Insights Into The Origin of Selectivity For [2+2] Cycloaddition Step Reaction Involved In The Mechanism of Enantioselective Reduction of Ketones With Borane Catalyzed By A B-Methoxy Oxazaborolidine Catalyst Derived From (–)-β-Pinene. A DFT And Combined Topological ELF, NCI And QTAIM Study

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Insights into the origin of selectivity for [2+2] cycloaddition step reaction involved in the mechanism of enantioselective reduction of ketones with borane catalyzed by a *B*-methoxy oxazaborolidine catalyst derived from (–)- β -pinene. A DFT and combined topological ELF, NCI and QTAIM study

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Abstract

Theoretical studies on [2+2] cycloaddition step involved in the Enantioselective Reduction of ketones with borane catalyzed by a *B*-MethoxyOxazaborolidine Catalyst Derived from Pinene has been performed by means of the Density Functional Theory method (DFT) at MPWB1K /6-31G (d,p). The formation of the **M5a(S)** complexes via transition state **TSa(S)** was the more favorable pathway among other [2+2]cycloaddition competing steps. The explanation of the formation of O-B and N-B through two-stage one-step mechanism was allowed by means of the electron localization function (ELF) topological analysis. NCI and QTAIM analysis of the two computed transition states **TSa(S)** and **TSa(R)** indicate that the difference between both in term of stability comes mainly from the orientation of the methanediyl group inside the pinene skeleton, which implies that CH-H...O interaction found at **TSa(S)** is the great factor that makes it more stable than **TSa(R)**.

Key Words: Oxazaborolidine;; Enantioselective reduction; [2+2] cycloaddition ; DFT ; ELF ; NCI ; QTAIM ; MPWB1K ; B3LYP ; M06.

1. Introduction

The asymmetric reduction of prochiral ketones catalyzed by chiral oxazaborolidine derived from amino alcohol has been a powerful protocol to induce high enantioselectivity^{1,2,3}, where the absolute configuration of the major enantiomer was determined to be *R* or *S* under the influence of B and/or N-substitutes as expected for the pathway of the mechanism established by Corey *et al*^{2,4}, which involves the following steps (see [Scheme 1](#)): formation of the **M2'** active catalyst and the catalyst-borane-ketone adduct **M3**; proton transfer from the borane moiety to the carbonyl carbon in **M3** generates four-membered ring(B(8)-N(3)-B(4)-O(7)) at the catalyst-alkoxyborane adduct **M5**; formation of the final product (chiral secondary alcohol) and the release of the catalyst. Somewhat surprisingly, several computational studies on the mechanism of the reaction show the change

of the selectivity of the oxazaborolidine-borane-ketone adduct complexes in the [2+2] cycloaddition step compared to that obtained in the remained steps involved in the mechanism^{5,6}. This finding urged me to disclose certain vital mechanistic insights into this step of the title reaction. Very recently I have considered an expanded conformational analysis of *B-methoxy* oxazaborolidine includes “**M1a**” and “**M1b**” conformations as preformed catalysts producing two catalytic cycles **a** and **b**⁷ (see Fig 1).

Fig. 1 The transfer of H(1') to O(2') and H(1'') to O(2'') in the catalyst **cata**

As shown in Fig. 1, the migration of H(1') from N(1) to O(2') pointed by the letter "**a**" gives rise, after removal of MeOH to **M1a**, while the other type of structure of oxazaborolidine **M1b** is obtained by transferring of H(1'') from N(1) to O(2'') which pointed by letter "**b**". Thus, there are two competing enantioselective cycles (mode **a** and **b**).

Scheme 1. Possible competing pathways for the title reaction

Therefore, the goal of this work is to understand the origin of the selectivity along the [2+2] cycloaddition step involved in the reaction mechanism of the reduction of acetophenone as prochiral ketone with borane catalyzed by B-methoxy-oxazaborolidine derived from (1R,2S,3R,5R)-3-amino-6,6-dimethyl-2-hydroxy-bicyclo[3.1.1]-heptane. Moreover, there are still some key issues that need to be shed light on and answered such as: (1) what is a suitable suite of density functional which can reproduce the correct and compatible selectivity? (2) What kind of active catalyst that will be involved in the reaction mechanism, consequently? (3) What is the conformation of the oxazaborolidine-boran-ketone adducts in the cycloaddition of the reaction? (4) Key factors governing the enantioselectivity of the title step

of the reaction? All these raised questions prompt us to explore the role of the conformation of the catalyst-borane-keton adduct to induce the *S*-selectivity in this [2+2] cycloaddition step of the mechanism. We would predict and validate which atoms involved in the 22CA reaction would be the best electrophilic sites by using Houk's rule. Additionally, we perform an Electron localization function(ELF)⁸, noncovalent interaction index (NCI)⁹ and Quantum Theory of atoms in Molecules(QTAIM)¹⁰ analysis to gain insight into the origin of selectivity of the title step by obtaining a chemical information relative to lone pair, bonding electron and especially investigate the hydrogen bonds (H-bonds) arising from the close contact of the H atom of the methanediyl group inside the pinene skeleton to atoms underneath in the oxazaborolidin ring.

2. Models and computation

In the present study, all theoretical calculations were performed using the GAUSSIAN 09¹¹ suite of programs. All structures were optimized by employing the MPWB1K¹² functional, which enhances thermodynamic calculations, together with the standard 6-31G(d,p)¹³ basis set. These 22CA structures were further optimized by means of B3LYP^{14,15} and M06¹⁶ functionals, where the corresponding energies were compared with the previously mentioned MPWB1K one. The stationary points were analyzed by frequency calculations, testing that all reactants, intermediates, products and transition states have zero and only one imaginary frequency, respectively, and are verified by the internal reaction coordinate (IRC)^{17,18} calculations, at the same level of theory, to identify all transition states. We then refined the energy by conducting single-point energy calculations for all the stationary points involved in the first step at a higher level of B3LYP/6-311++G(2df, 2pd)/IEF-PCM_{THF}, M06-2X/6-311++G(2df, 2pd)/IEF PCM_{THF}//M06-2X/6-31G(d, p), and MPWB1K /6-311++G(2df, 2pd)/IEF-PCM_{THF}// MPWB1K /6-31G(d, p) level based on the B3LYP/6-31G(p, d), M06-2X/6-31G(p,d), M06-2X/6-31G(d, p), and MPWB1K /6-31G(p, d) optimized geometries in the gas phase, where IEF-PCM^{19a,b} was used for the single points calculations to simulate the effects of solvent . It is worth noting that we will summarized the computational method of geometry optimization at the B3LYP/6-31G(d, p), M06-2X/6-31G(d, p), M06-2X/6-31G(d, p), and MPWB1K /6-31G(p,d) level in Table 1, the single point energy calculated at the B3LYP/6-311++G(2df, 2pd)/IEF-PCM_{THF}, M06-2X/6-311++G(2df, 2pd)/IEF PCM_{THF} and MPWB1K /6-311++G(2df, 2pd)/IEF PCM_{THF} in Table 2, and the energy refinement in Table 3.

Table 1. B3LYP/6-31G(d,p), M06/6-31G(d,p) and MPWB1K /6-31G(d,p) Total E (a.u) and relative energies ΔE (kJ/mol), in the gas phase of the stationary point SP involved in the [2+2] cycloaddition reaction along the reaction pathways (**a** and **b**).

	B3LYP		M06		MPWB1K	
	E	ΔE	E	ΔE	E	ΔE
M1a(S)	-1033.68651553		-1032.97455048		-1033.15708640	
M1a(R)	-1033.68192580		-1032.97597866		-1033.15959934	
M1b(S)	-1033.69202391		-1032.98312593		-1033.16797776	
M1b(R)	-1033.69680982		-1032.98724956		-1033.17297179	
TSa(S)	-1033.66439622	58.07	-1032.96198010	33.00	-1033.15094472	16.12
TSa(R)	-1033.66280448	50.20	-1032.96145491	38.13	-1033.15002231	25.14
TSb(S)	-1033.66789495	63.35	-1032.96467543	48.44	-1033.15037217	46.22
TSb(R)	-1033.67145749	66.56	-1032.96713722	52.80	-1033.15611826	44.25
M2a(S)	-1033.68429536	5.83	-1032.98126266	-17.62	-1033.17872432	-56.81
M2a(R)	-1033.68256875	-1.69	-1032.97967505	-9.70	-1033.17714210	-46.06
M2b(S)	-1033.68777972	11.14	-1032.98447205	-3.53	-1033.18163852	-35.87
M2b(R)	-1033.68890323	20.76	-1032.98369791	9.32	-1033.18151743	-22.44

Table 2. Comparison of the single-point energies calculated at B3LYP/6-311++G(2df, 2pd)/IEF-PCM_{THF}//B3LYP/6-31G(d, p), M06-2X/6-311++G(2df, 2pd)/IEF PCM_{THF}//M06-2X/6-31G(d, p), and MPWB1K /6-311++G(2df, 2pd)/IEF PCM_{THF}//MP1W/6-31G(d, p) Total E (a.u) and relative energies ΔE (kJ/mol), of the stationary point SP involved in the [2+2] cycloaddition reaction along the reaction pathways (**a** and **b**).

	B3LYP		M06		MPWB1K	
	E	ΔE	E	ΔE	E	ΔE
M1a(S)	-1033.99841174		-1033.26496359		-1033.44283384	
M1a(R)	-1033.99272126		-1033.26500755		-1033.44432460	
M1b(S)	-1034.00429741		-1033.27402925		-1033.45356296	
M1b(R)	-1034.01006063		-1033.27837707		-1033.45893569	
TSa(S)	-1033.97467172	62.33	-1033.25111290	36.36	-1033.43583219	18.38
TSa(R)	-1033.97430419	48.35	-1033.25149929	35.47	-1033.43629024	21.09
TSb(S)	-1033.97884869	66.82	-1033.25493926	50.12	-1033.42683420	70.17
TSb(R)	-1033.98215068	73.28	-1033.25659682	57.18	-1033.44080619	47.60
M2a(S)	-1033.99444560	10.41	-1033.27114838	-16.24	-1033.46364513	-54.64
M2a(R)	-1033.99228266	1.15	-1033.26869936	-9.69	-1033.46154073	-45.20
M2b(S)	-1033.99718268	18.68	-1033.27359733	-1.13	-1033.46536747	-30.99
M2b(R)	-1033.99930174	28.25	-1033.27418241	11.01	-1033.46687270	-20.84

Table 3. Comparison of the energies refinement of the single-point energies calculated B3LYP/6-311++G(2df, 2pd)/IEF-PCM_{THF}// B3LYP/6-31G(d, p), M06-2X/6-311++G(2df, 2pd)/IEF PCM_{THF}//M06-2X/6-31G(d, p), and MPWB1K /6-311++G(2df, 2pd)/IEF PCM_{THF}//MP1W/6-31G(d, p) plus thermal correction calculated at B3LYP/6-31G (d, p), M06/6-31G (d, p) and MPWB1K /6-31G (d, p), total E (a.u) and relative energies ΔE (kJ/mol) of the stationary point SP involved in the [2+2] cycloaddition reaction along the reaction pathways (a and b).

	B3LYP		M06		MPWB1K	
	E	ΔE	E	ΔE	E	ΔE
M1a(S)	-1033.59705974		-1032.85772559		-1033.02613084	
M1a(R)	-1033.59244726		-1032.85781455		-1033.0234046	
M1b(S)	-1033.60331841		-1032.86642025		-1033.03566596	
M1b(R)	-1033.61085663		-1032.87461207		-1033.03935769	
TSa(S)	-1033.57043072	69.91	-1032.84589190	31.07	-1033.01775419	21.99
TSa(R)	-1033.57075819	56.94	-1032.84607729	30.82	-1033.01416424	24.26
TSb(S)	-1033.57546869	73.12	-1032.85119026	39.99	-1033.00766620	73.51
TSb(R)	-1033.57855168	84.82	-1032.85372682	54.83	-1033.02455419	38.87
M2a(S)	-1033.5879216	23.99	-1032.86502038	-19.15	-1033.04160913	-40.64
M2a(R)	-1033.58601666	16.88	-1032.86136336	-9.32	-1033.03795573	-38.20
M2b(S)	-1033.59104468	32.22	-1032.86578433	-1.67	-1033.04236247	-17.58
M2b(R)	-1033.59323174	46.72	-1032.86792141	17.57	-1033.04482770	-14.36

The frontier molecular orbital (FMO) theory was used to interpret and investigate the reactivity and intramolecular interactions in concerted [2+2] cycladdition using houbt's rule based on the HOMO and LUMO energies obtained within the Kohn–Sham scheme. The electronic chemical potential μ ²⁰ and the global electrophilicity index ω ²¹ were calculated from the energies of the frontier molecular orbitals ε_{HOMO} and ε_{LUMO} , as $\mu = \varepsilon_{HOMO} + \varepsilon_{LUMO}/2$ and $\omega = \mu^2/2(\varepsilon_{LUMO} - \varepsilon_{HOMO})$.

Thermodynamic calculations such as enthalpies, entropies, and Gibbs free energies were computed at the standard statical thermodynamic at 298.15 K and 1 atm²². The electron localisation function (ELF)²³ topological analysis was done with Multiwfn software using the MPWB1K/6–31G(d,p) wave functions of the pertinent steps selected from the IRC diagram. The evaluation of the reduced density gradient and low-gradient isosurfaces^{24,25} was used to

perform Non-covalent interaction (NCI)²⁶ analysis using Multiwfn²⁷ package and visualized with VMD²⁸. In NCI plots, green indicates weakly attractive while blue reveals strongly attractive. QTAIM²⁹ were carried out with the same Multiwfn software and MPWB1K/6–31G(d,p) wave functions previously mentioned in ELF.

3. Result and discussion:

This study focused on the studying the 22CA step involved in the reaction mechanism of enantioselective reduction of ketones with borane catalyzed by a B-methoxy oxazaborolidine catalyst, which structured into three sections: the first is dedicated to a comparison between the energies of the B3LYP, M06 and MPWB1K functionals as for to choose the suitable one for this study. The second section is allowed to study the [2+2] cycloaddition step involved in the catalytic mechanism, which include the study of: regioselectivity study based on Houk's rule, energy profiles and geometries analysis of the [2+2] cycloaddition process, and nature of the molecular mechanism (ELF analysis). In the third one, the Origin of the S selectivity for the **a** catalytic cycle, which include Non-Covalent Interactions (NCI) in Transition States and Quantum Theory of Atoms in Molecules (QTAIM) Analysis, is studied in order to gain insight into the fact that **TSa(S)** is more favorable than **TSa(R)**.

3.1. Choice of the computational method

In order to assess the suitable suite of density functional for realizing this study, we have performed a comparative assessment between the B3LYP, M06 and MPWB1K functionals. Table 1 shows the relative and total energies generated with the three levels of theory investigated. We can observe from Table 1 that the employing of B3LYP fails to find the right and a compatible configuration of the oxazaborolidine-borane-ketone adduct involved in the [2+2] cycloaddition step, where the **TSa(R)** is more stable than **TSa(S)** by 7.87 kJ/mol which imply that the product of this 22CA step is of *R*- selectivity. In the other hand, as illustrated in Table 1, the product energy of the more stable cycloadduct **M5a(S)** shows that the result obtained with M06 is higher (-17,62 kJ/mol) than that obtained with MPWB1K (-56,81 kJ/mol) leading to a less exothermic reaction. Furthermore, the activation energies of the most favorable **TSa(S)** obtained with MPWB1K is 9.02 kJ/mol bellow that of the second **a** approach (**TSa(R)**), while the difference between **TSa(S)** and **TSa(R)** obtained with M06 is 5.13 kJ/mol. Furthermore, the accuracy of the chosen methods was tested by conducting

additional calculations at the b3LYP/6-311++G(2df, 2pd)/IEF-PCM_{THF}// B3LYP/6-31G(p, d), M06-2X/6-311++G(2df, 2pd)/IEF PCM_{THF}//M06-2X/6-31G(d,p), and MPWB1K/6-311++G(2df,2pd)/IEF PCM_{THF}// MPWB1K/6-31G(d,p) levels. As detailed in [Tables 2&3](#) of the supporting information, the computational outcomes (the single-point energies calculated with different levels, and the single-point energies plus thermal corrections to free energy calculated at the B3LYP/6-31G(d, p), M06-2X/6-31G(d, p), and MPWB1K /6-31G(d, p) level) illustrate that the same trend for the first step is clearly observed with different methods, indicating that the selected MPW1K functional with the 6-31G(d,p) basis set is the reliable and the suitable density functional for the both kinetic and thermodynamic studies of this 22CA step, that we will employ it to realize this work.

3.2. Regioselectivity study based on Houk's rule

To perform this preliminary study we have to define firstly which is the nucleophile and the electrophile agent within the single molecule involved in this intramolecular CA reaction and secondly, the atoms involved in this ICA.

We establish, according to the Tachibana and al scheme^{30,31,32}, that the complex **M4a(S)** consists of three areas corresponding fragment **A**, fragment **B** and the bulky that links the region **A** and **B**, where the two regions **A** and **B** are considered as nonhomogeneous electron gas having $\mu_A \neq \mu_B$ ($\mu_A = -0.142$ and $\mu_B = -0.118$) ([Fig 2](#), [table 4](#)). Then we study the chemical reactivity of IMCA by evaluating the reactivity indices, namely the electronic chemical potential μ and the global electrophilicity index ω .

Fig. 2 Fragmentation scheme for the intramolecular [2+2] cycloaddition reaction of the reduction of acetophenone with borane catalysed by a B-methoxy oxazaborolidine

Based on the Houk's rule³³, the IMCA reaction can be explained according to that "large-large and small-small FMO interactions are more favored than that of large-small and small-large FMO interactions." The FMO study of the intramolecular cycloaddition (IMCA) demonstrates that the principle interaction takes place between the HOMO of the fragment **B** and the LUMO of the fragment **A**. Additionally, FMO coefficients presented in Table 4 clearly shows that the most favored large-large interaction occurs between O(3) of the fragment **B** and B(4) of the fragment **A**, while the small-small interaction done between B(2) of the fragment **B** and N(1) of the fragment **A**.

Table 4 The FMO energies (a.u.), electronic chemical potential (a.u.), and global electrophilicity index (a.u.) indices for the reactants

Reactant	HOMO	LUMO	μ	ω
Frg A	-0.34434	0.06020	-0.142	0.025
Frg B	-0.27251	0.03684	-0.118	0.022

On the other hand, as shown in table 5, the large value of electronic chemical potential μ and the small one of the nucleophilic index ω for the fragment **B** regarding those of the

fragment **A**, indicates that the Fragment **B** act as nucleophile whereas the fragment **A** considered as electrophile, this finding is in line with the FMO study.

Table 5 FMOs coefficients of fragments **A** and **B**

Reactants						
Frag A		HOMO		LUMO		
	N(1)		B(4)		N(1)	B(4)
	0,43701		0,10950		-0.28303	0.43234
Frag B		HOMO		LUMO		
	O(3)	B(2)	O(5)	O(3)	B(3)	O(5)
	0.04667	0.00522	-0.01197	0.01194	0.03060	-0.01406

3.3. Energy profile and geometries analysis of the [2+2] cycloaddition process.

As illustrated in Fig 1, there are two possible kinds of oxazaborolidine **M1a** and **M1b** can be involved in the mechanism reactional of the enantioselective reduction of acetophenone with borane catalyzed by oxazaborolidine, which imply to rise two competing channels (channels **a** and **b**) for the [2 + 2] cycloaddition step each one has two stereoselective pathways (S & R), in which the kind of catalyst (**M1**) with its structure exerts a great effect on the reaction. Thus, there are four pathways involved in this 22CA reaction.

The formation of the four-membered ring (N(1)-B(2)-O(3)-B(4)) occurs through the coordination between the carbonyl oxygen of aromatic ketone and the B(4) site. In this reaction, the catalyst-borane-acetophenone adducts **M4(aS,aR,bS,bR)** are transformed into the catalyst-alkoxyborane adducts **M5(aS,aR,bS,bR)** via **TS(aS,aR,bS,bR)** as shown in Scheme 1 and Fig.3 The distance of newly formed bonds N(1)-B(2) and B(4)-O(3) changes from 2.189/ 2.060 Å in **TSa(S)**, 2.127/2.129 Å in **TSa(R)**, 2.377/1.814 Å in **TSb(S)** and 2.201/1.980 Å in **TSb(R)**, to 1.600/1.549 Å in **M5a(S)**, 1.575/1.550 Å in **M5a(R)**, 1.565/1.548 in **M5b(S)** and 1.585/1.546 Å in **M5b(R)**, respectively, which demonstrate that the B(1)-N(2) and O(3)-B(4) bonds have completely formed in **M5 (aS,aR,bS,bR)**, allowing the construction of the (B(1)-N(2)-O(3)-B(4)) 4-membered ring. The distances of the N(1)-B(4), and B(2)-O(3) bonds are 1.435, and 1.406 Å for **TSa(S)**, 1.436, 1.400 Å for **TSa(R)**, 1.450, 1.412 Å for **TSb(S)** and 1.440, 1.412 Å for **TSb(S)** as illustrated in Fig 3. It is emphasized here that these geometric parameters point to synchronous N(1)-B(2) σ and O(3)-

B(4) σ bonds formation process of this [2+2] cycloaddition reaction in along the transition states **TSa(R)** and slightly asynchronous in **TSa(S)**, in which the formation of the O(3)–B(4) bond is slightly advance the formation of N(1)–B(2) one, but an asynchronous one along the **TSb(S)** and **TSb(R)**.

From the Table 1, the MPWB1K/6-31G(d,p) activation energies related to this [2+2] cycloaddition reaction via transition states **TS(aS,aR,bS,bR)** are 16.12/25.14/46.22/44.25 kJ/mol respectively, indicating that the first step should be the most favorable process. Furthermore, the energies of products **M5(aS,aR,bS,bR)** are 56.81/46.06/35.87/22.44 kJ/mol lower than that of complexes **M4(aS,aR,bS,bR)**, respectively. Therefore, the reactions involved in the 22CA process via transition states **TS(aS,aR,bS,bR)** is an exothermic process, which makes the formation of **M5(aS,aR,bS,bR)** irreversible (see Table 1). This finding accounts for the complete *S*-selectivity.

On the other hand, as listed in the Table 6, the activation enthalpy values associated with 22CA process illustrates that the more favorable pathway is related to the **TSa(S)** ($\Delta H = 8.97$ kJ/mol), which is in line with what was obtained in electronic energies. An additional entropic contribution to the enthalpy augments the activation Gibbs free energy of these reactive transition states involved in the 22CA to 13.12 kJ/mol for **TSa(S)**, 19.97 kJ/mol for **TSa(R)** and to 41.93 kJ/mol for **TSb(S)**, while this Gibbs free energy value decreases to 31.13 kJ/mol for **TSb(R)** as the consequence of the unfavorable positive activation entropy ($\Delta S = 11.37$ J/mol. Thus, these values predict the same finding in term of predominance of *S*-selectivity obtained in electronic energies. Furthermore, this 22CA reaction is strongly exergonic by between 52.92 and 23.36 kJ/mol. Consequently, the **M5a(S)** is clearly the most favorable product to obtain over the **M5a(R)** ($\Delta\Delta G = 6.59$ kJ/mol) under both kinetic and thermodynamic controls (see Fig 4, Table 6).

Table 6: MPWB1K/6-31G(d,p) enthalpies (H, in a.u.), entropies (S, in cal/mol K) and Gibbs free energies (G, in a.u.), and the relative a ones (ΔH in kJ/mol, ΔS in cal/mol K and ΔG in kJ/mol K, respectively), computed at 398.15 K and 1 atm, for the **TSs** involved in the [2+2] cycloaddition reaction along the along the reaction pathways (**a** and **b**).

System	H	ΔH	S	ΔS	G	ΔG
M1a(S)	-1032.685540		169.187		-1032.765886	
M1a(R)	-1032.686574		163.746		-1032.764336	
M1b(S)	-1032.696022		165.501		-1032.774617	
M1b(R)	-1032.700962		165.706		-1032.779654	

TSa(S)	-1032.682125	8.97	165.857	-3.33	-1032.760889	13.12
TSa(R)	-1032.681966	11.68	157.433	-6.31	-1032.756730	19.97
TSb(S)	-1032.681897	37.08	161.614	-3.89	-1032.758646	41.93
TSb(R)	-1032.687815	34.52	168.422	2.72	-1032.767798	31.13
M2a(S)	-1032.709272	-62.31	161.655	-7.53	-1032.786041	-52.92
M2a(R)	-1032.707172	-54.08	157.529	-6.22	-1032.781982	-46.33
M2b(S)	-1032.712759	-43.94	152.098	-13.40	-1032.784989	-27.23
M2b(R)	-1032.712190	-29.48	160.795	-4.91	-1032.788550	-23.36

Fig. 3 The MPWB1K/6-31G(d,p) optimized structures for complexes **M4(aS,aR,bS,bR)**, **M5(aS,aR,bS,bR)** and transition states **TS (aS,aR,bS,bR)** involved in the 22CA step (unit in Å for bond lengths)

Fig. 4 Gibbs free energy profile (ΔG , in kJ mol^{-1}) of the 22CA step of the reduction of acetophenone with borane catalyzed by a *B*-methoxy oxazaborolidine

3.4. Nature of molecular mechanism (ELF analysis):

M4a(S)

P1

TSa(S)

P2

P3

P4

Fig. 5 Electron localisation function basin attractor positions of the relevant points of IRC **M4a(S)**-**M5a(S)** related to the formation of the N-B and O-B bonds along the most favorable **TSa(S)**

In order to gain insight on the most significant bonding changes along the reaction path of 22CA step of the most favorable transition state **TSa(S)**, by characterizing the electronic structures in which the reactivity and electronic structure of 22CA can be linked with each other, an ELF^{34,35} topological analysis of some appropriate path selected from IRC related to the formation of **M5a(S)** complex, was performed to calculate basins of attractors with the most representative valence basin populations of 22CA reaction. That is the space in which the probability of finding an electron pair is maximal³⁶. The valence basin populations ELF analysis of the selected structures associated with the formation of the O-B and N-B single bonds along the IRC of **M4a(S)**-**M5a(S)**, and their electronic population and position are shown in Fig 5.

The ELF analysis of **M4a(S)**, $d(\text{B},\text{N}) = 2.87 \text{ \AA}$ and $d(\text{O},\text{B}) = 3.24 \text{ \AA}$, point out the presence of the following basins: two disynaptic basins $V(\text{N},\text{B})$ and $V'(\text{N},\text{B})$ related to the N-B bonding region, integrating 1.93 e and 1.97e respectively, as well as one monosynaptic basin $V(\text{B},\text{O})$ with a population of 2.14e belonging to B-O single bond, and one monosynaptic basin $V(\text{O})$ integrating 4.22e associated with oxygen lone pair electron density at oxygen moiety.

ELF of **P1**, $d(\text{B},\text{N}) = 2.40 \text{ \AA}$ and $d(\text{O},\text{B}) = 2.35 \text{ \AA}$, illustrates an increase of both $V(\text{N},\text{B})$ and $V'(\text{N},\text{B})$ disynaptic basins to 3.84e for each one, while $V(\text{B},\text{O})$ monosynaptic basin decreases to a population of 2.01e. Noticeably, the monosynaptic basin $V(\text{O})$ shown in **M4a(S)** experiences a split into two disynaptic basins $V(\text{O})$ and $V'(\text{O})$ integrating 4.38e for each one.

In **TSa(S)**, $d(\text{B},\text{N}) = 2.18 \text{ \AA}$ and $d(\text{O},\text{B}) = 2.07 \text{ \AA}$, the most relevant change of this TS is the appearance of a new $V(\text{N})$ monosynaptic basin, integrating 0.96e which is an indicator for the beginning of the creation of the N lone pair. Meanwhile, the $V(\text{N},\text{B})$ and $V'(\text{N},\text{B})$ disynaptic basins gathered into one $V(\text{N},\text{B})$ monosynaptic basin with decrease of population towards 2.96 e. Whereas the pair disynaptic basins $V(\text{O})$ and $V'(\text{O})$ appeared in **P1** are merged into one monosynaptic $V(\text{O})$ with a population of 4.41e, while $V(\text{B},\text{O})$ monosynaptic basin remain almost unchanged with a population of 2.00e.

In **P2**, $d(\text{B},\text{O}) = 1.94 \text{ \AA}$ and $d(\text{N},\text{B}) = 2.07 \text{ \AA}$, the monosynaptic basin $V(\text{O})$ present at **TSa(S)** split again into two $V(\text{O})$ and $V'(\text{O})$ integrating 1.34e and 2.76e, respectively. Whereas, the $V(\text{N})$ monosynaptic basin formed at **TSa(S)** has increased to 1.34e, as a result of the depopulation of $V(\text{N},\text{B})$ disynaptic basin to 2.64e.

In **P3**, $d(\text{B},\text{O}) = 1.83 \text{ \AA}$ and $d(\text{N},\text{B}) = 1.94 \text{ \AA}$, several topological significant changes are observed related to the creation of the O-B and N-B single bonds: at the first most relevant topological change, the $V(\text{O})$ monosynaptic associated with one of the two non-bonding O lone pair experiences an increase of its population to achieve 1.59e, which is necessary for the creation of an O-B bond. At the same time, the population of the $V(\text{N})$ monosynaptic basin related to the nitrogen N lone pair continues to profit to more electron population reaching 1.58e, as a consequence of the depopulation of $V(\text{N},\text{B})$ to 2.41e, this second topology change is demanded for the formation of the second single bond N-B. Whereas, the population of the $V(\text{B},\text{O})$ disynaptic basin decreases slightly to achieve 1.98e and 1.96e, respectively.

ELF of **P4**, $d(\text{B},\text{N}) = 1.81 \text{ \AA}$ and $d(\text{O},\text{B}) = 1.72 \text{ \AA}$, shows a creation of a new $V(\text{O},\text{B})$ monosynaptic basin with an initial integration of 1.65e, which account for the beginning of the formation of the first O-B single bond (dative covalent bond) at a length of *ca* 1.72 $\text{\AA}$ through the total donation of the electron density of the non-bonding sp^2 -hybridised O lone pair to the empty orbital in the B atom. Meanwhile, the $V(\text{N},\text{B})$ disynaptic basin continues depopulating allowing to the increase of $V(\text{N})$ monosynaptic basin to 1.76 e, which becomes almost lone pair.

In **P5**, the most noticeable change is related to the apparition of a new $V(\text{B},\text{N})$ disynaptic Basin with a population of 1.81e, indicating the begun of the formation of the second B-N single bond (dative covalent bond) at length of *ca* 1.77 $\text{\AA}$, in which the losing electron-density at N is totally gathered at this newest forming bond. Whereas, the population of the $V(\text{O},\text{B})$ disynaptic basin, associated with the first formed O-B bond, remains almost unchanged.

Finally, ELF of **M5a(S)**, $d(\text{B},\text{N}) = 2.40 \text{ \AA}$ and $d(\text{O},\text{B}) = 2.35 \text{ \AA}$, illustrates an increase of the population of both disynaptic basins $V(\text{O},\text{B})$ and $V(\text{B},\text{N})$, to 1.84e and 1.93e,

respectively. The $V(N,B)$ disynaptic basin and the oxygen lone pair experience a decrease of their populations to reach 2.05e and 2.45e, respectively.

ELF topological analysis related to the formation of both B–N and N–B single bonds along the most favorable **TSa(S)**, resumes some relevant points: (1) This reaction pathway occurs through a two-stage one-step mechanism, in which the B–O began somewhat before the formation of the second single bond N–B, which account for an almost asynchronous. (2) The formation of the two O–B and N–B single bonds takes place through the donation of the lone pair of O and N into the empty orbital in the B.

3.5. Origin of the *S* selectivity for the a catalytic cycle

3.5.1. Non-Covalent Interactions in Transition States

Fig. 6 NCI analysis of the MPWB1K/6-31G(d,p) optimised transition states **TSa(S)** and **TSa(R)**. Blue for strong attractive, green for intermediate interactions.

Previous studies have illustrated that non-covalent interactions play an important role in determining the selectivity in the wide large of reactions ^{7,37}. Thus, for gain some

insight into the origin of the *S* selectivity obtained along the **TSa(S)**, which implies to justify the stabilization of **TSa(S)** with respect to **TSa(R)**. Thus, for explaining the stabilization of conformers and understanding of driving forces in our structures, a topological analysis NCI³⁸ of the MPWB1K/6-31G(d,p) optimized **TSs** was highlighted in Fig 6. The deep blue region shown in both **TSs** reveals that the forming N(1)-B(2) and O(3)-B(4) bonds are on the border of covalent, and non covalent. Along with the N(1)-B(2) and O(3)-B(4) formation, both **TSs** undergo other common HBs interactions, which comes mainly from the orientation of the methanediyl group inside the pinene skeleton towards atoms below. For the lowest-energy transition state **TSa(S)**, NCI plot (Fig 6) discloses three interactions involving H atom of the methanediyl: one located with H attached to boron atom, the second interaction occurs with the hydrogen of the aromatic ring of acetophenone and the third one done with the oxygen atom of oxazaborolidine, this latest interaction is more conducive to stabilizing the conformer. Whereas in **TSa(R)**, there are only two weak interactions: C-H...H-B and CH₂-H...H-CH₂. It's worth noting that all those hydrogen and dihydrogen bond interactions are validated by the presence of surfaces coloured with light and bluish green which indicates a weak to moderately strong attraction.

Consequently, the presence of more HBs interactions in **TSa(S)** with respect to **TSa(R)** supports a favorable conformation of the **TS3a(S)**, for giving the *S* chirality of the product along the **a** cycle, which is in-line with what it was evoked above.

3.5.2. Quantum Theory of Atoms in Molecules (QTAIM) Analysis

In order to deeply understand the difference in the amount of interaction shown in previously NCI study with both **TSa(S)** and **TSa(R)** and be more accurate with what is evoked in NCI analysis, we have performed a QTAIM topological analysis to shed light into conventional and non-conventional HB.

It has been suggested that QTAIM is a powerful tool to characterize hydrogen bonding interactions by correlation between electron density ρ at bond critical points and bond strength, which provides a series of critical points (cp). The existence of the binding interaction independent the nature bond is conditioned by the presence of CP (3, -1). Whereas, the Laplacian of the electron density in a bond critical point, $\nabla^2\rho_{bcp}$, plays a great role in determining electron density concentration in the interatomic space, which is measured on the basis of the value and the sign of Laplacien, where the positive sign of the Laplacian $\nabla^2\rho_{bcp}$

in the BCP is attributed to closed-shell-interaction, such as hydrogen where the electron density for this interaction is locally depleted, while the negative one is related to shared-interaction like covalent bonds as a consequence of a local concentration of ρ_{bcp} . Thus, the Laplacian electron density and electron energy density as a criterion of hydrogen bonds description was proposed

- 1) $\nabla^2\rho_{bcp} < 0$, $H_{cbcp} < 0$ - strong typ interactions like weakly polar covalent bonds.
- 2) $\nabla^2\rho_{bcp} > 0$, $H_{cbcp} < 0$ - medium typ interactions like strong hydrogen bonds and polar covalent bonds.
- 3) $\nabla^2\rho_{bcp} > 0$, $H_{bcp} > 0$ - weak typ interactions like Van der Waals bonds and weak hydrogen bonds.

As illustrated in [Table 7](#), Topological parameters and intramolecular hydrogen bond energies of **TSa(S)** and **TSa(R)** are compared. The Laplacian and electron energy of the new forming bonds B...O and N...B demonstrates that is intermediary non-covalent interactions present within the backbone of both **TSSs** which is characterized by $\nabla^2\rho_{bcp} > 0$ and $H_{bcp} < 0$ that is evidence of the closed-shell interaction. Moreover, the $H(r)$ value in the B...O bond at **TSa(S)** is considerably more negative ($H(r) = -0.105$ au) than that in the B...N ($H(r) = -0.705$ au) bond which makes the former interaction stronger than the latter one. Whereas, at **TSa(R)** the interaction in newly forming bond B...N ($H(r) = -0.1405$ au) is stronger than that in B...O ($H(r) = -0.0864$ au). Resulting, a more strength of the newly forming bond B...O in **TSa(S)** than N...B forming bond in **TSa(R)** as $H(r)_{B...O} > H(r)_{N...B}$. Additionally, beside to weak stabilized non-conventional H...H interactions pointed out by $\nabla^2\rho_{bcp} > 0$ and $H_{bcp} > 0$ of (3,-1) bcp which has been seen in both **TSSs**, another type of hydrogen bond associated with **TSa(S)** is found between H...O characterized by small $\rho_{H...O}$ values together with positive Laplacian which is a sign of closed-shell interactions observed in H-bond. Consequently, these interactions are significantly stabilising **TSa(S)** over **TSa(R)**, which is inline with what has been found above.

TSa(S)

TSa(R)

Table7 QTAIM parameters/ a.u. of the (3, -1) bond critical points for **TSa(S)** and **TSa(R)**.
Wavefunctions are obtained at the MPWB1K level using 6-31G (d,p) basis set.

	interaction	BCP	ρ_{cbcp}	$\nabla^2 \rho_{\text{bcp}}$	H_{bcp}
TSa(S)	H(42)-H(12)	70	0.439	0.900	0.137
	H(12)-H(50)	77	0.939	0.374	0.216
	H(12)-O(37)	87	0.102	0.374	0.948
	N(24)-B(26)	112	0.394	0.632	-0.705
	B(49)-O(37)	96	0.422	0.211	-0.105
TSa(R)	H(13)-H(30)	121	0.822	0.356	0.203
	H(23)-H(14)	108	0.128	0.507	0.223
	H(12)-H(53)	70	0.799	0.258	0.134
	H(12)-H(52)	76	0.653	0.226	0.118
	N(25)-B(27)	112	0.475	0.561	-0.140
	B(50)-O(38)	100	0.373	0.717	-0.864

4. Conclusions

This work has studied, using MPWB1K/6-31G(d,p) DFT methods, the [2+2] cycloaddition step involved in the mechanism reactional of the enantioselective reduction of ketones with borane catalyzed by a *B*-methoxy oxazaborolidine catalyst derived from (–)- β -Pinene. Thus, The calculated results indicate that this reaction takes place through four transition steps **TSa(S)**, **TSa(R)**, **TSb(S)** and **TSb(R)**, where the mode **a** denotes the implication of the kind **a** of oxazaborolidine, while the **b** one refers to the implication of **b** kind). The following findings can be drawn from our results:

1. Houk's rule and FMO studies show that intramolecular cycloaddition reaction takes place between the fragment **B** which act as nucleophile whereas the fragment **A** considered as electrophile, where the most favored large-large interaction occurs between O(3) of fragment B and B(4) of the fragment **A**, while the small-small interaction done between B(2) of the fragment **B** and N(1) of the fragment **A**.
2. **TSa(S)** is kinetically and thermodynamically the most favorable transition state relative to **TSa(R)**, **TSb(S)** and **TSb(R)**, thus, the chirality of the reduced products in this step is of *S* type, which is consistent with the experimental outcomes.
3. ELF topological analysis during the formation of the two new single bonds N...B and B...O with the more stable **TSa(S)** involved in the 22CA step of the enantioselective reduction of ketones with borane catalyzed by a *B*-methoxy oxazaborolidine, illustrates that the reaction intramolecular between the fragment A and fragment B occurs at a distance of *ca* 1.72 through the total donation of the electron density of the non-bonding sp²-hybridised O lone pair to the empty orbital in the B atom, while the formation of the second N...B single bond takes place at a distance of *ca* 1.77, where the losing electron-density at N is totally gathered at this newest forming bond. Thus, the formation of an O-B single bond precedes the formation of N-O, supporting two-stage-one step mechanism.
4. The NCI (Non Covalent Interaction) and QTAIM study of the most favorable transition state **TSa(S)** suggests the presence of moderately strong interaction between the H atom of the methanediyl group inside the pinene skeleton and the oxygen atom of the oxazaborolidine ring, which accounts for the stabilisation of the **TSa(S)** with respect to **TSa(R)**, explaining that the *S* selectivity obtained in this step is aligned with the chirality of the whole step of the reaction mechanism.

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Declarations

Conflicts of interest: I declare that I have no conflict of interest.

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