DOI: 10.1002/ejoc.200600988

Selectivity in 1,3-Dipolar Cycloadditions of β-Substituted Captodative Olefins – An Experimental and DFT Transition State Study

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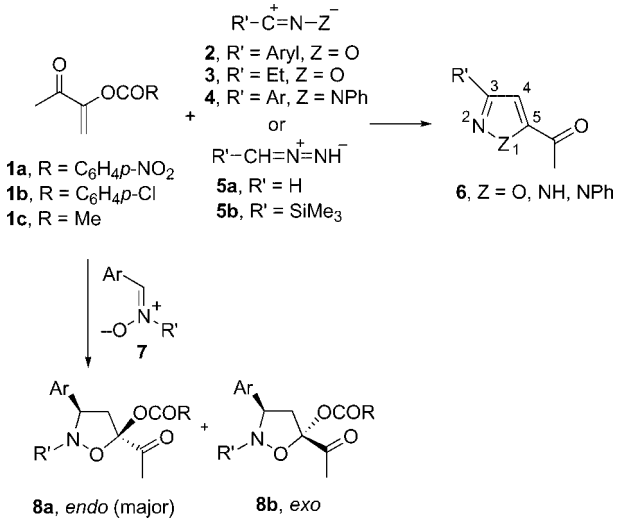
Keywords: Cycloadditions / Nitrones / Regioselectivity / Density functional calculations / Transitions states

Captodative olefins 1-acetylvinyl carboxylates substituted with alkyl groups at the β position, **12**, strongly modified the regioselectivity of 1,3-dipolar cycloadditions with respect to the behavior observed for their unsubstituted analogs, **1**. When the reaction of **12** was carried out with diphenyl nitrone (**7a**), the corresponding C-4 disubstituted isoxazolidines were obtained as a mixture or as single stereoisomers, in contrast to the isomeric C-5 disubstituted heterocycles yielded by olefins **1**. Nevertheless, olefins **12** reacted with benzonitrile oxide (**2a**) to give the C-5 acetyl isoxazoles, as observed with dipolarophiles **1**. This intricate behavior of the reactions between 1,3-dipoles and β-substituted captodative olefins was rationalized on the basis of DFT calculations [B3LYP/6-31(d)] of the transition states (TSs) for nitrone **7a** and olefin **12a**. Thus, the observed C-4 and *endo* regio- and stereoselectivities agreed with the most stable TSs, which are mainly stabilized by dipolar and electrostatic interactions.

Introduction

As a part of our ongoing research program concerning the synthesis of new captodative olefins and their study in cycloaddition reactions,[1] we have described the behavior of 1-acetylvinyl carboxylates **1** with a diverse set of dipoles such as nitrile oxides,[2] nitrile imines, diazo compounds, and nitrones.[3] We found that the addition of aryl and alkyl nitrile oxides, **2** and **3**, C-aryl-N-phenylnitrile imines **4**, and diazo compounds **5** provided exclusively the corresponding 5-substituted aromatic isoxazoles and pyrazoles **6** (Scheme 1). The reactions with nitrones **7** were also highly regioselective and yielded C-5 substituted heterocycles **8**; this process was stereoselective as well given that *endo* adduct **8a** was the major product.[3]

The regioselectivity observed in the 1,3-dipolar cycloadditions of monosubstituted alkenes can be explained in terms of FMO theory.[4] However, many incorrect predictions of this theory are reported for 1,3-dipolar reactions of captodative and disubstituted olefins.[5] Diverse factors are invoked to rationalize the preferred orientation of the cycloaddends; among them we can cite steric effects,[6] closed-shell repulsions,[7] and repulsive secondary orbital interactions.[8] Calculations of transition states have also suggested the presence of a diradicaloid or highly polarized species,[9] and pointed out the importance of electrostatic interactions and solvent effects in controlling the regiochemical outcome.[10]



Scheme 1. 1,3-Dipolar cycloadditions of captodative olefins **1** with diverse dipoles.

With respect to olefins **1**, FMO analysis of the reaction between benzonitrile oxide (**2a**) and nitrones **7** failed to predict the observed regioselectivity of the cycloaddition, which favors the opposite orientation.[2,3b] A correct predic-

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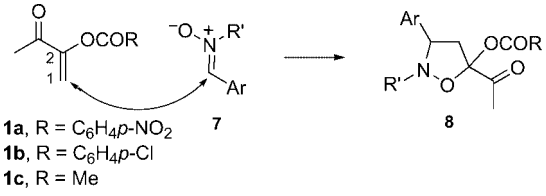
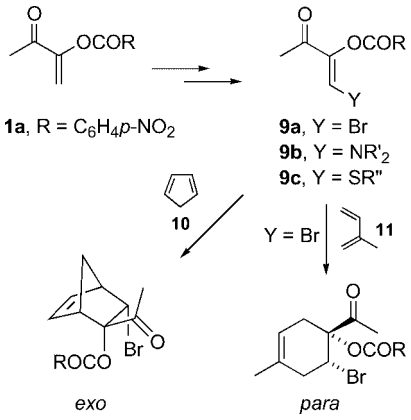
tion of the regioselectivity was obtained through the estimation of the interaction energy between the reactants in terms of density functional theory (DFT) and the hard–soft acid–base principle (HSAB).[11] The theoretical study of derivatives **1** under the principles of the DFT/HSAB model indicated that the regioselectivity depends mainly on the effect of the electron-donor group, which increases the nucleophilicity of the unsubstituted terminus C-1 of the olefin. A mutual electron donation between this carbon atom and the nitrone C atom (Scheme 2), or the interaction with the carbon atom of the nitrile oxide as the electrophilic center, would predict the C-5 substituted adducts, which matches the experimental results.[3b,11a]



Scheme 2. Mutual electron donation between olefins **1** and nitrones **7** (see text).

We have also assessed the perturbation effect of a third substituent at the β position of the double bond of **1** on the reactivity, regio-, and stereoselectivity of these olefins in Diels–Alder reactions.[12] We prepared β-functionalized 1-acetylvinyl arenecarboxylates **9**; however, they failed to react with cyclopentadiene (**10**) and isoprene (**11**), except for β-brominated olefin **9a**, which undergoes addition to these dienes to give the *exo* and *para* adducts, respectively, as the major isomers (Scheme 3).[12a] The ratio of regioisomers obtained with diene **11**, under thermal conditions, was similar to that observed for unsubstituted olefin **1a**. The low reactivity of dienophiles **9b** and **9c** can be ascribed to efficient delocalization of the electron lone pair of the heteroatom of the β-substituent towards the double bond.

With the aim of evaluating the effect of β-substitution in captodative olefins on 1,3-dipolar cycloaddition reactions, we decided to prepare cyclic and noncyclic captodative olefins substituted by groups with low polarizing strength, such as alkyl groups, and to study these alkenes in cycloadditions with benzonitrile oxide (**2a**) and nitrones **7**. The experimental results and a theoretical study are described herein.

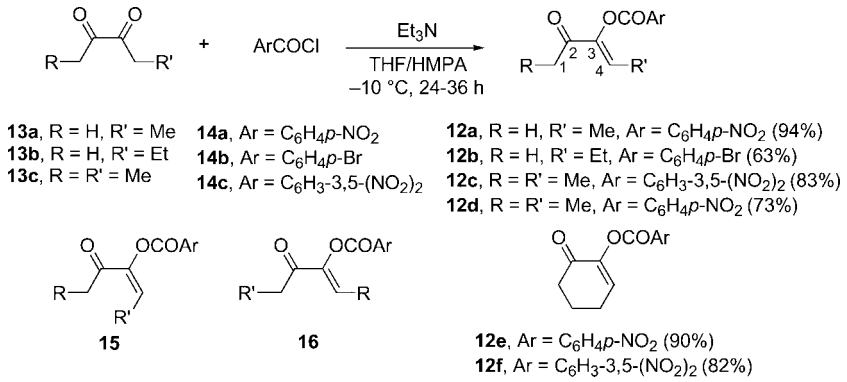


Scheme 3.

Results

Preparation of β-Substituted Captodative Alkenes 12

Acyclic β-alkyl-substituted olefins **12a**–**12c** were prepared by a straightforward method through treatment of the base-generated enolate of corresponding α-diketones **13** with acid chlorides **14**, under conditions similar to those used for the preparation of **1a** (Scheme 4).[13] In a previous report, we described the synthesis of olefin **12a** by a cross-coupling reaction between olefin **9a** and tetramethyltin in the presence of catalytic amounts of a Pd^{II} complex.[14] In contrast with that methodology, where **12a** was obtained by a four-step synthesis in 38% overall yield, the direct condensation of 2,3-pentanedione (**13a**) with *p*-nitrobenzoyl chloride (**14a**) provided **12a** in 94% yield. Similarly, by reacting 2,3-hexanedione (**13b**) and 3,4-hexanedione (**13c**) with acid chlorides **14b** and **14c**, respectively, olefins **12b** and **12c** were furnished in good yields. Under the thermodynamic conditions used in the reaction, neither geometric isomers **15** nor olefins **16** were obtained. NOE experiments confirmed the configuration of the double bond as en-



Scheme 4.

hancements of the signals attributed to the acyl methyl group, and to the β-substituted alkyl group, were measured upon irradiation of the vinylic 4-H. A procedure analogous to that above was employed for the preparation of cyclic enone **12e** by using 1,2-cyclohexanedione (**13d**) and acid chloride **14a**.

1,3-Dipolar Cycloadditions of Alkenes 12a–12c and 12e to Nitrone 7a

The 1,3-dipolar cycloadditions between diphenyl nitrone (**7a**) and olefins **12a**–**12c** were carried out under thermal conditions (Scheme 5) and provided the corresponding stereoisomeric mixtures of 4-disubstituted isoxazolidines **17**–**18** (Table 1). No evidence of the 5-disubstituted regioisomer was found either by chromatography or by ^{1}H NMR spectroscopy, even after the reaction was stopped before the dipolarophile had disappeared. This regioselectivity strongly contrasts that expected for both steric[6] and electronic points of view,[15] and with the behavior of olefin **1a**, which adds to **7a** to yield only the C-5 adduct (Scheme 1).[3] The C-4 orientation would be the most crowded one because the C-phenyl ring of the nitrone is vicinal to the geminal center of the olefin. In principle, one might not expect that an alkyl group at the β position would perturb the polarization of the double bond as far as to reverse it.[16] However, the 1,3-dipolar additions of nitrones to 1,2-disubstituted olefins bearing carbonyl and methyl groups with the (*E*) geometry, such as olefins **12**, yield only the C-4 regioisomer.[17] Other captodative olefins,[17,18] and most dipolarophiles monosubstituted with either electron-donating or electron-withdrawing groups add to nitrones[18f,19] to yield the C-5 orientation, preferentially.

As expected, dipolarophile **12c**, bearing the 3,5-dinitrobenzoyloxy group, was more reactive than **12a** and **12b**, although all these additions were slower than those of olefin **1a**.[3b] The steric hindrance and the hyperconjugative effect of the alkyl group in the double bond might be responsible for the lower reactivity of the former dipolarophiles.[4f,6,16] The faster addition of **12c** towards **7a**, in comparison with those of **12a** and **12b**, agrees with the observation that electron-withdrawing groups in the aroyloxy group of captodative olefins **1** increase the reaction rate in concerted Diels–Alder additions.[13a]

Table 1. 1,3-Dipolar additions of olefins **12a**–**12c** and **12e** with nitrone **7a**.[a]

Entry	Olefin	**7a** [mol equiv.]	*T* [°C]	*t* [h]	Products[b] (ratio)	Yield[c] [%]
1	**12a**	1.9	110	12	**17a/18a** (70:30)	50[d]
2	**12b**	3.6	110	12	**17b/18b** (55:45)	30[e]
3	**12c**	3.7	80	12	**17c/18c** (66:44)	40[f]
4	**12e**	2.0	140	24	**19**	63[g]

[a] All reactions were performed under a N_2 atmosphere in dry benzene heated at reflux. [b] Determined by ^{1}H NMR (300 MHz) spectroscopy of the crude mixture. [c] Of the mixture after column chromatography. [d] Olefin **12a** (27%) was recovered. [e] Olefin **12b** (36%) was recovered. [f] Olefin **12c** (30%) was recovered. [g] Olefin **12e** (31%) was recovered.

The *endo* stereoselectivity of these additions was not as high as that shown by olefin **1a**[3b] or by other captodative alkenes,[17a,17d,18b,18d,18e] although lower stereoselectivities were also reported.[18d,20] The *endo* approach is preferred, in spite of the possible steric repulsions at the transition state between the aroyloxy group and the C-phenyl group of the nitrone (Figure 1). Besides, this *endo* preference agrees with the steric interactions generated at the *exo* transition state between the nitrone N-phenyl group and both the aroyloxy group and the substituent in the β position of these dipolarophiles.[3b,19d] In addition to these interactions during the *exo* approach, further steric interactions could take place between the acyl group of olefins **12a**–**12c** and

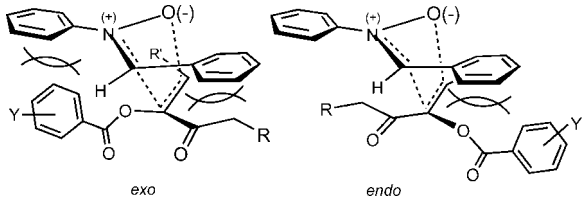
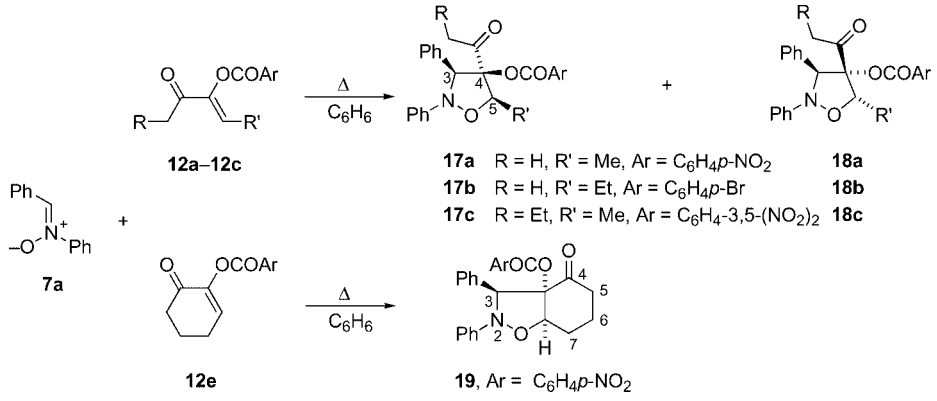


Figure 1. Possible steric interactions at the *exo* and *endo* transition states in the 1,3-dipolar cycloadditions of nitrone **7a** and olefins **12a**–**12c**.



Scheme 5.

the C-phenyl group of the nitrone (Figure 1). To investigate this hypothesis, we prepared olefin **12d** (Scheme 4) and its crystalline structure was determined by X-ray crystallography (Figure 2).[21] This structure confirmed that the configuration of the double bond was (*Z*), as anticipated by NOE experiments. In addition, it showed that the aroyloxy group adopts a conformation out of the plane formed by the enone conjugated moiety and that the latter adopts the *s-trans* conformation. These structural features are in agreement with those observed for analogous molecules,[12,14] and support the proposed transition states as long as the geometries of the starting materials are maintained (Figure 1).

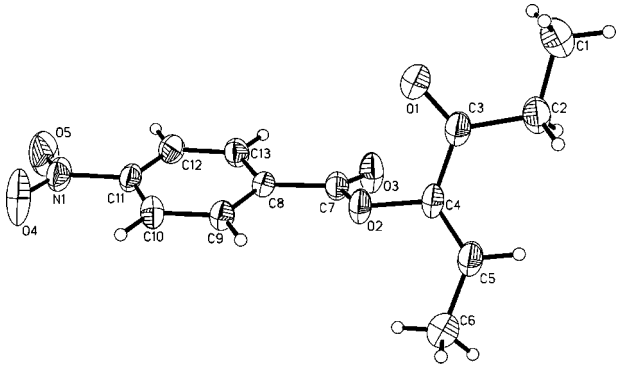


Figure 2. X-ray structure of **12d** (ellipsoids with 30% probability).

It is well known that nitrones substituted with bulky groups possess the (*Z*) configuration, with the N-alkyl or N-phenyl and the C-aryl groups in a *trans* relationship,[5d] as confirmed by X-ray crystallography and NOE experiments.[3b] We assumed that this configuration is maintained at the transition state, and that the reactants do not isomerize during the course of the cycloaddition.[22] The X-ray structure of **7b** (R′ = phenyl and Ar = C_6H_4*p*-OMe) showed both N-phenyl and C-anisyl groups in conformations slightly out of the plane formed by the 1,3-dipole (vide infra).[3b] In consequence, the steric interactions illustrated in Figure 1 become more important if the conformation of the aromatic rings of the nitrone is retained at such transition states.

The structures of adducts **17** and **18** were established on the basis of 2D NMR and NOE experiments. The multiplicity and coupling constants were consistent with the non-vicinal 3-H and 5-H protons in the isoxazolidine ring (Scheme 5). NOE enhancements of the signals of these protons were observed when the CH_3CO group on C-4 was irradiated in *endo* adducts **17a** and **17b**. In addition, for **17a**, an enhancement of the protons of the phenyl group at C-3 was recorded when the methyl group on C-5 was irradiated. This assignment was further confirmed by single-crystal X-ray diffraction of isoxazolidine **17a** (Figure 3).[21] The conformation of the heterocycle is different to that shown by the isoxazolidines arising from olefin **1a**.[3b] In contrast with the latter, where the *p*-nitrobenzoyloxy (PNB) group and the N-phenyl group are pseudoaxial, in **17a** only the N-phenyl group exhibits this arrangement. The heterocyclic ring adopts the envelope conformation with the N2–C3–C4–C5 atoms in the plane of the envelope (dihedral angle = 3.2°), and the oxygen out of this plane and *syn* to the C3-phenyl and C4-PNB groups. As a result of this arrangement, the latter two substituents are essentially eclipsed [dihedral angle O10–C4–C3–C22 = –4.3°], as are the corresponding substituents in the opposite face of the ring [dihedral angle C7–C4–C3–H3 = 0.7°]. The methyl group at C5 is also nearly eclipsed with the PNB group [dihedral angle C6–C5–C4–O10 = 22.1°], and it adopts the pseudoequatorial position with respect to the conformation of the ring. Conversely, the configuration of the nitrogen atom is such that the N-phenyl ring is *anti* with respect to the C3-phenyl.

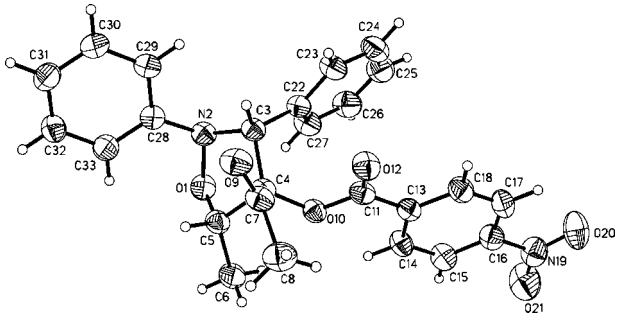


Figure 3. X-ray structure of isoxazolidine **17a** (ellipsoids with 30% probability).

The addition of nitrone **7a** to cyclohexenone **12e** was slower than those to olefins **12a**–**12c** because the former reaction took place at a higher temperature and with a longer reaction time (Table 1, Entry 4), to give adduct **19** as a single regio- and stereoisomer (Scheme 5). Notably, the regioselectivity was the same as that of dipolarophiles **12a**–**12c**; however, unlike these olefins, **12e** showed a preference for *exo* stereoselectivity. Therefore, the configuration of the olefin, (*Z*) in **12a**–**12c** or (*E*) in **12e**, does not appear to have a significant effect on the regiochemistry. Then again, the *endo* approach of **12e** would promote strong destabilizing interactions between the N-phenyl ring of the nitrone and the rest of the cyclohexenone σ skeleton. To gain further insight on the conformation of this kind of cyclohexenone derivatives, we undertook single-crystal X-ray analysis of a related compound. Thus, conjugated cyclohexenone **12f** was prepared through the method described in Scheme 4, and its structure was established by X-ray diffraction (Figure 4).[21] The ORTEP structure shows that the conformation of the cycle is a distorted half-chair. The crystal lattice exhibited static disorder due to the random presence of the

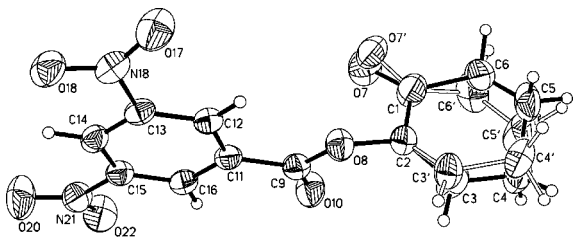


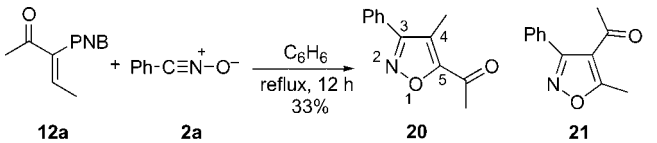
Figure 4. X-ray structure of cyclohexenone **12f** (ellipsoids with 30% probability).

two possible half-chair conformers of the cyclohexenone ring among different unit cells; the atoms involved in this disorder were C3, C4, C5, C6, and O7. Occupancy factors were determined for both conformers; a value of 0.56 for the half-chair in which C5 is pointing up with respect to the plane of the cyclohexenone ring (see Figure 4) and 0.44 for the other conformer was found. According to the above results, the *exo* preference found for enone **12e** might be attributed to repulsive interactions between the C4–C5–C6 cyclohexenone methylenes and the N-phenyl ring of the nitrone, at the *endo* transition state.

1,3-Dipolar Cycloadditions of Alkenes 12a and 12e to Benzonitrile Oxide (2a)

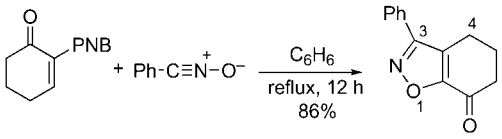
Nitrile oxides reacted with unsubstituted dipolarophile **1a** to give directly 3-aryl- and 3-alkyl-5-acetylisoxazoles (Scheme 1).[2] This regioselectivity parallels that obtained with nitrones as only the C-5 substituted heterocycle was observed.[3] From these results, one would expect that the C-4 regioselectivity observed in the reactions of olefins **12** with nitrones would be preserved in the reactions with nitrile oxides. With the goal of confirming this hypothesis, we carried out the reaction between benzonitrile oxide (**2a**) and olefins **12a** and **12e**.

Addition of **2a**, prepared in situ from benzohydroxyiminoyl chloride and triethylamine in benzene, to olefin **12a** and heated at reflux for 12 h furnished a single isoxazole [Equation (1)]. Expected 4-acetyl regioisomer **21** was not isolated from the reaction mixture; instead 5-acetyl-4-methyl-3-phenylisoxazole (**20**) was obtained pure in 33% yield. The low yield of **20** was mainly due to the difficulty of separating it from the dimer of **2a**, but the actual conversion to the adduct was higher, as shown by ^{1}H NMR spectroscopic analysis of the crude reaction mixture. The observed regiochemistry agreed either with that observed in the addition of nitrones to **1a** or with the trend observed for the reaction of diverse dipoles with **1a**.[3] Unless the electron-deficient olefin has a β substituent such as a methyl group, where the C-4 isomer will be preferred,[23] either captodative olefins[18b,24] or both electron-rich and electron-deficient alkenes,[19g,19h,23,24d,24f] will react with nitrile oxides to provide preferentially the C-5 regioisomer.



(1)

Although our previous results have suggested that steric interactions are not responsible for the regioselectivity observed in these 1,3-dipolar additions,[3] the relative stereochemistry of the β substituent in the dipolarophile may have an influence on the control of the regiochemistry observed with dipole **2a**. This prompted us to examine the cycloaddition of the latter with **12e**. Thus, under similar reaction conditions, **2a** added to **12e** to yield again a single product, whose structure corresponded to tetrahydrobenzoxazolone **22** in good yield (86%) [Equation (2)]; the reaction showed the same regioselectivity as that found for **12a**.



(2)

The structures of adducts **20** and **22** were established by NOE experiments. Irradiation of the methyl group at C-4 of **20**, and the C-4 methylene of **22**, resulted in enhancement of the signals corresponding to the *ortho* protons of the C-3 phenyl ring in both molecules.

Discussion

The opposite regioselectivity observed in the 1,3-dipolar cycloadditions of olefins **12** with nitrone **7a** and benzonitrile oxide (**2a**), which gives rise to the C-4 and C-5 heterocycle substitution of the captodative center, respectively, suggests that electronic rather than steric control is involved in the effect that the β substituent has on the polarization of the double bond. The evaluation of such effects in these reactions appears to be beyond the scope of FMO theory, as we have formally demonstrated in the case of olefins **1**. Owing to the success of DFT/HSAB theory in accounting for the regioselectivity of the 1,3-dipolar cycloadditions of olefins **1**,[3b,11a] we have also applied this theoretical approach to the rationalization of the behavior of olefins **12** in the additions described above, and these results will be reported elsewhere. Herein we describe the calculation and analysis of the geometries and energies of the possible transition states (TSs) derived from the reaction between nitrone **7a** and dipolarophile **12a**.[25]

The geometries of the reactants and transition states were fully optimized at the HF/3-21G, HF/6-31G(d), and B3LYP/6-31G(d) levels of theory[26] by using GAUSSIAN 94,[27] and by considering previous calculations of analogous molecules.[3b,28] Although the orthogonal conformation of the aroyloxy group with respect to the enone moiety for the calculated geometry of **12a** was similar to that observed in the X-ray structures of **12a**[14] and **12d** (Figure 2), the conformation of the enone conjugated system in the most stable conformer calculated for **12d** was not the *s-trans* form (Figure 5) as expected from the X-ray structures. However, the relative energy of the *s-cis* conformer was just 0.10 kcal mol^{-1} lower than that of the *s-trans* conformer.

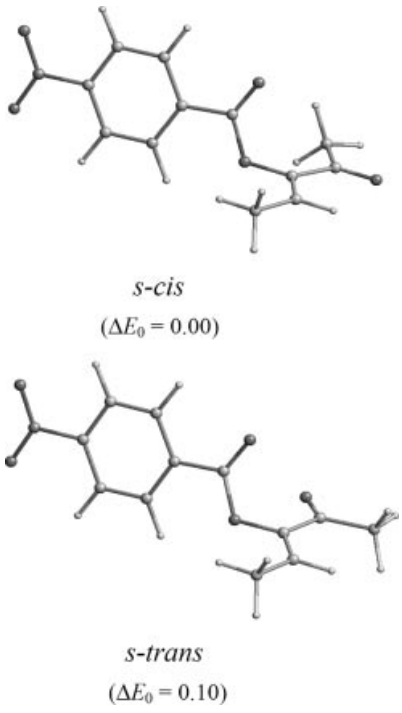


Figure 5. Optimized geometries [B3LYP/6-31G(d)] of olefin **12a** for the *s-cis* and *s-trans* conformations. In parenthesis the relative zero-point energies (kcal mol^{-1}).

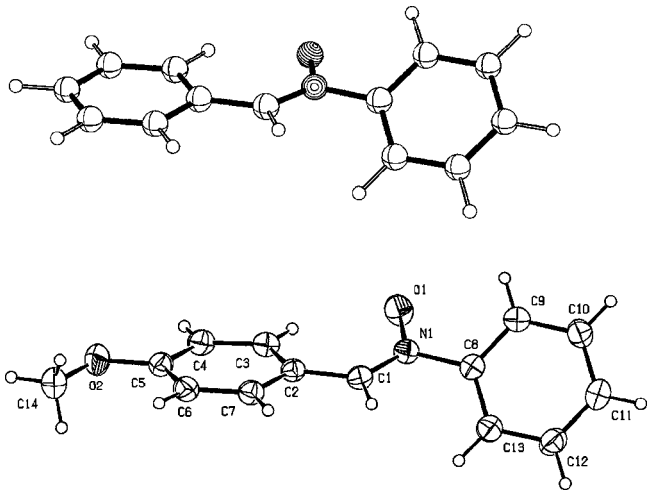


Figure 6. Optimized geometry [B3LYP/6-31G(d)] of nitrone **7a** (left) and X-ray structure (right) of **7b** (ellipsoids with 30% probability).

The calculated structure of nitrone **7a** shows a nonplanar conformation of the phenyl rings with respect to the plane of the dipole, with the N-phenyl ring having a larger twist out of the plane (Figure 6). This structure is in agreement with the X-ray structure of *N*-phenyl-*C*-(4-anisyl)nitrone (**7b**) (Figure 6), whose synthesis was previously reported.[3b] These and other nitrones prepared in precedent studies show,[3b] either in the solid phase or in solution, the (*Z*) configuration. There is evidence that this configuration does not isomerize within the course of the reaction;[22] hence, we assumed that it is maintained at the transition state.

In terms of the possible modes of approach between the reactants (**7a** + **12a**) leading to the transition states, we assumed that, in terms of the preferred conformation of the captodative olefin (Figure 5), the most favorable approach of the 1,3-dipole would take place onto the face of the double bond *anti* to the carbonyl oxygen of the PNB group. Thus, we took into account only three variables: (1) The C-4/C-5 regioisomerism, (2) the *endo*/*exo* approaches, and (3) the *s-cis*/*s-trans* conformation of the enone fragment in the captodative olefin. In all, eight transition states were located (Figures 7 and 8). The electronic energies (E_e), the electronic energies corrected by the inclusion of zero-point energies (E_0), and the corresponding relative energies (ΔE_e, ΔE_0) for all the calculated TSs are summarized in Table 2. Calculations were carried out in the gas phase; solvent effects were not included[10] because the experimental cycloadditions took place in a nonpolar solvent (benzene). Usually, a reliable account of regioselectivity can be obtained by means of theoretical calculations carried out in the gas phase or including solvent effects.[5f] It is noteworthy that both C4-*endo*-*s*-*cis* and C4-*endo*-*s*-*trans* TSs were the most stable, and that they were also those which lead to experimentally observed adduct **17a**. Then again, the C4-*exo* TSs were >3.4 kcal mol^{-1} more energetic than the C4-*endo* TSs. This energy difference would be enough to provide the C4-*endo* adduct **17a**, exclusively. However, adduct **18a**, which comes from the C4-*exo* TSs, was also observed in the product mixture. In contrast, the C5-*endo*-*s*-*cis* TS was found to be more stable than the C4-*exo* TSs but the corresponding adduct was not detected in the reaction mixture.

For the 1,3-dipolar cycloaddition of nitrones, it is likely that the reaction takes place through a concerted asynchronous transition state.[26,29,30] Indeed, for the C4 TSs, one can observe a highly asynchronous formation of the C–C and C–O bonds. The difference in distance between these bonds is smaller in the C5 TSs (Figure 8). Interestingly, the shortest distance at the C4 TS corresponded to the forming C–O bond,[31] which is perhaps a result of the interaction between the most polarized interacting sites: the oxygen of the nitrone as the electron-rich center and the β-carbon atom of the dipolarophile as the electron-deficient center.[32] This strong dipolar (electrostatic) interaction could be also one of the main factors controlling the regioselectivity of the process.[10] Although the β-carbon atom of the olefin is expected to be less electrophilic because of the electron-donating effect (+*R*) of the lone pairs of electrons on the oxygen atom of the aroyloxy group, it was demonstrated that, because of the conformational preference, this effect is not significant in comparison with the electron-withdrawing effect (–*R*) of the acetyl group[28] and the (–*I*) inductive effect of the aroyloxy group.[33] Another contribution to the C-4 regioselectivity might be ascribed to CH···π stabilizing interactions. Visual inspection of the TSs (Figures 7 and 8) shows a particularly close contact between the *ortho* protons of the aroyloxy group and the C-phenyl ring of the nitrone in both C4-*endo* geometries. The distance between the corresponding *ortho* proton of the aroyloxy group and

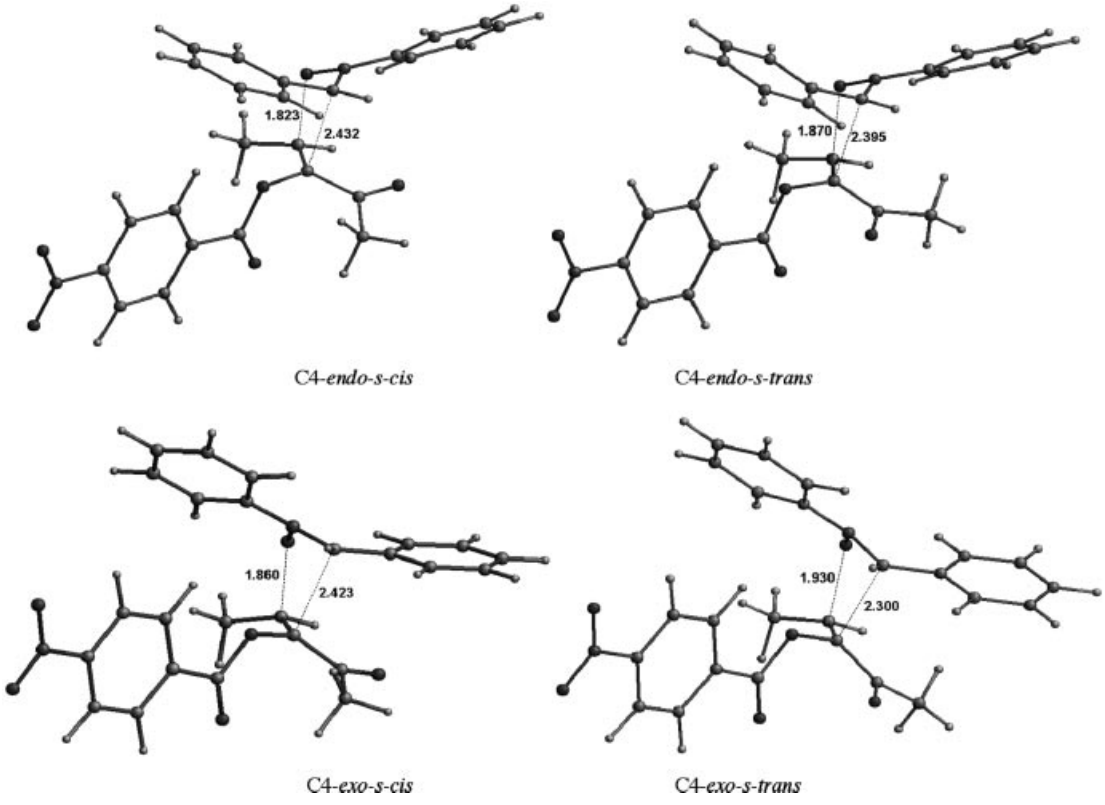


Figure 7. Calculated [B3LYP/6-31G(d)] geometries of the *endo* and *exo* C4 TSs for the cycloaddition of the *s-cis* and *s-trans* conformations of captodative olefin **12a** and nitrone **7a**.

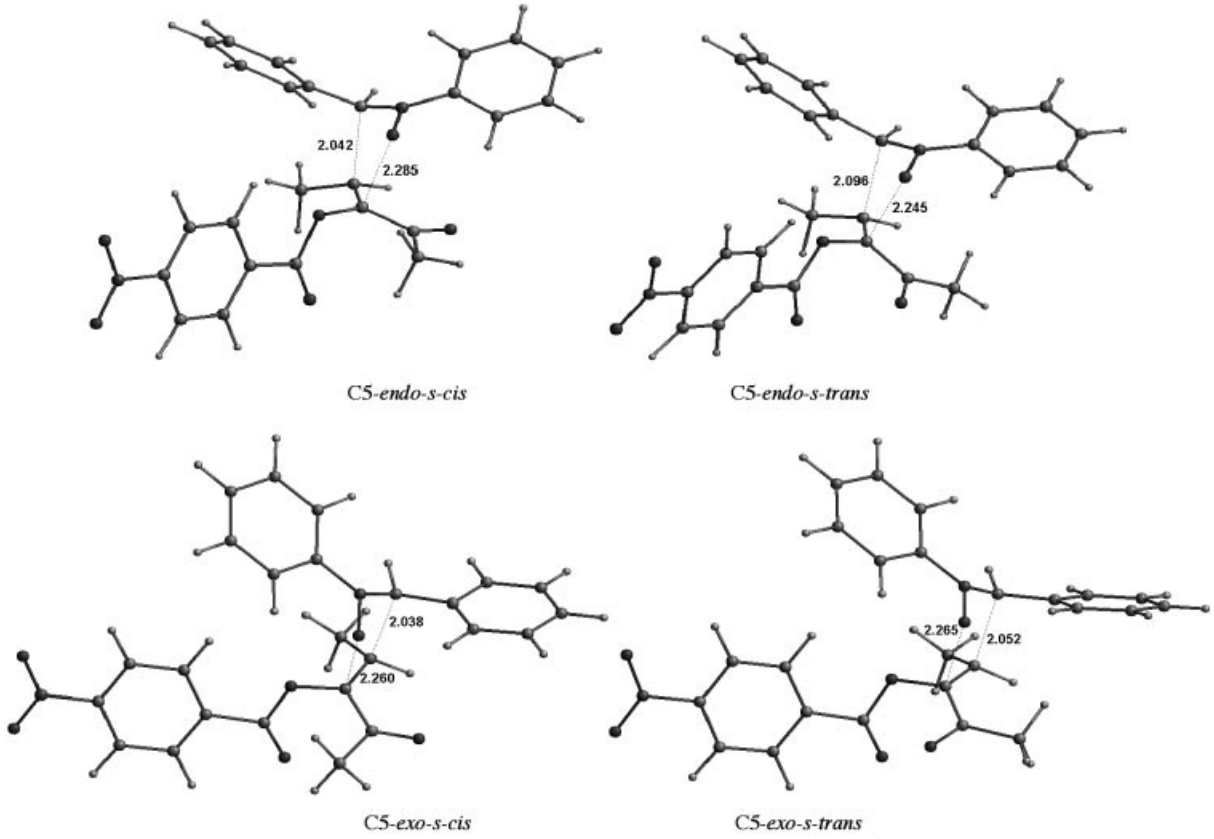


Figure 8. Calculated [B3LYP/6-31G(d)] geometries of the *endo* and *exo* C5 TSs for the cycloaddition of the *s-cis* and *s-trans* conformations of captodative olefin **12a** and nitrone **7a**.

Table 2. B3LYP/6-31G(d) electronic energies (E_e, HA), electronic energies including zero-point energy corrections (E_0, HA), and the corresponding relative energies (ΔE_e and ΔE_0 kcal mol^{-1}) for the C4 and C5 TSs of the cycloaddition between **7a** and **12a**.[a]

Energy	C4-*endo-s-cis*	C4-*endo-s-trans*	C4-*exo-s-cis*	C4-*exo-s-trans*
E_e	–1526.563685	–1526.560558	–1526.558143	–1526.557640
E_0	–1526.137190	–1526.134018	–1526.131697	–1526.130943
ΔE_e	0.00	1.96	3.48	3.79
ΔE_0	0.00	1.99	3.45	3.92
Energy	C5-*endo-s-cis*	C5-*endo-s-trans*	C5-*exo-s-cis*	C5-*exo-s-trans*
E_e	–1526.559104	–1526.554465	–1526.556804	–1526.553748
E_0	–1526.132638	–1526.127881	–1526.130482	–1526.127319
ΔE_e	2.87	5.79	4.32	6.24
ΔE_0	2.86	5.84	4.21	6.19

[a] The relative energies (ΔE_e and ΔE_0) are given with respect to the most stable transition state.

the centroid of the phenyl ring is 2.747 Å for the C4-*endo-s-cis* TS, and 2.704 Å for the C4-*endo-s-trans* TS. This interaction may also be associated with the *endo* stereoselectivity of the cycloaddition (Table 1).

All the *s-trans* TSs are more energetic than the corresponding *s-cis* (Table 2). This can be attributed to a stronger steric repulsion between the acyl Me group of the captodative olefin and either the C-phenyl or the N-phenyl ring of the nitrone in the *s-trans* TSs.

In both C5-*endo* TSs, steric hindrance between the β-methyl group of the dipolarophile and the C-phenyl group of the nitrone is progressively developed along the *endo* approach (Figure 8). In contrast, the less hindered TSs seem to be the C5-*exo* among all the series, although they are also among the most energetic. This supports the idea that the stability of the regioisomeric TSs is mostly affected by electronic and electrostatic effects.[34] However, steric hindrance might also contribute to the stereochemical outcome of the cycloadditions.[19d,19i]

Notably, the forming C–O bond at the C5 TSs is much longer than that of the C4 TSs. This is probably due to the fact that, in the former, the captodative center is not as electrophilic as the β-carbon center of the double bond; hence, the interaction would be less significant. Moreover, the methyl group at the β-carbon center will increase the π electron density of the captodative center by a hyperconjugative effect, which in consequence reduces its electrophilic character.[32]

Unlike the stability of the TSs, where the C4-*endo* geometries are the most stable, the stability of the adducts is reversed given that the C5-*exo-s-cis* adduct is the most stable product (Table 3), which is in disagreement with the experimentally obtained C4 adducts. Also in contrast with the TSs, the rest of the adducts are highly destabilized relative to the most stable C5-*exo-s-cis* adduct. These results supports the well-known hypothesis that the regio- and stereoselectivity of the 1,3-dipolar cycloadditions are kinetically and not thermodynamically controlled.[4]

It can be argued that the captodative substitution of our alkenes would favor the formation of free radicals and thus lead to a stepwise cycloaddition. However, the stereoselectivity observed in these reactions strongly supports the idea of concerted processes. Alternatively, a more subtle issue would be whether the transition states for these concerted processes have diradical character. One would expect that the highly polar nature of the 1,3-dipoles would lead to transition states with more polar than diradical character, a fact that is supported by our current transition state calculations; however, a transition state with diradical character cannot be ruled out on the basis of these results. One way to rule out or confirm the diradical character of the transition state would by means of TS calculations involving configuration interaction (CI) methods; nevertheless, the size of our system is very large for a study of this kind, at least with the computational resources we have at hand.

Table 3. B3LYP/6-31G(d) electronic energies (E_e, HA), electronic energies including zero-point energy corrections (E_0, HA), and the corresponding relative energies (ΔE_e and ΔE_0, kcal mol^{-1}) for the C4 and C5 adducts of the cycloaddition between **7a** and **12a**.[a]

Energy	C4-*endo-s-cis*	C4-*endo-s-trans*	C4-*exo-s-cis*	C4-*exo-s-trans*
E_e	–1526.607394	–1526.607921	–1526.605490	–1526.606231
E_0	–1526.177516	–1526.177973	–1526.175764	–1526.176497
ΔE_e	6.21	5.88	7.41	6.94
ΔE_0	6.61	6.32	7.71	7.25
Energy	C5-*endo-s-cis*	C5-*endo-s-trans*	C5-*exo-s-cis*	C5-*exo-s-trans*
E_e	–1526.612039	–1526.606679	–1526.617296	–1526.607955
E_0	–1526.182588	–1526.177031	–1526.188049	–1526.178146
ΔE_e	3.30	6.66	0.00	5.86
ΔE_0	3.43	6.91	0.00	6.21

[a] The relative energies (ΔE_e and ΔE_0) are given with respect to the most stable adduct.

An additional comment should be made on the adducts. Once these are formed, it does not really matter whether they arose from the *s-cis* or *s-trans* transition states, so that they can be described in terms of conformers of the C4/C5 or *endo*/*exo* adducts. Owing to the very high conformational flexibility of saturated five-membered rings, and to all the rotamers that can be generated on these adducts, no conformational analysis was carried out on any of them. The geometries whose energies are described in Table 3 correspond to those coming from full optimization of geometries that mostly resembled the corresponding TSs, and they might not correspond to the most stable conformers of the adducts. In particular, the conformer of **17a** observed in the solid state (a C4-*endo* adduct) was not obtained through this methodology. An additional optimization at the B3LYP/6-31G(d) level was carried out on the X-ray structure, which led to a geometry not very different from the experimental. Figure 9 shows a superposition of the experimental and theoretical geometries, which shows that most of the differences originate in a small change in the conformation of the five-membered heterocyclic ring, as well as in small rotations the bonds between the substituents and the heterocycle. The good agreement between the structures shown in Figure 9, despite the fact that one was obtained in the solid state and the other obtained through theoretical calculations in the gas phase, gives us confidence in the theoretical method employed.

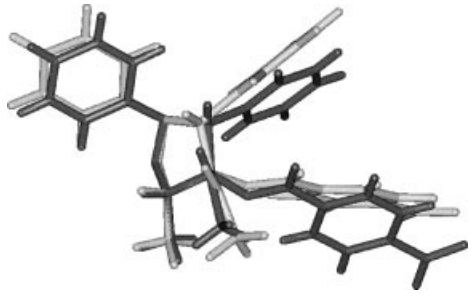


Figure 9. Superposition of the X-ray (dark) and calculated [B3LYP/6-31G(d)] (light) structures of **17a**, obtained by superimposing the N-2, C-4, and C-5 atoms of the heterocycle.

Conclusions

The presence of a β alkyl substituent in captodative olefins **12** modified their behavior substantially in 1,3-dipolar cycloadditions with nitrone **7a**, relative to unsubstituted dipolarophiles **1**, and provided the products corresponding to C-4 regioselectivity. The formation of the opposite regioisomer, the C-5 substituted aromatic heterocycle, with benzonitrile oxide (**2a**) also suggested a significant perturbation of the double bond by the third substituent.

The DFT calculations of TS energies and geometries for the most stable approaches in both C-4 and C-5 regioisomers, for the addition of nitrone **7a** to olefin **12a**, are in agreement with the C-4 regioselectivity experimentally observed. This preference might be associated with a stronger dipolar interaction between the oxygen atom of the nitrone and the β carbon atom of the captodative olefin, as well as to a steric interaction between the CH_3 group of the captodative olefin and the C-Ph group of the dipole at the C5-*endo* TSs. Moreover, these calculations also accounted for the *endo* stereoselectivity shown in these cycloadditions, as a consequence of supplementary stabilizing CH···π interactions at the C4-*endo* TSs that take place between the cycloaddends. Therefore, these calculations rationalize the apparently subtle electronic effect of the β alkyl group in the dipolarophiles, which reverses the regiochemical orientation with respect to their unsubstituted analogs, when they are adding to nitrones.

Experimental Section

General: Melting points are uncorrected. NMR spectra were recorded with Varian Mercury (300 MHz) and Bruker DMX-500 (500 MHz) spectrometers by using TMS as an internal standard. Mass spectra and high-resolution mass spectra (HRMS) were obtained in the electron impact (EI) mode at 70 eV and the fast-atom bombardment (FAB) mode, respectively. Microanalyses were performed by M-H-W Laboratories (Phoenix, AZ) and Centro de Investigaciones Químicas, Universidad Autónoma del Estado de Hidalgo. Analytical thin-layer chromatography was carried out with E. Merck silica gel 60 F_{254} coated 0.25 plates, visualized by long- and short-wavelength UV light. All air–moisture sensitive reactions were carried out under a nitrogen atmosphere by using oven-dried glassware. THF and benzene were freshly distilled from sodium, and dichloromethane from calcium hydride, prior to use. Triethylamine was freshly distilled from NaOH. All other reagents were used without further purification.

General Method for the Preparation of Captodative Olefins 12a–12d: To a solution of triethylamine in dry THF (19.0 mL) and HMPA (1.0 mL), at –20 or –10 °C and under an N_2 atmosphere, acid chloride **14** diluted in dry THF was slowly added. Then, a solution of α-diketone **13** in dry THF was added dropwise. After being stirred at room temperature for 24 to 36 h, the solvent was removed under vacuum, and the residue was dissolved in CH_2Cl_2 (70 mL) and washed successively with a cold 5% aqueous solution of HCl (2 × 30 mL), a cold aqueous saturated solution of NH_4Cl (3 × 30 mL), a cold 10% aqueous solution of $NaHCO_3$ (2 × 30 mL), and a cold saturated solution of NaCl (2 × 30 mL). The organic layer was dried ($MgSO_4$), and the solvent was evaporated under vacuum. The residue was successively purified by flash column chromatography on silica gel treated with 10% triethylamine (30 g/1.0 g of crude; hexane/EtOAc, 95:5), and by radial chromatography (hexane/EtOAc, 90:10), to give corresponding olefins **12a**–**12f**.

(*Z*)-3-(*p*-Nitrobenzoyloxy)-3-penten-2-one (12a): Following the general procedure, Et_3N (0.83 g, 8.26 mmol), **14a** (1.0 g, 5.4 mmol) in THF (25 mL), and **13a** (0.413 g, 4.13 mmol) in THF (10 mL) were mixed at –20 °C and stirred for 36 h to afford **12a** (0.97 g, 94%) as pale yellow crystals. R_f = 0.18 (hexane/EtOAc, 8:2). M.p. 104–106 °C (ethyl ether/hexane, 8:2) [ref.[14] 104–106 °C]. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.88 (d, J = 7.1 Hz, 3 H, CH_3C=), 2.39 (s, 3 H, CH_3CO), 6.74 (q, J = 7.1 Hz, 1 H, HC=), 8.28–8.34 (m, 4 H, H-Ar) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 12.0 (CH_3C=), 25.1 (CH_3CO), 123.7, 129.0, 131.3, 134.2, 147.2, 150.9, 162.4, 190.3 (CH_3CO) ppm. IR (CH_2Cl_2): $\tilde{\nu}$ = 1742, 1687, 1529, 1420, 1349, 1256, 1245, 1096, 1012 cm^{-1}. MS (70 eV): *m*/*z* (%) = 249 (0.6) [M]$^+$, 150 (100), 134 (2), 120 (6), 104 (20), 92 (10), 76 (14).

$C_{12}H_{11}NO_5$ (249.13): calcd. C 57.83, H 4.45, N 5.62; found C 57.81, H 4.60, N 5.56.

(*Z*)-3-(*p*-Bromobenzoyloxy)-3-hexen-2-one (12b): Following the general procedure, Et_3N (0.69 g, 6.84 mmol), **14b** (0.977 g, 4.45 mmol) in THF (20 mL), and **13b** (0.39 g, 3.42 mmol) in THF (10 mL) were mixed at –10 °C and stirred for 24 h to afford **12b** (0.64 g, 63%) as white crystals. R_f = 0.38 (hexane/EtOAc, 8:2). M.p. 55–56 °C (CH_2Cl_2/hexane, 7:3). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.10 (t, J = 7.6 Hz, 3 H, CH_3CH$_2$C=), 2.28 (q, J = 7.6 Hz, 2 H, CH$_3$CH_3C=), 2.36 (s, 3 H, CH$_3$CO), 6.58 (t, J = 7.6 Hz, 1 H, HC=), 7.61–7.64 (m, 2 H, H-Ar), 7.98–8.01 (m, 2 H, H-Ar) ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 12.6 (*C*H$_3$CH$_2$C=), 19.7 (CH$_3$*C*H$_2$C=), 25.1 (*C*H$_3$CO), 127.6, 128.8, 131.60, 131.65, 134.6, 145.7, 163.5, 191.0 (CH$_3$*C*O) ppm. IR (CH_2Cl_2): $\tilde{\nu}$ = 1738, 1687, 1589, 1484, 1399, 1366, 1300, 1282, 1241, 1141, 1109, 1093, 1067, 1013 cm^{-1}. MS (70 eV): *m*/*z* (%) = 298 (1) [M + 2]$^+$, 296 (1) [M]$^+$, 185 (100), 183 (99), 157 (13), 155 (14), 131 (1), 129 (1), 104 (2), 77 (1). $C_{13}H_{13}BrO_3$ (297.04): calcd. C 52.55, H 4.41; found C 52.67, H 4.53.

(*Z*)-4-(3,5-Dinitrobenzoyloxy)-4-hexen-3-one (12c): Following the general procedure, Et_3N (0.69 g, 6.84 mmol), **14c** (1.02 g, 4.45 mmol) in THF (20 mL), and **13c** (0.39 g. 3.42 mmol) in THF (10 mL) were mixed at –10 °C and stirred for 24 h to afford **12c** (0.88 g, 83%) as brown crystals. R_f = 0.48 (hexane/EtOAc, 8:2). M.p. 73–75 °C (CH_2Cl_2/hexane, 7:3). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.15 (t, J = 7.3 Hz, 3 H, CH_3CH$_2$CO), 1.94 (d, J = 7.1 Hz, 3 H, CH$_3$C=), 2.77 (q, J = 7.3 Hz, 2 H, CH$_3$CH_2CO), 6.81 (q, J = 7.1 Hz, 1 H, HC=), 9.23–9.25 (m, 2 H, H-Ar), 9.26–9.28 (m, 1 H, H-Ar) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 7.8 (*C*H$_3$CH$_2$CO), 11.9 (*C*H$_3$C=), 30.1 (CH$_3$*C*H$_2$C=), 122.8, 128.5, 129.8, 132.5, 146.6, 148.6, 160.3, 192.7 (CH$_3$CH$_2$*C*O) ppm. IR (CH_2Cl_2): $\tilde{\nu}$ = 1751, 1688, 1627, 1547, 1345, 1282, 1225, 1152 cm^{-1}. MS (70 eV): *m*/*z* (%) = 308 (4) [M]$^+$, 279 (4), 195 (100), 179 (3), 149 (24), 103 (5), 75 (19). $C_{13}H_{12}N_2O_7$ (308.14): calcd. C 50.66, H 3.92, N 9.09; found C 50.88, H 4.05, N 9.09.

(*Z*)-4-(*p*-Nitrobenzoyloxy)-4-hexen-3-one (12d): Following the general procedure, Et_3N (0.69 g, 6.84 mmol), **14a** (0.82 g, 4.45 mmol) in THF (20 mL), and **13c** (0.39 g, 3.42 mmol) in THF (10 mL) were mixed at –10 °C and stirred for 24 h to afford **12d** (0.66 g, 73%) as yellow crystals. R_f = 0.38 (hexane/EtOAc, 8:2). M.p. 98–100 °C (CH_2Cl_2/hexane, 7:3). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.15 (t, J = 7.3 Hz, 3 H, CH_3CH$_2$CO), 1.88 (d, J = 7.1 Hz, 3 H, CH$_3$C=), 2.74 (q, J = 7.3 Hz, 2 H, CH$_3$CH_2CO), 6.73 (q, J = 7.1 Hz, 1 H, HC=), 8.31–8.35 (m, 4 H, H-Ar) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 7.9 (*C*H$_3$CH$_2$CO), 11.8 (*C*H$_3$C=), 30.3 (CH$_3$*C*H$_2$C=), 123.6, 127.7, 131.2, 134.2, 146.7, 150.8, 162.4, 193.4 (CH$_3$CH$_2$*C*O) ppm. IR (CH_2Cl_2): $\tilde{\nu}$ = 1741, 1728, 1530, 1348, 1282, 1099 cm^{-1}. MS (70 eV): *m*/*z* (%) = 263 (1) [M]$^+$, 234 (1), 150 (100), 120 (22), 104 (21), 76 (19). $C_{13}H_{13}NO_5$ (263.14): calcd. C 59.31, H 4.98, N 5.32; found C 59.29, H 5.07, N 5.32.

2-(*p*-Nitrobenzoyloxy)-2-cyclohexen-1-one (12e): Following the general procedure, Et_3N (0.76 g, 7.5 mmol), **14a** (0.87 g, 4.71 mmol) in (15 mL) THF, and **13d** (0.41 g, 3.62 mmol) in THF (10 mL) were mixed at –10 °C and stirred for 24 h to afford **12e** (0.85 g, 90%) as pale brown needles. R_f = 0.32 (hexane/EtOAc, 8:2). M.p. 130–131 °C (EtOAc/hexane, 8:2). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.12–2.17 (m, 2 H, 5-H), 2.58–2.64 (m, 4 H, 4-H, 6-H), 6.78 (t, J = 4.3 Hz, 1 H, 3-H), 8.26–8.29 (m, 4 H, H-Ar) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 22.5 (C-5), 24.9 (C-4), 38.0 (C-6), 123.6, 131.3, 134.3, 136.7, 145.2, 150.8, 162.6, 191.2 (C-1) ppm. IR (CH_2Cl_2): $\tilde{\nu}$ = 1743, 1690, 1530, 1350, 1239, 1110 cm^{-1}. MS (70 eV): *m*/*z* (%) = 261 (2) [M]$^+$, 150 (100), 120 (8), 104 (24), 92 (12), 76 (14). $C_{13}H_{11}NO_5$ (261.14): calcd. C 59.77, H 4.24, N 5.36; found C 59.62, H 4.25, N 5.30.

2-(3,5-Dinitrobenzoyloxy)-2-cyclohexen-1-one (12f): Following the general procedure, Et_3N (0.76 g, 7.5 mmol), **14a** (1.09 g, 4.71 mmol) in THF (15 mL), and **13d** (0.41 g, 3.62 mmol) in THF (10 mL) were mixed at –10 °C and stirred for 24 h to afford **12f** (0.89 g, 82%) as pale brown needles. R_f = 0.26 (hexane/EtOAc, 8:2). M.p. 153–154 °C (EtOAc/hexane, 8:2). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.16–2.22 (m, 2 H, 5-H), 2.61–2.68 (m, 4 H, 4-H, 6-H), 6.90 (t, J = 4.2 Hz, 1 H, 3-H), 9.16–9.26 (m, 3 H, H-Ar) ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 22.3 (C-5), 24.7 (C-4), 37.7 (C-6), 122.7, 129.7, 132.5, 137.0, 144.9, 148.6, 160.4, 190.6 (C-1) ppm. IR (CH_2Cl_2): $\tilde{\nu}$ = 1748, 1696, 1630, 1541, 1349, 1142, 751 cm^{-1}. MS (70 eV): *m*/*z* (%) = 306 (9) [M]$^+$, 278 (2), 195 (100), 149 (18), 103 (7), 75 (24). $C_{13}H_{10}N_2O_7$ (306.14): calcd. C 50.99, H 3.29, N 9.15; found C 50.87, H 3.41, N 9.21.

General Procedure for the 1,3-Dipolar Addition of 12a–12d with Nitrone 7a. (3*R,4*S**,5*S**)-4-Acetyl-5-methyl-4-(*p*-nitrobenzoyloxy)-2,3-diphenylisoxazolidine (17a) and (3*R**,4*R**,5*R**)-4-Acetyl-5-methyl-4-(*p*-nitrobenzoyloxy)-2,3-diphenylisoxazolidine (18a):** A mixture of **7a** (0.30 g, 1.52 mmol) and **12a** (0.2 g, 0.8 mmol) in dry benzene (10 mL), in a threaded ACE glass pressure tube with a Teflon screw cap, was heated to 110 °C and stirred for 12 h under an N_2 atmosphere. The solvent was removed under vacuum to yield a mixture of **17a/18a** (70:30) as an oily residue. The mixture was purified by flash column chromatography on silica gel (30 g, hexane/EtOAc, 95:5) to give **17a** and **18a** (0.179 g, 50%) and recovered **12a** (0.054 g, 27%). Additional purification by flash column chromatography on silica gel (20 g, hexane/EtOAc, 10:2) allowed the isolation of **17a** (0.079 g, 22%) as pale green crystals, which were recrystallized from hexane/EtOAc (10:2), and **18a** (0.05 g, 14%) as a pale green oil. Data for **17a**: R_f = 0.64 (hexane/EtOAc, 7:3). M.p. 146–147 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.63 (d, J = 6.3 Hz, 3 H, CH$_3$), 2.24 (s, 3 H, COMe), 4.70 (q, J = 6.3 Hz, 1 H, 5-H), 5.39 (s, 1 H, 3-H), 6.97–7.03 (m, 3 H, H-Ph), 7.19–7.29 (m, 5 H, H-Ph), 7.46–7.54 (m, 2 H, H-Ph), 7.70–7.76 (m, 2 H, H-Ar), 8.13–8.20 (m, 2 H, H-Ar) ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 14.4 (CH$_3$), 25.3 (CO*C*H$_3$), 74.5 (C-3), 78.2 (C-5), 96.4 (C-4), 115.1, 122.5, 123.4, 128.2, 128.3, 128.9, 129.3, 130.7, 133.7, 136.1, 149.3, 150.7, 163.8 (CO$_2$Ar), 199.4 (COMe) ppm. IR (KBr): $\tilde{\nu}$ = 1730, 1598, 1489, 1349, 1279, 1099 cm^{-1}. HRMS (FAB): calcd. for $C_{25}H_{22}N_2O_6$ [M]$^+$ 446.1478; found 446.1495. Data for **18a**: R_f = 0.72 (hexane/EtOAc, 7:3). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.34 (d, J = 6.4 Hz, 3 H, CH$_3$), 1.82 (s, 3 H, COMe), 5.14 (s, 1 H, 3-H), 5.30 (q, J = 6.4 Hz, 1 H, 5-H), 6.93–7.03 (m, 3 H, H-Ph), 7.21–7.30 (m, 2 H, H-Ph), 7.34–7.45 (m, 3 H, H-Ph), 7.55–7.62 (m, 2 H, H-Ph), 8.04–8.12 (m, 2 H, H-Ar), 8.26–8.33 (m, 2 H, H-Ar) ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 14.9 (CH$_3$), 26.9 (CO*C*H$_3$), 76.7 (C-3), 77.6 (C-5), 98.1 (C-4), 115.3, 122.4, 123.7, 127.9, 128.8, 129.1 (2 C), 131.1, 133.9, 134.8, 150.8, 150.9, 163.7 (CO$_2$Ar), 199.2 (COMe) ppm. IR (film): $\tilde{\nu}$ = 1730, 1599, 1528, 1490, 1349, 1279, 1101 cm^{-1}. HRMS (FAB): calcd. for $C_{25}H_{22}N_2O_6$ [M]$^+$ 446.1478; found 446.1475.

(3*R,4*S**,5*S**)-4-Acetyl-4-(*p*-bromobenzoyloxy)-5-methyl-2,3-diphenylisoxazolidine (17b) and (3*R**,4*R**,5*R**)-4-Acetyl-4-(*p*-bromobenzoyloxy)-5-methyl-2,3-diphenylisoxazolidine (18b):** A mixture of **7a** (0.5 g, 2.5 mmol) and **12b** (0.2 g, 0.7 mmol) in dry benzene (15 mL), in a threaded ACE glass pressure tube with a Teflon screw cap, was stirred and heated to 110 °C for 12 h under an N_2 atmosphere. The solvent was removed under vacuum to yield an oily residue of a mixture of **17b/18b** (55:45). The mixture was purified by flash column chromatography on silica gel (30 g, hexane/EtOAc,

9:1) to give a mixture of **17b** and **18b** (0.11 g, 30%) as a green oil, and recovered **12b** (0.072 g, 36%). The mixture was separated by radial chromatography (hexane/EtOAc, 95:5) to isolate **17b** (0.07 g, 21%) as a colorless oil and **18b** (0.02 g, 6%) as a colorless oil. Data for **17b**: R_f = 0.7 (hexane/EtOAc, 7:3). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.23 (t, J = 7.4 Hz, 3 H, CH_3CH$_2$), 1.64–1.80 (m, 1 H, CH$_3$CH_2), 2.08–2.22 (m, 1 H, CH$_3$CH_2), 2.21 (s, 3 H, COMe), 4.44 (dd, J = 10.5, 2.8 Hz, 1 H, 5-H), 5.27 (s, 1 H, 3-H), 6.93–7.04 (m, 3 H, H-Ph), 7.17–7.30 (m, 5 H, H-Ph), 7.38–7.54 (m, 6 H, H-Ph, H-Ar) ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 10.9 (*C*H$_3$CH$_2$), 22.0 (CH$_3$*C*H$_2$), 25.3 (CO*C*H$_3$), 74.3 (C-3), 83.2 (C-5), 95.6 (C-4), 115.2, 122.3, 127.3 (2 C), 128.1, 128.2, 128.8, 129.3, 131.1, 131.6, 136.2, 144.0, 162.8 (CO_2Ar), 200.7 (COMe) ppm. IR (film): $\tilde{\nu}$ = 1720, 1591, 1486, 1285, 1087, 1011, 750 cm^{-1}. $C_{26}H_{24}BrNO_4$ (494.19): calcd. C 63.17, H 4.89, N 2.83; found C 63.23, H 5.03, N 2.86. Data for **18b**: R_f = 0.6 (hexane/EtOAc, 7:3). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.12 (t, J = 7.3 Hz, 3 H, CH_3CH$_2$), 1.48–1.68 (m, 2 H, CH$_3$CH_2), 1.79 (s, 3 H, COMe), 5.10 (dd, J = 10.0, 3.1 Hz, 1 H, 5-H), 5.10 (s, 1 H, 3-H), 6.94–7.06 (m, 3 H, H-Ph), 7.20–7.32 (m, 3 H, H-Ph), 7.34–7.64 (m, 6 H, H-Ph, H-Ar), 7.77–7.83 (m, 2 H, H-Ar) ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 10.9 (*C*H$_3$CH$_2$), 22.2 (CH$_3$*C*H$_2$), 26.8 (CO*C*H$_3$), 76.5 (C-3), 83.0 (C-5), 97.5 (C-4), 114.6, 122.0, 127.9, 128.7, 128.8, 128.9, 129.0, 129.2, 131.4, 132.0, 135.0, 150.8, 162.5 (CO_2Ar), 199.9 (COMe) ppm. IR (film): $\tilde{\nu}$ = 1686, 1497, 1421, 1360, 1277, 1218, 955, 769, 693 cm^{-1}. HRMS (FAB): calcd. for $C_{26}H_{24}BrNO_4$ [M]$^+$ 493.0889; found 493.0889.

(3*R,4*S**,5*S**)-5-Methyl-4-(3,5-dinitrobenzoyloxy)-2,3-diphenyl-4-propanoylisoxazolidine (17c) and (3*R**,4*R**,5*R**)-5-Methyl-4-(3,5-dinitrobenzoyloxy)-2,3-diphenyl-4-propanoylisoxazolidine (18c):** A mixture of **7a** (0.48 g, 2.43 mmol) and **12c** (0.20 g, 0.65 mmol) in dry benzene (15 mL), in a threaded ACE glass pressure tube with a Teflon screw cap, was stirred and heated to 80 °C for 12 h under an N_2 atmosphere. The solvent was removed under vacuum to yield a green oily residue of a mixture of **17c/18c** (66:44). The mixture was purified by flash column chromatography on silica gel (30 g, hexane/EtOAc, 9:1) to give a mixture of **17c** and **18c** (0.2 g, 40%) and recovered **12c** (0.06 g, 30%). By crystallization (hexane/CH_2Cl_2, 8:2) of the mixture, **17c** (0.128 g, 25%) was isolated as pale brown needles and **18c** (0.041, 8%) as a pale brown oil. Data for **17c**: R_f = 0.5 (hexane/EtOAc, 7:3). M.p. 152–153 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.14 (t, J = 7.1 Hz, 3 H, CH_3CH$_2$CO), 1.61 (d, J = 6.3 Hz, 3 H, CH$_3$), 2.59–2.63 (m, 2 H, CH$_3$CH_2CO), 4.82 (q, J = 6.3 Hz, 1 H, 5-H), 5.14 (s, 1 H, 3-H), 6.98–7.01 (m, 2 H, H-Ph), 7.21–7.50 (m, 8 H, H-Ph), 8.60 (br. s, 2 H, H-Ar), 9.14 (br. s, 1 H, H-Ar) ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 7.9 (*C*H$_3$CH$_2$CO), 14.9 (CH$_3$), 30.7 (CH$_3$*C*H$_2$CO), 74.6 (C-3), 77.9 (C-5), 99.4 (C-4), 115.6, 122.7, 122.8, 128.6, 128.8, 128.9, 129.0, 129.2, 132.9, 134.9, 148.8, 150.8, 161.5 (CO_2Ar), 201.3 (COEt) ppm. IR (KBr): $\tilde{\nu}$ = 1736, 1597, 1546, 1489, 1455, 1344, 1282, 1161, 1077 cm^{-1}. MS (70 eV): *m*/*z* (%) = 505 (79) [M]$^+$, 448 (1), 461 (4), 294 (10), 278 (20), 238 (10), 196 (48), 195 (77), 180 (50), 149 (28), 105 (25), 91 (100), 77 (37). HRMS (FAB): calcd. for $C_{26}H_{23}N_3O_8$ [M]$^+$ 505.1485; found 505.1486. Data for **18c**: R_f = 0.6 (hexane/EtOAc, 7:3). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.70 (t, J = 7.1 Hz, 3 H, CH_3CH$_2$CO), 1.39 (d, J = 6.5 Hz, 3 H, CH$_3$), 2.31 (q, J = 7.1 Hz, 2 H, CH$_3$CH_2CO), 5.25 (s, 1 H, 3-H), 5.28 (q, J = 6.5 Hz, 1 H, 5-H), 6.94–7.30 (m, 3 H, H-Ph), 7.21–7.29 (m, 2 H, H-Ph), 7.34–7.47 (m, 3 H, H-Ph), 7.58–7.62 (m, 2 H, H-Ph), 9.06 (d, J = 2.1 Hz, 2 H, H-Ar), 9.26 (t, J = 2.1 Hz, 1 H, H-Ar) ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 7.9 (*C*H$_3$CH$_2$CO), 14.8 (CH$_3$), 30.7 (CH$_3$*C*H$_2$CO), 74.5 (C-3), 77.9 (C-5), 99.1 (C-4), 114.8, 122.4, 122.9, 127.5, 128.9, 129.1, 129.2, 129.6, 132.7, 134.8, 148.7, 150.8, 161.7 (CO_2Ar), 201.4 (COEt) ppm. IR (film): $\tilde{\nu}$ = 1738, 1720, 1545, 1344, 1278, 1159, 1074 cm^{-1}. HRMS (FAB): calcd. for $C_{26}H_{23}N_3O_8$ [M]$^+$ 505.1485; found 505.1493.

(3*R,4*R**,5*S**)-3a-(*p*-Nitrobenzoyloxy)-4-oxo-2,3-diphenyl-2,3,3a,4,5,6,7,7a-octahydrobenzo-4*H*-isoxazole (19):** A mixture of **7a** (0.30 g, 1.52 mmol) and **12e** (0.20 g, 0.77 mmol) in dry benzene (10 mL), in a threaded ACE glass pressure tube with a Teflon screw cap, was stirred and heated to 140 °C for 24 h under an N_2 atmosphere. The solvent was removed under vacuum to yield a green oily residue, which was purified by flash column chromatography on silica gel (20 g, hexane/EtOAc, 100:6) to give **19** (0.22 g, 63%) as yellow crystals and recovered **12e** (0.062 g, 31%). Data for **19**: R_f = 0.4 (hexane/EtOAc, 7:3). M.p. 157–158 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.18–1.37 (m, 1 H, 6-H), 1.62–2.00 (m, 3 H, 6-H, 7-H), 2.23–2.43 (m, 2 H, 5-H), 4.86 (dd, J = 6.9, 6.5 Hz, 1 H, 7a-H), 5.56 (s, 1 H, 3-H), 7.02–7.08 (m, 1 H, H-Ph), 7.10–7.18 (m, 2 H, H-Ph), 7.26–7.44 (m, 7 H, H-Ph, H-Ar), 7.54–7.60 (m, 2 H, H-Ph), 8.02–8.10 (m, 2 H, H-Ar) ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 18.1 (C-6), 28.3 (C-7), 39.8 (C-5), 77.7 (C-3), 85.1 (C-7a), 96.7 (C-3a), 114.3, 122.1, 123.3, 128.4, 128.6, 128.7, 129.2, 130.8, 134.0, 134.1, 150.6, 151.1, 162.3 (CO_2Ar), 202.5 (C-4) ppm. IR (KBr): $\tilde{\nu}$ = 1717, 1599, 1527, 1489, 1347, 1277, 1102 cm^{-1}. MS (70 eV): *m*/*z* (%) = 458 (14) [M]$^+$, 291 (35), 262 (30), 234 (10), 180 (15), 150 (100), 104 (33), 76 (20). $C_{26}H_{22}N_2O_6$ (458.29): calcd. C 68.11, H 4.84, N 6.11; found C 68.29, H 5.07, N 5.95.

5-Acetyl-4-methyl-3-phenylisoxazole (20): To a solution of **12a** (0.15 g, 0.60 mmol) in dry benzene (10 mL), benzohydroxyiminoyl chloride (2.0 g, 12.8 mmol) and Et_3N (0.36 g, 3.59 mmol) were added at room temperature. After the mixture was stirred and heated to 80 °C for 12 h, the solvent was removed under vacuum, and the residue was dissolved in CH_2Cl_2 (20 mL), washed with a 5% aqueous solution of HCl (2 × 30 mL), and water (2 × 20 mL). The organic layer was dried ($MgSO_4$), and the solvent was evaporated under vacuum to yield a brown residue, which was purified by flash column chromatography on silica gel (15 g, hexane) to give **20** (0.04 g, 33%) as a pale brown oil. R_f = 0.66 (hexane/EtOAc, 8:2). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.42 (s, 3 H, CH$_3$), 2.66 (s, 3 H, COMe), 7.47–7.55 (m, 3 H, H-Ph), 7.62–7.67 (m, 2 H, H-Ph) ppm. ^{13}C NMR (75.4 MHz, [D$_6$]acetone): δ = 8.1 (CH$_3$), 27.3 (CO*C*H$_3$), 117.9, 128.3, 128.6, 129.0, 130.0, 161.8, 163.8, 188.5 (COMe) ppm. IR (film): $\tilde{\nu}$ = 1696, 1604, 1452, 1359, 1286, 1204, 924, 772, 701 cm^{-1}. HRMS (FAB): calcd. for $C_{12}H_{12}NO_2$ [M + H]$^+$ 202.0868; found 202.0866.

7-Oxo-3-phenyl-4,5,6,7-tetrahydrobenzo-7*H*-isoxazole (22): The same procedure used for **20** was followed: **12e** (0.1 g, 0.4 mmol), benzohydroxyiminoyl chloride (0.51 g 3.3 mmol), and Et_3N (0.73 g 7.2 mmol) reacted to afford a residue that was purified by column chromatography on silica gel (20 g, hexane/EtOAc, 8:2) to give **22** (0.07 g, 86%) as colorless crystals (hexane/EtOAc, 8:2). R_f = 0.5 (hexane/EtOAc, 7:3). M.p. 114–15 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.23–2.36 (m, 2 H, 5-H), 2.69–2.74 (m, 2 H, 6-H), 2.97 (t, J = 6.0 Hz, 2 H, 4-H), 7.49–7.55 (m, 3 H, H-Ph), 7.72–7.79 (m, 2 H, H-Ph) ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 21.6 (C-5), 24.4 (C-4), 38.6 (C-6), 127.5, 127.9, 128.2, 129.1, 130.3, 160.8, 160.9, 186.3 (C-7) ppm. IR (KBr): 1690, 1600, 1521, 1444, 1327, 1302, 928, 884 cm^{-1}. MS (70 eV): *m*/*z* (%) = 213 (100) [M]$^+$, 185 (47), 184 (95), 156 (64), 129 (65), 103 (25), 77 (32). HRMS (FAB): calcd. for $C_{13}H_{11}NO_2$ [M]$^+$ 213.0790; found 213.0805.

Single-Crystal X-ray Crystallography: Enones **12d** and **12f** and isoxazolidine **17a** were obtained as pale brownish, yellow, and green crystals, respectively. These were mounted on glass fibers. Crystallographic measurements were performed with a Siemens P4 dif-

fractometer with Mo (**12d** and **12f**) and Cu (**17a**) Kα radiation (λ = 0.7107 Å and 1.54178 Å, respectively; graphite monochromator) at room temperature. Three standard reflections were monitored periodically; they showed no appreciable change during data collection. Unit cell parameters were obtained from least-squares refinement of 50 (**12d**), 39 (**12f**), and 41 (**17a**) reflections in the ranges $10.2<2\theta<24.9°$, $9.8<2\theta<25.7°$, and $21.4<2\theta<56.1°$, respectively. Intensities were corrected for Lorentz and polarization effects. No absorption corrections were applied for **12d** and **12f**, whereas for **17a** an empirical absorption correction was employed. 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 by using SHELXTL[35] on a personal computer. Data of **12d**: Formula: $C_{13}H_{13}NO_5$; molecular weight: 263.24 g mol^{-1}; cryst. syst.: monoclinic; space group: $P2_1/n$; unit cell parameters: *a*, 8.1617 (9), *b*, 14.0618 (9), *c*, 11.7048 (12) (Å); α, 90, β, 104.131 (12), γ, 90 (°); V = 1302.7(2) Å^3; temp.: 293 (2)°K; Z: 4; no. of reflections collected: 2333; no. of observed reflections: 1700; R: 0.0370; wR = 0.0949; GOF: 1.043. Data for **12f**: Formula: $C_{13}H_{10}N_2O_7$; molecular weight: 306.23 g mol^{-1}; cryst. syst.: monoclinic; space group: $P2_1/n$; unit cell parameters: *a*, 10.7549 (11), *b*, 5.4943 (4), *c*, 22.919 (4) (Å); α, 90, β, 91.214 (9), γ, 90 (°); V = 1354.0(3) Å^3; temp.: 293 (2)°K; Z: 4; no. of reflections collected: 4321; no. of observed reflections: 3036; R: 0.0543; wR = 0.1304; GOF: 1.013. Data for **17a**: Formula: $C_{25}H_{22}N_2O_6$; molecular weight: 446.45 g mol^{-1}; cryst. syst.: triclinic; space group: $P\bar{1}$; unit cell parameters: *a*, 8.0780 (5), *b*, 12.2879 (8), *c*, 12.4725 (6) (Å); α, 67.057 (5), β, 87.978 (4), γ, 78.508 (6) (°); V = 1116.02(11) Å^3; temp.: 293 (2)°K; Z: 2; no. of reflections collected: 3685; no. of observed reflections: 2926; R: 0.0881; wR = 0.2691; GOF: 1.103.

Calculation Methods: All the calculations described in this work were carried out with the Gaussian 94 program package,[27] on personal computers running under the Linux operating system. All optimizations were first carried out at the at the HF/3-21G level of theory, and the resulting geometries were employed as starting points for further optimizations at the HF/6-31G(d) and B3LYP/6-31G(d) levels. In all optimizations (minima and transition states) the OPT = TIGHT keyword was employed; in addition, all the DFT calculations were carried out with the INT(GRID = 99590) keyword, to obtain better energies and vibrational frequencies by means of a finer integration grid. The initial geometries of the reactants were derived either from previous studies or from X-ray structures. For each one of the approaches of the reactants described in the main text, geometries were generated for the corresponding products (in this case a single conformer was optimized, no attempt was made to carry out a conformational search). From these geometries, and those of the reactants, the transition states were obtained employing the QST2 (QST3 at the highest levels) option of the OPT keyword. For all stationary points, vibrational analyses were carried out at each level of ab initio theory; each point was characterized by the appropriate number of imaginary vibrational frequencies. Each transition state was further characterized by visual inspection of the normal mode corresponding to its single imaginary frequency. Relative energies were obtained by subtracting the energy of the lowest-energy structures (TSs or minima) from the energies of all the other geometries and converting these differences into kcal mol^{-1}.

Acknowledgments

We thank Fernando Labarrios for his help in spectrometric measurements. J. T. would like to acknowledge DEPI/IPN (Grants 921769, 200410, 20050151, and 20060583) and CONACYT (Grants 1570P, 32273-E, and 43508Q) for financial support. F. M. acknowledges a grant from CONACYT (400200–5-29299E). H. A. J.-V. thanks CONACYT (Grant 3251P) for financial support. R. H. is grateful to CONACYT for a graduate fellowship and to the Ludwig K. Hellweg Foundation for a partial scholarship. M. A. M. thanks CONACYT for a Ph.D. scholarship. J. T., F. D., and H. A. J.-V. are fellows of EDI/IPN and COFAA/IPN.

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Received: November 15, 2006
Published Online: March 16, 2007

