# On the Origin of *Cis/Trans* Stereoselectivity in Intramolecular Diels−Alder Reactions of Substituted Pentadienyl Acrylates: A Comprehensive Density Functional Study

Michael N. Paddon-Row,*,† Damian Moran,† Garth A. Jones,† and Michael S. Sherburn‡

School of Chemistry, The University of New South Wales, Sydney, NSW 2052, Australia, and Research School of Chemistry, Australian National University, Canberra, ACT 0200, Australia

m.paddonrow@unsw.edu.au

endo-adduct preferred ✓   exo-adduct preferred ✗
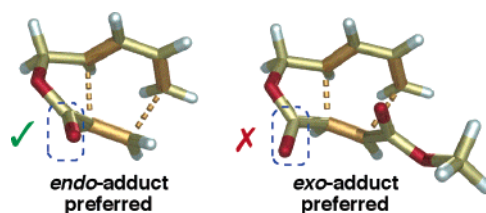
A gas-phase B3LYP/6-31+G(d) study of substituent effects on the stereochemistry of both *intra*molecular Diels−Alder (IMDA) reactions of 9-*E*- and 9-*Z*-substituted pentadienyl acrylates and *inter*molecular Diels−Alder (DA) reactions between butadiene and monosubstituted alkenes and 3-substituted acrylates is reported and involves the calculation of 230 transition structures. It was found that, although *exo* ("anti-Alder") addition of monosubstituted ethenes to butadiene is the norm, Alder *endo* selectivity is more widely predicted for 3-substituted methyl acrylate dienophiles, and this was explained in terms of secondary orbital interactions (SOIs). Whereas *cis/trans* selectivity for IMDA reactions involving 9-*E*-substituted pentadienyl acrylates generally follows the normal pattern found for the corresponding intermolecular DA reactions, the 9-*Z*-substituted stereoisomers generally displayed *trans* selectivity that was much stronger than can be attributed to effects of the isolated substituent. This is strikingly so with unsaturated electron-withdrawing substituents whose *endo* selectivities, displayed in intermolecular DA reactions, are reversed in the IMDA reactions of pentadienyl acrylates. The origin of this anomalous *Z*-effect is explained in terms of the twist-mode asynchronicity concept of Brown and Houk. These ideas are used to explain the stereochemical outcomes of IMDA reactions of other triene systems.

Introduction

We recently presented experimental and DFT computational studies of the intramolecular Diels−Alder (IMDA) reactions of some pentadienyl acrylates (Scheme 1) bearing substituents at C1 and C9.[1] These reactions can form two distinct diastereoisomeric products (**P**), namely *cis*-**P** and *trans*-**P**, which differ in the stereochemistry about the ring fusion. It was found experimentally that the IMDA reaction of the unsubstituted system **1** was *cis* selective, giving a *cis/trans* product ratio of 70:30. The B3LYP/6-31+G(d) gas-phase calculations reproduced this product ratio (62:38), predicting that the *cis* transition structure (TS), leading to formation of the *cis* product, is

about 1.9 kJ/mol more stable than the *trans*-TS, leading to formation of the *trans* product. Furthermore, calculations suggested that the overall energetic preference for the *cis*-TS is the net outcome from two opposing influences, namely torsional strain about the C4−C5 bond in the *cis*-TS, amounting to ca. 2.5 kJ/mol *destabilization* of the *cis*-TS relative to the *trans*-TS, and attractive electrostatic and/or secondary orbital interactions (SOIs)[2] in the *cis*-TS between the *endo* tether carbonyl group and

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SCHEME 1. *Intra*molecular DA Reaction *Cis* and *Trans* Transition Structures (TS) and Bicyclic Products (P)[a]
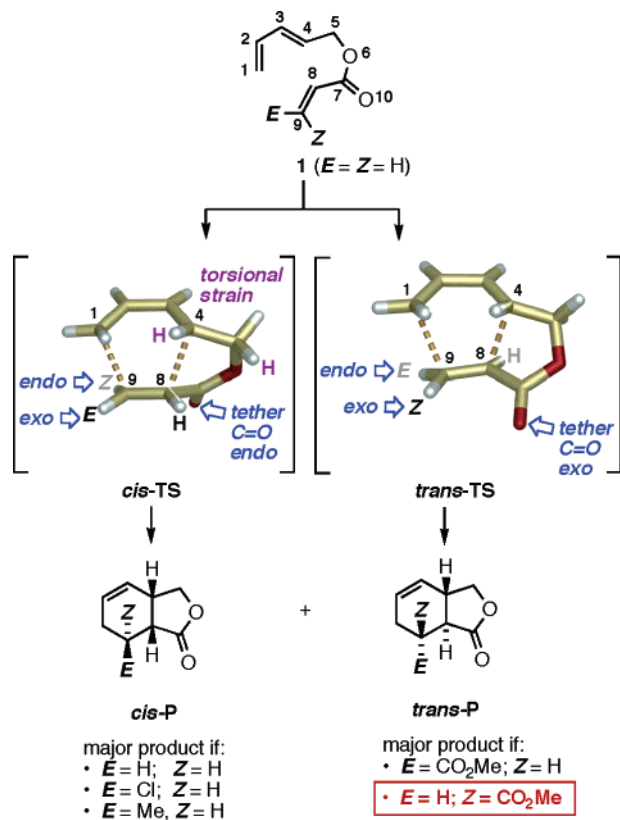
[a] The anomalous *trans* selectivity with *Z*-dienophiles is highlighted in red.

atoms C4 and possibly C3 of the diene unit.[1] Combining the net stabilization energy of 1.9 kJ/mol of the *cis*-TS, relative to the *trans*-TS, with the destabilizing torsional strain energy of 2.5 kJ/mol in the *cis*-TS gives a value of 4.4 kJ/mol for the attractive interactions between the *endo* tether carbonyl group and the diene moiety in the *cis*-TS.

Experimentally, it has been observed that substitution at C9 with Cl, Me, or CO_2Me groups influences the stereochemical outcome. Thus, placement of Me or Cl at the *E* position of **1** gave predominantly *cis* product, whereas the 9-*E*-CO_2Me substituent weakly favored formation of the *trans* product (*cis/trans* = 42:58).[1] This switchover in *cis/trans* selectivity, upon changing the 9-*E* substituent from Cl or Me to CO_2Me, may be explained in terms of repulsive electrostatic interactions between the diene unit and the *endo* Cl and Me in the *trans*-TSs, which are absent in the corresponding *cis*-TSs, and attractive electrostatic/SOIs between the diene and the *endo* ester group in the *trans*-TS. In the latter case, there is a competition between the *endo* preference for the tether in the *cis*-TS and the *endo* preference of the unsaturated, electron-withdrawing 9-*E* ester group which is realized in the *trans*-TS. Bearing in mind that the *endo* preference for the tether is not fully optimized, owing to the presence of the aforementioned torsional strain in the *cis*-TS, it is reasonable that the *endo* preference of the 9-*E* ester weakly prevails over the *endo* preference of the tether, even though the 9-*E*-CO_2Me group is slightly

further removed from the diene, compared to the tether carbonyl group.

In stark contrast, the IMDA reaction of the 9-*Z*-CO_2-Me stereoisomer is strongly *trans* selective (*cis/trans* = 17:83), meaning that *both 9-CO_2Me and tether carbonyl groups are in the* exo *orientation with respect to the diene in the favored TS*. Apparently, attractive electrostatic/ SOIs involving both 9-CO_2Me and tether carbonyl groups in the *cis*-TS are overwhelmed by some other effect which tilts the balance in favor of the *trans*-TS.[3] This anomalous *trans* selectivity has also been observed in the IMDA reaction of 1,3,8-nonatriene bearing the 9-*Z*-CO_2Me substituent.[4] This paper presents the results of a DFT computational study into *cis/trans* selectivity in the IMDA reactions of 9-*E*-substituted and 9-*Z*-substituted pentadienyl acrylates covering a wide range of 9-substituents, an important goal being to understand the origin of the anomalous *trans* selectivity displayed by the 9-*Z*-CO_2Me substituent and to learn whether unsaturated 9-*Z*-substituents other than ester groups also exhibit *trans* selectivity. *Endo/exo* selectivities of *inter*molecular DA reactions between substituted ethylenes and butadiene were also computed in order to understand better the origin of *cis/trans* selectivity in this synthetically important system.[3,5]

Computational Methods

Inter- and *intra*molecular TSs and, where appropriate, reactant and product structures were optimized using the B3LYP functional[6] and the 6-31+G(d) basis set.[7] Harmonic vibrational frequencies (at the same level of theory)

(3) For other examples of this anomalous *trans*-selectivity of *Z*-dienophiles in IMDA reactions, see: (a) White, J. D.; Sheldon, B. G. *J. Org. Chem.* **1981**, *46*, 2273−2280. (b) He, J. F.; Wu, Y. L. *Tetrahedron* **1988**, *44*, 1933−1940. (c) Batchelor, M. J.; Mellor, J. M. *J. Chem. Soc., Perkin Trans. 1* **1989**, 985−995. (d) Lilly, M. J.; Sherburn, M. S. *Chem. Commun.* **1997**, 967−968. (e) Turner, C. I.; Williamson, R. M.; Paddon-Row: M. N.; Sherburn, M. S. *J. Org. Chem.* **2001,** *66*, 3963−3969. (f) Cayzer, T. N.; Paddon-Row, M. N.; Sherburn, M. S. *Eur. J. Org. Chem.* **2003**, 4059−4068.
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TABLE 1. ZPVE-Corrected Energy Differences (E_{rel}^{TS}, kJ/mol) between Penta-1,3-dienyl *E/Z*-Acrylate *Cis*- and *Trans*-IMDA TSs[a]

Entry	R-group	$E_{rel}^{TS} E^{b,c}$	$E_{rel}^{TS} Z^{b,c}$	Entry	R-group	$E_{rel}^{TS} E^{b,c}$	$E_{rel}^{TS} Z^{b,c}$
1	—H	c1.88 (64%)	–	2	—CH₃	c4.17 (79%)	t2.24 (67%)
3	—C(CH₃)₃	c2.98 (72%)	t7.40 (91%)	4	—SiH₃	c0.23 (52%)	c0.52 (54%)
5	—Si(CH₃)₃	c2.39 (68%)	t2.42 (68%)	6	—GeH₃	c5.79 (86%)	t0.02 (50%)
7	—Ge(CH₃)₃	c5.67 (85%)	t1.96 (65%)	8	—CF₃	c2.06 (66%)	t5.40 (84%)
9	—CCl₃	c4.18 (79%)	t11.99 (98%)	10	—CBr₃	c3.73 (76%)	t11.32 (97%)
11	—F	c6.20 (87%)	t4.54 (81%)	12	—Cl	c6.64 (89%)	t8.71 (94%)
13	—Br	c5.10 (83%)	t8.23 (93%)	14	—NH₂	c0.81 (56%)	t5.66 (85%)
15	—N⁺H₃	t8.76 (94%)	c9.81 (96%)	16	—B⁻H₃	c13.48 (99%)	t30.84 (100%)
17	—BH₂	t22.07 (100%)	c9.28 (95%)	18	—B(CH₃)₂	t8.82 (94%)	t0.07 (51%)
19	—B(OCH₂CH₂O)	t1.70 (63%)	t5.81 (86%)	20	—C≡CH	c4.44 (80%)	t11.94 (98%)
21	—C≡N	c1.59 (62%)	t8.09 (93%)	22	—NO₂	t3.84 (77%)	t8.00 (92%)
23	ester (*s-cis*)	t0.71 (56%)	t8.85 (94%)	24	ester (*s-trans*)	t0.56 (54%)	t8.87 (94%)
25	—CH₃ ketone (*s-cis*)	t1.51 (62%)	t6.28 (88%)	26	—CH₃ ketone (*s-trans*)	t4.15 (79%)	t3.39 (74%)
27	—H aldehyde (*s-cis*)	t3.74 (76%)	t5.44 (85%)	28	—H aldehyde (*s-trans*)	t4.36 (80%)	t1.29 (60%)
29	(*s-cis-syn*)	t1.26 (60%)	t8.48 (93%)	30	(*s-cis-anti*)	c0.19 (51%)	t9.18 (95%)
31	(*s-trans-syn*)	t0.71 (56%)	t9.37 (95%)	32	(*s-trans-anti*)	t5.35 (84%)	c1.39 (61%)
33	H₂C= (*s-trans*)	c1.92 (65%)	t8.92 (93%)				

[a] See Figure 1 for entry details. [b] Note that the "*c*" and "*t*" E_{rel}^{TS} prefixes used throughout the manuscript indicate that the *cis*-TS and *trans*-TS are more stable, respectively. For example, the parent penta-1,3-dienyl acrylate **1** E_{rel}^{TS} is c1.88 kJ/mol, which indicates that the *cis*-TS is favored by 1.88 kJ/mol. [c] Boltzmann populations at 383 K are shown in parentheses.

were employed to characterize optimized geometries as either first-order saddle structures (one negative Hessian eigenvalue) or minima (all frequencies real) and to provide zero-point vibrational energy (ZPVE; unscaled) corrections. Salient TS relative energies are summarized in Tables 1 and 2, and geometrical parameters (Figure 1) are summarized in Tables S1−S3 in the Supporting Information.

ZPVE (0 K) corrected TS relative energies (E_{rel}^{TS}) were calculated using the electronic energies from optimized *cis*- and *trans*-IMDA TS isomers (i.e., $E_{rel}^{TS} = E_{cis-TS} -$ $E_{trans-TS}$) and *endo*- and *exo-inter*molecular DA reaction TS isomers (i.e., $E_{rel}^{TS} = E_{endo-TS} - E_{exo-TS}$). TS Boltzmann populations (383 K) were calculated from the electronic energies (ZPVE-corrected) and were used in place of enthalpies or free energies because they have been shown to give similar results.[8] *Inter*- and *intra*molecular DA E_{rel}^{TS} and Boltzmann populations are summarized in Tables 1 and 2. The Gaussian 98[9] and 03[10] program packages were used throughout. Optimized geometries (in Cartesian coordinate form) and their energies are provided as Supporting Information.

Justification of the Theoretical Model. The B3LYP functional, in conjunction with either the 6-31G(d) or 6-31+G(d) basis sets, is known to give acceptable relative

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TABLE 2.   ZPVE-Corrected Relative Energies (E_{rel}^{TS}; kJ/mol) for Intermolecular DA TSs between 1,3-Butadiene and Substituted Ethylenes, with Their Substituents Either *Endo*- or *Exo*-Oriented with Respect to the Diene[a]

Entry	R-group	$E_{rel}^{TS\,b,c}$	Entry	R-group	$E_{rel}^{TS\,b,c}$
da1	—H	–	**da2**	—CH_3	x0.70 (55%)
da3	—C(CH_3)(CH_3)CH_3	x2.96 (72%)	**da4**	—SiH_3	x0.07 (51%)
da5	—Si(CH_3)(CH_3)CH_3	x2.27 (67%)	**da6**	—GeH_3	x2.74 (70%)
da7	—Ge(CH_3)(CH_3)CH_3	x2.62 (89%)	**da8**	—C(F)(F)F	x2.17 (66%)
da9	—C(Cl)(Cl)Cl	x5.94 (87%)	**da10**	—C(Br)(Br)Br	x7.89 (92%)
da11	—F	x1.60 (62%)	**da12**	—Cl	x4.16 (79%)
da13	—Br	x1.38 (61%)	**da14**	—N(H)H	n6.03 (87%)
da15	—$\overset{\oplus}{N}$(H)(H)H	n13.81 (99%)	**da16**	—$\overset{\ominus}{B}$(H)(H)H	x18.67 (100%)
da17	—B(H)H	n20.78 (100%)	**da18**	—B(CH_3)CH_3	n8.24 (93%)
da19	—B(O–O)	n1.21 (59%)	**da20**	—C≡CH	x6.80 (89%)
da21	—C≡N	x3.28 (74%)	**da22**	—N(O)O	x1.18 (59%)
da23	C(=O)O—CH_3 (*s-cis*)	x1.01 (58%)	**da24**	C(=O)O—CH_3 (*s-trans*)	x1.18 (59%)
da25	C(=O)—CH_3 (*s-cis*)	x0.25 (52%)	**da26**	C(=O)—CH_3 (*s-trans*)	n2.56 (69%)
da27	C(=O)—H (*s-cis*)	n0.98 (58%)	**da28**	C(=O)—H (*s-trans*)	n2.58 (69%)
da29	C(=O)O—H (*s-cis-syn*)	x.1.05 (58%)	**da30**	C(=O)O—H (*s-cis-anti*)	x1.98 (65%)
da31	C(=O)O—H (*s-trans-syn*)	x1.52 (62%)	**da32**	C(=O)O—H (*s-trans-anti*)	n5.84 (86%)
da33	H_2C=C—H (*s-trans*)	x4.89 (82%)			

[a] See Figure 1 for R-group orientations. [b] Note that the "*n*" and "*x*" E_{rel}^{TS} prefixes used throughout the manuscript indicate that the *endo*-TS and *exo*-TS are more stable, respectively. For example, the **da2** E_{rel}^{TS} is x0.70 kJ/mol, which indicates that the *exo*-TS is favored by 0.70 kJ/mol. [c] Boltzmann populations at 383 K are shown in parentheses.

energies and geometries for a broad variety of Diels–Alder reactions.[1,2h,3e,f,8,11] Importantly, we have shown that the B3LYP/6-31+G(d) method correctly predicts *cis/trans* ratios for the IMDA reactions of several 9-substituted pentadienyl acrylates, often with an accuracy of 1 kJ/mol.[1] This level of theory is, therefore, adequate for this study. In this work, we focus exclusively on the

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influence of electronic, strain and steric factors on the *cis/trans* selectivities of IMDA reactions, without considering solvent effects; consequently, we have used *gas-phase* DFT calculations. The excellent agreement found between gas-phase B3LYP/6-31+G(d) predicted IMDA *cis/trans* ratios and the experimental ratios, obtained using toluene as solvent, suggests that weakly polar solvents—which are often used in IMDA reactions—have no significant influence on *cis/trans* selectivities.[1] A detailed computational and experimental study of solvent effects on IMDA stereoselectivity is currently underway in our laboratory.

Results and Discussion

The full list of 9-substituents studied in the IMDA reaction is presented in Table 1, together with their structure numbers. Five of these substituents, namely $CH=CH_2$, CO_2Me, CHO, COMe, and CO_2H, are capable

FIGURE 1. Important geometrical parameters associated with (left) *inter*molecular and (right) *intra*molecular Diels−Alder reaction transition structures.
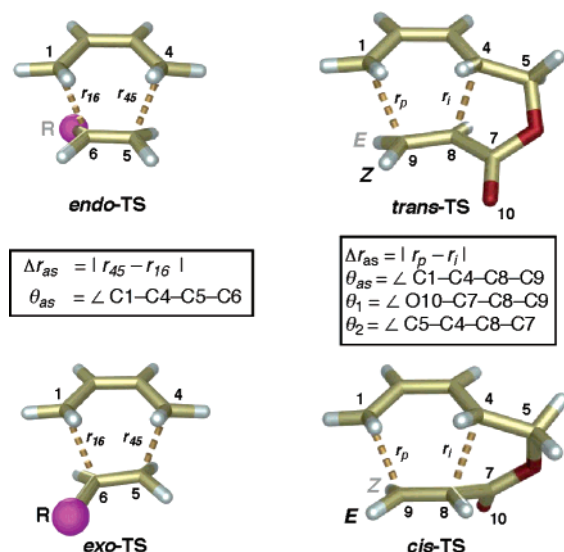
of adopting either the *s-cis* or *s-trans* orientations with respect to the adjacent C9=C8 double bond, and TSs associated with both orientations were calculated with one exception (see Table 1, **23**−**33**). The exception was the vinyl substituent, for which only results for the *s-trans* conformation are reported here, since the dimerization of *s-cis* butadiene occurs through a so-called bispericyclic TS discovered by Caramella et al.[12] In general, the *s-cis*-TS was found to be more stable than the corresponding *s-trans*-TS for these dienophiles.

Furthermore, the CO_2Me and CO_2H groups can adopt conformations in which the Me and H are *syn*- or *anti*- to the carbonyl group. Although the *syn* conformation is substantially more stable than the *anti* conformation,[13] the TSs for both conformations were located for the −CO_2H substituent (Table 1, **29**−**32**). Our purpose for studying the TSs possessing the less stable conformations of substituents was exclusively to investigate whether

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(12) Quadrelli, P.; Romano, S.; Toma, L.; Caramella, P. *Tetrahedron Lett.* **2002**, *43*, 8785−8789.

(13) For example, the *anti* conformation of acetic acid is 25 kJ/mol less stable than the *syn* conformation (B3LYP/6-31G(d)//HF/3-21G). The *anti* conformation can be preferred in the presence by external H-bonding acceptors (see later).

exo/endo selectivities were influenced by the conformation of the substituent and not to determine which particular TS conformation was more stable. Consequently, relative energies of various TS conformations are not explicitly discussed in this paper; this information is, however, available in the Supporting Information.

The computed *cis/trans*-product distribution and the relative energies of the *cis*- and *trans*-TSs are presented in Table 1. Referring to Figure 1, there are six significant geometrical parameters associated with the IMDA TSs. These are the peripheral and internal forming bonds, r_p and r_i, respectively; the bond-forming asynchronicity, Δr_{as} ($= |r_p - r_i|$); the twist-mode asynchronicity dihedral angle, θ_{as} ($=$ the dihedral angle C1−C4−C8−C9);[14] the dihedral angle, θ_1, made between the carbonyl group and the dienophile double bond; and finally, the dihedral angle, θ_2, which gives the degree of twisting about the C4−C8 internuclear axis in the forming γ-butyrolactone ring. Values for the parameters (with the exception of Δr_{as}) for the IMDA TSs for the 9-*E* and 9-*Z* systems are given in Tables S1 and S2 of the Supporting Information, respectively. The various substituents studied herein may be categorized according to their electronic structures, as summarized in Table 3.

General Comments on IMDA TS Geometries. For all IMDA TSs the forming peripheral bond is longer than the forming internal bond (see Tables S1 and S2, Supporting Information), with the bond-forming asynchronicity, Δr_{as}, in the *trans*- and *cis*-IMDA TSs becoming larger upon substitution at C9. The asynchronicity is generally larger for the *trans*-TS than for the *cis*-TS and for *Z*-substituents, compared to *E*-substituents, and becomes largest for conjugating groups (see Tables S1 and S2, Supporting Information). Even though Δr_{as} varies significantly throughout the series of 9-substituted TSs studied, the sum of the internal and peripheral bond lengths remains approximately constant (ca. 4.5−4.6 Å). Thus, any increase in the length of the developing peripheral bond is compensated by contraction of the forming internal bond, thereby maintaining as much bond-forming stabilization energy as possible.[1]

The direction of the twist-asynchronicity parameter, θ_{as}, depends on the stereochemistry of the IMDA TS, *cis* or *trans*.[1,14] With the exception of *cis-E*-**16TS** and *cis-Z*-**17TS**, θ_{as} is positive for all *cis*-TSs studied, representing twisting of the dienophile double bond about the developing C4−C8 bond in the *endo* direction, taking C9 further under the diene face; conversely, θ_{as} is negative for all *trans*-TSs studied, representing twisting of the dienophile in the *exo* direction, in which case C9 is moved further away from the diene face (see Figure 2 and Tables S1 and S2, Supporting Information). The numerical value of θ_{as} depends on the nature and stereochemical orientation (*E* or *Z*) of the 9-substituent. For the parent system **1**, the magnitude of θ_{as} is small, being 5.8° and −8.8° for the *cis*- and *trans*-TSs, respectively.

In general, 9-*E* substitution has little effect on the magnitudes of θ_{as}, notable exceptions being the borane systems *E*-**17TS** − *E*-**19TS**. The values of θ_{as} for the 9-BH_2 system are 11.1° for *cis-E*-**17TS**, and −19.6° for *trans-E*-**17TS**, the magnitudes of which reflect the ten-

(14) Brown, F. K.; Houk, K. N. *Tetrahedron Lett.* **1985**, *26*, 2297−2300.

TABLE 3. Substituents Categorized According to Their Electronic Structures

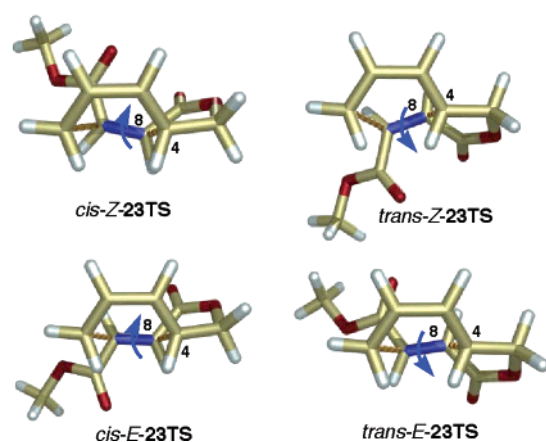| group	substituents
1	saturated alkyl, silyl, and germyl groups XY_3 (X = C, Si, Ge; Y = H, Me), trihalomethyl groups CX_3 (X = F, Cl, Br), and charged groups NH_3^+ and BH_3^-
2	F, Cl, Br, and NH_2 possess lone pairs of electrons on the atom which is covalently linked to C9
3	boranes (with a vacant *p* orbital on B), BR_2 (R = H, Me; $R_2 = -OCH_2CH_2O-$)[15]
4	conjugating groups, ethynyl, cyano, CO_2Me, CO_2H, CH=O, $C(CH_3)$=O, NO_2, and vinyl

FIGURE 2. *Cis-* and *trans*-IMDA TSs for **23**. Dienophiles are colored blue. Blue arrows depict direction of dienophile twisting about the C4−C8 axis seen in all *cis-* and *trans*-TSs except *cis-E-***16TS** and *cis-Z-***17TS**.

FIGURE 3. Schematic representation of the impact upon θ_1 (dihedral O10−C7−C8−C9) when θ_{as} (dihedral C1−C4−C8−C9) is increased.

dency for the boron vacant *p* orbital to interact maximally with C1. Indeed, the distance between C1 and C9 (2.627 Å) in *cis-E-***17TS** is greater than that between C1 and B (2.583 Å), and this is even more pronounced in *trans-E-***17TS** (C1−C8 = 2.644 Å; B−C1 = 2.169 Å). Singleton first identified this "boron" effect from MO calculations on the *inter*molecular DA reaction between butadiene and vinyl borane, calling it a [4 + 3] addition (vide infra), which underscores the proximity of the boron atom to C1 of the diene in these reactions.[2g] The magnitude of θ_{as} for both *cis-* and *trans*-TSs decreases along the series of 9-boranes *E-***17TS** > *E-***18TS** > *E-***19TS**, which reflects the decreasing electrophilicity of the boron along this series.

The magnitude of the dihedral angle θ_1, between the tether carbonyl group and the dienophile double bond is largely insensitive to the type of 9-*E*-substituent, generally lying within 5° of the value of 31° found in both *cis-* and *trans*-TSs of unsubstituted **1**. The TSs that exhibit anomalously high θ_{as} values also generally give high numerical values for θ_1, however, as evidenced by *trans-E-***17TS** ($\theta_1 = 44°$). The qualitative relationship that is often found to exist between θ_1 and θ_{as} has been discussed previously[1] and is summarized in Figure 3. Briefly, increasing θ_{as} in the *exo* direction in the *trans*-TS (arrow *a*) leads to a flattening of the developing five-membered ring (*b*) and, hence, to a concomitant increase in θ_1 (*c*). Similarly, increasing θ_{as} in the *endo* direction in the *cis*-TS leads to an increase in the magnitude of θ_1. Of course, any factor which causes θ_1 to change will induce a corresponding change in θ_{as}, in the manner described above. This is relevant to the discussion of selectivities in the IMDA reactions of 9-*Z*-substituted systems (vide infra).

9-*Z* substitution has a much stronger influence upon the magnitudes of both θ_{as} and θ_1, the numerical value of θ_{as} often exceeding 20° (see Table S2, Supporting Information). The origin of the enhanced magnitudes of θ_{as} lies in interactions between the 9-*Z* substituent and the tether carbonyl group. For the majority of 9-*Z*-substituents, e.g., alkyl group, halogen, RC=O, CO_2R, this interaction is repulsive, which leads to an increase in the magnitude of the out-of-plane twisting angle θ_1 and, hence, to a concomitant increase in the magnitude of θ_{as}, in the *endo* direction—in the *cis*-TS—and in the *exo* direction—in the *trans*-TS. An extreme example of this behavior is provided by the negatively charged 9-*Z*-BH_3^- substituent, with strong *destabilizing* electrostatic interactions between this substituent and the tether carbonyl group leading to $\theta_1 = 45°$ and $\theta_{as} = 20°$ for *cis-Z-***16TS**, and $\theta_1 = 54°$ and $\theta_{as} = -35°$ for *trans-Z-***16TS**. Electrostatic *stabilizing* interactions between the tether carbonyl group and positively charged Z-NH_3^+ group in *cis-Z-***15TS** and *trans-Z-***15TS** lead to diminished values of θ_1 and θ_{as}; for *cis-Z-***15TS**, $\theta_1 = -26°$ and $\theta_{as} = 7°$ and for *trans-Z-***15TS**, $\theta_1 = 23°$ and $\theta_{as} = -8°$.
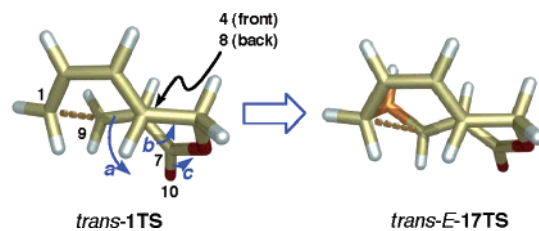
The *Z*-acetyl and *Z*-formyl substituents in their *s-cis* conformations have a greater effect on the magnitudes of θ_1 and θ_{as} than they do in their *s-trans* conformations, owing to the presence of increased repulsive interactions between the substituent's carbonyl group and the tether carbonyl group in the *s-cis* conformation. In contrast, both *s-cis* and *s-trans* conformations of the 9-*Z*-CO_2Me group have an equally strong effect on the magnitudes of θ_1 and θ_{as} because, in each conformation, there is a CO_2Me oxygen atom directed toward the tether carbonyl group (compare *Z-***29TS**s and unsubstituted **1TS**s in Figure 4). Likewise, the *s-cis-syn*, *s-cis-anti* and *s-trans-syn* conformations of the 9-Z-CO_2H groups have the same strong effect on the magnitude of θ_{as} (i.e. *Z-***29TS** − *Z-***31TS**). In marked contrast, the *s-trans-anti* conformation, *Z-***32TS**, has a negligible effect on the magnitudes of θ_1 and θ_{as}—note the close similarity between the *Z-***32TS**s and unsubstituted **1TS**s in Figure 4. This notable exception, which will be discussed in more detail later, is due to the presence of an intramolecular H-bond between the CO_2H *anti*-OH proton and the tether carbonyl oxygen atom.

The effect of 9-*Z*-BR_3 on TS geometries is discussed in the Supporting Information.
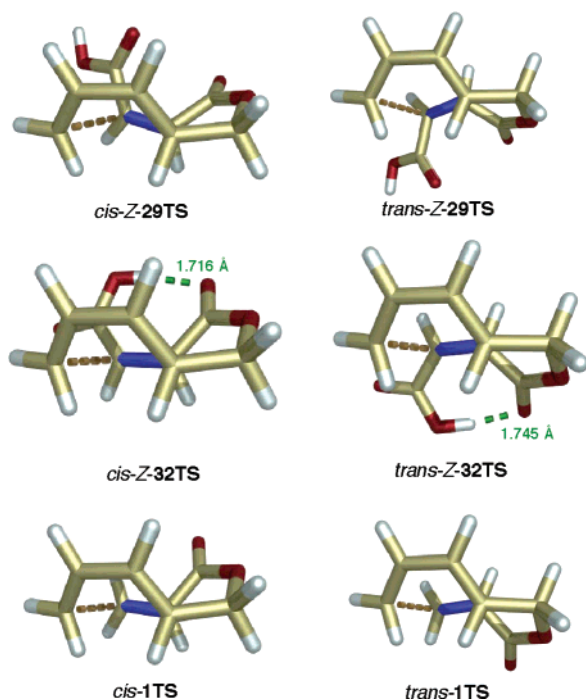
FIGURE 4. Views down forming internal (C4−C8) bond of optimized *cis-* and *trans-*TSs of **29** (no H-bond) and **32** (H-bond). TSs of **1** are provided for comparison. Dienophile bonds are highlighted in blue, and H-bonds are depicted with green dashed lines. The geometries of **29TS**s are representative of the 9-*Z*-CO₂R systems; **32TS**s are the exception. Note the pronounced dienophile twisting, butyrolactone flattening, and tether carbonyl twisting in **29TS**s, which is absent in **32TS**s.

FIGURE 5. Profiles of the least squares superposition of *cis-Z*-**23TS** and *trans-E*-**23TS**. Superfluous atoms have been hidden for clarity.

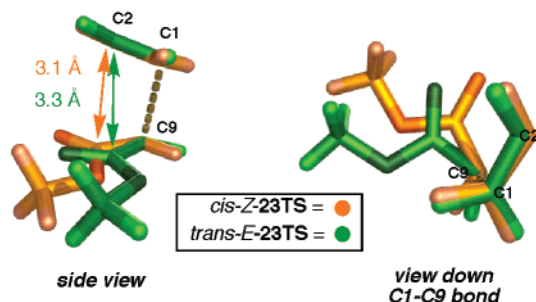In summary, the magnitude of θ_{as} is little affected by 9-*E* substituents but it is significantly affected by the presence of 9-*Z* substituents, the consequence of which is to drive the 9-*Z* substituent further under the diene face in the *cis*-TS and further from the diene face in the *trans*-TS. This is illustrated in Figure 5 for the case of the two 9-CO₂Me TSs, *cis-Z*-**23T**S and *trans-E*-**23TS**, in which the ester group is *endo* with respect to the diene face. As may be seen, the ester group in *cis-Z*-**23TS** penetrates more deeply into the *endo* region than in *trans-E*-**23TS**.

For comparison purposes, B3LYP/6-31+G(d) *endo* and *exo inter*molecular DA TSs between butadiene and monosubstituted alkene dienophiles were calculated (Figure 1). The *exo/endo* selectivities are presented in Table 2 and

TS geometrical parameters are given in the Supporting Information (Table S3).

Stereochemistry of DA Reactions

Exo/Endo **Selectivity in Intermolecular DA Reactions.** Substituent effects on *exo/endo* selectivities in *inter*molecular DA reactions between 1,3-butadiene and monosubstituted ethene dienophiles are listed in Table 2. As may be seen from the data, *exo* selectivity is predicted for all group 1 and group 2 substituents, with the exception of **da14** and **da15** (vide infra), and the *exo* selectivity increases with increasing size of the substituent. Thus, compare **da3** vs **da2**, **da5** vs **da4**, and **da9** vs **da8**. The *exo* selectivities displayed by these substituents is a consequence of the absence of SOIs and of the presence of repulsive electrostatic and Pauli, four-electron overlap, repulsion[16] interactions between these substituents and the diene in the *endo* TS.

In contrast, both amino, **da14**, and ammonium ion, **da15**, substituents are predicted to be *endo* selective by 6.0 and 14 kJ/mol, respectively. The strong *endo* directing character of the ammonium ion is no doubt due to the presence of stabilizing NH₃⁺···π electrostatic interactions in the *endo*-TS.[17] The surprising, fairly strong, *endo* selectivity predicted for the amino substituent in **da14** is probably due to the presence of weak (N)H···π(diene) electrostatic interactions in the *endo*-TS (see the Supporting Information for further discussion). The group 3 boranes, **da17**−**da19**, are *endo* selective, as a result of Singleton [4 + 3] SOIs,[2g] with the selectivity decreasing along the series **da17** > **da18** > **da19**.

For the conjugating group 4 substituents, only the formyl and acetyl substituents display *endo* selectivity. That the ethynyl, cyano, carbomethoxy, and nitro groups display *exo* selectivity imply that SOIs are unimportant in the *endo* DA TSs of **da20**−**da23**.[18] For the *exo* directing groups, the degree of selectivity decreases along the series C≡CH > CH=CH₂ > C≡N > NO₂ > *s-cis*-CO₂Me ≈ *s-cis-syn*-CO₂H. The HOMO energies of the dienophiles also generally decreases along this series,[19] which suggests that the *exo* selectivity is mainly due to overlap repulsion between the substituent and the diene in the *endo*-TS.

IMDA *Cis/Trans* **Selectivities in 9-*E*-Substituted Systems.** In the case of 9-*E*-substitution, formation of the *cis* product arises from the substituent and the tether carbonyl group occupying, respectively, *exo* and *endo* dispositions with respect to the diene face. Thus, when comparing the *cis/trans* selectivities for the IMDA reactions of 9-*E* substituted systems with *exo/endo* selectivi-

(15) For IMDA reactions on trienes containing vinylborane dienophiles, see: (a) Singleton, D. A.; Lee, Y.-K. *Tetrahedron Lett.* **1995**, *36*, 3473−3476. (b) Batey, R. A.; Lin, D.; Wong, A.; Hayhoe, C. L. S. *Tetrahedron Lett.* **1997**, *38*, 3699−3702.

(16) Albright, T. A.; Burdett, J. K.; Whangbo, M.-H. *Orbital Interactions in Chemistry*; Wiley-Interscience: New York, 1985; Chapter 1.

(17) (a) Ma, J. C.; Dougherty, D. A. *Chem. Rev.* **1997**, *97*, 1303−1324. (b) Caldwell, J. W.; Kollman, P. A. *J. Am. Chem. Soc.* **1995**, *117*, 4177−4178.

(18) Calculations suggest that the observed *endo* selectivity for the DA reaction between dienes and acrylonitrile in solution is due to solvent effects: Karcher, T.; Sicking, W.; Sauer, J.; Sustmann, R. *Tetrahedron Lett.* **1992**, *33*, 8027−8030.

(19) The B3LYP/6-31G(d) HOMO/LUMO energies (eV) are: *s-trans*-butadiene (−6.24/−0.57); but-2-en-1-yne (−6.57/−0.675); acrylonitrile (−7.96/−1.39); nitroethene (−7.86/−2.42); methyl acrylate (−11.1.1/0.001); methyl vinyl ketone (−6.74/−1.64); acrolein (−7.01/−1.84).
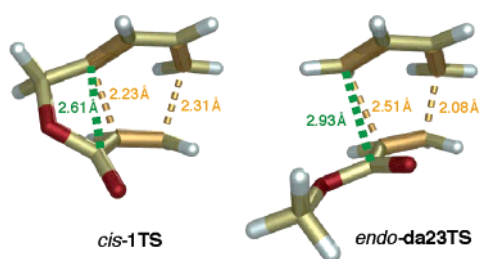
FIGURE 6. Tether carbonyl group prefers the *endo*-orientation in the *intra*molecular DA reaction of **1** (left-hand side), whereas the $-CO_2Me$ group of methyl acrylate prefers the *exo*-orientation in the *inter*molecular DA reaction (right-hand side).

ties of the corresponding *inter*molecular DA reactions, *cis* (*trans*) selectivity in the former reaction is synonymous with *exo* (*endo*) selectivity in the latter reaction.

Whereas the ester group is *exo* selective in *inter*molecular DA reactions involving methyl acrylate (**da23** and **da24**), it is *cis* directing in the IMDA reaction of the acrylate **1**, where it is part of the tether (Figure 6). The *cis* selectivity displayed by the ester group in the IMDA reaction may be due to the presence of stronger stabilizing electrostatic and SOIs in the *cis* IMDA TS than in the *endo* intermolecular DA TS because the distance between the ester carbonyl carbon atom and the nearer terminal carbon of the diene is 0.33 Å smaller in the IMDA TS, *cis*-**1TS**, than in the corresponding intermolecular DA TS *endo*-**DA23TS**.

Cis selectivity is predicted for all group 1 and group 2 substituents, with the exception of *E*-**15** (Table 1), which may be readily explained in terms of simple steric/electrostatic effects. The degree of *cis* selectivity is stronger in the IMDA reactions, than in the corresponding intermolecular DA reactions, because both 9-*E* substituent and tether carbonyl groups occupy their preferred positions in the *cis*-TSs, namely *exo* and *endo*, respectively.

As was found for the intermolecular DA reactions of the group 3 boranes, **da17**−**da19**, the corresponding 9-*E* boranes, *E*-**17**−*E*-**19**, are *trans* selective with the selectivity decreasing along the series *E*-**17** > *E*-**18** > *E*-**19**, in accordance with the diminishing electrophilicity of the boron along this series.

Turning to the group 4 conjugated substituents, there is a good qualitative correlation between IMDA *cis* selectivity and *inter*molecular DA *exo* selectivity, with the IMDA *cis* selectivity decreasing along the series: $C\equiv CH$ > $CH=CH_2$ > $C\equiv N$ > $CO_2Me \approx CO_2H$ > *s-cis*-$CH_3C=O$ > *s-cis*-$CH=O$ > NO_2 > *s-trans*-$CH_3C=O$ > *s-trans*-$CH=O$. The *exo* selectivity for the *inter*molecular DA reaction follows a similar sequence with the exception of the NO_2 group which now lies between the CN and CO_2Me substituents.

The crossover in selectivity, from *cis* to *trans*, in the IMDA reaction occurs with the *s-trans*-CO_2Me substituent, whereas it takes place further down the series, at *s-cis*-$CH=O$, in the *inter*molecular DA reactions. That the crossover does not occur at the same position in the series for both IMDA and *inter*molecular DA reactions is probably due to the perturbing influence of the tether carbonyl group on the electronic properties of the dienophile in the molecules undergoing the IMDA reaction. This possibility was explored by calculating *exo/endo*

TABLE 4. B3LYP/6-31+G(d)//B3LYP/6-31+G(d) Relative Energies of *Endo*- and *Exo*-TSs for Intermolecular Diels−Alder Reactions between Butadiene and 3-Substituted Methyl Acrylates[a,b]

		E_{rel} (kJ/mol)	
		exo−TS	endo−TS
E series (*Z* = H)			
E-**dda14**	NH_2	0	6.9
E-**dda20**	$C\equiv CH$	2.3	0
E-**dda21**	CN	0.32	0
E-**dda22**	NO_2	0	0.9
E-**dda27**	*s-cis*-CHO	0	1.0
E-**dda28**	*s-trans*-CHO	0	1.6
E-**dda29**	*s-cis-syn*-CO_2H	0	0.05
E-**dda33**	*s-trans*-$CH=CH_2$	0.45	0
Z series (*E* = H)			
Z-**dda20**	$C\equiv CH$	0	4.6
Z-**dda21**	CN	0	1.9
Z-**dda22**	NO_2	3.0	0
Z-**dda23**	*s-cis*-CO_2Me	1.0	0
Z-**dda28**	*s-trans*-CHO	1.1	0
Z-**dda29**	*s-cis-syn*-CO_2H	2.0	0
Z-**dda32**	*s-trans-anti*-CO_2H	2.7	0
Z-**dda33**	*s-trans*-$CH=CH_2$	0	2.7

[a] The stereochemical labels *exo* and *endo* refer to the position of the ester group of the acrylate with respect to the diene face. [b] Details of the geometries and energies of these TSs are given in the Supporting Information.

selectivities for selected intermolecular DA reactions between butadiene and 3-substituted methyl acrylate dienophiles (Table 4). The switchover, from *exo* selectivity to *endo* selectivity in this series, occurs at the same point as in the corresponding IMDA series; whereas the *E*-CN group is *exo* selective, the *E*-*s-cis-syn*-CO_2H group is mildly *endo* selective, as is found for the corresponding IMDA reaction of **29**.[20]

The selectivities displayed by the 3-*E*-substituted acrylates suggest that SOIs are more important in this series than in DA reactions involving monosubstituted dienophiles, being determined by competing strengths of SOIs associated with the ester and the 3-*E*-substituent. Why is this so and can we explain the *exo/endo* selectivities along the series of dienophiles listed in Table 4? Simple second-order perturbational molecular orbital (PMO) theory applied to frontier MOs offers answers to these questions.[21]

All Diels−Alder reactions treated herein involve dienes possessing normal electron demand which means that, within the context of PMO theory, the dominant stabilizing interaction in the DA TS is between the diene doubly

(20) In fact, the *cis-to-trans* crossover in the IMDA series occurs with the 9-*E*-CO_2Me substituent. The *exo/endo* preference of this substituent cannot be ascertained using the intermolecular DA strategy depicted in Table S3 (Supporting Information) because of the symmetry of the dimethyl fumarate dienophile. The case of the CO_2Me will be addressed later in this paper using perturbation theory.

(21) For a related treatment, applied to Lewis acid catalysis of Diels−Alder reactions, see: Houk, K. N.; Strozier, R. W. *J. Am. Chem. Soc.* **1973**, *95*, 4094−4096.
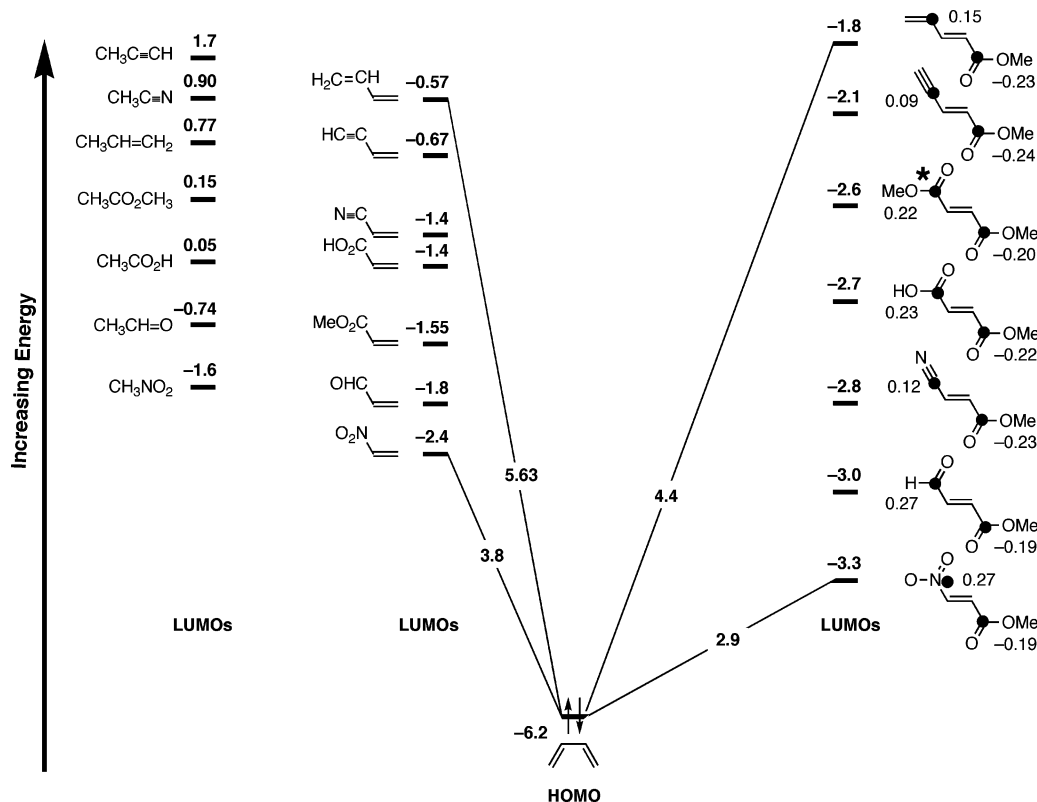
FIGURE 7. B3LYP/6-31G(d)//AM1 LUMO energies (eV) of various monosubstituted dienophiles and methyl derivatives (far left-hand side) and the HOMO energy of *s-cis*-butadiene. Also depicted are the inner-*p* orbital LUMO coefficients of the depicted atoms (bullets) of the substituted methyl acrylates (far right-hand side). For the dimethyl fumarate molecule, the ester group labeled by an asterisk is twisted 10° out-of-plane, and the other ester group is twisted 30° out-of-plane and is intended to serve as a model for the dienophile component in the IMDA TSs for **23** and **24**. Although orbital energies are ordered within each series of molecules, their spacings are NOT to scale for the purpose of visual clarity.

occupied HOMO and the dienophile LUMO.[22] The TS stabilization energy, ΔE^{SOI}, arising from SOIs is given, to second-order, by[23]

$$\Delta E^{SOI} \approx \frac{|H_{HL}|^2}{E_H - E_L} \quad (1)$$

where H_{HL} is the matrix element of the interaction between the diene HOMO (H) and the dienophile LUMO (L), the magnitude of which depends on the magnitudes of the atomic orbital coefficients of the HOMO and LUMO at the sites where the SOIs occur, and $(E_H - E_L)$ is the diene HOMO − dienophile LUMO energy gap. In applying this equation, we use the B3LYP/6-31G(d) MO energies[24] of various dienophiles and butadiene, displayed in Figure 7.

As may be seen from Figure 7, covalent attachment of an *E*-carbomethoxy group to a monosubstituted alkene dienophile, to give the *E*-3-substituted methyl acrylate, causes the dienophile's LUMO energy to drop by ~1 eV, thereby reducing the magnitude of the denominator of eq 1. Consequently, SOIs should be more important in the substituted acrylates than in the corresponding monosubstituted alkenes. Moreover, SOIs within the 3-*E*-

substituted acrylates should become stronger with decreasing dienophile LUMO energy, being strongest for the nitro acrylate and weakest for the vinyl and ethynyl acrylates.[25] Consequently, it is not unreasonable to expect that SOI effects might be evident in acrylate dienophiles bearing powerful electron-withdrawing groups, such as the nitro group.

Which group, the 3-*E*-substituent or the carbomethoxy group, prefers the *endo* position in *inter*molecular DA reactions of 3-*E*-substituted methyl acrylate? This question may be answered by considering the numerator in eq 1 and taking note of the following easily derived statement of PMO theory, namely that if two groups are attached to each other, either directly or indirectly via, say, a double bond, then the LUMO of the resulting "supermolecule" is polarized toward that group possessing the lower energy LUMO and that this polarization increases with increasing disparity in the LUMO energies of the two isolated groups. The LUMO energies of the various substituents are taken to be those of the methyl derivatives, and these are shown at the extreme left-hand side of Figure 7. Applying these data to the series of 3-*E*-substituted methyl acrylates, we predict LUMO polarization *away* from the 3-*E*-substituent, toward the carbomethoxy group, to *increase* along the series: CH=CH$_2$

(22) Fleming, I. *Frontier Orbitals and Organic Chemical Reactions*; Wiley-Interscience: New York, 1976; Chapter 4.

(23) Dewar, M. J. S.; Dougherty, R. C. *The PMO Theory of Organic Chemistry*; Plenum Press: New York, 1975.

(24) Strictly speaking, the orbitals are Kohn–Sham orbitals.
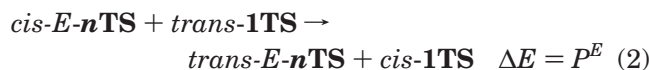
(25) Using a stronger electron withdrawing substituent will also polarize the dienophile LUMO towards the substituent, thereby increasing the magnitude of the numerator of eq 1 and further strengthening the SOI term.

< CN < C≡CH. Conversely, LUMO polarization *toward* the 3-*E*-substituent, away from the carbomethoxy group, is predicted to *increase* along the series CO_2H < CH=O < NO_2. Calculations confirm this prediction. We focus attention on the LUMO coefficients on those atoms which are largely responsible for SOIs and these are labeled by bullets on the extreme right-hand side of Figure 7.[26] As may be seen, the magnitude and direction of the LUMO polarization follow the same trends as predicted above.

Thus, the *endo* preference of the ester group wins against the substituents CH=CH$_2$ < CN < C≡CH, the *endo* preference *increasing* along this series, i.e., **dda33** < **dda21** < **dda20**. In contrast, the bullet-marked LUMO coefficients of the 3-CO_2H, 3-CH=O, and the 3-NO_2 acrylates lead to the prediction that these substituents have stronger *endo* selectivities than the CO_2Me group and that this *endo* preference should be strong and of comparable magnitude for CH=O and NO_2, but only marginal for CO_2H. The calculated *exo/endo* selectivities given in Table 4 generally confirm these predictions.

These PMO-based insights, gained from investigating *exo/endo* selectivities in intermolecular DA reactions, explain the *cis/trans* selectivities of the IMDA reactions of 9-*E*-substituted acrylates. The finding that the 9-*E*-CO_2Me substituent in **23** and **24** is mildly *trans* directing, preferring the *endo* position over the tether carbonyl group, might be due to the fact that, in the IMDA TS, the tether carbonyl group is twisted about 30° out of the dienophile double bond plane, whereas the 9-*E*-CO_2Me carbonyl group is twisted by only about 10°−15°. This difference in the out-of-plane twisting angles of the two ester groups is sufficient to cause a slight polarization of the LUMO toward the 9-*E*-CO_2Me group, leading to stronger SOIs at this site. This LUMO polarization is evident in the dimethyl fumarate system displayed in Figure 7 (right-hand side), in which the upper left ester substituent (labeled with an asterisk)—which models the 9-*E*-CO_2Me substituent in **23** and **24**—is twisted 10° out-of-plane, and the other ester group—modeling the tether carbonyl group—is twisted 30° out-of-plane. The increased canting of the tether carbonyl π orbital, away from the diene, compared to that of 9-*E*-CO_2Me is also expected to attenuate SOIs involving the former group.

The positional preference of a 9-*E*-substituent for either the *exo* or *endo* position with respect to the diene face is given by the energy P^E associated with eq 2

$$cis\text{-}E\text{-}n\textbf{TS} + trans\text{-}\textbf{1TS} \rightarrow$$
$$trans\text{-}E\text{-}n\textbf{TS} + cis\text{-}\textbf{1TS} \quad \Delta E = P^E \quad (2)$$

where **n** refers to the identity of the *E*-substituent. A positive (negative) value for P^E means that the *E*-substituent **X** prefers the *exo* (*endo*) disposition with respect to the diene, in which case the tether carbonyl group occupies the *endo* (*exo*) position and the favored TS has overall *cis* (*trans*) stereochemistry. Values for P^E are given in Table S4 (Supporting Information). Of the group 4 conjugating substituents, only the *E*-ethynyl group *E*-**20** prefers the *exo* position, the others preferring

the *endo* position, the strongest being displayed by the formyl and acetyl groups. The *E*-vinyl substituent, *E*-**33**, appears to have no positional preference.

IMDA *Cis/Trans* Selectivities in 9-*Z*-Substituted Systems. In the 9-*Z*-substituted IMDA TSs, the *cis* (*trans*) TS has both substituent and tether carbonyl groups occupying the *endo* (*exo*) position with respect to the diene. Adding the positional preference P^E of the 9-substituent, obtained from the 9-*E* series (Table S4, Supporting Information), to the value of −1.88 kJ/mol for the *endo* preference of the tether carbonyl group, gives the idealized *cis/trans* preference, P^Z, for the 9-*Z* series of TSs, in the absence of specific interactions between the tether carbonyl group and the *Z* substituent (Table S4, Supporting Information). A positive value for P^Z means that the *trans*-TS is predicted to be energetically favored over the *cis*-TS.

Considering the systems **1**−**28** and **33**, it is seen from the E_{rel}^{TS} *Z* values of Tables 1 and S4 (Supporting Information) that, with three exceptions (*Z*-**4TS**, *Z*-**15TS**, and *Z*-**17TS**), the *trans* IMDA TS is preferred over the *cis*-TS and that this *trans* preference generally exceeds the corresponding P^Z value, often by more than 10 kJ/mol. For example, the 9-*Z*-CCl_3 and 9-*Z*-CBr_3 substituents are almost exclusively *trans* selective although their P^Z value are close to zero. The 9-*Z* borane substituents have a markedly diminished *endo* preference, compared to the corresponding 9-*E* stereoisomers (**17TS** − **19TS**), implying that Singleton-type SOIs are of lesser importance in the *cis* TSs. The 9-*Z*-NH_3^+ substituent still produces a *cis* preferred IMDA TS, however, with the substituent and the tether carbonyl group both occupying *endo* positions.

The strong *trans* selectivity shown by the 9-*Z*-conjugated substituents, NO_2, CO_2Me, CH=O and CH_3C=O, **22**−**28**, is very surprising because the P^Z values for these *Z*-substituents predict fairly strong *cis* selectivity. In contrast, results for intermolecular DA reactions between butadiene and 3-*Z*-substituted methyl acrylates (Table 4) do, indeed, show that the NO_2, CO_2Me, CH=O, and CO_2H *Z*-substituents are *endo* selective. The *Z*-cyano system, *Z*-**dda21**, is *exo* directing, by about 1.9 kJ/mol, but even this selectivity is significantly smaller than the 8.1 kJ/mol *trans* selectivity for the IMDA reaction of *Z*-**21**. A similar situation holds for the *Z*-ethynyl and *Z*-vinyl substituents, the *exo* preferences for the DA reactions of *Z*-**dda20** and *Z*-**dda33** being significantly weaker − by about 6.5 kJ/mol—than those for *Z*-**20** and *Z*-**33**.

Drawing inspiration from, and building upon, Houk's pioneering insights into the role of twist-mode asynchronicity in influencing the stereoselectivity of IMDA reactions of decatrienes and nonatrienes,[4,14] we postulate that the origin of this "anomalous *Z*-effect", in which the 9-*Z* substituent in the IMDA reaction is *trans* directing *to an enhanced extent*, is a consequence of geometrical changes in the *Z*-TS brought about by *direct* interactions between the 9-*Z*-substituent and the tether carbonyl group.

Our reasoning is as follows. First, the majority of the 9-*Z* substituents studied herein interact in a repulsive manner with the tether carbonyl group (vide supra). This leads to an increased out-of-plane twisting angle θ_1 of the carbonyl group which causes a reduction in the strength of Singleton-type SOIs between the tether

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(26) Consideration of the LUMO coefficients of other atoms which might give rise to SOIs, such as the carbonyl oxygen atom of the ester and formyl groups, leads to the same conclusions that are derived from considering only the bullet-labeled atoms.

carbonyl group and the diene in the *cis Z*-TS.[1] Second, increasing the magnitude of θ_1 in the *endo-Z*-TS causes θ_{as} to increase which pushes the 9-*Z*-substituent further in the *endo* direction, the consequences of which, we postulate, are weakened stabilizing Singleton-type SOIs between C1 and increased electrostatic repulsive interactions between the 9-*Z*-substituent and the diene π electrons. The aforementioned 9-*Z*-substituent-induced geometric changes also take place in the *exo* TS but, in this case, SOIs are always unimportant and an increase in θ_{as} drives the 9-*Z*-substituent in the *exo* direction, further away from the diene, thereby reducing further any existing substituent-diene repulsive interactions.

The superpositions of *cis-Z*-**23TS** and *trans-E*-**23TS**, shown in Figure 5, illustrate these ideas. As may be seen, the CO$_2$Me group in *cis-Z*-**23TS** is both closer to, and better oriented with respect to the diene π-face to suffer electrostatic destabilizing interactions than in *trans-E*-**23TS**. The finding that the 9-*Z*-NH$_3^+$ substituent favors the *cis*-TS is consistent with our postulates because of the presence of strong stabilizing electrostatic interactions between the positively charged NH$_3^+$ group and the diene in *cis-Z*-**15TS**. In the case of 9-*Z*-BH$_3^−$, the interactions are now destabilizing, and consequently, *trans-Z*-**16TS** is strongly favored over the *cis*-TS.

A more convincing verification of our explanation of the anomalous *Z*-effect is provided by the IMDA TSs associated with the 9-CO$_2$H substituent, **29**−**32** (Tables 1 and S1, S2, Supporting Information). The IMDA reactions of the 9-*E*-CO$_2$H series, *E*-**29**−*E*-**32**, mainly display *trans* selectivity,[27] with the CO$_2$H group preferring the *endo* position. Likewise, the 9-*Z*-CO$_2$H series, *Z*-**29**−*Z*-**32**, display the anomalous *Z*-effect *with one notable exception*, namely the 9-*s-trans-anti-Z*-CO$_2$H stereoisomer **Z-32**, which is calculated to be predominantly *cis* selective. The geometries of *Z*-**29TS**−*Z*-**32TS** are revealing (Figure 4; Table S2, Supporting Information). For *Z*-**29TS**−*Z*-**31TS**, both θ_1 and θ_{as} display the characteristically dilated numerical values that are associated with *trans* selectivity: $43−46°$ and $11−23°$, respectively. In contrast, both *cis-Z*-**32TS** and *trans-Z*-**32TS** display "normal" values of 27° and 28° for θ_1 and 0.4° and 6° for θ_{as} (Table S2, Supporting Information), thereby restoring stabilizing SOIs between the diene and both CO$_2$H and tether carbonyl groups. The reason for the normal values of θ_1 and θ_{as} in *cis-Z*-**32TS** and *trans-Z*-**32TS** is the presence of an intramolecular hydrogen-bond between the *anti* hydroxy proton of the CO$_2$H group and the tether carbonyl group (Figure 4), in which the distance between the CO$_2$H hydrogen and the carbonyl oxygen is about 1.7 Å. This favorable distance is achieved by reducing the torsional angle θ_1 which leads to a decreased value of θ_{as} (vide supra). Interestingly, the observed *cis* IMDA stereoselectivity of pentadienyl citraconates was explained on the basis of such an *intra*molecular hydrogen bond in White's investigations into *intra*molecular cycloaddition reactions.[28] Although our studies appear to validate this work, we point out that *trans-Z*-**32TS** is 7−21 kJ/mol *less* stable than any of the corresponding *syn* TSs, *Z*-**29TS**

(27) The IMDA reaction of 9-*s-cis-anti-E*-CO$_2$H, **30**, constitutes an exception, being *cis*, rather that *trans*, selective. However the degree of selectivity for this molecule is insignificant.

(28) White, J. D.; Sheldon, B. G.; Solheim, B. A.; Clardy, J. *Tetrahedron Lett*. **1978**, *19*, 5189−5192.
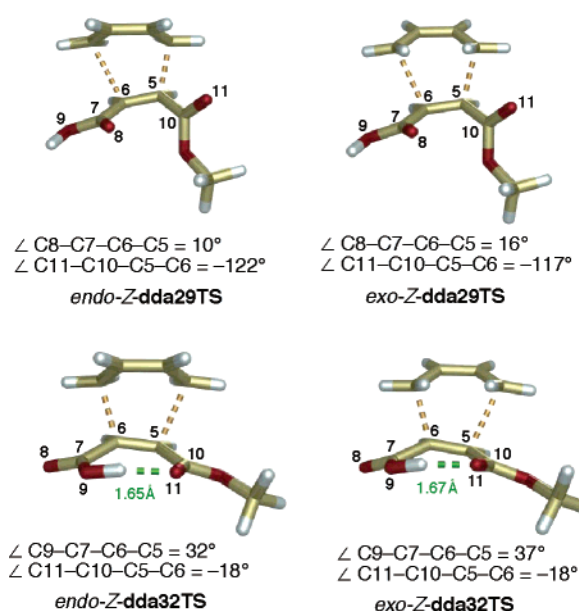

FIGURE 8. Transition structures for the *inter*molecular Diels−Alder reaction between butadiene and the half methyl ester of maleic acid. Top: *endo*-**29TS** and *exo*-**29TS** with the *s-cis-syn* conformation of the CO$_2$H group. Bottom: *endo*-**32TS** and *exo*-**32TS** with the *s-trans-anti* conformation of the CO$_2$H group. The internal H-bond in the latter two TSs is shown in green.

and *Z*-**31TS**, and, therefore, plays no noticeable role in the actual IMDA reaction of the 9-*Z*-carboxylic acid system.[29]

That the presence of an intramolecular H-bond in *Z*-**32TS** is not, in itself, responsible for the stabilization of *cis-Z*-**32TS**, relative to *trans-Z*-**32TS**, was confirmed by the finding that, for the corresponding *inter*molecular DA reactions between butadiene and the half-ester of maleic acid, both *Z*-**dda29** and *Z*-**dda32** display comparable *endo* selectivities (Table 4), even though only the latter isomer hosts an intramolecular H-bond (Figure 8).[30] Parenthetically, none of the *endo* selective 3-*Z*-substituted acrylates of Table 4 revealed any significant twist mode asynchronicity in their *endo* TSs ($\theta_{as} < 5°$).

Applications to Other Systems. (a) IMDA *Cis/Trans* Selectivity in the 9-CO$_2$Me-1,3,8-Nonatriene System. Experimentally, it is found that the IMDA reactions of the 9-*Z*-CO$_2$Me derivative of 1,3,8-nonatriene **34** (Scheme 2) give predominantly the *trans* fused product, whereas the parent 1,3,8-nonatriene **33** is *cis*-selective.[4] The *Z*-**34** system thus exhibits the anomalous *Z*-effect because both the trimethylene tether and the ester substituent separately prefer the *endo* position in the IMDA TS. We posit the same explanation that was
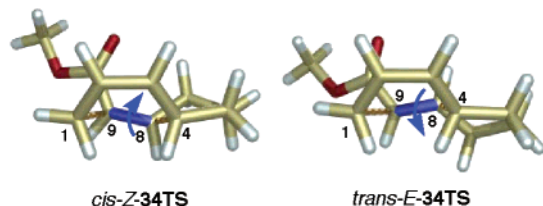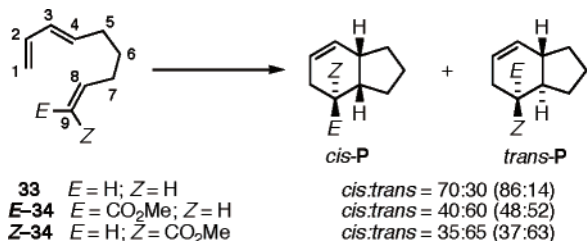
(29) Cayzer, T. N.; Lilly, M. J.; Williamson, R. M.; Paddon-Row, M. N.; Sherburn, M. S. *Org. Biomol. Chem.* **2005**, *3*, 1302−1307.

(30) The predicted *endo* selectivity for the reaction between *s-trans-anti*-acrylic acid and butadiene, **da32** (Table 2), in contrast to the *exo* selectivity predicted for the remaining conformations of acrylic acid, **da29**−**da31**, arises from stabilizing OH···diene−π electrostatic interactions in *endo*-**da32TS**; in this TS, the carboxyl group is significantly twisted, by 28°, out of the plane of the dienophile double bond, in the direction of the diene, bringing the OH hydrogen atom fairly close to both C2 and C3 atoms of the diene (ca. 2.7 Å). This effect is absent in *cis-Z*-**32TS**; in this TS, the OH forms a hydrogen bond with the tether carbonyl group, with the result that the OH bond is twisted 12° *below* the plane of the dienophile double bond, *away* from the diene.

SCHEME 2. *Cis/Trans* Product Ratios from IMDA Reactions of Trimethylene-Tethered 1,3,8-Nonatrienes at 423 K[4] [a]

33　$E = H$; $Z = H$
E–34　$E = CO_2Me$; $Z = H$
Z–34　$E = H$; $Z = CO_2Me$

cis:trans = 70:30 (86:14)
cis:trans = 40:60 (48:52)
cis:trans = 35:65 (37:63)

*cis-Z-**34TS***　　*trans-E-**34TS***

[a] The B3LYP/6-31+G(d) computed ratios are given in parentheses. The direction of dienophile twisting is represented with blue arrows in B3LYP/6-31+G(d)-optimized IMDA TSs.

advanced above to explain the anomalous *Z*-effect in the IMDA reaction of *Z*-**34**. As may be seen from the TSs for *cis-Z-**34TS*** and *trans-E-**34TS*** depicted in Scheme 2, both TSs display pronounced twist-mode asynchronicity, with $\theta_{as} = 14°$ and 10°, respectively. In *cis-Z-**34TS***, the ester group lies much deeper in the *endo* region than it does in *trans-E-**34TS*** and, consequently, stabilizing Singleton-type SOIs are weakened in the former TS, whereas electrostatic repulsive interactions are stronger.

(b) IMDA *Cis/Trans* Selectivity in Ester-Tethered 1,3,9-Decatrienes. Although the IMDA reactions of the hexadienyl acrylates will be discussed in detail in a forthcoming publication,[31] that for the 10-*Z*-CO_2Me system, **Z-35**, (Scheme 3) will be briefly mentioned because it is *cis* selective.[32] DFT predicts a *cis/trans* ratio of 62:38 whereas the experimental result is *exclusive* formation of the *cis* product. The absence of the anomalous *Z*-effect for this system is readily explained in terms of our proposals. DFT calculations show that in the IMDA TSs for hexadienyl acrylates, it is the peripheral (C1−C10) forming bond which is more highly developed and not the internal (C4−C9) forming bond, as is the case for the IMDA TSs for the pentadienyl acrylates. Not only is twist-mode asynchronicity modest in *cis-Z-**35TS***, amounting to 8° (Scheme 3), but it now takes place about the shorter C1−C10 forming bond[14] and in the *exo direction, away from the diene*. Thus, the 10-*Z*-CO_2Me group in *cis-Z-**35TS*** does not experience the energetically costly displacement in the *endo* direction, as suffered by the 9-*Z*-substituted pentadienyl acrylates. The reason for this is that, unlike the *cis-Z* TSs for the pentadienyl acrylates, in which the 9-*Z*-substituent induces a large out-of-plane

(31) Pearson, E. L.; Turner, C. I.; Kwan, L. C. H.; Jones, G. A.; Willis, A. C.; Paddon-Row, M. N.; Sherburn, M. S. Manuscript in preparation.

(32) Important experimental observations and detailed analyses of transition states of closely related decatrienone systems have reported by Roush and co-workers: (a) Coe, J. W.; Roush, W. R. *J. Org. Chem.* **1989**, *54*, 915−930. (b) Roush, W. R. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Paquette, L. A., Eds,; Pergamon: Oxford, 1991; Vol. 5, pp 513−550. (c) Dineen, T. A.; Roush, W. R. *Org. Lett.* **2005**, 7, 1355−1358. For an analysis of hexadienyl acrylate IMDA TSs, see ref 11c.

SCHEME 3. *Cis/Trans* Product Ratio from the IMDA Reaction of *Z*-35 at 383 K[31] (B3LYP/6-31+G(d) Value in Parentheses) and the B3LYP/6-31+G(d)-Optimized *Cis* TS[a]

*cis-**35P***　　*trans-**35P***
100:0 (62:38)

*cis-Z-**35TS***
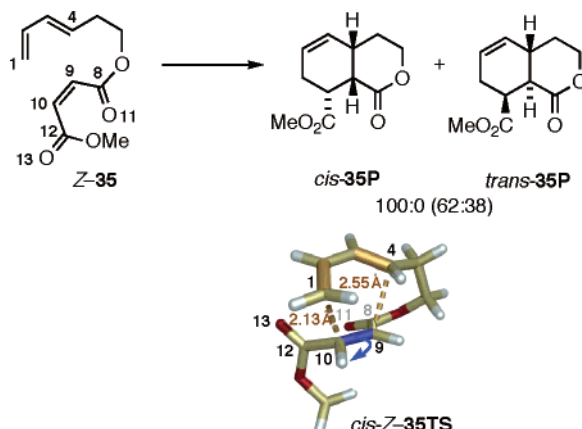
[a] The direction of dienophile (blue bond) twisting about the shorter C1−C10 peripheral bond axis is represented with the blue arrow. Note the essentially coplanar O11−C8−C9−C10 arrangement and the severely twisted C9−C10−C12−O13 group.

twisting of the tether carbonyl group, such an occurrence is not evident in *cis-Z-**35TS*** (θ_1 is only 12°). Instead, it is the 10-*Z*-CO_2Me substituent which suffers a large (75°) out-of-plane rotation (Scheme 3). As expected, this twisting mode has little influence on the magnitude of twist-mode asynchronicity.[33]

Concluding Remarks

We find that, for the gas-phase addition of monosubstituted ethene dienophiles to butadiene, *exo* (anti-Alder) selectivity is predicted for all but the last two of the following unsaturated substituents: *s-trans*-$CH=CH_2$, $C≡CH$, CN, NO_2, CO_2H, CO_2Me, $CH_3C=O$, and $CH=O$. In contrast, Alder *endo* selectivity is more widely predicted for 3-substituted methyl acrylate dienophiles. PMO-based arguments were used to explain these findings which led to the proposal that SOI effects—hence, *endo* selectivity—increase with diminishing magnitude of the diene HOMO − dienophile LUMO energy gap.

Whereas *cis/trans* selectivity for *intra*molecular DA reactions involving 9-*E*-substituted pentadienyl acrylates generally follows the normal pattern found for the corresponding *inter*molecular DA reactions, the 9-*Z*-substituted stereoisomers generally displayed *trans* selectivity that was much stronger than can be attributed to effects of the isolated substituent. This is strikingly so with unsaturated electron withdrawing substituents (e.g., CO_2Me) whose *endo* selectivities, displayed in *inter*molecular DA reactions, are reversed in the *intra*molecular DA reactions of pentadienyl acrylates. The origin of this so-called anomalous *Z*-effect is believed to be the consequence of destabilizing structural changes in the *cis*-TS—namely amplification of the twist-mode asynchronicity angle, θ_{as}, and the out-of-plane twisting

(33) The favored conformation of the forming six membered lactone ring in *cis-Z-**35TS*** has the tether carbonyl group nearly coplanar with the dienophile double bond. Coplanarity between tether carbonyl and dienophile cannot take place in the pentadienyl acrylate TSs, even in the absence of a 9-*Z*-substituent.

angle, θ_1, of the tether carbonyl group—caused by repulsive interactions between the 9-*Z*-substituent and the tether carbonyl group, which lead to diminished SOIs involving the tether carbonyl and to the 9-*Z* substituent being driven further into the *endo* region of the diene where electrostatic repulsion prevail over SOIs.

Our study has clarified the role and scope played by twist-mode asynchronicity[14] in influencing *trans/cis* selectivity in IMDA reactions. Significantly, we find that the Houk−Brown postulate, namely that "the outside (i.e., *exo*) movement of the C9 terminus is easier than the inside (i.e., *endo*) movement"[14] may not be applicable to 9-*E*-substituents. Thus, 9-*E*-substitution has negligible effect on the magnitude of θ_{as}, being nearly the same as that found for the IMDA TSs of the unsubstituted system **1** (Table S1, Supporting Information). Stereoselectivities for the 9-*E*-substituted systems are explicable in terms electrostatic, steric and secondary orbital interactions. The Houk−Brown postulate certainly plays a decisive role in the IMDA reactions of 9-*Z*-substituted pentadienyl acrylates; the magnitude of θ_{as} is markedly amplified by *Z*-substituents, often by more than 10°, compared to that found for the unsubstituted system, **1**.

Supporting Information Available: Cartesian coordinates and energies of B3LYP/6-31+G(d)-optimized TS geometries, geometrical parameters for intramolecular and intermolecular DA reactions, further computational details, and extended discussions of geometries and stereoselectivities of IMDA and DA reactions. This material is available free of charge via the Internet at http://pubs.acs.org.

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