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# Stereoelectronic Control in Diels−Alder Reaction of Dissymmetric 1,3-Dienes

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**ABSTRACT**

The Diels−Alder reaction is a widely employed protocol in which four stereogenic centers are generated in a predictable manner with olefin geometry, adjoining chiral center, and transition-state topology serving as the main controlling elements. However, when the Diels−Alder partners are in a dissymmetric environment, $\pi$-face selection is determined through the interplay of steric, orbital, and electrostatic factors whose relative importance is a subject of intense debate. Several new systems have been crafted to probe the mechanistic nuances of the $\pi$-face selection. The available data have enabled us to qualitatively define a hierarchy of various stereoelectronic effects that would aid predictability of the stereochemical outcome.

## Introduction

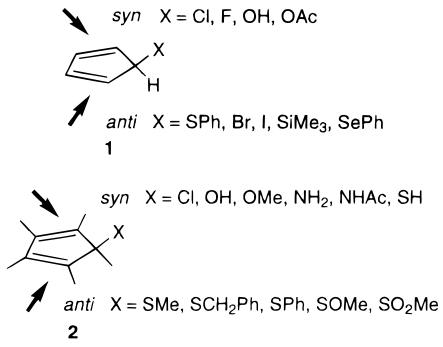
Stereogenic centers in organic synthesis are generated by the conversion of $sp^2$ centers into tetrahedral carbon(s). Nucleophilic additions to carbonyl groups and electrophilic additions to olefins constitute familiar examples, and the stereoelectronic factors that control facial selectivity in these additions have been subjected to incisive scrutiny.[1] Pericyclic reactions, under orbital symmetry control,[2] represent another commonly employed protocol for the installation of stereogenic centers. Among them, [$4\pi + 2\pi$] cycloadditions (Diels−Alder reaction) are the most versatile and synthetically[3] useful reactions in which four new contiguous stereogenic centers can be generated in a single laboratory operation. The advent of asymmetric and intramolecular variants of this reaction have added to its vast synthetic potential.[4]

The stereoselectivity, regioselectivity, and topographical (*endo* vs *exo)* selectivity in Diels−Alder reactions is largely predictable. However, the stereochemical outcome during the $\pi$-facial diastereoselection,[5] which arises when the two faces of the reacting partners, viz., the diene or the dienophile, are nonequivalent (dissymmetric), is still not fully understood. Both steric and electronic factors contribute significantly toward $\pi$-face selection in Diels−Alder reactions of dissymmetric 1,3-dienes.

Studies with acyclic 1,3-dienes such as substituted butadienes have revealed that the diastereoselectivities are more often controlled by dominant steric and conformational effects and therefore provide little insight into the contribution of electronic factors. However, cycloaddition studies with simple cyclic dienes, with minimal conformational effects, have revealed the importance of steric effects,[6] ground-state geometric distortions,[7] product stabilities,[8] torsional effects,[9] orbital mixing/tilting,[10,11] secondary orbital interactions,[12] hyperconjugative effects,[13] and electrostatic interactions[14] as additional factors in determining face selectivity. For a critical assessment of the relative importance of these effects in cycloadditions, substrates having a 1,3-diene moiety embedded in constrained, rigid polycyclic frames constitute useful probe systems. Such systems are free from conformational uncertainties, and facial discrimination can be fine-tuned through modulation of distal functionalities. In this Account, we consider various stereoelectronic factors that contribute toward $\pi$-face diastereoselection during Diels−Alder reactions and evaluate their relative importance. Our deductions are based on the results obtained with a range of facially perturbed mono- as well as polycyclic 1,3-dienes, with particular focus on our investigation of the hexacyclo[7.5.1.0.$^{1,6}$0.$^{6,13}$0.$^{8,12}$0$^{10,14}$]pentadeca-2,4-diene-7,15-dione system.

## Cycloadditions to 5-Substituted 1,3-Cyclopentadienes

Extensive studies with facially discriminated 1,3-cyclopentadienes have been very useful in eliciting various stereoelectronic responses. In the mid-1950s, Winstein and Woodward[15a] observed that the reaction of 5-acetoxycyclopentadiene with ethylene proceeded in a contrasteric manner, with the dienophile approaching exclusively from the face *syn* to the heteroatom substituent. Subsequent studies on several C-5-substituted cyclopentadienes **1** have highlighted the intriguing *syn* or *anti* directing role of the substituent. For example, while oxygen,[15] fluorine,[16] and chlorine[17] substituents are *syn* directing, heteroatoms such as bromine,[17] iodine,[17] silicon,[18] sulfur,[19] and selenium[19] are overwhelmingly *anti* directing.

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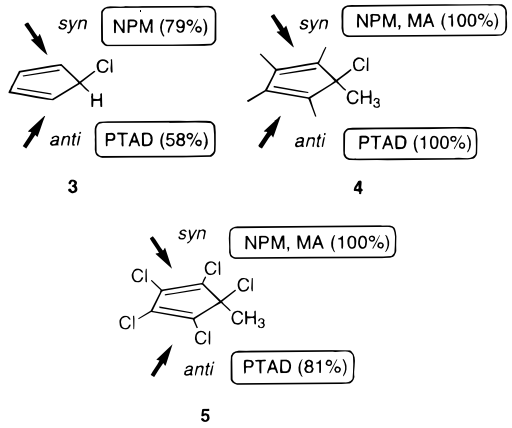
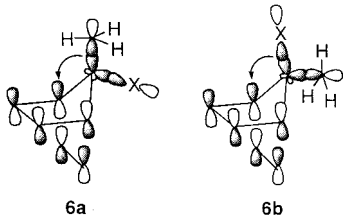
Macaulay and Fallis[20] systematically studied the cycloaddition between C-5-substituted permethylated cyclopentadienes **2** and maleic anhydride (MA) and/or *N*-phenylmaleimide (NPM). While chlorine, oxygen, and nitrogen substituents showed an overwhelming *syn* preference, substituents such as thiol exhibited only a modest *syn* selectivity. Expectedly, sterically demanding substituents bearing sulfoxide, phenylthio, and sulfone functionalities predominantly furnished *anti* addition products. Recently, Burnell et al.[17] have shown that diastereoselectivities in cycloadditions to C-5-substituted cyclopentadienes **3**–**5** also exhibit marked dependence on the nature of the dienophile. Thus, *N*-phenyl-1,2,4-triazolinedione (PTAD) adds to **4** and **5** overwhelmingly from the *anti* face (cf. *syn* face addition of MA). This reversal has been attributed to filled-orbital repulsion between the dienophile lone pair and the halogen substituent.

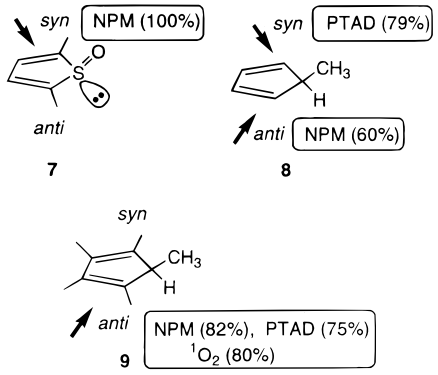



Several proposals have been advanced to explain the face selectivities observed in 5-substituted cyclopentadienes. Anh[21] invoked a favorable nonbonded interaction between the heteroatom (lone pair) and the dienophile (LUMO) to stabilize the *syn* transition state. On the other hand, Fukui et al.[10] explained the origin of the *syn* selectivity in the case of oxygen, fluorine, and chlorine substituents on the basis of the orbital mixing rule. Kahn and Hehre[14] proposed that electrostatic interactions could play an important role, with the more nucleophilic face of the facially perturbed diene being more reactive toward an electrophilic dienophile. Poirier and Burnell[22a] have evaluated the stereoselectivies in 5-substituted 1,3-cyclopentadiene cycloadditions computationally at the ab initio level and found the steric hindrance between the substituent and the incoming dienophile to be a dominant factor. The facial preference was attributed to the differences in energy required to deform the addends, especially the diene, into the *syn* and *anti* transition-state geometries, and this was manifest mainly in differences in the angles about C-5.

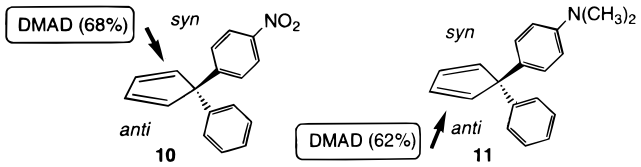
Macaulay and Fallis have rationalized their studies[20] on permethylated cyclopentadienes in terms of the Cieplak model,[13a] which proposes stabilization of the transition state by hyperconjugative participation[13] of the *anti* periplanar $\sigma$ bonds into the $\sigma^*$-orbitals of the newly forming bonds. Consequently, the Cieplak model predicts preferential addition *anti* to the best $\sigma$ donor (C–C bond), and therefore addition *syn* to C–O is expected as in **6a** (X = O), which parallels the experimental findings.[20]



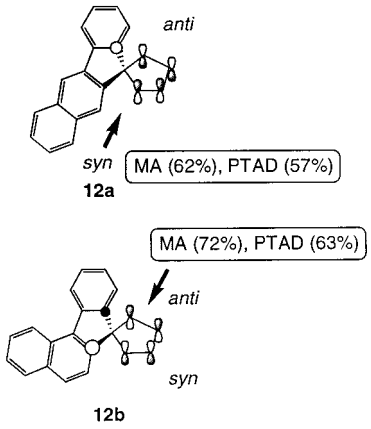

Likewise, when C–C and C–S bonds were positioned on either face of **2**, cycloaddition *anti* to the C–S bond in **6b** (X = S) was observed, as predicted by the Cieplak model. Further support for this model came from the contrasteric addition to the thiophene oxide **7**, from the face *anti* to the lone pair.[23] On the other hand, Burnell et al.[22b] have observed that, while a sterically less demanding dienophile such as PTAD was captured by 5-methylcyclopentadiene (**8**) predominantly from the *syn* face in accordance with the Cieplak model, sterically biased dienophiles such as NPM reacted predominantly from the more open *anti* face. It was further shown that, in the case of **9**, steric factors overwhelmed hyperconjugative effects, and addition of a variety of dienophiles was from the *anti* face.[6b,22b]




Halterman et al.[24] investigated the selectivities in 5,5-diarylcyclopentadienes, an isosteric probe, wherein one of the aryl groups is electronically fine-tuned by remote functionalization at the *para* position. The preferential approach from the face opposite to the better electron donor in **10** and **11** was in accordance with the Cieplak model.



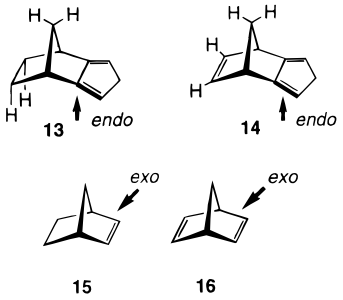

Ohwada et al.[25] have studied the selectivities in spiroconjugated, benzo-annulated fluorene-based dienes **12a,b**. While **12a** favored *syn* addition with respect to the naphthalene ring, **12b** exhibited a reversed selectivity.




Nonequivalent orbital interactions of the $\pi$ reaction center with the aromatic $\pi$-orbitals at the *ipso* position were considered to be crucial for facial preferences in these systems.

## Cycloadditions to Isodicyclopentadiene and Related Systems

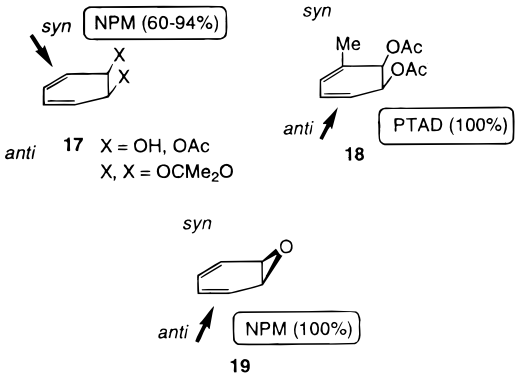
Gleiter and Paquette[11] have studied the cycloaddition in norbornyl-fused cyclopentadienes such as isodicyclopentadiene **13** and isodicyclopentatriene **14.** These dienes underwent cycloadditions preferentially from the *endo* face, i.e., *syn* to the ethano/etheno bridge with common dienophiles. These results were rather intriguing, as



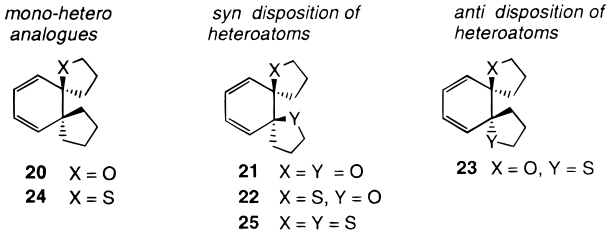

norbornene **15** and norbornadiene **16** reacted from their more open *exo* face. This striking deviation could not be of steric origin since cycloaddition occurred *syn* to the larger (sterically demanding) ethano bridge. Since **13** and similar hydrocarbons have low dipole moments, polar interactions were eliminated. A comprehensive analysis of the observed stereoselectivities was made in terms of the $\sigma/\pi$ interaction. On the basis of ab initio and semiempirical calculations, Gleiter and Paquette showed that, in **13** and **14**, mixing of high-lying $\sigma$-orbitals with the lowest occupied $\pi_s$-orbitals resulted in disrotatory tilting of the terminal $P_\pi$-lobes. This tilting was proposed to induce differences in the frontier electron distribution in the two faces of the diene, leading to greater antibonding interactions between the $\pi_s$-orbital of the diene and the HOMO of the dienophile when the reaction occurred from the *exo* face of **13**, which was in consonance with the observed *endo* selectivity.[11]

## Cycloadditions to 1,3-Cyclohexadienes

Cyclohexadienes are often less selective than the corresponding cyclopentadienes, as the diene system exhibits more flexibility and conformational effects often play a substantial role. Gillard and Burnell have studied the cycloaddition of 1,2-substituted cyclohexadienes **17** with NPM,[26a] and *syn* selectivity was uniformly observed. Interestingly, the diacetate derivative **18** exhibited a reversal in selectivity[26a] with a heterodienophile (PTAD), and this was attributed to repulsive electrostatic interactions. Likewise, epoxide **19** exhibited *anti* selectivity, and this reversal was due to steric encumbrance by the oxirane bridge.[26b]



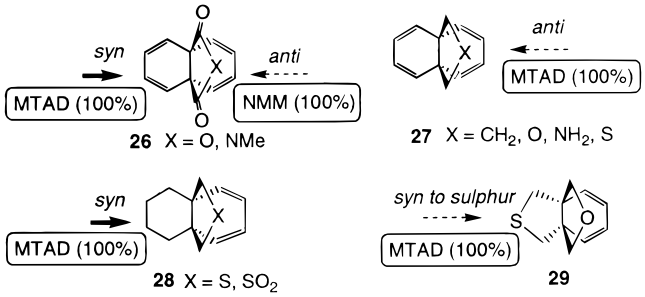

Paquette et al.[27] have recently studied the $\pi$-face selectivities in a series of dispiro-1,3-cyclohexadienes **20**–**25** with NPM and a heterodienophile, *N*-methyltriazolinedione (MTAD). Approach of NPM *syn* to the heteroatoms in **20**–**22** was favored (93–100%) for steric reasons. When the heteroatoms were *anti* disposed as in **23**, NPM




added *syn* to oxygen (100%) in order to avoid interaction with the larger sulfur atom. The diene **24** displayed little facial selectivity with NPM and was attributed to the comparable size of $S/CH_2$ and $CH_2/CH_2$ arrays on opposite faces. Interestingly, MTAD underwent reaction with **20**–**22** exclusively from the face *anti* to oxygen, in contrast to NPM, due to the repulsive interactions between the nonbonded electron pairs on the heteroatoms present in the dienes and on the nitrogen atoms of the dienophile. Likewise, **24** and **25** added MTAD predominantly (91–100%) *anti* to sulfur. It was surmized[27a] that electrostatic effects dominate in a *syn* dioxa system. However, steric factors need to be accorded proper consideration while accounting for the $\pi$-facial selectivity in the oxa/thia and dithia compounds.

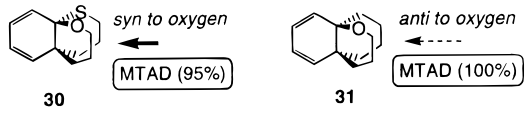
## Cycloadditions to [*l.m.n*]Propella-1,3-dienes

Gleiter and Ginsberg[12] have shown that, in cyclohexadienes embedded in a propellane skeleton, dienophiles stereoselectively add *syn* to the larger of the two flanking rings unless an opposing stereoelectronic effect intervenes. However, in the heteropropellane skeleton, which possesses homoallylic heteroatoms, stereoelectronic effects are turned on and exert a dominant role in addition to steric factors. Thus, diene **26** captured MTAD exclusively from the face *syn* to the anhydride/imide bridge (cf. *anti* addition in **27** and *syn* addition to **28**). On the other hand,




*N*-methylmaleimide (NMM) added to **26** from the sterically accessible *anti* face. Furthermore, in these homoallylic propelladiene systems containing both oxygen and sulfur bridges as in **29**, cycloaddition occurred *anti* to oxygen and *syn* to sulfur.[12] Gleiter and Ginsberg have rationalized these results by invoking stabilizing secondary orbital interaction[12] between the electron-rich heterodienophile and electron-poor anhydride functionality.

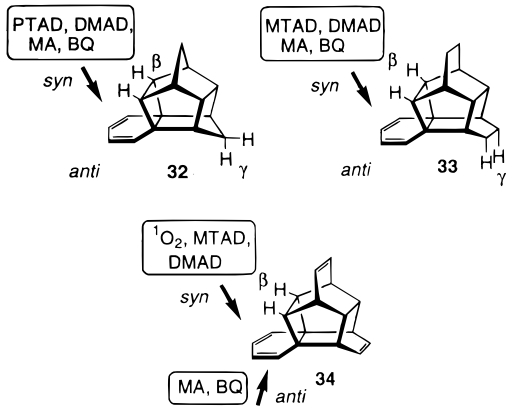
In sharp contrast, Paquette et al. have observed[27a] that, in a related propelladiene **30**, addition predominantly occurred from the direction *syn* to oxygen and *anti* to sulfur. The almost complete crossover observed with the




two closely related dienes **29** and **30**, though intriguing, can be reconciled as follows. In **30**, allylic sulfur directs MTAD from the *anti* face through Cieplak-type hyperconjugative interaction, subjugating the electrostatic repulsion between MTAD and the lone pairs on oxygen. However, Cieplak-type interactions are effectively turned off in **29**, as sulfur is far removed from the reaction center, and hence the electrostatic interactions gain dominance, favoring attack *anti* to oxygen and *syn* to sulfur. Similar arguments hold well for an earlier example **23**, wherein addition *syn* to oxygen is favored. When the choice is between an oxygen and methylene, as in mono-oxapropelladiene **31**, MTAD adds exclusively *anti* to oxygen, underscoring the importance of through-space electrostatic interactions.[27b]

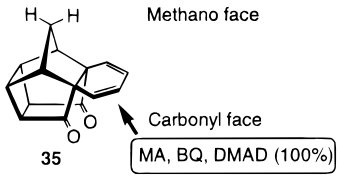
## Cycloadditions to 1,3-Cyclohexadienes in Constrained Polycyclic Systems

Prinzbach et al.[28] have studied cycloaddition face selectivities in rigid polycyclic dienes **32**–**34** to evaluate stereoelectronic factors. In dienes **32** and **33**, predominant




*syn* addition (82–98%) from the cyclobutane face was observed.[28a] The stereoselectivity was attributed to the relative magnitude of nonbonded steric repulsion during dienophile capture from the *anti* trajectory ($\gamma$-hydrogens) to be more effective. However, in diene **34**, additional unsaturation was also expected to exert an electronic interaction with the adjacent $\pi$-cloud with concomitant reduction in the steric requirements. A *syn*-to-*anti* reversal of face selectivity was observed in **34** for MA and BQ on account of steric factors. However, hetero and acetylenic dienophiles added predominantly from the sterically demanding *syn* face, and this was reconciled in terms of n–$\pi$ and $\pi$–$\pi$ repulsion among filled orbitals.[28b]

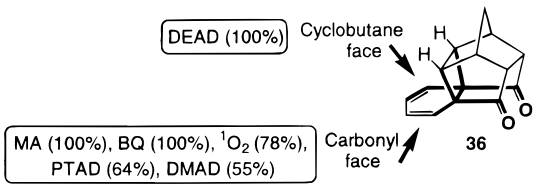
Diels–Alder cycloaddition to the polycyclic diene **35**, wherein the diene moiety is flanked by a methano and carbonyl face, occurred exclusively from the carbonyl face.




The observed selectivities were mainly attributed to greater nonbonded steric repulsion during dienophile capture on the methano face. However, orbital effects were also speculated to have cooperatively aided in the addition from the carbonyl face.[29]

## Cycloadditions to Hexacyclic 1,3-Diene System 36

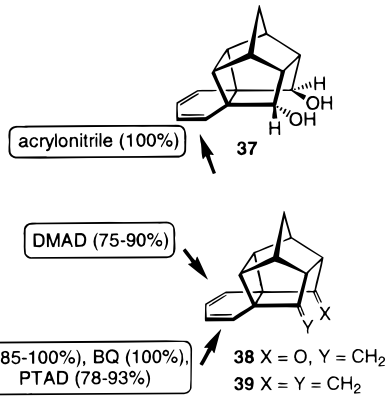
Among the various probes for exploring face selectivities, the hexacyclic system **36**, embodying a [4.4.2]propella-2,4-diene moiety and devoid of conformational uncertainties, is particularly attractive because of its accessibility, reactivity, and functional group maneuverability. In **36**,



facial discrimination in the cyclohexadiene moiety is manifested through the interplay of steric effects of cyclobutane hydrogens, hyperconjugative participation of the high-energy $\sigma$ bonds of the strained cyclobutane ring, and electrostatic interactions of the two carbonyl groups during the approach of a polar reagent. The relative importance of steric, electrostatic, and hyperconjugative interactions can be gleaned by fine-tuning the substrate functionalities, without altering the steric environment around the diene. The presence of a stereogenic center and a heteroatom at the homoallylic position in **36** provides an opportunity to study the effect of heteroatom on diastereoselection.

Initially, Coxon et al.[30a] and Pandey et al.[31a] probed the facial selectivity exhibited by **36** and observed some systematic trends, with the olefinic dienophiles (MA, BQ) being captured exclusively from the carbonyl face of the diene. On the other hand, alkynes and azo dienophiles (PTAD, DEAD) showed selectivities ranging from preferred carbonyl face attack to exclusive cyclobutane face attack (for DEAD). Calculations based on X-ray crystal structure[30a,31b] parameters of the diene **36** indicated that, for a normal Diels–Alder transition-state geometry, attack from the cyclobutane face resulted in unreasonably close interactions between the olefinic protons on the dienophile and the cyclobutane ring protons. Thus, the exclusive carbonyl face attack observed with olefinic dienophiles is a consequence of the inherent steric bias in the diene **36**. Coxon et al. qualitatively rationalized the observed preferences in azo- and alkyne-type dienophiles as an interplay of steric encumbrance on the cyclobutane face and the repulsive interaction between the $\pi$-bonding or nonbonding orbital electron density in the alkyne and azo dienophiles and the electron density of the carbonyl oxygen atoms.[30a]

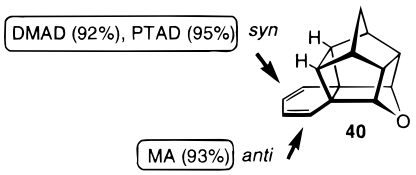
The role of carbonyl groups in $\pi$-facial selectivities in the diene **36** was further probed by studying the facial selection in the corresponding diol **37** and the ***mono***- and bis-methylidene derivatives **38** and **39**. Diol **37** captured




acrylonitrile exclusively from the hydroxy face,[31a] and as the directions of addition in the dione **36** and diol **37** were the same, it was surmised that the carbonyl groups are unimportant in determining the face selectivity in **36**. In **38** and **39**, the $\pi$-electron configuration was retained by replacing the lone pairs of the carbonyl oxygens with hydrogen atoms, and it was expected that this subtle variation might enhance the steric hindrance to the carbonyl face addition and encourage reaction from the cyclobutane face.[30b] Dienes **38** and **39** accepted alkene dienophiles (MA, BQ) with strong preference for the carbonyl face, but for DMAD, attack from this face decreased with successive methylidene substitution.

The selectivities in the hexacyclic dienes **36** and **38**–**39** were analyzed computationally by Coxon et al.[30b] Ground-state geometric distortions such as unsymmetrical pyramidalization[7] were ruled out on the basis of X-ray structure of **36**. The proposal of Vogel et al.[8] based on product stabilities was considered, but MMX calculations showed that the product stabilities do not parallel the observed selectivities. $\sigma/\pi$ interactions[11] in dienes **36** and **38**–**39** at the AM1 level indicated an inward tilting on the cyclobutane face of the terminal p lobes for the $\Psi_1$ MO of the diene unit. The inward orbital tilting was considered as a favorable factor for the carbonyl face attack observed with some of the dienophiles. The steric and torsional interactions resulting from bending at the "transition state" proposed by Houk et al.[9] were considered to account for the carbonyl face selectivity exhibited by **36**, **38**, and **39**. This approach explained the absence of alkene cycloaddition to the cyclobutane face but predicted carbonyl face preference for alkyne addition to dione **36**, contrary to experimental observation. Thus, while face selectivities for alkene-type dienophiles could be understood on the basis of steric bias, unfavorable orbital interaction of the closed shells of the carbonyl(s) and methylidene(s) *syn* to the incoming orthogonal $\pi$-orbital of DMAD was also considered important.[30b]

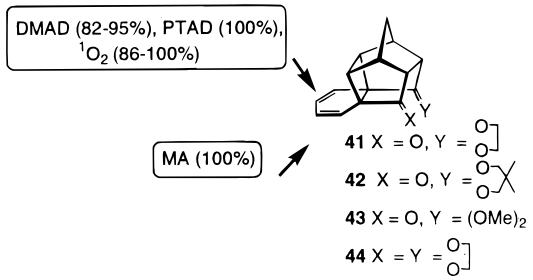
To validate this proposition, Coxon et al.[30c] investigated the $\pi$-face preferences in the caged ether **40**, wherein a lone pair of the ether oxygen is positioned to interact with the $\pi$-orbital of the alkyne or n-orbitals of the azo dienophile when addition occurs from the face bearing the ether oxygen. If this electronic repulsion were impor-




tant, acetylenic and azo dienophiles would react from the cyclobutane face and alkene dienophiles from the less hindered ether face. Indeed, such a variation in face selectivities with MA, DMAD, and PTAD was observed. Calculations at the AM1 level reproduced the observed selectivities and revealed an unfavorable interaction in the transition state between the filled $\pi$-orbital of acetylene (disposed orthogonal to the forming $\sigma$-bonds) and the lone pair on the ether oxygen during the *anti* approach. This was recognized as a factor undermining addition from the ether face.[30c]

We reasoned that rehybridization of the carbonyl carbon(s) in **36** and strategic disposition of hetero functionalities on the newly generated $sp^3$ center(s), without

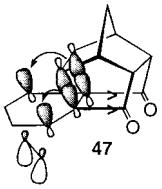
substantially altering the steric environment or sacrificing the skeletal identity of the substrate, would be insightful in revealing the stereoelectronic effects on face selectivity. This could be accomplished simply by protecting the carbonyl groups in **36** as corresponding acetals **41**–**44** or thioacetals **45** and **46**, through simple protective group modification of carbonyl groups. In our study, we em-




ployed three types of dienophiles: (a) alkene dienophiles, wherein the two olefinic protons could induce steric bias, (b) acetylenic dienophile with filled $\pi$-orbitals, and (c) $^1O_2$ and PTAD, heterodienophiles with filled n-orbitals.

Addition of MA to acetals **41**–**44** occurred as expected from the carbonyl face, as in the case of dione **36**. However, mono- and bis-acetals **41**–**44** underwent cycloaddition reactions with $^1O_2$, PTAD, and DMAD predominantly from the cyclobutane face. This was a dramatic reversal of face selectivity from the carbonyl face addition of these dienophiles in the dione **36** (vide supra). Clearly, face selectivities in the case of **41**–**44** were highly dienophile specific.[32]

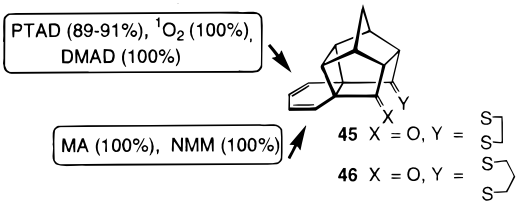
Since there is no marked change in the $\pi$-face selectivity of MA addition to acetals **41**–**44** as compared to the case with the parent dione **36**, any steric intervention by the acetal groups can be ruled out. According to the Cieplak model,[13a] the addition should occur from the side opposite to the most electron-rich bond, as shown in **47**.




This model can readily rationalize the predominant carbonyl face attack (addition opposite to electron-rich cyclobutane bonds) in MA but fails to rationalize the contrasteric approach of $^1O_2$, PTAD, and DMAD in acetals **41**–**44**. In particular, the key hyperconjugative interaction in the cycloaddition transition state should become more important when the newly formed C–X bonds involve highly electronegative X groups and should strongly favor carbonyl face addition.

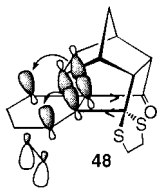
The observed selectivities can be rationalized as follows: when the addition occurs from the face of the diene bearing the acetal functionality in **41**–**44**, repulsive electrostatic interaction between the lone pair on the acetal oxygen with the $\pi$-orbital of DMAD or n-orbitals of PTAD or $^1O_2$ is turned on. Further, the variation in diastereoselectivity, with respect to the dienophile employed, reaffirms our surmise that the repulsive electrostatic interactions between the incoming dienophile and the acetal oxygens in **41**–**44** govern the $\pi$-facial selectivities. In addition, these results also provide a novel illustration of the stereodirecting effect of remote protective groups. Since acetal protection and deprotection are fairly routine manipulations, this tactic could find useful synthetic applications in achieving diastereoselection.[32]

The unusual findings with acetals **41**–**44** led us to direct our attention to their sulfur counterparts **45** and **46**, to gauge the effect of the change in the heteroatom on diastereoselection. The presence of sulfur in **45** and **46** was expected to exert a profound effect on diastereoselectivities through the Cieplak[13] and electrostatic effects.[33]




In the thioacetals **45** and **46**, addition of $^1O_2$, PTAD, and DMAD occurred from the sterically demanding cyclobutane face, whereas olefinic dienophiles (MA and NMM) were captured from the face bearing the thioacetal moiety. The results clearly indicate that the thioacetal functionality has a profound bearing on the $\pi$-facial selectivity and is generally consistent with the observed trends in the acetals **41**–**44**.[34] Most noteworthy is the 100% selectivity in the cases of MA, NMM, $^1O_2$, and DMAD with the introduction of barely a single thioacetal functionality in **36**.

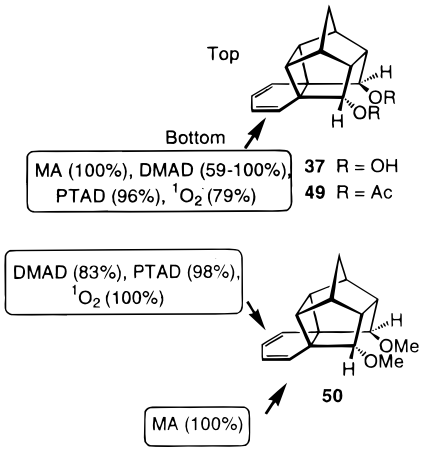
For olefinic dienophiles, possessing an intrinsic steric bias, addition to **45** and **46** is expectedly from the less hindered carbonyl face. Therefore, the observed preference for cyclobutane face in $^1O_2$, PTAD, and DMAD additions to thioacetals **45** and **46** is a contrasteric outcome. This preference for hetero and acetylenic dienophiles may be reconciled in terms of the Cieplak hyperconjugative model, according to which the preferred face of addition is *anti* to the most electron-rich bond (C–C bonds $\alpha$ to a thioacetal, see **48**). Additionally,




unfavorable electrostatic interactions between these dienophiles and the lone pairs on sulfur should encourage addition from the cyclobutane face. However, in thioacetals **45** and **46**, the relative contribution from such interactions is expected to be less as compared to their oxygen variants **41**–**44**, as these dienophiles are closer in energy to 2p lone pairs of oxygen rather than sulfur.[27a,33] Thus, if electrostatics were the major determinant, the

observed trends for cyclobutane face addition in **45** and **46** would be reduced as compared to the case of the acetals **41**–**44**. However, the exclusive selectivity for the cyclobutane face, observed in **45** and **46**, is indicative of both Cieplak-type hyperconjugative effects and through-space electrostatic interactions acting in concert.[34]

Once it was demonstrated that transformation of the carbonyl groups in **36** to acetal functionality as in **41**–**44** can lead to dramatic reversal of face selectivities, an attempt to further segregate the role of *inside oxygen* (within the cage) vs the *outside oxygen* was made. *endo,endo*-Diol **37**, diacetate **49**, and dimethoxy derivative **50** were selected as diagnostic probes to investigate the role of inside oxygen.[35] Addition of DMAD, $^1O_2$, and PTAD




to the *endo,endo*-diol **37** and diacetate **49** occurred preferentially from the bottom face, whereas complete reversal occurred in the case of the dimethyl ether **50**. However, MA added **37**, **49**, and **50** uniformly from the bottom face. It is noteworthy that a reversal in diastereoselectivity is observed on going from the diacetoxy derivative **49** to the dimethoxy derivative **50**, with the hybridization at the carbon center remaining unaltered; even the simplest derivatization can lead to crossover as observed in methoxy (top face) vs acetoxy (bottom face).[35] Considering our earlier studies with the acetals **41**–**44**, the expectation was that repulsion between *endo*-directed oxygens in **37**, **49**, and **50** and the hetero and acetylenic dienophiles would uniformly favor addition from the top face. While the observed selectivity in **50** was in consonance with this reasoning, the outcome in the case of **37** and **49** suggested intervention of some additional, unrecognized interactions. Transition-state modeling at the AM1 level indicated a repulsive interaction between the oxygen lone pairs and the approaching hetero and acetylenic dienophiles. Hence, the exclusive formation of the top face adduct in **50** is consistent with electrostatic control. For the diol **37**, a significant bottom face preference was computed, qualitatively in accord with the experimental trend. For the bottom face attack, an additional hydrogen-bonding interaction is evident for hetero and acetylenic dienophiles, which seem to provide enough stabilization to overcome electrostatic repulsions as noted in **50** (Figure 1a. Transition-state energies favor-

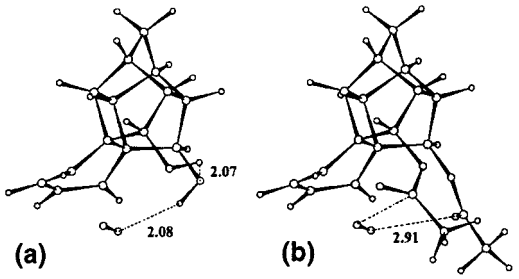
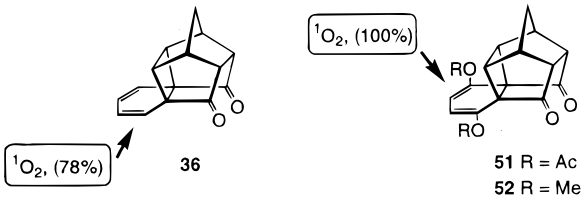



**FIGURE 1.** AM1-optimized transition-state structures for the bottom face addition of $^1O_2$ to (a) **37** and (b) **49**.

ing the bottom face attack for the diacetoxy derivative, **49**, were also consistent with experiment. While **37** allows hydrogen bonding between the substituent and the heterodienophile, the origin of the selectivity in **49** is intriguing. We propose that stabilizing orbital interactions between the reagent (n-orbital) and the remote substituent ($\pi^*$ of ester linkages) direct the approach of the heterodienophiles (Figure 1b). These attractive effects are not translated into any reaction at the substituent but only result in the delivery of the reagent to the nearby diene face.[35a]

Attention was next turned to fine-tune the face selectivities by introducing 1,4-substituents on the diene unit of the hexacyclic dione **36**. Accordingly, the dione **36** and the 1,4-substituted derivatives **51** and **52** were subjected to singlet oxygen cycloaddition to furnish the corresponding endoperoxides. While **36** furnished both the diaster-




eomers, the 1,4-disubstituted derivatives **51** and **52**, quite unexpectedly, afforded exclusively a single diastereomer through contrasteric cyclobutane face addition.[36] The influence of 1,4-substituents on the $\pi$-face selectivity of the diene **36** is quite remarkable, since the groups are expected to remain in the $\pi$-plane in the reactant and in the sterically neutral bridgehead positions in the product. The Cieplak model can rationalize the predominant carbonyl face attack (addition opposite to electron-rich cyclobutane bonds) in **36** but fails to rationalize the contrasteric approach of $^1O_2$ in **51** and **52**.

Therefore, the origin of this dramatic reversal of face selectivities in **51** and **52** as opposed to **36** was probed through transition-state modeling at the MNDO level. The computed energies for $^1O_2$ addition to **36** revealed preference for the carbonyl face addition, consistent with the experimental trend. The reversal of face selectivity in the dimethoxy derivative **52** is also reproduced by MNDO calculations. The computed geometry of these structures reveals a possible reason for this reversal. The diene is twisted at the 1,4-position such that the substituents move toward the dienophile; this is a requirement for maximiz-

ing frontier orbital interactions.[9,37] For carbonyl face addition of $^1O_2$ to **52**, the methoxy lone pairs are brought closer to the carbonyl oxygen atoms at the transition state. The consequent repulsion leads to relative destabilization of the corresponding transition state. The same effect can account for the face selectivity in the diacetoxy derivative **51**. It may be emphasized that the critical geometric distortion (out-of-plane bending) which subtly controls face selectivity in these systems is not present either in the reactant or in the product but is specific to the transition state.[36] These interpretations provide an interesting complement to earlier suggestions of face selectivity being influenced by out-of-plane bending at the 2,3-positions of isodicyclopentadiene **13**.[9,37]

## Concluding Remarks

Studies on Diels–Alder reactions with a range of carefully crafted dissymmetric 1,3-dienes highlight the importance of several factors such as steric and torsional effects, through-space electronic interactions, Cieplak-type hyperconjugation, and ground-state orbital effects to account for the observed diastereoselectivities. Systematic investigations with different types of dienophiles have been particularly useful, as the nature of the interaction between the diene and the dienophile is crucial to the stereochemical outcome.

The large body of results now available enables apportioning of relative importance to the various stereoelectronic factors that govern diastereoselection. Steric effects invariably play a dominant role, more so when both of the reacting partners are sterically biased, subjugating all other effects, and the outcome is predictable. However, when the steric effects are less pronounced, subtle electronic effects must be reckoned with. For example, when steric interaction between **8** and the dienophile is relaxed, Cieplak effect begins to dominate, and reversal in face selectivity is observed.

In near-isosteric environments, the direct through-space interaction between the substituent and the reagent generally governs selectivities. The outcome may be attractive or repulsive, depending upon the nature of the interacting groups. Through-space, filled-orbital repulsions between the substrate functionality and the dienophile are the main determinants of face selectivity in **34**, **40,** and **41**–**44**. On the other hand, secondary orbital (in **26**), stabilizing orbital (in **49**), and hydrogen-bonding (in **37**) interactions provide ample evidence of the role of attractive interactions. However, through-space interactions are intricately related to the geometrical requirements, as exemplified by the contrasting behavior of acetoxy groups in different environments, as seen in **18** vs **49**.

In systems not amenable to through-space interaction with the approaching reagent (see **10** and **11**), hyperconjugative interactions, though smaller in magnitude, are decisive and are the main determinants of diastereoselection. Cieplak effect gains further dominance in sulfur-containing systems where the sulfur atom is positioned to participate through hyperconjugative $\sigma$-assistance. Finally, in systems which do not possess polar substituents, steric (**32** and **33**) or ground-state orbital effects (**13**) play a key role.

Available data have been evaluated to qualitatively define a hierarchy for the expression of stereoelectronic effects: steric > through-space (electrostatic repulsion/attractive stabilizing orbital interactions) > hyperconjugative > ground-state orbital distortion (generally in substrates devoid of polar substituents). The effects may reinforce or oppose each other, and the observed selectivities can thus be deduced and, to an extent, predicted.

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