HAL
open science

A combined experimental and theoretical study of the thermal [3+2] cycloaddition of carbonyl ylides with activated alkenes

Samira Hamza-Reguig, Ghenia Bentabed-Ababsa, Luis R Domingo, Mar Ríos-Gutiérrez, Stephanie Philippot, Stéphane Fontanay, Raphaël E. Duval, Sandrine Ruchaud, Stéphane Bach, Thierry Roisnel, et al.

To cite this version:

Samira Hamza-Reguig, Ghenia Bentabed-Ababsa, Luis R Domingo, Mar Ríos-Gutiérrez, Stephanie Philippot, et al.. A combined experimental and theoretical study of the thermal [3+2] cycloaddition of carbonyl ylides with activated alkenes. Journal of Molecular Structure, 2018, 1157, pp.276-287. 10.1016/j.molstruc.2017.12.052 . hal-01695551v2

HAL Id: hal-01695551

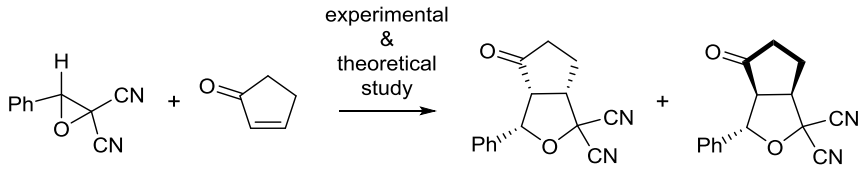
https://hal.univ-lorraine.fr/hal-01695551v2

Submitted on 26 Nov 2018

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

Graphical Abstract



A combined experimental and theoretical study of the thermal [3+2] cycloaddition of carbonyl ylides with activated alkenes

Samira Hamza-Reguig,[a] Ghenia Bentabed-Ababsa,[a,b,*] Luis R. Domingo,[c,*] Mar Ríos-Gutiérrez,[c] Stéphanie Philippot,[d] Stéphane Fontanay,[d] Raphaël E. Duval,[d,*] Sandrine Ruchaud,[e] Stéphane Bach,[e,*] Thierry Roisnel,[f] and Florence Mongin[b,*]

[a] *Laboratoire de Synthèse Organique Appliquée, Faculté des Sciences Exactes et Appliquées, Université d'Oran 1 Ahmed Ben Bella, BP 1524 El M'Naouer, 31000 Oran, Algeria*

[b] *Chimie Organique et Interfaces, Institut des Sciences Chimiques de Rennes, UMR 6226, CNRS-Université de Rennes 1, Bâtiment 10A, Case 1003, Campus de Beaulieu, 35042 Rennes, France*

[c] *Department of Organic Chemistry, University of Valencia, Dr. Moliner 50, 46100 Burjassot, Valencia, Spain*

[d] *UMR 7565, SRSMC, CNRS-Université de Lorraine, Faculté de Pharmacie, 5 rue Albert Lebrun, BP 80403, 54001 Nancy, France*

[e] *Sorbonne Universités, UPMC Univ Paris 06, CNRS USR3151, "Protein Phosphorylation and Human Disease" Unit, Plateforme de criblage KISSf, Station Biologique de Roscoff, Place Georges Teissier, 29688 Roscoff, France*

[f] *Centre de Diffractométrie X, Institut des Sciences Chimiques de Rennes, UMR 6226, CNRS-Université de Rennes 1, Bâtiment 10B, Campus de Beaulieu, 35042 Rennes, France*

* Corresponding authors. E-mail addresses:
badri_sofi@yahoo.fr (G. Bentabed-Ababsa), domingo@utopia.uv.es (L. R. Domingo), raphael.duval@univ-lorraine.fr (R. E. Duval), bach@sb-roscoff.fr (S. Bach), florence.mongin@univ-rennes1.fr (F. Mongin).

Abstract:

4-Benzoyl-3,5-diaryltetrahydrofuran-2,2-dicarbonitriles were first synthesized from 2,2-dicyano-3-aryloxiranes and chalcones at toluene reflux; the 4,5-*cis* products proved to be predominantly formed and were isolated. Whereas shortened reaction times were observed by using microwave irradiation or catalytic cuprous chloride, no significant stereoselectivity change was in general noticed. Reacting 2,2-dicyano-3-aryloxiranes with 2-cyclopentenone next afforded 3-aryl-4-oxohexahydro-1*H*-cyclopenta[*c*]furan-1,1-dicarbonitriles, and the *endo* stereoisomers were isolated. That no stereoselectivity change was noticed in the presence of cuprous chloride rather suggests an impact of the salt on the epoxide ring opening. Finally, treatment of 2,2-dicyano-3-aryloxiranes by 2-morpholinoacrylonitrile yielded 3-cyano-3-morpholino-5-phenyltetrahydrofuran-2,2-dicarbonitriles from which the preponderant *trans* isomers were isolated. Importantly, the molecular mechanism of the domino reaction between 2,2-dicyano-3-phenyloxirane and 2-cyclopentenone was studied. The rate-determining thermal ring opening of the oxirane is followed by a non-concerted *pseudoradical*-type reaction of the carbonyl ylide with 2-cyclopentenone. Using the bond evolution theory also allowed the regioselectivity of this non-polar reaction to be explained.

Keywords: [3+2] cycloaddition; carbonyl ylides; enones; enamines; tetrahydrofurans; theoretical calculations

1. Introduction

Tetrahydrofurans are found in various natural products, and many of these heterocycle-containing products show potent biological activities.[1] Consequently, the synthesis of tetrahydrofuran derivatives has attracted great attention due to their wide applications, notably in medicinal industry.[2]

[3+2] Cycloaddition (32CA) reactions, whose general concept was introduced by Huisgen and co-workers in 1960s,[3] have been established as one of the most powerful methods for the construction of oxygen-containing heterocycles[4] and led to combined experimental and theoretical studies in order to understand their underlying principles.[5] Carbonyl ylides (CYs), generated by thermal ring opening of epoxides, are known to react with multiple bonds of alkynes,[6] alkenes,[6a,b,7] imines,[8] aldehydes[8c,d,9] ketones[10] and thioketones,[11] affording highly substituted dihydrofurans, tetrahydrofurans, oxazolidines, dioxolanes and oxathiolanes, respectively. In general, CYs are three-atom-components that react very quickly with either species containing a multiple bond, both in non-polar and polar *pseudodiradical*-type 32CA reactions with very low activation energies, below 1 kcal·mol^{-1}.[12]

We previously performed studies on 32CA reactions between CYs generated by thermal ring opening of epoxides, on the one hand, and aldehydes,[8d] imines,[8d] ketones[10] and alkynes,[6g] on the other hand. In particular, we investigated the mechanisms of these reactions through theoretical calculations using density functional theory (DFT) methods. In order to extend the knowledge on reactions involving such CYs, we studied the reactivity of these CYs toward enones (impact of microwave irradiation and presence of a Lewis acid) and enamines. More importantly, through suitable calculations, we could get important information on the pathway by which the cycloadducts are formed, and rationalize the regioselectivity observed.

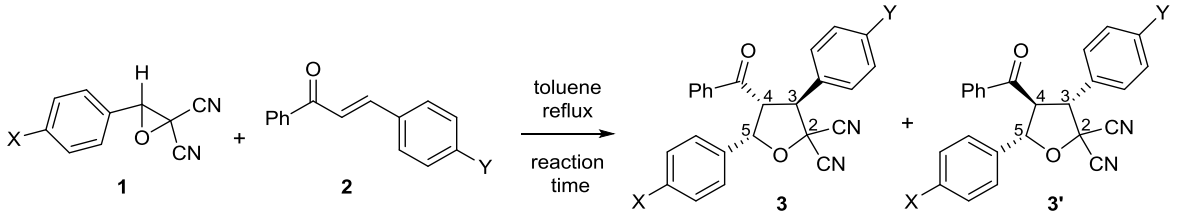
2. Results and Discussion

2.1. Synthetic aspects

We considered 32CA reactions between the different 2,2-dicyano-3-aryloxiranes **1a-c** and chalcones **2a-c** (Table 1). The reactions carried out in refluxing toluene and monitored by NMR (by taking samples from the reaction mixtures) afforded 4-benzoyl-3,5-diphenyltetrahydrofuran-2,2-dicarbonitriles. Under classical heating in the absence of

catalyst, the reactions were completed in times ranging from 24 h to 62 h; the presence of an electron-donating group (OMe) at the 4 position of the chalcone phenyl group favors the reaction (entries 5, 6, 12 and 13), as well as the presence of an electron-donating group (OMe) at the 4 position of the epoxide phenyl group (entries 8-13).

Table 1. Cycloaddition reaction between CYs generated from the epoxides **1** and chalcones **2**.



Entry	X (**1**)	Y (**2**)	Catalyst (equiv)	Reaction time (h)	**3**:**3'** ratio[a]	Product(s), yield(s)[b] (%)
1	Cl (**1b**)	H (**2a**)	-	56 (0.9)[c,d]	52:48 (65:35)[c]	**3ba**, 42 (51)[c]
2			CuCl (0.3)	22	65:35	**3ba**, 50
3		Cl (**2b**)	-	48	62:38	**3bb**, 35
4			CuCl (0.3)	24	69:31	**3bb**, 43
5		OMe (**2c**)	-	38	80:20	**3bc**, 38
6			CuCl (0.3)	20	79:21	**3bc**, 45
7	H (**1a**)	H (**2a**)	-	62 (0.9)[c,d]	51:49 (68:32)[c]	**3aa**, 31 (45)[c]
8	MeO (**1c**)	H (**2a**)	-	48 (0.7)[c,e]	57:43 (83:17)[c]	**3ca**, 50 (53)[c]
9			CuCl (0.3)	18	56:44	**3ca**, 53
10		Cl (**2b**)	-	36	71:29	**3cb**, 37, **3'cb**, 10
11			CuCl (0.3)	20	75:25	**3cb**, 45, **3'cb**, 15
12		OMe (**2c**)	-	24	77:23	**3cc**, 30
13			CuCl (0.3)	18	72:28	**3cc**, 48

[a] Determined from the ^{1}H NMR spectra of the crude. [b] After purification by column chromatography. [c] The values in brackets correspond to reactions performed without solvent with recourse to microwave irradiation (120 W). [d] 6 min to reach 80 °C, 9 min to reach 120 °C, and maintain at 120 °C for 40 min. [e] 3 min to reach 60 °C, 6 min to reach 80 °C, and maintain at 80 °C for 35 min.

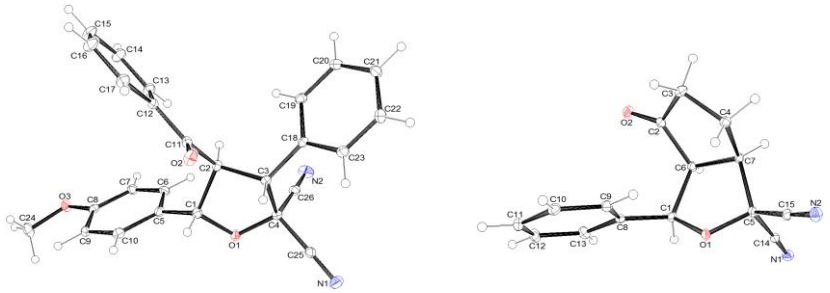
In order to reduce the reaction times required for these cycloaddition reactions, we performed experiments involving the epoxides **1a-c** and chalcone (**2a**) using microwave irradiation[13] at different powers and irradiation times. The best results were obtained without solvent (power = 120 W), with shortened reaction times in comparison to the corresponding reactions in toluene at reflux (55 min instead of 56 h for **3(')ba** (entry 1), 55 min instead of 62 h for **3(')aa** (entry 7), and 44 min instead of 48 h for **3(')ca** (entry 8).

If cuprous chloride has been recognized as a suitable catalyst for Huisgen's type reactions giving 1,2,3-triazoles from azides and alkynes,[15] its use to catalyze other 1,3-dipolar cycloadditions is far from common. In the present case, shortened reaction times were noticed for all the tested substrates by using 0.3 equivalent of this salt (Table 1).

As evidenced by recording the ^{1}H NMR spectra of the crudes, the 4,5-*cis* products **3** were formed preponderantly in all the reactions whereas the 4,5-*trans* products **3'** could not be avoided. The former were all isolated by column chromatography over silica gel in yields ranging from 30 to 53% (Table 1) whereas the latter were only separated similarly in the case of **3'cb** (10-15% yield, entries 10 and 11). If microwave irradiation tends to favor the formation of the 4,5-*cis* products **3** in the case of **2a**, the impact of cuprous chloride on the stereoselectivity is less obvious.

HMBC and HMQC sequences were performed on a $CDCl_3$ solution of the product **3ba** in order to assign the ^{1}H and ^{13}C NMR signals (see Supplementary data). The NOESY experiment showed a relationship between H4 (triplet at 5.13 ppm, coupling constant of 11 Hz) and H5 (doublet at 5.95 ppm, coupling constant of 9.6 Hz), but no relationship between H4 and H3 (doublet at 4.89 ppm, coupling constant of 11.5 Hz), in accordance with the structure proposed for **3ba** (concerning numbering, see Table 1). In addition, suitable crystals for X-ray diffraction of the minor diastereoisomer **3'ca** could be obtained, and allowed us to identify unequivocally its structure (Figure 1, left).

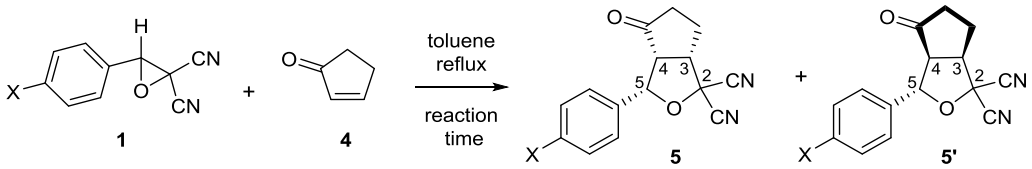
Figure 1. ORTEP diagram (30% probability) of **3'ca** and **5a**.



We next turned to the reaction of the 2,2-dicyano-3-aryloxiranes **1a-c** with 2-cyclopentenone (**4**) (Table 2). In refluxing toluene, two cycloadducts were formed regioselectively in reaction times ranging from 25 h (with the more reactive epoxide **1c**, entry 4) to 48 h (entry 1). The presence of cuprous chloride allowed the reaction times to be shortened, but did not modify significantly the stereoisomeric ratios (entries 2 and 5); this result is rather in agreement with an impact of the salt on the epoxide ring opening step of the reaction. Whereas Lewis acids such as BF_3 or $AlCl_3$ favor the ring aperture of epoxides by heterolytic rupture of their C–O bond to give zwitterionic species, the copper catalyst could favor the homolytic rupture of their C–C bond, yielding a carbonyl ylide (see Part 2.2).

In all the attempted reactions, the *endo* stereoisomers **5** were found to slightly predominate over the *exo* ones **5'**. Whereas the *endo* **5a** and **5b** were isolated by column chromatography over silica gel in about 50% yield (entries 1-3), the *exo* **5'b** and **5'c** were separated similarly in about 25% yield (entries 1, 4 and 5).

Table 2. Cycloaddition reaction between CYs generated from the epoxides **1** and 2-cyclopentenone (**4**).



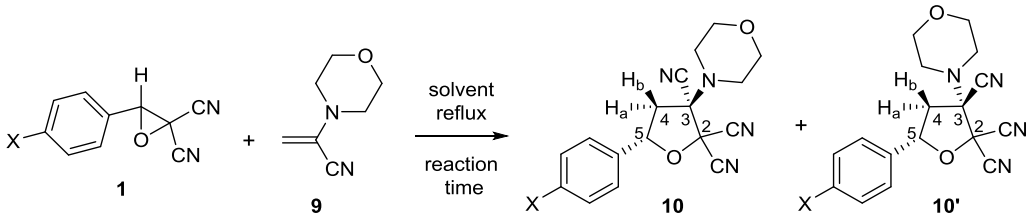
Entry	X (**1**)	Catalyst (equiv)	Reaction time (h)	**5:5'** ratio[a]	Product(s), yield(s)[b] (%)
1	Cl (**1b**)	-	48	60:40	**5b**, 45, **5'b**, 23
2		CuCl (0.3)	24	57:43	**5b**, 50
3	H (**1a**)	-	46	59:41	**5a**, 51
4	MeO (**1c**)	-	25	57:43	**5'c**, 23[c]
5		CuCl (0.3)	18	62:38	**5'c**, 29[c]

[a] Determined from the ^{1}H NMR spectra of the crude mixture. [b] After purification by column chromatography. [c] Attempts to isolate pure **5c** failed; estimated yields of **5'c** were given due to ~10% remaining **5c**.

Two-dimension NMR sequences were performed as before on a $CDCl_3$ solution of the products **5b** and **5'b**. After assignment of the ^{1}H and ^{13}C NMR signals, the performed NOESY experiment evidenced a relationship between H4 (triplet at 3.36 ppm (8.6 Hz) and triplet at 3.24 ppm (7.8 Hz), respectively) and H3 (signals at 3.68-3.81 ppm) for both **5b** and **5'b**, as expected. Correlations between H4 and H5 (doublet at 5.52 ppm (9.1 Hz) and doublet at 5.34 ppm (6.7 Hz), respectively) were also identified for both **5b** and **5'b**, albeit to a smaller extent in the case of the minor stereoisomer. Importantly, correlation between H3 and H5 was only detected in the case of the predominant stereoisomer, in accordance with an *endo* arrangement (stereoisomer **5b**). Finally, suitable crystals for X-ray diffraction of the major stereoisomer **5a** could be obtained, allowing us to elucidate unambiguously its structure (Figure 1, right).

The 2,2-dicyano-3-aryloxiranes **1a-c** were reacted with 2-morpholinoacrylonitrile (**9**) in refluxing toluene. 3-Cyano-3-morpholino-5-phenyltetrahydrofuran-2,2-dicarbonitriles were obtained. As expected due to the presence of the electron-withdrawing group, the oxirane **1d** is less reactive, and is only converted similarly in refluxing xylene (Table 3).

Table 3. Cycloaddition reaction between CYs generated from the epoxides **1** and 2-morpholinoacrylonitrile (**9**).



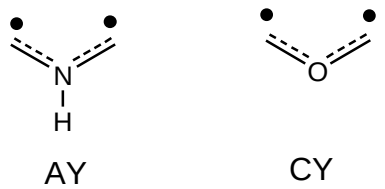
Entry	X (**1**)	Solvent	Reaction time (h)	**10**:**10'** ratio	Product(s), yield(s)[a] (%)
1	Cl (**1b**)	toluene	46	55:45	**10b**, 50
2	H (**1a**)	toluene	37	50:50	**10a**, 37
3	MeO (**1c**)	toluene	20	95:5	**10c**, 62
4	O_2N (**1d**)	xylene	38	62:38	**10d**, 45

[a] After purification by recrystallization.

Recording the ^{1}H NMR spectra of the crudes led to two sets of peaks. The preponderant *trans* products **10** were isolated from the mixture by recrystallization from ethanol in yields ranging from 37% to 62% (Table 3). From NMR data gathered from closely related 5-phenyltetrahydrofurans unsubstituted at their 4 position,[16] one could estimate the *cis* and *trans* coupling constants values between H4 and H5 at ~ 6-7 Hz and ~ 10-11 Hz, respectively, and the assignment of H_a and H_b of **10** was made on this basis. Next, in the absence of structural proof, we assumed a more downfield signal for the proton closer to the nitrile function (H_a for **10**),[17] and attributed the main sets of peaks of the crudes to **10**.

2.2. Theoretical aspects

Recent molecular electron density theory[18] studies devoted to 32CA reactions have established a very good correlation between the electronic structure of three-atom-components and their reactivity toward ethylene.[19] Thus, depending on their electronic structure, the non-polar 32CA reactions were classified into *pseudodiradical*-type (*pdr-type*),[19] *pseudoradical*-type (*pmr-type*),[19b] *carbenoid*-type (*cb-type*)[20] and *zwitterionic*-type (*zw-type*)[19a] reactions. The reactivity trend decreases in the following order: pseudodiradical > pseudoradical > carbenoid > zwitterionic. The simplest azomethine ylide (AY) and CY have a *pseudodiradical* structure that enables them to react quickly in non-polar *pdr-type* reactions (see Scheme 1).[19a] However, the substitution in these three-atom-components can modify their electronic structure, and consequently their reactivity.[12]



Scheme 1. *Pseudodiradical* structures of the simplest azomethine ylide (AY) and CY.

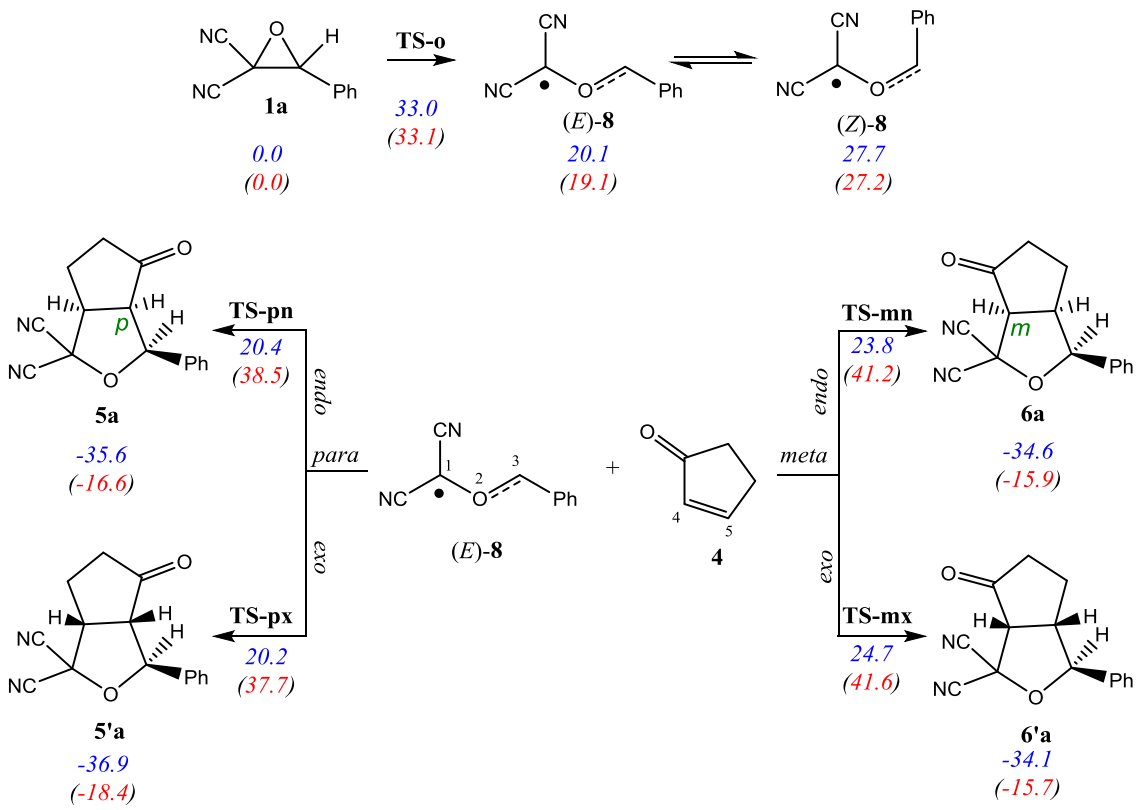
In order to explain the molecular mechanism of these domino reactions, the reaction between the oxirane **1a** and smaller electron-deficient 2-cyclopentenone **(4)**, yielding the tetrahydrofurans **5(')a** and **6(')a**, was theoretically studied using DFT methods. This theoretical study has been divided into two parts: (i) first, reaction paths associated with the domino reaction between the oxirane **1a** and 2-cyclopentenone **(4)** were explored and characterized; and (ii) then, a bonding evolution theory[21] study along the most favorable reactive channel associated with the 32CA between CY **8** and 2-cyclopentenone **(4)** was performed in order to characterize the molecular mechanism of these 32CA reactions.

2.2.1. Analysis of the reaction paths associated with the domino reaction between the oxirane 1a and 2-cyclopentenone (4)

The reaction between the oxirane **1a** and 2-cyclopentenone **(4)** is a domino process that comprises two sequential reactions: (i) first, the thermal ring opening of the oxirane **1a** to yield CY **8** and (ii) second, the 32CA reaction of CY **8** with 2-cyclopentenone **(4)** to give the tetrahydrofurans **5(')a** and **6(')a**. In order to explain the reactivity and the selectivities of this domino reaction, its energetic and geometrical aspects were theoretically studied within the molecular electron density theory,[18] using DFT calculations at the MPWB1K/6-311G(d) computational level. Total and relative electronic energies, in gas phase and in toluene, of the stationary points involved in the two processes are given in Table S2 of the Supplementary data, relative enthalpies and Gibbs free energies are displayed in Scheme 2 and complete thermodynamic data are gathered in Table S3.

The thermal ring opening of the oxirane **1a** to yield CY **8** takes place through a one-step mechanism with a very high activation enthalpy, 33.0 kcal·mol^{-1} (**TS-o**), the reaction being strongly endothermic by 20.1 kcal·mol^{-1}. Once CY **8** is formed, it can adopt the *E* or *Z* configuration through the restricted rotation of the O2–C3 bond. In this way, while (*E*)-**8**

presents a planar arrangement, (*Z*)-**8** is twisted as a consequence of the steric hindrance between the phenyl substituent and one cyano group. As this hindrance makes (*Z*)-**8** notably higher in energy than (*E*)-**8** (7.6 kcal·mol^{-1}), only the *E* configuration of CY **8** is considered in the present study. The Electron Localization Function (ELF) topological analysis of the electron density of CY **8** indicates that this three-atom-component has a *pseudoradical* structure (see (*E*)-**8** in Scheme 2 and the ELF analysis in the Supplementary data). Note that the presence of the phenyl substituent at the C3 carbon of CY **8** causes the delocalization of one of the two *pseudoradical* centers present in the simplest CY (see Scheme 1). Consequently, it is expected that CY **8** participates in *pmr-type* 32CA reactions.[19b]



Scheme 2. Domino reaction between the oxirane **1a** and 2-cyclopentenone **(4)**. Relative enthalpies, in blue, and Gibbs free energies, in red, are given in kcal·mol^{-1}.

Due to the non-symmetry of CY **8** and 2-cyclopentenone **(4)**, four reactive channels are feasible along the 32CA reaction between them (see Scheme 2). The two *endo* and *exo* stereoisomeric reactive channels are related to the two stereoisomeric approach modes of 2-

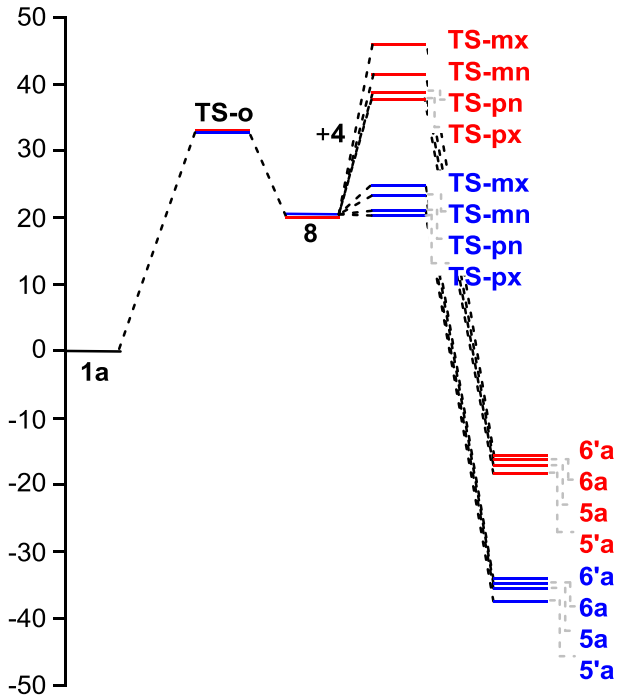
cyclopentenone **(4)** toward the sp^2 hybridized O2 oxygen atom of CY **8**, so that along the *endo* approach, the cyclopentenone ring is situated above the O2 oxygen of the CY framework. The two possible *meta* and *para* regioisomeric channels are related to the two regioisomeric approach modes of the C4 or C5 carbon atoms of 2-cyclopentenone **(4)** toward the C1 carbon of CY **8** in such a manner that, along the *meta* reactive pathway associated with the C1–C4 bond formation, the carbonyl group of the cyclopentenone framework is situated at the third position relative to the tetrahydrofuran oxygen atom. One TS and its corresponding cycloadduct were located and characterized for each of the four competitive reaction channels, thus indicating that the 32CA reaction between CY **8** and 2-cyclopentenone **(4)** takes place through a one-step mechanism (see Scheme 2).

The activation enthalpies associated with the four competitive reaction channels of the 32CA reaction between CY **8** and 2-cyclopentenone **(4)** are 0.2 (**TS-pn**), 0.1 (**TS-px**), 3.6 (**TS-mn**) and 4.6 (**TS-mx**) $kcal \cdot mol^{-1}$, formation of the corresponding tetrahydrofurans being strongly exothermic by between 54 and 57 $kcal \cdot mol^{-1}$. Two appealing conclusions can be drawn from these energy results: i) the 32CA reaction between CY **8** and 2-cyclopentenone **(4)** takes place with a very low activation enthalpy, 0.1 (**TS-px**) $kcal \cdot mol^{-1}$; ii) this 32CA reaction is completely *para* regioselective, as **TS-mn** is 3.5 $kcal \cdot mol^{-1}$ higher in energy than the most favorable **TS-px**, and presents poor *exo* stereoselectivity, as **TS-pn** is only 0.1 $kcal \cdot mol^{-1}$ higher in energy than **TS-px**. These results are in reasonable agreement with the experimental outcomes in which a mixture of *para endo/exo* adducts is obtained in a 59:41 ratio.

Figure 2 shows the enthalpy and Gibbs free energy profiles associated with the domino reaction between the oxirane **1a** and 2-cyclopentenone **(4)** in toluene. Along the ring opening of the oxirane **1a**, the relative Gibbs free energies are slightly higher than the enthalpy ones as a consequence of the unimolecular character of the reaction. Thus, while the activation Gibbs

free energy increases only by 0.1 kcal·mol^{-1}, the endergonic character of the reaction decreases by 1.1 kcal·mol^{-1} due to the slightly favorable relative entropy associated with the formation of CY **8** (see Table S3 of the Supplementary data). However, along the 32CA reaction, the relative Gibbs free energies considerably increase as a consequence of the unfavorable entropies associated with this bimolecular process. Thus, while the activation Gibbs free energies associated with the 32CA reaction increase by 17-18 kcal·mol^{-1}, the exergonic character of the reaction decreases by ca. 19 kcal·mol^{-1}.

Figure 2. Enthalpy, in blue, and Gibbs free energy, in red, profiles (in kcal·mol^{-1}) associated with the domino reaction between the oxirane **1a** and 2-cyclopentenone (**4**) in toluene. Relative energies are given with respect to **1a** + **4**.

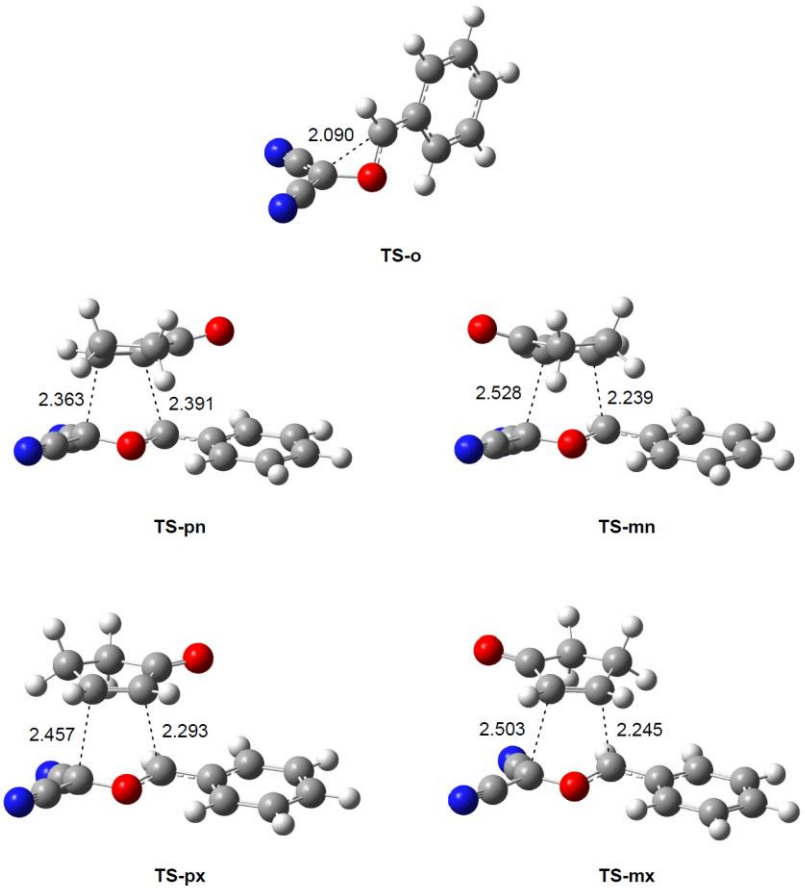


Some appealing conclusions can be drawn from these thermodynamic profiles: i) despite the very low activation enthalpy associated with the 32CA reaction, the endergonic character of the formation of CY **8** together with the unfavorable activation entropies associated with the 32CA reaction with 2-cyclopentenone **(4)** causes this reaction to be the rate-determining step of this domino process. The high activation Gibbs free energy associated with the rate-

determining step, 37.7 kcal·mol^{-1}, accounts for the hard thermal conditions required for obtaining the tetrahydrofurans **5(')a** and **6(')a**; ii) as the Gibbs free energy difference between **TS-px** and **TS-mn** is 3.5 kcal·mol^{-1}, this 32CA remains completely *para* regioselective, in complete agreement with the experimental outcomes; iii) inclusion of entropies to enthalpies increases the Gibbs free energy difference between **TS-pn** and **TS-px** to 0.8 kcal·mol^{-1}, in reasonable agreement with the experimental *endo/exo* ratio of ~60/40; and iv) finally, the high activation Gibbs free energy associated with the retro-32CA reaction, *ca.* 54 kcal·mol^{-1}, makes this domino reaction irreversible. Consequently, the observed reaction mixture of the tetrahydrofurans *endo* **5a** and *exo* **5'a** is obtained by kinetic control. In addition, the high exergonic character of this process makes this domino reaction thermodynamically very favorable.

The geometries of the TSs involved in the domino reaction between the oxirane **1a** and 2-cyclopentenone **(4)** in toluene are given in Figure 3. At **TS-o**, involved in the thermal ring opening of the oxirane **1a**, the distance between the two C1 and C3 carbons is 2.090 Å. At the *para* TSs, the distances between the C1 and C5, and the C3 and C4 carbons involved in the single bond formation are 2.363 and 2.391 Å at **TS-pn**, and 2.457 and 2.293 Å at **TS-px**, respectively. Likewise, at the *meta* TSs, the distances between the C1 and C4, and the C3 and C5 carbons involved in the single bond formation are 2.528 and 2.239 Å at **TS-mn**, and 2.503 and 2.245 Å at **TS-mx**, respectively. Three interesting conclusions can be drawn from these geometrical parameters: i) along the most favorable *para* regioisomeric reactive channels, while the C−C bond formation at the most favorable **TS-px** seems to be slightly asynchronous (Δl = 0.16), at **TS-pn** it appears to be practically synchronous (Δl = 0.03); ii) at the most favorable **TS-px**, the C−C bond formation involving the C1 *pseudoradical* carbon of CY **8** appears to be less advanced than that involving the C3 carbon; iii) in general, the most unfavorable *meta* TSs are slightly more asynchronous than the *para* ones (see Figure 3).

Figure 3. MPWB1K/6-311G(d) geometries of the TSs involved in the domino reaction between the oxirane **1a** and 2-cyclopentenone **(4)** in toluene; the distances between the carbons involved in the bond breaking and bond formation, as well as the asynchronicity Δl, are given in angstroms, Å.



Finally, the electronic nature of the 32CA reaction between CY **8** and 2-cyclopentenone **(4)** was evaluated by computing the Global Electron Density Transfer[22] (GEDT) at the TSs associated with the four reactive pathways in toluene. Along a polar reaction, there is an electron density transfer from the nucleophile to the electrophile, which is measured by the GEDT value at the TSs of the reactions; the larger the GEDT at the TS, the more polar the reaction is. 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; the more polar the reaction character, the faster the reaction is. It is

noteworthy that the GEDT[22] concept comes from the observation that the electron density transfer that takes place from a nucleophile to an electrophile along a polar reaction is not a local process, but a global one involving the two molecules.

The negligible values of GEDT computed at the cyclopentenone framework of the TSs, −0.02e (**TS-pn**), 0.01e (**TS-px**), 0.02e (**TS-mn**) and 0.01e (**TS-mx**), emphasize the non-polar character of this 32CA reaction, despite the strong electrophilic character of CY **8**, ω = 4.29 eV,[23] and the moderate nucleophilic character of 2-cyclopentenone **(4)**, N = 2.66 eV.[24] The relatively low activation energy associated with this 32CA reaction, together with the non-polar character of the reaction, and the topological analysis of the ELF of CY **8**, which shows a *pseudoradical* structure (see Supplementary data), is in agreement with a *pmr-type* of 32CA reaction.[19b]

2.2.2. Bonding evolution theory study of the molecular mechanism of the 32CA reaction between CY 8 and 2-cyclopentenone (4)

When trying to achieve a better understanding of bonding changes in organic reactions, the so-called bonding evolution theory[21] has proven to be a very useful methodological tool. This quantum-chemical methodology makes it possible to understand the bonding changes along a reaction path and, thus, to establish the nature of the electronic rearrangement associated with a given molecular mechanism.[25] Consequently, in order to establish the molecular mechanism of the 32CA reaction between CY **8** and 2-cyclopentenone **(4)**, such a study of the bonding changes along the most favorable *para/exo* reactive channel was performed (the complete study is provided in the Supplementary data).

Some appealing conclusions can be drawn from this bonding evolution theory study: i) the nine phases in which the *para/exo* reactive channel is divided allows the non-concerted nature of the reaction to be established, and consequently the pericyclic mechanism proposed for

these 32CA reactions to be ruled out;[26] ii) formation of the first C1−C5 single bond takes place at a C−C distance of 2.20 Å by the C-to-C coupling of the two C1 and C5 *pseudoradical* centers with an initial population of 1.17e, the former making a considerably larger contribution to the C1−C5 bond formation;[22] iii) formation of the second C3−C4 single bond takes place at a C−C distance of 1.97 Å by a C-to-C coupling of the two *pseudoradical* centers previously generated at the C3 and C4 carbons with an initial population of 1.25e;[22] iv) formation of the two C−C single bonds is slightly asynchronous; v) the topology of the ELF of **TS-px** reveals an inverse asynchronicity to that suggested by the geometrical analysis (see Figure 3): formation of the C1−C5 bond involving the *pseudoradical* C1 carbon already present in CY **8** is more advanced than the C3−C4 one; vi) the low activation energy associated to **TS-px** can be mainly related with the depopulation of the O2−C3 single bond of CY **8** and the C4−C5 double bond of cyclopentenone **(4)**. These behaviors, together with the fact that the activation energy relative to **MC-px** is 6.3 kcal·mol^{-1}, permit to classify this 32CA reaction as a *pmr-type* one, in clear agreement with the *pseudoradical* electronic structure of CY **8** (see Table S1 in Supplementary data).[19b] Consequently, the presence of the phenyl substituent at the C3 carbon of CY **8** changes the parent *pdr-type* reactivity to a *pmr-typ*e one; vii) in this non-polar 32CA reaction, the formation of the C4 *pseudoradical* center at the α position of the carbonyl group appears to be favored over that at the β one due to the electron-withdrawing character of the carbonyl group. This behavior accounts for the regioselectivity experimentally observed in this non-polar reaction.

2.3. Biological evaluation

Because tetrahydrofuran-containing scaffolds can exhibit bioactivities, some of the synthesized derivatives were evaluated. The compounds **3ba**, **3bc**, **5a** and **5'c** were assessed for their antibacterial activities against several bacterial species representative of those most

frequently encountered at the Hospital and responsible of healthcare-associated infections (HAI): *Escherichia coli*, *Klebsiella pneumoniae*, *Enterobacter cloacae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, *Staphylococcus aureus* and *Enterococcus faecalis*. Bacteria were treated with different concentrations of compounds (range 1 to 64 $\mu g.mL^{-1}$). For most of the bacteria tested, both Gram-positive and Gram-negative, we were able to determine antibacterial activities (i.e. determination of the Minimum Inhibitory Concentration, Table 4). Even if we observed globally a weak antibacterial activity for these compounds, most of them inhibit bacterial growth (PI = percentage of inhibition). Of particular interest, the cycloadduct **5'c** showed higher antibacterial activities, with MICs of 32 and 16 $\mu g.mL^{-1}$ against *S. aureus* and *E. faecalis*, respectively.

Table 4. Antibacterial activity MICs ($\mu g.mL^{-1}$) of the compounds **3ba**, **3bc**, **5a**, **5'c** and **ATB** (reference antibiotic) obtained by broth microdilution method, according to CLSI guidelines (n = 2, see Supplementary data), and/or PI% (percentage of inhibition) at 64 $\mu g.mL^{-1}$.

Bacteria	**3ba**	**3bc**	**5a**	**5'c**	**ATB**
Escherichia coli ABC 5	NI	NI	NI	NI	4[a]
Klebsiella pneumoniae ABC 12	>64 29%	>64 45%	>64	>64 42%	2[b]
Enterobacter cloacae ABC 291	>64 50%	>64 56%	>64 50%	>64 63%	2[b]
Acinetobacter baumannii ABC 14	>64 45%	>64 39%	>64 55%	>64 52%	8[c]
Pseudomonas aeruginosa ABC 4	>64 58%	>64 59%	>64 62%	>64 55%	8[c]
Staphylococcus aureus ABC 1	>64 28%	>64 31%	>64 38%	**32**	<1[d]
Enterococcus faecalis ABC 3	>64 78%	>64 89%	>64 78%	**16**	2[e]

NI: not interpretable. [a] Amoxicillin. [b] Amikacin.
[c] Ticarcillin. [d] Penicillin G. [e] Vancomycin.

These compounds were also assessed for their antiproliferative activities on both HeLa (Table 5) and L132 (Table 6) cell lines. Indeed, HeLa (an adenocarcinoma cell line from cervix) and L132 (an epithelial cell line originally thought to be derived from embryonic lung

tissue) are currently used as models for antiproliferative assays. Cells were treated with three concentrations of compounds (100, 50 and 10 μM). The discrimination was done at 100 μM. After 48 h treatment, **3ba** and **3bc** were found of interest. In fact, growth of HeLa and L-132 cells was inhibited by **3ba** and **3bc**, respectively (Table 5 and Table 6), with a very interesting antiproliferative activity of **3bc** on L132, even at 10 μM.

Table 5. Antiproliferative activity of the compounds **3ba**, **3bc**, **5a** and **5'c** on HeLa cell line (results are expressed as a percentage of survival determined by the MTT assay after 48 h of treatment at three different concentrations; results are mean ± SEM of two independent experiments).

Compound	3ba	3bc	5a	5'c
100 μM	0.53	57.90	89.71	95.58
50 μM	0.73 ± 0.17	82.84 ± 21.10	92.71 ± 5.78	103.12 ± 9.25
10 μM	30.42 ± 1.57	98.37 ± 9.53	106.13 ± 6.00	104.72 ± 2.75

Table 6. Antiproliferative activity of the compounds **3ba**, **3bc**, **5a** and **5'c** on L132 cell line (results are expressed as a percentage of survival determined by the MTT assay after 48 h of treatment at three different concentrations; results are mean ± SEM of two independent experiments; ND: not determined).

Compound	3ba	3bc	5a	5'c
100 μM	0.27	19.53	85.36	87.66
50 μM	16.03 ± 3.29	17.20 ± 9.99	ND	ND
10 μM	64.27 ± 5.50	19.94 ± 15.02	ND	ND

In order to study the mode of action of the compounds, we evaluated their bioactivity against a short panel of disease-related kinases: CDK2/Cyclin A; CDK5/p25; CDK9/Cyclin T; PIM1; GSK-3; RIPK3; Haspin; Aurora B. Among these selected targets, some are notably involved in cellular growth (including the control of the cell-division cycle for the human CDK2/Cyclin A). This class of enzymes should be putative targets of antiproliferative compounds described here (e.g. **5a**). The compounds were tested at 10 μM final concentration (15 μM ATP) and none of the derivatives was shown to inhibit significantly the enzymatic activities tested (data not shown).

3. Conclusions

Thus, different polysubstituted tetrahydrofurans were synthesized by reacting 2,2-dicyano-3-aryloxiranes with either enones, such as chalcones and 2-cyclopentenone, or enamines, here 2-morpholinoacrylonitrile. We showed, by using chalcones as enones, that microwaves can be efficiently used to shorten the reaction times and enhance the diastereoselectivities.

Importantly, the molecular mechanism of the reaction between the oxirane **1a** and 2-cyclopentenone **(4)**, yielding the tetrahydrofurans **5(')a** and **6(')a**, was theoretically studied using DFT methods. The reaction is a domino process that comprises two sequential reactions: (i) the thermal ring opening of the oxirane **1a** to yield CY **8** and (ii) its 32CA reaction with 2-cyclopentenone **(4)** to give the tetrahydrofurans **5(')a** and **6(')a**. The endergonic character of the formation of CY **8** together with the unfavorable activation entropies associated with the 32CA reaction with 2-cyclopentenone **(4)** causes this reaction to be the rate-determining step of this domino process.

The 32CA reaction between CY **8** and 2-cyclopentenone **(4)** takes place with a very low activation enthalpy, 0.1 kcal·mol^{-1}. This 32CA reaction is completely *para* regioselective, and presents poor *exo* stereoselectivity, in reasonable agreement with the experimental outcome. The negligible GEDT values computed at the TSs emphasize the non-polar character of this 32CA reaction.

The bonding evolution theory study of the most favorable *para/exo* reactive channel shows the non-concerted nature of the mechanism. ELF analysis of CY **8** indicates that this three-atom-component has a *pseudoradical* structure participating in a *pmr-type* 32CA reaction towards 2-cyclopentenone **(4)**. In this asynchronous process, the formation of the C1−C5 single bond takes place before the formation of the C3−C4 one, in disagreement with the asynchronicity showed by the lengths of the two C−C forming bonds at the corresponding TS.

The formation of the C1[3]−C5[4] single bonds takes place at C−C distances of 2.20[1.97] by a C-to-C coupling of the two C1[3] and C5[4] *pseudoradical* centers. The high electron density of the C1 *pseudoradical* center of CY **8** demands the asymmetric depopulation of the C4−C5 bonding region of 2-cyclopentenone **(4)**, in which the formation of the C4 *pseudoradical* center at the α position appears to be favored over that at the β one due to the presence of the electron-withdrawing carbonyl group. This behavior accounts for the regioselectivity experimentally observed in this non-polar reaction.

4. Experimental

4.1. General

Column chromatography separations were achieved on silica gel (40-63 μm). Melting points were measured on a Kofler apparatus. ^{1}H and ^{13}C Nuclear Magnetic Resonance (NMR) spectra were recorded with a Bruker ARX 200 P or a Bruker AC 300 P spectrometer (^{1}H at 200 or 300 MHz, respectively, and ^{13}C at 50 or 75 MHz, respectively). ^{1}H chemical shifts (δ) are given in ppm relative to the solvent residual peak, ^{13}C chemical shifts are relative to the central peak of the solvent signal.[27] Mass spectra (HRMS) measurements were performed at the CRMPO (Centre Régional de Mesures Physiques de l'Ouest) of Rennes by using a a Varian MAT 311 spectrometer in positive electrospray CI mode.

4.1.1. Starting materials

The oxiranes **1**[6b] and 2-morpholinoacrylonitrile (**9**)[28] were prepared according to a described procedure. Toluene was distilled before use. Reactions were performed under dry argon. Petrol refers to petroleum ether (bp 40–60°C).

4.1.2. Crystallography

The samples were studied with graphite monochromatized Mo-Kα radiation (λ = 0.71073 Å). X-ray diffraction data were collected at T = 100(2) K using APEXII Bruker-AXS

diffractometer. The structure was solved by direct methods using the SIR97 program,[29] and then refined with full-matrix least-square methods based on F^2 (SHELX-97)[30] with the aid of the WINGX program.[31] All non-hydrogen atoms were refined with anisotropic thermal parameters. H atoms were finally included in their calculated positions. Molecular diagrams were generated by ORTEP-3 (version 2.02).[31]

4.2. General procedures:

General procedure 1: A mixture of epoxide (2.0 mmol) and enone (2.0 mmol) in dry toluene (30 mL) was heated at reflux under N_2. The mixture was then evaporated to dryness and the residue was purified as specified in the product description.

General procedure 2: A mixture of epoxide (2.0 mmol) and enone (2.0 mmol) was heated in a microwave oven (power, temperature and time are given in the product description). The residue was purified as specified in the product description.

General procedure 3: A mixture of epoxide (2.0 mmol), enone (2.0 mmol) and CuCl (0.6 mmol) in dry toluene (30 mL) was heated at reflux under N_2. The mixture was then evaporated to dryness and the residue was purified as specified in the product description.

General procedure 4: A mixture of epoxide (2.0 mmol) and 2-morpholinoacrylonitrile (**9**, 2.0 mmol) in dry toluene (30 mL) was heated at reflux under N_2. The mixture was then evaporated to dryness and the residue was purified as specified in the product description.

4.3. Diastereoisomers of 4-benzoyl-5-(4-chlorophenyl)-3-phenyltetrahydrofuran-2,2-dicarbonitrile. The general procedure 1 (reflux of 56 h), using 3-(4-chlorophenyl)oxirane-2,2-dicarbonitrile (**1b**, 0.41 g) and chalcone (**2a**, 0.42 g), gave a 52/48 mixture from which the predominant diastereoisomer **3ba** was isolated by chromatography over silica gel (eluent: petrol/AcOEt 90:10) in 42% yield as a white powder: mp 182 °C; ^{1}H NMR ($CDCl_3$) δ 4.89 (d, 1H, J = 11.5 Hz, H3), 5.13 (t, 1H, J = 10.6 Hz, H4), 5.95 (d, 1H, J = 9.6 Hz, H5), 6.92-6.96 (m, 2H), 7.11-7.16 (m, 2H), 7.41-7.59 (m, 8H), 7.68-7.72 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 53.2

(CH), 56.5 (CH), 73.4 (C), 83.7 (CH), 112.3 (CN), 112.8 (CN), 128.4 (2CH), 128.4 (2CH), 128.5 (2CH), 128.7 (2CH), 129.2 (2CH), 129.7 (2CH), 129.8 (C), 130.1 (CH), 133.3 (C), 134.5 (CH), 135.4 (C), 136.3 (C), 192.6 (C=O); HRMS, *m*/*z*: 272.0931 found (calcd for $C_{18}H_{12}N_2O$, $[M\text{-}ClC_6H_4CHO]^{+\bullet}$ requires: 272.0950). The general procedure 2 (120 W, 6 min to reach 80°C, 9 min to reach 120°C, and 40 min at 120°C), using 3-(4-chlorophenyl)oxirane-2,2-dicarbonitrile (**1b**, 0.41 g) and chalcone (**2a**, 0.42 g), gave a 65/35 mixture from which the preponderant diastereoisomer **3ba** was isolated by chromatography over silica gel (eluent: petrol/AcOEt 90:10) in 51% yield. The general procedure 3 (reflux of 22 h), using 3-(4-chlorophenyl)oxirane-2,2-dicarbonitrile (**1b**, 0.41 g) and chalcone (**2a**, 0.42 g), gave a 65/35 mixture from which the preponderant diastereoisomer **3ba** was isolated by chromatography over silica gel (eluent: petrol/AcOEt 90:10) in 50% yield. The minor diastereoisomer **3'ba** was identified by selected NMR data: ^{1}H NMR ($CDCl_3$) δ 4.05 (t, 1H, *J* = 10.5 Hz, H4), 5.39 (d, 1H, *J* = 10.3 Hz).

4.4. Diastereoisomers of 4-benzoyl-3,5-diphenyltetrahydrofuran-2,2-dicarbonitrile. The general procedure 1 (reflux of 62 h), using 3-phenyloxirane-2,2-dicarbonitrile (**1a**, 0.34 g) and chalcone (**2a**, 0.42 g), gave a 51/49 mixture from which the preponderant diastereoisomer **3aa** was isolated by chromatography over silica gel (eluent: petrol/AcOEt 90:10) in 31% yield as a beige powder: mp 138-139 °C; ^{1}H NMR ($CDCl_3$) δ 4.93 (d, 1H, *J* = 11.6 Hz, H3), 5.13 (dd, 1H, *J* = 11.6 and 9.6 Hz, H4), 5.99 (d, 1H, *J* = 9.5 Hz, H5), 6.98-7.02 (m, 2H), 7.14-7.27 (m, 4H), 7.41-7.44 (m, 4H), 7.50-7.56 (m, 3H), 7.66-7.70 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 53.3 (CH), 56.5 (CH), 73.4 (C), 84.5 (CH), 112.4 (CN), 113.0 (CN), 127.1 (2CH), 128.4 (2CH), 128.5 (4CH), 130.0 (2CH), 129.6 (2CH), 129.4 (CH), 130.0 (CH), 130.1 (C), 134.2 (CH), 134.8 (C), 136.5 (C), 192.7 (C=O); HRMS, *m*/*z*: 378.1400 found (calcd for $C_{25}H_{18}N_2O_2$, $M^{+\bullet}$ requires: 378.1368). The general procedure 2 (120 W, 6 min to reach 80°C, 9 min to reach 120°C, and 40 min at 120°C), using 3-phenyloxirane-2,2-dicarbonitrile (**1a**,

0.34 g) and chalcone (**2a**, 0.42 g), gave a 68/32 mixture from which the preponderant diastereoisomer **3aa** was isolated by chromatography over silica gel (eluent: petrol/AcOEt 90:10) in 45% yield. The minor diastereoisomer **3'aa** was identified by selected NMR data: ^{1}H NMR ($CDCl_3$) δ 4.13 (t, 1H, *J* = 10.5 Hz, H4), 4.99 (d, 1H, *J* = 10.6 Hz), 5.48 (d, 1H, *J* = 10.4 Hz), 7.92-7.96 (m, 2H).

4.5. Diastereoisomers of 4-benzoyl-5-(4-methoxyphenyl)-3-phenyltetrahydrofuran-2,2-dicarbonitrile. The general procedure 1 (reflux of 48 h), using 3-(4-methoxyphenyl)oxirane-2,2-dicarbonitrile (**1c**, 0.40 g) and chalcone (**2a**, 0.42 g), gave a 57/43 mixture from which the preponderant diastereoisomer **3ca** was isolated by chromatography over silica gel (eluent: petrol/AcOEt 90:10) in 50% yield as a white powder: mp 204 °C; ^{1}H NMR ($CDCl_3$) δ 3.80 (s, 3H, OMe), 4.77-4.90 (m, 2H, H3, H4), 5.44 (d, 1H, *J* = 8.9 Hz, H5), 6.86-6.90 (m, 2H), 7.24-7.45 (m, 10H), 7.49-7.53 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 55.5 (OMe), 56.9 (CH), 60.5 (CH), 73.3 (C), 88.9 (CH), 112.9 (CN), 113.5 (CN), 114.7 (2CH), 127.9 (2CH), 128.3 (2CH), 128.1 (C), 128.7 (2CH), 128.9 (2CH), 129.6 (2CH), 130.1 (CH), 130.1 (C), 134.4 (CH), 136.1 (C), 160.7 (C), 194.8 (C=O); HRMS, *m*/*z*: 408.1491 found (calcd for $C_{26}H_{20}N_2O_3$, $M^{+\bullet}$ requires: 408.1474). The general procedure 2 (120 W, 3 min to reach 60°C, 6 min to reach 80°C, and 35 min at 80°C), using 3-(4-methoxyphenyl)oxirane-2,2-dicarbonitrile (**1c**, 0.40 g) and chalcone (**2a**, 0.42 g), gave a 83/17 mixture from which the preponderant diastereoisomer **3ca** was isolated by chromatography over silica gel (eluent: petrol/AcOEt 90:10) in 53% yield. The general procedure 3 (reflux of 18 h), using 3-(4-methoxyphenyl)oxirane-2,2-dicarbonitrile (**1c**, 0.40 g) and chalcone (**2a**, 0.42 g), gave a 56/44 mixture from which the preponderant diastereoisomer **3ca** was isolated by chromatography over silica gel (eluent: petrol/AcOEt 90:10) in 53% yield. **Crystal data for 3'ca** (CCDC 688220). $C_{26}H_{20}N_2O_3$, *M* = 408.44, triclinic, *P -1*, *a* = 8.5336(12), *b* = 10.6411(14), *c* = 13.899(2) Å, α = 101.087(6), β = 107.846(6), γ = 111.557(6) °, *V* = 1049.0(3) Å^3, *Z* = 2, *d* = 1.293 g cm^{-3}, μ = 0.085 mm^{-1}. A

final refinement on F^2 with 4754 unique intensities and 281 parameters converged at $\omega R(F^2)$ = 0.1151 ($R(F)$ = 0.055) for 4326 observed reflections with $I > 2\sigma(I)$.

4.6. Diastereoisomers of 4-benzoyl-3,5-di(4-chlorophenyl)tetrahydrofuran-2,2-dicarbonitrile. The general procedure 1 (reflux of 48 h), using 3-(4-chlorophenyl)oxirane-2,2-dicarbonitrile (**1b**, 0.41 g) and 4-chlorochalcone (**2b**, 0.49 g), gave a 62/38 mixture from which the preponderant diastereoisomer **3bb** was isolated by chromatography over silica gel (eluent: petrol/AcOEt 80:20) in 35% yield as a white powder: mp 147 °C; ^{1}H NMR ($CDCl_3$) δ 4.86 (d, 1H, *J* = 11.7 Hz, H3), 5.07 (dd, 1H, *J* = 11.7 and 9.7 Hz, H4), 5.96 (d, 1H, *J* = 9.7 Hz, H5), 6.90-6.94 (m, 2H), 7.11-7.15 (m, 2H), 7.39-7.50 (m, 6H), 7.60 (tt, 1H, *J* = 7.4 and 1.2 Hz), 7.68-7.71 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 53.3 (CH), 55.9 (CH), 73.0 (C), 83.7 (CH), 112.1 (CN), 112.6 (CN), 128.2 (C), 128.4 (4CH), 128.7 (2CH), 129.2 (2CH), 129.8 (2CH), 129.9 (2CH), 133.1 (C), 134.6 (CH), 135.5 (C), 136.1 (C), 136.3 (C), 192.3 (C=O); HRMS, *m*/*z*: 306.0564 found (calcd for $C_{18}H_{11}{}^{35}ClN_2O$, $[M\text{-}ClC_6H_4CHO]^{+\bullet}$ requires: 306.0560). The general procedure 3 (reflux of 24 h), using 3-(4-chlorophenyl)oxirane-2,2-dicarbonitrile (**1b**, 0.41 g) and 4-chlorochalcone (**2b**, only 0.245 g), gave a 69/31 mixture from which the preponderant diastereoisomer **3bb** was isolated by chromatography over silica gel (eluent: petrol/AcOEt 80:20) in 43% yield. The minor diastereoisomer **3'bb** was identified by selected NMR data: ^{1}H NMR ($CDCl_3$) δ 4.07 (t, 1H, *J* = 10.5 Hz, H4), 4.99 (d, 1H, *J* = 10.6 Hz), 5.35 (d, 1H, *J* = 10.5 Hz), 7.89-8.01 (m, 2H).

4.7. Diastereoisomers of 4-benzoyl-3-(4-chlorophenyl)-5-(4-methoxyphenyl)tetrahydrofuran-2,2-dicarbonitrile. The general procedure 1 (reflux of 36 h), using 3-(4-methoxyphenyl)oxirane-2,2-dicarbonitrile (**1c**, 0.40 g) and 4-chlorochalcone (**2b**, 0.49 g), gave a 71/29 mixture from which the preponderant diastereoisomer **3cb** was isolated by chromatography over silica gel (eluent: petrol/AcOEt 90:10) in 37% yield as a yellow oil; ^{1}H NMR ($CDCl_3$) δ 3.71 (s, 3H), 4.89 (d, 1H, *J* = 11.8 Hz, H3), 5.02 (dd, 1H, *J* =

11.8 and 9.5 Hz, H4), 5.95 (d, 1H, *J* = 9.5 Hz, H5), 6.64-6.68 (m, 2H), 6.90-6.94 (m, 2H), 7.39-7.44 (m, 4H), 7.48-7.52 (m, 2H), 7.56 (tt, 1H, *J* = 7.4 and 1.3 Hz), 7.65-7.70 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 53.5 (CH), 55.3 (CH_3), 55.9 (CH), 72.9 (C), 83.2 (CH), 112.3 (CN), 112.8 (CN), 113.9 (2CH), 126.6 (C), 128.4 (2CH), 128.6 (2CH), 129.0 (2CH), 129.8 (2CH), 129.9 (2CH), 133.6 (C), 134.3 (CH), 136.2 (C), 136.3 (C), 160.3 (C), 192.6 (C=O); HRMS, *m*/*z*: 442.1055 found (calcd for $C_{26}H_{19}{}^{35}ClN_2O_2$, $M^{+\bullet}$ requires: 442.1084). The minor diastereoisomer **3'cb** was isolated similarly in 10% yield as a white powder: mp 212 °C; ^{1}H NMR ($CDCl_3$) δ 3.80 (s, 3H), 4.13 (t, 1H, *J* = 10.5 Hz, H4), 4.97 (d, 1H, *J* = 10.6 Hz), 5.32 (d, 1H, *J* = 10.5 Hz), 6.87 (d, 2H, *J* = 8.5 Hz), 7.13-7.28 (m, 6H), 7.53 (t, 2H, *J* = 7.6 Hz), 7.68 (t, 1H, *J* = 7.2 Hz), 7.96 (d, 2H, *J* = 7.8 Hz); HRMS, *m*/*z*: 442.1061 found (calcd for $C_{26}H_{19}{}^{35}ClN_2O_2$, $M^{+\bullet}$ requires: 442.1084). The general procedure 3 (reflux of 20 h), using 3-(4-methoxyphenyl)oxirane-2,2-dicarbonitrile (**1c**, 0.40 g) and 4-chlorochalcone (**2b**, 0.49 g), gave a 75/25 mixture from which the preponderant and minor diastereoisomer **3cb** and **3'cb** were respectively isolated by chromatography over silica gel (eluent: petrol/AcOEt 90:10) in 45% and 15% yield.

4.8. Diastereoisomers of 4-benzoyl-5-(4-chlorophenyl)-3-(4-methoxyphenyl)tetrahydrofuran-2,2-dicarbonitrile. The general procedure 1 (reflux of 38 h), using 3-(4-chlorophenyl)oxirane-2,2-dicarbonitrile (**1b**, 0.41 g) and 4-methoxychalcone (**2c**, 0.48 g), gave a 80/20 mixture from which the preponderant diastereoisomer **3bc** was isolated by chromatography over silica gel (eluent: CH_2Cl_2/petrol 70:30) in 38% yield as a white powder: mp 152 °C; ^{1}H NMR ($CDCl_3$) δ 3.79 (s, 3H), 4.84 (d, 1H, *J* = 11.7 Hz, H3), 5.08 (dd, 1H, *J* = 11.8 and 9.7 Hz, H4), 5.94 (d, 1H, *J* = 9.7 Hz, H5), 6.92-6.95 (m, 4H), 7.11-7.15 (m, 2H), 7.41-7.48 (m, 4H), 7.59 (tt, 1H, *J* = 7.4 and 1.2 Hz), 7.68-7.71 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 53.3 (CH), 55.4 (CH_3), 56.0 (CH), 73.5 (C), 83.6 (CH), 112.4 (CN), 112.9 (CN), 115.0 (2CH), 121.3 (C), 128.4 (2CH), 128.4 (2CH), 128.7 (2CH), 129.2 (2CH), 129.6

(2CH), 133.4 (C), 134.4 (CH), 135.3 (C), 136.3 (C), 160.8 (C), 192.6 (C=O); HRMS, *m*/*z*: 442.1071 found (calcd for $C_{26}H_{19}{}^{35}ClN_2O_3$, $M^{+\bullet}$ requires: 442.1084). The general procedure 3 (reflux of 20 h), using 3-(4-chlorophenyl)oxirane-2,2-dicarbonitrile (**1b**, 0.41 g) and 4-methoxychalcone (**2c**, 0.48 g), gave a 79/21 mixture from which the preponderant diastereoisomer **3bc** was isolated by chromatography over silica gel (eluent: CH_2Cl_2/petrol 70:30) in 45% yield. The minor diastereoisomer **3'bc** was identified by selected NMR data: ^{1}H NMR ($CDCl_3$) δ 3.99 (t, 1H, *J* = 10.5 Hz, H4), 5.35 (d, 1H, *J* = 10.7 Hz).

4.9. Diastereoisomers of 4-benzoyl-3,5-di(4-methoxyphenyl)tetrahydrofuran-2,2-dicarbonitrile. The general procedure 1 (reflux of 24 h), using 3-(4-methoxyphenyl)oxirane-2,2-dicarbonitrile (**1c**, 0.40 g) and 4-methoxychalcone (**2c**, 0.48 g), gave a 77/23 mixture from which the preponderant diastereoisomer **3cc** was isolated by chromatography over silica gel (eluent: petrol/AcOEt 80:20) in 30% yield as a yellow oil; ^{1}H NMR ($CDCl_3$) δ 3.70 (s, 3H), 3.78 (s, 3H), 4.89 (d, 1H, *J* = 11.8 Hz, H3), 5.06 (dd, 1H, *J* = 11.8 and 9.6 Hz, H4), 5.95 (d, 1H, *J* = 9.6 Hz, H5), 6.64-6.67 (m, 2H), 6.92-6.95 (m, 4H), 7.38-7.43 (m, 2H), 7.47-7.50 (m, 2H), 7.54 (tt, 1H, *J* = 7.4 and 1.2 Hz), 7.68-7.71 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 53.4 (CH), 55.3 (CH_3), 55.4 (CH_3), 56.0 (CH), 73.3 (C), 84.2 (CH), 112.6 (CN), 113.1 (CN), 113.7 (2CH), 114.9 (2CH), 121.8 (C), 126.8 (C), 128.4 (2CH), 128.6 (2CH), 128.9 (2CH), 129.6 (2CH), 134.1 (CH), 136.4 (C), 160.1 (C), 160.7 (C), 192.9 (C=O); HRMS, *m*/*z*: 438.1583 found (calcd for $C_{27}H_{22}N_2O_4$, $M^{+\bullet}$ requires: 438.1580). The general procedure 3 (reflux of 18 h), using 3-(4-methoxyphenyl)oxirane-2,2-dicarbonitrile (**1c**, 0.40 g) and 4-methoxychalcone (**2c**, only 0.24 g), gave a 72/28 mixture from which the preponderant diastereoisomer **3cc** was isolated by chromatography over silica gel (eluent: petrol/AcOEt 80:20) in 48% yield. The minor diastereoisomer **3'cc** was identified by selected NMR data: ^{1}H NMR ($CDCl_3$) δ 4.07 (t, 1H, *J* = 10.5 Hz, H4), 5.33 (d, 1H, *J* = 10.5 Hz).

4.10. Diastereoisomers of 3-(4-chlorophenyl)-4-oxohexahydro-1*H*-cyclopenta[*c*]furan-1,1-dicarbonitrile. The general procedure 1 (reflux of 48 h), using 3-(4-chlorophenyl)oxirane-2,2-dicarbonitrile (**1b**, 0.41 g) and 2-cyclopentenone (**4**, 0.16 g), gave a 60/40 mixture from which the preponderant diastereoisomer **5b** was isolated by chromatography over silica gel (eluent: heptane/Et_2O 70:30) in 45% yield as a beige powder: mp 109 °C; ^{1}H NMR ($CDCl_3$) δ 2.18-2.45 (m, 4H), 3.36 (t, 1H, *J* = 8.6 Hz, H4), 3.68-3.81 (m, 1H, H3), 5.52 (d, 1H, *J* = 9.1 Hz, H5), 7.17 (d, 2H, *J* = 8.0 Hz), 7.36 (d, 2H, *J* = 8.1 Hz); ^{13}C NMR ($CDCl_3$) δ 24.9 (CH_2), 38.5 (CH_2), 52.6 (CH), 54.5 (CH), 71.7 (C), 84.7 (CH), 111.3 (CN), 113.1 (CN), 127.3 (2CH), 129.1 (2CH), 131.6 (C), 135.1 (C), 210.6 (C=O); HRMS, *m*/*z*: 286.0514 found (calcd for $C_{15}H_{11}{}^{35}ClN_2O_2$, $M^{+\bullet}$ requires: 286.0509). The minor diastereoisomer **5'b** was isolated similarly in 23% yield as a white powder: mp 144 °C; ^{1}H NMR ($CDCl_3$) δ 2.28-2.38 (m, 1H), 2.53-2.63 (m, 2H), 2.77-2.86 (m, 1H), 3.24 (t, 1H, *J* = 7.8 Hz, H4), 3.81 (q, 1H, *J* = 7.9 Hz, H3), 5.34 (d, 1H, *J* = 6.7 Hz, H5), 7.33 (d, 2H, *J* = 8.6 Hz), 7.39 (d, 2H, *J* = 8.7 Hz); ^{13}C NMR ($CDCl_3$) δ 23.2 (CH_2), 37.9 (CH_2), 54.2 (CH), 58.9 (CH), 71.8 (C), 84.5 (CH), 111.8 (CN), 113.5 (CN), 127.0 (2CH), 129.3 (2CH), 135.0 (C), 135.9 (C), 211.5 (C=O); HRMS, *m*/*z*: 286.0520 found (calcd for $C_{15}H_{11}{}^{35}ClN_2O_2$, $M^{+\bullet}$ requires: 286.0509). The general procedure 3 (reflux of 24 h), using 3-(4-chlorophenyl)oxirane-2,2-dicarbonitrile (**1b**, 0.41 g) and 2-cyclopentenone (**4**, 0.16 g), gave a 57/43 mixture from which the preponderant diastereoisomer **5b** was isolated by chromatography over silica gel (eluent: heptane/Et_2O 70:30) in 50% yield.

4.11. Diastereoisomers of 4-oxo-3-phenylhexahydro-1*H*-cyclopenta[*c*]furan-1,1-dicarbonitrile. The general procedure 1 (reflux of 46 h), using 3-phenyloxirane-2,2-dicarbonitrile (**1a**, 0.34 g) and 2-cyclopentenone (**4**, 0.16 g), gave a 59/41 mixture from which the preponderant diastereoisomer **5a** was isolated by chromatography over silica gel (eluent: heptane/Et_2O 70:30) in 51% yield as a beige powder: mp 158 °C; ^{1}H NMR ($CDCl_3$) δ 2.18-

2.48 (m, 4H), 3.36 (t, 1H, J = 8.8 Hz, H4), 3.72 (q, 1H, J = 7.6 Hz, H3), 5.55 (d, 1H, J = 9.3 Hz, H5), 7.22-7.24 (m, 2H), 7.35-7.42 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 24.8 (CH_2), 38.5 (CH_2), 52.7 (CH), 54.7 (CH), 71.7 (C), 85.5 (CH), 111.4 (CN), 113.3 (CN), 125.9 (2CH), 128.9 (2CH), 129.3 (CH), 133.1 (C), 210.8 (C=O); HRMS, *m*/*z*: 252.0912 found (calcd for $C_{15}H_{12}N_2O_2$, $M^{+\bullet}$ requires: 252.0899). **Crystal data for 5a** (CCDC 688217). $C_{15}H_{12}N_2O_2$, M = 252.27, orthorhombic, $P\ b\ c\ a$, a = 7.9165(4), b = 13.9702(9), c = 21.5846(13) Å, V = 2387.2(2) Å^3, Z = 8, d = 1.404 g cm^{-3}, μ = 0.095 mm^{-1}. A final refinement on F^2 with 2739 unique intensities and 172 parameters converged at $\omega R(F^2)$ = 0.1034 ($R(F)$ = 0.0477) for 2703 observed reflections with $I > 2\sigma(I)$. The minor diastereoisomer **5'a** was identified by selected NMR data: ^{1}H NMR ($CDCl_3$) δ 5.38 (d, 1H, J = 6.7 Hz, H5).

4.12. Diastereoisomers of 3-(4-methoxyphenyl)-4-oxohexahydro-1*H*-cyclopenta[*c*]furan-1,1-dicarbonitrile. The general procedure 1 (reflux of 25 h), using 3-(4-methoxyphenyl)oxirane-2,2-dicarbonitrile (**1c**, 0.40 g) and 2-cyclopentenone (**4**, 0.16 g), gave a 57/43 mixture from which the minor diastereoisomer **5'c** was isolated by chromatography over silica gel (eluent: heptane/Et_2O 70:30) in 23% yield as a beige oil; ^{1}H NMR ($CDCl_3$) δ 2.34-2.40 (m, 1H), 2.52-2.59 (m, 2H), 2.76-2.85 (m, 1H), 3.28 (s, 3H, OMe), 5.32 (d, 1H, J = 6.6 Hz), 6.93 (d, 2H, J = 8.7 Hz), 7.30 (d, 2H, J = 8.7 Hz); ^{13}C NMR ($CDCl_3$) δ 23.5 (CH_2), 37.8 (CH_2), 54.5 (CH), 55.5 (OMe), 58.9 (CH), 71.7 (C), 85.5 (CH), 113.8 (CN), 114.6 (2CH), 115.5 (CN), 127.4 (2CH), 129.0 (C), 160.3 (C), 212.2 (C=O); HRMS, *m*/*z*: 282.1020 found (calcd for $C_{16}H_{14}N_2O_3$, $M^{+\bullet}$ requires: 282.1004). The general procedure 3 (reflux of 18 h), using 3-(4-methoxyphenyl)oxirane-2,2-dicarbonitrile (**1c**, 0.40 g) and 2-cyclopentenone (**4**, 0.16 g), gave a 62/38 mixture from which the minor diastereoisomer **5'c** was isolated by chromatography over silica gel (eluent: heptane/Et_2O 70:30) in 29% yield. The major diastereoisomer **5c** was identified by selected NMR data: ^{1}H NMR ($CDCl_3$) δ 5.51 (d, 1H, J = 9.3 Hz).

4.13. Diastereoisomers of 5-(4-chlorophenyl)-3-cyano-3-morpholinotetrahydrofuran-2,2-dicarbonitrile. The general procedure 4 (reflux of 46 h), using 3-(4-chlorophenyl)oxirane-2,2-dicarbonitrile (**1b**, 0.41 g), gave a 55/45 mixture from which the preponderant diastereoisomer **10b** was isolated by recrystallization in EtOH in 50% yield as a white powder: mp 191 °C; ^{1}H NMR ($CDCl_3$) δ 2.70-2.87 (m, 5H), 3.00 (dd, 1H, *J* = 13.4 and 9.7 Hz, H4), 3.77-3.94 (m, 4H), 5.53 (dd, 1H, *J* = 9.6 and 4.8 Hz, H5), 7.33-7.45 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 43.4 (CH_2), 50.4 ($2CH_2$), 66.0 ($2CH_2$), 74.9 (C), 75.0 (C), 81.4 (CH), 109.6 (CN), 110.8 (CN), 113.2 (CN), 127.6 (2CH), 129.6 (2CH), 135.2 (C), 135.8 (C); HRMS, *m*/*z*: 340.0715 found (calcd for $C_{17}H_{13}{}^{35}ClN_4O_2$, $M^{+\bullet}$ requires: 340.0727). The minor diastereoisomer **10'b** was identified by selected NMR data: ^{1}H NMR ($CDCl_3$) δ 5.63 (dd, 1H, *J* = 11.5 and 4.9 Hz, H5).

4.14. Diastereoisomers of 3-cyano-3-morpholino-5-phenyltetrahydrofuran-2,2-dicarbonitrile. The general procedure 4 (reflux of 37 h), using 3-phenyloxirane-2,2-dicarbonitrile (**1a**, 0.34 g), gave a 50/50 mixture from which the diastereoisomer **10a** was isolated by recrystallization in EtOH in 37% yield as a beige powder: mp 188 °C; ^{1}H NMR ($CDCl_3$) δ 2.70-2.87 (m, 5H), 2.99 (dd, 1H, *J* = 13.4 and 9.6 Hz, H4), 3.77-3.92 (m, 4H), 5.54 (dd, 1H, *J* = 9.6 and 5.0 Hz, H5), 7.36-7.50 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 43.4 (CH_2), 50.4 ($2CH_2$), 66.1 ($2CH_2$), 74.8 (C), 75.0 (C), 82.2 (CH), 109.7 (CN), 111.0 (CN), 113.3 (CN), 124.7 (CH), 127.8 (2CH), 131.0 (2CH), 131.5 (C); HRMS, *m*/*z*: 306.1111 found (calcd for $C_{17}H_{14}N_4O_2$, $M^{+\bullet}$ requires: 306.1117).

4.15. Diastereoisomers of 3-cyano-5-(4-methoxyphenyl)-3-morpholinotetrahydrofuran-2,2-dicarbonitrile. The general procedure 4 (reflux of 20 h), using 3-(4-methoxyphenyl)oxirane-2,2-dicarbonitrile (**1c**, 0.40 g), gave a 95/5 mixture from which the preponderant diastereoisomer **10c** was isolated by recrystallization in EtOH in 62% yield as a yellow powder: mp 151 °C; ^{1}H NMR ($CDCl_3$) δ 2.75-2.84 (m, 5H), 2.94 (dd, 1H, *J*

= 13.4 and 9.7 Hz, H4), 3.83-3.89 (m, 4H), 5.48 (dd, 1H, *J* = 9.5 and 5.1 Hz, H5), 6.95-6.96 (m, 2H), 7.35-7.37 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 43.4 (CH_2), 50.4 ($2CH_2$), 55.5 (CH_3), 66.1 ($2CH_2$), 74.7 (C), 75.3 (C), 82.2 (CH), 109.8 (CN), 111.0 (CN), 113.5 (CN), 114.7 (2CH), 128.2 (2CH), 128.4 (C), 160.8 (C); HRMS, *m*/*z*: 336.1205 found (calcd for $C_{18}H_{16}N_4O_3$, $M^{+\bullet}$ requires: 336.1222). The minor diastereoisomer **10'c** was identified by selected NMR data: ^{1}H NMR ($CDCl_3$) δ 5.67 (dd, 1H, *J* = 11.5 and 4.8 Hz, H5).

4.16. Diastereoisomers of 3-cyano-3-morpholino-5-(4-nitrophenyl)tetrahydrofuran-2,2-dicarbonitrile. The general procedure 4 (but using xylene, reflux of 38 h), using 3-(4-nitrophenyl)oxirane-2,2-dicarbonitrile (**1d**, 0.43 g), gave a 62/38 mixture from which the preponderant diastereoisomer **10d** was isolated by recrystallization in EtOH in 45% yield as a beige powder: mp 228 °C; ^{1}H NMR ($(CD_3)_2CO$) δ 2.56-2.66 (m, 5H), 3.02 (dd, 1H, *J* = 14.1 and 4.1 Hz, H4), 3.15 (dd, 1H, *J* = 14.1 and 9.9 Hz, H4), 3.49-3.58 (m, 4H), 5.64 (dd, 1H, *J* = 9.8 and 4.0 Hz, H5), 7.23-7.25 (m, 2H), 7.75-7.76 (m, 2H); selected ^{1}H NMR ($CDCl_3$) δ 5.70 (dd, 1H, *J* = 9.85 and 4.0 Hz, H5); ^{13}C NMR ($(CD_3)_2CO$) δ 43.1 (CH_2), 51.2 ($2CH_2$), 66.6 ($2CH_2$), 75.8 (C), 76.1 (C), 82.2 (CH), 110.7 (CN), 112.3 (CN), 114.0 (CN), 124.7 (2CH), 127.9 (2CH), 145.8 (C), 149.2 (C); HRMS, *m*/*z*: 351.0972 found (calcd for $C_{17}H_{13}N_5O_4$, $M^{+\bullet}$ requires: 351.0968). The minor diastereoisomer **10'd** was identified by selected NMR data: ^{1}H NMR ($CDCl_3$) δ 5.78 (dd, 1H, *J* = 11.4 and 5.2 Hz, H5).

4.17. Computational methods

Density functional theory (DFT) calculations were carried out using the MPWB1K functional[32] together with the standard 6-311G(d) basis set.[33] Optimizations were carried out using the Berny analytical gradient optimization method.[34] The stationary points were characterized by frequency calculations to verify that the transition state structures (TSs) have one and only one imaginary frequency. The IRC paths[35] 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.[36] Solvent effects of toluene were taken into account by full optimization of the gas phase geometries using the polarisable continuum model (PCM) developed by Tomasi's group[37] in the framework of the self-consistent reaction field (SCRF).[38] Values of enthalpies, entropies and Gibbs free energies in toluene were calculated with the standard statistical thermodynamics at 386 K and 1 atm.[33] The Global Electron Density Transfer (GEDT)[22] is computed by the sum of the natural atomic charges (q), obtained by a natural population analysis (NPA)[39] of the atoms belonging to each framework (f) at the TSs; GEDT = Σq_f. The sign indicates the direction of the electron density flux in such a manner that positive values mean a flux from the considered framework to the other one. All the computations were carried out with the Gaussian 09 suite of programs.[40]

The ELF[41] analyses were performed with the TopMod program,[42] using the corresponding MPWB1K/6-311G(d) monodeterminantal wave functions over a grid spacing of 0.1 a.u.. For the bonding evolution theory study, the corresponding reaction channel was followed by performing the topological analysis of the ELF for 519 nuclear configurations along the IRC path.

Acknowledgements

The experimental study has been supported by the Centre National de la Recherche Scientifique, the Université de Rennes 1, the Institut Universitaire de France, Rennes Métropole, the Ministère de l'Enseignement supérieur, de la Recherche et de l'Innovation, and Région Lorraine. The theoretical study has been supported by the Ministry of Economy and Competitiveness (MINECO) of the Spanish Government, project CTQ2016-78669-P (AEI/FEDER, UE). M.R.-G. thanks MINECO for a pre-doctoral contract co-financed by the European Social Fund (BES-2014-068258). We also thank the Cancéropôle Grand Ouest (axis: natural sea products in cancer treatment), IBiSA (French *Infrastructures en sciences du*

vivant: biologie, santé et agronomie) and Biogenouest (Western France life science and environment core facility network) for supporting KISS*f* screening facility. FM thanks Dr. Keith Woerpel for helpful discussions.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/xxxxxxxxxxxxxxxxxxxxxxxx. It contains ^{1}H and ^{13}C NMR spectra of the new compounds, details of the theoretical calculations and of the biological evaluation.

References and notes

1. Lorente, A.; Lamariano-Merketegi, J.; Albericio, F.; Álvarez, M. *Chem. Rev.* **2013**, *113*, 4567-4610.
2. Rainier, J. D. *Top. Heterocycl. Chem.* **2014**, *35*, 1-41.
3. (a) Huisgen, R.; Grashey, R.; Sauer, J. The Chemistry of Alkenes **1964**, Interscience, New York; (b) Sustmann, R. *Heterocycles* **1995**, *40*, 1-18.
4. (a) Chiacchio, U.; Padwa, A.; Romeo, G. *Curr. Org. Chem.* **2009**, *13*, 422-447; (b) Zhang, W. *Chem. Lett.* **2013**, *42*, 676-681.
5. (a) Padwa, A. 1,3-Dipolar Cycloaddition Chemistry **1984**, Wiley-Interscience, New York, vol. 1-2; (b) Gothelf, K. V.; Jorgensen, K. A. *Chem. Rev.* **1998**, *98*, 863-909.
6. (a) Robert, A.; Pommeret, J. J.; Foucaud, A. *C. R. Acad. Sci. Paris, Ser. C* **1970**, *270*, 1739-1742; (b) Pommeret, J. J.; Robert, A. *Tetrahedron* **1971**, *27*, 2977-2987; (c) Derdour, A.; Texier, F. *Can. J. Chem.* **1985**, *63*, 2245-2252; (d) Clawson, P.; Lunn, P. M.; Whiting, D. A. *J. Chem. Soc., Perkin Trans. 1* **1990**, 159-162; (e) Ruf, S. G.; Dietz, J.; Regitz, M. *Tetrahedron* **2000**, *56*, 6259-6267; (f) Liu, R.; Zhang, M.; Zhang, J. *Chem. Commun.* **2011**, *47*, 12870-12872; (g) Bentabed-Ababsa, G.; Hamza-Reguig, S.; Derdour, A.; Domingo, L. R.; Saez, J. A.; Roisnel, T.; Dorcet, V.; Nassar, E.; Mongin, F. *Org. Biomol. Chem.* **2012**, *10*, 8434-8444; (h) Chen, W.; Fu, X.; Lin, L.; Yuan, X.; Luo, W.; Feng, J.; Liu, X.; Feng, X. *Chem. Commun.* **2014**, *50*, 11480-11483.
7. (a) Bentabed, G.; Derdour, A.; Benhaoua, H. *Synth. Commun.* **2003**, *33*, 1861-1866; (b) Yoakim, C.; Goudreau, N.; McGibbon, G. A.; O'Meara, J.; White, P. W.; Ogilvie, W. W. *Helv. Chim. Acta* **2003**, *86*, 3427-3444; (c) Tagliapietra, S.; Cravotto, G.; Gaudino, E. C.; Visentin, S.; Mussi, V. *Synlett* **2012**, *23*, 1459-1462; (d) Yuan, X.; Lin, L.; Chen, W.; Wu, W.; Liu, X.; Feng, X. *J. Org. Chem.* **2016**, *81*, 1237-1243.
8. (a) Pommeret, J. J.; Robert, A. *C. R. Acad. Sci. Paris, Ser. C* **1971**, *272*, 333-336; (b) Robert, A.; Pommeret, J. J.; Marchand, E.; Foucard, A. *Tetrahedron* **1973**, *29*, 463-468; (c) Bentabed, G.; Rahmouni, M.; Mongin, F.; Derdour, A.; Hamelin, J.; Bazureau, J. P. *Synth. Commun.* **2007**, *37*, 2935-2948; (d) Bentabed-Ababsa, G.; Derdour, A.; Roisnel, T.; Saez, J. A.; Pérez, P.; Chamorro, E.; Domingo, L. R.; Mongin, F. *J. Org. Chem.* **2009**, 2120-2133.

9. (a) Robert, A.; Pommeret, J. J.; Foucaud, A. *Tetrahedron Lett.* **1971**, 231-234; (b) Robert, A.; Pommeret, J. J.; Foucaud, A. *Tetrahedron* **1972**, *28*, 2085-2097; (c) Chen, Z.; Wei, L.; Zhang, J. *Org. Lett.* **2011**, *13*, 1170-1173; (d) Chen, W.; Lin, L.; Cai, Y.; Xia, Y.; Cao, W.; Liu, X.; Feng, X. *Chem. Commun.* **2014**, *50*, 2161-2163.
10. Bentabed-Ababsa, G.; Derdour, A.; Roisnel, T.; Saez, J. A.; Domingo, L. R.; Mongin, F. *Org. Biomol. Chem.* **2008**, *6*, 3144-3157.
11. Meier, K. R.; Linden, A.; Mloston, G.; Heimgartner, H. *Helv. Chim. Acta* **1997**, *80*, 1190-1204.
12. Domingo, L. R.; Aurell, M. J.; Pérez, P. *Tetrahedron* **2015**, *71*, 1050-1057.
13. Bougrin, K.; Benhida, R. Microwaves in Organic Synthesis (3rd Edition) **2012**, *2*, 737-809.
14. Using a monomode reactor (Prolabo Synthewave 402) with accurate control of power and temperature (infrared detection).
15. Heravi, M. M.; Tamimi, M.; Yahyavi, H.; Hosseinnejad, T. *Curr. Org. Chem.* **2016**, *20*, 1591-1647.
16. (a) Smith, D. M.; Woerpel, K. A. *Org. Lett.* **2004**, *6*, 2063-2066; (b) Shenoy, S. R.; Smith, D. M.; Woerpel, K. A. *J. Am. Chem. Soc.* **2006**, *128*, 8671-8677; (c) Parsons, A. T.; Johnson, J. S. *J. Am. Chem. Soc.* **2009**, *131*, 3122-3123.
17. Dilman, A. D.; Belyakov, P. A.; Struchkova, M. I.; Arkhipov, D. E.; Korlyukov, A. A.; Tartakovsky, V. A. *J. Org. Chem.* **2010**, *75*, 5367-5370.
18. Domingo, L. R. *Molecules* **2016**, *21*, 1319-1333.
19. (a) Domingo, L. R.; Emamian, S. R. *Tetrahedron* **2014**, *70*, 1267-1273; (b) Domingo, L. R.; Ríos-Gutiérrez, M. *Molecules* **2017**, *22*, 750-769.
20. Domingo, L. R.; Ríos-Gutiérrez, M.; Pérez, P. *Tetrahedron* **2016**, *72*, 1524-1532.
21. Krokidis, X.; Noury, S.; Silvi, B. *J. Phys. Chem. A* **1997**, *101*, 7277-7282.
22. Domingo, L. R. *RSC Adv.* **2014**, *4*, 32415-32428.
23. Parr, R. G.; von Szentpaly, L.; Liu, S. *J. Am. Chem. Soc.* **1999**, *121*, 1922-1924.
24. Domingo, L. R.; Chamorro, E.; Pérez, P. *J. Org. Chem.* **2008**, *73*, 4615-4624.
25. (a) Berski, S.; Andrés, J.; Silvi, B.; Domingo, L. R. *J. Phys. Chem. A* **2003**, *107*, 6014-6024; (b) Polo, V.; Andrés, J.; Berski, S.; Domingo, L. R.; Silvi, B. *J. Phys. Chem. A* **2008**, *112*, 7128-7136.
26. Houk, K. N.; González, J.; Li, Y. *Acc. Chem. Res.* **1995**, *28*, 81-90.
27. Gottlieb, H. E.; Kotlyar, V.; Nudelman, A. *J. Org. Chem.* **1997**, *62*, 7512-7515.
28. Boucher, J. L.; Stella, L. *Tetrahedron* **1985**, *41*, 875-887.
29. Altomare, A.; Burla, M. C.; Camalli, M.; Cascarano, G. L.; Giacovazzo, C.; Guagliardi, A.; Moliterni, A. G. G.; Polidori, G.; Spagna, R. *J. Appl. Crystallogr.* **1999**, *32*, 115-119.
30. Sheldrick, G. M. *Acta Crystallogr., Sect. A* **2008**, *A64*, 112-122.
31. Farrugia, L. J. *J. Appl. Crystallogr.* **2012**, *45*, 849-854.
32. Zhao, Y.; Truhlar, D. G. *J. Phys. Chem. A* **2004**, *108*, 6908-6918.
33. Hehre, W. J.; Radom, L.; Schleyer, P. v. R.; Pople, J. A. Ab initio Molecular Orbital Theory **1986**, Wiley: New York.
34. (a) Schlegel, H. B. *J. Comput. Chem.* **1982**, *3*, 214-218; (b) Schlegel, H. B. Modern Electronic Structure Theory **1994**, Ed.: D. R. Yarkony; World Scientific Publishing: Singapore.
35. Fukui, K. *J. Phys. Chem.* **1970**, *74*, 4161-4163.
36. (a) González, C.; Schlegel, H. B. *J. Phys. Chem.* **1990**, *94*, 5523-5527; (b) González, C.; Schlegel, H. B. *J. Chem. Phys.* **1991**, *95*, 5853-5860.

37. (a) Tomasi, J.; Persico, M. *Chem. Rev.* **1994**, *94*, 2027-2094; (b) Simkin, B. Y.; Sheikhet, I. Quantum Chemical and Statistical Theory of Solutions - Computational Approach **1995**, Ellis Horwood, London.
38. (a) Cances, E.; Mennucci, B.; Tomasi, J. *J. Chem. Phys.* **1997**, *107*, 3032-3041; (b) Cossi, M.; Barone, V.; Cammi, R.; Tomasi, J. *Chem. Phys. Lett.* **1996**, *255*, 327-335; (c) Barone, V.; Cossi, M.; Tomasi, J. *J. Comput. Chem.* **1998**, *19*, 404-417.
39. (a) Reed, A. E.; Weinstock, R. B.; Weinhold, F. *J. Chem. Phys.* **1985**, *83*, 735-746; (b) Reed, A. E.; Curtiss, L. A.; Weinhold, F. *Chem. Rev.* **1988**, *88*, 899-926.
40. Frisch, M. J., Gaussian 09, Revision A.02, Gaussian Inc., Wallingford CT.
41. Becke, A. D.; Edgecombe, K. E. *J. Chem. Phys.* **1990**, *92*, 5397-5403.
42. Noury, S.; Krokidis, X.; Fuster, F.; Silvi, B. *Comput. Chem.* **1999**, *23*, 597-604.