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A DFT study of the role of the Lewis acid catalysts in the [3+2] cycloaddition reactions of the electrophilic nitron isomer of methyl glyoxylate oxime with nucleophilic cyclopentene

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Abstract

The molecular mechanism and stereoselectivity of the BF₃ Lewis acid catalyzed [3+2] cycloaddition (32CA) reaction between C-methoxycarbonyl nitron and cyclopentene have been theoretically studied using DFT methods at the MPWB1K/6-31G(d) computational level. The BF₃ catalyst accelerates the 32CA reaction by decreasing the activation energy leading to the formation of the *trans* cycloadduct as the kinetic product, in agreement with the experimental data. Inclusion of solvent effects slightly increases the activation energy and decreases the exothermic character of the 32CA reaction as a consequence of a better solvation of nitron than the transition state and the cycloadduct. The use of the lithium cation as LA catalyst does not make any remarkable change with respect to the BF₃ catalyzed process. The nature of the mechanism has been also studied using the reactivity indices defined within the conceptual DFT.

Keywords: [3+2] Cycloaddition reaction, Molecular mechanism, Stereoselectivity, Lewis acid catalyst, DFT calculations.

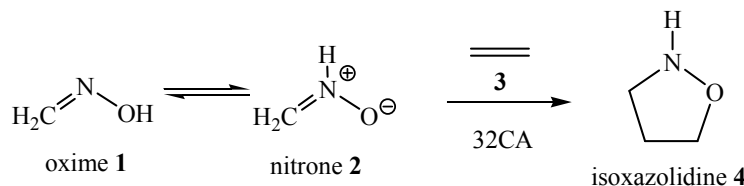
1. Introduction

[3+2] cycloaddition (32CA) reactions offer a versatile route for the construction of a variety of complex five-membered heterocycles that are synthetically useful compounds.¹ 32CA reactions of nitrones with alkenes leading to isoxazolidine derivatives have been intensively studied and have found general application in organic synthesis (see Scheme 1).² Oximes and their derivatives as useful synthons are widely utilized in organic synthesis, since they can be easily transformed into nitrones.³ A considerable amount of theoretical and

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experimental⁴ work devoted to the study of the mechanism and selectivity of 32CA reactions of oximes or nitrones with alkenes can be found in the literature.

Unlike Diels-Alder (DA) reactions, which can be classified as non-polar DA (N-DA) reactions with high activation energies and polar DA (P-DA) reactions with low activation energies,⁵ 32CA reactions lack a clear systematization of their reactivity based on the nucleophilic/electrophilic behavior of the reagents. Recently, the 32CA reactions of a series of twelve three-atom-components (TACs) with ethylene **3** were studied in order to find a structure/reactivity relationship.⁶ A good correlation between the *pseudodiradical* character, the hardness η , and the nucleophilicity N index of the TAC with the feasibility of these non-polar reaction was established. This study allowed establishing a useful classification of 32CA reactions into *pseudodiradical-type* (*pr-type*) reactions involving TACs with a high *pseudodiradical* character, which take place easily through an earlier TS with non-polar character, and *zwitterionic-type* (*zw-type*) reactions involving TACs with a high zwitterionic character, characterized by favorable nucleophilic/electrophilic interactions, taking place through polar TSs.⁶ Thus, the simplest nitron **2**, which has a zwitterionic character, presented a high activation energy towards ethylene **3**, 13.0 kcal mol⁻¹, with a very low charge transfer (CT) at the transition state (TS), 0.01e (see Scheme 1).

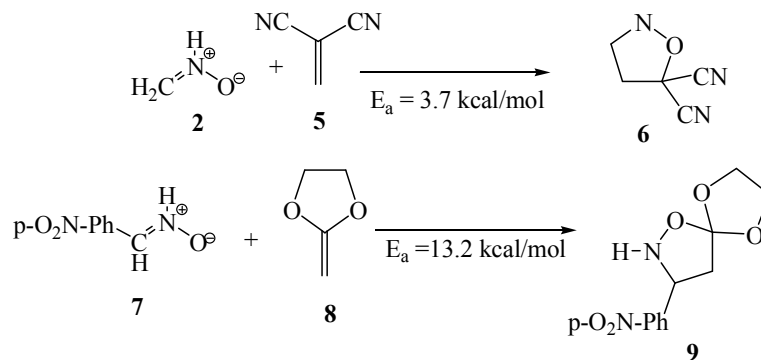


Scheme 1. 32CA reaction of nitron **2** with ethylene **3**.

In order to verify this hypothesis, a series of the most common TACs used in organic synthesis⁷ showing low reactivity in 32CA reactions towards ethylene **3** were recently explored to determine if the electrophilic/nucleophilic activation of both TACs and ethylene derivatives might favor the 32CA reactions *via* a polar *zw-type* mechanism⁸. To this end, a series of seven non-substituted TACs, including the simplest nitron **2**, having a zwitterionic structure were studied analyzing their electrophilic/nucleophilic behavior (see Scheme 2).

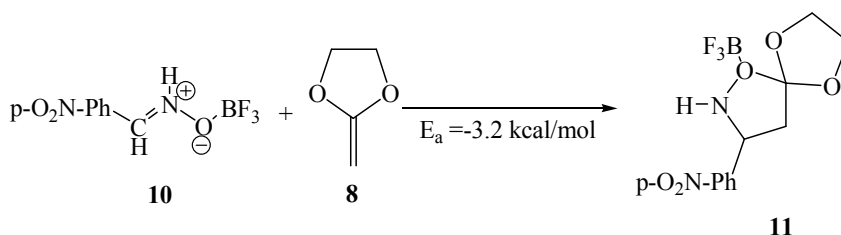
The general characteristic of zwitterionic TACs is their high nucleophilic and low electrophilic behavior. Thus, the simplest nitron **2** has an electrophilicity index $\omega = 1.06$ eV,⁹ being classified as a moderate electrophile¹⁰ and a nucleophilic index $N = 2.92$ eV¹¹ being on the borderline of strong nucleophiles.¹² The computed activation energies indicated that non-substituted TACs react quickly toward the electron-deficient 1,1-dicyanoethylene **5**, showing

their ability to react towards electrophilic ethylenes. Thus, the 32CA reaction of the simplest nitron **2** with 1,1-dicyanoethylene **5** was $3.7 \text{ kcal mol}^{-1}$, in clear agreement with the CT at the corresponding TS; 0.15e.



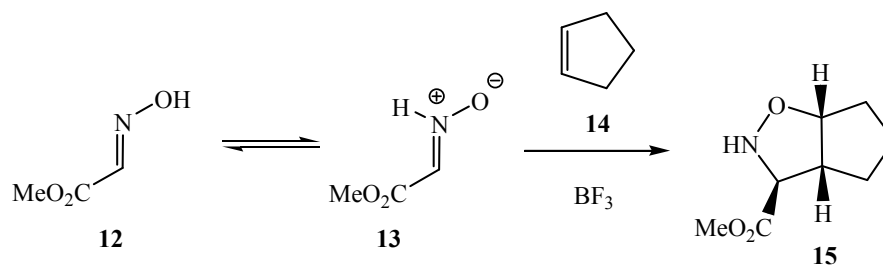
Scheme 2. 32CA reactions of nitrones and nucleophilic and electrophilic alkenes.

Interestingly, when the electrophilically activated phenyl nitrone **7**, $\omega = 3.13 \text{ eV}$, reacted with the electron-rich ethylene **8**, $N = 3.64 \text{ eV}$, the computed activation energy, $13.2 \text{ kcal mol}^{-1}$ was closer to that found in the 32CA reaction of the simplest nitrone **2** towards ethylene **3**. These energy results indicated that the electrophilic activation of the TACs by an electron-withdrawing substitution seems to be insufficient to favor the 32CA reaction toward electron-rich ethylenes. Only the coordination of nitrone **7** with a BF_3 Lewis acid (LA) activated it for a nucleophilic attack; the corresponding TS was found to be $3.2 \text{ kcal mol}^{-1}$ below reagents (see Scheme 3).



Scheme 3. LA-catalyzed 32CA reaction between electrophilic nitrone and nucleophilic alkene.

Recently, Sousa and co-workers¹³ studied experimentally the reaction of methyl glyoxylate oxime **12** with cyclopentene **14**, finding that this reaction gives exclusively the *trans* isoxazolidine **15**, originating from the *exo* approach (Scheme 4). The formation of cycloadduct **15** was explained by the 32CA reaction of the nitrone tautomer **13** of the methyl glyoxylate oxime **12** with cyclopentene **14**.



Scheme 4. LA catalyzed reaction between glyoxylate oxime and cyclopentene.

Herein, we present a MPWB1K-/6-31G(d) computational investigation of the role of the BF_3 LA catalyst and solvent effects in the 32CA reactions of electrophilically activated nitrones with electron rich ethylenes. For this purpose, the 32CA reaction between nitron 13 and cyclopentene 14, experimentally studied by Sousa, is analyzed. A predictive study on lithium metal as a LA catalyst is also performed.

Computational method

Several works have shown that the B3LYP functional^{14,15} is relatively accurate for kinetic data, although the reaction exothermicities are underestimated^{16–18}. Recently, the Truhlar's group has proposed some functionals, such as the MPWB1K¹⁹ hybrid meta functional which improve thermodynamic calculations. DFT calculations were carried out using the MPWB1K [19] functional together with the 6-31G(d) basis set²⁰. These 13DC reactions were also optimized using the M06-2X²¹ and B3LYP functionals and the corresponding energies were compared with the MPWB1K ones.

The stationary points were characterized by frequency calculations in order to verify that transition states (TSs) had one and only one imaginary frequency. The intrinsic reaction coordinate (IRC)^{22,23} have been further performed to check the energy profiles connecting each TS to the two associated minima. The electronic structures of critical points were analyzed by the natural bond orbital (NBO) method²⁴. Thermodynamic calculations were done with the standard statistical thermodynamics at 298.15K and 1 atm²⁰, and harmonic vibrational frequencies were scaled by a factor of 0.96²⁵. Solvent effects of dichloromethane (DCM) were considered at the same level of theory by single-point calculations of the gas-phase structures using a self-consistent reaction field (SCRF)²⁶ based on the polarizable continuum model (PCM) of Tomasi's group²⁷. All calculations were carried out with the Gaussian 09 suite of programs²⁸.

The global electrophilicity index, ω , is given by the following expression⁹ $\omega = (\mu^2 / 2\eta)$, in terms of the electronic chemical potential μ and the chemical hardness η . Both quantities may be approached in terms of the one-electron energies of the frontier molecular orbitals HOMO and LUMO, ϵ_H and ϵ_L , as $\mu \approx (\epsilon_H + \epsilon_L) / 2$ and $\eta \approx (\epsilon_L - \epsilon_H)$, respectively¹¹. Recently, Domingo introduced an empirical (relative) nucleophilicity index²⁹ N , based on the HOMO energies obtained within the Kohn-Sham scheme³⁰ and defined as $N = E_{\text{HOMO}}(\text{Nu}) - E_{\text{HOMO}}(\text{TCE})$. Nucleophilicity is referred to tetracyanoethylene (TCE). The P_k^+ electrophilic and P_k^- nucleophilic Parr functions³⁰ which allow for the characterization of the electrophilic and nucleophilic centers of a molecule, were obtained through the analysis of the Mulliken atomic spin density of the radical anion and the radical cation of the studied molecules, respectively.

2. Results and discussion

The present study has been divided into five sections: i) first, a comparison between the energies of the B3LYP, M06-2X and MPWB1K functionals is performed to choose the appropriate functional for this study ii) in the second part, the non-catalyzed 32CA reaction between nitron **13** and cyclopentene **14** is studied; iii) in the third part, the BF_3 LA catalyzed 32CA reaction of nitron **13** with cyclopentene **14** is analyzed; iv) in the fourth part, the role of the lithium cation as a LA catalyst in the 32CA reaction is also evaluated; v) in the last part, a DFT-based reactivity indices analysis is performed to shed light on the effect of the LA catalyst on the reaction mechanism.

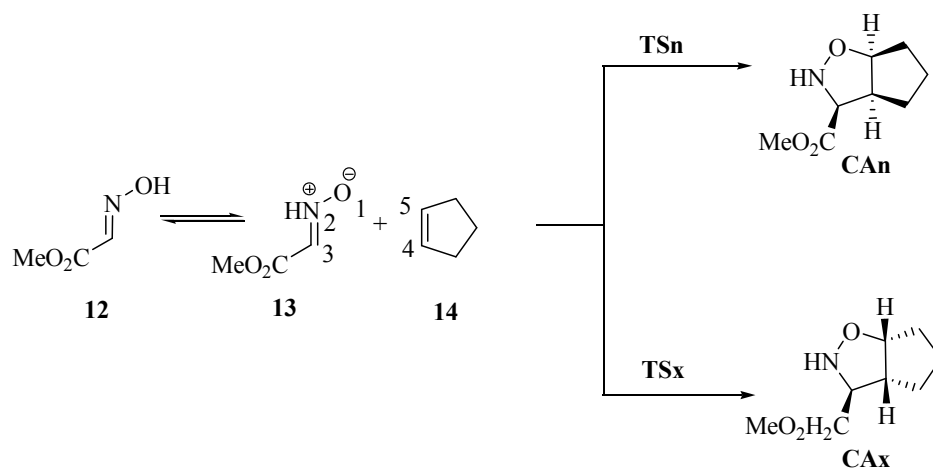
2.1. Choice of the computational method

In order to find the appropriate functional to realize this study, we have performed a comparative study between the B3LYP, M06-2X and MPWB1K functional. Relative energies are summarized in Table 1. Total energies are given in Tables S1 in Supplementary data. We can notice from Table 1 that the use of the three functional predicts an exo stereoselectivity, where the activation energies obtained with both B3LYP and MPWB1K are slightly similar (2 and 2.9 respectively), while the value obtained with the use of the M06-2X functional is different to them ($-0.2 \text{ kcalmol}^{-1}$) leading to a spontaneous reaction, thus it does not reproduce the experimental data. Thereby, B3LYP and MPWB1K functional are appropriate for kinetically controlled of these cycloaddition reactions. In the other hand, a comparison between the products energies of the more stable cycloadduct (**CAn-B**) reveals that the values

obtained with both M06-2X and MPWB1K functionals are also slightly similar (-38.9 and 37.0 kcalmol⁻¹, respectively), while the value obtained with B3LYP functional is more higher (-22.4 kcal mol⁻¹) leading to a less exothermic reaction. Thus, the B3LYP functional fail in thermodynamic controlled of these cycloaddition reactions. Consequently, the MPWB1K functional is the appropriate functional for both kinetic and thermodynamic controlled the BF₃ LA catalyzed 32CA reaction of nitrone **13** with cyclopentene **14**, that we will used it to performed this study.

2.1 Study of the non-catalyzed 32CA reaction between nitrone **13** and cyclopentene **14**.

In order for oximes to undergo a 32CA reaction with alkenes they should be transformed into the corresponding nitrone (see Scheme 5). The nitrone-tautomer is more reactive than the oxime one³². The 32CA reaction between C-methoxycarbonyl nitrone **13** and cyclopentene **14** can take place along two stereoisomeric pathways; namely, the *endo* and *exo* approaches (Scheme 5). Analysis of the stationary points involved along the two stereoisomeric channels indicates that this 32CA reaction takes place along a one-step mechanism. Consequently, two stereoisomeric TSs, **TSn** and **TSx**, and the corresponding [3+2] CAs, **CAn** and **CAs**, were located and characterized. Relative energies of the stationary points (TSs and CAs) involved in the 32CA reaction between nitrone **13** and cyclopentene **14**, in the gas phase and in DCM, are given in Table 2. Total energies are given in Table S2 in Supplementary Information.



Scheme 5. The possible stereoisomeric pathways for the 32CA reaction between nitrone **13** and cyclopentene **14**.

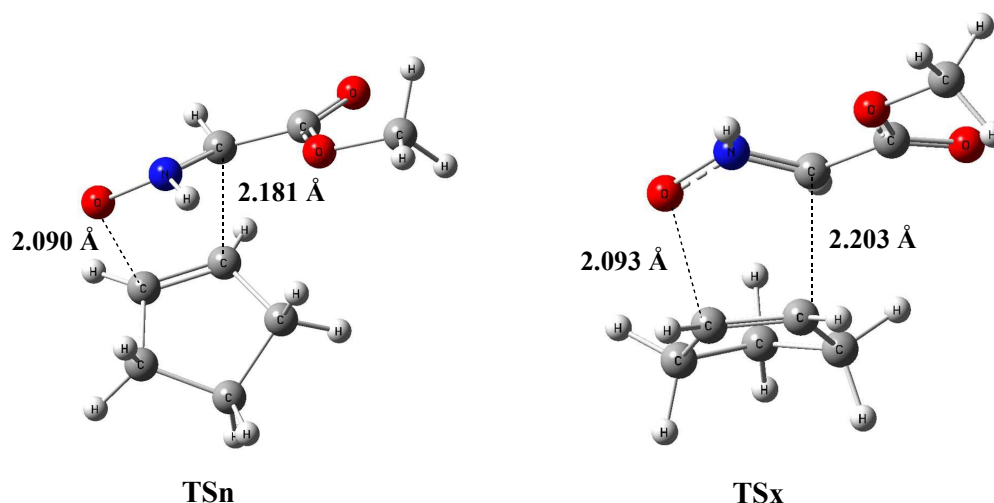


Figure1. Optimized structures of the TSs of the 32CA reaction of nitrone **13** and cyclopentene **14**.

The gas phase activation energies associated with this 32CA reactions are: 15.3 (**TSn**) and 11.2 (**TSx**) kcal mol⁻¹, the reaction being exothermic by 38.0 (**CAn**) and 39.7 (**CAs**) kcal mol⁻¹. The energy difference between the two stereoisomeric TSs, 4.1 kcal/mol, indicates that this 32CA reaction is completely *exo* stereoselective, allowing the formation of *trans* isoxazolidine **CAs** (Scheme 2). The unfavorable steric hindrance between the hydrocarbon system of cyclopentene **14** and the methyl group of the ester function present in nitrone **13** may be responsible for this *exo* selectivity. The high exothermic character of this 32CA reaction makes the cycloaddition irreversible.

Solvent effects stabilize the reactants, TSs and CAs relative to gas phase calculations. The most noticeable change with the inclusion of solvent effects is the increase in activation energies; the changes are 1.4 and 1.5 kcal mol⁻¹ for **TSn** and **TSx**, respectively. Moreover, solvent effects slightly decrease the exothermic character of the reaction; the changes are 1.4 and 1.5 kcal mol⁻¹ for **CAs** and **CAn**, respectively. The increase of the activation energies and the decrease of the exothermic character of this 32CA reaction are a consequence of a higher solvation of nitrone **13** than TSs and CAs in polar solvents³³.

Relative enthalpies, entropies and Gibbs free energies of the TSs and cycloadducts involved in the 32CA reaction of nitrone **13** with cyclopentene **14** are summarized in Table 3. The values of enthalpies, entropies and Gibbs free energies are given in Table S3 in Supplementary Information. Inclusion of thermal corrections to the electronic energies raises the activation entropies by ca. 2 cal mol⁻¹ K⁻¹. Analysis of the activation enthalpies associated with the 32CA reaction of nitrone **13** with cyclopentene **14** indicates that the more favorable

approach mode is that associated with the *exo* **TSx** ($\Delta H=13.8$ kcal mol⁻¹). Addition of the unfavorable entropic contribution associated to this bimolecular process to the enthalpies increases the Gibbs activation free energy of this reactive channel to 26.1 kcal mol⁻¹, which remains more favored than the *endo* approach mode ($\Delta\Delta G=3.9$ kcal mol⁻¹). Consequently, formation of the *exo* **CAx** is clearly favored over the *endo* **CA_n**, in good agreement with the experimental outcomes.

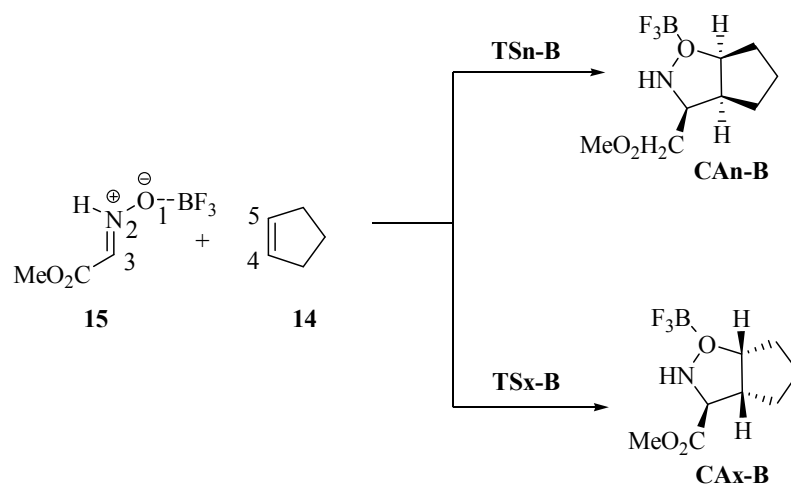
The geometries of the TSs associated with the 32CA reaction of nitrone **13** and cyclopentene **14** are given in Figure 1. The lengths of the O1-C5 and C3-C4 forming bonds at the TSs are 2.090 and 2.181 Å at **TS_n**, and 2.093 and 2.203 Å at **TSx**.

The extent of bond formation or bond breaking along a reaction pathway is provided by the concept of bond order (BO). The Wiberg bond indices³⁴ have been computed using NBO analysis. At the TSs associated with the non-catalyzed 32CA reaction the BO values for the O1-C5 and C3-C4 forming bonds are 0.33 and 0.30 at **TS_n** and 0.31 and 0.32 at **TSx**. These values point to synchronous single bond formation processes of this 32CA reaction.

The CT analyses at the TSs of this non-catalyzed 32CA reaction are done to shed light on the nature of the molecular mechanism. Natural population analysis (NPA) allows evaluating the CT along these 32CA reactions, and thus to establish the polar nature of these reactions. The MPWB1K/6–31G(d) natural atomic charges at the TSs were shared between the nitrone **13** and cyclopentene **14**. The CT value at both **TS_n** and **TSx** is 0.06e, thereby indicating that these TSs have a very low polar character, in clear agreement with the high activation energies⁶.

2.2 Study of the BF₃ catalyzed 32CA reaction between nitrone **13** and cyclopentene **14**

Nitrones are strong nucleophilic TACs that react with electron-deficient alkenes via a *zw-type* mechanism⁸. However, coordination of the oxygen atom of nitrone with a LA catalyst notably increases its electrophilicity, allowing its participations in *zw-type* 32CA reactions towards electron-rich alkenes. Accordingly, the 32CA reaction of the nitrone:BF₃ complex **15** with cyclopentene **14** was studied (see Scheme 6). Relative energies for the stationary points (TSs and cycloadducts) involved in 32CA reactions of nitrone:BF₃ complex **15** with cyclopentene **14**, in the gas phase and in DCM are displayed in Table 4. Total energies are given in Table S4 in Supplementary Information. The geometries of the TSs involved in the BF₃ catalyzed 32CA reaction are given in Figure 2.



Scheme6. The possible stereoselective pathways for the BF_3 catalyzed 32CA reaction between C-methoxycarbonylnitrone **15** and cyclopentene **14**.

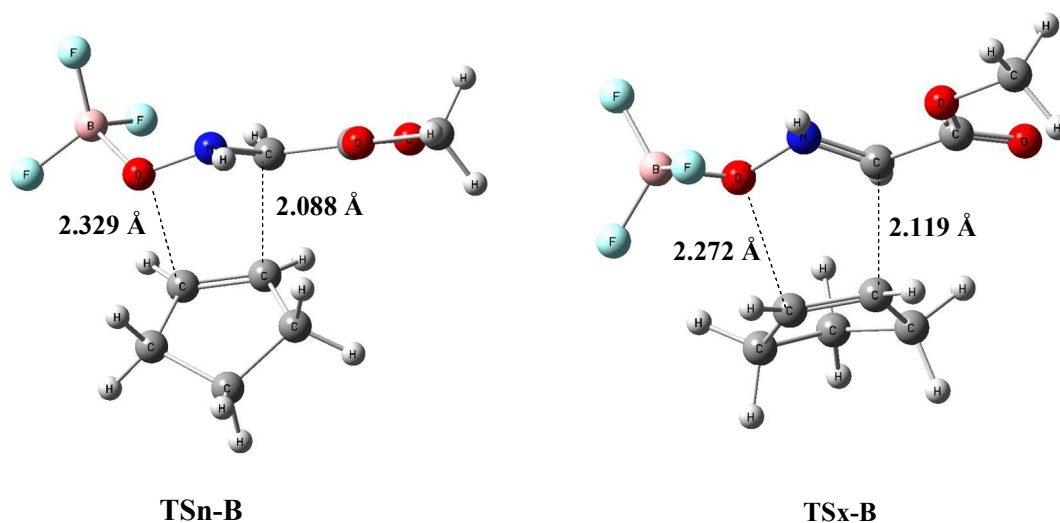


Figure2. Optimized structures of the TSs of the 32CA reaction of the BF_3 :nitrone complex **15** with cyclopentene **14**.

The gas phase activation energies associated with this BF_3 catalyzed 32CA reaction are 10.5 (**TSsn-B**) and 2.9 (**TSsx-B**) kcal mol^{-1} , the reaction being exothermic by 34.7 (**CAn-B**) and 37.0 (**CAx-B**) kcal mol^{-1} . These energy results clearly indicate that the coordination of the BF_3 catalyst to the oxygen atom of nitrone **13** favors the *exo* stereoisomeric channel to decrease the corresponding activation energy by 8.3 kcal mol^{-1} . This behavior makes the LA catalyzed 32CA reaction completely *exo* stereoselective to be **TSsx-B** 7.6 kcal mol^{-1} below **TSsn-B**. Note that according to the Boltzmann distribution equation³⁵, when ΔE between two isomers is above 3 kcal mol^{-1} , one isomer will exclusively be obtained.

Solvent effects of DCM stabilize all the structures; the BF_3 :nitrone complex **15** being the most stabilized one. Consequently, solvent effects increase the activation energies: $1.0 \text{ kcal mol}^{-1}$ for the *endo* approach and $2.8 \text{ kcal mol}^{-1}$ for the *exo* approach. In spite of the larger increase of the activation energy associated with the *exo* **TSx-B**, the solvent effect does not modify the *exo* stereoselectivity found in gas phase.

Relative enthalpies, entropies and Gibbs free energies of the BF_3 catalyzed 32CA reaction are summarized in Table 5. Values of absolute enthalpies, entropies and Gibbs free energies are given in Table S5 in Supplementary Information. Just as in the non-catalyzed reaction, inclusion of the thermal corrections with the electronic energies raises the activation entropies by ca. 2 kcal mol^{-1} ; the activation enthalpy associated to the catalyzed reaction being $7.0 \text{ kcal mol}^{-1}$. Addition of the unfavorable entropic contribution associated to this bimolecular process to the enthalpies raises the Gibbs activation free energy of the most favorable *exo* reactive channel to $20.3 \text{ kcal mol}^{-1}$, the reaction being exergonic by $12.9 \text{ kcal mol}^{-1}$.

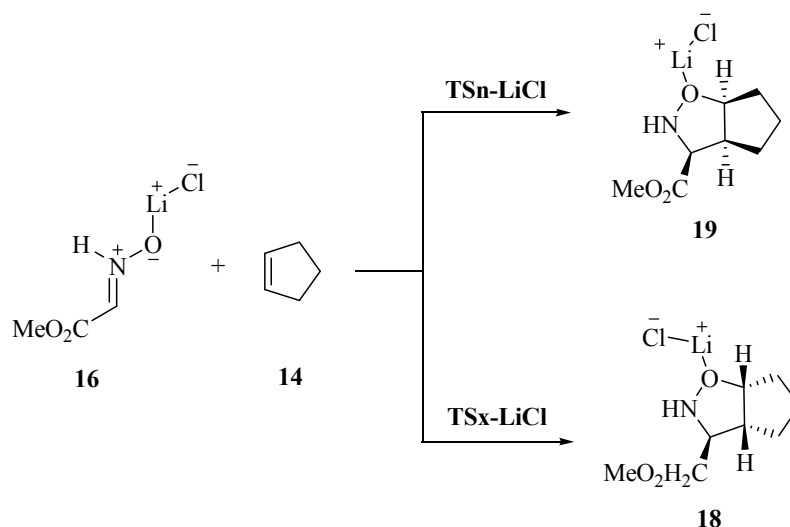
The geometries of the TSs associated with the 32CA reaction of BF_3 :nitrone **15** complex and cyclopentene **14** are given in Figure 2. The lengths of the O1–C5 and C3–C4 forming bonds at the TSs are 2.329 and 2.088 Å at **TSn-B**, and 2.272 and 2.119 Å at **TSx-B**, respectively. The BO values for the O1–C5 and C3–C4 forming bonds at the TS associated to the BF_3 catalyzed 32CA reaction are 0.18 and 0.37 at **TSn-B** and 0.20 and 0.36 at **TSx-B**, respectively, indicating that these TSs correspond to an asynchronous single bond formation process in which the C–C bond formation is more advanced than the C–O one.

The values of CT, which takes place from cyclopentene **14** to the electrophilically activated BF_3 :nitrone complex **15**, are 0.22e (**TSn-B**) and 0.21e (**TSx-B**). The CT found in these TSs accounts for the polar character of this LA catalyzed 32CA reaction. This analysis is in agreement with a *zw-type* mechanism.

2.3 Study of the effects of the lithium cation as LA catalyst in the 32CA reaction between nitrone **13** and cyclopentene **14**.

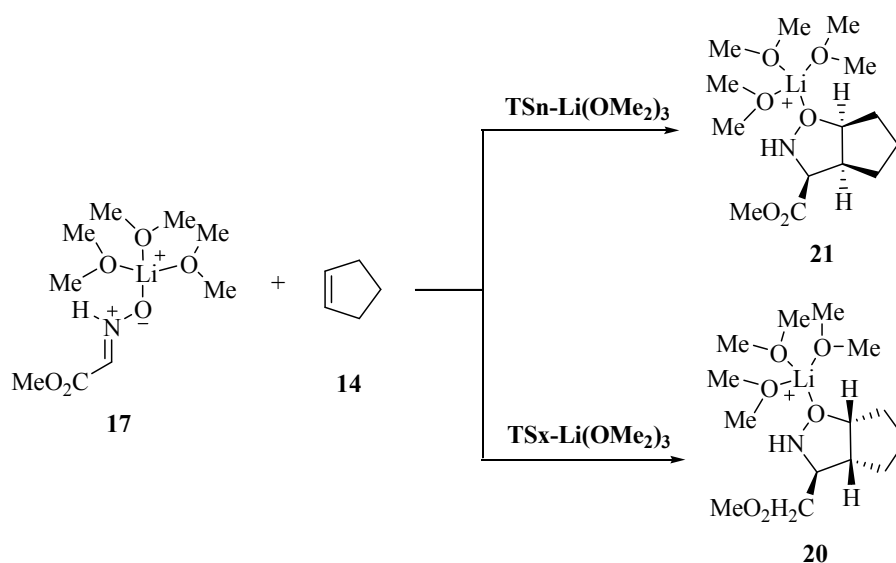
In this part, the effects of the lithium cation as a LA catalyst on the molecular mechanism and the reaction rate of the 32CA reactions between nitrone **13** and cyclopentene **14** is analyzed. Two models for nitrone:lithium complexes have been considered: i) in the first model, the lithium cation is coordinated to the nitrone oxygen and to a chlorine anion (**16**), having the corresponding complex charge 0 (see Scheme 7); ii) in the second model the lithium cation is coordinated to the nitrone oxygen and to three ether molecules to complete a

four coordination (**17**)³⁶, this complex presents a charge +1 (Scheme 8). Since both non-catalyzed and BF_3 catalyzed 32CA reactions between nitron **13** and cyclopentene **14**, presented a complete *exo* selectivity, only the *exo* approach mode was considered. Analysis of the stationary points involved in the *exo* channels associated with these 32CA reactions indicates that they also take place through a one-step mechanism. Consequently, the nitron:lithium complex, one TS and the corresponding CA were located and characterized. Relative energies of the stationery points associated with the 32CA reactions of nitron **13** with cyclopentene **14** in presence of LiCl and $\text{Li}^+(\text{OMe}_2)_3$ catalysts are given in Table 6. Total energies are given in Table S6 in Supplementary Information.



Scheme 7. The possible stereoselective pathways for the LiCl catalyzed 32CA reaction between C-methoxycarbonylnitron **16** and cyclopentene **14**.

The gas phase activation energies associated to these lithium promoted 32CA reactions are 10.0 (**TSx-LiCl**) and 10.8 (**TSx-Li(OMe)₂**)₃ kcal mol⁻¹, the 32CA reactions being strongly exothermic by 42.9 (**10**) and 40.8 (**12**) kcal mol⁻¹. When these activation energies are compared with the non-catalyzed process, it can be observed that the lithium cation produces an unappreciable acceleration of the reaction. These TSs are only 1.1 kcal mol⁻¹ lower in energy than the non-catalyzed **TS1x**. When solvent effects of DCM are considered, the interaction with the lithium cation becomes unfavorable. Similar to other 32CA reactions, inclusion of solvent effects produces a deceleration of the gas phase 32CA reaction as a consequence of a better solvation of the nitron:lithium complexes than TSs. In the two analyzed reactions the larger solvation of the two nitron:lithium complexes provokes the activation energies to be even higher than that of the non-catalyzed process.



Scheme 8. The possible stereoselective pathways for the $\text{Li}^+(\text{OMe}_2)_3$ catalyzed 32CA reaction between C-methoxycarbonylnitrone **17** and cyclopentene **14**.

Relative enthalpies, entropies and Gibbs free energies of the lithium catalyzed 32CA reactions of nitrone **13** with cyclopentene **14** are summarized in Table 7. Values of enthalpies, entropies and free energies are given in Table S7, in Supplementary Information. The use of LiCl and $\text{Li}^+(\text{OMe}_2)_3$ as catalysts increases the activation free energy in comparison with the BF_3 catalyst process ($\Delta\Delta G_{\text{activation}} = 7.9$ and $6.5 \text{ kcal mol}^{-1}$, respectively). Consequently, the Li cation catalyst is not an alternative catalyst, when compared to BF_3 .

The geometries of the TSs associated with the 32CA reaction of nitrone **13** and cyclopentene **14** in the presence of LiCl and $\text{Li}^+(\text{OMe}_2)_3$ are given in Figure 3. The lengths of the O1–C5 and C3–C4 forming bonds at the TSs are 2.286 and 2.120 Å at TSx-LiCl , and 2.256 and 2.117 Å at $\text{TSx-Li(OMe}_2)_3$, respectively. The BO values of the C–O and C–C forming bonds are 0.24 and 0.36 at TSx-LiCl and 0.23 and 0.36 at $\text{TSx-Li(OMe}_2)_3$, respectively. Therefore, these TSs are less asynchronous than that of the BF_3 catalyzed process. Thus, the lithium catalyzed 32CA reactions between nitrone **13** and cyclopentene **14** preceded via an asynchronous one-step mechanism in which the formation of the C–C single bond is more advanced than the C–O one.

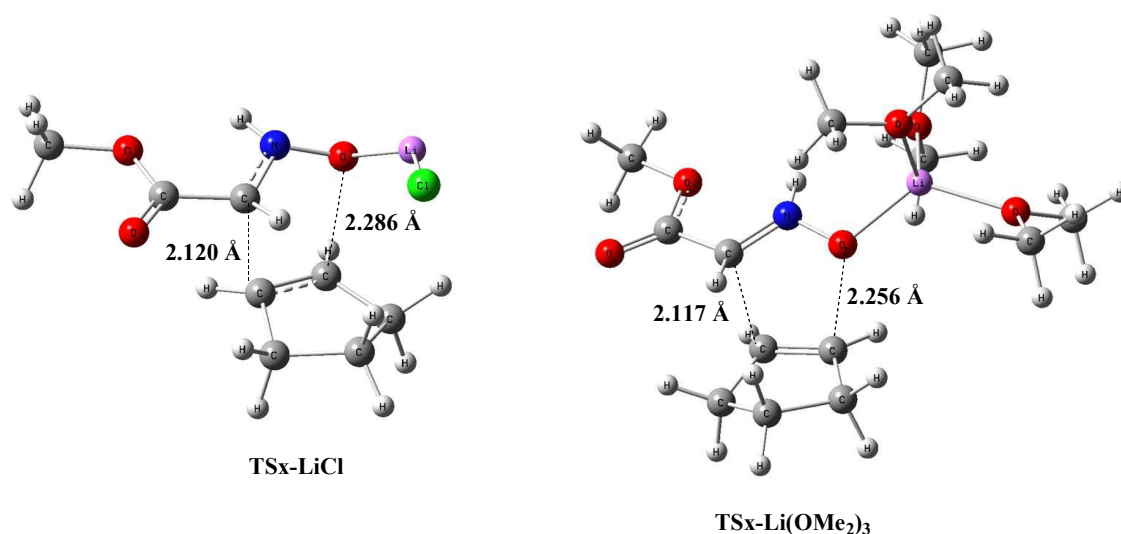


Figure 3. Optimized structures of the TSs for the 32CA reactions of nitronium **13** and cyclopentene **14** in the presence of LiCl and $\text{Li}^+(\text{OMe}_2)_3$

The CT at the TSs associated with the lithium promoted 32CA reactions is 0.16e (**TSx-LiCl**) and 0.17e (**TSx-Li(OMe₂)₃**), indicating that these 32CA reactions took place via some polar mechanism. It may be noted that these values are lower than those found in the BF_3 catalyzed process.

3. DFT-based reactivity indices analysis

Previous studies devoted to DA and 32CA reactions have shown that the analysis of the reactivity indices defined within the context of the conceptual DFT³⁷ is a powerful tool to understand the reactivity in polar cycloadditions. DFT reactivity indices, namely, electronic chemical potential, μ , hardness, η , electrophilicity, ω , and nucleophilicity, N , indices of nitronium, cyclopentene and nitronium- BF_3 are given in Table 8.

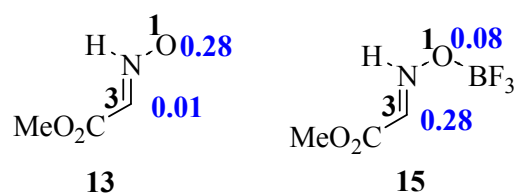
The electronic chemical potential μ of nitronium **13** and nitronium: BF_3 complex **15**, $\mu = -4.47$ eV and -6.13 eV, respectively, is lower than that of pentene **14**, -2.63 eV, indicating that along a polar 32CA reaction the CT will take place from cyclopentene towards nitronium, in agreement with the analysis performed at the TSs.

The electrophilicity and nucleophilicity indices of nitronium **13** are 1.46 and 2.63 eV, respectively, allows for its classification as a moderate electrophile and a moderate nucleophile, based on the electrophilicity¹⁰ and nucleophilicity¹² scales. Coordination of the BF_3 LA to nitronium **13** allowing its electrophilicity increases to $\omega = 2.54$ eV, and decreases the

nucleophilicity to $N = 0.69$ eV, of the corresponding nitron:BF₃ complex **15**. Consequently, it becomes a strong electrophile participating in polar reactions. On the other hand, the electrophilicity and nucleophilicity indices of cyclopentene are $\omega = 0.36$ eV and $N = 3.18$ eV, being classified as a marginal electrophile and strong nucleophile.

The electrophilicity difference $\Delta\omega$ between nitrone **13** and nitron:BF₃ complex **15**, $\Delta\omega = 1.08$ eV, accounts for the catalyst role of the BF₃ LA to favor a *zw-type* reaction *via* a polar process; in *zw-type* 32CA reactions the increase of the polar character of the TS goes accompanied by a decrease of the activation energy.

Recently, Domingo and coworkers³¹ proposed electrophilic, P_k^+ , and nucleophilic, P_k^- , Parr functions, based on the atomic spin density distribution in the radical anion and radical cation of the neutral molecules, to study the regioselectivity in polar reactions. The electrophilic and nucleophilic Parr functions, respectively, obtained through the analysis of the Mulliken atomic spin density of the radical anion and the radical cation. Accordingly, the electrophilic P_k^+ and nucleophilic P_k^- Parr functions for nitrone **13** and nitron-BF₃ **15** are shown in Scheme 8.



Scheme 8. MPWB1K/6-31G(d) electrophilic P_k^+ Parr functions in nitrone **13** and nitron-BF₃ **15**

Analysis of the electrophilic P_k^+ functions at the nitrone **13** indicates that the O1 oxygen atom is the most electrophilic center $P_k^+ = 0.28$. Thus, the formation of the new C–O single bond will be more advanced than the C–C one. For nitron:BF₃ complex **15**, the electrophilic P_k^+ Parr functions at the C3 carbon and O1 oxygen atoms are 0.28 and 0.08, respectively. Therefore, the C3 carbon atom is now the most electrophilic center of complex **15**. Consequently, coordination of the BF₃ LA catalyst to the nitron O1 oxygen atom makes the C3 carbon atom as the most electrophilicity center of complex **15** and thereby, the change the asynchronicity of the single bond formation along these 32CA reactions.

Conclusion

The mechanism and stereoselectivity of the non-catalyzed and BF_3 catalyzed 32CA reactions between the C-methoxycarbonyl nitrone **13** and cyclopentene **14** to yield exclusively the corresponding *trans* isoxazolidine has been studied using DFT methods at the MPWB1K/6-31G(d) computational level. In the absence of an LA catalyst, this 32CA reaction takes place through a near synchronous mechanism leading to the formation of the *exo* cycloadduct as the kinetic and thermodynamic product. The low CT found at the corresponding TS points to the low polar character of this 32CA reaction and the relative high activation energy. The inclusion of solvent effects slightly increases the activation energy and decreases the exothermic character of the 32CA reactions as a consequence of a larger solvation of nitrone **2** than TSs and CAs.

Coordination of the BF_3 catalyst to the oxygen atom of nitrone **2** accelerates the 32CA reaction to increase of the polar character of the reaction with lower activation energy for the *exo* approach leading to formation of a single *trans* cycloadduct. The BF_3 catalyzed 32CA reaction takes place via an asynchronous mechanism in which the C–C bond formation is more advanced than the O–C one. Inclusion of solvent effects has a similar trend to that observed in the non-catalyzed process. The computed activation Gibbs free energy of the TSs also favored kinetically the formation of the *exo* cycloadduct, in agreement with the energy analysis and experimental data.

Finally, the effects of the coordination of the lithium cation as a LA catalyst to nitrone **2** has been analyzed. Coordination of the lithium cation to the oxygen atom of nitrone **2** does not make any appreciable change along the *exo* stereoisomeric channel with respect to the non-catalyzed process. This analysis suggests that the lithium cation is not an effective metal catalyzing 32CA reactions. The computed activation Gibbs free energies of the *exo* TSs allow establishing that the coordination of the Li cation to the oxygen atom of nitrone does not provoke any appreciable catalytic effect on these 32CA reactions.

These findings are the basis of our future research, which we will try to make a platform for experimental chemists in the field of asymmetric synthesis, who would like to use a facile and an efficient metal catalysts.

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References

1. A. Padwa. *1,3-Dipolar Cycloaddition Chemistry*- Ed, Wiley- Interscience: New York, NY, 1984.
2. J. J. Tufariello. in *1,3-Dipolar cycloaddition chemistry*-ed. A. Padwa, J. Wiley & Sons Inc., New York, 1984.
3. a) A.Y. Sukhorukov, S. L. Ioffe. Chem. Rev. **111**, 5004 (2011). b) S. Enthaler, M. Weidauer, and F. Schroeder. Tetrahedron Lett. **53**, 882 (2012).
4. R. Huisgen, R. Grashey and J. Sauer, in *The Chemistry of Alkenes*, Interscience: New York, 1964. b) Luis R. Domingo, M. José Aurell, Rachid Jalal, M'hamed Esseffar, Computational and Theoretical Chemistry 986 (2012) 6–13. c) A. K. Nacereddine, W. Yahia, S. Bouacha, A. Djerourou, Tetrahedron Lett, **51**, 2617 (2010). d) H. Layeb , A. K. Nacereddine, A. Djerourou and L. R. Domingo. J. Mol. Model. **20**, 2347 (2014).
5. L. R. Domingo and J. A. Sáez, Org. Biomol. Chem., 2009, 7, 3576.
6. Domingo, L. R.; Emamian, S. R. Tetrahedron 2014, 70, 1267.
7. Padwa, A. Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry toward Heterocycles and Natural Products; John Wiley & Sons: New York, 2002, Vol. 59.
8. Domingo, L. R.; Aurell, M. J.; Pérez, P. Tetrahedron 2014, 70, 4519
9. Parr, R. G.; Von Szentpaly, L.; Liu, S. J. Am. Chem. Soc. 1999, 121, 1922-1924.
10. L.R. Domingo, M.J. Aurell, P. Pérez, R. Contreras, Tetrahedron 58 (2002) 4417–4423.
11. (a) Parr, R. G.; Szentpaly, L. V.; Liu, S. J. Am. Chem. Soc. 1983, 105, 7512-7516; (b) Parr, R. G.; Yang, W. Density Functional Theory of Atoms and Molecules; Oxford University Press: New York, 1989.
12. P. Jaramillo, L.R. Domingo, E. Chamorro, P. Pérez, J. Mol. Struct. (Theochem) 865 (2008) 68–76.
13. C.A.D. Sousa, M.L.C Vale, X. Garcia-Mera, and J. E. Rodriguez-Borges. Tetrahedron. **68**, 1682 (2012).
14. C. Lee, W. Yang, and R.G. Parr. Phys. Rev B. **37**, 785 (1988).
15. A.D. Becke. J Chem Phys. **98**, 5648 (1993).
16. C.E. Check, and T. M. Gilbert. J. Org. Chem. **70**, 9828 (2005).
17. G.O. Jones, V.A. Gune, and K. Houk. J. Phys. Chem. A. **110**, 1216 (2006).
18. G.A. Griffith, I. H. Hillier, A.C. Moralee, J.M. Percy, R. Roig, and M.A. Vincent. J Am. Chem. Soc. **128**, 13130 (2006).
19. B.J. Lynch, P.L. Fast, M. Harris, and D.G. Truhlar. J. Phys. Chem. A. **104**, 4811 (2000).

20. W. J. Hehre, L. Radom, P.V.R. Schleyer, and J.A. Pople. *Ab Initio Molecular Orbital Theory*-Wiley: New York, NY, 1986.
21. Y. Zhao, D. G. Truhlar. *Theor. Chem. Acc.* **120**, 215 (2008).
22. K. Fukui. *J. Phys. Chem.* **74**, 4161 (1970).
23. K. Fukui. *Acc. Chem. Res.* **14**, 363 (1981).
24. (a) A.E. Reed, L.A. Curtiss, and F. Weinhold. *Chem. Rev.* **88**, 899 (1988); (b) A.E. Reed, R. B. Weinstock, and F. Weinhold. *J. Chem. Phys.* **83**, 735 (1985).
25. A. P. Scott and L. Radom, *J. Phys. Chem.* **100**, 16502 (1996).
26. (a) J. Tomasi, and M. Persico. *Chem. Rev.* **94**, 2027 (1994); (b) B.Y. Simkin, and I. Sheikhet. *Quantum Chemical and Statistical Theory of Solutions A Computational Approach*, Ellis Horwood: London, 1995.
27. (a) E. Cancès, B. Mennucci, and J. Tomasi. *J. Chem. Phys.* **107**, 3032 (1997); (b) M. Cossi, V. Barone, R. Cammi, and J. Tomasi. *Chem. Phys. Lett.* **255**, 327 (1996); (c) V. Barone, M. Cossi, and J. Tomasi. *J. Comput. Chem.* **19**, 404 (1998).
28. Frisch. M. J. *et al*, Gaussian 09, Revision A.02; Gaussian: Wallingford, CT, 2009.
29. (a) Domingo, L. R.; Chamorro, E.; Pérez, P. *J. Org. Chem.* 2008, 73, 4615-4624; (b) Domingo, L. R.; Pérez, P. *Org. Biomol. Chem.* 2011, 9, 7168-7175.
30. Kohn, W.; Sham, L. J. *Phys. Rev.* 1965, 140, 1133-1138.
31. L.R. Domingo, P. Pérez, J.A. Sáez, *RSC Adv.* 3 (2013) 1486–1494.
32. J.A. Long, N. J. Harris, and K. Lammertsma. *J. Org. Chem.* **66**, 6762 (2001).
33. W. Benchouk., S.M. Mekelleche, B. Silvi, M.J. Aurell, and L.R. Domingo. *J. Phys. Org. Chem.* **24**, 611 (2011).
34. K. B. Wiberg. *Tetrahedron.* **24**, 1083 (1968).
35. G. Ujaque, P.S. Lee, K.N. Houk, M.F. Hentemann, and S.J. Danishefsky. *Chem. Eur. J.* **8**, 3423 (2002).
36. L.R. Domingo, S. Gil, R. Mestres, and M. Picher, *Tetrahedron*, 51, 7207 (1995).
37. Geerlings, P.; De Proft, F.; Langenaeker, W. *Chem. Rev.* 103, 1793 (2003); (b) Ess, D. H.; Jones, G. O.; Houk, K. N. *Adv. Synth. Catal.* 348, 2337 (2006).

Table1. B3LYP/6-31G(d), M06-2X/6-31G(d) and MPWB1K/6-31G(d) relative energies (ΔE in kcal mol⁻¹), in gas phase of the stationary points involved in the 32CA reaction of BF₃:nitron **15** complex with cyclopentene **14**

	ΔE Gas phase		
	B3LYP	M06-2X	MPWB1K
TSn-c	13.1	6.7	10.5
TSx-c	2.0	-0.2	2.9
CAn-c	-22.4	-38.9	-37.0
CAX-c	-20.5	-37.8	-34.7

Table2. MPWB1K/6-31G(d) , relative energies (ΔE in kcal mol⁻¹), in gas phase and in DCM, of the stationary points for the 32CA reaction of nitron **13** with cyclopentene **14**.

	ΔE Gas phase	ΔE DCM
TSn	15.3	16.7
TSx	11.2	12.7
CAn	-38.0	-36.5
CAX	-39.7	-38.3

Table 3. MPWB1K/6-31G(d) relative enthalpies (ΔH , in kcal mol⁻¹), entropies (ΔS , in cal mol⁻¹ K⁻¹), and Gibbs free energies (ΔG , in kcal mol⁻¹), for the TSs and CAs involved in the 32CA reaction between nitron **13** and cyclopentene **14**.

	ΔH	ΔS	ΔG
TSn	17.6	-42.0	30.0
TSx	13.8	-41.8	26.1
CAn	-32.9	-42.1	-20.5
CAX	-34.5	-45.6	-21.0

Table 4. MPWB1K/6-31G(d) relative energies (ΔE in kcal mol⁻¹), in gas phase and in DCM, of the stationary points for the 32CA reaction of the BF₃:nitron complex **15** with cyclopentene **14**.

	ΔE Gas phase	ΔE DCM
TSn-B	10.5	11.5
TSx-B	2.9	5.7
CAn-B	-37.0	-31.3
CAX-B	-34.7	-30.3

Table 5. MPWB1K/6-31G(d) relative enthalpies (ΔH , in kcal mol⁻¹), entropies (ΔS , in cal mol⁻¹ K⁻¹), and Gibbs free energies (ΔG , in kcal mol⁻¹), for the TSs and CAs involved in the 32CA reaction between BF₃:nitron **15** complex and cyclopentene **14**.

	ΔH	ΔS	ΔG
TSn-B	12.9	-43.9	25.9
TSx-B	7.0	-45.1	20.3
CAs-B	-27.0	-54.3	-11.0
CAn-B	-27.2	-48.6	-12.9

Table 6. MPWB1K/6-31G(d) relative energies (ΔE in kcal mol⁻¹), in vacuum and in DCM, of the stationary points for the 32CA reactions of nitron **13** with cyclopentene **14** in presence of LiCl or Li⁺(OMe₂)₃.

	ΔE Gas phase	ΔE DCM
TSx-LiCl	10.0	13.3
18	-42.9	-39.7
TSx-Li(OMe₂)₃	10.8	14.3
20	-40.8	-37.4

Table 7. MPWB1K/6-31G(d) relative enthalpies (ΔH , in kcal mol⁻¹), entropies (ΔS , in cal mol⁻¹ K⁻¹), and free energies (ΔG , in kcal mol⁻¹), for the TSs and CA reactions involved in the 32CA reaction between nitron **13** and cyclopentene **14** in the presence of LiCl or Li⁺(OMe₂)₃ catalyst.

	ΔH	ΔS	ΔG
TSx-LiCl	13.5	-49.5	28.2
18	-34.0	-41.6	-23.6
TSx-Li(OMe₂)₃	15.7	-37.4	26.8
20	-33.1	-43.4	-20.3

Table 8. Electronic chemical potential μ , chemical hardness η , global electrophilicity ω and global nucleophilicity N , in eV, for nitron, nitron-c and cyclopentene.

	μ	η	ω	N
Nitron:BF ₃ complex 15	-6.13	7.39	2.54	0.69
Nitron 13	-4.47	6.84	1.46	2.63
Cyclopentene 14	-2.63	9.42	0.36	3.18