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Highly Diastereoselective 1,3-Dipolar Cycloadditions of Chiral Non-Racemic Nitrones to 1,2-Diaza-1,3-dienes: An Experimental and Computational Investigation

Cite this: DOI: 10.1039/x0xx00000x

Received 00th January 2012,
Accepted 00th January 2012

DOI: 10.1039/x0xx00000x

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Asymmetric 1,3-dipolar cycloadditions between 1,2-diaza-1,3-dienes and chiral non-racemic nitrones to give 3-substituted-5-diazenyl isoxazolidines have been studied both experimentally and theoretically. Whereas cyclic nitrones provide complete selectivity for the cycloaddition reaction (only one isomer is obtained), acyclic nitrones derived from D-glyceraldehyde and D-galactose lead to 1:1 mixtures of two isomers. A DFT analysis based on reactivity indices correctly predicts the regiochemistry of the reaction in agreement with the high electron-withdrawing character of the diazenyl group. The same theoretical studies considering solvent effects (PCM model) based on transition state theory are in a qualitative agreement with the observed experimental results.

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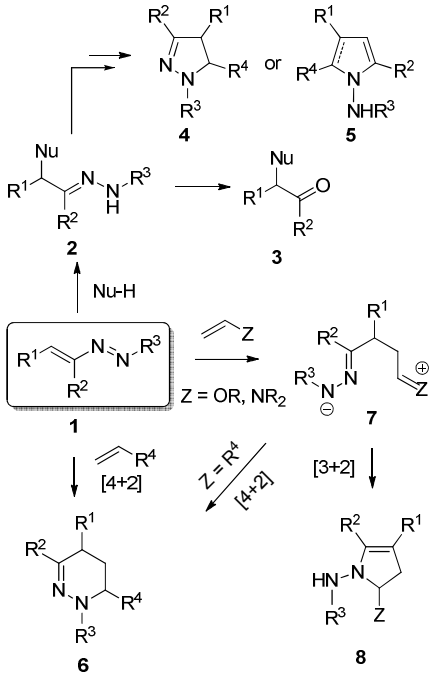
Introduction

1,2-Diaza-1,3-dienes (DDs, **1**) are important synthetic intermediates and very attractive building blocks for the construction of a great variety of heterocycles.[1] The conjugated system of 1 can be utilized as a Michael acceptor in 1,4-addition reactions of nucleophiles (Scheme 1). Among the nucleophiles are organometallic compounds such as Grignard derivatives[2] and a great number of carbanions derived from active methylene compounds including β-keto,[3] β-cyano,[4] β-phosphono[5] and β-nitro[6] carbonyl derivatives. The resulting hydrazones **2** can evolve towards the parent α-substituted carbonyl compounds **3** but in the case of β-functionalized carbonyls with the appropriate functionalities pyrazolines **4**[7] and N-amino pyrroles[8] and dihydropyrroles **5**[9] are obtained. Through the addition of diverse heterocyclic derivatives, bicyclic systems can also be prepared.[10]

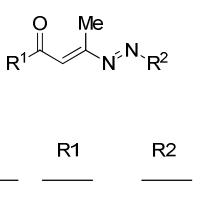
The scope of the DD chemistry has been enhanced by less studied cycloaddition reactions. Compounds **1** are electron-deficient systems and thus they are suitable of acting as dienes in inverse electron-demand [4+2] cycloadditions to give tetrahydropiridazines **6**.[11] In the case of enol ethers and enamines the cycloaddition is stepwise and intermediate **7** is formed. This intermediate can evolve to **6** through a formal [4+2] cycloaddition but also to *N*-amino pyrroles **8** through a competitive formal [3+2] cycloaddition.[12] The reactivity of DDs as dienophiles has been much less studied and only the reaction with cyclopentadiene has been reported,[13] besides the possibility of dimerization of compounds **1**.[14]



Scheme 1 Reactivity of DDs**1**

In 1,3-dipolar cycloadditions the C=C bond in compounds **1** can also act as dipolarophile as it has been demonstrated in reactions with diazomethane[15] and mesoionic heterocycles.[16] However, to the best of our knowledge no report has been communicated on the reaction between **1** and a typical 1,3-dipole as the nitrone functionality, which has been widely demonstrated its synthetic utility in the construction of several nitrogen heterocycles.[17]

Herein, we report a study of the reaction of DDs, **1** with cyclic and acyclic chiral non-racemic nitrones **9** (Chart 1). Thermal and microwave activated cycloadditions have been studied and the results have been rationalized by DFT calculations at several levels of theory considering solvent effects.



1	R1	R2
a	OMe	CONHPh
b	OMe	CO_2tBu
c	OMe	$CONH_2$
d	OMe	CO_2Me
e	OEt	$CONH_2$
f	Me_2N	CONHPh
g	OMe	4-$NO_2C_6H_4$

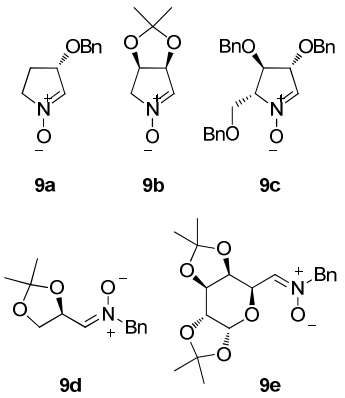


Chart 1 DDs **1** and nitrones **9**

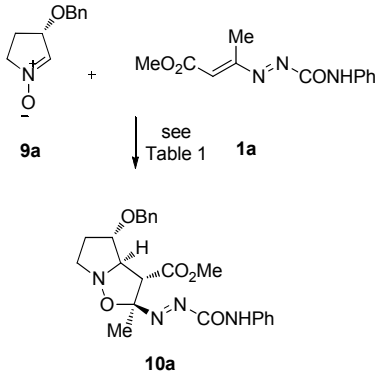
Results and Discussion

Experimental study

DDs **1a-f** were prepared according to previously reported procedures.[1] The starting nitrones **9** used for this study were prepared from L-malic acid for nitrone **9a**,[18] from D-erythrose for nitrone**9b**[19] from D-arabinose for nitrone**9c**,[20] from D-glyceraldehyde for nitrone **9d**[21] and from D-galactose for nitrone **9e**.[22]

Initially, we screened various solvents and ratios nitrone/DD for the cycloaddition between DD**1a** and nitrone **9a** to give **10a** (Scheme 3, Table 1). Among the various solvents tested, chloroform (Table 1, entries 1-3), ethyl acetate (Table 1, entries 4-6) and THF (Table 1, entries 7 and 8) gave moderate yields of the only observed cycloadduct**10a**. By using methanol as a solvent (Table 1, entries 9-10) no reaction was observed after 24 h. In the absence of any solvent (Table 1, entries 11 and 12) moderate to good results were obtained. The best solvent was found to be acetonitrile (Table 1, entries 13-15). Increasing the temperature resulted in shorter reaction times with similar chemical yields. On the other hand, a 2:1 ratio DD/nitrone showed the best results (Table 1, entries 3, 6, 8,12 and 15). In acetonitrile as a solvent, at 60 ºC and with a ratio **9a:1a** of 1:2, compound **10a** was obtained as the only product of the reaction in 91% yield (Table 1, entry 15). Thus, the reaction showed to be completely regio- and stereoselective with complete asymmetric induction.

With optimized conditions in hand, we next examined the reactivity and selectivity of nitrones **9** in cycloadditions with other DDs. As shown in Table 2 (entries 1-18), cyclic nitrones **9a-c** reacted with various DDs **1** under optimized conditions (ratio nitrone/diazadiene of 1:2, 60 ºC, neat or in MeCN as a solvent) from the less hindered side in an *exo* mode, with respect to the ester moiety, to give cycloadducts **10-12** as the main products. Typically, treatment of nitrone **9a** with DDs **1b-f** at 60 ºC gave cycloadducts **10b-f** (Table 2, entries 1-8) as the only products of the reaction in a similar way to **10a**. Reactions of nitrones **9b** and **9c** with other DDs also gave products **11** and **12**, respectively, bearing the same stereochemical sense (Table 2, entries 9-19). In sharp contrast to the above reactions, cycloaddition of open chain (*Z*)-nitrones **9d** and **9f**, derived from D-glyceraldehyde and D-galactose, respectively, with DD **1b** afforded adducts **13** and **14** as a 1:1 mixture of two isomers (Table 2, entries 20-25).



Scheme 2 Cycloaddition between nitrone**9a** and DD**1a** (see Table 1)

Table 1. Cycloaddition nitrone **9a** and DD **1a** (Scheme 2).

Entry	**1a:9**	solvent	T (ºC)	t (h)	yield (%)[a]	dr (%)[b]
1	1:1	$CHCl_3$	rt	24	28	1:0
2	1:1	$CHCl_3$	60	9	27	1:0
3	2:1	$CHCl_3$	60	17	44	1:0
4	1:1	EtOAc	rt	24	48	1:0
5	1:1	EtOAc	75	4	48	1:0
6	2:1	EtOAc	75	4	53	1:0
7	1:1	THF	60	9	46	1:0
8	2:1	THF	60	48	45	1:0
9	1:1	MeOH	rt	24	n.r[c]	1:0
10	2:1	MeOH	60	24	n.r[c]	1:0
11	1:1	neat	60	3	50	1:0
12	2:1	neat	60	3	71	1:0
13	1:1	MeCN	rt	24	27	1:0
14	1:1	MeCN	60	7	68	1:0
15	2:1	MeCN	69	9	91	1:0

[a] Isolated yield. [b] dr (diastereomeric ratio) was obtained from the ^{1}H NMR of the crude reaction mixture. [c] n.r. Not observed reaction.

The configurational assignments of the products were based on straightforward analysis of NMR spectra. The relative configuration could therefore be readily assigned on the basis of NOESY spectra. The most important information obtained from these experiments for compounds **10**, **11** and **12** is the absence of the NOE interaction between the protons H-3 and H-4 of the isoxazolidine ring and the presence of a clear NOE interaction between the ester group at C-4 and the methyl group at C-5 of the isoxazolidine ring (Figure 1, blue arrows). The products derived from cyclic nitrones **9a-c** are conformationally rigidified by the fused rings; consequently, the absolute configuration could be assigned through NOE relationship between H-3 and H-4, and the stereogeniccenter at the pyrrolidinering (Figure 1, red arrows). The structure of **10e** was elucidated by X-ray crystallography confirming the assigned configuration (Figure 2)[23] corresponding to an *exo* attack of DD by the less hindered *Re* diastereoface of the nitrone.

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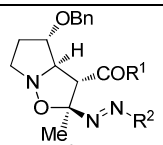
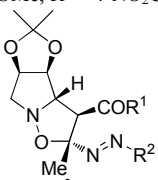
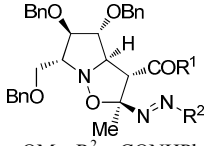
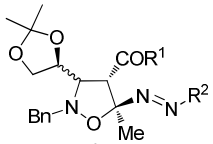
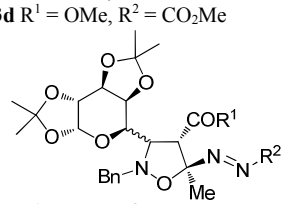
Table 2. Scope of the cycloaddition between nitrones **9** and DDs**1**.[a]

Entry	nitrone	diazadiene	adduct	solvent	t (h)	yield (%)[b]	dr (%)[c]
							
1	**9a**	**1b**	**10b** R^1 = OMe, R^2 = CO_2tBu	neat	3	69	1:0
2	**9a**	**1b**	**10b** R^1 = OMe, R^2 = CO_2tBu	MeCN	9	78	1:0
3	**9a**	**1c**	**10c** R^1 = OMe, R^2 = $CONH_2$	MeCN	5	52	1:0
4	**9a**	**1d**	**10d** R^1 = OMe, R^2 = CO_2Me	neat	1	44	1:0
5	**9a**	**1d**	**10d** R^1 = OMe, R^2 = CO_2Me	neat	2	54	1:0
6	**9a**	**1d**	**10d** R^1 = OMe, R^2 = CO_2Me	MeCN	2	68	1:0
7	**9a**	**1e**	**10e** R^1 = OEt, R^2 = $CONH_2$	MeCN	5	54	1:0
8	**9a**	**1f**	**10f** R^1 = NMe_2, R^2 = CONHPh	MeCN	9	74	1:0
9	**9a**	**1g**	**10g** R^1 = OMe, R^2 = 4-$NO_2C_6H_4$	MeCN	9	86	1:0
							
10	**9b**	**1a**	**11a** R^1 = OMe, R^2 = CONHPh	MeCN	3	66	1:0
11	**9b**	**1b**	**11b** R^1 = OMe, R^2 = CO_2tBu	neat	3	61	1:0
12	**9b**	**1b**	**11b** R^1 = OMe, R^2 = CO_2tBu	MeCN	3	72	1:0
13	**9b**	**1d**	**11d** R^1 = OMe, R^2 = CO_2Me	MeCN	3	67	1:0
14	**9b**	**1e**	**11e** R^1 = OEt, R^2 = $CONH_2$	MeCN	3	78	1:0
							
15	**9c**	**1a**	**12a** R^1 = OMe, R^2 = CONHPh	MeCN	3	76	1:0
16	**9c**	**1b**	**12b** R^1 = OMe, R^2 = CO_2tBu	neat	3	80	1:0
17	**9c**	**1b**	**12b** R^1 = OMe, R^2 = CO_2tBu	MeCN	3	82	1:0
18	**9c**	**1d**	**12d** R^1 = OMe, R^2 = CO_2Me	MeCN	3	80	1:0
19	**9c**	**1e**	**12e** R^1 = OEt, R^2 = $CONH_2$	MeCN	3	74	1:0
							
20	**9d**	**1a**	**13a** R^1 = OMe, R^2 = CONHPh	MeCN	9	74	8:1
21	**9d**	**1b**	**13b** R^1 = OMe, R^2 = CO_2tBu	neat	3	76	1:1
22	**9d**	**1b**	**13b** R^1 = OMe, R^2 = CO_2tBu	MeCN	9	77	3:2
23	**9d**	**1d**	**13d** R^1 = OMe, R^2 = CO_2Me	MeCN	9	72	1:1
							
24	**9e**	**1b**	**14b** R^1 = OMe, R^2 = CO_2tBu	neat	2	77	1:1
25	**9e**	**1b**	**14b** R^1 = OMe, R^2 = CO_2tBu	MeCN	9	68	1:1

[a] Isolated yield. [b] Obtained from the ^{1}H NMR of the crude reaction mixture.

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The cycloadducts **13b,d** and **14b**, obtained as 1:1 mixtures of isomers were separated by semipreparative HPLC. NOESY experiments confirmed the same relative configuration at the isoxazolidine ring for both isomers thus confirming the achievement of epimers at C-3 of the isoxazolidine ring (Figure 1, blue arrows). Due to the rotation of the bond Cα-C3 in **13** and **14** the absolute configuration of each epimer could not be unambigously assigned by NMR studies (for a tentative assignment see Supporting Information).

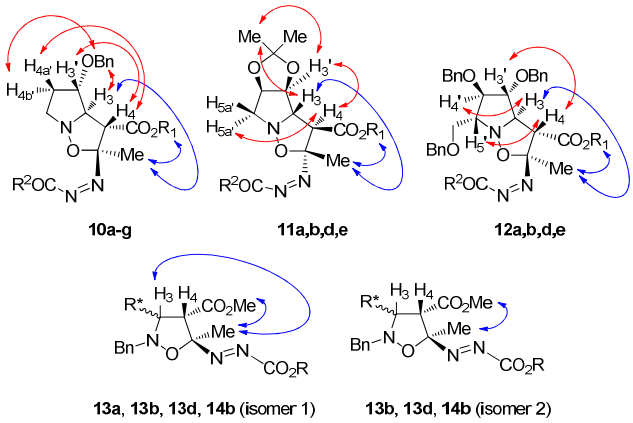


Figure 1 NOE relationships in cycloadducts. Blue and red interactions are related to relative and absolute configurations, respectively (see text), of the new formed isoxazolidine ring (for R^1, R^2 and R* see Table 2)

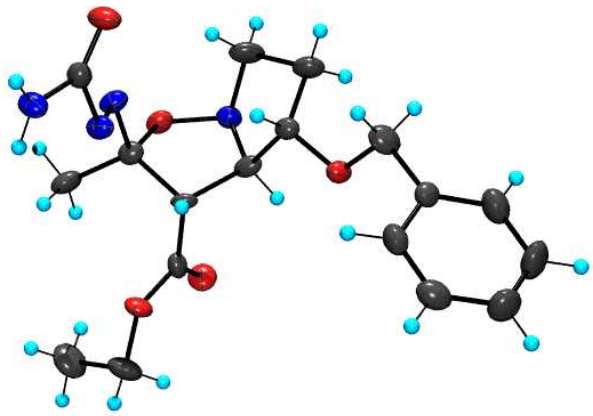


Figure 2 ORTEP representation of **10e**. Ellipsoids displayed at 50% probability.

In addition to the thermal conditions described above, two further additional approaches in an attempt to improve the cycloaddition reactions were explored: microwave irradiation and Lewis acid catalysis. With regard to Lewis acid, various catalysts including $MgBr_2$, $Zn(OTf)_2$, $ZnBr_2$, CuOTf, AgOTf, $Sc(OTf)_3$ and $Yb(OTf)_3$ were used in both catalytic and stoichiometric amounts. The ^1H NMR analysis of the corresponding reaction mixtures only revealed the disappearance of the DD and the complete recovery of the starting nitrone. Any attempt of isolating and/or identifying (by NMR of the crude mixture) any significative product derived from DDs failed and only complex mixtures were obtained. From these reaction mixtures only the starting nitrone could be recovered through column chromatography, likely due to the simple decomposition of starting DDs. The 1,3-dipolar cycloaddition between a nitrone and a DD is expected to be a normal-demand cycloaddition reaction, thus being controlled by a LUMO(dipolarophile)–HOMO(dipole) interaction. Accordingly, coordination of the Lewis acid to the dipolarophile (DD) should enhance the reactivity by lowering LUMO (dipolarophile) energy. DDs **1** bearing ester and/or amide groups have the possibility of forming chelates with Lewis acids thus favoring their coordination instead of undesired coordination of the nitrone species. Recovering of unreacted nitrone and disappearance of the DD is in agreement with the coordination of the latter but, unfortunately, also indicates the instability of DDs complexed with Lewis acids under reaction conditions. Indeed, parallel experiments subjecting DDs **1** in the presence of Lewis acids at 60ºC in MeCN and in the absence of nitrones showed, after 3 h, the complete disappearance of compounds **1**. Any attempt of recovering **1** from the reaction mixture by eliminating the Lewis acid was unsuccessful supporting the hypothesis of the above mentioned instability of **1** in the presence of Lewis acids.

Microwave irradiation (300 W, Tmax = 70 ºC) decreased dramatically the reaction time of the cycloadditions (Table 3).

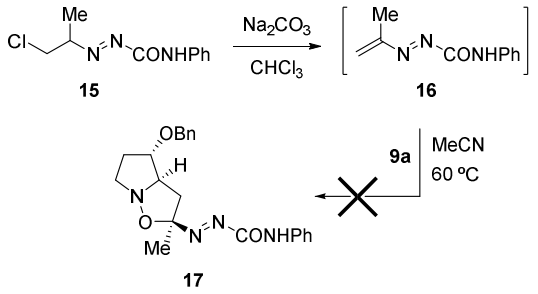
Table 3. Cycloaddition between nitrones **9** and DDs **1** under microwave irradiation.[a]

entry	nitrone	diazadiene	adduct	t (s)	Yield (%)[b]	dr[c]
1	**9a**	**1a**	**10a**	60	80	9:1
2	**9a**	**1b**	**10b**	60	73	5:1
3	**9a**	**1d**	**10d**	42	69	1:0
4	**9b**	**1a**	**11a**	62	68	1:0
5	**9b**	**1b**	**11b**	80	82	1:0
6	**9b**	**1d**	**11d**	100	80	1:0
7	**9c**	**1a**	**12a**	72	88	9:1
8	**9c**	**1b**	**12b**	72	86	5:1
9	**9c**	**1d**	**12d**	118	90	9:1
10	**9d**	**1a**	**13a**	240	75	1:1
11	**9d**	**1b**	**13b**	240	79	1:1
12	**9d**	**1d**	**13d**	240	78	1:1

[a] Reaction conditions: ratio **9**/**1** 1:1, neat, T_{max} 70ºC, 300 W. [b] Isolated yield. [c] obtained from the ^1H NMR of the crude reaction mixture.

For instance, in the case of the cycloaddition between nitrone **9a** and diazadiene **1b** (Table 3, entry 2), the reaction time decreased from 9 h to 1 min. In some cases, however, the NMR analysis of the crude mixture revealed the presence of a minor isomer (Table 3, entries 1-3 and 7-12) indicating a slightly lower selectivity with respect to thermal reactions. Also, in other cases, the chemical yield decreased considerably (Table 3, entries 4, 6 and 7). In all cases, the reactions were carried out without solvent and with a 1:1 ratio of nitrone/DD, what might contribute to the appearance of a minor isomer in some cases. Under microwave irradiation, the use of a 1:2 ratio of nitrone/DD did not enhance the chemical yield of the reaction and resulted in a more complex reaction mixture.

In order to evaluate the electronic influence of the substituents on sterical and electronic properties we replaced substituents by their most simplified version, when possible (due to stability of DDs). Thus, we attempted the reaction between DD **16**, generated *in situ* from precursor **15**, and cyclic nitrone **9a** (Scheme 3). However, under optimized conditions (MeCN or neat, 60 ºC, with or without MW irradiaton) no reaction was observed in any case, the starting nitrone being recovered almost completely, while degradation products deriving from DD were detected. This result evidences the necessity of using stabilized DDs with appropriate EWGs on the terminal carbon and nitrogen atoms of the azo-ene system that have been shown to enhance both stability and electrophilicity, such as compounds **1a-g**.[24]



Scheme 3 Cycloaddition between nitrone **9a** and DD **16**.

Theoretical Study

Computational Methods

Computations with density functional theory (DFT) were done using the exchange-correlation functional B3LYP[25]and Truhlar's functional M06-2X.[26] Standard basis sets 6-31G(d), 6-311G(d,p)[27] and ccpVTZ[28] were employed. For 3ζ optimizations with the B3LYP functional the recently developed[29] GD3BJ empirical correction for dispersion interactions was included. The nature of stationary points was defined on the basis of calculations of normal vibrational frequencies (force constant Hessian matrix). The optimizations were carried out using the Berny analytical gradient optimization method.[30] Minimum energy pathways for the reactions studied were found by gradient descent of transition states in the forward and backward direction of the transition vector (IRC analysis),[31] using the second order González–Schlegel integration method.[32] The solvent (MeCN) effects modeled as a continuum model were considered in all cases based on the polarizable continuum model (PCM) of Tomasi's group.[33] In previous work,[34] calculations using B3LYP functional failed in predicting the correct selectivity and thermodynamics of the reaction, even though recent studies[35] have demonstrated that B3LYP performed very well for geometries, in particular for cycloaddition reactions.[36] On the other hand, a recent report[37] conclude that M06-2X calculations provide best geometries than B3LYP. Thus, for the purpose of comparison the following 2ζ levels of theory were calculated for full optimizations: i) B3LYP/6-31G(d)/PCM=MeCN (level 1) and ii) M06-2X/6-31G(d)/PCM=MeCN. Single point calculations were carried out at a 3ζ level basis set and considering inclusion of diffuse functions as well as the same solvent; thus, single point calculations were carried out at M06-2X/6-311+G(d,p)/PCM=MeCN level using geometries calculated at M06-2X/6-31G(d)/PCM=MeCN (level 3). Finally, full optimizations at 3ζ levels were also carried out: B3LYP-GD3BJ/6-311G(dp)/PCM=MeCN (level 4) and M06-2X/cc-pVTZ/PCM=MeCN (level 5). Reactivity indices were calculated at M06-2X/6-311+G(d,p)/PCM=MeCN level of theory. All calculations were carried out with the Gaussian 09 suite of programs.[38] Structural representations were generated using CYLview.[39] Consistently with the experimental work and regarding the computational costs, the only changes made in the model is the use of methyl groups instead benzyl groups. The rest of the molecules have been preserved. We have studied regio- and stereoselectivity for the reaction between nitrones **N1** and **N2** (as models of nitrones **9a** and **9d**, respectively), and DDs **D1**(**1d**) and **D2**(**1c**) (Figure 3). For DDs **D1** and **D2** a total of eight conformations have been calculated.[40] Once evaluated the stability of reactants the most stable conformations have been chosen for performing the study. Figure 3 displays the conformational features of the DDs. These conformations have been further employed for locating the corresponding transition states.

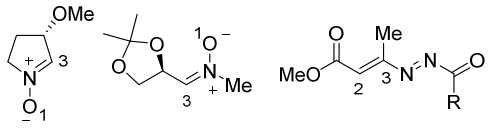


Figure 3. Reactants used in the theoretical study

Analysis based on reactivity indices

The 1,3-dipolar cycloadditions between nitrones **N1** and **N2**, and DDs **D1** and **D2** have been analyzed using the global indexes, as defined in the context of DFT,[41] which are useful tools to understand the reactivity of molecules in their ground states. For details and how to calculate the various reactivity indices, see Supporting Information. The values of μ,η, S and

ω for compounds **N1**, **N2**, **D1** and **D2**, calculated with the reported formulas, are listed in Table 4. The global electrophilicty indices (ω) for nitrones (1.04 and 1.05 for **N1** and **N2**, respectively) are lower than those of DDs (2.36 and 2.30 for **D1** and **D2**, respectively) indicating a normal demand character for the 1,3-dipolar cycloadditon reaction in which the nitrone acts as the nucleophile. In the same way, the electronic chemical potential, μ, of nitrones **N1** and **N2** is higher (-0.1501 and -0.1507) than that of the dipolarophiles **D1** and **D2** (2.0028 and 2.0581), thereby indicating that a net charge transfer will take place from the dipole (nitrone) to the dipolarophile (DD), i.e. HOMO(dipole)-LUMO(dipolarophile) interaction, in agreement with a normal-demand 1,3-dipolar cycloaddition.

Table 4 HOMO, LUMO and global properties (HOMO, LUMO, electronic chemical potential μ, chemical hardness η and chemical softness S values are in a.u.; electrophilicity power ω values are in eV) for nitrones and DDs calculated at M06-2X/6-311+G(d,p)/PCM=THF level.

	HOMO	LUMO	μ	η	S	ω	ΔN_{max}
N1	-0.29789	-0.00226	-0.1501	0.2956	1.6913	1.04	0.508
N2	-0.29824	-0.00320	-0.1507	0.2950	1.6947	1.05	0.511
D1	-0.33275	-0.08310	-0.2079	0.2497	2.0028	2.36	0.833
D2	-0.32428	-0.08134	-0.2028	0.2429	2.0581	2.30	0.835

The regioselectivity of the reaction can be predicted by considering that in a polar cycloaddition reaction between non-symmetrical compounds, the most favorable interaction is that between the most nucleophilic center of the nucleophile (characterized by the highest condensed Fukui function for electrophilic attack f_k^-) and the most electrophilic center of the electrophile (characterized by the highest local electrophilicity index ωk). The local electrophilic indices (ω_k) and the condensed Fukui functions (f_k^+ and f_k^-) of nitrones **N1** and **N2**, and DDs **D1** and **D2** are collected in Table 5.

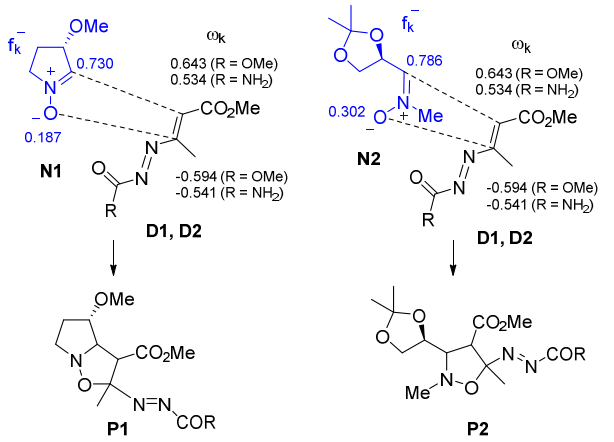
For DDs **D1** and **D2**, **C2** has the higher local electrophilicity index, ω_k thus being the preferred site for the nucleophilic attack of the nitrone. For nitrones **N1** and **N2** the carbon atom has higher f_k^- than the oxygen atom. Consequently, **C2** will be linked to the nitrone carbon atom predicting the formation of adducts **P1** and **P2**, respectively (Scheme 4), in complete agreement with the experimental findings.

Table 5 Calculated (M06-2X/6-311+G(d,p)/PCM=THF) reactivity indices of nitrones **N1** and **N2**, and DDs**D1** and **D2**. (k indicates the site at which the local property is evaluated according to Figure 3)

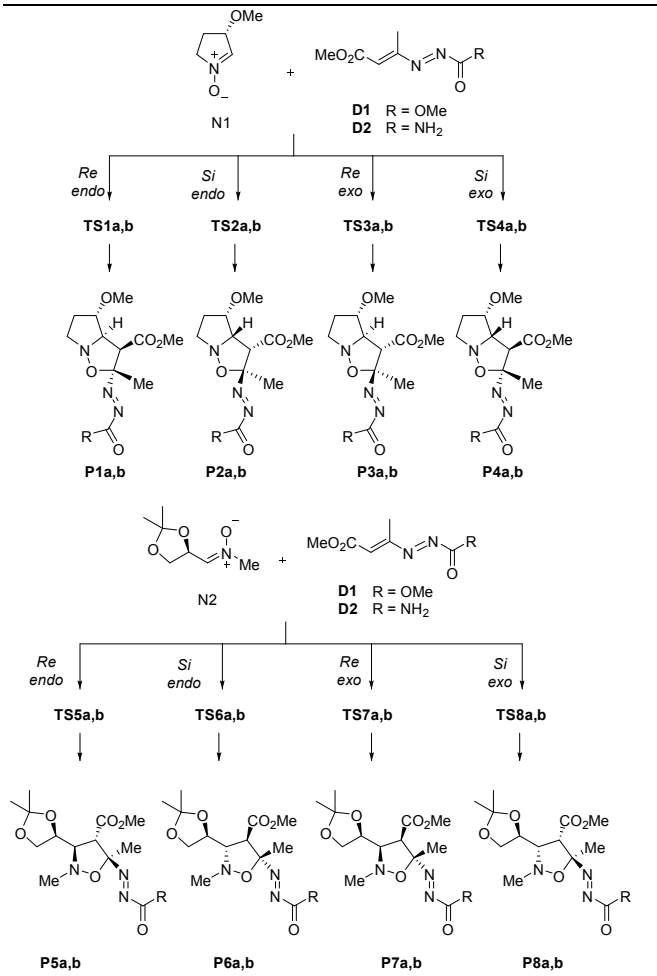
	k	ω_k	f_k^-	f_k^+
N1	O1	0.60	0.187	0.581
	C3	0.19	0.730	0.180
N2	O1	0.47	0.302	0.447
	C3	0.01	0.786	0.010
D1	C2	0.64	0.180	0.273
	C3	-0.59	-0.026	-0.252
D2	C2	0.53	0.176	0.232
	C3	-0.54	-0.044	-0.235

Analysis of transition structures

We have considered the formation of adducts predicted by the DFT analysis based on reactivity indices and observed experimentally. In consequence four model reactions have been studied (Scheme 5) corresponding to the cycloaddition between nitrones **N1** and **N2** and DDs **D1** and **D2**; *endo* and *exo* approaches to the nitrone by *Re* and *Si* faces completed the study. Consequently four transition states leading to the four possible cycloadducts have been located for each nitrone and dipolarophile (a total of 16 transition structures have been located). The nomenclature for defining stationary points is given in Scheme 5.



Scheme 4. Prediction of regioisomers on the basis of reactivity indices.



Scheme 5. Dipolar cycloadditions between nitrones **N1** and **N2**, and DDs **D1** and **D2**. *Re* and *Si* attacks refer to diastereofaces of the nitrones; *endo* and *exo* approaches refer to the methoxycarbonyl group; a and b series refer to R = OMe and R = NH_2, respectively.

Table 6. Calculated (PCM=MeCN/M06-2X/cc-pVTZ) free (ΔG, hartrees) and relative energies (ΔΔG, kcal·mol^{-1}) of the stationary points corresponding to the reaction of nitrone **N1** with DDs **D1** and **D2**.[a]

	ΔG	ΔΔG[b]		ΔG	ΔΔG[c]
N1	-400.937506		**N1**	-400.937506	
D1	-682.972361		**D2**	-623.828581	
C1a	-1083.892845	10.7	**C1b**	-1024.746127	12.5
C2a	-1083.894624	9.6	**C2b**	-1024.750889	9.5
C3a	-1083.892823	10.7	**C3b**	-1024.749485	10.4
C4a	-1083.895478	9.0	**C4b**	-1024.749139	10.6
TS1a	-1083.868630	25.9	**TS1b**	-1024.722840	27.1
TS2a	-1083.866330	27.3	**TS2b**	-1024.721385	28.1
TS3a	-1083.874825	22.0	**TS3b**	-1024.728752	23.4
TS4a	-1083.873403	22.9	**TS4b**	-1024.726466	24.9
P1a	-1083.913799	-2.5	**P1b**	-1024.767394	-0.8
P2a	-1083.908045	1.1	**P2b**	-1024.764285	1.1
P3a	-1083.908021	1.2	**P3b**	-1024.762595	2.2
P4a	-1083.922089	-7.7	**P4b**	-1024.776517	-6.5

[a] For nomenclature of stationary points see Scheme 5; **C1**, **C2**, **C3** and **C4** correspond to encounter complexes previous to the formation of **TS1**, **TS2**, **TS3** and **TS4**, respectively; **a** and **b** series correspond to the reactions of **N1** with **D1** and **D2**, respectively. [b]Referred to starting materials (**N1**+**D1**). [c]Referred to starting materials (**N1**+**D2**).

Table 7. Calculated (PCM=MeCN/M06-2X/cc-pVTZ) free (ΔG, hartrees) and relative energies (ΔΔG, kcal·mol^{-1}) of the stationary points corresponding to the reaction of nitrone **N2** with DDs **D1** and **D2**.[a]

	ΔG	ΔΔG[b]		ΔG	ΔΔG[c]
N2	-554.734824		**N2**	-554.734824	
D1	-682.972361		**D2**	-623.828581	
C5a	-1237.686327	13.1	**C5b**	-1178.541928	13.5
C6a	-1237.686152	13.2	**C6b**	-1178.545108	11.5
C7a	-1237.683416	14.9	**C7b**	-1178.539856	14.8
C8a	-1237.688901	11.5	**C8b**	-1178.543609	12.4
TS5a	-1237.664292	26.9	**TS5b**	-1178.517506	28.8
TS6a	-1237.657486	31.2	**TS6b**	-1178.518166	28.4
TS7a	-1237.661424	28.7	**TS7b**	-1178.514804	30.5
TS8a	-1237.668002	24.6	**TS8b**	-1178.520479	26.9
P5a	-1237.726429	-12.1	**P5b**	-1178.579236	-9.9
P6a	-1237.723389	-10.2	**P6b**	-1178.577129	-8.6
P7a	-1237.721230	-8.8	**P7b**	-1178.574930	-7.2
P8a	-1237.719691	-7.8	**P8b**	-1178.574580	-7.0

[a] For nomenclature of stationary points see Scheme 5; **C5**, **C6**, **C7** and **C8** correspond to encounter complexes previous to the formation of **TS5**, **TS6**, **TS7** and **TS8**, respectively; **a** and **b** series correspond to the reactions of **N2** with **D1** and **D2**, respectively. [b]Referred to starting materials (**N2**+**D1**). [c]Referred to starting materials (**N2**+**D2**).

The absolute and relative free and electronic energies with respect to reactants for the 16 transition structures located are collected in Table 6 for the reaction between nitrone **N1** and DDs **D1** and **D2,** and in Table 7 for the reaction between nitrone **N2** and DDs **D1** and **D2**. Starting situations, consisting

of calculation of the encounter complexes **C1a,b-C8a,b** using as initial geometries those provided by IRC calculations (see Supporting Information) have also been included. The energy differences between products and reactants are given, too. The geometry of the transition structures for the reaction between nitrone **N1** and DDs **D1** and **D2** are given in Figures 4 and 5, respectively, and for the reaction between nitrone **N2** and DDs **D1** and **D2** in Figures 6 and 7, respectively.

The energy values were calculated at five levels of theory, considering solvent effects (PCM=MeCN) in all cases: i) B3LYP/6-31G(d), ii) M06-2X/6-31G(d), iii) M06-2X/6-311+G(d,p)//M06-2X/6-31G(d), iv) B3LYP-GD3BJ/6-311G(dp) and v) M06-2X/cc-pVTZ.[43] All the discussions will be based on the highest level used (PCM=MeCN/M06-2X/cc-pVTZ). The analysis of relative free energies (ΔG) shows that, in general,*exo* attacks (referred to the ester group) are preferred to the corresponding *endo* approaches.[42]

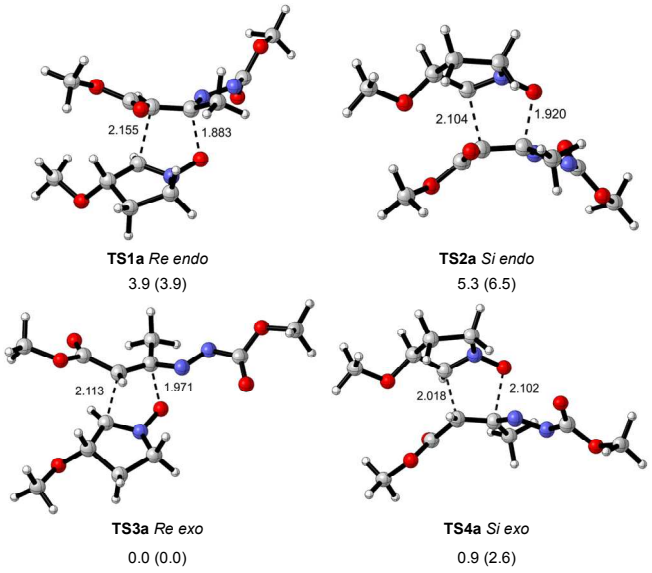


Figure 4. Transition structures (PCM=MeCN/M06-2X/6-31G(d))corresponding to the reaction between **N1** and **D1**. **TS1a**, **TS2a**, **TS3a** and **TS4a** correspond to *Re endo*, *Si endo*, *Re exo* and *Si exo* approaches leading to**P1a**, **P2a**, **P3a** and **P4a**. Relative energy values between TSs referenced to isolated reagents and the corresponding encounter complexes (in brackets) are calculated at PCM=MeCN/M06-2X/cc-pVTZ level on theory and given in kcal/mol. Bond distances are given in Å.

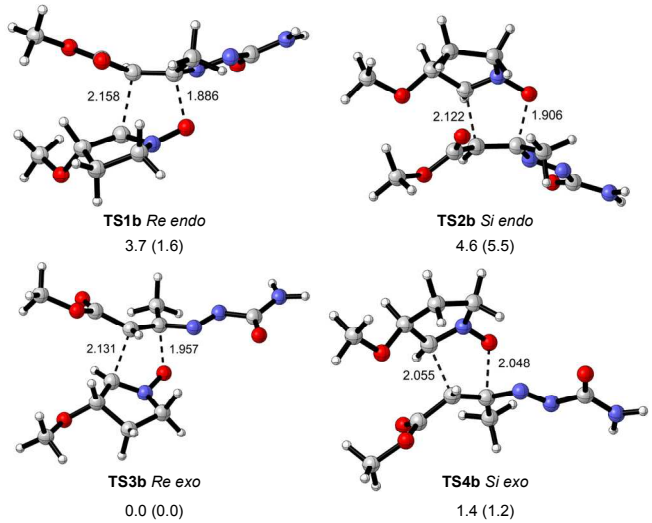


Figure 5. Transition structures (PCM=MeCN/M06-2X/6-31G(d))corresponding to the reaction between **N1** and **D2**. **TS1b**, **TS2b**, **TS3b** and **TS4b** correspond to *Re endo*, *Si endo*, *Re exo* and *Si exo* approaches leading to**P1b**, **P2b**, **P3b** and **P4b**. Relative energy values between TSs referenced to isolated reagents and the corresponding encounter complexes (in brackets) are calculated at PCM=MeCN/M06-2X/cc-pVTZ level on theory and given in kcal/mol. Bond distances are given in Å.

For cycloadditions of cyclic nitrone **N1** with DDs **D1** and **D2** all levels predict the *Re exo* approach as the preferred one. The barrier for the cycloaddition between **N1** and **D1** is 22.0 kcal/mol and the barrier for the cycloaddition between **N1** and **D2** is 23.4 kcal/mol. These results, predicting the formation of **P3a,b**(from a *Re exo*attack) are in good qualitative agreement with the experimental observations even though the small observed energy differences between transition states (less than 1.5 kcal/mol, within the experimental error) are more in agreement with the obtention of mixtures of isomers instead only one isomer as actually takes place. In this regard, all the calculations fail in predicting the observed complete diastereoselectivity. Initially, it should be possible to think that such a discrepancy might arise of using a methyl group instead the real benzyl group which could lead to higher energy differences between transition structures. However, we have calculated the stationary points corresponding to cycloaddition reactions of **9a** at level 4 (PCM=MeCN/B3LYP-GD3BJ/6-311G(dp)), including reagents, transition structures and products,and quite similar values (differences of 0.8 and 2.5 kcal/mol between the two more stable TSs for the reaction with **D1** and **D2**, respectively) to those obtained for **N1** have been obtained (see Supporting information). These data support the validity of our model and demonstrate that the failure in quantitative prediction is inherent to the calculation.[44] As expected for a cyclic biased system like nitrone **N1** the qualitatively predicted diastereoselectivity is in agreement with the addition of the dipolarophile by the less hindered *Re* face.

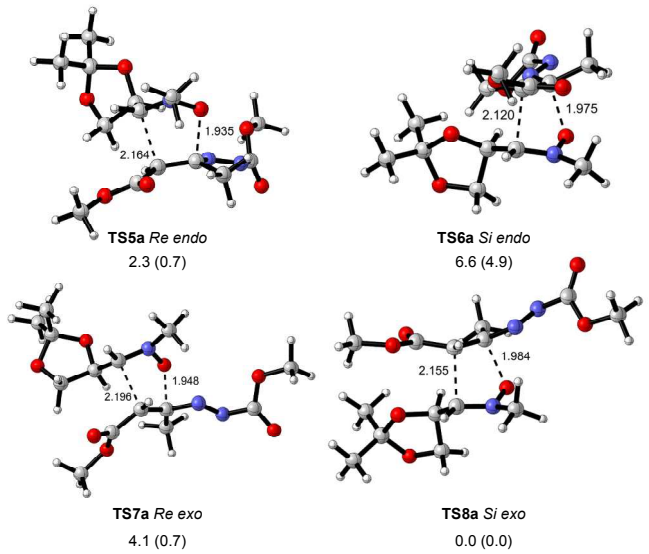


Figure 6. Transition structures (PCM=MeCN/M06-2X/6-31G(d))corresponding to the reaction between **N2** and **D1**. **TS5a**, **TS6a**, **TS7a** and **TS8a** correspond to *Re endo*, *Si endo*, *Re exo* and *Si exo* approaches leading to**P5a**, **P6a**, **P7a** and **P8a**. Relative energy values between TSs referenced to isolated reagents and the corresponding encounter complexes (in brackets) are calculated at PCM=MeCN/M06-2X/cc-pVTZ level on theory and given in kcal/mol. Bond distances are given in Å.

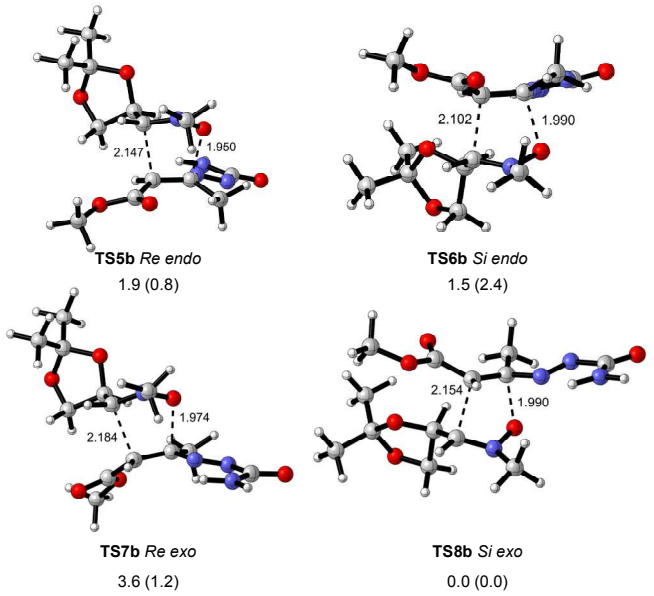


Figure 7. Transition structures (PCM=MeCN/M06-2X/6-31G(d))corresponding to the reaction between **N2** and **D2**. **TS5b**, **TS6b**, **TS7b** and **TS8b** correspond to *Re endo*, *Si endo*, *Re exo* and *Si exo* approaches leading to**P5b**, **P6b**, **P7b** and **P8b**. Relative energy values between TSs referenced to isolated reagents and the corresponding encounter complexes (in brackets) are calculated at PCM=MeCN/M06-2X/cc-pVTZ level on theory and given in kcal/mol. Bond distances are given in Å.

The preference by the *exo* approach with respect to the methoxycarbonyl group is a consequence of the presence of the diazo moiety which acts as directing-electron-withdrawing group and, as expected for normal-demand 1,3-dipolar cycloadditions, is oriented *endo* with respect to the dipole. For the acyclic nitrone **N2**, the barrier for the cycloaddition with **D1** is 24.6 kcal/mol and the barrier for the cycloaddition with **D2** is 26.9 kcal/mol. In this case, the differences observed between transition states (ca. 1.5-2.0 kcal/mol) are in agreement with the observed obtention of mixtures of isomers although there is a clear preference for the obtention of adducts **P8a,b** coming from a *Si exo* attack. Again, the preference by the *exo* approach with respect to the methoxycarbonyl group is a consequence of the presence of the diazo moiety which is oriented *endo* with respect to the dipole. The diastereofacial selectivity is in agreement with a classical Houk model in which the methylene and oxygen groups are placed as large and medium ones, respectively.

All the transition states are concerted asynchronous as expected for a typical normal-demand 1,3-dipolar cycloaddition. In the case of cyclic nitrone **N**1 the C-O forming bonds are in the range of 1.88-2.10 Å and the C-C forming bonds in the range of 2.02-2.16 Å. For nitrone **N2** the C-O forming bonds are in the range of 1.94-1.99 Å and the C-C forming bonds in the range of 2.10-2.20 Å. The geometry of the transition structures is very similar independently of the DD.

In general, shorter C-O forming bonds were found for the *endo* approaches. The C-C forming bonds were, however, shorter for the *exo* approaches. The same trend was observed for both nitrones **N1** and **N2** although with higher differences in the case of the cyclic one **N1**. A More O'Ferrall-Jencks plot[45] using as reaction coordinates C-C and C-O forming bonds can be employed for better understand the transition state variation depending on the DD and the orientation between the reagents. In order to evaluate in a realistic way the asynchronicity of the reaction, relative values (in %) to standard C-C (1.55 Å) and C-O (1.41 Å) bonds in isoxazolidines are used. The More O'Ferrall-Jencks diagrams for the cycloaddition reactions of **N1** and **N2** are given in Figures 8 and 9, respectively.

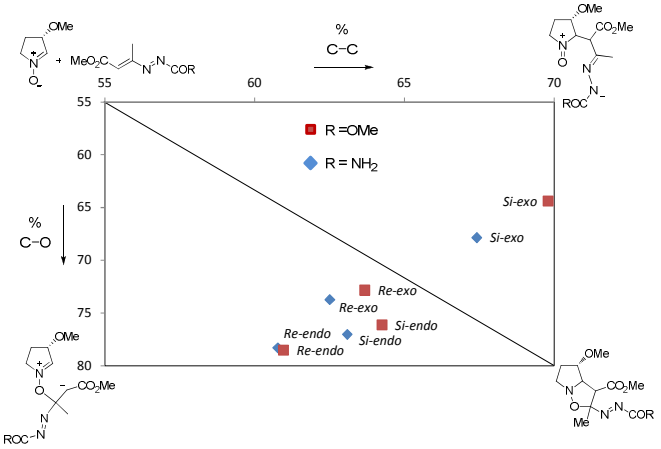


Figure 7. More O'Ferrall-Jencks diagram representing the cycloaddition between **N1** and DDs **D1** and **D2**. The horizontal axis corresponds to the C-C bond, while the vertical axis corresponds to the C-O bond. *Re endo*, *Si endo*, *Re exo* and *Si exo* points corresponds to **TS1a,b**, **TS2a,b**, **TS3a,b** and **TS4a,b.**

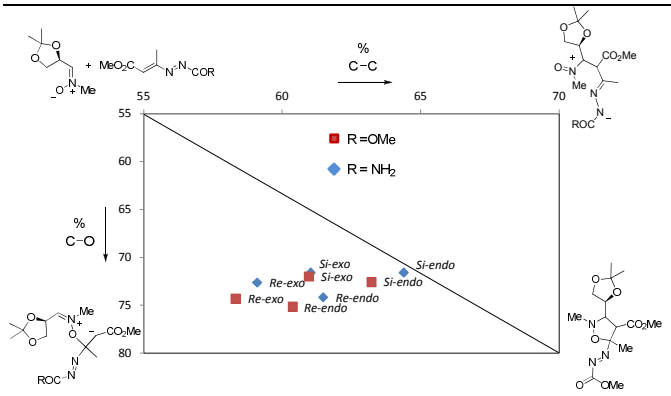


Figure 8. More O'Ferrall-Jencks diagram representing the cycloaddition between **N2** and DDs **D1** and **D2**. The horizontal axis corresponds to the C-C bond, while the vertical axis corresponds to the C-O bond.*Re endo*, *Si endo*, *Re exo* and *Si exo* points corresponds to **TS5a,b**, **TS6a,b**, **TS7a,b** and **TS8a,b.**

In the case of nitrone **N1** the difference between transition structures corresponding to a *Si-exo* attack (**TS4a,b**) and the rest of transition states is evident for both DDs **D1** and **D2**. Only in **TS4a** and **TS4b** the C-C bond is being formed more rapidly that the C-O bond. Notably, **TS4a** and **TS4b** are those which are close in energy to the experimentally preferred (and theoretically qualitatively predicted) *Re-exo* transition states **TS3a** and **TS3b**. This unexpected behaviour could be the origin for the inaccuracy observed in theoretical calculations for predicting quantitatively the diastereoselectivity of the reaction. For **TS1a,b**, **TS2a,b** and **TS3a,b** the C-O bond is formed more rapidly than the C-C bond. **TS1a** and **TS1b** corresponding to a *Re-exo* attack are the more asynchronous transition states for these reactions. On the other hand, similar situations regarding asynchronicity are found for the reactions of nitrone **N2**. For this nitrone, however, the C-O bond is formed more rapidly that the C-C bond in all cases, the less asynchronous transition states being **TS6a** and **TS6b**, corresponding to a *Si-endo* attack.

Conclusions

Diastereoselective 1,3-dipolar cycloadditions of chiral non-racemic nitrones with DDs have been studied both experimental and theoretically. Whereas cyclic nitrones only afforded one isomer showing a complete regio- diastereo- and enantioselectivity acyclic nitrones led to a 1:1 mixture of two isomers. Theoretical calculations based on reactivity indices correctly predict the regioselectivity of the cycloaddition reactions. The analysis of transition structures calculated at 3 3ζ levels of theory, i.e., M06-2X/6-311+G(d,p)//M06-2X/6-31G(d), B3LYP-GD3BJ/6-311G(dp) and M06-2X/cc-pVTZ, considering solvent effects (PCM=MeCN) in all cases, are in qualitative agreement with the observed experimental results. Noteworthy, while the complete diasereoselectivity observed for **N1** is not exactly predicted by the calculations, the obtention of diastereomeric mixtures observed for **N2** is correctly predicted in all cases. The geometry of the transition structures corresponds to typical asynchronous processes as confirmed by the corresponding More Jenks-O'Ferral diagram analyses. Further elaborations of the obtained cycloadducts will allow the preparation of a variety of heterocyclic systems and it will be reported on due course.

Experimental Section

The reaction flasks and other glass equipment were heated in an oven at 130 °C overnight and assembled in a stream of Ar. All reactions were monitored by TLC on silica gel 60 F254; the position of the spots were detected with 254 nm UV light or by spraying with either 5% ethanolicphosphomolybdic acid. Column chromatography was carried out in a Buchi 800 MPLC system or a Combiflash apparatus, using silica gel 60 microns and with solvents distilled prior to use. Melting points were uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on BrukerAvance 300, 400 or 500 instruments in the stated solvent. Chemical shifts are reported in ppm (δ) relative to $CHCl_3$ (δ = 7.26) in $CDCl_3$. Optical rotations were taken on a JASCO DIP-370 polarimeter. Elemental analysis were performed on a Perkin Elmer 240B microanalyzer or with a Perkin-Elmer 2400 instrument. The microwave reactions were carried out with a Discover Focused Microwave System (CEM Corporation)

General Procedure for the thermal cycloaddition between DDs 1 and nitrones 9.

A solution of the corresponding 1,2-diaza-1,3-diene **1** (2.0 mmol) and nitrone **9** (1 mmol) in dry acetonitrile (8 mL) was heated at 60 ºC in a sealed tube for the stated time (Table 2). The reaction mixture was cooled at room temperature, the solvent evaporated at reduced pressure and the crude product was purifiedby column chromatography (hexane/EtOAc, 3:2) to yield the pure product.

(2S,3S,3aR,4S)-methyl 4-(benzyloxy)-2-methyl-2-((phenylcarbamoyl)diazenyl)hexahydropyrrolo[1,2-b]isoxazole-3-carboxylate 10a

(0.4 g, 91%); oil. $[\alpha]^{25}_{D}$ +12 (c 1.3, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.48 (s,3H), 1.89–1.96 (m, 1H), 2.21–2.31 (m, 1H), 3.27–3.36 (m, 1H), 3.46–3.53 (m, 1H), 3.60 (d, 1H, J = 5.9 Hz), 3.78 (s, 3H), 3.89–3.93 (m, 1H), 4.37 (dd, 1H, J = 2.3, 5.9 Hz), 4.48 and 4.52 (AB system, 2H, J = 11.9Hz), 7.20–7.24 (m, 1H), 7.27–7.35 (m, 5H),7.39–7.43 (m, 2H), 7.64–7.67 (m, 1H), 0.11 (br s,1H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 18.9, 52.6,55.8, 58.6, 71.3, 74.1, 82.2, 107.5, 125.5, 127.6, 127.7, 128.3, 128.4, 129.3, 136.3, 137.6, 156.0, 169.6. Anal. Calcd for $C_{23}H_{26}N_4O_5$: C, 63.00; H, 5.98; N, 12.78; O, 18.24. Found: 63.12, H 6.14, N 12.55.

(2S,3S,3aR,4S)-methyl 4-(benzyloxy)-2-((tert-butoxycarbonyl)diazenyl)-2-methylhexahydropyrrolo[1,2-b]isoxazole-3-carboxylate 10b

(0.327 g, 78%); yellow oil. $[\alpha]^{25}_{D}$ +10 (c 1.7, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.39 (s, 3H), 1.59 (s, 9H), 1.84–1.91 (m,

1H), 2.16–2.25 (m, 1H), 3.25–3.31(m, 1H), 3.47 (dt, 1H, J = 7.2, 12.5 Hz), 3.54 (d, 1H, J = 5.2), 3.77 (s, 3H), 3.85–3.88 (m, 1H), 4.30 (dd, 1H, ^3J =2.6, 5.4),4.46 and 4.51 (AB system, 2H, J = 11.9 Hz), 7.28–7.35 (d, 2H, J = 7.2 Hz), 9.01 (s, 1H), 10.03 (s, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 18.6, 27.7, 52.4, 55.7, 58.1, 71.3, 74,0 82.5, 85.9, 107.6, 127,7 128.3, 137.6, 160.3, 169.8. Anal. Calcd for $C_{21}H_{29}N_3O_6$: C, 60.13; H, 6.97; N, 10.02; O, 22.89. Found: 59.94, H 6.86, N 10.27.

(2S,3S,3aR,4S)-methyl 4-(benzyloxy)-2-(carbamoyldiazenyl)-2-methylhexahydropyrrolo[1,2-b]isoxazole-3-carboxylate 10c

(0.188 g, 52%); yellow solid. mp 86-88 ºC. $[\alpha]^{25}_D$ +8 (c 1.2, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.43 (s, 3H), 1.88–1.96 (m, 1H), 2.19–2.28 (m, 1H), 3.34-3.51 (m, 1H), 3.53 (d, 1H, J = 6.0 Hz), 3.77 (s, 3H), 3.87–3.91 (m, 1H), 4.35 (dd, 1H, J = 2.3, 6.0 Hz), 4.47 and 4.53 (AB system, 2H, J = 11.9 Hz), 5.58 (br s, 1H), 5,94 (br s, 1H), 7.28–7.36 (m, 5H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 18.8, 52.6, 55.7, 58.3, 71.3, 74.1, 82.2, 107.5, 127.6, 127.7, 128.5, 137.6, 161.2, 169.6. Anal. Calcd for $C_{17}H_{22}N_4O_5$: C, 56.34; H, 6.12; N, 15.46; O, 22.08. Found: 56.48, H 6.21, N 15.36.

(2S,3S,3aR,4S)-methyl 4-(benzyloxy)-2-((methoxycarbonyl)diazenyl)-2-methylhexahydropyrrolo[1,2-b]isoxazole-3-carboxylate 10d

(0.257 g, 68%); yellow oil. $[\alpha]^{25}_D$ -11 (c 0.6, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.40 (s, 3H), 1.86–1.93 (m, 1H), 2.18-2.27 (m, 1H), 3.22–3.29 (m, 1H), 3.44–3.50 (m, 2H), 3.77 (s, 3H), 3.86-3.90 (m, 1H), 4.00 (s, 3H), 4.33 (dd, 1H, J = 2.3, 5.7 Hz), 4.49 (AB system, 2H, J = 11.9, 19.7 Hz), 7.27-7.35 (m, 5H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 18.6, 52.6, 55.0, 55.8, 58.3, 71.4, 74.1, 82.4, 107.9, 127.7, 127.8, 128.4, 137.7, 162.0, 169.6. Anal. Calcd for $C_{18}H_{23}N_3O_6$: C, 57.29; H, 6.14; N, 11.13; O, 25.44. Found: 57.39, H 6.11, N 10.92.

(2S,3S,3aR,4S)-ethyl 4-(benzyloxy)-2-(carbamoyldiazenyl)-2-methylhexahydropyrrolo[1,2-b]isoxazole-3-carboxylate 10e

(0.203 g, 54%); white solid. mp 110-112 ºC. $[\alpha]^{25}_D$ +8 (c 1.2, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.29 (t, 3H, J = 7.1 Hz), 1.45 (s, 3H), 1.88–1.92 (m, 1H), 2.20–2.28 (m, 1H), 3.23–3.29 (m, 1H), 3.44–3.51 (m, 2H), 3.88–3.91 (m, 1H), 4.18–4.28 (m, 2H), 4.36 (dd, 1H, J = 2.2, 6.2 Hz), 4.47 and 4.55 (AB system, 2H, J = 11.9 Hz), 5.71 (br s, 1H), 5.99 (br s, 1H), 7.28–7.36 (m,5H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.1, 18.4, 57.7.58.2, 61.7, 65.7, 71.2, 73.9, 82.2, 107.4, 127.6, 127.7, 128.4, 137.6, 161.3, 169.0. Anal. Calcd for $C_{18}H_{24}N_4O_5$: C, 57.44; H, 6.43; N, 14.88; O, 21.25. Found: 57.37, H 6.50, N 14.96.

(2S,3S,3aR,4S)-4-(benzyloxy)-N,N,2-trimethyl-2-((phenylcarbamoyl)diazenyl)hexahydropyrrolo[1,2-b]isoxazole-3-carboxamide 10f

(0.334 g, 74%); oil. $[\alpha]^{25}_D$ +9 (c 1.4, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.44 (s,3H), 1.90–1.98 (m, 1H), 2.25–2.33 (m, 1H), 2.99 (s, 3H), 3.04 (s, 3H), 3.08–3.15 (m, 1H), 3.47–3.53 (m, 1H), 3.76 (d, 1H, J = 7.4 Hz), 3.87–3.90 (m, 1H), 4.23 and 4.59 (AB system, 2H, J = 12.0 Hz) 4.71 (dd, 1H, J = 1.2, 7.3 Hz), 7.18–7.22 (m, 1H), 7.27–7.36 (m, 5H), 7.39 (t, 2H, J = 8.0 Hz), 7.66 (d, 2H, J = 8.5 Hz),8.42 (br s,1H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 19.2, 36.3, 37.8, 55.5, 55.7, 71.1, 74.7, 80.9, 113.9, 119.6, 125.5, 127.7, 127.8, 127.9, 128.3, 129.3, 136.3, 137.7, 167.5. Anal. Calcd for $C_{24}H_{29}N_5O_4$: C, 63.84; H, 6.47; N, 15.51; O, 14.17. Found: 63.97, H 6.62, N 15.36.

(2S,3S,3aR,4S)-methyl 4-(benzyloxy)-2-methyl-2-((E)-(4-nitrophenyl)diazenyl)hexahydropyrrolo[1,2-b]isoxazole-3-carboxylate 10g

(0.379 g, 86 %); orange powder. mp 58-60 ºC. $[\alpha]^{25}_D$ +19 (c 0.5, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.49 (s, 3H), 1.88-1.96 (m, 1H), 2.16-2.25 (m, 1H), 3.33-3.39 (m, 1H), 3.51 (dt, 1H, J = 7.3, 12.5 Hz), 3.63 (d, 1H, J = 5.5 Hz), 3.80 (s, 3H), 3.83-3.86 (m, 1H), 4.36 (dd, 1H, J = 2.6, 5.5 Hz), 4.48 and 4.51 (AB system, 2H, J = 12.1 Hz), 7.24-7.35 (m, 5H), 7.80 (d, 2H, J = 9.10Hz), 8.35 (d, 2H, J = 9.10 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 19.1, 52.6, 55.6, 58.6, 71.2, 74.1, 82.2, 107.7, 123.5, 124.8, 127.7, 127.8, 128.5, 137.7, 149.4, 170.0, 174.0. Anal. Calcd for $C_{22}H_{24}N_4O_6$: C, 59.99; H, 5.49; N, 12.72; O, 21.80. Found: 60.16, H 5.70, N 12.83.

(3aR,7S,8S,8aR,8bS)-methyl 2,2,7-trimethyl-7-((phenylcarbamoyl)diazenyl)hexahydro-[1,3]dioxolo[4',5':3,4]pyrrolo[1,2-b]isoxazole-8-carboxylate 11a

(0.267 g, 66%); yellow oil. $[\alpha]^{25}_D$ -21 (c 0.4, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.28 (s, 3H), 1.44 (s, 3H), 1.51 (s, 3H), 3.71 (dd, 1H, J = 12.5, 5.3 Hz), 3.59–3.67 (m, 2H), 3.77 (s, 3H), 4.46 (d, 1H, J = 9.2 Hz), 4.65 (d, 1H, J = 6.4 Hz), 4.83 (d, 1H, J = 5.6 Hz), 7.21 (t, 1H, J = 7.4 Hz), 7.40 (t, 2H, J = 7.8 Hz),7.66 (t, 2H, J = 7.9 Hz), 8.33 (br s,1H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 18.9, 24.8, 26.3, 52.7, 56.4, 61.6, 74.8, 78.5, 80.7, 109.4, 112.0, 119.7, 125.6, 129.3, 136.3, 156.2, 168.9. Anal. Calcd for $C_{19}H_{24}N_4O_6$: C, 56.43; H, 5.98; N, 13.85; O, 23.74. Found: 56.38, H 6.12, N 13.71.

(3aR,7S,8S,8aR,8bS)-methyl 7-((tert-butoxycarbonyl)diazenyl)-2,2,7-trimethylhexahydro-[1,3]dioxolo[4',5':3,4]pyrrolo[1,2-b]isoxazole-8-carboxylate 11b

(0.277 g, 72%); yellow oil. $[\alpha]^{25}_D$ -15 (c 1.4, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.27 (s, 3H,), 1.37 (s, 3H), 1.49 (s, 3H), 1.59 (s, 9H), 3.17 (dd, 1H, J = 5.6, 12.9 Hz), 3.49 (d, 1H, J = 8.3Hz), 3.59 (d, 1H, J = 1.7 Hz), 3.62 (d, 1H, J = 1.7 Hz), 3.76 (s, 3H), 4.41 (d, 1H, J = 8.2 Hz), 4.59 (dd, 1H, J = 0.8, 6.5 Hz), 4.79-4.83 (m, 1H,). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 18.6, 24.8, 27.7, 52.6, 56.1, 61.6, 74.7, 78.7, 81.3, 86.1, 109.4, 112.1, 160.4, 169.1. Anal. Calcd for $C_{17}H_{27}N_3O_7$: C, 52.98; H, 7.06; N, 10.90; O, 29.06. Found: 53.11, H 7.14, N 10.78.

(3aR,7S,8S,8aR,8bS)-methyl 7-((methoxycarbonyl)diazenyl)-2,2,7-trimethylhexahydro-[1,3]dioxolo[4',5':3,4]pyrrolo[1,2-b]isoxazole-8-carboxylate 11d

(0.230 g, 67%); white solid. mp 77-79 ºC. $[\alpha]^{25}_D$ +1 (c 0.8, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.29 (s, 3H), 1.39 (2,

3H), 1.51 (s, 3H), 3.15 (ddd, 1H, J = 0.5, 5.5, 12.7 Hz), 3.47 (d, 1H, J = 8.8 Hz), 3.63 (dd, 1H, J = 1.4, 12.7 Hz), 3.77 (s, 3H), 4.01 (s, 3H), 4.43 (d, 1H, J = 8.8 Hz), 4.62 (d, 1H, J = 6.5 Hz), 4.81–4.85 (m, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 18.6, 24.8, 26.3, 52.8, 55.1, 56.0, 61.4, 74.7, 78.6, 80.9, 109.7, 112.1, 161.9, 168.9. Anal. Calcd for $C_{14}H_{21}N_3O_7$: C, 48.98; H, 6.17; N, 12.24; O, 32.62. Found: 48.86, H 6.31, N 12.40.

(3aR,7S,8S,8aR,8bS)-ethyl 7-(carbamoyldiazenyl)-2,2,7-trimethylhexahydro-[1,3]dioxolo[4',5':3,4]pyrrolo[1,2-b]isoxazole-8-carboxylate 11e

(0.267 g, 78%); yellow oil. $[\alpha]^{25}_D$ -14 (c 0.8, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.27-1.29 (m, 6H) 1.40 (s, 3H), 1.50 (s, 3H), 3.15 (dd, 1H, J = 5.2, 12.9 Hz), 3.52 (d, 1H, J = 9.2 Hz), 3.63 (dd, 1H,J = 12.5, 1.1 Hz), 4.22 (q, 2H,J = 7.1 Hz), 4.43 (d, 1H,J = 9.2 Hz), 4.65 (d, 1H, J = 6.49 Hz), 4.82-4.84 (m, 1H) 6.29 and 6.24 (br s, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.1, 18.7, 24.7, 26.3, 56.1, 61.5, 61.9, 74.7, 78.5, 80.6, 109.4, 112.0, 161.5, 168.4. Anal. Calcd for $C_{14}H_{22}N_4O_6$: C, 49.12; H, 6.48; N, 16.37; O, 28.04. Found: 49.32, H 6.23, N 16.19.

(2S,3S,3aR,4R,5R,6R)-methyl 4,5-bis(benzyloxy)-6-((benzyloxy)methyl)-2-methyl-2-((phenylcarbamoyl)diazenyl)hexahydropyrrolo[1,2-b]isoxazole-3-carboxylate 12a

(0.505 g, 76%); yellow solid. mp 94-96 ºC. $[\alpha]^{25}_D$ +14 (c 1.4, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.49 (s, 3H), 3.46-3.40 (m, 1H), 3.65–3.79 (m, 2H), 3.80 (s, 3H), 3.95 (dd, 1H, J = 2.9, 6.6 Hz), 3.98-4.01 (m, 1H), 4.47 (s, 2H), 4.53 (d, 1H, J = 12.00 Hz), 4.54 (ABsystem, 2H, J = 12.00, 64.3 Hz), 4.58 (2, 2H),7.12–7.19 (m, 2H), 7.22–7.34 (m, 16H), 7.42–7.45(m, 2H),7.97 (br s, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 18.9, 52.6, 57.5, 70.4, 70.9, 71.5, 72.2, 73.4, 83.3, 84.3, 109.7, 119.7, 125.1, 127.6, 127.8, 127.8, 127.9, 128.2, 128.3, 128.4, 129.0, 136.3, 137.1, 137.2, 137.8, 157.2, 169.5. Anal. Calcd for $C_{38}H_{40}N_4O_7$: C, 68.66; H, 6.07; N, 8.43; O, 16.85. Found: 68.81, H 6.24, N 8.29.

(2S,3S,3aR,4R,5R,6R)-methyl 4,5-bis(benzyloxy)-6-((benzyloxy)methyl)-2-((tert-butoxycarbonyl)diazenyl)-2-methylhexahydropyrrolo[1,2-b]isoxazole-3-carboxylate 12b

(0.530 g, 82%); yellow oil. $[\alpha]^{25}_D$ +6.8 (c 1.6, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.43 (s, 3H), 1.57 (s,9H), 3.76-3.77 (m,1H), 3.65–3.78 (m, 2H), 3.80 (s, 3H), 3.91 (d, 1H, J = 9.0 Hz), 4.00–4.02 (m, 1H), 4.08 (dd, 1H, J = 3.1, 6.6 Hz), 4.46–4.67 (m, 7H), 7.22–7.24 (m, 2H), 7.28–7.39 (m, 13H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 18.6, 27.6, 52.4, 57.0, 69.0, 70.3, 71.1, 71.7, 72.0, 73.2, 83.7, 83.8, 85.7, 109.7, 127.4, 128.3, 137.4, 137.8, 138.3, 160.3, 169.6. Anal. Calcd for $C_{36}H_{43}N_3O_8$: C, 66.96; H, 6.71; N, 6.51; O, 19.82. Found: 67.13, H 6.93, N 6.80.

(2S,3S,3aR,4R,5R,6R)-methyl 4,5-bis(benzyloxy)-6-((benzyloxy)methyl)-2-((methoxycarbonyl)diazenyl)-2-methylhexahydropyrrolo[1,2-b]isoxazole-3-carboxylate 12d

(0.483 g, 80%); yellow oil. $[\alpha]^{25}_D$ +7 (c 1.2, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.32 (s, 3H), 3.32–3.36 (m, 1H), 3.52–3.66 (m, 2H), 3.69 (s, 3H), 3.77 (d, 1H, J = 9.5 Hz), 3.86 (s, 3H), 3.89–3.90 (m, 1H), 3.97 (dd, 1H, J = 2.7, 6.4 Hz), 4.34–4.57 (m, 7H), 7.10-7.12 (m, 2H), 7.16-7.28(m, 13H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 118.7, 52.6, 54.9, 57.1, 69.0, 70.6, 71.5, 71.8, 72.1, 73.3, 83.6, 83.9, 109.9, 127.4, 127.6, 127.7, 127.8, 127.9, 128.2, 128.3, 128.4, 137.4, 137.7, 138.7, 161.9, 169.4. Anal. Calcd for $C_{33}H_{37}N_3O_8$: C, 65.66; H, 6.18; N, 6.96; O, 21.20. Found: 65.79, H 5.99, N 7.13.

(2S,3S,3aR,4R,5R,6R)-ethyl 4,5-bis(benzyloxy)-6-((benzyloxy)methyl)-2-(carbamoyldiazenyl)-2-methylhexahydropyrrolo[1,2-b]isoxazole-3-carboxylate 12e

(0.446 g, 74%); yellow solid. mp 67-69ºC. $[\alpha]^{25}_D$ +6 (c 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.29 (t, 3H, J = 7.1 Hz), 1.42 (s, 3H) 3.41–3.59 (m, 1H), 3.61–3.77 (m, 2H), 3.84–3.95 (m, 2H), 3.97–3.99 (m, 1H), 4.43 (d AB system, 1H, J = 12.0 Hz), 1.46 (d, 2H, J = 1.40 Hz),4.49–4.52 (m, 1H),4.54 (s, 2H),4.66 (d AB system, 1H, J = 12.0 Hz),5.4(br s, 1H), 6.04 (br s, 1H),7.17–7.20(m, 2H), 7.27–7.34 (m, 13H);^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.1, 18.4, 57.7, 61.8, 70.6, 71.2, 71.6, 72.3, 72.4, 73.5, 83.7, 84.7, 109.5, 127.7, 127.9, 128.3, 128.4, 128.5, 137.2, 137.9, 162.2, 169.2. Anal. Calcd for $C_{33}H_{38}N_4O_7$: C, 65.77; H, 6.36; N, 9.30; O, 18.58. Found: 65.90, H 6.51, N 9.17.

(4S,5S)-methyl 2-benzyl-3-((2S)-2,2-dimethyl-1,3-dioxolan-4-yl)-5-methyl-5-(3-phenyltriaz-1-en-1-yl)isoxazolidine-4-carboxylate 13a

(0.3 g, 66 %); oil. $[\alpha]^{25}_D$ +12 (c 0.2, $CHCl_3$). ^{1}H NMR (C_6D_6, 500 MHz) δ 1.22 (s, 3H), 1.41 (s, 3H), 1.46 (s, 3H),3.39 (s, 3H),3.65 (dd, 1H, J = 6.7, 8.5 Hz), 3.87 (dd, 1H , J = 6.5, 8.7 Hz), 3.96 (c, 1H , J = 6.6 Hz), 4.06 (d, 1H, J = 7.7 Hz), 4.13 (t, 1H, J = 7.3 Hz), 4.25 (d, 1H, J = 14.5 Hz), 4.50 (d, 1H, J = 14.5 Hz), 6.95 - 7.00 (m, 1H), 7.10 - 7.19 (m, 3H), 7.22 - 7.26 (m, 2H),7.51 - 7.60 (m, 4H),8.06 (s, 1H). ^{13}C NMR (C_6D_6, 100 MHz) δ 18.3, 24.9, 26.2, 51.8, 56.1, 61.6, 65.9, 71.9, 75.6, 104.1, 109.9, 119.5, 124.7, 127.3, 128.3, 128.8, 129.1, 135.8, 137.7, 162.7, 171.1. Anal. Calcd for $C_{24}H_{30}N_4O_5$: C, 63.42; H, 6.65; N, 12.33; O, 17.60. Found: 63.29, H 6.72, N 12.50.

(4S,5S)-methyl 2-benzyl-5-((tert-butoxycarbonyl)diazenyl)-3-((2S)-2,2-dimethyl-1,3-dioxolan-4-yl)-5-methylisoxazolidine-4-carboxylate13b

Isomer 1: (0.176 g, 38%); oil. $[\alpha]^{25}_D$ +14 (c 0.3, $CHCl_3$).^{1}H NMR (C_6D_6, 500 MHz) δ 1.24 (s, 3H), 1.41 (s, 9H), 1.42 (s, 3H), 1.47 (s, 3H), 3.36 (s, 3H), 3.74 (dd, 1H, J = 7.0, 8.8 Hz), 3.95 (dd, 1H, J = 6.7, 8.8 Hz), 4.04 (c, 1H, J = 6.5 Hz), 4.11 (d, 1H, J = 7.7 Hz), 4.18 (dd, 1H, J = 7.3, 7.6 Hz), 4.24 (d, 1H, J = 14.5 Hz), 4.41 (d, 1H, J = 14.5 Hz), 7.13 - 7.19 (m, 1H), 7.23 - 7.26 (m, 2H), 7.54 - 7.60 (m, 2H). ^{13}C NMR (C_6D_6, 100 MHz) δ 18.0, 24.7, 26.2, 27.3, 51.5, 55.7, 61.3, 65.9, 72.1, 75.1, 84.9, 103.8, 109.6, 127.0, 128.5, 137.5, 161.1, 171.0. Anal. Calcd for

$C_{23}H_{33}N_3O_7$: C, 59.60; H, 7.18; N, 9.07; O, 24.16 Found: 59.73, H 7.31, N 8.87.

Isomer 2: (0.175 g, 38%); oil. $[\alpha]^{25}_D$ -10 (c 0.3, $CHCl_3$).^{1}H NMR (C_6D_6, 500 MHz) δ 1.32 (s, 3H), 1.40 (s, 12H), 1.44 (s, 3H), 3.35 (s, 3H), 3.75 - 3.82 (m, 2H), 4.09 - 4.13 (m, 1H), 4.15 (c, 1H, 6.5 Hz), 4.21 (d, 1H, J = 6.3 Hz), 4.29 (d, 1H, J = 14.8 Hz), 4.39 (d, 1H, J = 14.8 Hz), 7.15 - 7.19 (m, 1H), 7.25 - 7.29 (m, 2H), 7.60 - 7.64 (m, 2H). ^{13}C NMR (C_6D_6, 100 MHz) δ 18.3, 25.2, 26.2, 27.3, 51.5, 56.4, 62.1, 66.5, 70.2, 75.6, 84.8, 104.8, 109.0, 127.1, 128.2, 128.6, 137.7, 160.9, 171.2. Anal. Calcd for $C_{23}H_{33}N_3O_7$: C, 59.60; H, 7.18; N, 9.07; O, 24.16 Found: 59.52, H 7.28, N 9.14.

(4S,5S)-methyl 2-benzyl-3-((2S)-2,2-dimethyl-1,3-dioxolan-4-yl)-5-((methoxycarbonyl)diazenyl)-5-methylisoxazolidine-4-carboxylate13d

Isomer 1: (0.153 g, 36%); oil. $[\alpha]^{25}_D$ +4 (c 0.2, $CHCl_3$).^{1}H NMR (C_6D_6, 400 MHz) δ 1.31 (s, 3H), 1.36 (s, 3H), 1.69 (s, 3H), 3.38 (s, 3H), 3.46 (s, 3H), 3.63 (dd, 1H, J = 7.8, 8.6 Hz), 3.68 (dd, 1H, J = 6.0, 8.96 Hz), 3.71 (d, 1H, J = 12.0 Hz), 3.99 (dd, 1H, J = 6.0, 8.6 Hz), 4.26 - 4.34 (m, 2H), 4.74 (dt, 1H, J = 6.0, 8.5 Hz), 7.12 - 7.24 (m, 3H), 7.40 - 7.45 (m, 2H). 13C NMR (C_6D_6, 100 MHz) δ 19.1, 25.3, 26.7, 51.3, 54.0, 54.7, 64.0, 68.1, 70.3, 74.9, 109.0, 19.3, 128.1, 128.3, 129.4, 137.2, 162.4, 168.3. Anal. Calcd for $C_{20}H_{27}N_3O_7$: C, 57.00; H, 6.46; N, 9.97; O, 26.57. Found: 57.26, H 6.64, N 9.84.

Isomer 2: (0.152 g, 36%); oil. $[\alpha]^{25}_D$ +11 (c 0.2, $CHCl_3$).^{1}H NMR (C_6D_6, 500 MHz) δ 1.24 (s, 3H), 1.39 (s, 3H), 1.47 (s, 3H), 3.31 (s, 3H), 3.37 (s, 3H), 3.74 (dd, 1H, J = 6.7, 8.3 Hz), 3.93 (dd, 1H, J = 6.5, 8.4 Hz), 4.01 - 4.07 (m, 2H), 4.17 (dd, 1H, J = 6.8, 7.8 Hz), 4.11 (d, 1H, J = 14.8 Hz), 4.22 (d, 1H, J = 14.8 Hz), 7.13 - 7.18 (m, 1H), 7.23 - 7.26 (m, 2H), 7.55 - 7.60 (m, 2H). ^{13}C NMR (C_6D_6, 100 MHz) δ 17.9, 24.7, 26.1, 51.6, 53.9, 55.9, 61.5, 65.8, 72.2, 75.2, 104.1, 109.7, 127.1, 128.2, 128.4, 137.5, 162.4, 170.9. Anal. Calcd for $C_{20}H_{27}N_3O_7$: C, 57.00; H, 6.46; N, 9.97; O, 26.57. Found: 57.19, H 6.58, N 10.12.

(4S,5S)-methyl 2-benzyl-5-((tert-butoxycarbonyl)diazenyl)-5-methyl-3-((3aR,5aS,8aS,8bR)-2,2,7,7-tetramethyltetrahydro-3aH-bis([1,3]dioxolo)[4,5-b:4',5'-d]pyran-5-yl)isoxazolidine-4-carboxylate14b

Isomer 1: (0.202 g, 34%); oil. $[\alpha]^{25}_D$ -9 (c 0.2, $CHCl_3$).^{1}H NMR (C_6D_6, 500 MHz) δ 1.12 (s, 3H), 1.19 (s, 3H), 1.42 (s, 9H), 1.48 (s, 3H), 1.56 (s, 3H), 1.66 (s, 3H), 3.47 (s, 3H), 4.03 (dd, 1H, J = 1.8, 8.0 Hz), 4.18 - 4.24 (m, 3H), 4.25 - 4.33 (m, 2H), 4.43 (dd, 1H, J = 2.5, 7.9 Hz), 5.13 (d, 1H, J = 14.9 Hz), 5.48 (d, 1H, J = 4.8Hz), 7.15 - 4.21 (m, 1H), 7.29-7.23 (m, 2H), 7.71 - 7.79 (m, 2H). ^{13}C NMR (C_6D_6, 100 MHz) δ 17.9, 24.2, 24.8, 25.9, 27.4, 51.3, 55.1, 62.0, 70.1, 70.4, 71.1, 72.2, 84.4, 96.5, 103.9, 108.8, 109.3, 126.6, 128.0, 128.7, 138.9, 161.4, 170.8. Anal.Calcd for $C_{29}H_{41}N_3O_{10}$: C, 58.87; H, 6.98; N, 7.10; O, 27.04 Found: 58.75, H 7.11, N 6.92.

Isomer 2: (0.207 g, 35%); oil. $[\alpha]^{25}_D$ +5 (c 0.2, $CHCl_3$).^{1}H NMR (C_6D_6, 500 MHz) δ 1.11 (s, 3H), 1.16 (s, 3H), 1.41 (s, 9H), 1.52 (s, 3H), 1.72 (s, 3H), 3.33 (s, 3H), 4.14 (dd, 1H, J = 1.4, 8.0 Hz), 4.20 (dd, 1H, J = 1.5, 8.0 Hz), 4.22 (dd, 1H, J = 2.1, 5.0 Hz), 4.46 - 4.51 (m, 2H), 4.54 - 4.60 (m, 2H), 4.81 (d, 1H, J = 15.5 Hz), 5.60 (d, 1H, J = 5.0 Hz), 7.18 - 7.22 (m, 1H), 7.30 - 7.35 (m, 2H), 7.71 - 7.78 (m, 2H). ^{13}C NMR (C_6D_6, 100 MHz) δ 18.2, 23.8, 24.6, 25.7, 26.4, 27.3, 29.9, 51.3, 57.8, 61.9, 68.3, 69.2, 70.9, 70.9, 84.4, 104.6, 108.4, 109.0, 126.8, 128.3, 128.5, 138.8, 161.3, 171.8. Anal.Calcd for $C_{29}H_{41}N_3O_{10}$: C, 58.87; H, 6.98; N, 7.10; O, 27.04 Found: 58.99, H 7.18, N 7.25.

General Procedure for the microwave irradiated cycloaddition between DDs 1 and nitrones 9.

A mixture of nitrone **9** (1.0 mmol) and 1,2-diaza-1,3-diene **1** (1.0 mmol) was irradiated under microwave conditions at 300 W for the stated time (Table 3) min at a maximum temperature of 70ºC. The obtained crude material was purified by column chromatography (hexane/EtOAc, 3:2).

Acknowledgements

This study was supported by the Ministerio de Ciencia e Innovación (MICINN) and FEDER Program (Madrid, Spain, projects CTQ2010-19606 and CTQ2013-44367-C2-1-P) and the Gobierno de Aragón (Zaragoza, Spain. Bioorganic Chemistry Group. E-10). We thank MIUR (Italy) and CNMPS (Italy) for their financial support. O.K. thanks the Erasmus Program for a grant. We also acknowledge the Institute of Biocomputation and Physics of Complex Systems (BIFI) at the University of Zaragoza for computer time (Terminus, Memento and CesAr clusters).

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†Electronic Supplementary Information (ESI) available: Details on assignment of the absolute configuration of compounds **13** and **14**; theoretical analysis based on reactivity indices, absolute (hartrees) and relative (kcal/mol) electronic and free energies at B3LYP/6-31G(d)/PCM=MeCN, M062X/6-31G(d)/PCM=MeCN, M06-2X/6-311+G(d,p)/PCM=MeCN//M06-2X/6-31G(d)/PCM=MeCNB3LYP-GD3BJ/6-311G(dp)/PCM=MeCN and M06-2X/cc-pVTZ/PCM=MeCN levels; IRC analyses; calculations of cycloaddition reactions of nitrone **9a**; stationery points and Cartesian coordinates of optimized structures, and copies of ^{1}H, ^{13}C and NOESY RMN spectra of new compounds. See DOI: 10.1039/b000000x/

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