Substituent and Solvent Effects in the [2 + 2] Cycloaddition Reaction between Olefins and Isocyanates

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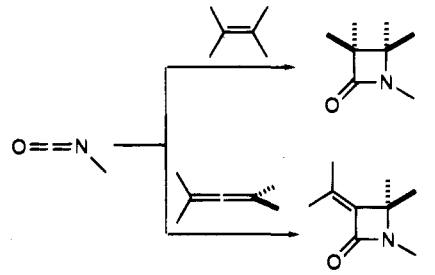
Abstract: *Ab initio* calculations provide with the models to explain the main features of the cycloaddition between olefins and isocyanates to yield 2-azetidinones (β-lactams). It is found that the reaction takes place *via* concerted transition structures involving retention of configuration in the starting olefins. These transition structures have zwitterionic character. The presence of olefins having π-donating groups and/or isocyanates with electron-withdrawing groups diminish the synchronicity as well as the activation energy of the reaction, yielding exclusively the 4-substituted regioisomers. The solvent enhances the asynchronicity of the reaction and can modify its profile from a concerted to a two-step process, thus explaining the loss of stereospecificity observed in the reaction between sulfonyl isocyanates and vinyl ethers.

Introduction

One of the most general methods to synthesize 2-azetidinone rings (β-lactams) in a convergent fashion consists in the cycloaddition reaction between alkenes and isocyanates[1] (Scheme 1). Similarly, the interaction between allenes and isocyanates provide a general access to α-alkylidene-β-lactams.[2] The practical importance of this reaction is due to its usefulness in the chemical synthesis of β-lactam antibiotics, mainly carbapenem compounds.[3] Thus, the cycloaddition between isocyanates and alkenes has been successfully applied to the synthesis of antibiotics such as PS-5,[4] PS-6,[5] thienamycin,[6] and 1β-methylcarbapenems.[7] Similarly, the reaction of isocyanates and allenes provides useful building blocks for the synthesis of carpetimycins[8] and asparenomycins.[9]

Scheme 1[a]



[a] The possible substituents at the different positions are not specified.

The main features and the scope of these cycloadditions have been reviewed.[10] From the experimental evidence available, the following observations emerge.

(i) **The Presence of Electron-Withdrawing Groups in the Isocyanates Facilitates the Reaction.** In particular, the isocyanates commonly employed in this reaction incorporate acyl and sulfonyl groups.[11] In this respect the most versatile reagent is chlorosulfonyl isocyanate (CSI).[12] Isocyanates without electron-withdrawing groups only react with electron-rich olefins, such as enamines[13] or ketene acetals.[10b]

(ii) **Olefins with Electron-Donating Substituents React Readily Yielding Markovnikov Regioisomers.** Thus, the reaction of chlorosulfonyl isocyanate with α-olefins such as allyl iodide[14] or vinyl acetate[15] yields exclusively the 4-substituted

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cycloadducts. Other substituted alkenes behave similarly.[10] When the reaction is carried out with 1,2-disubstituted olefins incorporating groups with comparable donating ability, variable mixtures of the two possible regioisomers are obtained.[16]

(iii) 1,2-Disubstituted Alkenes React with Retention of Configuration. This stereochemical outcome has been observed with dialkyl[16,17] or alkylaryl[17] olefins. Similarly, cyclic alkenes[16,18] yield the corresponding *cis* cycloadducts. Differently substituted norbornenes react *via* the *exo* face.[18a,19] However, one exception has been reported. In 1967, Effenberger and Kiefer[20a] observed that *trans*-1-butenyl ethyl ether reacts with *p*-tosyl isocyanate to yield exclusively the corresponding *trans*-4-ethoxy-3-ethylazetidin-2-one. By contrast, *cis*-1-butenyl ethyl ether forms firstly the corresponding *cis*-cycloadduct, but this compound epimerizes under the reaction conditions to form predominantly the thermodynamically more stable trans-β-lactam. (After 1440 min of reaction time, the *cis*/*trans* ratio is 27:73.) Some years later, Effenberger *et al.*[20b] reported a kinetic study on the epimerization of 4-alkoxy-1-tosylazetidin-2-ones.

(iv) Polar Solvents Accelerate the Reaction Rates.[12c] For example, it has been reported[12f] that in the [2 + 2] cycloaddition between CSI and 2-ethyl-1-hexene the rate acceleration in dichloromethane with respect to *n*-hexane is $k_2(CH_2Cl_2)/k_2(n\text{-}C_6H_{14}) = 1700$. This result suggests the participation of zwitterionic intermediates or highly polar transition states in the mechanism of the reaction.

In spite of the practical importance of the reaction and theoretical interest of thermal [2 + 2] cycloadditions,[21] this process has not been investigated using modern high-level computational tools, with the exception of a preliminary communication reported by our group.[22] Instead, qualitative concerted or stepwise models have been proposed in order to account for diverse experimental observations. The key intermediates or transition structures corresponding to these models have been collected in Figure 1. Thus, Graf[23] proposed a two-step mechanism involving the participation of zwitterionic intermediates **A**. Since then, these intermediates have been assumed to explain diverse epimerizations[20] and rearrangements observed in the reaction between electrophilic isocyanates and various conjugated olefins.[24] The total stereocontrol usually observed can be explained assuming a fast collapse between the N(1) and C(4) atoms of the zwitterionic intermediate, *via* transition states of type **B**[25] (Figure 1). On the other hand, in the course of his study on the thermolysis of several β-lactams to yield olefins and isocyanates, Paquette[26] suggested a concerted *supra-antara* transition state of type **C** (Figure 1), in line with the Woodward–Hoffmann[27] rules for [2 + 2] thermal cycloadditions. Finally, Huysgen[28] and others[17,29] have proposed concerted, although asynchronous, transition states of type **D** (Figure 1) to account for their experimental results. However, the reasons underlying these non-Woodward–Hoffmann geometries were not explained, although a possible participation of d-orbitals of sulfur atoms in sulfonyl isocyanates was suggested.[25,28]

In view of these precedents, and as part of our research program devoted to the study of [2 + 2] cycloadditions between cumulenes and double bonds,[22,30] we report here our results on the reaction between isocyanates and olefins to form 2-azetidinones. Our purpose has been to understand the origins of the regio- and stereocontrol observed in this reaction as well as to clarify whether one or several mechanisms are involved.

Computational Methods

All the results presented in this work have been obtained using *ab initio* MO theory, by means of the GAUSSIAN 92 series of programs,[31] with the standard 6-31G* and 6-31+G* basis sets.[32] Geometry optimizations have been carried out at the HF/6-31G* level, and some representative structures have also been optimized at the MP2/6-31+G* level of theory. No symmetry constrains were imposed during the optimizations. The energies have been then recalculated at the MP2/6-31G* level,[33] keeping the core electrons frozen. In some cases, single-point energies at MP3/6-31+G* and MP4SDQ/6-31+G* levels have also been computed. HF/6-31G* zero-point vibrational energies[34] (ZPVE) have been scaled[35] by 0.89. Stationary points were characterized by frequency calculations.[36] All reactants, intermediates, and products have positive defined Hessian matrices. Transition structures (TS's) showed only one negative eigenvalue in their diagonalized force constant matrices, and their associated eigenvectors were confirmed to correspond to the motion along the reaction coordinate under consideration. Atomic charges[37] were calculated with the natural bonding analysis (NBA) method.[38]

Solvent effects have been computed using a self-consistent reaction field (SCRF) method[39] based on the procedures developed by Rinaldi,

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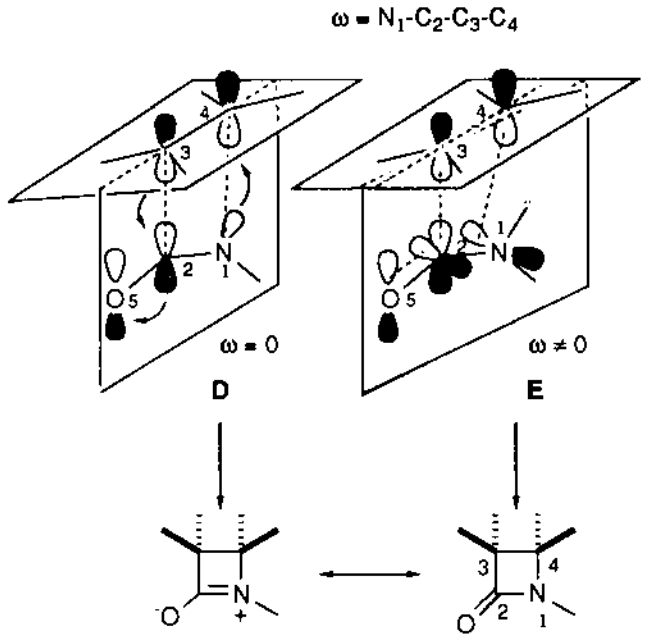
Scheme 2



Rivail *et al.*[41] The calculations have been carried out with a locally modified version of the GAUSSIAN 92 program suite, to incorporate the SCRFPAC link.[41] This program includes estimates of the cavitation and dispersion energies as well as the electrostatic free energy of solvation for an ellipsoidal cavity, defined from the geometry of the solute and a multipole expansion of the energy, computed at the center of the cavity.[19b,41] This methodology has been used successfully for the study of diverse cycloaddition reactions.[10c,42]

Results and Discussion

General Considerations. If we assume that the [2 + 2] cycloaddition between alkenes and isocyanates is a concerted reaction, then two alternative mechanisms can be envisaged. One possibility is the classical $[_\pi 2_s + _\pi 2_a]$ mechanism (Figure 1, structure **C**) or, in a more elaborated form, a $[_\pi 2_s + (_\pi 2_s + _\pi 2_s)]$ interaction mode, as it has been described for the [2 + 2] cycloaddition between alkenes and cumulenes such as allenes[43] or ketenes.[44,45] If we denote the dihedral angle between N(1), C(2), C(3), and C(4) atoms as ω, it is clear that the $[_\pi 2_s + (_\pi 2_s + _\pi 2_s)]$ geometry at the TS implies a value of ω different from zero (see structure **E** in Scheme 2). In addition, the degree of advancement of the N(1)−C(4) bond should be lower than bonding between the C(2) and C(3) atoms, because of the more favorable overlap in the latter case (Scheme 2).

An alternative mechanism consists in a push−pull interaction between the lone pair of the isocyanate, the nucleophilic π_{CC} of the alkene, and the electrophilic π_{CO}^* of the isocyanate. A similar mechanism could be also adscribed to the uncatalyzed thermolysis of β-lactones to yield alkenes and carbon dioxide.[46] As it can be appreciated looking at the structure **D** in Scheme 2, this interaction mode is favored when the dihedral angle ω is close to zero. Given that the alkene acts as a nucleophile, the N(1)−C(4) bond at the TS should be developed into a lesser extent than the C(2)−C(3) bond. Therefore, the main geometric difference between both mechanisms should be the value of ω.

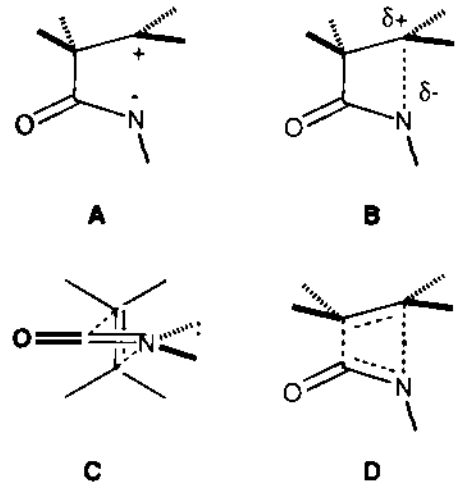


Figure 1. Transition structures and intermediates previously proposed in the cycloaddition reaction between alkenes and isocyanates. The possible substituents at the different positions are not specified.

As we have commented upon in the preceding section, if the reaction is stepwise, then it should take place *via* zwitterionic intermediates of type **A** (Figure 1). It is likely that these intermediates, if exist, could be stabilized even in moderately polar solvents such as ether or dichloromethane. Therefore, the mechanism of the reaction in gas phase could be different with respect to that in solution, depending upon the energy ordering of the possible reaction pathways.

In this study, we report our results on the [2 + 2] cycloaddition between alkenes **1a**−**e** and isocyanates **2a**−**d** to form β-lactams **3a**−**o**. These structures are collected in Figure 2 and have been chosen to cover the diverse structural and electronic effects which can be operating in the reaction. In the next sections we will report and discuss separately the results obtained in the gas phase and in solution.

Gas-Phase Calculations. We studied first the reaction between ethylene **1a** and isocyanates **2a**−**d** to form β-lactams **3a**−**d** (Figure 2). The total energies of the stationary points found in the HF/6-31G* potential energy hypersurface have been collected in Table 1 of the supporting information. In such a table we have also included the single-point MP2/6-31G* total energies and the ZPVE of the relevant species. Some relevant structures have also been computed at MP2/6-31+G*, MP3/6-31+G*//MP2/6-31+G*, and MP4SDQ/6-31+G*//MP2/6-31+G* levels. Unless otherwise stated, the differences in energy discussed in this section correspond to the MP2/6-31G*//HF/6-31G*+ΔZPVE level of theory.

The parent reaction (**1a** + **2a** -- **3a**) is predicted to be a concerted process at HF/6-31G*, HF/6-31+G*, MP2/6-31G*, and MP2/6-31+G* levels. We have found a sole transition structure **TSa** which connects reactants and product. In this TS, the N(1)−C(4) and C(2)−C(3) bonds are developed into a different extent, the latter being more advanced (see Figure 3). In addition, the C(4) atom still retains most of the sp^2 character present in the reactant **1a**. Thus, the natural bonding analysis of **TSa** assigns a strong carbocationic character to the C(4) atom, with an occupancy of 0.484 in the unhybridized p AO. This character is reflected by an NBA charge of +0.500 e (including the charges of the two hydrogens attached to C(4), see Table 2 of the supporting information).

It is noteworthy that the optimized geometries of **TSa** obtained at the HF/6-31G*, HF/6-31+G*, and MP2/6-31G* levels are compatible with the concerted push−pull mechanism **D** depicted in Scheme 2 and in Figure 1. However, when **TSa**

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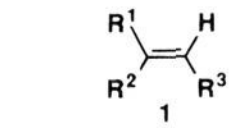

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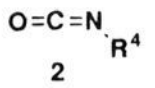
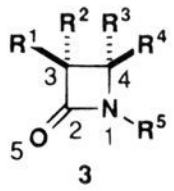


2

	R^1	R^2	R^3
1a	H	H	H
1b	H	H	CH_3
1c	H	H	OH
1d	$=CH_2$		H
1e	$=CH_2$		CH_3

	R^4
2a	H
2b	CH_3
2c	Cl
2d	SO_2Cl



3

	R^1	R^2	R^3	R^4	R^5
3a	H	H	H	H	H
3b	H	H	H	H	CH_3
3c	H	H	H	H	Cl
3d	H	H	H	H	SO_2Cl
3e	H	H	H	CH_3	H
3f	CH_3	H	H	H	H
3g	H	H	H	OH	H
3h	OH	H	H	H	H
3i	$=CH_2$		H	H	H
3j	H	H		$=CH_2$	H
3k	$=CH_2$		H	CH_3	H
3l	CH_3	H		$=CH_2$	H
3m	H	H	H	CH_3	Cl
3n	H	H	H	OH	Cl
3o	H	H	H	OH	SO_2Cl

Figure 2. Alkenes **1**, isocyanates **2**, and β-lactams **3** included in the present study. The same substitution patterns correspond to transition structures **TSa**–**o**.

Table 1. Activation Energies[a] (ΔE_a, kcal/mol) and Reaction Energies[a] (ΔE_{rxn}, kcal/mol) Obtained in the Reaction between Alkenes **1a**–**e** and Isocyanates **2a**–**d** to Form β-Lactams **3a**–**o**

	ΔE_a		ΔE_{rxn}	
reaction	HF/6-31G*	MP2/6-31G*	HF/6-31G*	MP2/6-31G*
1a + **2a** → **3a**	59.0	45.1	−6.2	−10.7
1a + **2b** → **3b**	60.1	44.0	−9.6	−15.7
1a + **2c** → **3c**	41.5	24.6	−17.2	−24.1
1a + **2d** → **3d**	46.8	34.5	−16.2	23.0
1b + **2a** → **3e**	53.4	41.1	−6.4	−12.0
1b + **2a** → **3f**	60.9	44.7	−4.8	−10.2
1c + **2a** → **3g**	42.7	34.9	−6.9	−10.5
1c + **2a** → **3h**	60.8	47.4	−0.4	−4.0
1d + **2a** → **3i**	61.8	46.4	−13.6	−17.9
1d + **2a** → **3j**	55.4	43.2	−19.1	−23.6
1e + **2a** → **3k**	54.1	40.2	−14.9	−20.4
1e + **2a** → **3l**	55.9	41.2	−19.1	−24.4
1b + **2c** → **3m**	35.2	18.9	−18.1	−26.5
1c + **2c** → **3n**	27.7	13.8	−18.4	−24.6
1c + **2d** → **3o**	20.8	6.2	−15.4	−22.0

[a] Single-point energies calculated on fully optimized HF/6-31G* geometries. ZPVE corrections (scaled by 0.89) are included.

was optimized at MP2/6-31+G* level, the push–pull mechanism of type **D** vanishes, the dihedral angle ω at this level being of 39.1° (see Figure 3). Therefore, inclusion of *both* electron correlation and a basis set incorporating diffuse functions leads to a $[{}_\pi 2_s + ({}_\pi 2_s + {}_\pi 2_s)]$ geometry for the parent reaction. Apart from this change in the value of ω, the rest of the geometrical parameters are similar. The calculated values of the energy of activation are similar at both MP2/6-31G*//HF/6-31G* and MP2/6-31+G* levels. Indeed, this value is not significantly affected as the Møller–Plesset expansion develops (see Table 2).

The reaction between ethylene **1a** and methyl isocyanate **2a** to form 1-methylazetidinone **3a** exhibits similar features with respect to those of the parent reaction. As in the preceding case, no evidence for the existence of intermediates of type **A**

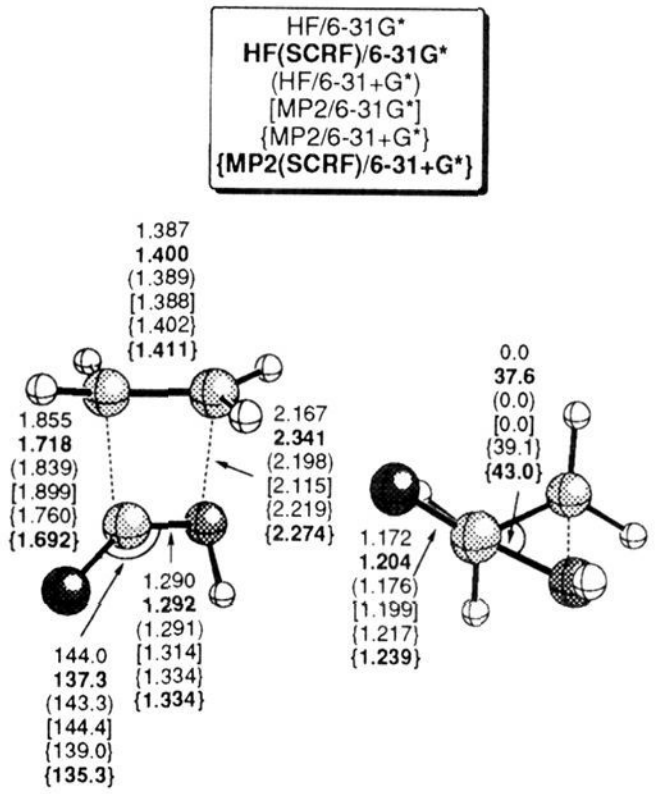


Figure 3. Computer plot (MP2/6-31+G*)and selected geometric data of **TSa** calculated at different levels of theory. Distances and angles are given in Å and deg, respectively. Atoms are represented by increasing order of shading as follows: H, C, N, and O.

(see Figure 1) could be found, and the reaction is again predicted to be concerted, the saddle point **TSb** being the only stationary point which connects reactants and product. Again, the geometry of **TSb** is predicted to correspond to a $[{}_\pi 2_s + ({}_\pi 2_s + {}_\pi 2_s)]$ mechanism only at the MP2/6-31+G* level (see Figure 2 of the supporting information). The calculated energies of activation of this reaction are similar to those found for the parent one (see Tables 1 and 2), in fair agreement with the experimental fact that alkyl isocyanates are usually inert toward unactivated olefins. This situation changes when isocyanates bearing electron-withdrawing groups are examined. Thus, the reaction between ethylene **1a** and the isocyanate **2c** is found to take place *via* the saddle-point **TSc** (see Figure 2 of the supporting information), whose geometrical features closely resemble those calculated for **TSa**. The activation energy for this reaction is found to be 26.1 kcal/mol (MP4SDQ/6-31+G*//MP2/6-31+G* result, see Table 2), 18.6 kcal/mol lower than that of the parent reaction. This value is similar at all the theoretical levels included in our study (see Tables 1 and 2).

In the case of the interaction between ethylene and the chemically more significant chlorosulfonyl isocyanate (CSI) **2d**, the trends outlined above are present again. In agreement with the experimental evidence, CSI is calculated to be very reactive toward a simple olefin such as ethylene, the activation energy being 10.6 kcal/mol lower than that calculated for the parent reaction. The saddle-point **TSd**, which connects the reactants with the product (1-chlorosulfonyl-2-azetidinone **3d**), is predicted to be less synchronous than the preceding ones (see Figure 2 of the supporting information).

The next step in our study was to investigate the reaction between monosubstituted olefins and isocyanic acid, in order to find out the effect of the substituents present in the olefin on the energetic and geometric variables of the cycloaddition as well as on its regiochemistry. First, we selected propene **1b** and vinyl alcohol **1c** as model alkenes which incorporate simple poor (methyl) and good (hydroxy) π-donors, respectively.

The main geometric features of the TS's leading to the regioisomeric β-lactams **3e** and **3f** are shown in Figure 4. The 4-substituted saddle point **TSe** shows similar features to those

Table 2. Activation Energies (ΔE_a, kcal/mol) and Reaction Energies (ΔE_{rxn}, kcal/mol) Calculated from Fully Optimized MP2-FC/6-31+G* Geometries

	ΔE_a			ΔE_{rxn}		
reaction	MP2/6-31+G*	MP3/6-31+G*	MP4SDQ/6-31+G*	MP2/6-31+G*	MP3/6-31+G*	MP4SDQ/6-31+G*
1a + **2a** → **3a**	42.2	44.9	44.7	−13.6	−16.2	−13.8
1a + **2b** → **3b**	38.7(−3.5)[a]	41.6(−3.3)[a]	42.6(−2.1)[a]	−18.3(−4.7)[a]	−21.2(−5.0)[a]	−18.4(−4.6)[a]
1a + **2c** → **3c**	21.1(−21.1)[a]	25.9(−19.0)[a]	26.1(−18.6)[a]	−26.9(−13.3)[a]	−28.1(−11.9)[a]	−25.7(−11.9)[a]
1b + **2a** → **3e**	37.1	39.3	39.2	−15.0	−17.4	−13.5
1b + **2a** → **3f**	41.6(4.5)[b]	45.0(5.7)[b]	44.4(5.2)[b]	−13.4(1.6)[b]	−15.7(1.7)[b]	−15.1(1.6)[b]
1d + **2a** → **3i**	43.6	48.3	45.8	−21.5	−23.3	−21.2
1d + **2a** → **3j**	39.7(−3.9)[c]	43.3(−5.0)[c]	42.6(−3.2)[c]	−26.7(−5.2)[c]	−28.5(−5.2)[c]	−26.1(−4.9)[c]

[a] Relative energies (kcal/mol) with respect to the **1a** + **2a** → **3a** process. [b] Relative energies (kcal/mol) with respect to the **1b** + **2a** → **3e** process. [c] Relative energies (kcal/mol) with respect to the **1d** + **2a** → **3i** process.

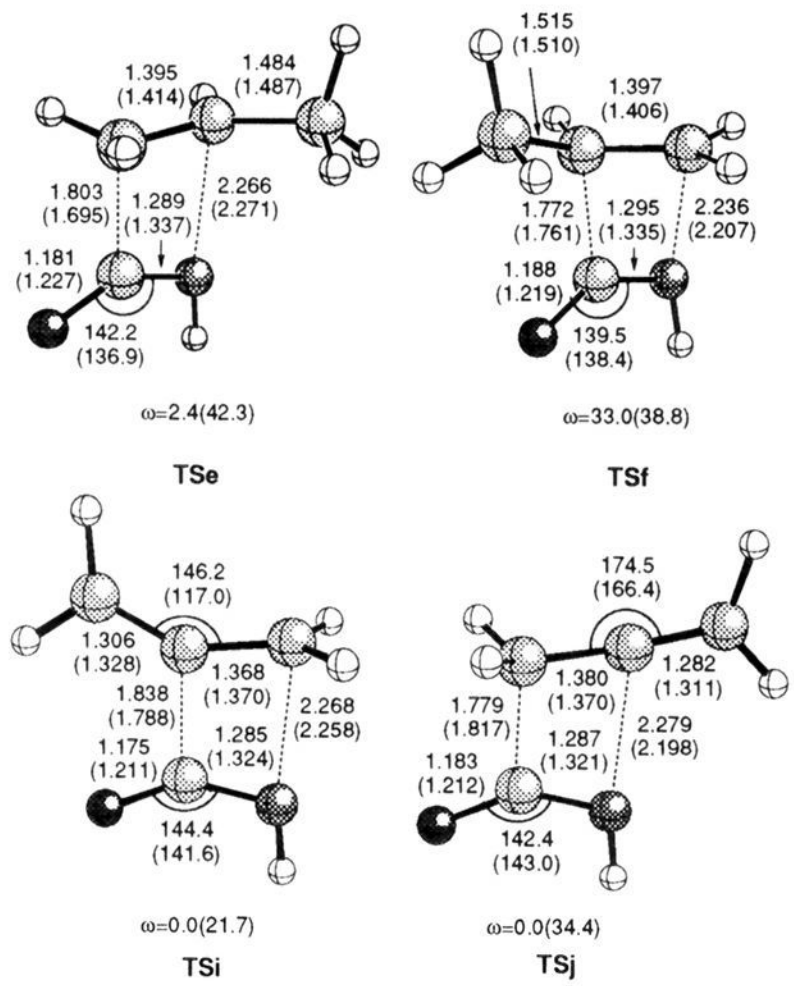


Figure 4. Computer plot and selected geometric data of the HF/6-31G* and MP2/6-31+G* (in parentheses) optimized transition structures corresponding to the interaction between isocyanic acid **2a** and alkenes **1b,d**. Distances and angles are given in Å and deg, respectively. Atoms are represented by increasing order of shading as follows: H, C, N, and O.

found in its analogs **TSa**−**d** at both HF/6-31G* and MP2/6-31+G* levels. As expected, we observed that the cationic character of C(4) is stabilized by the methyl group and consequently the activation energy is lower than that calculated for the parent **1a** + **2a** → **3a** reaction. Thus, the methyl group at C(4) is calculated to exert a stabilizing effect of *ca.* 3 kcal/mol at all the theoretical levels included in our study (see Tables 1 and 2). The saddle point **TSf**, which connects the reactants **1b** and **2a** with the product 3-methyl-2-azetidinone **3f**, is quite different with respect to **TSe**. The activation energy for the **1b** + **2a** → **3f** process is calculated to be of 44.7 kcal/mol, a 3.6 kcal/mol higher value than that obtained for the formation of the 4-substituted regioisomer **3e**. In addition, the reaction energy corresponding to the formation of this latter compound is 1.8 kcal/mol more exothermic (see Table 1). Interestingly, in the case of **TSf** the calculated value of ω differs significantly from planarity at both HF/6-31G* and MP2/6-31+G* levels (see Figure 4) the calculated value being 33.0°. Since **TSf** is consistently higher in energy than **TSe** (see Tables 1 and 2 and Table 1 of the supporting information), exclusive formation of the 4-substituted cycloadduct **3e** is predicted by our calculations, in agreement with the experimental evidence available.[10]

The same trends are observed in the study of the reaction of **2a** with vinyl alcohol **1c** to form the hydroxy-2-azetidinones **3g** and **3h**, but in this case the regiocontrol is amplified by the stronger π-donating ability of the exocyclic oxygen atom. Thus, the saddle point **TSg** leading to the 4-hydroxyazetidin-2-one **3g** is predicted to be 12.5 kcal/mol more stable than its 3-substituted analog **TSh** (see Table 1). Moreover, an analysis of the critical points of the gradient of the electron density[47] of **TSh** reveals a (3,−1) bond critical point between the hydroxylic hydrogen and the O(5) atom as well as the corresponding (3,+1) ring critical point corresponding to the H−O−C(3)−C(2)−O(5) pseudocycle (see Figure 3 of the supporting information). This result is generated by the hydroxy group included in our calculations instead of the alkoxy or acyloxy groups usually employed in practice. Therefore, the regioselectivity in the [2 + 2] cycloaddition between "real" vinyl ethers or esters and isocyanates should take place even with higher regiocontrol. In fact, in all the cases reported only the cycloadducts with the OR groups at C(4) have been obtained. In addition, the hydroxy group at C(4) induces a lowering of 10.2 kcal/mol with respect to the parent reaction. This result is consistent with the known experimental fact that activated olefins (i.e., those incorporating electron releasing groups) react smoothly with isocyanates, even with the less reactive ones.[10]

We have also studied the reaction of allenes with isocyanic acid. Firstly, we have computed the reaction profile for the reaction with allene itself to yield the regioisomeric methylidene β-lactams **3i** and **3j**. Surprisingly, **TSi** is found to be of higher energy than **TSj** and therefore the calculated activation energy for the **1d** + **2a** → **3i** reaction is found to be *ca.* 3.2 kcal/mol higher in energy than that predicted for the **1d** + **2a** → **3j** process (see Tables 1 and 2). The chief geometric features of **TSi** and **TSj** are reported in Figure 4. Inspection of such a figure indicates that both saddle points have C_s and C_1 symmetries at HF/6-31G* and MP2/6-31+G* levels, respectively. The main difference between **TSi** and **TSj** lies in their respective bond angles between C(3), C(4), and the exocyclic carbon atom. Thus, the values for these angles at MP2/6-31+G* level are 117.0° and 166.4° for **TSi** and **TSj**, respectively. Therefore, in **TSj** this angle is closer to the original value of 180.0° in the starting allene. The distortion of this angle in **TSi**, imposed by the higher degree of advancement in bond formation between C(2) and C(3), should be the responsible for the higher energy of this TS. This result apparently contradicts the experimental findings, since in all the cases reported in the literature,[2,10] only the 3-alkylidene regioisomers

(47) Bader, R. F. W. *Atoms in Molecules. A Quantum Theory;* Clarendom Press: Oxford, 1990. The critical points of **TSg** were located and characterized with the AIMPAC program, see: Biegler-Konig, F. W.; Bader, R. F. W.; Tang, T. *J. Comput. Chem.* **1982**, *3*, 317.

are formed in the reaction between allenes and isocyanates (Scheme 1). However, it is important to realize that all the chemically useful allenes incorporate π-donors such as alkyl, aryl, alkoxy, or acyloxy groups, and hence both the allenyl moiety and the substituents attached to it must be taken into account. Therefore, we have also calculated the reaction profiles for the reaction between methylallene **1e** and isocyanic acid **2a** to yield either 4-methyl-3-methylidene-azetidin-2-one **3k** or 3-methyl-4-methylidene-azetidin-2-one **3l**. In this case, our calculations predict the reverse regioselectivity, i.e., the **1e** + **2a** → **3k** process is now the preferred one. Thus, **TSk** is found to be 1.0 kcal/mol more stable than **TSl** (see Table 1). The main geometric features of these TS's are depicted in Figure 3 of the supporting information. It can be readily seen that the geometries of **TSk** and **TSl** are very similar to those found for **TSi** and **TSj**, respectively. Therefore, the lower energy of **TSk** should be attributed to the donating effect of the 4-methyl group in this TS. This stabilizing effect over the electron deficient C(4) atom is more important than the distortion of the allenic moiety from linearity. By contrast, the π-system of the methylidene group in **TSl** cannot exert any donation over C(4) because of its orthogonality with respect of the *p* AO of this atom. This lack of stabilization is not compensated by the low bending of the allenic moiety in **TSl**. As a consequence of these factors, this TS is more energetic than **TSk**. This result now agrees with the observed complete regiocontrol in the [2 + 2] cycloaddition between allenes and isocyanates.[9,10]

To conclude our studies in the gas phase, we investigated the [2 + 2] cycloadditions between the activated alkenes **1b** or **1c** and the electrophilic isocyanates **2c** and **2d**. In principle, in view of the combination of activated alkenes and electrophylic isocyanates it is expected that these reactions should be particularly favored. Thus, we have found that the methyl group at C(4) induces a decrease in energy of activation of $\Delta\Delta E_a$(4-Me) = −4.0 kcal/mol. Similarly, the variations induced by the remaining groups are $\Delta\Delta E_a$(4-OH) = −10.2 kcal/mol, $\Delta\Delta E_a$(1-Cl) = −20.5 kcal/mol, and $\Delta\Delta E_a$(1-SO_2Cl) = −10.6 kcal/mol. If we take the activation energy for the parent reaction **1a** + **2a** → **3a** as the base value (ΔE_a = 45.1 kcal/mol, see Table 1), then the expected values for the **1b** + **2c** → **3m**, **1c** + **2c** → **3n**, and **1a** + **2a** → **3o** processes are 20.6, 14.4, and 24.3 kcal/mol, respectively. The calculated activation energies resulted to be 18.9, 13.8, and 6.2 kcal/mol, respectively. These values are similar to the expected ones in the former reactions, whereas the latter reaction shows a higher difference between the expected and the calculated values. Therefore in this reaction there is a certain degree of synergism between the two activating substituents, and their effects are not simply additive. The main structural features of **TSm**−**o** are depicted in Figure 4 of the supporting information. It is important to note that, in spite of the high asynchronicity of **TSo**, associated to the **1c** + **2d** → **3o** process, no intermediates of type **A** (Figure 1) could be located. In addition, this is the process with the lowest activation energy (see Table 1) among the reactions included in our study. This result agrees with the well-known experimental fact that chlorosulfonyl isocyanate reacts particularly well with electron-rich olefins, even at low temperatures,[10] although our calculated reaction profile in the gas phase does not explain the loss of stereocontrol in the reaction between chlorosulfonyl isocyanates and alcoxy olefins.[20]

SCRF Calculations. We started our investigations studying the parent reaction, i.e., the **1a** + **2a** → **3a** process. Dichloromethane (ϵ = 9.08), a common solvent in cumulene chemistry, was chosen as model solvent. We have included the geometric data of **TSa** at HF(SCRF)/6-31G* and MP2(SCRF)/6-31+G* levels in Figure 3. One important feature of **TSa** in solution with respect to the gas phase is that the values of the dihedral angle ω are similar at both levels of calculation. It can also be seen that **TSa** in solution is less synchronous than in the gas phase. Therefore, we have found that in this reaction the solvent can act as a substantial factor of asynchronicity. However, we have not been able to find zwitterionic intermediates of type **A** in the parent reaction.

The energies of the stationary points found on the HF(SCRF)/6-31G* and MP2/6-31+G* potential energy hypersurfaces associated to this reaction have been collected in Tables 3 and 4 of the supporting information, respectively, as well as the principal axes of the corresponding ellipsoidal cavities. We have found that for the parent reaction the activation energy at the MP2(SCRF)/6-31G*//HF(SCRF)/6-31G*+ΔZPVE level is 46.6 kcal/mol (see Table 3 of the supporting information), a value higher than that found for the gas phase. Inclusion of the cavitation and dispersion energies in the solvation energy (HF(SCRF)/6-31G* level) promotes a lowering of 5.0 kcal/mol. In addition, the activation energy computed at our highest level (MP4SDQ(SCRF)/6-31+G*//MP2(SCRF)/6-31+G*) is of 42.3 kcal/mol (see Table 4 of the supporting information), a value 2.4 kcal/mol lower than that calculated *in vacuo* at the same level. According to the experimental data available,[12f,20b] it is expected that this rate acceleration should be more pronounced when a highly reactive isocyanate such as CSI were considered. Therefore, the next step in our SCRF study was to investigate the reaction profile for the reaction between vinyl alcohol **1c** and chlorosulfonyl isocyanate **2d** to yield 1-chlorosulfonyl-4-hydroxyazetidin-2-one **3o**. The reason for choosing this particular process is that it corresponds to a very important reaction in multistep synthesis of many carbapenem compounds and that it is the only one for which loss of stereospecificity has been reported. In addition, the TS associated to this reaction was found to be particularly asynchronous in the gas phase (*vide supra*). Since, as we have previously found, solvent effects can induce an additional lowering of synchronicity, formation of zwitterionic intermediates of type **A** could be specially favored in this case.

The stationary points found in this reaction are depicted in Figure 5. Inspection of such a figure reveals that the calculated geometries for **1c** and **2d** in solution are very similar to the data obtained *in vacuo*. In particular, the *s-cis* conformation for **1c** is the same to that found in the gas phase.[48] Similarly, the minimum energy conformation for **2d** is very similar to that reported by Nguyen *et al.*[49] in the gas phase at MP2/6-31G* level. However, the most important point is that the energy profile for the **1c** + **2d** → **3o** process changes completely with respect to that found in the gas phase (see Figure 5 and Table 3 of the supporting information). The first TS, denoted as **TS1**, corresponds to the formation of the C(2)−C(3) bond *via* the nucleophilic attack of the alkene over the *sp* hybridized carbon of chlorosulfonyl isocyanate. This TS is very early and therefore the alkene moiety still retains the *s-cis* conformation present in **1c** (see Figure 5, **TS1**). The activation energy of this first step is of 1.5 kcal/mol at the MP2(SCRF)/6-31G*//HF(SCRF)/6-31G*+ΔZPVE level. This value is probably too low, but it correctly reflects the fact that this particular reaction is very facile, even at low temperatures. Moreover, this activation energy is 4.7 kcal/mol lower than that calculated in the gas phase at the same level of theory (see Table 1 and Table 3 of the supporting information). The next stationary point found in the

(48) Nobes, R. H.; Radom, L.; Allinger, N. L. *J. Mol. Struct. (Theochem)* **1981**, *85*, 185.

(49) Nguyen, M. T.; Hajnal, M. R.; Vanquickenborne, L. G.; Ha, T.-K.; Stohner, J. *J. Chem. Soc., Faraday Trans.* **1993**, *89*, 2381.

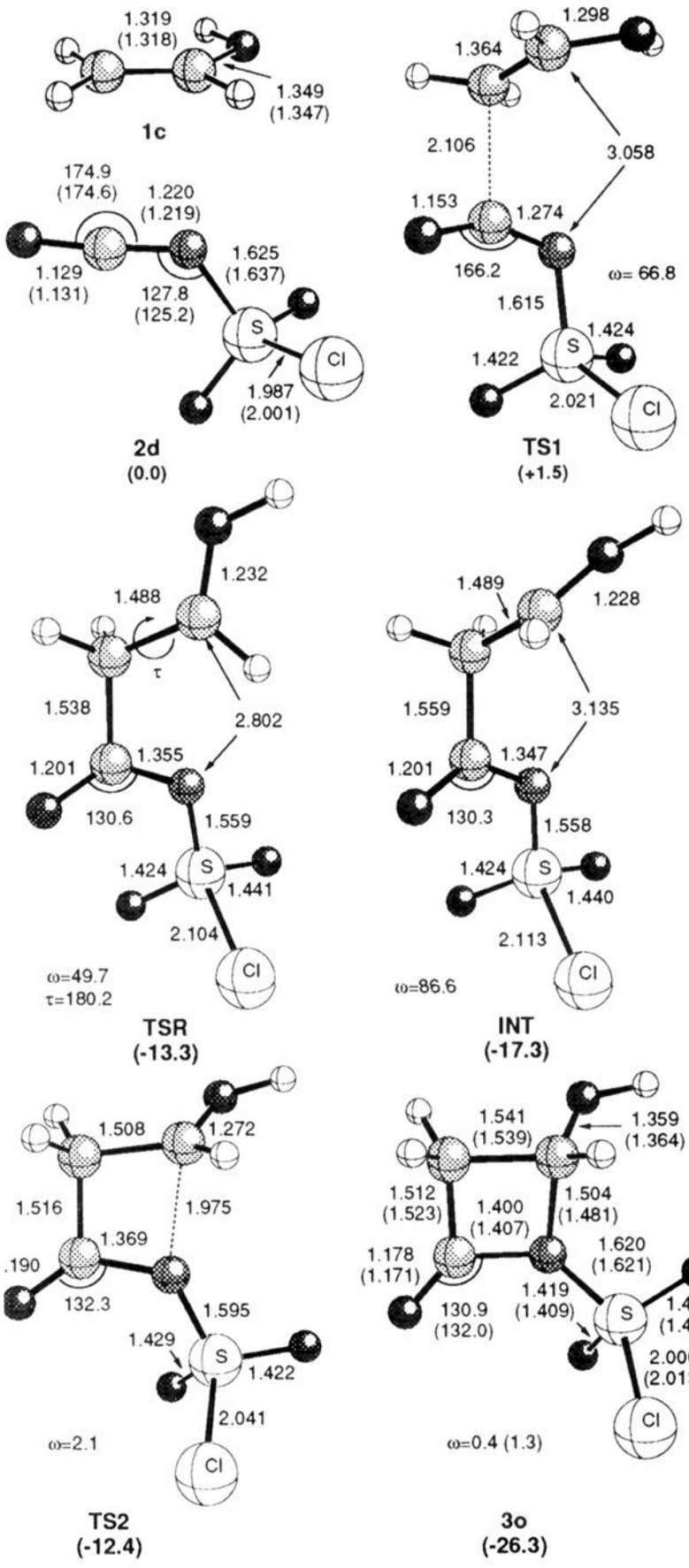
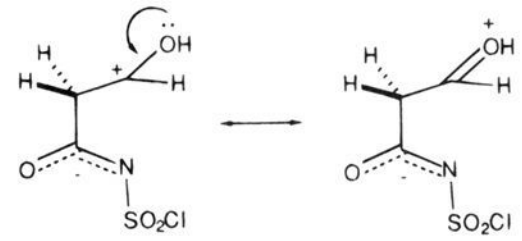


Figure 5. Computer plot and selected geometric data of the HF(SCRF)/6-31G* optimized stationary points corresponding to the interaction between chlorosulfonyl isocyanate **2d** and vinyl alcohol **1c** (HF/6-31G* data in parentheses). Distances and angles are given in Å and deg, respectively. Unless otherwise noted, atoms are represented by increasing order of shading as follows: H, C, N, and O. τ is the dihedral angle HO−C(4)−C(3)−C(2). Bold numbers in parentheses are relative energies (in kcal/mol) with respect to the reactants, computed at the MP2(SCRF)/6-31G*//HF(SCRF)/6-31G*+ΔZPVE level.

HF(SCRF)/6-31G* potential energy hypersurface corresponds to a local minimum, denoted as **INT** in Figure 5. This minimum, which lies 17.3 kcal/mol below the reactants, is similar to the zwitterionic intermediates of type **A** (Figure 1) proposed by Graf.[23] However, it is important to note that in **INT** the isocyanate and the alkene subunits are almost orthogonal each other, the value of the dihedral ω being 86.6°. As it is shown in Figure 5, the C(2)−C(3) bond is already formed at this stage of the reaction, the corresponding bond distance being 1.559 Å. It is also noteworthy that the hydroxy group in **INT** is in a *s-trans* conformation.[50] Another interesting feature of **INT** is that the bond distance between the hydroxylic oxygen and the C(4) atom is 1.228 Å, a relatively small value which indicates a strong stabilization of the carbocationic center at C(4) *via* π-donation:

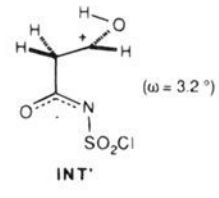


We have also found a TS whose imaginary frequency in its diagonalized hessian matrix corresponds to rotation along the C(3)−C(4) bond. This TS, denoted as **TSR** in Figure 5, is 4.0 kcal/mol higher in energy than **INT** at MP2(SCRF)/6-31G*//HF(SCRF)/6-31G*+ΔZPVE level (see Table 3 of the supporting information). Therefore, isomerization of the possible zwitterionic intermediates of this type can occur at low energy cost. The ability of the oxygen atom to stabilize electron-deficient centers facilitates the formation of these intermediates and decreases the energy of the TS's which interconnect them. Finally, we have found a TS which corresponds to the ring closure *via* formation of the N(1)−C(4) bond to yield the product, i.e., the β-lactam **3o**. This TS, denoted as **TS2** in Figure 5, shows an almost coplanar disposition of the N(1), C(2), C(3), and C(4) atoms, reflected by the value of ω of only 2.1°. The distance between N(1) and C(4) is calculated to be of 1.975 Å. The activation energy corresponding to this second step is 4.9 kcal/mol at our highest level of calculation.[51] This energy barrier is slightly higher than (although comparable to) that calculated for the rotation along the C(3)−C(4) bond. Therefore, given that this latter barrier is also low, it is possible to obtain mixtures of stereoisomers in the [2 + 2] cycloadditions between sulfonyl isocyanates and disubstituted vinyl ethers. This result is in agreement with the observations of Effenberger *et al.*[20] (*vide supra*). According to their results and our calculations, a *trans*-vinyl ether should yield the corresponding *trans*-β-lactam, which is the product which should be obtained under kinetic and thermodynamic control. However, if the reaction is carried out with a *cis*-vinyl ether, the product initially formed can be the corresponding *cis*-β-lactam, although the *trans* stereoisomer can be accessible *via* **TSR**, which connects the two possible intermediates (Scheme 3).

Conclusions

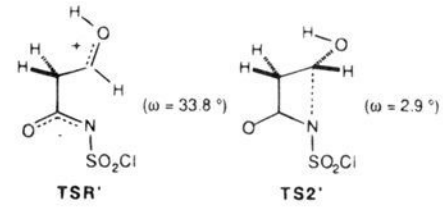
The following conclusions can be drawn from the *ab initio* calculations reported in this work: (i) The [2 + 2] cycloaddition

(50) We have also found a s-*cis* conformation for the hydroxy group at C(4), but this intermediate, denoted as **INT′** lies 11.8 kcal/mol above **INT** (MP2(SCRF)/6-31G*//HF(SCRF)/6-31G*+ΔZPVE level):



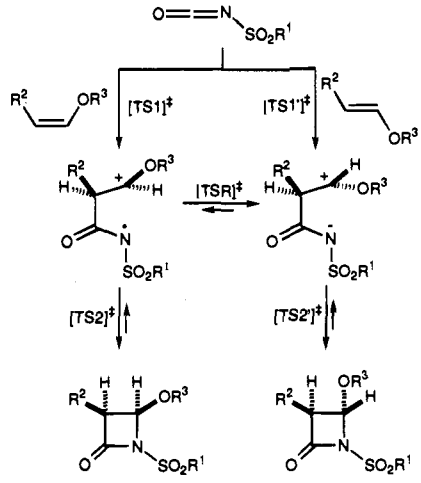
INT′

(51) The corresponding conformers of **TSR** and **TS2**, denoted as **TSR′** and **TS2′**, were found to be 14.9 and 5.5 kcal/mol higher in energy, respectively (MP2(SCRF)/6-31G*//HF(SCRF)/6-31G*+ΔZPVE level):



TSR′ TS2′

Scheme 3



between alkenes and isocyanates takes place *via* concerted $[_{\pi}2_s+(_{\pi}2_s+_{\pi}2_s)]$ mechanisms in the gas phase and, in some cases, in solution. (ii) Olefins with electron donating groups and/or isocyanates with electron withdrawing groups react more efficiently. (iii) Donating substituents in the starting alkene give exclusively the 4-substituted regioisomers. (iv) Substituted allenes give the corresponding 3-alkylidene-β-lactams. (v) The solvent contributes to the asynchronicity of the reaction and, in some cases, can modify its profile from a concerted to a two-step process, thus allowing a loss of stereoespecificity.

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Supporting Information Available: Tables including total energies of structures **1a–e**, **2a–d**, **3a–o**, and **TSa–o** and NBA charges of structures **1a–e**, **2a–d**, **TSa–o**, and **3a–o** and ball and stick drawings of the cycloadducts **3a–o** and **TSb–d,g,h,k–o** (9 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, can be ordered from the ACS, and can be downloaded from the Internet; see any current masthead page for ordering information and Internet access instructions.

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