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Unveiling the non-polar [3+2] cycloaddition reactions of cyclic nitrones with strained alkylidene cyclopropanes within a molecular electron density theory study†

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The role of cyclopropane substitution on the ethylene in *zw-type* [3+2] cycloaddition (32CA) reactions of cyclic nitrones has been studied within Molecular Electron Density Theory (MEDT) at the ωB97X-D/6-311G(d,p) computational level. Electron Localization Function (ELF) analysis of the ethylenes shows that the presence the cyclopropane only slightly increases the electron density in the C–C bonding region. Analysis of the Conceptual DFT reactivity indices indicates that the presence of the cyclopropane does not produce any remarkable change in the reactivity of these strained ethylenes. The marginal electrophilic character of ethylene makes the *zw-type* 32CA reactions of non-polar character. The presence of the cyclopropane in the ethylene decreases the activation enthalpy of the 32CA reactions by only 1.7 and 2.6 kcal mol^{-1}, and also decreases the *ortho* regioselectivity. The loss of the strain present in the cyclopropane is responsible for the reduction of the activation enthalpy and the increase of the reaction enthalpy in these non-polar 32CA reactions. The presence of the cyclopropane does not cause any change, neither in the transition state structure (TS) geometries nor in their electronic structure. The very low global electron density transfer (GEDT) computed at the TSs confirms the non-polar character of these 32CA reactions. The *ortho* regioselectivity experimentally observed in these non-polar 32CA reactions is determined by the most favorable two-center interaction between the less electronegative C1 carbon of nitrone and the non-substituted methylene C5 carbon of the ethylenes.

1. Introduction

[3+2] Cycloaddition (32CA) reactions are one of the most efficient synthetic methods for the construction of five-membered heterocyclic compounds due to their ability to build organic cyclic motifs with regio- and/or stereoselectively.[1–5] The 32CA reaction of nitrone **1** to an ethylene **2** is a classic synthetic strategy to generate isoxazolidines which constitute an interesting class of five-membered heterocycles which serve as valuable synthetic intermediates of fundamental significance in academia and industry.[6,7] The use of non-symmetric ethylenes such as **2** can afford the formation of two regioisomeric 5- and 4-isoxazolidines **3** and **4** (see Scheme 1).

The understanding of the 32CA reactions is a challenge for organic chemists as a consequence of the chameleonic electronic structures of the three-atom-components (TACs) participating in these reactions. Recent Molecular Electron Density Theory[8] (MEDT) studies on 32CA reactions of a wide diversity of

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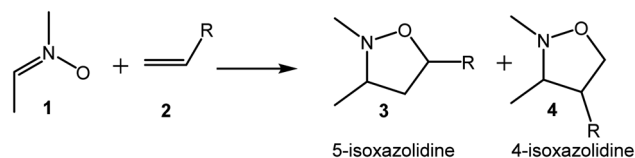
Scheme 1 32CA reaction of nitrone **1** with ethylenes **2** for the synthesis of isoxazolidines **3** and **4**.

TACs towards ethylene allowed establishing a good correlation between the electronic structure of TACs and their reactivity in 32CA reactions.[9] Nitrones are zwitterionic TACs participating in *zw-type* 32CA reactions with high activation energy towards ethylene **2** (R = H).[10,11] Due to the nucleophilic character of nitrones, their *zw-type* 32CA reactions are accelerated by increasing the electrophilic character of the ethylene. However, the 32CA reactions with electron-rich ethylenes does not take place easily,[11] demanding the use of Lewis acid catalysts.[12]

The *zw-type* 32CA reactions of cyclic nitrone **5** with acrolein **6** and with propene **8** have been recently studied within the MEDT (see Scheme 2).[11] The reactivity and selectivity were found to be very dependent on the polar character of the reaction. Due to the strong nucleophilic character of cyclic nitrone **5**, the *zw-type* 32CA reaction with acrolein **6** presented a very low activation energy of 1.4 kcal mol^{-1}, the reaction being completely *meta* regio- and *endo* stereoselective yielding the 4-isoxazolidine **7**, in complete agreement with the experimental outcome.[13] Interestingly, the 32CA reaction with the nucleophilic propene **8** presented a higher activation energy, 7.7 kcal mol^{-1}, and a reverse *ortho* regio- and *exo* stereoselectivity, yielding the 5-isoxazolidine **9**.[11]

Strained compounds are an interesting topic in organic chemistry as they enable the reactions to occur under milder conditions compared to unstrained species. In addition, these reactions permit the interplay between experiment and theory. In 1986, Brandi *et al.* reported an experimental study on the 32CA reaction of the cyclic nitrone **10** with methyl-enecyclopropane (MCP) **11**, a strained ethylene, yielding a mixture in the ratio of 5.5 : 1 for the regioisomeric isoxazoline-spiro derivatives **12** and **13** (see Scheme 3).[14] Likewise, the 32CA reaction of cyclic nitrone **14** with MCP **11** afforded a mixture of **15** and **16**. These 32CA reactions required high temperature (above 60 °C) and long reaction time (more than 2 days). The reactions were highly regioselective yielding the 5-iso-xazolidines **12** and **15** as the major products.[14]
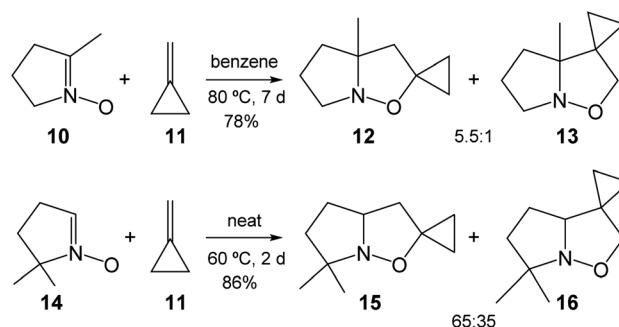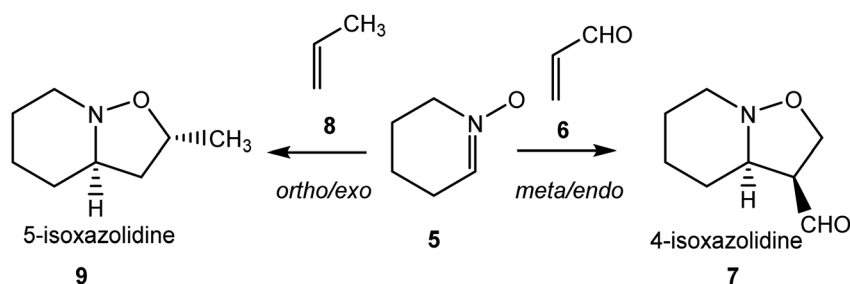

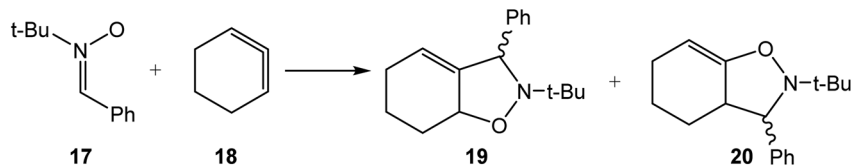**Scheme 3** 32CA reactions of cyclic nitrones with MCP **11**.

Thus, in 2017, the 32CA reaction of nitrone **17** with strained 1,2-cyclohexadiene **18** was studied within MEDT (see Scheme 4).[15] This non-polar 32CA reaction showed low stereo- and regioselectivity. The strain presents in 1,2-cyclohexadiene **18** causes the easy creation of a *pseudoradical* center[16] at the central carbon of the strained allene **18** at the beginning of the reaction with a relatively low energy cost, as it immediately promotes the formation of the first C–C single bond formation with an activation enthalpy of only 7.0 kcal mol^{-1}.[15] This scenario was completely different from that of the 32CA reaction involving the simplest allene, which presented an activation enthalpy of 27.0 kcal mol^{-1}.[15]

Recently, Pagliai *et al.* have reported a DFT study at the PBE0-GD3/6-311G(d,p) computational level of the 32CA reactions of cyclic nitrone **21** with methylpropene (MP) **22** and with a series of alkylidene cyclopropanes, including MCP **11**, in order to explain the regioselectivity in these 32CA reactions (see Scheme 5).[17] These authors concluded that the electronic effect of the substituents (donor or attractor groups) at the double bond of the ethylenes determines the polarization of the double bond and the reaction mechanism, consequently determining the electrostatic interactions with nitrones and controlling the regioselectivity of these 32CA reactions. However, regioselectivity in 32CA reactions is determined by the more favorable two-center interactions taking place at the transition state structures (TSs) along the C(O)–C single bond formation.[11,18]

The poor reactivity of strained MCP **11** together with the loss of the complete *ortho* regioselectivity as observed experimentally in the 32CA reactions of MP **22** prompted us to study the 32CA reactions of cyclic nitrones **14** and **21** with MP **22**, MCP **11** and dicyclopropylethylene (DCP) **27** within MEDT (see Chart 1).

Scheme 2 32CA reaction of cyclic nitrone **5** with acrolein **6** and propene **8**.

Scheme 4 Strain-promoted 32CA reaction of nitrone **13** with 1,2-cyclohexadiene **14**.
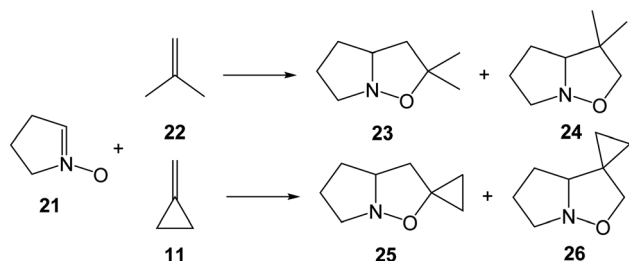
Scheme 5 32CA reactions of cyclic nitrone **21** with MP **22** and MCP **11**.
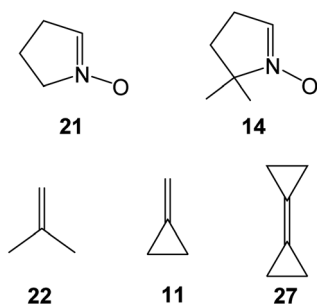

Chart 1 Series of cyclic nitrones and ethylenes herein studied.

The main purpose of this theoretical study is to understand how the strain present in MCP **11** and DCP **27** modifies the electronic structure and reactivity of these strained ethylenes, and to explain the origin of the *ortho* regioselectivity in these 32CA reactions.

2. Computational details

The ωB97X-D[19] functional, together with the standard 6-311G(d,p)[20] basis set, which includes d-type polarization for second-row elements and p-type polarization functions for hydrogens, were used throughout this MEDT study. The suitability of this DFT computational level for the study of these non-polar *zw-type* 32CA reactions was asserted by performing CCSD(T)/cc-pVTZ single point energy calculations at the stationary points involved in the 32CA reaction between cyclic nitrone **17** and MCP **7** (see Table S2 in the ESI†).[11] In addition, several studies of 32CA reactions emphasised that the inclusion of diffuse functions produces no notable changes in the relative energies.[21] The TSs were characterized by the presence of only one imaginary frequency. The Berny method was used in the optimizations.[22,23] The intrinsic reaction coordinate[24] (IRC) calculations were performed to establish the unique connection

given between the TSs and the corresponding minima.[25,26] Solvent effects of benzene were considered by full optimization of the gas-phase structures at the same computational level using the polarizable continuum model (PCM)[27,28] in the framework of the self-consistent reaction field (SCRF).[29–31] Enthalpies, entropies and Gibbs free energies were calculated in benzene at 80 °C and 1 atm.[20]

The GEDT[32] values were computed using the equation GEDT(f) = Σq_f, where q are the natural charges[33,34] of the atoms belonging to one of the two frameworks (f) at the TS geometries. Global and local Conceptual DFT (CDFT) indices[35,36] were calculated using the equations in ref. 36.

The Gaussian 16 suite of programs was used to perform the calculations.[37] Electron Localization Function[38] (ELF) analyses of the ωB97X-D/6-311G(d,p) monodeterminantal wavefunctions were done by using the TopMod[39] package with a cubical grid of step size of 0.1 Bohr. Molecular geometries and ELF basin attractors were visualized by using the GaussView program.[40]

3. Results and discussion

The present MEDT study has been divided into six sections: (i) first, the ELF topological analysis at the ground state (GS) of the reactants is performed to know their electronic structures; (ii) in the second part, the chemical behaviors of the reagents is studied from the analysis of reactivity indices defined within the CDFT; (iii) in the third part, the energy profile of the 32CA reactions of cyclic nitrone **21** with MP **22**, MCP **1** and DCP **27**, and that of cyclic dimethyl nitrone **14** with MCP **11** is studied; (iv) in the fourth part, a BET analysis along the more favorable *ortho* reaction path associated with the 32CA reaction of cyclic nitrone **21** with MCP **11** is performed; (v) an ELF comparative analysis of the *ortho* TSs involved in the 32CA reactions of cyclic nitrone **21**; and finally, (vi) the *ortho* regioselectivity observed in these non-polar *zw-type* 32CA reactions is analyzed.

3.1 ELF analysis of the electronic structures of cyclic nitrones 14 and 21, and the MP 22, MCP 11 and DCP 27

ELF[38] topological analysis of the electronic structure of cyclic nitrones **14** and **21**, and the MP **2**, MCP **11** and DCP **27** was first performed (Fig. 1) to correlate the electronic structure with reactivity.[41] Topological analysis of the ELF of cyclic nitrone **21** shows the presence of one disynaptic basin, V(C1,N2), integrating 3.84e, associated with a C1–N2 double bond, and one disynaptic basin, V(N2,O3), integrating 1.51e, associated with a depopulated N2–O3 single bond. ELF also shows the presence of two monosynaptic basins, V(O3) and V′(O3), integrating
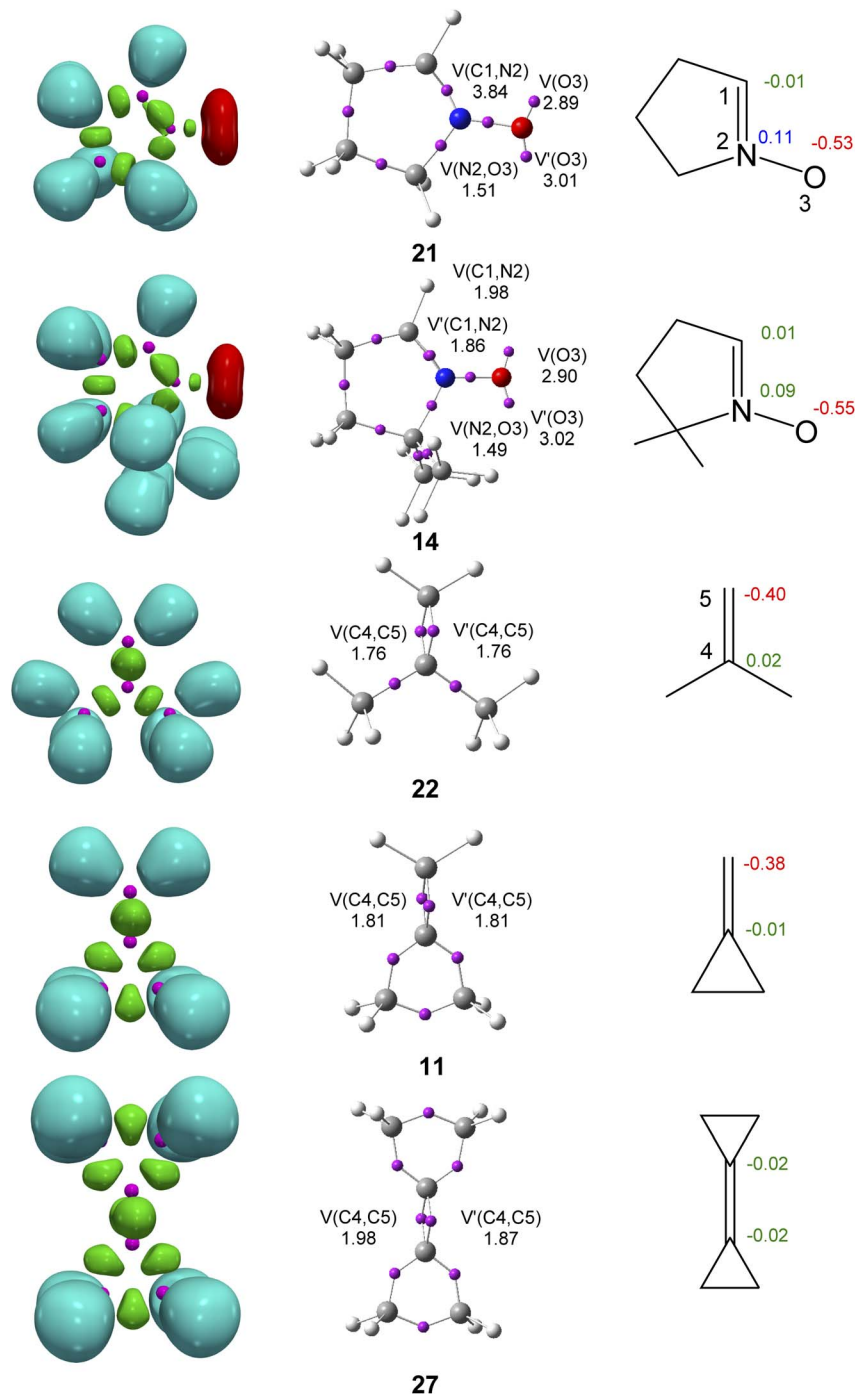
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Fig. 1 ωB97X-D/6-311G(d,p) ELF localization domains represented at an isosurface value of ELF = 0.75, ELF basin attractor positions together with the most relevant valence basin populations, and ELF-based Lewis-like structures together with natural atomic charges, of cyclic nitrones **14** and **21**, MP **22**, MCP **11** and DCP **27**. Valence basin populations and natural atomic charges are given in average number of electrons, e. Negative charges are colored in red, positive charges in blue, and negligible charges in green.

a total of 5.90e, associated with the non-bonding electron density of the O3 oxygen. ELF of the cyclic dimethyl nitrone **14** is very similar to that of nitrone **21**. The only difference is the split of the V(C1,N2) disynaptic basin present in nitrone **21** into two disynaptic basins, V(C1,N2) and V′(C1,N2), integrating a total of 3.84e. Due to the absence of *pseudoradical* and carbenoid

centres, cyclic nitrones **14** and **21** are classified as *zwitterionic* TACs participation in *zw-type* 32CA reactions.[9]

On the other hand, ELF topological analyses of MP **22**, MCP **11** and DCP **27** show the presence of two disynaptic basins V(C4,C5) and V′(C4,C5) integrating a total of 3.52e, 3.62e and 3.85e, respectively, associated with the C4–C5 double bond. The

inclusion of the cyclopropane group in the ethylene increases the electron density in the C4–C5 bonding region.

The natural atomic charges of these compounds, obtained by a natural population analysis[33,34] (NPA), were analyzed (see Fig. 1). At cyclic nitrones **21** and **14**, while the C1 carbon is negligibly charged, the O3 oxygen in negatively charged by *ca.* −0.54*e*. The N2 nitrogen are positively charged by *ca.* 0.10*e*. On the other hand, while the C5 carbon of MP **22** and MCP **11** is negatively charged by *ca.* −0.39*e*, the C4 is negligibly charged, *ca.* 0.00*e*. The loss of the strain present at the cyclopropyl ring of MCP **11** only slightly increases the polarization of the C4–C5 double bond of MP **22**. At DCP **27** the two ethylene C4 and C5 carbons are negligibly charged, −0.02*e*. The negative charges shown at the C5 carbons of MP **22** and MCP **11** is a consequence of the more electronegative character of the carbon atom than the hydrogen one.

3.2 Analysis of the CDFT reactivity indices of the reagents

The CDFT indices were calculated at B3LYP/6-31G(d) level of theory as it was used to define electrophilicity and nucleophilicity scales.[36] The global reactivity indices, namely, the electronic chemical potential, μ, chemical hardness, η, electrophilicity, ω, and nucleophilicity, N, at the GS of cyclic nitrones **14** and **21**, and the ethylenes MP **22**, MCP **11** and DCP **27** are summarized in Table 1.

The electronic chemical potentials[42] of cyclic nitrones **21** and **14**, $\mu = -2.90$ and -2.83 eV, are close to those of the ethylene derivatives, $\mu = -3.22$ (**11**), -3.07 (**27**) and -2.84 (**22**) eV, indicating that the corresponding 32CA reactions will have low or non-polar character.

The electrophilicity ω indices[43] of cyclic nitrones **21** and **14** are 0.77 and 0.72 eV, while the nucleophilicity N indices[44] are 3.48 and 3.53 eV, respectively, thus being classified as marginal electrophiles and strong nucleophiles within the electrophilicity and nucleophilicity scales.[36] The presence of the two electron-releasing methyl substituents in nitrone **14** slightly increases the nucleophilcity and decreases the electrophilicity with respect to cyclic nitrone **21**.

On the other hand, the electrophilicity ω and nucleophilicity N indices of MP **22** are 0.55 eV and 2.60 eV, respectively, thus being classified as a marginal electrophile and as moderate nucleophile. Thus, MP **22** will participate in polar reactions only towards strong electrophilic species. The inclusion of one or two cyclopropane rings in the ethylene increases the electrophilicity of MCP **11** and DCP **27** to 0.71 eV and 0.69 eV, respectively, while this substitution decreases the

nucleophilicity N index to 2.27 eV in the case of MCP **11** but makes no changes in the N index of DCP **27**, 2.62 eV. In any case, the inclusion of the cyclopropane rings does not produce any remarkable change in the reactivity of MCP **11** and DCP **27** with respect to MP **22**.

Consequently, despite the strong nucleophilic character of cyclic nitrones **14** and **21**, the marginal electrophilic character of MP **22**, MCP **11** and DCP **27** makes that the corresponding 32CA reactions will have non-polar character, in agreement with the similar electronic chemical potentials. Consequently, these *zw-type* 32CA reactions will be classified as of null electron density flux (NEDF).[45,46]

3.3. Study of the 32CA reactions of cyclic nitrone 21 with MP 22, MCP 11 and DCP 27, and that of cyclic dimethyl nitrone 14 with MCP 11

Due to the non-symmetry of ethylenes MP **22** and MCP **11**, two regioisomeric reactions paths, namely *meta* and *ortho*, are feasible for the 32CA reactions involving these species (see Scheme 6); while the *meta* reaction paths are associated with the formation of the C1–C5 and O3–C4 single bonds, the *ortho* reaction paths are associated with the formation of the O3–C5 and C1–C4 single bonds. These 32CA reactions take place through one-step mechanism involving only one TS. The relative enthalpies and Gibbs free energies, computed at 80 °C in benzene, are given in the Table 2, while the total electronic energies and thermodynamic data are given in the Tables S3 and S4 in ESI.†

These *zw-type* 32CA reactions present activation enthalpies in the range of 11.2–13.4 kcal mol⁻¹, the reactions being exothermic by between 27.8 – 46.3 kcal mol⁻¹. Some appealing conclusions can be obtained from the relative enthalpies given in Table 2: (i) the activation enthalpy of the 32CA reaction of cyclic nitrone **21** with MP **22** presents a high value, 13.8 kcal mol⁻¹. Note that the unfavorable activation enthalpy for the non-polar *zw-type* 32CA reaction of cyclic nitrone **21** with ethylene **31** is 13.3 kcal mol⁻¹ (see Table S1 in ESI†); (ii) the presence of the cyclopropane in MCP **11** and DCP **27** reduces the activation enthalpy of the 32CA reactions with cyclic nitrone **21** by only 1.7 and 2.6 kcal mol⁻¹, respectively, with respect to that with MP **11**; (iii) the presence of the two methyl groups in cyclic nitrone **14** increases the activation enthalpy of the 32CA reaction with MCP **11** by 1.3 kcal mol⁻¹ with respect to cyclic nitrones **21**; (iv) the 32CA of cyclic nitrone **21** with MP **22** is completely *ortho* regioselective as **TS-I-m** is located 4.5 kcal mol⁻¹ above **TS-I-o**, (v) a reduction of the regioselectivity in the 32CA reactions of nitrones **21** and **14** with MCP **11** is observed, as the *meta* TSs are located 1.7 and 1.3 kcal mol⁻¹, respectively, above the *ortho* TSs; (vi) the strong exothermic character of these 32CA reactions make them irreversible. Consequently, the corresponding isoxazoline-5-spiro derivatives are obtained by a kinetic control; and (vii) the exothermic character of the 32CA reactions involving nitrone **21** increases in the order −27.8 (**23**) < −36.7 (**25**) < −56.3 (**28**) kcal mol⁻¹. Thus, the inclusion of the cyclopropane in the ethylene framework increases the exothermic character of the 32CA reaction as

Table 1 B3LYP/6-31G(d) electronic chemical potential μ, chemical hardness η, electrophilicity ω, and nucleophilicity N indices, in eV, of cyclic nitrones **14** and **21**, and the ethylenes MP **22**, MCP **11** and DCP **27**

	μ	η	ω	N
Nitrone **21**	−2.90	5.47	0.77	3.48
Dimethyl nitrone **14**	−2.83	5.54	0.72	3.53
MCP **11**	−3.22	7.27	0.71	2.27
DCP **27**	−3.07	6.87	0.69	2.62
MP **22**	−2.84	7.37	0.55	2.60
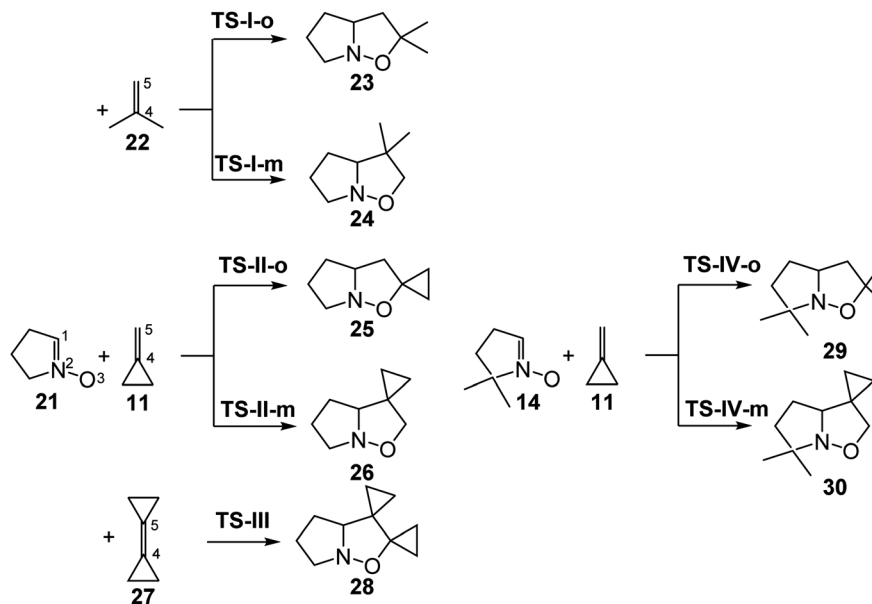
Scheme 6 Competitive reaction paths associated with the 32CA reactions of cyclic nitrone **21** with MP **22**, MCP **11** and DCP **27**, and that of cyclic dimethyl nitrone **14** with MCP **11**.

Table 2 ωB97X-D/6-311G(d,p) 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 80 °C in benzene, for the stationary points associated with the 32CA reactions of cyclic nitrone **21** with MP **22**, MCP **11** and DCP **27**, and that of cyclic dimethyl nitrone **14** with MCP **11**

	ΔH	ΔS	ΔG
TS-I-o	13.8	−46.0	30.0
TS-I-m	18.3	−47.3	35.0
23	−27.8	−49.9	−10.1
24	−24.3	−51.7	−6.0
TS-II-o	12.1	−45.1	28.0
TS-II-m	13.8	−44.7	29.6
25	−36.7	−50.1	−19.0
26	−34.0	−48.3	−17.0
TS-III	11.2	−46.2	27.5
28	−46.3	−52.6	−27.7
TS-IV-o	13.4	−43.3	28.7
TS-IV-m	14.7	−42.7	29.8
29	−32.5	−52.7	−13.9
30	−30.9	−46.4	−14.5

a consequence of the loss of the strain present at MCP **11** and DCP **27** at the cycloadducts **25** and **28**.

Inclusion of entropies and the reaction temperature to enthalpies increases the relative Gibbs free energies by between 15.1 and 18.6 kcal mol^{-1} due to the unfavorable activation entropies associated with these bimolecular reactions, which are found in the range −42.7 and −52.7 cal mol^{-1} K^{-1} (see in Table 2) The activation Gibbs free energies associated with these 32CA reactions *via* the more favorable *ortho* TSs rise between 27.5 and 30.0 kcal mol^{-1}, while formation of isoxazoline-5-spiro derivatives remains exergonic by more than 10.1 kcal mol^{-1}. Consequently, isoxazoline-5-spiro derivatives are formed by kinetic control.

Considering the Gibbs free energies associated to *meta* and *ortho* TSs given in Table 2, 4.4 (**I**), 1.6 (**II**) and 1.3 (**III**) kcal mol^{-1}, and the temperature reaction, 80 °C, the following relationship between the two regioisomeric isoxazoline-5-spiro and isoxazoline-4-spiro derivatives can be estimated by using the Eyring–Polanyi relation:[47] 99.8 : 0.3 (**I**), 90.0 : 10.0 (**II**) and 86.4 : 13.6 (**III**). The *ortho* regioselectivities found at the ωB97X-D/6-311G(d,p) computational level are in complete agreement with the experimental results in which the 32CA reactions of MP **22** are completely *ortho* regioselective, while the *ortho* regioselectivity decreases in the order **I** > **IV**.

A representation of the reaction enthalpies *versus* the activation enthalpies for the 32CA reactions of cyclic nitrone **21** with MP **22**, MCP **11**, DCP **27** and ethylene **31**, and that of cyclic dimethyl nitrone **14** with MCP **11**, shows that there is a good linear correlation between these enthalpies ($R^2 = 0.91$) (see Fig. 2). Thus, the loss of the strain present in the cyclopropane derivatives MCP **11** and DCP **27** along the formation of the corresponding isoxazoline-5-spiro derivatives might be responsible for both the reduction of the activation enthalpy and the increase of the reaction enthalpy in these 32CA reactions.

The geometries of the TSs involved in the 32CA reactions of cyclic nitrone **21** with MP **22**, MCP **11** and DCP **27**, and that of cyclic dimethyl nitrone **14** with MCP **11** are given in Fig. 3. In gas phase, the distances between the carbon and oxygen atoms participating in the 32CA reactions are found in the range of 2.05 and 2.26 Å, indicating a low geometrical asymmetry of both frameworks at the TSs. The C–C distances are slightly longer than that at **TS-V**, associated with the non-polar *zw-type* 32CA reaction of cyclic nitrone **21** with ethylene **31**, 2.141 Å, while the C–O distances are slightly shorter, 2.111 Å (see the geometry of **TS-V** in ESI). Consequently, the presence of the cyclopropane in the ethylene framework does not produce remarkable changes in the
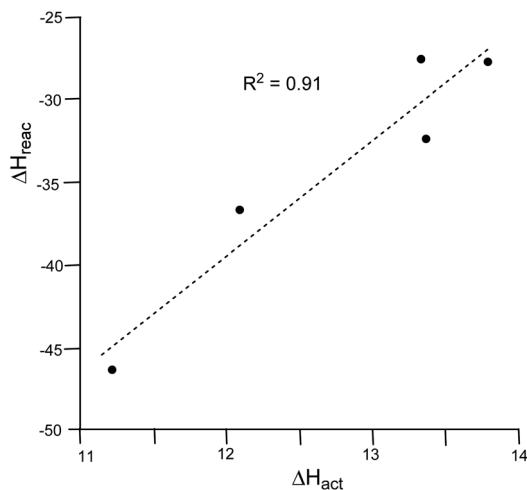
Fig. 2 Plot of the activation enthalpies, ΔH_{reac}, *versus* the activation enthalpies, ΔH_{act}, in kcal·mol^{-1}, for the 32CA reactions of cyclic nitrone **21** with MP **22**, MCP **11**, DCP **27** and ethylene **31**, and that of cyclic dimethyl nitrone **14** with MCP **11**.

Fig. 3 ωB97X-D/6-311G(d,p) geometries of the TSs involved in the The presence of 32CA reactions of cyclic nitrone **21** with MP **22**, MCP **11** and DCP **27**, and that of cyclic dimethyl nitrone **14** with MCP **11**. Distances in benzene are given in parentheses. Lengths are given in angstroms.

geometries. Considering that the formation of the C–C and C–O single bond take place in the short range of 2.0–1.9 and 1.8–1.7 Å, respectively,[9] these distances indicate the formation of any C–C and C–O single bonds have not yet begun at these TS (see later).

Inclusion of solvent effects of benzene in the geometry optimizations does not produce any remarkable change in the TS geometries (see Fig. 3). In benzene, the TSs are only slightly more delayed.

The non-polar nature of these 32CA reactions was characterized by evaluating the GEDT[32] at the corresponding TSs. The very low GEDT values found at the TSs, $-0.01e$ (**TS-I-o**), $0.01e$ (**TS-I-m**), $0.04e$ (**TS-II-o**), $0.06e$ (**TS-II-m**), $0.06e$ (**TS-III**), $0.02e$ (**TS-IV-o**) and $0.04e$ (**TS-IV-m**), establish the non-polar character of these 32CA reactions. The non-polar character of these 32CA reactions is a consequence of the marginal electrophilic character of these ethylene derivatives (see Table 1). Despite of this, the GEDT slightly increases in the order MP **22** > MCP **11** > DCP **27**. The very low GEDT computed at the most favorable *ortho* TSs allows classifying these 32CA reactions as of NEDF,[46] in clear agreement with the analysis of the CDFT indices.

3.4 BET analysis along the more favorable *ortho* reaction path associated with the 32CA reaction of cyclic nitrone 21 with MCP 11. Characterization of the *zw-type* mechanism

In order to characterize the C–C single bond formation along the 32CA reaction between cyclic nitrone **21** and MCP **11**, and thus characterize the type of 32CA reaction, a Bonding Evolution Theory[48] (BET) study along the more favorable *ortho* reaction path was performed. BET allows a full description of the bonding changes along a reaction path by analyzing the changes in the topology of the ELF at all the structures of the corresponding IRC path and selecting those which are chemically meaningful. Complete BET data are given in Table S5,† while ELF basin attractor positions of the more relevant
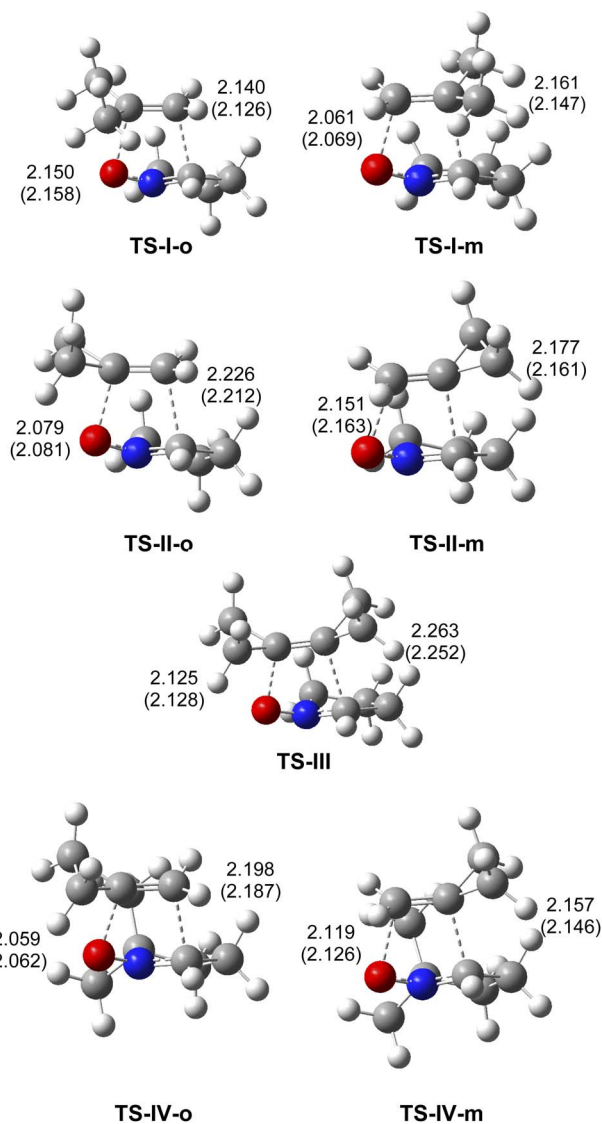
structures involved in the formation of the new C1–C5 and O3–C4 single bonds are represented in Fig. 4.

The most relevant mechanistic aspects obtained from the BET analysis can be summarized as follows: (i) at structure **S2** a new V(N2) monosynaptic basin is created with an initial population of $0.91e$. This monosynaptic basin, whose population is increased along the IRC, is associated with the non-bonding electron density present at the final isoxazoline-5-spiro **25**. The electronic changes required for the formation of the V(N2) monosynaptic basin have an energy cost from structure **S1** of 16.3 kcal mol^{-1}; (ii) at structure **S4**, two monosynaptic basins, V(C1) and V(C5), integrating 0.37 and 0.31e, respectively, are simultaneously created (see Fig. 4). These monosynaptic basins are related to the C1 and C5 *pseudoradical* centres[16] required for the subsequent C1–C5 single bond
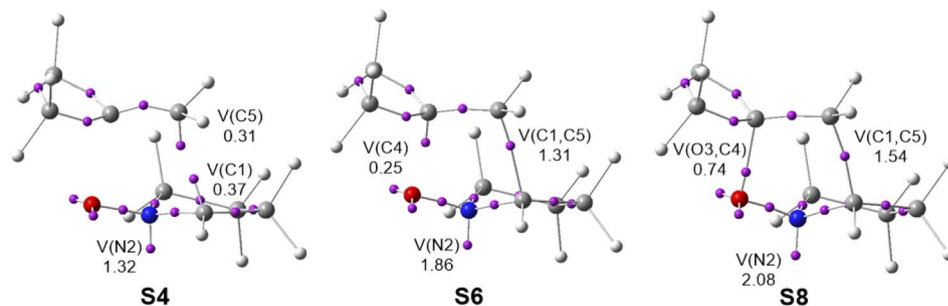
Fig. 4 ωB97X-D/6-311G(d,p) ELF basin attractor positions together with the most relevant valence basin populations, of the IRC structures **S4**, **S6** and **S8** involved in the formation of the C1–C5 and O3–C4 single bonds along the *ortho* reaction path of the 32CA reaction of cyclic nitrone **21** with MCP **11**.

formation;[32] (iii) at structure **S5**, a new V(C4) monosynaptic basin, integrating 0.18e, is created. It is required for the formation of the second O3–C4 singe bond; (iv) at structure **S6**, the first more relevant topological change along the IRC takes place. While the two V(C1) and V(C5) monosynaptic basins present at structure **S5** have disappeared, a new V(C1,C5) disynaptic basin, with an initial population of 1.31e, is created (see Fig. 4). These topological changes indicate that the new C1–C5 single bond has been created at a C–C distance of 2.01 Å by the C-to-C coupling of the two C1 and C5 *pseudoradical* centers; (v) at structure **S7**, the two V(O3) and V'(O3) monosynaptic basins associated with the non-bonding electron density of the nitrone O3 oxygen split into three monosynaptic basins, V(O3), V'(O3) and V'(O3); and finally, (vi) at structure **S8** the second more relevant topological change along the IRC takes place. While the two V''(O3) and V(C4) monosynaptic basins present at **S7** have disappeared, a new V(O3,C4) disynaptic basin, with an initial electron density of 0.72e, is created (see Fig. 4). These topological changes indicate that the new O3–C4 single bond has been created at a C–O distance of 1.76 Å by the sum of the electron density of the two V''(O3) and V(C4) monosynaptic basins.

Some relevant conclusions can be obtained from this BET analysis: (i) the bonding changes required to reach the TS are mainly associated to the depopulation (rupture) of the C1–N2 and C4–C5 bonding regions required for the formation of the non-bonding N2 electron density and the two C1 and C5 *pseudoradical* centres; (ii) the energy cost associated to these changes from the first structure of the IRC, **S1**, rises to

17.9 kcal mol^{-1}; (iii) these behaviors are characteristic of a non-polar *zw-type* 32CA reaction;[11] and finally, (iv) this BET analysis clearly characterizes the asynchronous non-concerted nature of the molecular mechanism of this *zw-type* 32CA reactions.

3.5 ELF comparative analysis of the *ortho* TSs involved in the 32CA reactions of cyclic nitrone 21

In order to analyze the role of the cyclopropane substitution in these non-polar *zw-type* 32CA reactions, a comparative ELF topological analysis of the electronic structure of the *ortho* TSs involved in the 32CA reactions of cyclic nitrone **21** with MP **22**, MCP **11** and DCP **27** was performed. The ELF basin attractor positions with the most relevant valence basin populations characterizing the TSs are shown in Fig. 5.

ELF of **TS-II-o**, involving MCP **11**, is identical to that of **TS-I-o**, involving MP **22**. It shows the presence of a V(N2) monosynaptic basin, integrating 1.35e, and two monosynaptic basins, V(C1) and V(C5), integrating 0.36 and 0.33e, respectively. These monosynaptic basins, which are not present at the reagents (see Fig. 5), are created along the reaction path (see Table S5†). While the V(N2) monosynaptic basin is related to the non-bonding electron density present at the final isoxazoline-5-spiro **25**, the two V(C1) and V(C5) monosynaptic basins are related to the C1 and C5 *pseudoradical* centers demanded for the subsequent creation of the new C1–C5 single bond.[32] The populations of these monosynaptic basins are slightly higher than those at **TS-I-o** as a consequence of its more advance character. ELF of **TS-I-o**
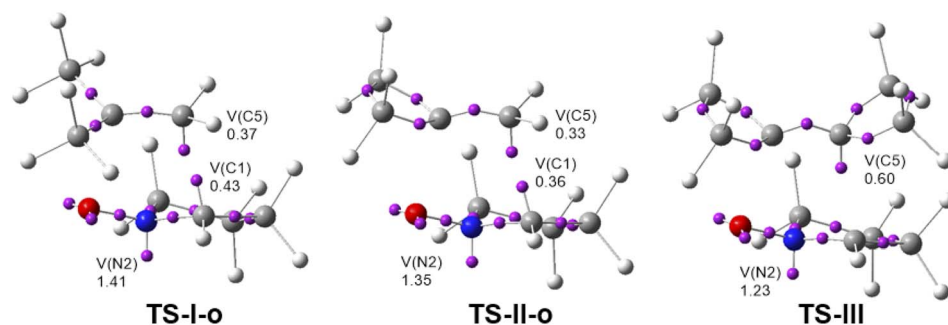

Fig. 5 ωB97X-D/6-311G(d,p) ELF basin attractor positions together with the most relevant valence basin populations, of the *ortho* TSs involved in the 32CA reactions of cyclic nitrone **21** with MP **22**, MCP **11** and DCP **27**. Valence basin populations are given in average number of electrons, *e*.

and **TS-II-o** are identical to that of **TS-V**, associated with the 32CA reaction involving ethylene **31** (see Fig. S1 in ESI†). Consequently, the presence of the two methyl groups at MP **22** or the cyclopropane at MCP **11** does not substantially modify its reactivity with respect to that of ethylene **31**. A slight difference is found at **TS-III**, involving DCP **27**. While the presence of the V(C1) monosynaptic basin is not observed, the population of the V(C5) monosynaptic basin is increased to 0.60e. Note that no V(C4) monosynaptic basin is observed. These topological changes with respect to the ELF of **TS-II-o** can by rationalized by two different behaviors: (i) **TS-III** is slightly more delayed than **TS-II-o**. Consequently, the formation of the V(C1) monosynaptic basin has not yet begun at **TS-V**; and (ii) the presence of the two cyclopropanes at DCP **27** makes this ethylene softer than MCP **11** (see Table 1), thus favoring the asynchronous formation of the C4 and C5 *pseudoradical* centers despite its symmetry.

3.6 What is the origin of the *ortho* regioselectivity in these non-polar *zw-type* 32CA reactions?

The 32CA reactions of cyclic nitrone **21** with MP **22**, MCP **11** or DCP **27** present a complete or high *ortho* regioselectivity. The presence of the strained cyclopropane at MCP **11** only slightly lowers the complete *ortho* regioselectivity observed in the 32CA reaction of MP **22**. The well-known Parr functions[49] predict regioselectivity in polar processes. However, the studied 32CA reactions are classified as NEDF reactions with non-polar character (Section 3.3). A recent MEDT study on the regioselectivity of non-polar 32CA reactions made it possible to conclude that the least electronegative C1 carbon of nitrones controls the asynchronicity in the C–X (X = C or O) single bond formation, and consequently, the regioselectivity.[18] This behavior is a consequence of the fact that the non-bonding electron density donation required for the formation of the two new C–X single bonds has a lower energy demand at the least electronegative C1 carbon than at the O3 oxygen.

On the other hand, the aforementioned study showed that in the non-polar 32CA reactions of nine different TACs towards MP **22**, the more favorable reaction paths always involved the non-substituted methylene C5 carbon of MP **22** (see **TS-I-o** in Fig. 3). Note that this behavior is not modified in the 32CA reactions involving MCP **11**.

NPA analysis of MP **22** and MCP **11** indicates that while the disubstituted C4 carbon is barely charged, the terminal methylene C5 carbon is considerably negatively charged as a consequence of the more electronegative character of the carbon than the hydrogen (see Fig. 1). Consequently, it is expected that along the rupture of the C4–C5 double bond, the C5 carbon will accumulate more electron density, thus favoring the earlier creation of the C5 *pseudoradical* center. In addition, the terminal methylene CH_2 carbon is also the less hindered.

4. Conclusions

The role of the cyclopropane substitution on the ethylene in *zw-type* 32CA reactions of cyclic nitrones has been studied within MEDT at the ωB97X-D/6-311G(d,p) computational level.

ELF topological analysis of MP **22**, MCP **11** and DCP **27** shows that the presence of the cyclopropane in **11** and **27** only increases the electron density in the C4–C5 bonding region with respect to that of MP **22**. Analysis of the CDFT indices indicates that the presence of the cyclopropane does not produce any remarkable change in the reactivity of MCP **11** and DCP **27** with respect to that of MP **22**. Despite the strong nucleophilic character of cyclic nitrones **14** and **21**, the marginal electrophilic character of ethylenes MP **22**, MCP **11** and DCP **27** makes the corresponding *zw-type* 32CA reactions to have non-polar character.

These *zw-type* 32CA reactions present activation enthalpies in the Range of 11.2–13.4 kcal mol^{-1}, the reactions being exothermic between 27.8 and 46.3 kcal mol^{-1}. The presence of the cyclopropane in MCP **11** and DCP **27** lowers the activation enthalpies of the 32CA reaction of cyclic nitrone **21** with ethylene **31** by only 1.7 and 2.6 kcal mol^{-1}, respectively, but also decreases the *ortho* regioselectivity. A linear correlation between reaction enthalpies *versus* the activation enthalpies is found; thus, the loss of the strain present in the cyclopropane is responsible for both the reduction of the activation enthalpies and the increase of the reaction enthalpies in these 32CA reactions.

Analysis of the geometrical parameters of the TSs indicates that the presence of the cyclopropane in the ethylene framework of MCP **11** and DCP **27** does not produce remarkable changes in the geometries. The very low GEDT computed at the more favorable *ortho* TSs, between 0.01e and 0.06e, permits establishing the non-polar character of these 32CA reactions, which are therefore classified as of NEDF.

ELF comparative analysis of the *ortho* TSs involved in the 32CA reactions of cyclic nitrone **21** shows the great similarity between them. The presence of the two methyl groups at MP **22** or the cyclopropane at MCP **11** does not substantially modify their reactivity with respect to that of ethylene **31**.

The present MEDT study establishes that the *ortho* regioselectivity in these non-polar *zw-type* 32CA reactions is determined by the most favorable two-center interactions between the less electronegative C1 carbon of the nitrones and the non-substituted methylene C5 carbon of MP **22** and MCP **11**.

Conflicts of interest

There are no conflicts to declare.

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