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Inductive and Resonance Effects of Substituents on π-Face Selection

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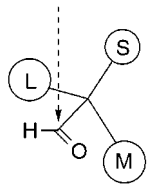
Contents

1. Introduction

The problem of π-face selection was first defined in modern terms in 1952.[1] The top and bottom additions to a trigonal center adjacent to a stereogenic center such as the one depicted in Scheme 1

Scheme 1



were proposed to occur at different rates because of the difference in size of the two out-of-plane groups M (medium) and S (small) that hinder the reagent's approach (Cram's rule). However, within only a few years after its introduction, limitations of the theory that attribute π-face selection solely to the steric

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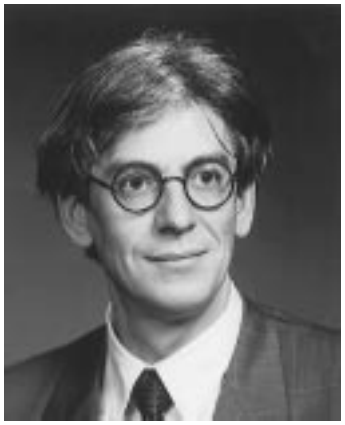
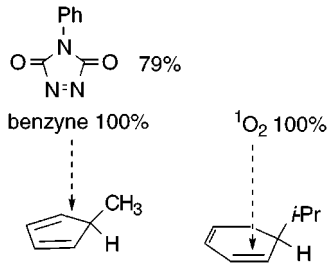


Andrzej Stanislaw Cieplak began studying chemistry at the University of Warsaw where in March 1968 he was expelled and detained for 5 months by the military for representing pro-democracy chemistry students in the university's strike committee but received, nonetheless, his undergraduate degree in 1971. He earned his Ph.D. in 1976 from the Institute of Organic Chemistry of the Polish Academy of Sciences for work on partial synthesis of a steroidal molting hormone under the supervision of Marian Kocor. He began his postgraduate studies with Oskar Jeger in the Laboratorium für Organische Chemie at ETH Zürich, which involved synthesis and photolysis of epoxyenones. In Switzerland, skiing in Davos, he met his future wife. In 1977, he joined Sir Jack Baldwin's group in the Department of Chemistry at MIT where he examined transformations of Arnstein's tripeptide and stereoelectronic effects in nucleophilic additions to penicillin. He joined William Lipscomb's group in the Department of Chemistry at Harvard in 1978, synthesizing inhibitors of aspartyl transcarbamylase. He continued to work with peptide-like enzyme inhibitors in 1980 in the Research Institute for Medicine and Chemistry, Cambridge, MA, headed by Sir Derek Barton, being involved there in the structure-based design of drugs controlling hypertension. While at Harvard, his longstanding interest in the puzzle of axial reduction of cyclohexanones by metal hydrides, dating back to the days of undergraduate research, and the newly developed understanding of stereoelectronic effects converged in the hypothesis of hyperconjugative assistance to bond formation presented in 1981 in the *Journal of the American Chemical Society* paper on the importance of two-electron stabilizing interactions in nucleophilic additions to cyclohexanone. In 1983 he joined the Department of Chemistry at Fordham University, New York, as Assistant Professor of Organic Chemistry, where the pursuit of implications of his theory for the transfer of chirality in conjugated systems led him to study conformational preferences and perturbations of peptide geometry in the crystal structures of oligopeptides. Leaving Fordham in 1990, he continued this work collaborating as Visiting Scholar with Hans-Beat Bürgi of the Laboratorium für Kristallographie, University of Berne, and with Ken Wiberg of the Department of Chemistry at Yale University, from 1992 to 1994, and teaching as Visiting Assistant Professor in the Department of Chemistry at the State University of New York at Stony Brook from 1994 to 1997. These studies have recently led to formulation of the first comprehensive theory of secondary structure propensities of Ala* amino acids described in the volume *The Amide Linkage: Structural Significance in Chemistry, Biochemistry and Materials Science*. He received an American Cyanamid Academic Award in 1988 and has lectured in the United States and Japan.

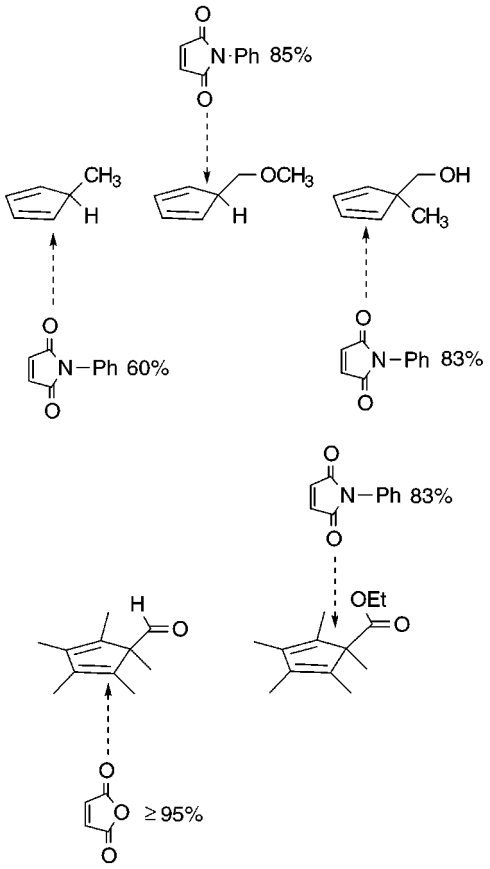
strain have become apparent in the examination of π-face selection in reactions of cyclic alkanones and 1,3-alkadienes. Several recent examples of cycloadditions serve well to illustrate these difficulties.[2−6] It seems that the steric strain can be readily overridden by some other interactions, Scheme 2, and that it is possible to enhance those interactions by modifying the reagent and the substitution of the stereogenic center, Scheme 3. Apparently, the preference for the hindered approach can be increased even in spite of the increased size of the larger ligand.

What is the nature of the effect that can override the steric demands of a reactant and an allylic ligand? One possible answer, proposed in 1981,[7] is

Scheme 2



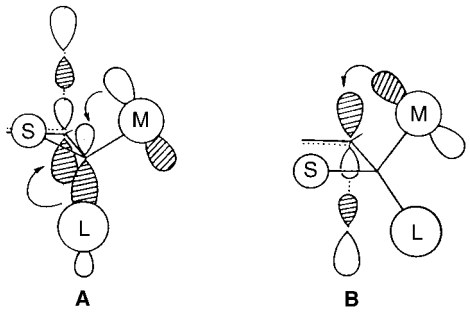
Scheme 3



that π-face selection is controlled not only by steric strain but also by resonance interactions between the incipient bond and the stereogenic center. The most important of those interactions is usually electron delocalization from the σ (hyperconjugation) or π (homoconjugation) orbitals of the stereogenic center into the σ^* orbital of the incipient bond ($\sigma^*_{‡}$), the low-lying LUMO of the transition state. Although such electron donation weakens the incipient bond, the net effect is stabilization of the transition state due to the increase in bonding between the stereogenic center and the incipient center. For most of the reaction paths for additions to C═O or C═C, this stabilizing effect is expected to be greater in the transition state than in the ground state. The reason for this increase in stabilization is that the $2p_z$ orbital at the reaction site becomes more electron deficient in the transition state as a result of π-charge polarization induced by the approaching reagent; in FMO parlance, the energy level of the $\sigma^*_{‡}$ orbital (the transition state LUMO) is lower than that of the π^* orbital (the ground state LUMO).

Thus, the relative stability of the transition states for bond formation at a trigonal center depends not only on the size of the allylic ligands S, M, and L but also on their σ- and π-donor capability, cf. Scheme 4.

Scheme 4

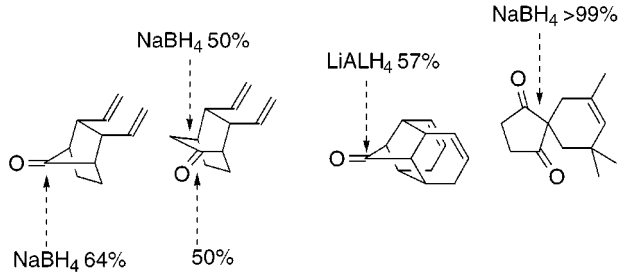


In this example, the S, M, and L ligands might be a hydrogen, an alkoxy group, and an alkyl group, respectively. The most important resonance interactions of the incipient bond would then involve, in transition state **A**, hyperconjugative donation from the C−C bond of the alkyl group (ligand L) into the $\sigma^*_{\ddagger}$ orbital which is assisted (enhanced) by the back-donation from the O lp (ligand M) or, in transition state **B**, direct homoconjugative donation from the O lp (ligand M) into the $\sigma^*_{\ddagger}$ orbital.

This hypothesis has numerous consequences which can be readily spelled out and verified. For instance, σ bonds of the stereogenic center can be replaced by bonds that are better or poorer electron donors due to remote substitution or due to introduction of allylic heteroatoms, while electron affinity of the incipient bond can be varied by changing the reagent's substitution. Each modification should result in a shift of π-facial preference that would correlate with the ensuing change in the energy of two-electron stabilizing interactions SE proportional to the overlap of the interacting σ and $\sigma^*_{\ddagger}$ orbitals and inversely proportional to the difference in their energy levels, SE $\propto S^2/\Delta\epsilon$.[8,9] The major trends in the data on the stereochemistry of nucleophilic additions to cyclohexanones and polycycloalkanones available at the time were indeed consistent with the predictions derived in this way. Moreover, some evidence has already suggested that the effects of structural modifications found in reactions of cyclohexanones and 7-norbornenones will also be observed in reactions of methylenecyclohexanes and 7-methylenebenzonorbornenes, thianes, piperidines, and 7-azabenzonorbornenes, i.e., that π-face selection in nucleophilic and electrophilic additions is controlled in the same way, as indeed implied by the postulate of hyperconjugative and homoconjugative assistance.[7]

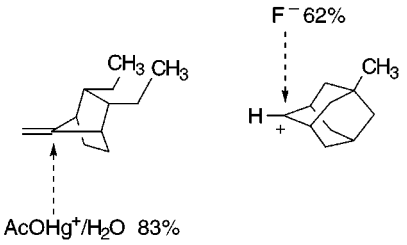
The early studies that followed publication of the 1981 hypothesis readily confirmed its main predictions.[10−12] Regardless of the mechanism of bond formation, the inductive effect of remote substitution of the stereogenic center was found to play a prominent role in the control of π-face selection and the corresponding Hammett and Taft plots were found to be reasonably linear. The subsequent accumulation of experimental data began, however, to complicate this simple picture. The more recent evidence often shows that the inductive effect is not the sole substituent property which determines stereochemical bias and that the dependence of π-face selection on the inductive effect is not linear and not even monotonic. For instance, the vinyl group with the positive inductive effect can be *anti*-directing,[13] silent,[14,15] or *syn*-directing,[16,17] depending on the probe, Scheme 5, and the inductively neutral alkyl groups

Scheme 5



can be astonishingly effective as the *anti*-[18] or *syn*-directing groups,[19] depending on the probe, Scheme 6; the use of two electronegative substituents instead

Scheme 6

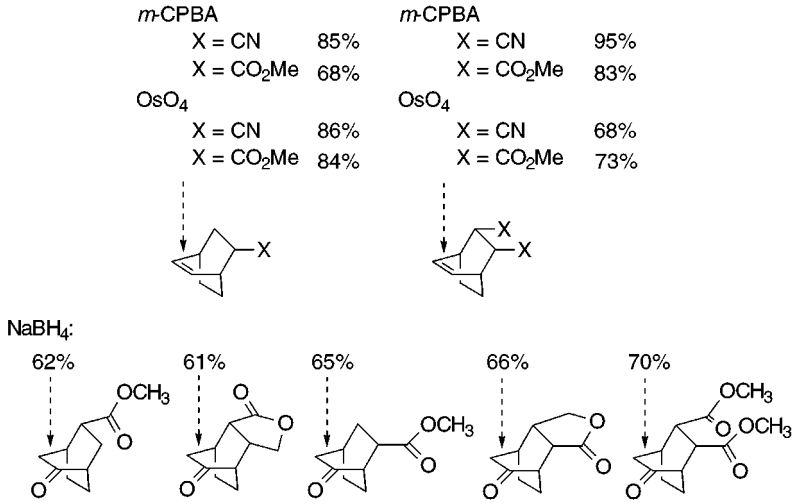


of one may increase the *syn* preference,[20,21] decrease the *syn* preference,[20,22] or not matter much,[15] depending on the reaction probed and the probe, Scheme 7; and the groups with a relatively small positive inductive effect can be equally good or better at *syn*-directing than those with a large one, Scheme 8.[23]

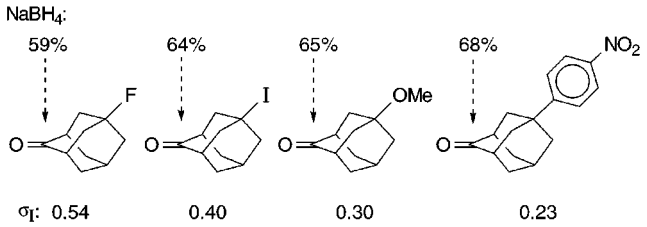
Furthermore, introduction of an allylic heteroatom in the stereogenic center turned out to be anything but a simple replacement of one σ-donor by another. The few data available by the end of the 1970s suggested that homoconjugation of the unshared electron pairs and π-bond electrons, likely to be important as long as proper overlap is possible, can nonetheless be ignored in case of allylic substituents. This expectation was refuted by findings that the alkoxy and acyloxy groups can act either as *syn*- or *anti*-directing groups depending on the probe and the reaction probed, Scheme 9.[24−29]

The relationship between the reagent's properties and π-face selection has also proven difficult to understand. Electron-withdrawing substitution of the reagent was first assumed to simply increase the electron deficiency of the incipient bond.[7] Thus, the hypothesis of hyperconjugative assistance to bond formation, as originally applied to the problem of the stereochemistry of nucleophilic additions to cyclohexanone, predicted that the axial preference should increase in a series of isosteric nucleophiles as their

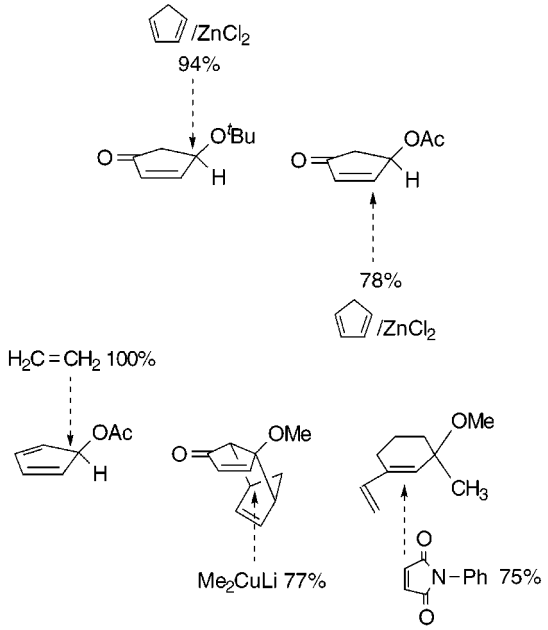
Scheme 7



Scheme 8

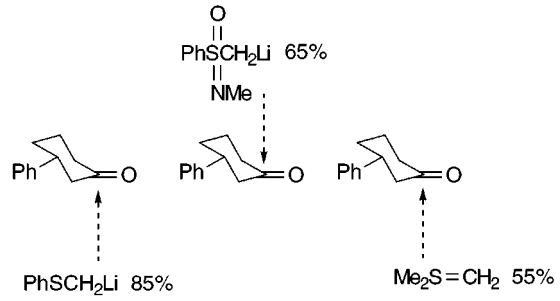


Scheme 9

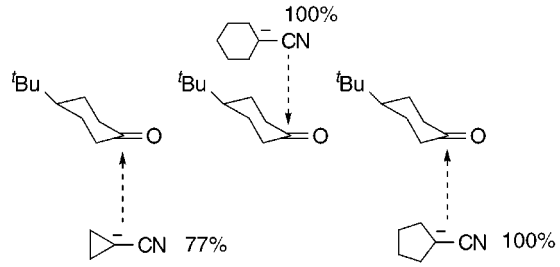


basicity decreases. The major trends in the data available by the end of the 1970s were indeed consistent with a linear Hammett relationship, e.g., lithiated thioanisol was reported to preferentially add to 4-*tert*-butylcyclohexanone on the equatorial face ($C_6H_5SCH_2Li$ 20% axial approach),[30] metalated *N*-tosyl methylsulfimine to be nonselective (e.g., $C_6H_5S(=NTs)CH_2Li$ 50%,[31] $C_6H_5S(=NTs)CH_2Na$ 33%[32] axial approach), and dimethylsulfonium ylide to be axially selective ($(CH_3)_2S^+CH_2Na$ 83% axial approach[33]). However, the subsequent studies of sulfur-stabilized carbanions[12,34,35] have revised the ylide result and

Scheme 10



Scheme 11



suggested a U-shaped dependence, Scheme 10, and the study of the carbonyl- and nitrile-stabilized carbanions[36] also failed to confirm a linear relationship between the π-face preference and basicity, Scheme 11.

Those and other recently encountered difficulties in the interpretation of the effects of remote, allylic, and reagent substitution in terms of hyperconjugation of the incipient bond raise the questions as to whether and how to modify or supplement the 1981 hypothesis. To address these questions, all the evidence concerning substitution effects on π-face selection, which is sufficiently extensive to quantify or at least qualitatively assess the corresponding Hammett or Taft relationships, is now reviewed. The review consists of three parts. The first part focuses on the studies that examine sterically neutral modifications (remote substitution) of aliphatic stereogenic centers using cyclic and polycyclic stereochemical probes. Systematic studies of effects of remote substituents on acyclic stereoselection have been far less frequent,

and conformational freedom in such fragments makes it more difficult to ascertain that the change in substitution is truly "sterically neutral". The second part deals with the effects of allylic substitution defined as the substitution that introduces homoallylic n or π orbitals, that is excluding from consideration, for instance, the effect of silyl substitution. This part extensively reviews examples of acyclic stereoselection which are quite important in the case of π-face selection controlled by the oxaalkyl stereogenic centers. The third part summarizes the data on the relationship between π-face selection and reactivity of the reagents and π-substrates.

The status of the experimental evidence is not discussed in this article since nearly all the reviewed evidence is obtained from the routine studies of diastereoselection where care is taken that the examined reactions are kinetically controlled, conversion complete or nearly complete, and the measurements reasonably accurate and reproducible. The data and their correlations are analyzed from the point of view of the resonance interactions between the incipient bond and the stereogenic center. No attempt is made to systematically cover other theories or ad hoc explanations of π-face selection phenomena. The reader will find some of those other theories discussed elsewhere in the current issue. Critical appraisals of underpinnings of the concepts such as π-orbital desymmetrization, torsional strain, electrostatic interactions, and approach angle-dependent variation in the transition-structure steric strain have been presented earlier.[12,37−39] Finally, the scope of the review is limited to π-face selection processes where the stereogenic center and the incipient center are separated by just one bond. Thus, the classic examples of π-face selection such as the atrolactic synthesis or alkylation of metalated Meyers' oxazolines,[40] where the stereogenic and incipient centers are separated by two intervening trigonal centers, are not included in the present discussion.

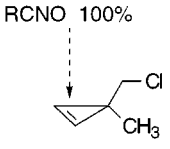
2. Remote Substitution

2.1. Bis-Alkyl Stereogenic Center Free of Steric Bias

2.1.1. β-(Homoallylic)-Substitution

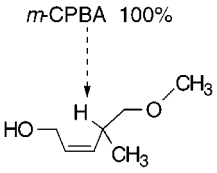
The β-substituted bis-alkyl stereogenic centers can be effective in controlling both cyclic, Scheme 12,[41]

Scheme 12

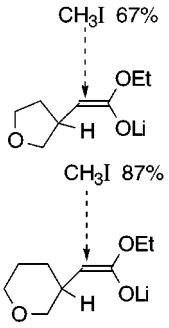


and acyclic stereoselection, Scheme 13.[42] Such stereogenic centers were incorporated in two types of stereochemical probes. The first type is obtained by embedding the center in a ring structure, either in an acyclic fragment with conformational freedom reduced by the 1,3-allylic strain, Scheme 14,[43] or in a spirocyclic fragment, Scheme 15.[17]

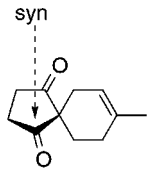
Scheme 13



Scheme 14



Scheme 15



	syn/anti	
	CH_3Li	$NaBH_4$
	4:1	2.5:1
	5:1	6:1
	6:1	7:1
	3:1	7:1
CO_2Et		12:1
	6:1	14:1
	63:1	>99:1

The results suggest that while the effect of some β-substituents may depend on conformation (cf. Schemes 13 and 14, where the effects of oxy substitution are opposite), their electronegativity certainly plays an important role. In particular, the study of $NaBH_4$ reductions and CH_3Li alkylations of spiro[4.5]dec-7-ene-1,4-diones, Scheme 15,[17] demonstrates the control of π-face selection by the inductive effect of the remote substitution. The plot of log [*Z*]/[*E*] vs the σ_I constants of the remote substituents,[44] prepared for the symmetry-expanded sample of the $NaBH_4$ reduction data,[45,46] Figure 1, shows a surprisingly steep increase in the [*Z*]/[*E*] ratio upon increase in the electronic bias. The preferred nucleophile

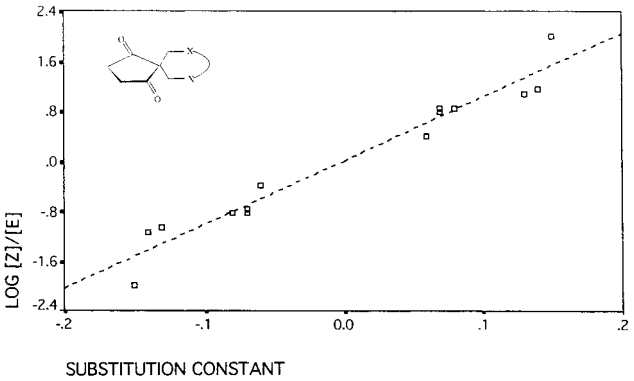
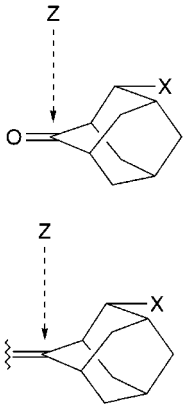


Figure 1. Effect of remote substitution on $NaBH_4$ reduction of spiro[4.5]dec-7-ene-1,4-diones (symmetry expansion,[45] see Scheme 15 for the list of data) log [*Z*]/[*E*] vs Grobb's σ_I constants,[44c] $\hat{Y} = 10.2X$, SE $b_1 = 0.67$, $r^2 = 0.951$.

approach is *syn* to the electron-withdrawing β-substituent and *anti* to the electron-releasing β-substituent; these preferences were attributed to σ-hyperconjugative assistance to bond formation.[17]

The second type of stereochemical probes where bias-introducing substitution is separated from the reaction site by two tetrahedral C atoms (β-substitution) is obtained by attaching sterically remote substituents to highly symmetrical polycycloalkane structures. This approach was first used in the study of $LiAl(O\text{-}t\text{-}Bu)_3H$ reduction of 4-eq-haloadamantan-2-ones.[47] Subsequent investigations of reactions of 4-eq- and 4-eq-9-eq-haloadamantane derivatives included examination of $NaBH_4$ reduction of adamantan-2-ones[48,49] as well as examination of epoxide, diazetidine, and dioxetane formation by biadamantylidenes.[50] The results are summarized in Scheme 16.

Scheme 16



%Z X	$LiAl(O^tBu)_3H$	$NaBH_4$
F	47	67
Cl	55	
Br	57	76
I	66	

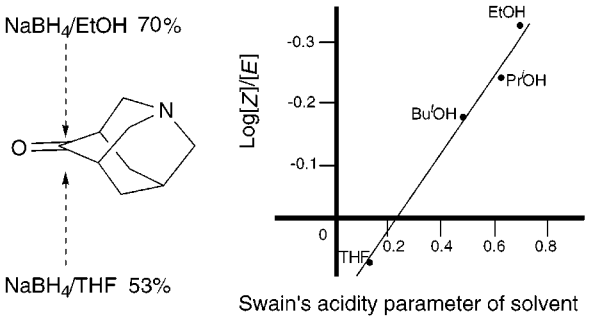
%Z X	*m*-CPBA	N=N	$^1O_2{}^a$
F	72	71	90
Cl	75	74	96
Br	71	70	

[a]addition to the radical cation.

The dependence of log [*Z*]/[*E*] on σ_I is inverse (negative slope), i.e., it appears to be opposite to that found in the case of spiro[4.5]dec-7-ene-1,4-diones, Scheme 15 and Figure 1. It has also been noted that only a small increase in selectivity is observed upon adding the second β-substituent (e.g., 4-eq-bromo vs 4-eq-9-eq-dibromo).[49]

5-Azaadamantan-2-one represents another variant of the β-substituted adamantane-based probe. The CH_3Li alkylation and $NaBH_4$ reduction of this ketone occur with a small *anti* preference,[51] in spite of a subtle distortion which makes the *syn* face slightly more accessible.[52] This preference is dramatically

Scheme 17



reversed in the corresponding *N*-oxide and ammonium iodide.[53] The results of $NaBH_4$ reductions in different alcohols show a large dependence of π-face selection on solvent properties; this is not observed in reductions of other adamantan-2-ones, Scheme 17.[54]

Among the most intensely investigated β-substituted probes are 5,6-*exo*-X,X′-bicyclo(2.2.2)octan-2-ones[14,15] and bicyclo(2.2.2)oct-2-enes.[20−22]

The dependence of π-face selection on the inductive effect of the remote substituents in oxidations of and 1,3-dipolar cycloadditions to 5,6-*exo*-X,X′-bicyclo(2.2.2)oct-2-enes, Scheme 18, is shown in Figure 2.

In the presence of moderately electron-withdrawing groups, the expected *syn* preference initially increases with the increase in the inductive effect. Subsequently, however, as the substitution becomes highly electronegative, this preference may diminish and disappear altogether. The height of the resulting maximum and its distance from the origin decrease on going from epoxidation and osmylation, Figure 2A and 2B, to cycloadditions, Figure 2C and 2D. Thus, the height and the position of the maximum along the σ_I coordinate seem to depend on how electron deficient the reaction site is.

Finally, 2,3-*endo*-X,X′-7-methylenebicyclo(2.2.1)heptanes[18,55] and bicyclo(2.2.1)heptan-7-ones were often used as β-substituted probes as well.[13,16,56−58] The dependence of π-face selection on the inductive effect in $NaBH_4$ reductions of 2,3-*endo*-X,X′-bicyclo(2.2.1)heptan-7-ones,[13,16,56−58] Scheme 19, and 5,6-*exo*-X,X′-bicyclo(2.2.2)octan-2-ones,[14,15] Scheme 20, is shown in Figure 3.

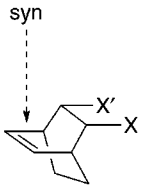
There is no correlation in the first case, Figure 3A, since the log [*Z*]/[*E*] vs σ_I distribution does not go through the origin. The neutral or weakly electron-withdrawing substituents such as alkyl, vinyl, phenyl, and ethynyl groups appear to act as electron-releasing groups. The latter effect is clearly less pronounced in the case of bicyclo(2.2.2)octan-2-ones, Figure 3B, but is still present.

Reactions of 2,3-*endo*-X,X′-7-methylenebicyclo(2.2.1)heptanes[18,55] are presented in Scheme 19. Interestingly, the effect of β-substitution on π-face selection in nucleophilic and electrophilic additions is identical in this system. Sensitivity of log [*Z*]/[*E*] to the change in substitution does not seem to correlate with the negative charge on the reagent.

2.1.2. γ-Substitution

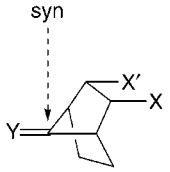
2.1.2.1. Kinetic Evidence. The kinetic competition studies of metal hydride additions and CH_3Li

Scheme 18



X	X′	*m*-CPBA	OsO_4	% syn PhCNO	% syn PhCOCNO	% syn 	% syn CH_2N_2
CH_3	H	52	54				
CH_2OCH_3	H	50	60				
CH_2OTs	H	63	63				
CONHPh	H	81	62				
CO_2H	H	74	76				
CO_2CH_3	H	68	84				
CN	H	85	86				
OH	OH	83		70	64	48	
$-OC(CH_3)_2-O-$		90		75	73	58	
CO_2CH_3	CO_2CH_3	83	73				
$-OC(=O)-O-$		96	80	71	71	51	38
$OCOCH_3$	$OCOCH_3$	82		50	54	46	
OSO_2CH_3	OSO_2CH_3	96		45			30
CN	CN	95	68		53	52	31

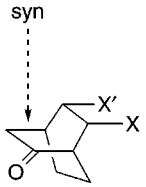
Scheme 19



X	X′	Y = O $NaBH_4$	syn % CH_3Li	Y = CH_2 $AcOHg^+/H_2O$	syn % *m*-CPBA	BH_3
CH_2CH_3	CH_2CH_3	20	17	17	30	38
$-CH_2CH_2CH_2-$		24	14			
$-CH=CH-CH_2-$		37	22			
$C_6H_4NH_2$	H	40				
$C_6H_4CH_3$	H	45				
C_6H_5	H	45				
C_6H_4F	H	46				
$CH=CH_2$	$CH=CH_2$	36				
CH_2OCH_3	CH_2OCH_3	40	34	40		44
$-CH_2-O-CH_2-$		50				
$-C(=O)-CH_2-CH_2-$		53				
$C_6H_4NO_2$	H	58				
$C\equiv CH$	H	69				
CO_2CH_3	H	68			62[a]	
CH_2Br	CH_2Br	45				
CN	H	82			77[a]	
CO_2CH_3	CO_2CH_3	84	90	>95	74	59

[a] Y = $C(CH_3)_2$

Scheme 20



X	X′	$NaBH_4$	$^iBu_2AlH$	CH_3Li
CH_2CH_3	CH_2CH_3	39	34	34
CH_2OCH_3	CH_2OCH_3	50		
$CH=CH_2$	$CH=CH_2$	50	50	54
H	CO_2CH_3	62	61	
$-CH_2OC(=O)-$		61		
CO_2CH_3	H	65	66	
$-C(=O)-O-CH_2-$		66		
CO_2CH_3	CO_2CH_3	70	67	

alkylation of 5-X-adamantan-2-ones were made using X = H, F, Br.[59] According to the hypothesis of σ-assistance, remote electron-withdrawing substitution improves the inductive stabilization of the extra negative charge (electron-rich carbonyl O) in the transition state for nucleophilic addition but decreases the resonance stabilization of the incipient bond (electron-deficient carbonyl C). Given a proper balance of the two effects in addition to a symmetrical probe, a paradoxical kinetic divergence might be observed as a result of the remote electron-withdrawing substitution: acceleration of the *syn* approach and retardation of the *anti* approach of a nucleophile. The data summarized in Table 1 show such retardation of the *anti* CH_3Li alkylation by both C(5)−F and C(5)−Br.

Table 1. Results of Competition Experiments with 5-X-Adamantan-2-ones

X nucleophile	*N* [a]	k_{obs}^X/k_{obs}^H	*Z*/*E*	k_Z^X/k_Z^H	k_E^X/k_E^H
		F			
CH_3Li	6	1.30 ± 0.05	1.94	1.71	**0.89**[b]
$LiAlH_4$	6	1.36 ± 0.02	1.44	1.61	1.11
$LiBH_4$	6	4.90 ± 0.47	1.50	5.88	3.92
$NaBH_4$	11	5.85 ± 0.37	1.44	6.90	4.80
		Br			
CH_3Li	8	1.21 ± 0.07	1.70	1.52	**0.90**
$LiAlH_4$	5	1.40 ± 0.02	1.27	1.57	1.23
$LiBH_4$	6	5.26 ± 0.38	1.22	5.78	4.74
$NaBH_4$	9	6.01 ± 0.62	1.17	6.48	5.54

[a] Number of observations. [b] $k_E^X/k_E^H = 2(k_{obs}^X/k_{obs}^H)/(1 + E/Z)$. *Z*/*E* ratio determined by GC integration. The experiments were run under conditions that are pseudo-first order in each ketone by using a large excess of reducing or alkylating agent. There was no change in the *Z*/*E* ratio in the course of the reaction.

2.1.2.2. Stereochemical Evidence. The γ-substituted probes include 5-X-2-methyleneadamantanes,[10,19,23,60] adamantan-2-ones,[10,19,23,61,62] 4-X-penta-

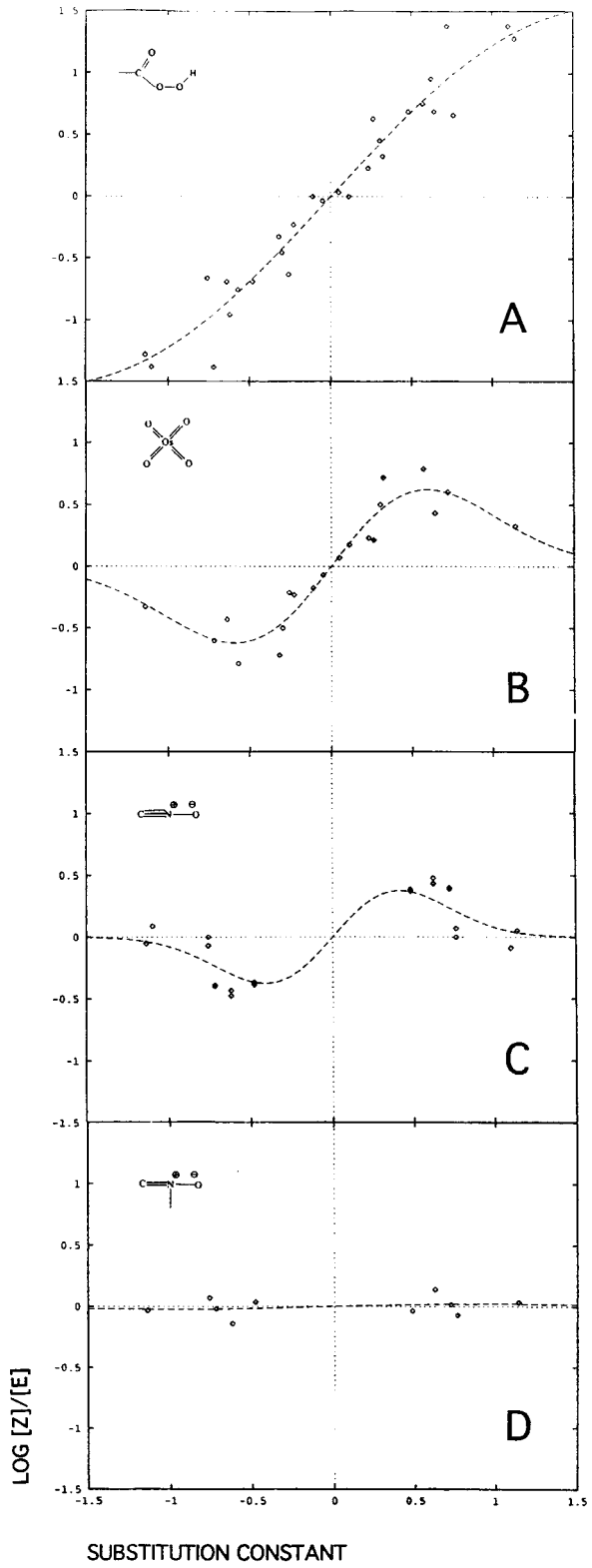


Figure 2. Effect of remote substitution on additions to 5- and 5,6-*exo*-substituted bicyclo(2.2.2)oct-2-enes, log [*Z*]/[*E*] vs $\sum\sigma_I$[44a] (symmetry expansion,[45] see Scheme 18 for the list of data): (A) *m*-CPBA epoxidation; (B) OsO_4 dihydroxylation; (C) RCNO (nitrile oxides, PhCNO, and PhCOCNO) cycloaddition; (D) $R_2C{=}N^+(O^-)R$ (nitrone, 3,4-dihydroisoquinoline-*N*-oxide) cycloaddition. The curves log [*Z*]/[*E*] = $b_1\sigma_I/\exp(b_2\sigma_I^2)$ are obtained by omitting the $b_3\sigma_R$ term from the equations given in Table 2.

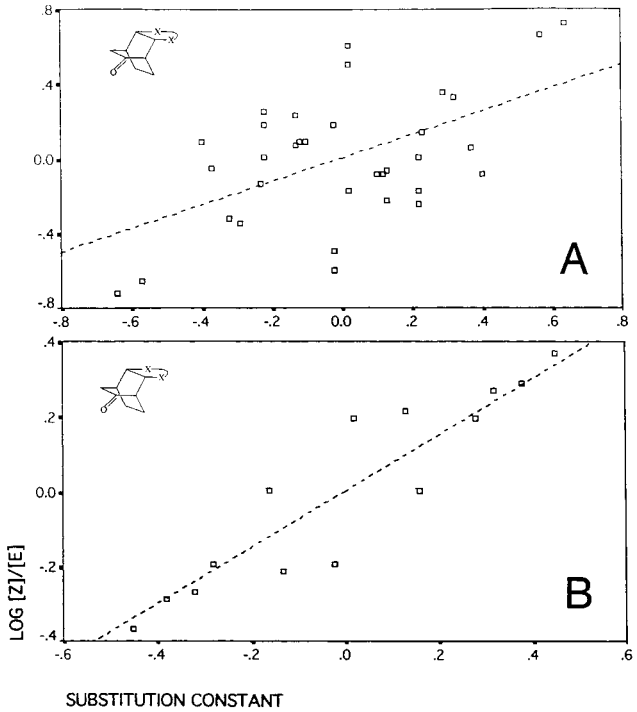


Figure 3. Effect of remote substitution on $NaBH_4$ reductions, log [*Z*]/[*E*] vs σ_I:[44a] (A) 2,3-*endo*-substituted bicyclo(2.2.1)heptan-7-ones, $\hat{Y} = 0.63X$, SE $b_1 = 0.17$, $r^2 = 0.287$; (B) 5,6-*exo*-substituted bicyclo(2.2.2)octan-2-ones, $\hat{Y} = 0.75X$, SE $b_1 = 0.09$, $r^2 = 0.814$ (symmetry expansion,[45] see Schemes 19 and 20 for the lists of 2,3- and 5,6-substituents).

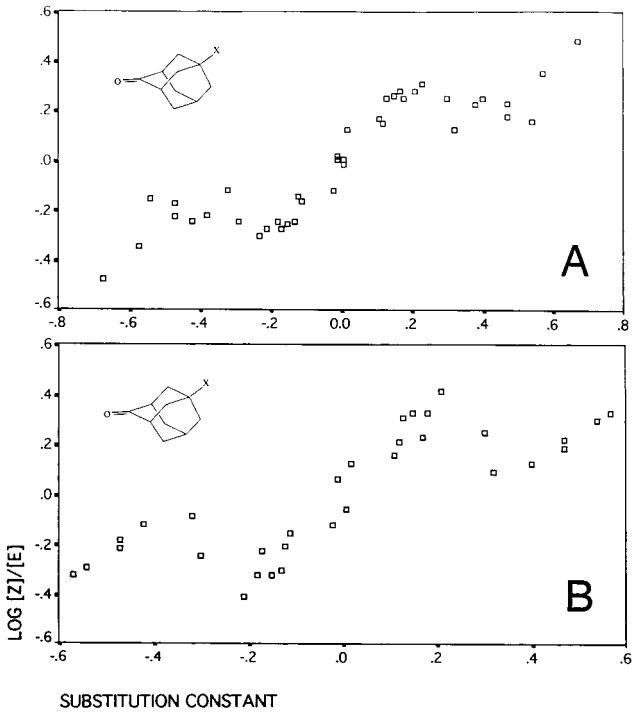


Figure 4. Effect of remote substitution on nucleophilic additions to 5-X-adamantan-2-ones, log [*Z*]/[*E*] vs σ_I:[44a] (A) $NaBH_4$ reduction; (B) CH_3Li alkylation. Symmetry expansion,[45] the substituents X are (in order of increasing σ_I): *t*Bu, Me, C_6H_4-*p*-X′ (X′ = NMe_2, OMe, H, F, Br), NMe_2, C_6H_4-*p*-X′ (X′ = CO_2Me, CN, NO_2), OMe, CO_2Me, OAc, CF_3, I, Br, Cl, F, CN, NO_2 (see Tables 2, 4, and 5 in ref 23).

cyclo(4.3.0.$0^{2,4}$.$0^{3,8}$.$0^{5,7}$)decan-9-ones,[63,64] and 4-X-pentacyclo(4.4.0.$0^{2,4}$.$0^{3,8}$.$0^{5,7}$)undecan-9-ones (norsnoutan-9-ones and snoutan-9-ones, see section 2.3.2.2.).[64] The results obtained with these probes are sum-

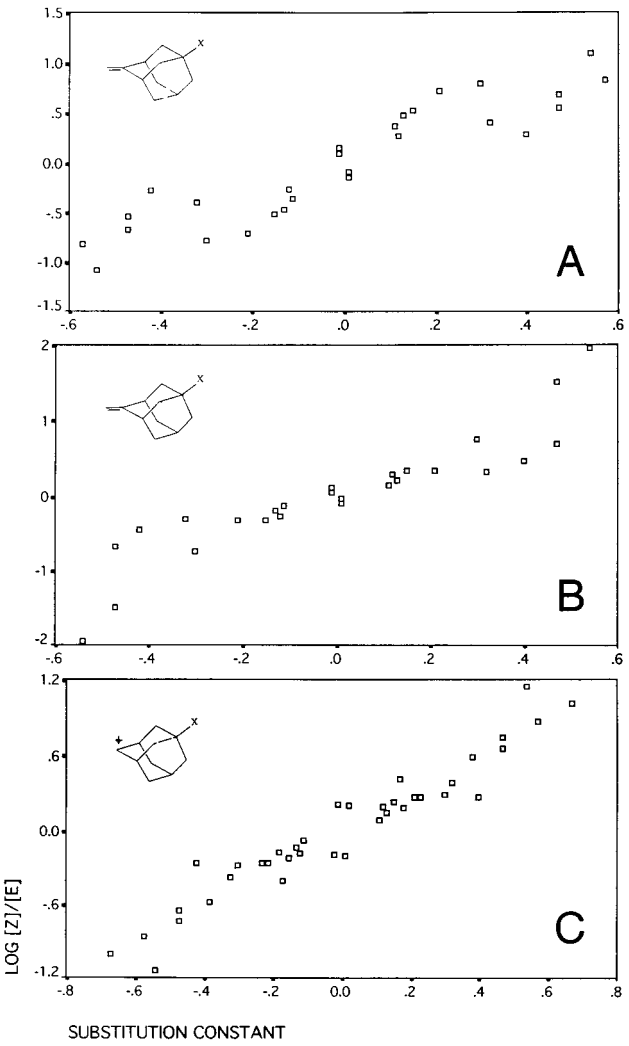


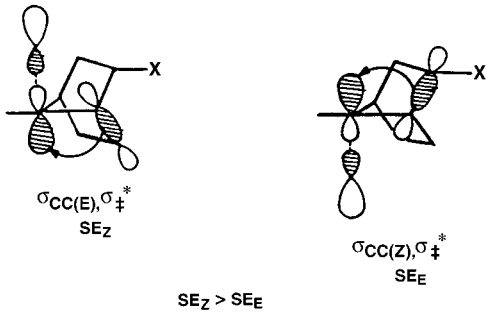
Figure 5. Effect of remote substitution on anion capture by 5-X-adamantyl-2 cations, log [*Z*]/[*E*] vs σ_I:[44a] (A) HCl addition to 2-methylene-5-X-adamantanes in CH_2Cl_2 (2-CH_3, tertiary cations); (B) HCl addition to 2-methylene-5-X-adamantanes in CH_3NO_2 (2-CH_3, tertiary cations); (C) DAST fluorination of 5-X-adamantan-2-ols in CH_2Cl_2 (2-H, secondary cations). Symmetry expansion,[45] X as listed in the caption for Figure 4, see Tables 3, 6, and 8 in ref 23 for the lists of data.

marized elsewhere in previous articles; the corresponding log [*Z*]/[*E*] vs σ_I plots for the adamantane-based probes are shown in Figures 4 and 5. It can be seen that the initial increase in the inductive effect of the 5-substituents brings about a maximum of the *syn* preference in $NaBH_4$ reductions and CH_3Li alkylations of adamantan-2-ones, Figure 4A and 4B, and in Cl^- capture by the tertiary 2-methyl-2-adamantyl cation in CH_2Cl_2, Figure 5A.[19,23] As noted previously, Figure 2, this maximum is further away from the origin when the reaction site is more electron-deficient, i.e., in the cation additions, cf. Figures 4A and 5A. In contrast, however, to the behavior of bicyclo(2.2.2)oct-2-enes, the very electronegative C(5) groups reverse the decline of the *syn* preference, which increases again at $\sigma_I > 0.45$. Interestingly, this complex pattern is not observed in the case of F^-, capture by the secondary 2-adamantyl cation,[19,23] Figure 5C.

2.1.3. Inductive Effect of Remote Substitution: Rise and Fall of Electronic Bias

The data in Figures 2, 4, and 5 suggest that as the positive inductive effect of the remote substitution increases, it can obliterate the electronic bias that it initially creates. The less electron deficient the transition state, the faster the turnaround occurs. This phenomenon can be explained within the framework of the hypothesis of hyperconjugative σ-assistance to bond formation.[7] The electron-withdrawing groups introduce electronic bias promoting the *syn* preference and initially increase it because the directly substituted C−C bond ($\sigma_{CC(Z)}$) becomes a poor σ-electron donor and cannot assist formation of a bond oriented *anti* with respect to the substituent: the $\epsilon(\sigma_{CC(Z)})$ level becomes lower than the $\epsilon(\sigma_{CC(E)})$ level, Scheme 21.

Scheme 21



Recall, however, that the σ-donor ability of the unsubstituted bond of bicyclo(2.2.2)oct-2-enes ($\sigma_{CC(E)}$), assisting the *syn* approach, eventually must also be affected as the inductive effect increases: this bond corresponds to the substituted bond of 5-X-adamantan-2-ones. Thus, in the presence of highly electronegative groups, all the C−C bonds in the probe become poorer σ-electron donors, i.e., all the σ_{C-C} levels go down. The energy gaps $\Delta\epsilon = \epsilon(\sigma^*_‡) - \epsilon(\sigma_{CC(Z)})$ and $\Delta\epsilon = \epsilon(\sigma^*_‡) - \epsilon(\sigma_{CC(E)})$ between the donor orbitals $\sigma_{CC(Z)}$ and $\sigma_{CC(E)}$ and the acceptor orbital $\sigma^*_‡$ increase, and the difference between $\epsilon(\sigma_{CC(Z)})$ and $\epsilon(\sigma_{CC(E)})$ that is perceived by the transition state (incipient bond) decreases. The electronic bias declines and with it the *syn* preference. The resulting nonlinear dependence of π-face selectivity on the inductive effect is predicted by the PMO formulation

$$\log k_Z/k_E \propto SE_Z - SE_E \propto \epsilon(\sigma_{CC(E)}) - \epsilon(\sigma_{CC(Z)})/(\Delta\epsilon)^2$$

where $\Delta\epsilon$ is the energy gap between the vicinal σ-donor orbitals and the vacant orbital of the incipient bond, $\Delta\epsilon = \epsilon(\sigma^*_‡) - \epsilon(\sigma_{CC(Z)}) \approx \epsilon(\sigma^*_‡) - \epsilon(\sigma_{CC(E)})$.[65] The σ_{CC} energy levels depend on σ_I, and consequently, log k_Z/k_E is expected to be proportional to $f(\sigma_I)/f(\sigma_I)^2$. Since the exponential function in the quadratic term responds better to the change in σ_I in the actual data samples than a polynomial one, a convenient analytical form of the above model is[66]

$$\log k_Z/k_E = b_1\sigma_I/\exp(b_2\sigma_I)^2$$

The plots in Figure 2 show that this function accounts rather well for the surprising response of oxidations and cycloadditions to the electron-withdrawing sub-

Table 2. Regression Analysis of the Data on π-Face Selection in Reactions of Bicyclo(2.2.2)octane-Based Probes Using the Function log $[Z]/[E] = b_1\sigma_I/\exp(b_2\sigma_I)_2 + b_3\sigma_R$

reagent	$N+1$	b_1, SE	b_2, SE	b_3, SE	adjusted r^2	ref
5,6-*exo*-X,X′-Bicyclo(2.2.2)oct-2-enes						
m-CPBA	15	1.4 (0.1)	0.2 (0.1)	0.0 (0.1)	0.948	20−22
OsO_4	11	1.7 (0.2)	1.4 (0.3)	0.0 (0.2)	0.917	20−22
$RC{\equiv}N^+-O^-$	11	1.5 (1.3)	2.9 (0.9)	0.0 (0.2)	0.832	22
5,6-*exo*-X,X′-Bicyclo(2.2.2)octan-2-ones						
$NaBH_4$	9	0.7 (0.1)	1.2 (0.6)	0.9 (0.1)	0.969	14, 15

stitution of bicyclo(2.2.2)oct-2-ene. The corresponding regression data are listed in Table 2, entries 1−4 (the complete function used includes the term $b_3\sigma_R$ to account for the resonance effect of the β-substituents, see the following section, 2.1.4.). Interestingly, it seems that the turnaround occurs sooner along the σ_I coordinate in the latter probes than in the 7-methylenebicyclo(2.2.1)probes for which the linear approximation is adequate.[66] Another comparison of the responses of these two skeletons can be made in the case of $NaBH_4$ reductions of 4-substituted pentacyclo(4.3.0.0^{2,4}.0^{3,8}.0^{5,7})decan-9-ones and pentacyclo(4.4.0.0^{2,4}.0^{3,8}.0^{5,7})decan-9-ones (norsnoutan-9-ones and snoutan-9-ones),[63,64] see section 2.3.2.2.

The initial change in the *syn* preference in reactions of the 5-substituted adamantane-based probes, Figures 4 and 5A, strongly resembles the phenomenon observed in reactions of bicyclo(2.2.2)oct-2-enes, Figures 2A−C, where the inductive effect gradually appears to obliterate the electronic bias that it created. Indeed, the 5-X-substituted adamantane derivatives can be considered as β-substituted probes when the −C(5)−X groups are taken as the remote substituents. The −C(5)−X groups are only moderately electron withdrawing (separation by a saturated C lowers the inductive effect of the X groups by a factor of ∼0.4), but there are three routes available to affect the C−C bonds interacting with the reaction site, and the C(5)−X impact is therefore enhanced.[50] The course of change in log $[Z]/[E]$ cannot, however, be described solely by the function log $k_Z/k_E = b_1\sigma_I/\exp(b_2\sigma_I)^2$ because an additional contribution is clearly involved: log $[Z]/[E]$ increases again in the presence of highly electronegative groups. The nature of this other contribution is discussed in section 2.1.4.2.

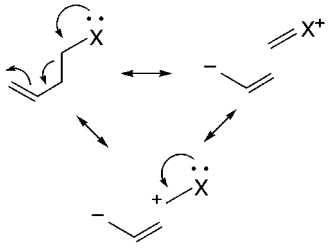
2.1.4. Extended Hyperconjugation

2.1.4.1. Resonance Effect of β-Substituents. The inverse correlation between π-face selection and the inductive effect of 4-eq-halogen substitution, cf. section 2.1.2.1., has been explained as a result of back-donation of the halogen unshared electron pair that assists σ_{CC}-hyperconjugative stabilization of the incipient bond during the *anti* approach of a reagent, Scheme 22.[67] Such interactions are often depicted in terms of the bond−no bond resonance as shown above.[43] However, it is also useful to think of the back-donation assistance in terms of n-donor interaction with the vacant σ^*_{CC} orbital which enables the σ_{CC} orbital to be a better electron donor in the interaction with the incipient bond, Scheme 23. This model emphasizes the similarity of the halogen back-donation to the anomeric effect in Altona's interpretation[68] and predicts that the importance of such participation ought to depend on the properties of the substituted C−C bond that interacts with the reaction site: the higher its electron affinity, i.e., the lower the σ^*_{CC} energy level, the more important this contribution will be (the σ^*_{CC} energy level can be lowered, e.g., by electron-withdrawing substitution or by incorporation of the C−C bond into a smaller ring). The importance of back-donation also depends on the donor ability of the electron-donating orbital. Ab initio calculations indicate that the inherent π-donor capacity of the heavier elements is as large or larger than their second-row counterparts.[69] However, the σ_P^+ and σ_R constants for halogens and chalcogens decrease going down the column,[70] and the experimental evidence, such as ionization potentials of 4-eq- and 5-halogenated biadmantylidenes,[50] often suggests that fluorine back-donation into σ-bonds is more effective than that of the heavier halogens. In fact, this back-donation is sometimes sufficient to offset the depletion of electron density in the substituted bond caused by the inductive effect; an example is the change in the ^{35}Cl NQR frequency differences $\nu(XCH_2Cl)-\nu(CH_3Cl)$ for halochloromethanes X−CH_2−Cl: F −0.23 (net electron transfer to Cl), Cl 1.96, Br 2.05, I 2.35,[71] or in the charge density at the bond critical point.[72] It is therefore not surprizing that the *syn* preferences are relatively small for 4-eq-F derivatives and increase in the order F < Cl < Br < I.

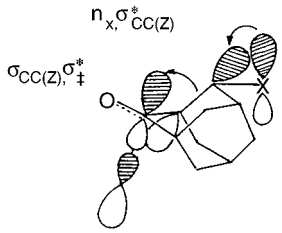
The n back-donation was also invoked to explain the high *anti* preference in alkylation of β-(2′-tetrahydropyranyl)- and β-(2′-tetrahydrofuranyl)-ester enolates, Scheme 24,[43] and the *anti* preference in $NaBH_4$ reduction of 5-azaadamantan-2-one in THF, Scheme 25.[54] It was proposed that the N lp assistance is diminished in protic solvents by H-bonding, and therefore π-face selection correlates with the alcohol acidity.[54] The difference in effectiveness of the six-membered and five-membered ring, Scheme 25, was attributed to the difference in O lp, σ^*_{CC} overlap; it should also be noted that the ionization potential of THP is lower than that of THF.[73]

Besides the n back-donation, π back-donation was invoked in the discussion of the effect of remote substitution on π-face selection, namely, to explain

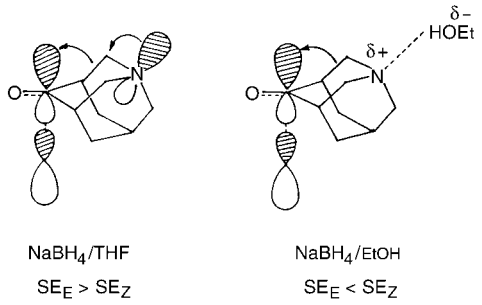
Scheme 22



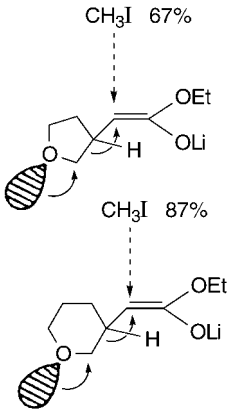
Scheme 23



Scheme 24



Scheme 25



why the *endo*-vinyl group acts as an electropositive, *anti*-directing group in nucleophilic additions to bicyclo(2.2.1)heptan-7-one.[13] Regression of the $NaBH_4$ reduction data for 2-*endo*- and 2,3-*endo*-substituted bicyclo(2.2.1)heptan-7-ones[13,16,56−58] on both σ_I and σ_R constants of the 2,3-substituents, Figure 6A,[46] indeed leads to a satisfactory correlation which could not be obtained with σ_I alone, cf. Figure 3A. This result implies that not only π but also σ back-donation is important in this probe. The same regression reveals that the resonance contribution is smaller in the case of 5,6-*exo*-substituted bicyclo(2.2.2)octan-2-ones,[14,15] Figure 6B, which is consistent with the fact that the σ^*_{CC} energy levels are lower in the bicyclo(2.2.1)-heptan-7-one skeleton.

The apparently nonlinear distribution for 5,6-*exo*-X,X′-bicyclo(2.2.2)octan-2-ones, cf. Figure 6B,[14,15] reminiscent of the plots for additions to bicyclo(2.2.2)oct-2-enes, Figure 2, suggested that these data were fitted using the function $\log k_Z/k_E = b_1\sigma_I/\exp(b_2\sigma_I)^2 + b_3\sigma_R$, which yielded a b_1/b_3 ratio of ∼0.8, see Table 2.

2.1.4.2. Resonance Effect of γ-Substituents. The C(5)−$Si(CH_3)_3$ and C(5)−$Sn(CH_3)_3$ groups promote *anti* approach of nucleophiles in additions to 5-X-adamantan-2-ones and 5-X-2-adamantyl cations, Scheme 26.[10,19,23,61,74] The *anti* preference increases as the transition state becomes more dependent on σ-assistance, on going from ketone reduction with $NaBH_4$ and $LiAlH_4$ to alkylation with CH_3Li, then to silane Et_3SiH and $PhSiH_3$ reduction, and eventually to cation capture. This effect was attributed to double hyperconjugation,[75] with participation of the C(5)−X (X = Si, Sn) and C(7)−H bonds, which is referred to in the present review as extended hyperconjugation involving C_γ σ-bonds.

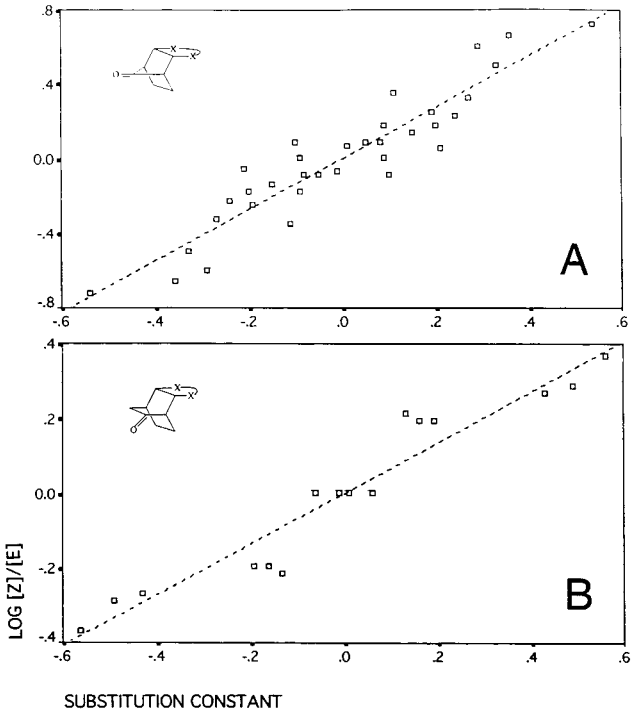
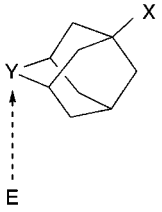


Figure 6. Effect of remote substitution on $NaBH_4$ reductions, log [*Z*]/[*E*] vs σ_π,[46] $\sigma_\pi = \lambda\Sigma\sigma_I + \Sigma\sigma_R$ (symmetry expansion,[45] see Schemes 19 and 20 for X): (A) 2,3-*endo*-substituted bicyclo(2.2.1)heptan-7-ones, $\lambda = 0.5$, $\hat{Y} = 1.37X$, SE $b_1 = 0.09$, $r^2 = 0.869$; (B) 5,6-*exo*-substituted bicyclo-(2.2.2)octan-2-ones, $\lambda = 1.0$, $\hat{Y} = 0.68X$, SE $b_1 = 0.05$, $r^2 = 0.923$. The result of fitting the latter data with the function $\log [Z]/[E] = b_1\sigma_I/\exp(b_2\sigma_I^2) + b_3\sigma_R$ is given in Table 2.

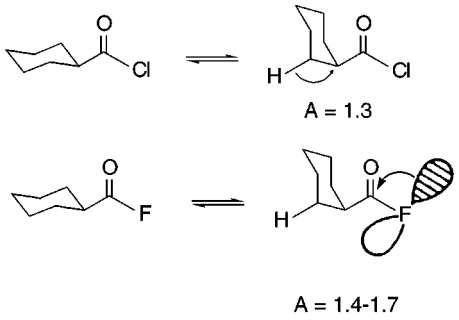
Scheme 26



Reactants	E% X = $Si(CH_3)_3$	E% X = $Sn(CH_3)_3$
Y = C=O		
$NaBH_4$, CH_3OH	50	52
$NaBH_4$, ^iPrOH	55	57
$LiALH_4$, Et_2O	56	62
sBu_2AlH, toluene	52	58
CH_3Li, Et_2O	51	64
Y = $C=CH_2$		
m-CPBA, CH_2Cl_2		50
Y = $\overset{+}{C}-OCH_3$		
Et_3SiH, CH_2Cl_2, PPHF	65	70
$PhSiH_3$, CH_2Cl_2, PPHF	59	75
Y = $\overset{+}{C}-CH_3$		
HCl, CH_3NO_2	50	
HCl, CH_2Cl_2	65	
Y = $\overset{+}{C}-H$		
DAST, CH_2Cl_2	86	100

The difference in the resonance-donor capability of the C(5)−X and C(7)−H bonds may be relevant not only in the case of X = Si or Sn. In fact, its importance is expected to increase along the σ_I coordinate for two reasons: (1) the σ-hyperconjugative capability of the C(5)−X bonds is likely to inversely correlate with the inductive effect of X, and (2) the increase in the inductive effect of X should lower all the σ^*_{CC} energy levels and thereby increase the magnitude of extended hyperconjugation. Thus, the latter effect is likely to be responsible for reversal of the decline of *syn* preference along the σ_I coordinate in Figures 4 and 5. In the reactions that display

Scheme 27



O X, X	H	CH_3	OMe	OH	Cl	F	O^-K^+
A, T < 200 K	0.82 (CD_2Cl_2)	1.02 (CD_2Cl_2/CS_2)	1.18 (Et_2O/PhMe)				
	0.84 (CD_2Cl_2/CS_2)	1.21 ($C_6D_5CD_3$)	1.31 (CS_2)				
A, T = 298 K		1.52 (CH_3OH)	1.27 (CH_3OH)	1.36 (diglyme/H_2O)	1.29 (dodecane)	1.4-1.7 (hexane)	1.96 ($HOCH_2CH_2OH$)
				1.38 (dodecane)			

strong dependence on extended hyperconjugation, Figure 5C, the extrema of log [*Z*]/[*E*] vs σ_I distribution cannot be detected. It should be noted that such extended hyperconjugation also seems to control π-face selection in some β-substituted probes, possibly generating, for instance, high *anti* preference in nucleophilic additions to 2,3-*endo*-diethylbicyclo-(2.2.1)heptan-7-one,[13] cf. Figure 6A.

2.1.4.3. Resonance Effect in Ground-State Conformational Equilibria. The structural and spectroscopic evidence to support the notion of extended hyperconjugation of remote substituents is rather scarce so far.[76] Therefore, it is important to note that examination of conformational equilibria, a major tool of the studies of hyperconjugative interactions (e.g., anomeric effect), can also be employed to study the extended hyperconjugation. The following two areas of conformational analysis seem particularly promising as the source of information about the latter effects.

A. Cyclohexane Substituent *A* Values. It has been suggested[77] that the constants for the axial−equatorial equilibria of monosubstituted cyclohexanes are determined not only by the bulk of the substituents X but also by σ,σ^*-hyperconjugation since the *A* values ($A = -\Delta G°$ for the ax−eq equilibrium) decrease and even change sign upon electron-withdrawing substitution of X and decrease when X is exchanged going down the main groups of the periodic table, i.e., whenever the σ^*_{CX} level is lowered.[78,79] The decrease in the σ^*_{CX} energy improves stabilization of the axial conformer by $\sigma_{CH},\sigma^*_{CX}$ interaction and thereby lowers the *A* value. This proposition was later supported by the correlation between the *A* values of the oxy substituents and the pK_a values of the corresponding O-acids.[80] Consequently, halogen substitution of the group X should lower its *A* value by lowering the σ^*_{CX} level due to the inductive electron-withdrawing effect in the order F > Cl > Br > I. However, if the extended hyperconjugation is important, that order would be reversed. The two available examples indicate that this might in fact be true. Thus, the conformational energy *A* of the fluorocarbonyl group has been reported to be greater than that of the chlorocarbonyl or methoxycarbonyl group, Scheme 27.[81−84]

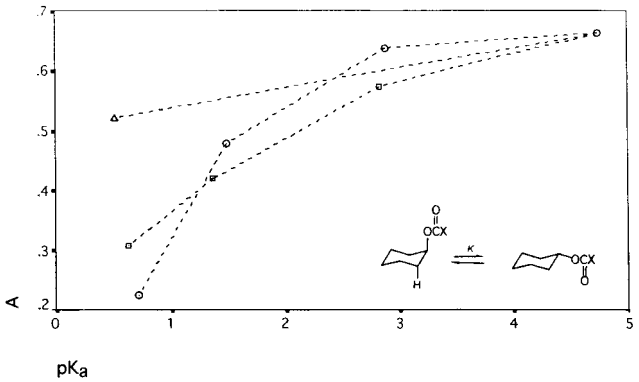
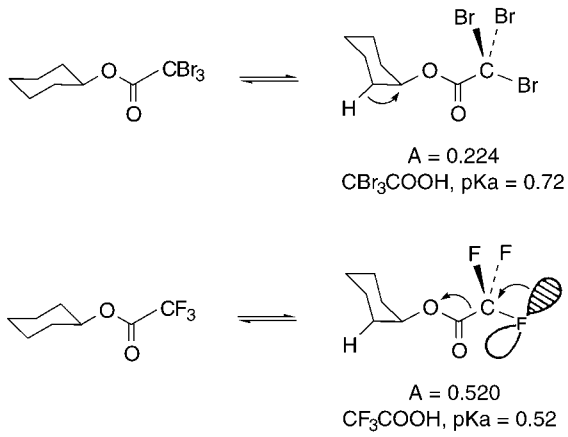


Figure 7. Effect of acyl halo substitution on conformational equilibria of cyclohexyl acetates ($X_1X_2X_3CC(=O)OR$, R = cyclohexyl): *A* values vs pK_a of haloacetic acids, (△) X = F; (□) X_i = Cl; (○) X_i = Br.

The above evidence concerning *A* values of the acyl substituents C(=O)X′ is apparently tentative,[85] but the observed trend is confirmed by the data on *A* values of haloacetates, Figure 7.[86] In the case of trihaloacetates, the correlation between the *A* values and the pK_a's of the trihaloacetic acids is inverse, which would be expected only if the σ^*_{CO} energy levels are raised here by halogen back-donation, as shown in Scheme 28.

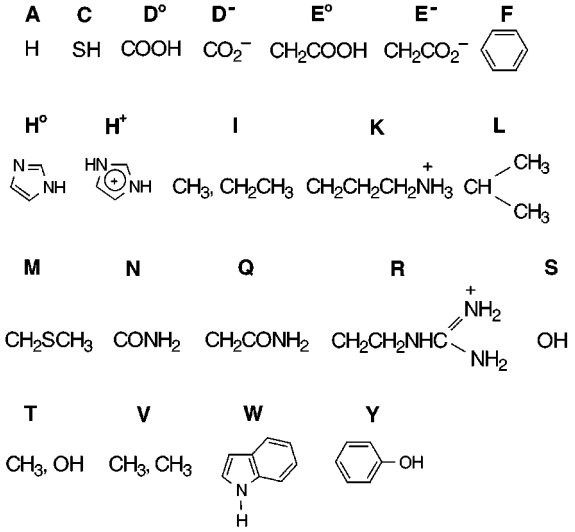
B. Secondary Structure Propensities of Ala* Amino Acids.[87] It is worthwhile to note that just like the reaction site during nucleophilic addition to carbonyls, the peptide backbone chain is moderately electron deficient due to the electronegativity of the carbonyl O and might be stabilized by electron donation from the side-chain $C_\alpha-C_\beta$ bonds. The σ^*_{CC} energy level of the $C_\alpha-C_\beta$ bond is low because this bond carries strongly electron-withdrawing groups (two amide groups). Thus, its donor and acceptor capabilities should be controlled by extended hyper-

Scheme 28



conjugation, i.e., the inductive and resonance effects of the side-chain C_β substituents. The sample of coded amino acids conveniently comprises a set of such C_β substituents of a wide range of acceptor and donor properties, cf. Scheme 29.

Scheme 29



The importance of the side-chain inductive and resonance effect is in fact indicated by the correlations between the ^{13}C and ^{15}N NMR chemical shifts of amino acids in H_2O ($^{13}C'$=O) and *N*-acetylamino acids in DMSO,[88] Figure 8, or the relative rates of base-catalyzed isotope exchange in amino acid *N*-acetyl-*N*′-methylamides,[89] Figure 9, and the σ_I and σ_R constants of the C_β substituents.[90]

The ^{13}C chemical shift of a trigonal C is expected to be determined by the dominant paramagnetic term and therefore by partial occupancy of the $2p_z$-orbital,[91] which would make it a sensitive probe of hyperconjugative donation. Regression analysis on σ_I and σ_R of the C_β substituents,[92,93] Figure 8A, reveals that the amino acid C′=O ^{13}C chemical shift depends largely on the inductive effect: $\sigma_{Ala}* = \sigma_I - 0.5\sigma_R$. The electron-withdrawing effect of the side chain R causes an upfield shift of the $^{13}C'$=O signal with respect to Ala, presumably due to the π-charge depolarization of the carboxylate ion. The small σ_R contribution is consistent with the hyperconjugative transfer of electron density from the $C_\alpha-C_\beta$ bond into

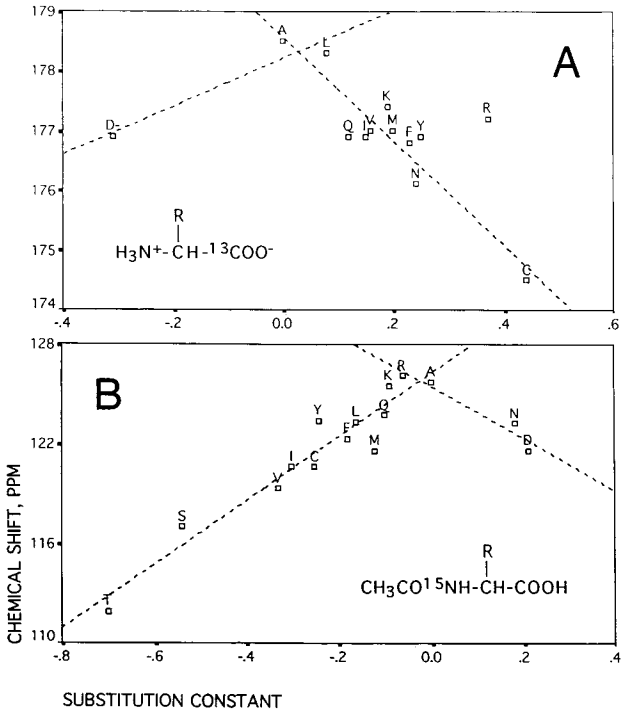


Figure 8. Effect of Ala* side-chain substitution on chemical shifts: (A) C′=O ^{13}C (amino acids, H_2O) vs $\sigma_{Ala}* = \sigma_I - 0.5\sigma_R$, $r^2 = 0.864$ for $\sigma_{Ala}* > 0$ (R not included in the correlation).[93] (B) ^{15}N (*N*-acetyl amino acids, DMSO) vs $\sigma_{Ala}* = 0.33\sigma_I + \sigma_R$, $r^2 = 0.922$ for $\sigma_{Ala}* < 0$ (E omitted since $\sigma_{Ala}*$ is highly dependent on the ionization state which is unknown).

the C′ $2p_z$ orbital. On the other hand, the upfield shift of the Ala* ^{15}N signals with respect to the Ala signal, in the case of the net electron donors at C_β, $\sigma_{Ala}* < 0$ in Figure 8B, depends mostly on σ_R, the resonance effect: $\sigma_{Ala}* = 0.33\sigma_I + \sigma_R$. This suggests that the upfield shift occurs mainly due to hyperconjugative transfer of electron density from the $C_\alpha-C_\beta$ bond into the N $2p_z$ orbital depleted by π-bonding to C=O. In the case of the net electron-acceptor substituents, the upfield shift probably occurs due to the π-charge depolarization of the amide bond.

The rate of base-catalyzed isotope exchange is likely to reflect stabilization of the incipient N anions, i.e., the magnitude of resonance donation into N $2p_z$ (destabilizing) and inductive withdrawal (stabilizing). Indeed, the rate of the N-acylamine exchange, Figure 9A, depends mostly on σ_R (the $C_\alpha-C_\beta$ bond interaction with the N $2p_z$ orbital), and the rate of the N-methylamide exchange, Figure 9B, depends mostly on σ_I (C_α interaction with C′).

In the conformational analysis of proteins, the simple two-state approximation is used to describe helix−coil or strand−coil transitions and the parameters equivalent to the cyclohexane substituent *A* values are thermodynamic secondary structure propensities of amino acids. Such data became available by the mid-1990s as a result of careful host−guest studies measuring the change in free energy of folding caused by a single-site mutation.[94] The method compares the stability of a standard protein with that of mutants in which other amino acids are individually substituted into the guest site. Using, for instance, Gly as the reference residue, the secondary structure propensity is given as the change in protein

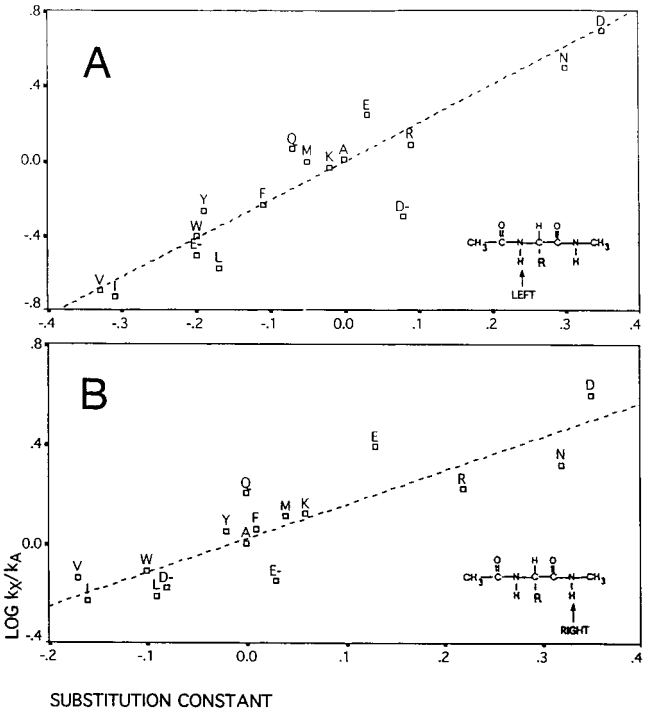


Figure 9. Effect of Ala* side-chain substitution on the relative rates of base-catalyzed hydrogen exchange in Ac−Ala*−NHMe dipeptides, log k_{ex}(Ala*)/k_{ex}(Ala) vs σ_{Ala}*: (A) left N−H in the diagram, $\sigma_{Ala}* = 0.8\sigma_I + \sigma_R$, $r^2 = 0.918$; (B) right N−H in the diagram, $\sigma_{Ala}* = \sigma_I + 0.5\sigma_R$, $r^2 = 0.774$. The data for C, S, and T are omitted from these plots since the σ_R constants cannot adequately describe the relative electron-donor ability of these residues in the acidic aqueous solution (pD < 6).[93]

stability relative to the Gly mutant: $\Delta\Delta G°(X) = \Delta G°$(mutant X) − $\Delta G°$(mutant G). Regression analysis of the secondary structure propensities obtained in these studies on the inductive and resonance constants of the Ala* side-chain C_β substituents confirms that extended hyperconjugation might play an important role in controlling conformational equilibria of the polypeptide chains. The major trends in the data are best shown using the plots of the relative secondary structure propensities against σ_{Ala}* defined by those regression analyses, see Figure 10.[95−98] The resonance effect appears to play a major role in stabilization of β-sheet strands, Figure 10C, and destabilization of the α-helix, Figure 10A,B. The stability of a turn, Figure 10D (C-cap residue), seems to depend mostly on the inductive effect of the side chain.[99] These results are consistent with the spectroscopic and structural evidence which indicates that conformational transitions of the polypeptide chain are accompanied by changes in the electronic configuration of the peptide bonds and are well accommodated by the theory based on this evidence and the analysis of crystal structures of oligopeptides.[90] Thus, a range of characteristics of amino acids, peptides, and proteins appear to depend on extended hyperconjugation of the amino acid side chains.

2.1.5. Inverse Correlations of π-Face Selectivity and Inductive Effect

Investigation of the symmetric probes discussed in the previous sections has yielded several examples

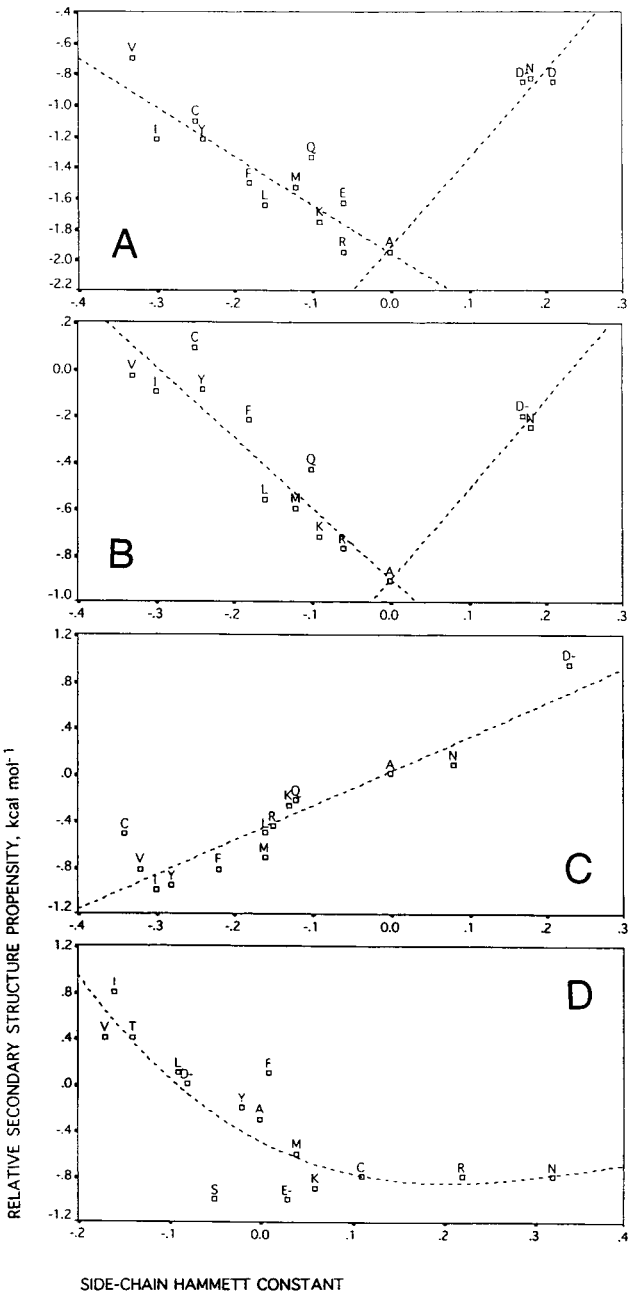


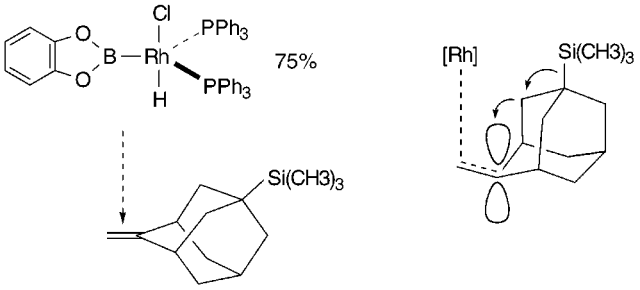
Figure 10. Effect of Ala* side-chain substitution on secondary structure propensities: (A) Relative α-helix propensity $\Delta\Delta G°_{Gly}$, SE = 0.01−0.03 kcal mol^{-1}, vs $\sigma_{Ala}* = 0.33\sigma_I + \sigma_R$: Ac−YSEEEEKKKKXXXEEEEKKKK−NH_2 peptide $r^2 = 0.795$ for $\sigma_{Ala}* < \overline{0.}$ (B) Relative α-helix propensity $\Delta\Delta G°_{Gly}$, SE = 0.03 kcal mol^{-1}, vs $\sigma_{Ala}* = 0.33\sigma_I + \sigma_R$: barnase (ribonuclease from *Bacillus amyloliquefaciens*, site 32), $r^2 = 0.852$ for $\sigma_{Ala}* < 0$. (C) Relative β-sheet propensity $\Delta\Delta G°_{Ala}$, SE = 0.06 kcal mol^{-1}, vs $\sigma_{Ala}* = \sigma_R$: IgG binding B1 domain of streptococcal protein G (I6A/T44A/T51S/T55S mutant, site 53), $r^2 = 0.856$. (D) Relative turn (C-cap) propensity $\Delta\Delta G°_{Asp}$, SE = 0.15 kcal mol^{-1}, vs $\sigma_{Ala}* = \sigma_I + 0.5\sigma_R$: Rop protein from plasmid ColE1 (site 30), $r^2 = 0.712$ (Q data set is omitted from the plot). The E, S, and T data sets are omitted from the plots in panels A, B, and C since the σ_R constants cannot adequately describe the relative electron-donor ability of these residues in the aqueous solution.[93]

of π-face selectivity that are unexpected insofar as the correlations between log [*Z*]/[*E*] and σ_I appear to be inverse, but the reversal of π-face preference cannot be attributed to extended hyperconjugation:

diazomethane cycloaddition to 5,6-*exo*-X,X-bicyclo(2.2.2)oct-2-enes (relative yield of the approach *anti* with respect to the 5,6-*exo*-substituents X,X = OC(=O)O 62%, CN 69%, OSO_2CH_3 70%),[22] rhodium-catalyzed hydroboration of 2-methylene-5-X-adamantanes (in THF: X = $Si(CH_3)_3$ 75% *syn* approach, C_6H_5 57%, F 54% *anti* approach),[100] $NaBH_4$ reduction of 5-*H*-perfluoroadamantan-2-one (*syn* with respect to C(5)−H 53%),[101] Paterno−Buchi photocycloaddition to 5-(trimethylsilyl)adamantan-2-one (*syn* approach 53%),[62] and Et_3SiH reduction of 5-(*p*-X-phenyl)adamantan-2-ones (*anti* approach X = H 53.0%, Br 53.5%, NO_2 55.5%).[61]

Assuming irreversible formation of the alkene−rhodium complex, i.e., carbon−metal bond formation as the stereoselection-controlling step,[100] π-face selectivity in rhodium-catalyzed hydroboration of 2-methylene-5-X-adamantanes was proposed to be determined by delocalization of the C−Rh bond into the vicinal antiperiplanar σ^*_{CC} orbitals.[100,102] The assumption of irreversible formation of the alkene−rhodium complex is now corroborated in the case of 1,1-dialkylethenes by the isotope incorporation experiments.[103] However, the large effect of the C(5)−Si bond on π-face selection in this reaction suggests participation of an electron-deficient center in the rate-determining step, cf. section 2.1.4.2, and the effect of the O-protecting groups on π-face selection is the same in the catalyzed and noncatalyzed hydroboration, see section 3.5.2.2.A, although π-face selectivity in those two reactions is opposite. These observations can be reconciled by assuming that the C=C···Rh complex is not symmetrical and that C(2) is pyramidalized *anti* with respect to the C···Rh bond as well as charge-polarized by the approach of the reagent, i.e., electron deficient on the *syn* face. Consequently, the preferred approach is *syn* to the C−C bonds that provide better hyperconjugative stabilization because their delocalization is assisted by the C−Si bond, Scheme 30.[104] This explanation

Scheme 30

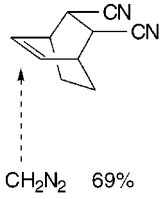


implies that the π-face selection here is not the case of 1,2-induction but rather an example of the situation where the inducing and the incipient centers are separated by a trigonal center.[105]

The *anti* preferences in Et_3SiH reductions of 5-phenyladamantan-2-ones were proposed to result from the sensitivity of large Et_3SiH to small distortions of the adamantane skeleton induced by the C(5)-phenyl substituents;[61] $C_6H_5SiH_3$, a smaller silane, in fact displays the expected *syn* preference in additions to the same adamantanones.

The *anti* preference in $NaBH_4$ reduction of 5-*H*-perfluoroadamantan-2-one was proposed to result from the Anh-type stabilization.[101] Indeed, the C−C bonds are expected to be incapable of hyperconjugation in the perfluorinated compound. However, the transition state for the hydride addition to this reactive ketone ought to be quite early and highly ionic, which makes hyperconjugation of the incipient bond improbable too. On the other hand, the hypothesis of σ^*_{CC} involvement offers a plausible explanation of the inverse log [*Z*]/[*E*] vs σ_I correlation in cycloadditions of CH_2N_2 to 5,6-*exo*-X,X-bicyclo(2.2.2)-oct-2-enes, Scheme 31.

Scheme 31



Diazomethane is a relatively nucleophilic 1,3-dipolar reagent, and its reactions with bicyclo(2.2.2)-octenes are exceedingly slow;[22] the olefinic reaction sites are not likely to be very electron deficient during these additions. Thus, the Anh-type hyperconjugation, $\sigma_\ddagger \rightarrow \sigma^*$, which is not observed in nucleophilic additions to cycloalkanones for which it was postulated, might actually be important during cycloadditions of diazomethane to unactivated alkenes.

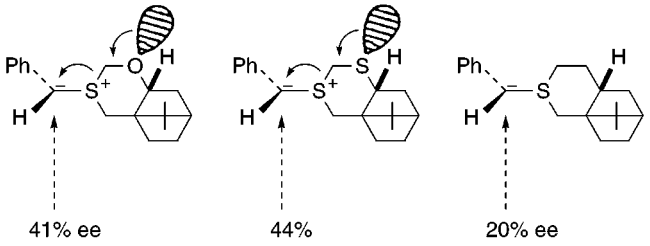
2.2. Bis-Alkyl S-Stereogenic Center Free of Steric Bias

As shown earlier, section 2.1.1 and Schemes 14, 15, and 24, embedding of the β-substituted bis-alkyl stereogenic center in a ring structure constrained in its mobility with respect to the incipient center can create an effective system of π-face selection. Interestingly, this principle also forms the underpinning of stereoselection in reactions of benzyl sulfonium ylides based on chiral oxathianes. Such ylides were recently used in catalytic asymmetric epoxidation of aldehydes and asymmetric cyclopropanation of acrylates.[106−108] The tendency of sulfonium ylides to maintain the bisected conformation creates a situation where π-face selection in their addition reactions is controlled by the sulfur stereogenic center with two methylene groups flanking the faces of the trigonal C, i.e., β-substituted bis-alkyl S-stereogenic center.

High face selectivity in C−C bond formation in addition of mercaptoisoborneol-based ylide to aldehydes was attributed to a combination of the anomeric and Cieplak effects, i.e., C−S bond hyperconjugation assisted by O lp back-donation into the σ^*_{CS} (extended hyperconjugation).[106] The enantiomeric excess is indeed lower when O is replaced by the methylene C, Scheme 32.

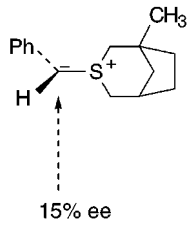
In the latter ylide, the difference in donor capability of the C−S bonds is smaller because it is determined solely by the inductive effect of the alkyl groups. Its direction, however, is the same as in the oxa ylide, most likely because the five-membered ring carbon

Scheme 32



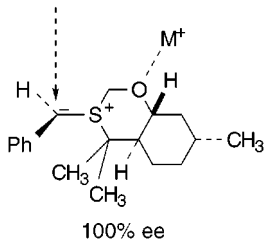
(β-methine group) is more electronegative than the six-membered ring carbon (β-methylene group). The electron-releasing effect of alkyl substitution also appears to control π-face selection in reactions of the ylide obtained from 1-methyl-3-thiabicyclo(3.2.1)-octane, Scheme 33.[107]

Scheme 33



The π-face preference is reversed in the second chiral oxathiane ylide where the cation and solvent effects suggest that the Na^+ complexation of O occurs in the transition state, which precludes O lp back-donation. Thus, hyperconjugation does not compete with the steric strain. On the contrary, RO···Na^+ is a strongly electron-withdrawing group, and here it is the bis-CH_3-substituted C−S bond which is a better hyperconjugative electron donor, Scheme 34.[108]

Scheme 34



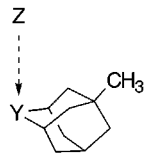
2.3. Alkyl Stereogenic Center: Steric vs Electronic Bias

2.3.1. C–H vs C–C

The C(5) of 5-methylcyclopenta-1,3-diene, cf. Schemes 2 and 3, is a prototype of the alkyl stereogenic center that introduces steric and electronic bias due to the differences in the properties of the C−C and C−H bonds and in the size of the out-of-plane groups, H and alkyl. As long as the addition to the adjacent trigonal center involves a reasonably early transition state (reactant-like transition state), the π-face of cyclopentadiene flanked by the methyl group at C(5) is sterically more hindered. Nonetheless, a number of reactions are known to occur in such situations *syn* to the methyl or even homologous groups or, in the case of cyclic and bicyclic alkenes and alkanones, on the concave face of the molecule. Those results are discussed below following a brief summary of the evidence on the crucial matter of hyperconjugative capabilities of the C−H and C−C σ-bonds.

2.3.1.1. C−H vs C−C Hyperconjugation. Beginning with the early observations of selectivity in Grignard alkylation of 5-methyladamantan-2-one,[109] the *syn*-directing effect of the C(5)−CH_3 group has often been found in reactions of related probes, Scheme 35.[19,23,61] These results can be explained as

Scheme 35



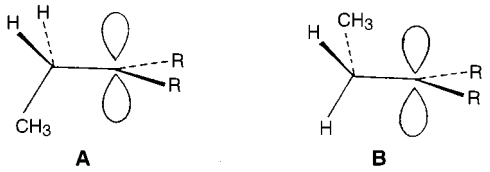
Reactants	Z %
Y = C = O	
$NaBH_4$, CH_3OH	51
CH_3Li, Et_2O	54
Y = $\overset{+}{C}-CH_3$	
HCl, CH_3NO_2	56
HCl, CH_2Cl_2	56
Y = $\overset{+}{C}-H$	
DAST, CH_2Cl_2	62

a result of extended hyperconjugation in which the C(5)−CH_3 bond is a poorer electron donor than the C(7)−H bond. Indeed, the *syn* preference induced by the C(5)−CH_3 group increases when the *anti* preference induced by the C(5)−$Si(CH_3)_3$ group increases, cf. Schemes 26 and 36, that is when the reaction is more sensitive to σ-assistance.

The assumption that C−H hyperconjugation is more important than C−C hyperconjugation challenges the opposite conclusion that was widely accepted in theoretical and physical organic chemistry by the mid-1970s. This conclusion was supported by two major arguments, related to two ways to approach the problem: one can compare electron release from two rotamers of Et (*i*-Pr, etc.) or one can compare electron release from Me and *t*-Bu.

First, the results of early ab initio MO calculations (STO-3G and 4-31G basis sets), including the energy, the 2p(C^+) orbital populations, the π(C−C^+) overlap, and the optimized C−C^+ bond distances in the two conformers of the 1-propyl cation (comparing rotamers of Et, **A** and **B** in Scheme 36, R = H), were

Scheme 36



concluded to indicate that C−C hyperconjugation is more important than C−H hyperconjugation.[110]

This argument is no longer tenable. The high-level calculations presently available (ab initio examination of the $C_3H_7^+$ potential energy surface and the *tert*-pentyl cation,[111] MP2/6-311G**, and MP4(fc)/6-311G**, including ZP vibrational energies from the MP2 frequencies) show that two rotamers of the *tert*-pentyl cation (**A** and **B**, R = CH_3) are equally stable in spite of the strain due to eclipsing of methyl groups, which contributes ~2.5 kcal mol^{-1} to the

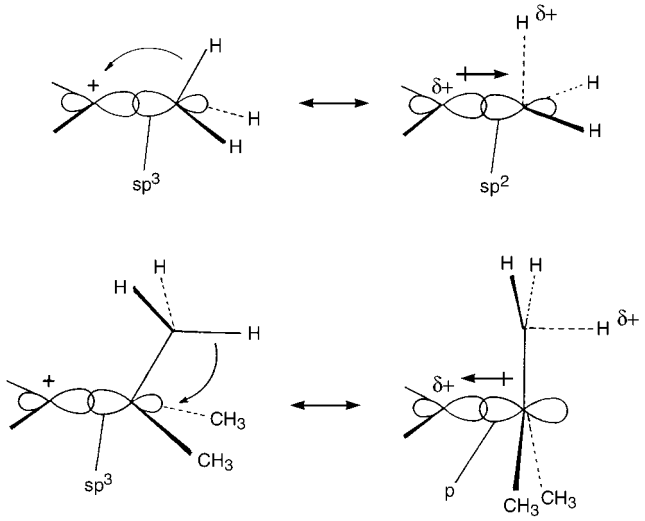
rotation barrier in *n*-butane. The analogous rotamers of the 1-propyl cation (**A** and **B**, R = H) correspond to the saddle points on the $C_3H_7^+$ surface, and the energy of **B**, which is sterically more strained, is actually lower by 1.4 kcal mol^{-1}. The latter result has been mistakenly quoted in the reverse order as evidence that the C−C bonds are better electron donors,[112] and this mistake is repeated in a recent review.[113] Both pairs of rotamers have a conventional geometry of classical cations which is similar to the geometry of alkylboranes. The ethyl group attached to a trigonal boron also displays the tendency to adopt the sterically more strained eclipsed conformation (C_s), which places the C−CH_3 bond in the nodal plane of boron.[114]

Second, the results of examination of carbocation stability in the gas phase (comparing Me and *t*-Bu) were concluded to indicate that C−C hyperconjugation is more important than C−H hyperconjugation. The typical examples are gas-phase stability of cations such as alkylbenzenonium ions[115] or the rates of gas-phase pyrolysis involving formation of *p*- and *m*-alkyl benzyl cations,[116] which show the *t*-Bu > Me order of electron release. The assumption that the inductive effects of alkyl groups are small relative to their conjugative effects and negative leads to the above conclusion. For instance, the gas-phase σ_R^+ constants for Me and *t*-Bu were calculated by subtracting Taft's σ_I values (−0.05 and −0.07) from the gas-phase σ_p^+ constants (−0.29 and −0.36), and the result was taken as evidence that C−C hyperconjugation is greater.[116] Reversal of the gas-phase *t*-Bu > Me order of electron release observed when alkylbenzenonium or alkylacylium ions are transferred into a solution, and often found when reactions involving formation of carbocations occur in solution (Me > *t*-Bu, the Baker−Nathan order), was consequently attributed to steric inhibition of solvation.[117]

This argument is no longer tenable either. Me and *t*-Bu cannot be assumed to be weak inductive electron donors regardless of the molecular context. NMR and reactivity data from polycycloalkyl derivatives were argued to demonstrate that Me is a σ-electron-withdrawing group both in the neutral ground state and electron-deficient species.[23] The ^{13}C NMR spectra of carbonium ions confirm that Me is an inductive electron acceptor.[118] Me becomes a σ-acceptor in these ions because rehybridization that accompanies hyperconjugation sends s-character to its C−C^+ bond. Thus, in the interactions with highly electron-deficient species, the inductive effect of the methyl group offsets the stabilizing effect of its hyperconjugation. On the other hand, the *tert*-butyl group attached to an electron-deficient center can become a more effective σ-donor because extended hyperconjugation (delocalization of the C−H bonds) sends p-character to its C−C^+ bond, see Scheme 37. In this context, extended hyperconjugation would be responsible for the bulk effect of the alkyl groups otherwise often attributed to polarizability.

This is consistent with the smaller electron release from *p*-Me on going from solvolysis of α,α-dimethylbenzyl chlorides (σ^+ −0.311) to detritiation in CF_3-COOH (σ^+ −0.303) and to gas-phase pyrolysis of

Scheme 37



1-arylethyl acetates (σ^+ −0.290), that is as the polarity of the medium decreases and electron demand of the cationic intermediate increases.[116] In contrast, the electron-releasing effect of *t*-Bu increases in the same series: σ^+ −0.256, −0.312, and −0.365, in accord with expectation. The recent studies of gas-phase substituent effects on the stability of α-*p*-substituted benzyl cations provide additional evidence of the dependence of electron release on the cation demand.[119] In the series of cations characterized by the Yukawa−Tsuno r^+ coefficient (the resonance demand parameter),[119] $ArC^+(OH)NMe_2$ 0.23, $ArC^+(OH)OMe$ 0.45, $ArC^+(OH)Me$ 0.78, ArC^+Me_2 1.00, $ArC^+(OH)H$ 1.04, ArC^+MeH 1.14, $ArC^+(OH)CF_3$ 1.20, ArC^+H_2 1.29, ArC^+MeCF_3 1.40, excellent linear relationships between the gas-phase stability and the σ^+ values in solution were obtained for the α-cumyl cations ArC^+Me_2 $r^+ = 1.00$ and the protonated benzaldehydes $ArC^+(OH)H$ $r^+ = 1.04$ while poor correlations were found for the benzyl cations ArC^+H_2 $r^+ = 1.29$ (positive deviations for π-donors) and the protonated benzoates $ArC^+(OH)OMe$ $r^+ = 0.45$ (negative deviations for π-donors). The gas-phase resonance constants for Me and *t*-Bu used in these studies are $\Delta\bar{\sigma}_{R(g)}(Me) = -0.20$ and $\Delta\bar{\sigma}_{R(g)}(t\text{-Bu}) = -0.17$, and the same Me > *t*-Bu order of the resonance constant values is obtained from Taft−Topsom three-parameter analysis of the protonated benzaldehyde data.[120] Furthermore, the electron-releasing effect of alkyl substituents on the transition energies for the 0−0 bands of the gas-phase UV spectra of alkylbenzenes or the enthalpies of gas-phase hydrogenation of *trans*-disubstituted ethylenes, i.e., in the case of species that are less electron deficient than carbonium ions, is unequivocally of the order Me > *t*-Bu; C−H hyperconjugation is found here to be 2−3 times more effective than C−C hyperconjugation.[121]

Thus, the order of the total electron release from Me and *t*-Bu seems to depend primarily on the electron demand of the substituted species. In the case of low electron demand, the Me > *t*-Bu order is observed both in the gas phase and in solution; in the case of high electron demand, the opposite order, *t*-Bu > Me, is observed both in the gas phase and in solution.[116] The intrinsic hyperconjugative order is

C−H > C−C, but because Me becomes an inductive electron acceptor as a result of a strong hyperconjugative interaction,[113] the apparent order is reversed when Me and *t*-Bu interact with highly electron-deficient centers. The reversal of the order of electron release by the solvent could be the result of both the classical effect of a continuous dielectric (attenuated hyperconjugation) and specific solvation because both effects can lower electron demand of the substituted center.

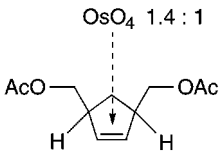
Over the last three decades, a wealth of additional evidence became available as the spectroscopic techniques were applied to study the stability of rotamers, distribution of electron density, and bond properties in alkyl derivatives.

Electron release from rotamers of Et (*i*-Pr, etc.) was investigated in a number of ways, cf. the studies of conformations of the alkylbenzene radical cations (ESR, 77 K, solid Freon)[122] and the effect of Lewis acid complexation on conformations of the β-alkyl groups in α,β-unsaturated aldehydes and esters,[123] NBO analysis of the charge distribution in rotamers of 2-chloropropanal[124] and structure correlation analysis of the alkyl ligand rotation in carbonyls,[125] the data on conformational equilibria of cyclohexyl derivatives[77,80] and the 1-methylcyclohexyl cations,[126] on conformational preferences of Et attached to the trigonal boron (MW, X-ray, ab initio MO calculations),[114] and on the effect of internal rotation on bond strength and polarization in alkyl derivatives.[7] All this evidence is consistent with the intrinsic C−H > C−C hyperconjugative order.

Electron release from Me and *t*-Bu was investigated by NMR in the studies of 2-alkylindenes, *p*-alkylbenzyl cations, and *p*-alkyl-α,α-difluorostyrenes.[127] In each case, the Me > *t*-Bu order of electron release was found, and examination of the solvent effect led to the conclusion that the observed Baker−Nathan order cannot be attributed to solvation. Thus, this evidence also is consistent with the intrinsic C−H > C−C order of hyperconjugation.

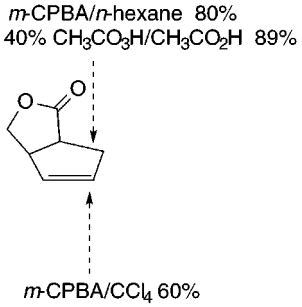
2.3.1.2. Cyclopentane Probes: Bridgehead Stereogenic Center in Bicyclo(3.3.0)alkanes. The studies of π-face selection in reactions of cyclopentane derivatives included examination of the stereochemistry of oxidation of 4-[128] and 3,5-substituted[129,130] cyclopentenes as well as reduction and alkylation of 2-substituted cyclopentanones.[131] The additions often occur *trans* except for ethynylation and hydride additions[131] and some OsO_4 dihydroxylations where the *syn* preference was explained as a result of C−H hyperconjugative assistance, Scheme 38.[130]

Scheme 38



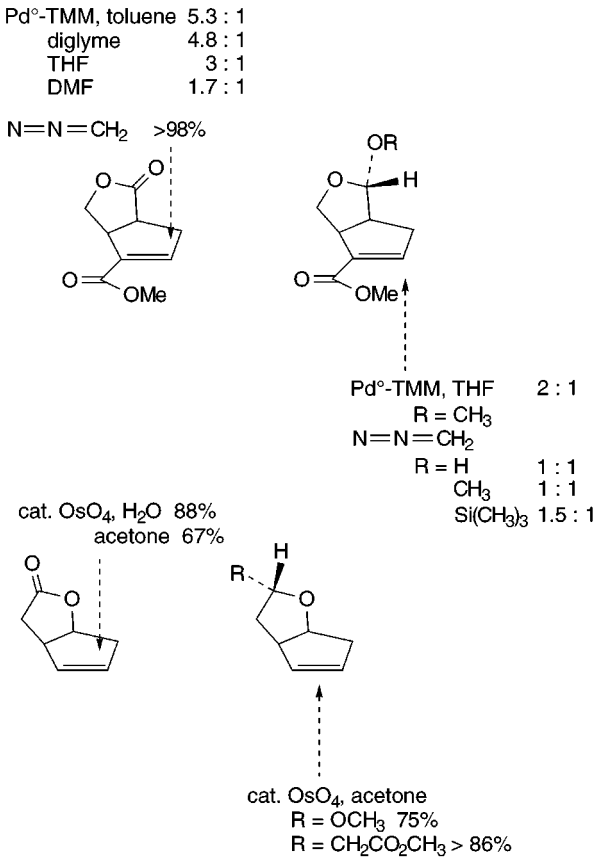
However, flexibility of the five-membered ring makes it difficult to assume that steric hindrance remains constant upon the change of substitution, i.e., no substituent is truly "sterically remote" in this ring. This difficulty disappears in the case of rigid bicyclo(3.3.0)octanes. Such derivatives were found in the course of early work on the synthesis of prostaglandins to display an unexpected tendency to react on the more hindered concave face of the molecule. Thus, 2-oxa-3-oxobicyclo(3.3.0)oct-6-ene can be preferentially epoxidized on either face depending on the peracid and solvent, see Scheme 39.[132]

Scheme 39

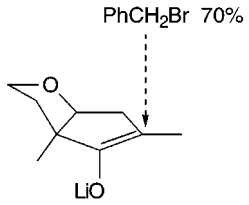


The presence of the carbonyl group was shown to be crucial for the *syn* preference in additions to related alkenes, see Scheme 40,[133,134] although it is not a sufficient factor per se, cf. OsO_4 oxidation of bicyclo(3.2.0)hept-2-en-6-one, section 2.3.2.3, Scheme 56. It should be noted that π-face selection in Michael-like[134] additions to 6-(methoxycarbonyl)-3-oxa-2-oxobicyclo(3.3.0)oct-6-ene, Scheme 40, most likely do not involve 1,2-induction, i.e., the incipient bond−stereogenic center interaction, but 1,3-π^1-induction, i.e., the incipient bond−enolate−stereo-

Scheme 40



Scheme 41



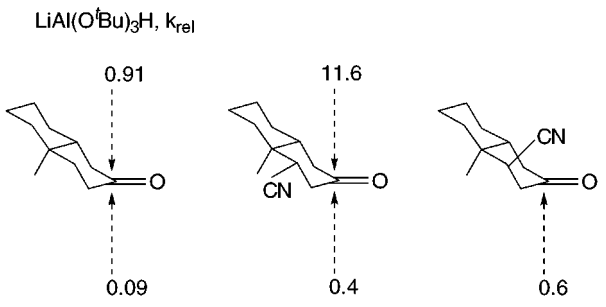
genic center interaction,[105] reminiscent of the situation in alkylation of bicyclic ketoenolates shown in Scheme 41, as well as lactam enolates, see section 3.5.2.1.B.

The role of the carbonyl group in controlling π-face selection in CH_2N_2 addition to 6-(methoxycarbonyl)-3-oxa-2-oxobicyclo(3.3.0)oct-6-ene, Scheme 40, was attributed to the electrostatic effect.[134] It is also consistent with the hypothesis of σ-assistance, since the electron-withdrawing effect of the carbonyl group increases the difference in C−C and C−H hyperconjugation.

2.3.1.3. Cyclohexane Probes. A. Kinetic Evidence. 1-Hetera-4-cyclohexanones can be considered as an example of β-substituted cyclohexanone probes. A number of kinetic studies of additions to such ketones have been reported.[135−137] The rates of $NaBH_4$ reduction of 2,6-diphenyltetrahydropyran-4-one, 4-piperidone, thian-4-one, and selenan-4-one (mostly axial) increase in the order O > N > S > Se, that is in the order of increasing electron-withdrawing effect of the heteroatom.[135] The only surprise is the effect of *N*-alkylation of 4-piperidone since the replacement of *N*-H by *N*-CH_3 accelerates the reduction.[137]

The 3-eq-X-cyclohexanones, 4-ax, 4-eq-, and 9-ax-X-*trans*-decal-2-ones, 2-eq- and 2-ax-X-cholestan-3-ones, and 5-ax-X-cholestan-3-ones represent the second type of β-substituted cyclohexanone probes, Schemes 42−44. Here, the effect of the electron-withdrawing substitution on the rates of hydride addition or organometallic alkylation is far from uniform acceleration. Thus, the β-cyano group accelerates $LiAl(OtBu)_3H$ reduction of 4-cyano-*trans*-decal-2-ones, but the axial approach is considerably more affected than the equatorial one, Scheme 42.[138]

Scheme 42



Furthermore, the β-ethoxycarbonyl group in 9-carbethoxy-*trans*-decal-2-one actually slows down equatorial addition of reactive organometallics such as $(CH_3)_3Al$ and $CH_3Li/(CH_3)_2CuLi$ and only accelerates addition of $(CH_3)_2Zn$, which is relatively sluggish.[139] This is consistent with the earlier reports that the β-alkyl substitution of cyclohexanone slows down, as expected, the equatorial addition of $NaBH_4$ but accelerates the equatorial addition of $LiAlH_4$, Scheme 43.[140]

The equatorial reduction of 5-X-5α-cholestan-3-ones and 3-ax-F-3,5,5-trimethylcyclohexanone with $LiAl(OtBu)_3H$ shows an apparently nonlinear effect of β-halo and cyano substitution, Scheme 44.

The effect of γ-substitution was examined in the series of 4-X-cyclohexanones and 10-X-*trans*-decal-2-ones.[35,139,142,143] The results obtained with the latter ketones confirm that the effect of substitution on the reaction rate depends on the nature of the nucleophile, see Figure 11 and Scheme 45. The axial

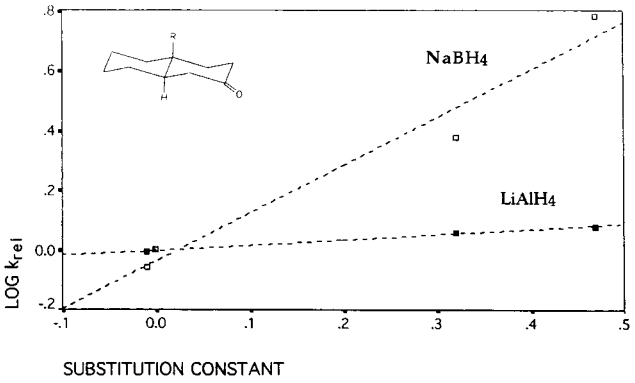


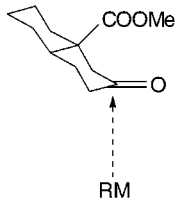
Figure 11. Effect of remote substitution on the rate of metal hydride addition to 10-X-*trans*-2-decalones, log k_{rel} vs σ_I[44a] (X = CH_3, H, $COOCH_3$, Cl): (□) $NaBH_4$ $\hat{Y} = 1.59X$, SE $b_0 = 0.06$, SE $b_1 = 0.21$, $r^2 = 0.966$; (■) $LiAlH_4$ $\hat{Y} = 0.18X$, SE $b_0 = 0.00$, SE $b_1 = 0.01$, $r^2 = 0.993$.

γ-ethoxycarbonyl group in 10-carbethoxy-*trans*-decal-2-one slows down the equatorial alkylation reactions within the series $(CH_3)_3Al$ 1:1/C_6H_6, $CH_3Li/(CH_3)_2CuLi$, CH_3Li, CH_3MgI (no effect on $(CH_3)_3Al$ 3:1) but accelerates the axial alkylations except for $(CH_3)_3Al$ 1:1/C_6H_6.[139]

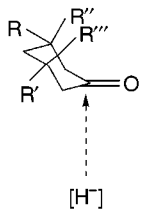
Similarly, the effect of the C(10)-methoxycarbonyl group on the rate of reduction of *trans*-decal-2-one depends on the hydride.[142] Both equatorial and axial $NaBH_4$ reductions are accelerated, but in the case of $LiAlH_4$ and $LiBEt_3H$, acceleration of the axial reductions is minimal, see Figure 11, while the equatorial reductions are slowed down. Similarly, the C(10)−Cl group considerably accelerates axial $NaBH_4$ reduction but accelerates axial $LiAlH_4$ and $LiBEt_3H$ reductions little or not at all, Figure 11. It probably slows down equatorial $LiAlH_4$ and $LiBEt_3H$ reductions; its effect on equatorial $NaBH_4$ reduction cannot be ascertained because of the very large rate of axial reduction.

A somewhat more detailed picture of the relationship between reactivity and sensitivity to the remote electronegative substitution emerges from the studies of organometallic alkylation and sulfur ylide epoxidation of 4-X-cyclohexanones, Figures 12−14. It was found in the early 1960s that polar C(4)-substituents "reverse" the normal stereochemistry of reduction of cyclohexanones observed when C(4) carries an alkyl group.[144] This effect was later explained as a result of reversal of conformational preference of the substrate: axial conformers of 4-X-cyclohexanones (X = O, Cl) are more stable than equatorial ones in the

Scheme 43

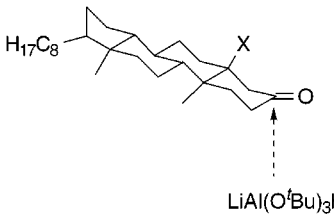


RM	k_{COOMe}/k_H
$Al(CH_3)_3$ 1:1	0.6
3:1	0.7
$(CH_3)_2CuLi \cdot CH_3Li$	0.7
CH_3Li, 20 °C	1.1
−78 °C	1.1
CH_3MgI, Et_2O	1.5
benzene	3.5
$(CH_3)_2Zn$	7.2

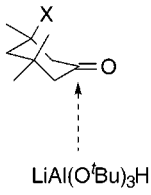


	k_{rel} $LiAlH_4$	k_{rel} $NaBH_4$
R = R′ = R″ = R‴ = H	1.0	1.0
R = R′ = CH_3, R″ = R‴ = H	1.8	1.2
R = R′ = R″ = CH_3, R‴ = H	4.0	0.44
R = R′ = R″ = R‴ = CH_3	3.7	0.36

Scheme 44

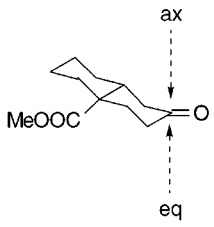


X	$k_{eq} \times 10^3$ l•mol^{-1}•sec^{-1}
H	140
CH_3	8.9
Cl	4.5
F	24
CN	224

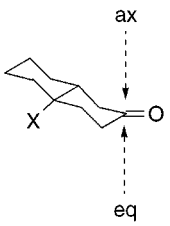


H	11.5 ± 1
F	5.3 ± 0.4

Scheme 45



RM	k_{COOMe}/k_H ax	eq
$Al(CH_3)_3$ 1:1	0.7	0.5
3:1	1.05	1.0
$(CH_3)_2CuLi \cdot CH_3Li$	2.5	0.4
CH_3Li, 20 °C	2.3	0.4
, −78 °C	3.2	0.4
CH_3MgI, Et_2O	7.8	0.8
benzene	2.0	0.8



hydride	k_X/k_H X=COOMe eq	X=COOMe ax	X=Cl ax
$LiBEt_3H$	0.10	1.16	1.0
	0.38	1.14	1.2
$NaBH_4$	1.15	2.37	6.0

gas phase, and this preference is retained in solution, in particular in solvents of lower dielectric constant.[145] Interestingly, even though the change in free energy in favor of the axial conformer is not large, a number of data suggest, vide infra section 2.3.1.3.B, that reductions and organometallic additions occur mostly on the axial conformer. Thus, it is assumed here for the purpose of calculating partial rate factors that 4-X-cyclohexanones exist in solution primarily as equatorial conformers when X = C_{sp^3} or Ph and as axial conformers when X = O or Cl.

In agreement with the *trans*-decal-2-one data in Schemes 43 and 45, the plots in Figure 12 show that the equatorial approach (□) is slowed down by X = OMe, Cl in the case of $(CH_3)_3Al$ 1:1/C_6H_6, Figure 12A, and CH_3Li/Et_2O, Figure 12B, little affected in the case of CH_3MgCl/THF, Figure 12C, and accelerated in the case of $CH_3Zn/MgI_2/Et_2O$, Figure 12D. The axial approach (■) is little affected in the first case, Figure 12A, and accelerated in all other cases, Figure 12B−D.[143] However, the slope is clearly largest for Grignard alkylation, Figure 12C.

The data on S-ylide epoxidations of 4-X-cyclohexanones are most extensive to date in terms of the number and variety of C(4) substituents.[35] Inclusion of the C(4) C_6H_5, *p*-F-C_6H_4, and CF_3 groups along with the oxy groups allows for separation of the inductive effect from other effects of the polar axial C(4)-substituents. The difference is revealed by the plots of partial rate factors vs σ_I[44a] for $(CH_3)_2S^+CH_2^-$ addition in THF in Figure 13A.

The distribution is very similar for the axial (◆) and equatorial (□) approach, but in both cases the addition to C(4)−O cyclohexanones is slower than addition to C(4)−C cyclohexanones. Interestingly, regression on σ_I and σ_R gives substitution constants[46] $\sigma_\pi = 0.8\sigma_I + \sigma_R$ (equatorial) and $\sigma_\pi = 0.6\sigma_I + \sigma_R$ (axial) and a reasonable correlation, Figure 13B. The outcome is qualitatively similar in the case of additions in DMSO and benzene. For the discussion of a possible role of this resonance contribution, see section 2.3.1.3.C.

The situation is even more complex in the case of $(CH_3)_2SO^+CH_2^-$ additions, Figure 14. These results have to be considered with some caution since additions of the less reactive ylide might be reversible.[32] Nonetheless, partial factors for the equatorial approach (THF) are plotted against σ_I[44a] in Figure 14A and show a distribution which is quite similar to that found previously for $(CH_3)_2S^+CH_2^-$ additions in THF, Figure 13A, both in terms of gradients and the split in two clusters (C(4)−C, □; C(4)−O, ■) due to the lower rates of addition to C(4)−O cyclohexanones. Indeed, regression on σ_I and σ_R gives an almost identical substitution constant[46] $\sigma_\pi = 0.75\sigma_I + \sigma_R$ (equatorial) and a reasonable correlation, Figure 14B.

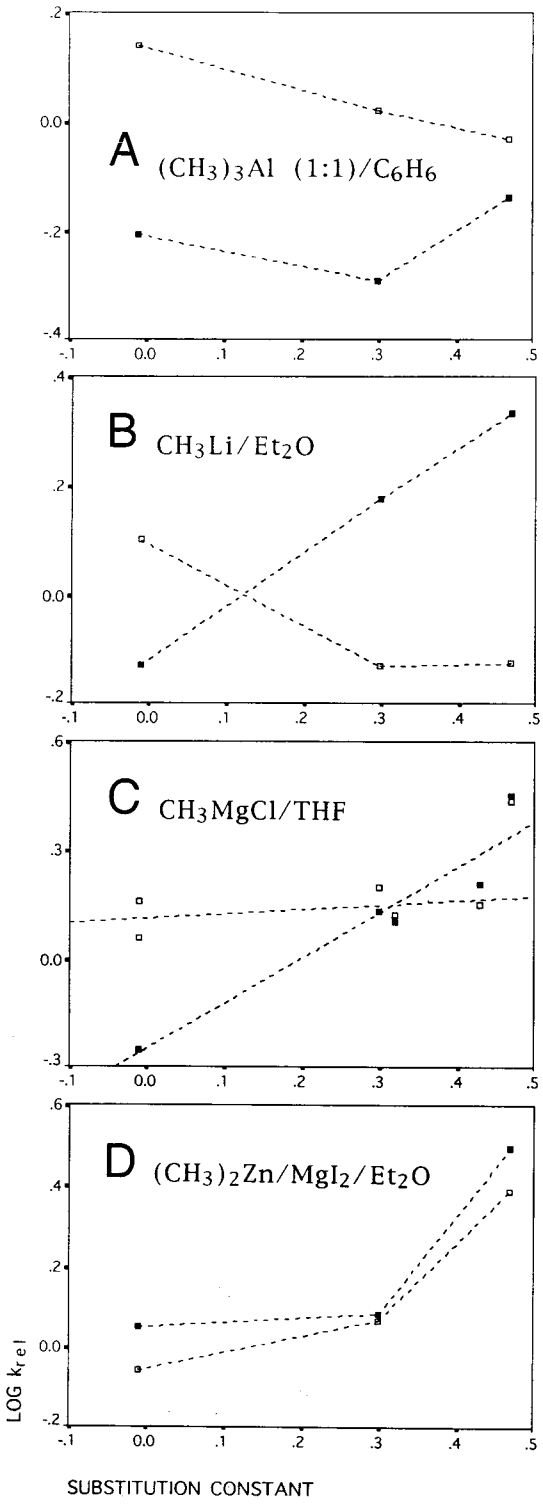


Figure 12. Effect of remote substitution on the rate of organometallic alkylation of 4-X-cyclohexanones, log k_{rel} vs σ_I[44a]: (■) axial approach, (□) equatorial approach. (A) $(CH_3)_3Al$ (1:1)/C_6H_6 (X = $C(CH_3)_3$, OCH_3, Cl). (B) CH_3Li/Et_2O (X = $C(CH_3)_3$, OCH_3, Cl). (C) CH_3MgCl/THF; (■) axial approach $\hat{Y} = -0.25 + 1.26X$, SE $b_0 = 0.05$, SE $b_1 = 0.15$, $r^2 = 0.943$; there is no correlation for the equatorial approach (X = CH_3, $C(CH_3)_3$, OCH_3, $COOCH_3$, $OCOC_6H_5$, Cl). (D) $(CH_3)_2Zn/MgI_2/Et_2O$ (X = $C(CH_3)_3$, OCH_3, Cl).

However, the plot of the axial partial rate factors reveals that the sensitivity to the electron-withdrawing substitution is much lower, as if the axial transition state were less advanced than the equatorial one, Figure 14C. Furthermore, the two separate clusters

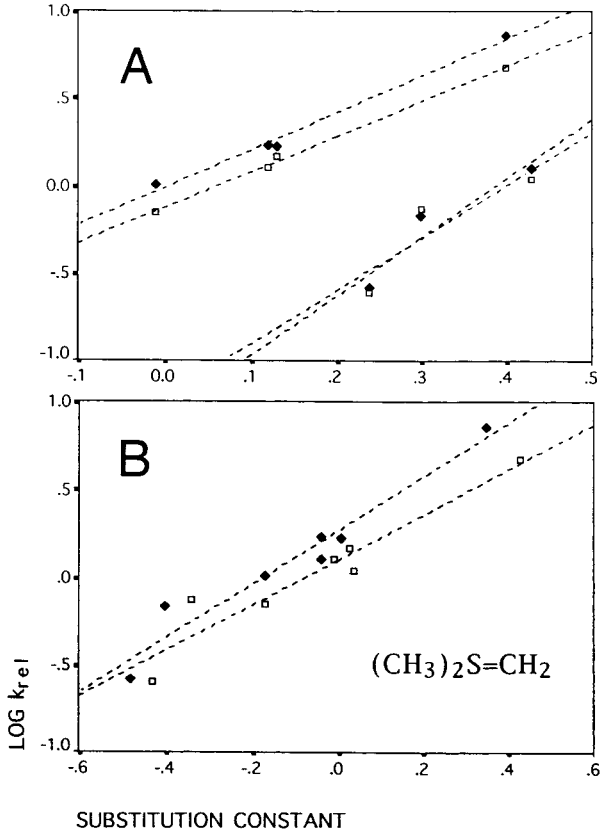


Figure 13. Effect of remote substitution on the rate of $(CH_3)_2S{=}CH_2$ epoxidation of 4-X-cyclohexanones: (□) equatorial approach, (◆) axial approach (X = CH_3, C_6H_5, C_6H_4-*p*-F, OH, OCH_3, CF_3, $OCOC_6H_5$). (A) log [*Z*]/[*E*] vs σ_I.[44a] X = CH_3, C_6H_5, C_6H_4-*p*-F, CF_3: (□) $\hat{Y} = -0.13 + 2.02X$, SE $b_0 = 0.02$, SE $b_1 = 0.08$, $r^2 = 0.997$; (◆) $\hat{Y} = -0.01 + 2.12X$, SE $b_0 = 0.03$, SE $b_1 = 0.13$, $r^2 = 0.992$. X = OH, OCH_3, $OCOC_6H_5$: (□) $\hat{Y} = -1.21 + 3.02X$, SE $b_0 = 0.52$, SE $b_1 = 1.57$, $r^2 = 0.788$; (◆) $\hat{Y} = -1.31 + 3.38X$, SE $b_0 = 0.39$, SE $b_1 = 1.13$, $r^2 = 0.899$. (B) log [*Z*]/[*E*] vs σ_π.[46] (□) $\sigma_\pi = 0.8\sigma_I + \sigma_R$, $\hat{Y} = 0.09 + 1.29X$, SE $b_0 = 0.05$, SE $b_1 = 0.18$, $r^2 = 0.910$; (◆) $\sigma_\pi = 0.6\sigma_I + \sigma_R$, $\hat{Y} = 0.26 + 1.54X$, SE $b_0 = 0.05$, SE $b_1 = 0.16$, $r^2 = 0.947$.

for C(4)−C ketones (□) and C(4)−O ketones (■) are found here, too, but their relative positions are reversed! The additions to C(4)−O cyclohexanones are now accelerated, and regression on σ_I and σ_R gives a substitution constant[46] with the opposite sign for σ_R, $\sigma_\pi = 0.7\sigma_I - \sigma_R$ (axial), Figure 14D. The possible significance of this reversal is discussed in section 2.3.1.3.C.

Thus, the Hammett ρ constants for additions to cyclohexanones appear to depend on the reactivity of the nucleophiles, direction of approach, and orientation and/or properties of the C(4) substituents. The dependence of ρ on the nature of the nucleophile was first noted in the studies of rates of nucleophilic additions to aromatic carbonyls: Grignard 0.36, 0.41; NH_2OH 0.32; sulfite ion SO_3^{2-} 1.27; cyanide CN^- 2.33; BH_4^- 2.81, 3.06.[146] It was proposed that the charge born by the carbonyl C in the reactant-like transition state for the organometallic alkylations is still positive.[146,147] In contrast, in the more advanced product-like transition states for BH_4^- and CN^- ion additions, the charge at the reaction site is close to zero or even slightly negative. This view is supported by studies of the secondary kinetic isotope effect in

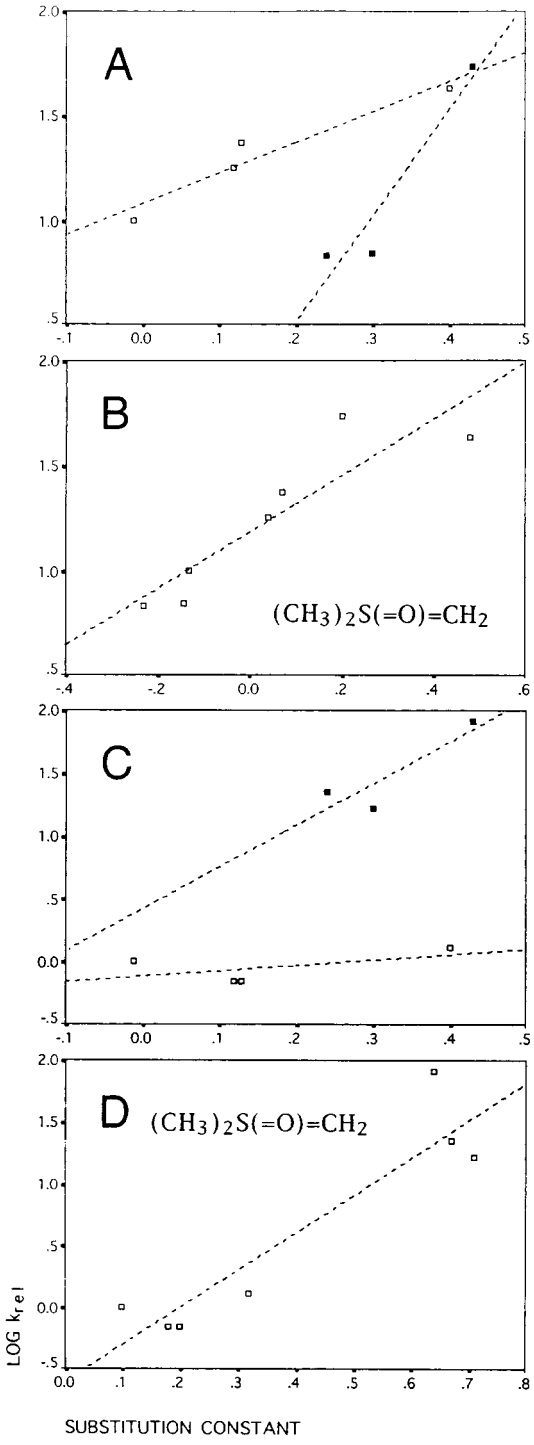
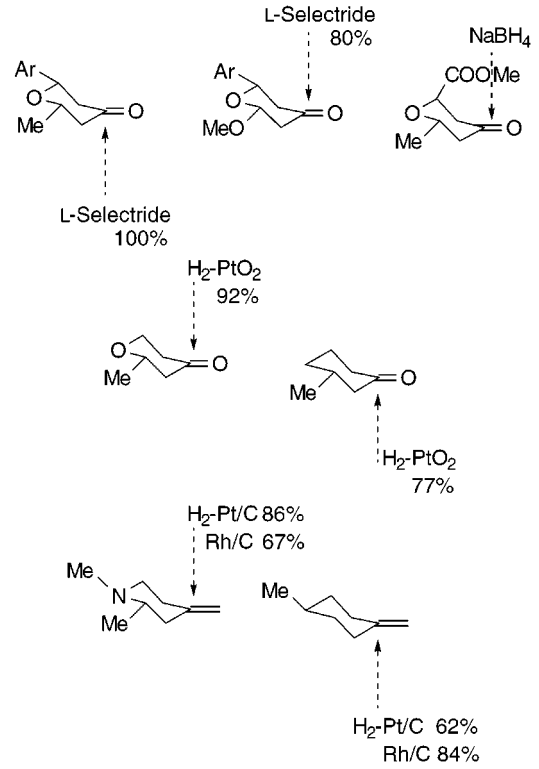


Figure 14. Effect of remote substitution on the rate of $(CH_3)_2SO{=}CH_2$ epoxidation of 4-X-cyclohexanones (X = CH_3, C_6H_4-*p*-F, OH, OCH_3, CF_3, $OCOC_6H_5$). (A) Equatorial approach, log [*Z*]/[*E*] vs σ_I:[44a] (□) X = CH_3, C_6H_5, C_6H_4-*p*-F, CF_3, $\hat{Y} = -1.08 + 1.46X$, SE $b_0 = 0.07$, SE $b_1 = 0.30$, $r^2 = 0.920$; (■) X = OH, OCH_3, $OCOC_6H_5$, $\hat{Y} = -0.51 + 5.10X$, SE $b_0 = 0.53$, SE $b_1 = 1.59$, $r^2 = 0.912$. (B) Equatorial approach, log [*Z*]/[*E*] vs σ_π[46] $= \sigma_I + 0.75\sigma_R$, $\hat{Y} = -1.18 + 1.35X$, SE $b_0 = 0.07$, SE $b_1 = 0.30$, $r^2 = 0.806$ (X = CH_3, C_6H_5, C_6H_4-*p*-F, OH, OCH_3, CF_3, $OCOC_6H_5$). (C) Axial approach, log [*Z*]/[*E*] vs σ_I:[44a] (□) X = CH_3, C_6H_5, C_6H_4-*p*-F, CF_3, $\hat{Y} = -0.12 + 0.43X$, SE $b_0 = 0.10$, SE $b_1 = 0.44$, $r^2 = 0.321$; (■) X = OH, OCH_3, $OCOC_6H_5$, $\hat{Y} = 0.42 + 3.31X$, SE $b_0 = 0.60$, SE $b_1 = 1.82$, $r^2 = 0.768$. (D) Axial approach log [*Z*]/[*E*] vs σ_π[46] $= \sigma_I + 0.7\sigma_R$, $\hat{Y} = -0.61 + 3.02X$, SE $b_0 = 0.26$, SE $b_1 = 0.55$, $r^2 = 0.856$ (X = CH_3, C_6H_5, C_6H_4-*p*-F, OH, OCH_3, CF_3, $OCOC_6H_5$).

nucleophilic additions to cyclohexanones.[148] The C−D bonds are poorer hyperconjugative donors than the C−H bonds.[149] Consequently, reactions with the negative or very small ρ (electron-deficient transition state) should display normal KIE in additions to cyclohexanones-2,2,6,6-d_4, and the ones with the greater positive ρ (electron-rich transition state) should display inverse KIE. A trend consistent with this expectation is indeed apparent in the available data (KIEs NH_2OH 1.054, 1.048; SO_3^{2-} 0.918; BH_4^- 0.890, 0.883).[148]

B. Stereochemical Evidence. A number of examples of additions to 1-hetera-4-cyclohexanones show that electron-withdrawing β-substitution can override the steric bias increasing, sometimes dramatically, axial preference in metal hydride additions or catalytic hydrogenation, Scheme 46.[150−152]

Scheme 46



This effect was examined in a more systematic way using a series of cyclohexanones and methylenecyclohexanes with polar substituents at C(3) that were sufficiently large to lock the conformation of the ring.[12] As with the polycyclic probes discussed earlier, electronegative β-substitution was found to increase the *syn* preference (the relative yield of axial approach) in several reactions, widely differing from the point of view of the transition-state polarization, geometry, and electron deficiency, Figure 15. Regression on σ_I reveals the largest slope coefficients b_1 for $(CH_3)_2CuLi$-catalyzed CH_3Li alkylation, Figure 15A, and hydroxymercuration $Hg(OAc)^+/H_2O$, Figure 15C, and the smallest for the S-ylide alkylation $(CH_3)_2S^+CH_2^-$, Figure 15B, while CH_3Li alkylation, Figure 15A, *m*-CPBA epoxidation, and OsO_4 dihyroxylation, Figure 15C, have similar intermediate values. The rank order of the coefficients b_1 resembles

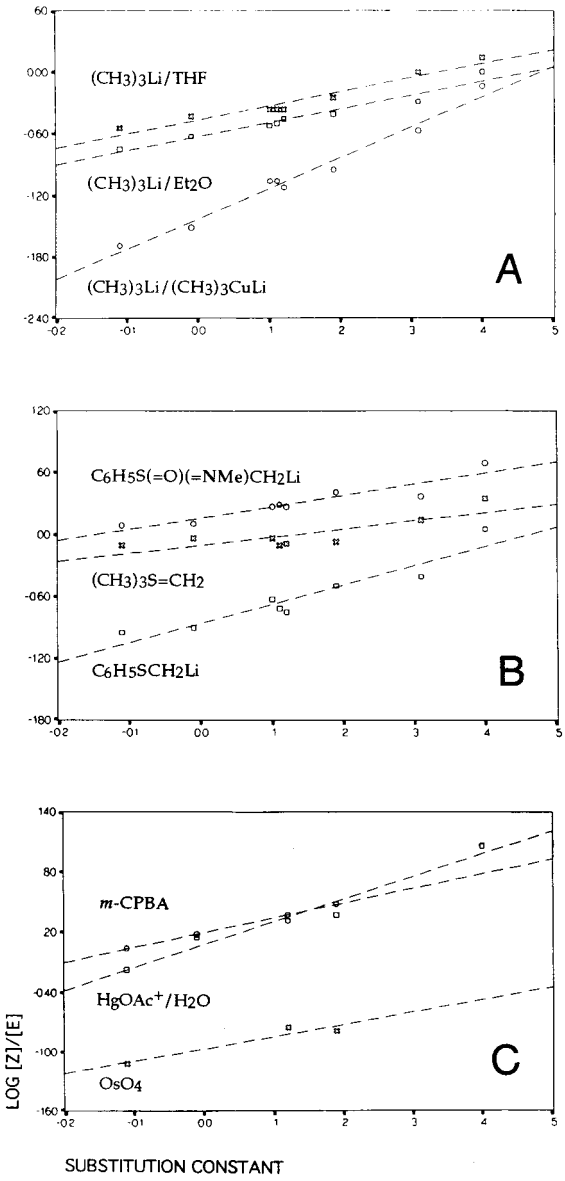


Figure 15. Effect of remote substitution on the stereochemistry of additions to 3-X-cyclohexanones and methylenecyclohexanes, log [*Z*]/[*E*] vs σ_I[44a] (X = $Si(CH_3)_3$, $C(CH_3)_3$, H, C_6H_4-*p*-OCH_3, C_6H_4-*p*-CH_3, C_6H_5, C_6H_4-*p*-CF_3, C_6F_5, CF_3): (A) (○) $CH_3Li/(CH_3)_2CuLi/Et_2O$, $\hat{Y} = -1.425 + 2.962X$, SE $b_0 = 0.038$, SE $b_1 = 0.186$, $r^2 = 0.977$; (□) CH_3Li/Et_2O, $\hat{Y} = -0.634 + 1.359X$, SE $b_0 = 0.026$, SE $b_1 = 0.124$, $r^2 = 0.952$; (×) CH_3Li/THF, $\hat{Y} = -0.465 + 1.373X$, SE $b_0 = 0.029$, SE $b_1 = 0.142$, $r^2 = 0.940$. (B) (□) $PhSCH_2Li/THF$ $\hat{Y} = -0.862 + 1.869X$, SE $b_0 = 0.054$, SE $b_1 = 0.262$, $r^2 = 0.894$; (○) $PhS(O)(NMe_2)CH_2Li/THF$ $\hat{Y} = 0.160 + 1.086X$, SE $b_0 = 0.035$, SE $b_1 = 0.169$, $r^2 = 0.873$; (×) $(CH_3)_2S{=}CH_2/DMSO$ $\hat{Y} = -0.104 + 0.794X$, SE $b_0 = 0.047$, SE $b_1 = 0.229$, $r^2 = 0.667$. (C) (×) $OsO_4-Me_3NO/THF-H_2O$ $\hat{Y} = -0.971 + 1.239X$, SE $b_0 = 0.058$, SE $b_1 = 0.398$, $r^2 = 0.906$; (□) $Hg(OAc)_2/THF-H_2O$ $\hat{Y} = 0.0711 + 2.276X$, SE $b_0 = 0.058$, SE $b_1 = 0.274$, $r^2 = 0.958$; (○) *m*-CPBA $\hat{Y} = 0.191 + 1.473X$, SE $b_0 = 0.002$, SE $b_1 = 0.018$, $r^2 = 1.000$.

the results obtained in bicyclo(2.2.1)heptane and bicyclo(2.2.2)octane series: $Hg(OAc)^+/H_2O > CH_3Li \approx BH_4^- >$ *m*-CPBA $> OsO_4 > BH_3$, see Scheme 19.[66] One indication that the sensitivity of log [*Z*]/[*E*] to C(3) substitution is related to electronic characteristics of the transition state is the decrease in the slope with decreasing basicity of the S-stabilized nucleophiles, Figure 12B: $PhSCH_2Li$ 1.869 (0.262), $PhS(=O)(=NMe_2)CH_2Li$ 1.086 (0.169), $(CH_3)_2S{=}CH_2$ 0.794 (0.229).

The effect of γ-substitution on the stereochemistry of nucleophilic additions to cyclohexanones was investigated in metal hydride reductions, organometallic alkylations, and sulfur ylide alkylations of 4-X-cyclohexanones,[35,145,153] 2-, 3-, and 4-*tert*-butyl-4-X-cyclohexanones,[154−156] 10-X-*trans*-decal-2-ones,[138,139,141,142,157] and 4-X-*trans*-decal-1-ones.[112,157] It is useful in this discussion to consider separately the effect of the equatorial and axial γ-substitution.

The equatorial γ-substitution does not uniformly increase the axial preference; again, the effect appears to depend on the nucleophile and ketone. Thus, the equatorial C(4) OCH_3 and CN groups in 3-methyl- and 3-*tert*-butylcyclohexanones increase axial preference of C_2H_5MgBr alkylations but slightly decrease axial preference of $NaBH_4$ reduction and ethynylation.[155] However, in the series of 2-*tert*-butyl-4-X-cyclohexanones[154] and 4-X-*trans*-decal-1-ones,[112,157] the equatorial C(4) substitution moderately increases axial preference in $NaBH_4$ reductions, cf. Figure 16 (□ in panels A and B).

In 4-X-cyclohexanones, the ring conformation can be considered locked as long as the C(4) groups are large, e.g. X = CH_3, C_6H_5, *p*-F-C_6H_4, CF_3 can be assumed to adopt predominantly equatorial orientation. Thus, in accord with the results for the C(3)-substituted cyclohexanones, it is found that the equatorial electron-withdrawing substitution at C(4) does not affect the stereochemistry of additions of the ylide $(CH_3)_2S^+CH_2^-$ (modest axial preference).[35] On the other hand, the low axial preference of $(CH_3)_2SO^+CH_2^-$ is further decreased![35]

In contrast, the axial γ-substitution always seems to increase the axial preference, and the effect is sometimes quite dramatic. Small increases were found in $NaBH_4$ and $LiAlH_4$ reductions of 4-X-3-*tert*-butyl- and 4-X-4-*tert*-butylcyclohexanones, but in Grignard alkylation, the preference for equatorial addition is reversed by the C(4)−OCH_3 group in 3-*tert*-butylcyclohexanone.[155,156] In the series of 2-*tert*-butyl-4-X-cyclohexanones,[154] the increases of the axial preference induced in $NaBH_4$ reductions by the axial C(4) substituents are comparable to those induced by the equatorial substituents, see Figure 16A, with one exception of the 4-ax-Br group. The latter effect is illustrated in Scheme 47. On the other hand, in the series of 4-X-*trans*-decal-1-ones,[112,157] all the examined polar groups induce slightly larger axial preferences in $NaBH_4$ reduction when they are in the axial orientation, see Figure 16B.

In the series of 10-X-*trans*-decal-2-ones,[139,142,157] the axial C(10)−COOMe group increases axial preference in $LiAlH_4$, $NaBH_4$, and $LiBEt_3H$ reductions (with the largest effect in the case of $LiBEt_3H$[142]) and in Grignard and CH_3Li alkylations (again with much larger effect in the case of CH_3Li that results in a reversal of the stereochemistry of addition[139]) but does not affect $(CH_3)_3Al$ alkylations. In the presence of the axial C(10)−Cl, $LiAlH_4$, $NaBH_4$, and $LiBEt_3H$ reduce *trans*-decal-2-one exclusively via axial addition.[142] In all these reactions the C(10)−CH_3 group

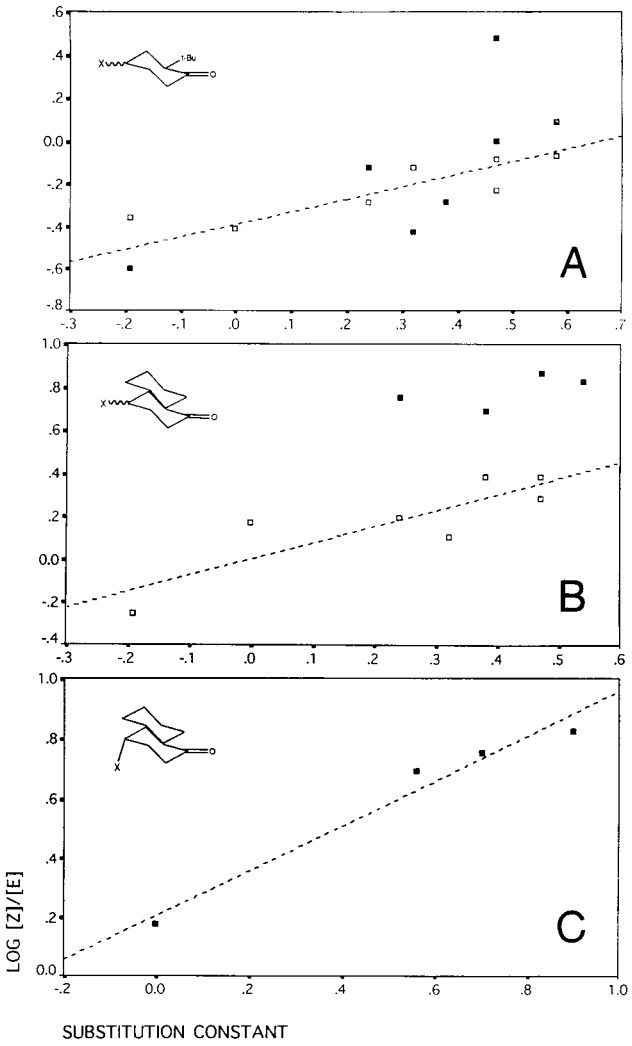


Figure 16. Effect of remote axial (■) and equatorial (□) substitution on $NaBH_4$ reduction of cyclohexanones: (A) 2-*tert*-butyl-4-X-cyclohexanones, log [*Z*]/[*E*] vs σ_I;[44a] $\hat{Y} = -0.39 + 0.59X$, SE $b_0 = 0.05$, SE $b_1 = 0.14$, $r^2 = 0.635$ (X = COO^-, H, OH, COOMe, OAc, Cl, Br, OTs); ax Br omitted from the regression, see text. (B) 4-X-*trans*-1-decalones, log [*Z*]/[*E*] vs σ_I;[44a] (□) equatorial 4-X, $\hat{Y} = 0.16 + 0.41X$, SE $b_0 = 0.06$, SE $b_1 = 0.18$, $r^2 = 0.635$; (■) axial 4-X (eq X = COO, H, OH, COOMe, OAc, Cl, Br; ax X = H, OH, OAc, Cl, F). (C) 4-X-*trans*-1-decalones, axial 4-X, log [*Z*]/[*E*] vs σ_π[46] = $\sigma_I - 0.75\sigma_R$, $\hat{Y} = 0.16 + 0.41X$, SE $b_0 = 0.06$, SE $b_1 = 0.18$, $r^2 = 0.635$ (X = H, OAc, OH, F).

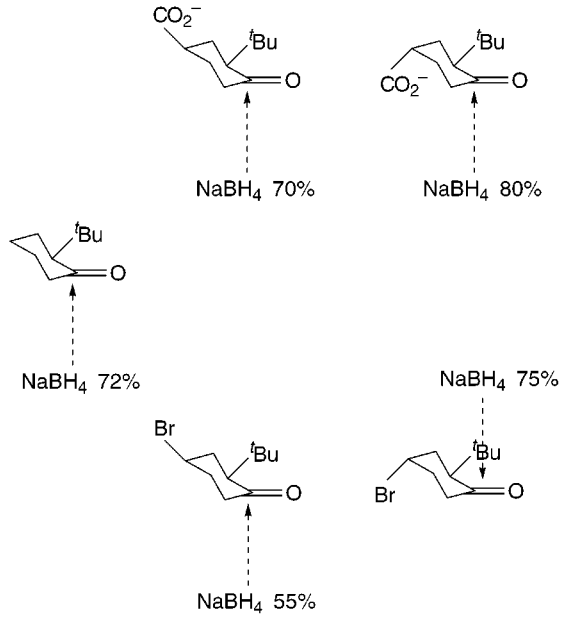
induces very small increases in the axial preference.[139,142]

Reversals of the normal stereochemistry of addition of some reducing and alkylating agents are also found in reactions with 4-X-cyclohexanones when X = O or Cl; several examples are shown in Scheme 48.

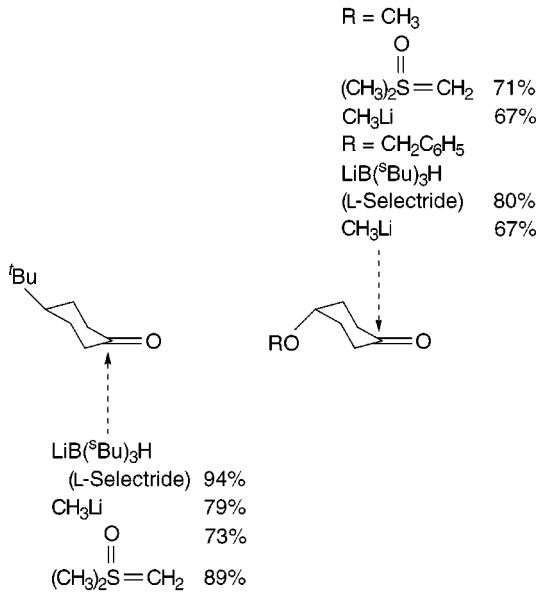
As mentioned earlier it is assumed that such ketones react mostly in the axial conformation. The most compelling evidence to support this assumption comes from the low-temperature study of *i*-Bu_2AlH (DIBAH, DIBAL, or DIBAL-H) reductions of 4-benzyloxy- and 4-TBDMSO-cyclohexanones in the presence and absence of $EtAlCl_2$, see Scheme 49.[153]

In the case of 4-benzyloxycyclohexanone, the stereochemistry of reduction is reversed by the addition of ~5 equiv of $EtAlCl_2$. This result was explained by the shift of the conformational equilibrium, indicated

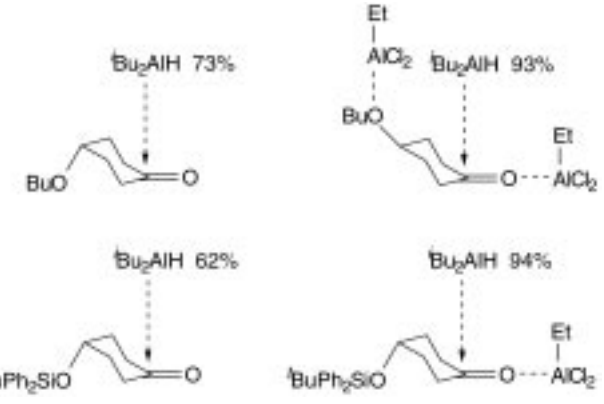
Scheme 47



Scheme 48

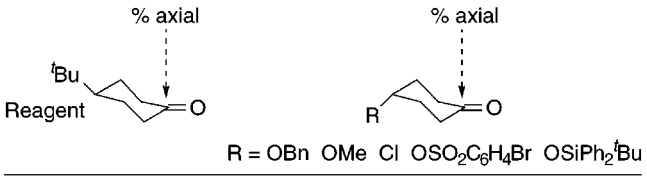


Scheme 49



by the NMR spectra, upon complexation of C(4) ether by $EtAlCl_2$.[153] The silyloxy group does not interact with the Lewis acid, and the stereochemistry of

Scheme 50



	R = OBn	OMe	Cl	$OSO_2C_6H_4Br$	$OSiPh_2{}^tBu$
$LiAlH_4$	91	80		75	73
$^tBu_2AlH$	72	73			62
$LiB(^sBu)_3H$ (L-Selectride)	19	80		82	
CH_3Li	31,37	67	67 74		62
$(CH_3)_2S=CH_2$	65		49		
$(CH_3)_2S(=O)=CH_2$	11		71		
$(CH_3)_3Al$ (1:1)	31		33 44		
CH_3MgCl/THF	28		46 50		
$(CH_3)_2Zn$	56		51 56		

reduction is not reversed. The data on the effect of the axial C(4)−OR and −Cl groups on several alkylations, epoxidations, and hydride additions is shown in Scheme 50. The possible reasons for different responses of reducing or alkylating agents to the axial C(4) substitution are discussed in the next section.

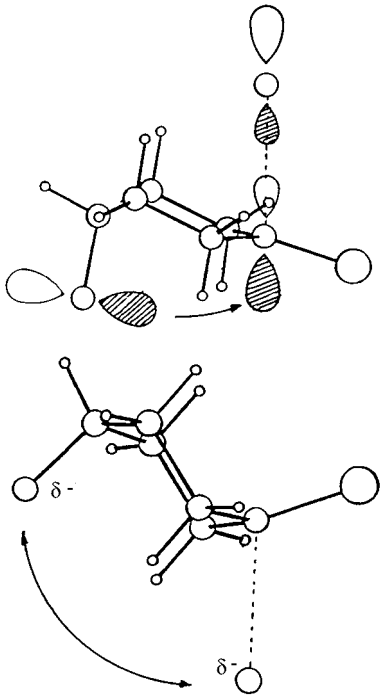
C. Inductive and Resonance Effects in Cyclohexane Probes. The available data suggest that the remote electron-withdrawing substitution of cyclohexanones can increase either preference, axial or equatorial, in additions of nucleophiles. The increase in axial preference seems to occur when the substituent accelerates the axial approach but slows down or accelerates the equatorial approach less. This is consistent with the notion, section 2.1.2.1, that such substitution diminishes C−C hyperconjugation and the resulting loss of stabilization of the equatorial transition state offsets the inductive effect; C−H hyperconjugation is somewhat diminished, too, but the C(2)−H and C(6)−H bonds are further away from the substitution site and thus less affected.

The increase in equatorial preference could occur for two reasons. First, in the case of the less electron-deficient transition states, it is possible that the diminished C−H and C−C hyperconjugative assistance no longer offsets the steric strain that favors the equatorial approach, see section 2.1.3. Second, in the case of sterically strained transition states, it is possible that the axial transition state is much less advanced than the equatorial one, and thus the ρ constant for the axial addition is smaller since the negative charge born by the carbonyl group is smaller. Among the reactions reviewed in the two preceding sections, epoxidation of cyclohexanone by $(CH_3)_2SO^+CH_2^-$ can be expected to lead to the most strained axial transition state because of the stereoelectronic requirement that the leaving sulfonium group be oriented *anti* with respect to the carbonyl O. Accommodation of this orientation on the axial face is more difficult for the $(CH_3)_2SO^+$ group than for the $(CH_3)_2S^+$ group. Consequently, the axial transition state for the $(CH_3)_2SO^+CH_2^-$ addition could be much less advanced than the equatorial one (or the two transition states for the $(CH_3)_2S^+CH_2^-$ addition), and therefore the axial approach would be less accelerated by the electron-withdrawing substitution. $NaBH_4$ reduction of pivalophenones is believed to involve a transition state which is more hindered and therefore less advanced than that for reduction of acetophenones, and the corresponding Hammett ρ constants are 2.33 and 2.52, respectively (for correlations with σ), and 1.12 and 1.82 (for correlations with σ^+).[158] The plots in Figures 13A, 14A, and 14C show that indeed the axial transition state for the $(CH_3)_2SO^+CH_2^-$ addition is less sensitive to the inductive effect (cf. □, Figure 14C), and that is why the electron-withdrawing effect increases the equatorial preference in $(CH_3)_2SO^+CH_2^-$ epoxidation of 4-X-cyclohexanones in the series X = $(CH_3)C$, C_6H_5, p-F-C_6H_4, CF_3.[35]

The difference in electronic properties of the axial and equatorial transition states for the $(CH_3)_2SO^+CH_2^-$ epoxidation is manifested in an even more dramatic way in the series X = OH, OAc, OBz. Assuming that these ketones react mostly in their axial conformations, vide supra, one has to conclude that the stereochemistry of this epoxidation is reversed here. The plots in Figure 14A and 14C reveal that the C(4)−oxy groups accelerate the axial addition but slow down the equatorial one compared to the C_6H_5, p-F-C_6H_4, and CF_3 groups.

Reversals of the normal stereochemistry of addition due to the polar axial C(4)-substitution were found in a number of other reactions, see Schemes 45, 47, 48, and 50. Two hypotheses were proposed to explain this effect of the axial C(4) groups, one invoking stabilization of the axial transition state by charge transfer,[7] the other destabilization of the equatorial transition state by electrostatic repulsion, Scheme 51.[112]

Scheme 51



The latter hypothesis was corroborated by the ab initio (3-21G) finding that the increased preference for axial approach of LiH to 4-ax-fluoro and 4-ax-

chlorocyclohexanone is a result of the large barrier for equatorial approach since the barriers for axial and equatorial additions to 4-eq-fluoro- and 4-eq-chlorocyclohexanone are nearly equal.[72] However, the magnitude of these barriers crucially depends on the choice and reproduction of the reference level. This level was defined by the authors as the energy of the linear LiH complexes with the corresponding ketones, which at the 3-21G level of the theory is lower for 4-ax-halocyclohexanones by ~0.6−1.2 kcal mol^{-1}. The decrease of this difference at the higher level of the theory or the choice of another model for the reference level might lead to the conclusion that the barriers for equatorial approach of LiH to 4-ax-fluoro- and 4-ax-chlorocyclohexanone are nearly equal, and thus the increased preference for axial approach is a result of the low barrier for axial approach. Furthermore, an important contribution of electrostatic repulsion between polar groups separated by more than 4.5 Å seems unlikely in the light of recent observations that the interactions of ion pairs (solvent separated) at such distances (between the α-helix or β-sheet residues) are negligible.[159]

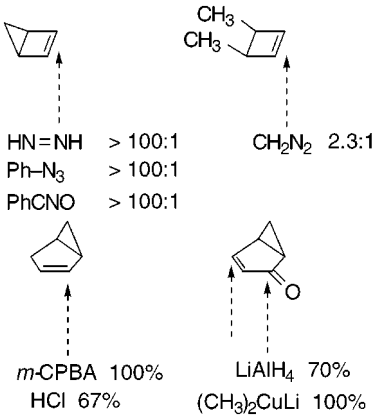
On the other hand, the charge-transfer interaction between OCH_3 and the carbonyl group in 4-methoxycyclohexanone (mostly axial OCH_3 in the gas phase[145]) is indicated by the fact that this group *lowers* the cyclohexanone $n_O(C{=}O)$ ionization potential, from 9.27 to 9.17 eV.[160] The corresponding transannular stabilization of the incipient carbonium ions is well-known.[161] The ground-state stabilization of the ketone might be more important than the transition-state stabilization in the case of advanced transition states for the $(CH_3)_2S^+CH_2^-$ and equatorial $(CH_3)_2SO^+CH_2^-$ epoxidation, and those reactions would be slowed down by X = OAc compared to X = CF_3, cf. Figures 13A and 14A. In the case of the less advanced transition state for the axial $(CH_3)_2SO^+CH_2^-$ epoxidation, the overall effect might be opposite,[39] i.e., resulting in acceleration of addition by X = OAc compared to X = CF_3, cf. Figure 14C.

This interpretation is consistent with the fact that the effect of Cl and Br (≥III row) is greater than the effect of II-row and even anionic (CO_2^-) substituents, see Scheme 47 and Figure 16A and 16B. The data sample is insufficient for a reliable analysis, but it is interesting to find that regression of log [*Z*]/[*E*] for $NaBH_4$ reduction of axially substituted 4-X-*trans*-decal-1-ones[112,157] (X = Cl omitted) on σ_I and σ_R gives substitution constant[46] $\sigma_\pi = \sigma_I - 0.75\sigma_R$ and improves correlation over the one on σ_I alone, Figure 16C.

2.3.2. Small-Ring C–C vs C–C

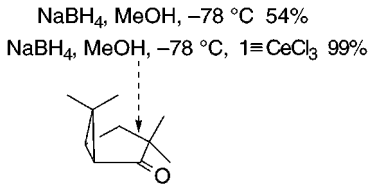
2.3.2.1. Allylic Cyclopropane C−C. Incorporation of the stereogenic center into the cyclopropane ring introduces the endocyclic C−C bond in the α-position whose σ_{CC} orbital is higher in energy and more diffuse than the σ_{CC} orbital of a nonstrained aliphatic C−C bond. A number of reactions of bicyclo(2.1.0)pent-2-ene[162,163] and bicyclo(3.1.0)hex-2-ene, Scheme 52,[164−166] suggest that the cyclopropyl group promotes *anti* approach more effectively than a comparable alkyl group.[167] However, examination of

Scheme 52



the stereochemistry of metal hydride reductions of bicyclo(3.1.0)hexen-2-one derivatives, Scheme 53,

Scheme 53



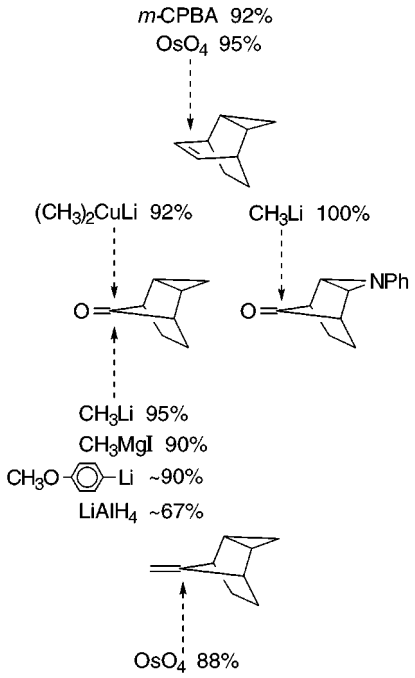
reveals that the π-face preference may also be opposite in these reactions, depending on the properties of the reducing agents.[168] The likely reason for this dependence is discussed in section 4.1.8.

2.3.2.2. Homoallylic Cyclopropane C−C. Incorporation of the cyclopropane ring as a ligand of the stereogenic center, separated from the incipient center by a tetrahedral C, introduces an excellent homoallylic σ-donor (diffuse, high-energy σ_{CC} orbital). On the other hand, the exocyclic C−C bond of cyclopropane, which has a relatively high s character and therefore a lowered electron-donor capability, becomes the vicinal (allylic) bond of the stereogenic center. This reduces the σ-assistance to bond formation. The latter effect seems to prevail in oxidations and hydroborations of tricyclo(3.2.2.0^{2,4})non-6-ene where *syn* π-face selectivity is observed,[169] but the *anti* preference is often observed in nucleophilic additions to *endo*-tricyclo(3.2.1.0^{2,4})octan-8-one and electrophilic additions to 8-methylene-*endo*-tricyclo(3.2.1.0^{2,4})octane, Scheme 54.[170,171] These results suggest that π-face selection is controlled by the homoconjugation of the cyclopropane endocyclic C−C bond. The C−C bond of the cyclopropane ring indeed offers better anchimeric asistance than the C=C bond in the solvolysis of bicyclo(2.2.1)heptyl derivatives.[171]

The competition between homoconjugative and hyperconjugative assistance is also expected to control π-face selection in reactions of the corresponding alkene. Since the oxirane and aziridine C−C bonds have also been shown to be powerful anchimeric-assistance donors in this system, the same should be true for 3-aza- and 3-oxa-8-methylene-*endo*-tricyclo(3.2.1.0^{2,4})octanes.[171] The available evidence is consistent with this expectation, Scheme 55.[172]

The difference in the importance of the cyclopropane C−C donation in the bicyclo(2.2.1)heptane- and

Scheme 54



bicyclo(2.2.2)octane-based probes, cf. Schemes 53 and 54, might be caused by the difference in the overlap of the incipient bond $\sigma^*_{\ddagger}$ orbital with the homoallylic cyclopropane C−C bond in the two skeletons. This could also explain the results of reduction of the γ-substituted bis-cyclopropyl probes, 4-substituted pentacyclo(4.3.0.$0^{2,4}$.$0^{3,8}$.$0^{5,7}$)decan-9-ones, and pentacyclo(4.4.0.$0^{2,4}$.$0^{3,8}$.$0^{5,7}$)decan-9-ones (norsnoutan-9-ones and snoutan-9-ones).[63,64] The regression slope for $NaBH_4$ reductions in the first case is much larger than in 5-X-adamantan-2-ones, in the second case smaller, cf. Figure 17. One of the differences between the two probes is the orientation of the endocyclic

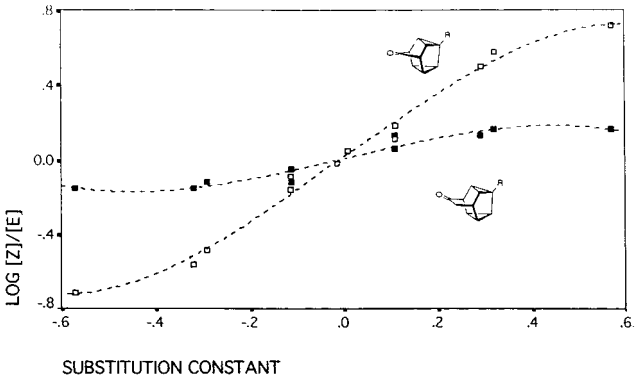
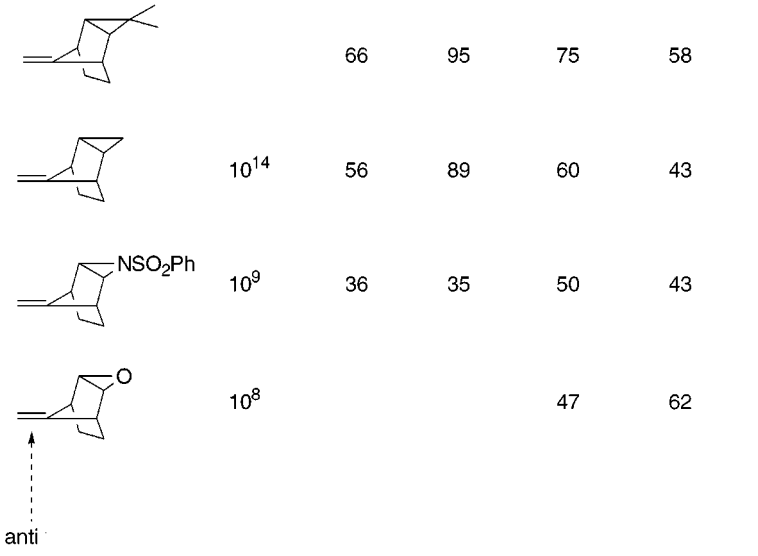


Figure 17. Effect of remote substitution on $NaBH_4$ reduction of snoutanones and norsnoutanones, log [*Z*]/[*E*] vs σ_I[44a] (X = CH_2CH_3, CH_2OMe, $CH{=}CH_2$, $C{\equiv}CH$, CO_2-Me, $C{\equiv}N$; symmetry expansion[45]): (■) snoutanones $\hat{Y} = 0.37X$, SE $b_1 = 0.05$, $r^2 = 0.861$ (cubic fit shown $r^2 = 0.949$); (□) norsnoutanones $\hat{Y} = 1.43X$, SE $b_1 = 0.08$, $r^2 = 0.971$ (cubic fit shown $r^2 = 0.989$).

cyclopropane bond with respect to the incipient bond. Good overlap, and consequently effective homoconjugative assistance, can be expected only in norsnoutan-9-ones. The *syn* approach in the reduction of snoutan-9-ones is promoted by the difference in hyperconjugative σ-assistance by one pair of vicinal (allylic) bonds and therefore less effectively than in reductions of 5-X-adamantan-2-ones.

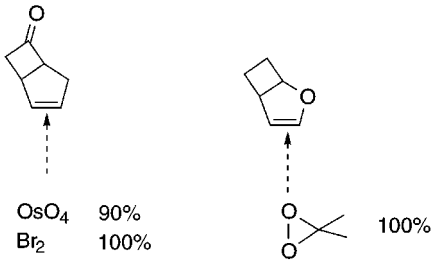
2.3.2.3. Allylic and Homoallylic Cyclobutane C−C. As was the case for the cyclopropane ring, introduction of the cyclobutane ring in the stereogenic center introduces an allylic or homoallylic σ_{CC} orbital that is high in energy and diffuse. Indeed, the electrophilic additions to bicyclo(3.2.0)hept-2-en-6-one and 2-oxabicyclo(3.2.0)hept-3-ene, Scheme 56,[133,173] and to *endo*-tricyclo(4.2.2.$0^{2,5}$)dec-7-ene occur *anti*, Scheme 57.[169]

Scheme 55

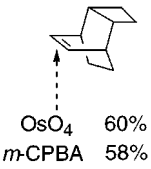


[a] Solvolysis of corresponding tosylates, k_{rel} = 1 for 7-tosyloxybicyclo(2.2.1)heptane

Scheme 56

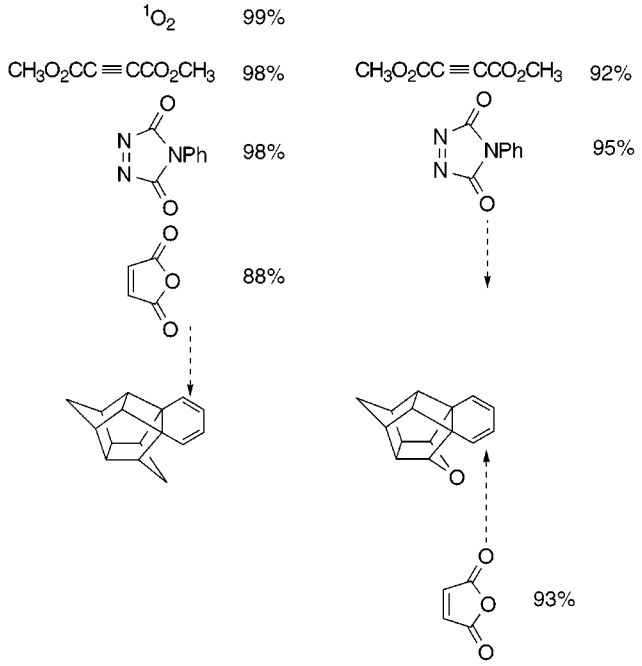


Scheme 57



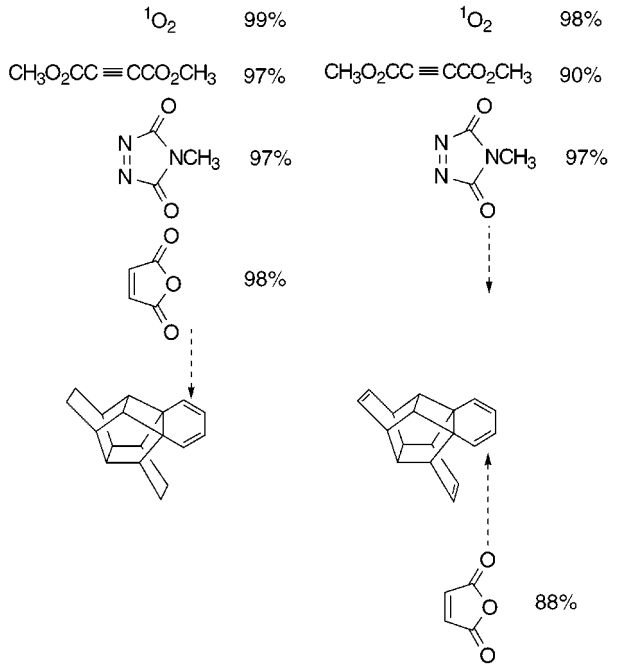
The classical stereochemical probes that incorporate the stereogenic center into the cyclobutane ring are Ginsburg's propellanes where cyclobutane is condensed along with another (larger) ring in the C(5) and C(6) positions of cyclohexadiene.[174] The closely related birdcage-annulated cyclohexadienes, heptacyclo(8.5.1.$0^{2,9}$.$0^{3,8}$.$0^{3,14}$.$0^{8,12}$.$0^{11,15}$)hexadeca-4,6-diene (Scheme 58) and heptacyclo-

Scheme 58

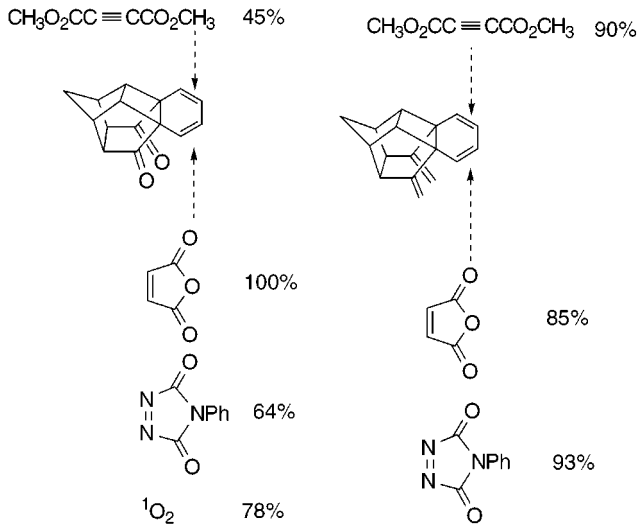


(8.6.2.$0^{2,9}$.$0^{3,8}$.$0^{3,15}$.$0^{8,12}$.$0^{11,16}$)octadeca-4,6,13,17-tetraene (Scheme 59), were recently synthesized and studied as intermediates of dodecahedrane synthesis (pagodanes).[175] The *syn* approach to these cyclohexadienes is believed to be less sterically hindered. Replacement of the C(13) methylene group by the oxygen atom, cf. Scheme 58, or the C(13), C(14) methylene groups by the double bond, cf. Scheme 59, decreases the difference in steric strain during the *syn* and *anti* approach, which is sufficient for some dienophiles to reverse π-face selectivity,[175,176] apparently promoted by the hyperconjugation of the cyclobutane endocyclic C−C.

Scheme 59



Scheme 60



In contrast, in hexacyclo(7.4.2.$0^{1,9}$.$0^{3,7}$.$0^{4,14}$.$0^{6,15}$)-pentadeca-10,12-diene-2,8-dione (Scheme 60), it is the*anti* face that is believed to be less hindered. Thus, in this case, the cyclobutane endocyclic C−C hyperconjugation and the steric strain would work in the same direction. The more hindered *syn* addition might be promoted, however, by the cyclobutane exocyclic C−C hyperconjugation, which is enhanced by the back-donation from the carbonyl O.[177−179] The likely reasons for the differences in dienophiles sensitivity to steric hindrance and hyperconjugation of the cyclobutane endo- and exocyclic C−C bonds are discussed in section 4.3.4.

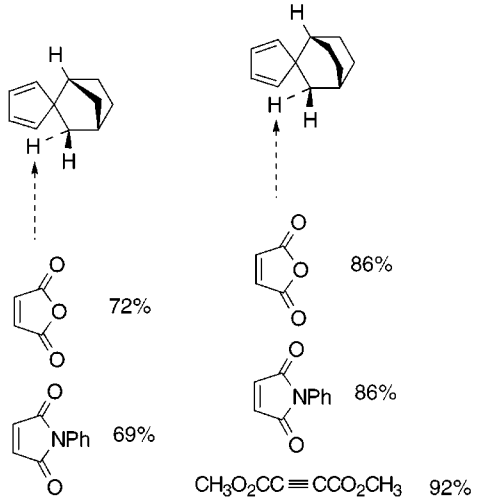
Yet another example of the effect of introduction of the cyclobutane ring as a ligand of the stereogenic center is described in the case of reduction and alkylation of cyclohexanones. The axial preference in additions to *trans*-bicyclo(4.2.0)octan-3-one is greater than in additions to *trans*-2-decalone.[180,181] This was explained as a result of flattening of the six-

membered ring, but it can also be expected as a result of decreased σ-assistance by the cyclohexanone C−C bond which in *trans*-bicyclo(4.2.0)octan-3-one becomes the exocyclic C−C bond of cyclobutane.

2.3.3. C–C vs C–C: Steric Demand of Rotamers or Electronic Effect of Alkyl Groups?

The stereochemistry of Diels−Alder additions to spiro(bicyclo[2.2.1]heptane-2,1′-[2,4]cyclopentadiene) and spiro(bicyclo[2.2.2]octane-2,1′-[2,4]cyclopentadiene) was attributed to the difference in the steric demand of the bridgehead C and the methylene C, corresponding to the isopropyl and ethyl groups, respectively, in the conformations extending their C−H bonds toward the incoming dienophile, Scheme 61.[182]

Scheme 61



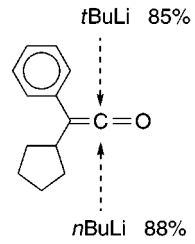
The effect is largest, however, for dimethyl acetylenedicarboxylate (DMAD), a dienophile with a small steric demand with respect to the cyclopentadiene C(5) stereogenic center, and it increases upon Lewis acid catalysis of addition. It is also larger for bicyclo(2.2.2)octane-annulated diene than for bicyclo(2.2.1)heptane-annulated diene. These observations are consistent with the hypothesis of σ-assistance, since the preferred approach occurs in each case *anti* to the more substituted C−C bond which has higher electron density at the bond critical point. The latter difference is greater in bicyclo(2.2.2)octane.[183]

3. Allylic Substitution

In this review, the term allylic substitution refers to the situation when modification of the stereogenic center involves one or two out-of-plane ligands carrying a homoallylic occupied p_z-orbital, bonding (e.g., C=C π-bond) or nonbonding (e.g., unshared electron pair of a heteroatom). Since the σ-assistance is likely to be either shut down or dominated by extended hyperconjugation as a consequence of highly electronegative substitution and rehybridization, cf. sections 2.1.3 and 2.1.4, involvement of the homoallylic π or n orbitals through $2p_z$-homoconjugation and through enhancement of σ-assistance due to back-donation (extended hyperconjugation) can be expected to control π-face selection.[184,185]

The prototype of such a center is C(1) of phenylcyclopentylketene or fluoroallene.[186,187] To explain the stereochemistry of alkyllithium additions to phenylcyclopentylketene, Scheme 62, one has to assume

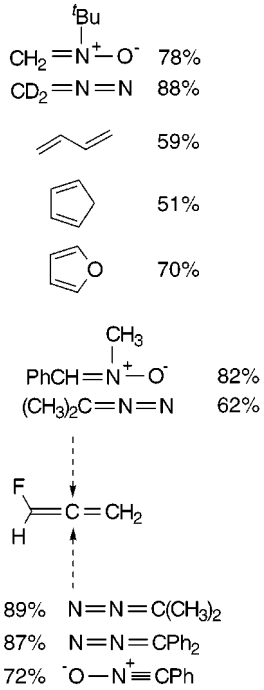
Scheme 62



that it is controlled by at least two and possibly three effects. One is the steric strain. The phenyl ring is usually believed to offer less steric hindrance to the approaching nucleophile than an aliphatic ring since it can turn its "flat" side toward the reagent. This difference could explain the *syn* preference of the bulky *tert*-butyllithium. The *syn* approach might also be promoted by extended hyperconjugation: $C(sp^3)-C(sp^2)$ delocalization (assisted by π-back-donation) will be more effective than $C(sp^2)-C(sp^2)$ delocalization. On the other hand, the *anti* approach can be promoted by π-homoconjugation of the phenyl ring and the incipient bond.

The stereochemistry of cycloadditions to fluoroallene appears to result from a similar interplay of these three effects. The *syn* approach is somewhat more hindered but is preferred in the case of C(2)-additions of primary, secondary, and even tertiary C (C−C bond formation). In contrast, the C−O and C−N bond formation at C(2) occur in a predominantly *anti* fashion, Scheme 63. As in the previous

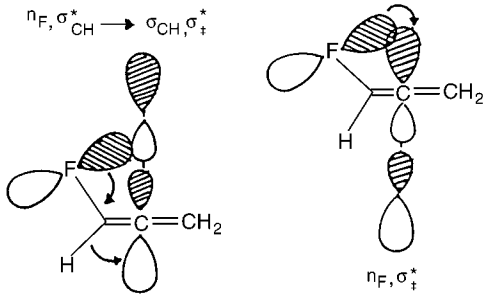
Scheme 63



example, the more hindered approach seems preferred because it is promoted by the C−H hypercon-

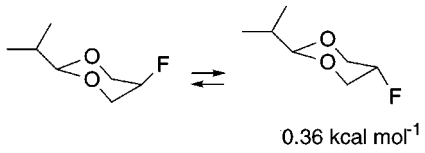
jugative assistance which is possible due to extended hyperconjugation, i.e., F lp back-donation in this case, Scheme 64.

Scheme 64



The *anti* preference in such situations is presently often attributed to electrostatic repulsion. This interpretation ignores the fact that O and F are found to "attract" each other rather than repel in 1,2-disubstituted ethanes or 5-substituted 1,3-dioxanes, Scheme 65.[188] The failure of classical electrostatic

Scheme 65



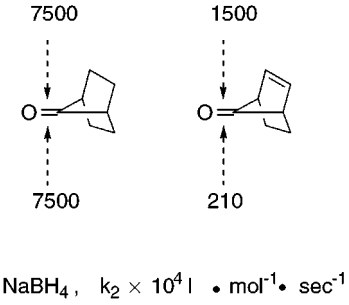
analysis to account for these phenomena is not surprising since they involve intramolecular interactions at nearly bonding distances. It seems significant that the classical models of π-face selection inevitably employ atomic point charges as the representation of the electrostatic force field. One cannot expect such treatment to be reliable,[189] and this necessity suggests that classical electrostatics actually play a small role in stabilization or destabilization of the transition state. The interaction that promotes the *anti* approach is more likely homoconjugation of the F $2p_z$ orbital and the incipient bond $\sigma^*_‡$ orbital, see Scheme 64. The possible reasons for the different response of the C−C and C−O incipient bonds to the presence of F unshared electron pairs are discussed in section 4.3.

3.1. Alkenylalkyl Stereogenic Center

3.1.1. Bicyclo(2.2.1)hept-2-en-7-one

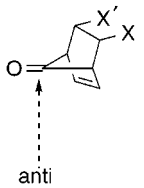
The stereochemistry of nucleophilic addition to bicyclo(2.2.1)hept-2-en-7-one was first examined in the pursuit of evidence of homoconjugation of the double bond and the carbonyl group.[190] The effect of the double bond on the rates of $NaBH_4$ reduction suggests that no such effect operates in this case because the preferred approach is *syn*, Scheme 66. However, these rate constants also indicate that the *syn* preference of the hydride addition is not simply a result of lesser steric demand of the alkene bridge.[191] The addition is unexpectedly slowed down by the double bond, and the *anti* approach is slowed down more.

Scheme 66



The lack of homoconjugative stabilization is perhaps not surprising since the C=C bond is a somewhat less potent anchimeric donor than the cyclopropane C−C bond,[172] while the transition state for $NaBH_4$ reduction is rather advanced and perhaps not sufficiently electron deficient. The *anti* approach is actually preferred by some alkylating reagents, see section 4.1.7, which means that π-homoconjugation can play a more important role in the addition of some C nucleophiles.[131,192−197] The involvement of σ-donor assistance has been confirmed by the effect of the ethane-bridge substitution on π-face selection, Scheme 67 and Figure 18.[198,199]

Scheme 67



X	X′	% anti $NaBH_4$	% anti CH_3Li
COONa	H	>90	
H	H	85	74
CH_2OCH_3	CH_2OCH_3	88	74
CH_2OAc	CH_2OAc	87	
$COOCH_3$	H	68	
CN	H	44	
$COOCH_3$	$COOCH_3$	45	10

3.1.2. 7-Substituted Bicyclo(2.2.1)hepta-2,5-dienes

The observations of large effects of remote 7-substituents on π-face selection in cycloadditions to bicyclo(2.2.1)hepta-2,5-dienes have prompted numerous kinetic and theoretical studies of their origin.[200−202] For most, and in particular for the bulky reagents, three π-faces are available in such reactions, Scheme

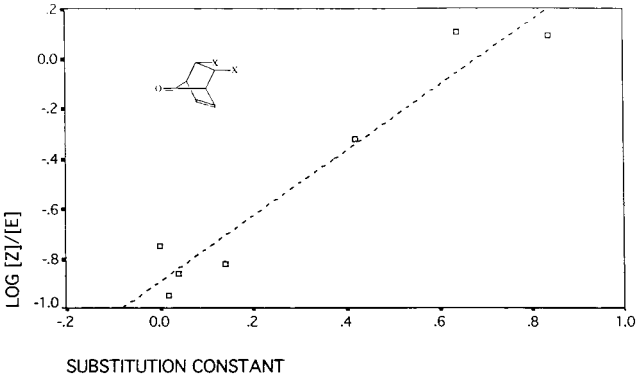


Figure 18. Effect of remote substitution on $NaBH_4$ reduction of bicyclo(2.2.1)hept-2-en-7-one, log [*Z*]/[*E*] vs σ_π[46] (X = COO^-Na^+, H, bis-CH_2OMe, bis-CH_2OAc, COOMe, C≡N, bis-COOMe): $\sigma_\pi = \sigma_I + 0.9\sigma_R$, $\hat{Y} = -0.90 + 1.30X$, SE $b_0 = 0.07$, SE $b_1 = 0.15$, $r^2 = 0.935$.

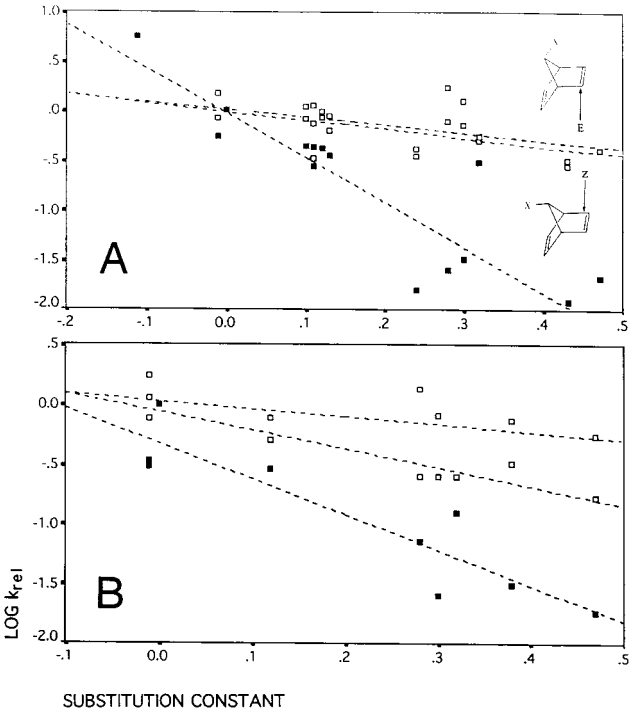
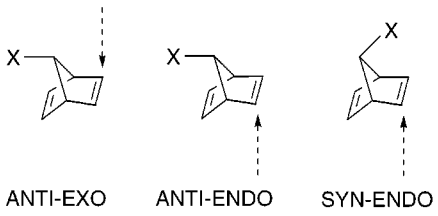


Figure 19. Effect of remote substitution on cycloadditions to bicyclo(2.2.1)hepta-2,5-diene, log k_{rel} vs σ_I.[44a] (A) Diels−Alder addition of hexachlorocyclopentadiene to 7-X-bicyclo-(2.2.1)hepta-2,5-dienes (X = $SiMe_3$, H, *t*Bu, CH_2OMe, OH, OMe, COOMe, O*t*Bu, OBz, C_6H_4-*p*-OMe, C_6H_4-*p*-Me, C_6H_5, C_6H_4-*p*-F, Cl): (■) anti-*exo* addition $\hat{Y} = -0.03 - 4.52X$, SE $b_0 = 0.12$, SE $b_1 = 0.53$, $r^2 = 0.935$ (the COOMe data set omitted from the regression, see text); (□) anti-*endo* additions $\hat{Y} = -0.01 - 0.87X$, SE $b_0 = 0.08$, SE $_1 = 0.31$, $r^2 = 0.426$. (B) CCl_2 carbene addition to 7-X-bicyclo(2.2.1)-hepta-2,5-dienes (X = H, COOMe, C_6H_5, *t*Bu, O*t*Bu, OMe, OAc, Cl): (■) anti-*exo* addition, $\hat{Y} = -0.33 - 2.96X$, SE $b_0 = 0.14$, SE $b_1 = 0.51$, $r^2 = 0.827$; (□) anti-*endo* additions $\hat{Y} = -0.06 - 1.55X$, SE $b_0 = 0.05$, SE $b_1 = 0.18$, $r^2 = 0.911$. Very poor correlations are obtained for both syn-*endo* cycloadditions, $r^2 < 0.25$.

Scheme 68



68. The plots of partial rate factors for such additions of hexachlorocyclopentadiene and dichlorocarbene are shown in Figure 19. The inductive effect of the 7-substituents has little effect on the *endo* additions but strongly affects the *exo* additions. It seems reasonable to propose that the small retardation effect on the *endo*-addition rate is due to inductive deactivation of the C=C double bonds. The effect on the *exo*-addition rate is larger because it results from superimposition of the above inductive deactivation and the decrease in electron-donor capability of the C(1)−C(6) and C(4)−C(5) bonds and the C(5)−C(6) double bond, i.e., decrease in hyperconjugative and homoconjugative assistance. The unusual acceleration of the *exo*-addition by the 7-methoxycarbonyl group, see Figure 16A, might be due to electron delocalization from its O $2p_z$-orbitals into the C(1)−C(6) and C(4)−C(5) bonds and/or the C(5)−C(6) double bond (extended homoconjugation).

The alternative explanation of the data in Figure 19 proposes that the inductive deactivation of the double bonds causes large retardation of *exo*-cycloadditions; during the *endo*-additions this effect is partly offset by the decrease in repulsion between the incipient bond and the C(1)−C(6) and C(4)−C(5) bonds.[202]

3.2. Bis-Aryl Stereogenic Center

The probes that incorporate bis-aryl stereogenic centers provide yet another model system to investigate stereoelectronic control of π-face selection in the absence of steric bias. Dibenzobicyclo(2.2.2)octa-2,5,7-triene was used first as such a probe.[203] The illustrative examples of the currently available evidence are shown in Figures 20−22: $NaBH_4$ reduction of dibenzobicyclo(2.2.2)octa-5,7-dien-2-ones,[204] epoxidation of dibenzobicyclo(2.2.2)octa-2,5,7-trienes and 1,3-butadiene cycloaddition to 9,10-dihydro-9,10-ethenoanthracene-11,12-dicarboxylic anhydrides[205,206] (Figure 20), $NaBH_4$ reduction of 2,2-diarylcyclopentanones[207] and spiro[cyclopentane-1,9′-fluoren]-2-ones[208] (Figure 21), and OsO_4 dihyroxylation of 3,3-diarylcyclopentenes[209] and dimethyl acetylenedicarboxylate cycloaddition to 5,5-diarylcyclopentadienes[210] (Figure 22).

There are two patterns of dependence of log [*Z*]/[*E*] on the substitution of the benzene rings in dibenzobicyclo(2.2.2)octane- and 1,1-diphenylcyclopentane-based probes. The electron-donating groups promote either *anti* approach, consistent with π-homoconjugation as the stereoinducing factor, Figures 20A,B, 21A, and 22, or *syn* approach, consistent with σ-hyperconjugation enhanced by π-back-donation (extended hyperconjugation), Figure 20C. The possible reasons for the different response of Diels−Alder additions to the bis-aryl stereogenic center are discussed in section 4.3.

The third pattern is found in the case of spiro-[cyclopentane-1,9′-fluoren]-2-ones, Figure 21B. Here, neither π-homoconjugation nor extended hyperconjugation can be effective because of the constraints of the spiro geometry. Consequently, electronic bias is mostly due to the inductive effect of the remote substituents (δ-substitution). The dependence of log [*Z*]/[*E*] on σ_I,[44a] Figure 21B, suggests that the electronic bias begins to decrease when $\sigma_I > 0.3$, as observed in the case of 5,6-*endo*-X,X′-bicyclo(2.2.2)-oct-2-enes (Figure 2), 5-X-adamantan-2-ones (Figure 3), 2-methyl-5-X-adamantyl cations (Figure 4A), 4-X-pentacyclo(4.3.0.$0^{2,4}$.$0^{3,8}$.$0^{5,7}$)decan-9-ones, and 4-X-pentacyclo(4.4.0.$0^{2,4}$.$0^{3,8}$.$0^{5,7}$)undecan-9-ones (norsnoutan-9-ones and snoutan-9-ones, Figure 17); see also section 2.1.3.

The data are insufficient to determine whether the poorer correlation for Diels−Alder additions to 5,5-diarylcyclopentadienes is an indication of yet another case of nonlinear distribution of log [*Z*]/[*E*] vs substitution constant.

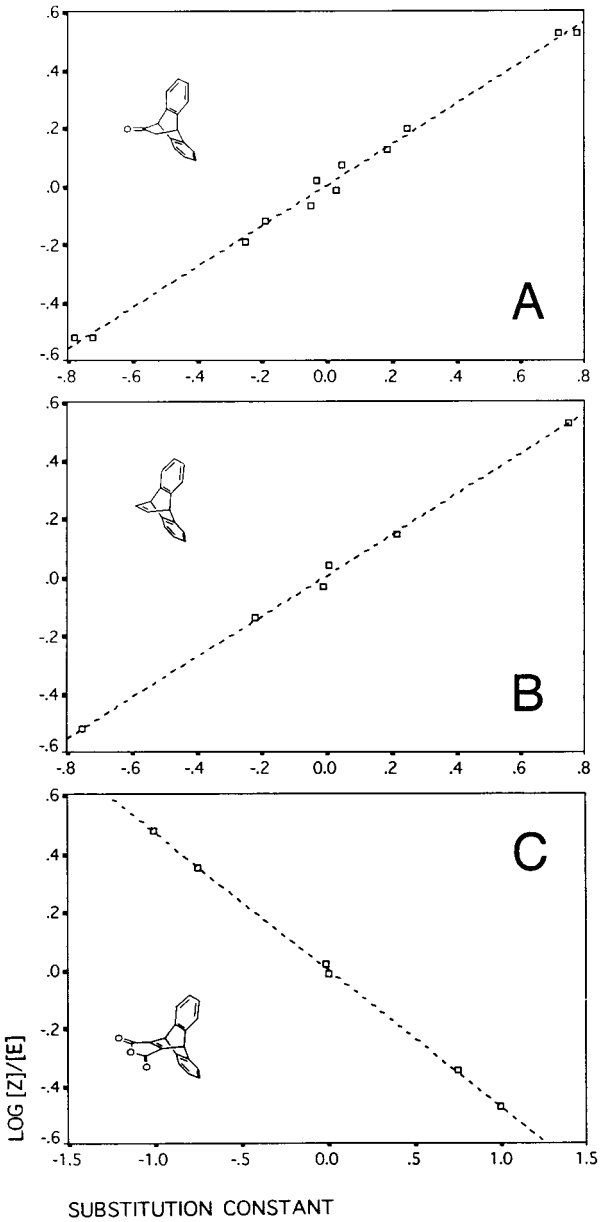


Figure 20. Effect of remote substitution on reactions of dibenzobicyclo(2.2.2)octa-2,5-diene-based probes, log [*Z*]/[*E*] vs σ_p and σ_m Hammett constants (in the gas phase[44f]) (symmetry expansion[45]): (A) $NaBH_4$ reduction of dibenzobicyclo(2.2.2)octa-5,7-dien-2-ones (*m*,*p*-X = OMe, F, NO_2), $\hat{Y} = 0.70X$, SE $b_1 = 0.02$, $r^2 = 0.993$. (B) *m*-CPBA epoxidation of dibenzobicyclo(2.2.2)octa-2,5,7-trienes (*m*,*p*-X = OMe, F, NO_2), $\hat{Y} = 0..70X$, SE $_1 = 0.02$, $r^2 = 0.997$. (C) Diels−Alder addition of 1,3-butadiene to dibenzobicyclo-(2.2.2)octa-2,5,7-triene-2,3-dicarboxylic acid anhydrides (*m*,*p*-X = OMe, NO_2, bis-CF_3), $\hat{Y} = -0.47X$, SE $b_1 = 0.01$, $r^2 = 0.999$.

3.3. Arylalkyl Stereogenic Center

A number of reactions have been examined in the series of 7-keto- and 7-methylenebenzobicyclo(2.2.1)-hept-2-enes[211,212] and benzobicyclo(2.2.2)oct-5-en-2-ones.[213] These probes are very similar to bicyclo-(2.2.1)hept-2-ene in terms of the operating effects: the *syn* approach can be promoted by the lesser steric hindrance and better σ-hyperconjugation, possibly assisted by π-back-donation (extended hyperconjugation, see sections 3.1.1 and 3.2 and Figure 21B), while the *anti* approach can be promoted by π-ho-

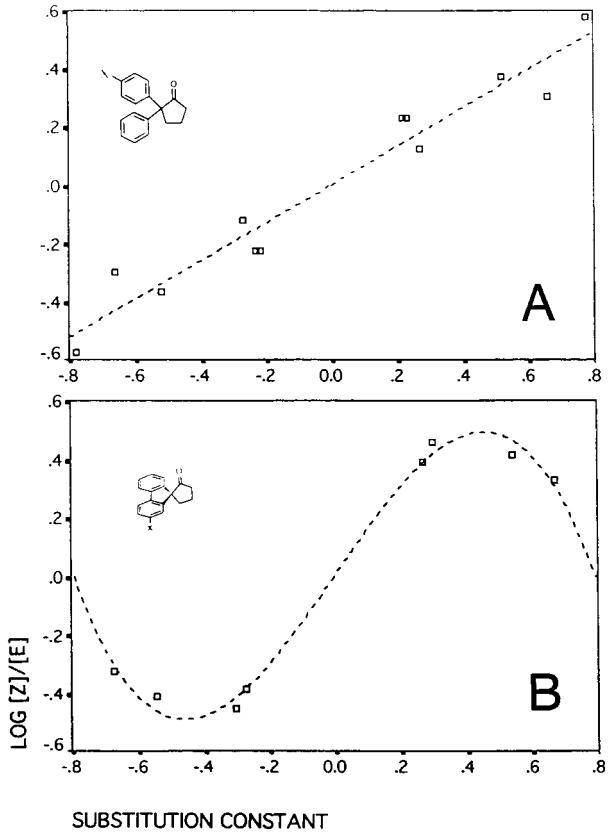
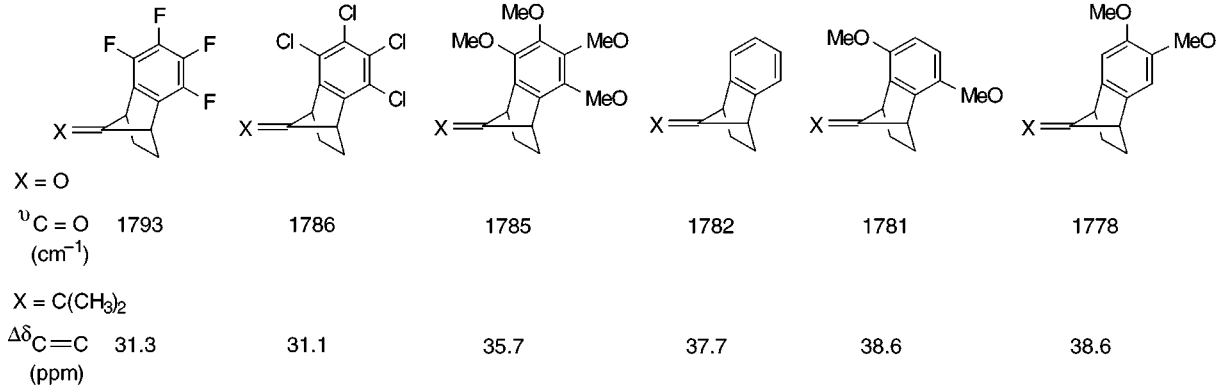


Figure 21. Effect of remote substitution on $NaBH_4$ reduction of 2,2-diarylcyclopentanones (symmetry expansion[45]): (A) 2,2-diphenylcyclopentanone (*p*-X = NH_2, O, OMe, Cl, Br, NO_2), log [*Z*]/[*E*] vs σ_p Hammett constants (in water[44f]) $\hat{Y} = 0.65X$, SE $b_1 = 0.05$, $r^2 = 0.942$. (B) spiro-[cyclopentane-1,9′-fluoren]-2-one (X = OMe, F, NO_2, =CH−NO_2), log [*Z*]/[*E*] vs σ_I,[44a] $r^2 = 0.992$ (cubic fit).

moconjugation. In lieu of the appropriate inductive and resonance constants for the multisubstituted phenyl rings, the change in the ring π-electron density can be gauged by its effect on charge polarization of the exocyclic C=O or C=C bond reflected in the C=O IR stretching frequency and the difference in ^{13}C chemical shifts of the distal and proximal olefinic carbons, respectively, see Scheme 69.

The corresponding plots of log [*Z*]/[*E*] for borohydride and aluminum hydride reductions of benzobicyclo(2.2.1)hept-2-en-7-ones and benzobicyclo(2.2.2)-oct-5-en-2-ones are shown in Figures 23 and 24. Among the two parent ketones, benzobicyclo(2.2.1)-hept-2-en-7-one is considerably more reactive and, due to the different orientation of the carbonyl with respect to the ethane bridge, more sterically biased. These differences are reflected in the fact that its reductions are more sensitive to remote substitution (regression slopes) and display greater *syn* preference. The increasing electron density in the phenyl ring promotes the *anti* approach with one exception, reduction of benzobicyclo(2.2.2)oct-5-en-2-ones with $LiAl(OtBu)_3H$, Figure 24A. In the case of benzobicyclo-(2.2.1)hept-2-en-7-ones, Figure 23A, reduction with $LiAl(OtBu)_3H$ also displays reversed dependence when the phenyl ring becomes a more effective electron donor. Thus, $LiAl(OtBu)_3H$ seems to be particularly sensitive to σ-assistance and extended hyperconjugation. The response of other hydrides to

Scheme 69



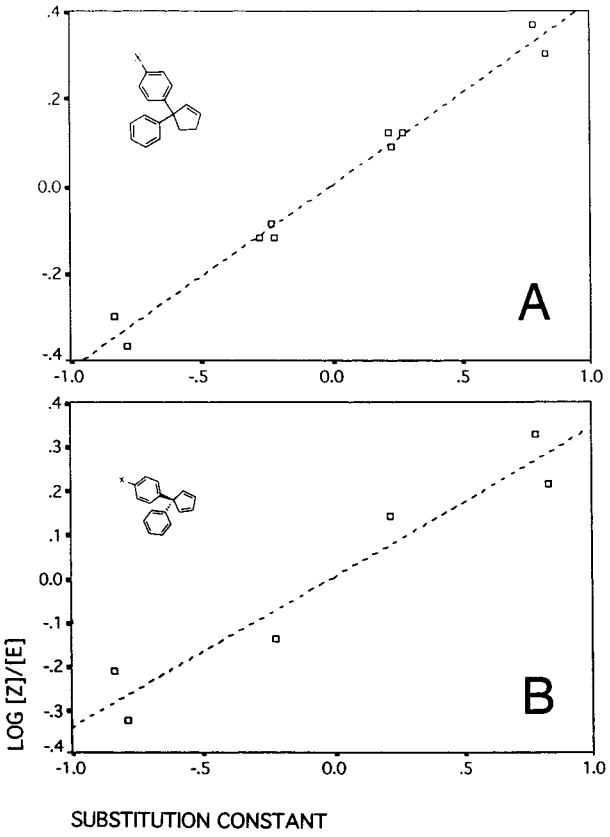


Figure 22. Effect of remote substitution on reactions of diphenylcyclopentane-based probes, log [*Z*]/[*E*] vs σ_p Hammett constants (in water[44f]) (symmetry expansion[45]): (A) OsO_4 dihydroxylation of 3,3-diphenylcyclopentenes (X = NMe_2, OMe, Cl, Br, NO_2) $\hat{Y} = 0.42X$, SE $b_1 = 0.002$, $r^2 = 0.981$. (B) Diels–Alder addition of dimethyl acetylenedicarboxylate DMAD to 5,5-diphenylcyclopentadienes (X = NMe_2, Cl, NO_2), $\hat{Y} = 0.34X$, SE $b_1 = 0.05$, $r^2 = 0.925$.

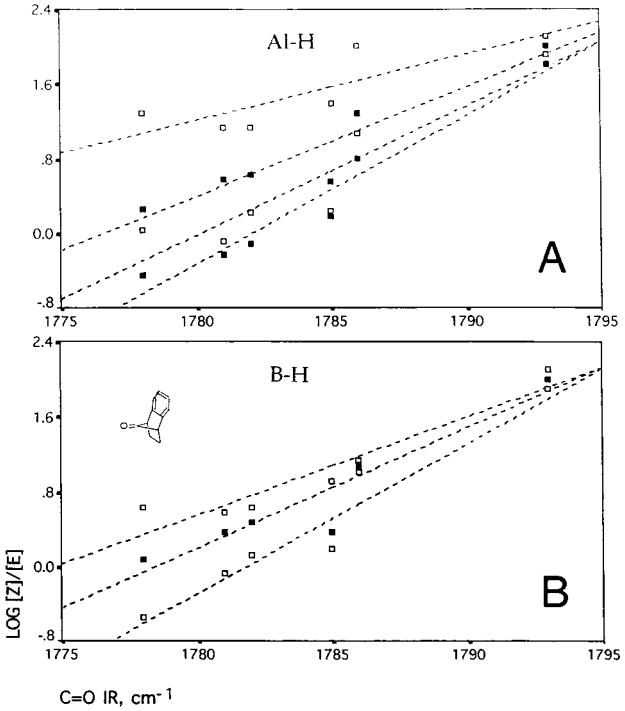


Figure 23. Effect of remote substitution on metal hydride additions to benzobicyclo(2.2.1)hept-2-en-7-one, log [*Z*]/[*E*] vs C=O IR absorption frequency $\nu_{C=O}$ (cm^{-1}) (see Scheme 69 for the type of the probe substitution): (A) aluminum hydrides from top to bottom (□) $LiAl(OtBu)_3H$ $\hat{Y} = -124.1 + 0.07X$, SE $b_0 = 41.3$, SE $b_1 = 0.02$, $r^2 = 0.698$; (■) $LiAlH_4/Et_2O$ $\hat{Y} = -207.4 + 0.12X$, SE $b_0 = 37.5$, SE $b_1 = 0.02$, $r^2 = 0.885$; (□) $LiAlH_4$/THF $\hat{Y} = -245.2 + 0.15X$, SE $b_0 = 53.4$, SE $b_1 = 0.03$, $r^2 = 0.841$; (■) iBu_2AlH $\hat{Y} = -281.3 + 0.16X$, SE $b_0 = 31.4$, SE $b_1 = 0.02$, $r^2 = 0.953$. (B) boron hydrides from top to bottom (□) $NaBH_4$ $\hat{Y} = -186.7 + 0.11X$, SE $b_0 = 32.9$, SE $b_1 = 0.02$, $r^2 = 0.890$; (■) B_2H_6 $\hat{Y} = -229.5 + 0.13X$, SE $b_0 = 40.9$, SE $b_1 = 0.02$, $r^2 = 0.888$; (□) $s\text{-}Am_2BH$ $\hat{Y} = -284.3 + 0.16X$, SE $b_0 = 32.2$, SE $b_1 = 0.02$, r^2, $= 0.963$.

the change in substitution is consistent with the dominant contribution of π-homoconjugation.[211,213] No correlation is apparent between the slopes and the negative charge borne by the reagent. The patterns of sensitivity of the aluminum and boron hydrides to π-homoconjugation are discussed later, see section 4.1.6.

The results of Friedel–Crafts alkylation, dichlorocarbene addition, oxidation ($^1O_2$, *m*-CPBA), and halogenation of 7-methylenebenzobicyclo(2.2.1)hept-2-enes are shown in Figure 25.

Compared to hydride additions to benzobicyclo(2.2.1)hept-2-en-7-ones, these reactions show little sensitivity to remote substitution. There is a wide range of the *syn* preference which may in part reflect the differences in the steric demand and in chelating effect of the benzene ring. In particular, the high *syn* preference in addition of the acetylium cation, Figure 25A (and in the Prins reaction, not shown, where the reactive species is the hydroxymethyl cation), and the increase in the *syn* preference of chlorination by *t*-BuOCl in acidic medium (increased concentration of *t*-BuO(Cl)H^+), Figure 25B, were attributed to the latter effect. It should be noted that the stereochem-

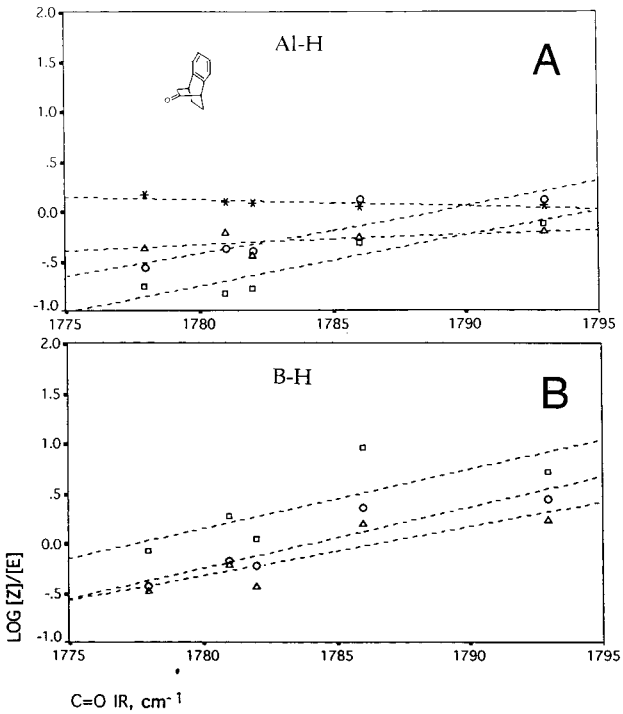


Figure 24. Effect of remote substitution on metal hydride additions to benzobicyclo(2.2.1)oct-5-en-2-ones, log [*Z*]/[*E*] vs C=O IR absorption frequency $\nu_{C=O}$ (cm^{-1}) as in Figure 20 (see Scheme 69 for the type of the probe substitution): (A) aluminum hydrides from top to bottom (∗) $LiAl(OtBu)_3H$ $\hat{Y} = 10.9 - 0.01X$, SE $b_0 = 5.7$, SE $b_1 = 0.00$, $r^2 = 0.543$; (△) $LiAlH_4/Et_2O$ $\hat{Y} = -22.2 + 0.01X$, SE $b_0 = 14.6$, SE $b_1 = 0.01$, $r^2 = 0.428$; (○) iBu_2AlH $\hat{Y} = -82.5 + 0.05X$, SE $b_0 = 21.8$, SE $b_1 = 0.01$, $r^2 = 0.826$; (□) $LiAlH_4$/THF $\hat{Y} = -92.9 + 0.05X$, SE $b_0 = 24.7$, SE $b_1 = 0.01$, $r^2 = 0.823$; (B) boron hydrides from top to bottom (□) B_2H_6 $\hat{Y} = -106.1 + 0.06X$, SE $b_0 = 49.9$, SE $b_1 = 0.03$, $r^2 = 0.603$; (○) *s*-Am_2BH $\hat{Y} = -108.7 + 0.06X$, SE $b_0 = 25.1$, SE $b_1 = 0.01$, $r^2 = 0.862$; (△) $NaBH_4$ $\hat{Y} = -87.5 + 0.05X$, SE $b_0 = 28.6$, SE $b_1 = 0.02$, $r^2 = 0.756$.

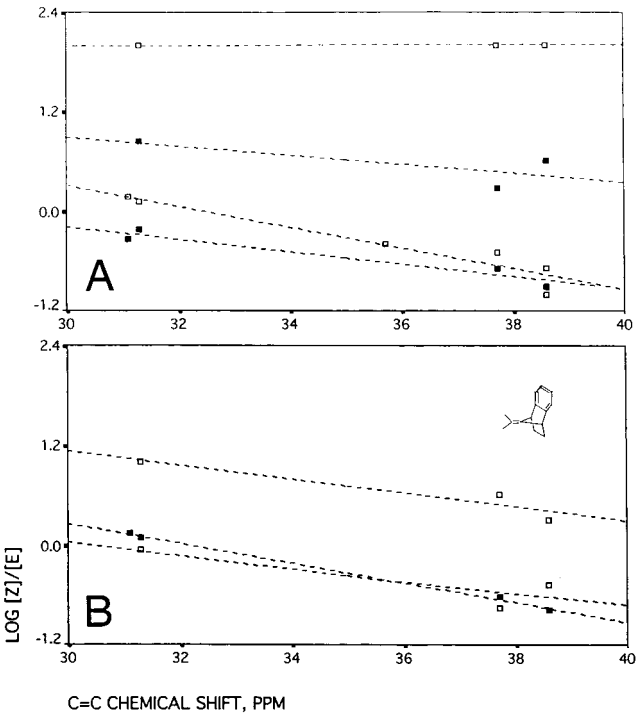
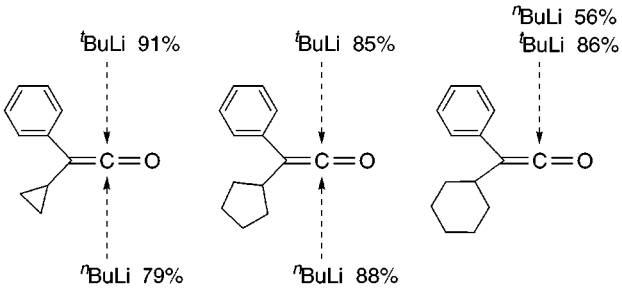


Figure 25. Effect of remote substitution on additions to 7-isopropylidenebenzobicyclo(2.2.1)hept-2-ene, log [*Z*]/[*E*] vs the difference in ^{13}C chemical shifts of the 7-isopropylidene olefinic C's (see Scheme 69 for the type of the probe substitution): (A) from top to bottom (□) acetylium ion CH_3CO^+; (■) CCl_2 carbene $\hat{Y} = 2.49 - 0.05X$, SE $b_0 = 1.73$, SE $b_1 = 0.05$, $r^2 = 0.552$; (□) $^1O_2$ $\hat{Y} = 4.01 - 0.12X$, SE $b_0 = 0.68$, SE $b_1 = 0.02$, $r^2 = 0.915$; (■) *m*-CPBA $\hat{Y} = 2.01 - 0.07X$, SE $b_0 = 0.51$, SE $b_1 = 0.01$, $r^2 = 0.927$; (B) from top to bottom (□) $tBuO(Cl)H^+$ $\hat{Y} = 3.63 - 0.08X$, SE $b_0 = 1.00$, SE $b_1 = 0.03$, $r^2 = 0.900$; (■) NBS $\hat{Y} = 3.81 - 0.12X$, SE $b_0 = 0.15$, SE $b_1 = 0.00$, $r^2 = 0.997$; (□) *t*BuOCl $\hat{Y} = 2.41 - 0.08X$, SE $b_0 = 1.48$, SE $b_1 = 0.04$, $r^2 = 0.788$.

istry of the chlorination of 7-azabenzobicyclo(2.2.1)-hept-2-ene displays a similar pattern of moderate dependence on the substitution of the benzene ring.[214]

The previously discussed phenyl(cycloalkyl)ketenes, Schemes 62 and 70, incorporate another version of

Scheme 70



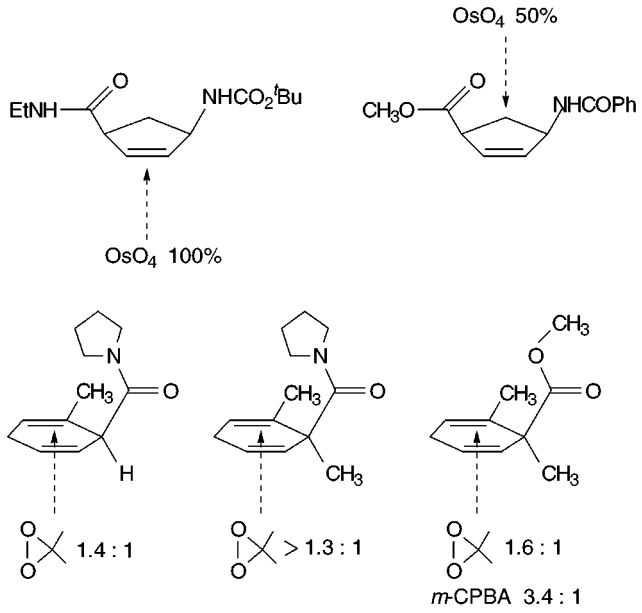
the arylalkyl stereogenic center.

In principle, σ-assistance would be expected to be less important in additions to phenyl(cycloalkyl)-ketenes since the stereogenic C is not only sp^2 but also carries strongly electron-withdrawing substituents. Nonetheless, since the electron-donor capability of the exocyclic C−C bonds increases with the ring size (section 2.3.2), the increase in σ-hyperconjugative assistance to the *syn* approach on going from phenylcyclopropylketene to phenylcyclohexylketene could precipitate the reversal of π-face selectivity in additions of *n*-butyllithium. Indeed, ketene reactivity in acid-catalyzed hydration, which depends on the ability of the substituents to directly stabilize the cationic transition state for protonation, increases in the order *c*-$Pr_2C{=}C{=}O$ < $Et_2C{=}C{=}O$.[186] The alternative explanation might invoke the change in reactivity of ketenes caused by the inductive effect of the cycloalkyl groups (e.g., *c*-PrCPh=C=O is more reactive than *i*-PrCPh=C=O in neutral hydration in H_2O/CH_3CN[186]). The resulting shift of the transition state along the reaction coordinate could change the balance of the steric strain and hyperconjugative and homoconjugative stabilization (vide infra section 4.1.3).

3.4. Carbonylalkyl Stereogenic Center

The few examples available indicate that modification of the carbonyl ligand of the stereogenic center can have a large effect on π-face selection, Scheme 71.[4,5,215,216] In both alkene oxidations, the carboxamide groups are more effective *anti* directing ligands that the carboxylate groups. The differences can be attributed to the changes in σ-assistance by the $C-C_{sp^2}$ bonds, enhanced in carboxamides by the back-

Scheme 71



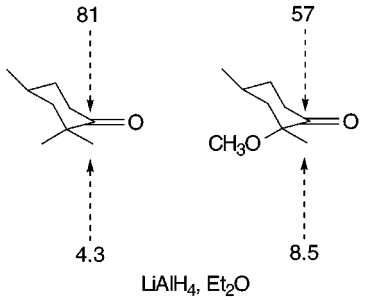
donation from the carbonyl O lp (the carboxylate carbonyl O is less basic and hence a poorer n donor), and to the changes in rotamer stability and consequently in steric hindrance.[216] The exclusive *anti* addition of *N*-phenylmaleimide (NPM) to 5-formyl-1,2,3,4,5-pentamethylcyclopenta-1,3-diene was explained as a result of distortion of the π-HOMO of the diene due to the perturbation by a low-lying π^* orbital on the C(5) substituent.[5] The π^* orbitals of the (hydroxyimino)methyl and vinyl groups are high-lying, and consequently the addition of NPM is less selective, Scheme 72. However, the observed shift of π-face selectivity is also consistent with the notion that in the case of 5-formyl-1,2,3,4,5-pentamethylcyclopenta-1,3-diene σ-assistance is enhanced by extended hyperconjugation (O lp back donation).

3.5. Heteraalkyl Stereogenic Center

3.5.1. Kinetic Evidence

3.5.1.1. Nucleophilic Additions to Ketones. As was the case for β- and γ-substitution of ketones, section 2.3.1.3, the effect of α-substitution on the rates of nucleophilic addition also depends on the nature of the reactants. Aldol condensation of lithium enolate of pinacolone with 4-*tert*-butylcyclohexanone, which occurs on the equatorial face, is strongly accelerated by the electron-withdrawing C(2) substitution.[217] On the other hand, the α-OR substitution of carbonyls was reported to slow down $(CH_3)_2Mg$ and $CH_3Ti(OiPr)_3$ additions in the absence of chelation, e.g., the relative rates of $(CH_3)_2Mg$ alkylations in the series 2-hexanone, cyclohexanone, and 2-methoxycyclohexanone are 1.0, 4.56, and 1.18.[218−220] Furthermore, the axial C(2)−OCH_3 group was shown to slow down the axial but not the equatorial $LiAlH_4$ reduction of 4-*tert*-butylcyclohexanone.[221] This effect was attributed to the absence of stabilization of the axial approach when the antiperiplanar C−H bond is replaced by the C−O bond, in accord with the hypothesis of hyperconjugative assistance to bond formation, Scheme 73.

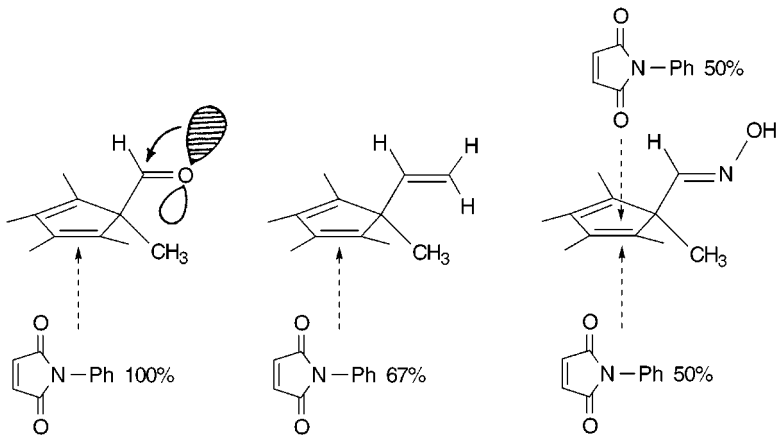
Scheme 73



In contrast, the results of reductions of 5-substituted 5,7-dihydro-1,11-dimethyl-6*H*-dibenzo[*a*,*c*]cyclohepten-6-ones have recently been interpreted as evidence that such an antiperiplanar effect does not operate in hydride additions.[222] The structure of the unsubstituted ketone (C_2 symmetry) and the two approaches that are free of steric strain because they are *anti* to the C(5) substituent, either when the substituent is equatorial (*anticlinal* approach) or when it is axial (*antiperiplanar* approach), are shown in Scheme 74.

The log k_R/k_H data for $NaBH_4$, $LiAlH_4$, and Et_3SiH *anticlinal* reductions are plotted against σ_I in Figure 26A. The two metal hydride reductions are accelerated by the electron-withdrawing groups, while the

Scheme 72



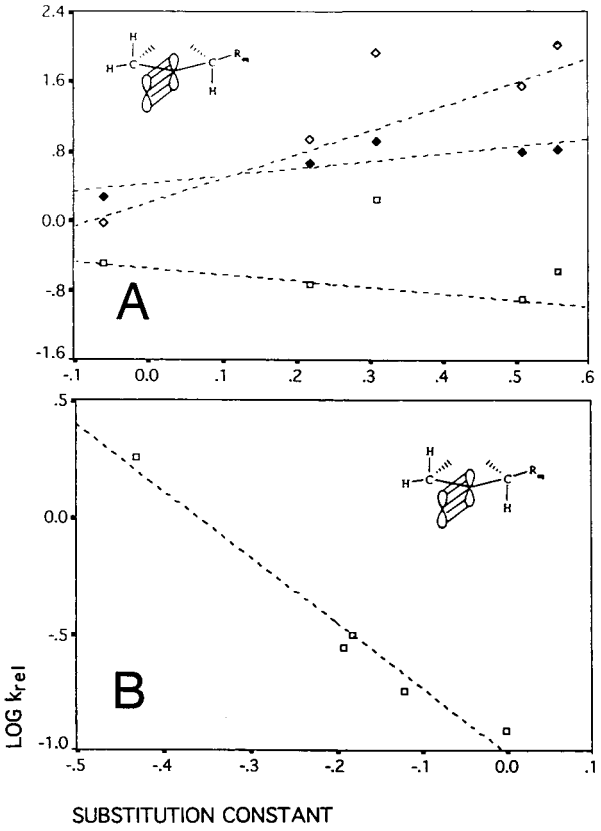
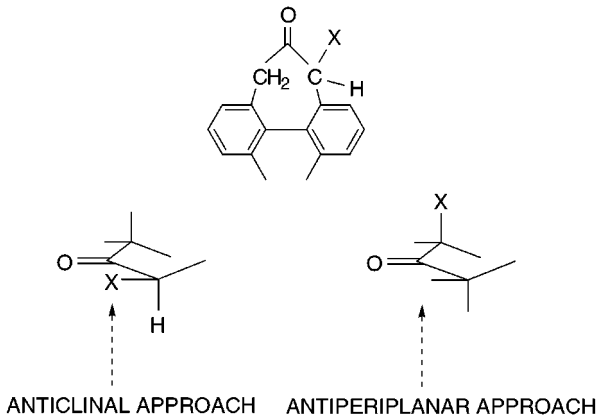


Figure 26. Effect of allylic substitution on trans addition of hydrides to 5-eq-X-5,7-dihydro-1,11-dimethyl-6*H*-dibenzo[*a*,*c*]cyclohepten-6-ones (anticlinal approach, X = Me, SMe, OMe, Cl, F): (A) log k_{rel} vs σ_I[44g] from top to bottom (◆) $NaBH_4$ $\hat{Y} = 0.42 + 0.85X$, SE $b_0 = 0.12$, SE $b_1 = 0.32$, $r^2 = 0.698$; (◇) $LiAlH_4$ $\hat{Y} = 0.33 + 3.05X$, SE $b_0 = 0.34$, SE $b_1 = 0.89$, $r^2 = 0.797$; (□) Et_3SiH $\hat{Y} = -0.40 - 0.30X$, SE $b_0 = 0.39$, SE $b_1 = 1.03$, $r^2 = 0.027$. (B) Et_3SiH, log k_{rel} vs $\sigma_\pi = 0.6\sigma_I + \sigma_R$, $\hat{Y} = -1.02 - 2.81X$, SE $b_0 = 0.07$, SE $b_1 = 0.29$, $r^2 = 0.970$.

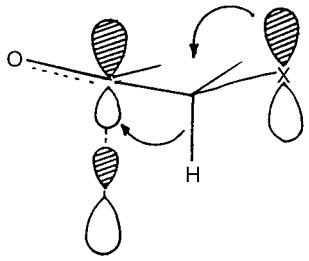
Scheme 74



silane reduction is considerably slowed down, which is consistent with development of positive charge at the carbonyl C in the transition state. The most remarkable characteristic of these plots are positive deviations for O and F which render the correlation with σ_I very poor. Such deviations suggest that O and F lp back-donation might play a role in stabilization of the electron-deficient transition state. Indeed, regression of log k_R/k_H for the silane reductions on $\lambda\sigma_I + \sigma_R$ gives $\lambda = 0.6$, and the correlation significantly improves; the plot of log log k_R/k_H vs σ_π[46] is shown in Figure 26B.

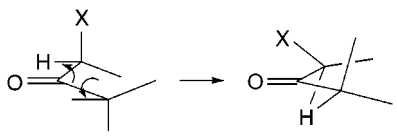
Explanation of this result is suggested by the recent finding that the electron-deficient C(1) reaction site in cyclohexanone can be stabilized both in the staggered and eclipsed conformations about the C(1)−C(2) and C(1)−C(6) bonds.[39] Thus, since the transition states for the *anticlinal* additions are probably similar to the parent ketone in terms of the C_2 skeletone symmetry, the incipient bond can be assumed to be stabilized both by the antiperiplanar C(7)−H_{ax} bond and the synperiplanar C(5)−H_{ax} bond, much like the 2-propyl cation is stabilized by the C(1)−H and C(3)−H bonds pointing in the opposite direction in the C_2-symmetrical conformation.[223] The C(5)−H_{ax} hyperconjugation, especially important in the case of silane reductions ($\rho < 0$), is enhanced by the OCH_3 group due to O lp back-donation (extended hyperconjugation), Scheme 75.

Scheme 75



Examination of the plots of log k_R/k_H vs σ_I for the *antiperiplanar* reductions reveals a similar picture of the general dependence of rates on the inductive effect of the C(5) substituents and, unexpectedly, again a large positive deviation for the 5-OCH_3 ketone in the silane reduction, Figure 27A. This surprising similarity suggests that the geometry of the two approaches is not as different as is implied by the diagrams above and the assumption of rigidity of the parent ketone. In fact, the transition states for the *antiperiplanar* reductions are unlikely to retain the skeletal C_2 symmetry: the X-ray crystal structures show that the strain of introducing the 5_{ax}−CH_3 group leads to a rotation about the C(5)−C(6) and C(6)−C(7) bonds.[224] The transition structure for LiH addition to 5_{ax}-methyl-5,7-dihydro-1,11-dimethyl-6*H*-dibenzo[*a*,*c*]cyclohepten-6-one located at the 3-21G level shows the same distortion.[225] As a result, the C(5)−H_{eq} bond has a better overlap with the reaction site than the C(5)−O_{ax} bond, Scheme 76. Conse-

Scheme 76



quently, the incipient bond in the *antiperiplanar* transition state can be stabilized by the antiperiplanar C(7)−C_{sp^2} bond or C(8)-π-homoconjugation *and* by the synperiplanar C(5)−H_{eq} bond, assisted by O lp back-donation. Again, extended hyperconjugation results in the increase of the reaction rate due to the transition-state stabilization. In this case, regression

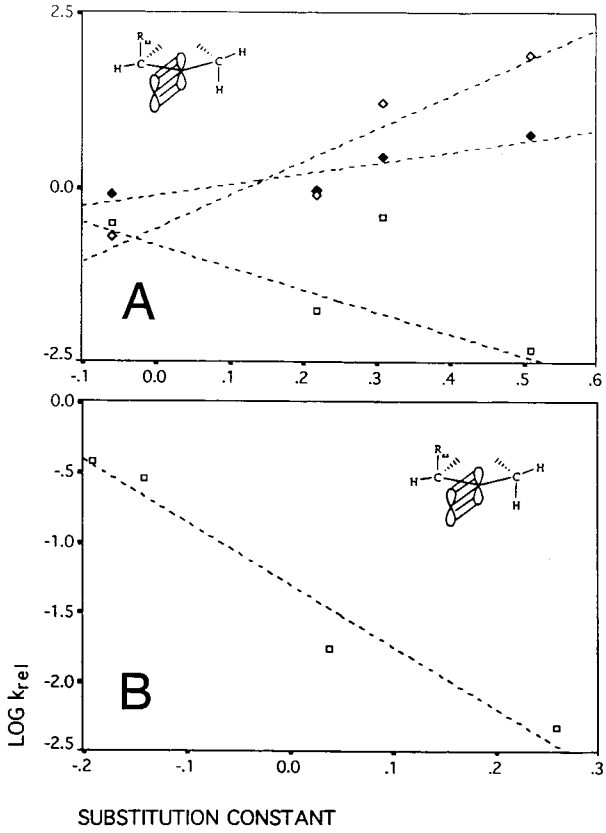


Figure 27. Effect of allylic substitution on trans addition of hydrides to 5-ax-X-5,7-dihydro-1,11-dimethyl-6*H*-dibenzo[*a*,*c*]cycloheptene-6-ones (antiperiplanar attack, X = Me, SMe, OMe, Cl): (A) log k_{rel} vs σ_I[44g] from top to bottom (◆) $NaBH_4$ $\hat{Y} = -0.13 + 1.56X$, Se $b_0 = 0.18$, SE $b_1 = 0.55$, $r^2 = 0.801$; (◇) $LiAlH_4$, $\hat{Y} = -0.59 + 4.76X$, SE $b_0 = 0.37$, SE $b_1 = 1.17$, $r^2 = 0.892$; (□) Et_3SiH $\hat{Y} = -0.64 - 2.57X$, SE $b_0 = 0.67$, SE $b_1 = 2.10$, $r^2 = 0.430$. (B) Et_3SiH, log k_{rel} vs $\sigma_\pi = \sigma_I + 0.75\sigma_R$, $\hat{Y} = -1.30 - 4.45X$, SE $b_0 = 0.12$, SE $b_1 = 0.69$, $r^2 = 0.954$.

of log k_R/k_H for the silane reductions on $\sigma_\pi = \sigma_I + \lambda'\sigma_R$ gives $\lambda' = 0.75$; the plot of log log k_R/k_H vs σ_π[46] is shown in Figure 27B.

3.5.1.2. Diels−Alder Additions to 5-Substituted Cyclopenta-1,3-dienes. The effect of substituents on π-face selection in Diels−Alder additions was studied using 5-substituted 1,2,3,4,5-pentamethylcyclopenta-1,3-dienes, Scheme 77.[27]

The reported reaction times can be used to approximate the relative rate constants. Regression of the partial rate factors for the *syn* approach on σ_I and σ_R yields a satisafctory correlation and the substitution constant[46] $\sigma_\pi = \sigma_I - \lambda'\sigma_R$, $\lambda' = 0.85$, Figure 28. No correlation is obtained for the *anti* partial rate factors.

The effect of cyclopentadiene C(5) substituents on the energy of activation for Diels−Alder addition was also studied by means of the ab initio MO calculations.[226] In this study, the energy of deformation of the cyclopentadiene ring to its transition-state geometry was found to correlate with the activation energies. The dependence of the ab initio activation and deformation energies on the inductive and resonance constants of the C(5) substituents is shown in Figures 29 and 30.

To capture the difference in the steric demand of the groups X, the second-row X and the third- and

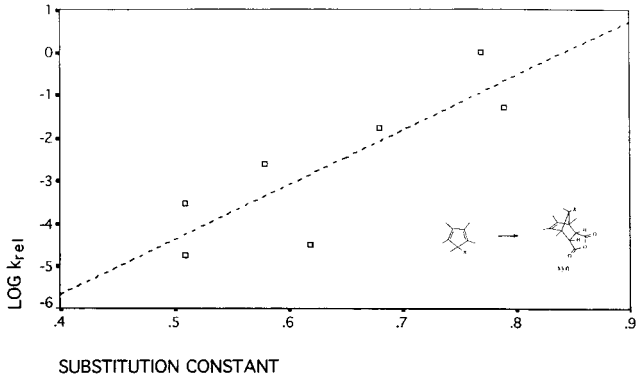
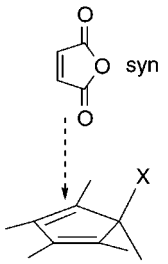


Figure 28. Effect of allylic substitution on Diels−Alder *syn*-addition of maleic anhydride MA to 5-X-1,2,3,4,5-pentamethylcyclopenta-1,3-dienes (XOMe, OH, NHAc, Cl, SBn, SPh, SMe): log k_{rel} (approximate) vs $\sigma_\pi = \sigma_I - 0.85\sigma_R$, $\hat{Y} = -10.8 + 12.8X$, SE $b_0 = 2.4$, SE $b_1 = 3.7$, $r^2 = 0.705$.

Scheme 77



X	anti	syn	reaction time	approximate K_{rel} (syn)
Cl	0	10	30 min	1.67×10^{-2}
OH	0	10	<30 sec	1.00
OCH_3	0	10	<10 min	5.00×10^{-2}
NHAc	0	10	3.5 h	2.38×10^{-3}
SMe	9	1	27.5 h	3.03×10^{-5}
SCH_2Ph	9	1	48 h	1.74×10^{-5}
SPh	9.7	0.3	1 h	2.53×10^{-4}
SOMe	10	0	48 h	—
SO_2Me	10	0	9 days	—

higher-row X are plotted separately and the X = H data sets are omitted. In agreement with the experimental data, regression of the ab initio E_{act} and E_{def} for the *syn* approach on σ_I and σ_R, Figures 29A and 29B, suggests that both effects make important contributions ($\sigma_\pi = \sigma_I - \lambda'\sigma_R$, $\lambda' = 0.6$ and 0.75).

In contrast, regressions of E_{act} and E_{def} for the *anti* approach reveal that the resonance effect does not make an important contribution ($\sigma_\pi = \sigma_I - \lambda'\sigma_R$, $\lambda' <$ 0.2, no significant improvement of the correlation with σ_I). The plots of E_{act} and E_{def} against the inductive constant[44d] are shown in Figures 30A and 30B.

The acceleration of Diels−Alder addition by the electron-withdrawing C(5) substitution of cyclopentadiene is unexpected. The most likely explanation for this unique response is based on Bent's rule:[227] the positive inductive effect facilitates deformation of cyclopentadiene because increasing the electronegativity of the C(5) substituents sends s-character to the olefinic C(1) and C(4) and thereby stabilizes rehybridization $2p_z \rightarrow sp^3$.

As for the resonance effect, the C(5)−X lp backdonation stabilizes the deformation and the transi-

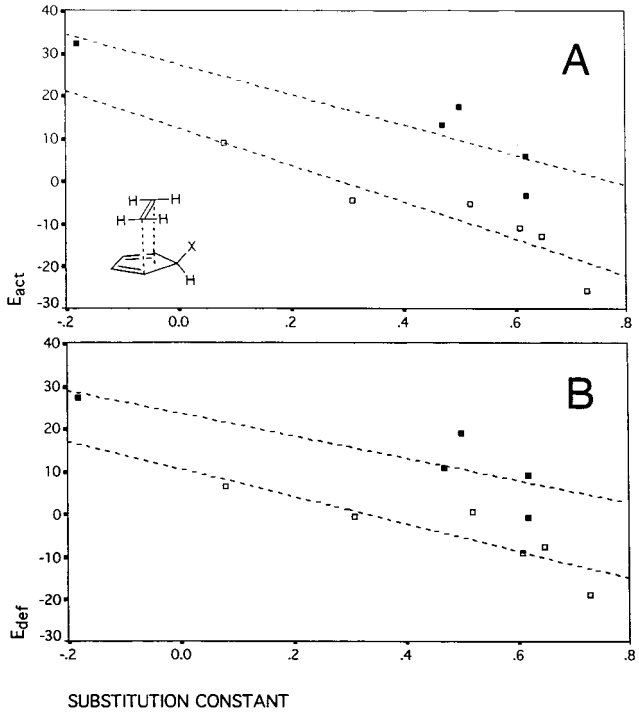


Figure 29. Effect of allylic substitution on Diels−Alder *syn*-addition of ethylene to 5-X-cyclopenta-1,3-dienes (■) ≥II-row X = SiH_3, SH, Cl, Br, I and (□) I-row X = CH_3, C≡CH, OH, NH_2, F, C≡N: (A) E_{act} (ab initio 3-21G) vs $\sigma_\pi = \sigma_I - 0.6\sigma_R$, (□) $\hat{Y} = 12.3 - 43.2X$, SE $b_0 = 4.8$, SE $b_1 = 9.0$, $r^2 = 0.853$; (■) $\hat{Y} = 27.2 - 35.5X$, SE $b_0 = 5.3$, SE $b_1 = 10.5$, $r^2 = 0.791$. (B) E_{def} (ab initio 3-21G, energy of cyclopentadiene deformation to the transition-state geometry) vs $\sigma_\pi = \sigma_I - 0.75\sigma_R$, (□) $\hat{Y} = 10.4 - 31.9X$, SE $b_0 = 4.7$, SE $b_1 = 8.8$, $r^2 = 0.767$; (■) $\hat{Y} = 23.5 - 26.0X$, SE $b_0 = 5.2$, SE $b_1 = 10.3$, $r^2 = 0.678$.

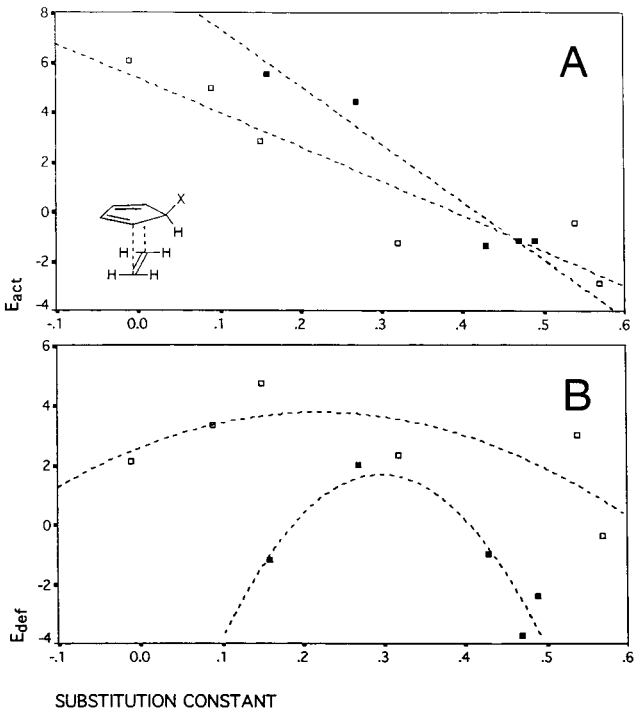
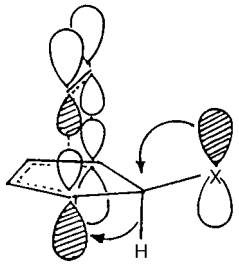


Figure 30. Effect of allylic substitution on Diels−Alder *anti*-addition of ethylene to 5-X-cyclopenta-1,3-dienes (■) ≥II-row X = SiH_3, SH, Cl, Br, I; (□) I-row X = CH_3, C≡CH, OH, NH_2, F, C≡N: (A) E_{act}, kcal mol^{-1} (ab initio 3-21G) vs σ_F[44d], (□) $\hat{Y} = 5.3 - 13.9X$, SE $b_0 = 1.0$, SE $b_1 = 2.8$, $r^2 = 0.864$; (■) $\hat{Y} = 9.7 - 23.3X$, S $b_0 = 1.3$, SE $b_1 = 3.3$, $r^2 = 0.944$. (B) E_{def}, kcal mol^{-1} (ab initio 3-21G, energy of cyclopentadiene deformation to the transition-state geometry) vs σ_F,[44d] (□) quadratic fit, $r^2 = 0.503$, (■) quadratic fit, $r^2 = 0.834$.

tion state during the *syn* approach because it improves hyperconjugation of the C(5)−H bond (extended hyperconjugation), Scheme 78. Thus, for most C(5)

Scheme 78



substituents used in the two studies, the inductive and resonance effect work in the same direction during the *syn* approach.

The positive inductive effect ought to facilitate deformation of the ring during the *anti* approach as well, but now the deformation is not stabilized by the σ-hyperconjugation assisted by back-donation: the C−X σ-bonds for the electronegative C(5) substituents are poorer electron donors than the C−H bond. On the other hand, destabilization of the deformation by the electropositive groups X (third and higher row) is offset by the improved σ-hyperconjugation of the C−X bonds. Thus, for many X groups, the two effects work in the opposite direction during the *anti* approach. The relative contribution of σ-hyperconjugation of the C−X bonds is greater in the case of the *anti* deformation energy than in the case of the *anti* activation energy, which results in the difference in the plots in Figures 30A and 30B.

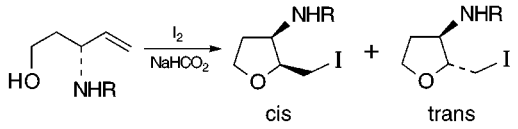
This interpretation accounts for the fact that the range of activation energies is very wide for the *syn* approach and quite narrow for the *anti* approach. The hypothesis of hyperconjugative assistance to bond formation was recently concluded to predict the opposite outcome since all the *syn* transition states would be stabilized by the same σ-donor, the C(5)−H bond, while each of the *anti* transition states would be stabilized by a different antiperiplanar C(5)−X bond.[226] It seems, however, that no such conclusion should have been drawn and that the ab initio data support rather than refute the hypothesis of σ-assistance.

3.5.2. Stereochemical Evidence: Azaallyl and Oxaalkyl Stereogenic Centers

3.5.2.1. Azaalkyl Stereogenic Center. There are few systematic studies of the effect of N-substitution on π-face selectivity induced by the azaalkyl stereogenic center. An interesting example is examination of iodoetherification of N-substituted 3-amino-4-penten-1-ols which yield mixtures of *cis*- and *trans*-3-amino-2-iodomethyltetrahydrofurans, Scheme 79.[228]

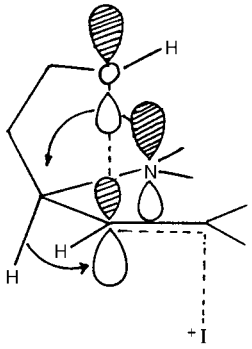
The *cis*-product, formed via the more sterically strained transition state shown in Scheme 80, is promoted by the least and most electron-withdrawing

Scheme 79



R	% cis
$CO_2{}^tBu$	85
CO_2Et	83
$COCH_3$	23
COPh	30
SO_2NMe_2	70
$COCF_3$	69
SO_2-*p*Tol	71
SO_2CH_3	79
$SO_2CH_2CF_3$	85
SO_2CF_3	93

Scheme 80



substituents at N, cf. Figure 31. It seems reasonable to assume that the properties of the stereogenic center depend both on the inductive and resonance effect of the N-substituents. However, separation of these two effects is not possible in the present sample, and the log [*Z*]/[*E*] is plotted simply against the inductive constant. The plot reveals a sharp transition from the *syn* preference (formation of the *cis*-product via the transition state in Scheme 80) to the *anti* preference when the N ligand changes from an alkoxycarbonyl group (urethane) to an acyl group (amide) and then a gradual return to the *syn* preference as the positive inductive (and resonance) effect of N-substituents increases. Interestingly, the urethane and amide ligands also induce opposite preferences in OsO_4 dihydroxylation of alkenes, Scheme 81,[229] and in Eu(fod)$_3$-catalyzed Diels−Alder additions of 1-methoxy-1,3-butadiene to *N*-acyl-L- and *N*-acyl-D-alaninals.[230]

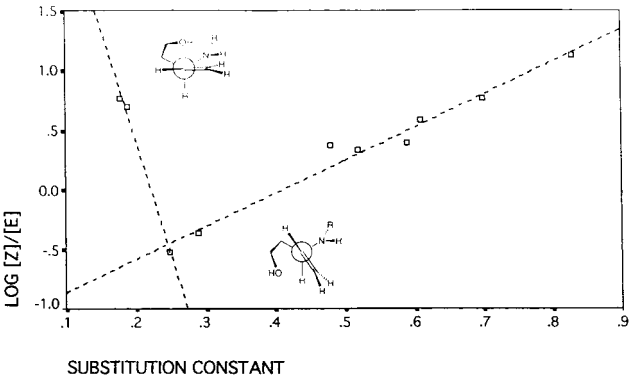
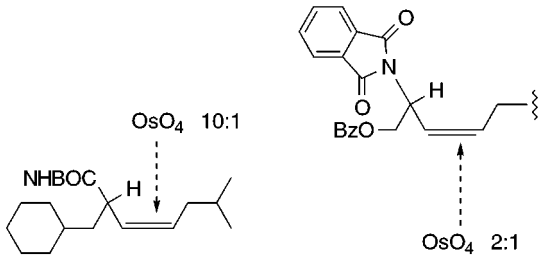


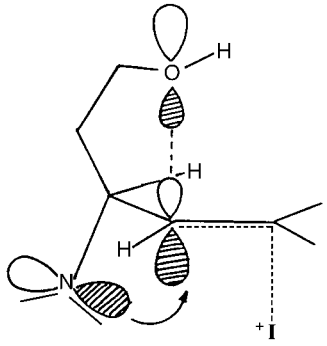
Figure 31. Effect of allylic substitution on formation of tetrahydrofuran in intramolecular iodoetherification of 3-amino-5-hydroxy-1-pentene, log [*Z*]/[*E*] vs σ_F[44d] (see Scheme 79 for the list of data): when $\sigma_F > 0.2$, $\hat{Y} = -1.14 + 2.76X$, SE $b_0 = 0.10$, SE $b_1 = 0.18$, $r^2 = 0.974$.

Scheme 81



The urethane N lp can be expected to be more effective than the amide N lp in back-donation into σ^*_{C-H} (extended hyperconjugation), while the opposite should be true for homoconjugation.[231] The urethane ligand promotes, therefore, the *syn* approach, Scheme 80, and the amide ligand promotes the *anti* approach, Scheme 82. As the N-substitution becomes more electron-withdrawing in sulfonamides, homoconjugative assistance dimishes; σ_{C-H}-hyperconjugative assistance becomes relatively more important again.

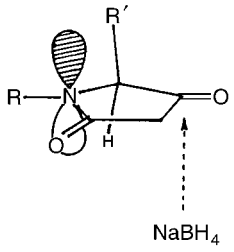
Scheme 82



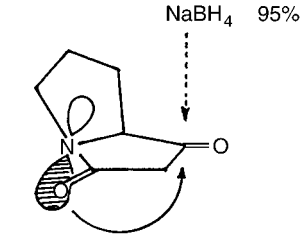
The effect of N-substitution on π-face selectivity of $NaBH_4$ reduction was examined in a series of ketolactams where the N ligand is in the plane of the keto group.[232] The electron-withdrawing effect of the N ligand is expected to inhibit the C−C and C−H hyperconjugation and thereby increase the relative importance of the steric strain. This seems to be corroborated by the experimental results, Scheme 83. However, the reversal of π-face preference in the bicyclic lactam 1-azabicyclo(3.3.0)octan-2,4-dione is unexpected on this hypothesis, although the change is in the right direction.[231] As pointed out,[232] pyramidalization of the lactam N is the likely cause of the reversal. Indeed, nonequivalent extension of the N 1p should improve homoconjugative stabilization of the more hindered *syn* approach.

The preference for approach to the more hindered concave face was also found in OsO_4 and Br^+ additions to 1-azabicyclo(4.3.0)non-7-en-2-one, Scheme 84. The *syn* preference was attributed to σ-assistance by

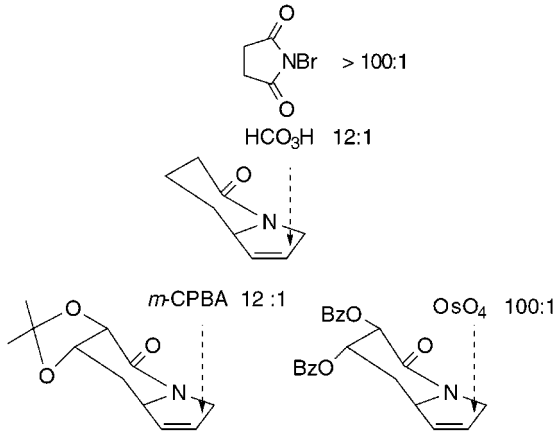
Scheme 83



R	% anti
R′ = CH_3	
H	66
^{i}Pr	97
BnOCO	100
R′ = ^{i}Bu	
H	68
CH_3	85
^{i}Pr	100
^{t}BuOCO	100
CH_3CO	100



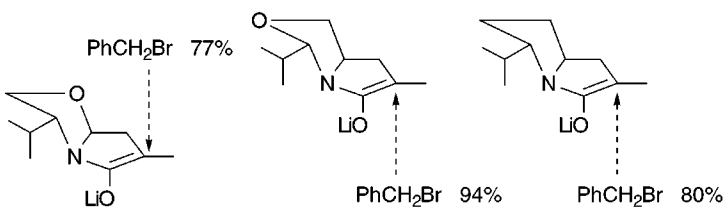
Scheme 84



the C−H bonds.[233] The N pyramidalization is much less pronounced in this lactam.

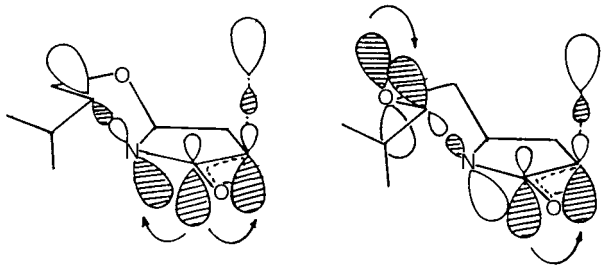
There is a degree of similarity between those two bicyclic lactam systems and Meyers' lactams based on 1-aza-4-oxabicyclo(3.3.0)octan-8-one, cf. Schemes 83, 84, and 85.[234] However, the effect of the azaoxaalkyl C(5)-stereogenic center has to be considered in the case of [2+*n*] cycloadditions ($n = 1-4$) to 1-aza-4-oxabicyclo(3.3.0)oct-6-en-8-ones, vide infra section 3.5.2.2.B, Schemes 104 and 105, while the effect of the stereogenic N(1)-center has to be considered in the case of alkylations of 1-aza-4-oxabicyclo(3.3.0)-octan-8-one enolates, Scheme 85.

Scheme 85



The *syn* preference in the latter alkylations might be a result of 1,3-π^1-induction involving the enolate C′ $2p_z$-orbital interactions with the σ^*_{CN} and $\sigma^*_{\ddagger}$ orbitals, see Scheme 86.[105] When the σ^*_{CN} energy

Scheme 86

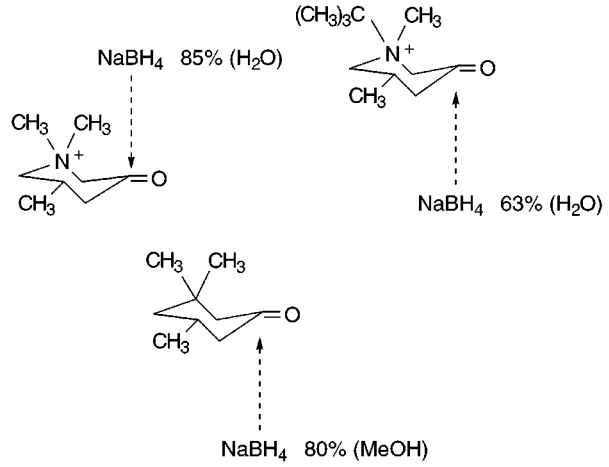


level is high due to lack of electron-withdrawing substitution, as in 1-azabicyclo(3.3.0)octan-8-one enolate, or due to O lp back-donation, as in 1-aza-3-oxabicyclo(3.3.0)octan-8-one enolate, Scheme 86, such 1,3-π^1-induction is not effective and the *anti* approach is preferred.

The *anti* directing effect of the nitrogen lone pair of the lactam enolate, analogous to that proposed to explain reductions of 1-azabicyclo(3.3.0)octan-2,4-dione, Scheme 83, does not seem to operate in alkylations of 1-azabicyclo(3.3.0)octan-8-one or 1-aza-3-oxabicyclo(3.3.0)octan-8-one enolates, Scheme 86. However, this effect was recently invoked to explain very high π-face selectivity of alkylation of 1,5-dimethylpyrrolidinone enolate.[235]

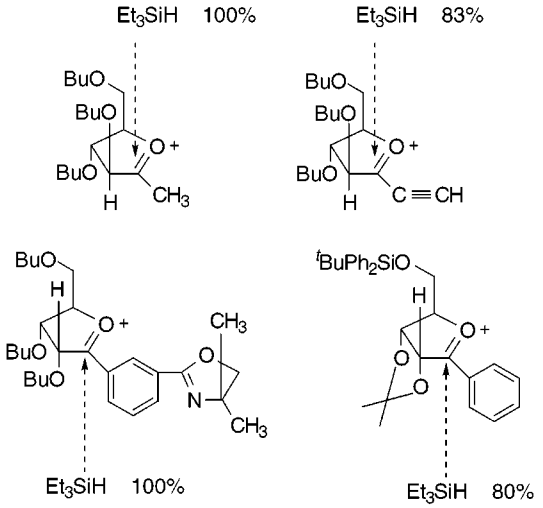
Finally, the effect of the *N*-alkyl substitution on the *syn* (axial) preference in $NaBH_4$ reductions of quaternized 3-piperidones was reported, Scheme 87.[236]

Scheme 87

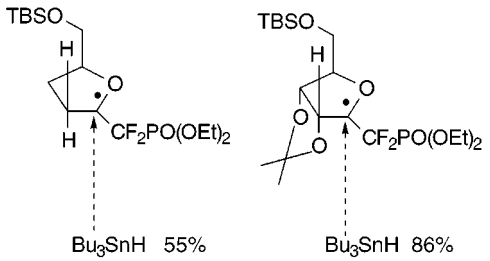


The trend is consistent with the important role of hyperconjugative σ-assistance of the C−N bond; indeed, ammonium ions are often argued to be

Scheme 88



Scheme 89



mesomeric electron donors,[237] and resonance constants for the ammonium groups are comparable or greater than those for the alkyl groups, e.g., R^+ parameters are CH_3 −0.32, $C(CH_3)_3$ −0.17, and $N^+(CH_3)_3$ −0.45.[44e]

3.5.2.2. Oxaalkyl Stereogenic Center. In the early 1980s, the interest in polyoxygenated antibiotics and related natural products stimulated the studies of acyclic stereoselection controlled by oxaalkyl stereogenic centers. The efforts to develop effective methods of such stereoselection both in nucleophilic addition to carbonyls (aldol renaissance) and electrophilic or electrocyclic additions to alkenes have generated a wealth of experimental evidence. This evidence often shows that the electron-withdrawing or -donating properties of the O-protecting groups have a large effect on π-face selection controlled by the oxy function of the oxaalkyl stereogenic center. The following sections focus on those effects that appear to primarily involve changes in the resonance-donor capability of the oxy ligands. The data such as resonance constants σ_R,[44] indicators of Lewis basicity,[238] or ionization potentials[73,184] suggest the following rank order of the electron-donor capability for the commonly used oxy groups: TBDMSO > TMSO > methoxy > benzyloxy > THPO > benzoyloxy > acetoxy > sulfonyloxy. The hydroxy group is usually excluded from consideration because the hydrogen bonding can offset the differences in electronic properties;[239] furthermore, as the ionization potentials indicate, the σ_R constants overestimate its donor capability compared to the alkoxy groups, most likely because of the difference in steric demand. Finally, it should be noted that it is not always possible to separate the resonance and inductive effects of the protecting groups, and the latter effect can cause large changes in the rate constants. The resulting shifts of the transition states along the reaction coordinate may affect π-face selectivity by changing the relative importance of different stabilizing (secondary bonding) and destabilizing (steric strain) interactions, see section 4.

A. C−H Bond Formation. The oxy group at the conformationally constrained stereogenic center is often found to promote the *syn* approach of the reducing agents even if that approach is more hindered. Thus, the *syn* preference is consistently observed in silane reductions of 2-oxyfuranosyl oxonium ions, Scheme 88, and radicals, Scheme 89.[240] Interestingly, no selectivity is observed without the 2-oxy function;[240] in this example, however, the steric demand of the phosphonate group can play a role in directing the reduction.

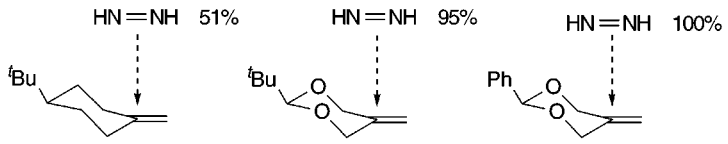
Replacement of C by O in methylenecyclohexane increases the *syn* (axial) preference in diimide reduction, see Scheme 90.[241]

The *syn* preference is also found in reductions of the tertiary radicals whose conformations are controlled by the 1,3-allylic strain, Scheme 91.[242] The effects of modification of the stereogenic center suggest that the *syn* preference depends on the effective C−C hyperconjugation, since it is increased by the electron-releasing substitution of the C−C bond that is antiperiplanar to the incipient bond during the *syn* approach, cf. the series H, Me, *i*Pr, *t*Bu in Scheme 91, and decreased by the electron-withdrawing substitution, cf. the series Me, H, *t*BuMe$_2$SiO, F, AcO in Scheme 91, where the F and O back-donation also seem to play a role.

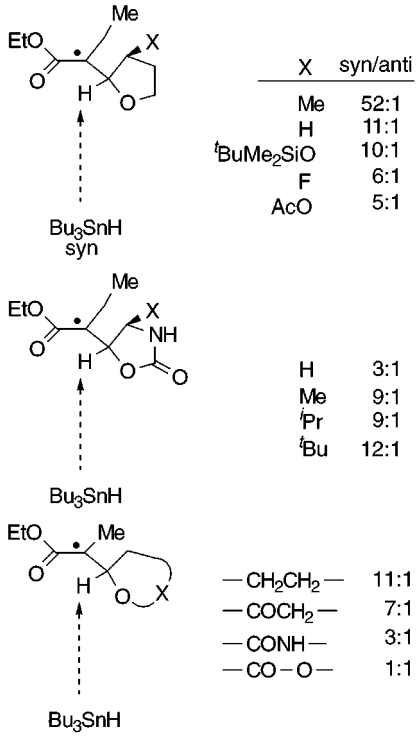
In contrast, the *anti* preference is found in reductions of the secondary radicals with conformationally unconstrained oxy groups, Scheme 92.[243] The evidence is insufficient to decide whether this preference is a result of steric hindrance or stereoelectronic control since the observed effect of the O-protecting groups is not inconsistent with U-shaped dependence on the electron-withdrawing effect of the O-substitution, cf. section 3.5.2.1.

The 9-BBN (uncatalyzed) hydroborations proceed *syn* regardless of the nature of the O-protecting group, but the data again suggest a U-shaped dependence of π-face selectivity on the electron-withdrawing effect of the O-substitution. Interestingly, the stereochemistry of Rh-catalyzed hydroboration,

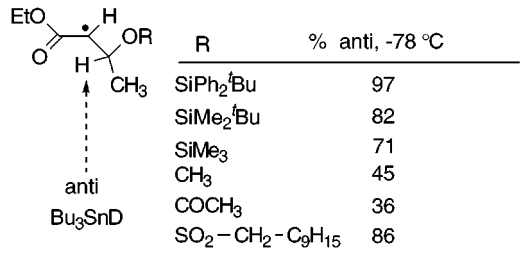
Scheme 90



Scheme 91



Scheme 92



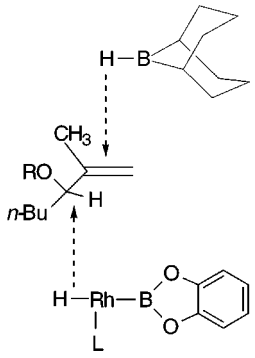
while exactly opposite, shows the same pattern of dependence on the properties of the O-protecting groups, Scheme 93.[244] This supports the argument that Rh-catalyzed hydroboration is an example of 1,3-π^1-induction, cf. section 2.1.5. The latter mechanism implies that the C−Rh bond forms at the distal C of the double bond and is preferably aligned *syn* with the C−C bond at the stereogenic center, hence the *anti* preference with respect to the oxy group. Indeed, an increase in the bulk of the alkyl group at the stereogenic center, which usually increases π-face selectivity, has the opposite effect.[245]

The *syn* preference in uncatalyzed hydroborations is consistent with the C−H or C−C assistance to bond formation, enhanced by the O lp back-donation (extended hyperconjugation, as shown in Schemes 4, 64, 75, 78, and 80). The unexpected preference for the more hindered approach in reactions of the chelated radical can perhaps be explained as a result of the same transition-state stabilization, Scheme 94.[246]

On the other hand, interactions leading to the *anti* preference might involve the direct O 1p assistance to bond formation (n-homoconjugation, as shown in Schemes 4, 64, and 82).

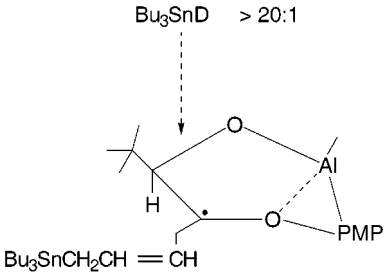
B. C−C Bond Formation. As shown in Scheme 9, the directing effect of the oxy groups on the C−C

Scheme 93

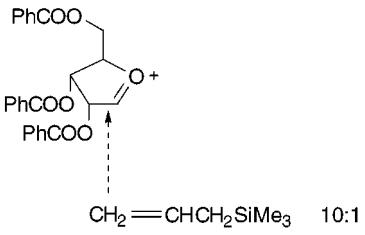


R	anti : syn	
	Rh-cat.	9-BBN
Me_3Si		1.0:10.5
$^tBuMe_2Si$	24.0:1.0	1.0:9.0
$^tBuPh_2Si$	24.0:1.0	1.0:6.0
Ph_3C	18.0:1.0	1.0:5.5
$PhCH_2OCH_2$		1.0:5.0
	8.4:1.0	1.0:3.7
Me_2NCO	2.4:1.0	
MeCO	2.7:1.0	1.0:7.5
^tBuCO	6.5:1.0	1.0:15.4
CF_3CO	7.5:1.0	1.0:14.0

Scheme 94



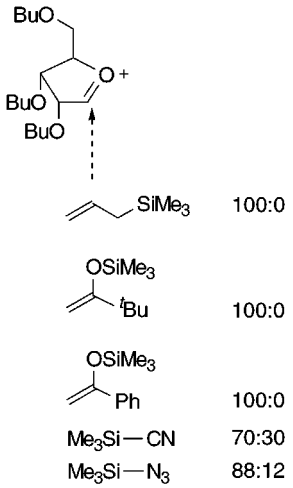
Scheme 95



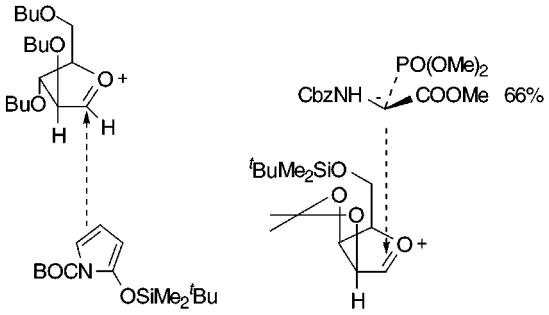
bond formation depends not only on the O-substitution but also on the probe and the probed reaction. This is indeed observed in reactions of a number of conformationally constrained, cyclic and polycyclic probes.

Thus, alkylations of furanosyl oxonium ions are often directed *syn* by the adjacent oxy groups regardless of whether the protecting group is benzoate, Scheme 95,[247,248] or benzyl ether, Scheme 96, or ketal, Scheme 97, but the stereoelectronic control might be insufficient to offset the steric strain in the case of some more bulky nucleophiles.

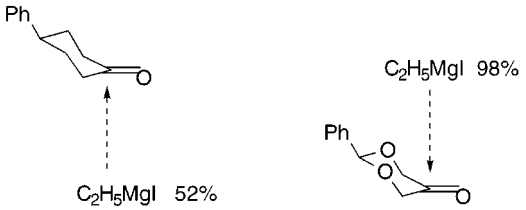
Scheme 96



Scheme 97



Scheme 98

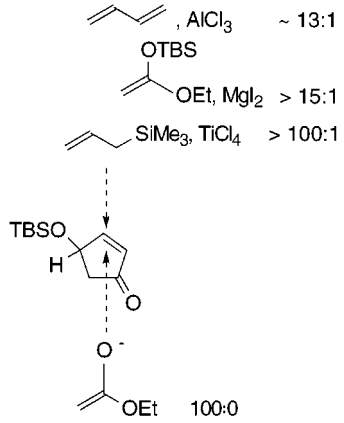


Replacement of the methylene group by O in cyclohexanone also has the *syn* (axial) directing effect, Scheme 98.[249]

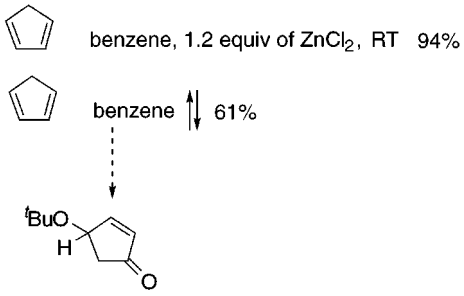
Extensive studies of the stereochemistry of Lewis-acid-catalyzed Mukaiyama and related alkylations,[250,251] Michael-like additions,[252,253] and Lewis-catalyzed Diels−Alder reactions[24,25] of 4-alkoxy-, -acyloxy-, and -silyloxycyclopent-2-en-1-ones followed the discovery that the 4-silyloxy group *syn* directs the β-C−C bond formation as long as the transition state is sufficiently electron deficient, Schemes 99−101.[250] However, the *syn* preference in these reactions depends not only on the Lewis catalyst[25] but also on the O-protecting groups, Schemes 102 and 103. Interestingly, the *t*BuMe$_2$SiO group is a better *syn* directing ligand than the Me$_3$SiO group, while the tosyloxy group is an *anti* directing group in ylide additions to cyclopentenone, Scheme 103. The increase in the *syn* directing effect in cyclopentenone-based probes with the increase in electron-donor capability of the acyloxy groups is confirmed by the correlation of log [*Z*]/[*E*] with the *R* constants of the corresponding acyl groups, Figure 32.

The example of the dependence of π-face selectivity on the properties of the reagent is found in cycloadditions to α,β-unsaturated bicyclic lactams, derivatives of 1-aza-4-oxabicyclo(3.3.0)oct-6-en-8-one, where β-C−C bond formation is likely to be controlled by the C(5)-stereogenic center, Scheme 104. The stereochemistry of these cycloadditions seems to be controlled by both steric and stereoelectronic effects, Scheme 105. It should be noted, however, that extended hyperconjugation (O lp back-donation) might be more effective in the case of the C−C bonds which are better acceptors than the C−H bonds. Further-

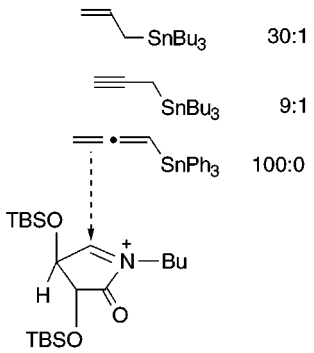
Scheme 99



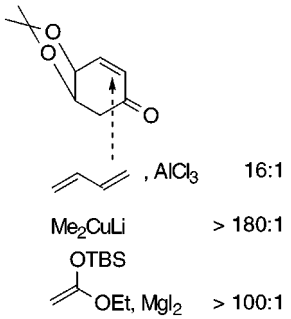
Scheme 100



Scheme 101



Scheme 102



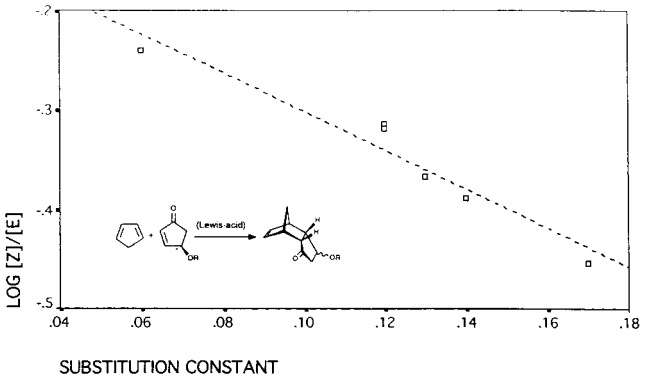
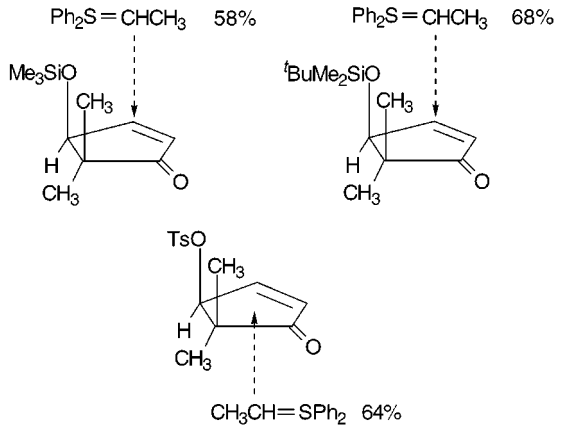
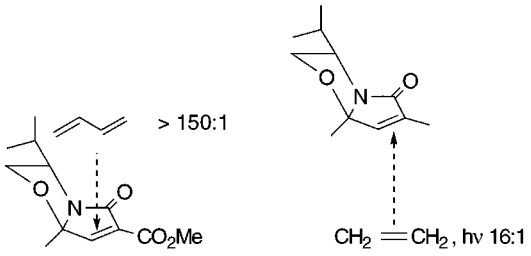


Figure 32. Effect of allylic substitution (acyloxy) on Diels−Alder addition of cyclopentadiene to 4-acycloxycyclopent-2-enones, log [*Z*]/[*E*] vs modified Swain−Lupton constant R^{44b} (4-acyloxy = OX, X = COMe, COEt, COPr, CO*i*Pr, COPh, CO*t*Bu), $\hat{Y} = -0.11 - 1.95X$, SE $b_0 = 0.03$, SE $b_1 = 0.27$, $r^2 = 0.930$.

Scheme 103



Scheme 104



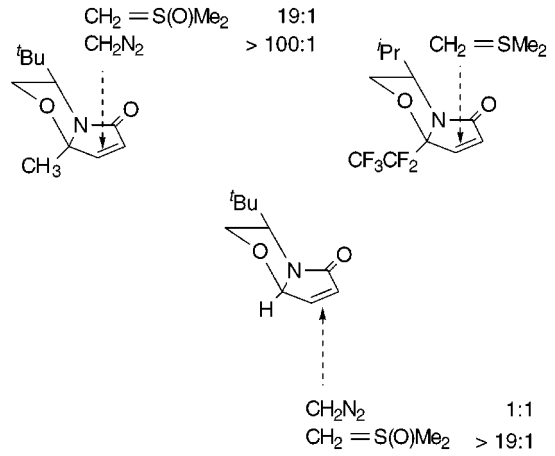
more, the role of N lp-homoconjugative assistance, section 3.5.2.2.A, in promoting the more hindered approach of some reagents has not been explored.

Large effects of the O-protecting groups on π-face selectivity are also found in Diels−Alder additions to 1,3-dienes carrying the oxaalkyl stereogenic centers. The data shown below corroborate the trends found in reactions of cyclopentenones and reveal that the impact on the rate constants is not a simple function of the inductive effect of the O-substitution, Scheme 106. Finally, numerous studies of Diels−Alder additions to 5-alkoxy-1,3-hexadienes suggest that the *syn*/*anti* ratio depends not only on the dienophile and the protecting group, but also on the reactivity of the diene.[254−262] This dependence will be discussed in section 4.3.4.

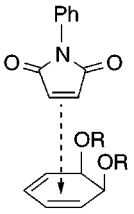
The available examples of acyclic stereoselection where the conformational freedom is restricted by 1,3-allylic strain show the *syn* preference in cycloadditions to nitrones[263] and alkenes,[264,265] electrophilic additions to enolates,[266] and radical[267] and nucleophilic additions to alkenes, Schemes 107−110,[268] although the *anti* preference is observed in cyanide additions to nitrone, Scheme 111.[269]

The apparent *anti* preference in nucleophilic additions to acyclic alkenes devoid of 1,3-allylic strain is suggested by calculations,[270] see Scheme 112, to

Scheme 105

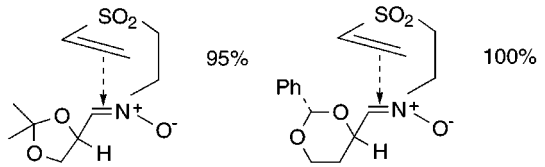


Scheme 106

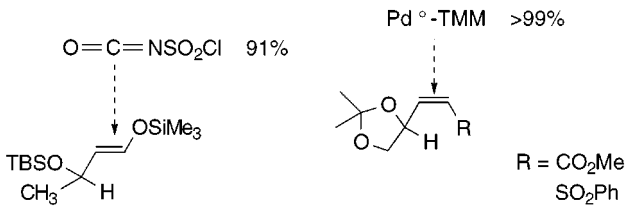


R, R	k_{rel} (1, 3-cyclohexadiene = 1)	% syn
$COCH_3$, $COCH_3$	0.002	88
$SiMe_3$, $SiMe_3$	0.03	100
H, H	0.1	95
CH_3, CH_3	0.2	99
— $SiMe_2$ —	2.7	60
— CMe_2 —	>100	60
— BEt —	—	45

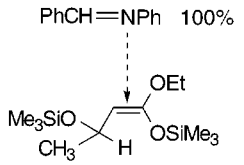
Scheme 107



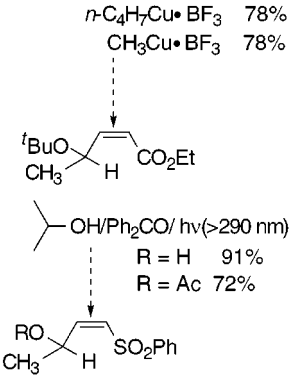
Scheme 108



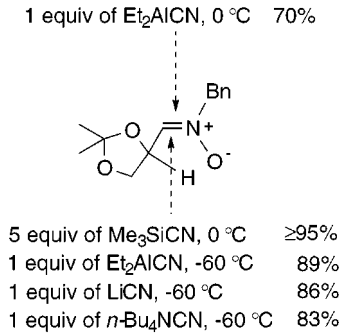
Scheme 109



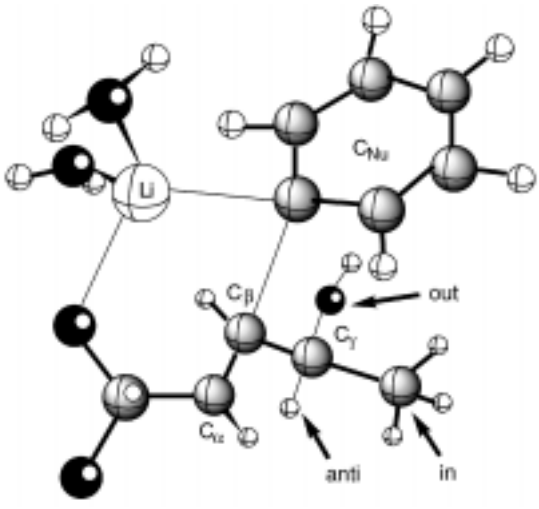
Scheme 110



Scheme 111



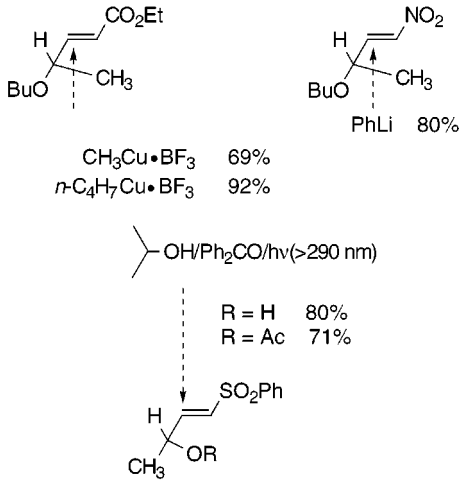
Scheme 112



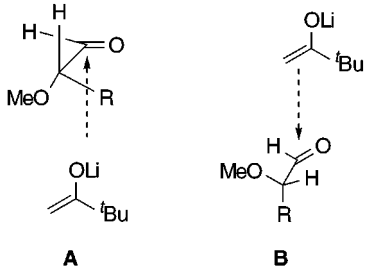
result not from reversal of the intrinsic π-face selectivity but from reversal of the transition-state conformational preference when either the alkyl group or the alkoxy group become synperiplanar with the double bond, see Scheme 113.

Thus, the nonchelation-controlled nucleophilic addition to α-alkoxy aldehydes is likely to involve the two transition states shown in Scheme 114, one stabilized by the C−H bond assisted by the O back-donation (extended hyperconjugation) and the other

Scheme 113



Scheme 114



R	A%	B%
Me	42	58
Et	24	76
^{i}Pr	8	92
^{t}Bu	7	93

stabilized by the C−C bond and the O back-donation. This model explains the bulk effect of the alkyl ligands at the stereogenic center.[271]

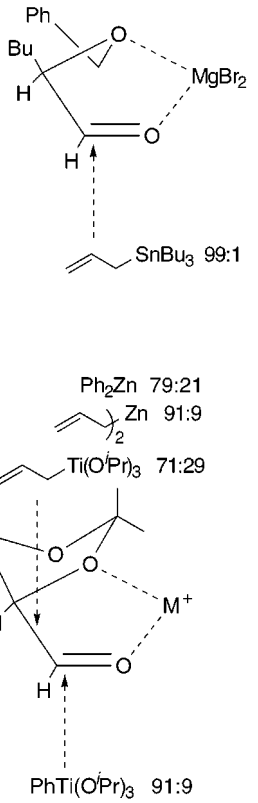
In the case of chelation-controlled additions, π-face preference depends on whether the oxy group is acyclic or incorporated in a five-memebered ring, Scheme 115.[272−277]

The oxy group becomes strongly electron withdrawing (oxonium ion), and therefore stereoelectronic control can be important only if the C−C or C−H hyperconjugation is assisted by the O lp back-donation. Since O lp can interact with the C−H bond but not with the C−C bond when O is incorporated in the five-membered ring and the chelate ring, extended hyperconjugation supports the more hindered *cis* approach; when the oxy group is acyclic, the O lp can effectively interact only with the C−C bond, and extended hyperconjugation supports the less hindered *trans* approach (the gauche conformation of the alkoxy group, required for the interaction with the C−H bond, is more strained).

C. C−O Bond Formation. The data on the C−O bond formation provide further evidence of the effect of the probe, reagent, and O-protecting group properties on the control of π-face selection by the oxaalkyl stereogenic center.

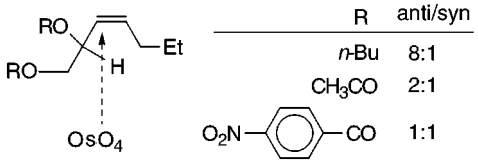
Thus, in additions of O nucleophiles to 2-oxyfuranosyl oxonium ions, the 2-oxy groups are *syn* directing.[278,279] It should be added that it is also true for N nucleophiles.[280]

Scheme 115



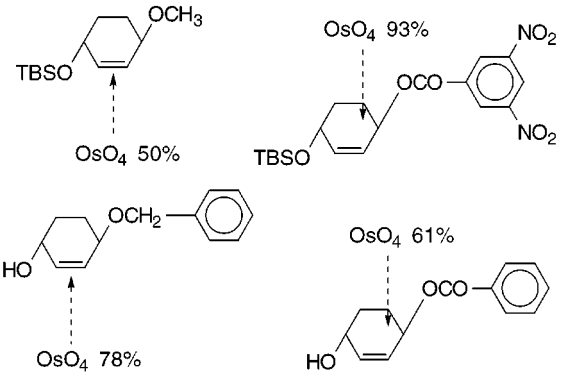
On the other hand, in additions of electrophilic oxidation reagents to alkenes, the oxy ligands are often *anti* directing. For instance, in OsO_4 dihydroxylation of relatively nucleophilic alkenes such as the alkyl-substituted alkenes, the allylic oxy group promotes the *anti* approach (Kishi effect) depending on the electron-withdrawing effect of the O-protecting group.[281−283] The evidence is found in reactions of acyclic *Z*-alkenes where the conformation of the allylic stereogenic center is controlled by 1,3-allylic strain, Scheme 116, in reactions of C_2-symmetric

Scheme 116

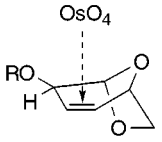


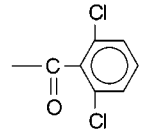
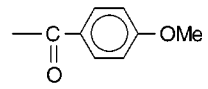
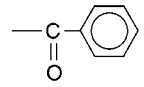
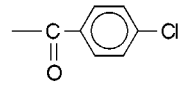
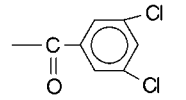
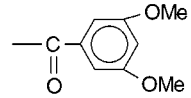
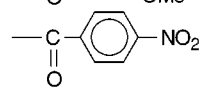
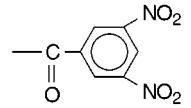
trans-3,6-dioxycyclohexenes, Scheme 117, and in reactions of 2-*O*-derivatives of 1,6-anhydro-3,4-dideoxy-*β*-D-*erythro*-hex-3-enopyranose where only the *t*-$BuMe_2$SiO group induces the *anti* approach 2:1 while the 3,5-dinitrobenzoyloxy group induces the *syn* approach >20:1, Scheme 118. The increase in the *anti* directing effect in these oxidations with the increase in the electron-donor capability of the benzoyloxy groups is confirmed by the correlation of log [*Z*]/[*E*] with the σ_p Hammett constants, Figure 33. The effect of O-substitution is observed in oxidations of *cis*-3,4-dioxycyclobutenes as well, Scheme 119. However, the *anti* directing effect is also a function of reactivity of the alkene. It is diminished by electron-withdrawing substitution of alkenes, Scheme 120, and no longer important in reactions of electron-deficient, deactivated alkenes such as acrylates, Scheme 121.[284,285]

Scheme 117



Scheme 118



R	syn / anti
CO^{t}Bu	4:1
COMe	3.5:1
Bu	1:1
^{t}BuMe$_2$Si	1:2
	2:1
	6:1
	7:1
	8:1
	9:1
	10:1
	12:1
	>20:1

The effect of O-substitution on the stereochemistry of OsO_4 oxidation of *trans*-2-oxy-4-*tert*-butylmethylenecyclohexanes is shown in Scheme 122.[286] The axial 2-OMe group appears to be equal in size to the axial 2-ethyl group, whereas the 2-OAc group appears to be smaller. Incorporation of the axial 2-oxy group in the spiro-cyclopentane ring drastically reduces its effective size, which suggests that the *anti* directing effect also depends on the orientation of the oxy function.[286] This conclusion is supported by the results of oxidations of *cis*-3,4-dioxycyclobutenes, where the *anti*-directing effect of the acyloxy ligands seems to depend on the conformation about the C−O bond at the stereogenic center as well, Scheme 123.[287]

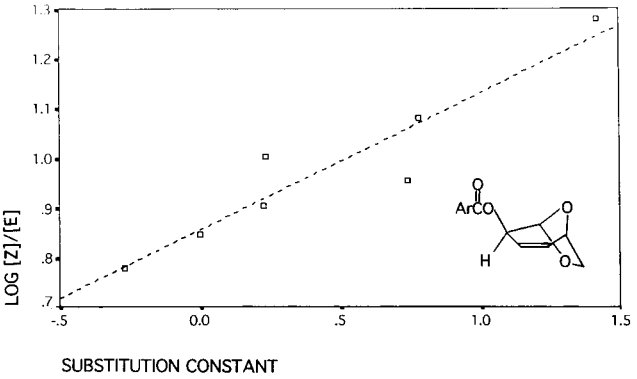
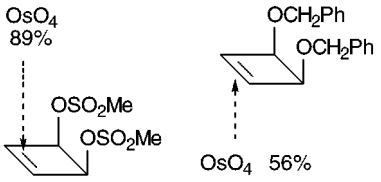
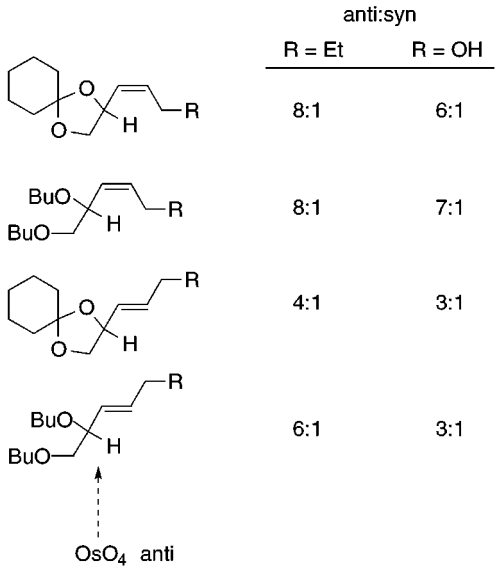


Figure 33. Effect of allylic substitution (benzyloxy) on OsO_4 dihydroxylation of 1,6-anhydro-2-*O*-benzoyl-3,4-dideoxy-β-D-*erythro*-hex-3-enopyranose, log [*Z*]/[*E*] vs Hammett constants σ_p and $\sum\sigma_m$ (see Scheme 118 for the list of data): $\hat{Y} = 0.85 + 0.27X$, SE $b_0 = 0.03$, SE $b_1 = 0.04$, $r^2 = 0.887$.

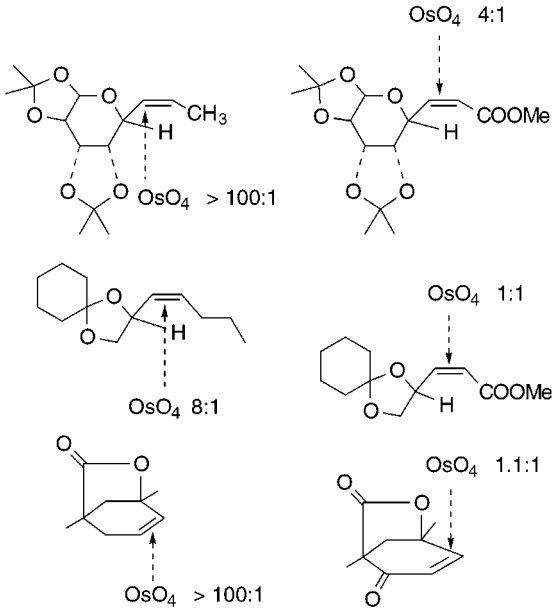
Scheme 119



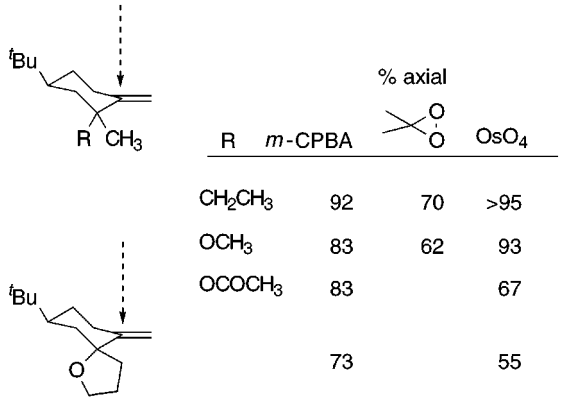
Scheme 120



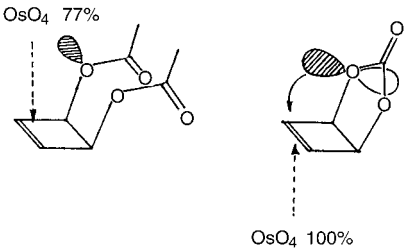
Scheme 121



Scheme 122



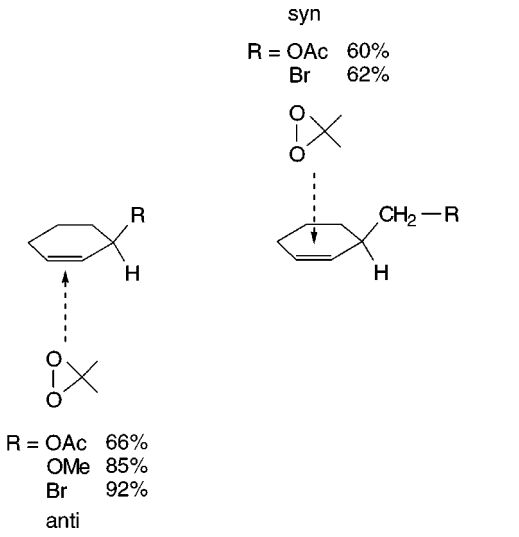
Scheme 123



These observations are readily explained if the *anti* directing effect is assumed to involve O lp homoconjugative assistance. In the preferred conformation of esters of the secondary alcohols, the acetoxy groups in *cis*-3,4-diacetoxycyclobutene cannot provide such assistance to the *anti* approach. In contrast, the conformation of the ester moiety in the carbonate derivative assures optimal overlap of the O $2p_z$ and $\sigma^*_{\ddagger}$ orbitals. It should be added, however, that π-face selectivity in additions to *cis*-3,4-X,X-cyclobutenes may also depend on the degree of splaying of the two substituents.[288] OsO_4 oxidations of *cis*-3,5-dioxycyclopentenes occur with strong *anti* preference.[131]

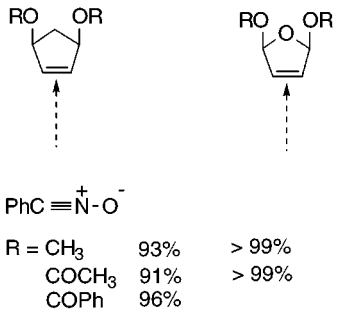
The second reaction of alkenes involving electrophilic addition and C−O bond formation which was extensively studied in this context is peracid and dioxirane epoxidation. However, the results of peracid epoxidation are not reviewed here since the contribution of H-bonding to the allylic oxy groups is difficult to gauge.[42] The data for dimethyldioxirane epoxidation of cyclohex-2-en-1-ol derivatives are shown in Scheme 124.[289,290] In these additions, the effective sizes of all the oxy and halo groups are considerably greater while the effective sizes of CH_2OAc, CH_2Br, etc., are considerably smaller than those of Me or Et. Yet another reaction involving the C−O bond formation which was often studied in this context is 1,3-dipolar cycloaddition of nitrile oxides to alkenes. In general, the behavior of these reactions is similar to that of OsO_4 oxidations. Thus, additions to *cis*-3,5-dioxycyclopentenes and *cis*-2,5-dioxyoxacyclopent-3-enes are not dependent on the O-protecting groups

Scheme 124



R	acetone	CCl_4/acetone (90:10)	acetone
	% anti		% anti
CH_2COOEt	35	27	
CH_2Br	38	27	
CH_2OAc	40		
CH_3	48	47	73
CH_2CH_3	55		
$CH_2CH(CH_3)_2$	55	54	
$OCOCH_3$	66	65	87
$OCOCH_2CH_3$	66	62	
OCH_3	85	92	95
$OSi(CH_3)_3$	87	99	95
Cl	90		
Br	92		

Scheme 125

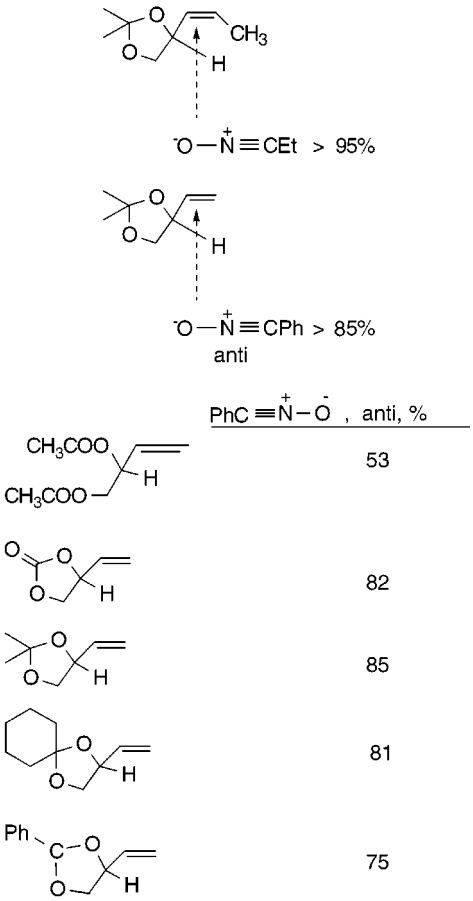


and occur with the strong *anti* preference, Scheme 125.[129]

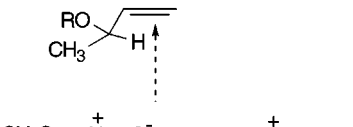
The *anti* preference is also often observed in cycloadditions to acyclic alkenes and seems to correlate in a familiar way with the resonance-donor capability of the oxy functions, Schemes 126 and 127.[291]

Furthermore, the same effects of O-substitution and conformation are observed in cycloadditions of nitrile oxides to *cis*-3,4-X,X-cyclobutenes.[292] However, the effect of the oxaalkyl stereogenic centers on cycloadditions of nitrile oxides also depends on their substitution.[293] This dependence was examined in

Scheme 126



Scheme 127

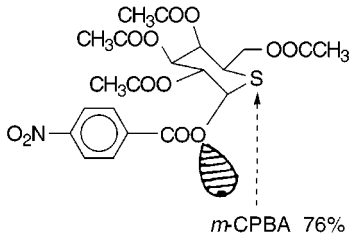


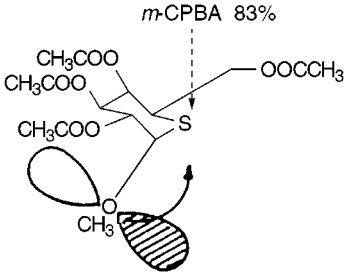
R	anti %	
$^tBuMe_2Si$	73	72
$^tBuPh_2Si$	66	64
CH_3CO	52	
C_6H_5		64
THP		62

reactions of 2,3-dioxabicyclo(2.2.2)oct-5-ene and is discussed in section 4.3.1.

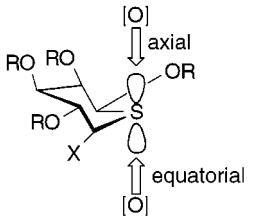
D. S−O Bond Formation. The effect of C(1)-substituents on the stereochemistry of oxidation of 5-thio-α-D-glucopyranosides to sulfoxides was examined including a series of the oxy groups OCH_3, $OCOCH_3$, and $OCOC_6H_4$-*p*-X (X = H, OCH_3, Cl, CF_3, NO_2). The examined reactions included *m*-CPBA and BSNPO (2-benzenesulfonyl-3-(*m*-nitrophenyl)oxaziridine) oxidations, Schemes 128 and 129.[294] The multivariate analysis of the results has indentified the resonance effect of the C(1) substituents as a major determinant of the stereochemistry of these reactions. It seems that the extensive electron-withdrawing substitution of the 5-thioglucopyranose ring decreases the importance of hyperconjugation, and the stereochemistry of oxidation is a result of competition

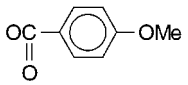
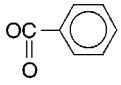
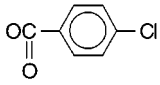
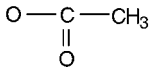
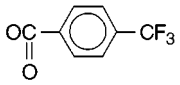
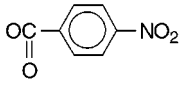
Scheme 128





Scheme 129



X	% axial *m*-CPBA	% axial BSNPO
SPh	100	
OMe	83	68
$(CH_2)_2CN$	66	60
F	62	54
	42	59
	38	57
	36	49
	29	36
	27	46
	24	36

between the steric strain and O lp homoconjugation. When C(1)−O lp is a good resonance donor like in OCH_3, the axial approach is preferred; when the C(1)−O lp donor capability is lowered by an electron-withdrawing acyl group, the equatorial approach is preferred. The correlations between π-face selectivity and the substituent constants (σ_R constants for the F and O groups, σ_p constants for the benzoates) are shown in Figure 34.

It should be added here that the stereochemistry of the oxidation of sulfur in 2-thiaadamantane was shown to be controlled by 5-X-substitution in the manner consistent with hyperconjugative σ-assistance to bond formation.[295] The *anti* directing effect of fluorine was observed in the oxidation of an acyclic sulfide.[296]

E. C−Cu Bond Formation. Both S_N2' alkylation of allylic halides and esters and Michael addition-

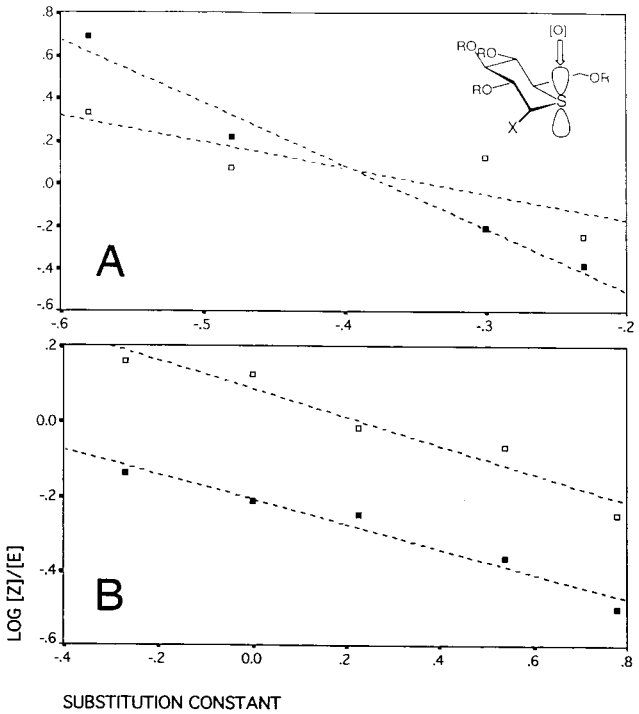
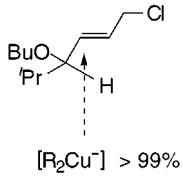


Figure 34. Effect of allylic substitution on oxidation of tetraacetyl-5-thioglucose: (A) log [*Z*]/[*E*] vs σ_R[43a] (X = OMe, F, OCOPh, OCOMe) (■) *m*-CPBA $\hat{Y} = -1.10 - 2.95X$, SE $b_0 = 0.14$, SE $b_1 = 0.34$, $r^2 = 0.975$; (□) BSNPO $\hat{Y} = -0.42 - 1.23X$, SE $b_0 = 0.25$, SE $b_1 = 0.59$, $r^2 = 0.684$. (B) log [*Z*]/[*E*] vs σ_p (X = $OCOC_6H_4$-*p*-*X*′, *X*′ = OMe, H, Cl, CF_3, NO_2) (■) *m*-CPBA $\hat{Y} = -0.21 - 0.33X$, SE $b_0 = 0.02$, SE $b_1 = 0.04$, $r^2 = 0.959$; (□) BSNPO $\hat{Y} = 0.09 - 0.38X$, SE $b_0 = 0.03$, SE $b_1 = 0.06$, $r^2 = 0.939$.

Scheme 130

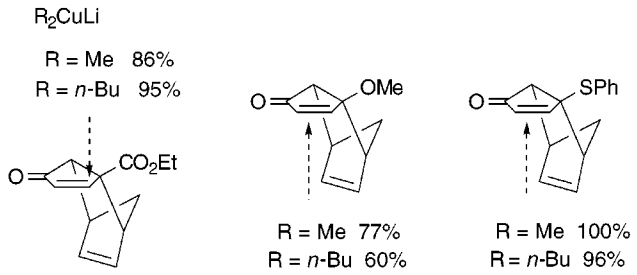


like alkylation of enones by cuprates occur with high *anti* selectivity, Schemes 130 and 131.[29,297]

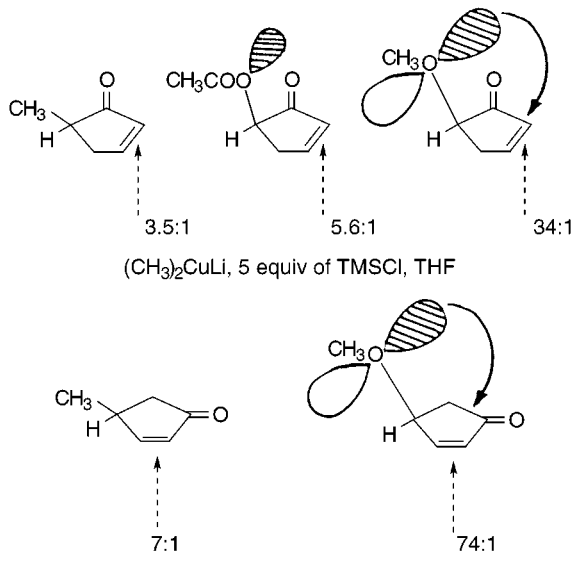
The study of alkylations of 4- and 5-X-cyclopent-2-en-1-ones has demonstrated that the effect of steric strain is reinforced by a stereoelectronic effect dependent on the substitution of the oxy function, Scheme 132.[298]

It has been proposed that the irreversible formation of the C=C···Cu complex is facilitated by electron donation into the antiperiplanar C−O bond (two-electron stabilizing interaction $\sigma_{CCu^{\ddagger}} \rightarrow \sigma^*_{CO}$).[84] As later pointed out, however, when the sulfide shown

Scheme 131



Scheme 132



in Scheme 132 is oxidized, the *anti* addition is slowed down rather than accelerated.[29] Thus, homoconjugative assistance of the O lp, as shown in Scheme 131, might be the more important contribution to the transition-state stabilization.

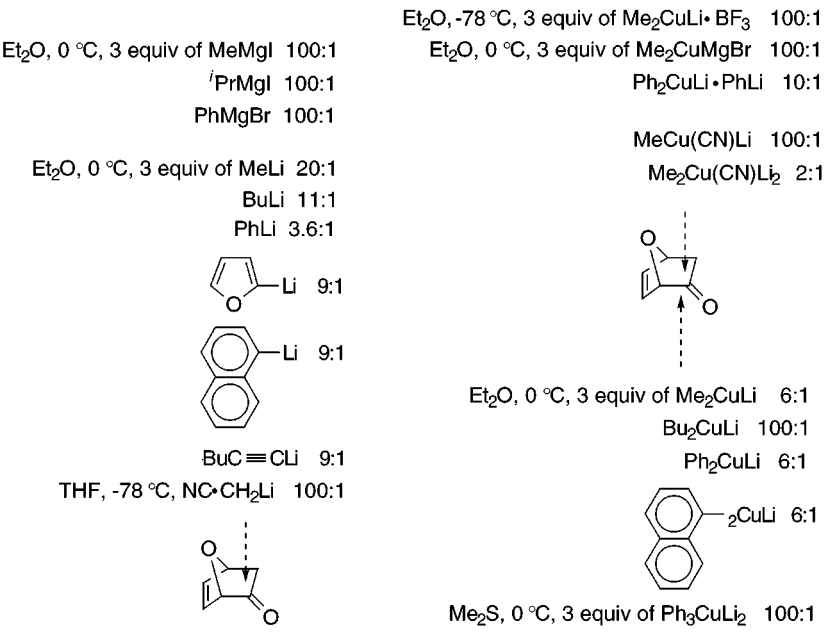
This assistance could also explain reversal of π-face selectivity in alkylation and arylation of 7-oxabicyclo-(2.2.1.)hept-5-en-2-one with alkyllithiums, aryllithiums, and dialkyl- and diaryllithium cuprates, Scheme 133.[299] The unexpectedly high preference for the more hindered *endo* approach is observed in reactions with the excess of cuprates in Et_2O but not in THF. It seems, therefore, that the ketone must be activated by complexation to increase the stereoelectronic effect that offsets the steric strain. Furthermore, in the series of both organolithiums and organocuprates, the relative yield of the more hindered approach is largest for the moderately reactive organometallics, see Scheme 131. Such dependence of the stereoelectronic effect on reactivity often seems consistent with σ-hyperconjugative or n-homoconjugative assistance, cf. section 4. Extended hyperconjugation, which would promote the *syn* (*exo*) approach, is unlikely to play an important role since mixing of the O $2p_z$ orbital into C−C orbitals apparently does not occur in this skeleton.[300] The *anti* (*endo*) approach would be promoted by homoconjugation. A similar transannular interaction was proposed to explain the effect of heteroatoms on the stereochemistry of reduction of a bicyclic keto lactam, see section 3.5.2.2.A, Scheme 83, and of catalytic hydrogenation of methylenecyclohexanes, Scheme 134.[301]

4. Reagent Substitution and Variation in Reactivity

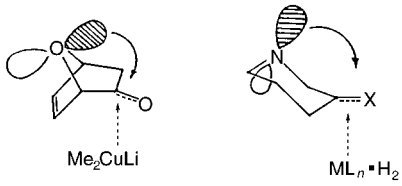
The notion that the transition state shifts along the reaction coordinate when the reagent reactivity is varied has often been invoked in discussions of the structure effects on π-face selection. It was perhaps most systematically explored in the area of nucleophilic additions to cyclohexanones.[302] The studies of the progress of bonding in the transition states for additions of metal hydrides to carbonyls were inspired by the hypothesis that the stereochemistry of hydride additions to cyclohexanones is controlled not only by the steric hindrance to nucleophile approach, but also by the product stability,[303] generally understood to imply that the sources of steric strain are different in the early and late transition states.[140,304] It was difficult, however, to explain in this way the fact that the two commonly used metal hydrides, $LiAlH_4$ and $NaBH_4$, which are quite different in terms of reactivity, display very similar π-face preferences in reductions of unhindered cyclohexanones. That π-face selectivity may be related to the electronic properties of nucleophilic reagents was first recognized only in the early 1970s in the course of studies of the alkylation of cyclohexanones. The explanation of this dependence, rooted in the FMO theory, proposed that hard C-nucleophiles add to carbonyls via early transition states stabilized by coulombic interactions (charge control) and soft C-nucleophiles react via advanced transition states (frontier control).[305] Since in the early region of the reaction coordinate for additions to cyclohexanone the steric strain is small and the effect of LUMO desymmetrization relatively large, hard nucleophiles prefer the axial approach. In the late region of this reaction path, the nucleophile suffers greater steric strain while the importance of the ground-state distortion of the LUMO is smaller, and soft nucleophiles prefer the equatorial approach. Clearly, the stereoelectronic effect is expected to steadily decrease along the reaction coordinate.

A different picture was suggested several years later by the hypothesis of hyperconjugative assistance to bond formation.[7] This hypothesis postulated that the axial preference in additions to cyclohexanones should increase in a series of isosteric nucleophiles as their basicity decreases. However, the recent ab initio study of π-face selection in addition of the substituted acetylide ions to cyclohexanone and cyclohexanethione found the relationship between the basicity of the nucleophile and the axial preference to be parabolic,[39] which implies that the stereoelectronic effect initially increases along the reaction coordinate, reaches a maximum, and dissipates only in the latest stages of addition. This concept appeared to better accomodate the experimental evidence. A similar conclusion was reached in the study of acyclic stereoselection in nucleophilic additions to aldehydes, which suggested that stereoelectronic control reaches a maximum in the mid-region of the reaction coordinate while the relative stability of the early and late transition states reflects conformational preferences of the reactant and product.[306] To address the question of whether in fact stereoelectronic control of π-face selection depends on the location of the transition state along the reaction coordinate, the

Scheme 133



Scheme 134



pertinent evidence is reviewed in the following sections.

4.1. Nucleophilic Addition to Ketones

4.1.1. Alkylation of Cyclohexanones

4.1.1.1. S-, C=O-, and C≡N-Stabilized Carbanions. The reactivity of C nucleophiles can, in principle, be described in terms of an inductive and a resonance effect of C-substitution as long as they are stabilized by heteroatom-containing groups (pK_a of the conjugated C acid ≤40); the metal ion is usually bonded in this situation to a heteroatom.[307,308] However, the substituent constants for such metal-bonded groups are not known, and therefore, the basicity of the stabilized carbanions is taken here as a measure of the summary effect of electronic properties of such substituents.

The results of alkylation of 4-*tert*-butylcyclohexanone by the primary carbanions $Z-CH_2^-$ are compiled in Table 3 and listed according to the pK_a values of the corresponding conjugated C acids in DMSO.[309] The counterions are alkali metals and cerium, magnesium, and zinc halides. In principle, such carbanions might be more reactive in the cation-solvating media (liquid NH_3, HMPT, and DMSO, neat or used as a cosolvent, DN[310] > 20) than in the nonsolvating media (ethers and hydrocarbons, DN < 20) due to depolymerization or extrusion from the aggregate nucleus.[308] However, the large dependence of π-face selectivity on the properties of the solvent is observed only in the case of ester enolates. Thus, the results of alkylation with those enolates are listed separately for the solvating and nonsolvating media, taking this change in solvent properties as equivalent to lowering enolate basicity.[30−36,311−324]

Table 3. Relative Yield of Axial Approach in Alkylations of 4-*tert*-Butylcyclohexanone by Sulfur, Carbonyl, Thiocarbonyl, Nitro, and Cyano Group-Stabilized Carbanions and pK_a of the Conjugated Acid

ZCH_3	pK_a[309]	axial %	ref
$C_6H_5SeCH_3$		0	311
$C_6H_5SCH_3$	42.0	17, 20	30
$Li^+OC(=O)CH_3^-$		30, 41	312
$(CH_3)_2NC(=O)CH_3$		35, 45	312
$(C_2H_5)_2NC(=O)CH_3$	34.5	38, 45, 58, 68	312
$C_6H_5S(=NTs)CH_3$		33, 50	31, 32
$C_6H_5S(=O)(=NCH_3)CH_3$	33.0	60	313
$(CH_3)_2NS(=O)_2CH_3$		61, 62, 62, 62, 65	314, 315
$N\equiv CCH_3$	31.3	64, 65, 65, 66, 67 71, 72, 72, 75, 80 84, 84, 85, 85	36, 312, 316 317, 318
$(CH_3)_3COC(=O)CH_3$[a]		81, 82	319, 320
$C_2H_5OC(=O)CH_3$[a]	30.5	54, 67, 68, 69, 69	312
$(CH_3)_3SiOC(=O)CH_3$[b]		56, 72	312
$(CH_3)_3COC(=O)CH_3$[b]		4, 10, 15, 25 40, 53	319
$C_2H_5OC(=O)CH_3$[b]		37, 43	312
$C_6H_5S(=O)(=NTs)CH_3$	27.7	0	32
$(CH_3)_3CC(=O)CH_3$	26.5	5, 20, 21	217, 321
$(CH_3)_2NC(=S)CH_3$	25.7	25	322
$(CH_3)_2S^+CH_3$	18.2	55, 62, 65, 67, 83	33, 34, 35
O_2NCH_3	17.2	~90	323
$(CH_3)_2S^+(=O)CH_3$		0, 8, 10, 14	33, 35
$C_6H_5((CH_3)_2N)S^+(=O)CH_3$	14.4	0	324

[a] Solvent DN[310] > 20. [b] Solvent DN < 20.

The data for the secondary and tertiary anions, all obtained in liquid NH_3 (Na^+ as the counterion),[36] are plotted in Figure 35 against the rank order of reactivity based on the pK_a values of the model compounds and the assumption that the pK_a values of the cyclic derivatives reflect the ring-size effect on the delocalization of the unshared electron pair.[325]

In contrast to the secondary carbanions, the stereochemistry of the addition of the primary and tertiary carbanions appears to strongly depend on their basicity. Assuming that these two series do map out reaction coordinates for the additions to 4-*tert*-butylcyclohexanone, the available evidence suggests

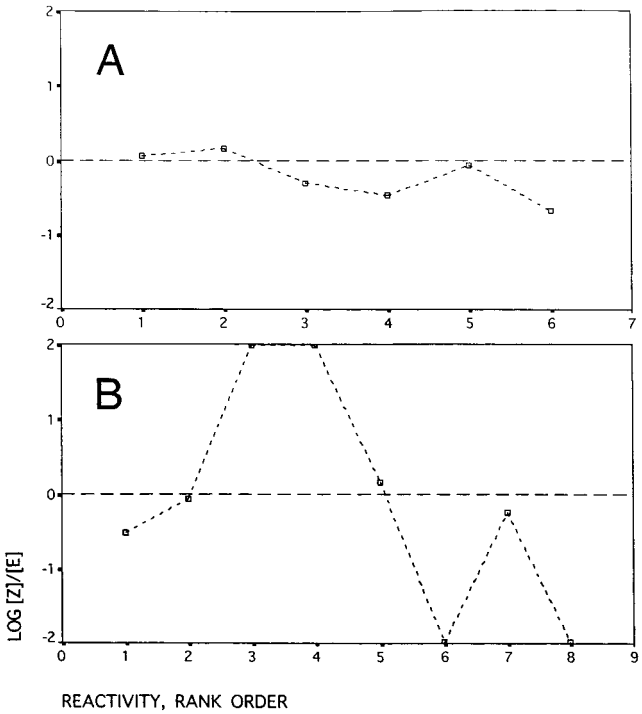


Figure 35. Effect of nucleophile basicity on alkylation of 4-*tert*-butylcyclohexanone (Na^+, liquid NH_3): (A) log [*Z*]/[*E*] vs rank order of pK_a (DMSO) for the secondary carbanions $CH_3CH^-CON(CH_2)_4$, $CH_3CH^-CO_2tBu$, $CH_3CH^-C{\equiv}N$, $PhCH^-CON(CH_2)_4$ (pK_a 26.6), $PhCH^-CO_2tBu$ (pK_a 23.6), $PhCH^-C{\equiv}N$ (pK_a 21.9). (B) log [*Z*]/[*E*] vs rank order of pK_a for the tertiary carbanions $(CH_2)_2C^-C{\equiv}N$, $(CH_2)_5C^-CO_2tBu$, $(CH_2)_5C^-C{\equiv}N$, $(CH_3)_2C^-CON(CH_2)_4$, $(CH_3)_2C^-CO_2tBu$, $(CH_3)_2C^-C{\equiv}N$, $(CH_2)_4C^-CO_2tBu$, $(CH_2)_4C^-C{\equiv}N$.

that the axial preference reaches two maxima in the mid-region of this coordinate.

4.1.1.2. Alkylmetals and Allylmetals. An example of the substituent effect on the stereochemistry of alkylation of 4-*tert*-butylcyclohexanone by organometallics where the metal is bonded to carbon (pK_a of the conjugated C acid > 40) is provided by the series of halodimethylaluminum reagents $(CH_3)_2AlX$ which display a wide range of axial preferences, see Figure 36.[326] The axial preference increases in the case of monomer addition in benzene (reagent to ketone stoichiometry 1:1) in the series X = CH_3 24% ax, Cl 43% ax, Br 60% ax, I 80% ax. On the other hand, little effect is observed when the coordination of Al is completed by the solvent molecule, as is probably true for the monomer addition in THF, or by the second molecule of the organometallic in case of the dimer addition in benzene (reagent to ketone stoichiometry 3:1). Thus, the axial preference seems to increase when the X back-donation, which probably assists the C−Al bond cleavage in the monomer addition in benzene, see Scheme 135 and sections 2.1.4.1 and 2.1.4.3.A, becomes less effective.

For a measure of the reactivity of the C−M bonds, the data on alkylation of 4-*tert*-butylcyclohexanone by other such organometallics are listed in Table 4 in order of increasing Pauling electronegativity of M.[327] To gauge the electron-donor effect of metal M (activating the nucleophile) separated from its effect as the electron acceptor (activating the carbonyl), all the methylmetal reactions included in Table 4, the

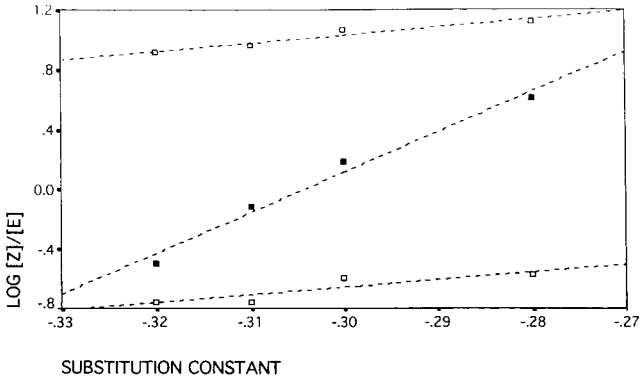
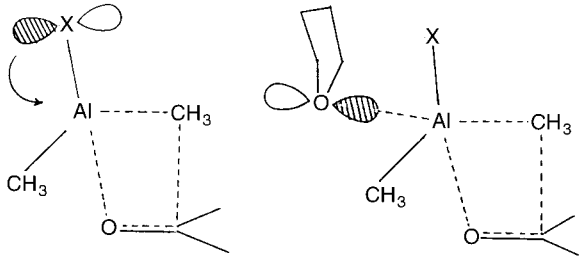


Figure 36. Effect of nucleophile halo substitution on addition to 4-*tert*-butylcyclohexanone, log [*Z*]/[*E*] vs R^- [44e] (X = CH_3, Cl, Br, I), from top to bottom: (□) Me_2AlX:ketone 3:1/benzene $Y = 0.87 + 5.10X$, SE $b_0 = 0.55$, SE $b_1 = 1.83$, $r^2 = 0.796$; (■) Me_2AlX:ketone 1:1/benzene $Y = 8.22 + 27.03X$, SE $b_0 = 0.82$, SE $b_1 = 2.72$, $r^2 = 0.980$; (□) Me_2AlX:ketone 1:1/THF $Y = 2.69 + 5.53X$, SE $b_0 = 0.29$, SE $b_1 = 0.96$, $r^2 = 0.944$.

Table 4. Relative Yield of Axial Approach in Organometallic Alkylations of 4-*tert*-Butylcyclohexanone and Pauling Electronegativities of Metals

M	χ[327]	$(CH_3)_nM$	$CH_3ML_n^-$	$(C_3H_5)ML_n$	$(CH_2CN)ML_n$
K	0.82			63[340]	80, 85[317] 84[316]
Na	0.93			65[340]	85[317]
Li	0.98	99[328] 6,[329] 8[330] 16,[331] 21[329] 35[332]		65[340]	65,[312] 71[36] 75,[317] 84[316]
Ce	1.12		29, 29[338]		66[318]
Sm	1.17			13,[341] 50[342]	
Mg	1.31	35,[333] 41[332]	31[339]	55,[340] 56[343]	64[316]
Ti	1.54	62[334]	67[334]	77, 80[344] 57[344]	
Mn	1.55			31, 43[345]	
Al	1.61	83, 88[335]	69, 82[339] 58[339]	32[340]	30[316]
Zn	1.65	54, 62[336]	36[339]	15[340,346] 16,[343] 23[340]	67, 72[312] 71[316]
Cr	1.66			12, 19[347]	
Cd	1.69	48,59[336]		22[343,348]	
In	1.78			18[349]	
Fe	1.83	1[337]			
Cu	1.90	32[331]			
Si	1.90			13[350]	
Sn	1.96			8, 15[351]	
B	2.04		30[339]	45[352]	

Scheme 135



first column, involve dimers or occur in the presence of Lewis acid catalysts.[328−337] The CH_3Li results are listed according to the strength of those catalysts, and therefore, the high axial preference of addition in the presence of $MeAl(BHT)_2$ is followed by the high equatorial preference of addition in the presence of

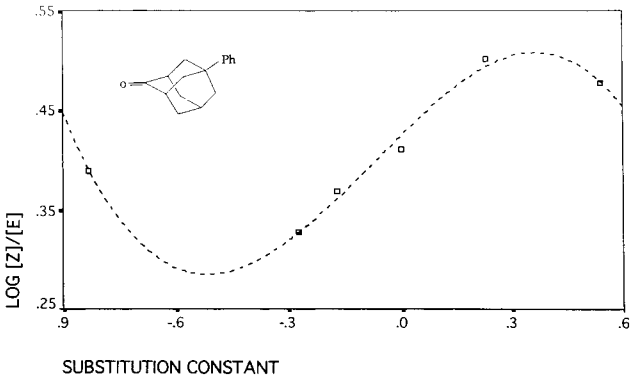


Figure 37. Effect of nucleophile substitution *p*-X-C_6H_4-MgBr on addition to 5-phenyladamantan-2-one: log [*Z*]/[*E*] vs Hammett constant σ_p (X = NMe_2, OMe, Me, H, Br, CF_3), cubic fit $r^2 = 0.985$.

$LiClO_4$ or $(CH_3)_2CuLi$. As noted in the case of the stabilized carbanions in the previous section 4.1.1.1, these data indicate that axial preference reaches certainly one and possibly two maxima along the reaction coordinate.

The alkylations by methylmetalates, the second column, occur in the presence of Li^+ as the counterion.[334,338,339] These data also indicate a maximum of axial preference along the coordinate of ionicity of the C−M bond.

The π-face selectivity of the allylmetal reagents, the third column,[340−352] except the allylboron entry, conforms to the picture of possibly two maxima of axial preference along the reaction coordinate, although these reagents are quite diverse in terms of the C−M bonding, solution structure, properties of the metal ligands, and possibly even the mechanism of addition. The electronegativity of boron is probably inadequate to describe the reactivity of the C−B bond in the transition state with the high negative charge developing on the borate-like moiety.

4.1.2. Arylation of Adamantanones

The only attempt to probe the effect of the nucleophilicity on π-face selection in additions to 5-X-adamantan-2-one involved phenylmagnesium halide additions and yielded an inconclusive result since the range of the obtained *Z*/*E* ratios was very small, from 2.1 (68/32) to 3.2 (76/24).[353] Nonetheless, the plot of log *Z*/*E* vs Hammett's σ_p is quite remarkable insofar as it suggests two maxima of the *syn* preference, reminiscent of the previously seen picture of the relationship between the basicity and π-face selection in additions to cyclohexanone, Figure 37.

4.1.3. Hydride Reduction of Cyclohexanones

The recent study of secondary deuterium kinetic isotope effects in metal hydride reductions of benzaldehyde has shown wide variation in the extent of the transition-state hydride transfer in the series $LiAlH_4$, $LiBEt_3H$, $NaB(OMe)_3H$, $LiBH_4$, $LiAl(OtBu)_3H$, $NaBH_4$, and $NaB(OAc)_3H$.[354] The magnitude of the inverse SDKIE increases in this series with the decrease in apparent reactivity of the hydrides (in the indicated order) estimated on the basis of the relative reaction times and the reactivity toward

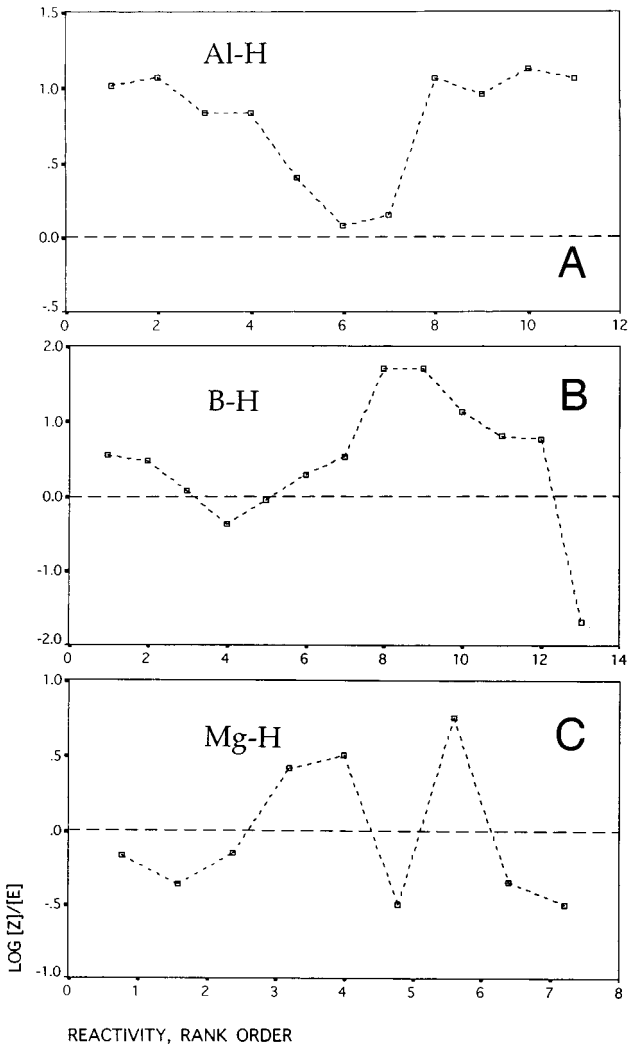


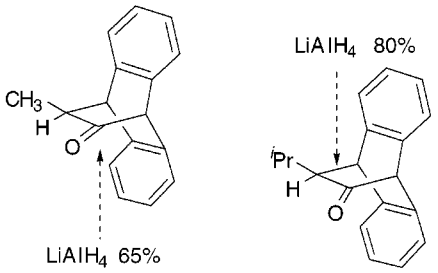
Figure 38. Effect of nucleophile reactivity on addition to 4-*tert*-butylcyclohexanone log [*Z*]/[*E*] vs rank order of hydride reactivity: (A) $LiAlH_4/Et_2O$, $LiAlH_4$/THF, $NaAlH_4$, AlH_3/THF, iBu_2AlH, AlH_3/Et_2O, $LiAl(OMe)_3H$, $NaAl(OC_2H_4OMe)_2H_2$, $LiAl(OtBu)_3H$, $LiAl(OPh)_3H$, $LiAl(OPhpCl)_3H$; (B) $LiBEt_3H$, $H_3B{\cdot}NMe_2/AlCl_3$, $H_3B{\cdot}NMe_2/BF_3{\cdot}Et_2O$, $KB(OsBu)_3H$, $KB(OiPr)_3H$, $KB(OtBu)_3H$, $KB(OC(CH_2)_4)_3H$, $LiBnBuH_3$, $LiBMeH_3$, $LiBH_4$, $NaBH_4$, $KB(OPh)_3H$, $NaB(OC_6F_5)_3H$; (C) $LiMg(OMe)H_2$, $LiMg(OiPr)H_2$, $LiMg(OtBu)H_2$, $LiMg(OPh)H_2$, MgH_2, HMg(OMe), HMg(O*i*Pr), HMg(O*t*Bu), HMg(OPh).

different carbonyl derivatives. Thus, in lieu of a better measure of hydricity,[355] the axial preference in the reduction of 4-*tert*-butylcyclohexanone by the aluminum, boron, and magnesium hydrides is plotted in Figure 38 against the rank order of the apparent reactivity. It is assumed that the alkoxy substitution of the metal, and possibly the alkyl substitution as well, lower the reactivity of Al and Mg hydrides but enhance the reactivity of B hydrides while the aryloxy substitution lowers the reactivity of all hydrides.[356−366] Furthermore, it is assumed that the effect of the alkoxy substitution is modified by the O lp back-donation, which increases the nucleophilicity of the M−H bond.[367] The importance of this interaction is suggested by the correlation of the B−O stretching frequencies (i.e., the B−O bond order) with the axial preference in the reduction of cyclohex-

Table 5. Relative Yield of Axial Approach in Reductions of Cyclohexanones by Alkoxymetal Hydrides and the Metal−Oxygen Bond Order

R	ν_{BO}[362] (cm^{-1})	4-*tert*-butylcyclohexanone				4-methyl-cyclohexanone	3-methyl-cyclohexanone	2-methyl-cyclohexanone	3,3,5-trimethyl-cyclohexanone
		$KB(OR)_3H$[362]	$LiAl(OR)_3H$	$LiMg(OR)H_2$[365]	$HMgOR$[366]	$KB(OR)_3H$			
sec-C_4H_9−	1385	29.5				30.0	17.5	7.0	2.5
$(CH_3)_2CH$−	1375	47.0		30	85	33.5	26.0	9.0	4.5
$(CH_3)_3C$−	1365	66.0	90[140]	41	31	67.0	54.0	38.0	12.5
$(CH_2)_4CH$−	1365	77.0				72.5	66.5	60.5	9.5
C_6H_5−	1330	85.0	93[360]	72	24	85.0	79.0	65.0	19.0
p-ClC_6H_4−			92[360]						
C_6F_5−		0.0[364]							

Scheme 136

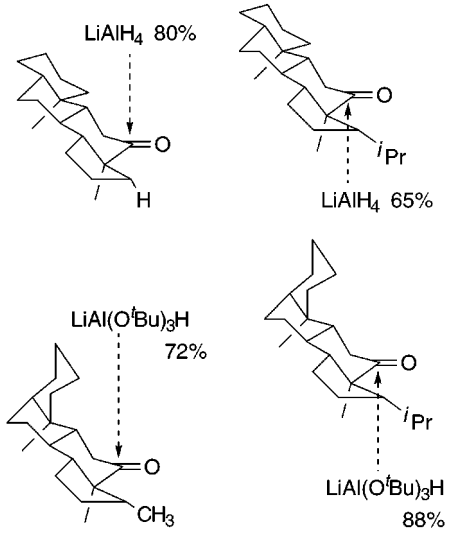


anones by potassium trialkoxyhydroborates, see Table 5.

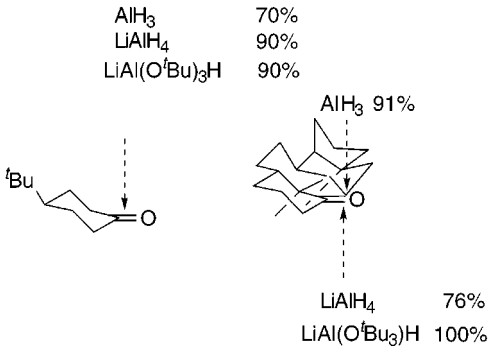
The data in Figure 38, although preliminary and qualitative, seem to support the notion that the axial preference in metal hydride additions (sensitivity to stereoelectronic control) varies along the reaction coordinate. The course of this change is not inconsistent with the picture of two maxima of the axial preference that emerges from the data on the stereochemistry of alkylation.

In principle, the shift of a transition state from one region of the reaction path to another and the associated shift of π-face preference can occur not only as a result of the change in the nucleophilicity of the hydride, but also as a result of the change in the reactivity of the ketone. It should be noted that this somewhat controversial concept[302] and the model of two maxima of stereoelectronic control along the reaction path for nucleophilic addition to cyclohexanones offer an attractive way to interpret a number of puzzling effects of alkyl substitution on the stereochemistry of these additions. Thus, the effect of the C(3)-alkyl groups on the stereochemistry of reduction of bicyclo(2.2.2)octan-2-ones and dibenzobicyclo(2.2.2)-octa-5,7-dien-2-ones would be explained as the in-plane effect of the electron-releasing substitution that shifts the transition states along the reaction path, Scheme 136.[368] More specifically, the C(17)-alkyl substitution of 12-oxo steroids would be assumed to shift the early $LiAlH_4$ transition state toward the mid-region and the advanced $LiAl(tBuO)_3H$ transition state toward the late region of the reaction path, i.e., decreasing in both cases the stereoelectronic control, Scheme 137,[369] while the extensive alkyl substitution of the cyclohexanone ring in 1-oxo steroids would be assumed to shift the $LiAlH_4$ (early), AlH_3 (mid-region), and $LiAl(tBuO)_3H$ (late) transition states for the reductions of 4-*tert*-butylcyclohexanone toward the mid, late, and very late (respectively) regions of the reaction path, Scheme 138.[356−358,370]

Scheme 137



Scheme 138



4.1.4. Ir-, Rh-, and Zr-Catalyzed Meerwein–Ponndorf–Verley Reduction of Cyclohexanones

The data on the kinetic axial preference in Zr-(O*i*Pr)$_3$-catalyzed reduction by a series of benzyl alcohols, plotted against their oxidation potentials in Figure 39, suggest that the axial preference possibly reaches two maxima along the reaction coordinate, Scheme 139.[371]

The data on the stereochemistry of the Ir- and Rh-catalyzed Meerwein−Ponndorf−Verley reductions of 4-*tert*-butylcyclohexanone are listed according to the pK_b constants of the ligands of the reduction catalysts, Scheme 140.[372]

4.1.5. Metal Hydride Reduction of Tetrakis(methylene)-bicyclo(2.2.2)octan-2-one·Fe(CO)$_3$

The *syn* approach is preferred in all investigated metal hydride additions to tetrakis(methylene)bicyclo-

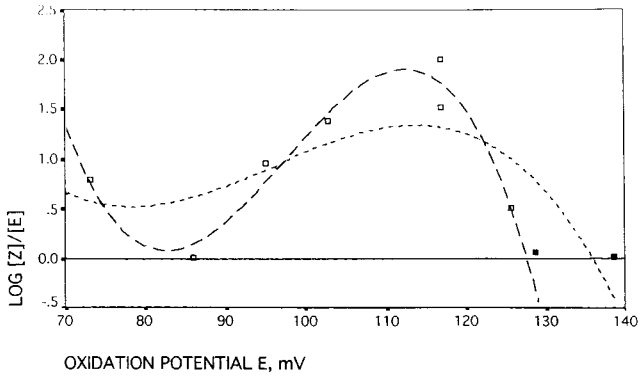


Figure 39. Effect of nucleophile reactivity on addition to 4-*tert*-butylcyclohexanone log [*Z*]/[*E*] vs oxidation potential of Meerwein−Ponndorf−Verley reducing agents (see Scheme 139 for the list of data and structures of the alcohols used): (- - -) the set of reported oxidation potentials, cubic fit $r^2 = 0.931$; (•••) the combined set of reported (□) and extrapolated (■) (from *E* vs $v_{initial}$ correlation) oxidation potentials, cubic fit $r^2 = 0.541$.

(2.2.2)octan-2-one where the remote substituent that introduces electronic bias is $Fe(CO)_3$.[373] However, the magnitude of the effect strongly depends on the reactivity of the metal hydride. When the reported reaction times are used to arrange the results, the *syn* preference seems to reach two maxima along the reaction coordinate. As expected, the *syn*-tosyloxy derivative of the complex (not shown in Scheme 141) solvolyzes faster than the *anti* derivative but the effect is very small.[373] Apparently, both diene moieties are relatively poor homoconjugative electron donors and π-face selection is most likely controlled by the σ-assistance rather than by the π-assistance, as is also the case for the reductions of bicyclo(2.2.1)-hept-2-en-7-one, section 3.1.1.

4.1.6. Metal Hydride Reduction of Benzobicyclo(2.2.1)-hept-2-en-7-ones and Benzobicyclo(2.2.2)oct-5-en-2-ones

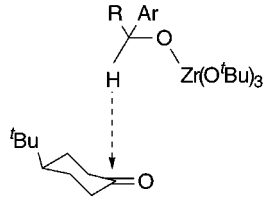
The rank order of the apparent reactivity of the metal hydrides established for cyclohexanones, cf. section 4.1.3, is used here to plot π-face selectivity in reductions of benzobicyclo(2.2.1)hept-2-en-7-ones, vide supra section 3.3. The *anti* preference, which results from homoconjugative π-assistance, appears to reach a maximum for the reagents whose transition states for addition to cyclohexanone occur in the center of the mid-region of the reaction coordinate where the axial preference is lowered, Figure 40.

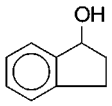
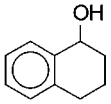
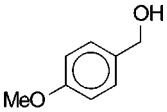
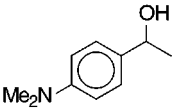
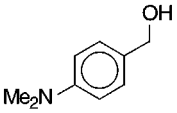
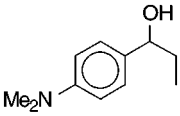
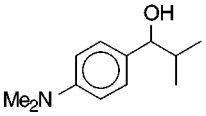
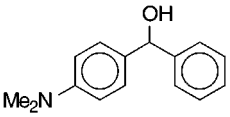
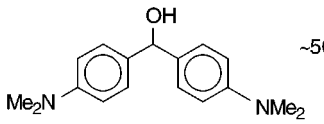
Sensitivity of π-face selection to homoconjugative π-assistance in reductions of benzobicyclo(2.2.2)oct-5-en-2-ones is smaller, cf. Figures 23 and 24. Nonetheless, the stereochemistry of methylmetal alkylation of the parent ketone seems to strongly depend on the subtle changes in reactivity, Scheme 142.[374]

4.1.7. Alkylation of Bicyclo(2.2.1)hept-2-en-7-one

The data on the stereochemistry of the addition of alkyllithium, aryllithium, and arylmagnesium reagents to bicyclo(2.2.1)hept-2-en-7-one are arranged in Scheme 143 approximately in the order of decreasing nucleophilicity, along with the two least reactive

Scheme 139



RR^{1}CHOH	%ax	E, mV	v•10^2, mol l^{-1}h^{-1}
	86	73	8.65
	50	86	5.32
	90	95	4.03
	96	103	5.69
	99	117	3.66
	97	117	3.51
	76	126	0.32
	53	(129)[a]	1.32
	~50	(139)[a]	0.13

[a] Extrapolated from *E* vs $v_{initial}$ correlation.

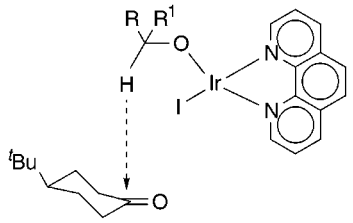
C nucleophiles, sulfonium ylide and diazomethane, Scheme 143.[131,211−213] This preliminary assessment indicates that the *anti* preference which seems to be promoted by π-homoconjugation reaches a maximum along the reaction coordinate here as well.

4.1.8. Metal Hydride Reduction of Bicyclo(3.1.0)-hexan-2-ones

The effect of the C(4)-substitution of 3,3,6,6-tetramethylbicyclo(3.1.0)hexan-2-one and the effect of nucleophilicity of metal hydrides on π-face selection suggest that the puzzling preference for the more hindered *syn* approach increases when the transition state is more advanced, Scheme 144.[168,253]

Given the rigid planar geometry of the ketone, the forming bond cannot remain in the transition state antiperiplanar with respect to the vicinal bonds and eventually has to eclipse those bonds. Therefore, the

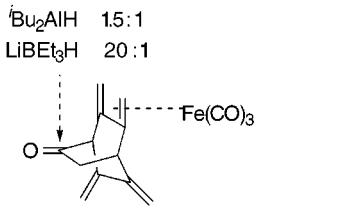
Scheme 140



Relative yield of the axial approach in catalytic reductions of 4-*tert*-butylcyclohexanone with propan-2-ol in the presence of Ir^I and Rh^I chelates and PK_a of the chelating ligand.

		Ir^I, counterion		Rh^I
ligand	pK_a	Cl^-	ClO_4^-	
4, 7-dimethoxy-1,10-phenanthroline	6.45			43.5
3, 4, 7, 8, -tetramethyl-1,10-phenanthroline	6.31	81.8	93.3	
4, 7-dimethyl-1,10-phenanthroline	5.95	61.5	80.4	81
5, 6-dimethyl-1,10-phenanthroline	5.60	66.7	90.4	
4, 4′-dimethylbipyridine	5.32		75.6	
1,10-phenanthroline	4.93	72.2	86.8	77
4, 7, diphenyl-1,10-phenanthroline	4.84	61.5	86.1	76.5
bipyridine	4.44		71.4	
4, 4′-diphenylbipyridine	·····		56.5	

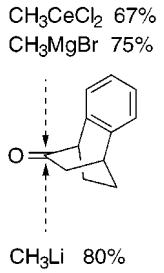
Scheme 141



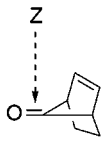
	reagent	time, min	syn/anti
-78 °C	$LiAlH_4$	30	11.5:1
	$^i Bu_2AlH$	90	1.5:1
	$NaAl(OC_2H_4OCH_3)_2H_2$	120	6.5:1
	$LiBEt_3H$	180	20.7:1
	$LiBH_4$	360	7.7:1
20 °C	$NaBH_4$, THF/ ^{i}PrOH	3	4:1
	THF/H_2O	10	4:1
	THF	1020	2:1

only hyperconjugative interaction that might be maximized in a relatively advanced transition state is the *syn*-periplanar stabilization of the incipient bond.[39] The cyclopropane C−C bond, a high-energy and diffuse σ-bond, can be a good resonance donor provided that the location of the transition state along the reaction path secures effective overlap, both in terms of the geometry of the transition state and extension of the $\sigma^*_{‡}$ orbital. It seems that both conditions are met in the case of reduction with the Luche reagent ($NaBH_4$/MeOH/$CeCl_3$), which most likely involves an alkoxy-substituted hydroborate ion.[375]

Scheme 142



Scheme 143

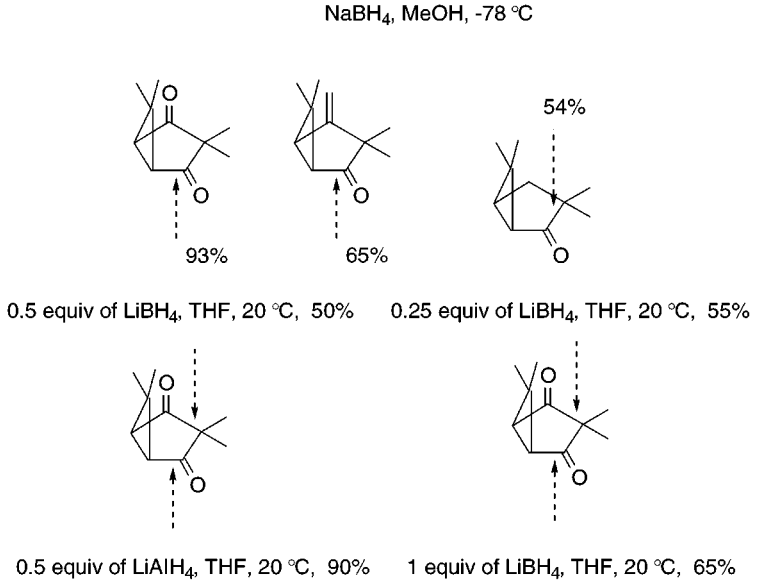


nucleophile	% Z
CH_3Li	77
C_4H_9Li	50
C_2F_5Li	25
C_6H_5Li	28
CH_2N_2	100
$(CH_3)_2S=CH_2$	100
$CH_3OC_6H_4Li$	76
C_6H_5Li	28
C_6H_5MgBr	74

4.1.9. Alkylation and Metal Hydride Reduction of 1,3-Oxathiolane Mono-Ketal of 1,2-Acenaphthylenedione

The stereochemistry of nucleophilic addition to another rigid, planar cyclopentanone, this time with the 1,3-oxathiolane ketal ring adjacent to the carbonyl, was investigated using a wide range of organometallic reagents and metal hydrides.[376] In the series of metal hydride reductions, a reversal of stereoselectivity is observed: $LiAlH_4$, $LiAl(OtBu)_3H$, and related hydrides add *syn* to S, while iBu$_2$AlH (DIBAH)

Scheme 144



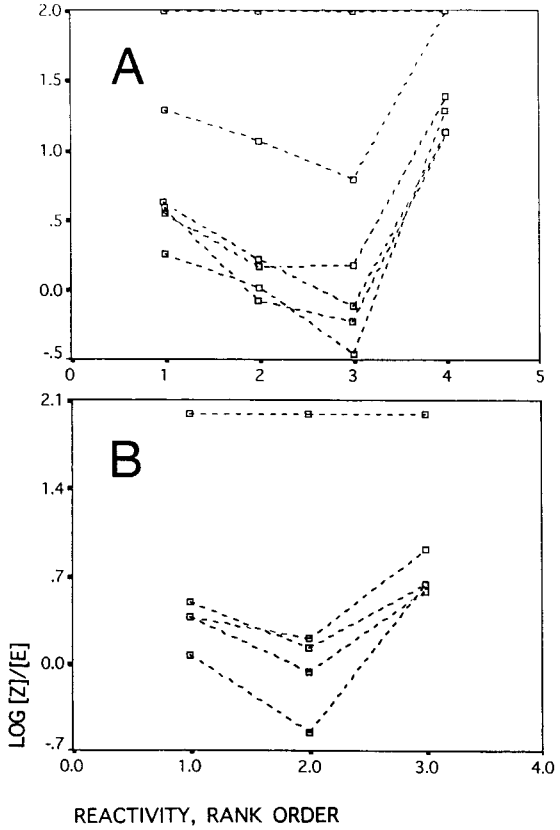
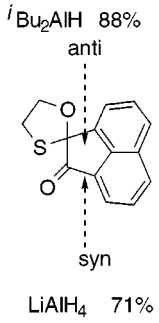


Figure 40. Effect of nucleophile reactivity on addition to benzobicyclo(2.2.1)-hept-2-en-7-ones, log [*Z*]/[*E*] vs rank order of hydride reactivity: (A) $LiAlH_4/Et_2O$, $LiAlH_4$/THF, i-Bu_2AlH, $LiAl(OtBu)_3H$; (B) B_2H_6, sAm_2BH, $NaBH_4$.

adds *anti* with respect to S. All the methyllithium and methylmagnesium reagents add *anti*, Scheme 145.

The C−S bond participation is expected to dominate interactions between the stereogenic center and the incipient bond in terms of both σ- and π-assistance. In this case, however, the two effects oppose each other because, as previously noted in section 4.1.8, reaction progress during nucleophilic addition to such ketones brings about eclipsing rather than

Scheme 145



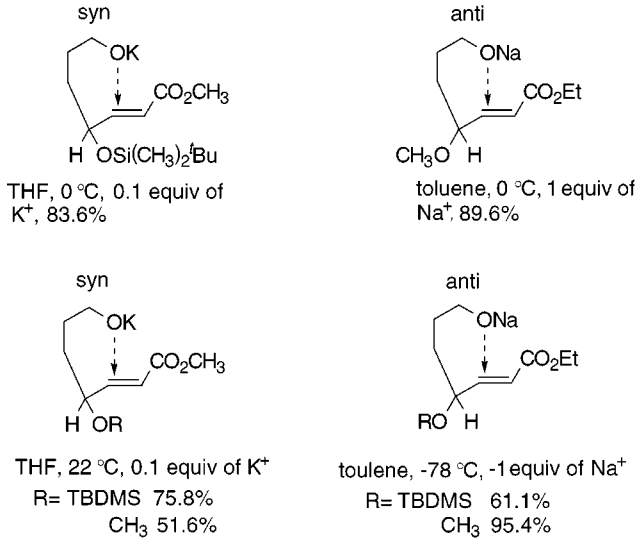
reagent	anti:syn
$LiAlH_4$, Et_2O, 0 °C	29 : 71
$^iBu_2AlH$, Et_2O, -78 °C	88 : 12
$NaAl(OC_2H_4OCH_3)_2H_2$, Et_2O, 0 °C	9 : 91
$LiAl(O^sBu)_3H$, Et_2O, -78 °C	11 : 89
$Zn(BH_4)_2$, Et_2O, 0 °C	50 : 50
$LiB(^sBu)_3H$, THF, 0 °C	26 : 74
$LiBH_4$, THF, 0 °C	31 : 69
$NaBH_4$, MeOH, 22 °C	24 : 76
MeLi, Et_2O, 0 °C	98 : 2
MeMgI, Et_2O, 0 °C	84 :16
MeMgBr, $ClCl_3$, THF, 0 °C	77 : 23
MeMgBr, THF, 0 °C	76 : 24
MeMgBr, $ZnCl_2$, THF, 0 °C	63 : 37

staggering of the vicinal bonds. In fact, the behavior of metal hydrides is consistent with their behavior in the reduction of benzobicyclo(2.2.1)hept-2-en-7-ones, cf. sections 3.3 and 4.1.6. The hydride which is most sensitive to homoconjugative π-assistance is the moderately reactive i-Bu_2AlH (DIBAH), which also displays high *anti* preference in the reduction of benzobicyclo(2.2.1)hept-2-en-7-ones and lower axial preference in the reduction of 4-*tert*-butylcyclohexanone. The more and less reactive hydrides ($LiAlH_4$, $LiAl(OtBu)_3H$, etc.) that are more sensitive to σ-assistance in cyclohexanone reduction and less sensitive to π-assistance in benzobicyclo(2.2.1)hept-2-en-7-one reduction add *syn*.

4.2. Nucleophilic Additions to Alkenes

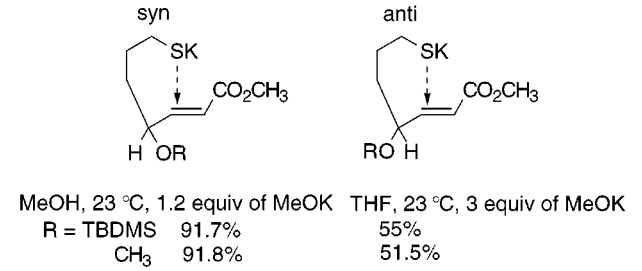
The effect of the solvent and Lewis acid strength (and concentration) on intramolecular alkoxide or sulfide additions to α,β-unsaturated esters suggests the importance of the reactivity in determination of π-face selectivity, Scheme 146.[377,378] The stereochemistry of these cyclizations also seems to depend on the protecting-group O lp back-donation. Thus, the more hindered *syn* approach is favored when the

Scheme 146



alkoxide is relatively reactive (large cation K^+ in catalytic amount, cation-solvating solvent) and the O lp back-donation more effective (silyloxy group). As the transition states become more advanced (less reactive alkoxide: smaller cation Na^+ in at least equivalent amount, nonsolvating solvent) and the O lp assistance to C−H hyperconjugation less effective (methoxy group), the less hindered *anti* approach is favored. The analogous sulfide is highly reactive, and the more hindered *syn* approach is strongly preferred regardless of the protecting group, Scheme 147.[378]

Scheme 147



The reaction becomes nonselective when the sulfide reactivity is lowered by a larger amount of Lewis acid and a less polar solvent.

Similarly, addition of sodium ethylmercaptide to α,*β*-unsaturated lactone becomes somewhat more sensitive to homoconjugative asistance when the mercaptide reactivity increases in a more polar solvent, Scheme 148.[379]

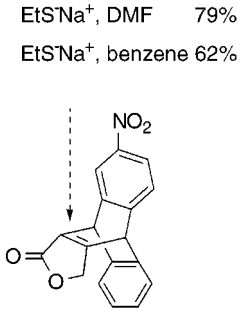
4.3. Cycloadditions

4.3.1. 1,3-Dipolar Additions to 2,3-Dioxabicyclo(2.2.2)-oct-5-ene

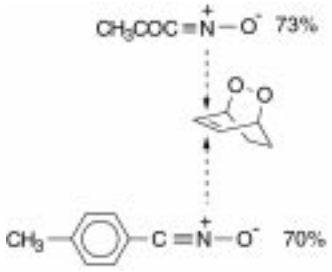
The relationship between the reactivity of the 1,3-dipoles and *π*-face selection was investigated in the nitrile oxide additions to 2,3-dioxabicyclo(2.2.2)oct-5-ene where the nitrile substitution can reverse *π*-face selectivity, Scheme 149.[293]

Assuming that in a structurally homogeneous sample reactivity should depend on the inductive and

Scheme 148



Scheme 149



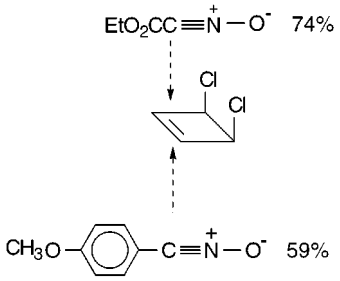
resonance effects of the nitrile oxide substituents, log [*Z*]/[*E*] for these reactions are plotted against the substituent constants, see Figure 41A.

The scattergram suggests a parabolic relationship between the reactivity and *π*-face selection, and it is the *anti* preference that is maximized in the mid-region of the reaction path, although the *anti* approach to 2,3-dioxabicyclo(2.2.2)oct-5-ene is more hindered. This is consistent with the notion that the *anti* approach is promoted by the O lp homoconjugation.

4.3.2. 1,3-Dipolar Additions to cis-3,4-Dichlorocyclobutene

The dependence of log [*Z*]/[*E*] on the inductive and resonance effects of the nitrile oxide substituents in additions to *cis*-3,4-dichlorocyclobutene is shown in Scheme 150 and Figure 41B.[380] Again, the *anti*

Scheme 150



preference is maximized in the mid-region of the reaction path. This pattern is confirmed when a wider range of 1,3-dipoles is examined[381] and the LUMO energy levels[383] are taken as a measure of reactivity, see Scheme 151.

The *anti* approach to *cis*-3,4-dichlorocyclobutene is less hindered. The more hindered *syn* approach is most likely promoted by the C−H hyperconjugation. This means that the sensitivity of these cycloaddi-

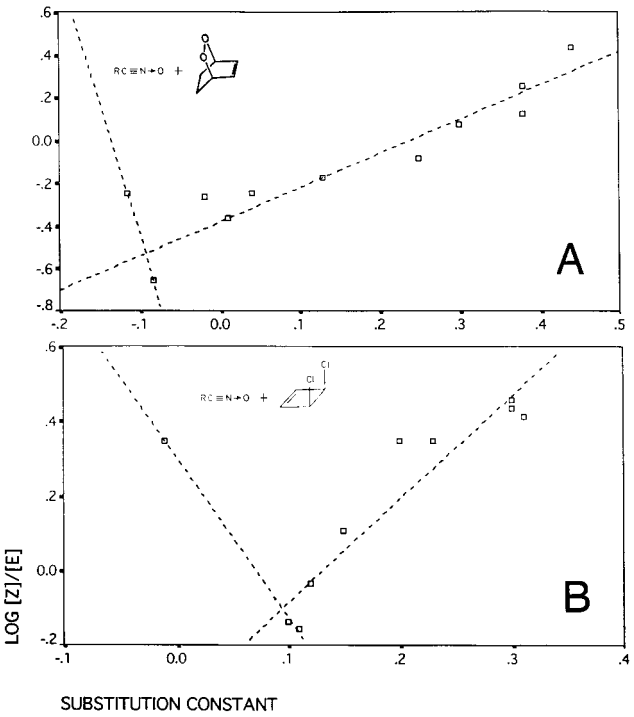


Figure 41. Effect of 1,3-dipole substitution on additions to alkenes. (A) RCNO additions to 2,3-dioxabicyclo(2.2.2)-oct-5-ene (R = Me, *t*Bu, C_6H_4-*p*-X′ (X′ = OMe, Me, H, Cl, NO_2), Br, EtOCO, MeCO, PhCO), for $\sigma_\pi > -0.1$: log [*Z*]/[*E*] vs $\sigma_\pi = \sigma_I + 0.7\sigma_R$ (σ_R estimate is used for *t*Bu based on refs 126 and 127 as well as extrapolation of R^+ constants[44e]) $\hat{Y} = -0.38 + 1.60X$, SE $b_0 = 0.04$, SE $b_1 = 0.17$, $r^2 = 0.915$. (B) RCNO additions to *cis*-3,4-dichlorocyclobutene (R = Me, C_6H_4-*p*-X′ (X′ = OMe, Me, H, Cl, NO_2), C_6H_4-*m*-NO_2, EtOCO, MeCO, C_6F_5), log [*Z*]/[*E*] vs σ_I,[44a] for $\sigma_I > 0.1$: $\hat{Y} = -0.36 + 2.77X$, SE $b_0 = 0.08$, SE $b_1 = 0.36$, $r^2 = 0.895$.

tions to σ-assistance might reach two maxima along the reaction coordinate, in a manner analogous to that observed in nucleophilic additions to cyclohexanones.

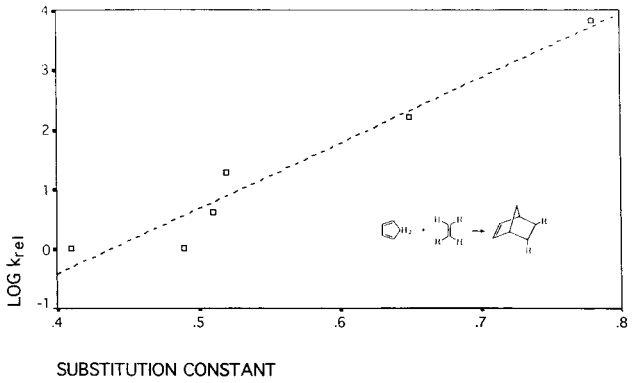
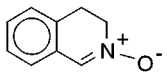


Figure 42. Effect of dienophile substitution X (*E*-XCH=CHX) on Diels–Alder additions to 1,3-cyclopentadiene: log k_{rel} vs R^- [44e] (X = CO_2Me, C≡N, COMe, COPh, SO_2Ph, COCl), $\hat{Y} = -4.78 + 10.89X$, SE $b_0 = 0.75$, SE $b_1 = 1.31$, $r^2 = 0.945$.

4.3.3. Diels–Alder Additions to 1,2,3,4,5-Pentachlorocyclopenta-1,3-diene

Regression analysis of the rates of Diels–Alder addition of *trans*-1,2-bis-substituted ethylenes to cyclopentadiene on Swain–Lupton constants shows that a good correlation is obtained for this small sample applying R^- constants,[43e] cf. Figure 42.[383] Thus, for a structurally homogeneous set of dienophiles, cycloaddition reactivity can be described in terms of the substituent constants. However, in the case of a structurally diverse set of reagents, consisting of mono- and bis-substituted acyclic and cyclic alkenes, the rate constants are necessary as a measure of reactivity to establish its relationship to π-face selection. This question was first investigated using Diels–Alder additions of mono- and disubstituted ethylenes to 1,2,3,4,5-pentachlorocyclopenta-1,3-diene.[384,385] A comparison of the approximate reaction times of these additions[384] with the rate constants for additions to 9,10-dimethylanthracene and cyclopentadiene[383] indicates that for most of the

Scheme 151

1,3-dipole	LUMO, ev	X, X = OAc, OAc	OCO	Cl, Cl	Syn %
$CH_2{=}\overset{+}{N}{=}\overset{-}{N}$	1.8	100	36	96	91
	~0	82	5	73	
$CH_2{=}\overset{t\text{Bu}}{\overset{|}{\overset{+}{N}}}{=}O^-$	~0	77	2		
$PhC{\equiv}\overset{+}{N}\overset{-}{N}Ph$	-0.5	77	≤5		
$PhC{\equiv}\overset{+}{N}{-}O^-$	-1.0	90	17	48	36
$PhCOC{\equiv}\overset{+}{N}{-}O^-$		95	34	73	64

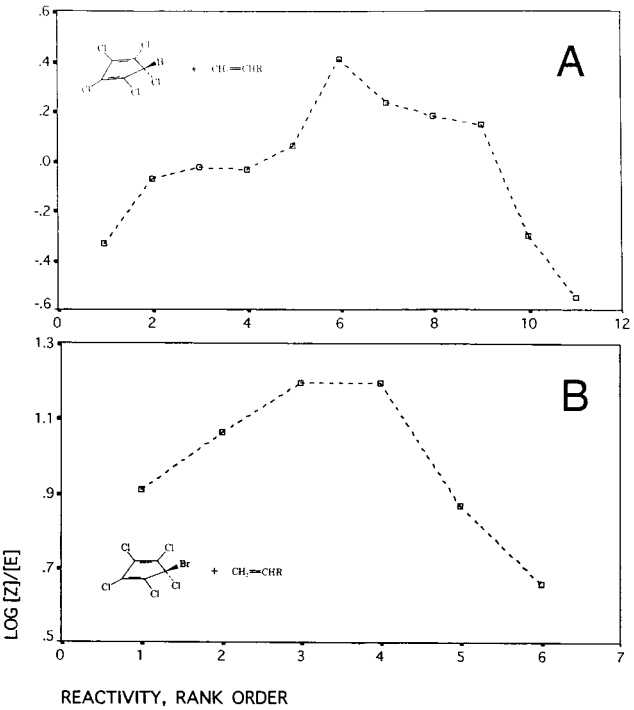


Figure 43. Effect of dienophile reactivity on additions to 1,2,3,4,5-pentachlorocyclopenta-1,3-dienes, log [*Z*]/[*E*] vs rank order of reactivity. (A) 1,2,3,4,5-Pentachlorocyclopenta-1,3-diene: propene, vinyl chloride, vinyl bromide, vinyl acetate, methyl acrylate, acrylonitrile, maleic anhydride (MA), *p*-benzoquinone (BQ), *N*-phenylmaleimide (NPM), styrene, *N*-phenyl-1,2,4-triazoline-3,5-dione (PTAD). (B) 5-Bromo-1,2,3,4,5-pentachlorocyclopenta-1,3-diene: 1,4-naphthoquinone, *N*-phenylmaleimide (NPM), 3-nitrostyrene, styrene, vinylene carbonate, *N*-phenyl-1,2,4-triazoline-3,5-dione (PTAD).

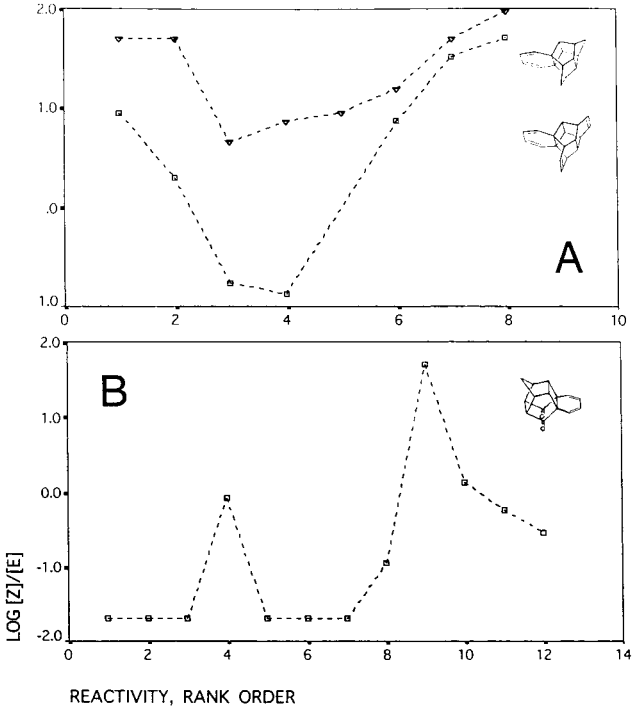


Figure 44. Effect of dienophile reactivity on Diels−Alder additions to birdcage-annulated cyclohexadienes, log [*Z*]/[*E*] vs rank order of dienophile reactivity. (A) (▽) Heptacyclo(8.5.1.$0^{2,9}$.$0^{3,8}$.$0^{3,14}$.$0^{8,12}$.$0^{11,15}$)hexadeca-4,6-diene, Scheme 58, and (□) heptacyclo(8.6.2.$0^{2,9}$.$0^{3,8}$.$0^{3,15}$.$0^{8,12}$.$0^{11,16}$)octadeca-4,6,13,17-tetraene, Scheme 59: dimethyl acetylenedicarboxylate (DMAD), dicyanoacetylene, *p*-benzoquinone (BQ), maleic anhydride (MA), *N*-phenylmaleimide (NPM), tetracyanoethylene, *N*-phenyl-1,2,4-triazoline-3,5-dione (PTAD), $^1O_2$. (B) Hexacyclo(7.4.2.$0^{1,9}$.$0^{3,7}$.$0^{4,14}$.$0^{6,15}$)pentadeca-10,12-diene-2,8-dione, Scheme 60: methyl propiolate, acrylonitrile, methyl acrylate, dimethyl acetylenedicarboxylate (DMAD), *p*-benzoquinone (BQ), maleic anhydride (MA), *N*-phenylmaleimide (NPM), benzyne, diethyl azodicarboxylate (DEAD), *N*-phenyl-1,2,4-triazoline-3,5-dione (PTAD), $^1O_2$.

series the order of relative reactivity is the same. One clear-cut exception is styrene whose high reactivity toward pentachlorocyclopentadiene is characteristic of the inverse electron-demand Diels−Alder and places it, in terms of relative reactivity, near 4-phenyl-1,2,4-triazoline-3,5-dione.[386] The resulting scale of rank order of reactivity is used to plot log [*Z*]/[*E*], Figure 43A. The scattergram indicates that the *syn* preference, the preference for the more hindered approach, reaches a maximum along the reaction coordinate, suggesting that hyperconjugative C−H σ-assistance which most likely promotes that preference, is maximized in the mid-region of the reaction path.

The results of a recent similar study of π-face selection in Diels−Alder reactions of 5-bromo-1,2,3,4,5-pentachlorocyclopenta-1,3-diene are shown in Figure 43B.[387] The preference for the *syn* approach with respect to Cl cannot be expected on steric grounds. Furthermore, the Cl-*syn* preference apparently reaches a maximum in the same region of the reaction path where the maximum of Cl-*syn* preference is found for 1,2,3,4,5-pentachlorocyclopenta-1,3-diene additions, Figure 43A. This is consistent with the notion that here too π-face selection is controlled by σ-assistance enhanced by extended hyperconjugation. The difference in the C−Cl and C−Br σ-assistance would reflect the fact that the Cl lp back-donation into σ^*_{CBr} ought to be more effective than the Br lp back-donation into σ^*_{CCl}.

4.3.4. Diels–Alder Additions to Hexacyclo(7.4.2.$0^{1,9}$.$0^{3,7}$.$0^{4,14}$.$0^{6,15}$)pentadeca-10,-12-diene-2,8-dione and Related Birdcage-Annulated Cyclohexadienes

The birdcage-annulated dienes, heptacyclo(8.5.1.$0^{2,9}$.$0^{3,8}$.$0^{3,14}$.$0^{8,12}$.$0^{11,15}$)hexadeca-4,6-diene and heptacyclo(8.6.2.$0^{2,9}$.$0^{3,8}$.$0^{3,15}$.$0^{8,12}$.$0^{11,16}$)octadeca-4,6,-13,17-tetraene, readily undergo the Diels−Alder additions described earlier, section 2.3.2.3.[174−180] These dienes, flanked by cyclobutane on one side and bicyclo(2.2.1)heptane or bicyclo(2.2.2)octane on the other side, display high preference for the *syn* approach with respect to cyclobutane, which is consistent with greater steric hindrance to the *anti* approach. However, when the difference in the steric strain is smaller, in the oxa and the unsaturated derivatives, stereoelectronic control sometimes prevails, that is the *syn* preference decreases and even reverses, as shown in Figure 44A.

The σ-assistance involves cyclobutane endocyclic C−C bonds (promoting the *anti* approach) and cyclobutane exocyclic C−C bonds (promoting the *syn* approach). Interestingly, hyperconjugation of the endocyclic σ_{CC}, which are higher in energy but more diffuse, appears most effective in the case of the moderately reactive dienophiles, i.e., in the mid-

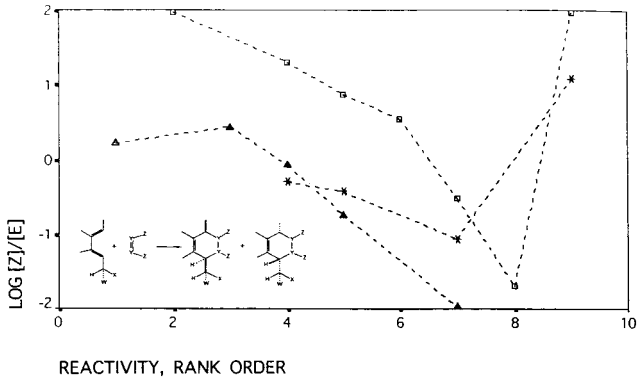


Figure 45. Effect of diene reactivity on Diels−Alder additions of (□) *N*-phenylmaleimide (NPM), (▲) *N*-phenyl-1,2,4-triazoline-3,5-dione (PTAD), and (∗) dimethyl acetylenedicarboxylate (DMAD): log [*Z*]/[*E*] vs rank order of reactivity of 5-alkoxy-1,3-hexadienes and related cyclic and semicyclic dienes, see Scheme 152.

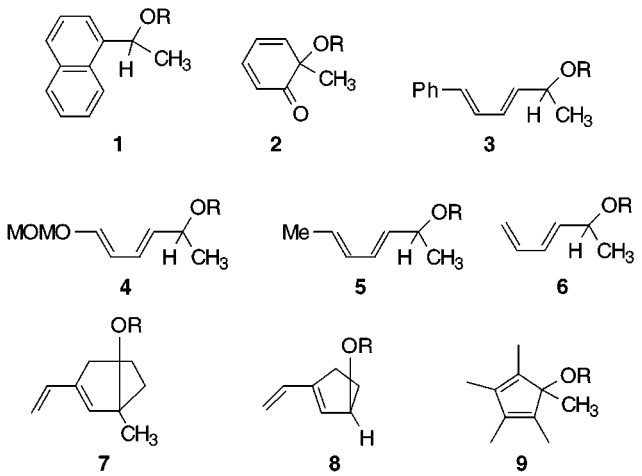
region of the reaction coordinate. It is assumed that the transition state for TCNE addition is early because of the high steric strain, see section 2.3.1.3.C, even though the reported reaction time is quite long.

Reactions of hexacyclo(7.4.2.$0^{1,9}$.$0^{3,7}$.$0^{4,14}$.$0^{6,15}$)-pentadeca-10,12-diene-2,8-dione might be controlled by the same interactions. Here, however, the *anti* approach is less hindered while hyperconjugation of cyclobutane exocyclic C−C bonds is assisted by the carbonyl O lp back-donation (extended hyperconjugation). The available data suggest that the *syn* preference, promoted by the latter interaction, reaches two maxima along the reaction coordinate, see Figure 44B.

4.3.5. Diels–Alder Additions to 5-Alkoxy-1,3-Hexadienes and Related Semicyclic and Cyclic Dienes

The log [*Z*]/[*E*] data for Diels−Alder additions of 4-phenyltriazolidin-3,5-dione (PTAD), $^1O_2$, *N*-phenylmaleimide (NPM), and dimethylacetylenedicarboxylate (DMAD) to a number of 5-alkoxy(silyloxy)-1,3-hexadienes and related semicyclic and cyclic dienes are plotted in Figure 45 in order of increasing reactivity of the dienes, shown in Scheme 152.[255−261]

Scheme 152



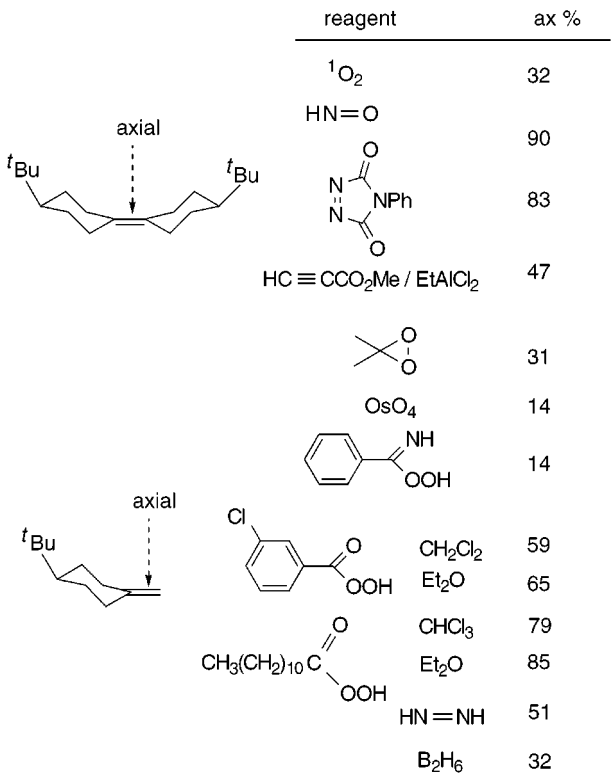
The oxaalkyl stereogenic center appears to induce the *syn* preference in Diels−Alder additions to the least and most reactive dienes, while the *anti* approach is preferred in reactions of dienes of moderate reactivity.

The view along the perpendicular coordinate of dienophile reactivity (DMAD, NPM, PTAD) changes depending on where along the coordinate of diene reactivity the projection is made. In general, however, the dependence appears to go through a maximum, vide supra section 4.3.3. It should be added that the change in reactivity might also be involved in the reversal of π-face selectivity in cycloadditions to thiophene 1-oxide and related dienes.[255,388]

4.4. Electrophilic Addition to Alkenes

A number of ene and oxidation reactions of methylenecyclohexanes, including $^1O_2$ addition, OsO_4 dihydroxylation, and perimidic acid or dioxirane epoxidations, occur faster on the equatorial π-face.[389−392] This preference is puzzling in light of the propensity for the axial attack on methylenecyclohexanes displayed, e.g., by peracids,[393,394] halonium ions,[395] and [2+2]-cycloaddition reagents.[396] The available examples of ene additions, epoxidations, and related electrocyclic additions to methylenecyclohexanes are listed in Scheme 153.[389−398] The set of listed reactions

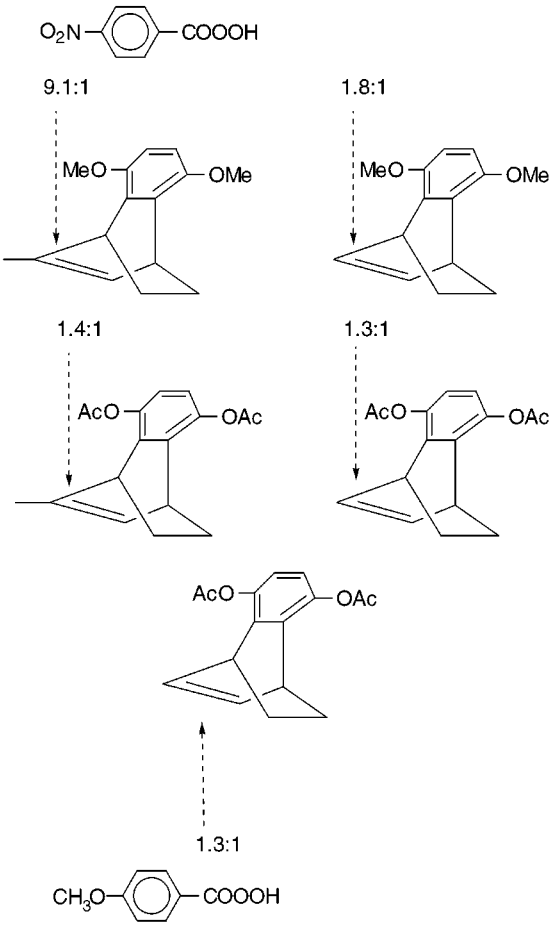
Scheme 153



seems too diverse to map out a reaction coordinate for additions to the exocyclic double bond. However, if it does, the axial preference reaches two maxima along that path, i.e., variation in the sensitivity of electrophiles to stereoelectronic control of additions to methylenecyclohexane resembles the corresponding variation among nucleophiles and could perhaps be related to reactivity.

Indeed, in the case of perimidic acid epoxidation, the equatorial preference was attributed to the fact that the reaction is relatively fast and its transition state located early on the reaction coordinate.[392] The

Scheme 154



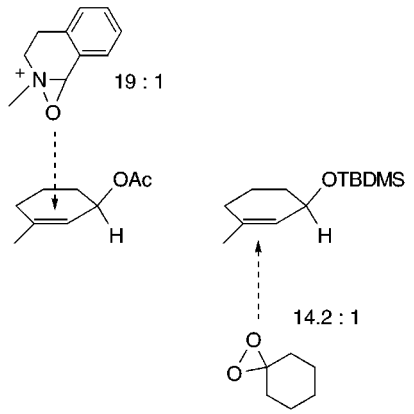
change in reactivity of alkenes and peracids was also proposed to explain the changes in π-face selectivity in epoxidation of 1,4-dihydro-1,4-ethanonaphthalenes caused by the substituent and solvent effects; homoconjugative π-assistance, postulated by the authors to promote *anti* approach, would depend on the reaction progress in the transition state.[399] Since the rate of epoxidation is lower in solvents that the peracid can be H-bonded to (e.g., Et_2O),[400] the chelating effect of the phenyl ring was assumed not to operate in this system. The effect of substitution of the probe and peracid on the *anti* preference in peracid epoxidation of 1,4-dihydro-1,4-ethanonaphthalenes is shown in Scheme 154, where the illustrative examples are arranged in the order of decreasing reaction rate. Furthermore, a large solvent effect on the [*Z*]/[*E*] ratio, presumably related to the known effect of solvents on the rate of peracid epoxidation,[400] was observed in epoxidation of 2-oxa-3-oxobicyclo-(3.3.0)oct-6-ene, see section 2.3.1.2.[133]

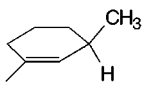
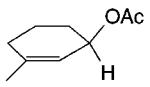
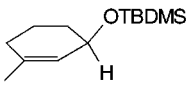
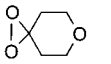
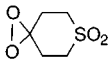
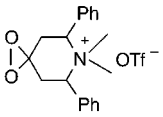
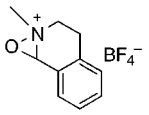
On the other hand, the effect of electron-withdrawing substitution of dioxirane on π-face selection in epoxidation of cyclohex-2-en-1-ol derivatives and the unexpected π-face preference of oxaziridinium tetrafluoroborate was attributed to electrostatic stabilization and destabilization of the *syn* and *anti* transition states, Scheme 155.[401]

4.5. Electrophilic Addition to Amines

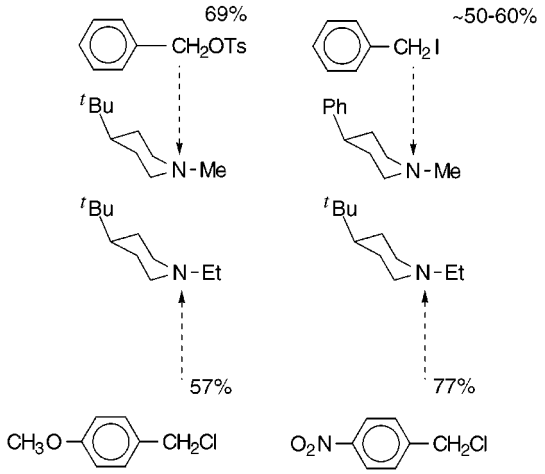
The *syn* (axial) preference in quaternization of *N*-alkylpiperidines by primary alkylating agents was reported to depend on the leaving group, substitution

Scheme 155



Reagent			
	anti / syn		
	4.4 : 1	6.6 : 1	14.2 : 1
	4.4 : 1	5.0 : 1	10.4 : 1
	4.7 : 1	4.7 : 1	6.3 : 1
	3.8 : 1	3.4 : 1	4.3 : 1
		1 : 19	

Scheme 156



of the alkyl moiety (e.g., *p*-substitution of the benzyl group), *N*-alkyl group, and the solvent.[402] The emerging pattern of the dependence of the stereochemistry of quaternization on the reactivity of the benzylating agents is shown in Scheme 156.

5. Concluding Remarks

The present review focuses on the studies of π-face selection that involve systematic variation in the

electronic properties of the stereogenic center or the reagent. This scope, while wide enough to discuss all the basic types of bond-forming reactions, leaves out a vast amount of evidence, in particular in the area of acyclic stereoselection, generated over the last several decades by intense efforts to develop methods of controlling and predicting the stereochemistry of additions to trigonal carbon. Nonetheless, the limitation seems justified for understanding how remote substituents affect π-face selection may well be the key to understanding diastereoselection and it is central to the development of the hypothesis of transition-state stabilization by resonance interactions between the incipient bond and the adjacent stereogenic center.

This hypothesis, proposed in 1981,[7] attempted to generalize the concept of the kinetic anomeric effect[403] by considering the σ,σ^* hyperconjugation and introducing the notion of a low-lying vacant orbital associated with the incipient bond ($\sigma^*_{\ddagger}$). It was initially applied to explain the stereochemistry of nucleophilic additions to cyclohexanone, challenging two widely accepted, at the time, tenets of organic chemistry. First, it implied that C−H hyperconjugation is more important than C−C hyperconjugation, contrary to the conclusion of the early ab initio and gas-phase studies reached in mid-1970s,[404] and was for that reason immediately rejected by some authors.[405] Second, it was perceived to be in conflict with the FMO theory.[406,407] It was pointed out that the proposed hyperconjugative stabilization essentially involves donation into the transition-state LUMO which develops when the nucleophile HOMO interacts with the C=O π^* orbital. Thus, such hyperconjugation not only must be diminished by the progress in bonding since the LUMO energy level steadily increases along the reaction coordinate, but it also additionally raises the LUMO level (i.e., weakens the incipient bond) slowing down the addition instead of accelerating it.[407] To compound these difficulties, the concept of the kinetic anomeric effect[403] soon became controversial when a number of authors questioned, in mid-1980s, the Deslongchamps theory of the antiperiplanar lone pair effect,[408] and skepticism regarding the n,σ^* effects implied that the energy gap between the σ and σ^* orbitals is much too large for the σ,σ^* hyperconjugation to be significant.

On the other hand, however, the hypothesis of σ-assistance to bond formation offered readily verifiable clear-cut predictions concerning the effect of sterically remote substituents on π-face selection. Consequently, the theoretical objections notwithstanding, it attracted the attention of a number of research groups, and the ensuing investigations of this effect largely corroborated its major predictions.[113] As a result, 10 years after the 1981 publication, the notion that σ-assistance plays an important role in π-face selection seemed at least partly accepted but the apparent conflict with the FMO interpretation of the carbonyl and alkene reactivity continued to hamper its reception.[409]

"[...] Cieplak provocatively pointed out that the incompletely formed bond in the transition structure was, in essence, electron deficient, and should therefore be stabilised, both for nucleophilic and for electrophilic attack, by an antiperiplanar π-donor substituent. [...] Whether Cieplak's suggestion proves to be generally true for nucleophilic attack on a carbonyl group, and it is still currently a subject of much debate, it is very probably true for electrophilic attack on a double bond."

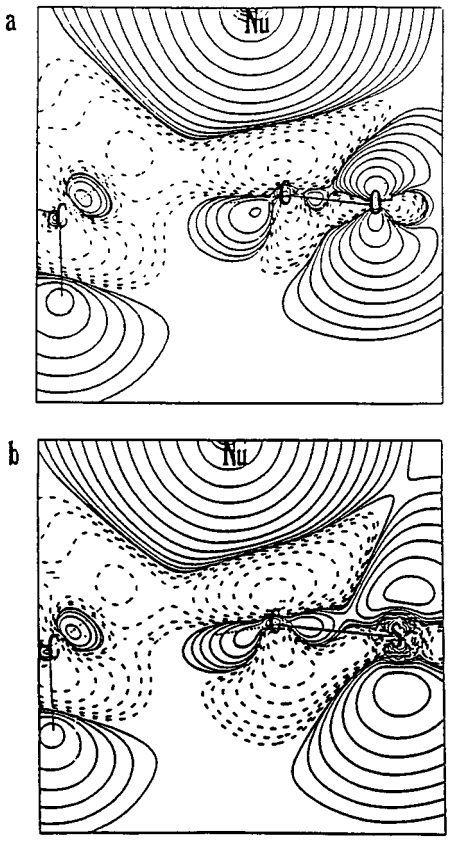


Figure 46. Electron density shifts upon approach of a nucleophile to (a) cyclohexanone (axial approach of the acetylide ion, the C(1)···C(7) distance of 2.7 Å and (b) cyclohexanethione (transition-state structure for the axial addition of the fluoroacetylide ion). In both cases, the ρ function is plotted in the C_s plane of the fragment, x size 10.0 B, x increment 0.1 B; y size 10.0 B, y increment 0.1 B; outermost contour = 10^{-4} e/B^3, each successive contour represents a factor of 2.0 increase.

The debate will undoubtedly continue. Over the last decade, however, a number of developments occurred that are noteworthy for the potential impact on its outcome.

First, the postulate, referred to as "provocative" in the above quote, has been recently validated by the ab initio study of the reaction path and transition structures for nucleophilic addition to cyclohexanone.[39] Examination of electron density shifts during the acetylide additions to cyclohexanone and cyclohexanethione at the HF/6-31G* level has shown that the atomic charge on the carbonyl C becomes more positive upon approach of the nucleophile; the density deformation maps, Figure 46, suggested that the charge polarization occurs to a large extent in the π bond.

This effect is not compensated for by charge transfer until the late stage of addition. Consequently, the reaction site is considerably electron deficient (more so than the carbonyl C in the sub-

strate) for most of the reaction paths, and its interactions with the ligands are dominated by hyperconjugation with the C−H and C−C bonds. No structural evidence of repulsion between the incipient bond and the eclipsing C−H bonds or delocalization of the incipient bond into the antiperiplanar C−H bonds is found along the reaction path. The NBO analysis of the B3LYP/6-31G* transition structures for LiH addition to cyclohexanone has confirmed that the density of electron population of the incipient bond orbital is very low, and therefore, neither repulsion nor incipient bond delocalization can be significant.[410]

It seems reasonable to assume that during electrophilic or electrocyclic addition to alkene, the reaction site also becomes more electron deficient in the transition state. Thus, one can expect it to be generally true that the energy level of the $\sigma^*_{\ddagger}$ orbital of the transition state (transition-state LUMO) is lower than that of the π^* orbital of the substrate (ground-state LUMO), except perhaps in the very advanced transition states. This picture is indeed inconsistent with the one usually considered within the framework of the FMO theory[406,407] but it better accommodates the ab initio results that map out the reaction path for nucleophilic addition to cyclohexanone[39] and the experimental evidence that stereoelectronic control of π-face selection in carbonyl and alkene additions involves the same interaction. The 1981 hypothesis proposed that this interaction is electron delocalization from the σ (hyperconjugation) or π (homoconjugation) orbitals of the stereogenic center into the $\sigma^*_{\ddagger}$ orbital which stabilizes the transition state. Such delocalization weakens of course the incipient bond but its net effect is stabilizing because of the increase in bonding between the stereogenic center and the incipient center.[411]

Second, the continuing interest in the substitution effect on π-face selection has led to an increase in the kinetic and stereochemical evidence and brought about several attempts to develop a quantitative description of such effects while new stereochemical probes were investigated, including those where the synperiplanar rather than antiperiplanar interactions of the incipient bond might control the relative stability of the transition states. The present survey and analysis of these data suggest that the common assumptions about the substituent effects ought to be revised on the following accounts.

First, the dependence of log [*Z*]/[*E*] on the inductive effect of remote substituents is often nonlinear. It is particularly well documented in the case of the symmetrical probes free of steric bias that the increase in the electron-withdrawing effect of substitution, which initially creates the electronic bias, eventually shuts down hyperconjugative σ-assistance and decreases π-face selectivity. The lower the electron affinity of the reaction site (incipient bond), the sooner along the inductive-constant coordinate that turnaround occurs.

Second, the change in log [*Z*]/[*E*] often depends on the resonance effect of remote or allylic substitution as well as the inductive effect and sometimes can be accounted for by the resonance effect alone. This evidence suggests that π-face selection can be controlled by extended hyperconjugation, i.e., electron donation from the remote or allylic substituents which assists vicinal σ-hyperconjugation, and by homoconjugation of homoallylic n- and π-donor orbitals.

Third, the dependence of log [*Z*]/[*E*] on variation in the reagent structure (reactivity) often suggests that stereoelectronic control of π-face selection reaches a maximum along the reaction coordinate and sometimes unexpectedly indicates occurence of two such maxima.

The first two findings are readily accommodated by the 1981 hypothesis and allow one to complete its treatment of π-face selection controlled by allylic substituents. The σ-bonds are likely to play an important role in the case of arylalkyl or oxaalkyl stereogenic centers primarily as a result of extended hyperconjugation, i.e., when the C−H and C−C delocalization is assisted by back-donation. However, homoallylic unshared electron pairs and π-electrons can also directly delocalize into the incipient bond (n- or π-homoconjugation). Thus, stereoelectronic control of π-face selection exerted by such centers would be determined by the competition between hyperconjugation of alkyl groups promoting the *syn* approach and homoconjugation of allylic heteroatoms or phenyl groups promoting the *anti* approach, as shown in Scheme 4.

The evidence that stereoelectronic control of π-face selection depends on the location of the transition state along reaction coordinate is generally consistent with the ab initio study of the relationship between the basicity of the acetylide ions and π-face selection in additions to cyclohexanone and cyclohexanethione.[39] Stereoelectronic effects appear to be relatively small in the very early and late stages of addition to a trigonal center and prominent in the mid-region of the reaction path. The reason for the occurrence of two maxima is not clear at present, assuming that it is not an artifact, e.g., a result of projecting two reaction coordinates onto one plane.

Thus, in response to the questions raised in the Introduction, one can conclude that the core postulates of the 1981 hypothesis remain unchanged. The present review suggests that indeed it is necessary and sufficient to invoke resonance interactions of the incipient bond to account for stereoelectronic control of π-face selection, although more data and rigorous quantitative examination will perhaps be necessary to determine whether, when, and to what degree other interactions (electrostatic) may contribute to the transition-state stabilization. The future comprehensive theory of diastereoselection, as any future theory of reactivity, ought to be based therefore on the analysis of the transition-structure wavefunctions rather than wavefunctions of the reactants in their isolated states. The complete theory will also have to consider each π-face selection event as a point on a hypersurface comprising the dimensions of the educts' reactivity along with those of electron-donor capability and size of the stereogenic-center ligands. For all the complexity and subtlety of the interactions controlling π-face selection, such a theory seems now well within our reach.

6. Acknowledgments

The author thanks Professors William le Noble and Ken Wiberg for granting access to the computer facilities at Stony Brook and Yale and for numerous invaluable comments and suggestions. Special thanks are extended to Ms. Victoria Petrova for her essential contribution to the problem of analytical representation of π-face selection in additions to 5,6-*exo*-X,X′-bicyclo(2.2.2)oct-2-enes and her enthusiastic, thorough, and insightful effort in the investigation of H bonding in the crystal structures of linear oligopeptides.

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(symmetry expansion) automatically ensures that the regression goes through the origin. The expansion does not affect the correlation coefficient, although it increases of course the significance.
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(411) The metaphor that helps to understand this point is the donor−acceptor interaction in an acetal-like fragment. Delocalization of an unshared electron pair into the vicinal polar bond weakens that bond but strengthens the intervening bond. The relationship of the two bond distances is hyperbolic. In the region of the hyperbolic curve that corresponds to weak interactions of a lone pair with the vicinal polar bond, large changes in secondary bonding cause only small changes in primary bonding and the stabilization offsets the loss of the latter. In the region that corresponds to strong interactions, small changes in the secondary bonding cause large elongation of the vicinal polar bond and the loss of primary bonding is no longer compensated for. Thus, the axial conformer of 2-chlorotetrahydropyran is more stable than the equatorial conformer even though the axial C−Cl bond is weaker, while the axial conformer of 2-chloropiperidine is the case of ultimate destabilization, i.e., it cannot exist. Extending this metaphor, the interactions between the transition state and the stereogenic center are assumed to be sufficiently weak to place the fragment in the "safe" region of the corresponding hyperbolic curve.

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