

Catalytic and Solvent Effects on the Cycloaddition Reaction between Ketenes and Carbonyl Compounds To Form 2-Oxetanones

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Abstract: *Ab Initio* calculations (MP2/6-31G*//HF/6-31G*, including zero-point vibrational energy (ZPVE) corrections and solvent effect) predict that the reaction between ketenes and carbonyl compounds takes place *via* unusually synchronous [$\pi_2s + (\pi_2s + \pi_2s)$] transition structures (TS's). The reaction between formaldehyde and activated monosubstituted ketenes such as chloroketene is predicted to be more synchronous and to take place through an *exo* TS, whose shape is consistent with the experimentally reported low stereoselectivity in the cycloaddition between monosubstituted ketenes and aldehydes. The catalyzed reaction is predicted to be a concerted two-stage process, in which the Lewis acid in the TS is bonded to the carbonyl oxygen of the aldehyde and adopts an *exo* disposition with respect to the 2-oxetanone ring in formation. The shape of this latter TS accounts for the preferential formation of *cis* 2-oxetanones when bulky Lewis acid catalysts are used.

Introduction

2-Oxetanones¹ (β -lactones) are versatile and useful synthetic intermediates in the preparation of alkenes,² allenes,³ carboxylic acid derivatives⁴ (including amino acids⁵), and polymers.⁶ In addition, some β -lactones exhibit interesting biological properties.^{2b,7} One of the methods usually employed in the chemical

synthesis of these strained heterocycles is the [2 + 2] cycloaddition between ketenes and carbonyl compounds¹ (Scheme 1). This reaction was first reported by Staudinger⁸ in 1911. Since then, different authors have extended its scope and applicability, specially when a variety of methods for generating ketenes *in situ* became available.⁹ However, two intriguing features are present in this cycloaddition: Firstly, the reaction very often requires the use of Lewis acids as catalysts,¹⁰ and secondly, the stereocontrol of the cycloaddition is, in general, low.¹¹ For example, the reaction between chloroketene and chloral leads to a 62:38 mixture of *cis*- and *trans*-3-chloro-4-trichloromethyl-2-oxetanone.^{11a,12} Recently, it has been reported^{10c} that a bulky catalyst such as methylaluminum bis(4-bromo-2,6-di-*tert*-butylphenoxide) (MABR) leads to a highly stereoselective formation of the corresponding *cis*-2-oxetanones. In addition, chiral alkaloids such as quinine and quinidine are known to catalyze the formation of 4-(dihaloalkyl)-2-oxetanones with large enantiomeric excesses.¹³

In spite of the theoretical and synthetic interest of this reaction the elucidation of its mechanism has received little attention,¹⁴

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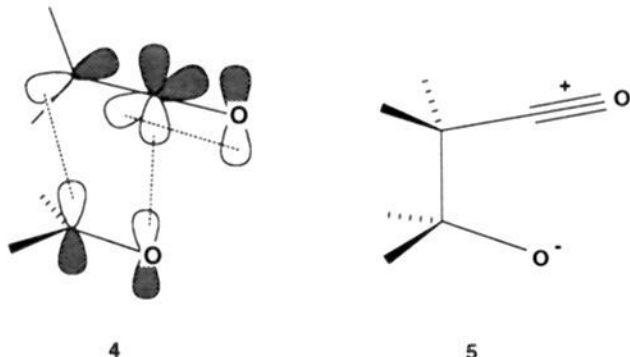
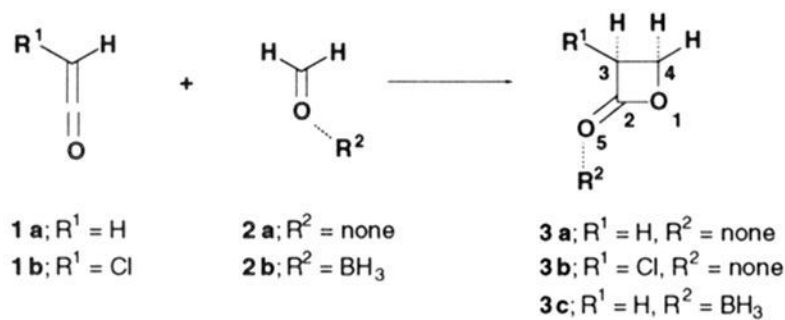
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(12) This poor stereocontrol contrasts with the high stereoselectivity usually observed in the reaction between ketenes and olefins (see, for example: Valentí, E.; Pericás, M. A.; Moyano, A. *J. Org. Chem.* **1990**, *55*, 3582) and between ketenes and imines (for a recent review see: Georg, G. L.; Ravikumar, V. T. In *The Organic Chemistry of β -lactams*; Georg, G. L., Ed.; Verlag Chemie: New York, 1993; pp 295–381).

Scheme 1



in comparison with that directed at other similar reactions such as the reaction of ketenes with alkenes^{12,15} or imines^{16,17} or the dimerization of ketenes,¹⁸ for which detailed discussions based on both *ab initio* and semiempirical calculations have been reported. Some authors,^{14,9b,14} however, have suggested that formation of β-lactones **3** could occur in a single step involving a [$\pi 2_s + (\pi 2_s + \pi 2_s)$] transition structure (TS) **4**, although the possibility of a two-step reaction path involving the zwitterionic intermediate **5** cannot be ruled out.

Within the above context, and as a part of a research program devoted to the study of the reactivity of cumulenes and double bonds to form four-membered rings,^{16,19} we have studied the possible reaction paths between ketenes **1a,b** and aldehydes **2a,b** to form the 2-oxetanones **3a–c** (see Scheme 1). The final goal of this investigation is to understand the origins of the abnormally low stereoselectivity of the reaction as well as the influence of the solvent and Lewis acid catalysts on its mechanism.

Computational Methods

All results presented in this paper have been obtained with the GAUSSIAN 92 suite of programs,²⁰ using the 6-31G* basis set.²¹ All the geometries have been optimized at the RHF/6-31G* level of theory and the energies have been recalculated at the MP2/6-31G* level.²² Zero-point vibrational energies (ZPVE) calculated at HF/6-31G* have

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been scaled²³ by 0.89. Stationary points were characterized by frequency calculations.²⁴ All reactants and products have positive defined Hessian matrices. TSs showed only one negative eigenvalue in their diagonalized force constant matrices, and their associated eigenvectors were confirmed to correspond to motion along the reaction coordinate. Atomic charges²⁵ and bond indices were calculated with the Natural Population Analysis (NPA) method.²⁶

According to Pericàs and Moyano^{2a}, the relative variation of bond index (δB_i) for a given bond (i) at the TS can be defined as:

$$\delta B_i = \frac{B_i^{\text{TS}} - B_i^{\text{R}}}{B_i^{\text{P}} - B_i^{\text{R}}} \quad (1)$$

where the superscripts R, TS, and P refer to reactants, transition structure, and products, respectively. The corresponding average value (δB_{av}) is:

$$\delta B_{\text{av}} = n^{-1} \sum_{i=1}^n \delta B_i \quad (2)$$

where the sum runs over the n bonds directly involved in the reaction. According to the definition exposed in (2), δB_{av} can be used as a measure of the degree of advancement of the transition structure. Therefore, the values of δB_{av} can be used to quantify the "earlyness" or "lateness" of a given TS. In addition, using the Pericàs and Moyano^{2a} ideas, we have computed the synchronicity of the reaction (S_y) by means of the following expression:

$$S_y = 1 - \frac{\sum_{i=1}^n \frac{|\delta B_i - \delta B_{\text{av}}|}{\delta B_{\text{av}}}}{2n - 2} \quad (3)$$

where the various symbols have the same meaning as indicated for (1) and (2). According to this definition, if all the intervening bonds were broken or formed to the same extent at the TS, then $\delta B_i = \delta B_{\text{av}}$ for $i = 1, 2, \dots, n$ and therefore $S_y = 1$. On the other hand, if one bond is completely broken at the TS while the other $(n - 1)$ bonds remain unchanged, then $S_y = 0$, as should be expected for a completely asynchronous mechanism. We find it convenient to use this precise definition of the synchronicity, since there has been, and probably still is, a great deal of controversy on the synchronous nature of concerted reactions.²⁷

As outlined above, the hypothetical mechanism that can be operating in the cycloaddition reaction between ketenes and carbonyl compounds could involve zwitterionic intermediates **5**. These highly polar minima are likely stabilized in solution. The solvents usually employed in this reaction vary from diethyl ether to dichloromethane. Therefore, we decided to study the mechanism of the reaction not only *in vacuo* but also in the presence of an organic solvent of intermediate polarity such as dichloromethane ($\epsilon = 9.08$). One useful form to describe nonspecific solute-solvent interactions is provided by the continuum models.²⁸ In these models, the liquid is represented by a dielectric continuum, characterized by its dielectric relative permittivity ϵ . The solute is placed in a cavity created in the continuum, at the cost of spending out some cavitation energy. The electronic distribution of the solute polarizes the

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continuum which generates an electric field inside the cavity which in turn affects the solute's geometry and electronic structure. The implementation of this interaction scheme is achieved through the so called self-consistent reaction field (SCRf) method,²⁹ whose simplest form within the MO theory framework relies on the Onsager³⁰ reaction field theory. In this particular model, the shape of the cavity is approximated to a sphere of radius a_0 , and the solute-solvent interaction energy is simply the electrostatic contribution to the free energy of solvation, *via* the interaction of the dipole of the solute and the continuum. Therefore, the cavitation and dispersive energy contributions to the solvation energy are neglected. The Onsager reaction field method has been implemented^{29c} in the GAUSSIAN 92 series of programs and has proven to be quite successful in reproducing, among other phenomena,³¹ the general features of a number of concerted processes, such as the Diels-Alder reaction between dienes and aldehydes, imines and related dienophiles.³²

A more rigorous implementation of the SCRf formalism consists of the methodology developed by Rinaldi, Rivail, *et al.*³³ In this model, the solute is placed in an ellipsoidal cavity, and the electrostatic free energy of solvation is computed according to:

$$\Delta A_{\text{solv}} = -\frac{1}{2} \sum_{l=0}^{\infty} \sum_{m=-l}^l R_l^m \langle M_l^m \rangle \quad (4)$$

where $\langle M_l^m \rangle$ represents the (l, m) component of the multipole expansion of the electrostatic potential of the solute evaluated at the center of the cavity and R_l^m is the corresponding component of the reaction field given by

$$R_l^m = \sum_{l'=0}^{\infty} \sum_{m'=-l'}^{l'} f_{ll'}^{mm'} \langle M_{l'}^{m'} \rangle \quad (5)$$

where the $f_{ll'}^{mm'}$ are constants that depend on the dielectric properties of the medium and on the cavity shape. In the case of an ellipsoidal cavity characterized by three independent axes, analytical expressions for the solvation energy and for their derivatives with respect to the nuclear coordinates are available.^{33a-c} It is important to note that, although in (4) and (5) l varies from 0 to ∞ , reasonable convergence of the series is in general obtained for $l = 6$. For the particular case of a spherical cavity (one independent axis instead of three) and considering only the dipole contribution to the solvation energy (i.e., sums in (4) and (5) being truncated at $l = 1$ and $l' = 1$, respectively), the Onsager formula is recovered. In this paper we have studied the solvent effects using both Onsager and Rinaldi-Rivail methods. The calculations using the latter procedure have been carried out with a locally modified version of the GAUSSIAN 92 program suite, to incorporate the SCRFPAC link,³⁴ which also includes estimates of cavitation and dispersion energies. In principle, it is expected that the electrostatic contribution should play a major role in this reaction. Expansions (4) and (5) have been truncated at $l = 6$ and $l' = 6$, respectively. Application of this method to similar reactions has been successful. For example, Ruiz-López *et al.* have used

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in their study of the [2 + 2] cycloaddition between ketenes and imines³⁵ and in Diels-Alder reaction between cyclopentadiene and methyl acrylate.³⁶

Results and Discussion

Gas-Phase Calculations. We started our study investigating the reaction between ketene **1a** and formaldehyde **2a** to form 2-oxetanone **3a**. Intensive search on the potential energy hypersurface did not permit the location of zwitterionic-like intermediates of type **5**. Instead, a transition structure **4a** was located and characterized. The chief geometric features of this TS are shown in Figure 1. Inspection of such a figure reveals that **4a** appears to be a quite synchronous TS, particularly if we compare it to those found by Wang and Houk in their study on the interaction between ketene and ethylene. Thus, the distances O₁-C₂ and C₃-C₄ corresponding to **4a** were found to be 2.091 and 1.918 Å, respectively, whereas the equivalent values found by Wang and Houk were 1.756 and 2.441 Å, respectively. These data and the calculated bond indices (see Table 3) indicate that bonding between O₁ and C₂ is less advanced at the TS than binding between C₃ and C₄, the values found for B_{12} and B_{34} being 0.172 and 0.525, respectively. In addition, the calculated value of δB_{av} was found to be 0.476, thus indicating that **4a** is almost a "halfway" TS. The computed synchronicity for the **1a** + **2a** → **3a** reaction is 0.79, a higher value than a mere inspection of the O₁-C₂ and C₃-C₄ bond orders and distances would suggest. It is noteworthy that the values for δB_{23} , δB_{34} , and δB_{14} are quite similar (0.614, 0.521, and 0.591, respectively). Therefore, the low development of the O₁-C₂ bond is almost exclusively responsible for the partial asynchronicity of the reaction. The analysis of the NPA charges is also illustrative of this aspect (see Table 1 of the supplementary material). Thus, the charge of the C₄ atom is 0.242e in TS **4a**, whereas in formaldehyde **1a** and 2-oxetanone **3a** the same atom has a charge of 0.331e and -0.038e, respectively. In addition, the formaldehyde fragment of **4a** bears a net excess of 0.29 electrons, while the ketene unit is deficient by an equal amount of charge (see the value of Σq in Table 1 of the supplementary material). The corresponding value in the product **3a** is 0.26. Therefore, the electron transfer from **1a** to **2a** is completed at the TS **4a**. All these results indicate that **4a** corresponds to a [π_2s + (π_2s + π_2s)] mechanism, the main interaction being between the ketene's HOMO and the LUMO of formaldehyde. This results in a higher development of the C₃-C₄ bond at TS **4a**. In addition, the calculated value of the C₂-C₃-C₄-O₁ dihedral angle is 24.7°, as should be expected for an approaching mode of this type.

The calculated activation energy for the **1a** + **2a** → **3a** reaction is 28.9 kcal/mol at the MP2/6-31G*//HF/6-31G* + $\Delta ZPVE$ level (see Table 2). This value is similar to the activation energy reported by Wang and Houk for the cycloaddition reaction between ketene and ethylene.^{15a} However, it is likely that these activation energies might be somewhat low, although it should be pointed out that energies computed at the MP2/6-31G* level are of high enough quality for comparative purposes between different TS's in cycloaddition reactions.^{32,36} In this respect it may be noted that the activation energy corresponding to the reaction of ketene and ethylene calculated at MP2/6-31G*//HF/6-31G* and MP2/6-31G* levels is *ca.* 5.1 kcal/mol (without ZPVE corrections) lower than the experimental value.^{15a} Also, Houk *et al.*³² have reported that activation energies of other cycloadditions such as the Diels-Alder reaction are 6.8-9.9 kcal/mol less than the experimental values when they are calculated at the MP2/6-31G* level.

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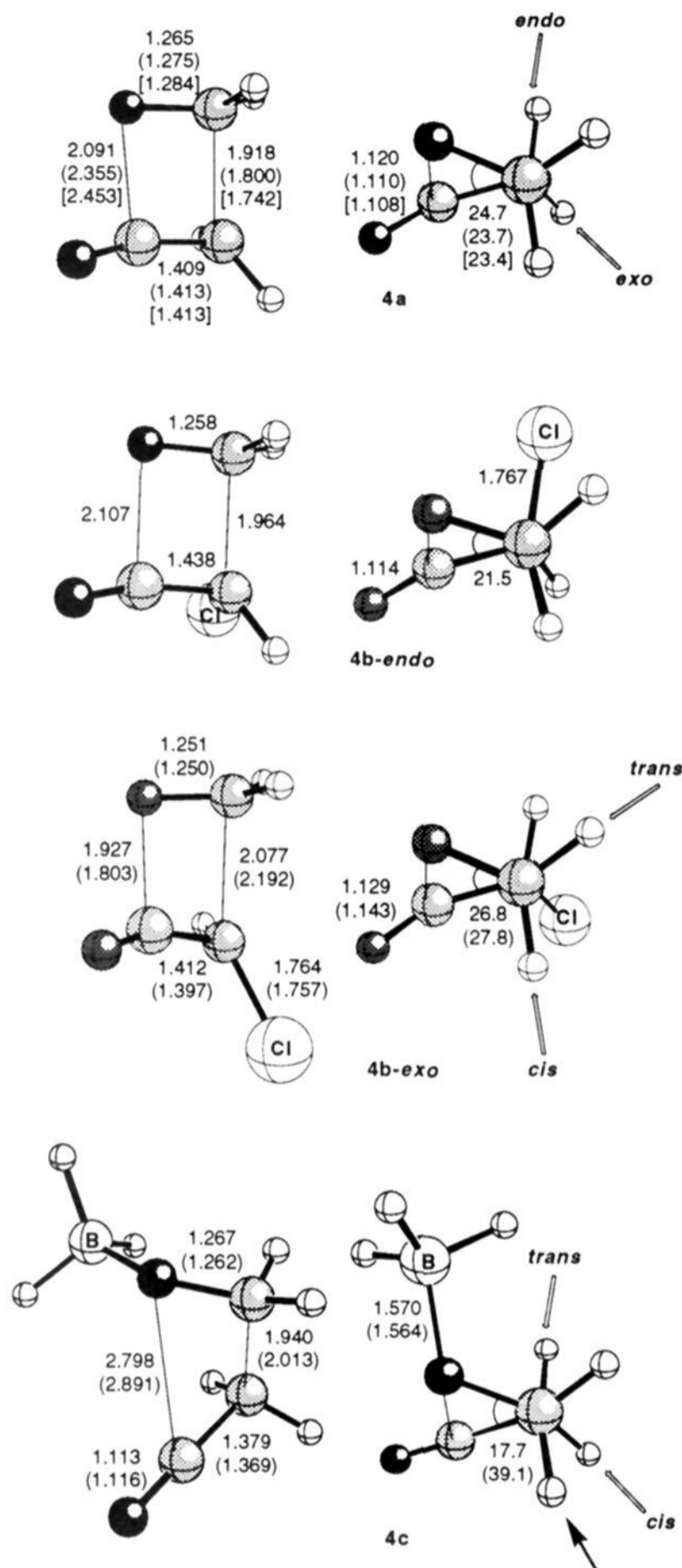


Figure 1. HF/6-31G* optimized geometries of the transition structures **4a-c**. Bond distances and angles are given in Å and deg, respectively. Numbers in parentheses and square brackets correspond to the values obtained in dichloromethane solution using the Onsager and Rinaldi-Rivail SCRF models, respectively (see text).

The $[\pi 2_s + (\pi 2_s + \pi 2_s)]$ interaction mode in TS's **4** imposes a certain torsion around the C_2-C_3 bond within the ketene moiety. As a consequence, the two substituents at the C_3 position are not equivalent. The Newman projection of TS **4a**, depicted in Figure 1, shows open arrows to indicate the two possible *endo* or *exo* orientations of the two hydrogens at C_3 . In order to obtain some information about the preferred interaction mode of a mono-substituted ketene, we have studied the reaction profile for the interaction between an electrophilic ketene such as chloroketene **1b** and formaldehyde. Two different TS's **4b**, corresponding to the *endo* and *exo* approaches, were found and characterized. The most important feature of TS's **4b** is the remarkable energy difference between the *endo* and *exo* structures (see Tables 1 and 2). The higher energy of **4b-endo** can be attributed to the

Table 1. Total Energies^a (au), Zero-Point Vibrational Energies^{a,b} (ZPVE, kcal/mol), and Spherical Cavity Radii^c (a_0 , Å) of the Stationary Points **1a**, **2a**, **3a-c**, and **4a-c**

structure	HF/6-31G*	ZPVE	MP2/6-31G*	a_0
1a	-151.72467 (-151.72564) [-151.72774]	21.5 (21.4) [21.3]	-152.14449 (-152.14534) [-152.14686]	3.13 [2.04, 2.39, 2.85]
1b	-610.60939 (-610.60989)	16.5 (16.4)	-611.15814 (-611.15857)	3.45
2a	-113.86633 (-113.86949) [-113.87174]	18.3 (18.3) [18.4]	-114.16525 (-114.16770) [-114.16898]	2.89 [2.12, 2.37, 3.70]
2b	-140.26802 (-140.27643)	39.9 (40.2)	-140.65461 (-140.66258)	3.43
3a	-265.64125 (-265.64678) [-265.65221]	46.8 (46.8) [46.8]	-266.36973 (-266.37433) [-266.37829]	3.51 [2.35, 2.98, 3.72]
3b	-724.53414 (-724.53775)	41.0 (40.9)	-725.39300 (-725.39595)	3.77
3c	-292.03925 (-292.05314)	67.1 (67.6)	-292.85250 (-292.86723)	3.89
4a	-265.52604 (-265.53273) [-265.54565]	42.9 (42.7) [42.8]	-266.26711 (-266.26728) [-266.27581]	3.52 [2.44, 3.09, 3.78]
4b-endo	-724.40417	36.6	-725.27194	3.79
4b-exo	-724.42069 (-724.42250)	37.1 (36.9)	-725.29615 (-725.29785)	3.80
4c	-291.96987 (-291.98356)	64.4 (64.0)	-292.79422 (-292.80611)	3.92

^a Single-point energies on HF/6-31G* optimized geometries. The numbers in parentheses and in square brackets correspond to values obtained in dichloromethane solution using the Onsager and the Rinaldi-Rivail models, respectively. ^b Vibrational energies calculated from frequencies obtained at the HF/6-31G* level. ^c Numbers in square brackets are the principal axes of the ellipsoids associated to the optimized solute structures.

electrostatic repulsion between the *endo* chlorine and the O_1 atoms, readily appreciable in the Newman projection of **4b-endo** in Figure 1. Consequently, the dihedral angle $C_2-C_3-C_4-O_1$ in **4b-endo** is 21.5° in order to minimize this repulsion, whereas in **4b-exo** this dihedral angle is 24.7° . In view of these results, it can be concluded that monosubstituted ketenes should interact exclusively through *exo* TS's, at least in the gas phase. As it can be appreciated in Tables 3 and 1 of the supplementary material, the TS **4b-exo** is earlier than **4a**, the calculated values for δB_{av} and Σq being 0.428 and 0.10, respectively. On the other hand, the bond order between O_1 and C_2 atoms is 0.256, whereas the bond order corresponding to the C_3-C_4 bond is now 0.376. As a consequence, **4b-exo** is a more synchronous TS than **4a**, the calculated synchronicity being 0.83. These results are consistent with the higher electrophilicity of chloroketene,^{16a} thus favoring the nucleophilic attack of O_1 over C_2 . The calculated activation energy for the reaction of chloroketene **1b** with formaldehyde is 9.8 kcal/mol lower than in the parent **1a** + **2a** → **3a** transformation (MP2/6-31G*//HF/6-31G*+ Δ ZPVE level, see Table 2). Therefore, the reaction between ketenes and carbonyl compounds is calculated to be facilitated using ketenes bearing electronegative atoms, in agreement with the available experimental data.¹

The reaction between nonactivated ketenes (i.e., ketenes incorporating stabilizing electrodonor substituents³⁷) is more difficult and usually requires the presence of Lewis acids to achieve acceptable yields.¹⁰ In order to study the catalytic effect of Lewis acids on this cycloaddition, we investigated the reaction profile corresponding to the interaction between ketene **1a** and the formaldehyde-BH₃ complex **2b** to yield the 2-oxetanone-BH₃ complex **3c** (see Figure 2). Extensive search on the potential energy surface led to the location of TS **4c**. Inspection of the structural data reported in Figure 1 for **4c** shows that this saddle point corresponds to a rather asynchronous TS, the distances

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Table 2. Activation Energies (ΔE_a) and Reaction Energies (ΔE_{rxn}) Obtained^{a,b} in the Reaction between Ketenes **1a,b** and Aldehydes **2a,b** To Form 2-Oxetanones **3a-c**

reaction	TS	level of theory	ΔE_a		ΔE_{rxn}	
			vacuum	CH ₂ Cl ₂	vacuum	CH ₂ Cl ₂
1a + 2a → 3a	4a	HF/6-31G*	40.8 (43.6)	39.2 (41.9) [33.8 (36.6)] ^c	-31.5 (-25.3)	-32.4 (-26.1) [-33.1 (-26.8)] ^c
		MP2/6-31G*	26.8 (28.9)	28.7 (30.7) [25.1 (27.9)] ^c	-37.6 (-31.4)	-38.5 (-32.2) [-39.2 (-32.9)] ^c
1b + 2a → 3b	4b-endo	HF/6-31G*	44.9 (46.5)		-36.7 (-31.2)	
		MP2/6-31G*	32.3 (33.9)		-43.7 (-38.2)	
1b + 2a → 3b	4b-exo	HF/6-31G*	34.5 (36.5)	35.7 (37.7)	-36.7 (-31.2)	-36.6 (-31.1)
		MP2/6-31G*	17.1 (19.1)	17.8 (19.8)	-43.7 (-38.2)	-43.7 (-38.2)
1a + 2b → 3c	4c	HF/6-31G*	14.3 (17.0)	11.6 (13.7)	-29.2 (-24.1)	-32.0 (-26.7)
		MP2/6-31G*	3.1 (5.8)	1.1 (3.2)	-33.5 (-28.4)	-37.2 (-31.9)

^a Single-point energies calculated on optimized HF/6-31G* geometries. All the differences in energy are given in kcal/mol. ZPVE corrected values in parentheses. ^b The values obtained in dichloromethane solution have been computed using the Onsager model, unless otherwise stated. ^c Values obtained using the Rinaldi-Rivail model.

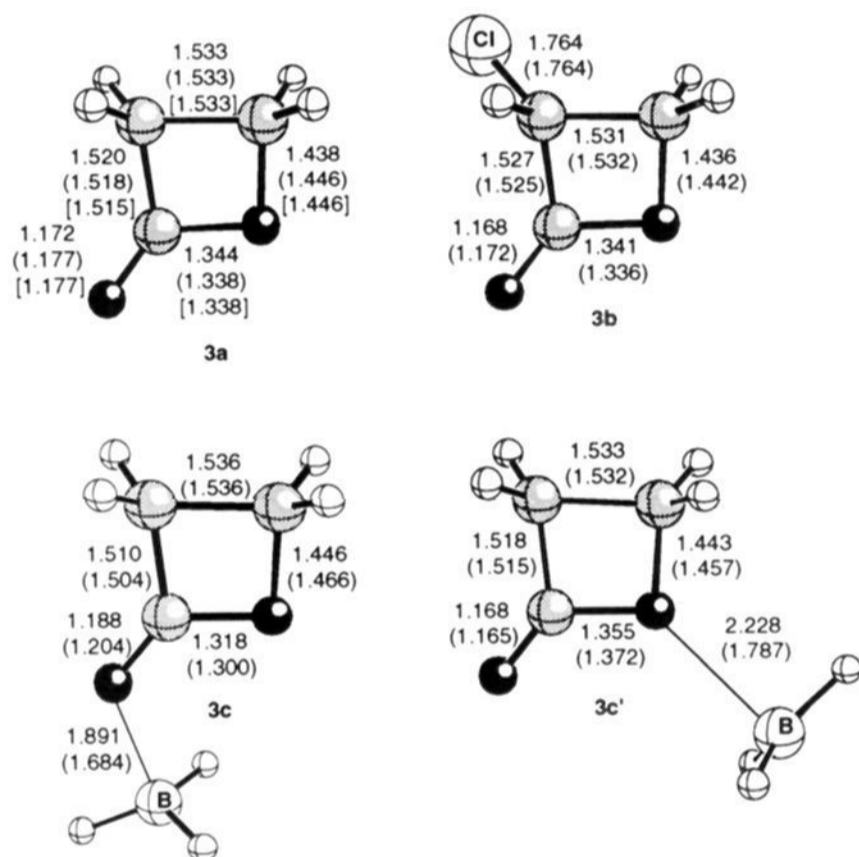


Figure 2. HF/6-31G* optimized geometries of β -lactones **3a-c**. Bond distances are given in Å. Numbers in parentheses and square brackets correspond to the values obtained in dichloromethane solution using the Onsager and Rinaldi-Rivail SCRF models, respectively (see text).

O_1-C_2 and C_2-C_3 being 2.798 and 1.940 Å, respectively. Moreover, the bond indices B_{12} and B_{34} are calculated to be 0.02 and 0.51 and the average value δB_{av} is 0.413 (see Table 3). Hence, **4c** is a relatively early and asynchronous TS. The calculated synchronicity is 0.68, the lowest value for S_y obtained in our study (see Table 3). Again, the virtually negligible value of the bond index B_{12} is almost exclusively responsible for the calculated asynchronicity. The distance between the boron atom and O_1 is 1.570 Å, which corresponds to a bond order of 0.53. These results evidence a strong interaction between both atoms. The calculated dihedral angle $C_2-C_3-C_4-O_1$ in **4c** is found to be very low in the gas phase (17.7°, see Figure 1). The conclusion of these results is that **4c** corresponds to a concerted two-stage reaction, according to the definition proposed by Dewar,^{27a} and consequently the orbital symmetry is not involved in its mechanism. In fact, the geometric and electronic features of **4c** are quite similar to those expected for intermediates of type **5**. The zwitterionic character of **4c** is also evidenced by the fact that in this TS the formaldehyde-BH₃ subunit bears an excess of almost a half electron ($\Sigma q = 0.40$, see Table 1 of the supplementary material) at the expense of the ketene fragment. All these data are consistent with the increasing electrophilicity of formaldehyde induced by the BH₃ group, resulting in a higher availability of the formaldehyde-BH₃ unit to accept charge from the ketene. It is also interesting to note

that in **4c** the BH₃ moiety has an *exo* disposition with respect to the forming 2-oxetanone ring. All our attempts to locate a similar TS bearing an O_1 atom having *exo* lone pairs failed. Therefore, for this reaction we have found the reverse lone pair effect with respect to that reported by Houk *et al.*^{32,38} for hetero-Diels-Alder reactions. This is not surprising, since these authors attributed the *exo* lone pair effect to electrostatic repulsions between the heteroatom lone pairs and the diene π electrons when the lone pairs are *endo*. In our case, the electron deficient character of the ketene moiety of TS **4a** favors the *endo* orientation of the O_1 lone pairs. The calculated activation energy for the **1a + 2b → 3c via 4c** is found to be only 5.8 kcal/mol at the MP2/6-31G*//HF/6-31G*+ Δ ZPVE level. As we have commented above, this value is probably somewhat low, but it correctly reflects the catalytic effect of the Lewis acid. Thus, the calculated decrease in activation energy with respect to the parent transformation **1a + 2a → 3a via 4a** is 23.1 kcal/mol at the same level of theory. This decrease in activation energy is much higher than those found by Houk *et al.*³² for the Diels-Alder reaction between butadiene and formaldehyde coordinated to BH₃ (12.0 kcal/mol at the MP2/6-31G*//HF/6-31G* level). According to our calculations the reaction energy of the catalyzed reaction is not more exothermic than the parent **1a + 2a → 3a** process. This is due to a slightly higher strength in the binding interaction between the BH₃ complex **2b** with respect to **3c**. The binding energy for **3c** is calculated to be 8.7 kcal/mol (MP2/6-31G*//HF/6-31G*+ Δ ZPVE level), whereas for **2b** it is 12.1 kcal/mol at the same level (see Table 2 of the supplementary material). Figure 2 shows the main geometric features of the 2-oxetanone-BH₃ complex **3c**. It is interesting to note that the calculated bond index between O_5 and the boron atom is 0.28. It may be noted also that the O_1-C_2 distance is shorter for **3c** than for **3a**, and the C_2-O_5 distance is higher. In addition, the charge of O_1 is lower in **3c** than in **3a**. These results indicate that the polar resonance structure **IV** contributes significantly to the actual structure of **3c** (Scheme 2). We have also located another minimum **3c'** for the 2-oxetanone-BH₃ complex, in which the boron atom interacts with the O_1 atom, the corresponding bond index being 0.12. This structure is calculated to be 2.2 kcal/mol less stable than **3c** at the MP2/6-31G*//HF/6-31G*+ Δ ZPVE level of theory (see Table 2 of the supplementary material). This agrees with experimental evidence, for it is known that Lewis acids preferably interact with carbonyl oxygens in esters and related carboxylic acid derivatives.³⁹

SCRF Calculations. The next step in our investigation was to study the solvent effect on the basic features of the reaction and to compare these features with those observed for the gas phase. First, we reoptimized the stationary points **1a-4a** using the

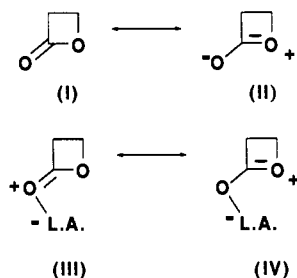
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Table 3. Bond Indices^{a,b} of TSs **4a–c** and Synchronicities^{a,c} (S_y) Obtained for the Reaction^d between Ketenes **1a,b** and Aldehydes **2a,b** To Yield 2-Oxetanones **2a–c**

TS	B_{12}		B_{23}		B_{34}		B_{14}		δB_{av}		S_y	
	$\epsilon = 1$	$\epsilon = 9.08$	$\epsilon = 1$	$\epsilon = 9.08$	$\epsilon = 1$	$\epsilon = 9.08$	$\epsilon = 1$	$\epsilon = 9.08$	$\epsilon = 1$	$\epsilon = 9.08$	$\epsilon = 1$	$\epsilon = 9.08$
4a	0.172	0.072	1.279	1.231	0.525	0.635	1.277	1.249	0.476	0.498	0.79	0.72
4b-endo	0.148		1.185		0.471		1.310		0.466		0.79	
4b-exo	0.256	0.345	1.293	1.348	0.376	0.306	1.336	1.339	0.428	0.402	0.83	0.88
4c	0.018	0.019	1.322	1.372	0.508	0.449	1.240	1.268	0.413	0.368	0.68	0.68

^a Properties computed from RHF/6-31G* wave functions. ^b Natural localized molecular orbital bond indices. ^c Synchronicities calculated from eqs 2–4 (see text). ^d The quantities obtained in dichloromethane solution ($\epsilon = 9.08$) have been computed using the Onsager model.

Scheme 2^a

^a L.A. = Lewis acid.

Table 4. Multipole Contributions, Total Values of the Electrostatic Part of the Solvation Energy (ΔE_e , kcal/mol), and Total Solvation Energies (ΔE_T , kcal/mol) Using the HF/6-31G* Calculations at the Gas-Phase Geometry with the Gas-Phase Electronic Distributions^a

structure	$l = 1$	$l = 2$	$l = 3$	$l = 4$	ΔE_e	ΔE_T
1a	-0.43 (-0.83)	-0.74 (-0.89)	-0.05 (-0.17)	-0.09 (-0.03)	-1.43	(-2.08)
2a	-1.10 (-3.47)	-0.34 (-0.24)	-0.01 (-0.20)	-0.03 (-0.03)	-1.48	(-3.92)
3a	-2.17 (-5.94)	-1.55 (-1.31)	-0.20 (-0.42)	-0.14 (-0.07)	-4.23	(-8.09)
4a	2.56 (-11.80)	-0.80 (-1.92)	-0.93 (-2.06)	-0.31 (-0.54)	-4.83	(-16.62)

^a Numbers in parentheses correspond to the values (in kcal/mol) obtained for the optimized geometries and for the polarized density matrices.

Onsager model as implemented in GAUSSIAN 92. The geometric features of TS **4a** and product **3a** are shown in Figures 1 and 2, respectively. The total and zero-point vibrational energies are reported in Table 1, as well as the corresponding spherical cavity radii. Inspection of these data indicates that the purely electrostatic Onsager model predicts a slight increase of the asynchronicity of the reaction. Thus, the O_1-C_2 and C_3-C_4 bond distances are now 0.264 Å higher and 0.118 Å lower, respectively, than the corresponding values obtained *in vacuo*. The bond indices B_{12} and B_{34} vary accordingly (see Table 3) and, as a consequence, the synchronicity of the reaction is calculated to be lower than those obtained for the gas phase. Inspection of the data reported in Table 2 reveals that the electrostatic solvation energies computed using the Onsager model stabilize similarly the reactants **1a** and **2a**, product **3a**, and TS **4a**. Therefore, the activation and reaction energies should not vary significantly with respect to those obtained in the gas phase. In order to find out whether the rather drastic simplifications introduced in the Onsager model could cause an incorrect description of the reaction profile, we have recalculated all the stationary points **1a–4a** using the more sophisticated Rinaldi–Rivail model. The energies and the structural features of these stationary points can be found in Tables 1 and 4, as well as in Figures 1 and 2. Our results indicate that the profile of the reaction does not change significantly when a more elaborated model of the solute–solvent interaction is used. The Rinaldi–Rivail model describes, however, saddle point **4a** as a slightly more asynchronous TS, the O_1-C_2 and C_3-C_4 bond distances being 2.453 and 1.742 Å (see Figure 1). The optimized geometries of reactants **1a** and **2a** as well as those of product **3a**

(see Figure 2) are almost coincident to those obtained with the Onsager model. In Table 4 we have included the multipole contributions to the electrostatic part of the solvation energy, computed using the isolated geometries of the stationary points **1a–4a** and the gas-phase density matrix. We have also included the same data obtained from the optimized solvated structures and the polarized density matrix. As can be seen, the dipole contributions to the solvation energy ($l = 1$ values) are more important than those attributable to higher multipoles, with the only exception being ketene **1a**. Thus, the dipole contributions in formaldehyde **2a** and 2-oxetanone **3a** are approximately 88% and 73% of the total electrostatic part of the solvation energy. In the case of the TS **4a**, the dipole contribution constitutes 71% of that energy. In addition, although the differences between the electrostatic and total solvation energies are not negligible (see the values of ΔE_e and ΔE_T in Table 4), the activation and reaction energies are found to be comparable to those obtained with the Onsager model. Thus, the activation energy of the **1a** + **2a** → **3a** reaction is found to be 27.9 kcal/mol at MP2/6-31G*//HF/6-31G*+ $\Delta ZPVE$ level. This activation energy is 2.8 kcal/mol lower than those computed with the Onsager model. The calculated reaction energy is -32.9 kcal/mol, at the same level of theory, which is almost coincident with those found by means of the Onsager model. All these results suggest that not accounting for the contribution of higher multipoles, as well as the cavitation and dispersion energies, can be considered a reasonable approximation for this particular reaction. Therefore, the simple Onsager model constitutes an accurate enough tool for studying the principal variables that can be significant in the [2 + 2] cycloaddition reaction between ketenes and carbonyl compounds. The remaining results discussed in this study have been obtained with the Onsager model.

As has been found in the preceding section, the reaction of a monosubstituted ketene such as chloroketene **1b** can take place *via* the corresponding *endo* and *exo* TS's. However, all our attempts to optimize the **4b-endo** TS in dichloromethane solution failed. We used as a starting point the previously optimized gas-phase geometry, and we tried all the algorithms available in GAUSSIAN 92. In all the cases studied, the initial geometries converged to either the reactants, the products, or the **4b-exo** TS upon optimization. We have also explored the potential energy hypersurface in the neighborhood of **4b-endo** in order to locate an *endo* TS which could differ substantially from the gas-phase geometry. However, all our efforts were in vain. By contrast, the TS **4b-exo** was readily located and characterized. In the preceding section we have shown that **4b-endo** is much higher in energy than **4b-exo**, so it is expected that, even assuming that in other cases the *endo* TS's could be located, the [2 + 2] cycloaddition between activated ketenes and carbonyl compounds should take place through *exo* TS's. Although the activation and reaction energies of the **1b** + **2a** → **2b** reaction in solution are similar to those obtained for the gas phase, the main features of **4b-exo** reveal significant differences with respect to the *in vacuo* results. Thus, this TS is now slightly earlier ($\delta B_{av} = 0.402$) and more synchronous ($S_y = 0.88$) than its gas-phase analog. Inspection of Table 3 reveals that the presence of the solvent favors the nucleophilic attack of O_1 over C_2 , and as a consequence

the O₁-C₂ bond is more advanced ($B_{12} = 0.345$) than the C₃-C₄ bond ($B_{34} = 0.306$) at **4b-exo**, thus resulting in a more synchronous TS. The C₃-C₄ bond distance is 0.115 Å higher than in the gas phase and therefore the substituent of the ketene lies away from the substituents of the C₄ atom. In addition, looking at the Newman projection of **4b-exo** depicted in Figure 1, we can observe that the *cis* and *trans* positions, which could be occupied by the substituents of an aldehyde, are nearly equivalent because of the large C₃-C₄ bond distance, the value of the C₂-C₃-C₄-O₁ dihedral angle, and the *exo* disposition of the chlorine atom. As a consequence the TS's leading to the corresponding *cis*- and *trans*-2-oxetanones should be of comparable energy. Therefore, the geometry of **4b-exo** provides a model for explaining the low stereocontrol observed¹¹ in the [2 + 2] cycloaddition reaction between monosubstituted ketenes and aldehydes.

In the case of the catalyzed reaction corresponding to the interaction between the BH₃-formaldehyde complex **2c** and ketene **1a**, it was expected that the highly polar character of the TS **4c** (*vide supra*) should produce significant changes in its geometry and in the energy of activation corresponding to the **1a** + **2b** → **3c** process. This was indeed the case, and the activation energy for the catalyzed reaction in solution was found to be 2.6 kcal/mol lower than in the gas phase, at the MP2/6-31G*//HF/6-31G*+ΔZPVE level. In fact, the calculated energy of activation is only 3.2 kcal/mol at the same level, which seems too low. In any case, it is reasonable to conclude that the presence of a Lewis acid catalyst and, to a lesser extent, an organic solvent of intermediate polarity induces an important decrease in the activation energy of the [2 + 2] cycloaddition reaction between ketenes and carbonyl compounds. The electrostatic interaction between the solute and the solvent also generates substantial variations in the geometry of TS **4c**. As in the preceding cases, the geometry of **4c** in solution corresponds to an earlier TS, the δB_{av} magnitude being 0.368, the lowest value for this magnitude found in our study. The C₃-C₄ bond is developed to a slightly lesser extent than in the gas phase, with the corresponding bond distance and bond index being 2.013 Å and 0.449, respectively (see Figure 1 and Table 3). In addition, the O₁-C₂ distance is also *ca.* 0.1 Å higher than in the gas phase, and the bonding between the O₁ and C₂ atoms is still negligible. As a result, **4c** is an earlier TS in solution, whereas the synchronicity of the process remains unchanged with respect to the gas phase. However, the most important feature of **4c** in solution is the higher value of the C₂-C₃-C₄-O₁ dihedral angle (39.1° in solution, whereas the value of this dihedral angle is 17.7° *in vacuo*, see Figure 1). Again, the BH₃ subunit is in an *exo* disposition with respect to the 2-oxetanone ring in formation. These results in solution provide a model for understanding why the Lewis acid catalyzed reaction between monosubstituted ketenes and aldehydes leads predominantly to *cis*-2-oxetanones, specially when bulky catalysts are used.^{10c} First, let us assume that the aldehyde coordinates to the Lewis acid using the lone pair which is *anti* with respect to the substituent,⁴⁰ represented by a black arrow in the Newman projection of **4c** depicted in Figure 1. With this disposition, the *cis*- and *trans*-2-oxetanones will be generated from the positions indicated by the open arrows pointing to the C₄ hydrogens of structure **4c**. Therefore, the Newman projection

of this TS reveals that the *trans* position interacts unfavorably with the Lewis acid, because of the steric repulsion imposed by the high value of the C₂-C₃-C₄-O₁ dihedral angle. Although a favorable electrostatic interaction could stabilize the *trans* TS, the nature of the catalysts as well as the aldehydes usually employed in this reaction¹⁰ suggests that this kind of interaction should not play a significant role. Therefore, preferential formation of the *cis* isomer should be expected. Of course, a bulky catalyst is required in order to achieve good stereocontrol.

The main variation in the equilibrium geometries of solvated 2-oxetanones **4a-c** with respect to those found in the gas phase is the shortening of the O₁-C₂ bond distances and the corresponding enlargement of the C₂-O₃ bond distances (see Figure 2). This variation in the bond distances is particularly remarkable for BH₃-coordinated 2-oxetanone **3c**. In addition, this latter structure exhibits a considerable shortening in the O₅-B bond distance (*ca.* 0.2 Å, see Figure 2), thus resulting in a 0.43 bond index between both atoms. These results suggest that solvation causes a higher contribution of the resonance forms **II** and **IV** represented in Scheme 2. The binding energy in solution for **3c** is 14.6 kcal/mol at the MP2/6-31G*//HF/6-31G*+ΔZPVE level, 5.9 kcal/mol higher than in the gas phase. Complex **3c'** also shows a considerable shortening in the O₅-B distance (0.441 Å, see Figure 2) and a concomitant enhancement of the corresponding bond index (0.32 instead of the 0.12 value found in the gas phase). However, the **3c** complex is still 3.4 kcal/mol more stable than **3c'** (MP2/6-31G*//HF/6-31G*+ΔZPVE results, see Table 2 of the supplementary material), in agreement with experimental evidence (*vide supra*).

Conclusions

The following conclusions can be drawn from the results reported in this study: (a) the uncatalyzed [2 + 2] cycloaddition between ketenes and carbonyl compounds is predicted to be a relatively synchronous concerted process, with a [τ_2 + (τ_2 + τ_2)] arrangement in the transition state; (b) monosubstituted ketenes interact preferentially through *exo* transition states, resulting in a low stereocontrol in the *cis/trans* ratio of the corresponding 2-oxetanones; (c) Lewis acid catalysis produces an important decrease in the activation energies of the process, *via* a two-stage concerted mechanism, in which the catalyst is *exo* with respect to the 2-oxetanone forming ring. The solvated TS explains the changes in stereoselectivity observed in the catalyzed reaction.

In our opinion, the simple models exposed in this work provide an explanation of the origins of the stereochemical outcome of the reaction and could stimulate new experimental efforts in this area, in order to improve the stereoselectivity of the process, specially for the catalyzed reaction.

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Supplementary Material Available: Tables including the NPA charges of structures **1-4** and binding energies for structures **2b**, **3c** and **3c'**; Cartesian coordinates of all the structures discussed in this work (9 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(40) This is in agreement with the experimental evidence available. See ref 39. See also: (a) Reetz, M. T.; Hüllmann, M.; Massa, W.; Berger, S.; Rademacher, P.; Heymanns, P. *J. Am. Chem. Soc.* **1986**, *108*, 2405. (b) Denmark, S. E.; Henke, B. R.; Weber, E. *J. Am. Chem. Soc.* **1987**, *109*, 2512. (c) Mahadevan, C.; Seshasayee, M.; Kothival, A. S. *Cryst. Struct. Commun.* **1982**, *11*, 1725. (d) Honeychuck, R. V.; Bonnesen, P. V.; Farahi, J.; Hersh, W. H. *J. Org. Chem.* **1987**, *52*, 5293.