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Regio- and Stereochemistry of [2 + 2] Photocycloadditions of Imines to Alkenes: A Computational and Experimental Study

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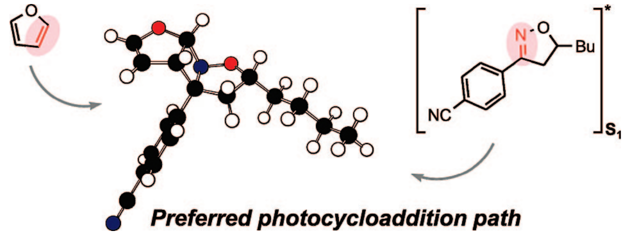

The [2 + 2] photocycloaddition of isoxazolines to alkenes has been studied by means of CASPT2/6-31G*//CASSCF/6-31G*. The reaction outcome is influenced by the relative ratio of imine deactivation and photocycloaddition. Analysis of the conical intersection points involved in the photoreaction shows that fast deactivation is prevented when an electron-withdrawing group is placed in any position that can affect the imine moiety. Computational data predict that the photoreaction will be regiospecific but without stereoselectivity. Furthermore, the favored regioisomer will be different for alkenes with electron-withdrawing or electron-releasing substituents. The results of a complementary experimental study correlate well with the computational data. Several conclusions included in the present work could prove useful for the generalization of the photocycloaddition of imines.

Introduction

[2 + 2] Photocycloadditions of olefins to C=C, C=O, and C=S bonds to yield four-membered cycles are now well-documented reactions and are useful tools in the synthesis of cyclobutanes,[1] oxetanes,[2,3] and thietanes,[4] respectively. However, similar photocycloaddition reactions of olefins to imines are less common.[5] Several isolated examples of this type of reactivity have been reported and reviewed,[6] although a systematic study to explain such different behavior has yet to be carried out. One of the required features of the C=N bond to yield successful photocycloadditions to olefins is to have the imine moiety constrained in a five- or six-membered ring, but few other structural requirements are clear. For instance, reports of photocycloadditions of different olefins to oxadiazoles,[7] azauracils,[8] isoindolones, oxazolinones,[9] and isoxazolines[10] have appeared. In order to shed some light on the reaction mechanism, we carried out a computational study of the photocycloaddition of imines to alkenes.[11] This step is necessary before this reactivity can be converted into a more general synthetic tool. Our initial results[11] showed that there are some structural requirements beyond the confinement of the imine moiety in a cycle for a successful photocycloaddition. Whereas pyrroline (**1**) and isoxazoline (**2**) share the cyclic structure, our calculations showed that photocycloaddition of **1** to ethylene is hampered by fast deactivation to the ground state, whereas in **2** deactivation is not that fast due to the presence of an energy barrier in the excited state. Similar results were obtained for compounds for

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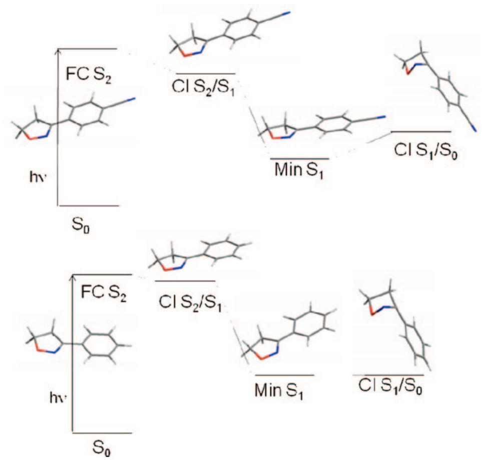

FIGURE 1. Critical points along the potential energy surfaces of isoxazolines **3** and **4** (top).

which the experimental outcome is available. In the case of 3-phenyl-2-isoxazoline (**3**), fast deactivation takes place, whereas 3-(*p*-cyanophenyl)-2-isoxazoline (**4**) successfully undergoes cycloaddition to alkenes. The reason behind this behavior seems to lie not only in the feasibility of the photocycloaddition but also in the competition between this reaction and fast deactivation to the ground state. We wish to report here the results of a theoretical study into the effect of alkene substitution and regiochemistry issues in the [2 + 2] photocycloaddition of alkenes to isoxazolines and an experimental study carried out to confirm the theoretical data.

Computational Details. All critical points were computed using fully unconstrained ab initio quantum chemical computations in the framework of a CASPT2//CASSCF strategy.[12] This process requires the reaction coordinate to be computed at the complete active space self-consistent field (CASSCF) level of theory and the corresponding energy profile to be re-evaluated at the multiconfigurational second order Møller−Plesset perturbation theory level (here we used the CASPT2 method implemented in MOLCAS-6.4)[13] to take into account the effect of electron dynamic correlation. All computations were carried out at the CASSCF level with the 6-31G* basis set. The active space was chosen depending on the compounds considered but in each case included the π and π^* orbitals of the imine and alkene moieties and the N lone pair. Depending on the alkene considered, the active space also included ketone π and π^* orbitals, N or O lone pairs. The zeroth order wave function used in the single-point CASPT2 calculations needed for the re-evaluation of the energy profile is a three root (S_0, S_1, S_2) state average CASSCF wave function with the 6-31G* basis set. The same type of wave function was used where necessary in order to avoid convergence problems. The structure of the conical intersection (CI) funnels associated with each path were optimized by applying the methodology included in GAUSSIAN 03.[14]

Results and Discussion

On the basis of our previous results, it is clear that the key feature of these reactions is the competition between fast deactivation and photocycloaddition, with the relative ratio controlled by the energy of the CI points involved. Compounds **3** and **4**, in which fast deactivation (**3**) and photocycloaddition (**4**) were detected experimentally, show potential energy surfaces (PES) consistent with these facts (Figure 1). When the energy of the CI point is low enough, fast deactivation can occur and photocycloaddition, although energetically available, does not take place. In contrast, when the CI point has a higher energy, the system has to spend some time in the excited state, thus allowing the reaction to occur. Accordingly, if we manage to understand the geometrical aspects that affect the CI point and its relative energy, we could gain a deeper understanding of the reaction mechanism, and this information could be used to predict the feasibility of any reaction and even design a system that is able to successfully photocycloadd to olefins. With this aim in mind, we analyzed the CI points for **3** and **4** (see Figure 2).

It can be seen that most of the geometric parameters for the two CI points are very similar, with differences no greater than 0.003 Å. Clearly these small differences in the geometry can hardly account for such different reactivity, in that **3** is known not to photocycloadd to olefins and **4** yields azetidines after irradiation. However, one of the distances, marked in red in Figure 2, is sufficiently different in the two structures to allow an explanation to be put forward. The key feature of these geometries is the triangular shape of the C═N−O moiety, which is planar in the ground state. This deformation causes the ground-state energy to increase while the excited state is stabilized, a situation that leads to the CI. The only distinction between **3** and **4** is the cyano group. The electron-withdrawing effect of the CN transmitted by the phenyl ring causes a partial positive charge to appear on the carbon atom of the C═N−O moiety in **4**. This partial positive charge interacts with the O atom, causing the C−O distance to shorten from 1.830 Å in **3** to 1.818 Å in **4**. Perhaps this deformation contributes to an increase in the energy of the CI point, thus allowing the system to spend some time in the excited state and yield photocycloaddition. To check that the enlargement of the active space is not essential, we carried out further calculations on **4** including the π orbitals of the cyano group (CAS(14,11)). Both geometries and relative energies remained almost unaltered.

Having assessed the effect of substitution on the CI geometry and thus on the course of the reaction, we aimed to study the regioselectivity of the reaction. For this purpose, we calculated the critical points for the photocycloaddition of **2** to methyl vinyl ether. We chose **2** for this part of the study because of its similar behavior and deformation in the excited state as **4**[11] and its smaller size. It has been reported[15] that a singlet excited state is involved in the photochemistry of this kind of compound.

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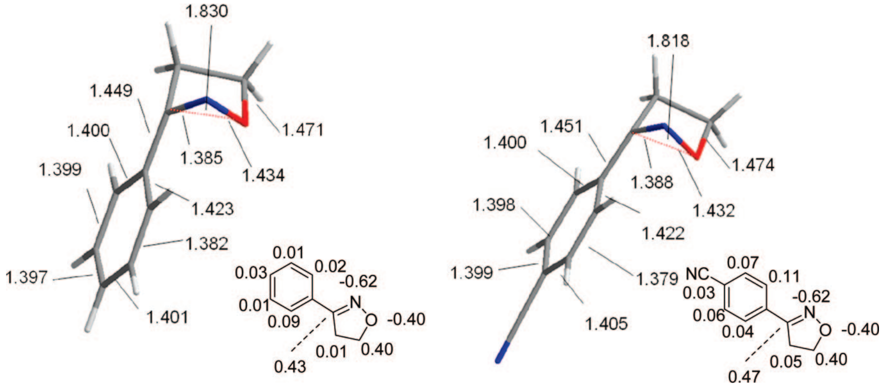


FIGURE 2. Optimized CI geometries and charges for **3** and **4**.

TABLE 1. CASPT2/6-31G* Relative Energies for Critical Points along the Potential Energy Surface for the Reaction of 2 with Methyl Vinyl Ether

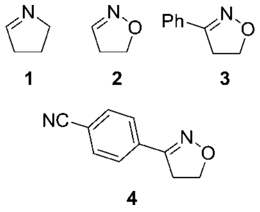
structure	state	energy[a]
FC	S_0	0.0
	S_1	158.4
	S_2	203.2
Min S_1	S_1	124.5
CI-a	S_0	68.9
	S_1	76.0
CI-b	S_0	85.3
	S_1	88.7
CI-c	S_0	69.6
	S_1	76.8
CI-d	S_0	82.5
	S_1	85.5
Prod-a	S_0	−9.8
Prod-b	S_0	−4.2
Prod-c	S_0	−4.6
Prod-d	S_0	−8.0

[a] CASPT2 energy (kcal/mol) relative to the ground-state minimum.

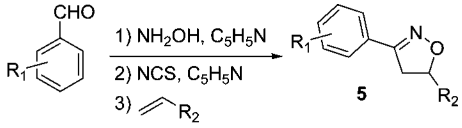
Accordingly, we found no experimental evidence of the participation of triplet states. The results are shown in Table 1 and Figure 3.

As can be seen, four approaches between the two molecules are possible, which implies the presence of up to four different CI points and four different photoproducts. These four possibilities correspond to two regioisomers, each with *endo* and *exo* descriptions available. Geometries for the CI points reflect the concerted reaction between the imine and alkene moieties. Both C═C (ca. 1.43 Å) and C═N (ca. 1.36 Å) distances increase compared to the ground state, and pyramidalization is clear in the atoms involved. The forming C−C bond in the azetidine has distances of 2.09 Å in **CI-a** and **CI-c** (lower in energy) and 2.17 Å in **CI-b** and **CI-d**. The forming N−C bond varies from ca. 2.18 Å in **CI-a** and **CI-c** to ca. 2.05 Å in **CI-b** and **CI-d**. Comparison of the energetics for the formation of these four possible compounds reveals that, although all four are achievable, there is a clear preference of at least 10 kcal/mol for one regioisomer (**CI-a**, **CI-c**) with respect to the other (**CI-b**, **CI-**

SCHEME 1. Model Compounds



SCHEME 2. Synthesized 3-Arylisoxazolines



R_1 = Ph	R_2 = Bu	40%	**5a**
p-MeO	Bu	48%	**5b**
p-CO_2Me	Bu	59%	**5c**
p-CN	Bu	62%	**5d**
m-CN	Bu	46%	**5e**
p-CN	Ph	67%	**5f**

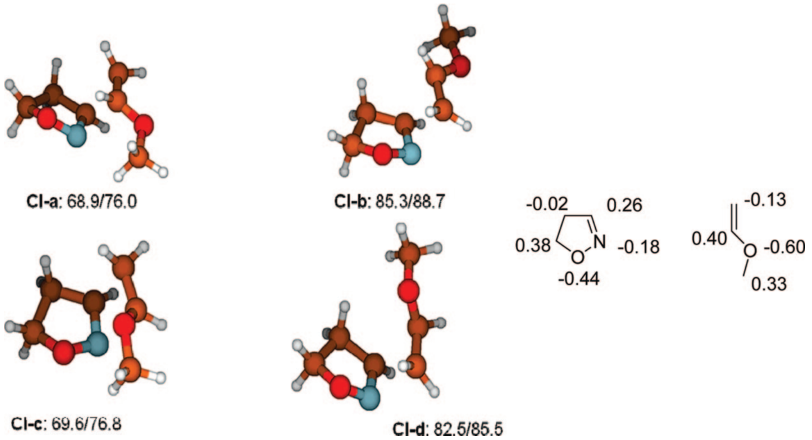


FIGURE 3. Optimized CI geometries and CASPT2 relative energies (S_0/S_1, kcal/mol) for the reaction of **2** with methyl vinyl ether. Atomic charges are also shown.

TABLE 2. CASPT2/6-31G* Relative Energies for Critical Points along the Potential Energy Surface for the Reaction of 2 with Dimethyl Vinyl Amine

structure	state	energy[a]
FC	S_0	0.0
	S_1	140.8
	S_2	200.2
Min S_1	S_1	112.8
CI-e	S_0	86.7
	S_1	92.5
CI-f	S_0	60.7
	S_1	69.0
Prod-e	S_0	1.1
Prod-f	S_0	0.3

[a] CASPT2 energy (kcal/mol) relative to the ground-state minimum.

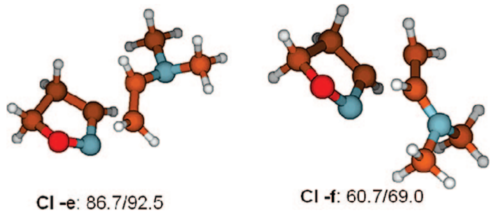


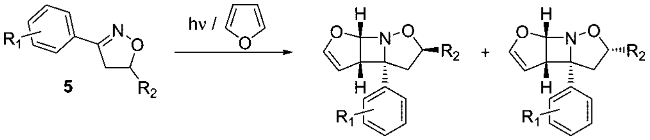
FIGURE 4. Optimized CI geometries and CASPT2 relative energies (kcal/mol) for the reaction of **2** with dimethyl vinyl amine.

TABLE 3. CASPT2/6-31G* Relative Energies for Critical Points along the Potential Energy Surface for the Reaction of 2 with Acrylaldehyde

structure	state	energy[a]
FC	S_0	0.0
	S_1	122.6
	S_2	191.0
Min S_1	S_1	74.4
CI-g	S_0	73.2
	S_1	74.8
CI-h	S_0	79.8
	S_1	84.0
Prod-g	S_0	3.4
Prod-h	S_0	−6.4

[a] CASPT2 energy (kcal/mol) relative to the ground-state minimum.

SCHEME 3. Irradiation of 3-Arylisoxazolines in the Presence of Furan



R_1 = *p*-CO_2Me	R_2 = Bu	**6c** (19%)	**6'c** (29%)
p-CN	Bu	**6d** (9%)	**6'd** (26%)
m-CN	Bu	**6e** (11%)	**6'e** (48%)
p-CN	Ph	**6f** (20%)	**6'f** (18%)

d). Thus, for the reaction of **2** with methyl vinyl ether (and by extension any O-substituted alkene with similar electronic and steric factors), the experimental outcome should show mainly one regioisomer, represented by **Prod-a** and **Prod-c**. The reason behind this seems to be related to the partial charges in the atoms involved. In the isoxazoline C═N moiety, the nitrogen atom is electron-rich and thus will preferentially interact with the electron-poor carbon in the olefin moiety to yield **Prod-a** and **Prod-c** (Figure 3). For each regioisomer, two different possibilities are still available, i.e., the *endo* and *exo* approaches. As can be seen from the results shown in Figure 3 and Table 1, there is little difference, if any, between these two approaches for each regioisomer. Thus, the computational data predict that a preference for the *endo* or the *exo* products is *not* expected and **Prod-a** and **Prod-c** are equally probable. However, the CASPT2 correction to the CASSCF energy causes an energy gap between states to appear that could conceal the relative stability of the *endo* and *exo* approaches. It should be noted that conclusions drawn from the study of **2** could be extrapolated to other isoxazolines with the same photochemical behavior (such as **4**).

We found it of interest to confirm the prediction from the calculations by means of experimental photoreactions. We synthesized several 3-arylisoxazolines[16] (see Scheme 2) and carried out irradiation experiments in the presence of an excess of furan using acetonitrile as the solvent.

In agreement with the theoretical predictions, photoadducts could not be detected upon irradiation of the phenyl or *p*-methoxyphenyl derivatives (**5a** and **5b**, respectively) and furan, but the presence of an electron-withdrawing group on the phenyl ring (**5c**−**5f**) enables the reaction to proceed (Scheme 3). The photoreaction led to the formation of only one regioisomer but as two diastereoisomer pairs, which were obtained in pure form by column chromatography on silica gel. The configuration was assigned on the basis of X-ray structure (**6f**, see Supporting Information) and difference NOESY (**6′f**) experiments. Interestingly, the reaction led to the formation of *exo* cycloadduct products. Although the formation of the *endo* products cannot be excluded, we were unable to isolate them or even detect them in the photomixture. This fact is very important because we were unable to predict the stereochemical outcome of the reaction from our computational results.

According to our calculations, the electron-withdrawing effect of the cyano group, transmitted along the phenyl ring, leads to a certain partial positive charge on the CI point, and this favors the photocycloaddition. This effect does not depend on the position of the cyano group as far as the geometries and energies for the structures of the *meta* and *para* isomers are very similar, although experimentally we found a higher yield when the cyano group was in the *meta* position.

The next step was to extend the study of the photocycloaddition to different olefins. This served not only to check the experimental feasibility of azetidines with diverse substitution patterns but also to obtain information on the effect that the alkene substitution has on the course of the reaction. We therefore calculated the critical points on the potential energy surface for the photocycloaddition of **2** to dimethyl vinyl amine, an N-substituted olefin. The results are shown in Table 2 and Figure 4.

Similar results were found for the dimethyl vinyl amine, and this is not surprising given that both electronic and steric factors are analogous to those in methyl vinyl ether. For the sake of simplicity, comparison of *endo* versus *exo* photocycloaddition was not considered. Two regioisomers are still possible in this reaction, but as in the case of O-substituted olefins, one of them should be formed preferentially as a result of interactions between partial charges. The geometries for the CI points have parameters similar to those obtained in the case of methyl vinyl ether. The distances for the C═C (ca. 1.44 Å) and C═N (ca. 1.36 Å) bonds together with the pyramidalization observed are consistent with a concerted reaction. The forming C−C bond

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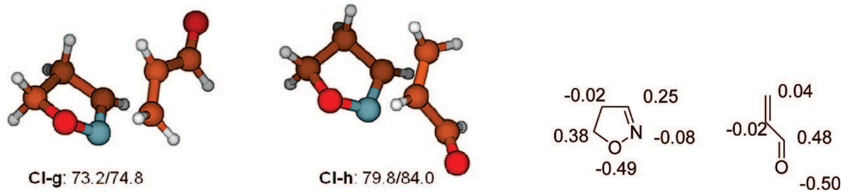
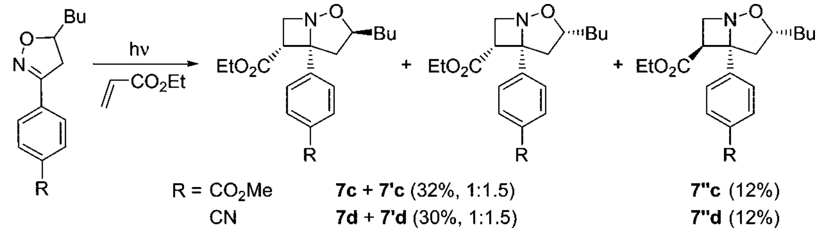


FIGURE 5. Optimized CI geometries and CASPT2 relative energies (S_0/S_1, kcal/mol) for the reaction of **2** with acrylaldehyde. Charge distributions are also shown.

SCHEME 4. Irradiation of Isoxazoline 5d in the Presence of Ethyl Acrylate



in the azetidines have distances of 2.18 Å in **CI-e** (higher in energy) and 1.94 Å in **CI-f**, while the forming N−C bond varies from 2.02 Å in **CI-e** to 2.33 Å in **CI-f**.

A very different outcome could result when the electronic character of the olefin is sufficiently different.[17] To test this hypothesis, we calculated the critical points for the photocycloaddition of **2** to acrylaldehyde. The results of these calculations are shown in Table 3 and Figure 5.

Once again, two different regioisomers are available. In this case the regioisomer predicted to be formed predominantly is different from the one formed for methyl vinyl ether and dimethyl vinyl amine. The reason for the preference, however, remains the same: the electrostatic interactions account for the regiochemistry. Once again, very similar geometries were found for the CI points. Values of ca. 1.44 Å were obtained for the C=C distances and ca. 1.36Å for the C=N. The forming C−C bond in the azetidine has a distance of 2.27 Å in **CI-g** (lower in energy) and 2.16 Å in **CI-h**, while the forming N−C bond has a distance of 1.97 Å in **CI-g** and 2.00 Å in **CI-h**.

We therefore investigated the irradiation of **5c** and **5d** in the presence of an alkene bearing an electron-withdrawing group, in this case ethyl acrylate (Scheme 4). In agreement with the theoretical calculations, the reaction led to the formation of only one regioisomer, which correlates with **CI-g**, but three diastereoisomer pairs, one corresponding to the *endo* addition and two to the *exo* addition. This is in contrast with the reaction with furan, where only the *exo* products were isolated (Scheme 3). From the reaction mixture only the *endo* diastereomer pair (**7″**) was obtained in pure form after column chromatography on silica gel. The configuration was assigned on the basis of difference NOESY experiments (**7″c**) and the ^{1}H NMR chemical shifts of the signal corresponding to H_{COOEt}, since these ethyl protons are shielded by the diamagnetic anisotropy of the phenyl ring (**7** and **7′**).[18]

The results described here allow an explanation for some previous data[10] and could be used to shed light on the mechanism of the photocycloaddition of imines. Some structural requirements for isoxazolines are made clear, but further computational and experimental effort will be needed to generalize this reaction to other imines.

Conclusions

The [2 + 2] photocycloaddition of alkenes to imines has been explored by computational methods. Interpretations based on the energy and geometry of critical points along the potential energy surface enabled the identification of some structural requirements of the imine moiety needed to yield azetidines. We also studied the regio- and stereochemistry of the reaction using a model compound for the imine and different olefins. It was found that the regiochemistry is completely dependent on the alkene used, as illustrated by the fact that the regioisomer obtained is different when olefins substituted by electron-withdrawing or electron-releasing groups are involved. A preference for a particular stereoisomer was not found, and as a consequence, mixtures of stereoisomers were predicted. To test the computational data, we carried out a complementary experimental study. A high correlation was found between data obtained in the calculations and in the experiments, a finding that supports the mechanistic proposals. Our results also provide an explanation for previous experimental data and could be used as a guide for the generalization of the photocycloaddition of imines to alkenes.

Experimental Section

Irradiation of 3-Arylisoxazolines 5. General Procedure. 3-Arylisoxazolines **5** (0.6 mmol) and 10 equiv of furan or ethyl acrylate (6 mmol) were dissolved in 50 mL of deoxygenated acetonitrile and irradiated at room temperature under Ar atmosphere through Pyrex glass with a 400 W medium-pressure mercury lamp, until **5** was consumed (TLC, hexane/AcOEt, 9:1). Solvents were then removed with a rotary evaporator, and the products were separated by column chromatography (silica gel, hexane/AcOEt, 9:1).

(2*S,6*S**,7*S**,9*R**)-9-Butyl-7-(4-cyanophenyl)-3,10-dioxa-1-azatricyclo[5.3.0.0^{2,6}]deca-4-ene (6d).** R_f = 0.30 (silica gel, hexane/AcOEt, 9:1), yield 16 mg, 9%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.65

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[17] The experimental outcome in the case of N-substituted olefins should be the same that the one found for O-substituted olefins, as predicted by the theoretical data. Thus, experimental exploration of the regio- and stereochemistry is well represented by methyl vinyl ether. Nevertheless, we tried to carry out the reaction with *N*-vinyl pyrrolidinone to further confirm the mechanism. Unfortunately, although some reaction took place, we found the product to be photoactive and no conclusive data could be obtained from the reaction mixture. Further efforts are currently under way.

[18] Silverstein, R. M.; Webster, F. X. *Spectrometric Identification of Organic Compounds*, 6th ed.; Wiley: New York, 1998.

(d, J = 8.5 Hz, 2H), 7.54 (d, J = 8.5 Hz, 2H), 6.35−6.33 (m, 1H), 5.61 (d, J = 7 Hz, 1H), 4.74 (m, 1H), 4.06−4.02 (m, 1H), 4.05−3.96 (m, 1H), 2.63 (dd, J = 13, 5.5 Hz, 1H), 2.40 (dd, J = 13, 10 Hz, 1H), 1.85−1.77 (m, 1H), 1.65−1.58 (m, 1H), 1.44−1.26 (m, 4H), 0.90 (t, J = 6 Hz, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 148.9, 147.3, 132.1, 126.6, 118.7, 110.6, 102.1, 100.0, 83.2, 79.0, 49.7, 49.0, 33.6, 28.5, 22.6, 13.9; ES(+) *m*/*z* 297.2 (M + 1). HRMS(+) *m*/*z* 229.1339 ([(M − furan)H$^+$], calcd 229.1341. Anal. Calcd for $C_{18}H_{20}N_2O_2$: C, 72.95; H, 6.80; N, 9.45. Found: C, 73.05; H, 6.85; N, 9.36.

(2*S,6*S**,7*S**,9*S**)-9-Butyl-7-(4-cyanophenyl)-3,10-dioxa-1-azatricyclo[5.3.0.0^{2,6}]deca-4-ene (6′d).** R_f = 0.15 (silica gel, hexane/AcOEt, 9:1), yield 46 mg, 26%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.64 (d, J = 8.5 Hz, 2H), 7.46 (d, J = 8.5 Hz, 2H), 6.35−6.33 (m, 1H), 5.73 (d, J = 6.5 Hz, 1H), 4.73−4.71 (m, 1H), 4.70−4.58 (m, 1H), 3.92−3.86 (m, 1H), 2.83 (dd, J = 12, 5 Hz, 1H), 1.89 (dd, J = 12, 11 Hz, 1H), 1.75−1.67 (m, 1H), 1.57−1.49 (m, 1H), 1.42−1.25 (m, 4H), 0.92−0.87 (m, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 148.4, 148.2, 132.2, 126.3, 118.8, 110.6, 102.1, 96.4, 82.2, 81.5, 49.5, 47.3, 32.5, 28.5, 22.6, 13.9; ES(+) *m*/*z* 297.2 (M + 1). HRMS(+) *m*/*z* 229.1339 ([(M − furan)H$^+$], calcd 229.1341. Anal. Calcd for $C_{18}H_{20}N_2O_2$: C, 72.95; H, 6.80; N, 9.45. Found: C, 73.10; H, 6.96; N, 9.38.

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Supporting Information Available: Experimental procedures, characterization data for new compounds, X-ray structure details for compound **6g** in CIF format, and Cartesian coordinates for the calculated geometries. This material is available free of charge via the Internet at http://pubs.acs.org.

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