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Stereoselectivity Control by Oxaspiro Rings during Diels−Alder Cycloadditions to Cross-Conjugated Cyclohexadienones: The *Syn* Oxygen Phenomenon

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Abstract: The diastereofacial selectivity operating in Diels−Alder additions involving spirocyclic cross-conjugated cyclohexadienones with dienes of varying reactivity has been investigated. The study has included the ether series **1a**−**c** as well as the lactone/ketone pair **2a**/**2b**. In all cases, the preferred [4+2] cycloaddition pathway consisted of bonding from that π-surface syn to the oxygen atom. 4-Substituted-4-methyl-2,5-cyclohexadienones (monocyclic systems) were also examined and found to undergo bond formation preferentially from the face bearing the more electron-withdrawing of the two groups at the 4 position. Kinetic parameters were determined for the cycloaddition of **1a** and **2a** to cyclopentadiene. The rate acceleration profile of solvents was in the order $CF_3CH_2OH \gg CH_3CN \sim CH_2Cl_2$ for the production of **9a** from **1a** and $CF_3CH_2OH \gg CH_2Cl_2 > CH_3CN$ for the production of **21a** from **2a**, respectively. This spread in polarity had no major impact on product distribution, a phenomenon also reflected in the behavior of 4-substituted-4-methyl-2,5-cyclohexadienones under comparable conditions. Theoretical assessment of these experimental facts was undertaken at the HF/6-31G* level. The facial selectivity is understandable in terms of the secondary interaction between the HOMO of the diene and LUMO of the dienophile as well as the effective hyperconjugation between the newly forming bond and the 4-*anti*-C−C σ-orbital due to the more electron-donating bond, as defined by the Cieplak model.

The capacity for generating four contiguous stereogenic centers in a single laboratory operation is obviously responsible for the widespread interest in the synthetic utility of the Diels−Alder reaction.[1] The stereochemical features of such cycloadditions have more recently been recognized to be capable of modulation by a neighboring heteroatomic substituent. Desymmetrization in this manner with continued operation of high diastereoselectivity offers additional stereochemical advantages.[2] Previous studies involving functionalized facially unsymmetric semicyclic dienes,[3] cyclopentadienes,[4] and 1,3-cyclohexadienes[5] have given evidence that high facial selectivity can be attained during [4+2] cycloaddition to symmetric dienophiles. Relatively rigid cyclic dienophiles have been the least studied.[6]

In select cases, steric effects control selectivity.[7] When structural inequities are brought more into balance, increasingly subtle effects gain prominence. Under these circumstances, the observed facial selectivities have been accounted for in terms of hyperconjugative,[8] electrostatic,[9] torsional,[10] and orbital interactions.[11−15] A rationale consistent with all of the experimental observations continues to be sought.

Our own interest in this area stems from two divergent directions. The Ohio State group has had a long-standing interest in the chemistry of spirotetrahydrofurans,[16] and ultimately became interested in the stereochemical issues surrounding the participation of cyclohexadienone **1a** in cycloadditions to appropriately reactive dienes.[17] Pursuit by the Hiroshima team of a total synthesis of scyphostatin necessitated that appreciation be gained of the π-facial selectivity capable of being exhibited by **2a**.[18] These preliminary considerations have since been

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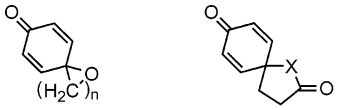
expanded to include spirooxetane **1b** and spirooxirane **1c** as well as the spirocyclic diketone **2b**. The discoveries made in the context of these investigations have been amalgamated in the present joint contribution.

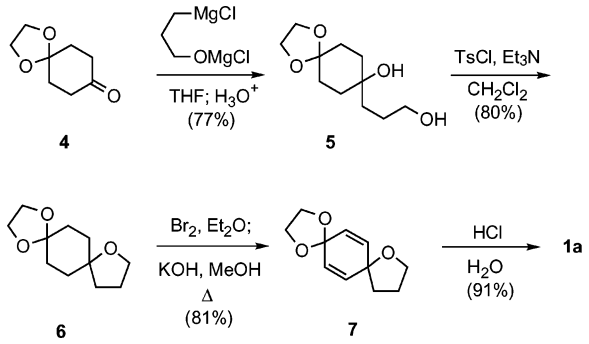


1a, n = 3
1b, n = 2
1c, n = 1

2a, X = O
2b, X = CH_2

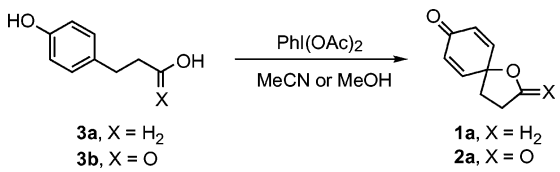
The series **1a**−**c** was probed in the expectation that alterations in the size of the heterocyclic ring would be accompanied by changes in the basicity of the ethereal oxygen center.[19] Would a ground-state parameter of this nature exercise any influence on kinetic selectivity? Do the steric changes that accompany spiro ring contraction facilitate attack from the same or opposite face? And what can be expected of differences in hyperconjugation? The chemical nuances separating **2a** from **2b** are more disparate. Are the prospects for recognizing an electrostatic control mechanism thereby enhanced? These cross-conjugated dienones appeared well suited for critical analysis of the source of stereocontrol in their Diels−Alder reactions.

Scheme 1



Results and Discussion

Synthesis. Substrates **1a** and **2a** were prepared by oxidative cyclization of 3-(4-hydroxyphenyl)propanol (**3a**) and its carboxylic acid derivative **3b** with iodobenzene diacetate.[20] The rather modest yield associated with the production of **1a** via this protocol prompted alternate advance on this dienone by way of the pathway given in Scheme 1. Addition of the Normant reagent to **4**



3a, X = H_2
3b, X = O

1a, X = H_2
2a, X = O

followed by monotosylation was met with spontaneous cyclization to give **6**.[21,22] Introduction of the pair of double bonds were achieved by 2-fold bromination-dehydrobromination.[23] Following arrival at **7**, the acetal functionality was hydrolyzed in dilute acid to unmask the keto group.

The preparation of **1b** was accomplished by irradiation of benzene solutions of *p*-benzoquinone with a 125 W medium-pressure mercury arc with concomitant bubbling of ethylene through the medium.[24] 1-Oxaspiro[2.5]octa-4,7-dien-6-one (**1c**) was formed by the oxidation of **8** with sodium bismuthate.[25] Diketone **2b** was conveniently available by several routes reported earlier.[26]

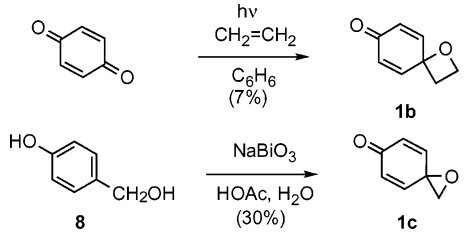


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Table 1. Stereoselectivities Determined for Diels−Alder Reactions Involving **1a**−**c** and **CP** or **SH**

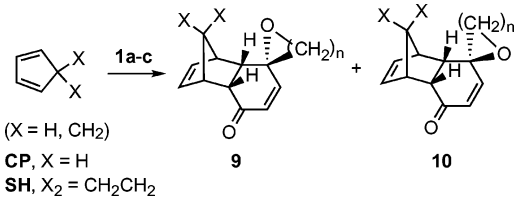
run no.	dienone	solvent	reaction conditions	**9**: **10**[a]	yield, %[b]
		A. cyclopentadiene (CP):			
1	**1a**	CH_2Cl_2	25 °C, 7 days	97:3	61
2	**1a**	CH_3CN	25 °C, 7 days	94:6	46
3	**1a**	CF_3CH_2OH	25 °C, 1 day	94:6	86
4	**1a**	CF_3CH_2OH	36 °C, 6 h	92:8	90
5	**1b**	CF_3CH_2OH	36 °C, 6 h	86:14	96
6	**1b**	CF_3CH_2OH	36 °C, 8 h	85:15	95
7	**1c**	CF_3CH_2OH	36 °C, 13 h	81:19	82
8	**1c**	CF_3CH_2OH	36 °C, 15 h	83:17	86
		B. spiro[2,4]hepta-4,6-diene (SH):			
9	**1a**	CF_3CH_2OH	55 °C, 15 h	77:23	86
10	**1b**	CF_3CH_2OH	55 °C, 18 h	67:33	83
11	**1b**	CF_3CH_2OH	55 °C, 21 h	64:36	84
12	**1c**	CF_3CH_2OH	55 °C, 11 h	65:35	67
13	**1c**	CF_3CH_2OH	55 °C, 17 h	66:34	59

[a] The ratios were determined by integration of the ^{1}H NMR spectra of unpurified field fragments. [b] Isolated yields after chromatographic purification.

Cycloaddition of Cyclopentadiene (CP) and Spiro[2.4]-hepta-4,6-diene (SH) to 1a−c. The first candidate reactions involved **CP** and its somewhat more sterically shielded homologue **SH**.[27] These studies, which were initially performed in the absence of Lewis acid catalysis to simplify mechanistic considerations, are summarized in Table 1.

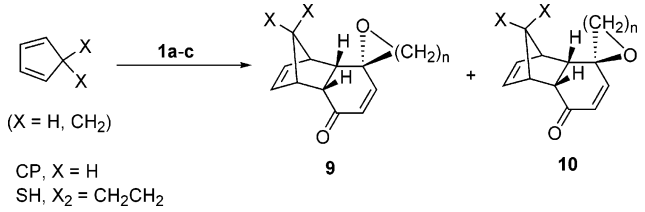
As for **CP**, *endo* adduct **9** and/or **10** can result in each example depending on the level and direction of π-facial selection that is operative. These reactions were found to proceed very slowly in CH_2Cl_2 and CH_3CN at room temperature or in toluene at 90 °C. For this reason, a switch was made to the more polar trifluoroethanol as solvent. As seen for runs 1−4, diastereoselectivity was not hardly eroded in this medium even as the temperature was increased to 36 °C.

Further use was made of the kinetic acceleration realized with trifluoroethanol in the Diels−Alder reactions involving **SH** as the diene. This less reactive 4π donor, like **CP**, gives rise to chromatographically separable mixtures of *endo* adducts **9** and **10**, with a very respectable kinetic preference for utilization of the π surface syn to the ethereal oxygen. An interesting point is that the formation of **9**, which dominates significantly under all circumstances (runs 1−8) involving reaction with **CP**, is met with a drop-off in its relative percentage when the slower reacting **SH** is involved.

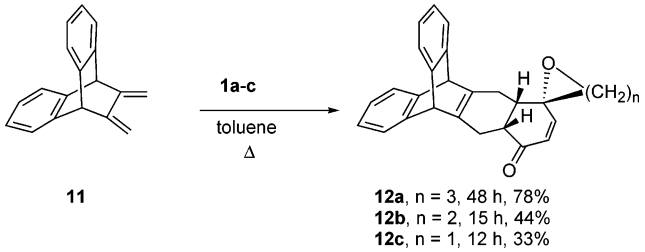


The relative configuration of adducts **9** and **10** was in all instances assigned on the bases of ^{1}H NMR NOE experiments (Supporting Information). These compounds serve as representative examples of the characteristic long-range ^{1}H/^{1}H interactions that are featured. The consistent adoption of *endo* transition states was further reflected in those coupling constants involving the bridgehead protons (J = 3.4−4.3 Hz).

Response of 1a−c to Other Dienes. Our interest in examining **11**[28] arises from its rigid conformational features, which lock the exocyclic double bonds into the reactive cisoid geometry. When **11** was heated with **1a**−**c** in refluxing toluene for several hours, a sole product was isolated in all three examples. Definition of these adducts as the result of exclusive syn capture as in **12** was validated by X-ray crystallographic analysis of **12a** and detailed NOESY studies involving **12b** and **12c**.[17]



The next candidate diene was the sterically more demanding diphenylisobenzofuran **13**.[29] Heating this co-reactant with **1a** and **1b** in benzene afforded uniquely the adducts **14a** and **14b**, respectively. The relative configuration of these products was assigned on the basis of NOESY data for **14a** and X-ray crystallographic data for **14b** (Supporting Information). When the same experiment was performed with **1c**, adducts **14c** and **15** were isolated in the proportion of 78:22. In this example, the minor constituent of the product mixture was subjected to three-dimensional crystallographic analysis.



Heating **16** in diglyme is recognized to allow for the in situ generation of isobenzofuran (**17**).[30] When this process was brought about in the presence of **1a**, three adducts **18**−**20** were formed. These proved to be amenable to chromatographic separation and independent characterization. The two less polar bridged ethers **18** and **19** were readily identified as the end products of endo addition, since both exhibited J values for interaction of the bridgehead and fused-ring protons of the

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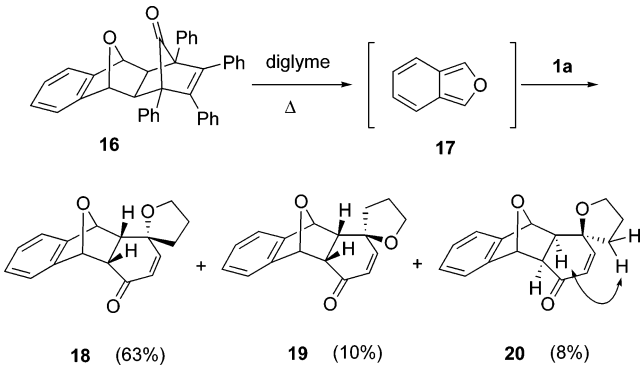
Table 2. Stereoselectivities Determined for Diels−Alder Reactions Involving **2a** and **2b**

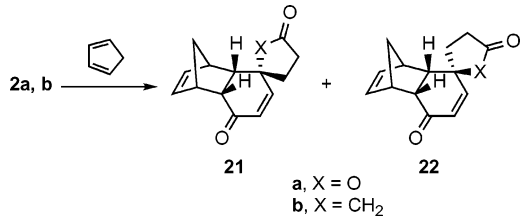
run no.	diene	solvent	reaction conditions	**21**: **22**[a]	yield, %[b]
		A. spirolactone 2a:			
14	**CP**	CH_2Cl_2	35 °C, 3 days	96:4	99
15	**CP**	CH_3CN	35 °C, 3 days	91:9	72
16	**CP**	CF_3CH_2OH	37 °C, 4 h	96:4	87
		B. spiroketone 2b:			
17	**CP**	CH_2Cl_2	25 °C, 7 days	66:34	7
18	**CP**	CH_3CN	25 °C, 7 days	61:39	7
19	**CP**	CF_3CH_2OH	25 °C, 7 days	60:40	82

[a] The ratios were determined by integration of the ^{1}H NMR spectra of unpurified field fragments. [b] Isolated yields after chromatographic purification.

proper magnitude (5.9, 4.8 Hz).[31] The coupling constant between the pair of fused-ring protons is 9.0 Hz. In contrast, no coupling between the fused-ring and bridgehead protons is seen in the ^{1}H NMR spectrum of **20**, thereby defining it as an *exo* adduct. The relative configuration of the spirotetrahydrofuran unit in **18** and **20** was established as before by X-ray and NOESY methods, respectively. [17]



π-Facial Selectivity Characteristics Exhibited by 2a and 2b. The spiro lactone system **2a** was found to exhibit appreciable diastereoselectivity upon reaction with **CP** (Table 2). The levels of selectivity favoring **21a** exceeded the 90% level irrespective of the reaction medium (runs 14−16). In contrast, the [4+2] cycloaddition of **CP** to spiro ketone **2b** occurs with the lowest level of discrimination (60:40) observed thus far in this investigation (runs 17−19). The facial selectivity involving **2b**



is not generated by the presence of an ethereal-type oxygen atom positioned homoconjugatively to the dienone part structure. Greater spatial separation between the reaction centers is also at play. Detailed NOE data were secured for **21b** and **22b**. These measurements compared remarkably closely with the long-range interactions observed for **21a** and **22a** (Supporting Information).

The highly crystalline nature of **21a** provided the opportunity to derive added structural proof by X-ray methods (Supporting Information). Therefore, there exists no doubt that **2a** and **2b**, like **1a**−**c**, possess an inherent structural feature that causes all of these spiro dienones to capture cyclopentadiene with a kinetic preference for that face syn to oxygen.

(31) Marchand, A. P. *Stereochemical Applications of NMR Studies in Rigid Bicyclic Systems*; Verlag Chimie International: Deerfield Beach, FL, 1982.

Table 3. Pseudo-First-Order Rate Constants (k_{obs}) and Second-Order Rate Constants (k_2) for the Production of **9a** in the Diels−Alder Reaction of **1a** with **CP**

solvent	T[a]	10^2[subst][b]	[CP][b]	$10^6 k_{obs}$[c]	$10^6 k_2$[d]
CH_2Cl_2	37.2	5.26	2.63	9.83	3.75
CH_2Cl_2	37.2	7.21	3.61	1.22×10	3.38
CH_2Cl_2	25	7.83	4.03	7.73	1.92
CH_2Cl_2	20	7.11	3.56	5.73	1.61
CH_3CN	37.2	6.71	3.36	2.38×10	7.08
CH_3CN	37.2	8.18	4.12	2.33×10	5.66
CH_3CN	30	7.93	4.02	1.03×10	2.57
CH_3CN	20	8.32	3.80	5.80	1.53
CF_3CH_2OH	11	5.65	1.13	2.11×10^2	1.86×10^2
CF_3CH_2OH	0	4.68	1.41	1.07×10^2	7.56×10
CF_3CH_2OH	−10	6.06	1.82	4.54×10	2.49×10
CF_3CH_2OH	−15	4.41	1.42	2.37×10	1.67×10

[a] °C. [b] bmol/L. [c] 1/s. [d] l/mol·s.

Table 4. Pseudo-First-Order Rate Constants (k_{obs}) and Second-Order Rate Constants (k_2) for the Production of **21a** in the Diels−Alder Reaction of **2a** with **CP**

solvent	T[a]	10^2[subst][b]	[CP][b]	$10^6 k_{obs}$[c]	$10^6 k_2$[d]
CH_2Cl_2	43	4.21	0.34	2.05×10	6.02×10
CH_2Cl_2	40	4.87	0.97	4.90×10	5.03×10
CH_2Cl_2	34.1	1.95	0.39	1.18×10	3.04×10
CH_2Cl_2	30.2	2.37	0.47	1.36×10	2.87×10
CH_2Cl_2	30.2	6.24	1.25	3.08×10	2.48×10
CH_2Cl_2	10	1.33	2.65	1.40×10	5.28
CH_3CN	43	4.19	0.32	7.26	2.24×10
CH_3CN	37.2	4.41	0.32	4.13	1.29×10
CH_3CN	19	14.6	2.92	1.00×10	3.43
CH_3CN	19	8.18	1.64	4.74	2.90
CF_3CH_2OH	52	0.45	0.03	4.46×10^2	1.48×10^4
CF_3CH_2OH	0	2.02	0.23	2.84×10^2	1.20×10^3
CF_3CH_2OH	−20	3.67	0.73	6.63×10	9.05×10
CF_3CH_2OH	−30	3.55	0.71	4.67×10	6.58×10

[a] °C. [b] bmol/L. [c] 1/s. [d] l/mol·s.

Kinetic Parameters for the Cycloaddition of 1a and 2a to Cyclopentadiene. To evaluate relative reactivities in different organic solvents (CH_2Cl_2, CH_3CN, CF_3CH_2OH), rate measurements of the Diels−Alder reactions of **1a** and **2a** with cyclopentadiene were carried out and kinetic parameters were calculated. Substrates **1a** and **2a** were treated with an excess of cyclopentadiene at a thermostated temperature and the appearance of major products **9a** and **21a**, respectively, was monitored by HPLC. The pseudo-first-order (k_{obs}) and second-order rate constants (k_2) for these processes are summarized in Tables 3 and 4.

The kinetic parameters in Table 5 were evaluated on the basis of Eyring plots (Figures S1 and S2: Supporting Information). The Gibbs free energies of activation ($\Delta G^{\ddagger}$) followed the order $CH_3CN \sim CH_2Cl_2 \gg CF_3CH_2OH$ for **1a** and $CH_3CN > CH_2Cl_2 \gg CF_3CH_2OH$ for **2a**, respectively. The activation free energies for **2a** were smaller than those associated with **1a** when compared in the same solvent. As anticipated from the bimolecularity of the Diels−Alder reaction, all of the activation entropies ($\Delta S^{\ddagger}$) were significantly negative. The ($\Delta S^{\ddagger}$) value for the reaction of **1a** in CH_2Cl_2 is particularly noteworthy. The smallest free energy of activation ($\Delta G^{\ddagger}$), which is observed for

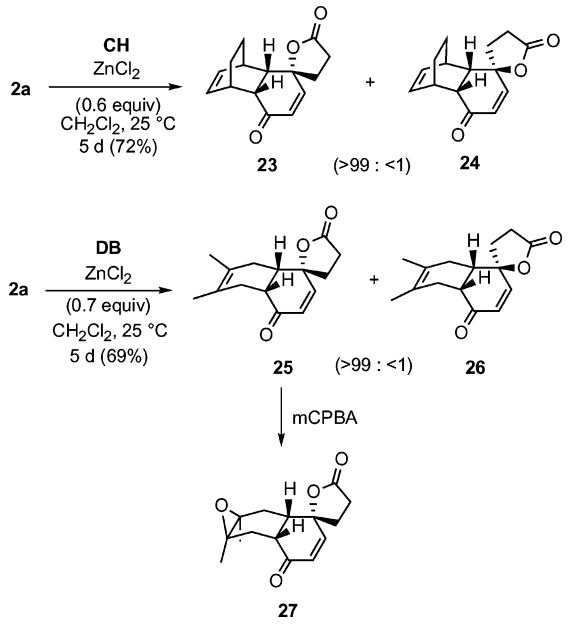
Table 5. Kinetic Parameters for the Production of **9a** and **21a** in the Diels−Alder Reactions of **1a** and **2a** with **CP**, Respectively

	1a → 9a			**2a → 21a**		
solvent	$\Delta G^{\ddagger}_{298}$[a]	$\Delta H^{\ddagger}$[a]	$\Delta S^{\ddagger}$[b]	$\Delta G^{\ddagger}_{298}$[a]	$\Delta H^{\ddagger}$[a]	$\Delta S^{\ddagger}$[b]
CH_2Cl_2	25.2 ± 1.52	7.98 ± 0.8	−57.8 ± 2.5	23.9 ± 1.1	12.5 ± 0.5	−38.5 ± 1.8
CH_3CN	25.2 ± 5.8	14.6 ± 2.9	−35.4 ± 9.6	24.7 ± 1.7	14.1 ± 0.9	−35.5 ± 2.9
CF_3CH_2OH	21.8 ± 1.2	13.3 ± 0.6	−28.6 ± 2.1	20.8 ± 2.8	10.3 ± 1.3	−35.0 ± 4.9

[a] kcal/mol. [b] e.u.

the reaction of **2a** in trifluoroethanol, may be attributed to hydrogen bonding at the transition state. In particular, the presence of a carbonyl group in the lactone ring of **2a** may enhance stabilization more effectively than that available to **1a** by hydrogen bonding. This effect would give rise to a small activation enthalpy ($\Delta H^{\ddagger}$).

Consequences of Lewis Acid Catalysis. Reaction of spiro lactone **2a** with **CP** in the presence of 0.7 equiv of anhydrous zinc chloride in CH_2Cl_2 at 25 °C for 2 days afforded exclusively the endo cycloadduct **21a** (>99%) in 96% yield. The sluggishness exhibited by 1,3-cyclohexadiene (**CH**) and 2,3-dimethylbutadiene (**DB**) toward spirolactone **2a** prompted us to probe the consequences, if any, of Lewis acid catalysis on these [4+2] cycloadditions. As expected, the co-addition of 0.6−0.7 equiv of anhydrous zinc chloride in CH_2Cl_2 led to the consumption of these dienes at room temperature, although at very different rates. For **CH**, the conversion to **23** and **24** was essentially complete after 5 days. For **DB**, a comparable level of completion required 5 days. In both examples, the overwhelmingly major diastereomer was that resulting from π-facial stereoselectivity syn to oxygen. This selectivity was opposite that of Liotta's cyclohexadienone 4-tertiary carbinol system in the presence of $SnCl_4$, which favored facial attack opposite to the oxygen atom.[6a] These workers rationalized the observed diastereoselectivity under Lewis acid conditions to steric hindrance introduced upon complexation of $SnCl_4$ to the hydroxyl group. In the present system, $ZnCl_2$ is a considerably weaker Lewis acid than $SnCl_4$ and furthermore is generally known to prefer coordination to a carbonyl moiety rather than to an ether group.



The tentative structural assignments to **23** and **25** were validated by means of NOE methods. Finally, the relative configuration of **23** was established by X-ray crystallographic analysis (Supporting Information). The stereochemistry of **25** was likewise secured by crystallographic examination of its epoxide **27**. The extent to which **2a** adopts the indicated reaction pathway is impressive not only on its own merits, but also because it reflects an enhancement of the stereoselectivity pattern that is operative in the absence of a Lewis acid promoter.

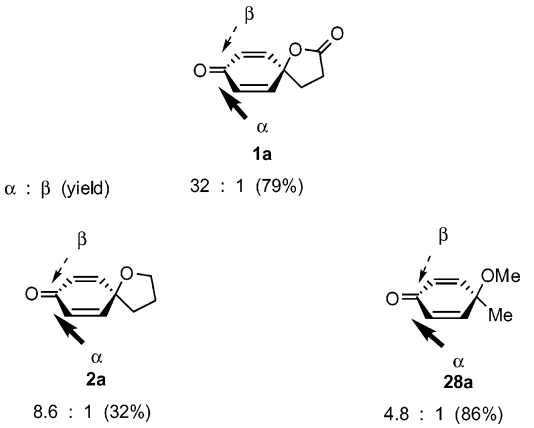
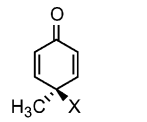


Figure 1. Stereoselectivities observed for the 1,2-addition of CH_3MgBr to **1a, 2a**, and **28a**. Note that α attack is favored for nucleophilic capture at C-1.

4-Substituted-4-methyl-2,5-cyclohexadienones as Dienophiles. The spatial orientation of the polar substituents in **28a-c**[20c,32−34] can be regarded to be closely similar to the situation in **1** and **2**. Methoxy derivative **28a** and ester **28c** are able to populate orientations of their polar substituent that are not available to the spiro analogues. This somewhat increased steric demand is recognized for **28a**



28a, X = OCH_3
28b, X = CN
28c, X = $COOCH_3$

to result in a deceleration of nucleophilic attack. The level of π-facial stereoselection observed for approach of the methyl Grignard reagent (note that π-attack on the opposite side with respect to the oxygen atom substituent is favored here) is also eroded as reflected in Figure 1. To what extent and in what direction will the release of those cyclic constrains embedded in spirocyclic cyclohexadienones impact on dienophilic response?

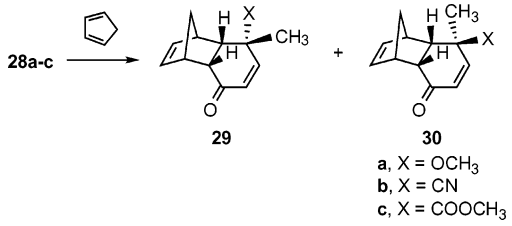
Table 6 summarizes the results of reacting **28a-c** with **CP** in CH_2Cl_2 as well as trifluoroethanol. As anticipated, all three dienophiles underwent cycloaddition in the more polar solvent after 2 days at room temperature. When CH_2Cl_2 was the reaction medium (25 °C), methoxy ketone **28a** failed to capture **CP** (run

Table 6. Stereoselectivities Determined for [4+2] Cycloaddition of **CP** to **28a−c**

run no.	solvent	reaction conditions	**29**: **30**[a]	yield, %[b]
		A. methoxy ketone 28a:		
20	CH_2Cl_2	25 °C, 3 days		0
21	CF_3CH_2OH	25 °C, 2 days	91:9	70
		B. cyano ketone 28b:		
22	CH_2Cl_2	25 °C, 3 days	97:3	61
23	CF_3CH_2OH	25 °C, 2 days	96:4	78
		C. keto ester 28c:		
24	CH_2Cl_2	25 °C, 3 days	100: 0	trace
25	CF_3CH_2OH	25 °C, 2 days	97:3	100

[a] The ratios were determined by integration of the ^{1}H NMR spectra of unpurified products. [b]Isolated yields after chromatographic purification.

20) and keto ester **28c** gave rise to only a trace of adduct **29c** (run 24).



The results derived from runs 21−25 reflect a pronounced π-facial bias favoring bonding from the surface syn to X. The relative configurations of **29** and **30** were readily deduced by NOE methods (Supporting Information). Although the Diels−Alder reactions were again accelerated in trifluoroethanol, little or no change in the proportion of **29** to **30** was seen. Dienone **28a** proved to be the least selective in its discriminating capability.

Theoretical Assessment of the π-Facial Stereoselectivity. Notwithstanding considerable variation in the substitution pattern, including that of the monocyclic systems **28a−c**, no switch away from the adoption of facial selectivity favoring predominant β attack was seen in any example. Therefore, predominant dienophile approach syn to the heteroatomic substituent constitutes a general reactivity trend for 4,4-disubstituted cyclohexadienones whether they be spirocyclic or monocyclic. This remarkable kinetic bias operates irrespective of whether an alkoxy, acyloxy, cyano, or carbomethoxy substituent resides at C-4. The downward progression in size from tetrahydrofuran to oxetane and finally to oxirane in the spiro oxygenated heterocycle causes no deviation in an otherwise consistent stereochemical outcome. The ineffectiveness of FMO theory as a tool for explaining this phenomenon is now widely accepted.[35] Kahn and Hehre have suggested more recently that electrostatic interactions likely play a major role in dictating the diasterofacial selectivity of Diels−Alder reactions.[9a]

Houk and co-workers have calculated the energies of all four possible transition states associated with [4+2] cycloadditions to 4,4-disubstituted cyclohexadienones at the PM3 level.[7b] The two exo transition state options were found as expected to be less stable than their endo counterparts. The most stable alternative involved endo addition syn to the heteroatom. This isomer, which features positioning of the oxygen atom in the interior of the developing adduct in a notably asynchronous manner offers positive electrostatic attraction rather than untoward repulsions. These authors concluded that the observed high levels of stereoselectivity arise from the lower steric demands of oxygen relative to a methylene group.

To investigate this matter further, MO calculations on spiro compounds **1**, **2**, and their related congeners **28** were performed at the HF/6−31 G* level.[36] The LUMO orbitals of dienophiles **1a−c**, **2a**,**b**, and **28a−c** are illustrated in Figure 2. The size of the lobes of the LUMOs at C3 (and C5) appear to be similar in size with respect to the plane of symmetry (cyclohexadienone ring) and thus cannot directly account for the high selectivity. However, there is another feature to take into consideration. A common feature of the LUMOs is that the orbitals of the σ bonds involving the C4 carbon are all out of phase in relation to the neighboring C3 (or C5) π lobe. Furthermore, the shape of the orbital is also important. The LUMO orbitals associated with C4−CH_2 or C4−CH_3 are more extended in the direction being attacked by the diene than that of the C−X. (X = O, CN, CO_2-CH_3). For dienophiles with high facial selectivity, the difference in size and shape between the two out-of-phase orbitals at C4 happens to be large with the larger of the two out-of-phase orbitals residing opposite to the face that is preferentially attacked. Thus, one explanation for the facial selectivity could be that attack occurs upon the face which has less undesirable secondary orbital interactions. For the series **1a−1c**, the size differences in the lobes at C4 do not vary significantly. However, the unfavorable C4 interaction appears to be alleviated as the size of the ring becomes smaller. Although the ineffectiveness of FMO theory as a tool for explaining this phenomenon is now widely accepted, the facial selectivity in these [4+2] cycloaddition can be explained in large part by considering the secondary orbital interaction of the FMO.[37]

The total electron densities of **1a−c**, **2a**, **2b**, and **28a−c** in their respective ground states were evaluated by HF/6-31G* calculations (Figure 3, Supporting Information). For **1a** and **2a**, the electron cloud over CH_2 of the spiro ring extends slightly more to the direction of the reaction site than that of the oxygen atom. Thus, the electron repulsion buildup between oxaspiro compounds **1a** and **2a** and π-electrons of the diene during the reaction may be a contributing factor to the π-facial selectivity in the Diels−Alder reaction as described by Houk et al.[10b] For **1b−c**, **2b,** and **28a−c**, extension of the electron cloud over both sides of the reaction site is universally comparable. The low reactivity of **1b−c**, **2b**, and **28a−c** can also be explained in terms of van der Waals repulsion.

Atomic distances between the proton at C10 of the attacking diene and the closest atom within the X or Y moiety in the transition state should be related to the van der Waals repulsion (Table S2, Supporting Information). The atomic distances in the transition states are shorter than the sum of van der Waals radii of the corresponding atoms, except for those of $\mathbf{TS_{1c-9c}}$, $\mathbf{TS_{1c-10c}}$, $\mathbf{TS_{28b-29b}}$, and $\mathbf{TS_{28b-30b}}$ (beyond the van der Waals

(32) (a) Schultz, A. G.; Macielag, M. *J. Org. Chem.* **1986**, *51*, 4983. (b) Schultz, A. G.; Lavieri, F. P.; Macielag, M.; Plummer, M. *J. Am. Chem. Soc.* **1987**, *109*, 3991. (c) Schultz, A. G.; Harrington, R. E.; Macielag, M.; Mehta, P. G.; Taveras, A. G. *J. Org. Chem.* **1987**, *52*, 5482.
(33) Marx, J. N.; Zuerker, J.; Hahn, Y.-S. P. *Tetrahedron Lett.* **1991**, *32*, 1921.
(34) Danishefsky, S.; Yan, C.-F.; Singh R. K.; Gammill, R. B.; McCurry, P. M.; Fritsch, N.; Clardy, J. *J. Am. Chem. Soc.* **1979**, *101*, 7001.
(35) For reviews, consult: (a) Anh, N. T. *Tetrahedron* **1973**, *29*, 3227. (b) Reference 15a.
(36) The calculations were performed with PC Spartan Pro, Wavefunction, Inc., Irvine, CA 92715.
(37) Huang, X. L.; Dannenberg, J. J.; Duran, M.; Bertrán, J. *J. Am. Chem. Soc.* **1993**, *115*, 4024.

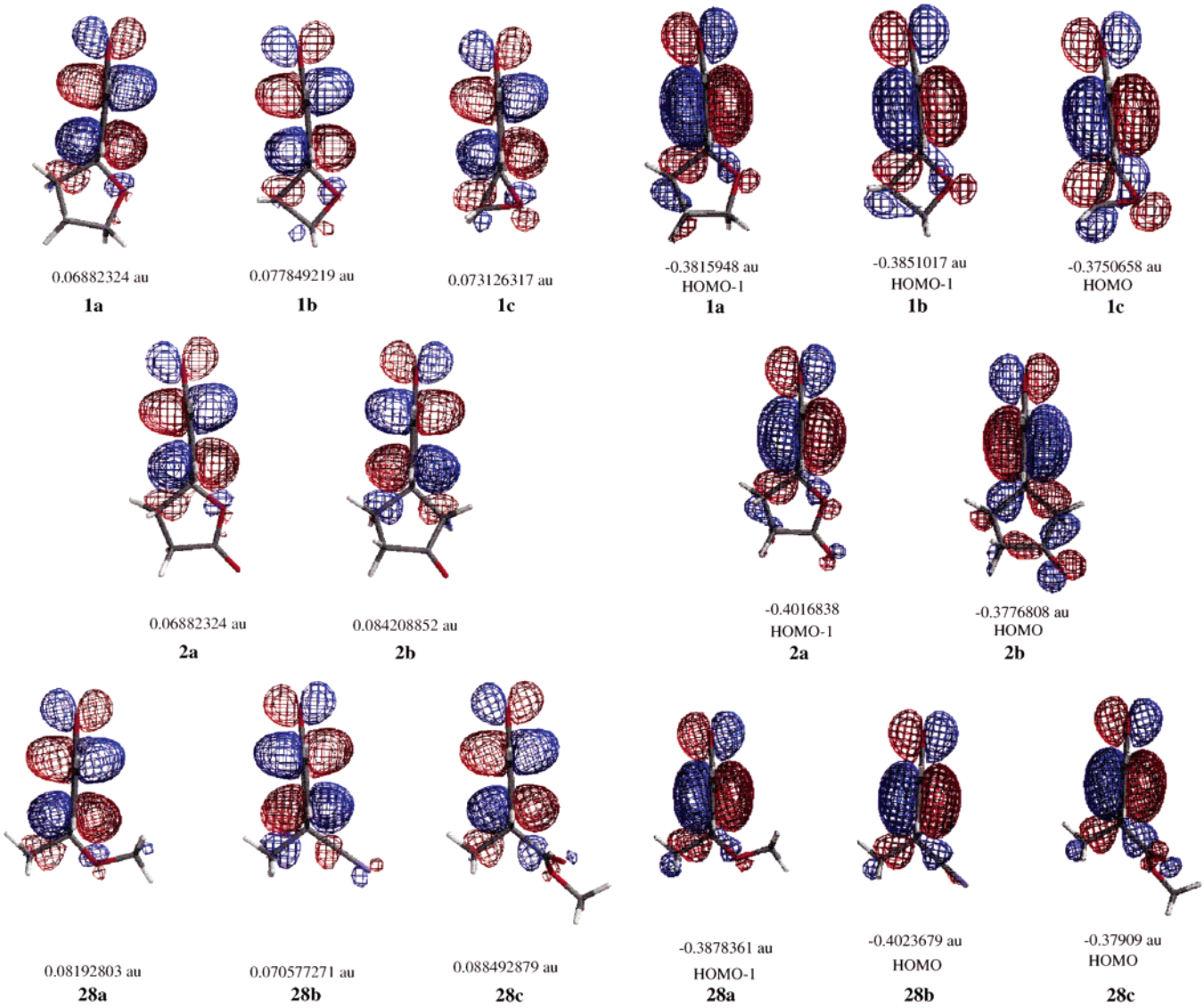


Figure 2. LUMO's and HOMO's of the dienophiles **1a**−**c, 2a, 2b**, and **28a**−**c** evaluated by HF/6-31G* calculations.

radial distance). In the transition states for the reaction of **2b** to give the adducts **21b** and **22b**; however, the distances are 2.30 Å for **21b** and 2.33 Å for **22b**, respectively, indicating their values to be essentially identical. Thus, the selectivity in the reactions (60/40 in CF_3CH_2OH) of **2b** that cannot be disregarded is better explained in terms of electronic effects rather than steric effects (electron-donating ability: $CH_2-CH_2 > CH_2-CO$). Although the 60/40 selectivity was very small, the electron-donating ability ($CH_2-CH_2 > CH_2-CO > CH_2-O$) at C4 position is qualitatively reflected in the selectivity. This explanation is not inconsistent with the Cieplak model (Figure 4).[38]

Thermodynamic parameters ($\Delta H°$ and ΔH^*_{calcd}) and dipole moment values (μ) for **1a**−**c**, **2a**,**b**, and **28a**−**c** were determined by ab initio calculations at the HF/6-31G* basis set level (Table 7). The calculated enthalpy values ($\Delta H°$) are consistent with the observed major adducts being thermodynamically more stable than the minor counterparts. The activation enthalpies (ΔH^*_{calcd}) were calculated on the basis of the corresponding heats of formation between the transition state and the reactant. These results show the major adducts **9a**−**c**, **21a**,**b**, **23**, **25**, and **29a**−**c** to be favored both kinetically and thermodynamically. The differences ($\delta\Delta H_{calcd}$) in the activation enthalpies between the major and minor reactions for **1a**, **1b**, **21a**, and **29a-c** are more than 4 kcal/mol, while those for **1c** and **21b** are 2.76 and 0.60 kcal/mol, respectively. The calculated sense of the Diels−Alder reactions is clearly consistent with that of the observed reactions, although the degree of difference itself ($\delta\Delta H_{calcd}$) varies to some extent.

Wipf et al. pointed out that the major product in the 1,2-nucleophilic addition of **1a** and **2a** with Grignard reagents may arise from favorable cancellations of dipole moment within the reactants as shown in Figure 1.[9c−e] Although the dipole moments of major adducts **9a**−**c**, **21a,b**, **23**, and **25** and their corresponding TS structures are smaller than those of the minor congeners **10a**−**c**, **22a**,**b**, **24**, and **26** and the transition state structures leading to the corresponding products (Table 7, entries 1−14), the dipole moments of the transition states in the Diels−Alder reactions of **28a**−**28c** with cyclopentadiene are not necessarily consistent with the observed high facial selectivities. Thus, rationalization based upon dipole moment does not appear

(38) (a) Cieplak, A. S. *J. Am. Chem. Soc.* **1981**, *103*, 4540. (b) Cieplak, A. S.; Tait, B. D.; Johnson, C. R. *J. Am. Chem. Soc.* **1989**, *111*, 8447.

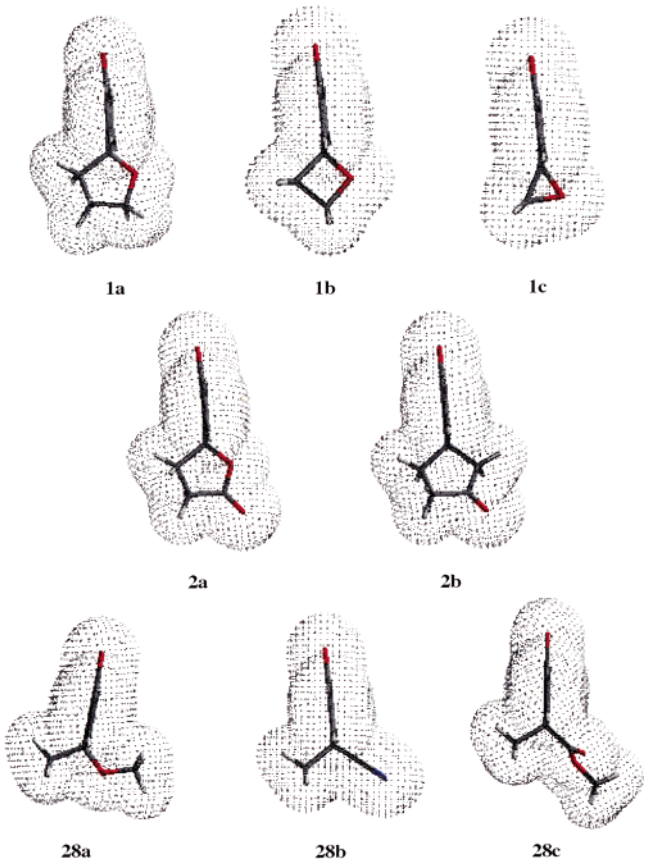


Figure 3. Total electron density in the ground state of dienophile (**1a**−**c**, **2a**, **2b**, and **28a**−**c** at the 6−31G* level.

Table 7. HF/6-31G* Calculations for the Diels−Alder Reaction of **1a**−**c**, **2a**−**c**, and **28a**−**c**

substrate				transition state			product		
entry		μ^a	diene		$\Delta H^{\ddagger}_{calcd}$ [b]	μ^a	product	$\Delta H^{\circ b}$	μ^a
1	**1a**	5.45	CP	$\mathbf{TS_{1a-9a}}$	39.53	4.77	**9a**	−13.29	4.53
2				$\mathbf{TS_{1a-10a}}$	43.53	5.90	**10a**	−10.69	5.25
3	**1b**	4.76	CP	$\mathbf{TS_{1b-9b}}$	37.89	4.03	**9b**	−13.49	3.86
4				$\mathbf{TS_{1b-10b}}$	41.86	5.83	**10b**	−11.83	3.75
5	**1c**	3.72	CP	$\mathbf{TS_{1c-9c}}$	38.33	3.10	**9c**	−13.81	3.08
6				$\mathbf{TS_{1c-10c}}$	41.09	5.14	**10c**	−13.31	2.65
7	**2a**	4.17	CP	$\mathbf{TS_{2a-21a}}$	37.75	1.51	**21a**	−14.51	2.45
8				$\mathbf{TS_{2a-22a}}$	42.05	7.37	**22a**	−12.05	6.09
9	**2a**	CH		$\mathbf{TS_{2a-23}}$	45.55	1.66	**23**	−20.00	1.89
10				$\mathbf{TS_{2a-24}}$	50.10	7.34	**24**	−18.00	6.50
11	**2a**	DB		$\mathbf{TS_{2a-25}}$	45.56	1.74	**25**	−37.42	3.53
12				$\mathbf{TS_{2a-26}}$	50.11	7.32	**26**	−36.65	4.92
13	**2b**	3.29	CP	$\mathbf{TS_{2b-21b}}$	44.19	1.62	**21b**	−8.99	1.41
14				$\mathbf{TS_{2b-22b}}$	44.79	5.11	**22b**	−8.76	4.00
15	**28a**	1.42	CP	$\mathbf{TS_{28a-29a}}$	43.91	4.66	**29a**	−8.73	4.17
16				$\mathbf{TS_{28a-30a}}$	47.45	4.55	**30a**	−8.06	4.03
17	**28b**	3.63	CP	$\mathbf{TS_{28b-29b}}$	39.79	1.42	**29b**	−12.53	1.84
18				$\mathbf{TS_{28b-30b}}$	43.59	6.58	**30b**	−10.56	5.20
19	**28c**	5.25	CP	$\mathbf{TS_{28c-29c}}$	42.44	4.32	**29c**	−9.61	3.37
20				$\mathbf{TS_{28c-30c}}$	46.35	3.99	**30c**	−9.42	2.06

[a] dipole moment: D. [b] calculated from heat of formation: kcal/mol.

sufficient because the Diels−Alder reactions are not as polar as the nucleophilic reactions.

Figure 5 illustrates the molecular structures of the Diels−Alder transition states involving dienophiles **1a**−**c**, **2a,b**, and **28a**−**c** as evaluated by HF/6-31G* calculations. All of the structures show capability for hyperconjugative interaction between the newly forming C−C bond (σ^*-orbital) (C5−C10) at C10 and the C4−X bond (minor products) or the C4−Y bond

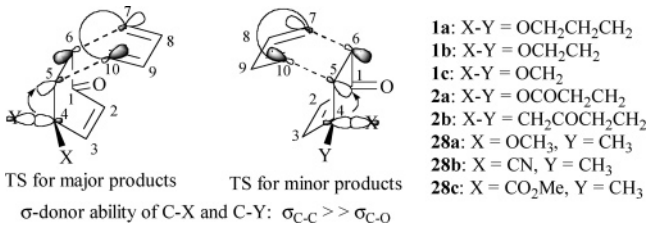


Figure 4. Cieplak model for the Diels-Alder reaction.

(major products) at an antiperiplanar position. Selected dihedral angels (∠X−C4−C5−C10 and ∠Y−C4−C5−C10) involving atoms in anti and syn relationships were compared (Table S3, Supporting Information). The angles for anti-positioned atoms reside in the border region between anti-periplanar and anti-clinal while those for syn-positioned atoms are between syn-periplanar and syn-clinal. In each example, the dihedral angle of the minor transition state arrived at by α-attack is larger than that by β-attack.

The anti dihedral angles of the transition states for the major Diels−Alder products of **1b** and **1c** (136.9° for **9b** and 111.3° for **9c**, respectively) are smaller than those (142.1−151.2°) of the other systems (**1a, 2a, 28a**, **28b**, and **28c**). Likewise, the syn-periplanar dihedral angle of **1c** (44.1° for **9c**) is larger than that (28.1−38.2°) of the other systems (**1a, 1b, 2a, 28a**, **28b**, and **28c**). Since the most favorable dihedral angle for hyperconjugation is 180°, this structural feature may be one of the factors underlying the somewhat lower stereoselectivity (86/16−81/19) of **1b** and **1c** relative to that (92/8−96/4) of the other systems.[39] On the other hand, the dihedral angles of **29a,b** (150.6° and 148.6° for the major product and 153.3° and 153.0° for the minor product, respectively) are similar to each other. In the **29a**−**c** subset, the electronic factor may perhaps be more effective in stereoselectivity control relative to the steric factor (anti-periplanarity).

Selected bond lengths (or distances) around the reaction site (C5−C10, C4−X, and C4−Y) in the transition states are summarized in Figure 5 (Table S4, Supporting Information). A comparison of these bond lengths reveals that the anti-bond lengths for both major (C4−Y) and minor (C4−X) products are 0.01−0.02 Å longer than the corresponding *syn*-bonds lengths (C4−X and C4−Y, respectively), suggesting effective orbital interaction of these *anti*-C−C bonds with the newly forming C5−C10 bonds. The C5−C10 distances in the major products are 0.03−0.07 Å shorter than those of the minor products except for the case of $\mathbf{TS_{2b-21b}}$ and $\mathbf{TS_{2b-22b}}$ transition states where selectivity was low. The shortening of the newly forming bonds may partially contribute to the stabilization of the transition state for the major product relative to that of the minor product. From a stereoelectronic point of view, the shortening of the C5−C10 distance peculiar to the transition states for the major adducts may be attributed to the larger electron-donating ability of the C−C bond relative to the C−O bond ($\sigma_{C-C} > \sigma_{C-O}$).[39] On the other hand, from a structural point of view, the lengthening of the C5−C10 distance in the minor products compared with the major products by 0.03−0.07 Å may be attributed to the steric repulsion between the dienophile and the diene in the transition state. In the case of $\mathbf{TS_{2b-21b}}$ and $\mathbf{TS_{2b-22b}}$, the steric environments around the

(39) Li, H.; Silver, J. E.; Watson, W. H.; Kashyap, R. R.; le Noble, W. J. *J. Org. Chem.* **1991**, *56*, 5932.

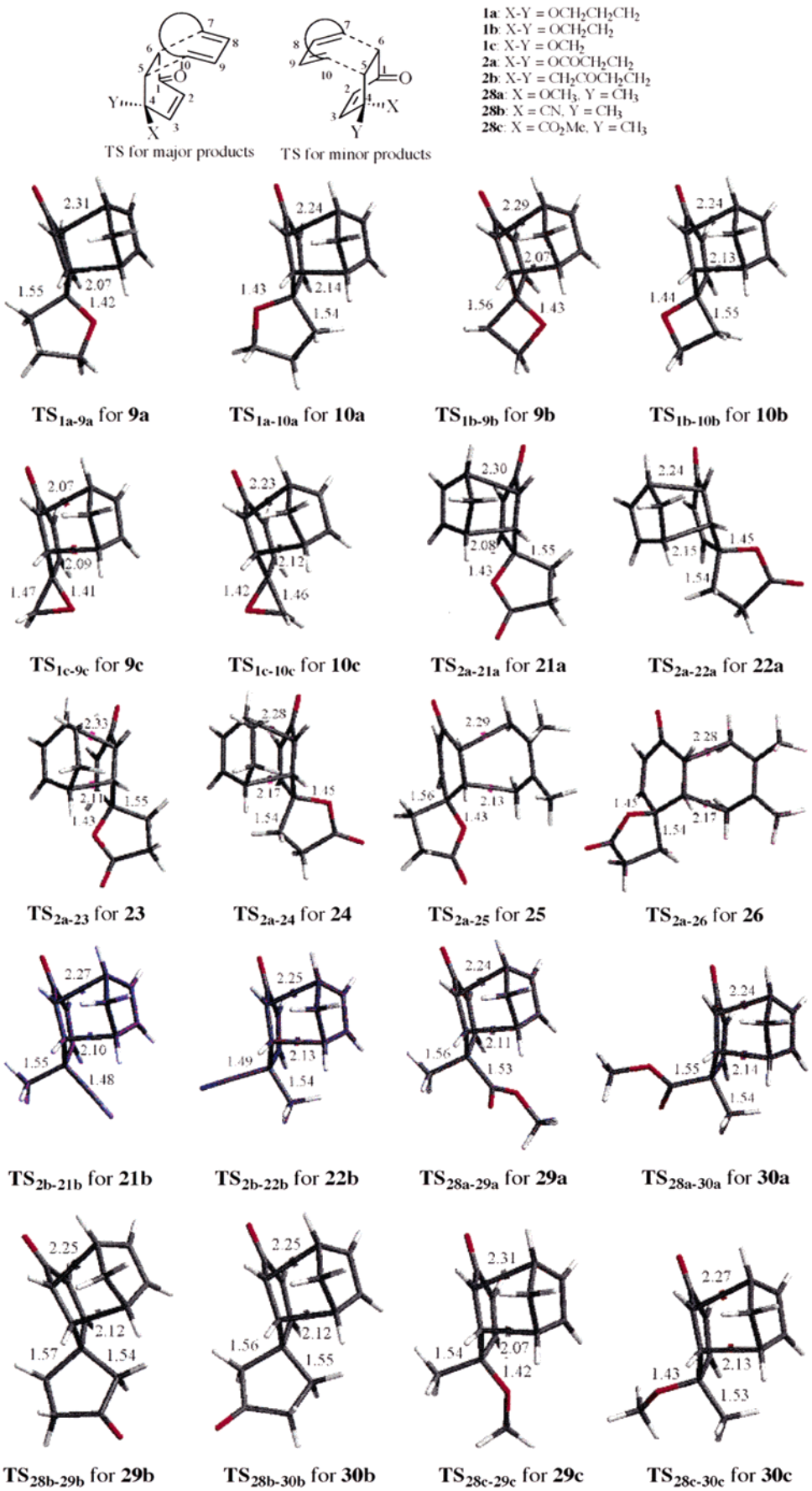


Figure 5. Molecular structures of the Diels-Alder transition state evaluated by HF/6-31G* calculations.

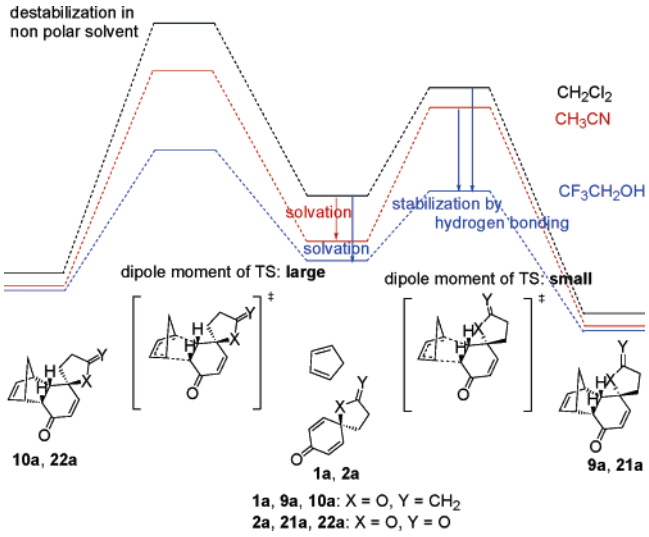


Figure 6. Solvent effects in Diels-Alder reaction of **1a**, and **2a** with **CP**.

reaction sites are virtually the same. Consequently, the observed stereoselectivity can be considered to result from stereoelectronic factors (difference between $-CH_2CO$ and $-CH_2CH_2$ at the *anti*-position) rather than steric repulsion.

According to the calculated dipole moments compiled in Table 7, solvent effects in the Diels−Alder reaction of **1a** and **2a** with cyclopentadiene can be explained in terms of the differences in solvation between the ground and transition states (the rate-determining and the product-determining steps) as illustrated in Figure 6. The dipole moments (μ) of the stable conformers of **1a** and **2a** in the ground state are 5.45 and 4.17 D, respectively, while those of the transition states ($\mathbf{TS_{1a-9a}}$ and $\mathbf{TS_{2a-21a}}$) leading to products **9a** and **21a** are 4.77 and 1.51 D, respectively. From the dipole moment of $\mathbf{TS_{2a-21a}}$, especially, it can be anticipated that cycloaddition will proceed less readily in a more polar solvent such as CH_3CN relative to CH_2Cl_2, since CH_3CN should stabilize the ground state of dienophile **2a** by solvation more than CH_2Cl_2. In fact, the rates of **2a** in CH_2Cl_2 are faster than those in polar CH_3CN. Furthermore, the higher stereoselectivity in CH_2Cl_2 compared with CH_3CN can also be rationalized in terms of transition state dipole moments. The transition state dipole moments are $\mu = 4.77$ D for $\mathbf{TS_{1a-9a}}$ (major product) and 5.91 D for $\mathbf{TS_{1a-10a}}$ (minor product), and $\mu = 1.51$ D for $\mathbf{TS_{2a-21a}}$ (major product) and 7.37 D for $\mathbf{TS_{2a-22a}}$ (minor product). The adduct arising from the less polar TS predominates and is expected to be favored more in the less polar CH_2Cl_2 relative to CH_3CN (Figure 6). On the other hand, the rate acceleration observed in reactions involving CF_3CH_2OH can be rationalized in terms of the protic solvent behaving as a Brønsted acid to activate the dienophile **1a** and **2a** or to stabilize the transition state rather than ground state. This explanation is not inconsistent with the activation parameters of the reactions performed in CF_3CH_2OH.

Conclusion. The diastereofacial selectivity operating in the Diels−Alder additions involving spirocyclic cross-conjugated cyclohexadienones with dienes of varying reactivity has been investigated. The study has included the ether series **1a**−**c** as well as the lactone/ketone pair **2a**/**2b**. In all cases, the preferred [4+2] cycloaddition pathway consisted of bonding from that π-surface syn to the oxygen atom. 4-Substituted-4-methyl-2,5-cyclohexadienones **28a**−**c** (monocyclic systems) were also examined and found to undergo bond formation preferentially from the face bearing the more electron-withdrawing of the two groups at the 4 position. The facial selectivity is understandable in terms of seconary orbital interactions between the HOMO of diene and the LUMO of dienophile and the orbital interactions (effective hyperconjugation) between the newly forming bond and the higher 4-*anti*-C−C4 σ-orbital (the more electron-donating bond) relative to the counterpart 4-*anti*-substituent−C4 σ-orbital in the transition state.

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Supporting Information Available: General experimental, spectroscopic characterization of all adducts, crystallographic data for **14b,c**, **21a**, **23**, and **27** (including Table S1), Figures S1 and S2, as well as relevant NOE of **9a**, **10a**, **21a,b**, **22a,b**, **23**, **29a,b**, and **30a,b**, and last Tables S2, S3, and S4. This material is available free of charge via the Internet at http:pubs.acs.org.[40]

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(40) Crystallographic data for structures in this paper have been deposited with the Cambridge Crystallographic Data Center; **21a**: CCDC-193077, **23**: CCDC-193078; **27**: CCDC-193079. For a discussion of the structures of **14b** and **14c**, consult Gallucci, J. C.; Tamura, Y.; Paquette, L. A. *Acta Cryst.* **2004**, *C60*, 656.