Regio- and Stereoselectivity of Captodative Olefins in 1,3-Dipolar Cycloadditions. A DFT/HSAB Theory Rationale for the Observed Regiochemistry of Nitrones

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Captodative olefins 1-acetylvinyl carboxylates proved to be highly regioselective dipolarophiles in 1,3-dipolar cycloadditon to propionitrile oxide, arylphenylnitrile imines, diazoalkanes, and nitrones to yield the corresponding 5-substituted heterocycles. The addition of the latter was also stereoselective, being slightly susceptible to steric demand of the carboxylate substituent in the olefin. All atempts to cleave the isoxazolidine N−O bond under reductive conditions failed, providing diverse products with side-group reduction. FMO theory was unsuccessful to explain the regioselectivity observed with nitrones, since the opposite orientation was predicted. The recently formulated DFT/HSAB theoretical model was able to rationalize this regioselectivity, identifying the nucleophilic and electrophilic atoms involved in the process via calculation of interaction energies, suggesting the specific direction of the electronic process at each of the reaction sites.

Introduction

1,3-Dipolar cycloaddition is among the most important pericyclic reactions, due to the versatile and straightforward way to generate a great number of heterocycles, and to the relevance of the mechanistic aspects involved in these processes.[1] Multiple substituted olefins with diverse electron-demand substituents have been extensively studied in order to determine the factors which control the regio- and stereoselectivity in these cycloadditions.[2] Thus, it has been established that in the addition of nitrile oxides to monosubstituted olefins, regardless of the electron-demand of the substituent, the 5-susbtituted isoxazoles are preferentially obtained.[3] Diazo compounds undergo 1,3-dipolar addition with a variety of olefins, providing also the pyrazole substituted on the C-5 position.[4] Similar regioselectivity was observed when diarylnitrile imines were used.[5] In contrast, nitrones react with olefins bearing strong electron-withdrawing substituents, such as the nitro group, to give the C-4 substituted isoxazolidines, while the C-5 regioisomer was preferred when electron-releasing and moderate electron-withdrawing substituted olefins were added.[3a,6] Addition to 1,2-disubstituted olefins has proven to be regioselective as well, but they were restricted to have reverse electron-demand substituents.[7] Although some studies have been devoted to captodative olefins in 1,3-dipolar additions,[8] for most of the reports, they have been only treated as occasional examples.[6h,9] However, they have attracted especial interest in Diels−Alder

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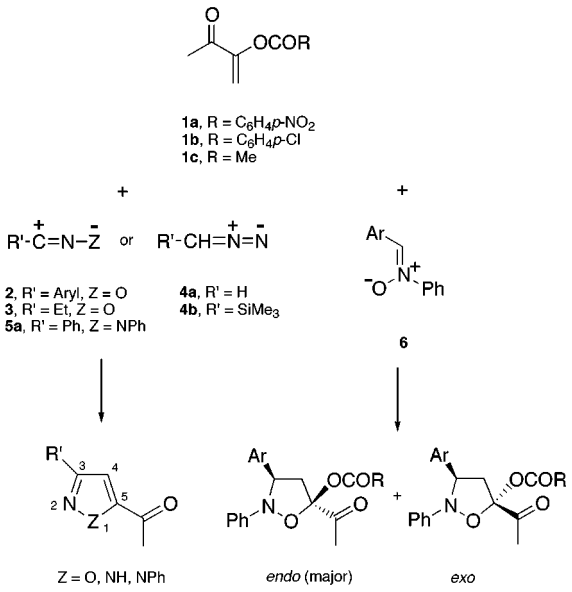
reactions, because of the opposite electronic effect displayed by their geminally substituted functional groups.[10]

Regioselectivity in 1,3-dipolar cycloadditions has been traditionally explained in terms of FMO theory, providing a quite successful agreement with the experimental result.[1b,3a,11] Indeed, the prediction of monosubstituted olefins with electron-withdrawing or electron-donating groups appears to match very well, assuming a normal and reverse electron-demand FMO interaction, respectively.[12] Several explanations have been furnished for the unreliable predictions, including repulsive secondary orbital interactions,[13] and closed-shell repulsions.[14] The high level ab initio calculations of transition structures and activation parameters of the regioisomeric approaches have satisfactorily accounted for the 1,3-dipolar additions between dipoles and dipolarophiles with diverse electron-demand.[1e,15] A less predictable behavior may be ascribed to captodative olefins, owing to the antagonic electronic effect upon the double bond, and to the steric hindrance generated around the disubstituted olefinic carbon. Indeed, FMO theory fails to rationalize the orientation observed with some captodative and disubstituted olefins.[1d,4,8b,9a,16] Steric effects have been invoked as controlling the cycloaddition.[17] The presence of a radicaloid or dipolaroid transition state generated by these strongly polarized dipoles at the ground state has also been suggested.[10a,18]

Recently, we reported the 1,3-dipolar cycloaddition of captodative 1-acetylvinyl carboxylates **1** with arylnitrile oxides **2**,[19] and preliminary results with propionitrile oxide (**3**), diazoalkanes **4**, diphenylnitrile imine (**5a**), and nitrones **6** (Scheme 1).[20] In all cases, the reactions were highly regioselective, yielding the C-5 substituted heterocycle. For dipoles **2**−**5a**, the aromatic products were isolated as a consequence of the elimination of the aroyloxy group, in contrast with nitrones for which the adducts were stable, giving the *endo* stereoisomers preferentially. Because FMO theory failed to account for the regiochemistry observed in the additions with benzonitrile oxide, an alternative novel theoretical model was investigated, including density functional theory (DFT) and the hard and soft acids and bases principle (HSAB), proving to be in agreement with the experimental results.[21]

Scheme 1



With the aim to improve our knowledge of the factors which govern the reactivity and selectivity of captodative olefins in cycloadditon reactions, we herein describe an extensive study of regioselectivity and stereoselectivity of 1,3-dipolar additions of dienophiles **1** to diverse dipoles. We also disclose full details about our calculations which rationalizes the reactivity and regiochemistry found with nitrones.

Results

The 1,3-dipolar cycloadditions between olefin **1a** and *C*-aryl-*N*-phenylnitrile imines **5a**−**d** under thermal conditions provided the corresponding 5-acetyl pyrazoles **9a**−**d** in good yields (Scheme 2). The nitrile imines were prepared in situ by treatment of arylaldehyde phenylhydrazones **7a**−**d** with chloramine-T in dry dioxane under reflux. These aromatic heterocycles might have been formed as a result of β-elimination of the *p*-nitrobenzoyloxy group (PNB) from the first formed cycloadducts **8a**−**d**. No evidence of the latter was found either by chromatography or by NMR, even after stopping the reaction before the dipolarophile had disappeared. The stabilization of the adducts by aromatization of the ring could be the driving force to give the pyrazoles.

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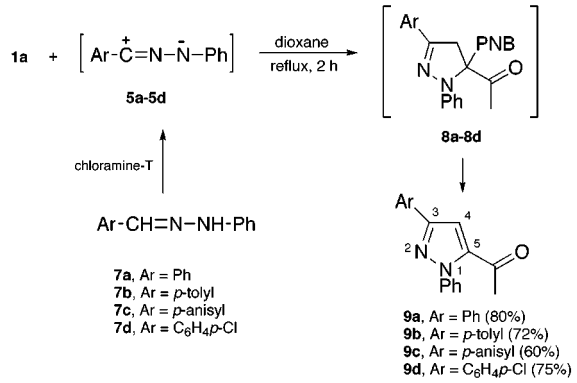
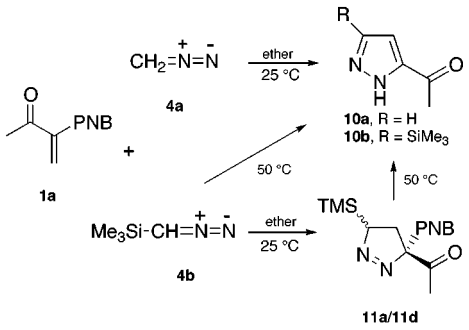
Scheme 2



Scheme 3

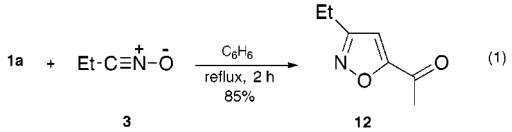


On the other hand, no traces of the 4-acetyl regioisomers were detected in the crude mixtures by ^{1}H NMR. The structure of pyrazoles **9** was confirmed by NOE experiments, since enhancements of the signals of aromatic protons of the C-3 aryl group and acetyl protons were observed when proton H-4 was irradiated.

The cycloaddition of **1a** with diazoalkanes such as diazomethane (**4a**) took place efficiently at room temperature to yield only pyrazole **10a** (Scheme 3). In contrast, with trimethylsilyl diazomethane (**4b**), a mixture of stereoisomeric adducts **11a**/**11b** (79:21), along with product **10a** in a ca. 1:1 ratio, were isolated. Interestingly, the expected silylated pyrazole **10b** was not detected. Adducts **11a**/**11b** seem to be precursors of pyrazole **10a**, as suggested by the transformation into this pyrazole (80%) by thermal (50 °C) treatment of **11a**/**11b**. Additional support for the above was obtained from the reaction of dipole **4b** with **1a** at 50 °C for 1 h, to give the expected single product **10a**.

Thus, this reaction gives evidence that the cycloadduct is the primary product formed in the reaction, and then it is transformed into the more stable aromatic product. A similar event might be taking place in the reaction with the other dipoles which give rise to aromatic heterocycles, including nitrile imines and nitrile oxides.

Addition of the aliphatic nitrile oxide **3** (C_6H_6, reflux, 2 h) to olefin **1a** furnished the single isoxazole **12** in 85% yield (eq 1). The formation of the heterocycle and the regiochemistry agreed with analogous results observed for the reaction of arylnitrile oxides **2** with olefin **1a**.[19]



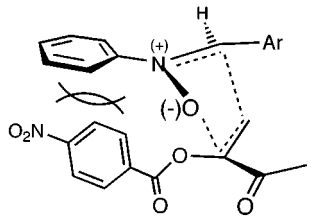


Figure 1. Steric interactions between the *N*-phenyl and aroyloxy groups at the *exo* transition state.

Table 1. 1,3-Dipolar Additions of 1c with Dipoles 3 and 5a[a]

dipole (mol equiv)	solvent	*T* (°C)	*t* (h)	product	yield (%)[b]
3 (6.0)	C_6H_6	80	2.0	**12**	63
5a (3.0)	dioxane	90	2.0	**9a**	60

[a] All under N_2 atmosphere. [b] After column chromatography and/or recrystallization.

It has been suggested that steric interactions are responsible for the regioselectivity observed in many 1,3-dipolar additions.[16,17] This prompted us to examine the steric effect of the PNB group on the control of the regiochemistry observed with the aforementioned dipoles. The aromatic ring could give rise to strong nonbonding interactions, since the X-ray structure and the gas-phase calculations of **1a** have shown that the PNB group is out of the plane formed by the enone π system.[22] Therefore, the sterically less hindered captodative olefin **1c** was evaluated, keeping the potential electron-donor effect of the carboxylate group on the olefin. Table 1 summarizes the results obtained in the cycloaddition reactions with dipoles **3** and **5a**. As observed with olefin **1a**, the aromatic heterocycles were isolated and they showed the same regiochemistry.

Similar results were obtained when olefins **1a** and **1c** were added to *N*-phenylnitrones **6a**−**g**: only the C-5 substituted isoxazolidines were observed as a mixture of stereoisomers **13**/**14** and **15**/**16**, respectively (Table 2). However, comparatively, the *endo* stereoselectivity was higher in the case of olefin **1a**. Despite the predominance of one or another diastereoisomer depending on a subtle interplay of several steric and electronic factors,[1d] this *endo* preference of **1a** could be rather associated with stronger steric interactions leading to an *exo* transition state between the *N*-phenyl group of the nitrone and the PNB group in the dipolarophile (Figure 1). That steric interactions would be controlling the *endo* preference in the additions might be supported by the fact that no traces of isomers *exo* **14h** and **16h** were detected when the more crowded nitrone **6h** was used with both olefins **1a** and **1c** (Table 2, entries 8 and 13).[23] Therefore, the presence of the bulky *N*-*tert*-butyl group influences the distribution of diastereomers, although it does not affect the regiochemistry of the cycloaddition.

Additions of olefin **1c** to nitrones **6c** and **6f** were, however, slower than those with olefin **1a** (Table 2, entries 11 and 12), correlating with their relative reac-

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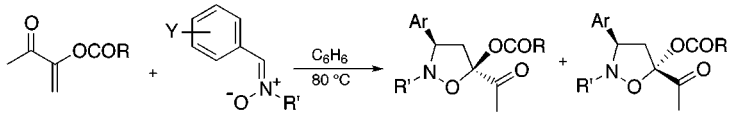
Table 2. 1,3-Dipolar Additions of Olefins 1a and 1c with Nitrones 6a−6j[a]



1a, R = C_6H_4*p*-NO_2 **1c**, R = Me | **6** | **13**, R = C_6H_4*p*-NO_2 **15**, R = Me | **14**, R = C_6H_4*p*-NO_2 **16**, R = Me

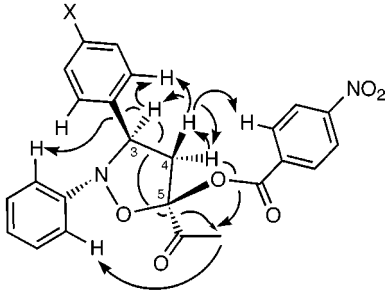
entry	olefin[b]	nitrone	R′	Y	*t* (h)	products (ratio)[c]	yield (%)[d]
1	**1a**	**6a**	Ph	H	8	**13a**/**14a** (89:11)	70
2	**1a**	**6b**	Ph	*p*-Cl	8	**13b**/**14b** (90:10)	75
3	**1a**	**6c**	Ph	*p*-Br	8	**13c**/**14c** (87:13)	70
4	**1a**	**6d**	Ph	*p*-NO_2	8	**13d**/**14d** (85:15)	70
5	**1a**	**6e**	Ph	*p*-MeO	8	**13e**/**14e** (83:17)	80
6	**1a**	**6f**	Ph	*p*-Me	8	**13f**/**14f** (95:5)	80
7	**1a**	**6g**	Ph	*m*-NO_2	8	**13 g**/**14g** (89:11)	75
8	**1a**	**6h**	*t*-Bu	H	24	**13h**/**14h** (100:0)	44
9	**1a**	**6i**	Bn	*p*-MeO	24	**13i**/**14i** (85:15)	50
10	**1a**	**6j**	Bn	*p*-Me	24	**13j**/**14j** (60:40)	30
11	**1c**	**6c**	Ph	*p*-Br	12	**15a**/**16a** (73:27)	70
12	**1c**	**6f**	Ph	*p*-Me	12	**15b**/**16b** (82:18)	50
13	**1c**	**6h**	*t*-Bu	H	12	**15c**/**16c** (100:0)	45

[a] All under N_2 atmosphere, in dry benzene under reflux. [b] 1.0 mol equiv of **1a**, and 1.5 mol equiv of **1c**. [c] Determined by ^{1}H NMR (300 MHz) from the crude. [d] Of the major isomer after column chromatography and recrystallization.

tivities.[24] An analogous trend is noticed with *N*-benzylnitrones **6i** and **6j** in comparison with *N*-phenylnitrones, since the former reacted with olefin **1a** at longer reaction times.

It has been well established that nitrones substituted with bulky groups possess the *Z* configuration, with *N*-alkyl or *N*-phenyl and *C*-aryl groups in a *trans* relationship.[9a] Nevertheless, we have also examined the stereochemistry of some of the nitrones used in this study. X-ray crystal structures of **6e** and **6k** (*N*-benzyl-*C*-phenylnitrone),[25] and NOE experiments of the less studied nitrones **6i**−**k**, confirmed that in the solid phase and in solution they show the *Z* configuration. For this reason, we assumed that the same configuration is maintained at the transition state, and they do not isomerize during the course of the cycloaddition.[9f] A further interesting feature to notice in the X-ray structure of **6e** is that the *N*-phenyl and *C*-anisyl groups present conformations slightly out of the plane formed by the dipole. Accordingly, the steric interactions illustrated in Figure 1 become significant if the conformation of the *N*-phenyl group of the nitrone is retained at the transition state. An analogous argument could be invoked for the low *endo* selectivity recorded in the reaction of nitrone **6j** (Table 2, entry 10), considering the motion of the *N*-benzyl group around the C−N bond.

The structures of the major isomers were established by ^{1}H NMR spectroscopy. In the case of isomers **13** and **15**, double irradiation, COSY, and HETCOR experiments were determined in order to correlate the isoxazolidine ring protons. The multiplicity and coupling constants were consistent with vicinal CH and methylene groups. The relative configuration on carbons C-3 and C-5 was provided by NOE experiments. For example, in adducts **13b** and **13c**, an enhancement of the signals of H-4α and the acetyl group on C-5 was observed when H-3 was irradiated (Figure 2). At the same time, the latter produced, as expected, a strong NOE enhancement of the



13b, X = Cl
13c, X = Br

Figure 2. NOE observed upon irradiation of protons in **13b** and **13c**.

signals attributed to the protons of the C-3 aromatic ring and, in lesser extent, of the aromatic protons of the *N*-phenyl group. This group appears to be oriented in the α position with an *anti* relationship with respect to the aryl group on C-3. This relative configuration also agrees with the NOE effect observed in the signals of these protons when the acetyl group was irradiated. A further support for the above was the observable enhancement of the protons of the *p*-nitrobenzoyloxy group by irradiation of H-4*β*.

This assignment was confirmed by X-ray crystallography of isoxazolines **13h** and **14j**,[25] which were crystallized from a mixture of hexane/EtOAc (7:3) (Figure 3). In the adduct **13h**, the heterocycle exhibits a conformation with the C-3 aryl ring and PNB group in pseudoaxial positions, leaving the acetyl group in a pseudoequatorial conformation. A similar conformation is displayed in the crystal structure of **14j**, the PNB group shows a quasi-axial conformation, leaving the *p*-tolyl ring in the pseudo-equatorial position. This preference of the PNB group for the pseudoaxial conformation (as previously observed in the half-chair conformation of cyclohexene adducts of dienes with olefin **1a**[10d,26]) could be associated with the

(24) Tamariz, J.; Vogel, P. *Helv. Chim. Acta* **1981**, *64*, 188.

(25) The authors have deposited the atomic coordinates for these structures with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.

(26) Ochoa, M. E. Nuevos Equivalentes de Cetenas en Reacciones de Diels−Alder. Síntesis de γ−Hidroxiciclohexenonas. M.S. Thesis, Escuela Nacional de Ciencias Biológicas, IPN: México, D. F., Mexico, 1997.

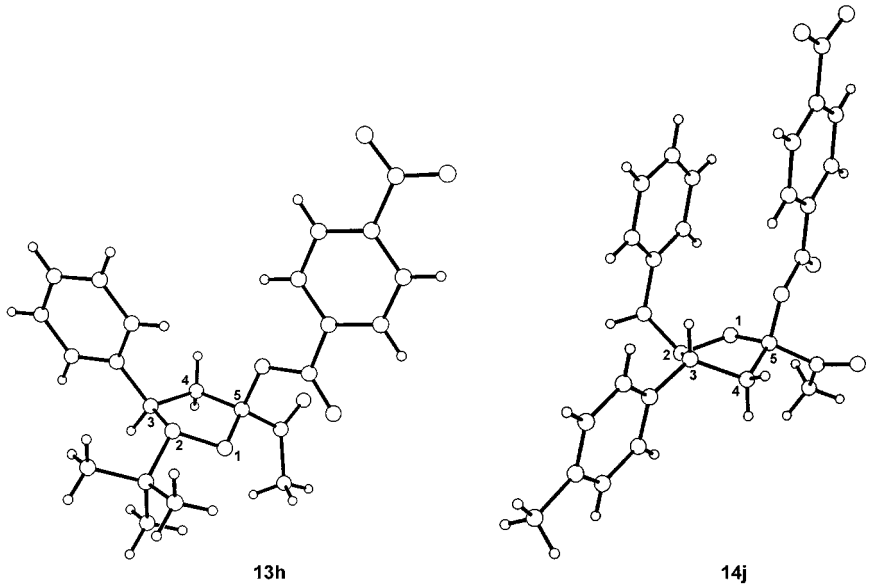
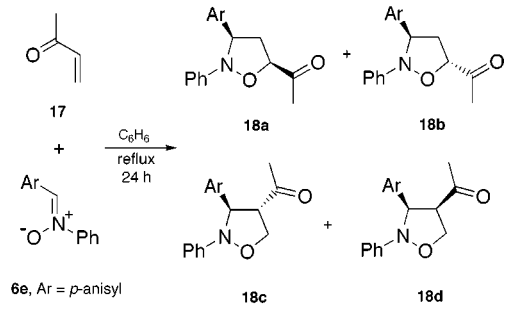


Figure 3. Structures of compounds **13h** and **14j**. They were constructed from their X-ray crystallographic data.

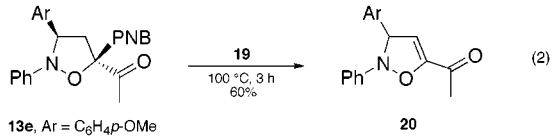
Scheme 4



anomeric effect, as previously indicated in analogous C-5 oxygenated isoxazolidines.[9f] In both structures, **13h** and **14j**, the *anti* relationship between the *N*-substituent and the aryl group on C-3 is preferred, as evidenced by the NOE experiments.

To evaluate the effect of the electron-donating group on the captodative center of olefins **1** on the control of both regio- and stereoselectivity, we carried out the cycloaddition of nitrone **6e** with methyl vinyl ketone (**17**) (Scheme 4). The reaction took place in benzene at reflux for 24 h, to give a mixture of the four possible isomers **18a**, **18b**, **18c**, and **18d** in ca. 2:10:7:1 ratio.[27] The regioselectivity (acetyl on C-5/C-4, 60:40) was practically lost in reference to olefins **1**, even though the *endo* selectivity remained in higher proportion. In accord with these results, it seems that the aroyloxy and the acetoxy groups of olefins **1** are playing a significant role in the orientation of the dipole during the addition.

It is noteworthy that the PNB group in the nitrone adducts **13**/**14** did not undergo β-elimination, as found for the nitrile imines, nitrile oxides, and diazo compounds. This suggests that the presence of a double bond in the adducts induces the elimination of the carboxylate group, giving rise to the most stable aromatic compound. Nevertheless, the PNB group could be eliminated by treatment of adduct **13e** with 2,4,6-collidine (**19**) at 100 °C for 3 h, producing isoxazoline **20** as an oil in 60% yield (eq 2). This compound has an interesting structure, which could be considered as an endocyclic β-substituted captodative olefin.[28]



Isoxazolidines have been useful synthons for the preparation of, among others, substituted amines, natural β-amino alcohols, and alkaloids by reductive cleavage of the N−O bond.[1a−d,29] With the aim to assess the synthetic potential of isoxazolidines **13**/**14**, we intended to cleave the N−O bond by hydrogenation. Several catalysts were used with derivatives **13e** and **13j**, and diverse products were isolated and characterized, but the heterocycle was not opened (Table 3). The hydrogenation of **13e** with Raney nickel produced alcohol **21** along with a small amount of the nitro group reduction product **22**; whereas isoxazolidine **13j** underwent reduction with the same catalyst, but in the presence of a different solvent (*i*-PrOH), to yield the product of reduction of the nitro group **24** (Scheme 5). In contrast, compound **22** was isolated as the major product by using PtO_2 in both solvents ethyl acetate and ethanol (entries 2 and 3). Palladium on charcoal (10%) provided diol **23** as the main product; however, it was unstable under purification conditions, and it was not fully characterized. Other catalysts were used such as $Pd(OH)_2$ which has been efficient for analogous substrates,[30] but a mixture of

(27) Mixtures of regioisomers have been also obtained in the presence of **6a** with this and other olefins: (a) Asrof Ali, Sk.; Senaratne, P. A.; Illig, C. R.; Meckler, H.; Tufariello, J. J. *Tetrahedron Lett.* **1979**, 4167. (b) Joucla, M.; Hamelin, J. *J. Chem. Res. (S)* **1978**, 276.

(28) β-Substituted captodative olefins have been prepared, and they display interesting structural and reactivity features. See: (a) Peralta, J.; Bullock, J. P.; Bates, R. W.; Bott, S.; Zepeda, G.; Tamariz, J. *Tetrahedron* **1995**, *51*, 3979. (b) Villar, L.; Bullock, J. P.; Khan, M. M.; Nagarajan, A.; Bates, R. W.; Bott, S. G.; Zepeda, G.; Delgado, F.; Tamariz, J. *J. Organomet. Chem.* **1996**, *517*, 9.

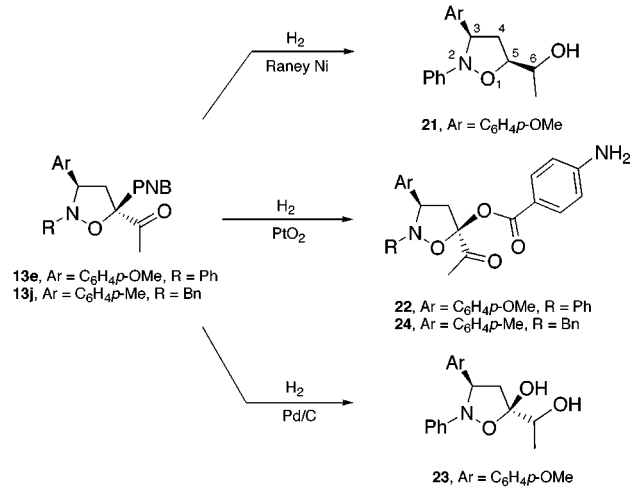
(29) (a) Curran, D. P. *J. Am. Chem. Soc.* **1982**, *104*, 4024. (b) Keck, G. E.; Fleming, S.; Nickell, D.; Weider, P. *Synth. Commun.* **1979**, *9*, 281. (c) Stork, G.; Danishefsky, S.; Ohashi, M. *J. Am. Chem. Soc.* **1967**, *89*, 5459. (d) Tufariello, J. J. *Acc. Chem. Res.* **1979**, *12*, 396. (e) Gothelf, K. V.; Jørgensen, K. A. *Chem. Rev.* **1998**, *98*, 863. (f) Frederickson, M. *Tetrahedron* **1997**, *53*, 403.

Table 3. Hydrogenation of Isoxazolidines 13e and 13j[a]

entry	isoxazolidine	catalyst	solvent	pressure (atm)	*t* (h)	products (ratio)[b]	yield (%)[c]
1	**13e**	Raney Ni	EtOAc	1.3	3.0	**21**/**22** (92:8)	79
2	**13e**	PtO_2	EtOAc	1.3	2.0	**21**/**22**/**23** (9:86:5)	40
3	**13e**	PtO_2	EtOH	1.3	3.0	**21**/**22**/**23** (23:69:8)	*d*
4	**13e**	Pd/C, 10%	EtOAc	1.3	3.0	**21**/**23** (5:95)	*e*
5	**13e**	$Pd(OH)_2$	EtOH	1.3	3.0	**21**/**22**/**23** (16:8:76)	*e*
6	**13e**	$Pd/CaCO_3$	EtOH	1.3	3.0	**22**/**23** (25:75)	*e*
7	**13j**	Raney Ni	*i*-PrOH	2.6	5.0	**24**	30

[a] All at room temperature. [b] Determined by ^{1}H NMR (300 MHz). [c] After column chromatography and recrystallization of the major product. [d] The mixture of products was obtained in almost quantitative yield, but the major product was not separated. [e] **23** decomposes under purification conditions.

Scheme 5



compounds **21**/**22**/**23** (entry 5) was isolated. Despite hydrogenolysis of the isoxazolidine N−O bond seeming to be slowed by steric encumbrance,[1d] the overstability found in these isoxazolidines could be also due to the presence of an oxygenated functionality on carbon C-5, base of the endocyclic oxygen, as previously suggested.[31]

Discussion

The precedent results have shown that captodative olefins **1** undergo highly regio- and stereoselective cycloaddition reactions with a variety of 1,3-dipoles. No significant effect on the regioselectivity could be detected by changing the substituent in the electron-donating group of the captodative olefin, suggesting a similar electronic perturbation of this group on the double bond. Moreover, the regioselectivity observed, furnishing the C-5 heterocycle substitution in these cycloadditions with all dipoles and olefins **1**, suggests a steric control, keeping far away the crowded centers of the olefin (the captodative carbon C-3) and the nitrone (the substituted carbon atom). However, neither the formation of the less crowded C-5 substituted adducts from **1** could be explained only by steric interactions, nor the loss of regiochemistry when adding the noncaptodative olefin **17**.[32] Mostly electronic demand of the dipolarophile substituents seems to account for these results.[33] The captodative effect,[10a] involving diradicaloid intermediates or transition states,[18] has also been considered in controlling the orientation of the cycloaddends.[34] Both experimental and theoretical investigations have revealed the increased importance of electrostatic interactions in controlling the approach to the transition state:[35] A dipolaroid character of the transition state may agree with the 5-substituted adducts for the interaction with nitrile oxides and nitrones as the dipoles, when the transition states are simulated in diverse polarity solvents.[1e]

Table 4. Ab Initio 6-31G* Energy Gaps (eV) of Frontier Orbitals[a] for Olefin 1a and Nitrones 6

nitrone	HOMO−LUMO	LUMO−HOMO	diff
6a	10.4187	13.0406	2.6219
6d	11.1034	11.8756	0.7722
6e	10.0582	13.2401	3.1819
6h	10.4781	13.6208	3.1427
6k	10.5396	13.4788	2.9392

[a] HOMO-nitrone/LUMO-olefin and LUMO-nitrone/HOMO-olefin.

It is generally agreed that 1,3-dipolar cycloadditions are concerted,[1,34,36] and the regiochemistry appears to be controlled by frontier orbital interactions.[11,29e,32] To rationalize the exclusive C-5 regioselectivity displayed by olefins **1** with nitrones **6**, in contrast with other captodative olefins,[8a] we performed an FMO analysis of the calculated (RHF/3-21G, and 6-31G*) frontier orbitals.[37] They show that the interaction between **1a** and **6a**, **6d**, **6e**, **6h**, and **6k** is governed by the HOMO-dipole/LUMO-dipolarophile (Table 4). According to FMO theory, regioselectivity is controlled by the magnitudes of the atomic orbital coefficients at the terminal atoms of the dipole,

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(31) DeShong, P.; Lander, S. W., Jr.; Leginus, J. M.; Dicken, C. M. Dipolar Cycloadditions of Nitrones with Vinyl Ethers and Silane Derivatives. In *Advances in Cycloaddition*; Curran, D. P., Ed.; JAI Press: Greenwich, 1988; Vol. 1, pp 112−113.

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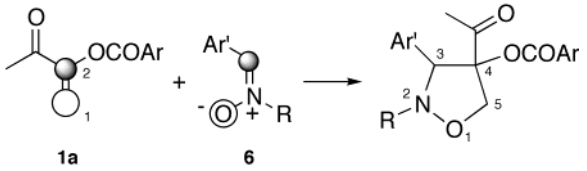
(37) Calculated with GAUSSIAN94, Revision E.2: Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Gill, P. M. W.; Johnson, B. G.; Robb, M. A.; Cheeseman, J. R.; Keith, T.; Petersson, G. A.; Montgomery, J. A.; Raghavachari, K.; Al-Laham, M. A.; Zakrzewski, V. G.; Ortiz, J. V.; Foresman, J. B.; Cioslowski, J.; Stefanov, B. B.; Nanayakkara, A.; Challacombe, M.; Peng, C. Y.; Ayala, P. Y.; Chen, W.; Wong, M. W.; Andres, J. L.; Replogle, E. S.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Binkley, J. S.; Defrees, D. J.; Baker, J.; Stewart, J. P.; Head-Gordon, M.; Gonzalez, C.; Pople, J. A. Gaussian, Inc., Pittsburgh, PA, 1995. See the Supporting Information for details.

Scheme 6. FMO Coefficients Interaction of the LUMO of 1a and HOMO (estimated average values) of Nitrones 6



and by those of the double bond of the dipolarophile.[11c] Thus, the preferred orientation should be the result of the interaction of the atoms with the largest coefficients. For olefin **1a** and calculated nitrones **6**, the FMO arguments predict the formation of the regioisomer C-4 substituted, in contrast to the observed regiochemistry (Scheme 6). An analogous prediction is furnished from the LUMO−HOMO interaction for olefin **17** and nitrones **6**, respectively, minimizing the fact that the more abundant C-5 regioisomer was obtained.

Therefore, this model did not provide a satisfactory explanation of cycloadditions of our molecules with nitrones, as anticipated from analogous results concerning the use of FMO theory with arylnitrile oxides,[19] and in similar cycloadditions.[15,35b,38] Owing to this conclusion, we investigated a novel theoretical approach which is based on the formulation of the interaction energy ΔE_{int} of the reactants, in terms of density functional theory (DFT)[39] and the hard and soft acids and bases principle (HSAB),[40] for the 1,3-dipolar cycloaddition of benzonitrile oxide and olefin **1a**. The results we obtained provide a successful rationalization of the experimental regiochemistry.[21]

The essence of this treatment of chemical reactivity is based, as already discussed in previous papers,[41] in the assumption that when molecule A and molecule B interact with each other in order to form product AB, a mutual perturbation of the molecular densities of both reactants occurs. The resulting change in energy for the reaction A + B → AB may be divided into two steps which take place in succession: $A + B \xrightarrow{i} A^* + B^* \xrightarrow{ii} AB$, (i) partial charge-transfer accompanied by soft−soft interactions (covalent interactions),[42] and (ii) electronic reorganization accompanied by hard−hard interactions (electrostatic interactions).[42]

The interaction energy $\Delta E_{int} = \Delta E_\nu + \Delta E_\mu$ represents the energy involved in the two steps. The energy of the first step, ΔE_ν, corresponds to the charge-transfer process between molecule A and molecule B at constant external potential ($\nu(\mathbf{r})$, which is generated by the nuclei), and it is a consequence of the chemical potential equalization principle.[43] The energy of the second step, ΔE_μ, comes from the reshuffling of charge distribution at constant chemical potential (μ), and is usually a manifestation of the maximum hardness principle.[44]

In this perturbational treatment we can visualize the various phenomena which occur during the process of nitrone−olefin bonding, thus gaining more insight into the factors that govern the reaction. We have recently used such a method to study the chemical reactivity of carbenes with olefins.[45]

For the study of the interaction from a global viewpoint, which does not specify the interaction sites (atomic sites) for nitrone A and olefin B, ΔE_{int} is given by eq 3.[41b]

$$\Delta E_{int} = \Delta E_\nu + \Delta E_\mu \approx -\frac{1}{2}\frac{(\mu_A - \mu_B)^2}{S_A + S_B} S_A S_B - \frac{1}{2}\frac{\lambda}{S_A + S_B} \quad (3)$$

where μ_A and μ_B are the electronic chemical potentials (identified as the negative of the electronegativities χ_A and χ_B)[46] and S_A and S_B are the global softnesses of the HSAB principle (identified as the inverse of the hardnesses η_A and η_B)[47] for nitrone and olefin, respectively. λ is a constant related to an *effective number of valence electrons*.[41b,44b]

From a local viewpoint, nitrone A and olefin B interact through their C, O, and C_1 (unsubstituted carbon), C_2 (captodative carbon) atoms, respectively. We assume that only these atoms participate in the charge transfer and the reshuffling of the charge distribution involved in the bond formation processes. Therefore, ΔE_{int} is given by eq 4.[41c,d]

$$\Delta E_{int} = \Delta E_\nu + \Delta E_\mu \approx -\frac{1}{2}\frac{(\mu_A - \mu_B)^2}{s_{Aa} + s_{Bb}} s_{Aa} s_{Bb} - \frac{1}{2}\frac{\lambda}{s_{Aa} + s_{Bb}} \quad (4)$$

where s_{Aa} and s_{Bb} are the condensed softnesses and characterize the softness of the C (or O) atom in the nitrone and the C_1 (or C_2) atom in the olefin, respectively.

According to eq 3, when the first term $(-1/2(\mu_A - \mu_B)^2 S_A S_B/(S_A + S_B))$ becomes predominant, strong electron transfer occurs between nucleophiles of low electronegativity and electrophiles of high electronegativity, decreasing the ionicity of the reagents. Chemical potential differences $(\mu_A - \mu_B)^2$ (electronegativity differences) drive electron transfer, and electrons tend to flow from a region of high chemical potential (low electronegativity) to a region of low chemical potential (high electronegativity). High values of the $S_A S_B/(S_A + S_B)$ term enhance the magnitude of the ΔE_ν term: high softness values of nucleophile and electrophile lead to soft−soft interactions and can be associated with covalent interaction.[42] The same reasoning may be extended to eq 4 at a local level.

Also in accord to eq 3, when the $(-\lambda/(S_A + S_B))$ term becomes predominant, very little electron transfer occurs between nucleophile and electrophile. The ΔE_μ term is enhanced by low softness values of the nucleophile and electrophile, the magnitude of the $(S_A + S_B)^{-1}$ term

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(47) Yang, W.; Parr, R. G. *Proc. Natl. Acad. Sci. U.S.A.* **1985**, *82*, 6723.

increases. All these properties correspond to those associated with a hard−hard interaction, and the electrostatic effect can be identified with it. Such an effect reflects an ionic type of interaction and will be predominant between highly charged species. It leads to a low covalent interaction.[42] Again, the same reasoning may be extended to eq 4 at a local level.

Once the necessary DFT and HSAB parameters for nitrones and olefins are known, we can characterize the global and local interactions using eqs 3 and 4. The electronic chemical potential (μ_A and μ_B) and the global softness (S_A and S_B) can be calculated in terms of the vertical ionization potential (I) and the vertical electron affinity (A) by the expressions[39] $\mu = -(I + A)/2$, $S = \eta^{-1}$ and $\eta = (I - A)/2$, where η is the global hardness of the HSAB principle.[48]

The condensed softness s_{Aa} for the C (or O) atom in the nitrone and s_{Bb} for the C_1 (or C_2) atom in the olefin, can be obtained for nucleophilic $s^-_{Aa} = S_A f^-_{Aa}$ and electrophilic $s^+_{Aa} = S_A f^+_{Aa}$ attacks.[39] The f^-_{Aa} and f^+_{Aa} are the condensed fukui functions for nucleophilic and electrophilic attacks respectively; they can be evaluated by $f^+_{Aa} = q_{Aa}(N_A + 1) - q_{Aa}(N_A)$ and $f^-_{Aa} = q_{Aa}(N_A) - q_{Aa}(N_A - 1)$,[49] where $q_{Aa}(N_A - 1)$, $q_{Aa}(N_A)$, and $q_{Aa}(N_A + 1)$ are the charges of the reactive atom in the cation, neutral, and anion of the nitrone, respectively. The superscript (+) in the f^+_{Aa} term indicates the electrophilic tendency of the C (or O) atom in the nitrone to increase its charge ($q_{Aa}(N_A) \rightarrow q_{Aa}(N_A + 1)$) when the olefin carries out a nucleophilic attack with its C_1 (or C_2) atom. The superscript (−) in the f^-_{Aa} term indicates the nucleophilic tendency of the C (or O) atom in the nitrone to decrease its charge ($q_{Aa}(N_A) \rightarrow q_{Aa}(N_A - 1)$) when the olefin carries out an electrophilic attack with its C_1 (or C_2) atom.

The statement *hard likes hard and soft likes soft* at global and local levels, the DFT perturbational approximation, and the orbital molecular calculation will be used to provide a rationalization of the experimental regioselectivity in the addition of nitrones and olefins. The electronic structures of the eight nitrones **6a**, **6d**−**f**, and **6h**−**k** and the two olefins **1c** and **17** were calculated at the equilibrium geometry of the neutral species at the RHF and UHF/6-31G** level with GAUSSIAN98.[50] The electronic structure for **1a** has been previously calculated.[21]

Table 5 summarizes the chemical potential and the global softness values for the nitrones and olefins; they were calculated in terms of the vertical ionization potential and electron affinity. The global parameter values for olefin **1a** were obtained from ref 21.

To study the process of nitrone−olefin bonding at a global level, we calculated from eq 3 the interaction energy for each nitrone−olefin pair, using the global properties of the eight nitrones and three olefins, and with a λ value of one.[21,45] Table 6 shows that the interaction energy becomes, in general, predominant when the global softnesses of the nitrones decrease. The same trend is observed for olefins **1c** and **17** except for olefin **1a**. This is probably due to a small contribution of the covalent interaction in the latter (vide infra). According to eq 3 the hard−hard interactions will be very important, and the noncovalent contribution will dominate the interaction (electrostatic interaction). This would imply that the ΔE_v term (energy involved in the charge-transfer process between nitrone and olefin) should be not as important as the ΔE_μ term (the reshuffling of the charge distribution). The calculations of the ΔE_μ and ΔE_v terms confirm this suggestion, since for olefins **1c** and **17**, the 99% of the interaction energy is coming from the ΔE_μ term. However, for olefin **1a**, 93% of the interaction energy is coming from the ΔE_μ term, and a small but significant contribution of covalent interactions (7%) is provided.

Our results supports the idea suggested by Sustman and Sicking[4,38] that noncovalent interactions are important in some 1,3-dipolar cycloadditions. Recently, Cossío et al. investigated, via transition state calculations, the regiochemistry of several 1,3-dipolar cycloadditions, and they concluded that electrostatic interactions and solvent effects can modify the regiochemical outcome.[1e]

To determine the regiochemistry of each nitrone−olefin pair, it is necessary to study the interaction at a local level. In accord to eq 4, only the C and O atoms of the nitrone and the C_1 and C_2 atoms of the olefin will be involved in the bonding process. Table 7 shows the condensed fukui functions for nucleophilic and electrophilic attacks for the C and O atoms for the eight

Table 5. Global Property Values (eV) for Nitrones 6a, 6d−f, and 6h−k, and Olefins 1a, 1c, and 17

compd	chemical potential (μ)[a]	global softness (S)[b]
6a	−2.59	0.153
6d	−3.12	0.178
6e	−2.45	0.154
6f	−2.52	0.155
6h	−2.25	0.142
6i	−2.23	0.143
6j	−2.31	0.144
6k	−2.36	0.143
1a[c]	−4.56	0.107
1c	−3.63	0.095
17	−3.17	0.099

[a] Calculated as $-(I + A)/2$. [b] Calculated as $S = \eta^{-1}$ and $\eta = (I + A)/2$, S values in eV^{-1}. [c] See ref 21.

Table 6. Global Interaction Energy (ΔE_{int}) Values (kJ/mol) for the Pair Nitrone−Olefin, Calculated with Eq 3

		ΔE_{int}		
nitrone	S[a] (eV^{-1})	olefin **1c** (S = 0.095 eV^{-1})	olefin **17** (S = 0.099 eV^{-1})	olefin **1a** (S = 0.107 eV^{-1})
6d	0.178	−177.614	−173.919	−175.966
6f	0.155	−196.761	−190.993	−196.964
6e	0.154	−198.062	−192.081	−198.629
6a	0.153	−197.749	−192.102	−197.396
6j	0.144	−206.717	−200.172	−207.127
6i	0.143	−208.340	−201.575	−209.086
6k	0.143	−206.999	−200.551	−207.042
6h	0.142	−209.195	−202.432	−209.733

[a] Calculated as in Table 5.

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Table 7. Values of the Condensed Fukui Functions for the C and O Atoms in the Nitrone and the C_1 and C_2 Atoms in the Olefin, Respectively, Values in eV^{-1}

nitrone	f_C^+ [a]	f_C^- [b]	f_O^+ [a]	f_O^- [b]
6d	0.283	0.089	−0.079	0.442
6k	0.182	0.110	0.152	0.438
6h	0.180	0.112	0.145	0.450
6j	0.183	0.111	0.149	0.438
6i	0.202	0.117	0.148	0.438
6a	0.194	0.114	0.156	0.443
6f	0.195	0.114	0.152	0.443
6e	0.211	0.121	0.149	0.443
olefin	$f_{C_1}^+$ [c]	$f_{C_1}^-$ [d]	$f_{C_2}^+$ [c]	$f_{C_2}^-$ [d]
1c	0.316	−0.085	0.128	−0.008
1a [e]	0.034	−0.067	−0.059	−0.035
7	0.335	0.002	0.052	0.098

[a] Calculated as $f_{Aa}^+ = q_{Aa}(N_A + 1) - q_{Aa}(N_A)$. [b] Calculated as $f_{Aa}^- = q_{Aa}(N_A) - q_{Aa}(N_A - 1)$. [c] Calculated as $f_{Bb}^+ = q_{Bb}(N_B + 1) - q_{Bb}(N_B)$. [d] Calculated as $f_{Bb}^- = q_{Bb}(N_B) - q_{Bb}(N_B - 1)$. [e] See ref 21.

nitrones, and C_1 and C_2 for the three olefins. The charges of the reactive atoms were obtained from the Mülliken population analysis of the neutral and ionic species.

In the cycloaddition of a nitrone and an olefin there are four pairs of possible atomic interactions (C−C_1, C−C_2, O−C_1, and O−C_2), and two kinds of condensed softness for each atom (nucleophilic and electrophilic attacks). Therefore, by statistics, there will be 16 probable interactions involved in the nitrone−olefin bond process: ($s_C^+ s_{C_1}^-$, $s_C^- s_{C_1}^+$, $s_C^+ s_{C_1}^+$, $s_C^- s_{C_1}^-$, ...). The $s_C^+ s_{C_1}^-$ term means that the nitrone C atom is the electron-acceptor (electrophilic center) and the olefinic C_1 atom is the electron-donor (nucleophilic center), while the $s_C^- s_{C_1}^+$ term means that the nitrone C atom is the electron-donor (nucleophilic center) and the olefinic C_1 atom is the electron-acceptor (electrophilic center). We consider the $s_C^+ s_{C_1}^+$ and $s_C^- s_{C_1}^-$ terms in agreement with Klopman et al., who suggested that an electron transfer occurs between the 1,3-dipole and the dipolarophile, but the specific direction of the electronic transfer process is not defined.[51] The $s_C^+ s_{C_1}^+$ term indicates that the nitrone C atom and the olefinic C_1 atom are electron-acceptors (electrophilic centers), while the $s_C^- s_{C_1}^-$ term indicates that the nitrone C atom and the olefinic C_1 atom are electron-donors (nucleophilic centers).

To predict the main interaction term in the bond process nitrone−olefin, we calculated the interaction energy considering the 16 probable interactions for each pair nitrone-olefin. The results show that the most important interaction corresponds to the $s_C^- s_{C_1}^-$ term, and suggests that the interaction will occur between the nitrone C atom and the olefinic C_1 atom with a mutual electron donation between these atoms in the addition process. These results are very interesting, because a mutual donation has been supported by experimental and theoretical evidence. For example, Fujitake and Hirota[52] corroborated by millimeter and submillimeter wave spectrum of dichlorocarbene (:CCl_2) the calculations made by Carter and Goddard,[53] who found a pπ donation from Cl to C ($\pi_c = 0.25$) and a σ electron donation from C to Cl ($i_\sigma = 0.20$).

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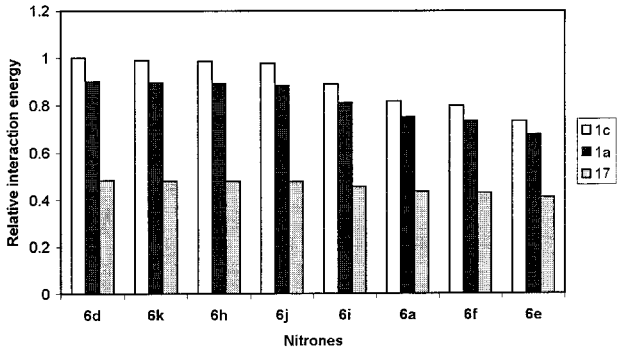

Figure 4. Histogram of the relative interaction energy ΔE_{int} between olefins an nitrones. Values relative to the value of the interaction energy of the pair olefin **1c** - nitrone **6d**. This energy is calculated using eq 4, where s_C^- of nitrone and $s_{C_1}^-$ of olefin are used. The values of s_C^- and $s_{C_1}^-$ were calculated from $s_C^- = S_{Nitrone} f_C^-$ and $s_{C_1}^- = S_{Olefin} f_{C_1}^-$. They increase from nitrone **6d** to **6e** and from olefin **1c** to **17**, respectively.

Figure 4 depicts a histogram of the relative calculated $s_C^- s_{C_1}^-$ values for the interaction energy term for each pair nitrone-olefin versus the nucleophilic condensed softness s_C^- and $s_{C_1}^-$, in relation to the value of the pair $s_{C_1}^-$ (olefin **1c**)−s_C^- (nitrone **6d**). In general, the interaction energies increase when the nucleophilic condensed softness of both atoms decreases. At a local level, these results suggest that the hard−hard interactions will be very relevant in the nitrone-olefin bond process, also supporting our previous analysis obtained at a global level. In addition, noncovalent interactions will be present in the most important local interaction: nitrone C atom-olefin C_1 atom (eq 4), since 99% of the interaction energy is provided by the ΔE_μ interaction term.

The experimental results would suggest that the control of regioselectivity depends mainly on the presence of the electron-donating group, and not only from the effect of the electron-withdrawing group on the olefins **1**. The theoretical results confirm this idea: Figure 4 shows that the interaction energy increases in the order of olefins **1c** > **1a** > **17**, (1:0.9:0.5). The electron-donating groups $OCOCH_3$ and $OCOPhNO_2$, in the captodative olefins **1c** and **1a**, respectively, increase the interaction energy $s_C^- s_{C_1}^-$ term (approximately at the same extent), enhancing the electron-donor capacity and the nucleophilicity of the olefinic C_1 atom, and consequently a high regioselectivity should be observed. While the electron-withdrawing group $OCOCH_3$ in olefin **17** cuts by half the energy of the interaction $s_C^- s_{C_1}^-$ term, decreasing the electron-donor capacity and the nucleophilicity of the olefinic C_1 atom, hence the reaction would not be regioselective, and a mixture of regiosomers should be obtained, as observed experimentally (Scheme 4).

Conclusions

Captodative olefins 1-acetylvinyl carboxylates **1** underwent 1,3-dipolar cycloadditions with diverse dipoles in highly regio- and stereoselectivities. The formation of the 5-substituted aromatic heterocycle with propionitrile oxide, nitrile imines, and diazo compounds and olefin **1a** was the result of the succesive dipolar addition and elimination of the PNB group, as confirmed by the reaction with trimethylsilyl diazomethane (**4b**). The cycloaddition with nitrones **6** also proceeded with the

exclusive formation of the 5-substituted isoxazolidines, and yielding the *endo* adduct as the major stereoisomer. No significant effect on the regiochemistry was detected by modifying the electron-donating group of the captodative olefin, in contrast with olefin **17**, which bears a single electron-withdrawing group, where the reaction was not regioselective. The structural characterization of the adducts was supported by NMR experiments and X-ray crystallography. Thus, the preference of the PNB group in the isoxazolidines for the pseudoaxial conformation was determined, which may be associated to the anomeric effect. Cleavage of the isoxazolidine N−O bond was not successfully made, despite the diverse catalytic hydrogenation conditions applied. This may be explained as an overstability of this bond due to the presence of the C-5 oxygenated functionality.

FMO theory has been used to rationalize the regioselectivity observed in 1,3-dipolar cycloadditions with nitrones. However, the calculations furnished a prediction of the regiochemistry opposite to the experimental results. In contrast, the chemical reactivity of nitrones **6** and olefins **1** and **17**, and the various factors which affect the process of nitrone−olefin bonding, were estimated in terms of interaction energy values obtained from the HSAB principle and DFT, predicting a regiochemistry in agreement with the experimental results.

To the best of our knowledge, this seems to be the first theoretical study of captodative olefins that provides an insight into the relevance of the electron-donor group of these molecules, as the main controlling factor of the regiochemistry in 1,3-dipolar additions with nitrones, and probably also with other dipoles.

Experimental Section

General. Melting points are uncorrected. NMR spectra were recorded at 300 and 500 MHz for ^{1}H, and at 75.4 and 125.0 MHz for ^{13}C, using TMS as internal standard. Mass spectra (EI) were obtained at 70 eV. X-ray analyses were collected using Mo Kα radiation (graphite crystal monochromator, l = 71073 Å). Microanalyses were performed by M−H−W Laboratories (Phoenix, AZ). Analytical thin-layer chromatography was carried out using E. Merck silica gel 60 F_{254} coated 0.25 plates, visualizing by long- and short-wavelength UV lamp. All air moisture sensitive reactions were carried out under nitrogen using oven-dried glassware. Dioxane, ethyl ether, THF, toluene, and xylene were freshly distilled from sodium, and methylene chloride from calcium hydride, prior to use. K_2CO_3 was dried overnight at 120 °C before using. Triethylamine was freshly distilled from NaOH. All other reagents were used without further purification.

General Method for the Preparation of 5-Acetyl-3-aryl-1-phenylpyrazoles 9a−d. To a solution of arylaldehyde phenylhydrazones **7a**−**d** (3.0 mmol) and 0.24 g (1.0 mmol) of olefin **1a** in dry dioxane (15 mL) was added 0.68 g (3.0 mmol) of chloramine-T·H_2O at room temperature, under an N_2 atmosphere. The mixture was heated to reflux for 2 h, and the solvent was removed under vacuum. The residue was purified by column chromatography on silica gel (30 g, hexane/EtOAc, 7:3) to give the corresponding pyrazoles **9a**−**d**.

5-Acetyl-1,3-diphenylpyrazole (9a). Method A. Following the general procedure with **7a** (0.59 g) afforded 0.21 g (80%) of **9a** as colorless prisms. **Method B.** Following the same conditions as method A, but using 0.13 g (1.0 mmol) of **1c** to give 0.157 g (60%) of **9a**: R_f 0.37 (hexane/EtOAc, 8:2); mp 112−113 °C; IR (CCl_4) 1694, 1498, 1424, 1356, 1276, 1214 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.58 (s, 3H, CH_3CO), 7.31 (s, 1H, H-4), 7.36−7.58 (m, 8H, Ph-H), 7.90−7.98 (m, 2H, Ph-H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 29.0 (*C*H_3CO), 110.9 (C-4), 126.5, 126.8, 129.1, 129.3, 129.4, 129.7, 133.5, 142.1, 142.4, 152.1, 188.6 (CH_3*C*O); MS (70 eV) 262 (M^+, 100), 247 (82), 233 (4), 219 (12), 171 (8), 116 (27), 89 (21), 77 (33). Anal. Calcd for $C_{17}H_{14}N_2O$: C, 77.84; H, 5.38; N, 10.68. Found: C, 77.97; H, 5.19; N, 10.85.

5-Acetyl-1-phenyl-3-(*p*-tolyl)pyrazole (9b). Following the general procedure with **7b** (0.63 g) afforded 0.2 g (72%) of **9b** as colorless crystals: R_f 0.23 (hexane/EtOAc, 8:2); mp 88−89 °C; IR (KBr) 1690, 1614, 1504, 1424, 1175 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.36 (s, 3H, CH_3Ar), 2.51 (s, 3H, CH_3CO), 7.20−7.23 (m, 2H, Ar−H), 7.22 (s, 1H, H-4), 7.39−7.47 (m, 5H, Ph-H), 7.73−7.75 (m, 2H, Ar−H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.3 (*C*H_3Ar), 28.8 (*C*H_3CO), 109.5 (C-4), 125.6, 125.9, 128.6, 128.7, 129.3, 129.4, 138.4, 140.6, 140.7, 151.4, 187.8 (CH_3*C*O). Anal. Calcd for $C_{18}H_{16}N_2O$: C, 78.24; H, 5.84; N, 10.14. Found: C, 78.39; H, 6.04; N, 10.02.

5-Acetylpyrazole (10a). Method A. A solution of 0.24 g (1.0 mmol) of **1a** in dry ether (15 mL) and 0.21 g (5.0 mmol) of **4a** (2.5 mL solution in dry ether) was stirred in dark at room temperature, under an N_2 atmosphere, for 5 h. The solvent was removed under vacuum, and the residue was purified by column chromatography on silica gel (30 g, hexane/EtOAc, 7:3) to give 0.075 g (68%) of **10a** as an yellow oil. **Method B.** A solution of 0.24 g (1.0 mmol) of **1a** in dry ether (15 mL) and 0.34 g (5.0 mmol) of **4b** (2.5 mL, 2 M solution in hexane) was stirred in dark at room temperature, under an N_2 atmosphere, for 24 h. The solvent was removed under vacuum, affording a mixture of **11a**/**11b** (71:29) and **10a** in 1:1 ratio. The mixture was heated in dry ether (10 mL) to 50 °C for 1 h, to yield an oily residue, which was purified by column chromatography on silica gel (30 g, hexane/EtOAc, 7:3) to give 0.088 g (80%) of **10a** as an yellow oil: R_f 0.65 (hexane/EtOAc, 7:3); IR (film) 3224, 1656, 1467, 1348, 1299, 792 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.61 (s, 3H, CH_3CO), 6.79 (d, J = 2.3 Hz, 1H), 7.67 (d, J = 2.3 Hz, 1H), 10.90 (br s, 1H, NH); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 26.9 (*C*H_3CO), 107.4, 134.2, 147.4, 191.9 (CH_3*C*O). Anal. Calcd for $C_5H_6N_2O$: C, 54.54; H, 5.49; N, 25.44. Found: C, 54.39; H, 5.31; N, 25.21.

5-Acetyl-3-ethylisoxazole (12). Method A. A solution of 1.08 g (12.0 mmol) of **3** and 1.20 g (12.0 mmol) of triethylamine in dry benzene (15 mL) was stirred at room temperature, under an N_2 atmosphere, for 30 min. At 0 °C, 1.44 g (12.0 mmol) of phenyl isocyanate and 0.47 g (2.0 mmol) of **1a** were added, and the mixture was stirred for 2 h at room temperature and then heated to reflux for 2 h. The suspension was filtered, and the solvent was removed under vacuum. The residue was purified by column chromatography on silica gel (40 g, hexane/EtOAc, 7:3) to give 0.236 g (85%) of **12** as an yellow oil. **Method B.** Following the same conditions as Method A, but using 0.26 g (2.0 mmol) of **1c**, to give 0.175 g (63%) of **12**: R_f 0.65 (hexane/EtOAc, 7:3); IR (CH_2Cl_2) 2982, 1603, 1474, 1453, 1431, 1036, 954 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.30 (t, J = 7.6 Hz, 3H, C*H*$_3$CH$_2$), 2.60 (s, 3H, CH_3CO), 2.77 (q, J = 7.6 Hz, 2H, CH_3C*H*$_2$), 6.79 (s, 1H, H-4); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 12.6 (*C*H$_3$CH$_2$), 19.6 (CH_3*C*H$_2$), 27.2 (*C*H_3CO), 106.6, 166.0, 166.5, 187.0 (CH_3*C*O); MS (70 eV) 139 (M^+, 61), 124 (7), 96 (33), 68 (100). HRMS (EI) calcd for [M^+] $C_7H_9NO_2$: 139.0633. Found: 139.0630.

General Procedure for the 1,3-Dipolar Addition of 3-*p*-Nitrobenzoyloxy-3-buten-2-one (1a) with Nitrones 6a, 6d, 6e, and 6f. (3*R,5*R**)-5-Acetyl-2,3-diphenyl-5-(*p*-nitrobenzoyloxy)isoxazolidine (13a) and (3*R**,5*S**)-5-Acetyl-2,3-diphenyl-5-(*p*-nitrobenzoyloxy)isoxazolidine (14a).** A mixture of 0.50 g (2.54 mmol) of **6a**, and 0.60 g (2.5 mmol) of **1a** in dry benzene (20 mL) was stirred and heated to 80 °C for 8 h, under an N_2 atmosphere. The solvent was removed under vacuum, to yield an oily residue of a mixture of **13a**/**14a** (89:11). The major isomer **13a** was isolated by crystallization from EtOH/CH_2Cl_2, 5:1, to yield 0.77 g (70%) as brownish yellow crystals: R_f 0.5 (hexane/EtOAc, 8:2); mp 100−101 °C; IR (CH_2Cl_2): 1706, 1601, 1529, 1492, 1348, 1263, 756, 696 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.55 (s, 3H, COMe), 3.12 (dd, J = 14.1, 6.4 Hz, 1H, H-4β), 3.27 (dd, J = 14.1, 9.1 Hz, 1H, H-4α), 4.68 (dd, J = 9.1, 6.4 Hz, 1H, H-3), 7.01−7.08 (m, 3H, H-9, Ar−H), 7.20−7.27 (m, 2H, Ar−H), 7.33−7.42 (m, 3H, Ar−H), 7.50−7.55 (m, 2H, Ar−H), 8.03−

8.07 (m, 2H, Ar−H), 8.22−8.26 (m, 2H, Ar−H). Further signals attributed to isomer **14a**: 2.59 (s, COMe), 4.99 (dd, J = 9.9, 7.1 Hz, H-3); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 25.9 ($CO\mathit{C}H_3$), 47.7 (C-4), 69.5 (C-3), 105.9 (C-5), 117.2, 123.5, 124.1, 126.9, 128.2, 128.8, 129.1, 131.1, 134.5, 139.3, 148.9, 150.9, 163.3 (CO_2Ar), 198.5 (COMe); MS (70 eV) 432 (M^+, 2), 352 (12), 275 (10), 256 (11), 222 (76), 198 (72), 167 (100), 154 (45), 121 (43), 77 (34), 65 (53). Anal. Calcd for $C_{24}H_{20}N_2O_6$: C, 66.66; H, 4.66; N, 6.48. Found: C, 63.70; H, 5.01; N, 6.04.

(3*R,5*R**)-5-Acetyl-3-(*p*-chlorophenyl)-5-(*p*-nitrobenzoyloxy)-2-phenylisoxazolidine (13b) and (3*R**,5*S**)-5-Acetyl-3-(*p*-chlorophenyl)-5-(*p*-nitrobenzoyloxy)-2-phenylisoxazolidine (14b).** The same procedure as for **13a**/**14a** was used, with 0.23 g (1.0 mmol) of **6b**, and 0.24 g (1.0 mmol) of **1a** in dry benzene (15 mL), to give a mixture of **13b**/**14b** (90:10). Purification by column chromatography on silica gel (30 g, hexane/EtOAc, 7:3), yielded 0.35 g (75%) of **13b**, which was recrystallized from hexane/CH_2Cl_2, 95:5, to give pale yellow crystals: R_f 0.48 (hex/EtOAc, 7:3); mp 57−58 °C; IR (KBr) 1730, 1663, 1600, 1521, 1346, 1263, 1097 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.52 (s, 3H, COMe), 2.94 (dd, J = 14.1, 6.4 Hz, 1H, H-4β), 3.30 (dd, J = 14.1, 9.0 Hz, 1H, H-4α), 4.65 (dd, J = 9.0, 6.4 Hz, 1H, H-3), 6.98−7.02 (m, 2H, Ar−H), 7.03−7.10 (m, 1H, Ar−H), 7.22−7.29 (m, 2H, Ar−H), 7.35−7.40 (m, 2H, Ar−H), 7.43−7.48 (m, 2H, Ar−H), 8.04−8.09 (m, 2H, Ar−H), 8.27−8.31 (m, 2H, Ar−H). Further signals attributed to isomer **14b**: 2.59 (s, COMe), 4.98 (dd, J = 9.6, 6.8 Hz, H-3); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 25.8 ($CO\mathit{C}H_3$), 47.7 (C-4), 69.0 (C-3), 106.1 (C-5), 117.5, 123.6, 124.5, 128.2, 128.7, 129.3, 131.1, 134.2, 134.3, 137.8, 148.7, 151.1, 163.4 (CO_2Ar), 198.4 (COMe). Anal. Calcd for $C_{24}H_{19}N_3O_8$: C, 60.38; H, 4.01; N, 8.80. Found: C, 60.40; H, 4.09; N, 9.00.

(3*R,5*R**)-5-Acetyl-2-(*tert*-butyl)-5-(*p*-nitrobenzoyloxy)-3-phenylisoxazolidine (13h).** The same procedure as for **13a**/**14a** was used, with 0.10 g (0.56 mmol) of **6e**, and 0.13 g (0.56 mmol) of **1a** in dry benzene (15 mL), and heating to reflux for 24 h, to give **13h** as a pale yellow oil. Purification by column chromatography on silica gel (15 g, hexane/EtOAc, 7:3), yielded 0.1 g (44%) of **13h**, which was recrystallized from EtOH/CH_2Cl_2, 4:1, to give pale yellow needles: R_f 0.43 (hex/EtOAc 8:2); mp 129−130 °C; IR (KBr) 1728, 1529, 1354, 1284, 1095, 846, 719 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.12 (s, 9H, *t*-Bu), 2.44 (s, 3H, COMe), 2.82 (dd, J = 14.1, 5.2 Hz, 1H, H-4β), 3.07 (dd, J = 14.1, 9.7 Hz, 1H, H-4α), 4.46 (dd, J = 9.7, 5.2 Hz, 1H, H-3), 7.23−7.37 (m, 3H, Ph-H), 7.50−7.55 (m, 2H, Ph-H), 7.95−8.00 (m, 2H, Ar−H), 8.20−8.26 (m, 2H, Ar−H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 25.7 ($CO\mathit{C}H_3$), 26.1 (*t*-Bu), 48.7 (C-4), 59.5 ($\mathit{C}Me_3$), 61.3 (C-3), 106.3 (C-5), 123.4, 127.3, 127.9, 128.5, 131.1, 134.6, 142.4, 150.7, 163.4 (CO_2Ar), 199.4 (COMe). Anal. Calcd for $C_{22}H_{24}N_2O_6$: C, 64.07; H, 5.87; N, 6.79. Found: C, 60.10; H, 5.76; N, 6.85.

(3*R,5*R**)-5-Acetyl-2-benzyl-5-(*p*-nitrobenzoyloxy)-3-(*p*-tolyl)isoxazolidine (13j) and (3*R**,5*S**)-5-Acetyl-2-benzyl-5-(*p*-nitrobenzoyloxy)-3-(*p*-tolyl)isoxazolidine (14j).** The same procedure as for **13a**/**14a** was used, with 0.103 g (0.458 mmol) of **6j**, and 0.107 g (0.458 mmol) of **1a**, to give a mixture of **13j**/**14j** (60:40). The major isomer **13j** was isolated by radial chromatography (hexane/EtOAc, 8:2), yielding 0.063 g (30%) of **13j**, which was recrystallized from hexane/CH_2Cl_2, 3:1, to give pale yellow needles: R_f 0.3, hex/EtOAc, 7:3; 131−132 °C; IR (KBr) 1726, 1527, 1350, 1286, 1064 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.37 (s, 3H, Me-Ar), 2.49 (s, 3H, COMe), 2.66 (dd, J = 13.2, 11.3 Hz, 1H, H-4β), 2.86 (dd, J = 13.2, 5.4 Hz, 1H, H-4α), 3.90 (d, J = 14.7 Hz, 1H, $PhCH_2$), 4.28 (d, J = 14.7 Hz, 1H, $PhCH_2$), 4.30 (dd, J = 11.3, 5.4 Hz, 1H, H-3), 6.98−7.14 (m, 3H, Ar−H), 7.18−7.26 (m, 4H, Ar−H), 7.37−7.43 (m, 2H, Ar−H), 8.04−8.09 (m, 2H, Ar−H), 8.24−8.29 (m, 2H, Ar−H). Further signals attributed to isomer **14j**: 3.20 (dd, J = 14.1, 7.8 Hz, H-4), 3.94 (d, J = 14.8 Hz, $PhCH_2$), 4.16 (d, J = 14.8 Hz, $PhCH_2$); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 21.2 (Ar−CH_3), 25.5 ($CO\mathit{C}H_3$), 47.7 (C-4), 59.8 ($Ph\mathit{C}H_2$), 65.3 (C-3), 106.1 (C-5), 123.4, 127.4, 127.6, 128.0, 129.7, 129.9, 131.0, 133.1, 134.5, 135.1, 138.5, 150.8, 163.1 (CO_2Ar), 201.6 (COMe). Anal. Calcd for $C_{26}H_{24}N_2O_6$: C, 67.82; H, 5.25; N, 6.08. Found: C, 67.62; H, 5.23; N, 6.03.

General Procedure for the 1,3-Dipolar Addition of 3-Acetoxy-3-buten-2-one (1c) with Nitrones 6c, 6f, and 6h. (3*R,5*R**)-5-Acetoxy-5-acetyl-3-(*p*-bromophenyl)-2-phenylisoxazolidine (15a) and (3*R**,5*S**)-5-Acetoxy-5-acetyl-3-(*p*-bromophenyl)-2-phenylisoxazolidine (16a).** A mixture of 0.28 g (1.0 mmol) of nitrone **6c** and 0.13 g (1.0 mmol) of **1c** in dry benzene (15 mL) was stirred and heated to 80 °C for 12 h, under an N_2 atmosphere. The solvent was removed under vacuum, to yield an oily residue of a mixture of **15a**/**16a** (73:27). This residue was purified by column chromatography on silica gel (15 g, hexane/EtOAc, 7:3) to give a mixture **15a**/**16a** (73:27). The major isomer was isolated by recrystallization from hexane/CH_2Cl_2 (95:5), to afford 0.283 g (70%) of **15a** as white needles: R_f 0.6 (hexane/EtOAc, 7:3); mp 122−123 °C; IR (KBr) 1735, 1595, 1481, 1360, 1233, 1067, 1000 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.12 (s, 3H, CH_3CO_2), 2.41 (s, 3H, CH_3CO), 2.70 (dd, J = 14.1, 7.4 Hz, 1H, H-4β), 3.19 (dd, J = 14.1, 9.0 Hz, 1H, H-4α), 4.43 (dd, J = 9.0, 7.4 Hz, 1H, H-3), 6.93−7.00 (m, 2H, Ph-H), 7.01−7.07 (m, 1H, Ph-H), 7.17−7.25 (m, 2H, Ph-H), 7.32−7.38 (m, 2H, Ar−H), 7.47−7.53 (m, 2H, Ar−H). Signals attributed to isomer **16a**: 2.22 (s, CH_3CO_2), 2.34 (s, CH_3CO), 3.03 (dd, J = 12.7, 6.7 Hz, H-4), 4.84 (dd, J = 9.9, 6.7 Hz, H-3); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 20.8 ($\mathit{C}H_3CO_2$), 25.6 ($\mathit{C}H_3CO$), 48.0 (C-4), 69.3 (C-3), 104.6 (C-5), 117.8, 122.1, 124.4, 128.7, 128.9, 132.1, 132.3, 138.1, 148.6, 169.9 ($CH_3\mathit{C}O_2$), 199.1 ($CH_3\mathit{C}O$). Anal. Calcd for $C_{19}H_{18}BrNO_4$: C, 56.45; H, 4.49; N, 3.46. Found: C, 56.32; H, 4.68; N, 3.41.

(3*R,5*R**)-5-Acetoxy-5-acetyl-2-phenyl-3-(*p*-tolyl)isoxazolidine (15b) and (3*R**,5*S**)-5-Acetoxy-5-acetyl-2-phenyl-3-(*p*-tolyl)isoxazolidine (16b).** The same procedure as for **15a**/**16a** was used, with 0.10 g (0.47 mmol) of **6f**, and 0.10 g (0.76 mmol) of **1c**, to give a mixture of **15b**/**16b** (82:18). This residue was purified by column chromatography on silica gel (30 g, hexane/EtOAc, 7:3) to give a mixture **15b**/**16b** (82:18) as pale green oil. The major isomer was isolated by crystallization from hexane/CH_2Cl_2, 8:2, to afford 0.08 g (50%) of **15b** as colorless crystals: R_f 0.37 (hexane/EtOAc, 8:2); mp 126−127 °C; IR (CH_2Cl_2) 1732, 1720, 1597, 1488, 1359, 1230, 1184, 1074 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.15 (s, 3H, CH_3CO_2), 2.36 (s, 3H, CH_3Ar), 2.42 (s, 3H, CH_3CO), 2.76 (dd, J = 14.1, 8.0 Hz, 1H, H-4β), 3.19 (dd, J = 14.1, 8.8 Hz, 1H, H-4α), 4.40 (dd, J = 8.8, 8.0 Hz, 1H, H-3), 6.97−7.06 (m, 3H, Ar−H), 7.17−7.23 (m, 4H, Ar−H), 7.32−7.37 (m, 2H, Ar−H). Signals attributed to isomer **16b**: 1.87 (s, CH_3CO_2), 2.35 (s, CH_3Ar), 2.50 (s, CH_3CO), 2.99 (dd, J = 13.0, 6.9 Hz), 4.81 (dd, J = 10.2, 6.9 Hz, H-3); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 20.4 ($\mathit{C}H_3Ar$), 20.8 (CH_3CO_2), 26.1 ($\mathit{C}H_3CO$), 48.7 (C-4), 69.3 (C-3), 104.9 (C-5), 118.0, 124.0, 127.3, 128.5, 129.6, 129.9, 135.8, 137.9, 149.0, 170.0 ($CH_3\mathit{C}O_2$), 199.7 ($CH_3\mathit{C}O$). Anal. Calcd for $C_{20}H_{21}NO_4$: C, 70.78; H, 6.24; N, 4.13. Found: C, 70.69; H, 6.12; N, 4.18.

(3*R,5*S**)-5-Acetyl-3-(*p*-anisyl)-2-phenylisoxazolidine (18a), (3*R**,5*R**)-5-Acetyl-3-(*p*-anisyl)-2-phenylisoxazolidine (18b), (3*R**,4*S**)-4-Acetyl-3-(*p*-anisyl)-2-phenylisoxazolidine (18c), and (3*R**,4*R**)-4-Acetyl-3-(*p*-anisyl)-2-phenylisoxazolidine (18d).** A mixture of 0.50 g (2.2 mmol) of nitrone **6e** and 0.15 g (2.2 mmol) of **17** in dry benzene (20 mL) was stirred and heated to 80 °C for 24 h, under an N_2 atmosphere. The solvent was removed under vacuum, to yield an oily residue of a mixture of **18a**/**18b**/**18c**/**18d** (2:10:7:1). This residue was purified by column chromatography on silica gel (30 g, hexane/EtOAc, 9:1) to give 0.52 g (80%) of a mixture of four stereoisomers and pure oily small fractions of each one: 0.026 g (4%) of **18a**, R_f 0.57 (hexane/EtOAc, 8:2); 0.052 g (8%) of **18b**, R_f 0.48 (hexane/EtOAc, 8:2); 0.039 g (6%) of **18c**, R_f 0.40 (hexane/EtOAc, 8:2); 0.02 g (3%) of **18d**, R_f 0.31 (hexane/EtOAc, 8:2); Data of **18a**: IR (CCl_4) 1703, 1604, 1578, 1511, 1485, 1258, 1161, 1036 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.38 (s, 3H, CH_3CO), 2.62 (ddd, J = 12.7, 6.4, 5.0 Hz, 1H, H-4β), 2.96 (ddd, J = 12.7, 9.0, 8.4 Hz, 1H, H-4α), 3.80 (s, 3H, CH_3O), 4.44 (dd, J = 8.4, 6.4 Hz, 1H, H-3), 4.58 (dd, J = 9.0, 5.0 Hz, 1H, H-5), 6.58−7.35 (m, 9H, Ar−H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 25.8 ($\mathit{C}H_3CO$), 41.9 (C-4), 55.2 (MeO), 69.1 (C-3), 81.5 (C-5), 114.2, 116.6, 123.1, 128.0, 128.7, 132.1, 149.9, 159.1, 200.5 ($CH_3\mathit{C}O$). Anal. Calcd for $C_{18}H_{19}NO_3$: C, 72.71; H, 6.44;

N, 4.71. Found: C, 72.90; H, 6.59; N, 4.75. Data of **18b**: IR ($CHCl_3$) 1718, 1676, 1512, 1492, 1251, 1176, 1029 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.31 (s, 3H, CH_3CO), 2.55 (ddd, J = 12.5, 8.2, 5.8 Hz, 1H, H-4β), 2.89 (ddd, J = 12.5, 8.0, 6.3 Hz, 1H, H-4α), 3.76 (s, 3H, CH_3O), 4.54 (dd, J = 8.0, 5.8 Hz, 1H, H-3), 4.66 (dd, J = 8.2, 6.3 Hz, 1H, H-5), 6.85−7.03 (m, 5H, Ar−H), 7.14−7.22 (m, 2H, Ar−H), 7.29−7.35 (m, 2H, Ar−H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 26.7 (CH_3CO), 41.4 (C-4), 55.1 (MeO), 67.6 (C-3), 81.4 (C-5), 114.1, 116.2, 122.3, 128.0, 128.4, 132.1, 149.4, 159.0, 207.6 (CH_3CO). Anal. Calcd for $C_{18}H_{19}NO_3$: C, 72.71; H, 6.44; N, 4.71. Found: C, 72.80; H, 6.18; N, 4.94. Data of **18c**: IR (CCl_4) 1720, 1612, 1598, 1512, 1490, 1249, 1173, 1040 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.12 (s, 3H, CH_3CO), 3.61−3.70 (m, 1H, H-4), 3.80 (s, 3H, CH_3O), 4.21 (dd, J = 8.2, 6.9 Hz, 1H, H-5β), 4.41 (dd, J = 8.2, 8.0 Hz, 1H, H-5α), 4.65 (d, J = 6.1, 1H, H-3), 6.89−6.99 (m, 5H, Ar−H), 7.16−7.24 (m, 2H, Ar−H), 7.38−7.44 (m, 2H, Ar−H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 29.7 (CH_3CO), 55.3 (MeO), 66.8 (C-4), 68.2 (C-5), 71.5 (C-3), 114.4, 115.5, 122.3, 127.9, 128.7, 133.1, 150.4, 159.3, 204.2 (CH_3CO). Anal. Calcd for $C_{18}H_{19}NO_3$: C, 72.71; H, 6.44; N, 4.71. Found: C, 72.92; H, 6.33; N, 4.75. Data of **18d**: IR (CCl_4) 1719, 1617, 1599, 1513, 1500, 1250, 1183, 1042 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.81 (s, 3H, CH_3CO), 3.80 (s, 3H, CH_3O), 3.80−3.92 (m, 1H, H-4), 4.26 (t, J = 8.4 Hz, 1H, H-5β), 4.61 (dd, J = 8.4, 6.7 Hz, 1H, H-5α), 5.02 (d, J = 8.8, 1H, H-3), 6.85−7.09 (m, 5H, Ar−H), 7.23−7.31 (m, 2H, Ar−H), 7.32−7.38 (m, 2H, Ar−H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 30.4 (CH_3CO), 55.2 (MeO), 60.5 (C-4), 66.9 (C-5), 71.5 (C-3), 114.1, 115.2, 122.1, 128.9, 129.1, 129.5, 150.4, 159.4, 204.2 (CH_3CO). Anal. Calcd for $C_{18}H_{19}NO_3$: C, 72.71; H, 6.44; N, 4.71. Found: C, 72.94; H, 6.56; N, 4.70.

Δ^4-5-Acetyl-3-(*p*-anisyl)-2-phenylisoxazoline (20). A mixture of 0.10 g (0.22 mmol) of **13e**, and **19** (10 mL) was stirred and heated to 100 °C for 3 h, under an N_2 atmosphere. The mixture was diluted with CH_2Cl_2 (50 mL) and washed with a 20% aqueous solution of HCl (3 × 30 mL), a saturated aqueous solution of $NaHCO_3$ (3 × 30 mL), and brine (3 × 30 mL). The organic phase was dried (Na_2SO_4), and the solvent was removed under vacuum, to give an oily residue, which was purified by column chromatography on silica gel (30 g, hexane/EtOAc, 9:1) to yield 0.038 g (60%) of **20** as a pale yellow oil: R_f 0.2 (hexane/EtOAc, 8:2); IR (CCl_4) 1706, 1600, 1535, 1510, 1260, 1249, 1124, 1086 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.43 (s, 3H, CH_3CO), 3.84 (s, 3H, MeO), 5.85 (d, J = 10.0 Hz, 1H, H-3), 6.90−7.45 (m, 9H, Ar−H), 8.37 (br d, J = 10.0 Hz, 1H, H-4); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 24.0 (CH_3CO), 55.5 (MeO), 96.5 (C-3), 114.8, 115.2, 122.1, 125.6, 128.2, 129.6, 129.8, 144.5, 151.4, 159.5, 185.5 (CH_3CO); MS (70 eV) 295 (M^+, 5), 252 (100), 209 (25), 180 (5), 77 (6). Anal. Calcd for $C_{18}H_{17}NO_3$: C, 73.20; H, 5.80; N, 4.74. Found: C, 73.37; H, 5.83; N, 4.93.

Single-Crystal X-ray Crystallography. Isoxazolidines **13h** and **14j** were obtained as pale yellow and colorless crystals, respectively. These were mounted in glass fibers. Crystallographic measurements were performed on a Siemens P4 diffractometer with Mo Kα radiation (λ = 0.7107 Å; graphite monochromator) at room temperature. Two standard reflections were monitored periodically; they showed no change during data collection. Unit cell parameters were obtained from least-squares refinement of 26 reflections in the range $2 < 2\Theta < 20°$. Intensities were corrected for Lorentz and polarization effects. No absorption correction was applied. Anisotropic temperature factors were introduced for all non-hydrogen atoms. Hydrogen atoms were placed in idealized positions and their atomic coordinates refined. Unit weights were used in the refinement. Structures were solved using SHELXTL[54] on a personal computer. Data for **13h**: Formula: $C_{22}H_{24}N_2O_6$; molecular weight: 412.43; cryst syst: triclinic; space group: $P\bar{1}$; unit cell parameters: a, 9.1316 (6), b, 11.266 (2), c, 11.7911 (8) (Å); α, 82.150 (7), β, 68.905 (4), γ, 75.488 (6) (deg); temp (K): 293 (2); Z: 2; R: 0.0421; GOF: 1.060. Data for **14j**: Formula: $C_{26}H_{24}N_2O_6$; molecular weight: 460.47; cryst syst: triclinic; space group: $P\bar{1}$; unit cell parameters: a, 6.778, b, 10.1390 (10), c, 18.013 (2) (Å); α, 79.610 (10), β, 79.330 (10), γ, 82.320 (10) (deg); temp (K): 293 (2); Z: 2; R: 0.0391; GOF: 1.042.

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Supporting Information Available: X-ray structures of nitrones **6e** and **6k**, tables of crystal data, structure solution and refinement, bond angles, lengths, and anisotropic thermal parameters for the structures **13h** and **14j**. Preparation methods and spectroscopic data for nitrones **6**, and compounds **9c**, **9d**, **13c**/**14c**, **13d**/**14d**, **13e**/**14e**, **13f**/**14f**, **13g**/**14g**, **13i**/**14i**, **15c**, **21**, **22**, **23**, and **24**. Table of ab initio (RHF/3-21G, and 6-31G*) calculated energies and coefficients of the frontier molecular orbitals of olefins **1a** and **17**, and nitrones **6a**, **6d**, **6e**, **6h**, and **6k**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(54) SHELXTL, v. 5.03, Siemens Energy & Automation, Germany, 1995.