sulfur and iodine is very stable but not between sulfur and fluorine, and such a bond is of marginal stability between sulfur and chlorine.[14] On this basis oxygen is not a prime candidate for 2c,3e interaction with an oxidized sulfur atom unless a suitable steric arrangement facilitates p-orbital overlap. This is in accord with our results which have identified rigid five- and six-membered cyclic structures as a necessary prerequisite for an observable sulfur–oxygen stabilization. Structure b takes into account that the unpaired electron could be subject to easy delocalization depending on suitably located energy levels in the MO diagram and may resemble radicals with σ as well as with π character. An example which is probably best characterized by a three-center or perhaps better multicenter arrangement is found in the work of Perkins et al. on the photolysis of *tert*-butyl 2-(methylthio)peroxybenzoate.[19] Steric demands are, however, probably high for such an aligned system. Localization of the unpaired electron at sulfur, finally, is another realistic alternative. This may occur in the form of a typical sulfuranyl radical as depicted in c or in a system with more Coulombic interaction d which may specifically be envisaged for the oxidized thioether acids. The latter appears reasonable in view of the electron delocalization in the carboxylate group. A crude ESR experiment on a γ-irradiated sample of the endo-acid **5b** in a Freon matrix at 77 K indicated $g \sim 2.03$. This high value certainly points toward strong localization of the unpaired electron at sulfur.

Generally, it is probably realistic to view a–d as different geometric structures which may even exist in equilibrium. Which of these electronic situations prevails or describes best certain chemical properties will depend on structural parameters and substitution patterns. The nonspecific S$^{\bullet}$↔O notation represents this.

Conclusion

From the results presented in this paper and some related earlier investigations a number of general conclusions can be drawn, but also some questions are raised. Our data provide further supporting evidence for the concept of neighboring group participation[22,39,44] and, in fact, clearly establish it now for radical species. The oxidation of the sulfur function in our compounds as well as the properties of the resulting radical species have been demonstrated to depend significantly on the influence of functional groups. However, the latter have to be located in a position suitable for interaction with the sulfur.

Acknowledgment. We are very thankful to Dr. M. J. Davies, for the ESR measurement, and to Professors T. F. Slater and R. L. Willson (all from Brunel University West—London) for providing the facilities for these experiments. K.-D.A. and S.M. gratefully acknowledge the support given by the Deutsche Forschungsgemeinschaft (DFG). R.S.G., M.H., and G.S.W. gratefully acknowledge support given by the U.S. Public Health Service, National Institutes of Health, Grant HL 15104. We also gratefully acknowledge support from NATO, Travel Grant RG85/0644.

Registry No. **1**, 13532-18-8; **2**, 646-01-5; **3**, 32391-97-2; **4**, 111-17-1; **5a**, 64887-94-1; **5b**, 64887-93-0; **5c**, 109216-48-0.

(44) (a) Capon, B. *Neighboring Group Participation*; Plenum: New York, 1976; Vol 1. (b) Kirby, A. J. *Adv. Phys. Org. Chem.* **1980**, *17*, 183.
(45) Jaffe, H.; Orchin, M. In *Theory and Applications of Ultraviolet Spectroscopy*; Wiley: New York, 1962; p 475.
(46) Sweigart, D. A.; Turner, D. W. *J. Am. Chem. Soc.* **1972**, *94*, 5599.
(47) Bock, H.; Wagner, G. *Angew. Chem.* **1972**, *84*, 119.
(48) Setzer, W. N.; Coleman, B. R.; Wilson, G. S.; Glass, R. S. *Tetrahedron* **1981**, *37*, 2743.
(49) Angyán, J. G.; Poirier, R. A.; Kucsman, A.; Csizmadia, I. G. *J. Am. Chem. Soc.* **1987**, *109*, 2237.
(50) Alder, R. W.; Sessions, R. B.; Mellor, R. B.; Rawlins, J. M. *J. Chem. Soc., Chem. Commun.* **1977**, 747.
(51) Alder, R. W.; Sessions, R. B. *J. Am. Chem. Soc.* **1978**, *101*, 3651.
(52) Nelsen, S. F.; Alder, R. W.; Sessions, R. B.; Asmus, K.-D.; Hiller, K.-O.; Göbl, M. *J. Am. Chem. Soc.* **1980**, *102*, 1429.
(53) Mohan, H.; Asmus, K.-D. *J. Chem. Soc., Perkin Trans 2*, in press. Mohan, H.; Asmus, K.-D. *J. Am. Chem. Soc.*, in press.
(54) Chaudhri, S. A.; Asmus, K.-D. *Angew. Chem.* **1981**, *93*, 690; *Angew. Chem., Int. Ed. Engl.* **1981**, *20*, 672.
(55) Clark, T. *J. Comput. Chem.* **1981**, *2*, 261.

A General Treatment of Nucleophilic Chemistry†

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A mechanistic model of nucleophilic chemistry has been developed and implemented in the computer program CAMEO. The program can make predictions on the outcome of nucleophilic processes by applying mechanistic reasoning and rules governing competing reactions that are based on literature precedents. The general procedure is divided into four steps: perception of reactive sites, recognition of applicable electron-push mechanisms, evaluation of the mechanisms for each nucleophilic site, and overall analysis of competing pathways. The model and the chemical rules used in these steps are described in this paper. The approach has general utility for synthetic analyses and allows the program to make sophisticated predictions on the outcome of a great variety of nucleophilic reactions.

I. Introduction

CAMEO is an interactive computer program designed to predict the products of organic reactions given starting materials and reaction conditions. It arrives at its predictions largely by mimicking the traditional mechanistic reasoning of chemists. The program is divided into modules which process different classes of reactions. These classes are distinguished primarily by the nature of the intermediates generated during the course of the reactions. They currently cover nucleophilic,[1-5] electrophilic,[6,7] rad-

† Computer-Assisted Mechanistic Evaluation of Organic Reactions. 13.

(1) Salatin, T. D.; Jorgensen, W. L. *J. Org. Chem.* **1980**, *45*, 2043.
(2) Salatin, T. D.; McLaughlin, D.; Jorgensen, W. L. *J. Org. Chem.* **1981**, *46*, 5284.

0022-3263/87/1952-3724$01.50/0

ical, carbenoid, thermal pericyclic,[8,9] and oxidative/reductive processes.

Organic synthesis, by design is generally oriented around a number of key strategic steps that involve construction of the target molecule skeleton. Nucleophilic chemistry, in turn, constitutes the major tool typically used to effect these carbon–carbon linkages. Accordingly, it is very important for the chemist and the CAMEO program to be able to accurately evaluate the feasibility of these key steps. The nucleophilic package in CAMEO has been under development for over 10 years, during which time the depth and scope of the program have increased dramatically. New mechanisms have been implemented while the application of existing mechanisms has been refined and extended. Most recently, the program has been restructured to account for a new pK_a algorithm[10] that provides a more general and accurate means of perceiving nucleophilic and electrophilic sites. As a result, the program is now able to make accurate predictions on a vast number of reactions with a relatively limited set of chemical rules. The search for such organizing principles governing organic reactivity is a key aspect of the CAMEO project. In this paper, we describe the modeling and the fundamental rules and conclude with a discussion of the capabilities and limitations of the nucleophilic package. Many of the rules deal with competing reactions; hopefully, their documentation will lead to some debate and further refinements. The overall presentation is sufficiently general to be of use to organic chemists outside of the context of the program, especially in pedagogical settings.

II. Overview of the Program and Nucleophilic Model

Operationally, CAMEO is run on Digital Equipment Corporation VAX computers. A session begins by entering the potentially reacting substrate(s) at a Tektronix-compatible computer graphics terminal. Additional common reagents can also be input in the same way, though some may be supplied from a reagent menu that is provided for convenience. The user subsequently selects a chemistry module corresponding to the reaction classes described above and the processing begins. A perception phase is first entered and information is garnered on structural features such as rings and stereochemistry and on chemical characteristics including pK_a's for proton removal. This information is used by the different mechanistic modules that actually create and evaluate the mechanisms and form the products. The viable products are subsequently displayed at the graphics terminal and stored on a "synthetic tree". They can be retrieved from the tree and further processed to build up a complete reaction sequence. The program provides substantial feedback to the user including text describing decisions that were made by the program to reach its predictions and sometimes quantitative data on relative reactivities and activation energies. The key issue is the recognition and analysis of competing processes in the mechanistic segments.

The fulcrum in the case of the nucleophilic module is evaluation of the coming together of a nucleophilic atom and an electrophilic atom. All mechanistic decisions revolve about these two atoms. The general organization of this module is as follows: (1) perception of nucleophilic and electrophilic sites in the input reagents, (2) determination of applicable mechanisms for a given nucleophilic/electrophilic site pairing, (3) evaluation of the best mechanisms for a given nucleophilic site, and (4) general comparison and screening of all reaction pathways. The predicted products are then output to the graphics terminal with one of three designations: major, minor, or disfavored. The disfavored product designation is reserved for products that are probably not formed during the course of the reaction but are shown because the rule applied is not strict enough to unequivocally reject them.

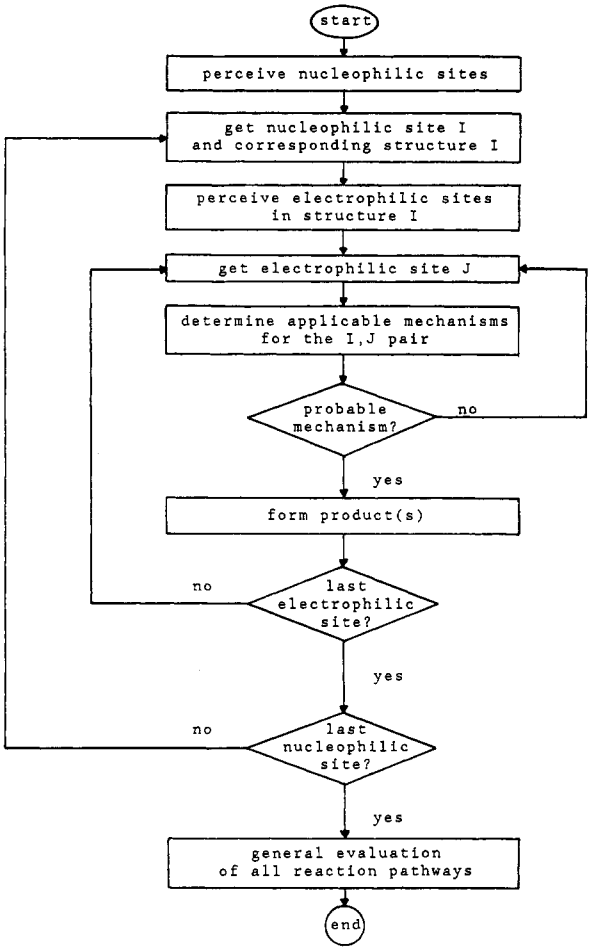
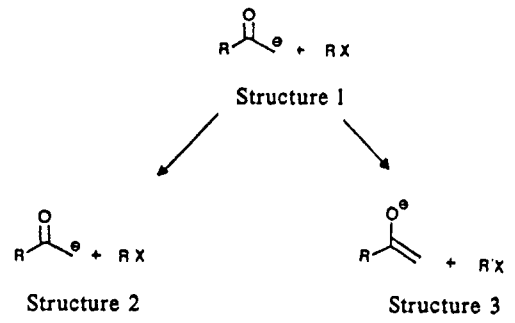


Figure 1. Flow chart outlining the organization of the nucleophilic module.

This procedure is diagrammed in Figure 1 and discussed below. Internally, the program considers the input reagents as one "structure". This structure is first perceived and nucleophilic sites determined. For every nucleophile, a new structure is generated reflecting the active form of each incorporated nucleophilic site. For example, if an enolate is input, two nucleophilic sites (C and O) are perceived corresponding to the two resonance forms. Hence, two structures are stored reflecting the appropriate charge and bond representations for the two nucleophilic sites. Following this perception, each nucleophilic site and its corresponding structure are retrieved sequentially and the potential electrophilic sites are perceived. Each electrophilic site is then paired up with its corresponding nucleophilic site for evaluation. The first evaluation determines the mechanisms that are applicable for the pair of sites, including proton transfer, halogen–metal exchange, E1cb (paths 1–2, 1–4, and 1–6), E2, S_N1, S_N2, S_N2', addition, addition–elimination, and a variety of 1,2-carbon

(3) Peishoff, C. E.; Jorgensen, W. L. *J. Org. Chem.* **1983**, *48*, 1970.
(4) Peishoff, C. E.; Jorgensen, W. L. *J. Org. Chem.* **1985**, *50*, 1056.
(5) Peishoff, C. E.; Jorgensen, W. L. *J. Org. Chem.* **1985**, *50*, 3174.
(6) McLaughlin, D. Ph.D. Thesis, 1983, Purdue University.
(7) Bures, M. G.; Roos-Kozel, B. L.; Jorgensen, W. L. *J. Org. Chem.* **1985**, *50*, 4490.
(8) Burnier, J. S.; Jorgensen, W. L. *J. Org. Chem.* **1983**, *48*, 3923.
(9) Burnier, J. S.; Jorgensen, W. L. *J. Org. Chem.* **1984**, *49*, 3001.
(10) Gushurst, A. J.; Jorgensen, W. L. *J. Org. Chem.* **1986**, *51*, 3513.



shifts such as the benzil–benzilic acid and Hoffman rearrangements. The applicable mechanisms are then evaluated and only the probable ones are allowed to lead to initial product formation. After all nucleophilic and electrophilic sites have been processed in this manner, the potential products are further screened before the final predictions are made.

An additional feature of this module is that products of addition reactions are resubmitted and allowed to undergo a subsequent intramolecular substitution, neutralization, or E1cb process. This procedure is desirable because it allows up to four elementary processes in one execution cycle. For example, the Wittig reaction shown in eq 1[11]

$$Ph_2P^+-CH_3 \xrightarrow[2.\ Ph_2CO]{1.\ PhLi} Ph_2C{=}CH_2 + Ph_3P{=}O \quad (1)$$

is performed in one pass through the program via proton transfer, addition, neutralization (oxaphosphetane formation), and decomposition. It should be noted that the decomposition step is triggered by the full perception of structural features for the products just before they are output. This includes the recognition and decomposition of unstable functional groups. Tautomers[12] and hemiacetal- and hemiketal-type species are likewise transformed appropriately in order to maintain a systematic representation of the chemical system.

Details on the four steps in the treatment of nucleophilic processes are described in turn in the following sections.

III. Perception of Nucleophilic and Electrophilic Sites

The perception of nucleophilic and electrophilic sites is closely linked to pK_a perception. pK_a values are used to initially gauge the rankings of the reactive sites. Of course, the pK_a values and consequently the reactivity of the sites are dependent on the choice of solvent for the reaction. By default, all reactions are processed in CAMEO assuming a dipolar aprotic solvent unless the menu "button" designating a "protic solvent" is selected. The pK_a values given in this paper correspond to the acidities predicted in dimethyl sulfoxide (Me_2SO).[10]

A. Nucleophile Perception. Nucleophilic sites can be anionic or neutral and may be perceived directly in the starting material or after a "mechanistic prestep". The mechanistic presteps currently implemented in the program include proton transfer, halide–alkyllithium exchange, and metal insertion reactions as shown below.

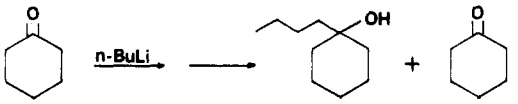
$$R{-}H + B^- \rightarrow R^- + B{-}H$$

$$R{-}X + R'{-}Li \rightarrow R{-}Li + R'{-}X$$

$$R{-}X + 2M \rightarrow R{-}M + M{-}X \text{ (monovalent M)}$$

$$R{-}X + M \rightarrow R{-}M{-}X \text{ (divalent M)}$$

These mechanisms are typically faster than substitution, elimination, and addition reactions and are therefore considered first. Organometallic addition, however, can be competitive with these processes under certain circumstances (e.g., eq 2[13]). Therefore, this competition must



(2)

be dealt with at this point to determine whether the organometallic base should be kept as a potential nucleophile for further examination. In the case presented, the program keeps both the butylate and the enolate for mechanistic evaluation.

The program recognizes two types of proton transfer: fast proton transfer, which takes place from nonmetal atoms of groups V, VI, or VII and from sp-hybridized carbon, and slow proton transfer, which takes place from sp^2- and sp^3-hybridized carbon. Having defined these types of proton transfer, the kinetic hierarchy for the mechanistic presteps is as follows: fast proton transfer > halide–alkyllithium exchange and organometallic addition > slow proton transfer ≫ metal insertion. Proton transfer from sp^3-hybridized carbon, however, can in fact be faster than halide–alkyllithium exchange or organometallic addition if the anion generated is particularly stabilized (e.g., eq 3).

$$CH_2(CO_2Et)_2 + n\text{-BuLi} \rightarrow Li^+{}^-CH(CO_2Et)_2 + n\text{-BuH} \quad (3)$$

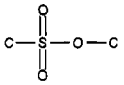
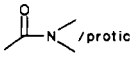
Hence, proton transfer from sp^3-hybridized carbon sites that have pK_a's less than 20 is treated as fast proton transfer. Additionally, since slow proton transfer is a side process in many organometallic addition reactions, e.g., eq 2, slow proton transfer is performed along with addition if the slow proton transfer site has a pK_a of 30 or less.

For all mechanistic presteps, the most stable anion and any others within a specified pK_a window are generated. The default pK_a window for all mechanistic presteps is 4 pK_a units. For example, the initial base in a proton-transfer reaction is allowed to generate the weakest base and any others within 4 pK_a units. The basicity of organolithium reagents, however, requires special attention. Increasing alkyl substitution increases basicity, i.e., *t*-BuLi is a stronger base than *sec*-BuLi which is stronger than *n*-BuLi. This reactivity is handled as follows: tertiary, secondary, and primary alkyllithium reagents are allowed to deprotonate acids with pK_a's up to 54, 50, and 46, respectively. Grignard and cuprate reagents behave as weaker bases than the corresponding organolithium compounds and are therefore only allowed to deprotonate compounds that have a pK_a of 42 or below.

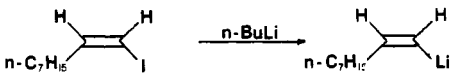
Halide–alkyllithium exchange and metal insertion reactions are analogous to proton-transfer reactions in that an atom is displaced to form the most stable anion. Halide–alkyllithium exchange is usually effected on iodides and bromides whereas metal insertion reactions are effected on chlorides as well. All other things being equal, the reactivity order is I > Br > Cl. Metal insertion reactions can be carried out with a variety of metals (Li, Mg, Zn, Na, Cd, K, and Cs), the most common being the first

(11) Wittig, G.; Geissler, G. *Liebigs Ann. Chem.* **1953**, *580*, 44.
(12) Roos-Kozel, B. L.; Jorgensen, W. L. *J. Chem. Inf. Comput. Sci.* **1981**, *21*, 103.
(13) Buhler, J. D. *J. Org. Chem.* **1973**, *38*, 904.
(14) Cahiez, G.; Bernard, D. B.; Normant, J. F. *Synthesis* **1976**, 245.
(15) Wiberg, K. B.; Lampman, G. M. *Tetrahedron Lett.* **1963**, 2173.
(16) Cripps, H. N.; Kiefer, E. F. *Org. Synth.* **1962**, *42*, 12.

Table I. Calculations Illustrating the Ranking Procedure for a Number of Representative Electrophilic Sites

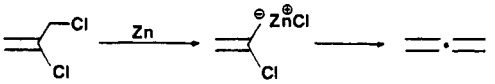
electrophilic site	leaving group	initial ranking	adjustment	final ranking
C–Cl	Cl^-	1	0	1
C–O–C	^-O–C	30	0	30
		30	−25	5
		30	−12	18
	^-O–C	30	−16	14
C=O	C–O^-	30	0	30
C=O/protic	C–OH	1	0	1
	$^-$N<	42	0	42
	HN<	15	0	15
	$^-$N<	42	12	54
	$^-$N<	42	−13	29
		30	−10	20
=·=O	=·—O^-	30	−25	5

three listed. The following equations provide some illustrations.



(4)[14]

(5)[15]

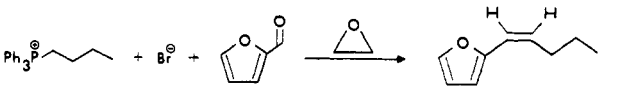


(6)[16]

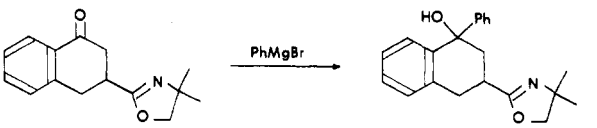
Once all nucleophilic sites have been perceived, they are given "nucleophilic qualification values" (NQVs) in order to gauge their relative tendency to behave as nucleophiles or as bases. These values range from 1 to 4 and are determined primarily by the basicity of the nucleophilic atom and by its steric environment. A value of 1 is associated with a very strong, hindered base (e.g., LDA and DBU), whereas a value of 2 identifies a less intense case of 1 (e.g. *t*-BuOK). A value of 3 is for a weak, nucleophilic base (e.g., F^-, NH_3, and PhS^-), and a value of 4 identifies a strong, nucleophilic base (e.g., EtO^-, *n*-BuLi, and $PhCOCH_2^-$). This classification scheme is important since it enables the program to distinguish the predominant mechanisms (e.g., S_N2 vs. E2) for a nucleophilic site by its NQV.

B. Electrophile Perception. An electrophilic site can be an atom in an X—Y, X=Y, or X≡Y bond, where X and Y are carbon or heteroatoms and X can equal Y. This broad definition encompasses carbon–oxygen double bonds, carbon–halogen bonds, epoxides, sulfenyl halides, bromine, peroxides, etc. Associated with each electrophilic site X is the leaving bond, X—Y, X=Y, X≡Y, and the leaving atom, Y.

The rankings of electrophilic sites are initially based on the pK_a of the conjugate acid of the leaving group. Adjustments to the initial ranking are then made to account for steric effects, relief of strain, and hetero–hetero fission. For example, the ranking of a simple epoxide is determined as follows (refer to the third entry in Table I). The initial ranking of the epoxide is 30, which corresponds to the pK_a of the alcohol that would result upon ring opening. An adjustment of −25 is then made to account for relief of ring strain and yields the final electrophilic site ranking of 5. In general, the adjustments have been determined such that the final electrophilic site ranking roughly coincides with the "limiting ranking" of the nucleophilic sites that are known experimentally to react at the electrophilic site. As an illustration, this ranking scheme permits bromide ion, which has a nucleophilic site ranking of 1, to open the epoxide in the following equation. The resultant base then



generates the phosphorus ylide for the Wittig reaction.[17a] Potential sites for addition bearing back-elimination groups are handled somewhat differently in that they are ranked according to the ultimate leaving group. For example, the carbonyl carbon in an acid chloride is ranked according to the leaving ability of the chloride anion. Additionally, adjustments are made to account for fundamental reactivity differences between different addition moieties. For instance, nucleophiles are observed to react selectively with ketones over imidates as shown below.[17b] If the



ranking for the imidate was based soley on the back-elimination group (alkoxide), the ketone and imidate would have the same ranking. Hence, adjustments have been determined empirically to reflect the base reactivity difference between reaction at a carbonyl carbon and alternate addition sites. Specifically, the ranking for the ultimate leaving groups in thionyl functionalities is lowered (made more reactive) by 13 units, and for imino functionalities is raised by 12 units when they bear back-elimination groups. Finally, the rankings for electrophilic sites can be markedly affected by designating that the solvent is protic. Due to the kinetics of protonation of leaving atoms such as oxygen and nitrogen in protic solvents, the initial pK_a rankings are no longer based on the conjugate acid of the leaving anion but rather on the conjugate acid of the protonated leaving anion. Thus, this treatment allows for the hydrolysis of amides in a protic solvent, a reaction that would not take place if run in an aprotic solvent. The rankings for a number of representative electrophiles are presented in Table I.

Two reactivity directories are used by the program to store information about electrophilic sites, the "All Path directory" and the "El directory".[1-5] The All Path directory is used to store electrophilic sites that can potentially undergo any type of mechanism. The E1 directory, in contrast, is used to store poorer electrophiles that are only able to participate in E1cb reactions. This classification scheme facilitates the elimination of some naive chemistry as shown below for a sulfone and nitro compound that

(17) (a) Buddrus, J. *Chem. Ber.* **1974**, *107*, 2050. (b) Meyer, A. I.; Temple, D. J. *J. Am. Chem. Soc.* **1970**, *92*, 6644.

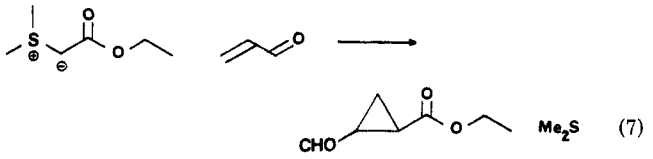
$$R\text{–}O^- + R^1\text{–}NO_2 \nrightarrow R\text{–}O\text{–}R^1 + NO_2^-$$

$$R\text{–}MgX + R^1\text{–}SO_2Ph \nrightarrow R\text{–}R^1 + PhSO_2MgX$$

would be in the E1 directory. More information on the actual representation of the data on nucleophiles, electrophiles, and acidic sites in CAMEO may be found in ref 1–5 and 10. In general, sets and arrays are the predominant data structures used in CAMEO.

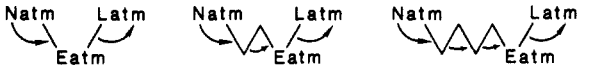
IV. Mechanistic Types

The different mechanisms applied by CAMEO are divided into three groups: eliminations, substitutions and additions, and 1,2-carbon shifts. The feasibility of each mechanism is first gauged via a ΔpK_a rule; namely, the pK_a of the conjugate acid of the nucleophilic site should be no more than 10 units above the ranking of the electrophilic site. This condition is only waived for stabilized ylides since these nucleophiles appear to yield intermediates up to 20 pK_a units above their own pK_a. This is demonstrated in eq 7[18] where the pK_a of the conjugate acid of the stabilized ylide is 7 and the ranking of the 1,4-addition site is 27.

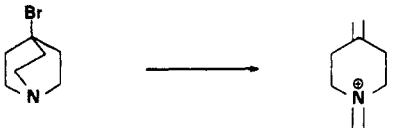


(7)

A. Elimination Mechanisms. 1. Unimolecular Eliminations. 1,*N*-E1cb processes are common unimolecular eliminations where *N* is an even number of bonds separating the nucleophilic atom (Natm) and the leaving



atom (Latm), and the electrophilic atom (Eatm) is in the pathway. Eliminations involving paths with more than six bonds are extremely rare. Consequently, the program only considers paths where *N* is equal to two, four, or six bonds as shown below. An example of an 1,4-E1cb fragmentation is shown in eq 8.[19]



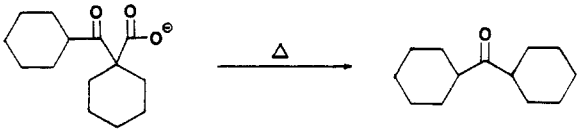
(8)

The program imposes several structural limitations on unimolecular elimination processes. First, atoms in row 1 of the periodic table are not allowed to form π bonds with atoms in row 2 (or greater) due to the relative weakness of such bonds. One exception is made for the formation of C=S bonds (e.g., eq 9[20]). Second, fragmentation pro-

$$PhCH_2SO_2Cl + Et_3N \rightarrow$$

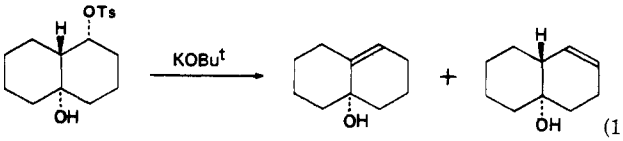
$$PhCH{=}SO_2 + Et_3NH^+Cl^- \xrightarrow{CH_2N_2} PhCHCH_2SO_2 \quad (9)$$

cesses involving the formation of a cumulene are not allowed unless a small stable molecule such as CO_2, SO_2, or SO_3 is extruded (e.g., eq 10[21]) or, in the case of a 1,2-E1cb



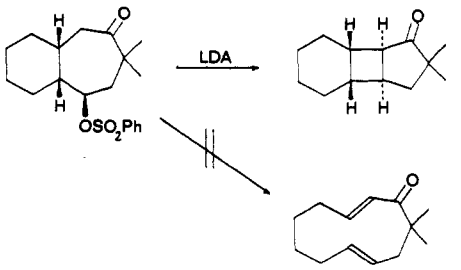
(10)

process in which the nucleophilic site ranking is greater than 20 units above the electrophilic site ranking (e.g., in eq 9 where sulfene formation is allowed, the nucleophilic and electrophilic site rankings are 24 and 1, respectively). Similarly, benzyne formation via an 1,2-E1cb process is not allowed unless the nucleophilic site ranking is more than 25 units above the electrophilic site ranking. Finally, 1,4-E1cb or Grob fragmentations involving the scission of a fusion bond are highly stereospecific.[22] They are not allowed in two cases: if the reaction is extrannular,[23] bears a trans fusion, and the relationship between the leaving atom and the nucleophilic atom is cis (e.g., eq 11[24]) or, if



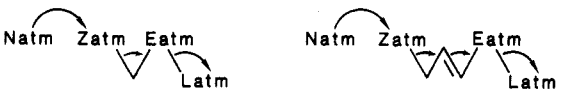
(11)

the reaction is intrannular[23] and the stereochemistry of the fusion bond and the relationship between the leaving atom and the adjacent fusion center are the same, i.e., cis/cis or trans/trans (e.g., eq 12[23]).

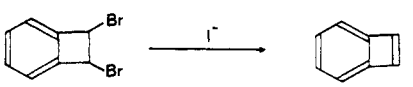


(12)

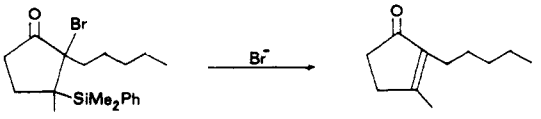
2. Simple and Conjugate Bimolecular Eliminations. The general forms for simple and conjugate bimolecular eliminations are presented below. Zatm can be hydrogen,



silicon, or halogen other than fluorine and Latm can be activated oxygen (e.g., OTs) or halogen other than fluorine. Special requirements are in effect for bimolecular eliminations not involving hydrogen. In particular, XY eliminations where X is halogen other than fluorine and Y is either equal to X or activated oxygen are only allowed for good nucleophiles that are weak bases, NQV = 3 (e.g., eq 13[25]). Furthermore, XY eliminations where X is silicon and Y is halogen other than fluorine are only allowed for good nucleophiles, NQV = 3 or 4 (e.g., eq 14[26]).



(13)

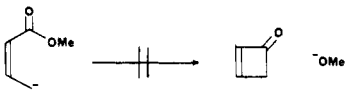


(14)

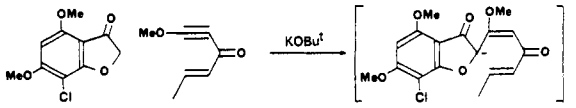
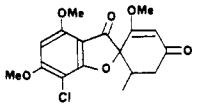
(18) Payne, G. B. *J. Org. Chem.* **1967**, *32*, 3351.
(19) Grob, C. A.; Fisher, H. P.; Raudenbush, W.; Zergenyi, J. *Helv. Chim. Acta* **1964**, *47*, 1003.
(20) King, J. G. *Acc. Chem. Res.* **1975**, *8*, 10.
(21) Krapcho, A. G.; Kashdan, D. S.; Janhgen, E. G. E., Jr. *J. Org. Chem.* **1977**, *42*, 1189.
(22) Grob, C. A. *Bull. Soc. Chim. Fr.* **1960**, 1360.
(23) Grob fragmentations of polycyclic systems have been classified according to the relationship of the assisting orbital and leaving group terminus; location within the same ring is intraannular and within different rings is interannular, and if the assisting orbital is external to the ring system, the relationship is termed extraannular. Clark, D. A.; Fuchs, P. L. *J. Am. Chem. Soc.* **1979**, *101*, 3567.
(24) Wharton, P. S.; Hiegel, G. A. *J. Org. Chem.* **1965**, *30*, 3254.
(25) Benson, R. E.; Cairns, T. L. *J. Am. Chem. Soc.* **1950**, *72*, 5355.

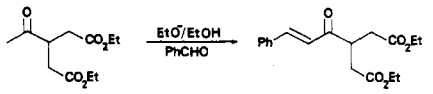
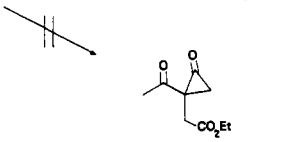
B. Substitution and Addition Mechanisms. This mechanistic class includes S_N2, S_N2', addition, addition–elimination, and neutralization ($X^+ + Y^- \rightarrow XY$) reactions. These mechanisms formally proceed via the same topological modifications of the reactive sites, i.e., a bond is formed between the nucleophilic atom and the electrophilic atom and a bond is broken between the electrophilic atom and the leaving atom. Neutralization is an exception in that no bond is broken. The structural and stereochemical rules used in CAMEO for this mechanistic class are presented next along with literature precedents.

Intermolecular substitutions have only one major structural limitation. Due to the strain in the transition state, S_N2 reactions do not occur on atoms in three- and four-membered rings unless the ring is opened. Hence, only the elimination pathway is followed with the dibromo compound in eq 13. Intramolecular reactions, in contrast, have many structural restrictions. First, a nucleophilic and an electrophilic site that are activated through the same chain of conjugation do not react (e.g., eq 15[27]). However,

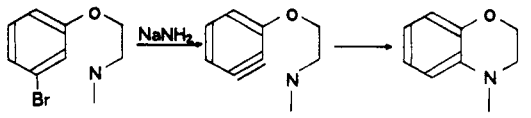

(15)

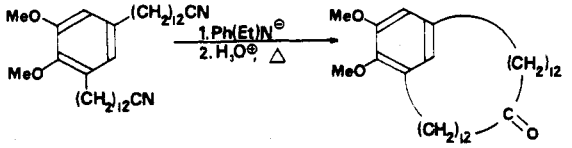
the sites may react if they are activated by the same group but through different chains of conjugation (e.g., eq 16[28]). Second, the formation of three-membered rings via an addition mechanism is not allowed (e.g., eq 17[29]). Note



(16)

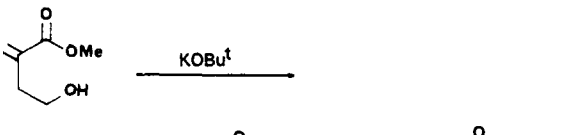


(17)

that formation of three-membered rings via a substitution reaction is allowed as demonstrated earlier in eq 7 and in many other processes such as Favorskii and Ramberg–Backlund rearrangements. Third, ring formation is not allowed if the ring has fewer than 9 atoms and contains a trans double bond or if it is smaller than size 10 and involves bridge formation about an aromatic ring. For example, in eq 18[30] only the fused product is formed, whereas in eq 19[31] bridge formation via a condensation reaction is possible owing to the long side chains. Finally, ring-forming processes involving first row electrophilic centers should be assessed according to Baldwin's rules.[32]


(18)

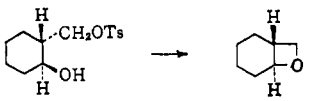

(19)

Since exceptions to Baldwin's rules are known, a violation does not prevent product formation in CAMEO. Instead, products of violations are displayed with a message indicating the offense as shown below.[33]

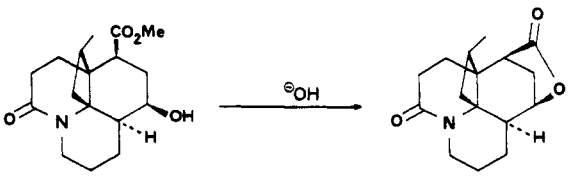

(20)

Baldwin's rule violator:
5-endo-trig

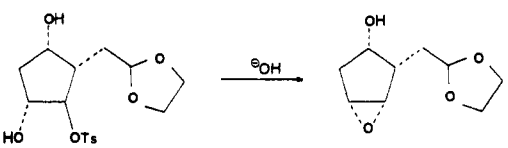
The stereochemical limitations imposed in CAMEO are primarily related to ring fusion or bridge formation.[5] First, trans fusions are highly disfavored if the envelope of the two fused rings that would form has fewer than 8 atoms. For example, trans-fused bicyclo[3.3.0]octanes and bicyclo[4.2.0]octanes have been synthesized as in eq 21.[34]


(21)

However, there are few examples of prepared systems that have a trans ring fusion with an envelope of 7 atoms due to the added strain of ca. 15 kcal/mol.[5,34] Second, if the nucleophilic, electrophilic, and leaving atoms are all off a ring, then the relationship between the branch bearing the nucleophilic atom and the branch bearing the leaving atom needs to be cis for reaction to occur (e.g., eq 22[35]). Third,


(22)

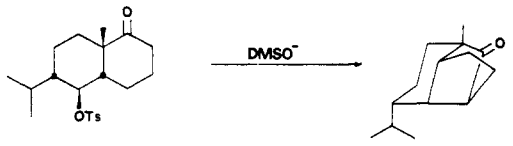
if both the nucleophilic atom and the leaving atom are off the ring and the electrophilic atom is in the ring, then the relationship between the branch bearing the nucleophilic atom and the leaving atom needs to be trans (e.g., eq 23[36]).


(23)

Finally, there are additional limitations for polycyclic ring systems in which the path between the nucleophilic and

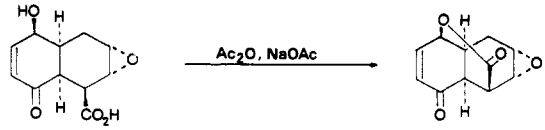
(26) Ager, D. J.; Fleming, I.; Patel, S. K. *J. Chem. Soc., Perkin Trans. 1* **1981**, 2520.
(27) Salatin, T. D. Ph.D. Thesis, Purdue University, 1981, 207.
(28) Stark, G.; Thomasz, M. *J. Am. Chem. Soc.* **1962**, *84*, 310.
(29) Mitschka, R.; Cook, J. M. *J. Am. Chem. Soc.* **1978**, *100*, 3973.
(30) Huisgen, R.; Konig, H. *Angew. Chem.* **1952**, *69*, 269.
(31) Shill, G.; Luttringhaus, A. *Angew. Chem., Int. Ed. Engl.* **1964**, *3*, 546.
(32) Baldwin, J. E. *J. Chem. Soc., Chem. Commun.* **1976**, 734.
(33) Baldwin, J. E.; Cutting, J.; Dupont, W.; Kruse, L.; Silberman, L.; Thomas, R. C. *J. Chem. Soc., Chem. Commun.* **1976**, 736.
(34) Meinwald, J.; Tufariello, J. J.; Hurst, J. J. *J. Org. Chem.* **1964**, *29*, 2914. Gassman, P. G.; Bonser, S. M. *J. Am. Chem. Soc.* **1983**, *105*, 667.
(35) Wiesner, K.; Poon, L.; Jirkowsky, I.; Fishman, M. *Can. J. Chem.* **1969**, *47*, 433.
(36) Fried, J.; Lin, C. H.; Sih, J. C.; Dalven, P.; Cooper, G. F. *J. Am. Chem. Soc.* **1972**, *94*, 4342.

electrophilic atoms involves one or more bridgehead or fusion atoms. If the path between the nucleophilic and electrophilic atoms contains one fusion bond, then this fusion needs to be cis (e.g., eq 24[37]). Additionally, the



(24)

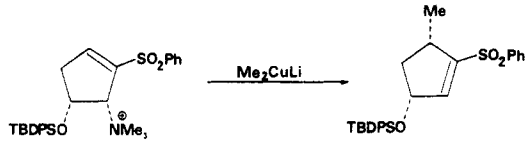
relationship between the branch bearing the nucleophilic atom and the nonring atom extending from the first fusion or bridge atom in the path must be trans (e.g., eq 25[38]).



(25)

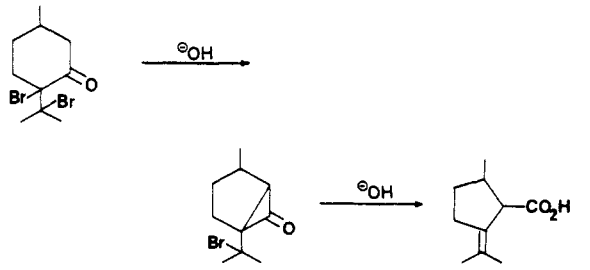
It should be noted that these stereochemical limitations are only applied in CAMEO when the stereochemistry has been explicitly designated in the starting material.

The stereochemistry at electrophilic centers is also considered by the program. S_N2 reactions at saturated carbon centers are performed with inversion of configuration. S_N2 at saturated silicon centers, however, may occur with retention or inversion of configuration.[39,40] Consequently, the stereochemistry at the stereocenter is currently deleted and the convergence product is shown. The predominant course for addition–elimination reactions at unsaturated electrophilic centers is retention of configuration.[41] While stereoconvergence is also common, full inversion is rarely seen. The stereochemistry for this mechanism is not considered by the program at this time and so the stereoconvergence product is shown. S_N2' reactions on ring systems typically occur via a synfacial mechanism, i.e., the nucleophilic atom attacks on the same side as the leaving group. The stereochemistry of this process is taken into account by the program as shown below.[42]



(26)

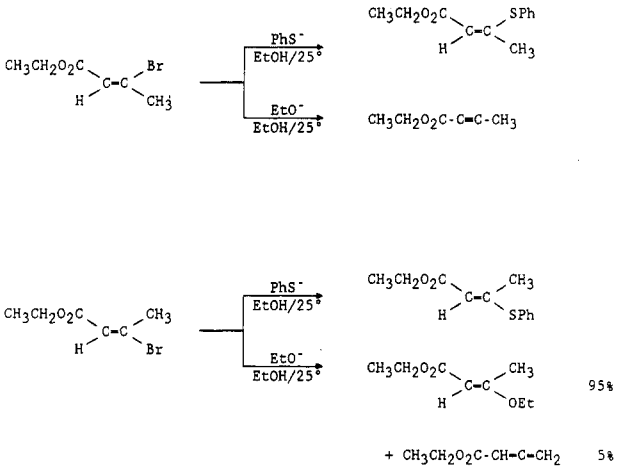
C. 1,2-Carbon Shifts. Many base-induced rearrangements can be decomposed into a series of the elementary mechanistic steps that have already been considered. For example, the Favorskii rearrangement depicted below[43]



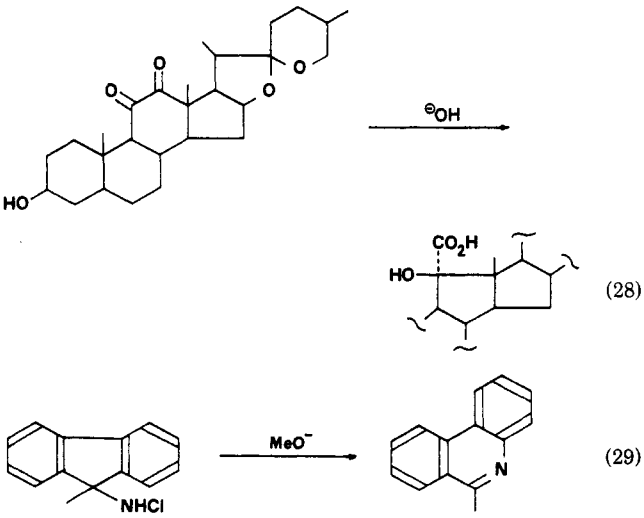
(27)

(37) McMurry, J. E. *J. Am. Chem. Soc.* **1968**, *90*, 6821.
(38) Woodward, R. B.; Bader, F. E.; Bickel, H.; Frey, A. J.; Kierstead, R. W. *J. Am. Chem. Soc.* **1956**, *78*, 2023.
(39) Fleming, I. *Comprehensive Organic Chemistry*; Pergamon Press: Oxford, 1979; Vol. 3, p 541.
(40) Mislow, K. *Acc. Chem. Res.* **1970**, *3*, 321.
(41) Modena, G. *Acc. Chem. Res.* **1971**, *4*, 73.
(42) Hutchinson, D. K.; Fuchs, P. L. *J. Am. Chem. Soc.* **1985**, *107*, 6137.

Scheme I. Reactions of (*E*)- and (*Z*)-β-(Bromoethyl)crotonates with Benzenethiolate and Ethoxide Ions

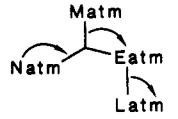


may be interpreted as a proton transfer/S_N2/Ad_N/1,4-Elcb progression which is, in fact, what the CAMEO program predicts. However, some base-induced rearrangements such as the benzil–benzilic (e.g., eq 28[44]) or the Stieglitz rearrangement (e.g., eq 29[45]) involve a different fundamental step, a 1,2-carbon shift. Three versions of this process may be identified and have recently been implemented in CAMEO as follows:

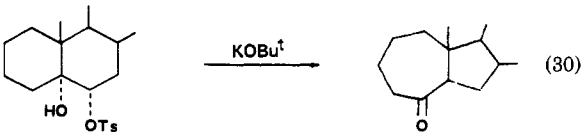


(28) (29)

1. Benzil–Benzilic and Related Rearrangements. The general form of this mechanism is shown below. The



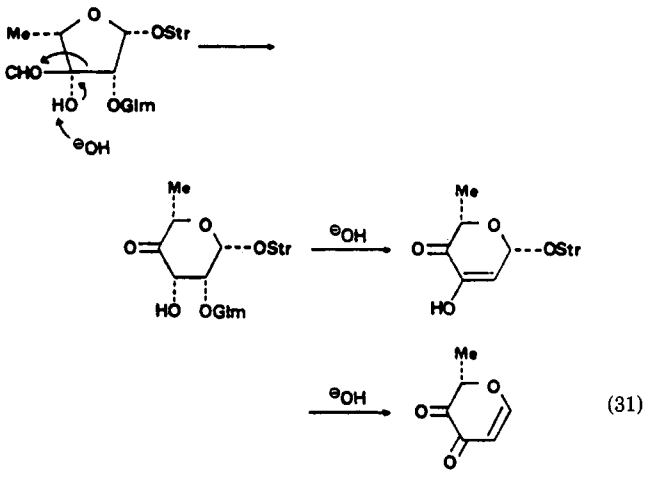
key features are that the leaving atom is β to the nucleophilic atom and that the migrating atom (Matm) must be able to attain an antiperiplanar relationship with the leaving atom. This is exemplified in eq 30 where only



(30)

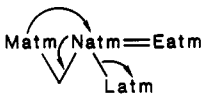
(43) Wallach, O. *Liebigs Ann. Chem.* **1918**, *414*, 233.
(44) Rajic, M.; Rull, T.; Ourisson, G. *Bull. Soc. Chim. Fr.* **1961**, 1213.
(45) Pinck, L. A.; Hilbert, G. E. *J. Am. Chem. Soc.* **1937**, *59*, 8.

migration of the fusion bond occurs.[46] The general mechanism has been applied extensively in natural product synthesis to effect ring expansions and contractions. For example, the synthesis of maltol, a precursor of the streptose portion of the antibiotic streptomycin, was affected by a ring expansion of this type.[47]

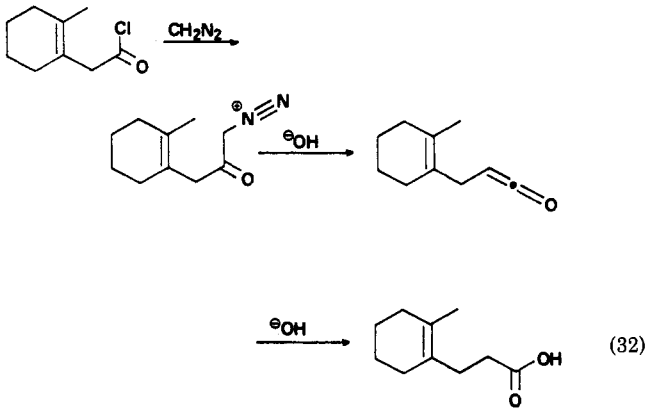


(31)

2. 1,2-Ene Rearrangements. The general form of this mechanism is shown below. The key features are that the

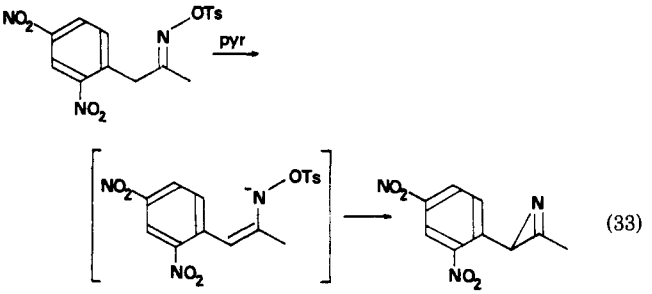


nucleophilic atom and the electrophilic atom are the same and that only carbon-carbon bonds beta to the nucleophilic atom are allowed to migrate. The Arndt–Eistert synthesis shown in eq 32[48] is illustrative. A great number of 1,2-



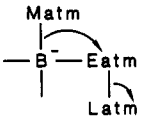
(32)

carbon shifts can be interpreted through this general mechanism including the Hoffman,[49] Stieglitz,[45] Fritsch–Buttenberg–Wiechell,[50] Curtius,[51] Lossen,[52] and Neber[53] rearrangements. Alternatively, these processes can be rationalized through the formation of a carbene or nitrene intermediate that subsequently rearranges. However, most studies give evidence for a concerted mechanism under basic conditions.[54] Incidentally, the Neber rearrangement (e.g., eq 33[55]), as interpreted by the program, is an example of a 1,2-multiple bond shift.

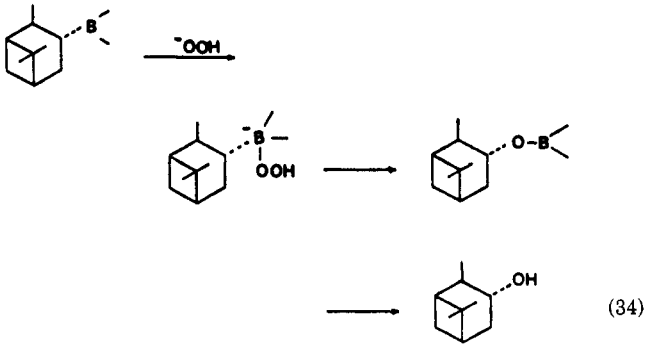


(33)

3. 1,2-Boron Rearrangements. The general form of this mechanism is shown below. The key features are the



presence of a borate anion and that the process occurs with retention of configuration at the migrating carbon. The standard example of this mechanism occurs in the conversion of alkylboranes to alcohols (e.g., eq 34[56]).



(34)

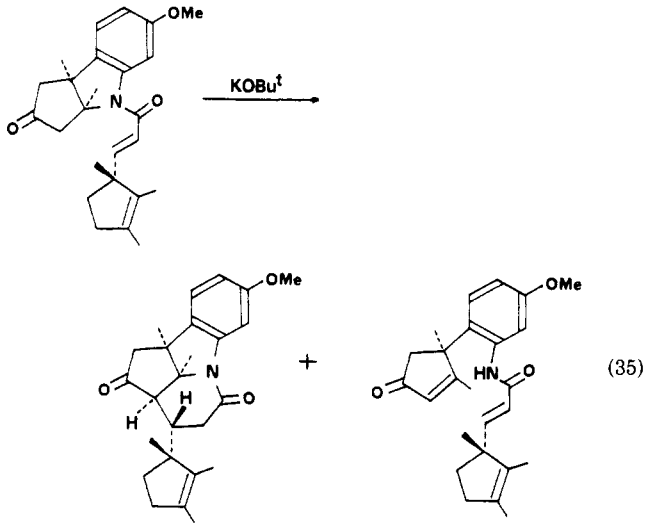
V. Mechanistic Evaluation

The "mechanistic evaluation" centers on the competitions between the different mechanisms available for *one* nucleophilic site. The competitions involving the reaction pathways for different nucleophilic sites are considered in the next section. Rules governing the competitions have been established empirically from literature data. In general, the philosophy is to err on the lenient side, allowing improbable products to form in some cases, rather than to be too strict and miss a legitimate possibility. The rules currently applied for the mechanistic evaluations are summarized in the following.

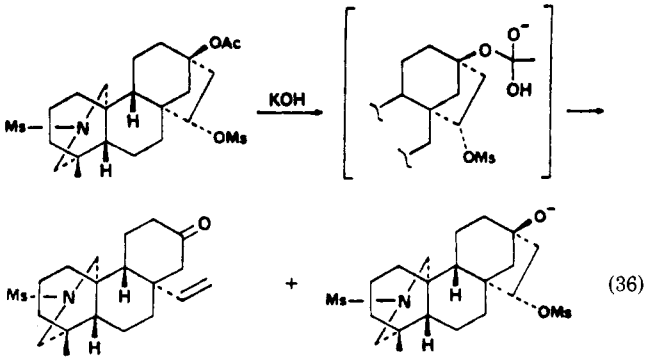
A. E1cb vs. Other Mechanisms. The program considers 1,2-E1cb reactions first since particularly high reaction rates are observed for simple E1cb reactions involving good leaving groups.[57] Consequently, this mechanism can preclude the consideration of other mechanistic types for a given nucleophilic site. A good leaving group is deemed to be one with a ranking that is more than 10 units below the pK_a of the conjugate acid of the base. For

(46) Mazur, Y.; Nussim, M. *J. Am. Chem. Soc.* **1961**, *83*, 3911.
(47) Lemieux, R. U.; Wolfrom, M. L. *Adv. Carbohydr. Chem.* **1948**, *3*, 372.
(48) Plentl, A. A.; Bogert, M. T. *J. Org. Chem.* **1941**, *6*, 669.
(49) Wallis, E. S.; Lane, J. F. *Org. React. (N.Y.)* **1946**, *3*, 267.
(50) Fritsch, P. *Justus Liebigs Ann. Chem.* **1894**, *279*, 319. Buttenberg, W. P. *Justus Liebigs Ann. Chem.* **1894**, *279*, 327. Wiechell, H. *Justus Liebigs Ann. Chem.* **1894**, *279*, 337.
(51) Smith, P. A. S. *Org. React. (N.Y.)* **1948**, *3*, 337.
(52) Yale, H. L. *Chem. Rev.* **1943**, *33*, 209.
(53) O'Brien, C. *Chem. Rev.* **1964**, *64*, 81.
(54) Lwowsky, *Nitrene*; Interscience Publishers: New York, 1970; pp 217–221. Curtin, D. W.; Flyn, E. W.; Nystrom, R. F. *J. Am. Chem. Soc.* **1958**, *80*, 4599.
(55) Neber, P. W.; Burgard, A.; Thier, W. *Liebigs Ann. Chem.* **1936**, *526*, 277.
(56) Brown, H. C. *Organic Synthesis Via Boranes*; Wiley Interscience: New York, 1975; p 8.
(57) Biale, G.; Cook, D.; Lloyd, D. J.; Parker, A. J.; Stevens, I. D. R.; Takahishi, J.; Winstein, S. *J. Am. Chem. Soc.* **1971**, *93*, 4737.

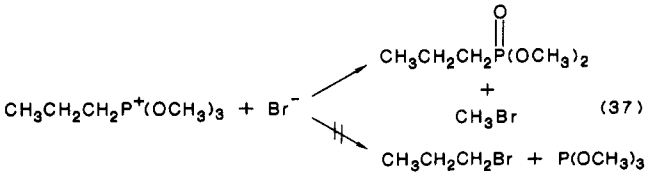
example, Ad_N/S_N2 to form an epoxide is not considered competitive with the Ad_N/E1cb process in the first step in eq 32. 1,2-E1cb reactions that do not involve sufficiently good leaving groups are considered competitive with other mechanisms. This is exemplified in eq 35[58] where the pK_a



of the ketone is 25 and the rankings of the E1cb leaving group and of the addition site are 19 and 27, respectively. As a result, both the 1,2-E1cb and the observed addition products are formed and displayed. Furthermore, if a 1,2-E1cb reaction is found to be part of a longer path fragmentation involving a better leaving group, both processes are allowed to occur. This feature is especially attractive because it allows the more complex process to be seen immediately without resubmission of the 1,2-E1cb product to the program (e.g., eq 36[59]). Since it is not always clear a priori that the longer path yields the best product, both processes are displayed.

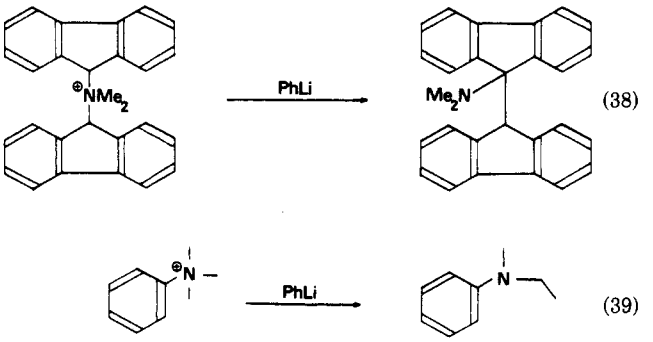


B. S_N2 vs. S_N2. The competition between reactions of one nucleophilic site at different substitution sites is handled by the ranking of the leaving groups, cf. Table I. Only the best substitution site and any others within a 4 "pK_a" unit window are considered by the program. This prevents the formation of some improbable products (e.g., eq 37[60]).



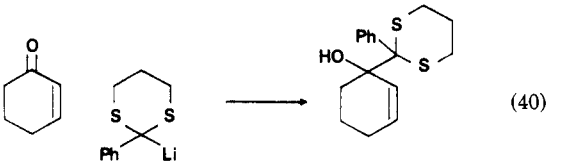
(58) Woodward, R. B. *Pure Appl. Chem.* **1968**, *17*, 519.
(59) Nagata, W.; Sugasawa, T.; Narisada, M.; Wakabagashi, Y.; Hayose, Y. *J. Am. Chem. Soc.* **1967**, *89*, 1483.

The Stevens, Wittig, and related rearrangements occur with the same structural modifications as substitution reactions. Hence, they are treated in CAMEO as a special class of S_N2 reactions. The general migratory aptitude for these rearrangements is as follows: benzyl and allyl > alkyl > aryl. This hierarchy is reflected below in eq 38[61] and 39.[62]

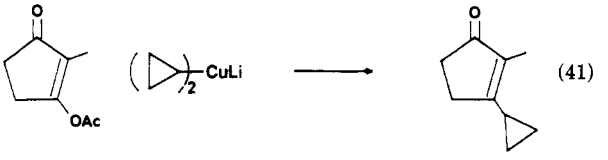


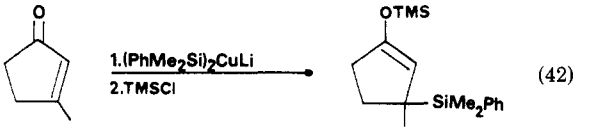
C. Ad_N vs. Ad_N. The competition between reactions of one nucleophilic site at different addition sites is also handled by the ranking of the electrophilic sites. Only the best addition site and any others within a 6 "pK_a" unit window are considered by the program. In addition to this general screening, rules have been developed to handle the competition between 1,2- and 1,4-addition. The rules presented next represent general tendencies that can, of course, be overcome by pronounced steric effects.

(1) Organolithium bases prefer 1,2- over 1,4-addition (e.g., eq 40[63]).

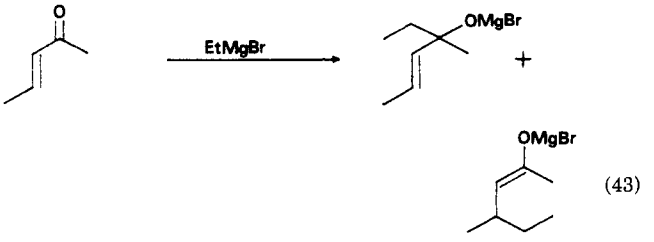


(2) Organocuprates and metallo silanes prefer 1,4- over 1,2-addition (e.g., eq 41[64] and 42[26]).



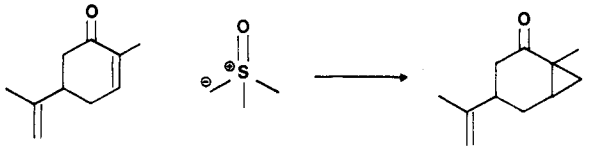


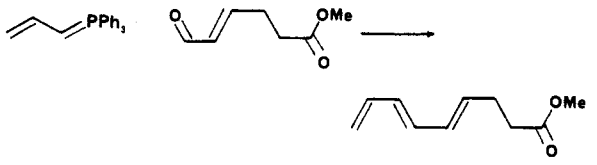
(3) Organomagnesium bases typically undergo both 1,2- and 1,4-addition (e.g., eq 43[65]).



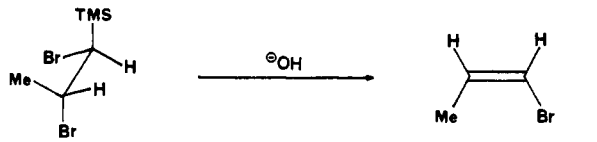
(60) Arbusow, B. A. *Pure Appl. Chem.* **1964**, *9*, 307.
(61) Wittig, G.; Tenhaeff, H.; Schoch, W.; Koenig, G. *Liebigs Ann. Chem.* **1951**, *572*, 1.
(62) Wittig, G.; Mangold, R.; Felletschin, G. *Liebigs Ann. Chem.* **1948**, *560*, 117.
(63) Ostrowsky, P. C.; Kane, V. V. *Tetrahedron Lett.* **1977**, 3549.
(64) Marino, J. P.; Browne, L. J. *J. Org. Chem.* **1976**, *41*, 3629.

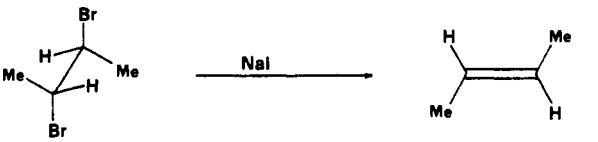
(4) Stabilized ylides prefer 1,4- over 1,2-addition to α,β-unsaturated ketones and esters (e.g., eq 44[66]) while they prefer 1,2- over 1,4-addition to α,β-unsaturated aldehydes (e.g., eq 45[67]). An ylide is deemed stabilized in CAMEO if the pK_a of its conjugate acid is less than or equal to 18. Nonstabilized ylides, in contrast, prefer 1,2- over 1,4-addition to α,β-unsaturated aldehydes and ketones.

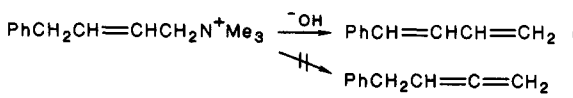

(44)


(45)

D. E2 vs. E2. The most general rule pertaining to the competition between different possible E2 reactions at one electrophilic site is that antiperiplanar elimination is faster than syn periplanar elimination. Hence, syn periplanar eliminations are only considered if the electrophilic site cannot adopt an antiperiplanar geometry. The reactivity order for different possible E2 reactions at one electrophilic site is Si–X or X–Y elimination > H–X elimination > E2 involving cumulene formation, where X and Y can be activated oxygen (e.g., OTs) or halogen other than fluorine. This reactivity order is exemplified in eq 46,[68] 47,[69] and 48.[70]

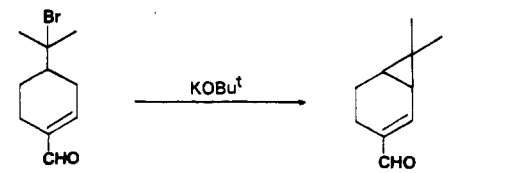

(46)


(47)


(48)

E. S_N2 vs. E2. The rules delineating the competition between S_N2 and E2 at one electrophilic site are presented below.

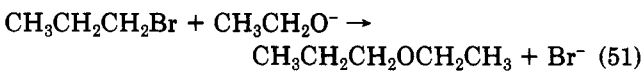
(1) Intramolecular S_N2 is always deemed a viable process regardless of the steric environment of the electrophilic site. Additionally, the program considers S_N2 to be a faster process than E2 for intramolecular reactions (e.g., eq 49[71]).


(49)

(2) S_N2 is not competitive with E2 if the base is nonnucleophilic, NQV = 1 or 2 (e.g., eq 50[57]).

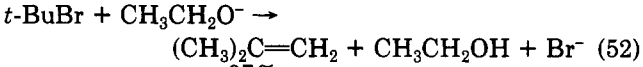

(50)

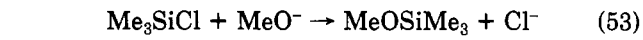
(3) E2 is not competitive with S_N2 for a nucleophilic base, NQV = 3 or 4, at unhindered electrophilic sites (e.g., eq 51[72]), or for a weak, nucleophilic base, NQV = 3, at


(51)

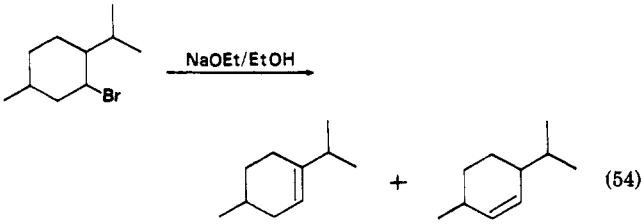
slightly hindered electrophilic sites. The term unhindered is reserved for primary electrophilic sites that do not bear a tertiary β-carbon, whereas slightly hindered refers to primary electrophilic sites that do bear a tertiary β-carbon and to secondary electrophilic sites. Note that elimination is important at primary electrophilic sites that have a tertiary β-carbon when a strong base is used. For instance, reaction of 1-bromo-2-methylpropane with $NaOC_2H_5$ gives 60% elimination at room temperature.[57] Additionally, considerations are made for activated E2 reactions with nucleophilic bases, NQV = 3 or 4, at primary and secondary electrophilic sites. For primary electrophilic sites, S_N2 is not competitive with E2 if the pK_a for loss of the hydrogen β to the electrophilic atom is less than or equal to 30, whereas S_N2 is deemed competitive with E2 if the pK_a is greater than 30 and less than or equal to 45. For secondary electrophilic sites, S_N2 is not competitive with E2 if the pK_a for loss of the β hydrogen is less than or equal to 45, whereas S_N2 is deemed competitive if the pK_a of that site is greater than 45.

(4) S_N2 is not competitive with E2 at hindered, electrophilic first-row atoms (e.g., eq 52[72]) but is considered for hindered electrophilic atoms not in row 1 (e.g., eq 53[39]).


(52)


(53)

(5) As mentioned earlier, on a structural basis nonring-opening S_N2 reactions are not allowed for three- or four-membered rings. Additionally, S_N2 is not competitive with E2 for attack on five- or six-membered rings when a strong base is used as in eq 54.[73a] However, for weaker, nucleophilic bases (NQV = 3), both S_N2 and E2 are observed, e.g., in the reaction of cyclohexyl bromide with sodium thiophenoxide.[73b]


(54)

F. Addition–Elimination vs. E2. Addition–elimination may be competitive with E2 at the same electrophilic site. Rules have been established to address this competition taking into account the nature of the nucleophilic and electrophilic sites.

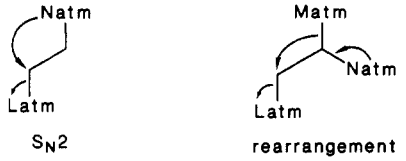
(65) Stevens, P. J. *J. Am. Chem. Soc.* **1935**, *57*, 1112.
(66) Corey, E. J.; Chaykovsky, M. *J. Am. Chem. Soc.* **1965**, *87*, 1353.
(67) Corey, E. J.; Snider, B. B. *J. Am. Chem. Soc.* **1972**, *94*, 2549.
(68) Jarvic, A. W. P.; Holt, A.; Thompson, J. *J. Chem. Soc. B* **1969**, 852.
(69) Winstein, S.; Pressman, D.; Young, W. G. *J. Am. Chem. Soc.* **1939**, *61*, 1645.
(70) Babayan, A. T.; Indzhikyan, M. G.; Minasyan, R. B. *J. Gen. Chem. USSR* **1963**, *33*, 1720.
(71) Buchi, G.; Hofheinz, W.; Paukstelis, J. V. *J. Am. Chem. Soc.* **1966**, *88*, 4113.
(72) Dhar, M. L.; Hughes, E. D.; Ingold, C. K.; Masterman, S. *J. Chem. Soc.* **1948**, 2055.
(73) (a) Hughes, Z. D.; Ingold, C. K.; Rose, J. B. *J. Chem. Soc.* **1953**, 3839. (b) McLellan, D. J. *J. Chem. Soc. B* **1966**, 705. Cook, D.; Parker, A. J.; Ruane, M. *Tetrahedron Lett.* **1968**, 5715.

(1) E2 is preferred over addition–elimination for strong, nonnucleophilic bases, NQV = 1 or 2 (e.g., LDA and *t*-BuOK).

(2) For strong, nucleophilic bases, NQV = 4 (e.g., EtO^-), the reactivity order is trans elimination > addition–elimination > elimination forming a cumulene > cis elimination, as in Scheme I.[74]

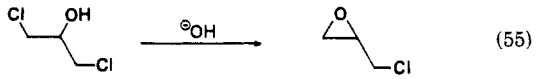
(3) For weak, nucleophilic bases, NQV = 3 (e.g., PhS^-), the reactivity order is addition–elimination > trans elimination > elimination forming a cumulene > cis elimination, as again reflected in Scheme I.[74]

G. S_N2 vs. Benzil–Benzilic. Substitution to form a three-membered ring and the benzil–benzilic rearrangement may both be structurally applicable for the same nucleophilic atom as shown below. Both processes are



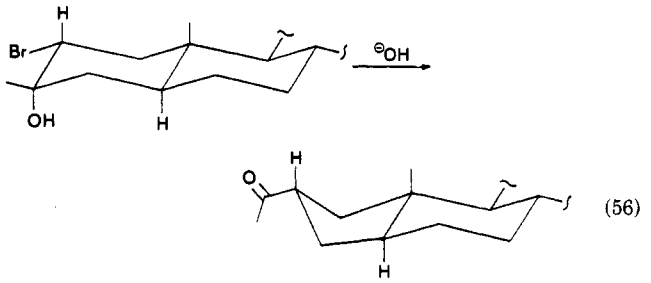
stereospecific. Hence, the geometry ultimately determines the product outcome. The S_N2 process is favored for systems that can adopt an antiperiplanar relationship between the nucleophilic atom and the leaving atom whereas the benzil–benzilic rearrangement is favored when this is not the case. The rules that have been developed to treat this competition are as follows.

(1) The benzil–benzilic rearrangement is not competitive with S_N2 for acyclic systems (e.g., eq 55[75]).



(55)

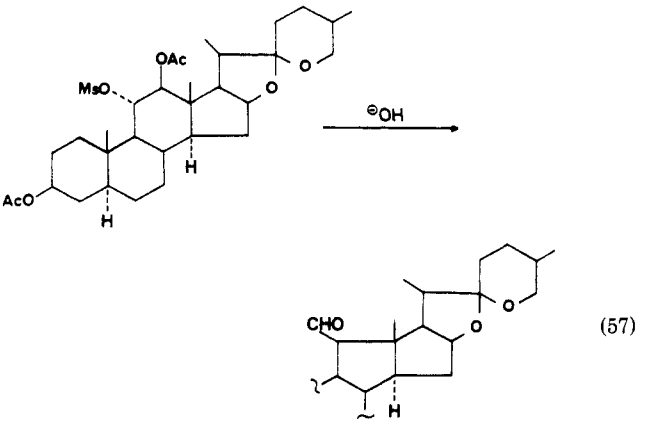
(2) S_N2 is not competitive with the benzil–benzilic rearrangement for cyclic systems in which the nucleophilic atom and leaving atom have a cis relationship. This is illustrated in eq 56.[76]



(56)

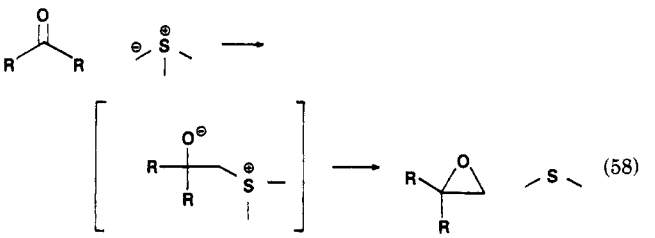
(3) The benzil–benzilic rearrangement is not competitive with S_N2 for simple cyclic systems in which the nucleophilic atom and the leaving atom have a trans relationship, as in formation of fused epoxides (e.g., eq 23[36]). It is assumed that the antiperiplanar orientation can be accessed through conformational equilibration. Exceptions are made for constrained ring systems that do not afford conformational equilibration to the proper geometry. This is demonstrated in the rigid steroid ring system shown in eq 57.[77]

(4) The benzil–benzilic rearrangement is not competitive with S_N2 following an addition when the nucleophilic atom in the addition step bears the leaving atom (e.g., eq 58[78]).



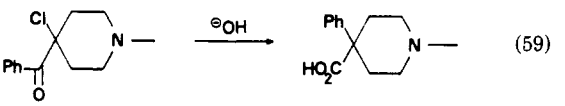
(57)

This is a kinetic phenomenon and suggests that the geometry of the addition intermediate directs the S_N2.



(58)

(5) The benzil–benzilic rearrangement is generally preferred over S_N2 following an addition when the nucleophilic atom in the addition step does not bear the leaving atom (e.g., eq 57[79]). Consequently, in this case both products are output, although the S_N2 product is indicated to be a minor product.



(59)

H. 1,2-Ene vs. 1,2-Ene. The general migratory aptitude for 1,2-ene rearrangements is as follows: carbon in a simple double bond > aryl carbon > alkyl carbon. This has been illustrated for the Stieglitz and Neber rearrangements shown in eq 29[45] and 33,[55] respectively.

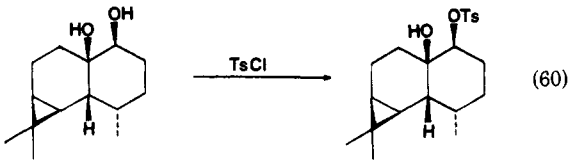
VI. Pathway Evaluation

The ranking of reaction pathways for different nucleophilic sites is a difficult problem due to the great number of factors that can affect the competitions. Therefore, any systematic evaluation must be carefully applied so as not to reject a valid reaction pathway. The rules governing competition between mechanisms issued for different nucleophilic sites can be broken down into two classes. The first class consists of the exclusive rules. These rules are fatal to the product, i.e., if one of these rules is violated, that pathway is rejected and the product is not shown. The second class consists of informative rules. These rules typically do not prevent the product from being shown except in special cases. A violation of an informative rule results in the transmission of a message that accompanies the product and indicates its relative likelihood in comparison to competing products. These rules, both exclusive and informative, are empirical and are not part of an absolute reactivity scale. Rather, they generally deal with competitions between defined reaction pathways, e.g., C- vs. O-alkylation.

(74) Theron, F. *Bull. Soc. Chim. Fr.* **1969**, 278.
(75) Clarke, H. T.; Hartman, W. W. *Org. Synth.* **1921**, *1*, 233.
(76) Mousseron, M.; Winternitz, F.; Craste de Paulet, A. *Comp. Rend.* **1958**, *246*, 2200. Mousseron, M.; Winternitz, F.; Caste de Paulet, A. *Bull. Soc. Chim. Fr.* **1960**, 1460.
(77) Anliker, R.; Rohr, O.; Heusser, H. *Helv. Chim. Acta* **1955**, *38*, 1171; **1956**, *39*, 1494.
(78) Bessiere-Chretien, Y.; El Gaied, M. M.; Meklati, B. *Bull. Soc. Chim. Fr.* **1972**, 1000.
(79) Smissman, E. E.; Hite, G. *J. Am. Chem. Soc.* **1959**, *81*, 1201.

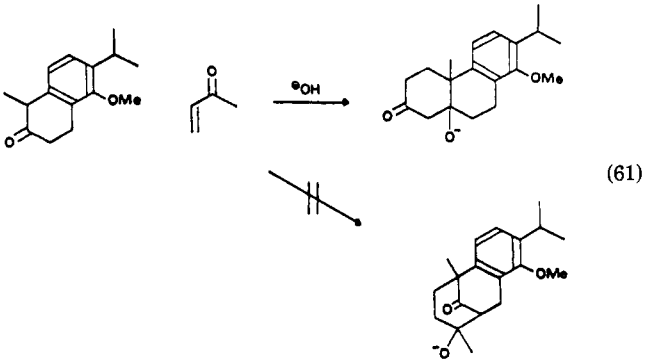
A. Exclusive Pathway Rules. The exclusive pathway rules are presented below.

(1) Good nucleophiles, NQV = 3 or 4, will react significantly faster than poor nucleophiles, NQV = 1 or 2. Thus, substitution products from reactions with nonnucleophilic bases are not considered competitive with substitution products from reactions with nucleophilic bases (e.g., in eq 60,[72] reaction with the more hindered alcohol is disfavored).



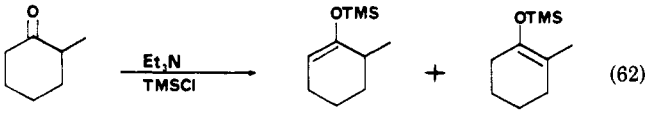
(60)

(2) Formation of a bridged ring is not competitive with formation of a fused ring for rings of size less than eight, except when the fusion bond is formed in violation of Baldwin's rules. Hence, only formation of the fused ring is allowed in the Robinson annulation that is shown in eq 61.[80]



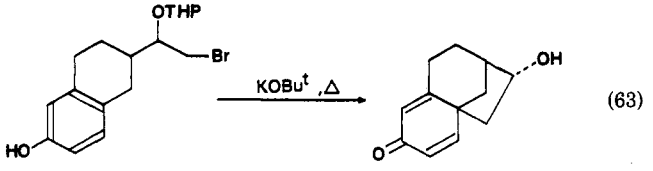
(61)

(3) The general order for substitution at electrophilic silicon for nucleophilic oxygen, nitrogen, and carbon is as follows: O > N > C. This is demonstrated in eq 62.[81]



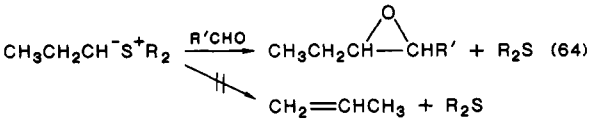
(62)

(4) Tautomeric forms of phenoxides typically do not undergo intermolecular reactions and are therefore only allowed to react via an intramolecular pathway (e.g., eq 63[82]).



(63)

(5) 1,2-Ene rearrangements are not competitive with faster ionic processes. For example, elimination of sulfur ylides is not competitive with addition (e.g., eq 64[83]).

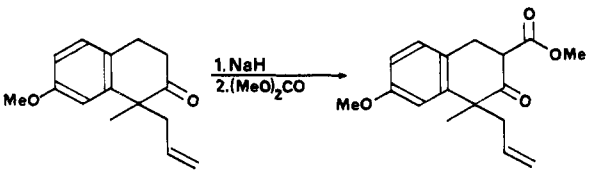


(64)

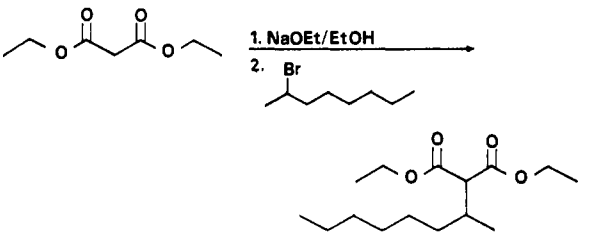
(6) 3-*Endo-Tet* reactions, e.g., Stevens and Wittig rearrangements, involving migration of alkyl or aryl groups are not competitive with faster ionic processes. For example, in eq 58[78] the program recognizes the possibility that the sulfur ylide might rearrange to form ethyl methyl sulfide. This pathway is rejected because it is not considered competitive with the Ad_N/S_N2 process to form the epoxide.

B. Informative Pathway Rules. The informative pathway rules are presented below.

(1) Enolate anions can react at carbon or oxygen. Generally, reaction at carbon is preferred over reaction at oxygen for unstabilized enolates (e.g., eq 65,[84] or if the reaction is run in a protic solvent, e.g., eq 66[85]). An enolate is deemed unstabilized if the pK_a of its conjugate acid is 24 or above.

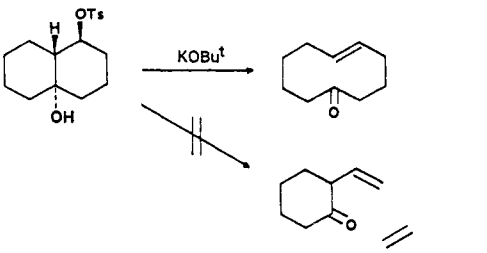


(65)



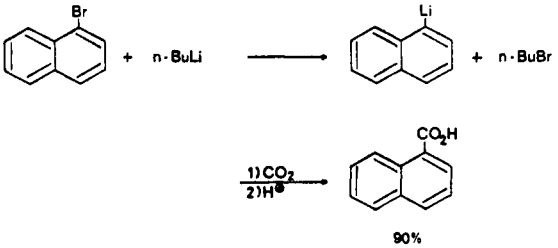
(66)

(2) All things being equal, E1cb fragmentations occur in the order 1,2-E1cb > 1,4-E1cb ≫ 1,6-E1cb (e.g., eq 67[24]). 1,6-E1cb fragmentations are typically so slow that they are not shown if any faster process such as 1,4-E1cb or S_N2 is found.



(67)

(3) Wurtz coupling with strongly basic organomagnesium and organolithium reagents, pK_a > 35, is slower than faster ionic processes such as addition, e.g., eq 68.[86]

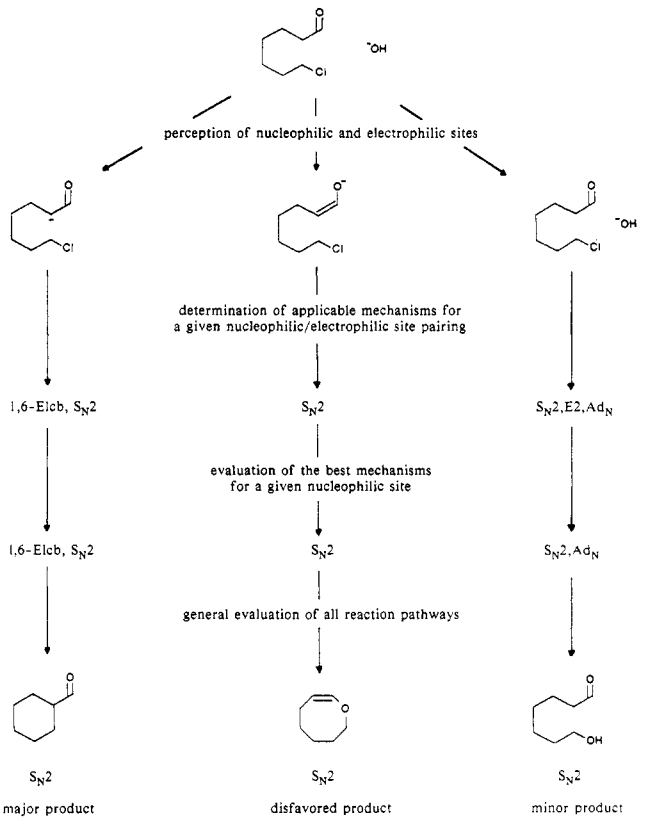


(68)

(4) The factors affecting ring formation are both kinetic and thermodynamic. In general, five-, six-, and seven-membered rings are comparatively easy to make, while

(80) Sher, F. T.; Berchtold, G. A. *J. Org. Chem.* **1977**, *42*, 2569.
(81) Stork, G.; Hudrlik, P. F. *J. Am. Chem. Soc.* **1968**, *90*, 4462.
(82) Masamune, S. *J. Am. Chem. Soc.* **1964**, *86*, 288.
(83) Trost, B. M.; Melvin, L. S., Jr. *Sulfur Ylides*; Academic Press: New York, 1975.
(84) Palmer, D. C.; Strauss, M. J. *Chem. Rev.* **1977**, *77*, 1.
(85) LeGoff, E.; Ulrich, S. E.; Denney, D. B. *J. Am. Chem. Soc.* **1958**, *80*, 662.
(86) Gilman, H.; Brannen, C. G.; Ingham, R. K. *J. Org. Chem.* **1957**, *22*, 685.

Scheme II. A CAMEO Analysis of the Treatment of 7-Chloroheptanal with Base



three-membered rings are easy to make but often break down again under the conditions of their formation.[87a] However, four-membered rings are typically difficult to synthesize via intramolecular nucleophilic pathways and alternate routes such as pericyclic reactions are preferred.[87b] Formation of larger rings by intramolecular reactions is also hindered by entropy effects that become pronounced above size 8. These considerations are reflected in CAMEO by designating the products of intramolecular nucleophilic processes as "minor" if an eight-membered ring is formed and "disfavored" if a ring of size 4 or greater than 8 is produced.

(5) Products arising from slow proton-transfer intermediates are generally disfavored vs. products from organometallic addition or halide–alkyllithium exchange intermediates. This is because the intermediates of organometallic addition or halide–alkyllithium exchange are formed in a greater percentage than are the intermediates of proton transfer, e.g., eq 2.[13]

(6) Due to the entropic factor, intramolecular processes are generally faster than intermolecular processes. This is the most general pathway rule and is applied after all the other rules have been considered. Equation 55[75] provides an example; epoxide formation via an intramolecular route is favored over intermolecular substitution with hydroxide.

VII. Sample Sequences

The previous sections have outlined the organization and rules used by the nucleophilic module in CAMEO. In this section, three schemes are discussed in detail, illustrating the program flow and application of rules.

Scheme II is a simple example that illustrates most of the major aspects of the program. Recalling Figure 1, nucleophilic sites are perceived first. The aldehyde is determined to activate the most acidic site in the starting materials. Hence, a proton-transfer prestep is performed generating the C-enolate and O-enolate resonance forms. The predicted pK_a's in Me_2SO for the aldehyde and hydroxide ion are 27 and 30, respectively. Since the hydroxide ion is within a 4 pK_a unit window of the aldehyde, it is also stored as a nucleophilic site. Electrophilic sites are then perceived for each intermediate structure. Each electrophilic site is paired with its corresponding nucleophilic site and the applicable mechanisms for that pairing are determined. The hydroxide ion, for example, is recognized to be able to participate in S_N2, E2, and Ad_N processes. In the mechanistic evaluation phase, however, the E2 process is rejected since E2 is not competitive with S_N2 for nucleophilic bases at unhindered electrophilic sites (rule V.E.3.). No other mechanisms are rejected during this evaluation phase for the other nucleophilic sites. After all nucleophilic and electrophilic sites are processed, all reaction pathways from all nucleophilic sites leading to products are evaluated. The C-enolate only yields the S_N2 product. The 1,6-Elcb reaction pathway is rejected by rule VI.B.2. Next, the hydroxide ion only yields the S_N2 product; the Ad_N product, a hydrate, is recognized as unstable and is broken down to starting materials in postmechanistic perception. The S_N2 product issued for the hydroxide ion, however, is deemed a minor product with respect to the S_N2 product from the C-enolate since intramolecular pathways are considered faster than intermolecular pathways (rule VI.B.6). Finally, the S_N2 product from the O-enolate is deemed disfavored with respect to the S_N2 product from the C-enolate since unstabilized enolates generally alkylate on carbon rather than on oxygen (rule VI.B.1).

Scheme III is a CAMEO analysis of two synthetic steps used in Wordward's synthesis of vitamin B_{12}.[58] The first step is a neutral nucleophilic reaction and is clear cut. The ranking of reactive sites yields the amine nitrogen and the acid chloride as by far the most reactive nucleophilic and electrophilic sites. Thus the only reaction pathway predicted by CAMEO is the Ad_N/Elcb which gives the amide, as observed.[58]

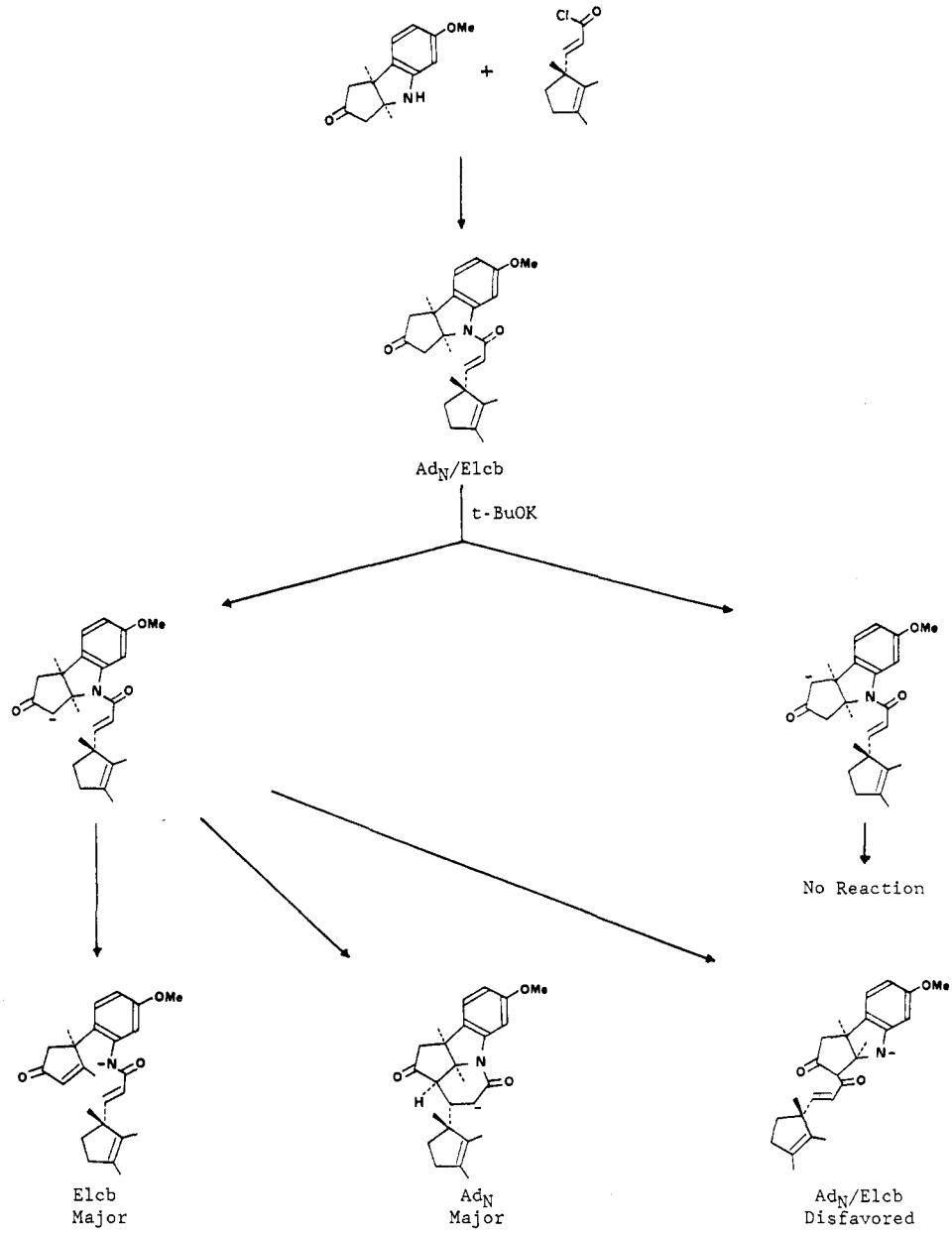
In the second step, the amide is treated with *t*-BuOK. A proton-transfer prestep is performed at both sites activated by the ketone to generate four intermediate structures, the two enolates shown in Scheme III and their resonance structures with the negative charge on oxygen. The only favorable reaction pathways predicted by the program are Elcb to give the stabilized amide and Ad_N to give the reported Michael product. The Ad_N/Elcb pathway is disfavored since it involves creation of a four-membered ring in forming the addition intermediate (rule VI.B.4). The three remaining intermediate structures generated by the proton transfer are not predicted to yield any products since they can only form strained rings that bear a bridge and/or a trans double bond (rules VI.A.2 and IV.B, respectively). The results predicted by CAMEO are quite reasonable. Although Woodward did not report any problems with the Elcb pathway, this pathway has literature precedent and cannot be ruled out a priori.

Scheme IV summarizes the analysis of a synthetic step used in a recent preparation of morphine.[88] The nucleophilic sites are determined according to the hierarchy for mechanistic presteps given in section III.A. The first

(87) (a) Carey, F. A.; Sundberg, R. J. *Advanced Organic Chemistry, Part A: Structure and Mechanisms*; Plenum Press: New York, 1984; p 147. (b) Roberts, J. D.; Sharts, C. M. *Org. React. (N.Y.)* **1962**, *12*, 1.

(88) Toth, J. E.; Fuchs, P. L., submitted for publication.

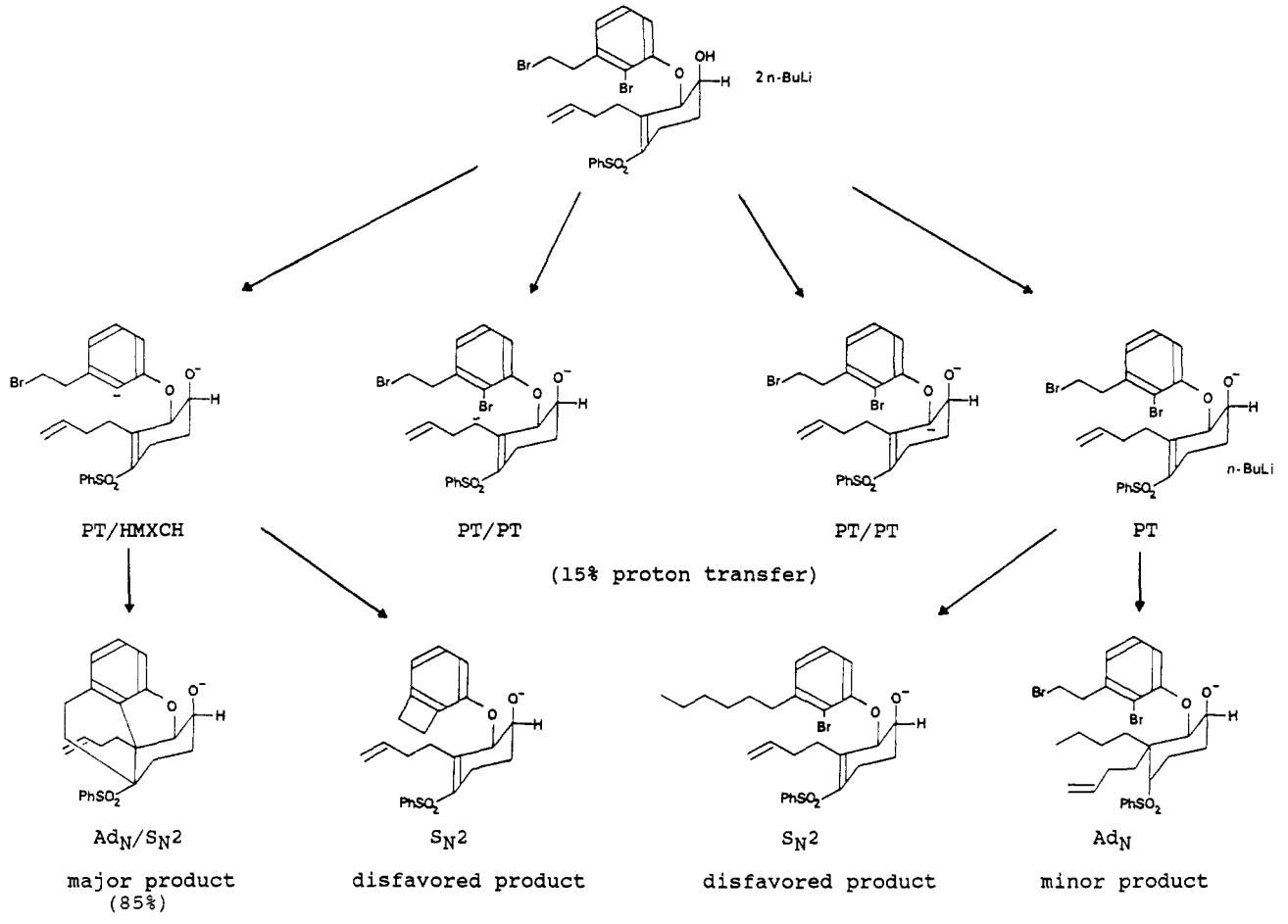
Scheme III. A CAMEO Analysis of a Synthetic Step Used in the Synthesis of Vitamin B_{12}



equivalent of base is spent in a fast proton transfer to yield the alkoxide. Since there are no other fast proton-transfer sites, the next most reactive class of mechanistic presteps is considered for the second equivalent of *n*-BuLi. Possibilities for halide–alkyllithium exchange and organometallic addition are both perceived. As a result, the halide–alkyllithium exchange is performed and the aryl anion is stored as a nucleophilic site, which can be designated PT/HMXCH. Since organometallic addition is not performed at this time, the second equivalent of *n*-BuLi is also stored as a nucleophilic site, PT, for later consideration in addition processes. Finally, two slow proton-transfer sites with pK_a's below 30 are stored as nucleophilic sites PT/PT and PT/PT, since the program deems such processes to be competitive with organometallic addition. It should be noted that their other resonance forms with the negative charge next to sulfur are also stored as nucleophilic sites but are not shown in this scheme.

The electrophilic sites for each intermediate structure are then perceived and the applicable mechanisms for each nucleophilic/electrophilic site pairing are determined. The possibilities for PT/HMXCH are S_N2 and Ad_N. The 1,2-Elcb elimination of the oxygen β to the aryl anionic site is rejected because the nucleophilic site ranking is not more than 25 units above the electrophilic site ranking (section IV.A.1). The two intermediates designated PT/PT and their resonance forms do not have any valid mechanisms for evaluation since addition–elimination on the aryl bromide is ruled out due to inadequate activation of the aromatic ring,[4] and since S_N2 on the alkyl bromide would create a bridged aromatic ring of size less than 10 (section IV.B.). Hence, the PT/PT intermediates are not subjected to any further evaluation. The applicable mechanisms for PT are Ad_N and S_N2. Once again, addition–elimination on the aromatic ring is not considered due to inadequate activation. During mechanistic evaluation for the individual nucleophilic sites, no additional mechanisms are rejected. Since PT/HMXCH and PT have undergone an addition reaction, their addition intermediates are resubmitted and allowed to react in a subsequent intramolecular substitution or Elcb process. The only valid mechanism for the PT/HMXCH addition intermediate is S_N2, whereas no valid substitution or Elcb processes are found for the PT addition intermediate since

Scheme IV. A CAMEO Analysis of a Synthetic Step Used in a Recent Synthesis of Morphine; PT and HMXCH Refer to Proton Transfer and Halogen-Metal Exchange, Respectively. The Percentages Shown in Parentheses Are Experimental Yields



substitution at the alkyl bromide would again result in a bridged aromatic ring of size less than 10. Note that the PT/HMXCH addition intermediate is also output by CAMEO but is not shown in this scheme. Now that all nucleophilic and electrophilic sites have been processed, a general evaluation of all reaction pathways is performed. The two S_N2 products issued for PT/HMXCH and PT are deemed disfavored since Wurtz coupling with strongly basic organolithium reagents is slower than faster ionic processes such as addition (rule VI.B.3). The Ad_N product from PT is deemed a minor product with respect to the Ad_N/S_N2 product from PT/HMXCH since intermolecular pathways are considered slower than intramolecular pathways (rule VI.B.6). The Ad_N/S_N2 pathway does not violate any rules and is therefore output to the graphics terminal as the major product. This analysis is in close agreement with observed experimental results.[88]

VIII. Conclusion

A general model for the treatment of nucleophilic chemistry has been presented. The efficiency of the model can be gauged by considering two opposing criteria; first, is the model able to predict the major products of a reaction, i.e., any products that are formed in over ca. 5% yield, and second, is the model able to screen out unlikely products, i.e., those that are formed in less than ca. 5% yield. A model that only satisfies the first criterion is easily realized by simply forming all products that satisfy the basic structural requirements for all mechanisms. The major products would undoubtedly be in the set of proposed products, but since the model would be totally unselective, it would not have practical value. Consequently, both criteria have been considered in the development of the model used in CAMEO. Numerous rules governing organic reactivity have been identified to provide the needed selectivity. However, due to the vast scope of nucleophilic chemistry, it has proved difficult to satisfy both criteria in all cases. As a result, some of the rules presented may favor one criterion over the other. However, this situation can be steadily improved as more literature data become available on competing reactions. As has been demonstrated, the present model provides a viable means of evaluating the feasibility of synthetic routes and can help identify side products of reactions.

Acknowledgment. Gratitude is expressed to the National Science Foundation for support of this work and to Procter and Gamble, Inc. and Rhone-Poulenc for fellowships awarded to A.G. and P.M., respectively.