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COMPUTATIONAL STUDY ON THE TRANSBORYLATION REACTION VIA DIBORANES

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1. Abstract

English

Through the use of DFT as the computational methods, with the hybrid functional ω B97XD, and the 6-31-G(d,p) basis set, a mechanistic analysis was performed on the transborylation reaction between an alkenyl boronate and a diborane reagent in order to explain the observed differences in activity and the stereospecificity.

A possible mechanism that satisfied the reactivity, selectivity and conformational details of the reaction was found. It consists in the diborane activation by the alkoxide generated from the solvent, followed by a nucleophilic attack from this activated diborane onto the other reagent, which after a series of rearrangements, leads to the desired final products, with a computed free-energy barrier of 27.2 kcal·mol⁻¹ (for methanol solvent). Another alternative mechanism starting by alkoxide coordination to the boryl substituent of the alkene substrate was also analysed, but calculations revealed that is less energetically favoured.

The free-energy barriers for other alcohols were also computed, with values that correlate with the experimental values of reactivity. Thus, the nucleophilic character of the alkoxides determines the reactivity in different solvents: the more nucleophilic the alkoxide is, the more activated the diboron reagent, and the lower the energy barrier. Moreover, the mechanistic proposal agrees with the observed lack of reactivity for non-protic solvents and the stereoselectivity retention of alkene configuration.

Catalan

Mitjançant l'ús de DFT com a mètode computacional, amb el funcional híbrid ω B97XD, i les funcions de base tipus 6-31-G(d,p), es va realitzar un anàlisi mecanístic de la reacció de transborilació entre un boronat d'alquenal i un reactiu diborà per poder explicar les diferències en activitat i estereoespecificitat observades experimentalment.

Es va trobar un possible mecanisme que satisfia la reactivitat i la selectivitat de la reacció observades experimentalment. Aquest consisteix en la activació del diborà per l'alcòxid generat pel dissolvent, seguit d'un atac nucleofílic del diborà activat a l'altre reactiu, i que seguit d'una sèrie de transposicions, s'obtenien els productes finals desitjats, amb una barrera d'energia lliure calculada de 27.2 kcal·mol⁻¹ (per al cas amb metanol com a dissolvent). També es va analitzar un mecanisme alternatiu que s'iniciés amb la coordinació del alcòxid al grup boril del alquè, però els càlculs van demostrar que això era energèticament menys afavorit.

També es van calcular les barreres d'energia lliure globals per la reacció en altres alcohols, i es van poder correlacionar amb la reactivitat experimental. El caràcter nucleofil dels alcòxids determina la reactivitat en els diferents dissolvents: quan més nucleòfil és el alcòxid, més activat està el reactiu diborà, i menor es la barrera energètica. Així mateix, la proposta mecanística és conseqüent amb la nula reactivitat en dissolvents apròtics i la retenció de la configuració dels alquens.

2. Objective

- The main objective of this work was to find a mechanism for the newly developed transborylation reaction between diboranes and alkenyl boronates by means of computational studies of the reaction using a DFT procedure.
- Another objective was to explain the difference in reactivity that this reaction presents on different solvents.
- The final objective was to try to find a reaction mechanism for a similar reaction, with a geminal bis-boron compound instead of a diborane as the source of the new borane group.

3. Introduction and experimental background

3.1 Case study

The reaction on which this project is focused, is the transborylation reaction between (E)-4,4,5,5-tetramethyl-2-(3-phenylprop-1-en-1-yl)-1,3,2-dioxaborolane, which will be referred as the substrate or the alkene; and 5,5,5',5'-tetramethyl-2,2'-bi(1,3,2-dioxaborinane), also known as Bis(neopentyl glycolato)diboron, which I will refer as B₂neop₂. This reaction has been recently discovered by the research group of Prof. Elena Fernández at the URV, and so the determination of its reaction mechanism would be important for its understanding.

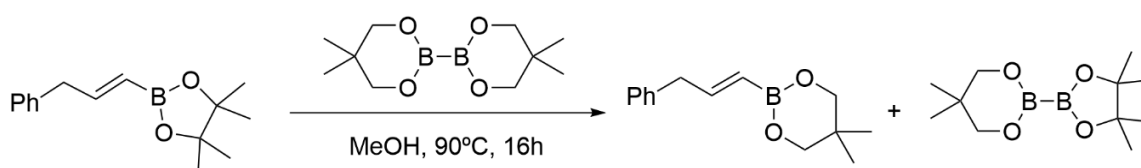


Figure 1. Transborylation reaction scheme

Structure	Systematic nomenclature	Identifyier
	4,4,4',4',5,5,5',5'-octamethyl -2,2'-bi(1,3,2-dioxaborolane)	B ₂ pin ₂
	5,5,5',5'-tetramethyl -2,2'-bi(1,3,2-dioxaborinane)	B ₂ neop ₂
	4,4,4',4',6,6'-hexamethyl -2,2'-bi(1,3,2-dioxaborinane)	B ₂ hex ₂

Figure 2. Nomenclature utilized in work for relevant species and moieties.

3.2 The transborylation reaction

The type of reaction studied here is of great interest, for it opens a new way to selectively synthesize new C-B bonds without the necessity of expensive and sometimes hazardous transition-metal catalysts. The transborylation reaction began as a consequence of expanding on the research of the hydroboration reaction.

Hoshi *et. al*¹² developed a novel reaction that allowed the formal hydroboration of alkynes with HB(OR)_2 reactants using HBCy_2 as catalyst. The high stability of dioxaborolanes (HB(OR)_2) prevented the reaction. However, the use of a more reactive borane (HBCy_2) to yield the alkenyl borane intermediate followed of the transborylation reaction with HB(OR)_2 allowed the formal addition to the triple bond.

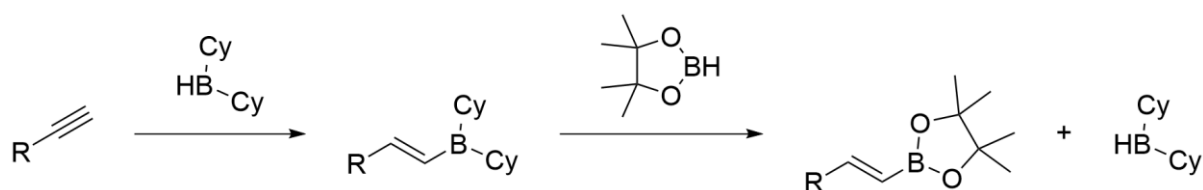


Figure 3. Alkyne hydroboration via a borane catalyst

In the second step, the exchange of borane groups was described computationally by a transition state that describes a σ -bond metathesis, where a pair of C-B and B-H bonds interchange groups, forming the desired alkenyl boronate moiety (Figure 4)³.

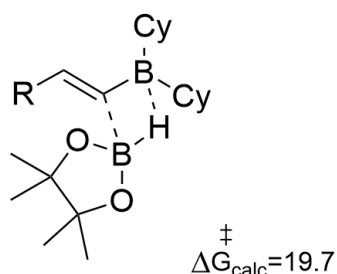


Figure 4. Proposed transition state for the transborylation step via σ -bond metathesis. Energy in $\text{kcal}\cdot\text{mol}^{-1}$

This reaction on itself is extremely useful for many synthetic applications, however the part with more relevance for this work, is the transborylation step. Depending on the boryl fragment bound to the $\text{C}(sp^2)$ further synthetic transformations can be achieved selectively or with more experimental ease.

Over the years, this type of transborylation related reaction has been studied and expanded onto more complex reactants¹⁴ or achieving double hydroborations².

However, one common factor on all of these reactions, was that these were hydroboration reactions, made use of a H-B(OR)_2 reagent, but in the reaction of this study we do not work with these, but with bis-diboron compounds which follow the formula $(\text{B(OR)}_2)_2$. This latter reactivity remains unexplored and therefore it is interesting to try to obtain more information including the characterization of the reaction mechanism.

3.3 Transition-Metal-Free reactivity of diboron compounds:

Reactivity of diboron reagents is usually related with diboration reactions of unsaturated bonds, usually accompanied by the use of transition-metal catalysts. Trivalent boron compounds are usually seen as electrophilic reactants. However, it has been computationally studied and reported²⁵ that diboron reagents can also react as a nucleophilic agent when activated by a Lewis Base in absence of transition-metal catalysts.

In this type of reactivity, the electron-rich Lewis Base can interact with the $(B(OR)_2)_2$ species donating its electron density to the empty p orbital of one of the boron atoms, quaternizing it in the process. The base polarizes the B-B σ -bond towards the non-quaternized boron, which provides it with a certain nucleophilic character.

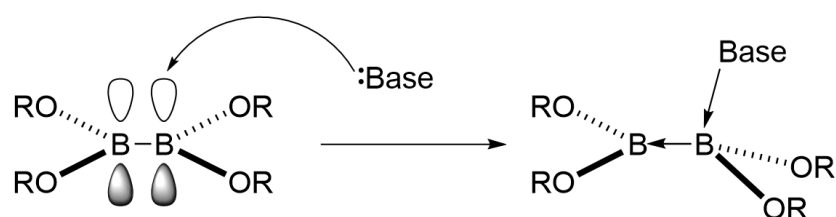


Figure 5. Schematic representation for the activation of the diboron reagent.

This type of reactivity has been applied experimentally, for example in the transition-metal-free monoborylation of 1,3-dienes⁵, and thus it was taken into account for a possible explanation for the reactivity of the diboron compound. As I will discuss below, this type of reactivity is important to understand the observed transborylation reaction.

3.4 Experimental background

When I started working on this project and during its duration, I received the latest information that the experimental group found on the laboratory. Alongside many other similar reactions, the main one, and the one that inspired this study would be the one between a E-vinylboronic ester (with the Bpin moiety) and either B_2neo_2 or B_2hex_2 , with the latter being more predominant, thanks to its ease of use in the laboratory compared with B_2neo_2 . Figure 1 shows one of the experimentally developed reactions.

From experimental outcome several hints were extracted (see Figure 6). For example, the reaction works well on methanol, but on THF did not work at all, and adding tiny amounts of methanol on the THF only produced yields of around 9%. The reaction is also very sensitive to the type of alcohol used. Figure 6 summarized the results of a selected reaction with different solvents.

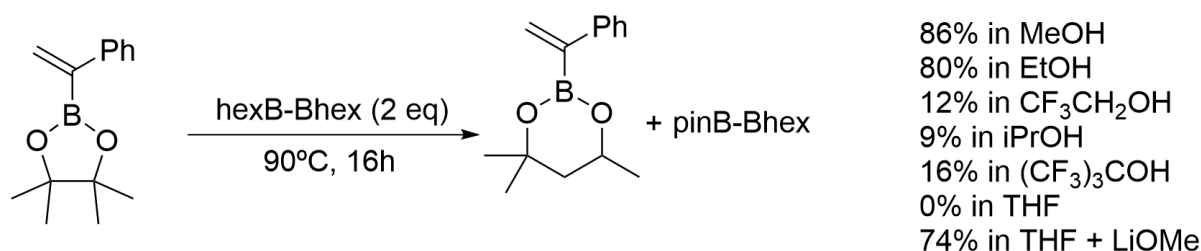


Figure 6. Yields of a transborylation reaction reproduced on different solvents

Although the reaction does not proceed at all in the aprotic solvent THF, when a base, lithium methoxide salt, was added the reaction proceeded with relatively high yields. This suggests that the alkoxide anions do have a fundamental role somewhere in the reaction mechanism. As we will describe in next section this observation prompted us to suggest that in the absence of base, the conjugate bases of protic solvents could act activating the substrates of the reactions.

Comparing the yield in methanol and in ethanol, we can see that the latter has a lower (although similar) yield compared with the methanol, and that the reaction in 2,2,2-trifluoroethanol (TFE for short) performs much worse than the previous two.

As part of the experimental input I received, I was informed that reaction depicted in Figure 7 was also achieved. This reaction is somewhat similar to the previous, with the difference being that the borane group on the alkene was Bhex instead of Bpin, that instead of working with a diborane compound, on this reaction, the other reagent was a geminal bis-boron compound, and that the Ph group of the alkene was directly bonded to the double bond.

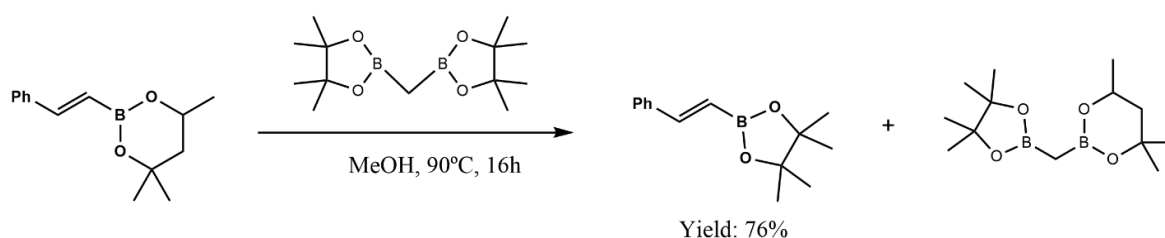


Figure 7. Reaction scheme and yield of the transborylation reaction with a gem bis-boron compound

3.5 Computational background

The research group where I did the TFG has done some attempts to elucidate the mechanism before I joined this project, however, they were unable to explain the observed reactivity. One hypothesis was that the reaction may follow a single step σ -bond metathesis, similar to the mechanism for the transborylation with HB(OR)₂ reagents. Nevertheless, the calculated energy barrier for this direct step was around 50 kcal·mol⁻¹ which would be too high.

Another hypothesis was that the alcohol solvent acts as a catalyst in the reaction. The acid-base equilibria of the alcohol can generate a methoxide that interacts with the substrate activating it. A related catalytic role of alcohol solvents has been recently reported by the host research group in the

telomerisation reaction with amines²⁴. As shown in Figure 8, the methoxy group would act as a Brønsted base deprotonating the alkene moiety, however the calculated free energy barriers indicate that the proposal is unviable.

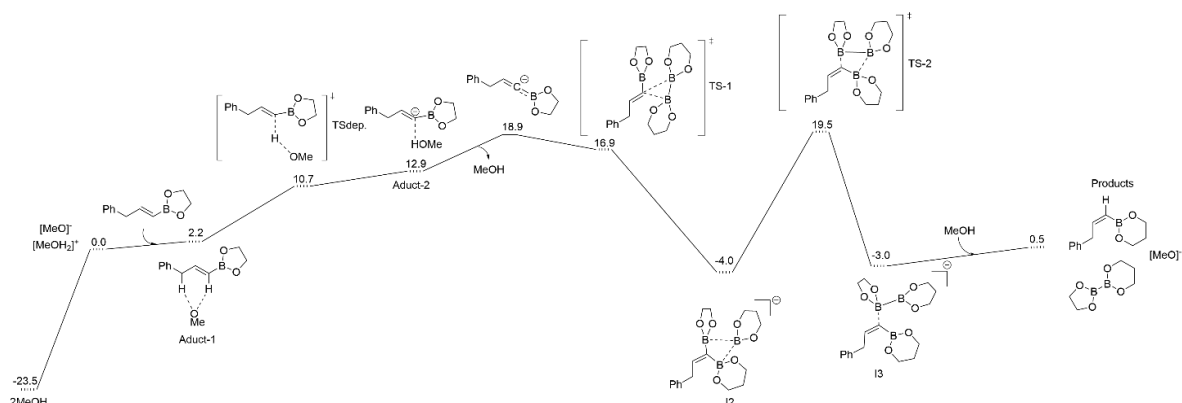


Figure 8. Free-energy profile of a proposed reaction mechanism for the transborylation reaction via carbanion formation. Free-energies in kcal·mol⁻¹

Having discarded that in the reaction mechanism the alkoxide acts as a Brønsted base, in this project we explore whether the alkoxide would act as a Lewis base, coordinating with the diboron reagents, donating its electron density, and thus activating it and starting the reaction mechanism. As seen in section 3.3, this is an already studied and reported reactivity of diboron compounds in presence of a Lewis base, so it wouldn't be far-fetched to think that the mechanism of the studied reaction could start this way.

4. Experimental section: Methods and computational details

4.1 Computational methods

For any quantum system, the wavefunction is the mathematical entity describes it and all its properties, with molecules being no exception to this statement. However, for most chemical systems we cannot obtain an analytical form of this function, in other words, we cannot solve the Schrödinger equation but obtain approximate solutions.

$$\hat{H}|\Psi\rangle = E|\Psi\rangle$$

In order to simplify the obtention of the wavefunction and therefore, determine the energy and many other properties of the system, we apply some approximations. One of these is the Born-Oppenheimer approximation, which states that due to the high mass of the atomic nuclei in relation to the electrons, the nuclei are considered static with the system, because for every little movement of the nuclei, the electron adapts instantaneously and therefore is like if they did not move.

However, to be able to obtain solutions to the Schrödinger equation, methods such as the Hartree-Fock (HF) method are needed. The HF method consists in approximating the complex multielectron wavefunction to a single determinant (the Slater determinant) composed of many one electron molecular orbitals. Through this approximation, solutions to the Schrödinger equations were achieved, and therefore, some properties and energies of atoms and molecules could be obtained.

However, this method is not perfect, and through the years some modifications and new methods have appeared. One of these methods would be the Density Functional Theory method, and to understand it, first we must look at how the HF energy is presented.

$$E_{HF} = V_{NN} + \hat{V}_{Ne} + \hat{T}_e + \hat{J}_{ee} - \hat{K}_{ee}$$

The energy in the Hartree Fock method is divided in groups: we have the nuclear repulsion energy (V_{NN}), the one-electron energy (kinetic + nuclei-electron potential) ($\hat{T}_e$), the electric repulsion energy ($\hat{J}_{ee}$) and the electron exchange energy that comes from the fermionic character of the electrons ($\hat{K}_{ee}$).

DFT proposes that the properties and interaction of the electrons is related to the electronic density of the system, and so it adds the exchange-correlation functional (E_{xc}) (electron correlation is not taken into account in HF), that substitutes the electron exchange exact value from HF, and depends on the electronic density function of the system (the density function being easier to work with compared to the wave-function).

$$E_{DFT} = V_{NN} + V_{Ne} + T_e + J_{ee} + E_{xc}[\rho]$$

Through applying the Hamiltonian operator to a wavefunction, its energy can be exactly known (although the wavefunction may be an approximated one), however the existence of a functional that being applied on a density function provides an exact energy is unknown, and so many types of functionals have appeared over the years trying to best achieve this goal.

4.2 Computational details

The DFT functional used on this work is the ω B97XD which is a hybrid functional²⁶, that meaning that on the exchange-correlation functional, the exact HF solution of the exchange energy is introduced to improve the functional. It includes Grimme's D2 dispersion model to describe long distance interaction between atoms. As for the basis set (which is the set of atomic orbitals that are used to build the final molecular orbitals), I used the 6-31G(d,p) set^{28,29}, which is a split valence double-zeta Pople's basis set. The 6-31G(d,p) basis set use 1 basis function for the non-valence orbitals, 2 basis functions for the valence orbitals, and one polarizable function (representing atomic orbitals with a higher orbital quantum number) in the form of d-type orbitals for the non-hydrogen atoms, and p-type orbitals for the hydrogens.

For calculating the energies and geometries of the reagents, products or stable intermediates Newton-Rapton method was used, and their nature as a minima en the potential energy surface was characterized by frequency calculations, ensuring that all of them are positive. Finding the transition states geometry suppose a greater degree of work and thought. The way the transition state structures were obtained was via a modified version of Newton-Raphson method that allows locating saddle points. The algorithm computes the first and estimates second derivatives of the energy and

uses them to move the atomic coordinates minimizing in all directions except in the coordinate connecting the reactants and products. Their characterization via frequency calculation should show that there is a negative value for a single direction, while all the others are still positive.

For this method to work correctly and for the algorithm to be able to reach the desired saddle point, one must start with a geometry that is sufficiently close to the transition structure. This represents the main difficulty of the search of the TS, for one does not know *a priori* how is said TS, therefore one must make use of their chemical intuition (alongside experience from other types of existing TS) to propose possible transition structures for the reaction.

Once a guess of the TS is made, one must do what is known as a partial geometry optimization, which is similar to a normal optimization but with some of the geometry parameters unchanging, usually bond distances. Using as starting geometry values the following distances: 2.10 Å for B-B bonds, or 2.0 Å for C-B bonds, turned out to be adequate to locate the key transition states.

Then a frequency calculation was performed in partially optimized structures in order to check that the largest negative frequency corresponds to the desired normal mode. When this happened, it meant that the proposed structure could be close in the PES to the saddle point, and the final geometry can be used as the initial point for TS search.

The free-energies were calculated at default values: 1 atmosphere of pressure and 298.15 K. The choice of temperature did not present a problem, for although it is not the same temperature as the one where the reaction is done, the general mechanism and its viability would not change drastically if done at more temperature. On the other hand, pressure did present a problem, which was the overestimation of the entropic component of the free energy for reactions occurring in solution.

This problem originates from the fact that the program is calculating the thermodynamic properties for a concentration of 1mol-atm⁻¹ which for 298.15K is equivalent to 1mol/24.5L. Thus, I changed the reference state to 1mol·L⁻¹ resulting in an energy correction of 1.893 kcal·mol⁻¹.

The solvent effects were evaluated with Polarizable Continuum Model (PCM)²¹⁻²³. This model creates a series of overlapping spheres where the desired molecule is contained and simulates the interaction of the solvent with the exterior of these spheres. Different solvents were used in this work, Methanol; 2,2,2-TriFluoroEthanol, and 2-Propanol, and their default dielectric constants were considered.

5. Results and discussion

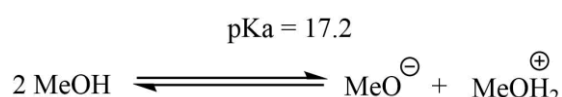
The proposed mechanism, in which the solvent can act as catalyst, is illustrated in Figure 9. According to this proposal, the reaction starts with the activation of diboron by an alkoxide acting as a Lewis base. In the case of aprotic THF solvent with the addition of lithium methoxide salt the formation of the MeO⁻→Bneop-Bneop adduct is straightforward. In next section, we discuss whether the formation of these species occurs also when in the absence of a base alcohol solvents are used.

5.1 Solvent autoprotolysis

Supposing that the reaction needs an activator like an alkoxide to take place, we must assume that when the reaction is done in an alcohol without any presence of an external base, the alkoxide that catalyses the reaction, is the one that is present in any protic solvent as a consequence of autoprotolysis.

To evaluate the free-energy cost associated to the solvent deprotonation to form the alkoxides we used the experimental pK_a values of alcohol autoprotolysis because DFT calculations produce large errors in charge separation processes. Autoprotolysis is defined by the IUPAC as: “A *proton (hydron) transfer reaction between two identical molecules (usually a solvent), autoprotolysis one acting as a Bronsted acid and the other as a Bronsted base.*”

In our case the solvent would be an alcohol (methanol for example) whose oxygen would act as a base deprotonating another alcohol molecule leaving us with a protonated alcohol-alkoxide pair (or the macrostructures that would form with the surrounding molecules).



Assuming a Boltzmann distribution of states, the free-energy differences can be calculated with the following expressions:

$$\begin{aligned} K_a &= 10^{-pK_a} = 10^{-17.2} \\ K_a &= e^{\frac{-\Delta G}{RT}} \\ \Delta G &= -RT \cdot \ln K_a = -1.987 \cdot 10^{-3} \frac{\text{kcal}}{\text{mol}} \cdot 298K \cdot \ln 10^{-17.2} \\ \Delta G &= 23.5 \frac{\text{kcal}}{\text{mol}} \end{aligned}$$

The purpose of this value is not to represent an accurate or factual energy barrier, but to show that the autoprotolysis does not represent a rate determining step of the reaction, for the energy required with it is smaller than some of the energy barriers calculated for the reaction profiles (see discussion of Figure 9 above).

5.2 Election of the Substrate

Although most of the experiments involved compounds with Bpin and Bhex moieties, in this TFG the Bhex moieties were substituted in favour of Bneop. The Bhex containing compounds are easier to handle experimentally compared to its Bneop compounds, but the latter is an easier moiety to work with in computational simulations. The reason behind that is that the Bneop group is more symmetric than Bhex, with Bhex lacking a symmetry plane that divides the group in two unlike Bneop.

The asymmetric nature of Bhex would have added another layer of complexity to this work, for the different conformations of the Bhex moiety must be taken into account when working with it, and thus the number of structures that should have been analysed would be extremely larger than when

working with Bneop. Therefore, and since the experimental results for both boryl moieties are very similar, we selected Bneop moiety for the computational study.

5.3 Characterization of transborylation mechanism

Figures 9 and 12 shows the computed free-energy reaction profiles for two different mechanisms: **(a)** the diborane activation mechanism, and **(b)** the substrate activation mechanism, respectively. In both mechanisms I assume that the methoxide can be naturally present in the medium due to autoprotolysis. Then it can interact either with the diborane, or with the boron from the substrate. The Lewis type coordination of the methoxy to the electrophilic boron with a formally empty p-orbital generates intermediate **1-a**. The adduct formed by methoxy coordination to the alkenyl boron is only slightly more stable than the activated diborane ($0.8 \text{ kcal}\cdot\text{mol}^{-1}$) The difference in energy is very small and so an equilibrium between the two species could exist.

More importantly, the overall activation free-energy required in mechanism **b**, initiated by substrate activation, is $38.1 \text{ kcal}\cdot\text{mol}^{-1}$ which is too high for this reaction (Figure 12). On the other hand, on the mechanism **a**, where the activated species is the diborane, the overall free-energy barrier ($27.2 \text{ kcal}\cdot\text{mol}^{-1}$) is not only a lot smaller than on the other path, but also falls into an energy value that is reasonable for a reaction that takes place at 90°C (Figure 9).

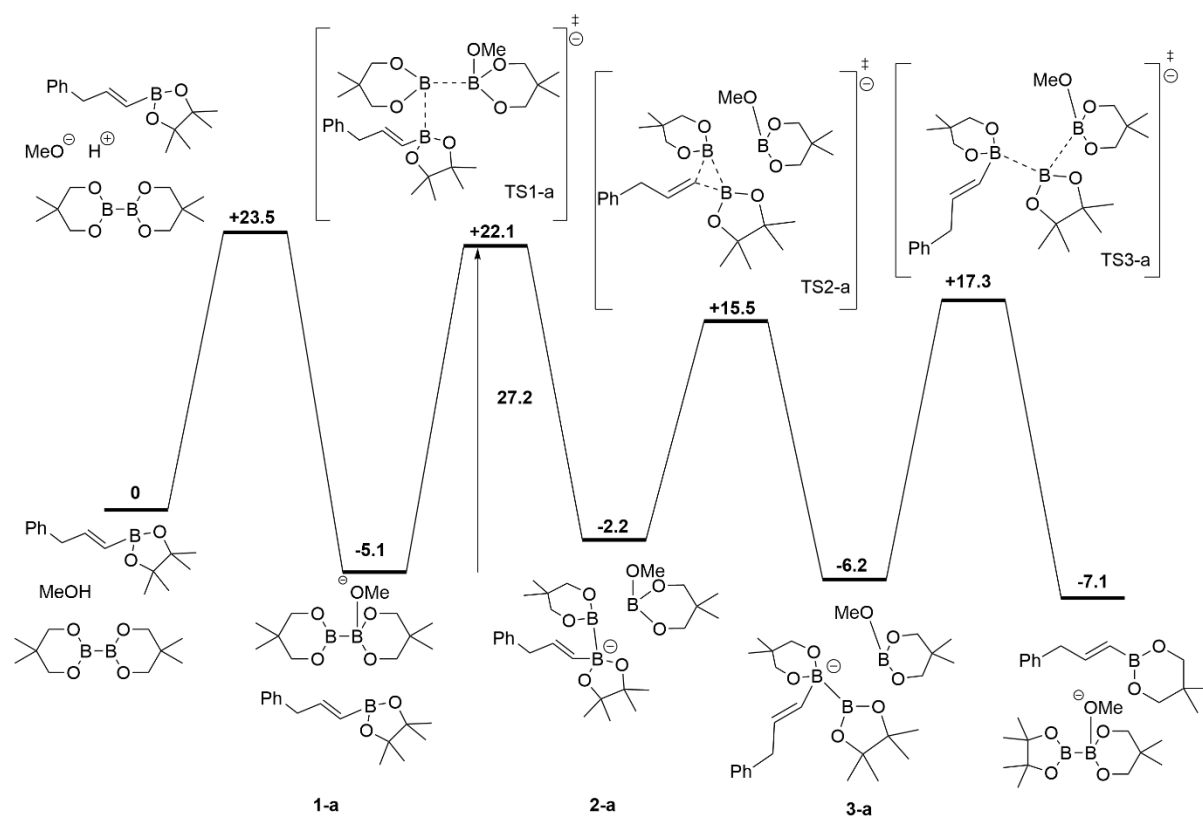


Figure 9. Free-Energy reaction profile ($\text{kcal}\cdot\text{mol}^{-1}$) for the transborylation reaction following the diborane activation by the methoxide.

The lower-energy mechanism **a** can be divided into 3 main steps, once the methoxide coordinates to the diborane. The B_2neop_2OMe species has now acquired a certain nucleophilic character, with the B-B bond polarized in favour of the non-quaternary boron. Thus, the first step of the reaction is an attack by the more electron-rich boron moiety of the diborane to the electrophile boron of the alkene substrate, breaking the previous B-B bond, and forming the intermediate **2-a**. This species consists of an asymmetric diborane (Bneo-Bpin) with the Bpin moiety quaternized by interaction with alkenyl moiety. This step is somewhat endergonic, and has an associated free-energy barrier ($27.2 \text{ kcal}\cdot\text{mol}^{-1}$) higher than the barrier of the alcohol autoprotolysis and so we can conclude that the alcohol autoprotolysis is not a determining factor on the reaction kinetics. The next step consists of the transposition of the boryl moieties at the alkenyl carbon resulting in the formation of a $C(sp^2)$ -B(neo) bond that is thermodynamically favoured by $4 \text{ kcal}\cdot\text{mol}^{-1}$. In the transition structure (**TS2-a**) the sp^2 carbon temporarily acquires a tetrahedral-like geometry with two almost equidistant C-B bonds (see Figure 10). The computed free-energy barrier ($17.7 \text{ kcal}\cdot\text{mol}^{-1}$) is moderate and lower than in the first step. The last step of mechanism **a**, corresponds to the formation of the new asymmetric diborane between the now leaving Bpin group and the Bneo-OMe molecule, yielding also the transborylated alkene product as the final products. This latter step has a moderate free-energy barrier ($23.5 \text{ kcal}\cdot\text{mol}^{-1}$) and is slightly exergonic with the products laying $2 \text{ kcal}\cdot\text{mol}^{-1}$ below the intermediate **1-a**.

The rate determining step (rds) of a reaction, is the step which has the largest associated energy barrier, and in this case, this would be the first one, the nucleophilic attack of the activated diborane to the alkene (**1-a** $\rightarrow$ **TS1a**). The kinetics of a reaction are usually related to the energy of the rds, and thus reaction activity is dependent on the chemical characteristics of the rds. As the rds is a nucleophilic attack, we suggest that by modifying the electron density of the activated diborane, the activity on the reaction could change. Because the electron density of the diborane is dependent on the type of alkoxide present, the overall activity can be related to the basicity of the alkoxide, with more basic alkoxides providing higher activities.

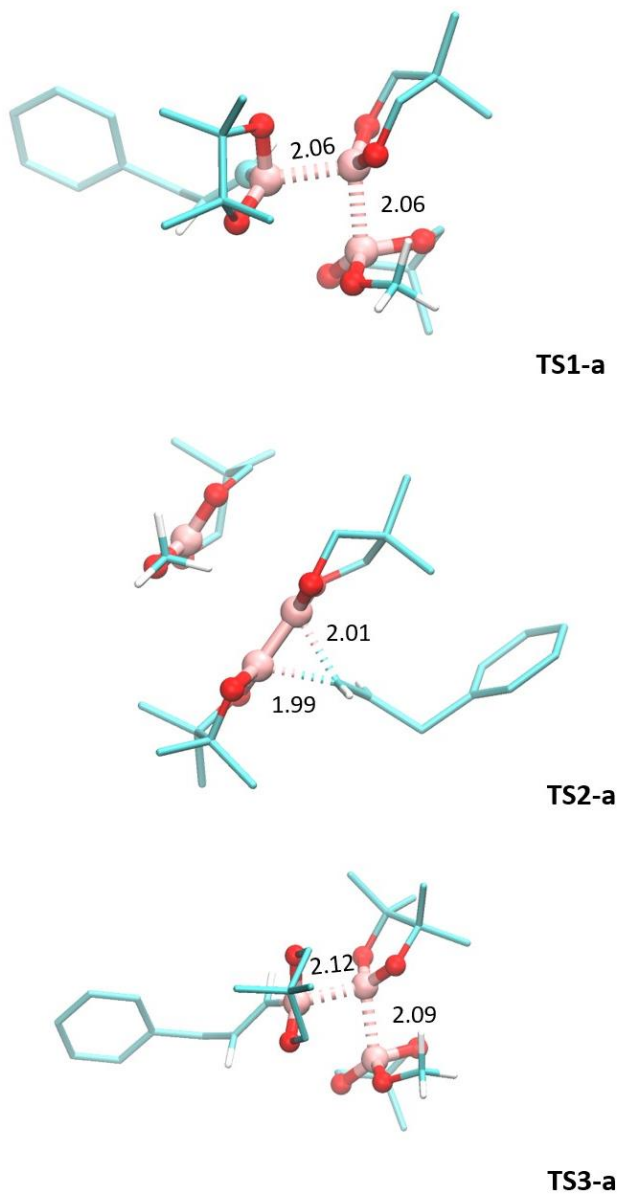


Figure 10. Molecular structure of the transition states for the mechanism a, with the chemically relevant atoms highlighted. Distances in Å.

As a way to analyse a bit of the electronic structure of the transition structures of the mechanism, a representation of their corresponding HOMO orbitals is presented in Figure 11. The HOMO is mostly localized around the reactive center (bond forming / breaking).

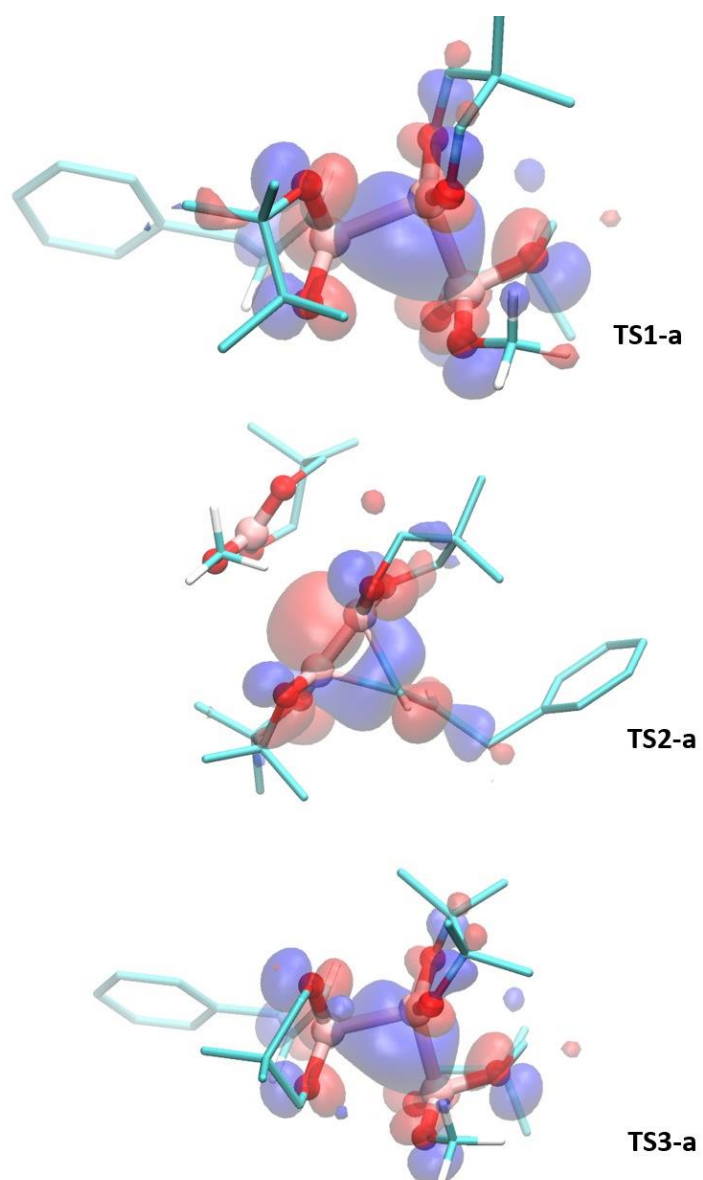


Figure 11. Visualization of the distributions of the electronic distribution of the HOMO orbitals for the three TS of the mechanism a (isovalue = 0.03)

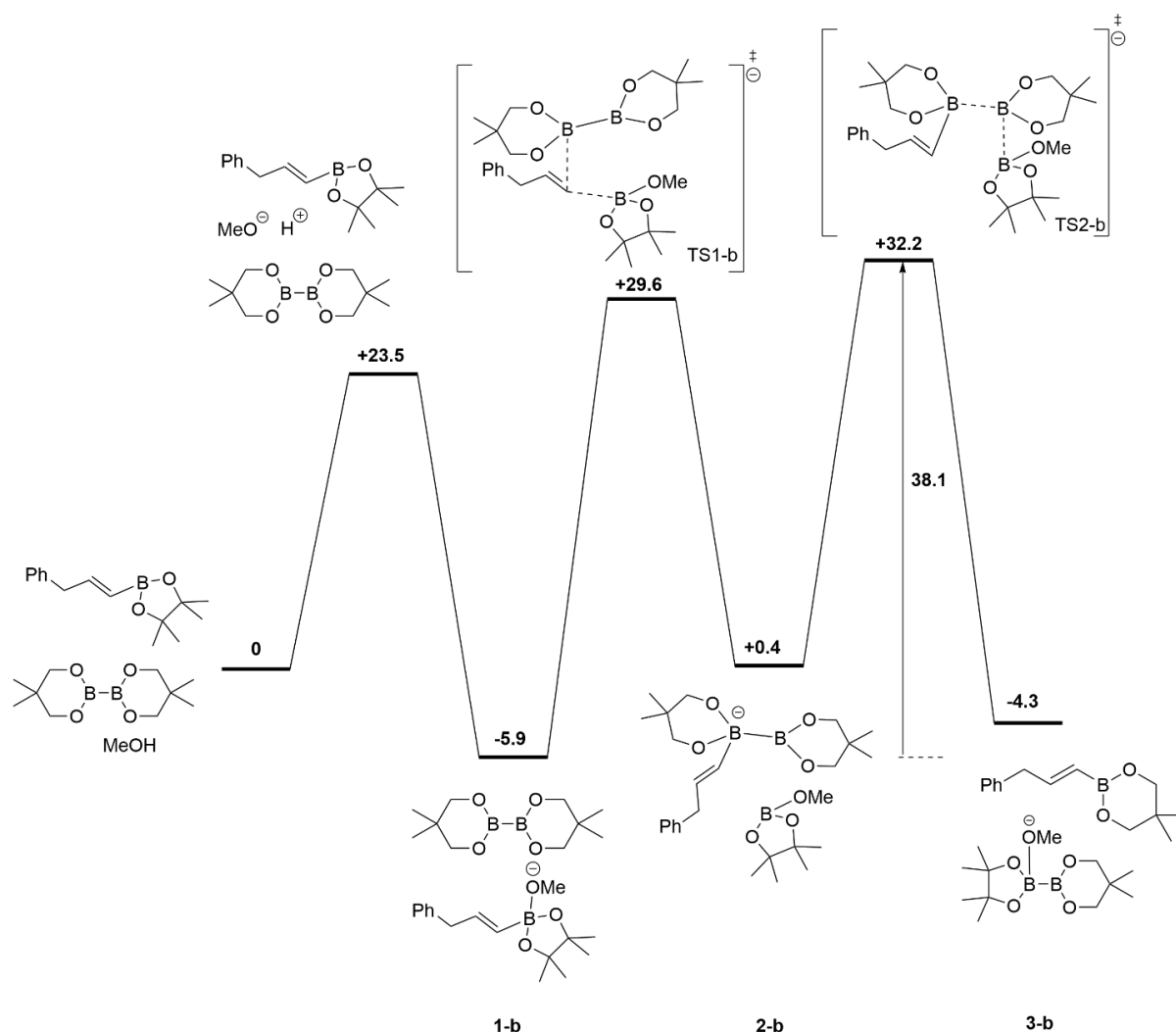


Figure 12. Free-Energy reaction profile (kcal·mol⁻¹) for the transborylation reaction following the substrate activation by the methoxide

In mechanism **b** (Figure 12), first the methoxide interacts with the boron atom of the olefin substrate, forming the corresponding adduct **1-b**. Then, the more nucleophilic sp^2 carbon of **1-b** interacts with the diborane. This leads to the formation of a new C-B bond with the Bneo2, while breaking one C-B bond of the Bpin moiety. Finally, the Bpin-OMe moiety would interact with the non-quaternary Bneo moiety, forming this new diborane, and the final product.

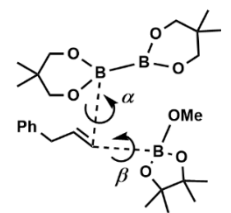
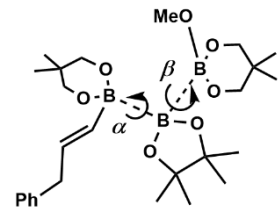
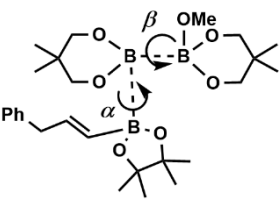
Now I will discuss in more detail why one reaction mechanism is more viable than the other. The reasoning behind that, is that although both reactions are thermodynamically favourable (as the start and end with the same reagents and products) one is kinetically more favoured due to having a free-energy barrier over 10 kcal·mol⁻¹ smaller. This huge difference in energy makes the alkene-activation mechanism much slower than its counterpart, which in practice translates to the last mechanism not being the one through which the reaction takes place.

As for the preservation of the E conformation of the alkene, the proposed mechanism **a** is consistent with the reaction stereochemistry. In all the reaction steps, the C(sp^2)-B bonds that formed and broke, always retain E configuration of the alkene, without forming any intermediate species that could lead to a conformation inversion.

5.4 The conformational problem

Something that became clear to me on the weeks of working on this project, is that for this particular reaction the stereoisomery of the intermediates/transition structures was important. Due to the conformational flexibility of the reactants and moieties, several orientations and conformations are possible for each structure. Moreover, this conformation differences can imply significant difference in energy. For example, in diborane molecule there are not any differentiable stable stereoisomers, for the molecules only has a single stable conformation. However, when the methoxide (or any other alkoxide) binds with one of its boron's, that boron acquires a quaternary configuration, and the previously simple planal trigonal geometry leads to a tetrahedral configuration. This, in junction with the other atoms of the Bneop moiety that form a cycle of 6 members, now that group does have two very distinct stable conformations: one similar the chair conformation and other resembling the boat or twist-boat (almost exactly the same that on cyclohexane). The computed difference of energy of the two conformations is 5.9 kcal·mol⁻¹ with the chair one being the lower of the pair. This conformational problem extended and magnified on the analysis of transition states, where extensive work was required in order to find the most stable configurations. Table 1 shows the different transition structures isomers that were studied and compared. Note that previous discussion was based on the lowest energy isomers.

Table 1. Free-Energy of different transition structures relative to their most stable counterpart (kcal·mol⁻¹)

General Structure	α	β	$\Delta\Delta G$
	-78.7 ^o	+55.1 ^o	0
	-73.3 ^o	-159.4 ^o	+4.7
	-178.6 ^o	+78.5	+2.8
	+162.7 ^o	-71.7 ^o	+1.9
	-88.6 ^o	-77.1 ^o	0
	+88.6 ^o	-58.8	+0.8
	-86.2 ^o	-82.5 ^o	0
	+85.1 ^o	+81.9 ^o	+1.7
	-89.3 ^o	+51.1 ^o	+4.1
	+179.0	+54.7	+7.4

5.5 Solvent effect on reaction activity

Knowing that the reaction yield is dependent on the alcohol used as solvent, I tried to understand the origin of this solvent effect. To do so, I will analyse how the reaction profile and the activation energies change when changing both the solvent used on the calculation and the activating alkoxide.

Initially, I selected 2,2,2-trifluoroethanol (TFE) which is more acid than methanol and for which a low yield was observed under the same conditions of methanol. Figure 13 shows the computed free-energy profile assuming the previously described mechanism **a** for methanol. Compared to methanol, the formation of the corresponding alkoxide in TFE has a lower energy cost due to its higher acidity. As a consequence of its higher acidity, the corresponding alkoxide is less basic, and thus the formation of the adduct is less stabilizing. We can see that both profiles follow similar tendencies, although with slightly different reaction barriers, the most significant of which, is the difference on the free-energy barrier of the nucleophilic attack of the diborane onto the alkene, which is larger for the TFE by about 1.0 kcal·mol⁻¹. Although the free-energy difference may seem to be low, we note that if we apply transition state theory an energy increase of 1 kcal·mol⁻¹ for the free-energy barrier means a rate constant 4 times larger at 90 °C. This ratio is not far from yield difference observed experimentally.

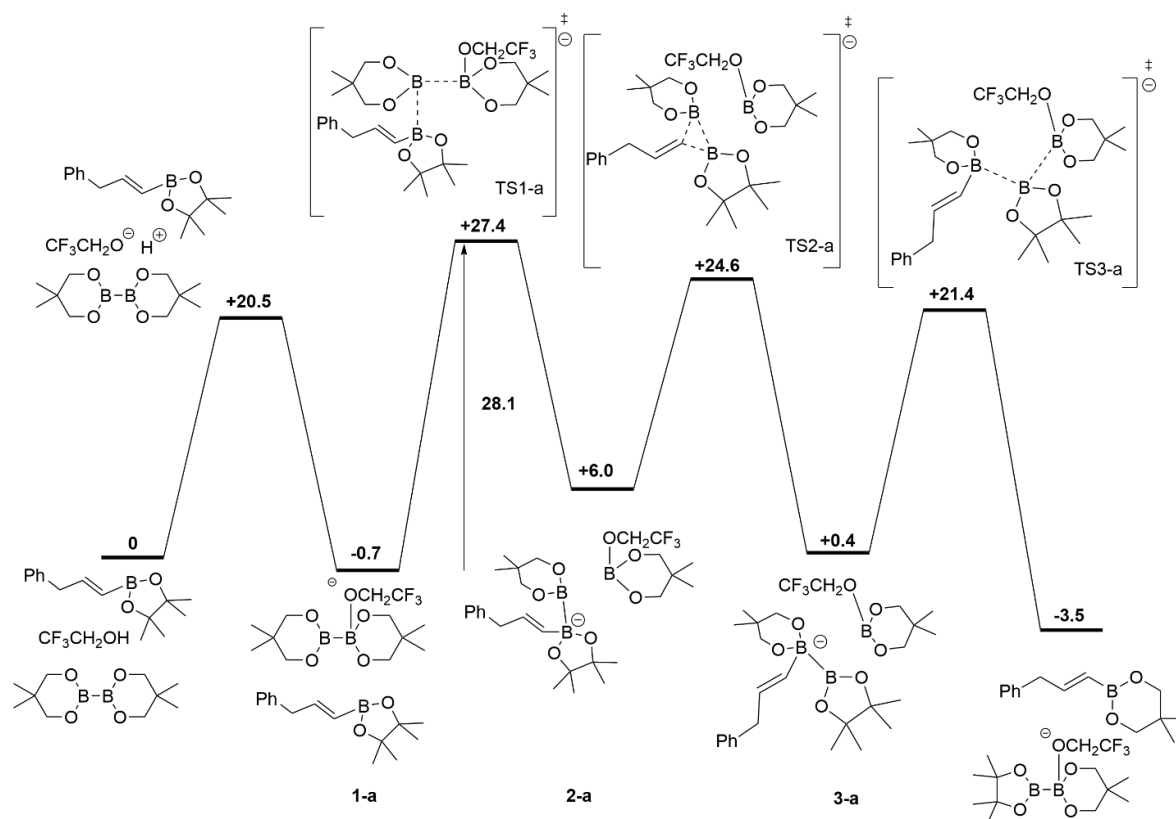


Figure 13. Free-Energy reaction profile (kcal·mol⁻¹) for the transborylation reaction following the diborane activation by TFE

I have also analysed the free-energy profile for other protic solvent, isopropanol. Table 2 compares the main energetic features for the 3 solvents studied. As a last solvent effect test, I calculated the free-energy barrier for the rate-determining step, the nucleophilic attack of the methoxy-diborane adduct to the alkenyl boron. What I observed was that the energy barrier was slightly higher than on TFE, with 28.22 kcal·mol⁻¹, which is 0.05 kcal·mol⁻¹ higher. The small free-energy difference agrees with

the observed similar yields on these solvents with the slightly higher yield in favour of TFE. This result may seem surprising because the alkoxide derived from isopropanol is more basic than that derived from TFE and similar to methanol (see pKa values in Table 2). We propose that for isopropanol the larger steric effects counterbalance the basicity.

Table 2. Relevant bibliographic and calculated values for the solvent effect analysis (kcal·mol⁻¹).

Solvent	Autoprotolysis pKa	Experimental yield	$\Delta G^{\ddagger}_{\text{rds}}$	$\Delta\Delta G^{\ddagger}$
Methanol ⁷⁻⁹	17.2	86%	27.21	0
2,2,2-Trifluoroethanol ⁶	15.0	12%	28.17	+0.96
Isopropanol ^{9,10}	20.8	9%	28.22	+1.01

5.6 Application of this mechanism onto a Geminal bis-boron compound

As part of TFG, I computed the mechanisms a and b for to the observed transborylation on geminal bis-boron reagent, trying to determine if its reaction mechanism is similar to the mechanism for the reaction with a diborane.

As in the diborane case, the substrate used in the computational simulation is not the same that the experimental one. As before, all Bhex moieties were substituted with Bneop, but in addition, a CH₂ was added between the Ph and the alkene of the substrate. These small changes made the find of the energy profiles much easier, while being similar enough to the experimental reagents.

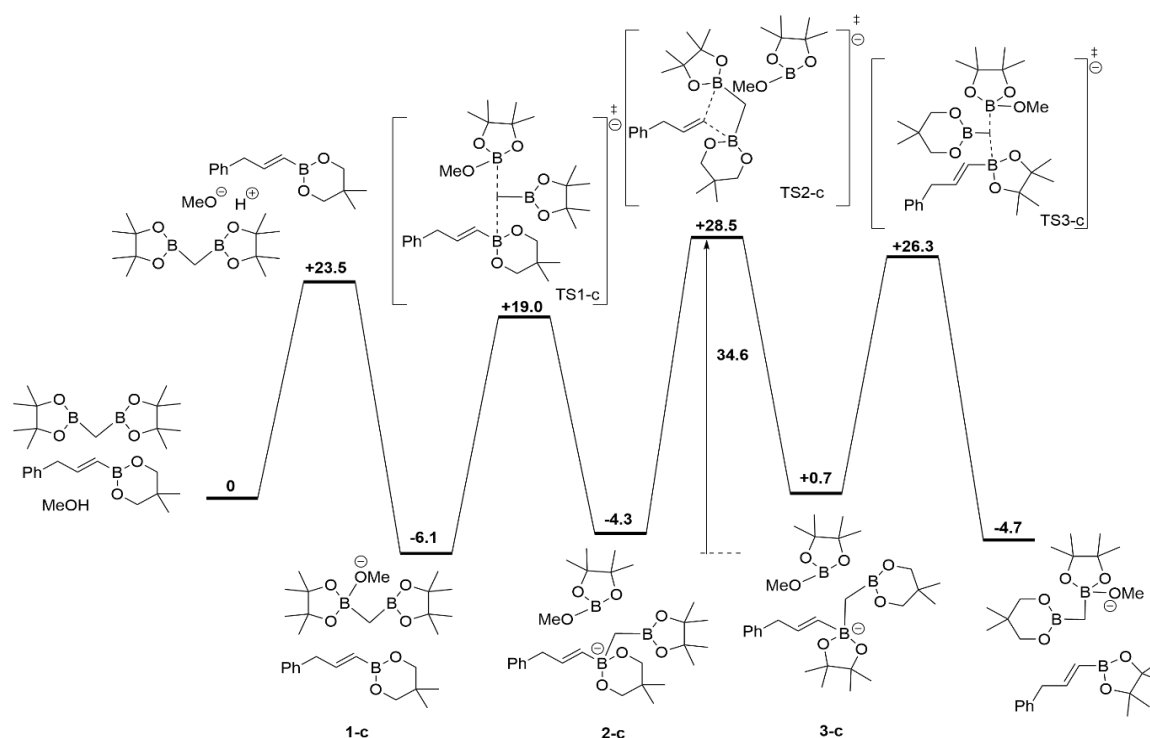


Figure 14. Free-Energy reaction profile (kcal·mol⁻¹) for the transborylation of the substrate with a geminal bis-boron reagent in methanol

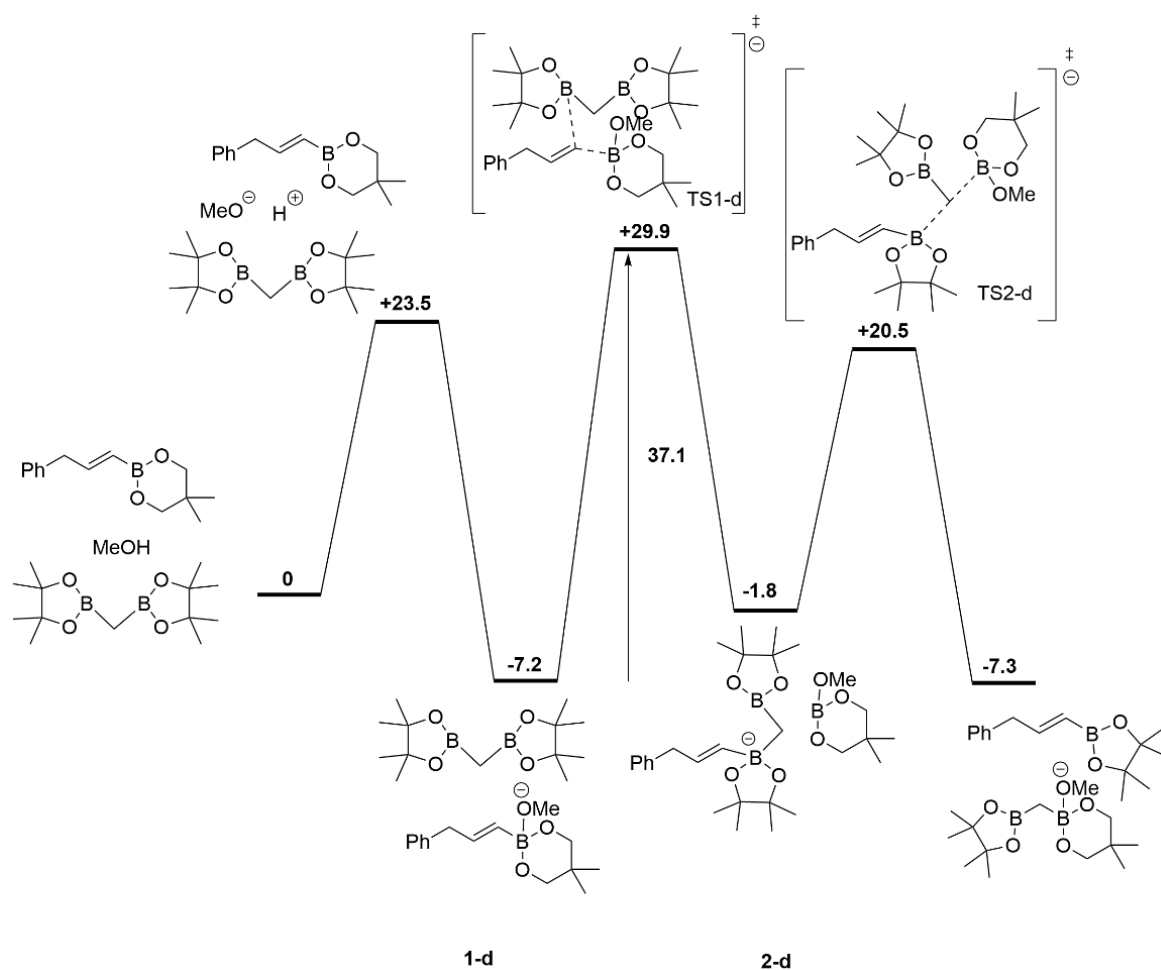


Figure 15. Free-Energy reaction profile (kcal·mol⁻¹) for the transborylation of the substrate with a geminal bis-boron reagent in methanol

As before, the mechanisms would start with the attack of the alkoxide present in the solution to either the alkene or the geminal compound, Figures 14 and 15, respectively.

When evaluating the pathway that follows the alkene activation (Figure 15) we obtain a too large free-energy barrier for the first step (37.1 kcal·mol⁻¹), discarding that viability of the mechanism.

In the mechanism depicted in Figure 14, the alkoxide would bind to a boron atom of the geminal molecule, inducing some nucleophilicity on the geminal carbon of the molecule. Next, the nucleophilic C of the adduct interacts with the boron of the alkene, at the same time weakening its bond with the quaternary boron, forming intermediate **1-c**. The reaction proceeds through transition state **TS1-c** with a distorted trigonal bipyramidal geometry of the geminal carbon, with the two hydrogens and the Bpin in the equatorial plane (Figure 16). The boryl fragments forming and breaking the bonds with the carbon atom are in axial position and the transition state resembles a S_N2 substitution. Following in the reaction direction, we would obtain a Bpin-OMe moiety and a new geminal-bis boron intermediate compound, where the alkenyl is bonded to the Bneop, intermediate **2-c**. In order to further progress on this reaction path I assumed a similar transposition reaction to the one that happens on the diborane example, where the compound evolves to the one that has the alkenyl fragment bonded to the Bpin moiety, intermediate **3-c**. The reaction proceeds through an transition state (**TS2-c**), where the carbon is at a similar distance from both boron atoms and is able to evolve to

form any of the two possible bonds. **TS2-c** structure (Figure 16) is too high in energy, $32.8 \text{ kcal}\cdot\text{mol}^{-1}$ above intermediate **1-c**, and a total reaction free-energy barrier is $34.6 \text{ kcal}\cdot\text{mol}^{-1}$. These values are not consistent with the high yields obtained experimentally. As for the explanation of the high energy value, I have two possible hypothesis. One would be that some other conformation exists, that would lower the steric repulsions and therefore the energy, however I don't really think that there exists an unseen conformation that would reduce the energy to the point of making this mechanism plausible. The other is that the cause of this high energy is the geminal carbon, because as seen in the transition structure (figure 16) the B-C-B angle is around 85° which is a very tensioned angle for a sp^2 carbon, making this compound more unstable. The last step of the reaction would be quite similar to the first, with the geminal carbon acquiring a trigonal bipyramidal structure again, and forming the asymmetric geminal compound, and the final alkene.

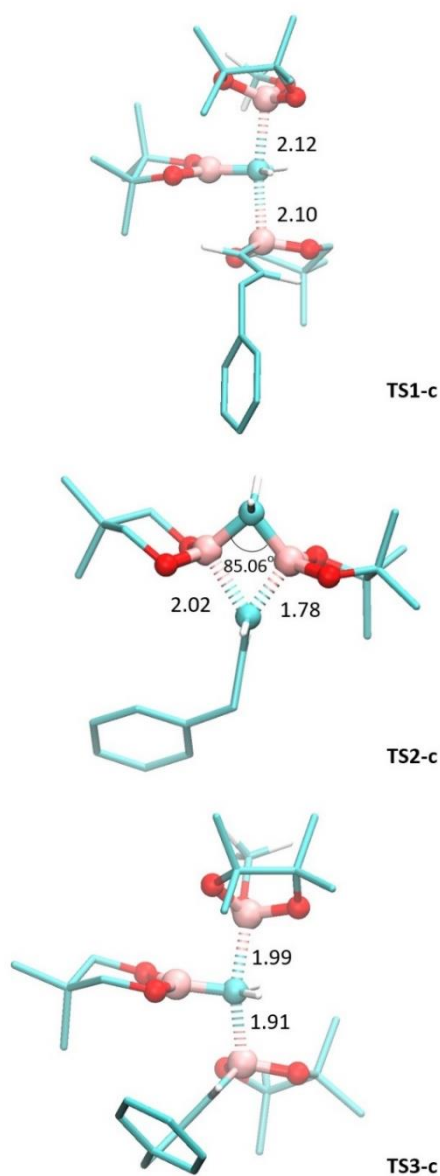


Figure 16. Molecular structure of the transition states for the mechanism d, with the chemically relevant atoms highlighted. Distances in Å.

The exploratory of the reaction mechanism for geminal bis boron compounds did not provide a plausible mechanism, but I hope that this study has discarded some reaction routes, helping to focus future computational studies in this reaction.

6. Conclusions

English

This work has proposed a plausible reaction mechanism for the recently developed transborylation reaction of alkenyl boronates with diboron reagents in methanol. The mechanism can be described as a nucleophilic attack of an activated diborane to the electrophilic boron of the substrate, followed by a series of transmutations that lead to the desired product. This mechanism successfully explains the observed conservation of the alkene E conformation, and the relatively high, computed free-energy barrier is consistent with the elevated temperature needed for this reaction to work. The rate-determining step corresponds to the nucleophilic attack of the $[\text{MeO} \rightarrow \text{Bneop-Bneop}]^-$ adduct to the alkenyl boron atom.

The effect of different solvents was also studied for the TFE and isopropanol case, with results that explain the experimental data. More acidic solvents have less basic alkoxides (conjugated bases), and consequently, their ability to activate diboron reagents is reduced. This correlation with the observed solvent effects further supports the proposed mechanism. Moreover, the steric effects of the alkoxide can also play a role on the reaction activity.

In summary, the main objective of this work was achieved by describing the underlying mechanism behind the newly found transborylation reaction. Moreover, the atomistic characterization of the mechanism could lead to new developments on C-B bond forming chemistry.

Catalan

Aquest treball ha proposat un mecanisme de reacció plausible per la recentment desenvolupada reacció de transborilació d'alquenil boronats amb reactius diborans en metanol. El mecanisme pot ser descrit com un atac nucleofílic d'un diborà activat al bor electrofílic del substrat, seguit d'una sèrie de transmutacions que condueixen al producte desitjat. Aquest mecanisme explica correctament la conservació de la conformació E de l'alquè, i la seva relativament alta barrera d'energia lliure calculada és consistent amb les elevades temperatures necessàries per dur a terme la reacció. El pas determinant de la velocitat correspon a l'atac nucleofílic de l'adducte $[\text{MeO} \rightarrow \text{Bneop-Bneop}]^-$ al bor de l'alquenil.

L'efecte dels diferents dissolvents també va ser estudiat per als casos del TFE i l'isopropanol, amb resultats que expliquen les dades experimentals. Els dissolvents més àcids tenen alcòxids menys bàsics (les seves bases conjugades), i en conseqüència, la seva habilitat per activar els diborans es redueix. Aquesta correlació amb l'efecte dels solvents observat experimentalment, suporta el mecanisme proposat. També, els efectes estèrics dels alcòxids poden tenir un paper important en la reactivitat.

En resum, l'objectiu principal d'aquest treball va ser aconseguit al poder descriure el mecanisme darrere la recentment descoberta reacció de transborilació. A més, la caracterització atomística del mecanisme pot portar a nous avenços en la química de la formació d'enllaços C-B.

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Annex

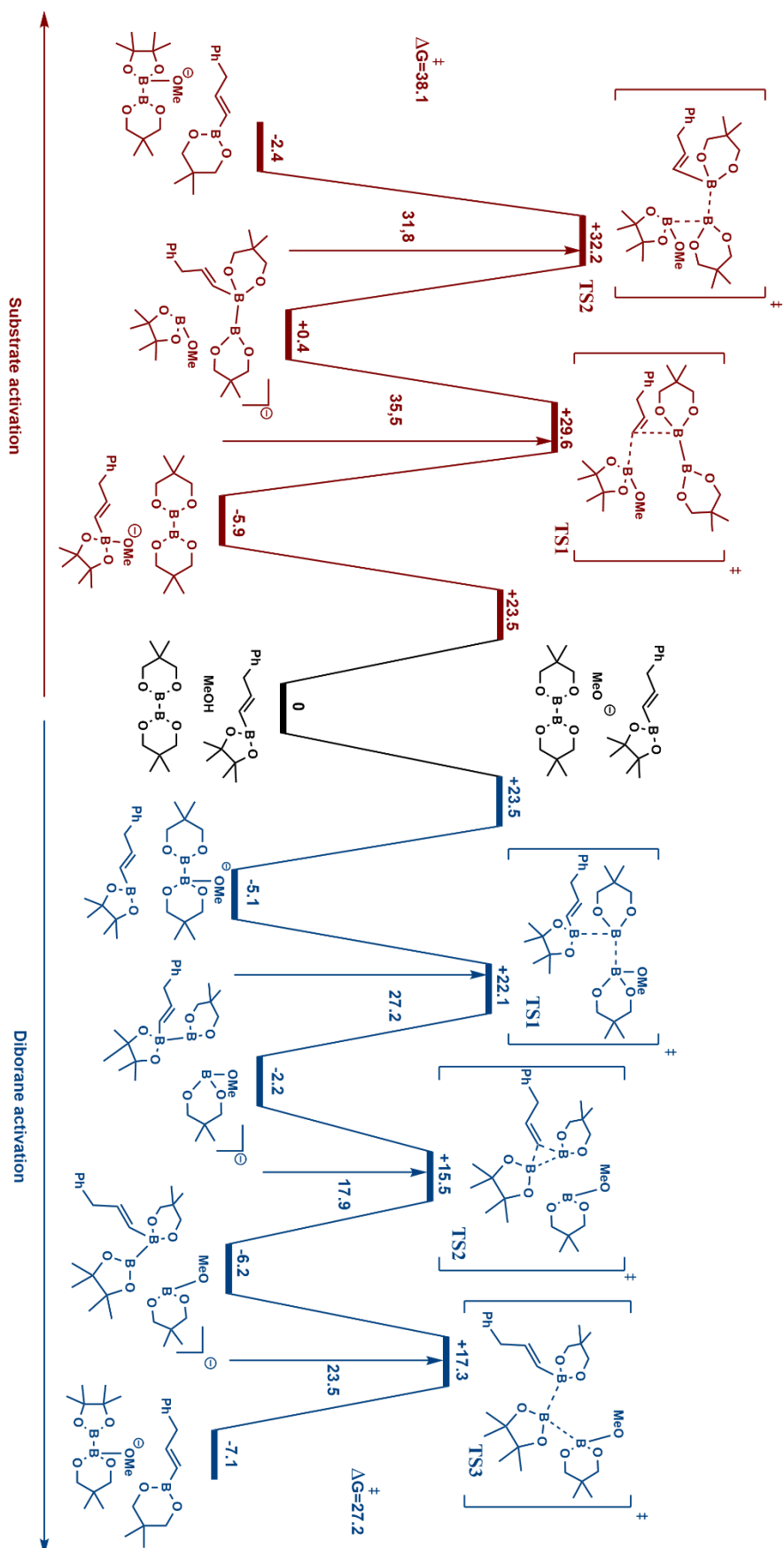


Figure A1. Reaction profile (kcal·mol⁻¹) for both reaction paths on the transborylation with a diborane

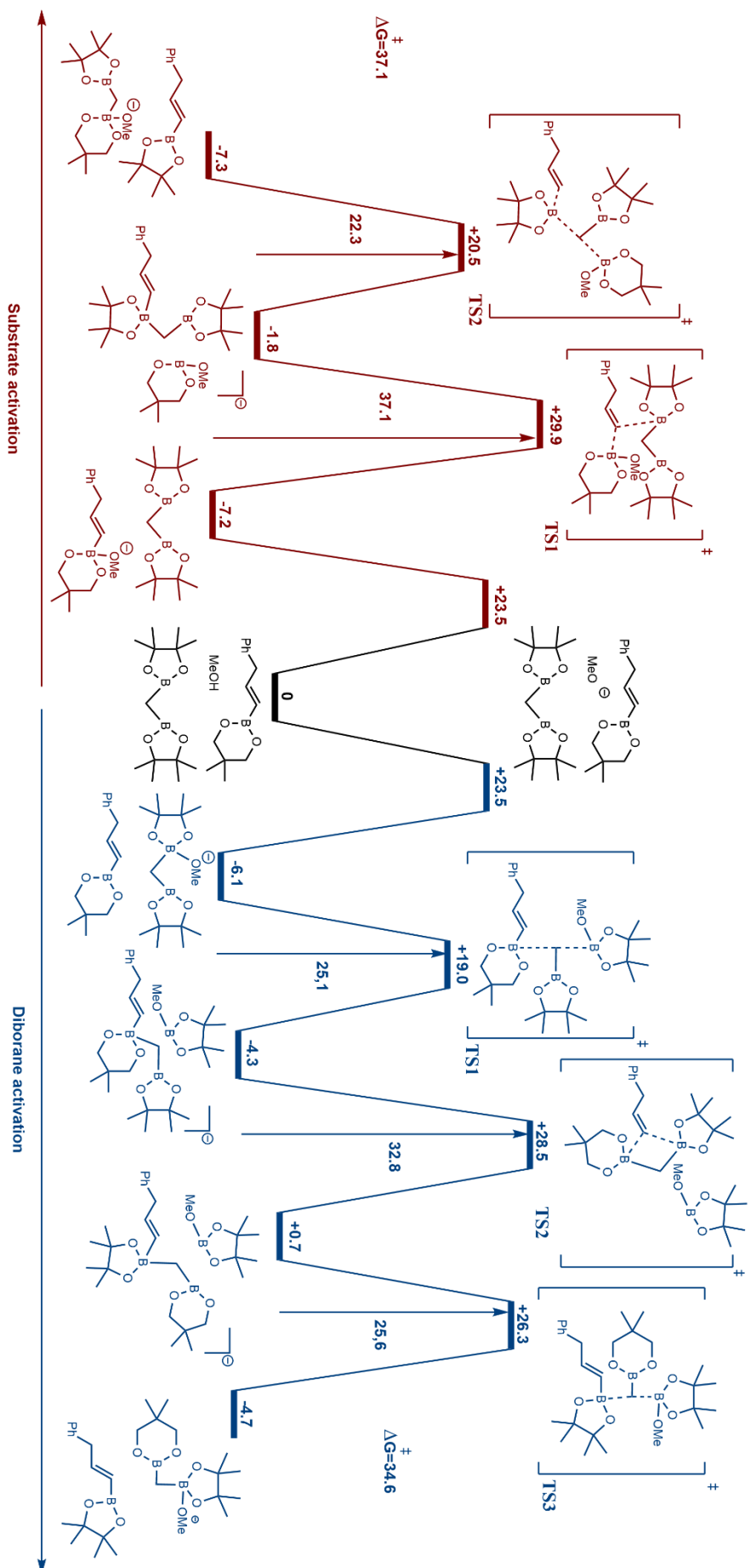


Figure A2. Reaction profile (kcal·mol⁻¹) for both proposed reaction paths on the transborylation with a geminal bis-boron compound.