[2 + 2]-Photocycloaddition of 1,1-Diethoxyethylene to Chiral Polyfunctional 2-Cyclohexenones. Regioselectivity and π-Facial Discrimination

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The photochemical [2 + 2]-cycloadditions of 1,1-diethoxyethylene to chiral polyfunctional 2-cyclohexenones have been carried out leading to the production of highly constrained unusual α-amino acids with excellent regioselectivity and satisfactory yields. Theoretical calculations have been done to rationalize the observed regio- and diastereoselectivity and show that regiochemistry is determined by the relative rate of formation of the 1,4-biradical intermediates and not by the stability of these species.

Introduction

The photochemical [2 + 2]-cycloaddition of olefins to cycloalkenones has been efficiently used in the synthesis of molecules of high structural complexity.[1] This reaction has been carried out both in its intra-[2] and intermolecular version. In the latter case, simple acyclic alkenes,[3] C_{60}-fullerene,[4] and functionalized linear[5] or cyclic[6] olefins have been employed. Compounds containing triple bonds such as acetylenes[5c,7] and ynamines[8] have also been successfully used.

Chiral auxiliaries and/or catalysts[2o,6b,c,e] have been utilized to induce π-facial discrimination in cyclic enones to produce single adducts in an enantio- and diastereoselective manner. Usually, π-facial diastereoselection occurs concomitant with the formation of the first C−C bond when using chiral enones.

Initially, this cycloaddition was assumed to occur through the interaction of a (n,π*) excited state of the enone, pressumably a triplet, with the alkene to produce a π-complex or exciplex. The dipole interactions between the polarized enone excited state and the olefin would govern the reaction regiochemistry according to the Corey−de Mayo exciplex mechanism,[5a,7a,10] thus favoring the formation of some 1,4-biradical intermediates over

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others. This hypothesis relied on the observation that head-to-tail (HT) adducts were predominant in the cycloadditions of electron-donating olefins to cyclohexenone or cyclopentenone, while head-to-head (HH) adducts were major regioisomers in the reactions with electron-deficient olefins. Later, HT adducts were also observed as major regioisomers in the reactions between cyclohexenone and electron-deficient olefins, the regiochemistry being justified by consideration of the relative stability of the biradical intermediates.[6f,11] Moreover, the enone excited state actually responsible for the reaction $(n,\pi)^*$ has a different polarization than the state (n,π^*) originally thought to be involved.[12] In 1970, Bauslaugh postulated a mechanism in which the only intermediates are enone triplet excited states, adduct triplet 1,4-biradicals, and the corresponding singlet 1,4-biradicals.[13]

At present, interpretation of regioselectivity in the cycloadditions of enones to alkenes is mainly based on the works by Weedon.[2m,14] This author trapped and studied the biradical intermediates in some reactions and suggested that regiochemistry is governed by competition between closure of the biradicals to adducts and their reversion to ground-state materials.

Photochemical [2 + 2]-cycloaddition reactions between α,β-unsaturated carbonyl compounds and alkenes have recently been the subject of theoretical studies.[15−17] The comparison of results obtained for reactions involving cyclic and acyclic carbonyl compounds has shown that the outcome of the reaction is governed by the competition between the deactivation of the $^3(\pi,\pi^*)$ carbonyl compound and its reaction with the alkene to form the triplet 1,4-biradical.[17] Regarding the regioselectivity, Houk et al.[18] have studied the addition of several monosubstituted ethylenes to acrolein showing that regioselectivity is determined by the formation of the first C−C bond.

In this article we present the results of the [2 + 2] photocycloaddition of 1,1-diethoxyethylene, **3**, to chiral polyfunctional cyclohexenones **1** and **2**. (Scheme 1) Ketene ketals such as **3** are useful reagents bearing a masked ketone function. Otherwise, enones **1** and **2** present an α-amino acid group at C_4. Therefore, this reaction allowed us the synthesis of conformationally constrained unusual amino acids containing four stereogenic centers. Moreover, we have performed theoretical calculations to rationalize the observed regioselectivity and π-facial diastereoselectivity.

SCHEME 1

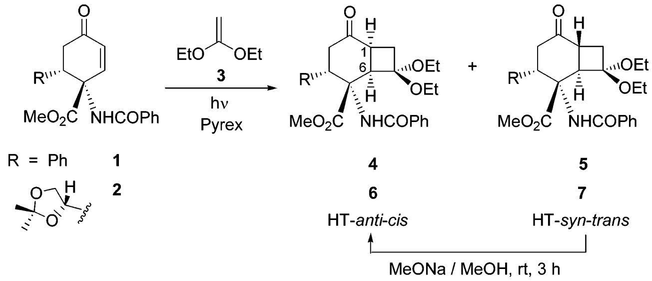

TABLE 1. Reactions of Enones 1 and 2 with 1,1-Diethoxyethylene, 3[a]

entry	enone	solvent	temp[b] (°C)	time (h)	yield[c] (%)	cis/trans ratio[d]
1	**1**	acetone	3	2.7	49	4.4
2	**1**	acetone	−40/−25	6.0	46	2.1
3	**1**	acetonitrile	3	3.7	77	2.2
4	**1**	acetonitrile	−40/−25	6.3	55	1.9
5	**2**	acetone	3	3.5	42	1.2
6	**2**	acetone	3	2.0	31	1.3
7	**2**	acetonitrile	3	1.2	27	0.8

[a] All experiments were performed with 14−16 equiv of **3**. [b] External bath. [c] Yield of purified products. [d] Determined for isolated isomers.

Results and Discussion

1. Reactions of 1 and 2 with 1,1-Diethoxyethylene, 3. Identification of Adducts. Enone **2** had been previously synthesized in our laboratory,[19] and the synthesis of **1** was decribed in the literature.[20] Reaction of racemic **1** with **3** was tried under several conditions shown in Table 1. Acetonitrile and acetone were used to test the role of the latter as a photosensitizer of the process. The best results were obtained in the conditions listed in entry 3 (Table 1). A 0.002 M solution of compound **1** in acetonitrile contained in a Pyrex reactor cooled at 3 °C was irradiated with a 125 W medium-pressure mercury lamp for 3.7 h in the presence of 15 equiv of **3**. In this way, a 2.2:1 mixture of adducts **4** and **5** was produced in 77% yield (Scheme 1). The *cis*-isomer was the major compound in all the conditions tried, the cis/trans ratio increasing with temperature (Table 1).

Products **4** and **5** were isolated by column chromatography, and the structure of **5** was unambiguously determined by X-ray structural analysis showing an HT-adduct with cyclobutane C1−C8 bond in syn disposition with respect to the benzamido group and trans stereochemistry at the ring junction. Therefore, compound **5** is a (HT-syn-trans)-adduct. The formation of the intramolecular hydrogen bond between the N*H* proton and the carbonyl of the methyl ester in the solid state is noteworthy (see Supporting Information), conferring a remarkable rigidity on the molecule. Otherwise, NOESY experiments show interaction between H1 and H6 protons allowing us to assign cis stereochemistry to the

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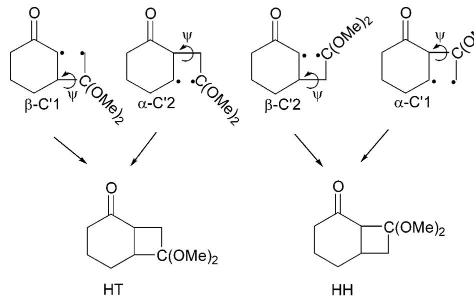
SCHEME 2



major adduct **4**, which is an oil. This product was also obtained by treatment of **5** with sodium methoxide in methanol in order to epimerize the α-carbonyl stereogenic center C1. Therefore, the structure of **4** was assigned as an (HT-anti-cis)-isomer (Scheme 1).

Optically active enone **2** reacted with **3**, affording two adducts in about the same ratio and moderate yield among other unidentified substances. The best conditions (entry 5 in Table 1) correspond to the use of acetone as a solvent, irradiation being performed at 3 °C for 3.5 h. Adducts **6** and **7** were thus obtained in 1.3:1 ratio and 40% yield. X-ray structural analysis of **6** showed an (HT-anti-cis)-adduct (Scheme 2). Moreover, treatment of **7** with base afforded a product whose ^{1}H NMR spectrum was superimposable with that of isomer **6** allowing us the assignment of the (HT-syn-trans)-adduct **7**.

From a synthetic point of view, treatment of trans-fused **5** and **7** with base to provide cis-fused **4** and **6**, respectively, is equivalent to the exclusive production of (HT-anti-cis)-adducts **4** and **6**, thus improving the yield in single isomeric amino acids.

At this step of our work, we could not account for the π-facial diastereoselectivity since we could not discern which C1−C8 or C6−C7 bond was first produced. For this reason, we performed theoretical calculations to establish the mechanism of the cycloaddition and to explain the observed regio- and stereochemistry.

2. Theoretical Calculations

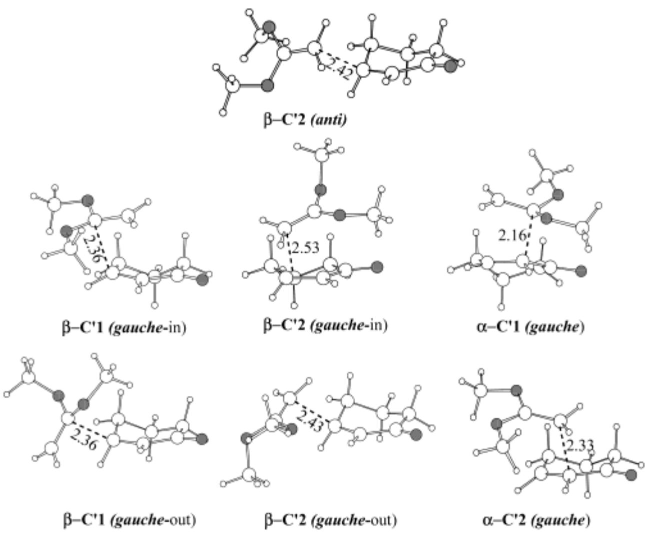
We have first studied the reaction between $^3(\pi\pi^*)$ 2-cyclohexenone and 1,1-dimethoxyethylene, which is used as a model of **3**. This process may lead to four different 1,4-biradicals, which are shown in Scheme 2. After intersystem crossing to the ground state, the ring closure of these biradicals may lead to two different regioisomers: HT and HH. Moreover, for each biradical, several conformers arising from the rotation around the new C−C bond are possible. For the reaction between 2-cyclohexenone and ethylene, it has been shown that the [2 + 2] cycloadduct can only be obtained if the 1,4-biradical is formed in a gauche conformation ($\psi \cong \pm 60°$).[17] For this reason, we have focused on the formation of such conformers. For the β-C′2 attack, which leads to the most stable intermediates, we have also studied the formation of the anti conformer ($\psi \cong 180°$).

Table 2 presents the energies and Gibbs energies of stationary points associated with the formation of these 1,4-biradicals, and the structures of the transition states are shown in Figure 1.

TABLE 2. Energies^a and Gibbs Energies^{a,b} for the Reaction between 1,1-Dimethoxyethylene and $^3(\pi\pi^*)$ 2-Cyclohexenone

attack^c	conformer^d	$\Delta E^\ddagger$	$\Delta G^\ddagger$	ΔE	$\Delta G°$
β-C′1	gauche-in	2.6 (7.3)	16.3 (21.0)	−20.7	−5.9
	gauche-out	9.9 (13.6)	22.0 (25.7)	−17.5	−2.9
β-C′2	anti	5.2 (7.9)	15.4 (18.1)	−27.7	−13.1
	gauche-in	2.0 (6.0)	14.4 (18.4)	−26.3	−11.6
	gauche-out	4.3 (7.4)	15.0 (18.1)	−27.7	−12.9
α-C′1	gauche^e	5.8 (11.3)	19.6 (25.1)	−5.9	7.8
α-C′2	gauche^f	−0.1 (4.1)	12.5 (16.7)	−17.0	−3.6

[a] In kcal/mol. In parentheses are values corrected for BSSE. [b] At 1 atm and 298.15 K. [c] See Scheme 2. [d] $\psi \cong +60°$ for gauche-in and $\psi \cong -60°$ for gauche-out. [e] Only one gauche transition state has been obtained with $\psi = 9°$. [f] Only one gauche transition state has been obtained with $\psi = 24°$.



β–C'2 (*anti*)

β–C'1 (*gauche*-in) β–C'2 (*gauche*-in) α–C'1 (*gauche*)

β–C'1 (*gauche*-out) β–C'2 (*gauche*-out) α–C'2 (*gauche*)

FIGURE 1. Structures of the transition states corresponding to the formation of 1,4-biradicals for the reaction between $^3(\pi\pi^*)$ 2-cyclohexenone and 1,1-dimethoxyethylene. Length of the forming bond in Å.

We can observe that β-C′2 biradicals are clearly the most stable ones, with all conformers being nearly degenerate. This result can be understood by taking into account that in these biradicals, the unpaired electrons can be efficiently delocalized, thus contributing to the stability of the system. However, the kinetically most favorable biradical is the one coming from the α-C′2 attack. The latter result would agree with the formation of a HT regioisomer, which is the major product experimentally observed.[5a]

It is to be noted that for the reaction between cyclohexenone and ethylene, the β-attack was kinetically and thermodynamically more favorable than the α-attack.[17,21]

Table 2 shows that the transition state for the α-C′2 attack is lower in energy than the reactants. We have located a precursor intermediate for this attack. This intermediate, which is shown in Figure 2, is 4.3 kcal/mol lower in energy than the reactants. Both fragments are in nearly parallel planes with an incipient interaction between the oxygen of cyclohexenone and a hydrogen atom of one of the methoxy groups and a weaker interaction between the C4−H of cyclohexenone and the oxygen of the other methoxy group. The inclusion of

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[21] For the reaction between cyclohexenone and ethylene, the energy barriers computed at the B3LYP/6-31G(d) level of calculation for α and β attacks are 3.7 and 1.8 kcal/mol, respectively.

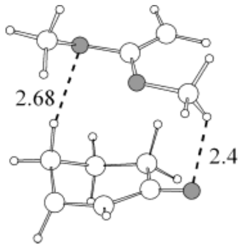


FIGURE 2. Structure of the precursor intermediate for the interaction between $^3(\pi\pi^*)$ 2-cyclohexenone and 1,1-dimethoxyethylene. Selected interatomic distances in Å.

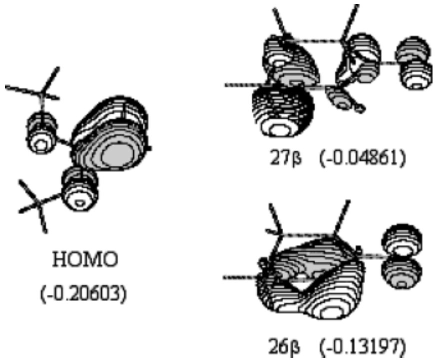


FIGURE 3. HOMO of 1,1-dimethoxyethylene and first two unoccupied β orbitals of $^3(\pi\pi^*)$ 2-cyclohexenone. Orbital energies in a.u.

entropy contribution leads to $\Delta G = 6.0$ kcal/mol. For this reason, this kind of intermediate is not relevant from a kinetic point of view and has not been further considered.

Figure 1 shows that the distances corresponding to the forming bond at the transition states range between 2.16 and 2.53 Å. The shortest value corresponds to the α-C′1 attack, whereas the larger values are obtained for the β-C′2 attack. The relative values of the potential energy barriers depend more on the relative orientation of both addends than on the values of these distances.

As we have already mentioned, there is not a direct relation between the stability of 1,4-biradicals and the potential energy barriers associated with their formation. So, the kinetic preference for a particular attack has to be rationalized through the electronic structure of the reactants.

The Mulliken population analysis shows that at the transition states, there is a charge transfer from dimethoxyethylene to cyclohexenone. This charge-transfer ranges between 0.07 au for β-C′2 (anti) and 0.25 au for β-C′1 (gauche-in) and α-C′2 attacks. So, the most important frontier orbital interaction is the one involving the HOMO of 1,1-dimethoxyethylene and the LUMO of triplet 2-cyclohexenone. Figure 3 shows that the HOMO of 1,1-dimethoxyethylene is polarized toward the nonsubstituted carbon atom (C′2), and thus this is the carbon atom that should be involved in the bond formation of the kinetically most favorable biradicals. Regarding triplet cyclohexenone, Figure 3 presents the first two unoccupied β orbitals. The one with the lowest energy (26β) is polarized toward to the Cα of cyclohexenone; thus, attack of dimethoxyethylene to this carbon atom is expected to be favored.

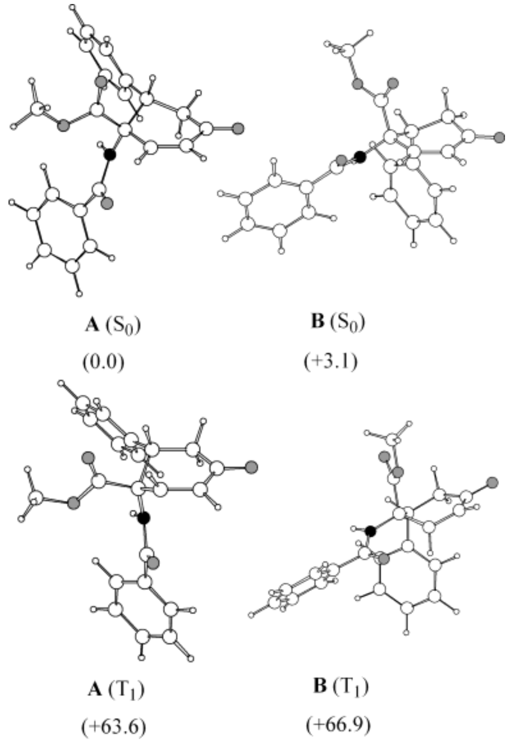
This analysis is in good agreement with the results reported by Houk et al.[18] for the reaction between triplet acrolein and substituted alkenes. According to these authors, a triplet enone may be considered as an alkyl radical (Cβ) linked to an α-acyl radical (Cα), the latter radical being more electrophilic than the first one. To verify the different electrophilic nature of both carbon atoms we have computed the interaction energy of triplet 2-cyclohexenone with a model nucleophile. We have placed an ammonia molecule at 2.50 Å from Cα or Cβ atoms of triplet cyclohexenone and optimized all the geometry parameters except the C−N distance. The computed interaction energies are −0.1 kcal/mol when ammonia approaches Cα and +3.4 kcal/mol when the interaction is with Cβ. So, there is a preference of 3.5 kcal/mol for the interaction of triplet cyclohexenone with this model nucleophile through Cα.

For the reaction between 2-cyclohexenone and ethylene, the potential energy barrier corresponding to the formation of the 1,4-biradical was about 2 kcal/mol (no correction for BSSE applied).[17] This process was more favorable than deactivation of triplet 2-cyclohexenone to the ground state. The results obtained for 1,1-dimethoxyethylene (see Table 2) predict that the formation of the α-C′2 1,4-biradical will be very fast. This biradical can then evolve to the ground-state potential energy surface. We have tried to optimize the geometry of such an intermediate, but the system evolved to the corresponding cyclobutane. This result indicates that ring closure is expected to be very fast, and thus the formation of the HT cyclobutane from the α-C′2 attack of dimethoxyethylene to triplet cyclohexenone will be very favorable. This result is in good agreement with experiments showing that the quantum yields for the photocycloadditions of cyclohexenone with electron-rich olefins are larger than those for reaction with ethylene.[12]

Once we have established that the first bond to be formed is the one between Cα of 2-cyclohexenone and C′2 at 1,1-dimethoxyethylene, we can analyze the π-facial diastereoselectivity. For this purpose, we have extended our study to the substituted cyclohexenone **1**. The presence of substituents leads to a considerable number of conformers. We have first studied the ground state of **1**. There are two different conformers associated with the six-membered ring, **A** and **B**, which are shown in Figure 4.

The most stable conformer (**A**) has the amide group in an axial position while phenyl and ester groups are equatorial, whereas in **B**, the amide is equatorial and phenyl and ester are axial.

Starting from these two structures, an exploration of the conformations associated with the amide, ester, and phenyl groups has been performed first through molecular mechanics calculations and then using the AM1 method. The most stable structures have been reoptimized at the ONIOM level of calculation. A similar procedure has been followed for the triplet state. In this case, the molecular mechanics exploration has been done for the C−C hydrogenated substrate. The results obtained show that structures **A** are energetically more favorable than structures **B** both in the ground and triplet excited states. The energy differences (3.1 and 3.3 kcal/mol) are large enough to consider that only structures **A** are significantly populated, and the [2 + 2]-cycloaddition therefore takes place from this conformer. However, we have located the transition states corre-



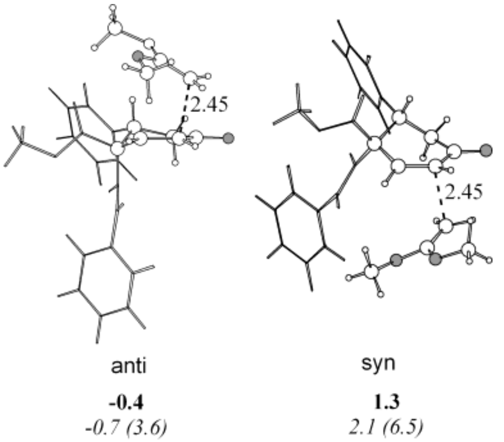
A (S_0) (0.0)

B (S_0) (+3.1)

A (T_1) (+63.6)

B (T_1) (+66.9)

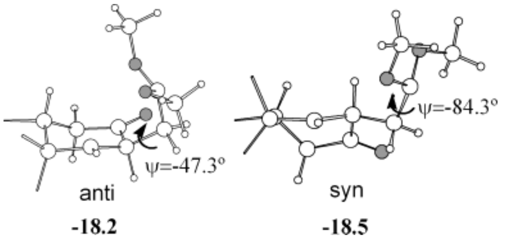
FIGURE 4. Structures of two conformers of cyclohexenone **1** in the ground state and in the first triplet state. Relative energies computed at the ONIOM level of calculation in kcal/mol.



anti **-0.4** *-0.7 (3.6)*

syn **1.3** *2.1 (6.5)*

FIGURE 5. Structures of the transition states corresponding to the α-C′2 attack of 1,1-dimethoxyethylene to the anti and syn faces of $^3(\pi\pi^*)$ **1**. Energies relative to separated reactants in kcal/mol computed at the ONIOM (boldface) and B3LYP//ONIOM (italics) levels of calculation. In parentheses are values corrected for BSSE.



anti **-18.2**

syn **-18.5**

FIGURE 6. Structures of the 1,4-biradicals corresponding to the α-C′2 attack of 1,1-dimethoxyethylene on the anti and syn faces of $^3(\pi\pi^*)$ **1**. Energies relative to separated reactants computed at the ONIOM level of calculation in kcal/mol. Substituents of the cyclohexenone ring have been omitted for clarity.

sponding to the α-C′2 attack of 1,1-dimethoxyethylene to both conformers of **1**. In each case, we have considered the attacks anti and syn to the amide group. The transition states corresponding to the attacks on conformer **A** (see Figure 5) involve lower energy barriers than attacks on **B**. The energy barriers for the reactions on **B** obtained at the ONIOM level of calculation (relative to **A** and dimethoxyethylene) are 1.7 and 3.6 kcal/mol for the anti and syn attacks, respectively.

The results presented in Figure 5 show that the attack anti to the amide group is the most favorable one. The corresponding transition state is lower in energy than the reactants, as we have already found for the reaction of parent cyclohexenone. The potential energy barriers computed through single-point B3LYP calculations are similar to the ONIOM values, but the difference between them increases from 1.7 to 2.8 kcal/mol (2.9 kcal/mol after correction for BSSE). These results are in excellent agreement with the stereochemistry of adduct **4**, which is the major stereoisomer produced in this reaction. We have also optimized the geometries of the corresponding 1,4-biradicals, and the obtained structures are shown in Figure 6.

The formation of cis- and trans-fused rings is determined during the ring-closure step, which takes place after intersystem crossing to the ground-state potential energy surface. As we have already mentioned, when we tried to optimize the geometry of an α-C′2 singlet 1,4-biradical for the reaction between 1,1-dimethoxyethylene and 2-cyclohexenone, the system evolved to the corresponding cyclobutane. For this reason, we have not studied the ring-closure step corresponding to the reaction of **1**. However, the structures of the triplet 1,4-biradicals represented in Figure 6 indicate that the intermediate corresponding to the anti attack presents a conformation suitable for a cis-fusion, whereas the conformation of the syn intermediate would lead to the formation of the trans-fused ring. These results are in excellent agreement with the experimentally observed stereochemistry of adducts **4** and **5**.

As we have already mentioned (see Table 1), the experimentally observed cis/trans ratio depends on the temperature in such a way that facial diastereoselectivity increases with temperature. This fact indicates that the final outcome of the cycloaddition is not only governed by the rate of formation of the 1,4-biradical intermediates. These intermediates can present different conformations associated with rotations around the new C−C bond. Once in the ground-state potential energy surface, gauche conformers are expected to evolve toward ring closure, whereas the most favorable process for anti conformers is reversion to reactants.[17] Figure 6 shows that the ψ torsional angle of the syn-face diastereomeric intermediate is notably larger than the value corresponding to the anti-face one. This might indicate a relatively easy gauche-anti rearrangement for the syn-face diastereomeric intermediate. The rate of this conformational rearrangement increases with temperature, and it can thus compete with intersystem crossing to the ground state. According to this reasoning, at low-temperature, most of the syn-face 1,4-biradical intermediates would evolve to ring closure, whereas at high temperatures, ring closure would be in competition with reversion to reactants.

Conclusion

We have successfully achieved the synthesis of highly rigid unusual α-amino acids through the photochemical [2 + 2]-cycloaddition of 1,1-diethoxyethylene to chiral polyfunctional 2-cyclohexenones. Head-to-tail regioisomers are the only identified adducts. Theoretical calculations on the reaction between 1,1-dimethoxyethylene and 2-cyclohexenone have shown that regiochemistry is determined by the rate of formation of the 1,4-biradical intermediates and not by the relative stability of these species. The most favorable attack leads to the formation of a 1,4-biradical containing a C−C bond between Cα of the enone and the nonsubstituted carbon (C′2) of the alkene. π-Facial diastereoselection in the reaction between 1,1-diethoxyethylene and enone **1** can be explained by considering the preferential attack of the alkene on the face anti to the benzamido group in the most stable conformation of **1**.

Experimental Section

Computational Details. Calculations were performed using the Gaussian 98 program.[22] The geometries of stationary points have been optimized using the B3LYP[23] density functional method with the 6-31G(d) basis set.[24] Open-shell systems have been described within a spin-unrestricted formalism. Harmonic vibrational frequencies have been calculated for all stationary points to characterize them as energy minima (all frequencies are real) or transition states (one and only one imaginary frequency). Basis set superposition error (BSSE) has been estimated for the transition states using the counter poise method.[25]

For the reaction between **1** and 1,1-dimethoxyethylene, we have used the ONIOM method.[26] The system has been divided in two layers. The first one includes cyclohexenone and 1,1-dimethoxyetylene, while the amide, ester, and phenyl groups are included in the second layer. We have described the first layer at the B3LYP/6-31G(d) level of calculation and the second layer using the semiempirical AM1 method.[27]

A preliminary conformational study has been done using the MM2 force field[28] implemented in the ChemBats3D package.[29]

The energies of the stationary points obtained using the ONIOM method have been recalculated through single-point calculations at the B3LYP/6-31(d) level of calculation.

General Procedure for the Photochemical Cycloaddition of 3 to Ketones 1 and 2. A mixture of ketone **1**[20] or **2**[19] (0.6 mmol) and **3** (8.4 mmol) in acetonitrile or acetone (60 mL) contained in a Pyrex reactor cooled with an external bath at 3°C was irradiated with a 125 W medium-pressure mercury lamp for 3.5−3.7 h under an argon atmosphere. Solvent was eliminated at reduced pressure, and the residue was chromatographed on silica gel (hexanes−ethyl acetate) to afford pure adducts. Analytical and spectroscopic data for the new compounds **4**−**7** are described in the Supporting Information.

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Supporting Information Available: Analytical and spectroscopic data for compounds **4**−**7**, Cartesian coordinates and total energies for stationary points obtained in the theoretical calculations, and crystal data, structure refinement, bond lengths, and angles for compounds **5** and **6**. This material is available free of charge via the Internet at http://pubs.acs.org.

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