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The Cycloaddition Reaction Between α-Bromo Vinylketenes and Imines: A Combined Experimental and Theoretical Study

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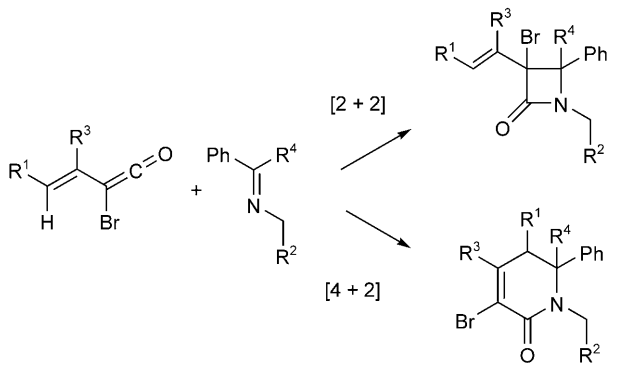
Abstract: The unusual behaviour of α-bromo vinylketenes in the cycloaddition reactions with imines is described. This class of vinylketenes behaves as dienophiles in [2+2] reactions, but also displays an unusual diene reactivity in [4+2] reactions. Interestingly, the reactivity of α-bromo vinylketenes can be modulated *via* a fine tuning of the substituents. For instance, a methyl group in the β-position completely inhibits the [2+2] reaction and the [4+2] pathway is almost exclusively followed. A more hindered ketimine (instead of a simple imine) is enough to activate again the [2+2] mechanism. We have carried out a DFT theoretical investigation to rationalise these experimental observations. We have considered two pathways for the [2+2] reaction involving imine, that is, the *endo* and *exo* pathways. The former is favoured in the case of α-bromo vinylketenes, while the latter is preferred for non-substituted vinylketenes. Since the [4+2] cycloaddition becomes possible only when the *s-Z*-conformation of vinylketene is significantly populated, the presence of bromine substituents in this substrate is crucial in determining the [2+2] or [4+2] mechanisms. For unsubstituted vinylketenes, the barrier connecting the *s-E*- to the *s-Z*-conformation is too high to be easily overcome. Thus, the *s-Z*-structure has a low population and the [2+2] mechanism is favoured. In the case of α-bromo vinylketenes (especially the β-methyl-substituted ones), this barrier can be surmounted and the [4+2] mechanism becomes available.

Keywords: azetidinones; α-bromo vinylketenes; cycloaddition; DFT computations; pyridinones; reaction mechanism

Introduction

Ketenes exhibit a very peculiar cycloaddition chemistry because of their structural and electronic properties.[1,2] One of the most valuable and exploited cycloaddition of ketenes is unquestionably the reaction with imines to afford β-lactams, which was discovered by Staudinger at the beginning of the 20th century.[3] In view of the importance of β-lactams in medicinal chemistry as antibacterial agents[4–8] and enzymatic inhibitors,[9–12] the Staudinger reaction has been extensively studied and a large number of experimental[13–25] and theoretical[26–40] papers are now available in the literature.

An interesting class of ketenes are vinylketenes, that have been demonstrated to be versatile building blocks in cycloaddition reactions with various double bonds.[41–45] They behave as electron-deficient dienophiles in [2+2] cycloadditions with electron-rich partners and as a diene component in [4+2] cycloadditions with electron-poor species.[28,46] Vinylketenes usually react with imines *via* the Staudinger reaction and, to the best of our knowledge, only silyl-vinylketenes have been shown to undergo [4+2] cycloaddition with imines.[47,48] However, we have recently carried out an experimental investigation on the reactivity of a new class of vinylketenes, the α-bromo-vinylketenes, with imines[49] and we have described successful synthetic routes toward α-bromo-substituted 4-alkyl-5,6-diyhdropyridin-2-ones. Halogen substituents[22,50–56] dramatically affect the α-bromo-vinylketene reactivity in the cycloaddition to imines, promoting an unusual diene behaviour. A fine tuning of the substituents on both vinylketene and imine moieties allows us to selectively obtain [2+2] or [4+2] products (Scheme 1). Moreover, these heterocycles are suitable for further manipulations that involve the substitution of the halogen atom and the transforma-



Scheme 1. Synthesis of 3-bromo-3-alkenylazetidin-2-ones and 3-bromo-4-alkyl-5,6-dihydropyridin-2-ones.

tion of the double bond.[57–63] Furthermore, it is interesting to note that derivatives of 3-bromo-3-alkenylazetidin-2-ones and 3-bromo-4-alkyl-5,6-diyhdropyridin-2-ones have been shown to behave as inhibitors of the ACAT enzyme and antagonists of $\alpha_v\beta_3$ and $\alpha_5\beta_1$ integrins, respectively.[64–67]

Herein we report an advanced investigation on the synthesis of four- and six-membered lactams *via* cycloaddition reactions between α-bromo vinylketenes and imines. Furthermore, we describe the results of a theoretical study aimed to elucidate the mechanism of these reactions and the origin of their stereoselectivity. Our work provides a rationalisation for the unusual behaviour of this class of vinylketenes.

Experimental Results

Reaction of Linear α-Bromo Vinylketenes with Imines

Recently, we have investigated the straightforward synthesis of 3-bromo-3-alkenylazetidin-2-ones *via* he Staudinger reaction between α-bromo vinylketenes and an imine. The α-bromo vinylketenes **1a** and **1b** were prepared *in situ* starting from α-bromohexenoyl chloride and α-bromocrotonyl chloride, respectively, in the presence of triethylamine.

The cycloaddition reaction of α-bromo vinylketenes **1a**, **b** with imines **2a–d** occurred preferentially *via* a [2+2] mechanism, affording, as major products, the *cis*-β-lactams **3a–d** and **6a**. The formation of the six-membered 5,6-dihydropyridin-2-ones **5a–d** and **8a** could not be avoided, even using a variety of experimental conditions (see Scheme 2).

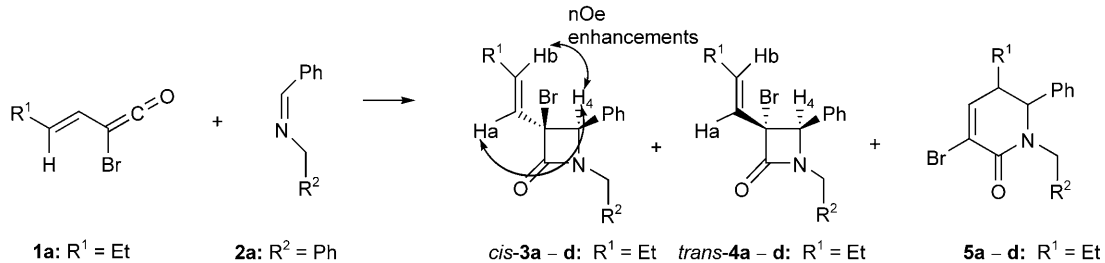
The reaction of vinylketenes with imines, reported several years ago by Bose and Manhas,[68–71] afforded 3-alkenyl-azetidin-2-ones exclusively, no traces of the six-membered lactams being observed. Thus, our results prompted us to investigate the effect of the halogen on the reactivity of the intermediate ketene.

The reaction of α-bromo vinylketene **1a** with imine **2a** was carried out under a number of different conditions in order to increase the yield and selectivity in the formation of the 3-Br-3-alkenyl-β-lactam. The best result in terms of diastereoselectivity could be obtained in CH_2Cl_2 at reflux by adding α-bromohexenoyl chloride to a hot solution of imine **2a** and TEA. Following this procedure, β-lactams **3a–d**, **4a–d** and **6a**, **7a** were obtained in good yield and high selectivity favouring the *cis*-isomer. However, these products were associated with a significant amount of **5a–d** and **8a** (see data reported in Table 1). Product distribution was determined by ^{1}H NMR integration of distinctive key signals and by the yields of the individual isomers obtained after chromatographic separation.

Table 1. Reaction of vinylketenes **1a–b** with imines **2b–d**.

Entry	Ketene	Imine	**3**+**4** [%][a]	**3**:**4** [%]	**5** [%][a]
1	**1a**	**2a**	57	95:5	22
2	**1a**	**2b**	60	80:20	27
3	**1a**	**2c**	50	80:20	23
4	**1a**	**2d**	55	93:7	14
5	**1b**	**2a**	30	90:10	15

[a] Reported yields refer to isolated products. A small amount of amide was observed in all the reactions.



1a: R^1 = Et
1b: R^1 = H

2a: R^2 = Ph
2b: R^2 = *p*-MeO-C_6H_4
2c: R^2 = CH=CH_2
2d: R^2 = CH_2COOEt

cis-**3a** – **d:** R^1 = Et
cis-**6a:** R^1 = H

trans-**4a** – **d:** R^1 = Et
trans-**7a:** R^1 = H

5a – **d:** R^1 = Et
8a: R^1 = H

Scheme 2. Reaction of **1a** and **1b** with imines **2a–d**.

The obtained compounds **3b–d** and **4b–d** were exclusively characterised by an *E* configuration at the double bond of the side chain, as shown by the coupling constant ($J = 15.6$ Hz). The *cis*-configuration of **3** was established by nOe experiments using DPFGSE pulse sequence (see Supporting Information for details).

Isomer **3** exihibited a strong nOe between H-4 and the double bond protons on C-3, which indicated a *cis* relationship between these two moieties. The same experiment performed on the minor isomer **4** did not show any nOe effect, thus suggesting a *trans* geometry between H-4 and the alkenyl group.

Staudinger reactions carried out with α-bromo vinylketenes **1a**, **b** and imine **2e** [obtained from benzaldehyde and (*S*)-1-phenylethylamine], afforded enantiomerically pure β-lactams (Scheme 3). Although four stereoisomers could possibly arise from this reaction, complete *cis*-diastereoselectivity was observed and mixtures of *cis*-β-lactams, together with a considerable amount of δ-lactams, were isolated both in the case of **1a** and **1b**.

The major isomer **3e** was isolated by flash chromatography as a sticky oil, while the minor isomer **4e** was a solid that was crystallised from methanol. The (1*S*′,3*S*,4*R*) absolute configuration of **4e** was established by X-ray diffraction (Figure 1). On the basis of these considerations, the assignment of the (1*S*′,3*R*,4*S*) absolute configuration to **3e** could be made. The comparison of the ^{1}H NMR data for **3e** and **4e** and the data for **6e** and **7e** showed a complete regularity that allowed the (1*S*′,3*R*,4*S*) configuration of **6e** and the (1*S*′,3*S*,4*R*) configuration of **7e** to be attributed.

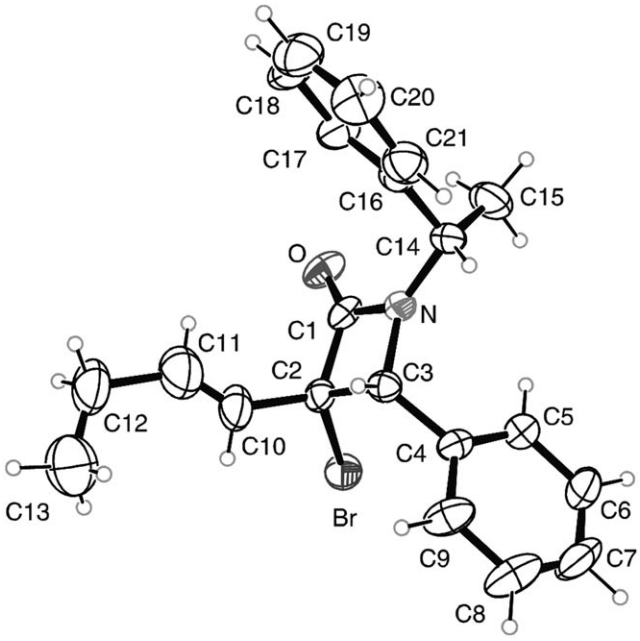
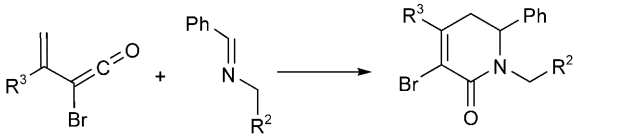


Figure 1. ORTEP diagram of **4e**.

Reaction of β-Substituted α-Bromo Vinylketenes with Imines

We observed that the diene behaviour of α-bromo vinylketenes could be enhanced by the introduction of a branch in the β position. Actually, the [4+2] pathway was exclusively followed in the reactions of **1c**, **d** with imines **2a–d**, and the dihydropyridinones **9a–e** could be obtained in high yields, as we reported in a previous paper.[57] Indeed, α-bromo vinylketene **1d** was prepared with excellent regioselectivity treating 2-bromo-3-methyl-2-hexenoyl chloride with 2equiv. of TEA, despite the possibility of deprotonation of the methylene group to give an isomeric vinylketene.[72]

No trace of the β-lactam was detected in the HPLC analysis and in the ^{1}H NMR spectra of the crude reaction mixture (Scheme 4).

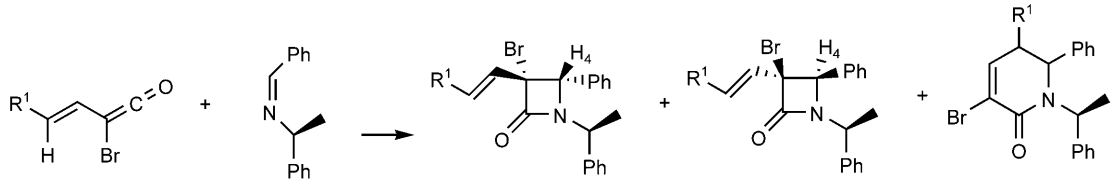


1c: $R^3 = CH_3$
1d: $R^3 = n\text{-}C_3H_7$

2a – d

9a: R^3 =Me, R^2 = Ph
9b: R^3 =Me, R^2 = PMP
9c: R^3 =Me, R^2 = CH=CH_2
9d: R^3 =Me, R^2 = CH_2COOEt
9e: $R^3 = n\text{-}C_3H_7$, R^2 = Ph

Scheme 4. Reaction of β-substituted-α-bromo vinylketenes **1c–d** with imines **2a–d**.



1a: R^1 = Et
1b: R^1 = H

2e

3e: R^1 = Et
6e: R^1 = H

4e: R^1 = Et
7e: R^1 = H

5e: R^1 = Et
8e: R^1 = H

Scheme 3. Reaction of **1a** and **1b** with imine **2e**.

The detailed investigation of the reaction conditions showed that the best results could be obtained when **1** and **2** were refluxed in CH_2Cl_2. Under these reaction conditions, **9a–e** were obtained in excellent yields (see Table 2).

Table 2. Formation of 3-bromo-4-alkyl-5,6-dihydropyridin-2-one **3** *via* ketene-imine cyclisation.

Entry[a]	Ketene	Imine	Product	Yield [%][b]
1	**1c**	**2a**	**9a**	92
2	**1c**	**2b**	**9b**	92
3	**1c**	**2c**	**9c**	96
4	**1c**	**2d**	**9d**	64
5	**1d**	**2e**	**9e**	94

[a] Reactions were performed in CH_2Cl_2.
[b] Yields correspond to the compounds purified by flash chromatography on silica gel.

Good yields and moderate diastereoselectivities were observed in the reactions of **1c** and **1d** with the chiral imine **2e** (98% yield and 62/38 *dr* for the reaction of **1c**, 55% yield and 68/32 *dr* for **1d**). The dihydropyridinones **10**/**11** and **12**/**13** (see Scheme 5) were easily separated and fully characterised by NMR spectroscopy and LC-MS analysis.

Reaction of α-Bromo Vinylketenes with Ketimines

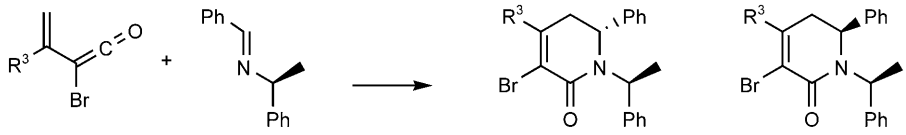
The results above reported indicate that linear α-bromo vinylketenes **1a** and **1b** react with imines preferentially giving β-lactams, while β-substituted-α-bromo vinylketenes **1c** and **1d** afford exclusively six-membered rings. In order to gain deeper insight into the problem, we studied the influence of the imine substitution on the reactivity, by treating α-bromo vinylketenes **1a–c** with the ketimines **2f** and **2g**, derived from benzophenone (Scheme 6).

The experimental results demonstrate that the substitution of the imine hydrogen with a phenyl group dramatically inhibits the strong preference of **1c** for the [4+2] mechanism, selectively leading to 3-bromo-3-alkenylazetidin-2-ones (Table 3).

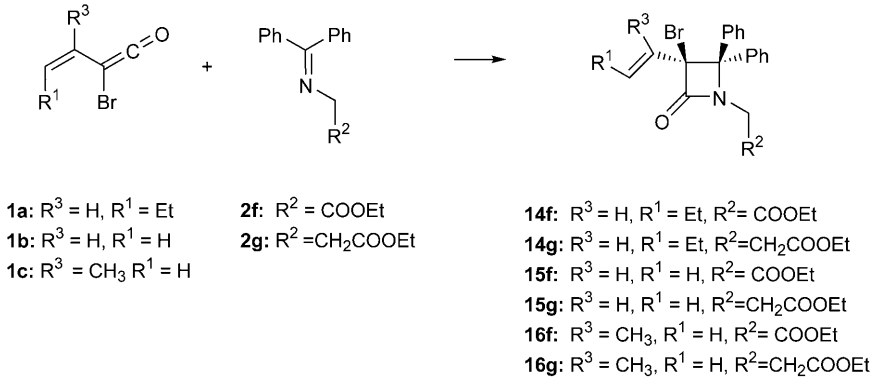
Table 3. Formation of 3-bromo-3-alkenylazetidin-2-ones *via* ketene-ketimine cyclisation.

Entry[a]	Ketene	Ketimine	Product	Yield [%][b]
1	**1a**	**2f**	**14f**	97
2	**1a**	**2g**	**14g**	84
3	**1b**	**2f**	**15f**	93
4	**1b**	**2g**	**15g**	90
5	**1c**	**2f**	**16f**	80
6	**1c**	**2g**	**16g**	87

[a] Reactions were performed in CH_2Cl_2.
[b] Yields correspond to the compounds purified by flash chromatography on silica gel.



Scheme 5. Reaction of **1c** and **1d** with the chiral Schiff base **2e**.



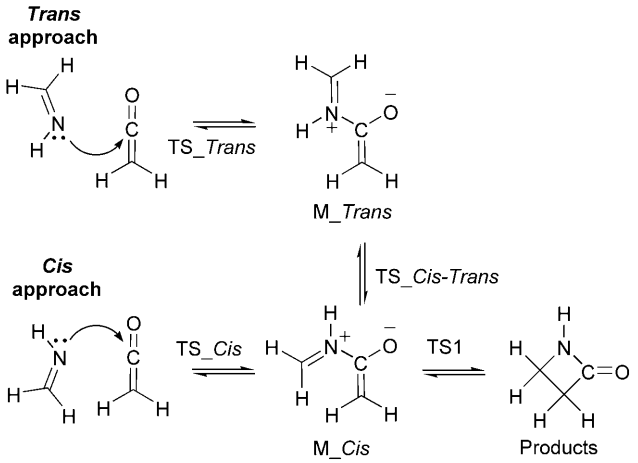
Scheme 6. Reaction of α-bromo vinylketenes with ketimines **2f** and **2g**.

These results clearly indicate that, in the cycloadditions between α-bromo vinylketenes and imines, substituents can be carefully changed to drive the reaction toward the [2+2] or the [4+2] pathway and to selectively obtain β-lactams or δ-lactams.

Computational Results

Choice of the Model System and Computational Details

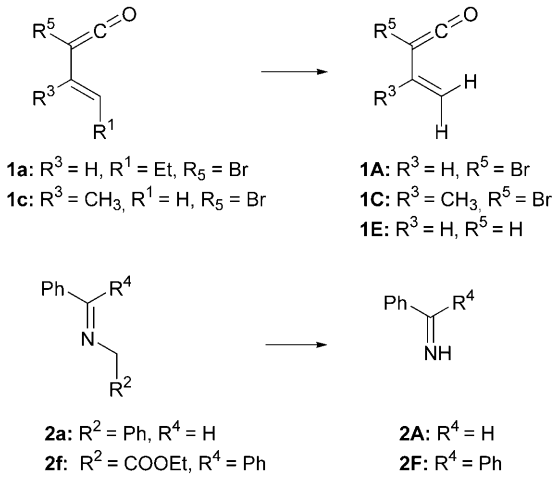
All computations have been performed at the DFT/B3LYP/DZVP[73–75] level, using the *Gaussian03* package.[76] Geometry optimizations have been carried out in the presence of solvent effects (dichloromethane), which have been simulated by the SCRF-CPCM[77–80] method. To validate this computational approach, we have investigated at the same theoretical level a model system where the addition involves an unsubstituted imine and an unsubstituted ketene (see Scheme 7). Then, we have compared our results to



Scheme 7. Possible paths for the reaction between ketene and imine.

those obtained for the same reaction by Venturini and Gonzalez at the CASSCF-CASPT2 level.[27] The DFT computations in the gas phase (see Figure S1 and Table S1 in the Supporting Information) have provided energy and structural data similar to the CASSCF ones. As outlined by Venturini[27] no transition state connecting the two intermediates **M**_*Cis* and **M**_*Trans* (i.e., **TS**_*Cis-Trans*) could be found in the gas phase. Besides, according to what was suggested by this author, the inclusion of the solvent (dichloromethane) effects *via* the SCRF method, afforded a different reaction profile. Since the solvent helps the stabilisation of the structures with charge separation (see Scheme 7), the transition state **TS**_*Cis-Trans*, which represents a "gate" between the two pathways corresponding to *Cis* and *Trans* approaches, could be easily located. Thus, the inclusion of the solvent is of paramount importance in determining the shape of the potential energy surface related to these reactions. Moreover, no influence of unpaired spin states has been detected: single point calculations on the various critical points, using either restricted (B3LYP) or unrestricted (UB3LYP) methods, provide identical results and stable wave functions. For these reasons, a restricted DFT formalism has been chosen and used throughout the work. Geometry optimisation has been carried out in redundant internal coordinates[81] and the nature of the various critical points has been determined by frequency calculations.

To lower the demand of computational time, all calculations have been carried out on model systems simpler than the real molecules used in the experiment (Scheme 8). In particular, vinylketenes have



Scheme 8. Model systems (**1A**, **1C**, **1E** and **2A**, **2F**) used in the computational study.

been emulated by **1A** (α-bromo-substituted), **1C** (α-bromo-β-methyl-substituted) and **1E** (unsubstituted). Two different molecules have been used to describe imines and ketimines that is, **2A** and **2F**, respectively. The presence and the nature of the N-substituents have been considered unimportant since experimentally they do not affect the outcome of the reaction. Thus, they have been replaced by a hydrogen atom in all calculations.

Discussion

The [2+2] reaction between ketene and imine leading to β-lactams is commonly considered a step-wise process. The first step is the nucleophilic attack of the imine nitrogen on the ketene *sp* carbon leading to a zwitterionic intermediate (as indicated in Scheme 7).

The intermediate can undergo a conrotatory electrocyclic ring closure to give the final product. Theoretical studies have provided an insight into the origins of the stereoselectivity,[34,36,38] which certainly is the most intriguing problem. Recently, a detailed study reported by Xu and co-workers[26] has elucidated the role of the substituents in controlling the stereoselectivity.

The conformations of vinylketenes have been computationally investigated.[28,46] The equilibrium between the *s-E*-conformation and the *s-Z*-conformation is of particular interest since it may be crucial for discriminating between the [2+2] and the [4+2] pathways. The *s-E*-conformation is more stable than the *s-Z*-conformation for all vinylketenes (Table 4). However, the energy values of the conformational transition state are markedly lower for **1A** and **1C** with respect to **1E**. This suggests that the bromine substituent plays a key role in stabilising the less favoured conformation. On the basis of these results it is clear that all examined ketenes adopt a *s-E*-conformation at the equilibrium. However, at ambient conditions the rotation around the single bond is possible and this process must be faster for **1C**.

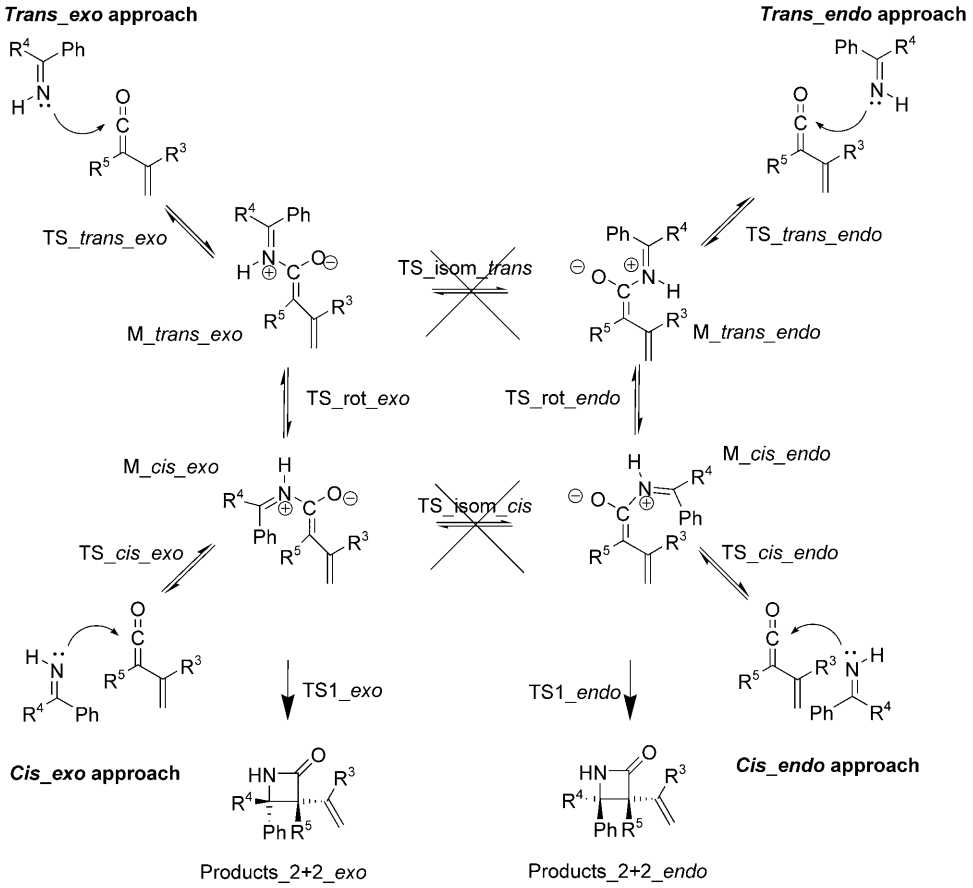
The possibility of *E*/*Z*-imine isomerisation has been taken into account,[26] and both experimental and computational evidences indicate that the model imine **2A** exists in the *E* configuration. Our data (see Table S3 in the Supporting Information) suggest a barrier of about 30 kcal mol^{-1} for the *E*/*Z*-isomerisation of **2A**.

Table 4. Energy values **E** for the conformational equilibrium of ketenes.

Molecule	E (kcal mol^{-1})[a]	ø (°)[b]
1A *s-Z*	3.09	0
1A_TS	5.81	108
1A *s-E*	0.00	180
1C *s-Z*	2.09	−43.39
1C_TS	5.07	−112.39
1C *s-E*	0.00	180
1E *s-Z*	2.18	0
1E_TS	7.01	98.24
1E *s-E*	0.00	180

[a] Energy values are relative to the *s-E* conformer.
[b] ø is the dihedral angle that describes the rotation around the central single bond.

As previously reported in the literature,[27,30] different approaches can lead to β-lactams: two *endo* approaches (*cis_endo* and *trans_endo*) and two *exo* approaches (*cis_exo* and *trans_exo*) as illustrated in Scheme 9. In the following discussion, *endo* indicates



Scheme 9. General scheme for all possible [2+2] pathways.

the approach of imine on the vinyl group side of ketene, while *exo* denotes the approach on the R^5 group side. As previously pointed out for both *exo* and *endo* pathways, the *cis* and *trans* approaches are connected by a rotational transition state (**TS**_rot_*exo* and **TS**_rot_*endo*) between the two minima **M**_*trans* and **M**_*cis*.

The energy values of the various critical points located for the [2+2] reaction between ketenes **1A, 1C** and **1E** and imine **2A** and ketimine **2F** are reported in Table 5. The energy profiles for the two reactions **1E+2A** and **1A+2A** are shown in Figure 2 and Figure 3, respectively. In all cases (i.e., the four pathways **1E+2A** *endo*/*exo* and **1A+2A** *endo*/*exo*) the rate-determining step coincides with the electrocyclic ring closure of the minimum **M**_*cis* to give the β-lactam. The comparison of the barriers associated to the corresponding transition state **TS1** in the *endo* and *exo* approaches (**TS1**_*endo* and **TS1**_*exo*) accounts for the preference of the system to give different β-lactam diastereoisomers. A qualitative relation was observed between the $\Delta E^{TS1}_{(exo\text{-}endo)}$ values reported in Table 5 (i.e., the difference between the energy of the two transition states) and the corresponding experimental ratio of products. In the case of vinylketene **1E** ($R^3=H$) the greatest barrier (see Table 5 and Figure 2) is associated with the *endo* approach (**TS1**_*endo* = 15.75 kcal mol^{-1}), while the rate-determining step of the *exo* approach has a much lower barrier (**TS1**_*exo* = 10.16 kcal mol^{-1}, the barrier difference being 5.60 kcal mol^{-1}). This result is in good agreement with the observed experimental data,[70] since the *exo* approach leads to *cis*-β-lactams. The opposite behaviour has been observed in the reaction between α-bromo vinylketene **1A** and aldimine **2A**, since the [2+2] *endo* pathway, leading to the (Br-Ph)-*cis*-β-lactam, is favoured with respect to the *exo* pathway by 4.46 kcal mol^{-1} (see Table 5 and experimental products ratio in Table 1). The analysis of the [2+2] pathway preference has been extended to other reacting pairs that is, **1C+2A**, **1E+2F**, **1A+2F**, **1C+2F**. In these cases the calculations have been carried out only on the most important critical points (i.e., reactants and **TS1**), since we have confidently assumed that all reaction surfaces considered here are qualitatively similar.

We have examined the isomerisation of the zwitterionic intermediates (see Scheme 9) from the more stable (*E*) to the less stable (*Z*) imine geometry. This pathway, if active, would connect the *endo* and *exo* pathways resulting in an opposite diasteroselectivity. Even if some authors have described the occurrence of this mechanism in the case of benzaldehyde imines[82], no connection between *endo* and *exo* pathways has been found in the present case. In spite of an extensive search no transition states connecting **M**_*cis*_*endo* and **M**_*cis*_*exo* (i.e., **TS**_isom_*cis*) or **M**_*trans*_*endo* and **M**_*trans*_*exo* (i.e., **TS**_isom_*trans*) were located.

To get a deeper understanding of the peculiar diene behaviour of α-bromo vinylketenes, [4+2] pathways have also been studied. First, on the basis of the computational evidences, we excluded that the zwitterionic intermediates located for the [2+2] pathway (i.e., **M**_*cis*_*endo* and **M**_*cis*_*exo*) could lead to the six-membered product by rotation of the vinyl group and subsequent ring closure. No minima and/or transition states related to this mechanism were found on the

Table 5. Energy values (kcal mol^{-1})[a] of the various critical points located for the [2+2] reaction.

	1E+2A	**1A+2A**	**1C+2A**	**1E+2F**	**1A+2F**	**1C+2F**
Reactants	0.0	0.0	0.0	0.0	0.0	0.0
TS_*trans_endo*	##[b]	##[b]				
M_*trans_endo*	−6.05	−12.62				
TS_*rot_endo*	−4.05	−11.13				
TS_*cis_endo*	3.95	2.01				
M_*cis_endo*	−4.19	−11.26				
TS1_*endo*	**15.75**	**6.72**	**10.83**	**11.01**	**2.95**	**9.56**
Products_*endo*	−28.05	−29.72				
TS_*trans_exo*	3.26	3.95				
M_*trans_exo*	−9.64	−13.21				
TS_*rot_exo*	−4.94	−10.94				
TS_*cis_exo*	##[b]	##[b]				
M_*cis_exo*	−5.40	−10.61				
TS1_*exo*	**10.16**	**11.18**	**13.80**	**5.45**	**6.10**	**8.11**
Products_*exo*	−26.89	−29.86				
$\Delta E^{TS1}_{(exo\text{-}endo)}$	−5.60	+4.46	+2.97	−5.57	3.14	−1.45

[a] Energy values are relative to reactants.

[b] The geometry obtained after the optimisation was found to be a saddle of order higher than 1 and so was considered irrelevant for a chemical point of view.

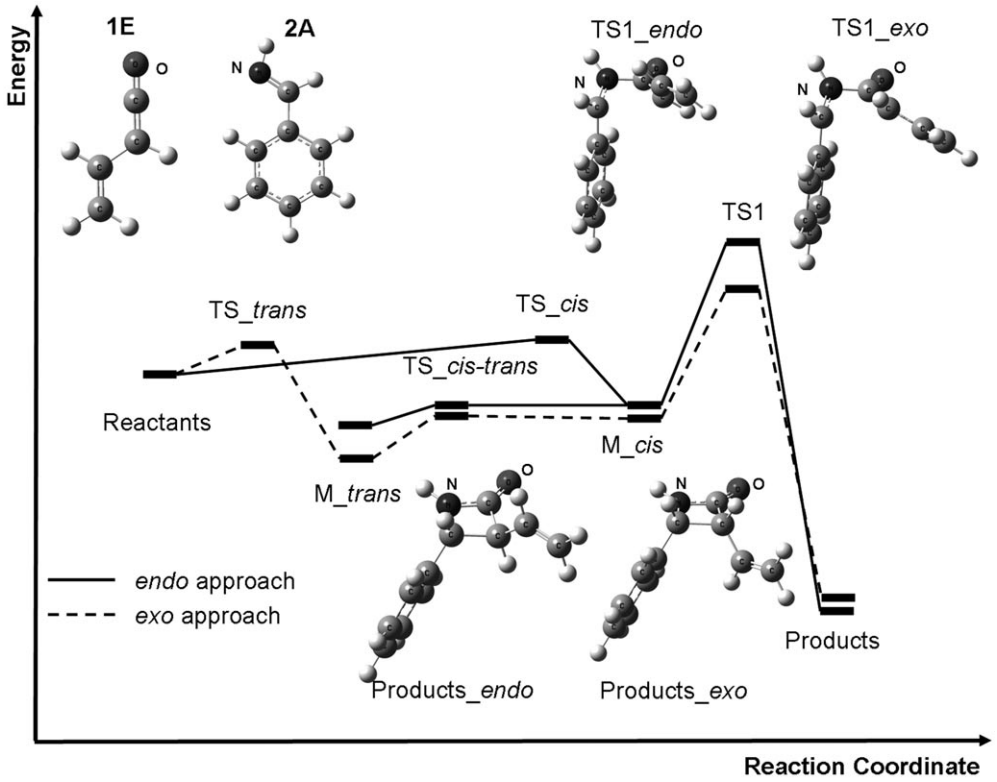


Figure 2. Energy profile for the **1E+2A** [2+2] reaction.

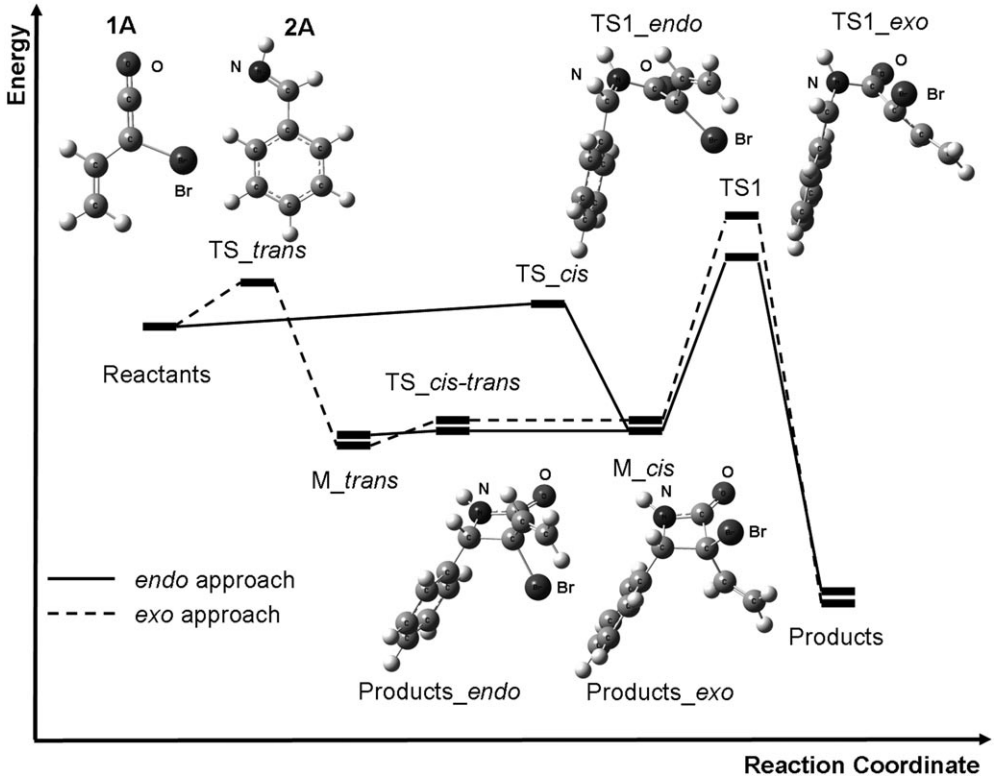
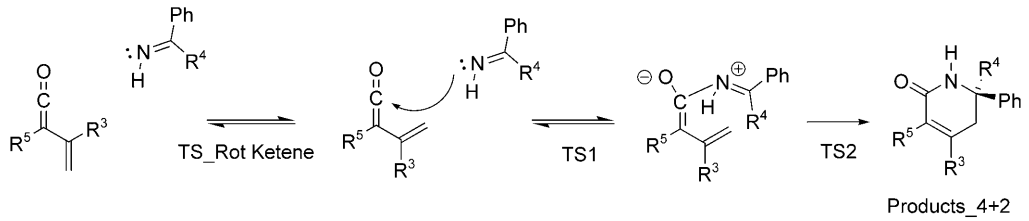


Figure 3. Energy profile for the **1A+2A** [2+2] reaction.



Scheme 10. General scheme for the [4+2] pathway.

potential surfaces (see Supporting Information for the structures conjectured for this pathway). On the contrary, an independent two-step mechanism originating from the *s-Z*-vinylketene has been discovered for the [4+2] cycloaddition. The capability of bromo substituents to stabilise the *s-Z*-conformation of α-bromo vinylketenes indeed enables a new reaction pathway. This path is schematically depicted in Scheme 10, where the conformational equilibrium between the *s-E* and *s-Z* conformations is also represented (**TS**_Rot_Ketene is the transition state connecting the *s-E*- and *s-Z*-structures).

The nucleophilic attack of the imine nitrogen on the *sp* carbon of the α-bromo vinylketene in the *s-Z*-conformation is the first step of the [4+2] reaction. The energy values for the various critical points located for this reaction are collected in Table 6. This attack, leading to the **M1** intermediate, corresponds to the rate-determining step (transition state **TS1**) of the process.[28] The subsequent ring closure (originating from **M1**), affords, through transition state **TS2**, the final six-membered product **M2** with the phenyl group in an axial position. A low barrier (transition state **TS3**) is required for the isomerisation process leading to the more stable conformer **M3** where the phenyl group is equatorial. A "ball and stick" representation of the [4+2] pathway for the **1A+2A** reaction is depicted in Figure 4. The energy diagrams for the [4+2] reaction of **2A** with **1E**, **1A** and **1C** are shown in Figure 5, Figure 6, Figure 7 and Figure 8 and are compared to the highest energy barriers that feature the competitive [2+2] pathways (i.e., **TS1**_*endo* and **TS1**_*exo*). It is worthwhile to note that the diasteroselectivity predicted by the proposed [4+2] mechanism is consistent with the observed stereo-

Table 6. Energy values (**E**, kcal mol^{-1})[a] of the various critical points located for the [4+2] reaction.

	1E+2A	**1A+2A**	**1C+2A**	**1C+2F**
Reactants	0.0	0.0	0.0	0.0
TS_rot_ketene	7.01	5.81	5.07	5.07
M0	2.18	3.09	2.09	2.09
TS1	10.63	8.26	7.27	8.68
M1	−1.30	−8.08	−8.11	−2.95
TS2	7.66	2.20	2.78	3.43
M2	−49.68	−53.93	−54.80	−46.76
TS3	−48.05	−52.02	−52.93	−43.43
M3	−51.51	−55.78	−56.72	−47.76

[a] Energy values are relative to reactants.

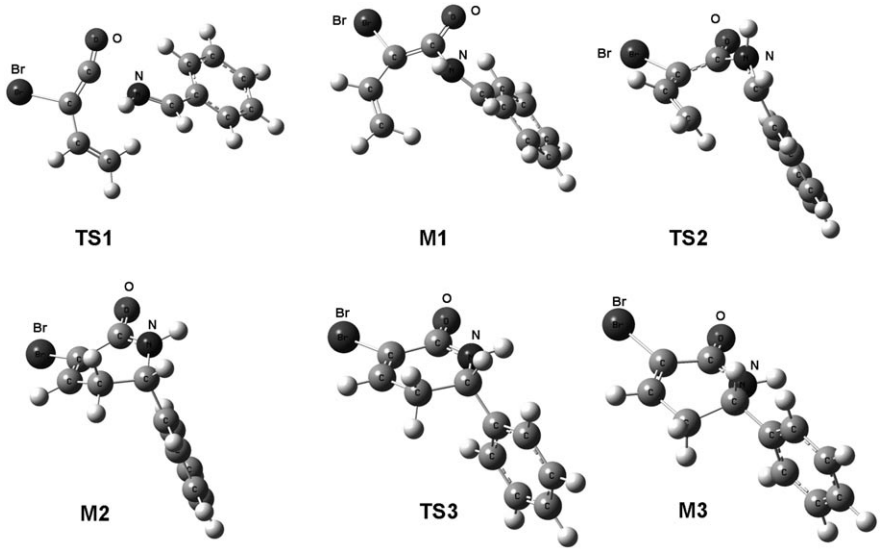


Figure 4. Structures of the various critical points located for the for **1E+2A** [4+2] reaction.

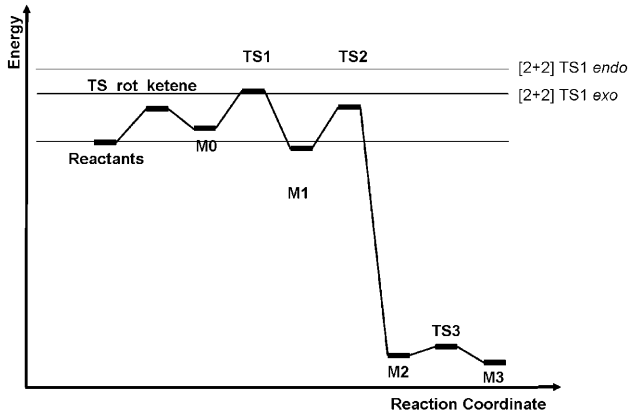


Figure 5. Energy profile for the **1E**+**2A** [4+2] reaction.

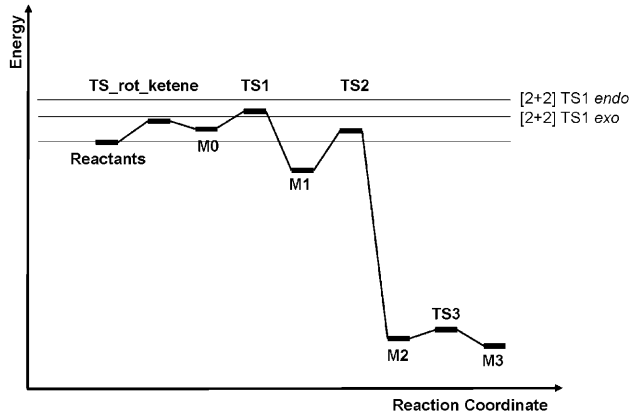


Figure 6. Energy profile for the **1A**+**2A** [4+2] reaction.

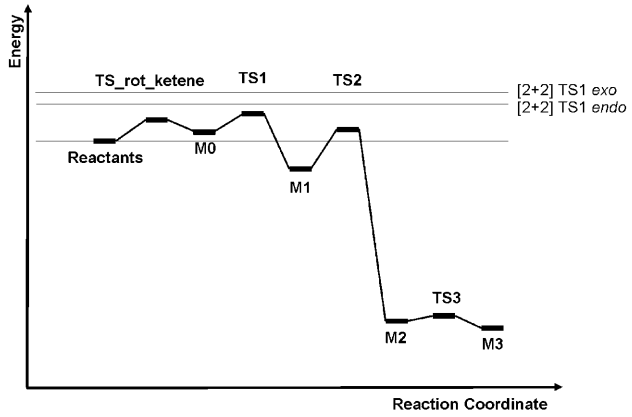


Figure 7. Energy profile for the **1C**+**2A** [4+2] reaction.

chemistry as reported in a previous paper (see Supporting Information for more details).[57]

In the **1E** + **2A** cycloaddition, the energies of **TS1** ([4+2] process) and **TS1** *exo* ([2+2] process) are similar. The exclusive formation of the β-lactam product may be ascribed to the more favoured attack of the imine (**TS**_*trans_exo*: 3.26 kcal mol^{-1}) on the *s-E*-vinylketene upon its isomerisation to give the *s-Z*-vi-

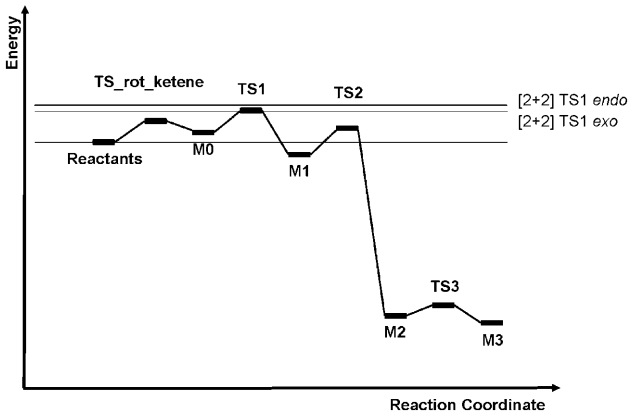


Figure 8. Energy profile for the **1C**+**2F** [4+2] reaction.

nylketene (**TS**_rot_ketene: 7.01 kcal mol^{-1}). In the reaction between **1A** and **2A**, the relative magnitude of the computed barriers of the rate-determining step for the [2+2] (**TS1** *exo*: 11.18 kcal mol^{-1}and **TS1** *endo*: 6.72 kcal mol^{-1}) and [4+2] reaction (**TS1**: 8.26 kcal mol^{-1}) are in good qualitative agreement with the experimental products ratio (Table 1). Concerning the cycloaddition **1C**+**2A**, the preference for the [4+2] product is fully explained by the difference between the barrier found for **TS1** (7.27 kcal mol^{-1}) and those for **TS1**_*exo* (13.80 kcal mol^{-1}) and **TS1**_*endo* (10.83 kcal mol^{-1}).

In general, we can state that the [4+2] pathway is available only for vinylketenes characterised by a significant population of the *s-Z*-structure. This explains the unusual behaviour of the α-bromo vinylketenes with respect to unsubstituted vinylketenes.

However, with ketimine **2F** (R^4 = Ph, Scheme 8) the energy of **TS1** increases (8.68 kcal mol^{-1}) and the [4+2] pathway is disfavoured with respect to the [2+2] one (**TS1**_*exo*: 8.11 kcal mol^{-1}; **TS1**_endo: 9.56 kcal mol^{-1} as reported in Table 5). This is also evident from the diagram of Figure 7.

Conclusions

In the present paper we have described the unusual behaviour of α-bromo vinylketenes in the cycloaddition reactions with imines. The peculiar feature of this class of vinylketenes is the fact that they behave as dienophiles in [2+2] reactions, but also display an unusual diene reactivity in [4+2] reactions. As a consequence α-bromo vinylketenes are versatile building blocks in the synthesis of highly functionalised heterocycles, since α-bromo substituted 3-alkenyl-azetidin-2-ones and 4-alkyl-5,6-diyhdropyridin-2-ones can be easily obtained from the [2+2] and [4+2] reactions with imines, respectively. Interestingly, the reactivity of α-bromo vinylketenes can be modulated *via* a fine tuning of the substituents. The introduction of a

methyl group in the β-position, for example, completely inhibits the dienophile reactivity and the [4+2] cycloaddition products are almost exclusively obtained. The usage of a more hindered ketimine in the place of a simple imine is enough to activate again the [2+2] mechanism (both β-methyl substituted and unsubstituted α-bromo vinylketenes give azetidinones when reacted with ketimines).

We have carried out a DFT theoretical investigation to rationalise these experimental evidences. We have considered two pathways for the [2+2] reaction involving imine, that is, the *endo* and *exo* pathways. The former has been found to be favoured in the case of α-bromo vinylketenes, while the latter is preferred for non-substituted vinylketenes. Since the [4+2] cycloaddition becomes possible only when the *s-Z*-conformation of vinylketene is significantly populated, the presence of Br substituents in this substrate is crucial in determining the [2+2] or [4+2] mechanisms. For unsubstituted vinylketenes, the barrier connecting the *s-E*- to the *s-Z*-conformation is too high to be easily overcome. Thus, the *s-Z*-structure has a low population and the [2+2] mechanism is favoured. In the case of α-bromo vinylketenes (especially the β-methyl-substituted ones), this barrier can be surmounted and the [4+2] mechanism becomes available. Interestingly, in the reactions involving ketimines, the presence of an additional phenyl group makes more difficult the formation of the zwitterionic intermediate along the [4+2] pathway. Consequently, the [2+2] path becomes again favoured with all α-bromo vinylketenes.

Experimental Section

General Remarks

Unless stated otherwise, solvents and chemicals were obtained from commercial sources and used without further purification. Flash chromatography was performed on Merck silica gel 60 (230–400 mesh). NMR spectra were recorded with Varian Gemini 200, Inova 300, Mercury 400 or Inova 600 MHz spectrometers. Chemical shifts are reported as δ values relative to the solvent peak of $CDCl_3$ set at $\delta = 7.27$ (^{1}H NMR) or $\delta = 77.0$ (^{13}C NMR). DPFGSE-nOe (double pulse field gradient-nuclear Overhauser effect) experiments have been performed in $CDCl_3$ at 25 °C on a Varian INOVA® 400 MHz (Oxford Magnet).

Melting points are uncorrected. MS analyses were performed on an HP1100 liquid chromatograph coupled with an electrospray ionisation-mass spectrometer (LC-ESI-MS), using H_2O/CH_3CN as solvent at 25 °C (positive scan 100–500 m/z, fragmentor 70 V). Imines **2a–e**[57] and ketimines **2f**, **g**[83] were prepared following a known procedure and characterised by comparison with literature data.

Complete characterization of compounds **3a**, **3c–e**, **4a**, **4c–e**, **6a**, **6e**, **7a**, **7e** have been reported in ref.[60] Complete characterisation of compounds **5e**, **9a–e**, **10**, **11**, **12**, **13** and X-ray data for compound **12** have been reported in ref.[59]

General Procedure for the Reaction of Ketene 1 with Imine 2 at Reflux

To a refluxing solution of the imine (1 mmol) and TEA (2 mmol, 2 equiv., 0.280 mL) in CH_2Cl_2 (10 mL) under a nitrogen atmosphere, acyl chloride (1.25 mmol, 1.25 equiv.) in CH_2Cl_2 (2 mL) was added dropwise very slowly. The solution was refluxed for 4 h and then allowed to reach room temperature. After quenching with 5 mL of 0.1 M HCl, the mixture was diluted with CH_2Cl_2 (10 mL) and washed twice with water. The organic layer was dried over Na_2SO_4 and solvent was removed under reduced pressure. The products were obtained, after purification by flash chromatography on silica gel (cyclohexane/Et_2O, 95/5), with the yields reported in Table 1.

Supporting Information

Full analytical characterisations of the [2+2] and [4+2] products, X-ray data for compound **4e** and the geometries of critical points are given in the Supporting Information.

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