DFT Study on the Molecular Mechanism of the [4 + 2] Cycloaddition between Thiobenzophenone and Arylalkenes *via* Radical Cations

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The mechanistic aspects of the radical cationic version of the [4 + 2] cycloaddition between thiobenzophenone **1** and three aryl-substituted alkenes **2a**−**c** have been studied using DFT methods at the UB3LYP/6-31G* level of theory. In the ground state, the Diels−Alder reaction follows an asynchronous concerted mechanism; the large activation energy associated with bond formation prevents this process. After generation of the radical cation (RC), formation of a molecular complex (MC) between **1** and **2a**−**c** initiates a stepwise mechanism, with attack of the sulfur atom of **1** to the aryl-conjugated position of **2a**−**c**. Subsequent ring closure is the rate-determining step of these cycloadditions. Methoxy or dimethylamino substitution at the aryl group, while stabilizing the corresponding RC, results in a less exothermic formation of MC and a significant increase of the cycloaddition barrier.

Introduction

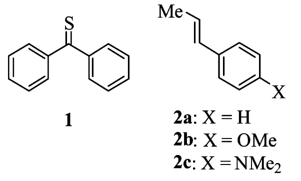
The Diels−Alder (DA) reaction is a classical process in organic chemistry that has been extensively used as a synthetic method for the construction of six-membered rings.[1] In addition, the DA reaction has been investigated to understand its mechanistic pathways from a theoretical point of view.[2] During the past few decades, hetero-DA cycloadditions have also attracted considerable interest and stimulated many experimental as well as theoretical investigations.[3] In this context, azadienes have been widely employed.[4] In comparison, the use of thiadienes has been less extensively explored; however, a number of processes of this type can be found in the literature.[5]

On the other hand, the electron-transfer (ET)-mediated DA reaction, where the diene or dienophile units are in the radical cationic form, has also been reported[6] and submitted to theoretical studies.[7] Recent density functional theory (DFT) and highly correlated molecular orbital calculations have studied the DA reaction of 1,3-butadiene radical cation with ethylene[7d–f] or acetylene,[7g] predicting a stepwise cycloaddition starting from ion−molecule complexes.

In a previous communication, we presented a novel ET-mediated DA cycloaddition between a thiadiene and a series of arylalkenes, using (thia)pyrylium salts as photosensitizers.[8] The scope of this reaction was investigated by using different types of electron-withdrawing or electron-releasing (ER) substituents. The mechanism was experimentally investigated by means of laser flash photolysis; it was found to involve formation of radical cations (RCs), which would react further in a concerted or stepwise fashion.

In order to obtain further insight into the mechanistic aspects of this novel process, we now performed theoretical calculations based on DFT methods at the UB3LYP/6-31G* level of theory. The reaction partners selected for the present work were thiobenzophenone (**1**) as thiadiene and three arylalkene derivatives (**2a**−**c**) as dienophiles, Chart 1.

CHART 1



In a first stage, the cycloaddition between **1** and **2a** has been analyzed in the ground state (GS), for comparison. Afterward, the studies have been focused on the [4 + 2] cycloaddition between **1** and **2a**−**c** in the radical cationic version as well as on the effect of ER substituents at the aryl group.

Computational Methods

DFT calculations were carried out using the B3LYP[9] exchange-correlation functional together with the standard 6-31G* basis set.[10] This methodology has been recently used in the study of the photodimerization of cyclohexadiene.[11] The spin-unrestricted (UB3LYP) formalism was used for the open-shell (doublet) RCs. The S^2 expectations for the doublet states of RCs all showed an ideal value (0.750) after spin annihilation, so the geometries and energetics are reliable for this study. Optimizations were carried out using the Berny analytical gradient optimization method.[12] Frequency calculations were performed on all structures to confirm that reactants, intermediates, and products do not have imaginary frequencies and that transition-state structures (TSs) have only one imaginary frequency. The relative energies were thus corrected for vibrational zero-point energies (ZPE, not scaled). The intrinsic reaction coordinate (IRC)[13] path

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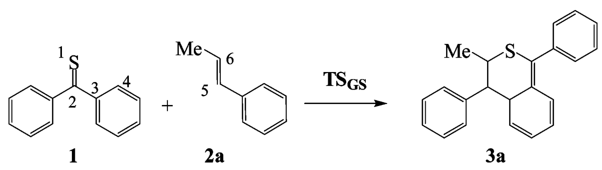
SCHEME 1



was traced in order to check the energy profiles connecting each TS with the two associated minima of the proposed mechanism by using the second-order González−Schlegel integration method.[14] The electronic structures of stationary points were analyzed by the natural bond orbital (NBO) method.[15] All calculations were carried out with the Gaussian 98 suite of programs.[16]

Results and Discussion

Ground-State [4 + 2] Cycloaddition Reaction Between 1 and 2a. Analysis of the B3LYP/6-31G* stationary points found at the potential-energy surface (PES) of the [4 + 2] cycloaddition reaction between **1** and **2a** (Scheme 1) to yield **3a** in the GS indicated that the process follows a concerted mechanism. A transition structure (**TS**$_{\mathbf{GS}}$) as well as the corresponding cycloadduct **3a** were located and characterized. Total and relative energies of the stationary points involved in this process are given in Table S1 of the Supporting Information.

Thus, the activation energy associated with **TS**$_{\mathbf{GS}}$ was found to be very large, 29.0 kcal/mol (see Figure 1). This value, which is close to that obtained for the DA between butadiene and ethylene (27.5 kcal/mol),[17] prevents cycloaddition at the GS. Moreover, the reaction was found to be an endothermic process (+17.1 kcal/mol). Thus, it is neither kinetically nor thermodynamically feasible. These unfavorable energies can be related with loss of the aromatic character of the aryl group of **1** involved in [4 + 2] cycloaddition.

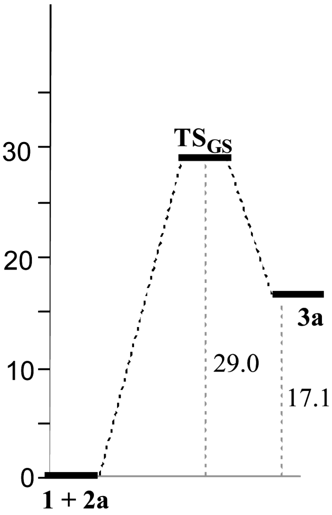
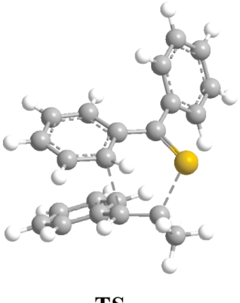


Figure 1. Energy profile, in kcal/mol, of the [4 + 2] cycloaddition of **1** with **2a**.



TS$_{\mathbf{GS}}$

Figure 2. Transition structure **TS**$_{\mathbf{GS}}$ involved in the [4 + 2] cycloaddition reaction between **1** and **2a**.

The geometry of **TS**$_{\mathbf{GS}}$ is depicted in Figure 2. The lengths of the two forming bonds were calculated as 2.10 (S1−C6) and 2.28 Å (C4−C5) (see Table S3 in Supporting Information), pointing to a concerted bond formation. However, the possible asynchronicity of the process could not be established from these data due to the fact that the C−S σ bond is larger than the C−C bond. Conversely, the extent of bond formation along the reaction pathway was provided by the bond order (BO) concept.[18] The BO values of the two forming bonds at the **TS**$_{\mathbf{GS}}$ were found to be 0.68 (S1−C6) and 0.33 (C4−C5), indicating an asynchronous process where formation of the S1−C6 bond is more advanced than that of the C4−C5 bond.

The natural population analysis (NPA) allowed us to evaluate a possible charge transfer (CT) through the cycloaddition reaction. The natural charges at **TS**$_{\mathbf{GS}}$ appeared to be shared between **1** and **2a**. The CT process from **2a** to **1** was negligible (0.04 e), indicating a nonpolar character of the **TS**$_{\mathbf{GS}}$ and supporting the large activation energy associated with this reaction at the GS.[19]

Radical Cationic [4 + 2] Cycloaddition Reaction Between 1 and 2a−c. Experimentally,[8] both the RCs of thiobenzophenone and the alkenes are generated by photosensitized electron transfer; these intermediates could in principle react further, following a concerted or a stepwise [4 + 2] cycloaddition mechanism. An exhaustive exploration of the PES for the RC version of the reaction between **1** and **2a−c** showed that the process actually occurs through a stepwise mechanism. In this context, after generation of the RCs, the reaction starts with formation of molecular complexes (MCs), irrespective of the nature of the ionized partner.

Thus, MCs formation was observed as an early step of the reaction, with distances between the two partners of 2.82 (**MCa**), 2.93 (**MCb**), and 3.21 Å (**MCc**). From these MCs, attack by the sulfur atom of **1** to the corresponding alkene **2a−c** would yield the intermediates **INa−c** via **TS1a−c**. In the subsequent step, ring closure would be achieved via **TS2a−c** with formation of the new six-membered heterocycle **3a−c**$^{\bullet+}$. (Scheme 2). Hence, six TSs, three INs, and the corresponding cycloadducts were located and characterized. Relative energies of the stationary points involved in the radical cationic version of the [4 + 2] cycloaddition between **1** and **2a−c** are shown in Table 1.

The RCs of **1** and **2a** had close relative energies, 171.8 (**1**$^{\bullet+}$) and 173.5 (**2a**$^{\bullet+}$) kcal/mol, respectively (see Table 1). Attachment of an ER methoxy group to the aryl moiety in **2b** decreased the relative energy of the corresponding RC **2b**$^{\bullet+}$ by 13.9 kcal/mol. A larger stabilization was found for the dimethylamino derivative **2c**, whose RC **2c**$^{\bullet+}$ was 28.9 kcal/mol more stable than **2a**$^{\bullet+}$. Formation of the MCs between **1** and **2a**$^{\bullet+}$, **2b**$^{\bullet+}$, and **2c**$^{\bullet+}$ was found to be exothermic by −19.2, −11.5, and −6.3 kcal/mol, respectively. Therefore, a qualitative relationship was observed between the ER character of the substituent (H < OMe < NMe$_2$) and the exothermic nature of MC formation.

Starting from the MCs, the TSs for generation of intermediates **INa−c** had very low energy barriers, namely, 0.0 (**TS1a**), 0.6 (**TS1b**), and 2.9 kcal/mol (**TS1c**). Formation of the S1−C6 bond at the intermediates can be considered nearly isothermic, between −0.1 and 3.0 kcal/mol. It has to be stated that due to the local bumpy surfaces more than one structure could be

SCHEME 2

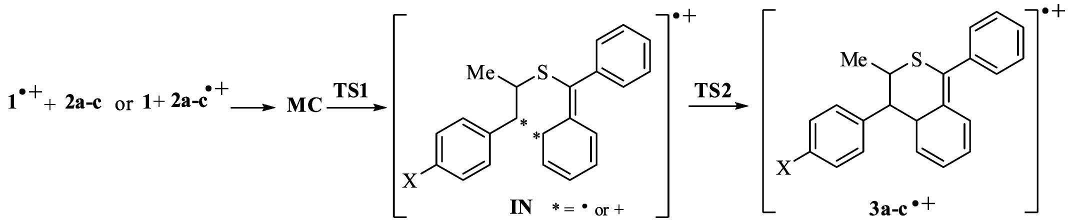


TABLE 1: B3LYP/6-31G* Relative Energies (ΔE,[a] in kcal/mol) of the Stationary Points Involved in the Cycloaddition Between 1 and 2a−c via RC

species	ΔE^a	species	ΔE^a	species	ΔE^a
1$^{\bullet+}$	171.8				
2a$^{\bullet+}$	173.5	**2b**$^{\bullet+}$	159.6	**2c**$^{\bullet+}$	144.6
MCa	−19.2	**MCb**	−11.5	**MCc**	−6.3
TS1a	−19.2	**TS1b**	−10.9	**TS1c**	−3.4
INa	−19.3	**INb**	−10.7	**INc**	−3.3
TS2a	−9.7	**TS2b**	0.0	**TS2c**	8.9
3a$^{\bullet+}$	−18.7	**3b**$^{\bullet+}$	−6.5	**3c**$^{\bullet+}$	4.1

[a] Relative to **1**, **2a−c, 1** + **2**, or **1** + **2a−c**$^{\bullet+}$.

obtained for these intermediates and that, among others, **INa−c** were the most appropriate ones as they lie along the reaction coordinate. The second step of the cycloaddition was ring closure with formation of the C4−C5 carbon bond; the energy barriers from the corresponding intermediates were found to be 9.6 (**TS2a**), 10.7 (**TS2b**), and 12.2 kcal/mol (**TS2c**). Again, as for MC formation, a qualitative relationship was observed between the ER character of the substituent and the energy barrier associated with the ring-closure step. Finally, formation of **3a**$^{\bullet+}$, **3b**$^{\bullet+}$, and **3c**$^{\bullet+}$ from the MCs was endothermic by 0.5, 5.0, and 10.4 kcal/mol, respectively.

In view of the ionic character of these cycloadditions and the presence of the sulfur atom on thiobenzophenone **1**, a more complete basis set was used for single-point energy calculations at the UB3LYP/6-311+G* level. The resulting total and relative energies are given in Table S2 (Supporting Information). They showed a lower stabilization of the stationary points with respect to the separated reagents through the process leading from **MCa** (0.5 kcal/mol) to **3a**$^{\bullet+}$ (1.9 kcal/mol) due to a decrease of the basis set superposition error (BBSE). However, the relative energies along cycloaddition remained unchanged. At this level, the reaction also had a very flat PES between **MCa** and **INa**. The activation barrier associated with **TS2a** remained 9.4 kcal/mol. These energetic results corroborate the B3LYP/6-31G* energies.

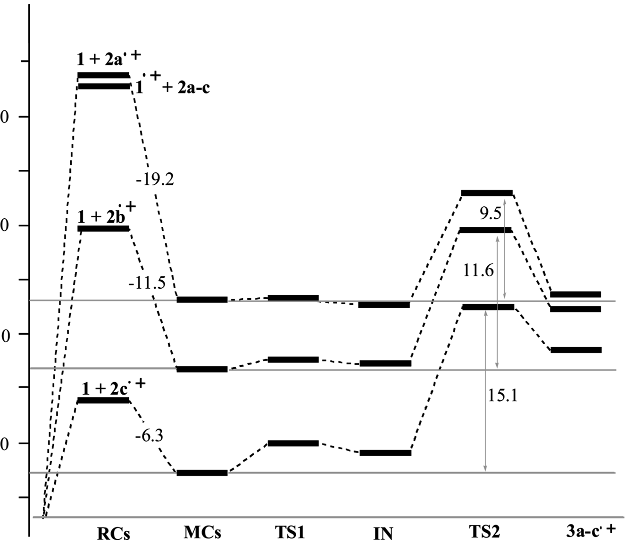


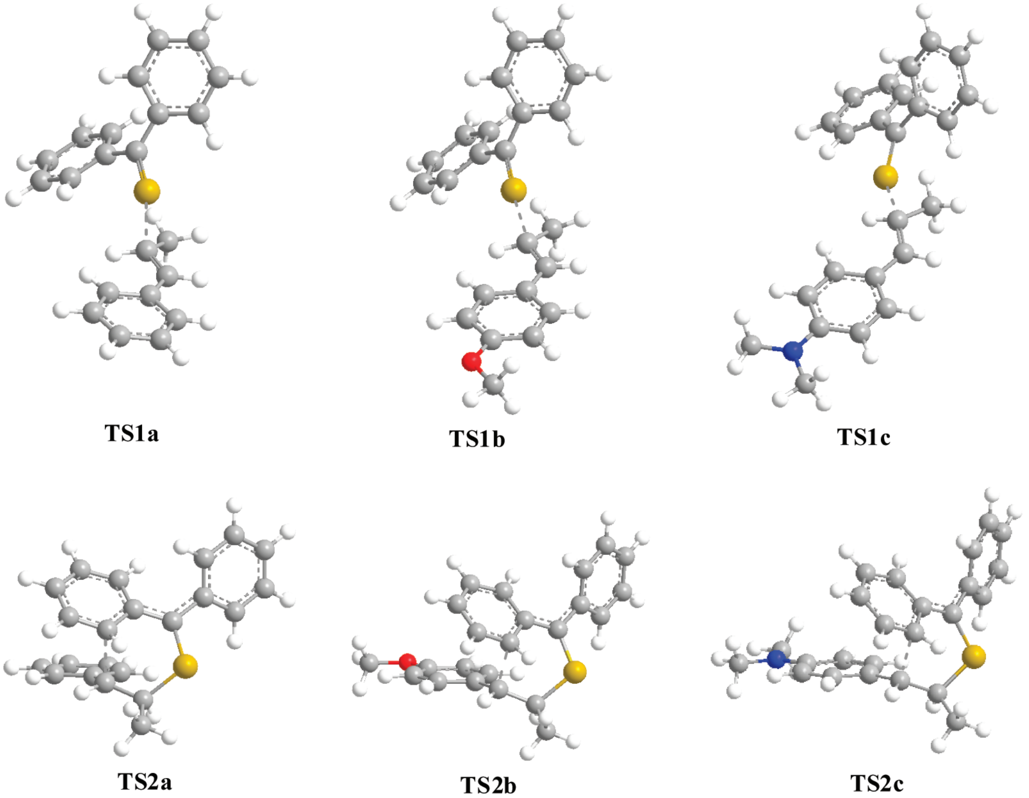
Figure 3. Energy profiles, in kcal/mol, for the stepwise [4 + 2] cycloaddition via RC between **1** and **2a−c**.

Figure 3 depicts the energy profiles for the cycloaddition between **1** and **2a−c** via RC with special attention to the ER substitution effects. It is worth mentioning that ring closure between C4 and C5 was the rate-determining step of these reactions. Thus, the exothermic character of MC formation was found to decrease with ER substitution, whereas the opposite was true with activation energies, whose values were 9.5 (via **TS2a**), 11.5 (via **TS2b**), and 15.2 kcal/mol (via **TS2c**). It is remarkable that the activation energy for the [4 + 2] cycloaddition between **1** and **2a**$^{\bullet+}$, via **TS2a**, was 19.5 kcal/mol lower in energy than that for the GS cycloaddition between **1** and **2a**, via **TS**$_{\mathbf{GS}}$. This dramatic decrease can be attributed to the ionic character of the cycloadditions via RC, which take place with a large degree of CT (see below).[20] Note that cycloadditions between **1** and **2a,b** via RC have a very flat PES around **MC**, **TS1**, and **IN**. In spite of their close energies, the nature of these stationary points was unambiguously characterized by frequency analysis (see Table S3 in Supporting Information).

The TS geometries involved in the radical cationic [4 + 2] cycloadditions of **1** with **2a−c** are shown in Figure 4, while the distances between S1−C6 and C4−C5 atoms at the stationary points involved in the cycloaddition reactions are given in Table S3 (Supporting Information). In the first step, the lengths of the forming S1−C6 bonds were found to be 2.29 Å at **TS1a**, 2.22 Å at **TS1b**, and 2.20 Å at **TS1c**; the distances between C4 and C5 were ca. 4.8 Å in all cases. In the intermediates INs, the S1−C6 bond length values were shorter, ca. 2.00 Å. Finally, at the TSs associated with ring closure the lengths of the forming C4−C5 bonds were found to be 2.16, 2.11, and 2.07 Å at **TS2a**, **TS2b**, and **TS2c**, respectively, Chart 1.

The electronic structure of the TSs and INs of these radical cationic DA reactions was analyzed by using the BOs and the natural charges obtained by a NBO analysis. The BO values of the S1−C6 forming bonds at the TSs associated with the first step of the cycloadditions were 0.55 at **TS1a**, 0.59 at **TS1b**, and 0.60 at **TS1c**. The corresponding BO values at the intermediates INs were 0.80 at **INa**, 0.78 at **INb**, and 0.80 at **INc**. Regarding the TSs associated with ring closure, the C4−C5 BO values were found to be 0.37 at **TS2a**, 0.40 at **TS2b**, and 0.43 at **TS2c**. Therefore, the shorter C4−C5 bond lengths in the alkenes with ER substituents, together with the higher BO values, clearly indicate that their TSs are more advanced.

The natural population analysis (NPA) was used for evaluation of CT in radical cationic [4 + 2] cycloadditions. In this way, it was found that the UB3LYP/6-31G* natural atomic charges at the stationary points are shared between the original **1** and **2a−c** fragments (see data in Table 2). Note that together with formation of two new σ bonds, a large amount of electron



TS1a **TS1b** **TS1c**

TS2a **TS2b** **TS2c**

Figure 4. Transition structures involved in the stepwise radical cationic [4 + 2] cycloadditions between **1** and **2a**−**c**.

TABLE 2: Charges (au) in 1 and 2a−c Fragments at the Stationary Points Involved in the Stepwise RC Cycloaddition

fragment	RC	MC	TS1	IN	TS2	3a−c$^{\bullet+}$
1	0.00	0.49	0.58	0.72	0.76	0.84
2a$^{\bullet+}$	1.00	0.51	0.42	0.28	0.24	0.16
1	0.00	0.36	0.53	0.60	0.69	0.82
2b$^{\bullet+}$	1.00	0.64	0.47	0.40	0.31	0.18
1	0.00	0.19	0.43	0.48	0.60	0.63
2c$^{\bullet+}$	1.00	0.81	0.57	0.52	0.40	0.37

density is transferred from thiobenzophenone **1** to the alkene RCs **2a**−**c**$^{\bullet+}$ along the reaction. Analysis of atomic Mulliken spin at the stationary points of these [4 + 2] cycloadditions indicated that charge and spin transfer are coupled. According to NPA, a large amount of electron density has already been transferred at the MCs; this accounts for the remarkable stabilization of the molecular complexes. Thus, CT goes from ca. 0.5 e at **MCa** to ca. 0.2 e at **MCc**. This trend can be related with ER substitution on the alkene, which stabilizes the corresponding RCs **2b,c**$^{\bullet+}$ by delocalization of the oxygen or nitrogen lone pair through the π system, thereby decreasing the exothermic character of MC formation.

At **TS1**, NPA showed an enhanced CT to the thiobenzophenone framework with the increasing ER character of the aryl substituent. Note that at this stage of the cycloaddition, CT increased on going from **MC** to **TS1** by 0.09 (**TS1a**), 0.17 (**TS1b**), or 0.24 (**TS1c**); this trend is opposite to that observed in formation of MCs. As a consequence of such counterbalance, the three TSs presented a close degree of CT: 0.58 (**TS1a**), 0.53 (**TS1b**), and 0.43 e (**TS1c**).[20]

At the intermediates **IN** an even higher amount of electron density had been transferred from thiobenzophenone to the alkenes. Accordingly, these species exhibited the following residual charges at the arylalkene framework: 0.28 (**INa**), 0.40 (**INb**), and 0.52 e (**INc**). Again, ER substitution resulted in less advanced CT, as expected from the relative stability of the corresponding intermediates: whereas formation of **INa** is exothermic, formation of **INc** is endothermic.

Following the general trend, the degree of CT at **TS2** (0.76 e at **TSa**, 0.69 e at **TSb**, and 0.60 e at **TSc**) revealed once more the effects associated with ER substitution. Because these TSs correspond to the rate-determining step, their electronic structures can in principle be correlated with the relative reactivities experimentally observed. In fact, the RC cycloaddition of **1** with **2c** had a larger activation energy (15.1 kcal/mol, **TS2c**) than the analogous reaction between **1** and **2a** (9.5 kcal/mol, **TS2a**) as a consequence of the reluctance of the alkene framework to accept additional electron density along the formation of the second σ bond.

Finally, full transfer of one electron from the original thiobenzophenone to the alkenes should be achieved at the end of the process, when formation of the [4 + 2] cycloadducts **3a**−**c**$^{\bullet+}$ is completed. However, some delocalization diminishes the positive charge at the thiobenzophenone fragment, where the following values were found: 0.84 (**3a**$^{\bullet+}$), 0.82 (**3b**$^{\bullet+}$), and 0.63 e (**3c**$^{\bullet+}$). Note that these values decrease with the ER character of the arylalkene substituent.

Conclusion

The mechanistic aspects of the [4 + 2] cycloaddition reaction between **1** and three aryl-substituted alkenes **2a**−**c** have been studied using DFT methods at the UB3LYP/6-31G* level of theory. At the ground state, the Diels−Alder reaction between **1** and **2a** follows an asynchronous concerted mechanism. The observed large activation energy associated with bond formation, 29.0 kcal/mol, prevents the cycloaddition reaction.

On the other hand, after generation of the RCs, formation of a molecular complex, MC, between **1** and **2a**−**c** initiates a stepwise mechanism with attack by the sulfur atom of **1** to the aryl conjugated position of the alkenes. Subsequent ring closure is the rate-determining step of these [4 + 2] cycloadditions. A clear effect of electron-releasing substituents at the arylalkenes on the reaction mechanism has been observed. In the presence of this type of substituents, charge delocation along the reaction pathway is delayed, decreasing the exothermic character of MC formation and increasing significantly the cycloaddition barrier.

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Supporting Information Available: UB3LYP/6-31G* total and relative energies, zero-point energies, and ZPE-corrected total and relative energies of the stationary points involved in the cycloadditions between **1** and **2a** or between **1** and **2a**−**c** via RCs; UB3LYP/6-311+G* total and relative energies of the stationary points involved in the cycloadditions between **1** and **2a** via RCs; Lengths of the C−S and C−C forming bonds, S^2 values of RCs, imaginary frequency of TSs, and lowest vibrational frequency of the molecular complexes, intermediates, and cycloadducts of the stationary points involved in the cycloadditions between **1** and **2a** or between **1** and **2a**−**c** via RCs; Cartesian coordinates of the stationary points involved in the cycloadditions between **1** and **2a**−**c** via RC. This material is available free of charge via the Internet at http://pubs.acs.org.

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