

Understanding the reaction mechanism of the Lewis acid (MgBr_2)-catalysed [3+2] cycloaddition reaction between *C*-methoxycarbonyl nitrone and 2-propen-1-ol: a DFT study

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Abstract The mechanism of the non-catalysed and the MgBr_2 -catalysed [3+2] cycloaddition (32CA) reactions between *C*-methoxycarbonyl nitrone and 2-propen-1-ol has been theoretically investigated within the molecular electron density theory using DFT methods at the B3LYP/6-31G(d) computational level. Analysis of DFT reactivity indices allows explaining the role of the MgBr_2 Lewis acid in the catalysed 32CA reaction. The 32CA reaction between *C*-methoxycarbonyl nitrone and 2-propen-1-ol takes place with a relative high activation enthalpy, 13.5 kcal mol⁻¹, as a consequence of the non-polar character of this *zw*-type 32CA reaction. Coordination of the MgBr_2 LA to *C*-methoxycarbonyl nitrone accelerates the corresponding *zw*-type 32CA reaction by taking place through a polar mechanism and with lower activation enthalpy, 8.5 kcal mol⁻¹. Both 32CA reactions, which take place through a one-step mechanism, are completely *meta* regioselective and present low *exo* stereoselectivity, which increases in the catalysed process. Energy and non-covalent interaction analyses at the transition-state structures indicate that the formation of an intramolecular H–Br hydrogen

bond in the catalysed process could be responsible for the *exo* selectivity experimentally observed.

Keywords [3+2] Cycloaddition reactions · Nitrones · Molecular mechanism · Molecular electron density theory, conceptual DFT indices · Non-covalent interactions

1 Introduction

[3+2] Cycloaddition (32CA) reactions are among the most powerful methods for the synthesis of five-membered heterocyclic compounds since 1961, when Huisgen experimentally developed their mechanistic study [1]. Starting from relatively simple and easily accessible molecules, 32CA reactions can offer a highly yielding and selective method for the synthesis of a wide variety of simple as well as complex heterocycles of great biological importance [2].

Nitrones **1** are stable and easily prepared compounds widely used as efficient three-atom components (TACs) in 32CA reactions with alkenes. In particular, the 32CA reaction of nitrones **1** with electron-deficient (ED) ethylenes **2** is one of the most attractive methods for the synthesis of isoxazolidines [3], which are important precursors for the synthesis of a large number of biologically active molecules with a diversity of applications, mainly as amino alcohols and alkaloids antiviral agents [4–7]. In addition, the use of non-symmetric alkenes opens up the possibility of obtaining two isomeric isoxazolidines (see Scheme 1).

Unlike 1,3-dienes participating in Diels–Alder reactions [8], the electronic structure of TACs participating in 32CA reactions strongly depends on the type and hybridisation of the atoms present in the TAC. Thus, depending on their electronic structure, TACs have recently been classified as *pseudodiradical*, carbenoid and zwitterionic TACs

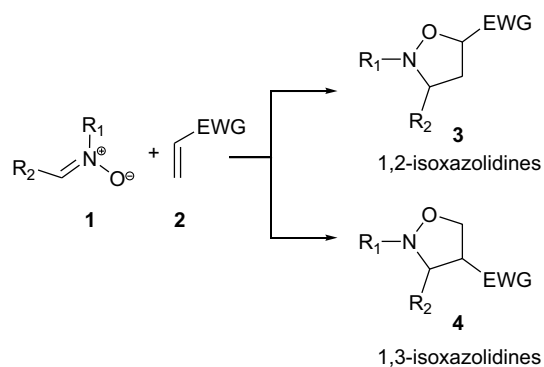
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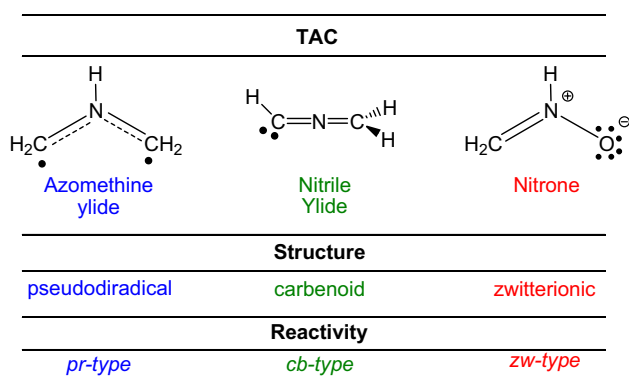
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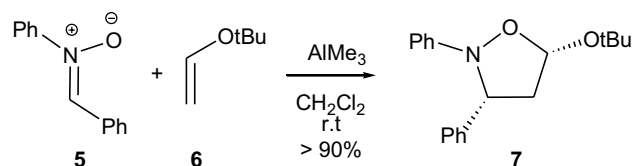
Scheme 1 32CA reactions of nitrones **1** with ED ethylenes **2**



Scheme 2 Electronic structure of TACs and the proposed reactivity types in 32CA reactions

(see Scheme 2) [9, 10]. Note that only 1,2-zwitterionic TACs such as nitrones **1** have the electronic structure of a 1,3-dipole as Huisgen proposed [1].

Very recently, Domingo has proposed a new reactivity model in organic chemistry named the molecular electron density theory (MEDT) [11], in which changes in the electron density along an organic reaction, and not MO interactions, are responsible for the feasibility of an organic reaction. Within MEDT, besides a deep exploration and characterisation of the potential energy surfaces (PESs) associated with the studied reaction, quantum chemical tools based on the analysis of the electron density, such as the analysis of the conceptual density functional theory (CDFT) reactivity indices at the ground state of the molecules [12, 13], the topological analysis of the electron localisation function (ELF) [14] focused on the progress of the bonding changes along the reaction coordinate and non-covalent interaction [15] (NCI) analysis at the TSs in order to characterise weak interactions determining the selectivity in organic reactions, are used to study the molecular reactivity in organic reactions rigorously.

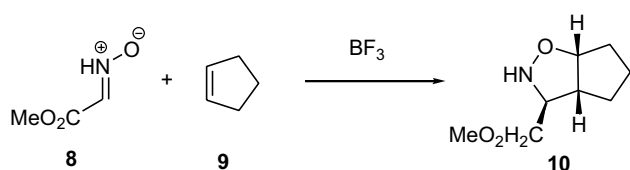


Scheme 3 LA-catalysed 32CA reactions of nitron **5** with ER vinyl ether **6** [20]

MEDT studies [10, 16] devoted to the understanding of the mechanisms of 32CA reactions have allowed establishing a useful classification of these reactions into *pseudoradical*-type [9] (*pr*-type), *carbenoid*-type (*cb*-type) [10] and *zwitterionic*-type [9] (*zw*-type) reactions, in such a manner that TACs with a *pseudoradical* character participate in *pr*-type 32CA reactions taking place easily through earlier transition-state structures (TSs) with a very low polar character [9, 17]; TACs with a *carbenoid* character participate in *cb*-type 32CA reactions whose feasibility depends on the polar character of the reaction, i.e. the nucleophilic character of the *carbenoid* TAC and the electrophilic character of the ethylene derivative [10]; and finally, TACs with a *zwitterionic* character participate in *zw*-type 32CA reactions controlled by nucleophilic/electrophilic interactions taking place at the TSs, similarly to *cb*-type reactions [9, 18].

Nitrones **1**, which present a high nucleophilic character, are able to participate in *zw*-type 32CA reactions with ED ethylenes **2**, usually via a polar one-step mechanism with low activation energy [18]. However, nitrones generally have no tendency to react with electron-rich (ER) ethylenes. In these cases, the presence of a Lewis acid (LA) catalyst coordinated to the nitron oxygen atom is required in order to increase its electrophilic character [18].

LA-catalysed 32CA reactions constitute a new research field and have attracted a continuous growing interest in some unexplored areas, which need to be investigated in both experimental and theoretical ways [19]. A considerable amount of experimental and theoretical studies of the mechanisms and selectivities of LA-catalysed 32CA reactions of nitrones with ethylene derivatives can be found in the literature. The 32CA reaction of nitron **5** with the ER ethylene **6** giving exclusively the 5-substituted isoxazolidine **7** was experimentally studied by Jorgensen et al. [20] (see Scheme 3). The reaction rate was enhanced by the presence of a LA. The 32CA reaction presented a total regioselectivity, while the *exo* stereoselectivity depended on the bulky chiral LA used as catalyst [20]. A further DFT study permitted establishing that inclusion of the BH_3 LA and solvent effects causes the corresponding nitron/ BH_3 complex and ER vinyl ether to behave as an electrophile and a nucleophile, respectively, in a polar reaction [21];



Scheme 4 32CA reaction of *C*-methoxycarbonyl nitron **8** with ER cyclopentene **9** yielding *trans*-isoxazolidine **10** [22]

thus, these reactions should be considered as a nucleophilic attack of the α -carbon of the vinyl ether on the carbon atom of the LA-coordinated nitron.

Sousa et al. [22] experimentally studied the 32CA reaction of *C*-methoxycarbonyl nitron **8** with ER cyclopentene **9**, finding that this reaction gives exclusively the *trans*-isoxazolidine **10** proceeding from the *exo* approach (see Scheme 4). A recent DFT study [23] of the role of the BF₃ LA in this *zw*-type 32CA reaction showed that in the absence of the LA catalyst, the reaction presents a high activation energy, 11.2 kcal mol⁻¹, as a consequence of the low electrophilic character of *C*-methoxycarbonyl nitron **8**, $\omega = 1.46$ eV [23]. Coordination of the BF₃ LA to the nitron oxygen atom accelerated the 32CA reaction by increasing markedly the polar character of the reaction, $\Delta E^\ddagger = 2.9$ kcal mol⁻¹. Both non-catalysed and catalysed 32CA reactions showed to be completely *exo* selective, in total agreement with the experimental outcomes [23].

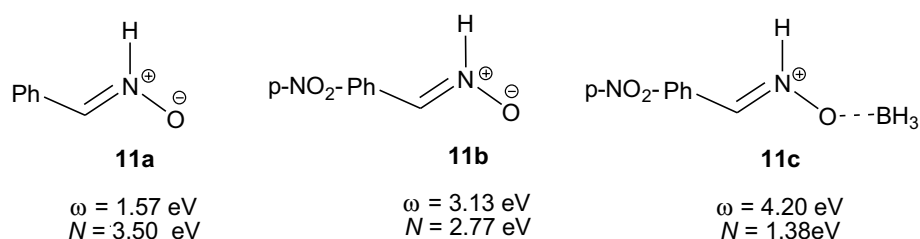
A recent DFT study [23] devoted to the participation of nitrones in *zw*-type reactions showed that the *C*-phenyl nitron **11a** presents a low electrophilicity ω index [24], $\omega = 1.57$ eV, and a high nucleophilicity N index [25, 26], $N = 3.51$ eV, being classified as a moderate electrophile and a strong nucleophile (see Scheme 5). Inclusion of a strong electron-withdrawing group (EWG) such as NO₂

in the phenyl substituent notably increases the electrophilicity of nitron **11b**, $\omega = 3.13$ eV. However, in spite of this strong electrophilic activation, the 32CA reaction of nitron **11b** with an ER ethylene presents a high activation energy, $\Delta E^\ddagger = 13.2$ kcal mol⁻¹ [13, 18]. This study revealed that coordination of the BF₃ LA to the nitron oxygen atom effectively activates the participation of complex **11c**, $\omega = 4.20$ eV, in *zw*-type 32CA reactions with ER ethylenes. In this case, the most favourable regioisomeric TS was energetically found below the separated reagents, $\Delta E = -3.7$ kcal mol⁻¹. The LA-catalysed 32CA reaction showed to be completely regioselective, giving the corresponding 1,2-isoxazolidine as single product [23].

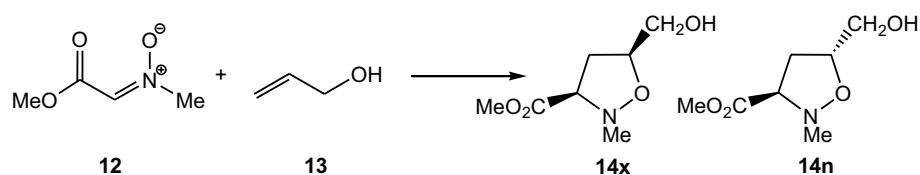
The 32CA reaction of *C*-methoxycarbonyl nitron **12** with 2-propen-1-ol **13**, yielding a 44:56 mixture of 3,5-*trans*- and 3,5-*cis*-isoxazolidines **14n** and **14x**, was experimentally studied by Kanemasa (see Scheme 6) [27]. Interestingly, a high rate acceleration was observed in the presence of an equimolar amount of MgBr₂·OEt₂ in dichloromethane (DCM), being the 3,5-*cis*-isomer **14x** obtained as single stereoisomer in 71% yield.

Herein, in order to understand the effects of the MgBr₂ LA catalyst on the molecular mechanism and the reaction rate of the 32CA reaction between *C*-methoxycarbonyl nitron **12** and 2-propen-1-ol **13**, as well as the origin of the selectivities experimentally found by Kanemasa et al. [27], a theoretical characterisation of the molecular mechanism of these *zw*-type 32CA reactions is carried out within the MEDT using DFT methods at the B3LYP/6-31G(d) computational level. To this end, besides the exploration and characterisation of the potential energy surfaces (PESs) associated with the studied reactions, quantum chemical tools based on the analysis of the electron density, such as CDFT reactivity indices [13, 28] and NCI [15] analysis, will be employed.

Scheme 5 Electrophilicity ω and nucleophilicity N indices of nitrones **11a**, **11b** and **11c**



Scheme 6 32CA reactions between *C*-methoxycarbonyl nitron **12** and 2-propen-1-ol **13** studied by Kanemasa [27]



2 Computational methods

All stationary points involved in these 32CA reactions were optimised using the B3LYP functional [29, 30] together with the standard 6-31G(d) basis set [31]. The optimisations were carried out using the Berny analytical gradient optimisation method [32, 33]. The stationary points were characterised by frequency computations in order to verify that TSs have one and only one imaginary frequency. The intrinsic reaction coordinate (IRC) paths [34] were traced in order to check the energy profiles connecting each TS to the two associated minima of the proposed mechanism using the second-order González–Schlegel integration method [35, 36]. Solvent effects of DCM were taken into account by full optimisation of gas-phase stationary points using the polarisable continuum model (PCM) developed by Tomasi's group [37, 38] in the framework of the self-consistent reaction field (SCRf) [39–41]. Values of enthalpies, entropies and Gibbs free energies in DCM were calculated with standard statistical thermodynamics at 298.15 K and 1 atm [31]. Natural atomic charges were obtained through a natural population analysis (NPA) within the natural bond orbital (NBO) method [42, 43]. NCI's were computed by evaluating the promolecular density and using the methodology previously described [15, 44, 45]. All computations were carried out with the Gaussian 09 suite of programs [46].

The global electrophilicity index [24], ω , is given by the following expression, $\omega = (\mu^2/2\eta)$, 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 $\mu \approx (\varepsilon_H + \varepsilon_L)/2$ and $\eta = (\varepsilon_L - \varepsilon_H)$, respectively [47, 48]. The empirical (relative) nucleophilicity index [25, 26] N , based on the HOMO energies obtained within the Kohn–Sham scheme [49], is defined as $N = E_{\text{HOMO}}(\text{Nu}) - E_{\text{HOMO}}(\text{TCE})$, where tetracyanoethylene (TCE) is the reference, because it presents the lowest HOMO energy in a long series of molecules already investigated in the context of polar organic reactions. This choice allows conveniently to hand a nucleophilicity scale of positive values. Nucleophilic P_k^- and electrophilic P_k^+ Parr functions [50] were obtained through the analysis of the Mulliken atomic spin density (ASD) of the corresponding radical cations or anions, respectively.

3 Results and discussion

The present theoretical study has been divided into four sections: (1) first, an analysis of DFT reactivity indices of the reagents involved in the non-catalysed and in the

Table 1 B3LYP/6-31G(d) electronic chemical potential (μ), chemical hardness (η), global electrophilicity (ω) and global nucleophilicity (N), in eV, of *C*-methoxycarbonyl nitron **12**, complex **12:Mg**, 2-propen-1-ol **13** and ethylene **16**

Reactants	μ	η	ω	N
<i>C</i> -methoxycarbonyl nitron 12	−4.17	4.82	1.81	2.54
Complex 12:Mg	−5.00	2.64	4.74	2.84
2-propen-1-ol 13	−3.27	7.29	0.74	2.20
Ethylene 16	−3.37	7.77	0.73	1.86

LA-catalysed 32CA reactions is carried out; (2) then, the PESs associated with the 32CA reaction between *C*-methoxycarbonyl nitron **12** and 2-propen-1-ol **13** are explored and characterised; (3) third, the 32CA reaction between complex **12:Mg** and 2-propen-1-ol **13** is studied; and (4) finally, the origin of the selectivity experimentally found in the LA-catalysed process is analysed.

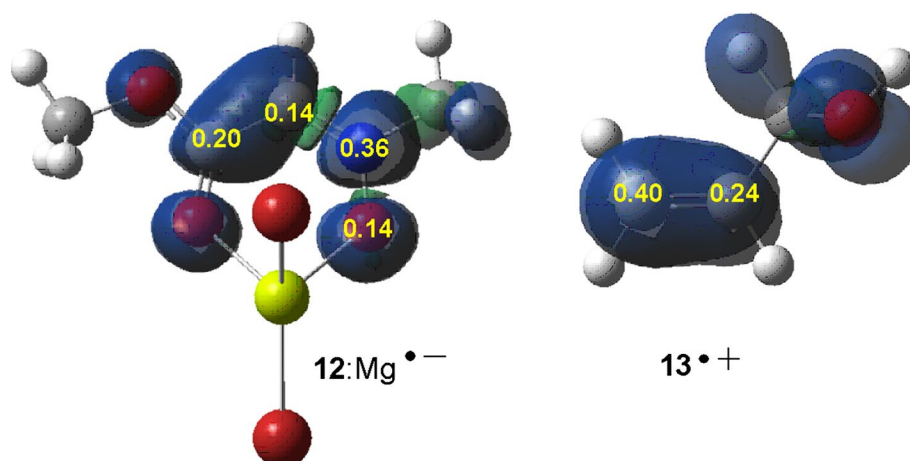
3.1 Analysis of CDFT reactivity indices

Global reactivity indices, as defined in the context of CDFT [16, 28], are useful tools to understand the reactivity of molecules in their ground state as shown in recent studies devoted to DA [8] and 32CA reactions [51]. Table 1 shows the static global properties: electronic chemical potential, μ , chemical hardness, η , and global electrophilicity, ω , and nucleophilicity, N , of *C*-methoxycarbonyl nitron **12**, complex **12:Mg**, 2-propen-1-ol **13** and ethylene **16**.

The electronic chemical potential of 2-propen-1-ol **13**, $\mu = -3.27$ eV, is higher than that of *C*-methoxycarbonyl nitron **12**, $\mu = -4.17$ eV, and complex **12:Mg**, $\mu = -5.00$ eV, suggesting that along a polar reaction, the global electron density transfer (GEDT) [52] will take place from 2-propen-1-ol **13** to *C*-methoxycarbonyl nitron **12** and complex **12:Mg**.

Along a polar reaction, there is an electron density transfer from the nucleophile to the electrophile, which is measured by the GEDT [52] value at the TS of the reaction; the larger GEDT at the TS is the more polar the reaction. Cycloadditions with GEDT values near 0.0e correspond to non-polar processes, whereas values higher than 0.2e correspond to polar processes. Interestingly, thorough studies have permitted to establish good correlations between the polar character of the reactions and their feasibility [8–10]. It is noteworthy that the GEDT concept comes from the observation that the electron density transfer taking place from a nucleophile to an electrophile along a polar reaction is not a local process, but a global one involving the two interacting frameworks [52] and depending on the electrophilic/nucleophilic interactions taking place between them.

Fig. 1 3D representations of the ASD of the radical anion complex **12**:Mg^{•−} and the radical cation **13**^{•+}, including the nucleophilic P_k^+ functions of complex **12**:Mg and the electrophilic P_k^- Parr functions of 2-propen-1-ol **13**



The electrophilicity and nucleophilicity indices of *C*-methoxycarbonyl nitrene **12**, $\omega = 1.81$ and $N = 2.54$ eV, allow its classification on the borderline of strong electrophiles and as a moderate nucleophile based on the electrophilicity [53] and nucleophilicity [54] scales. Coordination of MgBr₂ LA to nitrene **12** considerably increases the electrophilicity of complex **12**:Mg, $\omega = 4.72$ eV, and slightly increases the nucleophilicity, $N = 2.84$ eV, being now classified as a strong electrophile and remaining as moderate nucleophile.

On the other hand, the electrophilicity and nucleophilicity indices of 2-propen-1-ol **13** are $\omega = 0.74$ and $N = 2.20$ eV, being classified on the borderline of marginal electrophiles and as a moderate nucleophile. Note that 2-propen-1-ol **13** is only slightly more nucleophilic than ethylene **16**, which has no tendency to participate in polar cycloaddition reactions.

Analysis of these global reactivity indices indicates that the low electrophilic character of *C*-methoxycarbonyl nitrene **12** and the low nucleophilic character of 2-propen-1-ol **13** make that the corresponding *zw*-type 32CA reaction will have a very low polar character. Coordination of MgBr₂ to nitrene **12** considerably increases the electrophilicity of complex **12**:Mg, allowing the corresponding 32CA reaction to have somewhat polar character, thus having a lower activation energy than the non-catalysed process.

In polar cycloaddition reactions, the most favourable reactive channel is that involving the initial two-centre interaction between the most electrophilic and nucleophilic centres of both reagents. Recently, Domingo et al. [50] proposed the electrophilic P_k^+ and nucleophilic P_k^- Parr functions derived from the changes of spin electron density reached via the GEDT process from the nucleophile to the electrophile as powerful tools in the study of the local reactivity in polar processes. Accordingly, the electrophilic P_k^+ Parr functions for complex **12**:Mg and the nucleophilic P_k^- Parr functions for 2-propen-1-ol **13** were computed (see Fig. 1).

Analysis of the electrophilic P_k^+ Parr functions for complex **12**:Mg indicates that the nitrene nitrogen atom is the most electrophilic centre, $P_k^+ = 0.36$, being twice as electrophilically activated than the O1 and C3 atoms, which have the same electrophilic activation, $P_k^+ = 0.14$ (see Scheme 7 for atom numbering). The carbonyl carbon atom has a moderate electrophilic activation, $P_k^+ = 0.20$. On the other hand, analysis of the nucleophilic P_k^- Parr functions at 2-propen-1-ol **13** indicates that the C4 carbon, $P_k^- = 0.40$, is twice as nucleophilically activated as the C3 carbon, $P_k^- = 0.24$.

Although the O1 and C3 atoms of nitrene have the same electrophilic activation, the high electrophilic activation of the carbonyl carbon atom adjacent to the nitrene C3 carbon suggests that the most favourable regioisomeric reactive channel will correspond to that associated with the C3–C4 bond formation. Note the larger and overlapped ASD surfaces at the C3 and carbonyl carbon atoms at the radical anion of complex **12**:Mg in Fig. 1.

3.2 Study of the 32CA reaction between *C*-methoxycarbonyl nitrene **12** and 2-propen-1-ol **13**

Due to the non-symmetry of both reagents, four reactive channels for the 32CA reaction between *C*-methoxycarbonyl nitrene **12** and 2-propen-1-ol **13** are possible. They are related to the two regioisomeric approach modes of 2-propen-1-ol **13** to nitrene **12**, namely *meta* and *ortho*, and the two possible stereoisomeric approach modes, namely *endo* and *exo*. The *meta* and *ortho* regioisomeric channels are associated with the formation of the 3,5- and 3,4-isoxazolidines, respectively, while the *endo* and *exo* stereoisomeric channels are related to the relative position of the hydroxyl group of 2-propen-1-ol **13** with respect to the N2 nitrogen atom of *C*-methoxycarbonyl nitrene **12** (see Scheme 7). Analysis of the PESs associated with this

Scheme 7 32CA reaction between *C*-methoxycarbonyl nitrone **12** and 2-propen-1-ol **13**

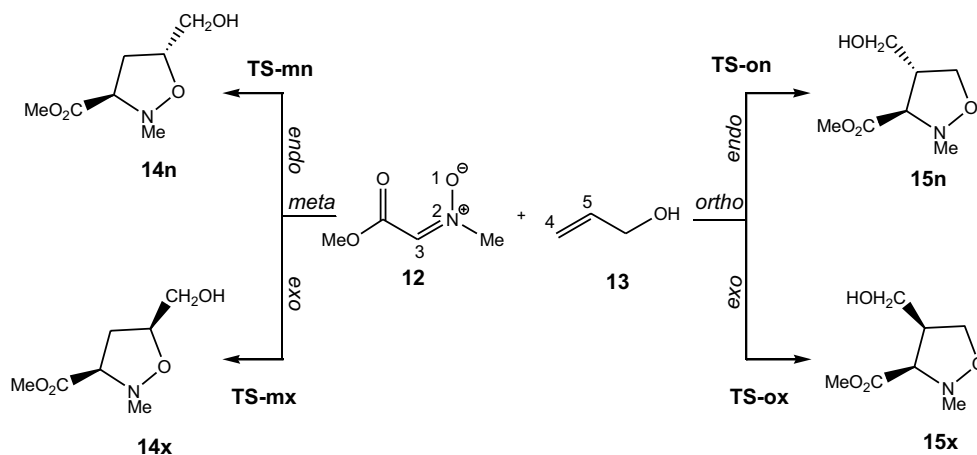


Table 2 B3LYP/6-31G(d) relative electronic energies (in kcal mol⁻¹), in gas phase and in the presence of DCM, for the species involved in the 32CA reaction between *C*-methoxycarbonyl nitrone **12** and 2-propen-1-ol **13**

	Gas phase	DCM
TS-mn	9.3	12.0
TS-mx	8.5	11.8
TS-on	14.7	17.5
TS-ox	12.7	16.3
14n	-31.2	-26.3
14x	-29.0	-24.8
15n	-27.3	-22.9
15x	-28.4	-23.4

32CA reaction allows locating and characterising four TSs, **TS-mn**, **TS-mx**, **TS-on** and **TS-ox**, and the corresponding CAs, **14-n** **14-x**, **15-n** and **15-x**, thus indicating that it takes place through a one-step mechanism. Relative energies, in the gas phase and in the presence of DCM, for the species involved in the 32CA reaction between *C*-methoxycarbonyl nitrone **12** and 2-propen-1-ol **13** are given in Table 2.

The gas-phase activation energies associated with the four competitive channels are 9.3 (**TS-mn**), 8.5 (**TS-mx**), 14.7 (**TS-on**) and 12.7 (**TS-ox**) kcal mol⁻¹. Thus, in gas phase, this 32CA reaction is completely regioselective as **TS-mx** is 4.2 kcal mol⁻¹ lower in energy than **TS-ox** and slightly *exo* stereoselective as **TS-mx** is 0.8 kcal mol⁻¹ lower in energy than **TS-mn**. This 32CA reaction is strongly exothermic, between 27 and 31 kcal mol⁻¹; consequently, it can be considered irreversible. These energy results indicate that the major product isoxazolidine **14x** is formed by kinetic control in good agreement with the experimental outcomes [27].

With the inclusion of solvent effects of DCM, the activation energies increase to 12.0 (**TS-mn**), 11.8 (**TS-mx**),

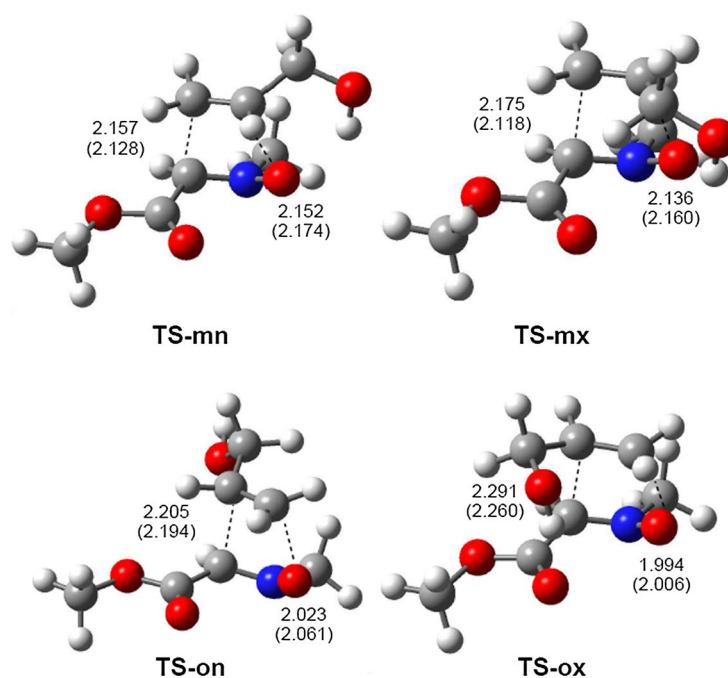
Table 3 B3LYP/6-31G(d) relative enthalpies (ΔH , in kcal mol⁻¹), entropies (ΔS , in cal mol⁻¹ K⁻¹) and Gibbs free energies (ΔG , in kcal mol⁻¹), computed at room temperature and 1 atm in DCM, for the stationary points involved in the 32CA reaction between *C*-methoxycarbonyl nitrone **12** and 2-propen-1-ol **13**

	ΔH	ΔS	ΔG
TS-mn	13.5	-44.1	26.7
TS-mx	13.3	-44.1	26.5
TS-on	18.7	-41.8	31.2
TS-ox	17.8	-45.4	31.3
14n	-22.5	-44.4	-9.3
14x	-21.1	-45.3	-7.6
15n	-19.1	-47.0	-5.1
15x	-19.4	-47.9	-5.1

17.5 (**TS-on**) and 16.3 (**TS-ox**) kcal mol⁻¹, as a consequence of a larger solvation of the reagents than the TSs and CAs [55]. In DCM, while the total regioselectivity found in gas phase remains unchanged, as the most favourable **TS-mx** is 4.5 kcal mol⁻¹ lower in energy than **TS-mn**, the *exo* stereoselectivity decreases, as now **TS-mx** is only 0.2 kcal mol⁻¹ more stable than **TS-mn**.

Values of relative enthalpies, entropies and Gibbs free energies of the stationary points involved in the 32CA reaction of *C*-methoxycarbonyl nitrone **12** with 2-propen-1-ol **13** are summarised in Table 3. Analysis of the relative activation enthalpies indicates that the most favourable approach mode remains associated with **TS-mx**, $\Delta H = 13.3$ kcal mol⁻¹. Addition of the entropic contribution to the enthalpy increases the activation Gibbs free energy of this reactive channel to 26.5 kcal mol⁻¹ as the consequence of the unfavourable negative activation entropy associated with this bimolecular process, $\Delta S = -44.1$ cal mol⁻¹ K⁻¹. Formation of the more favourable *meta* CAs is exergonic by 9.3 (**14n**) and 7.6 (**14x**) kcal mol⁻¹. Inclusion of the thermodynamic parameters

Fig. 2 B3LYP/6-31G(d) optimised geometries for the TSs involved in the 32CA reaction between *C*-methoxycarbonyl nitrene **12** and 2-propen-1-ol **13**. Geometries in DCM are given in *parentheses*. Distances are given in Angstroms



to the electronic energies does not modify the regio- and stereoselectivity previously found, in agreement with the experimental outcomes in which a 44:56 mixture of isoxazolidines **14n** and **14x** is obtained [27].

Figure 2 shows the geometries of the TSs involved in the 32CA reaction between *C*-methoxycarbonyl nitrene **12** and 2-propen-1-ol **13**. At the *meta* TSs, the lengths of the O1–C5 and C3–C4 forming bonds are 2.152 and 2.157 Å at **TS-mn** and 2.136 and 2.175 Å at **TS-mx**, while at the *ortho* TSs, the lengths of the O1–C4 and C3–C5 forming bonds are 2.023 and 2.205 Å at **TS-on**, and 2.291 and 1.994 Å at **TS-ox**, respectively. In addition, all TSs present a hydrogen bond (HB) between the nitrene O1 oxygen and the hydroxyl hydrogen of the propenol framework. Note that this 32CA reaction implies the formation of two single bonds C–C and C–O of different nature, and consequently, neither analysis of geometries nor of bond order values can be used as a measure of the extent of the bond formation, but an ELF topological characterisation of the bonding changes along the reaction path [56]. Inclusion of solvent effects of DCM in the geometry optimisation does not produce appreciable changes in gas-phase geometries (see Fig. 2).

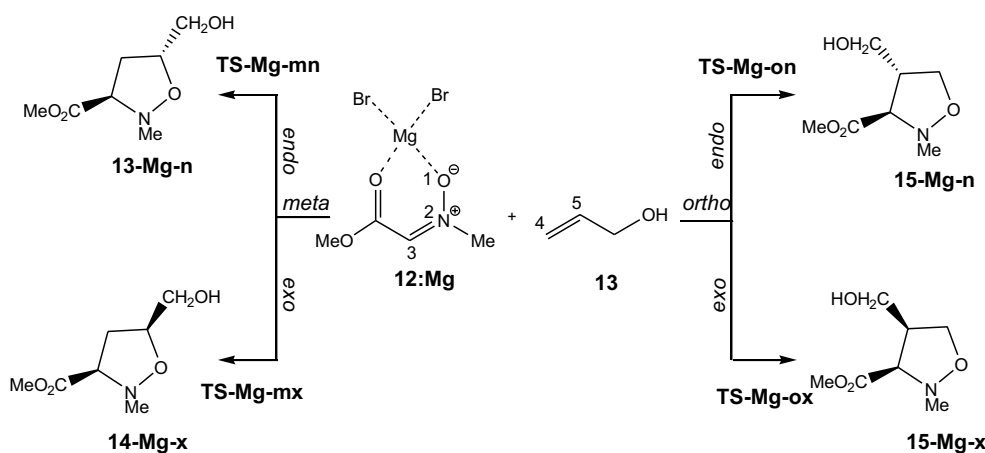
In order to evaluate the electronic nature of this 32CA reaction, the GEDT in the four competitive TSs was analysed. The GEDT at the TSs computed as the sum of the natural atomic charges, obtained through an NPA, of all the atoms belonging to the propenol framework is 0.06e at **TS-mn**, 0.06e at **TS-mx**, 0.03e at **TS-on** and 0.08e at **TS-ox**. These negligible GEDT values point out the low polar character of the non-catalysed process and account

for the computed high activation energy of this 32CA reaction [18]. This behaviour is in agreement with the relative low electrophilicity of *C*-methoxycarbonyl nitrene **12** and the relative low nucleophilicity of 2-propen-1-ol **13** (see Sect. 3.1).

3.3 Study of the MgBr₂ LA-catalysed 32CA reaction of *C*-methoxycarbonyl nitrene **12** with 2-propen-1-ol **13**

Coordination of the MgBr₂ LA to the carbonyl and nitrene oxygen atoms of *C*-methoxycarbonyl nitrene **12** allows the formation of complex **12:Mg**, thus increasing strongly the electrophilic character of *C*-methoxycarbonyl nitrene **12**. As the non-catalysed process, due to the non-symmetry of the reagents, the MgBr₂ LA-catalysed 32CA reaction of *C*-methoxycarbonyl nitrene **12** and 2-propen-1-ol **13** can take place along four competitive channels (see Scheme 8). Analysis of the stationary points found along the PESs associated with this LA-catalysed 32CA reaction indicates that it takes place also through a one-step mechanism. Thus, four TSs, **TS-Mg-mn**, **TS-Mg-mx**, **TS-Mg-on** and **TS-Mg-ox**, and the corresponding CAs, **14-Mg-n**, **14-Mg-x**, **15-Mg-n** and **15-Mg-x**, were located and characterised. Relative energies, in the gas phase and in the presence of DCM, for the species involved in the 32CA reaction between complex **12:Mg** and 2-propen-1-ol **13** are given in Table 4.

The gas-phase activation energies associated with the four reaction channels are: 8.3 (**TS-Mg-mn**), 5.7 (**TS-Mg-mx**), 11.0 (**TS-Mg-on**) and 11.9 (**TS-Mg-ox**)



Scheme 8 MgBr_2 LA-catalysed 32CA reaction between *C*-methoxycarbonyl nitron **12** and 2-propen-1-ol **13**

Table 4 B3LYP/6-31G(d) relative electronic energies (in kcal mol^{-1}), in gas phase and in the presence of DCM, for the species involved in the MgBr_2 LA-catalysed 32CA reaction between nitron **12** and 2-propen-1-ol **13**

	Gas phase	DCM
TS-Mg-mn	8.3	10.2
TS-Mg-mx	5.7	9.7
TS-Mg-on	11.0	14.3
TS-Mg-ox	11.9	15.8
14-Mg-n	-24.3	-20.9
14-Mg-x	-26.4	-20.2
15-Mg-n	-26.7	-24.4
15-Mg-x	-30.5	-27.1

kcal mol^{-1} (see Table 4). In gas phase, this LA-catalysed 32CA reaction is completely regioselective as **TS-Mg-mx** is $5.3 \text{ kcal mol}^{-1}$ lower in energy than **TS-Mg-on**, and highly *exo* selective as **TS-Mg-mx** is $2.6 \text{ kcal mol}^{-1}$ lower in energy than **TS-Mg-mn**. This 32CA reaction is strongly exothermic, between 24 and 30 kcal mol^{-1} ; consequently, this LA-catalysed 32CA reaction can also be considered irreversible, the major product isoxazolidine **14-Mg-x** being formed by kinetic control. Coordination of the MgBr_2 LA to the two oxygen atoms of *C*-methoxycarbonyl nitron **12** not only accelerates the *zw*-type 32CA reaction of complex **12:Mg** with 2-propen-1-ol **13**, but also notably increases the *exo* stereoselectivity, in complete agreement with the experimental outcomes [27].

Solvent effects of DCM increase the activation energies to 10.2 (**TS-Mg-mn**), 9.7 (**TS-Mg-mx**), 14.3 (**TS-Mg-on**) and 15.8 (**TS-Mg-ox**) kcal mol^{-1} as a consequence of a larger solvation of the reagents than TSs and CAs [55]. In DCM, the total regioselectivity found in gas phase remains unchanged as the most favourable **TS-Mg-mx** is

$4.6 \text{ kcal mol}^{-1}$ lower in energy than **TS-Mg-mn**, while the *exo* selectivity decreases, being **TS-Mg-ox** $0.5 \text{ kcal mol}^{-1}$ lower in energy than **TS-Mg-mn**.

Values of relative enthalpies, entropies and Gibbs free energies of the stationary points involved in the 32CA reaction of complex **12:Mg** with 2-propen-1-ol **13** are given in Table 5. Analysis of the relative activation enthalpies of the four reactive channels associated with the 32CA reaction of complex **12:Mg** with 2-propen-1-ol **13** shows that the most favourable approach mode remains associated with **TS-Mg-mx**, $\Delta H = 10.3 \text{ kcal mol}^{-1}$. Coordination of the MgBr_2 LA to *C*-methoxycarbonyl nitron **12** decreases the activation enthalpy by 3.0 kcal/mol with respect to that associated with the non-catalysed process. Addition of the entropic contribution to the enthalpy increases the activation Gibbs free energy of the most favourable *meta/exo* reactive channel to $26.5 \text{ kcal mol}^{-1}$ as the consequence of the unfavourable negative activation entropy associated with this bimolecular 32CA reaction, $\Delta S = -52.7 \text{ cal mol}^{-1} \text{ K}^{-1}$. Inclusion of the thermodynamic parameters to the electronic energies does not modify the regio- and stereoselectivity found by analysis of the electronic energies in DCM. At this computational level, formation of the most favourable isoxazolidine **14-Mg-x** is slightly endergonic.

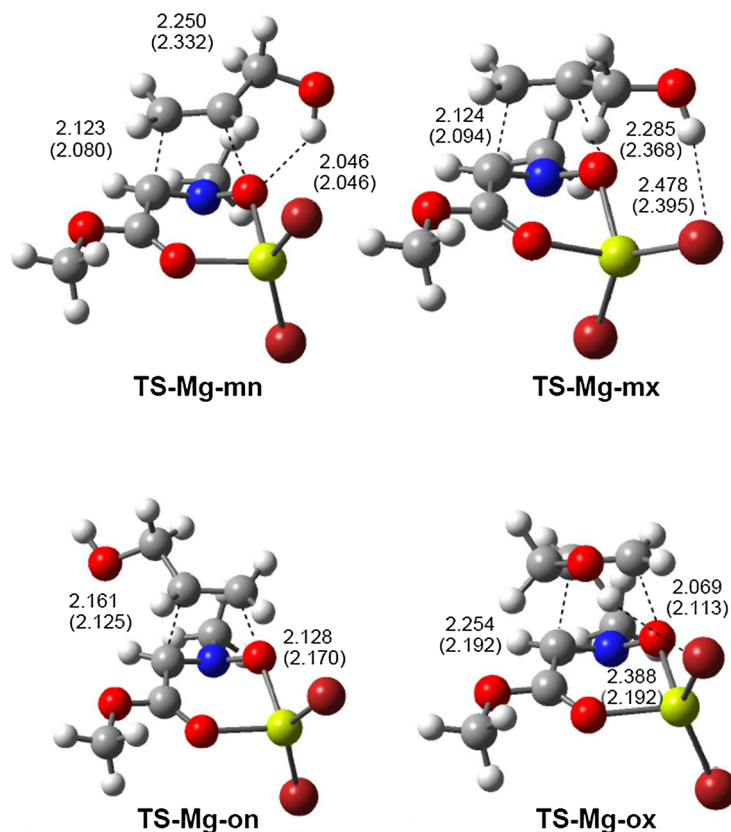
Figure 3 shows the geometries of the TSs involved in the LA-catalysed *zw*-type 32CA reaction between complex **12:Mg** and 2-propen-1-ol **13**. At the *meta* TSs, the lengths of the O1–C5 and C3–C4 forming bonds are 2.250 and 2.123 \AA at **TS-Mg-mn** and 2.285 and 2.124 \AA at **TS-Mg-mx**, while at the *ortho* TSs, the lengths of the O1–C4 and C3–C5 forming bonds are 2.128 and 2.161 \AA at **TS-Mg-on** and 2.069 and 2.254 \AA at **TS-Mg-ox**, respectively. Interestingly, while at the more favourable *exo* TSs the hydroxyl hydrogen atom of the propenol moiety is disposed towards one of the bromide anions of the MgBr_2 salt at Br–H distances of 2.478 \AA (**TS-Mg-mx**) and 2.388 \AA (**TS-Mg-ox**), at **TS-Mg-mn** this

Table 5 B3LYP/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), computed at room temperature and 1 atm in DCM, for the stationary points involved in the 32CA reaction between complex **12:Mg** and 2-propen-1-ol **13**

	ΔH	ΔS	ΔG
TS-Mg-mn	11.1	-52.1	26.6
TS-Mg-mx	10.3	-52.7	26.0
TS-Mg-on	15.0	-46.4	28.9
TS-Mg-ox	16.7	-53.8	32.7
14-Mg-n	-18.3	-59.1	-0.7
14-Mg-x	-17.4	-61.3	0.9
15-Mg-n	-21.3	-53.7	-5.3
15-Mg-x	-24.6	-60.6	-6.5

hydrogen is oriented towards the nitrone oxygen atom at a O–H distance of 2.046 Å. These geometrical arrangements suggest that while **TS-Mg-mn** presents an intramolecular HB between the hydroxyl hydrogen and the nitrone oxygen (O–H), the former forms a HB with the bromide anion of the LA catalyst (Br–H) in **TS-Mg-mx**. Note that due to the formation of these HBs, the C–C–O–H dihedral angles decrease from 180 to 42.9 (**TS-Mg-mn**) and -103.1 (**TS-Mg-mx**) degrees. Thus, the stronger interaction with the bromide anion could explain the *exo* selectivity experimentally

Fig. 3 B3LYP/6-31G(d) optimised geometries for the TSs involved in the 32CA reaction between complex **12:Mg** and 2-propen-1-ol **13**. Geometries in toluene are given in *parentheses*. Distances are given in Angstroms



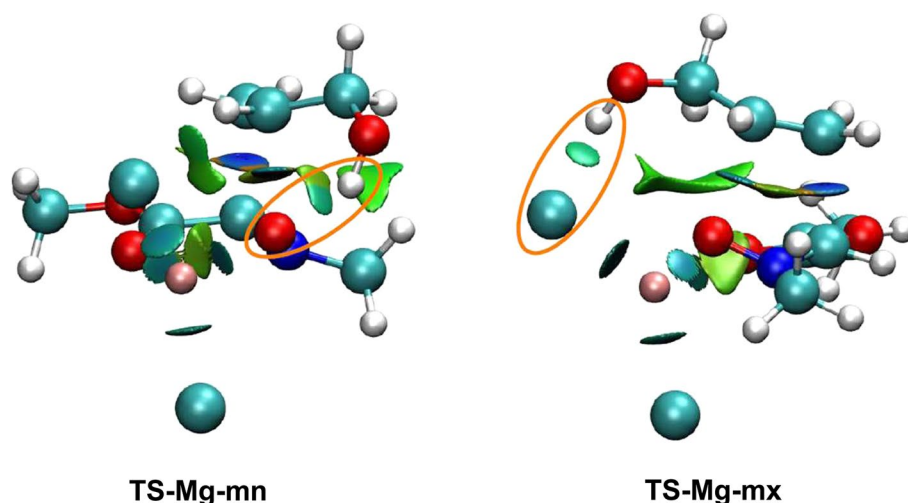
found in the LA-catalysed process. Inclusion of solvent effects of DCM in the geometry optimisation turns the TSs slightly more delayed (see Fig. 2). In DCM, the H–Br HB is 0.1 Å shorter than in gas phase.

The computed GEDT at the TSs associated with this LA-catalysed 32CA reaction, which fluxes from the propenol framework towards the complex one, is 0.19e at **TS-Mg-mn**, 0.16e at **TS-Mg-mx**, 0.15e at **TS-Mg-on** and 0.18e at **TS-Mg-ox**. These GEDT values account for the polar character of this LA-catalysed *zw*-type 32CA reaction, justifying the acceleration experimentally found as a consequence of the high electrophilic character of complex **12:Mg** [18]. Consequently, the role of the LA catalysis is to increase the electrophilicity of *C*-methoxycarbonyl nitrone **12**, favouring the corresponding *zw*-type 32CA reaction to take place via more polar TS with lower activation energy.

3.4 NCI analysis of the origin of the *meta/exo* selectivity in the LA-catalysed 32CA reaction of *C*-methoxycarbonyl nitrone **12** with 2-propen-1-ol **13**

As commented in previous sections, the LA-catalysed 32CA reaction of *C*-methoxycarbonyl nitrone **12** with 2-propen-1-ol **13** yields the 3,5-*cis*-isomer **14x**, resulting from the *meta/exo* approach mode of alkene **13**, as the

Fig. 4 NCI gradient isosurfaces of **TS-Mg-mn** and **TS-Mg-mx**



single stereoisomer in 71% yield. Analysis of the B3LYP/6-31G(d) gas-phase relative energies of the TSs associated with the two *meta endo/exo* competitive reactive channels gives a $\Delta E^\ddagger = 2.6 \text{ kcal mol}^{-1}$ between **TS-Mg-mn** and **TS-Mg-mx**, in reasonable agreement with the experimental outcomes.

As previously commented, analysis of the geometries of both TSs suggests the presence of a HB between the hydroxyl hydrogen and the nitrone oxygen (O–H) or bromide anion (Br–H), respectively (see Fig. 3); thus, the different nature of these non-covalent interactions could justify the preference for the *meta/exo* reactive pathway in the LA-catalysed 32CA reaction of *C*-methoxycarbonyl nitrone **12** with 2-propen-1-ol **13**.

In order to characterise the O–H and Br–H HBs, an NCI analysis [15] of the electron density of **TS-Mg-mn** and **TS-Mg-mx** was performed. NCI low-gradient isosurfaces for these *meta* TSs are displayed in Fig. 4.

Figure 4 reveals the presence of a small circular turquoise surface between the hydroxyl hydrogen of the propenol framework and the nitrone oxygen atom in **TS-Mg-mn** and between the former and the bromide anion of the MgBr_2 LA catalyst in **TS-Mg-mx**, confirming the existence of favourable O–H and Br–H HBs.

NCI gradient isosurfaces are coloured according to a colour scale ranging from blue, which is indicative of strong attractive interactions, to red, which is characteristic of strong repulsive interactions, in such a manner that this colour code can be used as a qualitative measure of the strength of NCI interactions. As shown in Fig. 4, the colour of the NCI gradient isosurfaces associated with the two HBs is indistinguishable, indicating the similar strength of both HBs. Consequently, in order to quantify the stabilisation of both *meta* TSs by the formation of these HBs, single-point energy calculations over the structures in which the C–C–O–H dihedral angles are set to 180 degrees were performed.

The energies of the corresponding structures in which the hydroxyl hydrogen is situated away from the oxygen atom or bromide anion, thus preventing the HB interaction, were found 6.7 (**TS-Mg-mn-rot**) and 8.3 (**TS-Mg-mx**) kcal mol^{-1} higher than those of the corresponding TSs. These energy results suggest that the Br–H HB is ca. 1.6 kcal mol^{-1} stronger than the O–H one, allowing establishing that the Br–H HB has an important role in the *exo* stereoselectivity experimentally found in the LA-catalysed 32CA reaction.

The present energy and NCI topological analyses allow concluding that although favourable HB interactions are distinguished in the two TSs associated with the more favourable *meta* regioisomeric channels, the stronger Br–H HB formed along the *meta/exo* approach could be responsible for the *exo* stereoselectivity experimentally found in the LA-catalysed 32CA reactions of *C*-methoxycarbonyl nitrone **12** with 2-propen-1-ol **13** [27].

4 Conclusions

The mechanisms of the non-catalysed and MgBr_2 LA-catalysed 32CA reactions between *C*-methoxycarbonyl nitrone **12** and 2-propen-1-ol **13** have been theoretically investigated within MEDT by using DFT methods at the B3LYP/6-31G(d) computational level.

Analysis of CDFT reactivity indices indicated that while the 32CA reaction of *C*-methoxycarbonyl nitrone **12** with 2-propen-1-ol **13** will have a non-polar character, coordination of MgBr_2 to nitrone **12** favours the corresponding *zw*-type 32CA reaction by taking place through a polar process as a consequence of the high electrophilic character of complex **12:Mg**.

Due the non-symmetry of both reagents, these 32CA reactions can take place through four competitive reactive

channels, the *ortho* and *meta* regioisomeric channels and the *endo* and *exo* stereoisomeric ones, following a one-step mechanism.

The 32CA reaction between *C*-methoxycarbonyl nitrene **12** and 2-propen-1-ol **13** takes place with a high activation enthalpy, 13.5 kcal mol⁻¹, as a consequence of the non-polar character of this *zw*-type 32CA reaction. This 32CA reaction is completely *meta* regioselective and very low *exo* stereoselective, in clear agreement with the experimental outcomes in which a 44:56 mixture of isoxazolidines **14n** and **14x** is obtained [27].

Coordination of the MgBr₂ LA to *C*-methoxycarbonyl nitrene **12** accelerates the corresponding *zw*-type 32CA reaction by taking place through a more polar mechanism. According to the *zw*-type mechanism, coordination of the MgBr₂ LA to *C*-methoxycarbonyl nitrene **12** increases the electrophilicity of the corresponding complex **12:Mg**, thus increasing the polarity of the reaction. The activation enthalpy associated with the catalysed process is 8.5 kcal mol⁻¹. The catalysed 32CA reaction is completely *meta* regioselective and presents a low *exo* stereoselectivity, but higher than in the non-catalysed process, in reasonable agreement with the experimental outcomes in which the isoxazolidine proceeding from the *meta/exo* approach is obtained as single product [27].

Analysis of the TS geometries involved in the catalysed 32CA reaction suggests the formation of an intramolecular HB between the hydroxyl hydrogen of 2-propen-1-ol **13** and one of the two bromide anions of the MgBr₂ salt. Energy and NCI topological analyses allow concluding that although favourable intramolecular HB interactions are distinguished in the two TSs associated with the more favourable *meta* regioisomeric channels, the stronger Br–H HB formed along the *meta/exo* approach could be responsible for the *exo* stereoselectivity experimentally found in the LA-catalysed 32CA reactions of *C*-methoxycarbonyl nitrene **12** with 2-propen-1-ol **13**.

4.1 Theoretical background of the NCI analysis

NCIs have a unique fingerprint, and their presence can be revealed solely by means of electron density analysis. They are highly non-local and manifest in real space as low-gradient isosurfaces with low densities. The sign of the Laplacian of the density, $\nabla^2\rho$, is a widely used tool to distinguish between different types of strong interactions [57]. To analyse bonding in more detail, the Laplacian is often decomposed into a sum of contributions. These components are the three eigenvalues λ_i of the electron density Hessian matrix, such that $\nabla^2\rho = \lambda_1 + \lambda_2 + \lambda_3$. Analysis of these components has been widely applied to chemical bonding. The sign of λ_2 can be used to distinguish bonded ($\lambda_2 < 0$) from non-bonded ($\lambda_2 > 0$) interactions. Analysis of

the sign of λ_2 thus helps to differentiate between different types of NCIs, whereas the density itself provides information about their strength.

The gradient isosurfaces provide a useful visualisation of NCIs as broad regions of real space, rather than simple pairwise contacts between atoms, and are coloured according to the corresponding values of $\text{sign}(\lambda_2)\rho$. Surfaces with very low density values ($\rho < 10.005|$ a.u.) generally represent weaker dispersion interactions, while surfaces with slightly higher density values ($10.005| < \rho < 10.05|$ a.u.) represent stronger NCIs, including both attractive HBs and steric clashes. Thus, large negative values of $\text{sign}(\lambda_2)\rho$ are indicative of attractive interactions (such as dipole–dipole or hydrogen bonding) and are coloured in blue, while if the $\text{sign}(\lambda_2)\rho$ is large and positive, the interactions are non-bonding and are coloured in red; values near zero indicate very weak van der Waals interactions and are coloured in green.

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