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Face-Selective Diels−Alder Reactions between Unsymmetrical Cyclohexadienes and Symmetric *trans*-Dienophile: An Experimental and Computational Investigation

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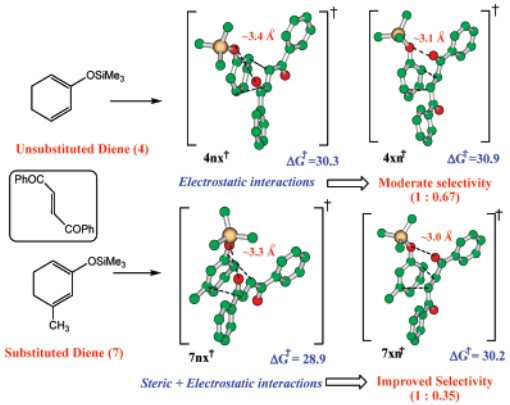

A combined experimental and theoretical study of the Diels−Alder reactions between 2-trimethylsiloxy-1,3-cyclohexadienes (**2**−**11**) and (*E*)-1,4-diphenylbut-2-ene-1,4-dione (**1**) is reported. Two diastereomeric products, 5-*endo*-6-*exo*- (**nx**) and 5-*exo*-6-*endo*- (**xn**) dibenzoyl derivatives, are possible with symmetric *trans*-dienophile (**1**). While in many cases 5-*endo*-6-*exo* product is preferred over the corresponding 5-*exo*-6-*endo* product, the product ratio **nx**:**xn** is found to vary with the position of substituents on the diene. The density functional theory studies with the mPW1PW91/6-31G* as well as the B3LYP/6-31G* levels reveal that the electrostatic repulsion between the oxygen lone pairs on the diene and the dienophile is critical to the observed product selectivities. The optimized transition state geometries though appeared to involve secondary orbital interactions, careful examination of the frontier Kohn−Sham orbitals as well as calculations with the natural bond orbital (NBO) analyses confirm the absence of SOI in these transition states. In the case of methyl-substituted dienes, a cumulative effect of steric and electrostatic interactions between the diene and the dienophile is found to be the controlling element toward the observed selectivity.

Introduction

The Diels−Alder (DA) reaction has been one of the most well-studied reactions both theoretically and experimentally. Over the years, a large variety of diene and dienophile combinations have been identified toward generating an interesting class of cycloadducts. One of the key features of the Diels−Alder reaction that generated considerable interest relates to the dramatic changes in the product selectivities depending on the nature of the reactants. The ubiquitous example of selectivity in the Diels−Alder reaction is the *endo*/*exo* stereoselectivity observed in [4+2] cycloadditions. The secondary orbital interaction (SOI) model has been widely employed as a conceptually effective framework in explaining the kinetically controlled *endo*-addition in the Diels−Alder reaction (earlier known as the Alder−Stein rule of maximum accumulation of

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double bonds).[1] However, this interpretation has also become a subject of considerable controversy.

A combination of effects such as electrostatic, steric, hydrogen bonding, as well as solvent effect could be alternatively invoked to explain the selectivity.[2] While the SOI is commonly considered to be a contributing factor for such selectivity,[3] several other considerations, such as the kinetic versus thermodynamic control,[4] differential volume of activation,[5] and polarities of the transition states in Diels−Alder reaction,[6] have also been proposed. A number of models based on the stabilization/destabilization of respective transition states leading to *endo* or *exo* products by the reaction medium,[7] electrostatic interactions,[8] hydrogen bonding,[9−10] as well as steric interactions are also available. For instance, in a series of interesting reports by Paddon−Row and Sherburn on the intramolecular Diels−Alder (IMDA) reactions, the π-facial selectivity has been explained with the help of steric and electrostatic interactions between the substituents attached to the diene and dienophile fragments.[11] There are other examples where the electrostatic interactions involving the oxygen of the silyloxy groups on the diene are considered to explain IMDA reactions.[12] In another study by Burnell and co-workers, the endo−exo as well as facial selectivity in the Diels−Alder reaction between substituted cyclopropenes and butandiene have been addressed primarily with the help of steric interactions in the transition structures.[13] Singleton and Sulikowski offered an elegant rationale in support of the experimentally observed selectivity in the Diels−Alder reaction between vinaylazepines with *N*-phenylmaleimide using the detailed structure of diene and dienophile as well as the interactions between them in the transition structures.[14]

The nature of substituents on the dienes or the dienophiles has been established to be a key factor in controlling the reactivity and selectivity in Diels−Alder reactions.[15] The dienes activated by electron-donating groups are known to be effective in Diels−Alder reactions.[16] Danishefsky's diene is one such example bearing alkoxy and trialkylsiloxy groups that is widely used in Diels−Alder as well as hetero-Diels−Alder reactions.[17] The DFT studies by Houk and co-workers on the cycloaddition of 1-methoxy-4-trimethylsiloxy-1,3-butadiene with acrylonitrile revealed that the regioselectivity is controlled by the direct electrostatic interactions between the substituents on the diene and dienophile, but not due to the SOI effects.[18]

Recently, we have reported the importance of steric factors in controlling the face-selectivity with diastereotopically nonequivalent π-facial dienes. The addition of trimethylsiloxy-substituted 1,6-annulated 1,3-cyclohexadienes to a *cis*-ethylenic dienophile like *N*-phenylmaleimide (NPM) was found to give an exclusive face- as well as *endo*-selectivity.[19] Encouraged by

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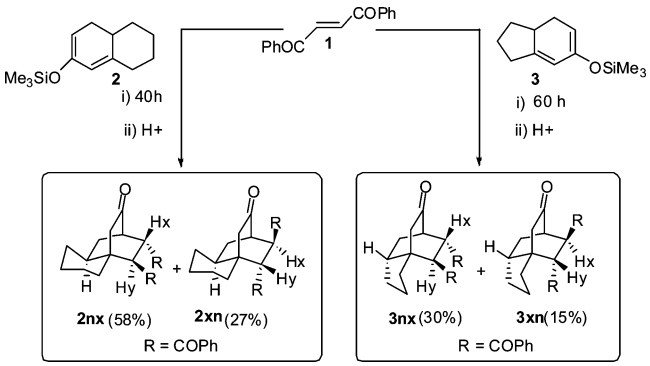
these results, we became interested in exploring the Diels−Alder reaction with *trans*-alkene as a dienophile under identical conditions, where the steric effect of substituents present in the unsymmetrical 1,3-cyclohexadienes might steer the *endo*/*exo* selectivity. It is worth noting that the number of reports on the *exo*/*endo* selectivities in cyclohexadienes is far fewer than that of other dienes such as cyclopentadiene or butadiene. Further, the known examples with *trans*-olefins as dienophiles in intermolecular Diels−Alder reactions are not as common as those with *cis*-olefins, except for some reports on chiral fumarates as well as crotonates.[20] On the basis of product selectivities, it has been proposed that the reactions involving cyclohexadienes proceed through an *endo* transition state.[21] The overview on the diastereoselective Diels−Alder reaction, as summarized in the earlier paragraphs, evidently conveys that the reasons behind selectivity are intricately related to the structural and electronic features of the diene and the dienophile. We have therefore chosen to employ density functional theory calculations to gain insights into the governing factors that influence the selectivity in the present group of molecules. The results are summarized in the following sections.

Results and Discussion

In this paper we report the Diels−Alder reactions of 2-trimethylsilyloxycyclohexa-1,3-dienes (**2**−**11**) with a symmetric trans-dienophile (*E*)-1,4-diphenylbut-2-ene-1,4-dione (**1**) in refluxing benzene. The trimethylsiloxy group in 2-trimethylsiloxy-1,3-cyclohexadiene derivatives has been reported to act as a very good *para* as well as *endo* director while reacting with unsymmetrical ethylenic dienophiles.[22] Since the resulting adducts with the silyl enol ether were difficult to work with, they were hydrolyzed in situ with methanolic HCl for 10 min to yield the stable ketones. Separate experiments showed that there is no epimerization of adducts due to hydrolysis. Reactions of both the bicyclic dienes **2** and **3** with **1** gave a ∼2:1 mixture of the diasteromeric adducts (**2nx** and **2xn**, **3nx** and **3xn**) and exclusive face-selective addition of the dienophile **1** was observed. (Scheme 1). For the purpose of maintaining consistency throughout the present discussion, the larger rings in **2** and **3** have been considered as simple 4,8-disubstitution. The product formed by the addition of dienophile leading to 5-*endo*-6-*exo*-dibenzoyl isomer is labeled as **nx** whereas the 5-*exo*-6-*endo*-dibenzoyl product is termed **xn**. Further, the *endo*-addition was found to be preferred for that dienophile substituent (COPh) which added *para* to the trimethylsilyloxy group. This could possibly be explained in terms of the directive influence imparted by the 2-siloxy group on the diene.[23] The structures were assigned from the analytical and ^{1}H NMR data and the structure of **3nx** was finally confirmed through X-ray crystallographic analysis.[24]

SCHEME 1. Adduct Formation from 2−3 and 1



In the case of dienes **4**−**11**, corresponding **nx** and **xn** isomers of the stable ketones were obtained after hydrolyses of the silyl enol ether adducts (Scheme 2, Table 1). With diene **4**, two different products 5-*endo*-6-*exo*- (**4nx**) and 5-*exo*-6-*endo*-dibenzoyl (**4xn**) derivatives in the ratio 1:0.67 were obtained after hydrolysis. Thus, as seen in the earlier cases of **2** and **3**, a low but definite 5-*endo*-selectivity of product formation from **1** has also been observed here. The structures of the adducts were arrived at from analytical and spectral data. For most of the 5-*endo*-6-*exo*-dibenzoyl derivatives (**nx**), a long-range coupling between H_y and one of the acyl protons H_b at the 3-position was indicative of the stereochemistry. Decoupling experiments further confirmed these assignments.

The steric effect exerted by the diene substituent has a strong directive effect in these reactions, which was further confirmed by the reaction of **1** with diene **5** where the 1-methyl substituent shifted the *endo*-selectivity in the opposite direction giving **5nx** and **5xn** in a 1:1.8 ratio. On the other hand, the 5-*endo*-6-*exo*-selectivity was much improved with dienes **7** and **11** (Scheme 2).

This result suggests the 5-*endo*-6-*exo* additions are more influenced by the steric effect of substituents at or near C_1 (**5**, **6**, **10**) than those near C_4 (**7**, **8**, **9**). Reactions with dienes **6** and **10** were found to be extremely sluggish and nearly 50% of the starting materials was recovered from the reaction mixtures. When C_1 and C_4 are identically substituted, as in **11**, the reaction followed the usual course similar to that for **4** and a preference for 5-*endo*-6-*exo* addition was observed. That the formations of 5-*endo*-6-*exo*-dibenzoyl isomers were all kinetically controlled ones was confirmed by the ready epimerization of **7nx** to the respective 5-*exo*-6-*endo*-dibenzoyl isomers (**7xn**) (Scheme 4). Interestingly, the 5-*exo*-6-*endo* product (**6xn**) did not epimerize at all under similar conditions.

When 2-trimethylsilyloxycyclohexa-1,3-dienes reacted with cyclic *cis*-dienophiles like NPM and maleic anhydride, formation of exclusive *endo* adducts has been reported.[25] So we decided to carry out the above reaction with the corresponding acyclic

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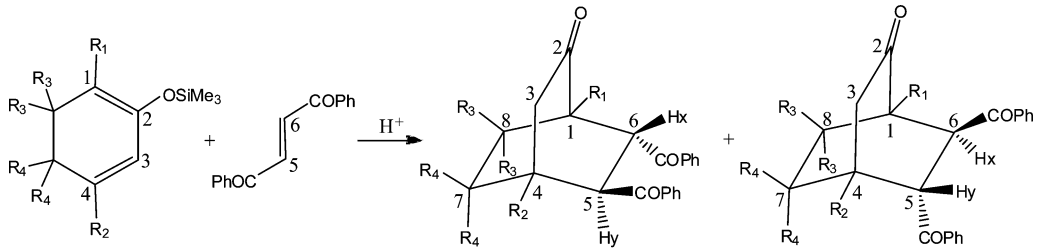
(24) The ORTEP diagram can be seen from Figure 1 in the Supporting Information. The X-ray data for **3nx** were collected at 293(2) K on a diffractometer with graphite monochromated Mo Kα radiation (λ = 0.71073 Å). The structure was solved by direct methods (SHELXS-97). Crystals of **3nx** are colorless with a size of 0.27 × 0.19 × 0.18 mm^3: prism, space group *P*21/*c*, a = 9.005(5) Å, b = 14.836 (8) Å, c = 14.242(8) Å, α = 90.00°, β = 91.149(9)°, γ = 90.00°, V = 1902.2(17) Å^3, Z = 4. Crystallographic data (excluding structure factors) for this structure have been deposited with the Cambridge Crystallographic Data Center as supplementary publication number CCDC 607025. Copies of the data can be obtained free of charge, on application to CCDC, 12, Union Road, Cambridge CB2 TEZ, UK [fax: +44(0)-1223-336033; e-mail:deposit@ccdc.cam.ac.uk].

SCHEME 2. Diels−Alder Adducts from 4−11 and 1



4 - 11 **1** **nx** 5-*endo*-6-*exo*-dibenzoyl adduct **xn** 5-*exo*-6-*endo*-dibenzoyl adduct

where,

4 - R_1= R_2= R_3= R_4 = H
5 - R_1= Me; R_2= R_3= R_4 = H
6 - R_1= R_2= R_4 = H; R_3= Me
7 - R_1= R_3= R_4 = H; R_2= Me
8 - R_1= R_2= R_3 = H; R_4= Me
9 - R_1= R_3= R_4 = H; R_2= OMe
10 - R_1= R_4 = H; R_2= R_3= Me
11 - R_1= R_2= Me; R_3= R_4 = H

TABLE 1. Diastereomeric Ratio of Cycloadducts from 1

diene	time (h)	recovered **1**[a] (%)	products **nx**:**xn**
2	40	nil	1:0.46
3	60	36	1:0.5
4	24	16	1:0.67
5	18	nil	1:1.82
6	16	51	6-*endo* (31%)
7	50	22	1:0.35
8	16	61	5-*endo* (20%)
9	16	nil	1:0.31
10	16	41	6-*endo* (33%)
11	24	3	1:0.48

[a] The rest part of the reaction mixture contained a tarry mass.

cis-dienophile, (*Z*)-1,4-diphenylbut-2-ene-1,4-dione (*cis*-dibenzoylethylene, **1′**). When the reaction of **1′** was carried out with diene **11**, the products isolated were identical with those isolated from the reactions of **1**. It was then found that under the experimental conditions as in refluxing benzene, **1′** was partially converted to the trans isomer (Scheme 5). In general the trans isomer of a dienophile reacts faster than its cis isomer.[26] The formation of the observed products, therefore, arose from the reaction of the *trans*-DBE (**1**) generated in the reaction medium while the absence of any product from reaction of the cis isomer (**1′**) was probably due to its very slow reactivity. Since only **1** and not **1′** could be recovered from the reaction mixture, acid-catalyzed isomerization of **1′** during the hydrolysis step cannot be ruled out.

From the comparison of the rates of reactions of symmetrical dienophiles with **4** and **6**−**8** it has been suggested that the steric hindrance experienced by the dienophiles is essentially the same with **6** and **8**.[27] In the present work we found while **8** yielded the expected 5-*endo*-6-*exo* product (**8nx**) exclusively and **7** yielded **7nx** preferentially, **6** as well as **10** gave the other diastereomers **6xn** and **10xn**, respectively. The results hitherto with symmetrical *trans*-alkene indicated that the steric effect of substituents on or near the C_1 of the diene plays an important role on the *endo*/*exo* selectivity.

We wanted to establish the key factors responsible for the observed selectivities as described in the preceding section. To achieve this goal, electronic structure calculations have been performed by using the hybrid Hartree−Fock density functional theory with the mPW1PW91 as well as the B3LYP functionals. The possible conformers such as (i) *s-cis*,*s-cis*-, (ii) *s-cis*,*s-trans*-, and (iii) *s-trans*,*s-trans*-dibenzoylethylene arising due to the C−C single bond rotation were first examined. The *s-cis*,*s-cis*-dibenzoylethylene was found to be the lowest energy conformer and therefore was employed for the evaluation of activation parameters in the present study. Further, the geometry of the dienophile in the initial guess transition structures with a variety of dienes was maintained in the *s-cis*,*s-cis* orientation. The transition states for the Diels−Alder reaction between a range of 2-trimethylsiloxy-1,3-cyclohexadienes and (*E*)-1,4-diphenylbut-2-ene-1,4-dione (**1**) were located. Since the dienophile is symmetric as well as diastereofacial two different modes of approaches between the dienophile (**1**) and trimethylsiloxy-substituted diene were considered. These transition states would lead to two diastereomeric cycloadducts as described in Scheme 2. The approaches are identified as *endo*/*exo* on the basis of the orientations of the benzoyl group at the C_5 and C_6 positions of the cycloadduct. The addition of dienophile leading to 5-*endo*-6-*exo*-dibenzoyl product is labeled as **nx**, whereas the addition resulting in 5-*exo*-6-*endo*-dibenzoyl product is termed **xn**. The corresponding transition states are designated as **nx**‡ and **xn**‡ along with a number designator representing the diene. The details on the relative activation barriers critical to the *endo*/*exo* selectivity and the underlying reasons are summarized in the following sections.

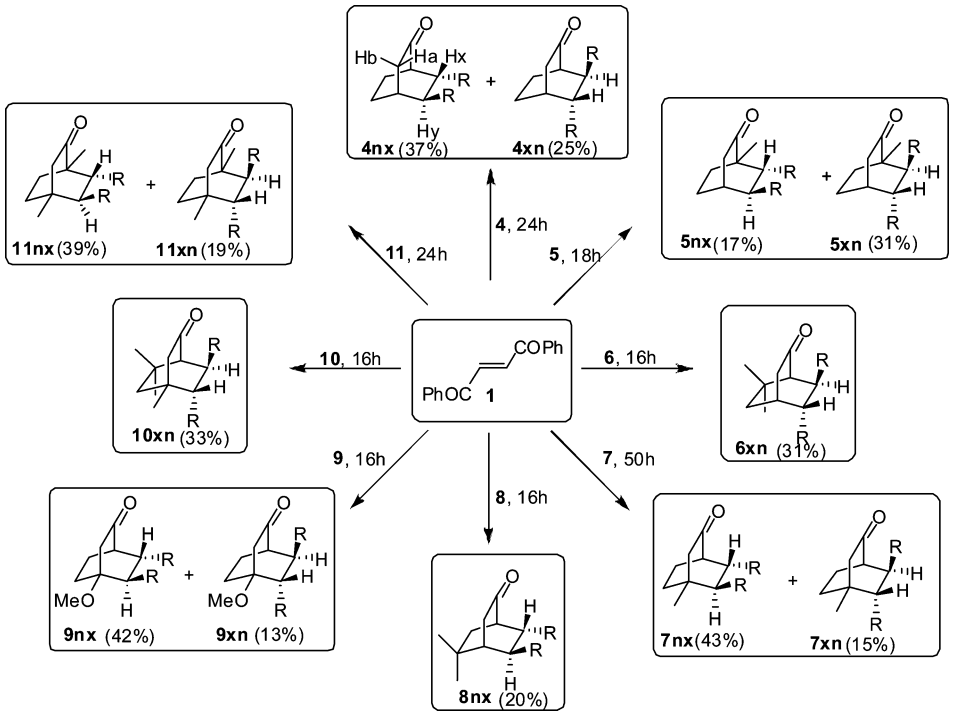
First, the Diels−Alder reaction between the unsubstituted diene (**4**) with the dienophile (**1**) was considered. Formation of **4nx** was found to be kinetically more favored as compared to the diastereomer **4xn**. Since the trimethylsiloxy group can have *syn* or *anti* orientations with respect to the C_1−C_2 π-bond, two important rotameric forms are possible for the unsubstituted diene. Four transition states were therefore identified for different modes of approaches between the diene and the dienophile as shown in Figure 1. The transition states **4nx**‡ and **4nx′**‡ will lead to 5-*endo*-6-*exo*-dibenzoyl products whereas **4xn**‡ and **4xn′**‡ result in 5-*exo*-6-*endo*-dibenzoyl products. On the basis of the computed Gibbs free energies of activation at the mPW1PW91/6-31G* level of theory for these additions, the pathway involving transition state **4nx**‡ was found to exhibit the lowest barrier. Interestingly, these predictions are in accordance with the experimental results, where **4nx** was found

(25) (a) Stork, G.; Baine, N. H. *Tetrahedron Lett.* **1985**, *26*, 5927. (b) Birney, D.; Lim, T. K.; Koh, J. H. P.; Pool, B. R.; White, J. M. *J. Am. Chem. Soc.* **2002**, *124*, 5091.

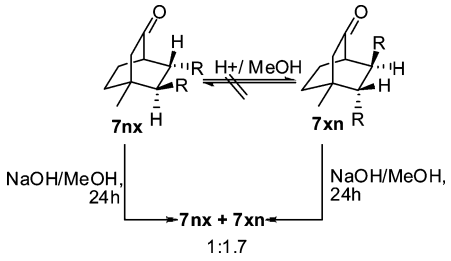
(26) (a) Sauer, J.; Wiest, H.; Mielert, A. *Chem. Ber.* **1964**, *97*, 3183. (b) Sauer, J.; Lang, D.; Wiest, H. *Chem. Ber.* **1964**, *97*, 3208.

(27) Buckle, R. N.; Liu, P. Y.; Roberts, E. W. D.; Burnell, D. J. *Tetrahedron* **1999**, *55*, 11455.

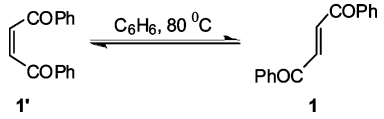
SCHEME 3. Final Products from Reactions of 1 with Dienes 4−11 (R = COPh) after Acid Hydrolysis



SCHEME 4. Epimerization of 7nx and 7xn



SCHEME 5. Isomerization of 1′ to 1



to be the major product. The same trends were also predicted at the B3LYP/6-311+G**//B3LYP/6-31G* level of theory.[28]

The secondary orbital interaction (SOI) protocol has been successfully employed in several situations toward rationalizing selectivities in Diels−Alder reactions.[3] In the present case, SOI between the C═O group of the dienophile and the developing C═C bond of the diene appears likely. However, the frontier Kohn−Sham orbital analyses of the transition states at the mPW1PW91/6-311+G** level indicated that the SOI is absent in both modes of approaches between the diene and dienophile.[29] Alternatively in the present case, two types of repulsive interactions were identified between the diene (**4**) and the dienophile (**1**) that can destabilize the transition states. These include the repulsive interactions between the lone pair of the diene oxygen (−OTMS) and (i) the lone pair on the carbonyl group or (ii) the π-bond of the dienophile. Interestingly, electrostatic interactions of similar kind have earlier been reported to be crucial in cases where the selectivity is not guided by the SOI.[8d,18]

The extent of electrostatic repulsion in the transition states will depend on the proximity as well as the orientation of the double bond or the groups bearing lone-pair electrons. A closer inspection of the transition state geometries suggested that the *lone pair−lone pair* repulsion holds the key to the relative stabilization between the diastereomeric transition states. In an effort to quantify the electrostatic interactions between the oxygen atoms of the diene and the dienophile (Figure 1), we have estimated the Coulombic forces using the partial charges. Analyses based on the Mulliken charges were found to be generally in good agreement with the relative energies between diastereomeric transition states. For instance, **4nx**‡ was found to exhibit relatively lower Coulombic interaction as compared to the **4xn**‡.[30] The trends were in good agreement with the predicted selectivities in that the Coulombic repulsions are found to be higher for the higher energy transition states.

In the case of the lowest energy 5-*endo*-6-*exo* transition state (**4nx**‡) the oxygens of the trimethylsiloxy and the carbonyl groups remained as far away as possible to minimize the destabilizing interactions.[31] However, when the trimethylsiloxy group was syn with respect to the C_1-C_2 π-bond, an unfavorable

(28) See Table S1 in the Supporting Information for activation parameters for diastereomeric transition states as well as the predicted selectivities obtained at the B3LYP/6-311+G**//B3LYP/6-31G* level of theory.

(29) The HOMO of both the transition state (**4nx**‡ and **4xn**‡) was found to be dominated only by the primary orbital interactions. However, HOMO-4 of **4nx**‡ exhibited a very weak secondary orbital interaction (see Figure S1 in the Supporting Information). The natural bond orbital (NBO) analysis of the transition states also showed a small delocalization energy for π-(C−C) to π*(C−O) suggesting that the SOI is insignificant. The difference between **nx**‡ and **xn**‡ delocalizations was found to be quite negligible, suggesting that this interaction cannot be responsible for the product selectivity in the present case. See Table S2 in the Supporting Information for further details.

(30) See Table S4 in the Supporting Information for a full list of Coulombic interactions calculated with use of the Mulliken partial charges obtained at the mPW1PW91/6-311+G**//mPW1PW91/6-31G* level of theory.

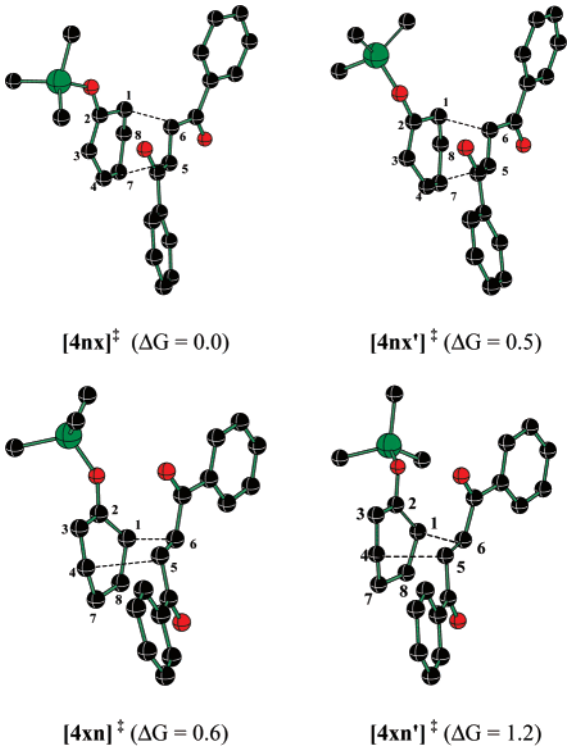


FIGURE 1. The mPW1PW91/6-31G* optimized transition state geometries of the reaction between different conformers of diene (**4**) and dienophile (**1**). Hydrogen atoms are omitted for improved clarity. [Atom colors: black = C, red = O, green = Si.]

electrostatic interaction between the oxygen lone pairs on the diene and the dienophile led to a slightly higher barrier for **4nx′‡**. Alternatively, when the dienophile approaches the diene using the opposite diastereotopic face, i.e., 5-*exo*-6-*endo* mode (**4xn‡** and **4xn′‡**), the oxygens of the trimethylsiloxy and carbonyl groups were found to be relatively closer and resulted in destabilization of the corresponding transition states. The electrostatic repulsion is evidently higher in **4xn′‡**, where the disposition of the lone pairs on the trimethylsiloxy is directed toward the carbonyl oxygen.[32] Hence, both these stereochemical modes leading to 5-*exo*-6-*endo*-dibenzoyl product are kinetically less favored as compared to 5-*endo*-6-*exo*-dibenzoyl product. Therefore, the observed selectivity in the Diels−Alder reaction between 2-trimethylsiloxy-1,3-cyclohexadiene and (*E*)-1,4-diphenylbut-2-ene-1,4-dione could be attributed to the electrostatic interactions between the oxygen lone pairs on the diene and the dienophile.[33] The predicted trends as noticed in the above discussions were found to remain the same at the B3LYP level of theory.[28]

The transition states for the Diels−Alder reaction between other substituted dienes (**5**−**11**) and the dienophile (**1**) were also identified at the mPW1PW91/6-31G* level of theory. We have considered the *anti* orientation of trimethylsiloxy group with respect to the C_1-C_2 π-bond for further discussions. The important bond distances of the optimized transition state geometries are provided in Table 2. While the reaction coordinate, as revealed by the imaginary vibrational frequencies, predominantly relates to a concerted C_4-C_5 and C_1-C_6 bond formation, the process was generally found to be asynchronous.[34] The degree of asynchronocity (d2/d1) at the transition state estimated as the ratio of C_4-C_5 to C_1-C_6 bond distances is summarized in Table 2. The transition states exhibited varying degrees of asynchronocity depending on the nature and position of the substituents on the diene. For instance, the C_1-substituted diene (**5**) was found to follow a relatively more synchronous pathway as compared to the C_4-substituted diene (**7**). All these transition states were subjected to intrinsic reaction coordinate (IRC) calculations, which enabled us to identify that the transition states connect to respective reactants and products on either side of the first-order saddle point.[34]

TABLE 2. The mPW1PW91/6-31G* Optimized Bond Distances (in Å) and Degree of Asynchronocity for Transition States for the Diels−Alder Reaction between 2-Trimethylsiloxy-1,3-cyclohexadiene (2−11) and (E)-1,4-Diphenyl-but-2-ene-1,4-dione (1)[a]

	nx‡			xn‡		
reaction	C_1-C_6(d1)	C_4-C_5(d2)	d2/d1	C_1-C_6(d1)	C_4-C_5(d2)	d2/d1
1 + 2	2.067	2.974	1.44	2.049	2.982	1.45
1 + 3	1.983	3.139	1.58	2.012	2.906	1.44
1 + 4	2.155	2.665	1.23	2.228	2.510	1.12
1 + 5	2.310	2.386	1.03	2.390	2.267	0.94
1 + 6	2.129	2.676	1.25	2.179	2.638	1.21
1 + 7	2.077	2.966	1.42	2.047	2.983	1.46
1 + 8	2.108	2.684	1.27	2.094	2.643	1.26
1 + 9	2.101	3.064	1.45	2.061	3.023	1.46
1 + 10	2.044	3.070	1.50	2.063	2.966	1.43
1 + 11	2.092	2.799	1.34	2.133	2.676	1.25

[a] See Figure 1 for atom numbers.

On the basis of the relative Gibbs free energies of activation between the diastereomeric transition states, the product selectivities were calculated (Tables 3). In general, the computed selectivity ratios predicted by using the DFT methods were found to be in good agreement with the experimentally determined product distributions. The concurrence between the computed selectivities obtained at the mPW1PW91/6-311+G**//mPW1PW91/6-31G* and B3LYP/6-311+G**//B3LYP/6-31G* levels of theories was very good.[28] It is evident from the product distribution that the selectivity varies with the position of the substituents on the diene. For instance, monosubstitution on C_1 or gem-dimethyl substitution on C_8 nearer to the trimethylsiloxy group of the diene (as in **5**, **6**, and **10**) led to opposite stereoselectivity as compared to the unsubstituted diene (**4**). In these cases, the 5-*endo*-6-*exo* transition state (**nx‡**) experiences

(31) (a) The effect was found to be quite similar even with an alternative orientation of the −OTMS group, see Figure 1. (b) Hydrogen bonding between the methyl group of the diene and the carbonyl of the dienophile (C_6−H(diene)···O═C(dienophile)) was noticed in both **4nx‡** and **4xn‡**, which could offer additional stabilization. See Table S5 in the Supporting Information.

(32) The distances between diene oxygen (−OTMS) and the oxygen of the nearest −C═O group in the transition states **4nx‡** and **4nx′‡** was respectively found to be 3.4 to 3.6 Å whereas for transition states **4xn‡** and **4xn′‡** it was much closer, 3.1 Å. See Table S4 in the Supporting Information.

(33) To obtain an approximate measure of Coulombic interactions due to the oxygen of the −OTMS group toward diastereoselectivity, we have carried out additional single-point energy calculations by replacing the oxygen of the −OTMS groups with a dummy atom. The difference in energies (bottom-of-the-well values) between the diastereomeric transition states **4nx‡** and **4xn‡** were found to be only 0.1 kcal/mol. The corresponding difference is about 0.5 kcal/mol in the real system, implying that the Coulombic interaction indeed contributes to the predicted diastereoselectivity.

(34) The concerted nature of these transition states was further confirmed by the Intrinsic Reaction Coordinate (IRC) calculations, starting from the transition state, toward the reactant and the product. It was noticed that the transition structures in general show a smooth connection to the products, without the involvement of any intermediates along the IRC trajectory. See Figure S2 in the Supporting Information for the IRC profile generated at the mPW1PW91/6-31G* level of theory.

TABLE 3. Computed Activation Parameters (in kcal mol^{-1})[a] and the Product Ratios for the Diels−Alder Reaction between 2-Trimethylsiloxy-1,3-cyclohexadiene (2−11) and (*E*)-1,4-Diphenylbut-2-ene-1,4-dione (1) Obtained at the mPW1PW91/6-311+G//mPW1PW91/6-31G* Level of Theory**

	nx‡		**xn**‡		predicted product ratio
reaction	$\Delta H^{\ddagger}$	$\Delta G^{\ddagger}$	$\Delta H^{\ddagger}$	$\Delta G^{\ddagger}$	nx:xn
1 + 2	11.9	28.2	12.6	29.2	1:0.18
1 + 3	14.0	29.8	16.5	33.2	1:0.01
1 + 4	13.8	30.3	14.2	30.9	1:0.36
1 + 5	15.1	32.0	15.1	31.1	0.21:1
1 + 6	18.8	36.1	15.9	32.8	0.01:1
1 + 7	12.6	28.9	13.7	30.2	1:0.11
1 + 8	15.7	31.9	18.7	35.6	1:0.01
1 + 9	10.3	27.4	11.6	28.1	1:0.31
1 + 10	18.4	35.9	15.6	32.8	0.01:1
1 + 11	14.8	31.5	15.9	32.0	1:0.44

[a] Barriers with respect to the separated reactants.

higher steric repulsion between the methyl substituent(s) on the diene and the benzoyl group of the dienophile. The transition state leading to 5-*exo*-6-*endo*-dibenzoyl product would therefore be favorable as it experiences relatively lower steric issues. Methyl substitutions on C_4 or C_7 carbon atoms with respect to the trimethylsiloxy group of the diene (as with **7** and **8**) led to same, but improved, selectivity as compared to the unsubstituted diene (**4**). The selectivity here can be attributed to (i) the steric interaction of the C_4/C_7 methyl substituents on the diene with the dienophile (ii) evidently higher than the lone pair−lone pair interactions with the 5-exo-6-endo transition states (e.g., **8xn**‡) as compared to the corresponding 5-endo-6-exo (**8nx**‡) transition states.

In the present case, the methyl substituents at two key positions on the diene were found to be effective in gaining improved control over the selectivities. The reaction of diene (**10**) having methyl substituents at the C_8 and C_4 positions resulted in 5-*exo*-6-*endo* diastereomer (**10xn)** as the only product. Here, the selectivity is controlled by the relative steric congestion in the transition state imparted by the methyl substituents on the diene with the benzoyl groups of the dienophile. While the steric interaction between the C_8 methyl group on the diene with the dienophile holds the key to relative stabilization of the transition state **10nx**‡, the C_4 methyl group was identified to be more crucial in the case of the other diastereofacial approach involving transition state **10xn**‡. The C_8 methyl group in **10nx**‡ is in closer proximity to the carbonyl carbon of the dienophile than the C_4 methyl group. Hence, the transition state destabilization due to steric interaction is expected to be higher in **10nx**‡ than in **10xn**‡. Additional stabilizing hydrogen bonding interactions between the dienophile carbonyl and diene methyl groups were also identified. These interactions were relatively more in favor of transition state **10xn**‡ than with **10nx**‡. The above examples illustrate the vital influence imparted by suitably placed methyl groups on the diene toward the product selectivity. Interestingly, methyl substitutions at C_1 and C_4 positions of the diene (as in **11**) provided nearly identical steric environments for both the diastereomeric transition states **11nx**‡ and **11xn**‡ and resulted in very similar selectivity as noticed for the unsubstituted diene (**4**).

To examine whether additional electronic factors contribute toward the relative stabilization between diastereomeric transition states, examination of electron delocalizations was performed by using the natural bond orbital method. It was noticed that the interactions between the incipient bonds (C_1-C_6 as well as C_4-C_5) and the carbonyl orbitals of the dienophile are noticed only in a few cases.[35] With dienes **3** and **10**, both diastereomeric transition states (**nx**‡ and **xn**‡) exhibited $\sigma(C_1-C_6) \rightarrow \pi^*$ (C═O) and π (C═O) $\rightarrow \sigma^*(C_1-C_6)$ delocalizations. Interestingly, the lower energy transition states **3nx**‡ and **10xn**‡ showed slightly improved delocalization than the corresponding diastereomeric transition states **3xn**‡ and **10nx**‡, in accordance with the predicted selectivities. A generalization on the basis of electronic delocalizations present in the transition states appears difficult at this point as all the diastereomeric transition states do not exhibit the orbital interactions of the above kind. Therefore, we propose that the stereoselectivity in the present series of dienes arises primarily due to differential steric and electrostatic interactions operating in diastereomeric transition states.

Conclusions

We have described the Diels−Alder reactions between variants of 2-trimethylsiloxycyclohexa-1,3-dienes with dienophile (*E*)-1,4-diphenylbut-2-ene-1,4-dione. The reaction exhibited moderate to high *endo*/*exo* (topographical) selectivity depending on the position of substituents on the diene. The product ratios computed at the mPW1PW91 and the B3LYP level of theories were found to be in very good agreement with the trends in the experimentally observed selectivities. In general, 5-*endo*-6-*exo* Diels−Alder product was preferred over the corresponding 5-*exo*-6-*endo* product for several dienes considered in this study. However, substitution of methyl groups at C_1 and C_8 positions resulted in an interesting reversal of selectivity in favor of 5-*exo*-6-*endo* cycloadduct. Further investigations on the transition states of the reaction involving unsubstituted diene indicated that the electrostatic interaction between the oxygen lone pairs on the diene and the dienophile is a crucial factor controlling the selectivity. The influence of secondary orbital interactions at the transition states of these reactions was found to be absent. In the case of cycloadditions involving methyl-substituted dienes, it was noticed that a combination of electrostatic, steric, and hydrogen bonding interactions are important and can be used to improve or even to change the selectivity.

Experimental Section

1. Computational Methods. The stationary points on the potential energy surfaces have been explored by using the mPW1PW91/6-31G* level of theory,[36] using the Gaussian98 and Gaussian03 suite of quantum chemical programs.[37] The performance of hybrid Hartree−Fock−DFT methods for pericyclic reactions has been quite impressive.[38] In particular, an increasing number of reports are now available on the successful applications of the modified Perdew−Wang functional in reactivity modeling, alongside the more popular B3LYP functional.[39] All geometries were

(35) (a) It appears that the bond length threshold at the mPW1PW91/6-311+G**//mPW1PW91/6-31G* level of theory is about 2.06 Å, beyond which the delocalizations involving the incipient bonds are absent. (b) See Table S3 in the Supporting Information for second-order perturbative stabilization energies involving the C_1-C_6 bond.

(36) Adamo, C.; Barone, V. *J. Chem. Phys.* **1998**, *108*, 664.

(37) (a) Frisch, M. J.; et al. *Gaussian 98*, Revision A.11.4; Gaussian, Inc.: Pittsburgh, PA, 2001. (b) Frisch, M. J.; et al. *Gaussian 03*, Revision C.02; Gaussian, Inc.: Wallingford, CT, 2004. See the Supporting Information for a full citation.

fully optimized at the above level of theory. The nature of stationary points was characterized by evaluating the corresponding Hessian indices. The single-point energies have been computed with a more flexible basis set, namely, 6-311+G**. All the energies are reported at the mPW1PW91/6-311+G**//mPW1PW91/6-31G* level of theory. The enthalpies and Gibbs free energies are calculated by adding unscaled zero-point energies and thermal energies, obtained at the mPW1PW91/6-31G* level of theory, to single-point energies, obtained at the mPW1PW91/6-311+G** level of theory. The transition states for Diels−Alder addition through the concerted pathway were located at the mPW1PW91/6-31G* level of theory and characterized by one and only one imaginary frequency.[40] These frequencies have been identified to represent the correct reaction coordinate. The intrinsic reaction coordinate (IRC) calculations have also been carried out at the mPW1PW91/6-31G* level to authenticate the transition states.[41] Natural bond orbital (NBO) analyses on all the transition states were performedby using the wave functions obtained at the mPW1PW91/6-311+G**//mPW1PW91/6-31G* level of theory.[42] Additionally, the geometry optimizations were repeated at the B3LYP/6-31G* level of theory. Single-point energies evaluated at the B3LYP/6-311+G** level are provided in the Supporting Information (Table S1).

2. Experimental Details. Starting Materials. The trimethylsilyloxy dienes **2**−**11**,[43] (*E*)-1,4-diphenylbut-2-ene-1,4-dione (**1**),[44] and (*Z*)-1,4-diphenylbut-2-ene-1,4-dione (**1′**)[45] were prepared following reported procedures.

Syntheses of Bicyclo[2.2.2]octanone Derivatives: General Procedure. To a solution of **1** in benzene was added 2 equiv of the appropriate diene, then the mixture was refluxed on an oil bath, under an atmosphere of argon, for the appropriate time. Benzene was then removed by distillation under reduced pressure and the residue was hydrolyzed with 5% methanolic-HCl (8−10 mL) for 10 min after which the reaction mixture was extracted with dichloromethane (DCM) (3 × 15 mL) and dried (Na_2SO_4). The solvent was then removed by distillation under reduced pressure and the residue was chromatographed over a column of silica gel (60−120 mesh). ^{1}H (300 MHz) and ^{13}C (75 MHz) NMR spectra for all compounds were recorded in $CDCl_3$ solution with tetramethylsilane as internal standard.

11,12-Dibenzoyltricyclo[6.2.2.0^{1,6}]dodecan-9-ones (2nx,xn). Reaction of **1** (0.33 g, 1.40 mmol) and (4,4a,5,6,7,8-hexahydronaphthalene-2-yloxy)trimethylsilane (**2**, 0.5 g, 2.25 mmol) in 10 mL of benzene for 40 h yielded **2nx** (0.315 g, 58%), mp 120−122 °C, after elution of the column with 10% ethyl acetate (EA)−petroleum ether (60−80 °C) (PE) mixture. IR (KBr) 1721, 1667 cm^{-1} (C═O); UV (CH_3CN) 247 nm (log ϵ 4.39), 278 (3.33), 320 (2.45); ^{1}H NMR δ 1.07−1.26 (m, 5H), 1.44−1.48 (m, 1H), 1.55−1.90 (m, 4H), 2.06 (ddd, J = 14, 11, and 3 Hz, 1H), 2.53 (d, J = 19 Hz, 1H), 2.64 (d, J = 19 Hz, 1H), 2.66 (m, 1H), 4.31 (br d, J = 6 Hz, 1H), 4.55 (br d, J = 6 Hz, 1H), 7.41−7.48 (m, 4H), 7.53−7.58 (m, 2H), 7.91−7.93 (m, 2H), 8.00−8.03 (m, 2H); ^{13}C NMR δ 22.0 (CH_2), 26.1 (CH_2), 27.6 (CH_2), 31.0 (CH_2), 35.3 (CH_2), 37.9 (CH_2), 38.6 (CH), 41.5 (C), 46.2 (CH), 46.5 (CH), 49.2 (CH), 128.9 (CH), 129.0 (CH), 129.1 (CH), 129.3 (CH), 133.8 (CH), 134.0 (CH), 135.6 (C), 139.2 (C), 199.0 (C═O), 204.5 (C═O), 213.3 (C═O). Anal. Calcd for $C_{26}H_{26}O_3$: C, 80.80; H, 6.78. Found: C, 80.23; H, 6.80.

Further elution with 12.5% ethyl acetate in petroleum ether gave **2xn** (0.145 g, 27%), mp 232−234 °C. IR (KBr) 1721, 1666 cm^{-1} (C═O); UV (CH_3CN) 247 nm (log ϵ 4.60), 276 (3.60), 314 (2.63); ^{1}H NMR δ 0.97−1.45 (m, 7H), 1.61−1.70 (m, 2H), 2.06 (dd, J = 19 and 1 Hz, 1H), 2.22−2.29 (m, 1H), 2.52−2.53 (m, 1H), 2.56−2.62 (m, 1H), 2.83 (d, J = 19 Hz, 1H), 4.35 (d, J = 7 Hz, 1H), 4.44 (dd, J = 7 and 1 Hz, 1H), 7.37−7.57 (m, 6H), 7.84−7.86 (m, 2H), 7.96−7.98 (m, 2H); ^{13}C NMR δ 22.1 (CH_2), 25.8 (CH_2), 30.1 (CH), 31.4 (CH_2), 32.2 (CH_2), 35.6 (CH_2), 40.9 (C), 44.3 (CH_2), 46.6 (CH), 47.9 (CH), 49.4 (CH), 128.8 (CH), 128.9 (CH), 129.16 (CH), 129.21 (CH), 133.8 (CH), 134.0 (CH), 135.6 (C), 139.3 (C), 200.5 (C═O), 203.6 (C═O), 212.9 (C═O). Anal. Calcd for $C_{26}H_{26}O_3$: C, 80.80; H, 6.78. Found: C, 80.64; H, 6.68.

8,9-Dibenzoylhexahydro-3a,6-ethanoinden-5-ones (3nx,xn). Reaction of **1** (0.84 g, 3.55 mmol) and trimethyl(2,3,7,7a-tetrahydro-1*H*-inden-5-yloxy)silane (**3**, 1.5 g, 0.720 mmol) in 15 mL of benzene for 60 h gave back unreacted **1** (0.305 g, 36%), mp 106−108 °C (mmp[35] 106−108 °C), on elution of the column with a 5% EA−PE mixture.

Further elution of the column with a 7.5% EA−PE mixture gave **3nx** (0.255 g, 19%), mp 174−176 °C. IR (KBr) 1734, 1668 cm^{-1} (C═O); ^{1}H NMR δ 1.17−1.24 (m, 1H), 1.86 (dd, J = 19 and 1 Hz) mixed with 1.43−2.09 (m, total 9 H), 2.70 (d, J = 5 Hz, 1H), 3.39 (d, J = 19 Hz, 1H), 4.33 (d, J = 8 Hz, 1H), 4.77 (dd, J = 8 and 1 Hz, 1H), 7.42−7.59 (m, 6H), 7.89−7.92 (m, 2H), 8.07−8.10 (m, 2H); ^{13}C NMR δ 23.9 (CH_2), 25.1 (CH_2), 29.5 (CH_2), 33.3 (CH_2), 38.8 (CH), 44.7 (CH), 45.9 (CH), 47.1 (CH_2), 47.7 (CH), 49.4 (C), 128.8 (CH), 129.0 (CH), 129.3 (CH), 133.9 (CH), 134.1 (CH), 134.1 (CH), 135.5 (C), 139.4 (C), 198.4 (C═O), 204.9 (C═O), 214.4 (C═O). Anal. Calcd for $C_{25}H_{24}O_3$: C, 80.62; H, 6.49. Found: C, 80.26; H, 6.60.

Further elution with a 7.5% EA−PE mixture gave **3xn** (0.125 g, 9%), mp 142−144 °C. IR (KBr) 1729, 1667 cm^{-1} (C═O); ^{1}H NMR δ 1.11−1.31 (m, 2H), 1.37−1.52 (m, 2H), 1.55−1.75 (m, 2H), 1.93−2.05 (m, 2H), 2.14 (d, J = 19 Hz) mixed with 2.11−2.17 (m, total 2H), 2.30 (dd, J = 19 and 1 Hz, 1H), 2.70−2.73 (m, 1H), 4.41 (dd, J = 4 and 3 Hz, 1H), 4.53 (dd, J = 4 and 1 Hz, 1H), 7.41−7.59 (m, 6H), 7.89−7.96 (m, 4H); ^{13}C NMR δ 22.0 (CH_2), 25.7 (CH_2), 29.5 (CH_2), 34.1 (CH_2), 38.7 (CH_2), 41.3 (CH), 44.2 (CH), 46.7 (CH), 47.4 (C), 49.5 (CH), 128.4 (CH), 128.45 (CH), 128.5 (CH), 128.8 (CH), 133.2 (CH), 133.5 (CH), 135.4 (C),

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137.9 (C), 199.0 (C═O), 202.4 (C═O), 212.8 (C═O). Anal. Calcd for $C_{25}H_{24}O_3$: C, 80.62; H, 6.49. Found: C, 80.89; H, 6.36.

5,6-Dibenzoylbicyclo[2.2.2]octan-2-ones (4nx,xn). Reaction of **1** (0.56 g, 2.37 mmol) and 2-trimethylsilyloxycyclohexa-1,3-diene (**4,** 0.8 g, 4.75 mmol) in 10 mL of benzene for 24 h gave back unreacted **1** (0.09 g, 16%), mp 106−108 °C (mmp[35] 106−108 °C), on elution of the column with 7.5% EA in PE.

Further elution of the column with 10% EA in PE gave **4nx** (0.29 g, 37%), mp 109−111 °C, after recrystallization from a DCM−PE (1:5) mixture. IR (KBr) 1732, 1666 cm^{-1} (C═O); ^1H NMR δ 1.64−1.73 (m, 2H), 1.80−1.92 (m, 1H), 2.09 (ddd, J = 19, 3, and 1 Hz) mixed with 2.05−2.16 (m, total 2H), 2.40 (ddd, J = 19, 3, and 3 Hz, 1H), 2.58−2.59 (m, 1H), 2.70−2.71 (m, 1H), 4.61 (br d, J = 7 Hz, 1H), 4.73 (br d, J = 7 Hz, 1H), 7.45−7.52 (m, 4H), 7.56−7.62 (m, 2H), 7.98−8.04 (m, 4H); ^{13}C NMR δ 18.2 (CH_2), 24.8 (CH_2), 32.5 (CH), 39.6 (CH_2), 41.5 (CH), 43.4 (CH), 45.3 (CH), 128.4 (CH), 128.5 (CH), 128.68 (CH), 128.71 (CH), 128.74 (CH), 133.3 (CH), 133.5 (CH), 135.2 (C), 135.6 (C), 198.4 (C═O), 202.2 (C═O), 212.3 (C═O). Anal. Calcd for $C_{22}H_{20}O_3$: C, 79.50; H, 6.06. Found: C, 79.31; H, 6.02.

Further elution with 10% EA in PE gave **4xn** (0.20 g, 25%), mp 161−163 °C, after recrystallization from DCM−PE (1:4). IR (KBr) 1722, 1674 cm^{-1} (C═O); ^1H NMR δ 1.40−1.49 (m, 1H), 1.58−1.69 (m, 1H), 1.79−1.90 (m, 1H), 2.12−2.23 (m, 1H), 2.35 (dd, J = 19 and 3 Hz, 1H), 2.60−2.63 (m, 2H), 2.70 (ddd, J = 19, 3, and 3 Hz, 1H), 4.25−4.27 (m, 1H), 4.86 (dd, J = 6 and 2 Hz, 1H), 7.42−7.62 (m, 6H), 7.94−7.99 (m, 4H); ^{13}C NMR δ 19.5 (CH_2), 22.2 (CH_2), 32.1 (CH), 43.4 (CH), 43.9 (CH_2), 45.1 (CH), 46.1 (CH), 128.3 (CH), 128.5 (CH), 128.67 (CH), 128.72 (CH), 133.4 (CH), 133.5 (CH), 135.1 (C), 135.4 (C), 199.8 (C═O), 200.7 (C═O), 212.4 (C═O). Anal. Calcd for $C_{22}H_{20}O_3$: C, 79.50; H, 6.06. Found: C, 79.42; H, 6.06.

5,6-Dibenzoyl-1-methylbicyclo[2.2.2]octan-2-ones (5nx,xn). Reaction of **1** (0.97 g, 4.10 mmol) and 1-methyl-2-trimethylsilyloxycyclohexa-1,3-diene (**5**, 1.5 g, 8.22 mmol) in 15 mL of benzene for 18 h gave a white solid of **5nx** (0.24 g, 17%), mp 118−120 °C, after elution of the column with a 10% EA−PE mixture. IR (KBr) 1720, 1682, 1663 cm^{-1} (C═O); UV (CH_3CN) 246 nm (log ϵ 4.57), 278 (3.60), 322 (2.68); ^1H NMR δ 0.85 (s, 3H), 1.39−1.48 (m, 1H), 1.71−1.82 (m, 1H), 2.14 (ddd, J = 19, 3, and 1 Hz, 1H), 2.40 (d, J = 19 Hz) mixed with 2.25−2.48 (m, total 3H), 2.58−2.60 (m, 1H), 4.27 (br d, J = 7 Hz, 1H), 4.66 (dd, J = 7 and 1 Hz, 1H), 7.43−7.48 (m, 4H), 7.53−7.56 (m, 2H), 7.92−7.99 (m, 4H); ^{13}C NMR δ 18.6 (CH_3), 25.7 (CH_2), 26.7 (CH_2), 33.1 (CH), 39.5 (CH_2), 42.6 (CH), 45.9 (C), 48.1 (CH), 128.9 (CH), 129.1 (CH), 129.2 (CH), 129.3 (CH), 133.8 (CH), 133.9 (CH), 135.9 (C), 138.7 (C), 200.4 (C═O), 202.0 (C═O), 213.1 (C═O). Anal. Calcd for $C_{23}H_{22}O_3$: C, 79.74; H, 6.40. Found: C, 79.48; H, 6.03.

Further elution with a 12.5% EA−PE mixture gave **5xn** (0.44 g, 31%), mp 160−162 °C, as colorless crystals after recrystallization from a DCM−PE (1:4) mixture. IR (KBr) 1728, 1661 cm^{-1} (C═O); UV (CH_3CN) 246 nm (log ϵ 4.50), 279 (3.46), 320 (2.51); ^1H NMR δ 0.96 (s, 3H), 1.44−1.68 (m, 3H), 1.94−2.04 (m, 1H), 2.42 (dd, J = 18 and 3 Hz, 1H), 2.59−2.62 (m, 1H), 2.85 (ddd, J = 18, 3, and 3 Hz, 1H), 3.87 (br m, 1H), 4.85 (d, J = 5 Hz, 1H), 7.41−7.57 (m, 6H), 7.90−8.00 (m, 4H); ^{13}C NMR δ 19.0 (CH_3), 21.2 (CH_2), 31.0 (CH_2), 32.9 (CH), 44.3 (CH_2), 45.3 (C), 48.4 (CH), 49.7 (CH), 128.8 (CH), 129.1 (CH), 129.2 (CH), 129.3 (CH), 133.9 (CH), 134.1 (CH), 135.8 (C), 136.9 (C), 200.0 (C═O), 203.5 (C═O), 213.7 (C═O). Anal. Calcd for $C_{23}H_{22}O_3$: C, 79.74; H, 6.40. Found: C, 79.57; H, 6.03.

5,6-Dibenzoyl-7,7-dimethylbicyclo[2.2.2]octan-2-one (6xn). 1 (0.63 g, 2.67 mmol) and 6,6-dimethyl-2-trimethylsilyloxycyclohexa-1,3-diene (**6,** 1.3 g, 6.62 mmol) were reacted in 10 mL of benzene for 16 h. After the usual workup the mixture was separated by column chromatography. Elution of the column with a 7.5% EA−PE mixture gave back unreacted **1 (**0.32 g, 51%), mp 106−108 °C (mmp[35] 106 °C).

Further elution of the column with 10% EA in PE gave white solid **6xn** (0.30 g, 31%), which was recrystallized from DCM−PE (1:5), mp 113−115 °C. IR (KBr) 1724, 1672 cm^{-1} (C═O); ^1H NMR δ 0.93 (s, 3H), 1.29 (dd, J = 14 and 2 Hz, 1H), 1.45 (s) mixed with 1.45−1.52 (total 4H), 2.19 (d, J = 2 Hz, 1H), 2.27 (dd, J = 19 and 3 Hz, 1H), 2.57−2.64 (m, 2H), 4.31 (br d, J = 6 Hz, 1H), 5.13 (dd, J = 6 and 2 Hz, 1H), 7.44−7.61 (m, 6H), 7.95−7.99 (m, 4H); ^{13}C NMR δ 28.1 (CH_3), 31.4 (C), 31.9 (CH_3), 32.9 (CH), 35.1 (CH_2), 39.9 (CH), 42.3 (CH_2), 45.2 (CH), 57.3 (CH), 128.3 (CH), 128.39 (CH), 128.45 (CH), 128.5 (CH), 128.68 (CH), 128.69 (CH), 133.2 (CH), 133.4 (CH), 135.4 (C), 135.6 (C), 199.8 (C═O), 200.4 (C═O), 211.6 (C═O). Anal. Calcd for $C_{24}H_{24}O_3$: C, 79.97; H, 6.71. Found: C, 79.90; H, 6.83.

5,6-Dibenzoyl-4-methylbicyclo[2.2.2]octan-2-ones (7nx,xn). Reaction of **1** (1.46 g, 6.18 mmol) and 4-methyl-2-trimethylsilyloxycyclohexa-1,3-diene (**7**, 2.25 g, 12.34 mmol) in 15 mL benzene for 50 h gave back unreacted **1** (0.32 g, 22%), mp 106−108 °C (mmp[35] 106−108 °C), after elution of the column with a 7.5% EA−PE mixture.

Further elution of the column with a 10% EA−PE mixture gave **7nx** (0.91 g, 43%), mp 144−146 °C, after recrystallization from DCM−PE. IR (KBr) 1726, 1678, 1666 cm^{-1} (C═O); UV (CH_3CN) 246 nm (log ϵ 4.36), 275 (3.36), 316 (2.63); ^1H NMR δ 0.89 (s, 3H), 1.40−1.50 (m, 1H), 1.66−1.89 (m, 3H), 1.91 (dd, J = 19 and 1 Hz, 1H), 2.71 (dd merged into triplet, J = 1.5 Hz, 1H), 2.96 (dd, J = 19 and 2 Hz, 1H), 4.33 (d, J = 7 Hz, 1H), 4.64 (dd, J = 7 and 1 Hz, 1H), 7.42−7.60 (m, 6H), 7.90−7.93 (m, 2H), 8.04−8.07 (m, 2H); ^{13}C NMR δ 19.5 (CH_2), 25.6 (CH_3), 34.4 (CH_2), 37.9 (C), 45.9(CH), 46.0 (CH), 46.1 (CH_2), 46.2 (CH), 129.0 (CH), 129.01 (CH), 129.2 (CH), 129.3 (CH), 133.9 (CH), 134.1 (CH), 135.5 (C), 138.9 (C), 198.7 (C═O), 204.4 (C═O), 213.3 (C═O). Anal. Calcd for $C_{23}H_{22}O_3$: C, 79.74; H, 6.40. Found: C, 79.40; H, 6.45.

Further elution with a 12.5% EA−PE mixture gave **7xn** (0.325 g, 15%), mp 140−142 °C, after recrystallization from a DCM−PE (1:7) mixture. IR (KBr, cm^{-1}) 1728, 1661 (C═O); UV (CH_3CN) 246 nm (log ϵ 4.35), 277 (3.36), 313 (2.69); ^1H NMR δ 0.86 (s, 3H), 1.26−1.35 (m, 1H), 1.89−1.99 (m, 1H), 2.12 (d, J = 19 Hz) mixed with 2.05−2.17 (m, total 2H), 2.31−2.41 (m, 1H), 2.45 (dd, J = 19 and 3 Hz, 1H), 2.63 (dd, J = 5 and 3 Hz, 1H), 4.33 (dd, J = 6 and 1 Hz, 1H), 4.40 (dd, J = 6 and 2 Hz, 1H), 7.38−7.46 (m, 4H), 7.50−7.58 (m, 2H), 7.83−7.86 (m, 2H), 7.91−7.95 (m, 2H); ^{13}C NMR δ 23.9 (CH_2), 26.3 (CH_3), 26.9(CH_2), 37.4 (C), 46.2 (CH), 47.9 (CH), 48.4 (CH), 52.3 (CH_2), 128.8 (CH), 129.0 (CH), 129.2 (CH), 129.3 (CH), 133.9 (CH), 134.1 (CH), 135.5 (C), 139.1 (C), 200.7 (C═O), 203.6 (C═O), 213.0 (C═O). Anal. Calcd for $C_{23}H_{22}O_3$: C, 79.74; H, 6.40. Found: C, 79.36; H, 6.48.

5,6-Dibenzoyl-8,8-dimethylbicyclo[2.2.2]octan-2-one (8nx). Reaction of **1** (1.2 g, 5.08 mmol) and 5,5-dimethyl-2-trimethylsilyloxycyclohexa-1,3-diene (**8,** 2.0 g, 10.18 mmol) in 20 mL of benzene for 16 h gave back unreacted **1 (**0.73 g, 31%), mp 106−108 °C (mmp[35] 106−108 °C), after elution of the column with a 7.5% EA−PE mixture.

Further elution of the column with 10% EA in PE gave **8nx** (0.37 g, 20%) as a white solid, which was recrystallized from DCM−PE (1:7), mp 113−114 °C. IR (KBr) 1732, 1676 cm^{-1} (C═O); ^1H NMR δ 1.00 (s, 3H), 1.48 (ddd, J = 14, 3, and 1 Hz, 1H), 1.53 (s, 3H), 1.69 (dd, J = 14 and 2 Hz, 1H), 2.13−2.14 (m, 1H), 2.27 (dd, J = 19 and 2 Hz, 1H), 2.38 (ddd, J = 19, 4, and 1 Hz, 1H), 2.67−2.68 (m, 1H), 4.70 (br d, J = 7 Hz, 1H), 5.01 (br d, J = 7 Hz, 1H), 7.45−7.63 (m, 6H), 7.97−8.06 (m, 4H); ^{13}C NMR δ 28.8 (CH_3), 29.2 (CH_3), 32.2(C), 35.2 (CH_2), 36.2 (CH_2), 40.6 (CH), 40.9 (CH), 43.6 (CH), 47.2 (CH), 128.41 (CH), 128.44 (CH), 128.71 (CH), 128.72 (CH), 133.3 (CH), 133.4 (CH), 135.3 (C), 135.7 (C), 198.3 (C═O), 200.5 (C═O), 212.8 (C═O). Anal. Calcd for $C_{24}H_{24}O_3$: C, 79.97; H, 6.71. Found: C, 79.74; H, 6.50.

5,6-Dibenzoyl-4-methoxybicyclo[2.2.2]octan-2-ones (9nx,xn). To a solution of **1** (0.75 g, 3.17 mmol) in benzene (15 mL) was added 1,5-dimethoxy-1,4-cyclohexadiene (**9,** 1.8 g, 12.84 mmol)

and 0.025 g of DCMA and the resulting mixture was refluxed on an oil bath for 16 h. The solvent was removed and the mixture was hydrolyzed by refluxing in a 1:5 mixture of DME−water (12 mL) for 8 h. After the usual workup the residue was chromatographed over a column of silica gel. Elution of the column with a 15% EA−PE mixture gave **9nx** (0.50 g, 42%), mp 156−158 °C, as colorless crystals on recrystallization from a DCM−PE (1:5) mixture. IR (KBr) 1732, 1666 cm^{-1} (C═O); UV (CH_3CN) 247 nm (log ϵ 4.25), 278 (3.32), 314 (2.72); ^1H NMR δ 1.67−1.73 (m, 1H), 1.81−1.93 (m, 2H), 2.00−2.09 (m, 1H), 2.45 (dd, J = 19 and 2 Hz, 1H), 2.68 (br s, 1H), 3.05 (s, 3H), 3.09 (dd, J = 19 and 3 Hz, 1H), 4.36 (d, J = 7 Hz, 1H), 4.96 (dd, J = 7 and 2 Hz, 1H), 7.42−7.47 (m, 4H), 7.51−7.58 (m, 2H), 7.90−7.93 (m, 2H), 8.03−8.06 (m, 2H); ^{13}C NMR δ 18.4 (CH_2), 28.9 (CH_2), 43.2 (CH_2), 45.8 (CH), 45.86 (CH), 45.89 (CH), 50.5 (CH_3), 79.0 (C), 128.8 (CH), 129.0 (CH), 129.2 (CH), 129.3 (CH), 133.5 (CH), 134.2 (CH), 135.3 (C), 139.0 (C), 198.0 (C═O), 203.5 (C═O), 209.7 (C═O). Anal. Calcd for $C_{23}H_{22}O_4$: C, 76.22; H, 6.12. Found: C, 76.06; H, 6.16.

Further elution with a 15% EA−PE mixture gave **9xn** (0.150 g, 13%), mp 173−175 °C, as colorless crystals on recrystallization from DCM−PE (1:6). IR (KBr, cm^{-1}) 1725, 1670 (C═O); UV (CH_3CN) 249 nm (log ϵ 4.46), 278 (3.49), 318 (2.81); ^1H NMR (300 MHz) δ 1.71−1.94 (m, 2H), 2.10−2.19 (m, 1H), 2.35−2.43 (m, 1H), 2.58 (d, J = 18 Hz, 1H) mixed with 2.62 (m), 2.67 (dd, J = 18 and 3 Hz, 1H), 3.04 (s, 3H), 4.42 (dd, J = 6 and 2 Hz, 1H), 4.60 (dd, J = 6 and 1 Hz, 1H), 7.39−7.44 (m, 4H), 7.50−7.55 (m, 2H), 7.83−7.85 (m, 2H), 7.94−7.97 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 22.1 (CH_2), 23.5 (CH_2), 45.8 (CH), 46.9 (CH), 47.8 (CH_2), 48.1 (CH), 50.5 (CH_3), 78.1 (C), 128.8 (CH), 129.0 (CH), 129.1 (CH), 129.3 (CH), 133.5 (CH), 134.2 (CH), 135.3 (C), 139.2 (C), 200.0 (C═O), 202.9 (C═O), 209.8 (C═O). Anal. Calcd for $C_{23}H_{22}O_4$: C, 76.22; H, 6.12. Found: C, 76.16; H, 5.94.

5,6-Dibenzoyl-4,7,7-trimethylbicyclo[2.2.2]octan-2-one (10xn). Reaction of **1** (1.46 g, 6.18 mmol) and 4,6,6-trimethyl-2-trimethylsilyloxycyclohexa-1,3-diene (**10**, 1.7 g, 8.08 mmol) in 15 mL of benzene for 16 h gave back unreacted **1** (0.60 g, 41%), mp 106−108 °C (mmp[35] 106−108 °C), after elution of the column with a 7.5% EA−PE mixture.

Further elution of the column with 10% EA−PE gave **10xn** (0.76 g, 33%), mp 178−180 °C, after recrystallization from a DCM−PE (1:6) mixture. IR (KBr) 1730, 1668 cm^{-1} (C═O); UV (CH_3CN) 246 nm (log ϵ 4.58), 277 (3.61), 312 (3.00); ^1H NMR δ 0.85 (s, 3H), 0.97 (s, 3H), 1.11 (dd, J = 14 and 1 Hz, 1H), 1.57 (s, 3H), 2.04−2.10 (m, 2H), 2.20 (d, J = 2 Hz, 1H), 2.33 (dd, J = 19 and 3 Hz, 1H), 4.39 (br d, J = 7 Hz, 1H), 4.69 (dd, J = 7 and 2 Hz, 1H), 7.40−7.47 (m, 4H), 7.52−7.57 (m, 2H), 7.84−7.86 (m, 2H), 7.96−7.99 (m, 2H); ^{13}C NMR δ 26.0 (CH_3), 28.4 (CH_3), 32.4 (CH_3), 32.5 (C), 37.9 (C), 42.2 CH_2), 44.3 (CH), 47.2 (CH), 50.8 (CH_2), 58.4 (CH), 128.8 (CH), 128.9 (CH), 129.1 (CH), 129.2 (CH), 133.8 (CH), 133.9 (CH), 135.7 (C), 139.1 (C), 200.2 (C═O), 203.6 (C═O), 212.2 (C═O). Anal. Calcd for $C_{25}H_{26}O_3$: C, 80.18; H, 7.00. Found: C, 80.06; H, 7.35.

5,6-Dibenzoyl-1,4-dimethylbicyclo[2.2.2]octan-2-ones (11nx,-xn). Reaction of **1** (1.2 g, 5.08 mmol) and 1,4-dimethyl-2-trimethylsilyloxycyclohexa-1,3-diene (**11,** 2.0 g, 10.18 mmol) in 20 mL of benzene for 24 h gave back unreacted **1 (**0.03 g, 2.5%), mp 106−108 °C (mmp[35] 106−108 °C), after elution of the column with a 7.5% EA−PE mixture.

Further elution of the column with a 10% EA−PE mixture gave **11nx** (0.72 g, 39%), mp 98−100 °C, after recrystallization from a DCM−PE (1:5) mixture. IR (KBr) 1720, 1661 cm^{-1} (C═O); ^1H-NMR δ 0.83 (s, 3H), 0.86 (s, 3H), 1.40−1.58 (m, 2H), 1.96 (dd, J = 19 and 2 Hz, 1H), 1.98−2.06 (m, 1H), 2.38−2.47 (m, 1H), 2.97 (dd, J = 19 and 3 Hz, 1H), 4.27 (br d, J = 8 Hz, 1H), 4.33 (br d, J = 8 Hz, 1H), 7.36−7.43 (m, 4H), 7.48−7.54 (m, 2H), 7.81−7.90 (m, 4H); ^{13}C NMR δ 18.1 (CH_3), 25.2 (CH_3), 26.1 (CH_2), 35.3 (CH_2), 37.2 (C), 45.2 (CH_2), 45.8 (C), 46.1 (CH), 49.4 (CH), 128.38 (CH), 128.43 (CH), 128.8 (CH), 133.5 (CH), 133.6 (CH), 138.1 (C), 138.2 (C), 201.3 (C═O), 203.6 (C═O), 213.2 (C═O). Anal. Calcd for $C_{24}H_{24}O_3$: C, 79.97; H, 6.71. Found: C, 79.74; H, 6.93.

Further elution with 12.5% EA−PE gave **11xn** (0.34 g, 19%), mp 122−124 °C, as colorless crystals after recrystallization from a DCM−PE (1:5) mixture. IR (KBr) 1728, 1661 cm^{-1} (C═O); ^1H NMR δ 0.82 (s, 3H), 0.95 (s, 3H), 1.28−1.38 (m, 1H), 1.60−1.70 (m, 1H), 1.97−2.08 (m, 1H), 2.19 (d, J = 19 Hz) mixed with 2.13−2.22 (m, total 2H), 2.62 (dd, J = 19 and 3 Hz, 1H), 3.88 (br d, J = 6 Hz, 1H), 4.38 (d, J = 6 Hz, 1H), 7.34−7.40 (m, 4H), 7.47−7.54 (m, 2H), 7.76−7.82 (m, 4H); ^{13}C NMR δ 18.3 (CH_3), 26.0 (CH_3), 27.7 (CH_2), 32.0 (CH_2), 37.0 (C), 45.4 (C), 51.6 (CH), 51.7 (CH), 51.8 (CH_2), 128.2 (CH), 128.4 (CH), 128.5 (CH), 128.6 (CH), 128.8 (CH), 128.9 (CH), 133.5 (CH), 133.8 (CH), 136.5 (C), 138.6 (C), 202.8 (C═O), 202.9 (C═O), 213.3 (C═O). Anal. Calcd for $C_{24}H_{24}O_3$: C, 79.97; H, 6.71. Found: C, 80.09; H, 6.67.

Addition Reaction of 4-Methyl-2-trimethylsilyloxycyclohexa-1,3-diene (7) with 1′. The above procedure was carried out with **1′** (0.38 g, 1.61 mmol) and 4-methyl-2-trimethylsilyloxycyclohexa-1,3-diene (**7**, 0.58 g, 3.2 mmol) in benzene (10 mL) for 50 h. After the usual workup and removal of the solvent, the residue was chromatographed over a column of silica gel. Elution of the column with 7.5% ethyl acetate in petroleum ether gave **1** (0.03 g, 8%), mp 106−108 °C (mmp[35] 106−108 °C).

Further elution of the column with 10% ethyl acetate in petroleum ether gave **7nx** (0.26 g, 47%), mp 144−146 °C (mmp 144−146 °C).

Further elution with 12.5% ethyl acetate in petroleum ether gave **7xn** (0.21 g, 19%), mp 140−142 °C (mmp 140−142 °C).

Epimerizatipn of 7nx and 7xn. In two separate experiments both of the diastereomers (**7nx**,**xn**, 50 mg) were stirred in 20% methanolic NaOH solution (8 mL) for 24 h. The mixtures were neutralized with dilute HCl and were extracted with DCM (3 × 10 mL). After removal of the solvents, the mixtures were analyzed by ^1H NMR spectroscopy, which showed the presence of **7nx** and **7xn** in a 1:1.7 ratio in both mixtures.

Isomerization of 1′ to 1. A solution of (*Z*)-1,4-diphenylbut-2-ene-1,4-dione (**1′**, 150 mg) in dry benzene (10 mL) was refluxed for 40 h under argon atmosphere. Removal of solvent followed by chromatography yielded (*E*)-1,4-diphenylbut-2-ene-1,4-dione (**1**, 16 mg, 10%), mp 106−108 °C (mmp[35] 106−108 °C), along with unreacted (*Z*)-1,4-diphenylbut-2-ene-1,4-dione (**1′**, 120 mg, 80%), mp 133−134 °C (mmp[36] 133−134 °C).

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Supporting Information Available: ORTEP diagram for **3nx**, ^1H NMR and ^{13}C NMR for all unknown compounds, total electronic energies, optimized coordinates, and single-point energies of all structures reported in the text (Tables S6 and S7), and a full list of citations for Gaussian98 and Gaussian03 (ref 37 in the text). This material is available free of charge via the Internet at http://pubs.acs.org.

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