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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†

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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 were 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 qualitative agreement with the observed experimental results.

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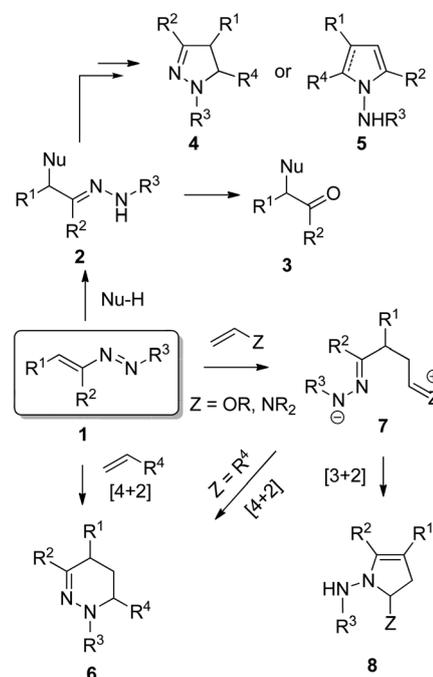
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### Introduction

1,2-Diaza-1,3-dienes (DDs, **1**) are important synthetic intermediates and very attractive building blocks for the construction of a large variety of heterocycles.<sup>1</sup> 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<sup>2</sup> and a great number of carbanions derived from active methylene compounds including  $\beta$ -keto,<sup>3</sup>  $\beta$ -cyano,<sup>4</sup>  $\beta$ -phosphono<sup>5</sup> and

$\beta$ -nitro<sup>6</sup> carbonyl derivatives. The resulting hydrazones **2** can evolve towards the parent  $\alpha$ -substituted carbonyl compounds **3** but in the case of  $\beta$ -functionalized carbonyls with the appropriate functionalities pyrazolines **4**<sup>7</sup>, *N*-amino pyrroles<sup>8</sup> and di-



Scheme 1 Reactivity of DDs 1.

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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<sup>-1</sup>) 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=MeCN/B3LYP-GD3BJ/6-311G(dp)/PCM=MeCN and M06-2X/cc-pVTZ/PCM=MeCN levels; IRC analyses; calculations of cycloaddition reactions of nitron **9a**; stationary points and Cartesian coordinates of optimized structures, and copies of <sup>1</sup>H, <sup>13</sup>C and NOESY RMN spectra of new compounds. CCDC 1002299. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c4ob01371a



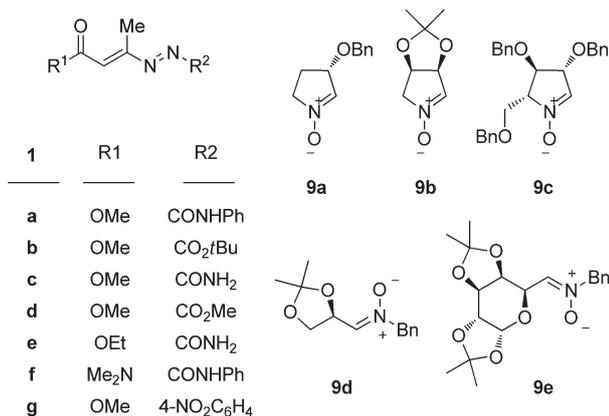


Chart 1 DDs 1 and nitrones 9.

hydropyrroles 5<sup>9</sup> are obtained. By the addition of diverse heterocyclic derivatives, bicyclic systems can also be prepared.<sup>10</sup>

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 for acting as dienes in inverse electron-demand [4 + 2] cycloadditions to give tetrahydropyridazines 6.<sup>11</sup> In the case of enol ethers and enamines the cycloaddition is stepwise and intermediate 7 is formed. This intermediate can evolve to 6 by a formal [4 + 2] cycloaddition but also to *N*-amino pyrroles 8 by a competitive formal [3 + 2] cycloaddition.<sup>12</sup> The reactivity of DDs as dienophiles has been much less studied and only the reaction with cyclopentadiene has been reported,<sup>13</sup> besides the possibility of dimerization of compounds 1.<sup>14</sup>

In 1,3-dipolar cycloadditions the C=C bond in compounds 1 can also act as a dipolarophile as has been demonstrated in reactions with diazomethane<sup>15</sup> and mesoionic heterocycles.<sup>16</sup> 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 nitron functionality, which has been widely demonstrated by its synthetic utility in the construction of several nitrogen heterocycles.<sup>17</sup>

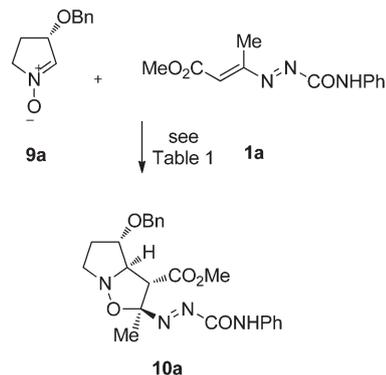
Herein, we report a study of the reaction of DDs, 1 with cyclic and acyclic chiral non-racemic nitrones 9 (Chart 1). Thermal and microwave activated cycloadditions have been studied and the results have been rationalized by DFT calculations at several levels of theory considering solvent effects.

## Results and discussion

### Experimental study

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

Initially, we screened various solvents and ratios of nitron/diastereomer (DD) for the cycloaddition between DD 1a and nitrone 9a to give 10a (Scheme 2, Table 1). Among the various solvents tested,



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

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

Entry	1a : 9	Solvent	<i>T</i> (°C)	<i>t</i> (h)	Yield <sup>a</sup> (%)	dr <sup>b</sup> (%)
1	1 : 1	CHCl <sub>3</sub>	rt	24	28	1 : 0
2	1 : 1	CHCl <sub>3</sub>	60	9	27	1 : 0
3	2 : 1	CHCl <sub>3</sub>	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. <sup>c</sup>	1 : 0
10	2 : 1	MeOH	60	24	n.r. <sup>c</sup>	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

<sup>a</sup> Isolated yield. <sup>b</sup> dr (diastereomeric ratio) was obtained from the <sup>1</sup>H NMR of the crude reaction mixture. <sup>c</sup> n.r. Not observed reaction.

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. Using methanol as a solvent (Table 1, entries 9 and 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 of DD/nitron showed the best results (Table 1, entries 3, 6, 8, 12 and 15). Using acetonitrile as a solvent, at 60 °C 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 stereo-selective 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 (nitron/diazadiene ratio of 1 : 2, 60 °C, 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



Table 2 Scope of the cycloaddition between nitrones **9** and DDs **1**

Entry	Nitron	Diazadiene	Adduct	Solvent	<i>t</i> (h)	Yield <sup>a</sup> (%)	dr <sup>b</sup>
1	<b>9a</b>	<b>1b</b>	<b>10b</b> R <sup>1</sup> = OMe, R <sup>2</sup> = CO <sub>2</sub> <i>t</i> Bu	Neat	3	69	1:0
2	<b>9a</b>	<b>1b</b>	<b>10b</b> R <sup>1</sup> = OMe, R <sup>2</sup> = CO <sub>2</sub> <i>t</i> Bu	MeCN	9	78	1:0
3	<b>9a</b>	<b>1c</b>	<b>10c</b> R <sup>1</sup> = OMe, R <sup>2</sup> = CONH <sub>2</sub>	MeCN	5	52	1:0
4	<b>9a</b>	<b>1d</b>	<b>10d</b> R <sup>1</sup> = OMe, R <sup>2</sup> = CO <sub>2</sub> Me	Neat	1	44	1:0
5	<b>9a</b>	<b>1d</b>	<b>10d</b> R <sup>1</sup> = OMe, R <sup>2</sup> = CO <sub>2</sub> Me	Neat	2	54	1:0
6	<b>9a</b>	<b>1d</b>	<b>10d</b> R <sup>1</sup> = OMe, R <sup>2</sup> = CO <sub>2</sub> Me	MeCN	2	68	1:0
7	<b>9a</b>	<b>1e</b>	<b>10e</b> R <sup>1</sup> = OEt, R <sup>2</sup> = CONH <sub>2</sub>	MeCN	5	54	1:0
8	<b>9a</b>	<b>1f</b>	<b>10f</b> R <sup>1</sup> = NMe <sub>2</sub> , R <sup>2</sup> = CONHPh	MeCN	9	74	1:0
9	<b>9a</b>	<b>1g</b>	<b>10g</b> R <sup>1</sup> = OMe, R <sup>2</sup> = 4-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	MeCN	9	86	1:0
10	<b>9b</b>	<b>1a</b>	<b>11a</b> R <sup>1</sup> = OMe, R <sup>2</sup> = CONHPh	MeCN	3	66	1:0
11	<b>9b</b>	<b>1b</b>	<b>11b</b> R <sup>1</sup> = OMe, R <sup>2</sup> = CO <sub>2</sub> <i>t</i> Bu	Neat	3	61	1:0
12	<b>9b</b>	<b>1b</b>	<b>11b</b> R <sup>1</sup> = OMe, R <sup>2</sup> = CO <sub>2</sub> <i>t</i> Bu	MeCN	3	72	1:0
13	<b>9b</b>	<b>1d</b>	<b>11d</b> R <sup>1</sup> = OMe, R <sup>2</sup> = CO <sub>2</sub> Me	MeCN	3	67	1:0
14	<b>9b</b>	<b>1e</b>	<b>11e</b> R <sup>1</sup> = OEt, R <sup>2</sup> = CONH <sub>2</sub>	MeCN	3	78	1:0
15	<b>9c</b>	<b>1a</b>	<b>12a</b> R <sup>1</sup> = OMe, R <sup>2</sup> = CONHPh	MeCN	3	76	1:0
16	<b>9c</b>	<b>1b</b>	<b>12b</b> R <sup>1</sup> = OMe, R <sup>2</sup> = CO <sub>2</sub> <i>t</i> Bu	Neat	3	80	1:0
17	<b>9c</b>	<b>1b</b>	<b>12b</b> R <sup>1</sup> = OMe, R <sup>2</sup> = CO <sub>2</sub> <i>t</i> Bu	MeCN	3	82	1:0
18	<b>9c</b>	<b>1d</b>	<b>12d</b> R <sup>1</sup> = OMe, R <sup>2</sup> = CO <sub>2</sub> Me	MeCN	3	80	1:0
19	<b>9c</b>	<b>1e</b>	<b>12e</b> R <sup>1</sup> = OEt, R <sup>2</sup> = CONH <sub>2</sub>	MeCN	3	74	1:0
20	<b>9d</b>	<b>1a</b>	<b>13a</b> R <sup>1</sup> = OMe, R <sup>2</sup> = CONHPh	MeCN	9	74	8:1
21	<b>9d</b>	<b>1b</b>	<b>13b</b> R <sup>1</sup> = OMe, R <sup>2</sup> = CO <sub>2</sub> <i>t</i> Bu	Neat	3	76	1:1
22	<b>9d</b>	<b>1b</b>	<b>13b</b> R <sup>1</sup> = OMe, R <sup>2</sup> = CO <sub>2</sub> <i>t</i> Bu	MeCN	9	77	3:2
23	<b>9d</b>	<b>1d</b>	<b>13d</b> R <sup>1</sup> = OMe, R <sup>2</sup> = CO <sub>2</sub> Me	MeCN	9	72	1:1
24	<b>9e</b>	<b>1b</b>	<b>14b</b> R <sup>1</sup> = OMe, R <sup>2</sup> = CO <sub>2</sub> <i>t</i> Bu	Neat	2	77	1:1
25	<b>9e</b>	<b>1b</b>	<b>14b</b> R <sup>1</sup> = OMe, R <sup>2</sup> = CO <sub>2</sub> <i>t</i> Bu	MeCN	9	68	1:1

<sup>a</sup> Isolated yield. <sup>b</sup> Obtained from the <sup>1</sup>H NMR of the crude reaction mixture.



main products. Typically, treatment of nitron **9a** with DDs **1b–f** at 60 °C 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).

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 (Fig. 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 stereogenic center at the pyrrolidine ring (Fig. 1, red arrows). The structure of **10e** was elucidated by X-ray crystallography confirming the assigned configuration (Fig. 2)<sup>23</sup> corresponding to an *exo* attack of DD by the less hindered *Re* diastereoface of the nitron.

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 (Fig. 1, blue arrows). Due to the rotation of the bond C $\alpha$ –C3 in **13** and **14** the absolute configuration of each epimer could not be unambiguously assigned by NMR studies (for a tentative assignment see ESI†).

In addition to the thermal conditions described above, two further additional approaches, in an attempt to improve the

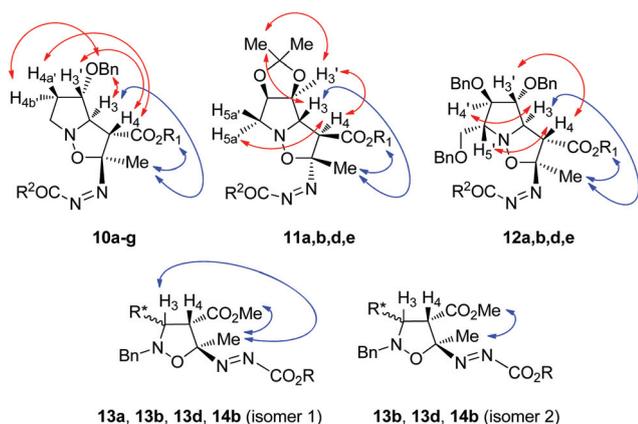


Fig. 1 NOE relationships in cycloadducts. Blue and red interactions are related to relative and absolute configurations, respectively (see text), of the newly formed isoxazolidine ring (for R<sup>1</sup>, R<sup>2</sup> and R\* see Table 2).

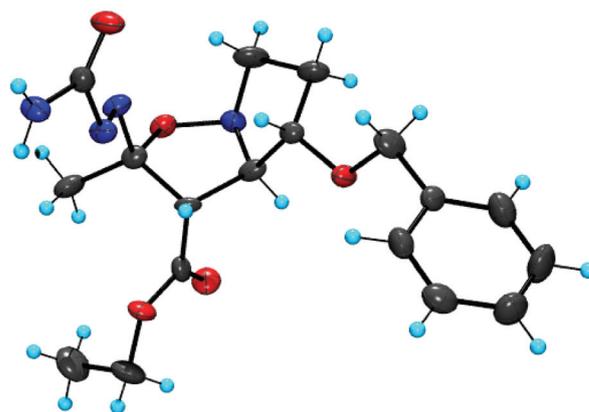


Fig. 2 ORTEP representation of **10e**. Ellipsoids displayed at 50% probability.

cycloaddition reactions, were explored: microwave irradiation and Lewis acid catalysis. With regard to Lewis acid, various catalysts including MgBr<sub>2</sub>, Zn(OTf)<sub>2</sub>, ZnBr<sub>2</sub>, CuOTf, AgOTf, Sc(OTf)<sub>3</sub> and Yb(OTf)<sub>3</sub> were used in both catalytic and stoichiometric amounts. The <sup>1</sup>H NMR analysis of the corresponding reaction mixtures only revealed the disappearance of the DD and the complete recovery of the starting nitron. Any attempt of isolating and/or identifying (by NMR of the crude mixture) any significant product derived from DDs failed and only complex mixtures were obtained. From these reaction mixtures only the starting nitron could be recovered by column chromatography, likely due to the simple decomposition of starting DDs. The 1,3-dipolar cycloaddition between a nitron 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 nitron species. Recovering the unreacted nitron and disappearance of the DD are in agreement with the coordination of the latter but, unfortunately, also indicate the instability of DDs complexed with Lewis acids under reaction conditions. Indeed, parallel experiments subjecting DDs **1** in the presence of Lewis acids at 60 °C 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, T<sub>max</sub> = 70 °C) decreased dramatically the reaction time of the cycloadditions (Table 3).

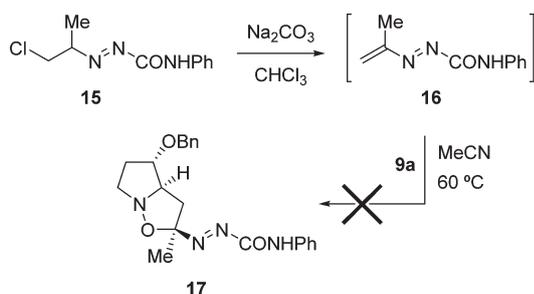
For instance, in the case of the cycloaddition between nitron **9a** and diazadiene **1b** (Table 3, entry 2), the reaction time decreased from 9 h to 1 min. In some cases, however, the NMR analysis of the crude mixture revealed the presence of a minor isomer (Table 3, entries 1–3 and 7–12) indicating a slightly lower selectivity with respect to thermal reactions.



**Table 3** Cycloaddition between nitrones **9** and DDs **1** under microwave irradiation<sup>a</sup>

Entry	Nitron	Diazadiene	Adduct	<i>t</i> (s)	Yield <sup>b</sup> (%)	dr <sup>c</sup>
1	<b>9a</b>	<b>1a</b>	<b>10a</b>	60	80	9 : 1
2	<b>9a</b>	<b>1b</b>	<b>10b</b>	60	73	5 : 1
3	<b>9a</b>	<b>1d</b>	<b>10d</b>	42	69	1 : 0
4	<b>9b</b>	<b>1a</b>	<b>11a</b>	62	68	1 : 0
5	<b>9b</b>	<b>1b</b>	<b>11b</b>	80	82	1 : 0
6	<b>9b</b>	<b>1d</b>	<b>11d</b>	100	80	1 : 0
7	<b>9c</b>	<b>1a</b>	<b>12a</b>	72	88	9 : 1
8	<b>9c</b>	<b>1b</b>	<b>12b</b>	72	86	5 : 1
9	<b>9c</b>	<b>1d</b>	<b>12d</b>	118	90	9 : 1
10	<b>9d</b>	<b>1a</b>	<b>13a</b>	240	75	1 : 1
11	<b>9d</b>	<b>1b</b>	<b>13b</b>	240	79	1 : 1
12	<b>9d</b>	<b>1d</b>	<b>13d</b>	240	78	1 : 1

<sup>a</sup> Reaction conditions: ratio 9/1 1 : 1, neat,  $T_{\max}$  70 °C, 300 W. <sup>b</sup> Isolated yield. <sup>c</sup> Obtained from the <sup>1</sup>H NMR of the crude reaction mixture.

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

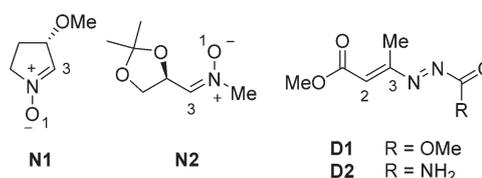
Also, in other cases, the chemical yield decreased considerably (Table 3, entries 4, 6 and 7). In all cases, the reactions were carried out without solvent and with a 1 : 1 ratio of nitron/DD, what might contribute to the appearance of a minor isomer in some cases. Under microwave irradiation, the use of a 1 : 2 ratio of nitron/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 steric and electronic properties we replaced the substituents by their most simplified versions, when possible (due to the stability of DDs). Thus, we attempted the reaction between DD **16**, generated *in situ* from precursor **15**, and the cyclic nitron **9a** (Scheme 3). However, under optimized conditions (MeCN or neat, 60 °C, with or without MW irradiation) no reaction was observed in any case, the starting nitron being recovered almost completely, while degradation products deriving from the 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**.<sup>24</sup>

## Theoretical study

**Computational methods.** Computations with density functional theory (DFT) were done using the exchange-correlation

functional B3LYP<sup>25</sup> and Truhlar's functional M06-2X.<sup>26</sup> Standard basis sets 6-31G(d), 6-311G(d,p)<sup>27</sup> and cc-pVTZ<sup>28</sup> were employed. For 3 $\zeta$  optimizations with the B3LYP functional the recently developed<sup>29</sup> 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 Bery analytical gradient optimization method.<sup>30</sup> Minimum energy pathways for the reactions studied were found by gradient descent of transition states in the forward and backward directions of the transition vector (IRC analysis),<sup>31</sup> using the second order González-Schlegel integration method.<sup>32</sup> 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.<sup>33</sup> In previous work,<sup>34</sup> calculations using the B3LYP functional failed in predicting the correct selectivity and thermodynamics of the reaction, even though recent studies<sup>35</sup> have demonstrated that B3LYP performed very well for geometries, in particular for cycloaddition reactions.<sup>36</sup> On the other hand, a recent report<sup>37</sup> concludes that M06-2X calculations provide the best geometries than B3LYP. Thus, for the purpose of comparison the following 2 $\zeta$  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 3 $\zeta$  level basis set and considering inclusion of diffuse functions as well as the same solvent; thus, single point calculations were carried out at the 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 3 $\zeta$  levels were also carried out: B3LYP-GD3BJ/6-311G(d,p)/PCM=MeCN (level 4) and M06-2X/cc-pVTZ/PCM=MeCN (level 5). Reactivity indices were calculated at the M06-2X/6-311+G(d,p)/PCM=MeCN level of theory. All calculations were carried out with the Gaussian 09 suite of programs.<sup>38</sup> Structural representations were generated using CYLview.<sup>39</sup> Consistently with the experimental work and regarding the computational costs, the only changes made in the model is the use of methyl groups instead of 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**) (Fig. 3). For DDs **D1** and **D2** a total of eight conformations have been calculated.<sup>40</sup> Once evaluated the stability of reactants, the most stable conformations have been chosen for performing the study. Fig. 3 displays the conformational features of the DDs. These conformations have been

**Fig. 3** Reactants used in the theoretical study.

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

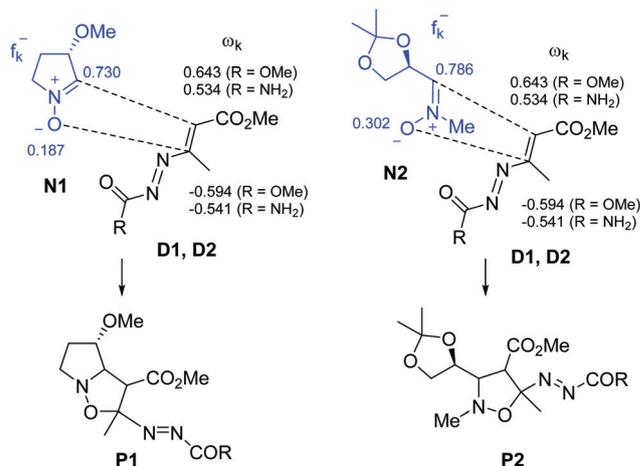
	HOMO	LUMO	$\mu$	$\eta$	$S$	$\omega$	$\Delta N_{\max}$
<b>N1</b>	-0.29789	-0.00226	-0.1501	0.2956	1.6913	1.04	0.508
<b>N2</b>	-0.29824	-0.00320	-0.1507	0.2950	1.6947	1.05	0.511
<b>D1</b>	-0.33275	-0.08310	-0.2079	0.2497	2.0028	2.36	0.833
<b>D2</b>	-0.32428	-0.08134	-0.2028	0.2429	2.0581	2.30	0.835

further employed for locating the corresponding transition states.

**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 indices, as defined in the context of DFT,<sup>41</sup> 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 ESI.† The values of  $\mu$ ,  $\eta$ ,  $S$  and  $\omega$  for compounds **N1**, **N2**, **D1** and **D2**, calculated with the reported formulas, are listed in Table 4. The global electrophilicity indices ( $\omega$ ) 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 cycloaddition reaction in which the nitrone acts as the nucleophile. In the same way, the electronic chemical potential,  $\mu$ , 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.

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  $\omega_k$ ). The local electrophilic indices ( $\omega_k$ ) and the condensed Fukui functions ( $f_k^+$  and  $f_k^-$ ) of nitrones **N1** and **N2**, and DDs **D1** and **D2** are shown in Table 5.

For DDs **D1** and **D2**, C2 has a higher local electrophilicity index,  $\omega_k$  thus being the preferred site for the nucleophilic

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

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.

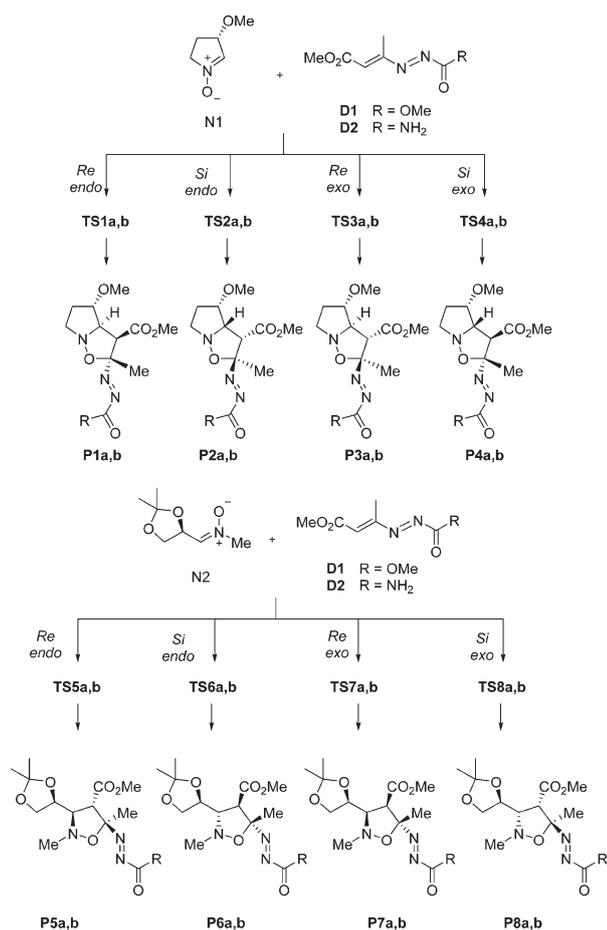
**Analysis of transition structures.** We have considered the formation of adducts predicted by the DFT analysis based on reactivity indices and observed experimentally. In consequence four model reactions have been studied (Scheme 5) corresponding to the cycloaddition between nitrones **N1** and **N2** 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.

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 ESI†) 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 Fig. 4 and 5, respectively, and for the reaction between nitrone **N2** and DDs **D1** and **D2** in Fig. 6 and 7, respectively.

**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 properties are evaluated according to Fig. 3)

	K	$\omega_k$	$f_k^-$	$f_k^+$
<b>N1</b>	O1	0.60	0.187	0.581
	C3	0.19	0.730	0.180
<b>N2</b>	O1	0.47	0.302	0.447
	C3	0.01	0.786	0.010
<b>D1</b>	C2	0.64	0.180	0.273
	C3	-0.59	-0.026	-0.252
<b>D2</b>	C2	0.53	0.176	0.232
	C3	-0.54	-0.044	-0.235





**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<sub>2</sub>, respectively.

**Table 6** Calculated (PCM=MeCN/M06-2X/cc-pVTZ) free ( $\Delta G$ , hartrees) and relative energies ( $\Delta\Delta G$ , kcal mol<sup>-1</sup>) of the stationary points corresponding to the reaction of nitron **N1** with DDs **D1** and **D2**<sup>a</sup>

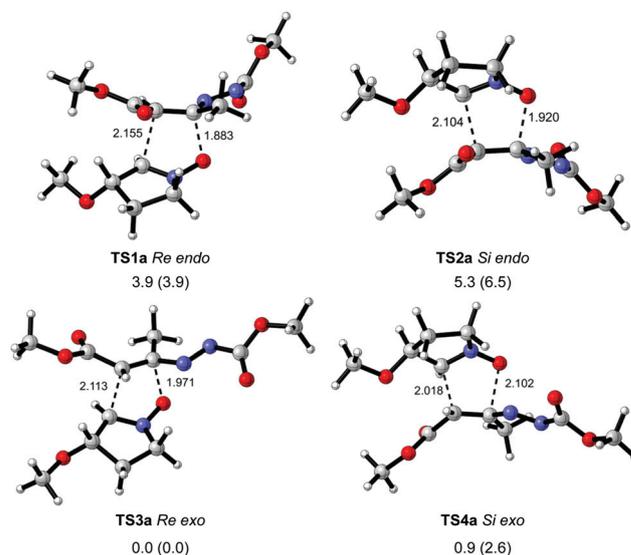
	$\Delta G$	$\Delta\Delta G^b$		$\Delta G$	$\Delta\Delta G^c$
<b>N1</b>	-400.937506		<b>N1</b>	-400.937506	
<b>D1</b>	-682.972361		<b>D2</b>	-623.828581	
<b>C1a</b>	-1083.892845	10.7	<b>C1b</b>	-1024.746127	12.5
<b>C2a</b>	-1083.894624	9.6	<b>C2b</b>	-1024.750889	9.5
<b>C3a</b>	-1083.892823	10.7	<b>C3b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

<sup>a</sup> 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. <sup>b</sup> Referred to starting materials (**N1** + **D1**). <sup>c</sup> Referred to starting materials (**N1** + **D2**).

**Table 7** Calculated (PCM=MeCN/M06-2X/cc-pVTZ) free ( $\Delta G$ , hartrees) and relative energies ( $\Delta\Delta G$ , kcal mol<sup>-1</sup>) of the stationary points corresponding to the reaction of nitron **N2** with DDs **D1** and **D2**<sup>a</sup>

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

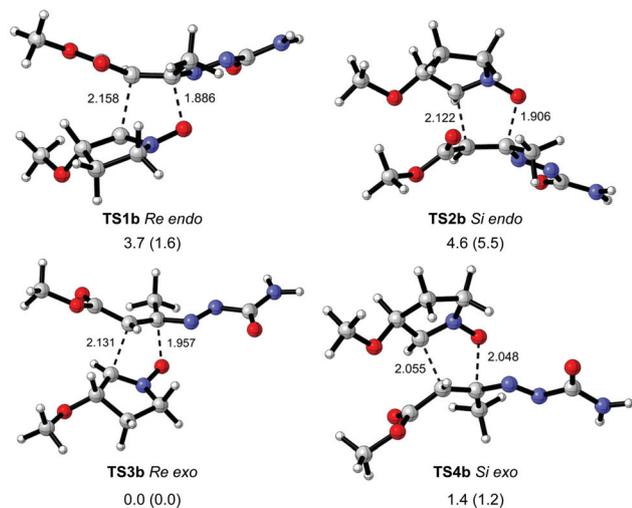
<sup>a</sup> For nomenclature of stationary points see Scheme 5; **C5**, **C6**, **C7** and **C8** correspond to encounter complexes previous to the formation of **TS5**, **TS6**, **TS7** and **TS8**, respectively; a and b series correspond to the reactions of **N2** with **D1** and **D2**, respectively.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



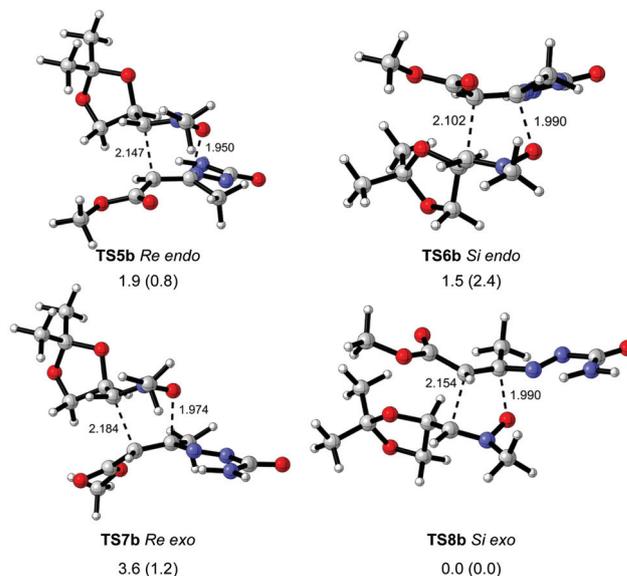
**Fig. 4** Transition structures (PCM=MeCN/M06-2X/6-31G(d)) corresponding to the reaction between **N1** and **D1**. **TS1a**, **TS2a**, **TS3a** and **TS4a** correspond to *Re endo*, *Si endo*, *Re exo* and *Si exo* approaches leading to **P1a**, **P2a**, **P3a** and **P4a**. Relative energy values between TSs referenced to isolated reagents and the corresponding encounter complexes (in brackets) are calculated at the PCM=MeCN/M06-2X/cc-pVTZ level of theory and are given in kcal mol<sup>-1</sup>. Bond distances are given in Å.

The energy values were calculated at five levels of theory, considering the 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.<sup>43</sup> All the discussions will be based on the highest level used (PCM=MeCN/M06-2X/cc-pVTZ). The analysis of relative free energies ( $\Delta G$ ) shows that, in general,

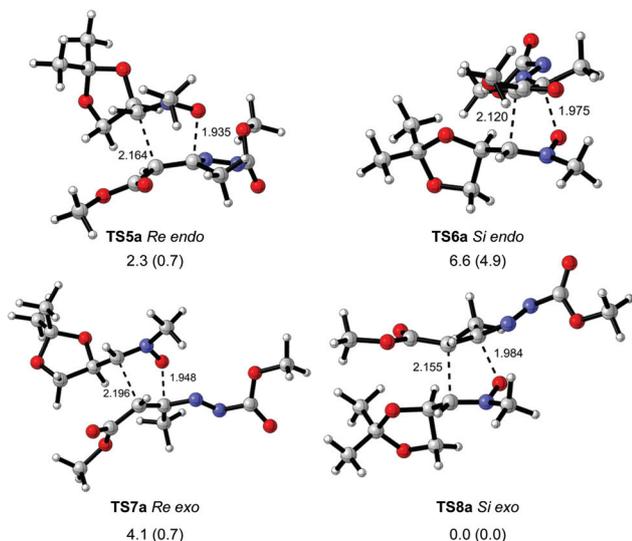




**Fig. 5** Transition structures (PCM=MeCN/M06-2X/6-31G(d)) corresponding to the reaction between N1 and D2. TS1b, TS2b, TS3b and TS4b correspond to *Re endo*, *Si endo*, *Re exo* and *Si exo* approaches leading to P1b, P2b, P3b and P4b. Relative energy values between TSs referenced to isolated reagents and the corresponding encounter complexes (in brackets) are calculated at the PCM=MeCN/M06-2X/cc-pVTZ level of theory and are given in kcal mol<sup>-1</sup>. Bond distances are given in Å.



**Fig. 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 the PCM=MeCN/M06-2X/cc-pVTZ level of theory and are given in kcal mol<sup>-1</sup>. Bond distances are given in Å.



**Fig. 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 the PCM=MeCN/M06-2X/cc-pVTZ level of theory and are given in kcal mol<sup>-1</sup>. Bond distances are given in Å.

*exo* attacks (referred to the ester group) are preferred to the corresponding *endo* approaches.<sup>42</sup>

For cycloadditions of cyclic nitron 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<sup>-1</sup> and the barrier for the cycloaddition between N1 and D2 is 23.4 kcal mol<sup>-1</sup>. These results, predicting the formation of P3a,b (from a *Re exo* attack) is in good qualitative agreement with the experimental observations even though the small observed energy differences between transition states (less than 1.5 kcal mol<sup>-1</sup>, within the experimental error) are more in agreement with the obtention of mixtures of isomers, instead only one isomer is actually obtained. In this regard, all the calculations fail in predicting the observed complete diastereoselectivity. Initially, it should be possible to assume that such a discrepancy might arise from using a methyl group instead of 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<sup>-1</sup> between the two more stable TSs for the reaction with D1 and D2, respectively) to those obtained for N1 have been obtained (see ESI†). These data support the validity of our model and demonstrate that the failure in quantitative prediction is inherent to the calculation.<sup>44</sup> As expected for a cyclic biased system like nitron N1 the qualitatively predicted diastereoselectivity is in agreement with the addition of the dipolarophile by the less hindered *Re* face.

The preference by the *exo* approach with respect to the methoxycarbonyl group is a consequence of the presence of

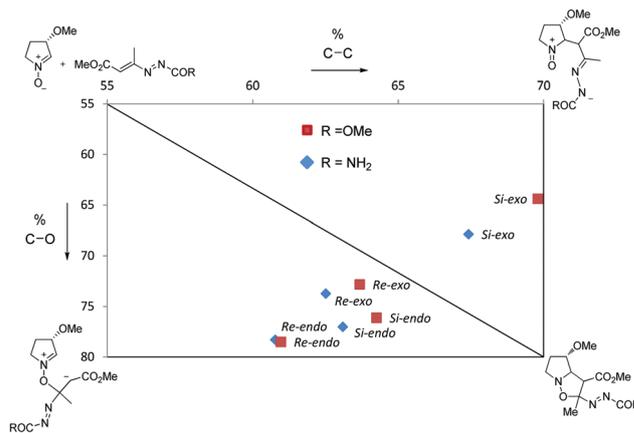


the diazo moiety which acts as a directing-electron-withdrawing group and, as expected for normal-demand 1,3-dipolar cycloadditions, is oriented *endo* with respect to the dipole. For the acyclic nitron **N2**, the barrier for the cycloaddition with **D1** is 24.6 kcal mol<sup>-1</sup> and the barrier for the cycloaddition with **D2** is 26.9 kcal mol<sup>-1</sup>. In this case, the differences observed between transition states (*ca.* 1.5–2.0 kcal mol<sup>-1</sup>) 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.

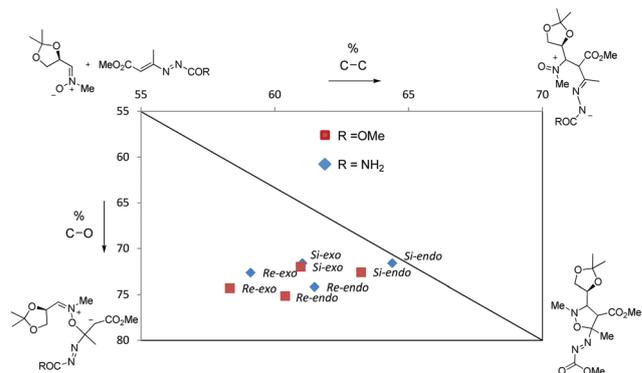
All the transition states are concerted asynchronous as expected for a typical normal-demand 1,3-dipolar cycloaddition. In the case of cyclic nitron **N1** the C–O forming bonds are in the range of 1.88–2.10 Å and the C–C forming bonds are in the range of 2.02–2.16 Å. For nitron **N2** the C–O forming bonds are in the range of 1.94–1.99 Å and the C–C forming bonds are in the range of 2.10–2.20 Å. The geometry of the transition structures is very similar independent 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<sup>45</sup> using as reaction coordinates C–C and C–O forming bonds can be employed for better understanding 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 Fig. 8 and 9, respectively.

In the case of nitron **N1** the difference between the 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 than 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 nitron **N2**. For this nitron, however, the C–O bond is formed more rapidly than the C–C bond in all cases, the less asynchronous



**Fig. 8** 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 correspond to **TS1a,b**, **TS2a,b**, **TS3a,b** and **TS4a,b**.



**Fig. 9** 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 correspond to **TS5a,b**, **TS6a,b**, **TS7a,b** and **TS8a,b**.

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 experimentally 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 3 $\zeta$  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 the solvent effects (PCM=MeCN) in all cases, is in qualitative



agreement with the observed experimental results. It is noteworthy that while the complete diastereoselectivity observed for **N1** is not exactly predicted by the calculations,<sup>46</sup> 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 O'Ferrall–Jencks diagram analyses. Further elaborations of the obtained cycloadducts will allow the preparation of a variety of heterocyclic systems and it will be reported in 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 positions 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. <sup>1</sup>H and <sup>13</sup>C NMR spectra were recorded on Bruker Avance 300, 400 or 500 instruments in the stated solvent. Chemical shifts are reported in ppm ( $\delta$ ) relative to CHCl<sub>3</sub> ( $\delta = 7.26$ ) in CDCl<sub>3</sub>. Optical rotations were taken on a JASCO DIP-370 polarimeter. Elemental analysis was 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 °C 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 purified by 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. [ $\alpha$ ]<sub>D</sub><sup>25</sup> +12 (*c* 1.3, CHCl<sub>3</sub>). <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz)  $\delta$  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* = 11.9 Hz), 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). <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz)  $\delta$  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<sub>23</sub>H<sub>26</sub>N<sub>4</sub>O<sub>5</sub>: 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. [ $\alpha$ ]<sub>D</sub><sup>25</sup> +10 (*c* 1.7, CHCl<sub>3</sub>). <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz)  $\delta$  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, <sup>3</sup>*J* = 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). <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz)  $\delta$  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<sub>21</sub>H<sub>29</sub>N<sub>3</sub>O<sub>6</sub>: 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 °C. [ $\alpha$ ]<sub>D</sub><sup>25</sup> +8 (*c* 1.2, CHCl<sub>3</sub>). <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz)  $\delta$  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). <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz)  $\delta$  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<sub>17</sub>H<sub>22</sub>N<sub>4</sub>O<sub>5</sub>: 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. [ $\alpha$ ]<sub>D</sub><sup>25</sup> –11 (*c* 0.6, CHCl<sub>3</sub>). <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz)  $\delta$  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). <sup>13</sup>C NMR (CDCl<sub>3</sub>, 75 MHz)  $\delta$  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<sub>18</sub>H<sub>23</sub>N<sub>3</sub>O<sub>6</sub>: 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 °C. [ $\alpha$ ]<sub>D</sub><sup>25</sup> +8 (*c* 1.2, CHCl<sub>3</sub>). <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz)  $\delta$  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). <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz)  $\delta$  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<sub>18</sub>H<sub>24</sub>N<sub>4</sub>O<sub>5</sub>: 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. [ $\alpha$ ]<sub>D</sub><sup>25</sup> +9 (*c* 1.4, CHCl<sub>3</sub>). <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz)  $\delta$  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). <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz)  $\delta$  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)diazanyl)hexahydropyrrolo[1,2-b]isoxazole-3-carboxylate 10g.** (0.379 g, 86%); orange powder. mp 58–60 °C.  $[\alpha]_D^{25} +19$  (c 0.5,  $CHCl_3$ ).  $^1H$  NMR ( $CDCl_3$ , 400 MHz)  $\delta$  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,  $J = 9.10$  Hz), 8.35 (d, 2H,  $J = 9.10$  Hz).  $^{13}C$  NMR ( $CDCl_3$ , 100 MHz)  $\delta$  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)diazanyl)hexahydro-[1,3]dioxolo[4',5':3,4]pyrrolo[1,2-b]isoxazole-8-carboxylate 11a.** (0.267 g, 66%); yellow oil.  $[\alpha]_D^{25} -21$  (c 0.4,  $CHCl_3$ ).  $^1H$  NMR ( $CDCl_3$ , 400 MHz)  $\delta$  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)  $\delta$  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)diazanyl)-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.  $[\alpha]_D^{25} -15$  (c 1.4,  $CHCl_3$ ).  $^1H$  NMR ( $CDCl_3$ , 400 MHz)  $\delta$  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,  $J = 8.3$  Hz), 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)  $\delta$  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  $C_{17}H_{22}N_3O_7$ : 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)diazanyl)-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 °C.  $[\alpha]_D^{25} +1$  (c 0.8,  $CHCl_3$ ).  $^1H$  NMR ( $CDCl_3$ , 400 MHz)  $\delta$  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)  $\delta$  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-(carbamoyldiazanyl)-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.  $[\alpha]_D^{25} -14$  (c 0.8,  $CHCl_3$ ).  $^1H$  NMR ( $CDCl_3$ , 400 MHz)  $\delta$  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)  $\delta$  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)diazanyl)hexahydropyrrolo[1,2-b]isoxazole-3-carboxylate 12a.** (0.505 g, 76%); yellow solid. mp 94–96 °C.  $[\alpha]_D^{25} +14$  (c 1.4,  $CHCl_3$ ).  $^1H$  NMR ( $CDCl_3$ , 400 MHz)  $\delta$  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 (AB system, 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)  $\delta$  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)diazanyl)-2-methylhexahydropyrrolo[1,2-b]isoxazole-3-carboxylate 12b.** (0.530 g, 82%); yellow oil.  $[\alpha]_D^{25} +6.8$  (c 1.6,  $CHCl_3$ ).  $^1H$  NMR ( $CDCl_3$ , 400 MHz)  $\delta$  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)  $\delta$  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)diazanyl)-2-methylhexahydropyrrolo[1,2-b]isoxazole-3-carboxylate 12d.** (0.483 g, 80%); yellow oil.  $[\alpha]_D^{25} +7$  (c 1.2,  $CHCl_3$ ).  $^1H$  NMR ( $CDCl_3$ , 400 MHz)  $\delta$  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)  $\delta$  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-(carbamoyldiazanyl)-2-methylhexahydropyrrolo[1,2-b]isoxazole-3-carboxylate 12e.** (0.446 g, 74%); yellow solid. mp 67–69 °C.  $[\alpha]_D^{25} +6$  (c 1.0,  $CHCl_3$ ).  $^1H$  NMR ( $CDCl_3$ , 400 MHz)  $\delta$  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)  $\delta$  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.

**(4*S*,5*S*)-Methyl 2-benzyl-3-((2*S*)-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.  $[\alpha]_D^{25} +12$  (c 0.2,  $CHCl_3$ ).  $^1H$  NMR ( $C_6D_6$ , 500 MHz)  $\delta$  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)  $\delta$  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.

**(4*S*,5*S*)-Methyl 2-benzyl-5-((*tert*-butoxycarbonyl)diazanyl)-3-((2*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)-5-methylisoxazolidine-4-carboxylate 13b.** Isomer 1: (0.176 g, 38%); oil.  $[\alpha]_D^{25} +14$  (c 0.3,  $CHCl_3$ ).  $^1H$  NMR ( $C_6D_6$ , 500 MHz)  $\delta$  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)  $\delta$  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.  $[\alpha]_D^{25} -10$  (c 0.3,  $CHCl_3$ ).  $^1H$  NMR ( $C_6D_6$ , 500 MHz)  $\delta$  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)  $\delta$  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.

**(4*S*,5*S*)-Methyl 2-benzyl-3-((2*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)-5-((methoxycarbonyl)diazanyl)-5-methylisoxazolidine-4-carboxylate 13d.** Isomer 1: (0.153 g, 36%); oil.  $[\alpha]_D^{25} +4$  (c 0.2,  $CHCl_3$ ).  $^1H$  NMR ( $C_6D_6$ , 400 MHz)  $\delta$  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).  $^{13}C$  NMR ( $C_6D_6$ , 100 MHz)  $\delta$  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.  $[\alpha]_D^{25} +11$  (c 0.2,  $CHCl_3$ ).  $^1H$  NMR ( $C_6D_6$ , 500 MHz)  $\delta$  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)  $\delta$  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.

**(4*S*,5*S*)-Methyl 2-benzyl-5-((*tert*-butoxycarbonyl)diazanyl)-5-methyl-3-((3*aR*,5*aS*,8*aS*,8*bR*)-2,2,7,7-tetramethyltetrahydro-3*aH*-bis[[1,3]dioxolo[4,5-*b*:4',5'-*d*]pyran-5-yl)isoxazolidine-4-carboxylate 14b.** Isomer 1: (0.202 g, 34%); oil.  $[\alpha]_D^{25} -9$  (c 0.2,  $CHCl_3$ ).  $^1H$  NMR ( $C_6D_6$ , 500 MHz)  $\delta$  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,  $J = 4.8$  Hz), 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)  $\delta$  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.  $[\alpha]_D^{25} +5$  (c 0.2,  $CHCl_3$ ).  $^1H$  NMR ( $C_6D_6$ , 500 MHz)  $\delta$  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)  $\delta$  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) at a maximum temperature of 70 °C. The obtained crude material was purified by column chromatography (hexane–EtOAc, 3 : 2).

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