Facial Stereoselectivity in Acyl Nitroso Cycloadditions to 5 5-Unsymmetrically Substituted Cyclopentadienes: Computational Exploration of Origins of Selectivity and the Role of Substituent Conformations on Selectivity

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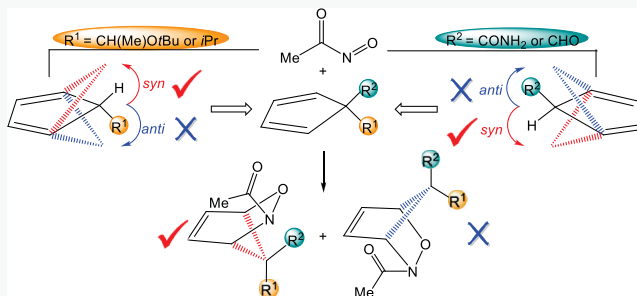Cite This: *J Org Chem* 2021 86 17082 17089

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ABSTRACT: The   -facial selectivity of Diels Alder cyclo-additions of 5-monosubstituted cyclopentadienes is known experimentally and has been extensively studied computationally. Previous studies on 5-monosubstituted cyclopentadienes by the Burnell and Houk groups showed that facial selectivity arises principally from hyperconjugative aromaticity or antiaromaticity of polar groups that cause distortion of the cyclopentadiene; steric e ects of nonpolar groups can also be important. We have now explored the stereoselective cycloaddition of 5,5-unsymmetrically substituted cyclopentadienes to an acyl nitroso dienophile reported by Kan and co-workers. Computational studies with M06-2X/6-311+G d,p) indicate that the stereoselectivity in the cycloadditions of 5,5-unsymmetrically substituted cyclopentadienes is not just a simple combination of e ects found for monosubstituted counterparts. Substituent conformations and diene dienophile steric and electronic interaction e ects all influence stereoselectivity. Predictions are made about several as-yet-unstudied cyclopentadiene cycloadditions.

INTRODUCTION

Stereoselective Diels Alder cycloadditions are widely used in organic synthesis, leading to six-membered rings often with full control of multiple stereogenic centers.[1,2] The Diels Alder reactions of cyclopentadienes are of particular interest due to the high reactivities of these dienes and the utility of the norbornene derivatives formed.[3,4] Burnell s group published a series of studies of the origin of the facial selectivity of Diels Alder reactions of substituted cyclopentadiene,[5] indicating that the facial selectivity can be attributed to steric[5a] and deformation e ects.[5c] Our group also studied and analyzed the Diels Alder reactions of 5-substituted cyclopentadiene with various dienophiles,[6,7] and we came up with a general model based on hyperconjugation of C5 substituents and the consequent ease of distortion in the transition state in one or the other direction toward the norbornene product geometry.[7]

Recently, Kan and co-workers reported a novel approach for the synthesis of pactamycin involving the Diels Alder reaction of chiral cyclopentadiene **2** and a chiral acyl nitroso compound **3** generated in situ from the treatment of acyl hydroxylamine derivative **1** in the presence of pyridine and copper catalyst) Scheme 1a).[8] They reported that product **4** was the only diastereomer obtained from the Diels Alder cycloaddition and carried out density functional theory DFT) calculations to study multiple reaction pathways. They proposed that the
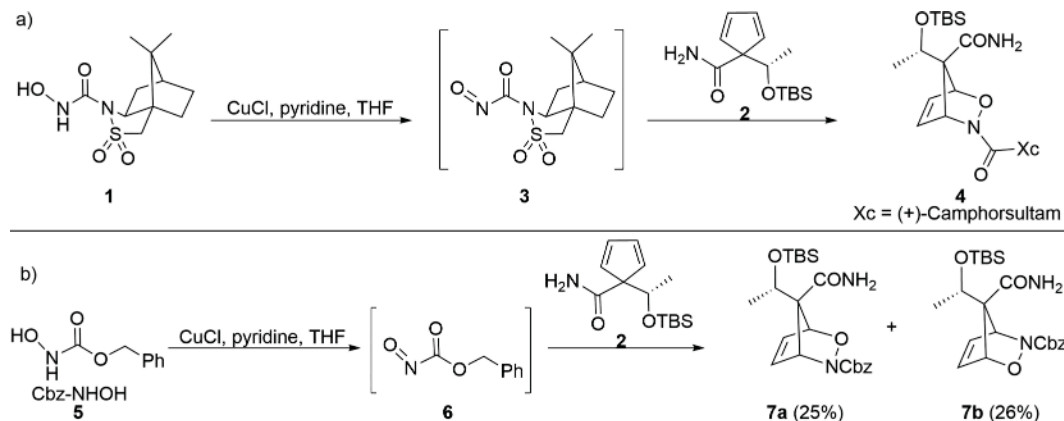
stereoselectivity and regioselectivity arise from steric hindrance between diene substituents and the dienophile. In the same study, Kan and co-workers reported the Diels Alder reaction of cyclopentadiene **2** with an achiral acyl nitroso dienophile **6** generated from **5**), where a 1:1 mixture of regioisomers, **7a** and **7b**, was obtained Scheme 1b). The same high facial selectivity was observed with the dienophile attacking syn to the amide group of cyclopentadiene. This example is fundamentally di erent from the previous examples studied since both substituents amide and alkyl groups) have carbons attached to the cyclopentadiene ring and do not di er significantly in electronegativity. Nitroso compounds partic-ipate in Diels Alder reactions as dienophiles.[9] Stevens s group reported hetero-Diels Alder reactions of 2-nitrosotoluene and other acyl nitroso dienophiles with a specific set of 1,3-dienes and found that no metal catalysts or specific additives are required to obtain the products 1,2-oxazines in good yields.[9c] Read de Alaniz s group showed novel application of nitro-
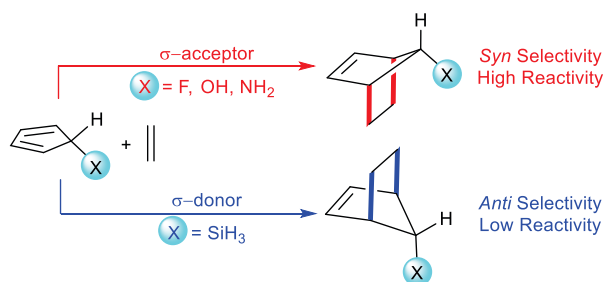
Scheme 1. Synthesis of Nitroso Compounds and Reactions with 5 5-Unsymmetrically Substituted Cyclopentadiene 2

socarbonyl chemistry in the field of block copolymer preparation, where they used polyethylene glycol hydroxamic acid and polystyrene cyclopentadiene in the nitroso hetero-Diels Alder reaction for polymer synthesis.[9d] Mechanistic studies of the intermolecular nitroso hetero-Diels Alder reaction by our group showed that the reaction proceeds in a concerted fashion.[9a,b] We undertook a theoretical study of the factors that control the stereoselectivity of this synthetically valuable reaction to probe the steric e ects cited by Kan et al. and to expand upon the previous discussions on the origins of -facial selectivity for Diels Alder reactions involving monosubstituted cyclopentadienes.

In previous studies of the reactivities and -facial stereoselectivities of the Diels Alder reactions of 5-substituted cyclopentadienes, both σ-donor and σ-acceptor substituents were investigated Scheme 2).[7] When the C5 substituent is a

Scheme 2. Hyperconjugative Aromaticity Model for the Facial Stereoselectivity of C5-Substituted Cyclopentadiene Diels Alder Reactions[7]

σ-acceptor, it bends away from the cyclopentadiene system in order to minimize the destabilizing hyperconjugation that amounts to 4-electron antiaromatic conjugation. This causes the molecule to resemble the transition-state geometry for syn cycloaddition, leading to the formation of syn products. In contrast, when the C5 substituent is a σ-donor, it causes distortion of the substituent toward the cyclopentadiene system in order to maximize stabilizing hyperconjugation, and this leads to anti products.[7]

RESULTS AND DISCUSSION

Cycloaddition of Experimental and Model Systems. We began our study with the computation of achiral nitroso dienophile **6** with chiral cyclopentadiene **2** that was studied experimentally by the Kan group Scheme 1b). Activation

barriers of cycloadditions with nitroso dienophile **6** attacking syn to the amide group are lower than those of the corresponding anti pathways 16.2 vs 21.7 kcal/mol and 16.4 vs 22.5 kcal/mol) Figure 1a). The calculated facial selectivity is consistent with experimental observation where only syn adducts with regard to the amide group were observed Scheme 1b).[8] Our calculations also confirmed that the diastereoselectivity within the syn cycloaddition is poor 16.2 vs 16.4 kcal/mol), in agreement with the absence of regiochemical selectivity shown in Scheme 1b.

A model reaction was then studied of achiral nitroso dienophile **8** as a simplification of **6**) with chiral cyclopentadiene **9** as a simplification of **2**). For simplicity, the CH Me)OTBS group in cyclopentadiene **2** was replaced with a   CH Me)OtBu group, and the benzyloxy group in the nitrosoester **6** was replaced with a methyl group. Four cycloaddition pathways, syn and anti with regard to the amide group, and the two regioisomeric alignments of nitroso with cyclopentadiene were studied Figure 1b). The facial selectivity syn vs anti) and diastereoselectivity within the syn or anti cycloaddition are consistent with the real system, confirming that the simplification made here is valid. A more detailed analysis will follow, but several points are of interest here. The ground-state structure of cyclopentadiene **9** is shown on the left side of Figure 1b. The preferred conformation of the amide group in the reactant [and when anti to the dienophile in the transition state TS)] is such that the   orbital of the carbonyl can interact in a stabilizing antarafacial spiro-type manner with the diene highest-occupied molecular orbital HOMO). On the other hand, the preferred conformation of the chiral   CH Me)OtBu group in the reactant has the methyl group antiperiplanar to the amide, presumably for steric reasons. When the nitroso dienophile approaches syn to this chiral group, it forces the chiral group to rotate into a less favorable arrangement with both   Me and   CH Me)OtBu gauche to the amide in order to place the small H atom near the approaching dienophile anti to the amide). This distortion, as we show in Figure S1, is large enough to disfavor these TSs by 1.6 2.2 kcal/mol.

The forming bond distances in **TS1a TS1d** are around 2.0 Å C N) and 2.4 Å C O), with slight di erences. We explored the influence of bond distance on the activation energy. The optimized structures of transition states with fixed bond distances **TS1a′ TS1d′** C N = 2.01 Å and C O = 2.40 Å) are shown in Figure S2. The energetics and corresponding distortion/interaction D/I) analyses Figure
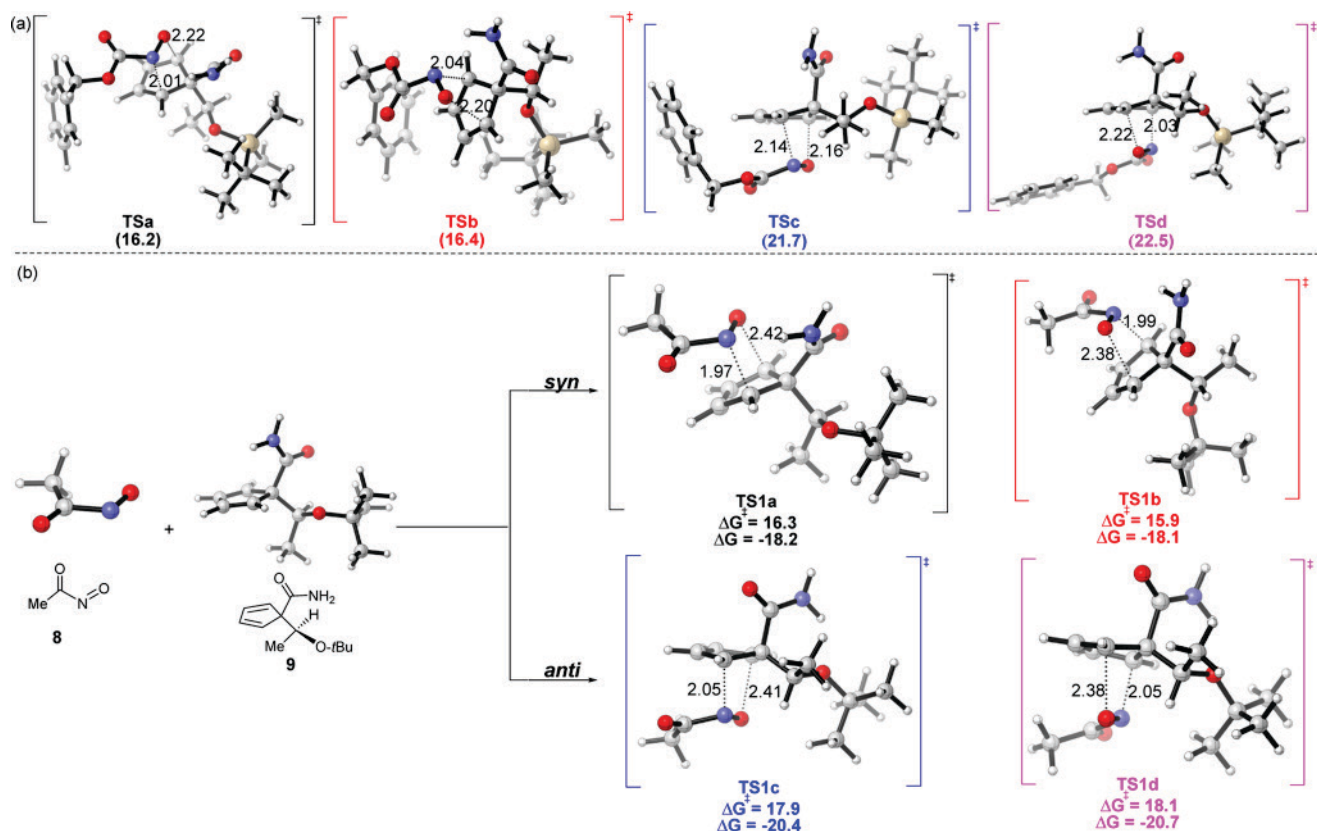
Figure 1. a) Calculated TS structures of the reaction between nitroso dienophile **6** and cyclopentadiene **2**. Gibbs free activation energies (Δ*G*‡) are shown in kcal/mol in parentheses. b) Calculated TS structures of the reaction between nitroso dienophile **8** and cyclopentadiene **9**. Gibbs free activation energies (Δ*G*‡) and reaction free energies (Δ*G*) are shown in kcal/mol. Bond lengths are given in Å.

S2) hardly change compared to the fully optimized cases (Figure S1), so the influence of bond distance is excluded.

To better understand the role of the alkyl group and amide group at the C5 position of cyclopentadiene, monosubstituted cyclopentadienes with alkyl groups (-CH(Me)O*t*Bu, *i*Pr, and *t*Bu), π-acceptor groups (-CONH₂ and -CHO), and a conjugating group (-Ph) were studied.

Cycloadditions of Monosubstituted Cyclopentadienes. The facial selectivities of cyclopentadienes with single -CH(Me)O*t*Bu, *i*Pr, and *t*Bu substituents at the C5 position were explored, and the results are shown in Figure 2. Syn selectivity (with regard to the C5 alkyl group) was observed for the cycloaddition of cyclopentadienes **10** and **11**. D/I analyses were done on each transition-state structure to identify the origin of selectivity. Figure 2a shows that with -CH(Me)O*t*Bu at C5, syn addition is favored over anti by 1.2 kcal/mol, and D/I analysis suggests that this is a result of stronger interaction (–18.4 kcal/mol in **TS2c** vs –13.4 kcal/mol in **TS2a**, Figure S3). The same facial selectivity is observed for *i*Pr substitution, where syn addition is favored over anti by 0.7 kcal/mol (Figure 2b). Stronger interaction energy accounts for this difference (–16.9 kcal/mol in **TS3c** vs –13.6 kcal/mol in **TS3a**, Figure S4). With *t*Bu substitution, the facial selectivity is reversed, where anti addition is favored over syn by 3.8 kcal/mol (Figure 2c). Distortion energy became the major factor controlling selectivity (10.1 kcal/mol in **TS4a** vs 15.2 kcal/mol in **TS4c**, Figure S5), and diene–dienophile steric effects dominate. Optimizations of transition states at fixed bond distances were again carried out. The energetics and corresponding D/I analyses (Figures S6–S8) hardly change

compared to the fully optimized cases (Figures S3–S5), so the influence of bond distance is not important.

The influence of the conformation of substituents at the C5 position in **10**–**12** was studied. Higher-energy conformations of alkyl substituents (CH(Me)O*t*Bu, *i*Pr, and *t*Bu) are shown in Figure S9.

In the previous study on cycloadditions of monosubstituted cyclopentadienes, we found that distortion of the cyclopentadiene toward the transition state was influenced by substitution. Electropositive substituents caused bending toward the diene π-system to maximize hyperconjugative aromaticity, while electronegative substituents distorted away from the diene π to minimize hyperconjugative antiaromaticity.[10] We explored if there is an effect of this type in the systems studied here, although neither the amide nor the alkyl group is particularly electropositive or electronegative. Figure 3 shows the energetics of out-of-plane distortion for each substituted cyclopentadiene in both syn and anti cycloadditions. The -CH(Me)O*t*Bu and -*i*Pr substituents bend most easily toward the π-system, which gives anti products; *t*Bu moves equally well in either direction. The out-of-plane angles measured in transition-state structures are marked on the graph with solid dots. The out-of-plane distortion energies are consistent with D/I analyses, which implies that syn addition requires larger distortion. With -CH(Me)O*t*Bu or -*i*Pr substitution, the syn transition state requires higher distortion energies, yet stronger interaction energies make this stereochemistry favorable (Figures S3 and S4). The interaction between alkyl substituents (-CH(Me)O*t*Bu or -*i*Pr) in cyclopentadiene and the nitroso group in the dienophile is
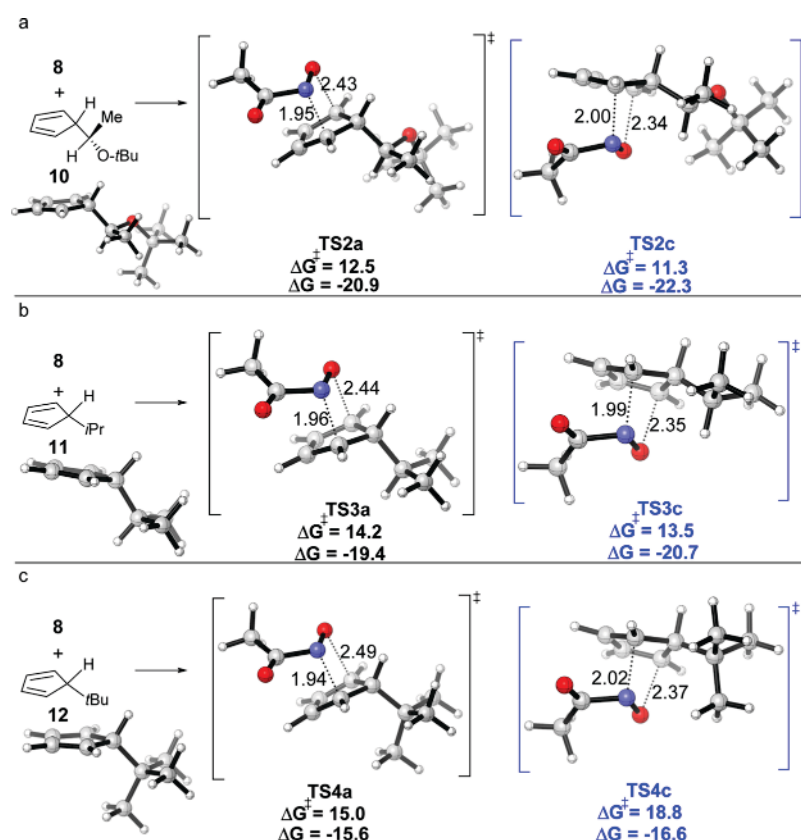
Figure 2. Calculated TS structures of the reaction between nitroso dienophile **8** with cyclopentadienes **10**, **11**, and **12**. Gibbs free activation energies and reaction free energies are shown in kcal/mol. Bond lengths are given in Å.
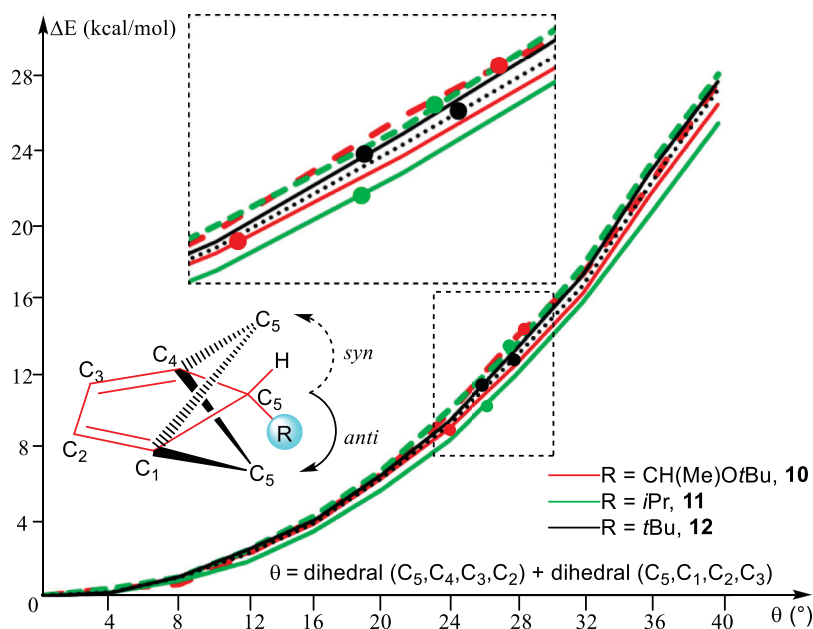

Figure 3. Distortion energy as a function of the out-of-plane angle of cyclopentadienes **10**–**12**. Two bending modes that correspond to anti and syn cycloadditions are shown in solid and dashed lines, respectively.

confirmed with noncovalent interaction (NCI) analyses (Figure S10). These show that there is a favorable electrostatic interaction between the nitroso group and the substituent. With *t*Bu substitution, anti cycloaddition reaches the transition state with a smaller out-of-plane angle and therefore less distortion, which overcomes the less favorable interaction

energy and becomes determinant (Figure S5). Here, steric effects favor the anti, less crowded, transition state.

The facial selectivity of cyclopentadienes **13**–**15** with other σ-acceptor (CONH$_2$ and CHO) and conjugating (Ph) substituents at the C5 position was further explored, and the results are shown in Figure 4. Syn-selectivity was observed for
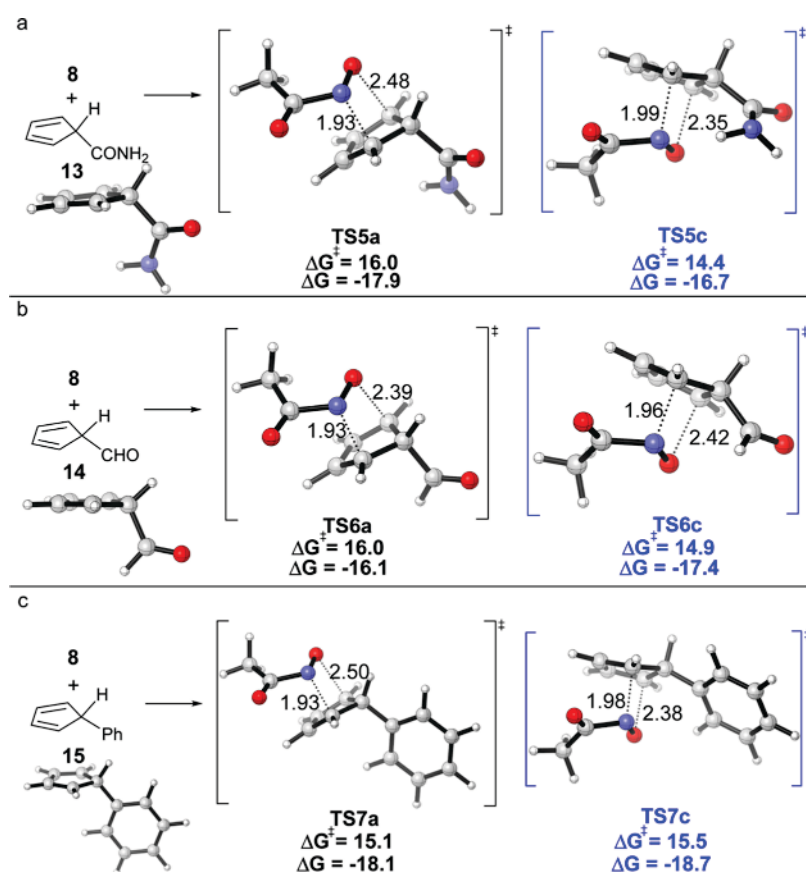
Figure 4. Calculated TS structures of the reaction between nitroso dienophile **8** with cyclopentadienes **13**, **14**, and **15**. Gibbs free activation energies and reaction free energies are shown in kcal/mol. Bond lengths are given in Å.
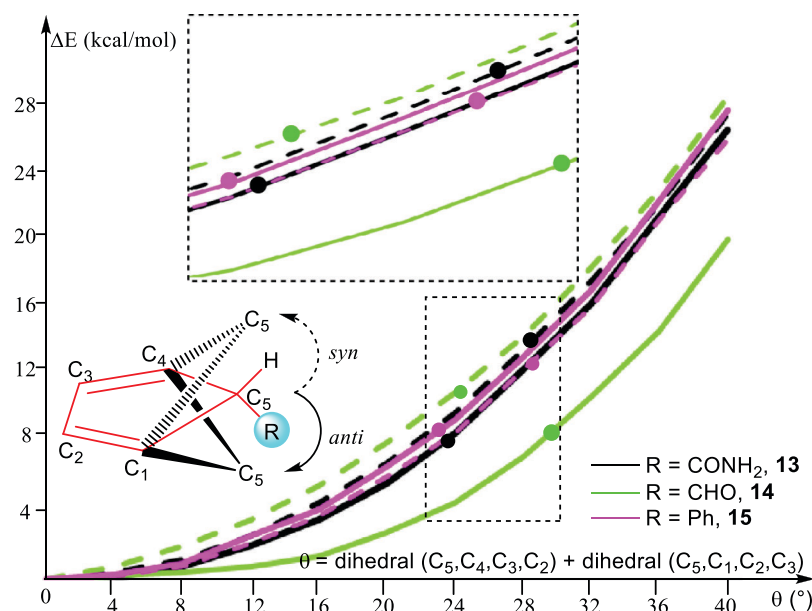

Figure 5. Distortion energy as a function of the out-of-plane angle of cyclopentadienes **13**–**15**. Two bending modes corresponding to the anti and syn cycloadditions are shown in solid and dashed lines, respectively.

13 and **14** (CONH$_2$ and CHO substitution), while **15** (Ph substitution) gives anti-selectivity. D/I analyses on transition-state structures are shown in Figures S11–S13. Figure 4a shows that with CONH$_2$ substitution at C5, syn addition is favored over anti by 1.6 kcal/mol. The selectivity mainly arises from favorable interaction energy (–18.6 kcal/

mol in **TS5c** vs –10.9 kcal/mol in **TS5a**, Figure S11). The same selectivity is observed for CHO substitution (Figure 4b), with syn addition favored over anti by 1.1 kcal/mol, as a result of stronger interaction (–15.7 kcal/mol in **TS6c** vs –11.4 kcal/mol in **TS6a**, Figure S12). Figure 4c shows that Ph substitution gives anti-selectivity, with the difference in
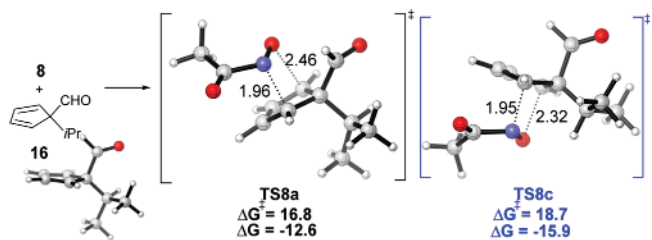
Figure 6. Calculated TS structures of the reaction between nitroso dienophile **8** and cyclopentadiene **16**. Gibbs free activation energies and reaction free energies are shown in kcal/mol. Bond lengths are given in Å.

activation free energies being only 0.4 kcal/mol. In this case, distortion energy (8.3 kcal/mol in **TS7a** vs 11.1 kcal/mol in **TS7c**, Figure S13) overrides the interaction energy and becomes the determining factor. As before, when optimizations of transition states at fixed bond distances were carried out, the energetics and corresponding D/I analyses (Figures S14–S16) do not change compared to the fully optimized cases (Figures S11–S13), so the influence of bond distance is not important for the D/I analysis.

Comparing the ground-state geometry with that in the transition state, the conformations of acceptor and conjugator substituents (CONH₂, CHO, and Ph) involve a significant rotation in syn addition transition states **TS5c**, **TS6c**, and **TS7c**). Di erent conformations of π-acceptor substituents at C5 in cyclopentadienes increase the energy by up to 4.7 kcal/mol (Figure S17). The attack of the nitroso group syn to π-acceptor forces it to rotate away from its favorable conformation, leading to larger distortion energies.

Figure 5 shows the out-of-plane distortion energies of cyclopentadienes **13**–**15** in both syn and anti additions. The –CONH₂ and –CHO substitutions bend easily in the anti addition fashion, while –Ph moves equally well in either direction. The out-of-plane angles in transition-state structures are marked with solid dots. The out-of-plane distortion energies are in accordance with the D/I analyses (Figures S11–S13). Syn addition requires larger distortion energies, but in the case of **13** and **14**, the stronger interaction makes syn addition more favorable (Figures S11 and S12). The NCI analyses also confirm the destabilizing strain interaction between the C5 substituent (–CONH₂ or –CHO) of cyclopentadiene and the nitroso group in the dienophile (Figure S18).

The preference for syn cycloaddition in **TS6c** is due to the stabilizing orbital overlap between the –CHO substituent and nitroso group in the syn addition transition state. The orbitals shown in Figure S19 are consistent with the observed stronger interaction energies in the syn addition of cyclopentadiene, a result from $n_{N,O} \to \pi^*_{CO}$ interactions.

Cycloaddition of Disubstituted Groups. The facial selectivity of the reaction of nitroso **8** and disubstituted cyclopentadiene **16** (iPr and –CHO groups at the C5 of cyclopentadiene) was also explored (Figure 6). The transition state with syn-formyl and anti-iPr is favored by 1.9 kcal/mol. The rotation of –CHO substitution in **TS8a** contributes to higher distortion energy (Figure S20), but the stronger interaction energy which comes from the stabilization between the π-acceptor and nitroso group is dominant (–15.2 kcal/mol in **TS8a** vs –13.7 kcal/mol in **TS8c**, Figure S20).

D/I Analysis and Energy Decomposition Analysis of the Experimental System. To explore the origin of the facial
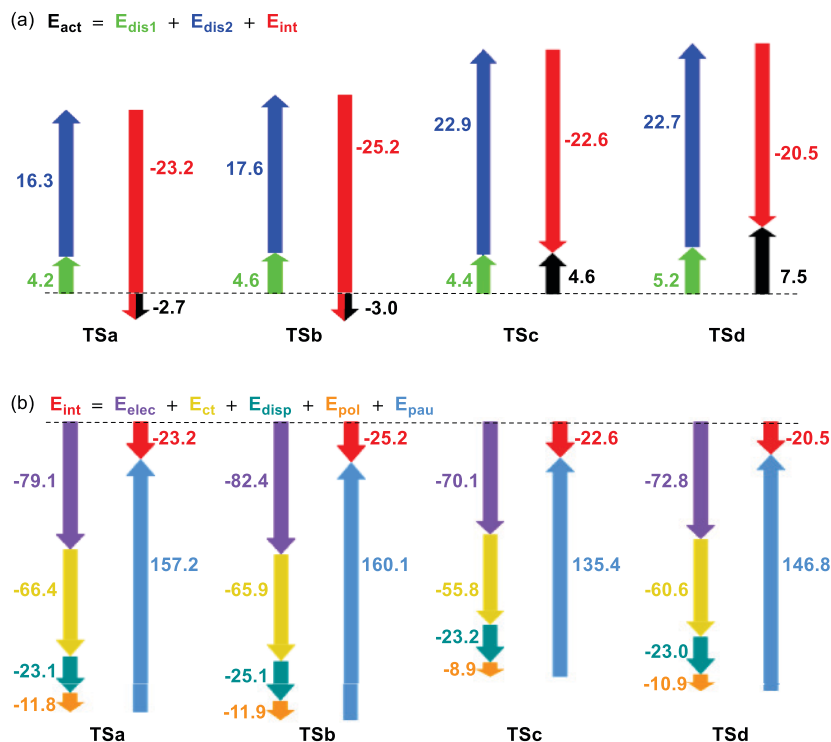

Figure 7. a) D/I analyses (in kcal/mol) of transition states **TSa**–**TSd**. Color code: green, distortion energy of the nitroso dienophile; blue, distortion energy of cyclopentadiene; red, interaction energy; and black, activation energy. b) Decomposition of interaction energies of **TSa**–**TSd**. Color code: purple, electrostatics; yellow: charge transfer; green, dispersion; orange, polarization energy; blue, Pauli repulsion; and red, interaction energy.

selectivity and regioselectivity, the D/I analysis and EDA were carried out and are shown in Figure 7, respectively. Figure 7a shows that there is variation in interaction energies between syn and anti cycloadditions 23.2 kcal/mol in **TSa** vs 22.6 kcal/mol in **TSc** and 25.2 kcal/mol in **TSb** vs 20.5 kcal/mol in **TSd**) and a more significant difference in distortion energies 16.3 kcal/mol in **TSa** vs 22.9 kcal/mol in **TSc** and 17.6 kcal/mol in **TSb** vs 22.7 kcal/mol in **TSd**). We have discussed the effect of conformation and how it contributes to distortion. Here, we analyze the individual components that give rise to interaction energy by carrying out EDAs with SAPT Figure S21) and ALMO-EDA Figure 7b) on **TSa** **TSd**. In comparison between syn and anti cycloadditions **TSa** and **TSb** vs **TSc** and **TSd**), the contributions of dispersion and polarization energies are less significant. The electrostatics and charge transfer are systematically more favorable for syn addition compared to anti addition, accompanied by more positive Pauli repulsions though. An overall effect is achieved with electrostatics and charge transfer overcoming the Pauli repulsion, which gives rise to a net stabilizing interaction.

CONCLUSIONS

Through investigations of the Diels Alder reactions of 5,5-unsymmetrically disubstituted cyclopentadienes, we find that additional factors to the distortion caused by substituent electronegativity, or the decreased original steric effects as suggested by Burnell, can control stereoselectivity. This difference arises because the groups studied here all involve carbon-substituents attached to the C5 of cyclopentadiene and do not differ much in electronegativities. We show that the conformational features of these substituents as well as direct substituent dienophile interactions can influence selectivity. In general, either an amide group or alkyl group, as a substituent on the C5 of cyclopentadiene, favors the formation of syn adducts. When both are present, syn selectivity with regard to the amide group is dominant.

COMPUTATIONAL METHODS

All DFT calculations were performed with Gaussian 16.[11] Preliminary molecular mechanics conformational searches were done with Schrödinger[12] Maestro 10.6. The low-energy conformers that are within 5 kcal/mol of the global minimum were re-optimized with M06-2X/6-31G d).[13] Normal mode vibrational frequency analyses were performed at the same level of theory to confirm that all vibrational frequencies are real for minima and only one imaginary frequency along the reaction coordinate is found for transition states, and to evaluate zero-point vibrational energies ZPVE) and thermal corrections at 298 K. Single point energies were calculated using the same functional with a larger basis set 6-311+G d,p), and CPCM[14] solvation model for tetrahydrofuran THF). Molecular orbitals were calculated with HF/6-311+G d,p) on optimized structure. Fragment distortion and interaction energies[15] were computed at the M06-2X/6-311+G d,p) level. The Q-Chem 4.3 software package[16] was used to perform absolutely localized molecular orbital energy decomposition analysis ALMO-EDA) with M06-2X/6-311+G d). Optimized structures were illustrated with CYLview.[17]

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.1c02191.

Optimized geometries of transition states **TS1a-TS8c** **TS1a′** **TS8c′**); D/I analyses of **TS1a-TS8c** **TS1a′** **TS8c′**); NCI analyses of **TS2a-TS7c**; HOMO and lowest-unoccupied molecular orbital energies of **TS6a** and **TS6c**; energy decomposition analyses with SAPT of **TSa-TSd**; and Cartesian coordinates of calculated structures PDF)

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Notes

The authors declare no competing financial interest.

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