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Selectivity in the Electron Transfer Catalyzed Diels−Alder Reaction of (*R*)-α-Phellandrene and 4-Methoxystyrene

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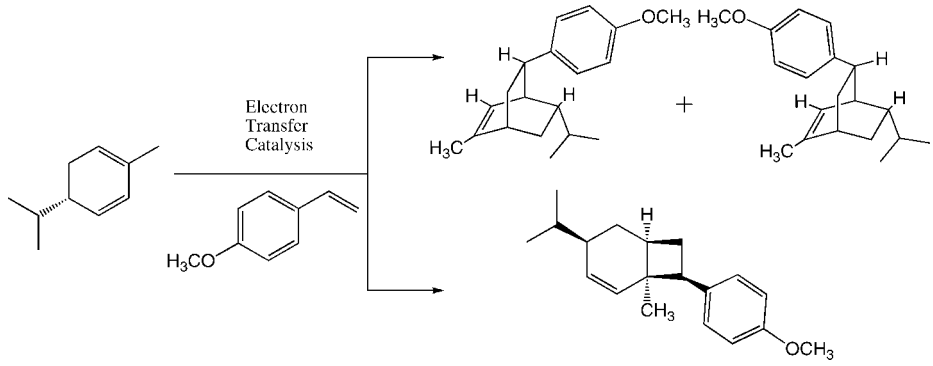

Electron transfer catalysis is an effective method for the acceleration of Diels−Alder reactions between two substrates of similar electron density. The dependence of the selectivity of the Diels−Alder reaction between (*R*)-α-phellandrene and 4-methoxystyrene catalyzed by photoinduced electron transfer with tris(4-methoxyphenyl) pyrylium tetrafluoroborate is studied. Despite the fact that the radical ions involved are highly reactive species, complete regioselectivity favoring attack on the more highly substituted double bond is observed. The *endo*/*exo* selectivity and the periselectivity between [4 + 2] and [2 + 2] cycloaddition is found to be solvent-dependent. Stereochemical analysis showed that the periselectivity is correlated with the facial selectivity, with attack *trans* to the isopropyl group leading to the [4 + 2] product and *cis* attack leading to the formation of the [2 + 2] product. A good correlation between the dielectric constant of the solvent and the *endo*/*exo* ratio is found, but more polar solvents lead to lower periselectivity. The effect of reactant and catalyst concentrations is found to be smaller. These results are rationalized in the context of the relative stability of the ion−molecule complexes and the singly linked intermediate of the reaction.

Introduction

The acceleration of pericyclic reactions through electron transfer catalysis (ETC) has been one of the most fruitful areas of radical ion chemistry.[1] Using a sequence of one-electron oxidation, pericyclic reaction, and back electron transfer, a wide range of electrocyclic reactions,[2] cycloadditions,[3] cycloreversions,[4] and sigmatropic shifts[5] can be accelerated by up to 13 orders of magnitude. As is the case in the thermal pericyclic reactions, the radical cation Diels−Alder reaction has been particularly useful because of the rapid construction of an important structural element, the possibility to react two substrates of similar electron density, and the fact that, unlike most other pericyclic reactions of radical cations, it could be extended to a variety of heterosubstituted compounds.[6]

Starting from the seminal work of Bauld and co-workers,[7] the mechanism of the radical cation Diels−Alder reaction has been studied extensively using a variety of experimental[8] and computational methods.[9] Stereochemical studies showed that for different substituted systems, the reaction proceeds through a stepwise process that allows the scrambling of stereochemistry.[10] This is confirmed by the calculation of the reaction pathways at different levels of theory by our group[11] and others[12]

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that indicate the presence of acyclic intermediates in different direct and indirect radical cation Diels−Alder pathways. The relative stabilities of these intermediates can be used to rationalize the experimentally observed regioselectivity of the reaction.[13] The structures of stationary points and the overall shape of the potential energy surface strongly resembles the ones calculated for the stepwise, biradical pathways of the thermal Diels−Alder reaction. In contrast, the concerted, symmetric transition structures analogous to the one calculated for the thermal reaction are distorted by vibronic coupling to low-lying excited states in a pseudo-second-order Jahn−Teller distortions and are therefore second-order saddle points much higher in energy.[1d,e,11]

Another useful feature of the radical cation Diels−Alder reaction is the empirical finding that the reaction is highly stereoselective. Even for combinations of nonpolar diene−dienophile combinations, good to excellent *endo*/*exo* ratios were obtained.[8] It is this dichotomy between the widely agreed upon stepwise pathway of electron transfer reactions, which can provide an assortment of products, versus the empirically observed selectivity that makes a variation of reaction conditions a useful study. When a chiral diene was used, complete facial diastereoselectivity of the reaction was observed.[14] In a rare application of a radical cation Diels−Alder reaction to a natural product synthesis, the ETC reaction of phenyl vinyl sulfide with a chiral diene only gave a 1.9:1.3:1 diastereoselectivity. Nevertheless, this reaction is still much more selective than the corresponding thermal reaction, which gives 11 isomers in approximately equal amounts.[15] These findings are surprising considering that the radical cations involved are highly reactive species and the calculated energy differences between the different stationary points on the potential energy surfaces of these reactions are typically very small.[11−13] It is therefore not obvious what the origin of the observed selectivity is and how it depends on the reaction conditions.

So far, there have been very few systematic investigations of the selectivity of radical cation Diels−Alder reactions. Martiny et al. studied the *endo*/*exo* selectivity in the radical cation Diels−Alder reaction of simple model systems as a function of the reaction conditions using the sensitizer 2,4,6-tris(4-methoxy phenyl) pyrylium tetrafluoroborate, which has been shown to successfully catalyze [4 + 2] and [2 + 2] cycloaddition reactions in the absence of oxygen.[16] This electron transfer sensitizer was deemed particularly useful in the study of the reaction conditions because the neutral pyrylium radical formed by the electron transfer does not strongly complex to the substrate radical cation, thus yielding free radical cations and less complex reaction mechanisms. Variable concentrations, stoichiometric ratios, solvents, and sensitizers were used in reactions to expose possible trends and mechanistic pathways. Depending on these variables, *endo*/*exo* ratios of 2.4:1 up to 24.3:1 were found for the electron transfer Diels−Alder reaction of 1,3-cyclohexadiene and styrenes.[16a]

Here, we present the first systematic study of chemo-, peri-, and stereoselectivity of electron transfer catalyzed Diels−Alder reactions of a chiral diene as a function of the reaction conditions. After identifying the main products, the regio- and diastereoselectivity of reacting (*R*)-α-phellandrene (**1**) and electron-rich 4-methoxystyrene (**2**) while varying solvent polarity, concentration, electron transfer catalysts, and catalyst concentration will be discussed. Although **1** has been used numerous times as a diene in radical cation Diels−Alder reactions,[6c,10b,14,17] the ETC reaction with the prototypical **2** as well as the factors controlling the chemo-, regio-, and diastereoselectivity of the reaction have to the best of our knowledge not been studied.

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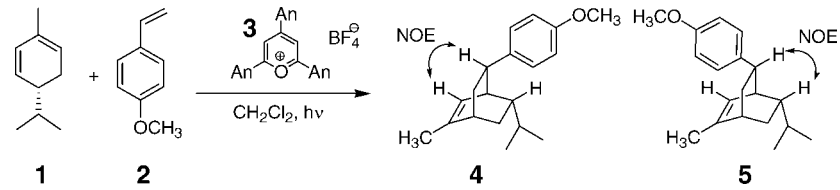

FIGURE 1. Main products of the ETC reaction of **1** and **2** and key NOE contacts.

TABLE 1. Effect of Absolute Concentration in CH_2Cl_2

	concentration [M]			
	1.51	0.50	0.15	0.05
dimers of **1**	1.00	1.00	1.00	1.00
mixed adducts	0.33	0.43	2.67	8.12
dimers of **2**	∼0	0.04	0.38	1.32
4	29%	28%	37%	35%
5	55%	53%	60%	63%
6	2%	2%	2%	2%
7	8%	9%	1%	0%
8	2%	3%	trace	0%
9	2%	2%	trace	0%
10	3%	2%	trace	trace

Results and Discussion

As a model diene for the study of the diastereoselectivity of the radical cation Diels−Alder reaction, the commercially available (*R*)-α-phellandrene (**1**) was chosen because it can reasonably be expected that only steric interactions will be relevant for the reaction outcome, simplifying the analysis of the results. GC/MS analysis of the reaction of **1** with 4-methoxystyrene (**2**) in dichloromethane under electron transfer catalysis induced by irradiation at 420 nm in the presence of 2% 2,4,6-tris(4-methoxyphenyl) pyrylium tetrafluorborate (**3**) leads to the formation of seven different isomers of the mixed adduct, **4**−**10**, in a combined isolated yield of 29% of which only two are present in sufficient amounts to be isolated and structurally characterized. Control experiments show that, in agreement with previous studies on related systems,[16] the presence of both **3** and irradiation is necessary for product formation, thus confirming the electron transfer catalysis of the reaction. Several dimers of **1** were formed in appreciable amounts as well (for a typical GC trace, see Supporting Information). Besides **4** and **5**, the other isomers were formed in small amounts. This and the very similar polarity of the isomers of essentially pure hydrocarbons made the isolation challenging. HPLC and normal phase silica column chromatography showed no useful separation of the mixture because of their similar polarity. However, effective separation was achieved using argentated silica. This technique, where silica gel is pretreated with silver by forming strong $Si-O-Ag^+$ interactions, has been used most commonly in separations of molecules with steroidal backbones.[18] The well-known ability of silver to complex with a double bond leads to a resolution of the diastereomers based on their steric accessibility. A combination of standard chromatography and this method can be used on a preparative scale and yielded 96% and 97% pure (by NMR) samples of **4** and **5** in 2% and 4% yield, respectively.

The structures of **4** and **5** were determined on the basis of the assignments of the protons by 2D NMR (see (5.91 ppm, 2.75 ppm) and (1.39 ppm, 2.83 ppm) ROESY crosspeaks for **4** and **5**, respectively, in Supporting Information), and the relative configuration was assigned using the ROESY cross peaks of the benzylic proton with olefinic and *exo* protons in **4** and **5**, respectively, as indicated in Figure 1. Compounds **4** and **5** are therefore assigned to be the *exo* and *endo* products of the cycloadditions, respectively. It is important to note that no significant amounts of the product resulting from the attack on the other side of the diene are observed under these reaction conditions. This very high facial selectivity is not only synthetically useful but also mechanistically interesting and can be understood on the basis of the calculations of simple model systems. The reaction is generally accepted to be stepwise, and the relative configuration is set in the formation of the singly linked intermediate. Earlier theoretical work[13] has shown that the reaction of the methyl-substituted 1,3-diene radical cation is ∼7 kcal/mol exothermic. Consequently, an early transition state would be expected, but the bond lengths for the formation of the first bond in the transition structure is with ∼2.0−2.1 Å shorter than expected. This is due to the initial formation of an ion−molecule complex that is approximately isoenergetic with the singly linked intermediate. These calculations also predicted very similar energies for the *endo* and *exo* pathways, in agreement with experiment.[13]

After elucidating the structure of the two major isomers, we then turned our attention to the effect of the reaction conditions on the diastereoselectivity of the reactions. First, we investigated the effect of the absolute concentration of diene and dienophile on the reaction. For this purpose, GC was used to quantify the relative amounts of **4** and **5**, as well as the minor isomers **6**−**10**. Coinjection of isolated and structurally characterized samples was used to distinguish the respective retention times of the hetero- and homodimers and assign the isomers. Although the minor isomers were not formed in sufficient amounts to allow for their detailed structural identification, analysis of the GC/MS data (see Supporting Information) showed that **6**−**10** are isomers of **4** and **5**.

The results for the variation of the absolute concentration of a 1:1 mixture of diene and dienophile in the reaction in dichloromethane are summarized in Table 1. The reaction is less selective with respect to heterodimer versus homodimer formation at high substrate concentrations, with the selectivity reversing over the concentration range studied here. The fact that both homodimers are found is consistent with the fact that although the exact oxidation potentials of **1** and **2** are not known due to the irreversibility of the redox reaction under typical cyclic voltametry conditions, the peak potentials are sufficiently close to indicate that both radical cations $\mathbf{1}^{\bullet+}$ and $\mathbf{2}^{\bullet+}$ are formed. In contrast, the concentration dependence of the relative yields for the homodimers as well as the mixed adducts is more difficult to understand. The finding that the relative amount of

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TABLE 2. Solvent Effect on ETC Reaction of 1 and 2

	conditions			
	CH_2Cl_2	acetone	acetonitrile	DMSO
dimers of **1**	1.00	1.00	1.00	1.00
mixed adducts	2.67	2.19	0.99	0.67
dimers of **2**	0.38	0.21	0.04	0.02
4	37.4%	34.9%	21.5%	9.5%
5	59.5%	57.9%	45.3%	29.8%
6	1.8%	1.4%	0.7%	5.4%
7	0.7%	3.3%	12.1%	26.4%
8	0.1%	1.2%	4.8%	9.9%
9	0.2%	1.0%	3.4%	7.2%
10	0.3%	0.3%	12.3%	11.7%

homodimers of **1** is lowest at low concentrations could be rationalized by the hypothesis that formation of these most sterically hindered homodimers relies on reduction of the singly linked intermediate to the biradical, which would then rapidly close. This hypothesis would be in analogy to the concentration dependence of the formation of the strained cyclobutane through ETC dimerization of **2**.[19] It is, however, noteworthy that from the practical point of view, the reaction should be run at lower concentrations of diene and dienophile to ensure the predominant formation of **4** and **5** and that this stepwise reaction of a highly reactive intermediate, which could be expected to have poor selectivity, shows in fact a ~98% facial selectivity in dilute solutions to give **4** and **5**.

Following the study of the concentration effects, various solvents were tested at a concentration of 0.15 M to observe the effect of solvent polarity on the reaction. It can be hypothesized that the solvent could have an effect at two points of the reaction pathway: first, a more polar solvent would solvate the substrate radical cation better and weaken the interactions in the initial ion−molecule complex, which are thought to contribute to the stereoselection; second, the solvent could stabilize the localized charges in the acyclic intermediate, which could lead to stereochemical scrambling. Due to the cyclic nature of the diene, no *trans* addition would be possible in the reaction studied here, but a rotation around the C_1-C_2 bond could interconvert the *endo* and *exo* products independently of the orientation of the initial attack. The results of these studies are summarized in Table 2.

Increasing the polarity of the solvent favors the dimerization of the diene **1** over the formation of mixed adducts. The free radical cation formed in a more polar solvent is more likely to react to form either a mixed or a homoadduct, giving the poorer selectivity that is observed. This conversely suggests that the ion−molecule complexes present in less polar solvents have a higher selectivity. The other chemoselectivity trend observed is that the amount of the homodimer of the dienophile **2** increases relative to the dimerization of the diene **1** in less polar solvents, even though the homodimer of **1** is still favored. This selectivity trend indicates that both substrates can be oxidized by the excited state of **3** in a diffusion controlled fashion but that in polar solvents $\mathbf{2}^{\bullet+}$ has a sufficiently long lifetime to oxidize **1**. The alternative explanation that the relative redox potentials of **1** and **2** changes as a function of the solvent appears to be less likely but cannot be excluded.

The effect of solvent polarity on the product distribution of the mixed adducts is two-fold. First, significantly larger amounts other isomers are formed in more polar solvent and **7** and **10** become the second and third most abundant product in DMSO. As will be discussed in more detail below, these two isomers

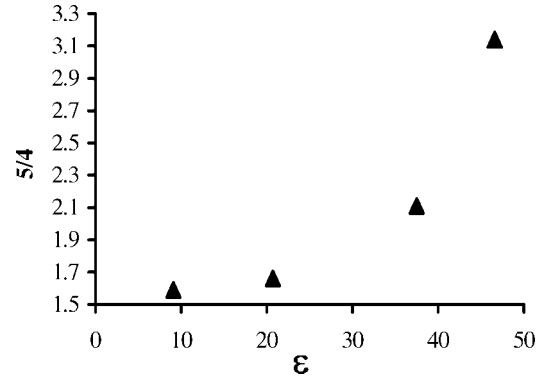

FIGURE 2. *Endo*/*exo* ratio of **4** to **5** as a function of dielectric constant.

correspond to [2 + 2] cycloadditions of **1** and **2** and are most likely formed through a back electron transfer of the singly linked intermediate to form the biradical, which then closes the cyclobutane ring.[19] Second, the solvent polarity has a substantial effect on the *endo*/*exo* ratio as shown in Figure 2. In contrast to the decreasing selectivity for the formation of **4** and **5**, an increase in stereoselectivity is observed with increasing polarity of the solvent. This and the data in Table 2 indicate that the effect of the solvent polarity is different for the pathway leading the *exo* isomer **4**, where the yield decreases 4-fold, than for the pathway leading the *endo* isomer **5**, where the yield decreases only 2-fold. This finding could be rationalized by the hypothesis that the larger solvent stabilization of the *exo* form of the ion−molecule complex or singly linked intermediate relative to the corresponding *endo* diastereomer can lead to larger amount of other isomers than the corresponding *endo* form. In polar solvents, the *exo* isomers are therefore more likely to react through other pathways than the *endo* isomers, which are more likely to collapse to **5**.

Finally, we investigated the effect of the sensitizer. Varying the reaction time and catalyst concentration in solution was tested and had no impact on mixed adduct selectivity (see Supporting Information). It is generally accepted that the use of a cationic sensitizer or cosensitizer in reactions catalyzed by oxidative electron transfer is beneficial because it does not lead to ion pairs of the substrate radical cation with the radical anion of the sensitizer after ET.[16] Thus, diffusion is not hindered by Coulomb attraction and will rapidly lead to the formation of free radical ions, which can then react with the respective neutral molecules. We tested this hypothesis by comparing the chemo- and stereoselectivity for the standard reaction conditions in dichloromethane and acetonitrile catalyzed by $\mathbf{3}^+$ and 1,10-dicyanoanthracene **11**. The effects of the solvent on ET reactions catalyzed by $\mathbf{3}^+$ have already been discussed earlier. In the reactions catalyzed by **11**, the selectivity for the formation of mixed adducts is higher even though the total amount of all products after the same reaction time is much smaller than in the case of the reactions catalyzed by $\mathbf{3}^+$ as shown by comparison of the GC peak areas to the ones of unreacted substrate. The selectivity is even higher in acetonitrile, but significant amounts of dimers of **2** are also formed in this case.

Interestingly, the *endo*/*exo* ratio is at ~2:1 nearly constant in all cases. The main differences in stereoselectivity between the two sensitizer systems is observed in the larger amounts of the minor products **6**−**10** that are formed. The reaction in dichloromethane sensitized by $\mathbf{3}^+$ is found to be the most selective, forming essentially only the two isomers of the mixed

TABLE 3. Variation of Sensitizer and Solvent

	conditions			
	$3^{+}/CH_2Cl_2$	3^{+}/acetonitrile	**11**/CH_2Cl_2	**11**/acetonitrile
dimers of **1**	1.00	1.00	1.00	1.00
mixed adducts	2.67	0.99	4.27	8.44
dimers of **2**	0.38	0.04	0.85	3.18
4	37.4%	21.5%	22.3%	24.6%
5	59.5%	45.3%	50.8%	53.9%
6	1.8%	0.7%	4.3%	0.8%
7	0.7%	12.1%	5.8%	1.0%
8	0.1%	4.8%	1.1%	0.4%
9	0.2%	3.4%	0.4%	0.2%
10	0.3%	12.3%	15.2%	19.2%

Diels−Alder product **4** and **5**. For the reactions sensitized by **11**, substantial amounts of **10** are formed even in dichloromethane. These conditions, in which reaction is most likely to proceed via an ion pair $\mathbf{1}^{\bullet+}/\mathbf{11}^{\bullet-}$, also give a relatively large amount of **6**. Interestingly, the only other set of reaction conditions that lead to the formation of substantial amounts of **6** is the reaction in the relatively viscous DMSO.

Three observations emerge from these experiments that provide some insights into the origin of the selectivity. First is the chemoselectivity of the formation of mixed cycloaddition products versus the homodimers of **1** and **2**. As can be seen from the results in Tables 2 and 3, polar solvents or sensitizers that are less likely to complex with an oxidized diene like **3** following electron transfer increase the amount of dimers of **1** relative to the mixed adducts. This data from catalyst variation supports the idea presented earlier that the formation of free ion pairs lead to an essentially statistical mixture of products that reflects the probability of collision of $\mathbf{1}^{\bullet+}$ with either **1** or **2**. The behavior of other forms of $\mathbf{1}^{\bullet+}$, e.g., as an ion pair with $\mathbf{11}^{\bullet-}$ or as a solvent-separated ion pair, is more complex but apprarently leads to the preferential formation of the mixed cycloadditions products.

The second question is the periselectivity of the reaction, leading to virtually exclusive formation of **4** and **5** in dichloromethane but yielding a substantial amount of other isomers in more polar solvents, as shown in Tables 2 and 3. Although none of the other isomers could initially be isolated under the standard reaction conditions, repeating the reaction in a 50:50 mixture of dichloromethane and acetone followed by rapid workup gave sufficient material for the spectroscopic characterization of **7**. The structure of **7** was then elucidated by 2D NMR and decoupling experiments that allowed the assignment of the *cis* (6.8 Hz) and *trans* (11.4 Hz) coupling for the hydrogen at C4 (see Supporting Information). As shown in Figure 3, **7** is the result of a dienophile attack on the same side as the isopropyl group forming a *cis*-diastereomer. Based on the similar MS (see Suppporting Information) and the fact that formation of **7** and **10** for the most part correlate as a function of solvent polarity as shown in Table 2, it can be hypothesized that **10** is an isomer of **7** with the methyl and anisyl groups in the *cis* position. However, multiple attempts to isolate **10** in an amount sufficient for structural characterization were not successful.

The formation of **7** and its dependence on the solvent polarity can be understood by considering the reactive intermediates involved. The electronic structure of $\mathbf{1}^{\bullet+}$ may be represented as shown in Figure 4 on the left, which is consistent with a B3LYP/6-31G* computed ChelpG charge of +0.18 at C4 and a spin density of 0.46 at C1. Attack of **2** could occur in principle at either position, whereas attacks at C2 and C3 can be excluded

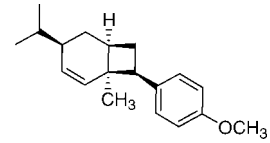

FIGURE 3. Structure of isomer **7**.

because they would force the formation of localized spin and/or charge. Previous computational studies on 2-methyl-substituted 1,3-butadiene radical cations[13a] indicate that attack at C1 is favored. More importantly, the experimentally observed regiochemistry of **4**, **5**, and **7** indicates that the major pathways attack at C1 because the formation of the experimentally observed major products via attack at C4 would require the formation of a primary radical or cation.

This attack can proceed *trans* or *cis* to the isopropyl group, initially leading to the two possible ion−molecule complexes $\mathbf{12}^{\bullet+}$ and $\mathbf{13}^{\bullet+}$, which are essentially equal in energy within the accuracy that can be reasonably expected for the method used here. On the basis of previous computational studies,[11,12] the potential energy surface around $\mathbf{12}^{\bullet+}$ and $\mathbf{13}^{\bullet+}$ is expected to be quite flat, resulting in several, presumably rapidly interconverting structures of the ion−molecule complexes. One such structure is shown for illustrative purposes in Figure 5 on the left. The first bond to yield the *trans* and *cis* singly linked intermediates $\mathbf{14}^{\bullet+}$ and $\mathbf{15}^{\bullet+}$ is formed through the transition structures $\mathbf{TS_{12,14}}$ and $\mathbf{TS_{13,15}}$ with activation energies of 2.4 and 3.8 kcal/mol, respectively. The lower activation energy for $\mathbf{TS_{12,14}}$ as well as the increased energy difference between the two singly linked intermediate is consistent with a stronger steric repulsion between the styryl and the isopropyl group. Consistent with earlier studies,[13a] the activation energy for the closure to the [4 + 2] product is at 0.6 kcal/mol very low.

Interestingly, we were unable to locate a transition structure for the ring closure to the [2 + 2] products **7** or a hypothetical *trans* analog **7′**. Attempts to calculate the structures of either $\mathbf{7}^{\bullet+}$ or $\mathbf{7'}^{\bullet+}$ led to a spontaneous opening of the cyclobutane ring, forming a "long bond intermediate"[19] that is stabilized by both benzylic and allylic resonance. It is therefore clear that the formation of the [2 + 2] products proceeds through the previously proposed back electron transfer (BET)−ring closure sequence.[19] This is further supported by the fact that the calculated activation energy for the closure of $\mathbf{15}^{\bullet+}$ to the [4 + 2] product, which is experimentally not observed, is at 6.5 kcal/mol substantially higher than in the case of $\mathbf{14}^{\bullet+}$. This is due to the larger steric repulsion in the case of $\mathbf{15}^{\bullet+}$, as can be seen in Figure 5. The increased lifetime of $\mathbf{15}^{\bullet+}$ therefore allows BET, which leads to larger amounts of **7**. If back electron transfer is not feasible or too slow, $\mathbf{14}^{\bullet+}$ and $\mathbf{15}^{\bullet+}$ could possibly equilibrate, giving larger amounts of the thermodynamically more stable **4** and **5**. This could also explain the larger amounts of **7** formed in polar solvents and, qualitatively, in the reactions using **11** as a sensitizer, even though it is not clear if the radical ions will occur in the form of free ion pairs, as discussed earlier.

An alternative and parallel explanation for the increased formation of **7** as a function of solvent polarity is the hypothesis that in polar solvents $\mathbf{1}^{\bullet+}$ is present as a free radical cation that has a lower facial selectivity, whereas in less polar solvents, it reversibly forms an ion−molecule complex that has a higher facial selectivity for attack. The high selectivity observed in dichloromethane would thus be a result of a double stereoselection in the two independent steps of the formation of the ion−molecule complex and the formation of the singly linked

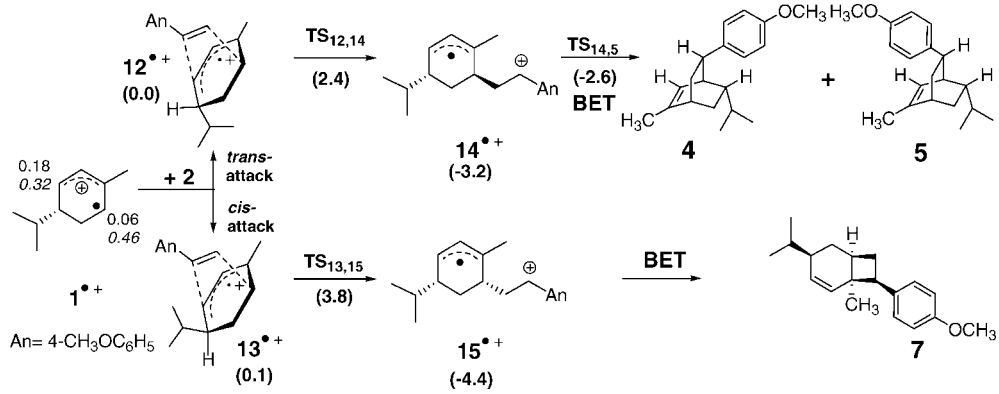

FIGURE 4. Possible reaction pathways with energies relative to $12^{\bullet+}$ (parenthesis), ChelpG charges (plain text), and spin densities (italics).

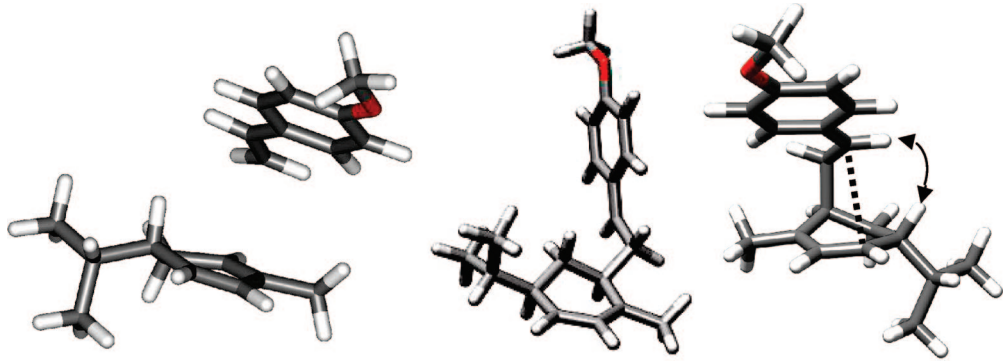

FIGURE 5. B3LYP/6-31G* calculated structures of ion−molecule complex $12^{\bullet+}$ (left), $15^{\bullet+}$ (middle), and reactive conformation of $14^{\bullet+}$ (right).

intermediate, which should be faster from the preferentially formed ion−molecule complex with a *trans* stereochemistry of the isopropyl group and **2**. However, these effects are likely to be too small to be studied by implicit solvent models.[19d]

Considering the structure of $14^{\bullet+}$ also helps to rationalize the third observation, the solvent dependence of the *endo*/*exo* ratio of **5** to **4** shown in Figure 2. Shown in Figure 5 on the right is the B3LYP/6-31G* calculated structure of the conformation of $14^{\bullet+}$ leading to the formation of the *endo* product **5**. In order for the [4 + 2] ring closure to occur, the vinyl anisole group has to be in the axial position. The preferred pseudoequatorial position of the isopropyl group then leads to a steric repulsion of the anisyl group with the axial hydrogen as shown in Figure 5. This repulsive interaction will be even stronger for the conformation leading to the *exo* isomer **4.** The solvent dependence of the *endo*/*exo* ratio can thus be rationalized as a competition between the ring closure, which will be faster in less polar solvents, and single bond rotation in $14^{\bullet+}$, which is stabilized by more polar solvents and thus gives a higher amount of the more stable *endo* isomer **5**. Thus, the *endo*/*exo* ratio is not governed by secondary orbital overlap as in the case of neutral Diels−Alder reactions but rather by the steric interactions in the singly linked intermediate $14^{\bullet+}$.

Conclusions

Electron transfer catalysis of the reaction of (*R*)-α-phellandrene with 4-methoxystyrene leads to the rapid formation of the mixed cycloaddition products in a surprisingly regio-, peri-, and stereoselective fashion. The systematic variation of the reaction conditions makes it possible to draw two sets of conclusions. From the synthetic point of view, the highest chemoselectivity favoring the formation of mixed Diels−Alder products relative to homodimers of **1** as well as other mixed cycloadducts is obtained in dilute (<0.15 M] dichloromethane solutions using 3^{+} as a sensitizer. Other reaction conditions lead to the formation of substantial amounts of other isomers of the mixed cycloadducts. Surprisingly, the *endo*/*exo* ratio is found to be highly solvent-dependent, with the highest diastereoselectivity obtained for DMSO, the most polar solvent studied here.

From the mechanistic viewpoint, the results of the study can be rationalized by considering a double stereoselection at the stage of an ion−molecule complex as well as at the stage of the singly linked intermediate. The fact that the highest selectivities are observed for low-polarity solvents is consistent with the idea that the ion−molecule complexes would be more stable and that the singly linked intermediate $14^{\bullet+}$ would rapidly collapse to give the product radical cations such as $4^{\bullet+}$ and $5^{\bullet+}$. The involvement of the ion−molecule complex could rationalize the almost complete facial selectivity of the dimerization. More polar solvents would stabilize free radical cations as well as the singly linked intermediate long enough to allow other reaction channels, including back electron transfer for form the biradical, which could then close to form the [2 + 2] cycloadducts such as **7**. Such a partitioning of the reaction pathway is similar to the better-studied case of the dimerization of **2**.[19]

Experimental Section

General Procedure. Commercially available, enantiomerically pure (95% GC) (*R*)-α-phellandrene **1** (24 μL) and 4-methoxystyrene **2** (20 μL) were dissolved in 1 mL of dichloromethane. After addition of 1.6 mg (2 mol %) of 2,4,6-tris(4-methoxyphenyl)

pyrylium tetrafluoroborate **3**[16a] as electron transfer sensitizer, the mixture was irradiated for 3 h under nitrogen with light of a wavelength of $\lambda = 422 \pm 20$ nm in a photoreactor equipped with eight UV lamps. The sensitizer was removed by passing the reaction through a short silica column with a mobile phase of methylene chloride and hexane in a 1:1 ratio. The reaction mixtures were then analyzed in a gas chromatograph using a standard 25 m column. These general reaction conditions were modified as specified in the text.

This procedure was scaled up to the synthesis of isomers **4**, **5**, and **7** used in the structure elucidation as follows. Using a microliter syringe 200 μL of 4-methoxystyrene (**2**) was added to 200 μL of (*R*)-(−)-α-phellandrene (**1**) in 15 mL of CH_2Cl_2 with 15 mg of **3** (1.9 mol %). Prior to individual isomeric separation, 97 mg of mixed adducts was collected for a 29% yield of cross addition. For the synthesis of **7**, a 50:50 mixture of dichloromethane and acetone was used as the solvent. The reaction mixture was degassed and irradiated at 420 nm for 3 h, and 57 mg of cross adducts (17% cross addition yield) was isolated using flash chromatography with 5% ethyl acetate in hexanes to separate the mixed adducts from other reaction products. Isomer separation was accomplished with argentated silica. $AgNO_3$ (2.75 g) was dissolved in 40 mL of water and added to 30 g of 60 Å silica. The mixture was stirred until homogeneity was achieved and left to oven dry overnight while covered with perforated aluminum foil. When dry, the silver-impregnated silica was slurry packed as one would with normal silica, and 2 mL fractions were collected.

(5*S*)-5-Isopropyl-8-((4*R*)-4-methoxyphenyl)-2-methylbicyclo-[2.2.2]oct-2-ene 4. A yield of 8 mg (2% isolated yield; 96% pure by NMR) was collected as a clear liquid. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.20 (d, ^3J = 8.8 Hz, 2H), 6.86 (d, ^3J = 8.8 Hz, 2H), 5.91 (dd, ^3J = 6.5 Hz, ^4J = 1.5 Hz, 1H), 3.81 (s, 3H), 2.75 (m, ^3J = 2.6 Hz, 6.5 Hz, 11.3 Hz, 1H), 2.53 (ddd, ^3J = 2.4 Hz, 2.2 Hz, 6.6 Hz, 1H), 2.38 (m, range = 13.2 Hz, 1H), 1.81 (d, ^4J = 1.6 Hz, 3H), 1.75 (m, range = 19.5 Hz, 1H), 1.70 (ddd, ^2J = 12.4 Hz, ^3J = 2.9 Hz, 9.2 Hz, 1H) 1.59 (ddd, ^2J = 12.8 Hz, ^3J = 2.1 Hz, 6.4 Hz, 1H) 1.35 (m, range = 14.0 Hz, 1H) 1.07 (m, ^3J = 2.5 Hz, 6.6 Hz, 1H) 0.98 (m, range = 22.8 Hz, 1H) 0.71 (d, ^3J = 6.6 Hz, 3H) 0.69 (d, ^3J = 6.6 Hz, 3H). ^{13}C NMR (500 MHz, $CDCl_3$) δ 20.1, 20.3, 20.9, 29.9, 33.3, 33.4, 36.7, 38.5, 39.4, 43.0, 55.2, 113.4, 125.8, 129.0, 136.7, 142.4, 157.4 ppm. IR (CCl_4) 1041.5, 1178.1, 1247.4, 1511.2, 1610.4, 2868.9, 3030.7 cm^{-1}. FABMS $[M + H]^+$ (relative intensity) 271 (17), 270 (27), 199 (25), 163 (26), 154 (30), 134 (100), 121 (58), 105 (17). Exact mass calculated for $C_{19}H_{26}O$ 270.1984, found 270.1978.

(5*S*)-5-Isopropyl-8-((4*S*)-4-methoxyphenyl)-2-methylbicyclo-[2.2.2]oct-2-ene 5. A yield of 15 mg (4% isolated yield; 97% pure by NMR) was collected as a clear liquid. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.08 (d, ^3J = 8.6 Hz, 2H), 6.81 (d, ^3J = 8.6 Hz, 2H), 5.64 (d, ^3J = 6.2 Hz, 1H), 3.80 (s, 3H), 2.83 (ddd, ^3J = 1.8 Hz, 5.6 Hz, 9.7 Hz, 1H), 2.59 (ddd, ^3J = 1.8 Hz, 1.8 Hz, 6.2 Hz, 1H), 2.42 (m, range = 11.7 Hz, 1H), 2.02 (ddd, ^2J = 12.8 Hz, ^3J = 2.8 Hz, 10.0 Hz, 1H), 1.89 (d ^4J = 1.4 Hz, 3H), 1.78 (ddd, ^2J = 12.0 Hz, ^3J = 2.4 Hz, 9.2 Hz, 1H), 1.44 (m, range = 18.6 Hz, 1H), 1.40 (m, range = 29.4 Hz, 1H), 1.11 (m, ^3J = 6.6 Hz, 2.9 Hz, 1H), 1.01 (m, range = 19.9 Hz, 1H) 0.88 (d, ^3J = 6.6 Hz, 3H), 0.84 (d, ^3J = 6.6 Hz, 3H). ^{13}C NMR (500 MHz, $CDCl_3$) δ 20.3, 20.8, 21.4, 31.7, 33.5, 35.3, 37.0, 41.0, 44.9, 48.5, 55.4, 113.5, 122.1, 128.9, 141.0, 143.4 157.7 ppm. IR (CCl_4) 1041.3, 1178.9, 1248.6, 1461.4, 1511.2, 1610.9, 2927.3, 3029.7 cm^{-1}. FABMS $[M + H]^+$ (relative intensity) 271 (24), 199 (34), 163 (23), 134 (83) 121 (100), 105 (30). Exact mass calculated for $C_{19}H_{26}O$ 270.1984, found 270.1979.

(1*S*,4*R*,6*R*,8*S*)-4-Isopropyl-8-(4-methoxyphenyl)-1-methylbicyclo[4.2.0]oct-2-ene 7. Compound **7** was formed following the general procedure but with a different solvent system. A 50:50 mixture of CH_2Cl_2/acetone was dried over $MgSO_4$. A yield of 3 mg (1% isolated yield; 62% pure by NMR) was collected as a clear liquid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.07 (d, ^3J = 8.7 Hz, 2H), 6.85 (d, ^3J = 8.7 Hz, 2H), 5.64 (d, ^3J = 10.4 Hz, 1H) 5.04 (dd, ^3J = 10.4 Hz, 2.7 Hz, 1H) 3.81 (s, 3H), 3.29 (t, ^3J = 9.4 Hz, 1H), 2.34 (m, range = 23.8 Hz, 1H), 2.11 (m, range = 22.6 Hz, 1H), 2.01 (dd, ^3J = 9.9 Hz, 8.5 Hz, 2H), 1.67 (m, ^3J = 6.8 Hz, 1H), 1.60 (m, range = 22.5 Hz, 1H), 1.22 (m, range = 29.0 Hz, 1H), 1.21 (s, 3H), 0.94 (d, ^3J = 6.8 Hz, 3H), 0.92 (d, ^3J = 6.8 Hz, 3H). ^{13}C NMR (500 MHz, $CDCl_3$) δ 158.0, 143.5, 133.4, 128.8, 113.4, 55.5, 51.4, 47.0, 43.7, 40.0, 37.9, 37.1, 32.0, 23.8, 19.8, 19.5 ppm. IR (CCl_4) 855.3 1052.3, 1175.9, 1233.4, 1455.4, 1507.2, 1623.1, 2934.2, 3033.7 cm^{-1}. FABMS $[M + H]^+$ (relative intensity) 271 (19), 269 (22), 255 (7), 199 (8), 149 (22), 137 (100), 121 (67), 105 (23). Exact mass calculated for $C_{19}H_{26}O$ 270.1984, found 270.1986.

Computational Studies. All computational studies were performed using the G03 series of programs[20] at the B3LYP/6-31G* level of theory. All geometries were fully optimized without constraints and the nature and identity of the stationary points was verified using harmonic frequency calculations and animation of the negative frequency. Energies are zero-point corrected and given in kcal/mol relative to the ion−molecule complex **12**$^{\bullet+}$. Partial charges were calculated using the CHelpG method.

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Supporting Information Available: Full citation for ref 20, Cartesian coordinates and energies for all structures discussed, GC/MS spectrum of the crude reaction, and 1D and 2D spectra of **4**, **5**, and **7**. This material is available free of charge via the Internet at http://pubs.acs.org.

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