



A theoretical investigation of the regio- and stereoselectivities of the 1,3-dipolar cycloaddition of C-diethoxyphosphoryl-N-methylnitrone with substituted alkenes

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ABSTRACT

A theoretical study of the regio- and stereoselectivities of the 1,3-dipolar cycloaddition of C-diethoxyphosphoryl-N-methylnitrone with substituted alkenes (allyl alcohol and methyl acrylate) is carried out using DFT at the B3LYP/6-31G(d,p) level of theory. The FMO analysis and DFT-based reactivity indices confirmed the experimental *ortho* regioisomeric pathway. Potential energy surface analysis shows that these 1,3-dipolar cycloaddition reactions favor the formation of the *ortho-trans* cycloadduct in both cases. The obtained results are in agreement with experimental data.

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1,3-Dipolar cycloadditions (1,3-DCs) are important processes in synthetic chemistry and are widely used for obtaining five-membered heterocyclic compounds.¹ Reactions between nitrones and alkenes leading to isoxazolidines are well-known processes of this kind.^{1,2} Substituted isoxazolidines have found numerous applications as enzyme inhibitors,^{3,4} and as intermediates for the synthesis of a variety of compounds after cleavage of the N–O bond.⁵ A significant amount of theoretical and experimental work has been devoted to the study of the selectivities of 1,3-dipolar cycloadditions. Pranata et al.⁶ studied the regioselectivity of nitrone cycloadditions. In 1,3-DCs between the simplest nitrone and electron-rich alkenes, the *ortho* regioisomers were predicted to be more favorable than the *meta*, and in the case of electron-poor alkenes, calculations predicted a lack of regioselectivity. The reaction of the simplest nitrone with nitroethylene has been investigated by Cosio et al.,⁷ their calculations predicted *endo* stereoselectivity and *meta* regioselectivity. Gandolfi⁸ also studied the 1,3-DC of the simplest nitrone with vinylboranes. The calculations showed that the vinylboranes may undergo very fast [3+2] cycloaddition resulting in a single *endo* adduct. It was also pointed out that the boronyl substituent is intimately involved in the reaction mechanism via very strong B–O interactions that are able to produce very low energy barriers, and complete *endo* selectivity, via a type of effective and selective intramolecular catalysis.⁹ Domingo¹⁰ studied the 1,3-

DC of C,N-diphenylnitrone with *tert*-butyl vinyl ether. His theoretical calculations predicted an *exo*-stereoselectivity with *ortho*-regioselectivity, which were in agreement with the experimental data. The *exo*-stereoselectivity was assigned, since in the case of the *endo* approach, steric hindrance develops between the phenyl group at the N atom and the *tert*-butyl group of the ether. Merino et al.^{11a} studied the 1,3-DCs of both electron-poor and electron-rich alkenes with D-glyceraldehyde nitrone,^{11b} glyoxylic nitrone,^{11c} and C-heteroaryl nitrones.^{11d} Taking into consideration the conformational lability of the nitrones, the predictions thus obtained were in good agreement with the experimental findings. Langlois et al.¹² performed calculations on frontier molecular orbital energies and coefficients of an oxazoline-type nitrone and electron-poor alkenes at the RHF/AM1 level. These studies confirmed the experimentally observed *endo* selectivity. The authors explained such preference by a second-order orbital interaction between the electron-withdrawing group of the olefin and the *endo*-ring oxygen atom of the nitrone.

Piotrowska¹³ found experimentally that the 1,3-DCs of C-diethoxyphosphoryl-N-methylnitrone with allyl alcohol and methyl acrylate were regiospecific affording the corresponding *ortho-trans* cycloadduct as the major regio- and diastereoisomer (Table 1). The major *trans* diastereoisomer originates from *endo* approach of the nitrone to the alkene, the minor *cis* derives from *exo* approach of the nitrone to the alkene (see Scheme 3).

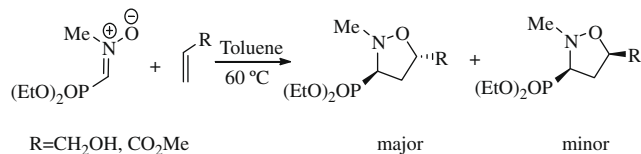
Our aim in this work was to undertake a theoretical investigation of the regio- and stereoselectivities of the 1,3-dipolar cycloadd-

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Table 1
Experimental regio- and stereoselectivity ratios

Reaction	R	<i>ortho:meta</i> ratio	<i>trans:cis</i> ratio
1	CH ₃ OH	100.0	(62:38)
2	CO ₂ Me	100.0	(90:10)



Scheme 1. 1,3-Dipolar cycloaddition of C-diethoxyphosphoryl-*N*-methylnitronium with alkenes.

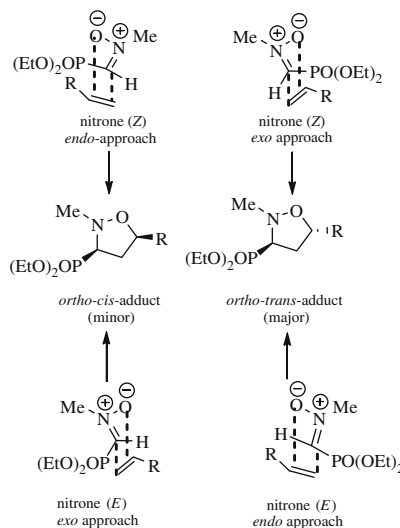
dition reactions of C-diethoxyphosphoryl-*N*-methylnitronium with substituted alkenes (Scheme 1) by analyzing the potential energy surfaces (PESs) corresponding to all possible regio- and stereocycloaddition channels, analysis of the frontier molecular orbital (FMO) interactions, and the global and local reactivity indices: the electronic chemical potential (μ) which is the opposite of electronegativity,¹⁴ and the electrophilicity (ω) which is a measure of the stabilization of the system.¹⁵ All calculations were carried out with GAUSSIAN 03.¹⁶ Geometry optimization of the stationary points (reactants, transition structures, and products) was carried out using DFT methods at the B3LYP/6-31G (d,p) level of theory.¹⁷ The stationary points were characterized by frequency calculations in order to verify that minima and transition states have zero and one imaginary frequency, respectively. The atomic electronic population and DFT-based reactivity indices were computed using natural population analysis (NPA).¹⁸

The electronic chemical potential, $\mu = \varepsilon_{\text{HOMO}} + \varepsilon_{\text{LUMO}}/2$.

The electrophilicity index, $\omega = \mu^2/\varepsilon_{\text{LUMO}} - \varepsilon_{\text{HOMO}}$.

As a computational model, we used the simplest phosphoryl nitronium **1** to investigate the regio- and diastereoselectivities of its reactions with allyl alcohol **2a** and methyl acrylate **2b**, and considered two reaction channels. The *endo* and *exo* approaches were investigated. Consequently, four transition states leading to four possible cycloadducts were located for each nitronium-alkene pair (Scheme 2). Table 2 shows the values of the FMO energies (a.u.) and molecular coefficients of the reactants. Figure 1 presents a schematic representation of the possible interactions between the FMOs (HOMO_{dipole}-LUMO_{dipolarophile}) and (HOMO_{dipolarophile}-LUMO_{dipole}).

According to Houk's rule,¹⁹ in general, the regioselectivity of these cycloadditions can be rationalized in terms of more favorable FMO interactions between the largest coefficient centers of the dipole and the dipolarophile. The FMO analysis for the studied cycloadditions shows that the main interactions occur between the HOMO_{dipolarophile} of alkene **2a** and the LUMO_{dipole} of nitronium **1** [in-



Scheme 3. The *endo* and *exo* approaches of nitronium **1** to alkenes **2a,b**.

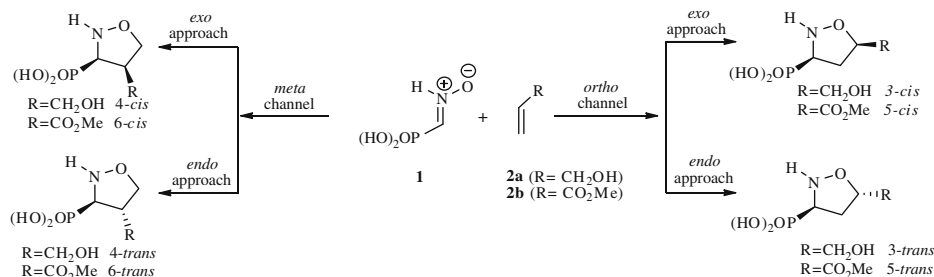
Table 2

The FMO energies (a.u.), electronic chemical potential (a.u.), and electrophilicity (a.u.) indices for the reactants

Reactant	HOMO	LUMO	μ	ω
1	-0.362	0.072	-0.144	0.024
2a	-0.366	0.175	-0.095	0.008
2b	-0.381	0.069	-0.156	0.027

verse electronic demand (IED) character], and in the reaction between nitronium **1** and alkene **2b** the main interaction occurs between the HOMO_{dipole} of nitronium **1** and the LUMO_{dipolarophile} of the alkene **2b** [normal electronic demand (NED) character]. In the reaction between nitronium **1** and alkene **2a**, the most favored large-large interaction takes place between C1 of the alkene **2a** and C3 of nitronium **1**, and the small-small interaction takes place between C2 of **2a** and O1 of nitronium **1** (*ortho* channel). In the reaction between nitronium **1** and alkene **2b**, the most favored interaction takes place between O1 of nitronium **1** and C2 of alkene **2b** (large-large) and the small-small interaction occurs between C3 of **1** and C1 of **2b** (*ortho* channel). Consequently, we conclude that Houk's rule, based on the FMO model, correctly reproduces the experimental regioselectivity of these 1,3-DC reactions.

Table 2 shows the values of the FMO energies, electronic chemical potentials, and the global electrophilicity indices of the reactants. The electronic chemical potential of the dipolarophile **2a** is (-0.095 a.u.) and is larger than that of dipole **1** (-0.144 a.u.) indicating that the charge transfer will take place from the alkene **2a** to nitronium **1**; this is in agreement with the FMO analysis. Moreover, the global electrophilicity of nitronium **1** (0.024 a.u.) is higher than



Scheme 2. 1,3-Dipolar cycloaddition reactions of nitronium **1** and alkenes **2a** and **2b**.

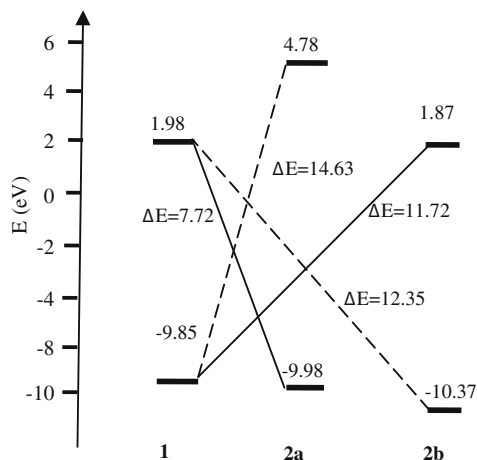


Figure 1. FMO interactions in the 1,3-DC reactions of nitrone **1** with alkenes **2a** and **2b**.

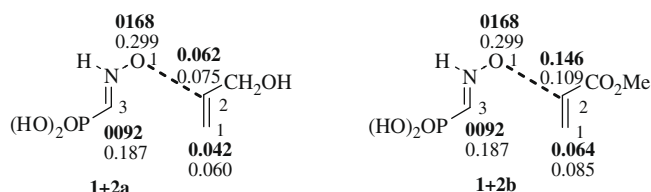
Table 3

Electrophilic and nucleophilic Fukui indices and local electrophilicities for the reactive atoms of the nitrone and the alkenes

	Nitrone 1		Alkene 2a		Alkene 2b	
	O1	C3	C1	C2	C1	C2
f^+	0.259	0.143	0.191	0.286	0.088	0.195
f^-	0.461	0.289	0.277	0.342	0.114	0.278
ω^+	0.168	0.092	0.042	0.062	0.064	0.146
ω^-	0.299	0.187	0.060	0.075	0.085	0.209

that of alkene **2a** (0.008 a.u.). Consequently, nitrone **1** will act as an electrophile whereas alkene **2a** will act as a nucleophile, and hence the reaction between **1** and **2a** possesses IED character. The electronic chemical potential of **2b** (−0.156 a.u.) is smaller than that of dipole **1** (−0.144 a.u.) indicating that charge transfer will take place from nitrone **1** to alkene **2b**, which is in agreement with the FMO analysis. Moreover, the global electrophilicity of alkene **2b** (0.027 a.u.) is higher than that of nitrone **1** (0.024 a.u.). Thus nitrone **1** will act as a nucleophile whereas alkene **2b** will act as an electrophile, and therefore the reaction of nitrone **1** with **2b** possesses NED character.

The local electrophilicity indices ω_k of atom k are easily obtained by projecting the global quantity into any atomic center k in the molecule by using the electrophilic Fukui index f . The Fukui function is $\omega_k = \omega f_k^+ = \omega[\rho_k(N+1) - \rho_k(N)]$ for nucleophilic attack, and $\omega_k = \omega f_k^- = \omega[\rho_k(N) - \rho_k(N-1)]$ for electrophilic attack. $\rho_k(N)$, $\rho_k(N+1)$, $\rho_k(N-1)$ are the gross electronic population of site k in neutral, anionic, and cationic systems, respectively.²⁰ The values of the Fukui indices f_k and local electrophilicity indices ω_k are reported in Table 3. For better visualization we have depicted these interactions in Scheme 4. In the reaction between **1** and **2a**, the most favorable two-center interaction takes place between C2 of alkene **2a** and O1 of the nitrone leading to the formation of the



Scheme 4. Illustration of the favorable interactions using local electrophilicity indices (ω^+ bold, ω^- normal).

Table 4

Molecular coefficients of the FMOs for nitrone **1** and alkenes **2a** and **2b**

Reactant				
1	O1	HOMO	C3	LUMO
		0.36276		−0.00014
2a	C1	HOMO	C2	LUMO
		0.28525		0.26538
2b	C1	HOMO	C2	LUMO
		−0.23147		−0.23311

Table 5

Energies and relative energies (ΔE) of the reagents, transition states, and products

Reaction	System	E (a.u.)	ΔE (kcal/mol)
1+2a	Nitrone 1	−737.508	
	Alkene 2a	−193.120	
	TS-3- <i>endo</i>	−930.607	13.83 ^a
	TS-3- <i>exo</i>	−930.601	17.87 ^a
	TS-4- <i>endo</i>	−930.573	35.11 ^a
	TS-4- <i>exo</i>	−930.590	24.90 ^a
	Pt-3- <i>cis</i>	−930.674	−27.86 ^a
	Pt-3- <i>trans</i>	−930.676	−29.00 ^a
	Pt-4- <i>cis</i>	−930.670	−25.24 ^a
	Pt-4- <i>trans</i>	−930.672	−27.01 ^a
1+2b	Alkene 2b	−231.243	
	TS-5- <i>endo</i>	−1043.957	16.56 ^b
	TS-5- <i>exo</i>	−1043.954	18.75 ^b
	TS-6- <i>endo</i>	−1043.956	17.61 ^b
	TS-6- <i>exo</i>	−1043.957	16.99 ^b
	Pt-5- <i>cis</i>	−1044.019	−21.80 ^b
	Pt-5- <i>trans</i>	−1044.019	−22.22 ^b
	Pt-6- <i>cis</i>	−1044.002	−11.22 ^b
	Pt-6- <i>trans</i>	−1044.010	−16.37 ^b

^a The energies of the TSs and products are referred to the sum $[E_1+E_{2a}]$.

^b The energies of the TSs and products are referred to the sum $[E_1+E_{2b}]$.

ortho-regioisomer. In the reaction between **1** and **2b**, the most favorable interaction takes place between O1 of the nitrone and C2 of the alkene **2b**; these results are in agreement with the experimental findings (see Table 4).

The 1,3-dipolar cycloaddition reaction of nitrone **1** with dipolarophiles **2a** and **2b** can take place along four reactive channels corresponding to the *endo* and *exo* approach modes in two regioisomeric pathways, *ortho* and *meta* (Scheme 2). For each nitrone–alkene pair, we studied four TSs and four cycloadducts. The geometries of the eight TSs are given in Figure 2 together with the newly forming bond lengths. Table 5 reports the energies (a.u.) and relative energies (kcal/mol). The PESS, corresponding to all the reaction channels, are illustrated in Figure 3.

Reaction between **1** and **2a**: from the calculated relative energies, the *ortho-endo* approach (TS-3-*endo*) is favored kinetically in comparison with the other approaches; in addition, the *ortho-trans* product Pt-3-*trans* is favored thermodynamically. The low energy difference (1.14 kcal/mol) between Pt-3-*trans* and Pt-3-*cis* may suggest the formation of a mixture of diastereoisomers as observed experimentally. The *meta*-regioisomeric channels are unfavorable kinetically and thermodynamically due to steric hindrance between the phosphoryl group of the nitrone and the CH₂OH group of the alkene **2a**.

Reaction between **1** and **2b**: analysis of the relative energies reveals that the low activation energy (16.56 kcal/mol) for the *ortho-endo* approach (TS-5-*endo*) favored the formation of Pt-5-*trans* as the kinetic product, this preference is explained by the secondary π orbital interaction of the *N*-nitroene *Pz* orbital with a vicinal *Pz*

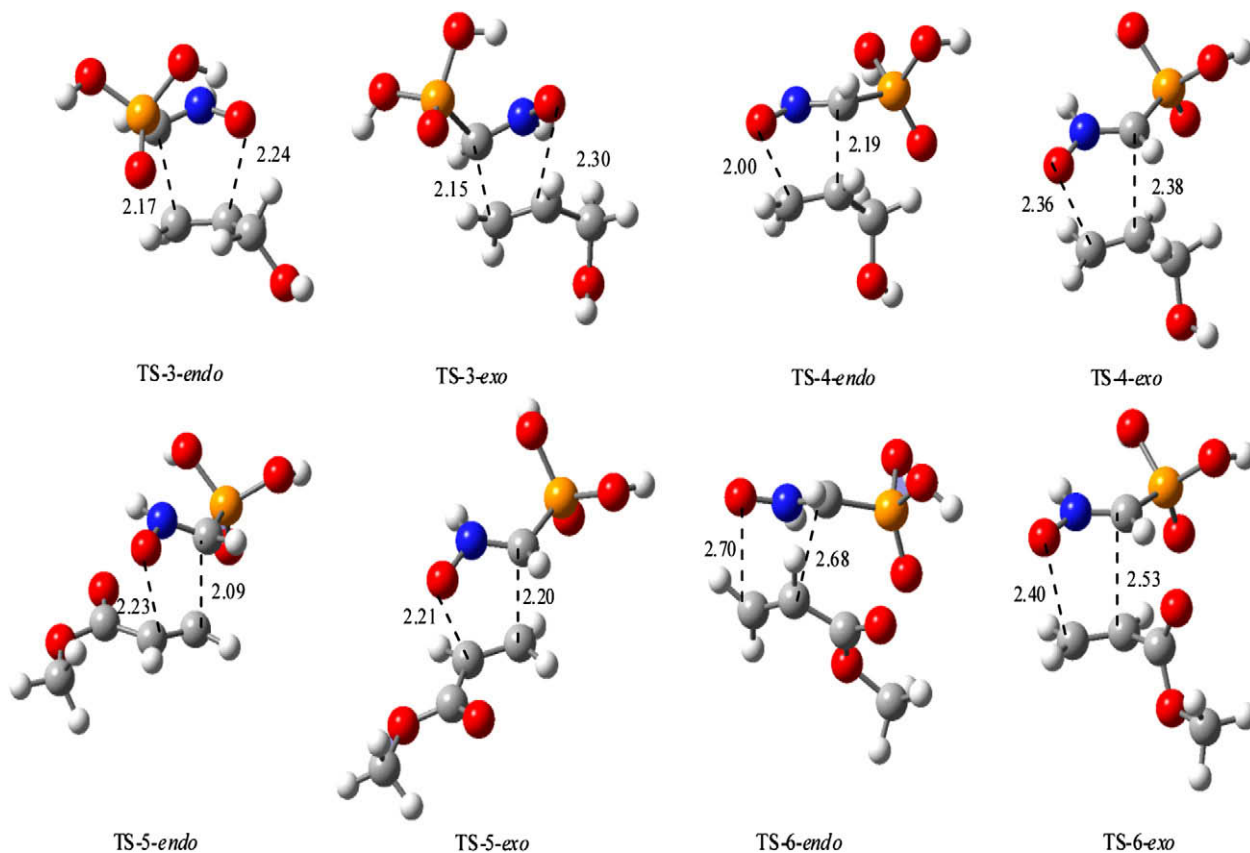


Figure 2. Transition structures of the two cycloaddition reactions of nitrone **1** with alkenes **2a** and **2b**.

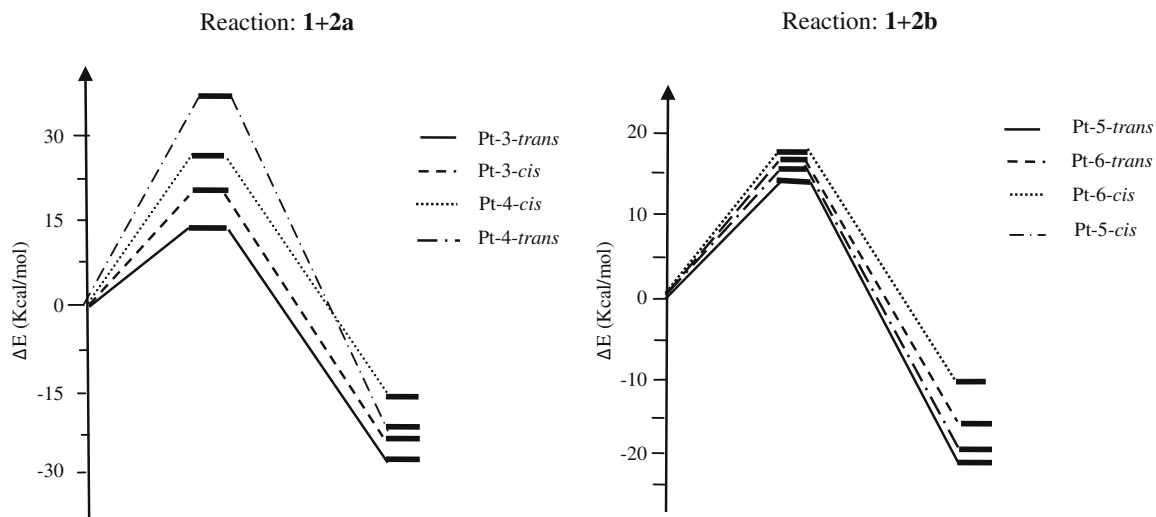


Figure 3. Energy profiles, in kcal/mol for the 1,3-DC reactions of nitrone **1** with alkenes **2a** and **2b**.

orbital on the alkene **2b**, and this interaction is small.²¹ The *meta* regioisomeric pathway is unfavorable due to steric hindrance between the phosphoryl group of the nitrone and the acyl group of alkene **2b**. On the other hand, for the *endo* approach (TS-6-*endo*), there are unfavorable interactions between the oxygen atoms of the phosphoryl group of the nitrone and the ester group of the alkene **2b** (Fig. 4). The distance between the oxygen atoms is 2.67 Å.

In conclusion the regio- and stereoselectivities of the 1,3-dipolar cycloaddition reactions of C-diethoxyphosphoryl-*N*-methylnit-

rone with substituted alkenes have been studied using DFT methods at the B3LYP/6-31G(d,p) level of theory. These calculations successfully explain the experimental results. The regioselectivity (*ortho/meta* channel) is controlled by FMO coefficients. We have shown that the most favorable interactions lead to the formation of the *ortho*-regioisomer in both reactions. The global and local DFT-based reactivity indices' analysis confirmed this regioselectivity. Comparison of the cycloadduct and TS energies indicates high *endo*-diastereoselectivity for both cycloadditions leading to the

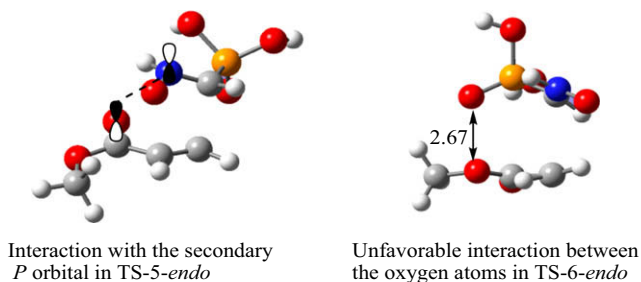


Figure 4. Geometries of both *endo*-TSs for the 1,3-DCs of nitrone **1** with alkene **2b**.

formation of Pt-3-*trans* in the reaction between **1** and **2a**, which is favored kinetically and thermodynamically. In the reaction between **1** and **2b** the formation of Pt-5-*trans* is favored thermodynamically and kinetically, the latter due to stabilization by the secondary π orbital interaction of the *ortho-endo* approach (TS-5-*endo*). These results corroborate very well with the experimental observations.

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