Theoretical Studies on Domino Cycloaddition Reactions

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Abstract: In this review some theoretical studies devoted to the mechanism of domino cycloaddition reactions are summarised. The analysis of the stationary points along the reaction pathways: transitions structures, intermediates and adducts, allows rationalising the chemoselectivity, regioselectivity and stereoselectivity experimentally observed.

Keywords: Domino cycloadditions, selectivity, mechanisms, transition structures, quantum chemistry calculations.

1. DOMINO CYCLOADDITIONS IN THE CONSTRUCTION OF COMPLEX POLYCYCLIC SYSTEMS

Domino cycloadditions play a key role in those organic syntheses where construction of complex polycyclic structures with adequate regio and stereochemical control is needed [1-5]. In this type of process, several bonds of the target molecule are formed alongside a continuous sequence of reactions, which does not require isolation of intermediates, changes of reaction conditions or addition of further reagents [6-14]. In these processes, every reaction takes place at the functionalities generated in the previous step. The interest in the subject is shown by numerous recent reviews [15-17].

Despite the obvious potential of the domino cycloaddition reactions and its many variations, the reaction pathways have not been theoretically studied so far. A deep knowledge of the molecular mechanism is fundamental, however, for the understanding of the experimental results. The structural information obtained by means of quantum mechanical studies of possible intermediates and transition structures (TSs) provides powerful assistance in the study of organic reaction mechanisms [18-20]. These methods are accepted as reliable tools for the interpretation of experimental results, as they provide data, which are rarely available from experiments [20].

The increase of the computational power in the last years has allowed the study of complex molecular systems. Recently, several theoretical studies for these complex domino reactions have been carried out with the aim of rationalise the experimental results. Chemoselectivity, regioselectivity and stereoselectivity have been analysed. In this review, I will only include studies on domino cycloadditions carried out in this laboratory. Some studies devoted to the stereochemistry of these complex domino cycloadditions [21-23] will not be discussed. This review has been organised according to the type of cycloaddition involved in the domino process: [4+2], [3+2] or [5+2] cycloadditions. The numbers given in brackets indicate only the number of atoms involved on each cycloaddition step. The computational levels used at the different studies are given in the corresponding schemes.

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2. DOMINO [4+2] / [4+2] CYCLOADDITION REACTIONS

One of the most historically important and having significant practical applications of this methodology involved the Diels-Alder reaction of bicyclic bisdienes with acetylenic derivatives, which can lead to a variety of bridged polycyclic ring systems.

2.1. Domino Reactions Involving Bicyclopentadiene

Paquette *et al.* [24] reported the domino reaction of the bicyclic bisdiene **1** with dimethyl acetylenedicarboxylate (**2**), DMAD, to give the bridged tetracyclic adducts **3** and **4** in similar amounts, 10% and 6%, respectively (see Scheme **1**).

Ab initio calculations [25] give similar energies for the attack of DMAD to both faces of the cyclopentenyl moiety of **1**, 26.04 kcal/mol for **TS1-1** and 25.98 kcal/mol for **TS1-2**, (see Scheme **2**) [26]. The electron-withdrawing ability of the two-carboxylate substituents on the dienophile fragment of the intermediate **IN-1** facilitates the intramolecular cycloaddition trough **TS2-1**. The first intermolecular [4+2] cycloadditions were more exothermic processes, in the range 7-10 kcal/mol, than the second intramolecular ones because of the increase of annular strain with the formation of bridged tetracyclic products. The large activation energies associated to the retro-cycloadditions of **3** and **4**, together with the low π–facial selectivity for the first step of this domino cycloaddition account for the similar amounts of **3** and **4** [26].

2.2. Domino Reaction Involving N,N'-dipyrrolylmethane

Visnick and Battiste [27] reported the domino reaction between N,N'-dipyrrolylmethane **5** and hexafluorobut-2-yne (**6**) (see Scheme **3**). In this case, the adduct **7** was obtained quantitatively as the only adduct at room temperature. However, on prolonged heating the adduct **8** was obtained quantitatively as the thermodynamic product. Formation of **7** and **8** was envisaged to occur in a synchronous two-stage

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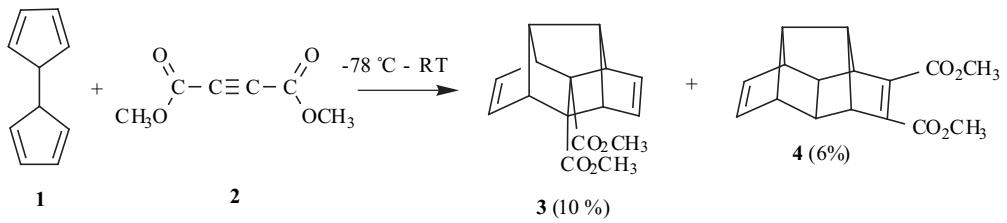
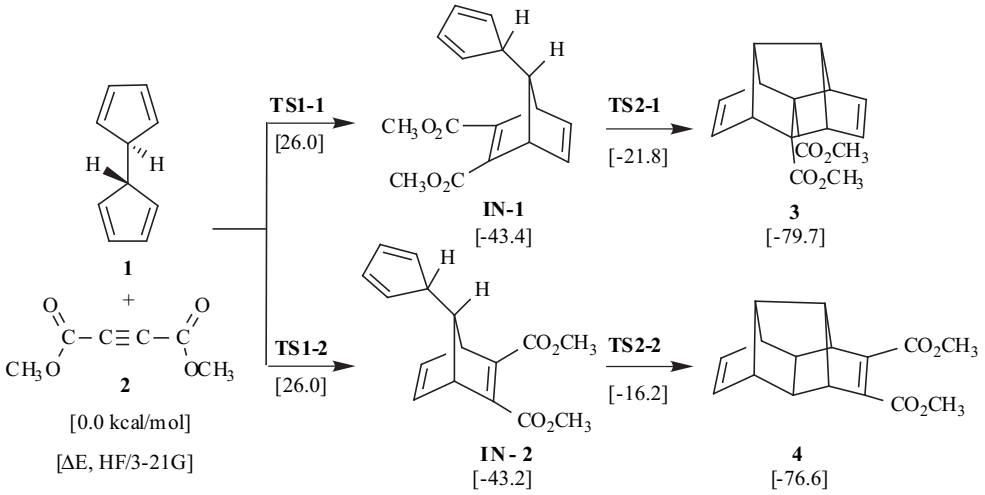


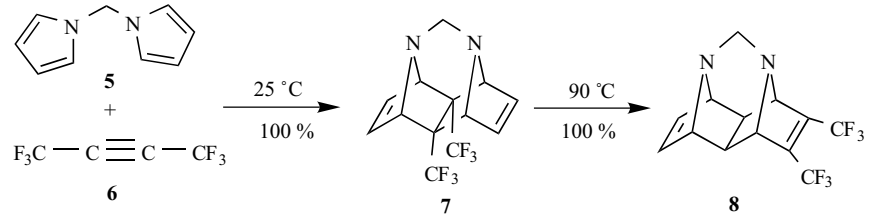
Scheme 1.



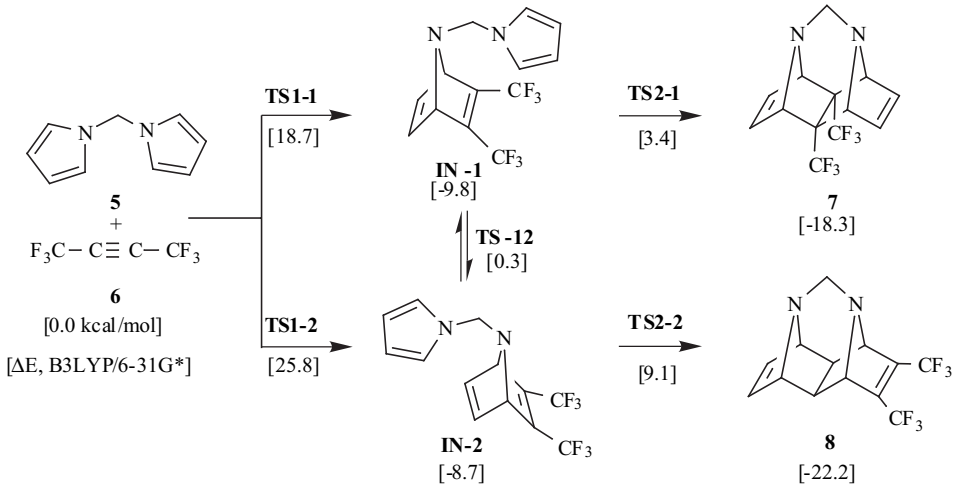
Scheme 2.

process, whereby the initially formed [4+2] cycloadduct is captured intramolecularly by the appended pyrrole ring.

A density functional theory [28-31] (DFT) analysis for this domino reaction indicated that the first intermolecular [4+2] cycloaddition *via* **TS1-1** corresponds to the rate-determining step of the global process, with activation energy of 18.7 kcal/mol (see Scheme **4**) [32]. The intermediate formed in the initial stage, **IN-1**, is unstable



Scheme 3.



Scheme 4.

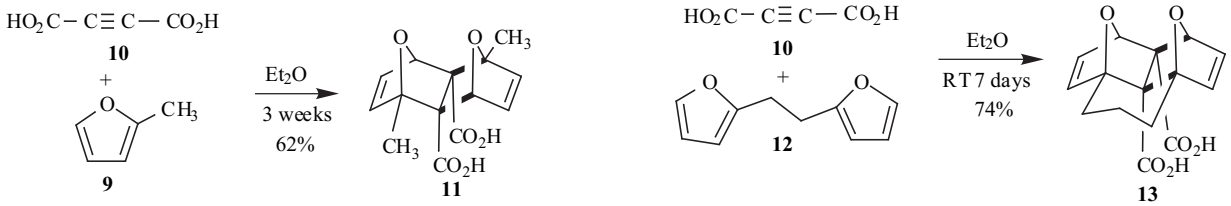
carrying out the intramolecular [4+2] cycloaddition by surmounting the low second activation energy, 13.2 kcal/mol. The activation energy for the second intramolecular [4+2] cycloaddition involving the more substituted double-bond, **TS2-1**, is ca. 4.5 kcal/mol lower than that for the cycloaddition involving the non-substituted double-bond, **TS2-2**; therefore only the adduct **7** is formed under kinetic control. However, the cycloadduct **8** is thermodynamically more stable than the cycloadduct **7**, the respective reaction energies being –22.2 kcal/mol and –18.3 kcal/mol, respectively.

The DFT calculations showed that by thermolysis the cycloadduct **7** can carry out a retro-cycloaddition reaction to give the intermediate **IN-1**, the activation energy being 21.7 kcal/mol. Furthermore, the easy interconversion between the azanorbornadiene intermediates **IN-1** and **IN-2** *via* **TS-12**, 10.1 kcal/mol, allows that under thermodynamic conditions the cycloadduct **8** can be preferentially formed [32].

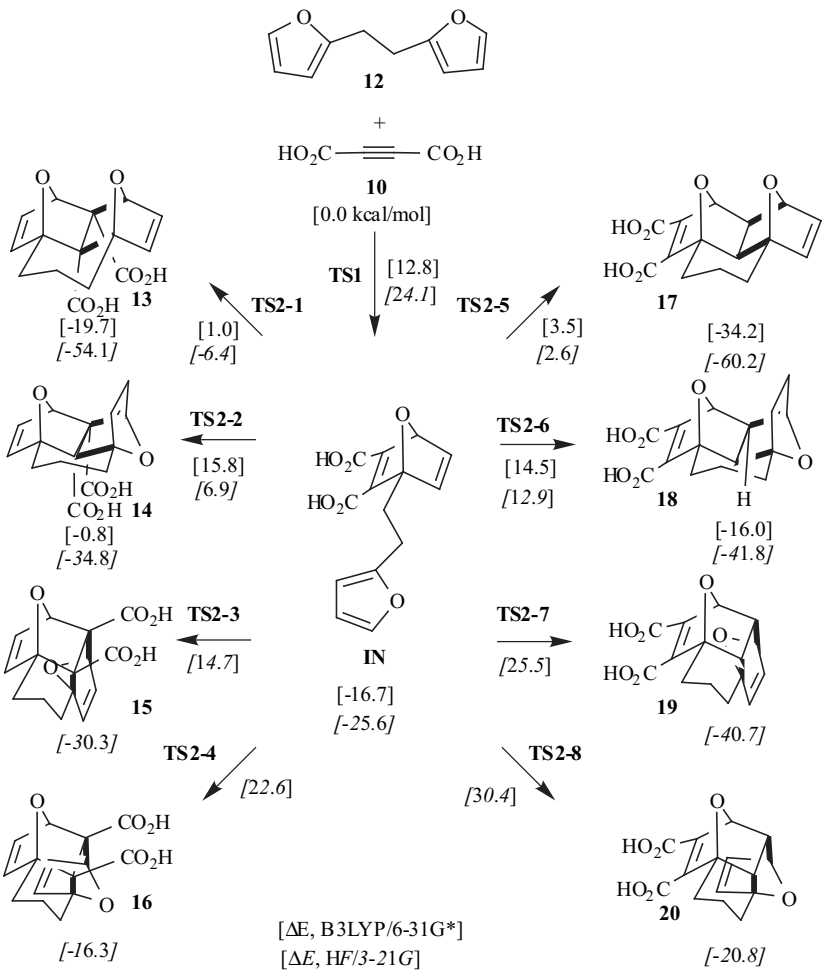
Similar results were obtained for the domino reaction between N,N'-dipyrrolylmethane (**5**) and acetylenedicarbaldehyde [33] as a computational model of the reaction of **5** with DMAD reported also by Visnick and Battiste [27].

2.3. Domino Reaction Involving 1,3-bis(-2-furanyl) propane

Lautens and Fillion [34] reported the domino reaction between furan derivatives and acetylenedicarboxylic acid (**10**) as the dienophile component, which would provide rapid access to dioxacycloadducts that may be useful in the synthesis of complex natural products. Thus, the domino reaction between 2-methylfuran (**9**) and **10** took place with a total regio, chemo, and stereoselectivity to obtain only an adduct, **11**, among the 16 possible isomers (see Scheme **5**) [34]. The source of regioselectivity was interpreted as steric repulsion between the methyl group on the incoming 2-methylfuran, which strongly favours the *anti*-product, while



Scheme 5.



Scheme 6.

formation of *endo* steresoisomer was interpreted in terms of crystal packing forces that cause selective crystallisation of the symmetric *endo-endo* adduct **11**. The reaction of the tethered difuran **12** was significantly faster than with 2-methylfuran to provide the *endo-endo* dioxapentacyclic adduct **13** in 74% yield after 1 week at room temperature (see Scheme **5**) [34]. Experimental data showed that the reaction takes place with a total chemo, facial, and stereoselectivity and only one adduct was isolated out of the other seven possible [34].

The theoretical study showed the complexity of the domino reaction between **10** and **12** (see Scheme **6**) [35]. This domino reaction comprises two consecutive [4+2] cycloadditions. The first intermolecular [4+2] cycloaddition to give the intermediate **IN** has activation energy of 12.8 kcal/mol; formation of the [4+2] cycloadduct is exothermic in -16.7 kcal/mol. A further analysis of the potential energy surface at the B3LYP/6-31+G* level showed that the intermolecular [4+2] cycloaddition takes place along a stepwise mechanism that is initiated by the nucleophilic attack of the furan ring on the acetylene conjugated moiety of acetylenedicarboxylic acid to give a zwitterionic intermediate, which by a subsequent ring closure affords the oxabicyclic intermediate **IN** [36].

The second step of this domino reaction is an intramolecular concerted [4+2] cycloaddition of this intermediate to give the final dioxapentacyclic adduct **13**. For the second cycloaddition, which corresponds with the step controlling of selectivities, eight alternative reaction pathways were characterised (see Scheme **6**) [35].

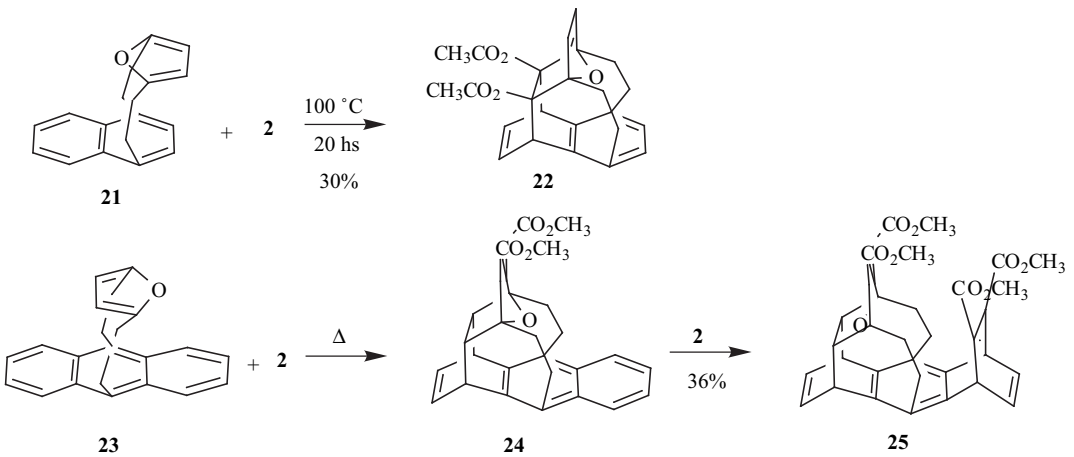
The different reactivity pattern was due to the different attack modes between the tethered furan and the oxanorbornadiene system of the intermediate **IN** formed in the first intermolecular [4+2] cycloaddition. An analysis of the energetic contributions to the activation energies corresponding to the second intramolecular [4+2] cycloadditions identified the different factors controlling the reaction pathways. The most favourable reaction pathway takes place along an *endo*/*syn* arrangement of the tethered furan ring relative to the oxygen atom of the oxanorbornadiene system together with the participation of substituted double-bond of the dienophile fragment, *via* **TS2-1**. The large strain imposed by the tether along the *exo* approach was responsible for the *endo* selectivity found in this domino reaction; the *exo* **TS2-2** is 14.8 kcal/mol higher in energy that the *endo* **TS2-1** [35]. The calculations provided an explanation of the observed *endo* stereochemistry instead of the crystal packing forces postulated by the experimentalists.

2.4. Domino Reactions Involving Naphthaleno and Anthracenofuranophanes

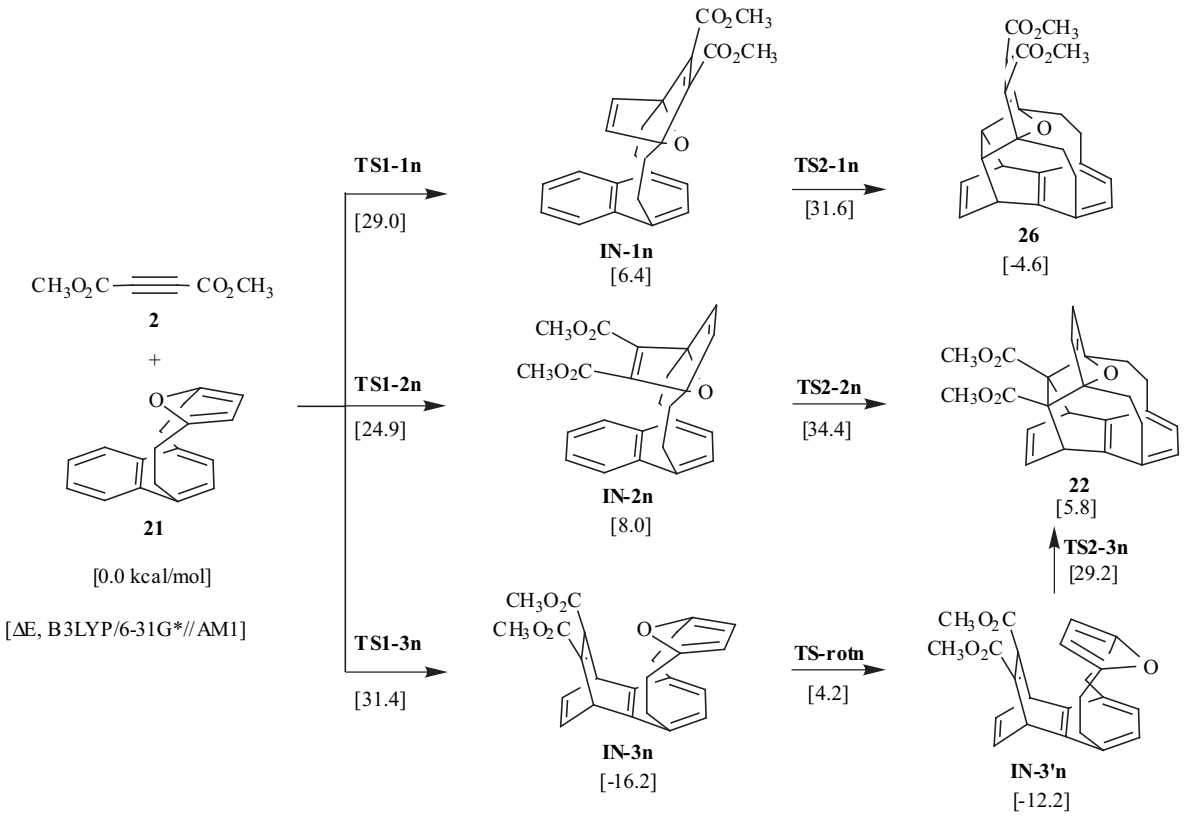
The domino reactions between DMAD and cyclophanes containing one furan ring were reported independently firstly by Wasserman and Kitzing [37], and later by Wynberg and Helder [38] (see Scheme **7**).

For the domino reaction between naphthalenofuranophane (**21**) and DMAD (**2**) Wasserman *et al.* [37] proposed that the reaction was initiated by an intermolecular [4+2] cycloaddition between the furan moiety of **21** and the acetylene moiety of DMAD to give an oxabicyclic intermediate. The second intramolecular [4+2] cycloaddition takes place between the activated double-bond of the oxanorbornadiene moiety and the non-substituted benzene ring. An unlike reactivity was found for the domino reaction between anthracenofuranophane (**23**) and DMAD. For this case, it was further proposed that the first intermolecular [4+2] cycloaddition takes place between furan moiety of **23** and the acetylene moiety of DMAD, while the second intramolecular [4+2] cycloaddition takes place with participation of the non-activated double-bond of the oxanorbornadiene moiety.

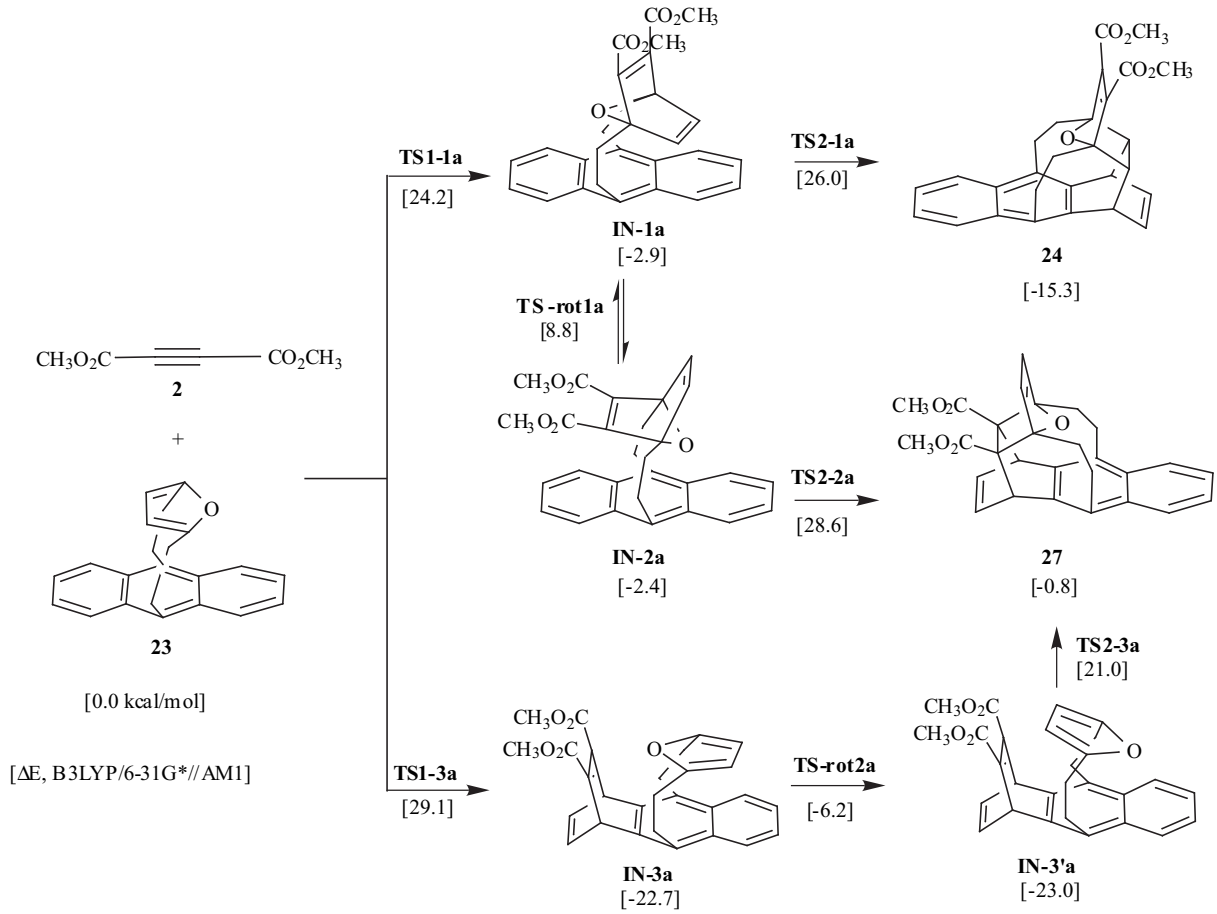
The factors controlling the reaction pathways leading to the formation of the cycloadducts **22** and **24** were investigated [39]. The different reactivity pattern was found as a result of the different attack modes of the acetylenic moiety of DMAD to the furan ring or to the naphthalene/anthracene systems. Thus, for naphthalenofuranophane (**21**) the most favourable reaction pathway takes place along the initial intermolecular [4+2] cycloaddition involving the naphthalene system, *via* **TS1-3n**, to give a benzobicyclo [2.2.2]octadiene intermediate **IN-3n**, which by rotation and subsequent intramolecular [4+2] cycloaddition involving the furan ring, *via* **TS2-3n**, gives the final product



Scheme 7.



Scheme 8.



Scheme 9.

22 (see Scheme **8**). On the other hand, for anthracenofuranophane (**23**) the most favourable reaction pathway takes place along an initial intermolecular [4+2] cycloaddition with participation of the furan ring, *via* **TS1-1a**, to give an oxanorbornadiene intermediate **IN-1a**, which by an intramolecular [4+2] cycloaddition involving the non-substituted double-bond affords, *via* **TS2-1a**, the final cycloadduct **24** (see Scheme **9**).

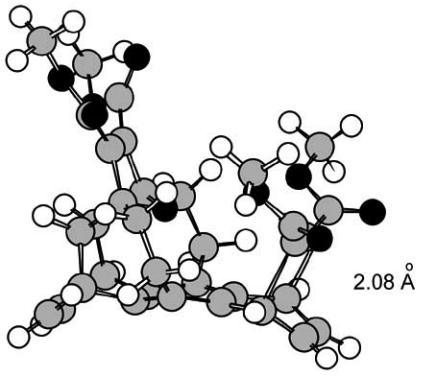
For these furanophanes the initial attacks of DMAD to the furan moiety, *via* **TS1-1n** (29.0 kcal/mol), **TS1-2n** (24.9 kcal/mol) and **TS1-1a** (24.2 kcal/mol), are lower in energy than the attack of DMAD to the naphthalene and anthracene moieties, *via* **TS1-3n** (31.4 kcal/mol) and **TS1-3a** (29.1 kcal/mol). On the other hand, the intramolecular [4+2] cycloadditions involving the most substituted double-bond of the oxanorbornadiene moiety, **TS2-2n** (34.4 kcal/mol) and **TS2-2a** (28.6 kcal/mol), are more energetic than those involving the non-substituted one, **TS2-1n** (31.6 kcal/mol) and **TS2-1a** (26.0 kcal/mol), as a consequence of the unfavourable interactions between the carboxylates and the fused aromatic rings in the former [39].

For the furanophane **21**, the TS associated of the intramolecular [4+2] cycloaddition involving the substituted double-bond, **TS2-2n**, is 3.0 kcal/mol higher in energy than that associated to the intermolecular [4+2] cycloaddition involving the naphthalene moiety, **TS1-3n** (see Scheme **8**). Therefore, formation of the cycloadduct **22** by heating takes place by the initial attack of DMAD to the naphthalene system *via* **TS1-3n**. For the domino reaction between **23** and DMAD, the activation energy for the intermolecular [4+2] cycloaddition involving the anthracene moiety *via* **TS1-3a** is 2.9 kcal/mol higher than that for the intramolecular cycloaddition *via* **TS2-1a** (see Scheme **9**). In consequence, in this domino reaction formation of the adduct **24** takes place trough the initial attack of DMAD to the furan moiety *via* **TS1-1a**, followed by the intramolecular [4+2] cycloaddition involving the non-substituted double-bond *via* **TS2-1a**.

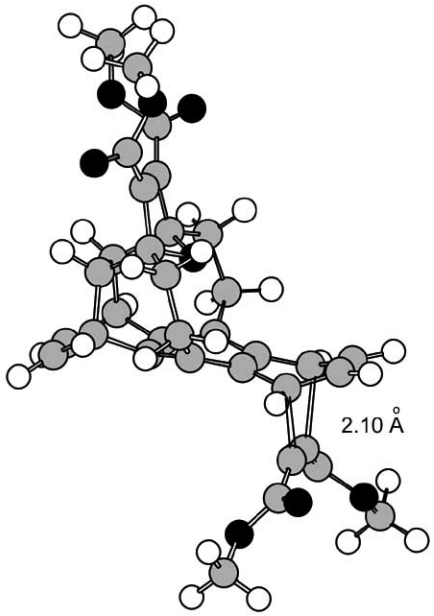
Finally, formation of the domino adduct **25** reported by Wynberg and Helder [38] involves an intermolecular [4+2] cycloaddition between **24** and a second molecule of DMAD. Calculations given the syn attack of DMAD to **24** *via* **TS-syn** 0.3 kcal/mol lesser in energy than the anti attack *via* **TS-anti** (see Fig. **1**) [40].

3. DOMINO [4+2] / [3+2] CYCLOADDITIONS OF NITROALKENES

The domino [4+2] / [3+2] cycloadditions of nitroalkenes have emerged as a powerful method for the rapid and stereoselective construction of complex polyheterocyclic systems [17]. The most extensively explored domino sequences have been those utilising the intermolecular [4+2] cycloadditions. A critical strategic feature in the intermolecular [4+2] cycloaddition with vinyl ethers is the ability of the Lewis acid to control the relative stereoselectivity of the reaction [41]. The ability to control the absolute configuration of the cycloadduct is allowed by the use of chiral vinyl ethers [42]. Denmark *et al.* [43-45] have reported several total syntheses where have relied on these two elements to selective manipulate the stereochemical outcome of these domino cycloaddition processes.



AM1 H^o_f = -101.47 kcal/mol
B3LYP/6-31G*//AM1 = -1990.458910 au
TS-*syn*

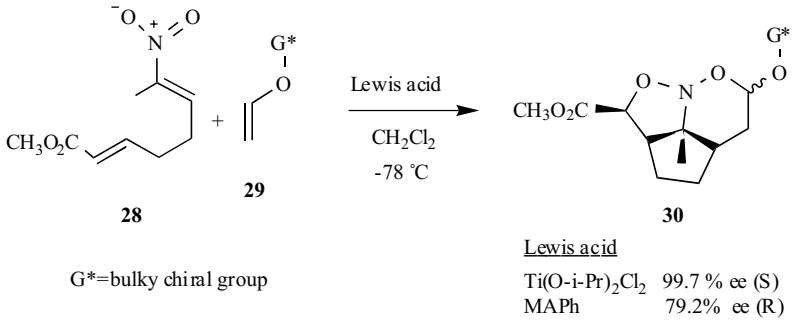


AM1 H^o_f = -101.52 kcal/mol
B3LYP/6-31G*//AM1 = -1990.458375 au
TS-*anti*

Fig. (1). Transition structures for the *syn* and *anti* intermolecular [4+2] cycloaddition between **24** and **2**.

3.1. Domino Inter [4+2] / Intra [3+2] Cycloadditions of Nitroalkenes: *Endo*/*Exo* Stereoselectivity and Facial Selectivity

Denmark *et al.* [41,46] described the domino inter [4+2]/intra [3+2] cycloadditions of the nitroalkene **28** with the chiral enol ethers **29** in the presence of Lewis acids, methylaluminum bis(2,6-dimethylphenoxide) (MAPh) or $Ti(O\text{-}i\text{-}Pr)_2Cl_2$, to give the nitroso acetals **30** (see Scheme **10**). These domino reactions take place with a total regioselectivity and with a high stereoselectivity to obtain mainly a final cycloadduct along with the formation of six



28 **29** **30**

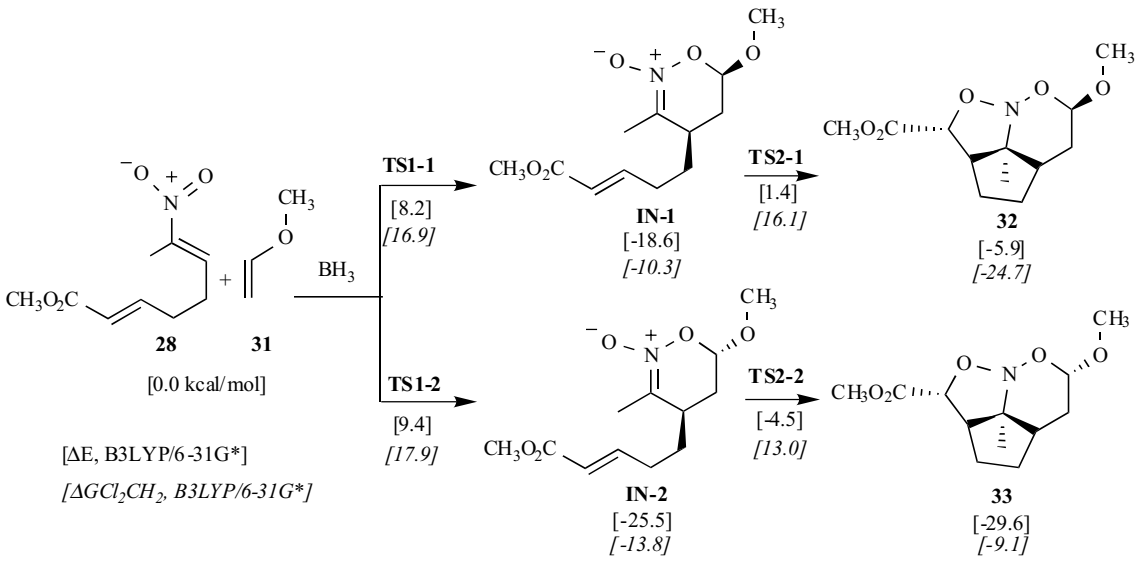
Scheme 10.

stereogenic centres, three of which are controlled by the outcome of the first [4+2] cycloaddition. The bulk of the Lewis acid together with the use of a bulky chiral enol ether determinate the *endo*/*exo* stereoselectivity for the first intermolecular [4+2] cycloaddition.

DFT calculations were performed for the domino inter [4+2] / intra [3+2] cycloaddition of the nitroalkene **28** with methyl vinyl ether (**31**) (see Scheme **11**) [47]. This domino process comprises two consecutive cycloaddition reactions: the first one is an intermolecular [4+2] cycloaddition between the nitroalkene **28** and the enol ether **31** to give a nitronate intermediate, **IN-1** or **IN-2**, whereas the second one is an intramolecular [3+2] cycloaddition at theses intermediates to afford the final nitroso acetal adduct, **32** or **33**.

between the more nucleophilic centre of the enol ether, the β position, and the more electrophilic centre of the nitroalkene, the conjugated position [48]. The *endo*/*exo* stereoselectivity depends on the bulk of the Lewis acid catalyst. Thus, while for small Lewis acid catalysts the addition presents an *endo* selectivity, **TS1-1** is 2.2 kcal/mol lesser in energy than **TS1-2** [48,49], for bulky Lewis acid catalysts and bulky chiral enol ethers the cycloaddition presents an *exo* selectivity as a consequence of the hindrance along the *endo* reaction pathway [41,46]. On the other hand, the intermolecular [3+2] cycloaddition presents total *exo* selectivity due to the constraints imposed by the tether [47].

Inclusion of Lewis acid catalyst and solvent effects decrease the activation energy for the first [4+2] cycloaddition and increase that for the second [3+2] one.



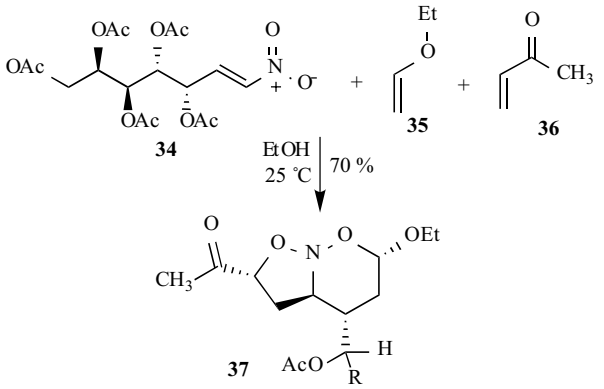
Scheme 11.

Calculations of the activation parameters along this domino reaction allowed validating the results obtained using the electronic energies in the study of the selectivity of these domino reactions (see ΔGCl_2CH_2 in Scheme **11**) [47].

Similar selectivities were found for the Lewis acid catalysed inter [4+2] / intra [3+2] domino cycloaddition reaction involving a nitroalkene and a silyl enol ether at the PM3 semi-empirical level [50].

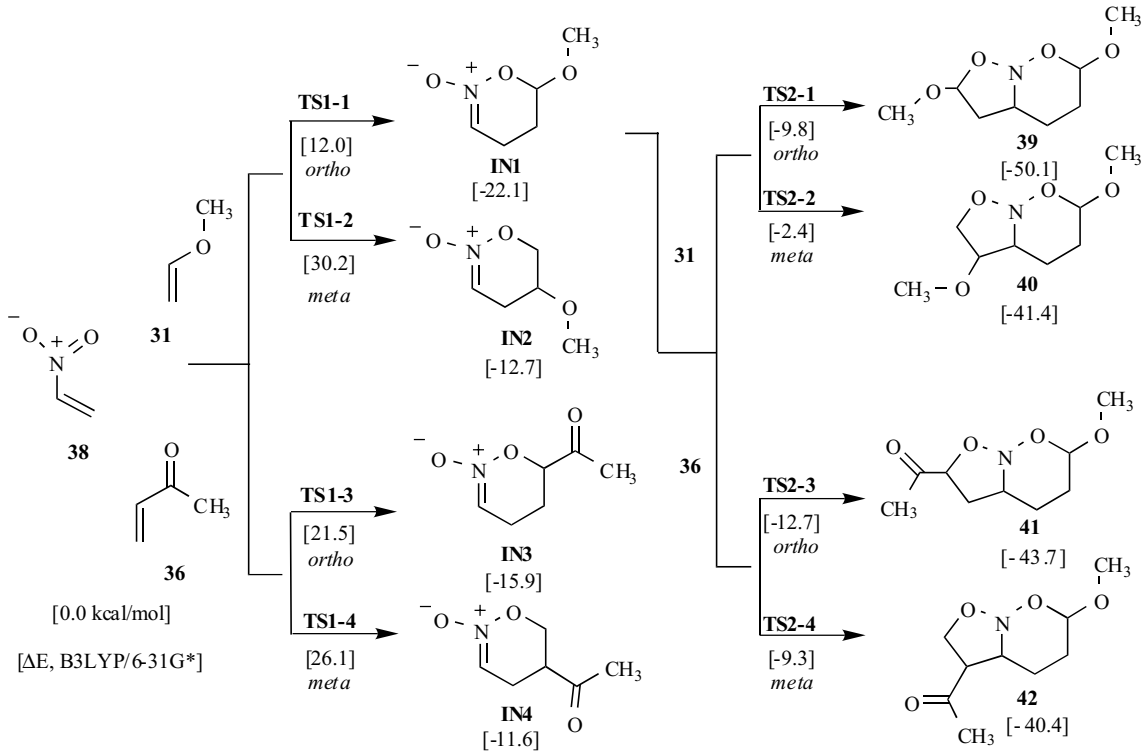
3.2. Domino Inter [4+2] / Inter [3+2] Cycloadditions of Nitroalkenes: Study of the Chemoselectivity and Regioselectivity

Avalos *et al.* [51] reported the domino inter [4+2] / inter [3+2] cycloaddition reaction of the nitroalkene **34** with ethyl vinyl ether (**35**) as an electron-rich alkene and methyl vinyl ketone (**36**) as an electron-poor alkene (see Scheme **12**). This three-component domino reaction takes place with a total chemo, regio, facial, and stereoselectivity to obtain mainly a single diastereomer **37** along with formation of six stereogenic centres. As the previously domino reaction, this process takes place along with an *endo*/*ortho* attack of ethyl vinyl ether to the nitroalkene, followed of an *exo*/*ortho* attack of methyl vinyl ketone to the corresponding nitronate intermediate to give the final nitroso acetal cycloadduct.



Scheme 12.

The chemo and regioselectivity of this three-component domino inter [4+2] / inter [3+2] cycloaddition were studied using nitroethylene (**38**) with methyl vinyl ether (**31**) and methyl vinyl ketone (**36**) as computational models (see Scheme **13**) [52]. This domino process comprises two consecutive cycloadditions: the first one is an intermolecular [4+2] cycloaddition of nitroethylene (**38**) with the vinyl ether **31** to give a nitronate intermediate **IN1**, *via* **TS1-1**, whereas the second one is an intermolecular [3+2] cycloaddition of this intermediate with the vinyl ketone **36** to afford the final nitroso acetal adduct **41**, *via* **TS2-3**. The calculations proved that the two cycloadditions present a total chemo and regioselectivity. While for the first intermolecular [4+2] cycloaddition reaction the attack of the electron-rich alkene **31** to nitroethylene (**38**) along the *ortho* approach corresponds to the more favourable reaction pathway, **TS1-1** (12.0 kcal/mol), for the second intermolecular [3+2] cycloaddition the most favourable reaction pathway corresponds to the attack of the electron-poor alkene **36** to the nitronate intermediate **IN1** along the *ortho* approach, **TS2-3** (9.4 kcal/mol). The lower activation energy found for the intermolecular [3+2] cycloaddition, *via* **TS2-3**, than that for the intermolecular [4+2] cycloaddition, *via* **TS1-1**, agrees with the domino nature of these consecutive cycloadditions. Finally, the lower chemoselectivity found at the [3+2] cycloaddition accounts for the fact that these domino reactions can take place experimentally without the participation of the electron-poor



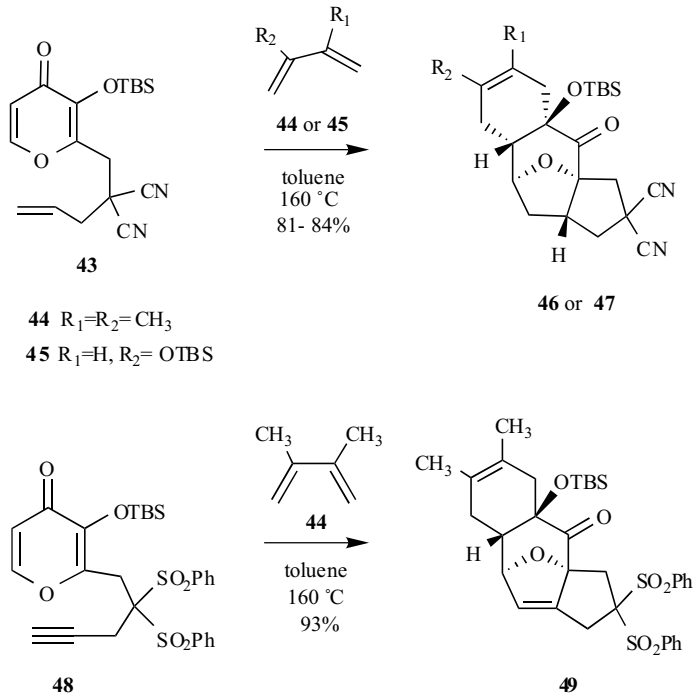
Scheme 13.

alkene [53]. Note that the activation energy for the intermolecular [3+2] cycloaddition between the intermediate **IN1** and the electron-rich alkene **31** *via* **TS2-1**, 12.3 kcal/mol, is similar to that for the formation of **IN1** *via* **TS1-1**.

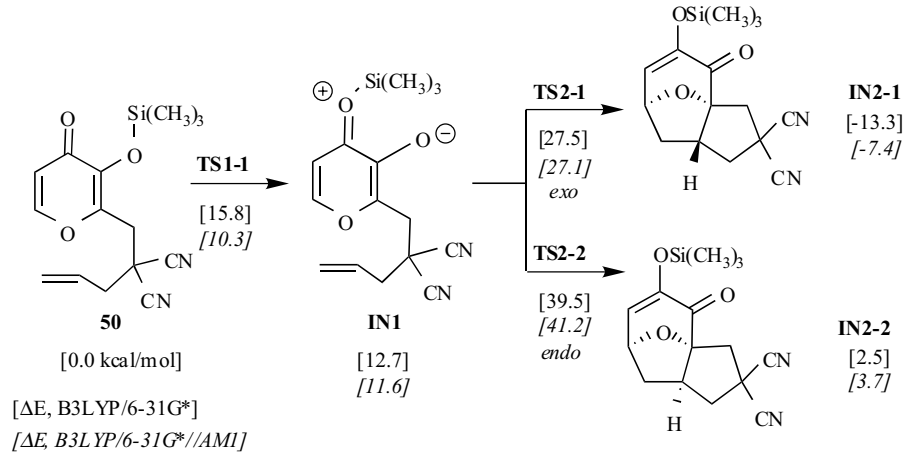
4. DOMINO INTRA [5+2] / INTER [4+2] CYCLOADDITIONS OF γ-PYRONES WITH SUBSTITUTED 1,3-BUTADIENES

The intramolecular [5+2] cycloaddition of β-alkoxy-γ-pyrones bearing tethered alkenes for rapidly assembling 8-oxabicyclo[3.2.1]octenone systems was extensively studied by Wender *et al.* [54-56] and more recently by Mascareñas *et al.* [57-59]. The dense functionalisation of the resulting oxabicycles allows their stereoselective elaboration into a variety of products. The presence of a conjugated double-bond prompted Mascareñas [60,61] to examine the ability of these compounds as dienophiles in Diels-Alder reactions. This provides a way to fuse a six-membered ring to the seven-membered carbocycles formed in the first [5+2] cycloaddition. Thus, heating a 1:5 mixture of the γ-pyrone **43** and 2,3-dimethyl-1,3-butadiene (**44**) at 160 ºC leaded to the tricarbocyclic adduct **46** in 81% yield (see Scheme **14**) [60]. A similar result was obtained using the diene **45** to give a unique regioisomeric adduct **47** [60] (see Scheme **14**). More recently, these authors studied the intra [5+2] / inter [4+2] domino cycloaddition of a γ-pyrone bearing a tethered alkyne, **48**, with **44** to give the tricarbocyclic adduct **49** in 93% yield (see Scheme **14**) [61]. These domino reactions take place with a high chemo, regio and stereoselectivity to obtain mainly an enantiomeric pair of adducts along with formation of five stereogenic centres.

The domino cycloaddition reactions between the γ-pyrone **50** bearing a tethered alkene and the substituted butadienes **44** and **45** comprise two consecutive



Scheme 14.



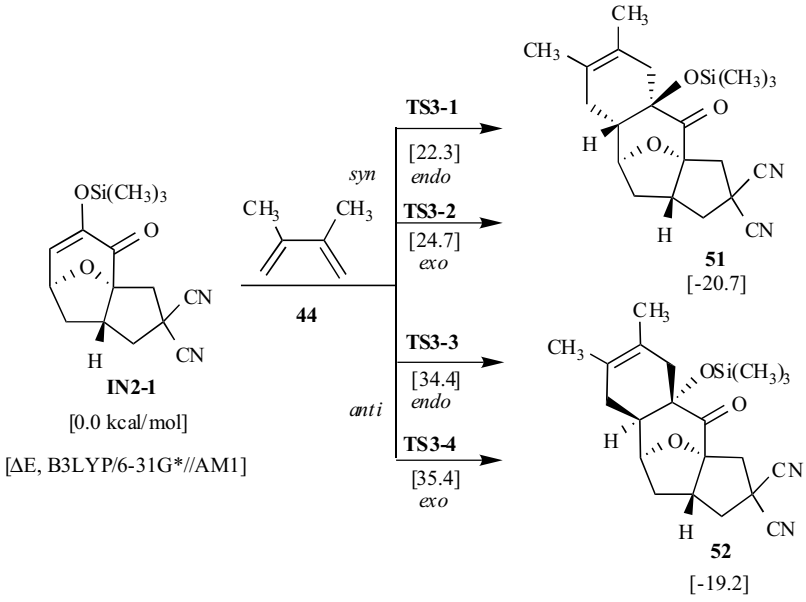
Scheme 15.

cycloadditions [62]. The first one is an intramolecular [5+2] cycloaddition that is initiated by the transfer of the trimethylsilyl group from the silyloxy oxygen to the carbonyl oxygen of the β-silyloxy-γ-pyrone **50**, with formation of a weak oxidopyrylium ylide intermediate **IN1** (12.7 kcal/mol), which by a subsequent intramolecular [5+2] cycloaddition affords the relatively complex 8-oxabicyclooctane adduct **IN2-1** (see Schemes **15**) [62,63]. The large activation energy associated to this [5+2] cycloaddition, 27.5 kcal/mol, demands an intramolecular process in order to minimise the unfavourable negative activation entropy associated to the intermolecular process. In addition, the constrain imposed by the tether along the *endo* approach is responsible for the large *exo* stereoselectivity found for this type of intramolecular processes; the *endo* **TS2-1** is 12.0 kcal/mol higher in energy than the *exo* **TS2-1** [63].

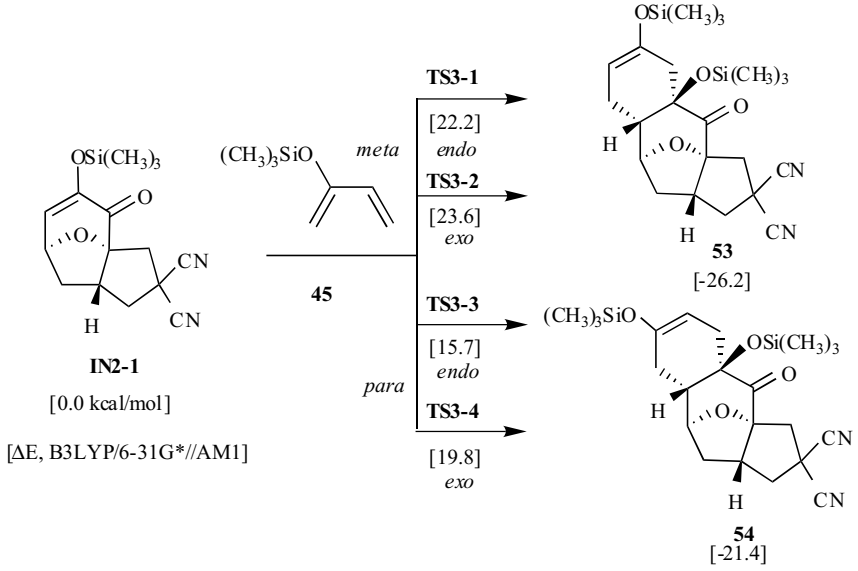
The second reactions correspond to intermolecular [4+2] cycloadditions of the cycloadduct **IN2-1** with the substituted butadienes **44** or **45**, to give the final tricarbocyclic compounds **51** or **54**, respectively (see Schemes **16** and **17**). These intermolecular [4+2] cycloadditions present a large *syn* diasterofacial selectivity due to hindrance that appears along the *anti* approach, the *syn* **TS3-1** is 12.1 kcal/mol lower in energy that the *anti* **TS3-3**. The presence of the silyloxy group on the butadiene **45** increases notably the rate of the [4+2] cycloaddition along the *endo*/*para* approach, being this cycloaddition very regioselective. The large activation entropy associated with the intermolecular processes together with the low activation of the double-bonds present in the γ-pyrone **50** are responsible for the chemoselectivity found in these domino reactions; the activation energies for the [4+2] cycloadditions between **50** and **44** or **45** are higher than that for the intramolecular [5+2] cycloaddition of **50** [62].

CONCLUSIONS

Quantum chemical based studies have proven to be of great use in the interpretation of the complex domino



Scheme 16.



Scheme 17.

cycloaddition reactions. Relative energies of the stationary points along the competitive reactive channels are found in reasonable agreement with the experimental outcome. Furthermore, the geometrical and electronic analysis of the transition structures and intermediates allow explaining the factor controlling the different selectivities. These studies provide an assessment of the current state of computational methods for the prediction of the products of these complicated organic reactions.

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