Nucleophilic Additions to 4,4-Disubstituted 2,5-Cyclohexadienones: Can Dipole Effects Control Facial Selectivity?

Peter Wipf* and Jae-Kyu Jung

Department of Chemistry, University of Pittsburgh, Pittsburgh, Pennsylvania 15260

Received August 19, 1998 (Revised Manuscript Received December 7, 1998)

Contents

I.	Introduction and Background	1469
II.	Preliminary Experimental Data for Nucleophilic Additions to Cyclohexadienones	1471
III.	1,2-Additions of Grignard and Organolithium Reagents to 4,4-Disubstituted 2,5-Cyclohexadienones	1473
IV.	Electrostatic vs Stereoelectronic Control	1474
V.	Quantitative Correlation between Facial Selectivity and Dipole Moment	1475
VI.	Solvent Effects and Design of a Long-Range Electrostatic Chiral Auxiliary	1476
VII.	Nucleophilic Additions to Naphthodiquinones	1477
VIII.	Conclusions	1479
IX.	Acknowledgments	1479
X.	References and Notes	1479

Peter Wipf received his Diploma in 1984 and his Ph.D. in 1987 from the University of Zürich under the direction of Prof. Heinz Heimgartner. His postdoctoral work as a Swiss NSF Postdoctoral Fellow with Prof. Robert E. Ireland led him to the University of Virginia in Charlottesville. In 1990, he joined the faculty at the University of Pittsburgh as an Assistant Professor and was promoted to Associate Professor in 1995 and Professor in 1997. His research interests focus on the total synthesis of natural products, heterocyclic and organometallic chemistry, and combinatorial chemistry. Among his recent awards are the Arthur C. Cope Scholar Award (1998), the Akron Section ACS Award (1998), and a Chancellor's Distinguished Research Award (1997).

Jae-Kyu Jung was born in Incheon, South Korea, in 1963 and received his B.S. in Chemical Technology in 1986 and his M.S. in 1988 from Seoul National University. From 1988 to 1994, he held a position at the Hanwha Research and Engineering Center in Taejon, Korea. Jae-Kyu joined the Wipf group in 1994 and has worked on methodology and natural products synthesis. He recently accomplished the total syntheses of palmarumycin CP_1, deoxypreussomerin A, and diepoxin σ. He will join Professor K. C. Nicolaou's group in the Scripps Research Institute as a postdoctoral fellow this summer.

I. Introduction and Background

> "It is a capital mistake to theorise before one has data. Insensibly one begins to twist facts to suit theories, instead of theories to suit facts." (Sherlock Holmes, *A Scandal in Bohemia*)[1]

The desymmetrization of the two faces of a planar carbonyl group[2] has emerged as one of the most important paradigms in the field of stereoselective synthesis since Cram[3] proposed a model to predict the facial selectivity of nucleophilic addition to α-chiral aldehydes and ketones. The Cram model correctly predicts the major diastereomer of most asymmetric addition reactions, with the notable exception of Grignard additions to α-chloro ketones. Cornforth proposed a modification where the halogen plays the role of the large substituent, so that the C═O and C−Cl dipoles are opposed.[4] The predictive value of Cram's rule notwithstanding, the rationale for the specific rotamer selection was speculative, and as spectroscopic methods developed, the validity of the ground-state conformation was increasingly questioned.

In 1968, Felkin noted that the Cram as well as the Karabatsos[5] models failed to account for the outcome of nucleophilic additions to cyclohexanones, and do not explain the effect of the R substituent on the selectivity.[6] In Felkin's original proposal, the incoming nucleophile attacked the carbonyl from a direction antiperiplanar to the large substituent (Figure 1). This model had major weaknesses, e.g., it assumed that intramolecular interactions in the substrate were responsible for the selectivity of a bimo-

10.1021/cr9803838 CCC: $35.00
Published on Web 03/23/1999

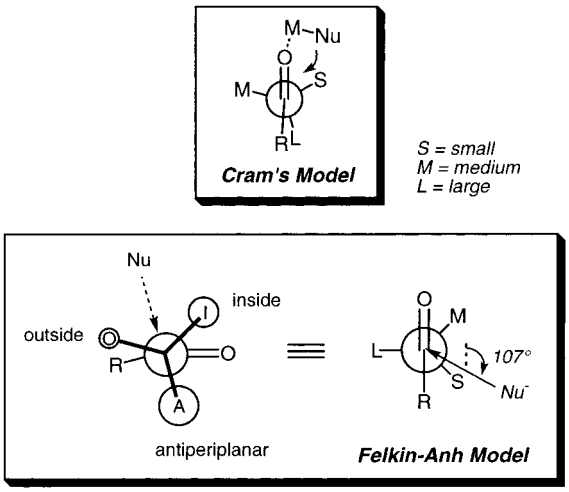


Figure 1.

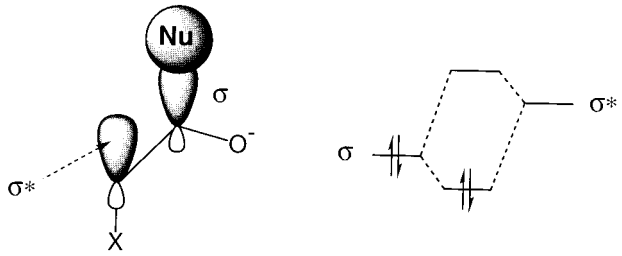
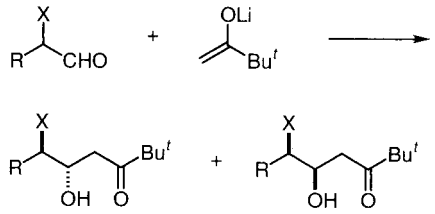


Figure 2.

lecular reaction (most distances are identical in both transition states); it was also hard to accept that R = H is more sterically demanding than oxygen as would be required for aldehydes. In 1977, Anh used ab initio methods to evaluate the energies for all postulated transition-state structures.[7] This clearly showed that Felkin's transition states were the lowest energy conformers for attack on either face of the ketone carbonyl C, including metal ion coordinated carbonyl groups. Anh and Eisenstein found that the energy difference between the two Felkin transition states was amplified when the angle of nucleophilic attack was adjusted to 105°.[8] Thus, the Felkin model was revised to include the Bürgi–Dunitz trajectory.[9] This work established the first sound theoretical basis for the selection of transition states in nucleophilic carbonyl additions.

Anh and Eisenstein also addressed the issue which substituent would assume the role of the large group anti to the incoming nucleophile.[8] An important aspect raised in Anh's study was the stabilization of the π^* orbital of the carbonyl group (LUMO) by overlapping with the σ^* antibonding orbital of the antiperiplanar α-substituent (L), as well as the stabilizing effect due to the σ–σ^* interaction between the newly forming C–Nu bond and the antiperiplanar C–L bond. A simple rule was offered: the substituents should be ordered according to the energies of the antibonding σ^* orbitals. The preferred anti substituent would be the one having the lowest lying σ^* orbital (Figure 2). This rule also explained the α-chloro ketone anomaly, since the σ^* of the carbon–chlorine bond is lower that a carbon–carbon bond.



% anti product

X	R = Me	Et	*i*-Pr	*t*-Bu	Ph
OMe	58%	76%	92%	93%	83%
Ph	78%	86%	70%	37%	-

Figure 3.

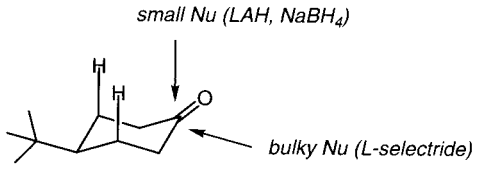


Figure 4.

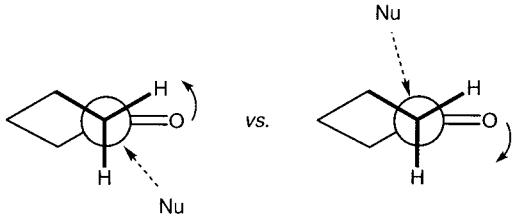


Figure 5.

Despite the substantial support[2,10] for the Felkin–Anh model, many alternative theoretical and computational models have been proposed. In 1987, Heathcock tested the Anh–Eisenstein σ^* hypothesis and concluded that it is only partially correct.[11] According to this hypothesis, one would expect a gradual increase in the *anti*-selectivity for the reaction shown in Figure 3 as the bulk of the remaining substituent R increases. However, this is clearly not the case; in fact, the syn-isomer is favored for the attack of the lithium enolate of *tert*-butyl methyl ketone to 2-*tert*-butylphenylacetaldehyde. The authors concluded that both steric and electronic effects determine the favored transition state in these nucleophilic additions.

In the more specialized facial selectivity of nucleophilic additions to cyclohexanones, experimental evidence clearly favored an axial attack for small nucleophiles and an equatorial addition of bulky groups (Figure 4).[12]

However, it was not clear whether stereoelectronic or purely steric factors determined axial versus equatorial facial selectivity. According to Felkin's torsional strain model, an equatorial attack leads to greater torsional strain in the transition state ($TS^{\ddagger}$) and is therefore intrinsically disfavored (Figure 5). This analysis was later supported by computational studies.[13]

In 1981, Cieplak attempted to use transition-state hyperconjugation to explain the facial selectivity of additions to cyclohexanone on the grounds of stereo-

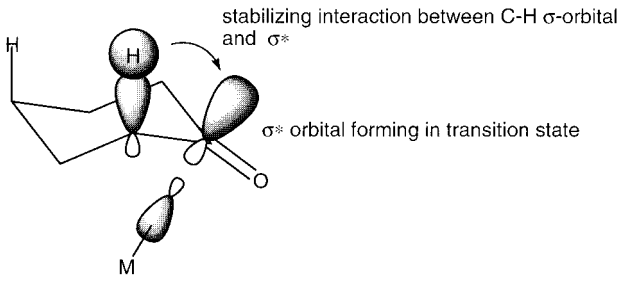


Figure 6.

electronic effects.[14] Accordingly, upon approach of a carbanion or hydride to the carbonyl carbon, the σ^* orbital that forms in the transition state is stabilized by overlap with the filled C−H σ orbital at the α-carbon (Figure 6). An equatorial attack is less stabilized since, according to Cieplak, the analogous σ^*/σ interaction for the β-C−C bond is less energetically favorable. This hyperconjugation of electron-deficient transition states explains[15] many experimental results that are more difficult to rationalize by other theories.

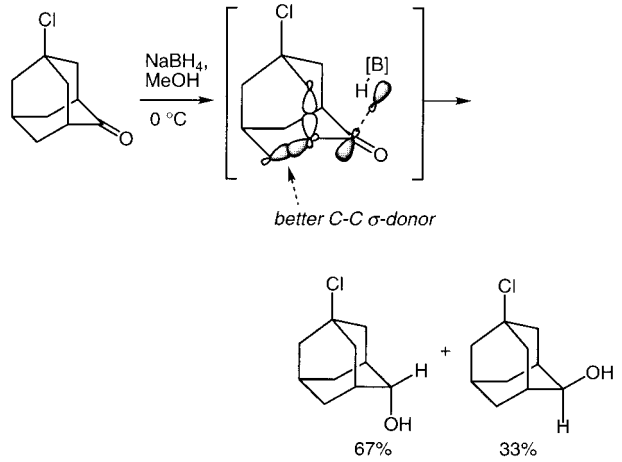


Figure 7.

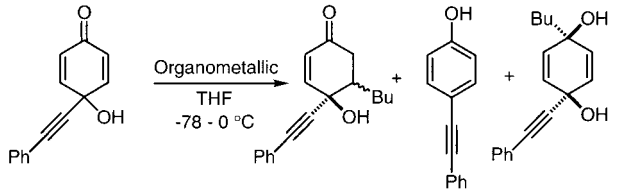
Some of the disagreements regarding Cieplak's interpretation are based on the relative electron-donor capacity of C−H bonds compared to C−C bonds.[2a] Some quantum chemical calculations do not agree with the Cieplak interpretation.[16,24] Nonetheless, his model succeeds in rationalizing a wealth of adamantanone addition chemistry, as demonstrated by le Noble's group. Addition of hydride to 4-chloroadamantanone, for example, provides a 2:1 ratio of axial versus equatorial alcohols (Figure 7).[15a] This experimental result was explained by the better σ donor effect of the C−C bond that is not in direct overlap with the electron-withdrawing chlorine substituent in the 4-position of the ketone.

The development of theoretical models for the analysis of the π-facial stereoselectivity in carbonyl additions is still one of the most active areas of physical organic chemistry. In many practical cases, the Cieplak hypothesis provides predictions for stereoselectivity that are just the reverse of the Anh−Eisenstein model, even though the attempt was made to unify the two concepts.[2b] Gung and Francis argued that an intramolecular 1,4-conjugate addition reaction which proceeds through an early TS should follow Anh's model while a reaction occurring through a late TS should follow Cieplak's model.[17] In an alternative approach, the importance of unsymmetrical extensions of π and π^* orbitals were pointed out by several groups.[18] Furthermore high-level ab initio calculations by Frenking have recently validated the latter concept for cyclohexanones,[19] whereas Dannenberg[20] and Tomoda[21] proposed PPFMO (polarized π frontier orbitals) and EFOE (exterior frontier orbital extension), respectively, as new methods for predicting and rationalizing diastereofacial selectivity. In the meantime, Shi and Boyd reported that there is no significant difference in the extent of charge depletion on the two sides of the carbonyl plane of cyclohexanone derivatives based on the AIM (atoms in molecules) theory.[22] They argued that instead of desymmetrization of the carbonyl orbital, electrostatic field differences between the two sides of the carbonyl plane affect the stereoselectivity. This electrostatic model was also emphasized by Paddon-Row[23] and Houk[24] for hydride additions to α-fluoroacetaldehyde, 4-substituted trans-decalones, and 3-substituted cyclohexanones.[25] Even though sometimes electrostatic effects are clearly eclipsed by other structural properties,[26] in many cases they appear to be one of the main control factors for the facial selection of planar carbonyl groups.[27] As the possibilities of computational models increase, calculations using semiempirical or ab initio algorithms become more important in reaching the elusive goal of a general prediction of facial selectivities in carbonyl additions.[28] To clarify the origin of facial selectivities in carbonyl additions, a number of sterically unbiased model compounds[15a−e,29] were designed and tested experimentally or theoretically in nucleophilic additions. In our work,[30,31] we have investigated 1,2-additions to 4,4-disubstituted cyclohexadienones, which are sterically unbiased probes ideally suited for the critical analysis of the various theoretical models for stereoelectronic control in carbonyl addition.[32] This review presents the data of our experimental studies that include variation of reaction parameters such as solvents, nucleophiles, and substrate structures. We have also discussed several current theoretical models for explanation of the observed selectivities. Electrostatic effects have thus far provided the best agreement with the experimental data.

II. Preliminary Experimental Data for Nucleophilic Additions to Cyclohexadienones

One of the first diastereoselective nucleophilic additions to sterically unbiased 4,4-disubstituted 2,5-cyclohexadienone was achieved by Swiss et al. in 1992.[33a] On the basis of prior results[33b,c] demonstrating that syn-additions of Grignard reagents to a variety of quinol alkoxides can be accomplished efficiently with complete diastereofacial control, they reasoned that it might be possible to achieve the complementary anti mode of addition by employing carbanions with coordinatively saturated counterions. Since complexation to the oxyanion is precluded under these circumstances, Coulombic repulsions

Table 1. Dibutylcuprate Additions to Dienone 1



Entry	Organometallic (equiv.)	Additive (equiv.)	Yield (%)		
			2α/2β (*anti*/*syn*)	3	4α
1	Bu_2CuLi (2)	-	22 (95:5)	27	20
2	Bu_2CuLi (2)	$BF_3{\bullet}OEt_2$ (1)	21 (>95:5)	36	-
3	$Li_2(Bu)_2CuCN$ (1.5)	-	85 (93:7)	-	-
4	$Li_2(Bu)_2CuCN$ (1.5)	$BF_3{\bullet}OEt_2$ (1)	61 (95:5)	-	-

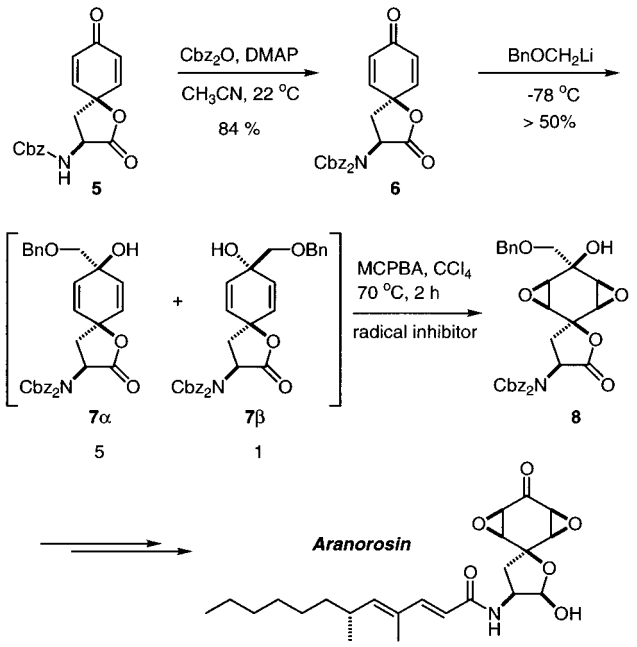
between the oxyanion and the approaching nucleophile should disfavor syn attack and thereby allow for the formation of the desired anti product. In an attempt to evaluate the legitimacy of this concept, they sought a substrate with minimal steric differences around the π faces of the enone β carbon, thereby allowing them to assess accurately the magnitude of the repulsive Coulombic interactions. Alkynyl quinol **1** was the substrate of choice for this study (Table 1).

In the case of simple homocuprate additions to **1** (either with or without diethyl ether−boron trifluoride complex), anti-selectivity was observed as expected, but in low chemical yields. The use of more basic cyanocuprates significantly improved the chemical efficiency of the addition without compromising the anti-selectivity. This observed facial selectivity might be originating from electrostatic interactions between nucleophile and substrate **1**. However, an Anh−Eisenstein-type hyperconjugation also predicts anti-preference for the 1,4-addition reactions. Accordingly, the major control factor is not clearly defined at this stage. Even though the 1,2-addition product **4**α was not explicitly discussed (entry 1 of Table 1), this isomer might also be formed stereoselectively by minimizing repulsive Coulombic interactions between the nucleophile and the hydroxyl group in **1**,[34] but again hyperconjugative effects cannot be excluded as an explanation.

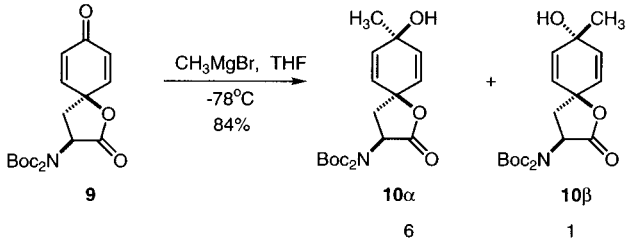
In the course of a total synthesis of the natural product aranorosin,[35] we observed an intriguing selectivity in the 1,2-addition of organometallic reagents to a 4,4-disubstituted cyclohexadienone intermediate. Treatment of spirolactone **6** with ((benzyloxy)methyl)lithium provided the bis-allylic alcohols **7**α and **7**β in a 5:1 ratio in >50% yield (Scheme 1). Similarly, addition of methyl Grignard reagent to **9** resulted in a 6:1 ratio of alcohols **10**α and **10**β (Scheme 2).

Molecular mechanics minimization of the geometry of dienones **6** and **9** revealed little if any steric bias for a face-selective 1,2-addition of organometallics.

Scheme 1



Scheme 2



The α face of the planar dienone appears to be sterically slightly more cumbersome due to the larger size of the methylene group and the carbamate substituent relative to the lactone oxygen (Figure 8), but the actual influence of these steric differences at the remote carbonyl group are questionable.

Recently, Winterfeldt et al. reported that the Diels−Alder reaction of conformationally rigid bicyclic and polycyclic prochiral cyclopentadienes such as **11** with spirolactone **12** and spiroether **13** provided a single endo-cycloadduct exclusively (Scheme 3).[36] Houk et al. argued that this high stereoselectivity arises from the lower steric demand of oxygen relative to methylene groups by PM3 and RHF/6-31G* calculation.[37]

Since obviously steric effects could not be used to rationalize the preferential α attack of nucleophiles to spirodienones **6** and **9**, we were considering electrostatic effects or stereoelectronic factors (e.g.,

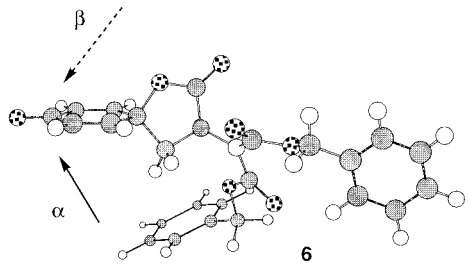
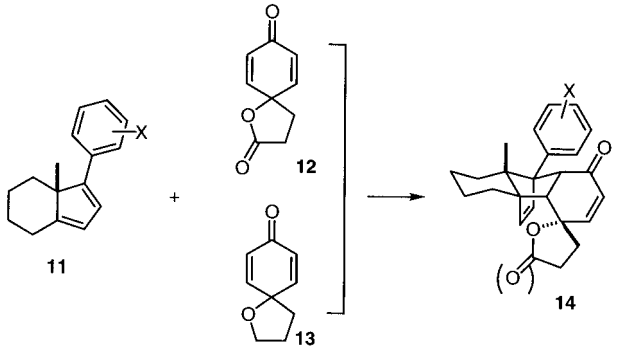


Figure 8.

Scheme 3



hyperconjugation, orbital distortion, etc.) for the control of the facial selectivity. First, however, it was necessary to investigate the general relevance of our experimental observations.

III. 1,2-Additions of Grignard and Organolithium Reagents to 4,4-Disubstituted 2,5-Cyclohexadienones

Due to the planar structure, the relative distance of the para-substituents of the dienone from the reaction center (approximately 4 Å), and the absence of charged, strongly haptophilic groups, steric and torsional effects, and ligand-assisted nucleophilic addition were likely to be of minor significance in the reactions of **6** and **9**. Therefore, 4,4-disubstituted dienones appeared ideally suited for the critical analysis of the various theoretical models for stereoelectronic control in carbonyl additions. The functionalization at the amino function of dienones **6** and **9** could possibly attenuate the impact of any electronic effects responsible for facial selectivity. Therefore, model compounds **15**−**22** were prepared as sterically unbiased substrates, in which the impact of any electronic effects on facial selectivity could be readily compared.[30]

The results of the nucleophilic addition of methylmagnesium bromide in THF at −78 °C to these model cyclodienones are summarized in Figure 9. An α facial selectivity as observed in the nucleophilic addition to aranorosin intermediates **6** and **9** was clearly a general trend for all 4,4-disubstituted cyclohexadienones. The observed α selectivities covered a surprisingly broad range from 4.8:1 for methyl ether **15** to 32:1 for spirolactone **21**. The low yields of 1,2-nucleophilic additions to dienones **17**, **18** and **20** were due to a competing *β*-selective 1,4-addition directed by the 4-oxygen substituents. As expected, a simple hydroxyl group provided the largest percentage of conjugate addition product (58%); however, tetrahydrofuran **17** and tetrahydropyran **18** were only slightly less effective 1,4-directing groups and provided 3-methylated product in 42 and 39% yield, respectively. Spirocyclic lactone **22** was considerably more base-sensitive than other substrates and a low yield of a 11:1 ratio of α versus *β* addition products was isolated in addition to intractable decomposed material. Interestingly, spirocyclic ether and esters provided uniformly higher facial selectivities than the corresponding monocyclic cyclohexadienone derivatives. This could be due to chelation phenomena leading to steric shielding of the *β* face. However, since both the silyl ether **16** and the hydroxy substrate **20** provided large α selectivities, and the competitive conjugate addition reaction was highly *β*-selective, chelation-induced steric shielding effects appear highly improbable for directing 1,2-carbonyl additions to the α face of these compounds.

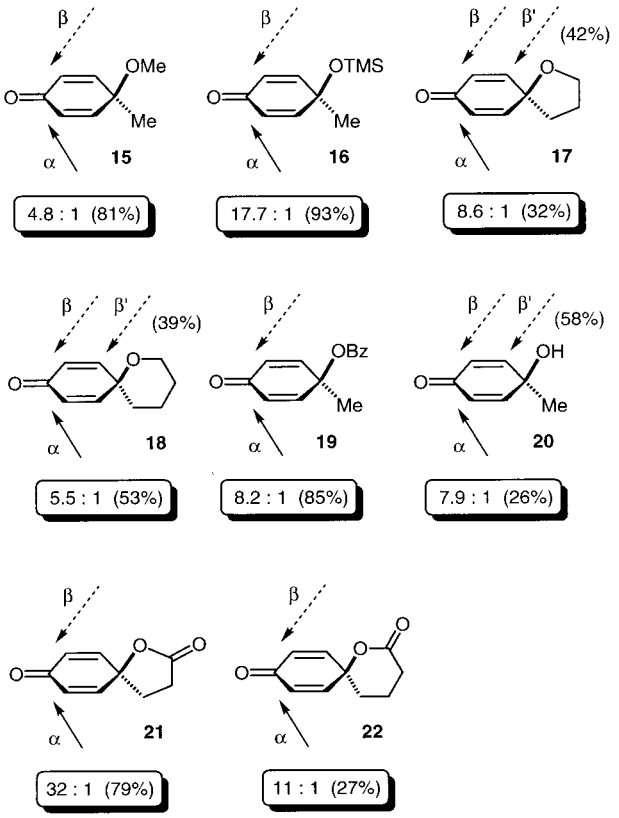


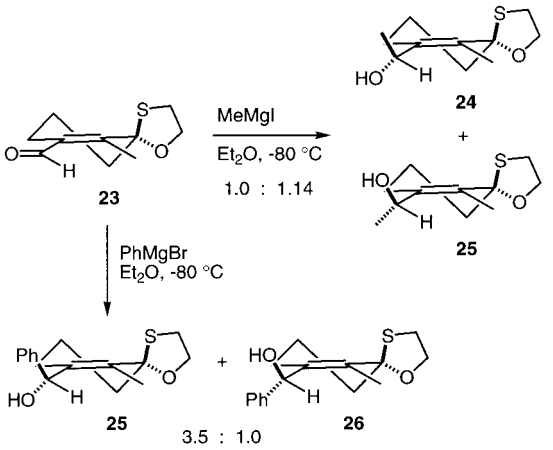
Figure 9.

Table 2. Nucleophilic Additions to Cyclohexadienone 15[38]

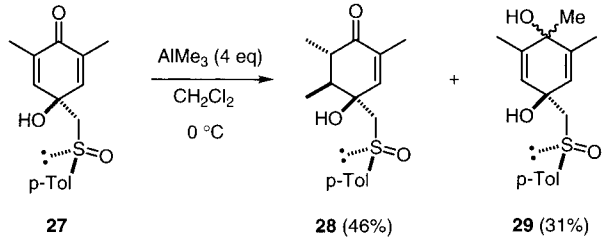
entry	nucleophile	yield (%)	α/*β* selectivity	solvent
1	MeMgBr	86	4.8:1	THF
2	$NaBH_4$ or $LiAlH_4$	100	1:1	MeOH or THF
3	HC≡CMgBr	70	1:1	THF
4	$H_9C_4C{\equiv}CLi$	26	1.1:1	THF
5	PhMgBr	83	3.6:1	THF
6	MeLi	87	2.1:1	THF
7	MeLi	77	3.3:1	Et_2O
8	$BnOCH_2Li$	84	3:1	THF

To expand the scope of our investigation of the facial selectivity in nucleophilic addition to these cyclohexadienones, we also studied the course of reaction with hydride reagents, organolithium compounds, and sp^2- as well as sp-hybridized C nucleophiles. In contrast to the addition of Grignard reagents, reduction of **15** with various hydride sources did not occur selectively and 1:1 mixtures of α and *β* addition products were isolated (Table 2, entry 2). Similarly, ethynylmagnesium bromide as well as hexynyllithium reacted without stereocontrol (Table 2, entries 3 and 4). Phenylmagnesium bromide, an example of an sp^2-hybridized carbon nucleophile, added to dienone **15** predominantly from the α face

Scheme 4



Scheme 5

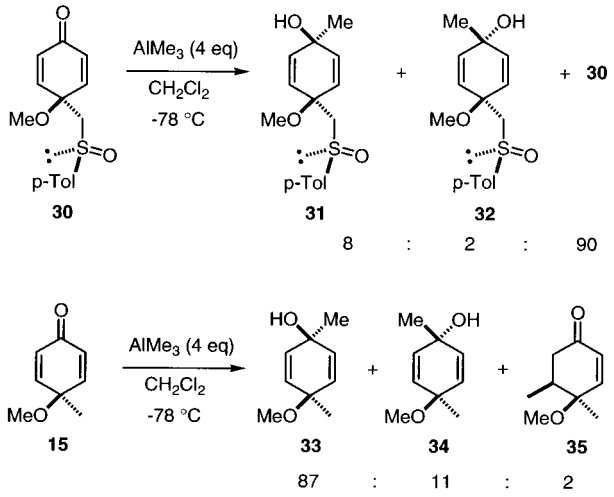


(Table 2, entry 5) and in lower selectivity than the methyl Grignard reagent. A slight drop in stereoselectivity versus this standard was also observed when alkyllithium reagents were employed (Table 2, entry 6). In contrast, a change in solvent from THF to the less polar Et_2O led to an improved α/β ratio with the organolithium reagent.

These results, especially the lack of selective addition observed with reducing agents and sp-hybridized carbon nucleophiles, clearly illustrate the high sensitivity of the stereoselectivity of the 1,2-addition process toward the solvent medium, as well as the electronic structure and, accordingly, the state of aggregation of the nucleophile. A related effect was recently reported by Yadav et al. for nucleophilic additions to 6-methyl-1-oxa-4-thiaspiro[4,5]dec-6-ene-7-carbaldehyde **23** (Scheme 4).[39] Whereas the 1,4-diastereoselectivity observed with sp^3-hybridized nucleophiles for this substrate was ca. 1.0:1.1 in favor of attack anti to sulfur, sp^2 and sp nucleophiles exhibited relatively much improved but reversed π selection under the same reaction conditions (1.4−3.5:1 in favor of attack syn to sulfur).

In another study related to our investigation of the facial selectivity of nucleophilic attack to cyclohexadienones, Carreño et al. observed a 1:1 mixture of 1,2-addition products **29** in addition to the conjugate addition product **28** when (*R*)-[*p*-tolylsulfinyl)methyl]-quinol (**27**) was treated with $AlMe_3$, (Scheme 5).[40] The authors proposed that this lack of diastereoselectivity was due to the electrophilic nature of the aluminum reagent compared to the nucleophilic nature of methyl Grignard or methyllithium organometallics. However, with methyl ether **30**, an 8:2 anti-selectivity was achieved at −78 °C, albeit in low yield, and substrate

Scheme 6



15 provided a large preference for the *anti*-addition product **33** (Scheme 6).[41]

IV. Electrostatic versus Stereoelectronic Control

For the nucleophilic additions to cyclohexadienones **6**, **9**, and **15**−**22**, all variations of reaction parameters only led to an erosion of α selectivity, and we were not able to observe a switch in the facial selectivity in favor of predominant β attack in any case.[30] Accordingly, attack anti to the 4-oxygen substituent represented indeed a general trend for 4,4-disubstituted cyclohexadienones. We were intrigued by the great variation of selectivity as a function of seemingly subtle changes at the 4-position, e.g., methyl ether **15** compared to spiroether **17**, or benzoate **19** compared to spirolactone **21** (Figure 9). Whereas the Anh−Eisenstein argumentation of transition state stabilization by $\sigma-\sigma^*$ interaction of the newly forming σ bond with the σ^* of the more electronegative substituent accounted for the general increase in selectivity from 4-alkoxy to 4-acyloxy dienones, this theory did not easily lend itself to an explanation of the significant differences between monocyclic and spirocyclic systems or the high selectivity of the 4-silyloxy dienone **16** and the oxyanion derived from **20**. Further complications in the use of the Anh−Eisenstein model arose by the vinylogous position of the polar substituents in 4,4-disubstituted dienones. In consideration of the phase inversion in the LUMO of the parent dienone, it could be argued that a nucleophile was expected to add from the β-face, syn to the C−O bond, to take advantage of $\sigma-\sigma^*$ stabilization (Figure 10). Alternatively, an application of the Cieplak hypothesis, e.g., the stabilization of the transition state by hyperconjugation of the newly

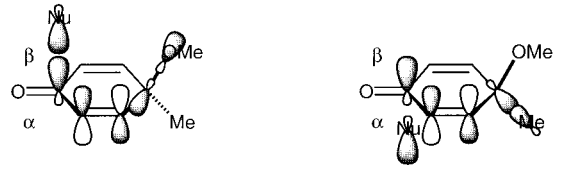


Figure 10.

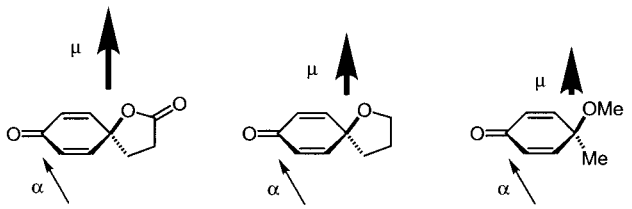
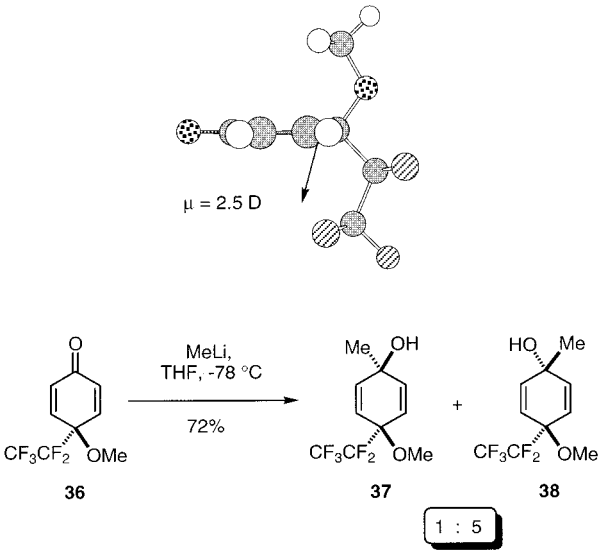


Figure 11.

forming σ^* bond by the σ orbital of the 4-alkyl substituent via a $\sigma^*-\sigma$ interaction, was similarly unsatisfactory in addressing the range of selectivities observed for **15**−**22**. Even though the consideration of a "vinylogous $\sigma^*-\pi^*-\sigma$ Cieplak effect", e.g., the phase inversion due to the double bond inserted between the carbonyl group and the 4-alkyl donor substituent, led to a correct prediction of the observed facial selectivity (Figure 10), no qualitative correlations between the ratio of isomers and the σ energy or the orbital overlap of the donor C−C bond of different dienones **15**−**22** were feasible with this model. Application of the principle of frontier orbital distortion as described by Klein, Burgess and Liotta would lead to an (experimentally incorrect) prediction for β-selectivity.[18a,b,f,42] Therefore we considered more closely the possibility of an electrostatic control mechanism in these dienone additions.

Qualitatively, there appeared to be a reasonable correlation between the observed α-selectivity and the expected dipole moments of dienones **15**−**22** (Figure 11). In physical terms, one can consider the nucleophilic attack of an organometallic reagent to a ketone to follow a potential energy curve that is, in a first approximation, related to the potential energy of interaction between a permanent dipole and a point charge (or another permanent dipole). The resulting potential is the sum of the repulsion of like charges and the attraction of opposite charges and proportional to the inverse of the square of the distance between dipole and point charge (or an inverse cubic dependence for a dipole−dipole interaction); typical values range from 2 to 4 kcal/mol.[43] Accordingly, an approach of the nucleophile toward the positive end of the dienone dipole moment vector should be favored. It is clear, however, that caution must be exercised in the qualitative use of a ground-state parameter such as the molecular dipole moment in the explanation of kinetic selectivity. An additional perturbation to the consideration of ground-state dipole moments derives from the complexation of the enone carbonyl oxygen with the organometallic reagent, in particular with the Lewis acidic counterion of the carbanionic species. However, it is feasible that in a closely related series of substrates the influence of Lewis acid coordination in the plane of the dienone would have a constant and minor influence on the component of the dipole moment perpendicular to the dienone plane. Accordingly, we argued that an appropriate test of the role of electrostatic control in the observed facial selectivity was the design of a substrate with an inverted perpendicular dipole moment opposing the C(4)-carbon−oxygen bond. In pentafluoroethyl dienone **36**, for example, electrostatic control should now lead to preferential β face

Scheme 7



attack, whereas hyperconjugative transition-state stabilization should still induce preferential α-selectivity.

Experimentally, fluorinated substrate **36** demonstrated indeed inverse selectivity, providing a 1:5 ratio α:β face methyl addition products (Scheme 7).[30] This unique β-selectivity represented clearly a significant support for dipolar control in our kinetically controlled nucleophilic additions.

The importance of electric fields imposed by ionic groups or salts on the substrate reactivity is evident in enzymes and can also be used for specific rate accelerations in organic transformations,[45] the design of a chiral auxiliary in organic synthesis,[46] and the design of enzyme inhibitors[47] as well as enzyme model reactions.[48,49] However, there was no information in the literature regarding the quantitative correlation of electrostatic effects and reaction selectivities.[50,51] Therefore, we were interested to probe for any quantitative structure−selectivity relationships in the 1,2-addition of organometallics to dienones.

V. Quantitative Correlation between Facial Selectivity and Dipole Moment

Our experimental studies with structurally closely related dienone substrates allowed us to address an intriguing question: Can the dipole moment be used for a quantitative prediction of facial selectivities? The electrostatic field of the substrate exercises a torque on any approaching reagent dipole and vice versa. The torque on the dipole is zero only when it is aligned with the electric field, and its potential energy is directly proportional to the dipole moment.[52] Accordingly, dipole moment and possibly also electrostatic potential at the site of attack should correlate linearly with the energy of activation of the addition process and the logarithm of the facial selectivity. This correlation would be analogous to a Hammett free-energy relationship.[53] However, in a series of 4,4-disubstituted dienones, only substrates with functional groups that are positioned in close vicinity to the dienone moiety could be expected to

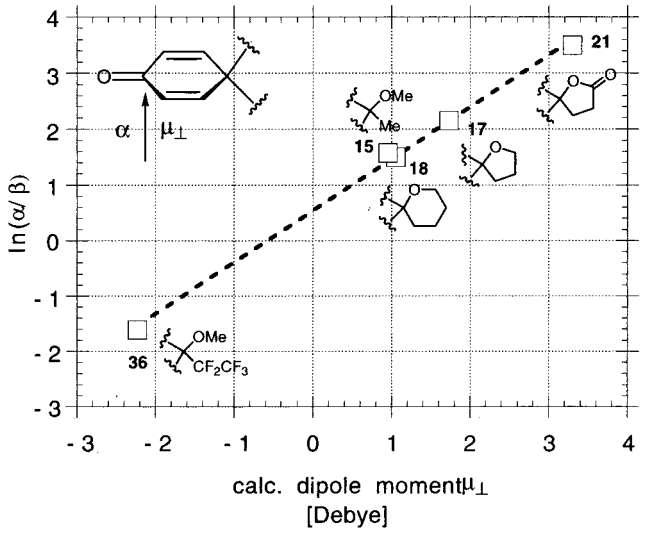


Figure 12. Least square linear regression correlation of calculated dipole moments of dienones **15**, **17**, **18**, **21**, and **36** versus the natural logarithm of the experimentally observed facial selectivities in the nucleophilic carbonyl addition. The values of the components of the dipole moments perpendicular to the dienone plane ($\mu_\perp$) are given in Debye [D]. Correlation coefficient $R = 0.998$.[30,55]

lend themselves to a good quantitative correlation of facial selectivities with overall dipole moments. Our dienones **15**, **17**, **18**, **21**, and **36** fulfilled this requirement, whereas **6**, **9**, **16**, and **19** appeared too highly functionalized or too conformationally flexible to be readily subjected to dipole moment calculations. The introduction of functional groups that are in greater spatial separation from the center of reaction should have a diminishing electrostatic directing effect on the carbonyl addition, but they still contribute evenly to a change in the overall dipole moment. In addition, dienones **20** and **22** were not included in this study, the former because the presence of a metal oxyanion caused problems in the calculation, and the latter because the yield of isolated product was quite low due to the unusual instability of this compound, and we were concerned that the experimentally determined ratio was not fully representative of the actual ratio of addition products. An additional concern was that the structure of the nucleophile, and the reaction conditions were kept as constant as possible, since obviously the electrostatic interaction is expected to be highly dependent on the nature of the nucleophile as well as solvent parameters.

We calculated the dipole moment of dienones **15**, **17**, **18**, **21**, and **36** with the semiempirical AM1 parameter set using the SPARTAN computational interface.[30,54] Optimized starting geometries were obtained from MM2 and Sybyl force fields implemented in SPARTAN. The vector components of the calculated dipole moments perpendicular to the plane of the dienones ($\mu_\perp$) were correlated to the natural logarithm of the observed facial selectivities and linearly extrapolated. On the basis of this extrapolation and the calculated dipole moment of dienones **15**, **17**, **18**, **21**, and **36**, the experimentally observed selectivity for nucleophilic 1,2-carbonyl addition was indeed very closely matched over a wide range of substrates and selectivities (Figure 12). The considerably more computer time intensive ab initio calculations of dienones **15**, **17**, **18**, **21**, and **36** with the 6-31G* and 6-31G** basis sets provided dipole moments $\mu_\perp$ within 10% of the AM1 values and only slightly parallel shifted graphical displays.[55] To the best of our knowledge, this study represented the first example of a quantitative correlation between dipole moments and kinetic selectivities.[30] The extraordinary fit between calculated perpendicular dipole moments and experimentally observed selectivities underlines the fundamental influence of ground-state electrostatic effects in directing the stereochemical course of organic reactions.[56] Interestingly, Figure 12 shows a small preference for α-attack even in the absence of a substituent-induced dipole moment (e.g., with $\mu_\perp = 0$). It is intriguing to speculate that this reflects a constant stereoelectronic contribution of the C(4) oxygen substituent on dienones **15**, **17**, **18**, **21**, and **36**. However, we do not have any additional experimental data to support this hypothesis, and the derivation from zero might simply be due to a systematic error of the AM1 calculation.[57,58]

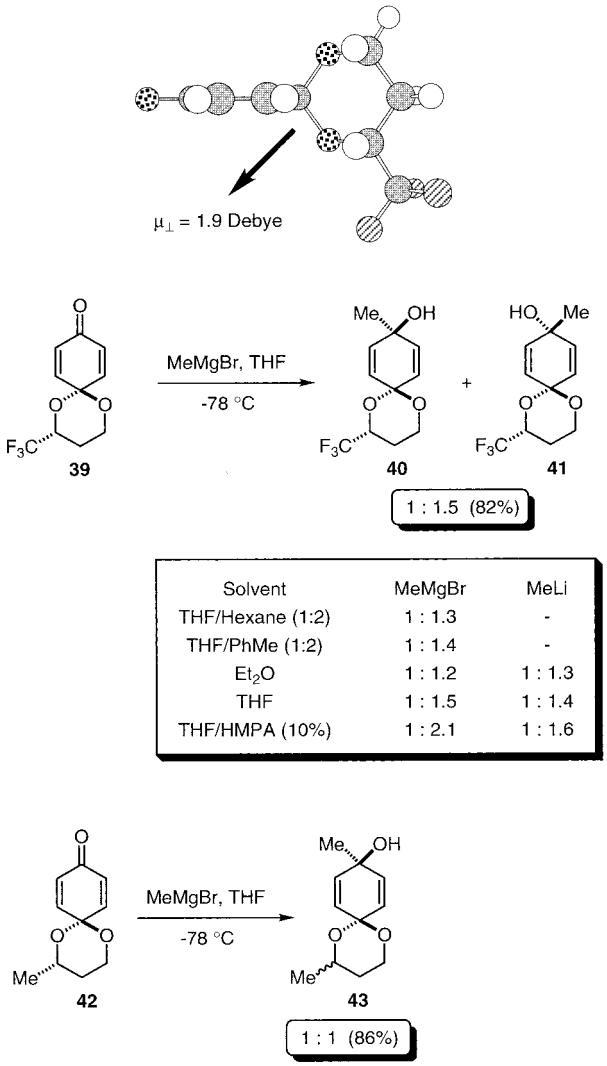
As mentioned previously, electrostatic effects are expected to be strongly influenced by substrate−reagent combinations, the presence of polar or ionic additives in the reaction medium, and solvent effects. In fact, the lack of information concerning solvent influences has been cited as a possible weakness in the argumentation for electrostatic effects,[59] and accordingly, we were interested in establishing relevant data for solvent effects in our dienone addition. We were also intrigued by the possibility of testing for long-range electrostatic effects by removing the polar functionality even further from the reaction center.

VI. Solvent Effects and Design of a Long-Range Electrostatic Chiral Auxiliary

On the basis of the quantitative relationship between the dipole moments and the facial selectivities of dienone derivatives (Figure 12), a novel chiral auxiliary (4,4,4-trifluoro-3-hydroxybutanol, **39**) was designed to induce diastereoselection at a remote carbon center by a dipole directing effect (Scheme 8).[31] The dipole moment of model compound **39** was calculated as $\mu_\perp = 1.9$ D [AM1]. According to Figure 12, this would correlate to an approximately 2:1 selectivity for the addition of methylmagnesium bromide anti to the CF_3 group. Experimentally, we detected a 1:1.5 ratio favoring the expected diastereomer **41** that was unambiguously assigned by X-ray structure analysis (Scheme 8).[31] In contrast, methylacetal **42** ($\mu_\perp = 0$ D) did not display any facial bias in the analogous addition reaction. Therefore, the modest but highly relevant diastereoselectivity observed for fluorinated acetal **39** was due to the long-range electrostatic field caused by the presence of the remote trifluoromethyl group and was not simply an effect of steric hindrance.

The 1,6-diastereoselection with **39** was significant given the distance of 5.1 Å between the carbonyl group and the asymmetric carbon atom. Also quite remarkable was the increase of diastereoselectivity experienced in reaction solvents of higher dielectric

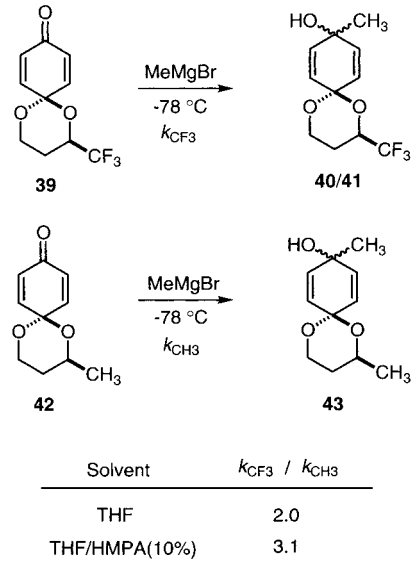
Scheme 8



constant. In a 9:1 mixture of THF and HMPA, methyl Grignard reagent gave a 1:2.1 ratio of **40** and **41**, whereas the selectivity dropped to 1:1.2 in ether. Since an increase in the dielectric constant of the medium leads to an increase in the induced dipole moment of the solute,[60] this solvent effect is, in a first-order approximation, in good qualitative agreement with an electrostatic control of the reaction. The use of the Cramer−Truhlar AM1−SM2 water solvation model,[61] for example, provides increases of 10−20% in the values of the perpendicular dipole moment of dienones compared to the gas-phase calculations used for Figure 12.[55] However, solvents with higher dielectric constants are expected to reduce the value of dipole−dipole or dipole−point charge interactions, and therefore the actual effect of increasing solvent polarity is not necessarily fully predictable. A further caveat is the influence of solvent changes or reaction additives on the aggregation state of the organometallic reagent. Clearly, more comprehensive studies will be necessary to assess the generality and elucidate the fundamental basis of the solvent effects listed in Scheme 8.

Quite often in synthetic chemistry, the price for increased selectivity is a drop in reactivity; e.g., a substrate that provides higher selectivity reacts often

Scheme 9



more slowly with the same set of reagents than a less selective compound. In terms of electrostatic control mechanisms, however, the reverse effect should occur, e.g., increasing the more favorable electrostatic interaction should accelerate the reaction rate. Dienones **39** and **42** provided us with the means to test this hypothesis in a competition experiment (Scheme 9). Exposure of a 1:1 mixture of **39** and **42** with 1 equiv of methyl Grignard reagent in THF at −78 °C provided an excess of **40** and **41**.[62] The relative rate of reaction of **39** compared to **42** (k_{CF_3}/k_{CH_3}) was 2.0:1 and further increased to 3.1:1 in THF/ HMPA (10%). Therefore, the electrostatically activated and more selective trifluoroacetal **39** was indeed reacting faster than methyl acetal **42** that did not show any facial selectivity in the carbonyl addition. Furthermore, the increase of the relative reaction rate to a ratio of 3.1:1 in the more polar solvent mixture was in excellent qualitative agreement with the solvent effects on selectivity shown in Scheme 8 and the general theme of an electrostatic control mechanism in these addition reactions.

VII. Nucleophilic Additions to Naphthodiquinones

In addition to being a useful tool for the investigation of long-range electrostatic and solvent effects, trifluoroacetal **39** also provided us with a welcome model for the use of electrostatically biased chiral auxiliaries. As a part of our work toward the total synthesis of epoxyketone natural products, we intended to apply this concept in a stereocontrolled synthesis of diepoxin σ and other bisacetal decalins.[31,63] Naphthodiquinone bisacetal **44** was designed to be an important test case for synthetic applications of the long-range chiral auxiliary concept. The use of two units of trifluoroacetal in the C_2-symmetrical **44** should guarantee a synthetically useful level of diastereoselectivity. The dipole moment of the bisacetal **44** was calculated as $\mu = 3.5$ D, with an perpendicular orientation of the dipole moment to the plane of the dienone carbonyl groups (Figure 13). According to Figure 12, this would translate into a

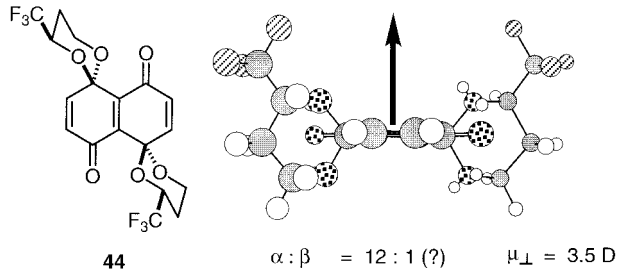
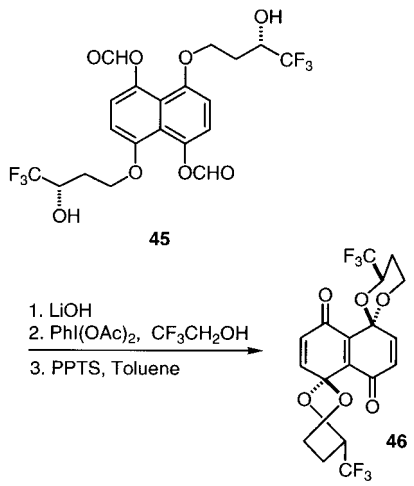


Figure 13.

Scheme 10



facial selectivity of >12:1 for the addition of methyl Grignard reagent to a single carbonyl function. A complication to the experimental realization of these plans presented itself when the tandem spirocyclization of naphthalenediol **45** provided chair−twist boat conformation **46** rather than the desired double chair **44** (Scheme 10).[62]

The formation of the unsymmetrical bisacetal **46** in preference to the C_2-symmetric bisacetal **44** is possibly due to the directing effect of the trifluoromethyl group after formation of the first acetal in the thermodynamically favored chair conformation. Formation of the second acetal in a twist boat conformation minimizes the overall dipole moment by positioning the two trifluoromethyl groups anti to each other on opposite faces of the decalin ring (Figure 14).[64]

To obtain the desired C_2-symmetric naphthodiquinone bisacetal, we changed the chiral auxiliary to the *syn*-1,1,1-trifluoropentane-2,4-diol on the basis of the realization that an additional syn methyl group attached to the acetal ring resulted in a severe steric repulsion with the β hydrogen of the naphthoquinone (Figure 15). Indeed, the desired syn cyclization product **48** was obtained even though this provided a compound with an unusually large ground-state dipole moment (Scheme 11).[31]

Reaction of naphthodiquinone bisacetal **48** with 1 equiv of methyllithium provided mixtures of two 1,2-carbonyl addition products. We were unable to stop the reaction after monoaddition, and therefore, we could not validate the predicted facial selectivity of 12:1 based on the quantitative correlation shown in Figure 12. However, when the reaction was allowed

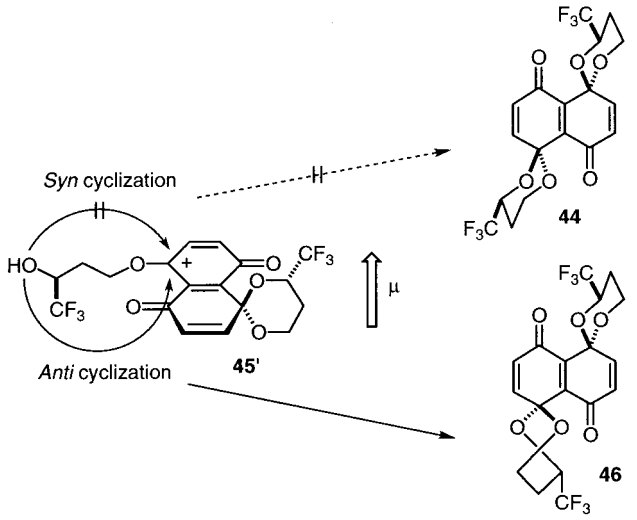


Figure 14.

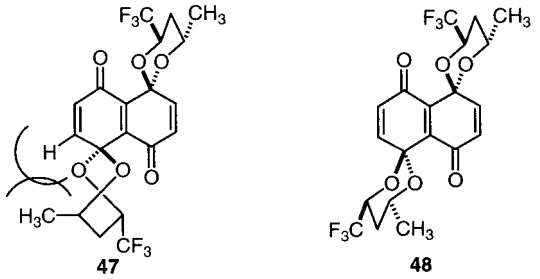
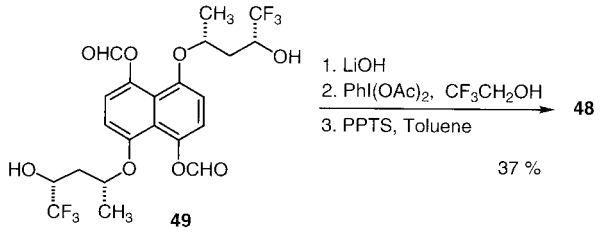


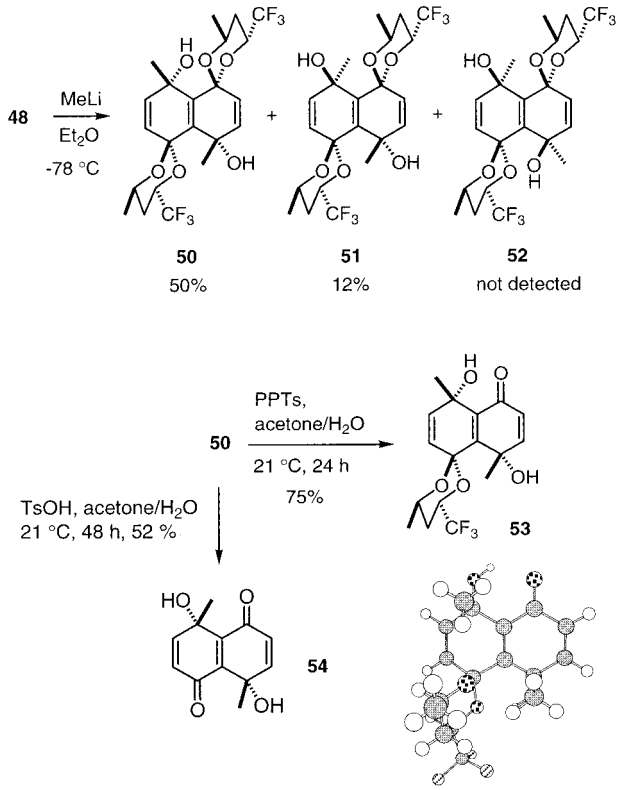
Figure 15.

Scheme 11



to proceed to completion using an excess of methyllithium, the symmetrical double anti addition product **50** was obtained as the major isomer in 50% yield (Scheme 12).[31] The minor diaddition product **51** where the two methyl groups had added opposite to each other, both syn and anti to the trifluoromethyl substituents, was obtained in 12% yield. We were unable to detect the formation of the double syn addition product **52**. After statistical correction, the ratio of **50**:**51** corresponds to a facial preference of 9:1 for preferential carbonyl attack anti to the trifluoromethyl substituents, a ratio that still corresponds very closely to the calculated value. The major isomer **50** was monodeprotected to give **53**, the structure of which was secured by X-ray analysis. Double deprotection of **50** provided the naphthodiquinol **54** in enantiomerically pure form. Both **53** and **54** served as key intermediates in a approach toward the asymmetric total synthesis of diepoxin σ.[62] Accordingly, the results observed in this synthesis are not only a remarkable demonstration of the directing power of strong dipole moments but also serve to underline the exciting possibilities of elec-

Scheme 12



trostatic models to predict quantitative diastereoselectivities in a reliable and synthetically useful fashion.

VIII. Conclusions

Do dipole effects control facial selectivity? Our investigations of the facial selectivity of 1,2-nucleophilic attack to 4,4-disubstituted cyclohexadienones provide strong experimental evidence for dominant dipolar control in these carbonyl addition reactions. Hyperconjugative orbital stabilization in the Felkin−Anh and the Cieplak sense or orbital distortion effects appear to be of secondary importance. A quantitative correlation of the calculated dipole moments of dienones with the facial selectivity is possible in analogy to Hammett linear free energy relationships. The excellent linear correlation of calculated dipole moments versus the logarithm of the facial selectivity and the considerable variation of the facial selectivity as a function of the polarity of the organic solvent support the notion that, in the absence of steric hindrance, the kinetic selectivity of irreversible C−C bond formation is strongly influenced by dipole−dipole interactions between reagents and substrates. Application of this concept to the design of novel chiral auxiliaries and the realization of a double chiral induction in the C_2-symmetric naphthodiquinone derivative **48** further showcases the possibility that electrostatic control can be harvested for quantitative reaction planning in asymmetric synthesis.

All stereoelectronic and electrostatic effects are substrate-, reagent-, and solvent-dependent. In consideration of the many electronic as well as steric features that can influence stereoselectivity in organic chemistry, it seems advisable to advocate a broad, unbiased analysis of all possible parameters until the elusive goal of a single, unified theory for the qualitative and quantitative prediction of selectivity and reactivity in organic transformations can be achieved. In our opinion, the analysis of the π facial stereoselectivity in carbonyl additions is one of the most suitable areas to develop and test new fundamental hypotheses of physical organic chemistry.

IX. Acknowledgments

This work was supported by the National Science Foundation, the National Institutes of Health, the American Cancer Society, and the Sloan and Camille Dreyfus Foundations.

X. References and Notes

(1) Doyle, A. C. *"The Original Illustrated Sherlock Holmes*; Castle Books: Edison, NJ, 1976; p 13.
(2) (a) Gung, B. W. *Tetrahedron* **1996**, *52*, 5263. (b) Li, H.; le Noble, W. J. *Recl. Trav. Chim. Pays-Bas* **1992**, *111*, 199. (c) Boone, J. R.; Ashby, E. C. *Top. Stereochem.* **1979**, *11*, 53. (d) Houk, K. N.; Wu, Y.-D. In *Stereochemistry of Organic and Bioorganic Transformations*; Bartmann, W., Shapless, K. B., Eds.; VCH: Weinheim, Germany, 1987; pp 247−260.
(3) Cram, D. J.; Elhafez, F. A. *J. Am. Chem. Soc.* **1952**, *74*, 5828.
(4) Cornforth, J. W.; Cornforth, R. H.; Mathew, K. K. *J. Chem. Soc.* **1959**, 112.
(5) Karabatsos, G. J. *J. Am. Chem. Soc.* **1967**, *89*, 1367.
(6) Cherest, M.; Felkin, H.; Prudent, N. *Tetrahedron Lett.* **1968**, 2199.
(7) Anh, N. T.; Eisenstein, O. *Tetrahedron Lett.* **1976**, 155.
(8) (a) Anh, N. T.; Eisenstein, O. *Nouv. J. Chim.* **1977**, *1*, 61. (b) Anh, N. T. *Top. Curr. Chem.* **1980**, *88*, 145.
(9) (a) Bürgi, H. B.; Dunitz, J. D.; Shefter, E. J. *J. Am. Chem. Soc.* **1973**, *95*, 5065. (b) Bürgi, H. B.; Lejn, J. M.; Wipff, G. *J. Am. Chem. Soc.* **1974**, *96*, 1956. (c) Bürgi, H. B.; Lejn, J. M.; Dunitz, J. D.; Wipff, G. *Tetrahedron* **1974**, *30*, 1563.
(10) (a) Kobayashi, Y. M.; Lambrecht, J.; Jochims, J. C.; Burkert, U. *Chem. Ber.* **1978**, *111*, 3442. (b) Terasama, T.; Okada, T. *J. Chem. Soc., Perkin Trans. 1* **1978**, 1252. (c) Kobayashi, Y. M.; Iitaka, Y. *Acta Crystallogr. Sect. B* **1977**, *33*, 923. (d) Mukherjee, D.; Wu, Y.-D.; Fronczek, F. R.; Houk, K. N. *J. Am. Chem. Soc.* **1988**, *110*, 3328. (e) Wu, Y.-D.; Houk, K. N.; Paddon-Row, M. N. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 1019. (f) Wong, S. S.; Paddon-Row, M. N. *J. Chem. Soc., Chem. Commun.* **1990**, 456. (g) Anh, N. T.; Maurel, F.; Lefour, J.-M. *New J. Chem.* **1995**, *19*, 353.
(11) Lodge, E. P.; Heathcock, C. H. *J. Am. Chem. Soc.* **1987**, *109*, 3353.
(12) For an excellent review of stereoelectronic effects in six-membered rings, see: Franck, R. W. In *Conformational Behavior of Six-Membered Rings*; Juaristi, E., Ed.; VCH: New York, 1995; pp 159−200.
(13) Wu, Y.-D.; Houk, K. N. *J. Am. Chem. Soc.* **1987**, *109*, 908.
(14) Cieplak, A. S. *J. Am. Chem. Soc.* **1981**, *103*, 4540.
(15) (a) Cheung, C. K.; Tseng, L. T.; Lin, M.-H.; Srivastava, S.; le Noble, W. J. *J. Am. Chem. Soc.* **1986**, *108*, 1598. (b) Lin, M.-H.; Silver, J. E.; le Noble, W. J. *J. Org. Chem.* **1988**, *53*, 5155. (c) Li, H.; le Noble, W. J. *Tetrahedron Lett.* **1990**, *31*, 4391. (d) Hahn, J. M.; le Noble, W. J. *J. Am. Chem. Soc.* **1992**, *114*, 1916. (e) Gonikberg, E. M.; le Noble, W. J. *J. Org. Chem.* **1995**, *60*, 7751. (f) Coxon, J. M.; Houk, K. N.; Luibrand, R. T. *J. Org. Chem.* **1995**, *60*, 418. (g) Okada, K.; Tomita, S.; Oda, M. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 459. (h) Metha, G.; Khan, F. A. *J. Am. Chem. Soc.* **1990**, *112*, 6140. (i) Sato, M.; Uehara, F.; Kamaya, H.; Murakami, M.; Kaneko, C.; Furuya, T.; Kurihara, H. *J. Chem. Soc. Chem., Commun.* **1996**, 1063. (j) Cieplak, A. S.; Tait, B. D.; Johnson, C. R. *J. Am. Chem. Soc.* **1989**, *111*, 8447. (k) Johnson, C. R.; Tait, B. D.; Cieplak, A. S. *J. Am. Chem. Soc.* **1987**, *109*, 5975. (l) Lau, J.; Gonikberg, E. M.; Hung, J.-t.; le Noble, W. J. *J. Am. Chem. Soc.* **1995**, *117*, 11421. (m) Senda, Y.; Sakurai, H.; Nakano, S.; Itoh, H. *Bull. Chem. Soc. Jpn.* **1996**, *69*, 3297. (n) Jones, C. D.; Kaselj, M.; Salvatore, R. N.; le Noble, W. J. *J. Org. Chem.* **1998**, *63*, 2758.
(16) (a) Rozeboom, M. D.; Houk, K. N. *J. Am. Chem. Soc.* **1982**, *104*, 1189. In contrast, see: (b) Laube, T.; Ha, T.-K. *J. Am. Chem. Soc.* **1988**, *110*, 5511.
(17) (a) Gung, B. W.; Francis, M. B. *Tetrahedron Lett.* **1995**, *36*, 2579. (b) Gung, B. W.; Francis, M. B. *J. Org. Chem.* **1993**, *58*, 6177.

(18) (a) Klein, J. *Tetrahedron Lett.* **1973**, *29*, 4307. (b) Klein, J. *Tetrahedron* **1974**, *30*, 3349. (c) Eisenstein, O.; Klein, J.; Lefour, J.-M. *Tetrahedron* **1979**, *35*, 225. (d) Ashby, E. C.; Noding, S. A. *J. Org. Chem.* **1977**, *42*, 264. (e) Giddings, M. R.; Hudec, J. *Can. J. Chem.* **1981**, *59*, 459. (f) Burgess, E. M.; Liotta, C. L. *J. Org. Chem.* **1981**, *46*, 1703. (g) Paquette, L. A.; Hsu, L.-Y.; Gallucci, J. C.; Korp, J. D.; Bernal, I.; Kravetz, T. M.; Hathaway, S. J. *J. Am. Chem. Soc.* **1984**, *106*, 5743.
(19) Frenking, G.; Kohler, K. F.; Reetz, M. T. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 1146.
(20) (a) Huang, X. L.; Dannenberg, J. J. *J. Am. Chem. Soc.* **1993**, *115*, 6017. (b) Huang, X. L.; Dannenberg, J. J.; Duran, M.; Bertran, J. *J. Am. Chem. Soc.* **1993**, *115*, 4024.
(21) Tomoda, S.; Senju, T. *Tetrahedron* **1997**, *53*, 9057.
(22) Shi, Z.; Boyd, R. J. *J. Am. Chem. Soc.* **1993**, *115*, 9614.
(23) (a) Wong, S. S.; Paddon-Row, M. N. *J. Chem. Soc., Chem. Commun.* **1991**, 327. (b) Wong, S. S.; Paddon-Row, M. N. *Aust. J. Chem.* **1991**, *44*, 765.
(24) Wu, Y.-D.; Tucker, J. A.; Houk, K. N. *J. Am. Chem. Soc.* **1991**, *113*, 5018.
(25) Even though more commonly attributed to hyperconjugation, stereoelectronics, and frontier orbital interactions, it is important to note that electrostatics have also been suggested as the origin of anomeric effects. See: Perrin, C. L.; Armstrong, K. B.; Fabian, M. A. *J. Am. Chem. Soc.* **1994**, *116*, 715, and references therein.
(26) (a) Okamoto, I.; Ohwada, T.; Shudo. K. *Tetrahedron Lett.* **1997**, *38*, 425. (b) Mehta, G.; Gunasekaran, G. *J. Org. Chem.* **1994**, *59*, 1953.
(27) (a) Ganguly, B.; Chandrasekhar, J.; Khan, F. A.; Mehta, G. *J. Org. Chem.* **1993**, *58*, 1734. (b) Adcock, W.; Cotton, J.; Trout, N. A. *J. Org. Chem.* **1994**, *59*, 1867. (c) Pudzianowski, A. T.; Barrish, J. C.; Spergel, S. H. *Tetrahedron Lett.* **1992**, *33*, 293. (d) Gandolfi, R.; Amade, M. S.; Rastelli, A.; Bagatti, M. *Tetrahedron Lett.* **1996**, *37*, 1321. (e) Fraser, R. R.; Faibish, N. C.; Kong, F.; Bednarski, K. *J. Org. Chem.* **1997**, *62*, 6164. (f) Adcock, W.; Head, N. J.; Lokan, N. R. *J. Org. Chem.* **1997**, *62*, 6177. (g) Mehta, G.; Kahn, F. A.; Adcock, W. *J. Chem. Soc., Perkin Trans. 2* **1995**, 2189.
(28) (a) Skancke, P. N. *Acta Chim. Scand.* **1993**, *47*, 629. (b) Jensen, F. *J. Comput. Chem.* **1994**, *15*, 1199. (c) Ando, K.; Houk, K. N.; Busch, J.; Menasse, A.; Sequin, U. *J. Org. Chem.* **1998**, *63*, 1761. (d) Jeyaraj, D.; Yadav, V. K. *Tetrahedron Lett.* **1997**, *38*, 6095. (e) Jeyaraj, D.; Yadav, A.; Yadav, V. K. *Tetrahedron Lett.* **1997**, *38*, 4483. (f) Gung, B. W.; Wolf, M. A. *J. Org. Chem.* **1996**, *61*, 232.
(29) (a) Halterman, R. L.; McEvoy, M. A. *J. Am. Chem. Soc.* **1992**, *114*, 980. (b) Mehta, G.; Khan, F. A.; Gadre, S. R.; Shirsat, R. N.; Ganguly, B.; Chandrasekhar, J. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1390. (c) Mehta, G.; Ravikrishna. C.; Ganguly, B.; Chandrasekhar, J. *J. Chem. Soc., Chem. Commun.* **1997**, 75. (d) Kaselj, M.; Gonikberg, E. M.; le Noble, W. J. *J. Org. Chem.* **1998**, *63*, 3218.
(30) Wipf, P.; Kim, Y. *J. Am. Chem. Soc.* **1994**, *116*, 11678.
(31) Wipf, P.; Jung, J.-K. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 764.
(32) (a) Jones, P. G.; Weinmann, H.; Winterfeldt, E. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 448. (b) Takano, S.; Moriya, M.; Higashi, Y.; Ogasawara, K. *J. Chem. Soc., Chem. Commun.* **1993**, 177. (c) Hiroya, K.; Kurihara, Y.; Ogasawara, K. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2287. (d) Clark, D. A.; Riccardis, F. D.; Nicolaou, K. C. *Tetrahedron* **1994**, *50*, 11391.
(33) (a) Swiss, K. A.; Hinkley, W.; Maryanoff, C. A.; Liotta, D. C. *Syhthesis* **1992**, 127. (b) Solomon, M.; Jamison, W. C. L.; MacCormick, M.; Liotta, D. C.; Cherry, D. A.; Mills, J. E.; Shah, R. D.; Rodgers, J. D.; Maryanoff, C. A. *J. Am. Chem. Soc.* **1988**, *110*, 3702. (c) Swiss, K. A.; Liotta, D. C.; Maryanoff, C. A. *J. Am. Chem. Soc.* **1990**, *112*, 9393.
(34) See also: Fischer, A.; Henderson, G. N. *Tetrahedron Lett.* **1980**, *21*, 701.
(35) (a) Wipf, P.; Kim, Y.; Fritch, P. C. *J. Org. Chem.* **1993**, *58*, 7195. (b) Wipf, P.; Kim, Y. *J. Org. Chem.* **1993**, *58*, 1649.
(36) (a) Winterfeldt, E.; Borm, C.; Nerenz, F. *Adv. Asymmetric Synth.* **1997**, *2*, 1. (b) Winfried, B.; Jones, P. G.; Nerenz, F.; Winterfeldt, E. *Tetrahedron* **1998**, *54*, 7273.
(37) Silvero, G.; Lucero, M. J.; Winterfeldt, E.; Houk, K. N. *Tetrahedron* **1998**, *54*, 7293.
(38) For the assignment of product ratios and relative configurations, see refs 30 and 31.
(39) Jeyaraj, D. A.; Yadav, V. K.; Parvez, M.; Gauniyal, H. H. *J. Org. Chem.* **1998**, *63*, 3831.
(40) Carreño, M. C.; Gonzalez, M. P.; Ribagorda, M.; Houk K. N. *J. Org. Chem.* **1998**, *63*, 3687.
(41) Carreño, M. C.; Gonzalez, M. P.; Ribagorda, M.; Fischer, J. *J. Org. Chem.* **1996**, *61*, 6758.
(42) Liotta, C. L.; Burgess, E. M.; Eberhardt, W. H. *J. Am. Chem. Soc.* **1984**, *106*, 4849.
(43) Atkins, P. *Physical Chemistry*, 6th ed.; Freeman: New York, 1997; Chapter 22, pp 655−660.
(44) Conformational flexibility and a slight variation in bond angles account for the decreased dipole moment of the acyclic versus that of the spirocyclic ether.
(45) a) Warshel, A. *Acc. Chem. Res.* **1981**, *14*, 284. (b) Smith, P. J.; Kim, E. I.; Wilcox, C. S. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1648.
(46) Boeckman, R. K., Jr.; Connell, B. T. *J. Am. Chem. Soc.* **1995**, *117*, 12368.
(47) Conroy, J. L.; Sanders, T. C.; Seto, C. T. *J. Am. Chem. Soc.* **1997**, *119*, 4285.
(48) Ohno, A.; Tsutsumi, A.; Yamazaki, N.; Okamura, M.; Mikata, Y.; Fujii, M. *Bull. Chem. Soc. Jpn.* **1996**, *69*, 1679.
(49) Westheimer, F. H. *Tetrahedron* **1995**, *51*, 3.
(50) For a recent general discussion of the role of electrostatic effects in organic chemistry, see: Wiberg, K. B. *J. Chem. Educ.* **1996**, *73*, 1089.
(51) A particular interesting variation of the principle of electrostatic reaction control is the use of highly electron-withdrawing groups, such as fluorinated residues, in asymmetric ligand design. For a recent example of a high asymmetric induction based on the ability of the trifluoromethyl group to interact with a chiral Ni-(II) complex of glycine, see: Soloshonok, V. A.; Avilov, D. V.; Kukhar, V. P. *Tetrahedron* **1996**, *52*, 12433.
(52) Weidner, R. T.; Sells, R. L. *Elementary Classical Physics*; Allyn and Bacon: Boston, MA, 1965; Vol. 2, pp 631−650.
(53) For correlations of log $K_{RSH,app}$ (the apparent equilibrium constant for addition of thiol to 4-heterocyclohexanones) versus the electrostatic substituent field constant (F) and pK_i (inhibition constant of ketone based inhibitors) vs log $K_{RSH,app}$, see ref 47.
(54) SPARTAN is a product of Wavefunction, Inc., Irvine, CA.
(55) Wipf, P.; Miehl, M. Unpublished results.
(56) A referee suggested that an anomeric stabilization of a half-boat reactant with the OR substituent in a pseudoaxial orientation would lead to a preference for pseudoaxial attack to form the product in a boat conformation. While the preference for such a conformation under Curtin−Hammett kinetics cannot be excluded, there is no indication from ground state X-ray analysis and calculations that a half-boat is thermodynamically preferred for 4,4-disubstituted dienones. In addition, it would have to be postulated that the introduction of the pentafluoroethyl substituent leads to a ring flip and places the OR group into the pseudoequatorial position.
(57) Dewar, M. J. S.; Zoebisch, E. G.; Healy, E. F.; Stewart, J. J. P. *J. Am. Chem. Soc.* **1985**, *107*, 3902. AM1 has been shown to reproduce dipole moments of organic molecules with good accuracy: Stewart, J. J. P. In *Reviews in Computational Chemistry*, Lipkowitz, K. B., Boyd, D. B., Eds.; VCH: Weinheim, 1991; pp 45−81.
(58) As pointed out by a referee, the nonzero intercept could also be due to changes in the relative volume of the dienones plotted in Figure 12. Depending on the size of the molecule, the effect of the calculated molecular dipole moment onto the reaction center is likely to vary.
(59) Kaselj, M.; Adcock, J. L.; Luo, H.; Zhang, H.; Li, H.; le Noble, W. J. *J. Am. Chem. Soc.* **1995**, *117*, 7088.
(60) J. Gao, X. Xia, *Science* **1992**, *258*, 631, and references therein.
(61) Cramer, C. J.; Truhlar, D. G. *J. Comput.-Aided. Mol. Des.* **1992**, *6*, 629.
(62) Wipf, P.; Jung, J.-K. Unpublished results.
(63) Wipf, P.; Jung, J.-K. *J. Org. Chem.* **1998**, *63*, 3530.
(64) The conformer with the larger dipole moment is often, but not always, the less stable one. See, for example: Perrin, C. L.; Young, D. B. *Tetrahedron Lett.* **1995**, *36*, 7185. The minimization of dipole moments in the transition state can also play an important role in determining the observed diastereoselectivity: Jones, D. K.; Liotta, D. C.; Choi, W.-B.; Volante, R. P.; Reider, P. J.; Shinkai, I.; Churchill, H. R. O.; Lynch, J. E. *J. Org. Chem.* **1994**, *59*, 3749.

CR9803838