Computer-Assisted Mechanistic Evaluation of Organic Reactions. 9. Reactions of Unsaturated Electrophiles Including Nucleophilic Aromatic Substitution

Catherine E. Peishoff and William L. Jorgensen*

Department of Chemistry, Purdue University, West Lafayette, Indiana 47907

Received September 10, 1984

The use of mechanistic reasoning to predict the products of organic reactions is the key feature of CAMEO, an interactive computer program. The program has been expanded to include nucleophilic reactions of singly bonded leaving groups attached to multiply bonded electrophiles, particularly nucleophilic aromatic substitution. This required refinements to electrophile perception as well as additions to the mechanistic reasoning; in particular, the importance of substituent effects in gauging electrophilicity is addressed. The paper begins with a review of the chemistry of aromatic and vinylic functional groups in which mechanisms, leaving groups, and substituent effects are discussed. The incorporation of these reactions into the existing module for base-catalyzed and nucleophilic processes is then presented along with general rules regarding competitions. Finally, sample reaction sequences predicted by CAMEO which illustrate these considerations are provided.

I. Introduction

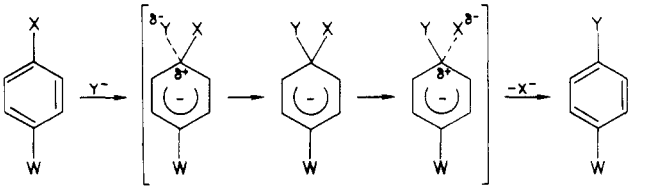
CAMEO, an interactive computer program, is being developed to predict the products of organic reactions given starting materials and conditions. Two key features are that it operates in the synthetic (forward) direction and that the predictions are not data driven but, rather, are made on the basis of mechanistic reasoning. Currently, the program contains modules for base-catalyzed and nucleophilic chemistry[1] including organometallic[2] and organosilicon[3] chemistry, acid-catalyzed and electrophilic reactions,[4] electrophilic aromatic substitution,[5] and thermal pericyclic processes including cycloadditions and sigmatropic and electrocyclic rearrangements.[6,7]

It is necessary in a project of this nature to not only increase the scope but also the sophistication of the predictions. Thus, with the groundwork for the base-catalyzed and nucleophilic module established,[1] refinements to the mechanistic reasoning have considered the effects of organometallic counter-ions,[2] ylide reactivity,[2] and the special reactivity of organosilicon compounds.[3] A more fundamental concept in the nucleophilic module which needs to be refined is electrophile perception. *Electrophiles are recognized in* CAMEO *as atoms* in an X—Y, X=Y, or X≡Y bond, where X and Y are carbon or heteroatoms and X can equal Y. As this definition covers a wide variety of functional groups (e.g., alkyl halides, esters, peroxides), a measure of the leaving group ability based on the effective pK_a of the leaving group (e.g., Y^-, $X—Y^-$, $X=Y^-$) is used to ascertain electrophilicity.[1] At the outset, both the best singly and multiply bonded electrophiles were retained by the program for later consideration in S_N2 and E2 or addition reactions, respectively, as well as in E1 processes. Furthermore, S_N2 reactions were not allowed on multiply bonded electrophiles and only aliphatic E2 reactions were performed.[2] Clearly, these definitions require expansion particularly to include the reactivity of unsaturated electrophiles via multistep mechanisms. At this time, the enhancements to CAMEO that permit the nucleophilic reactions of singly bonded leaving groups attached to multiply bonded electrophiles such as aromatic substitution, vinylic substitution, and aryne formation are presented. To begin, the chemistry of aromatic and vinylic functional groups is reviewed, followed by a discussion of its implementation in the program. The expansion of both electrophile perception and electrophile processing is explained and sample sequences are provided which illustrate the scope of the enhancements to the program.

II. Nucleophilic Aromatic Substitution

A. Mechanisms. Nucleophilic aromatic substitution reactions were intensively studied during the 1950s and 1960s; several reviews were written summarizing the mechanistic possibilities and activation parameters.[8-13] Although formally similar to aliphatic nucleophilic substitutions, the differing reactivity patterns require that this area be considered separately. In general, aromatic substitution reactions proceed via three main mechanisms: S_N1, addition–elimination, and elimination–addition. More recently, metal-catalyzed[14] and radical reactions[15] have also been established, particularly with substrates that are less reactive in the first three mechanisms. In the context of nucleophilic chemistry in CAMEO, the addition–elimination and elimination–addition mechanisms are the focus of this section.

1. Substitution via the Addition–Elimination Mechanism. Substitution on aromatic electrophiles which occur without rearrangement have been postulated to proceed through an intermediate complex as outlined in eq 1. Evidence for these intermediates, known as Meis-



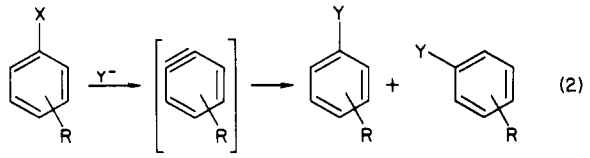
(1)

(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.
(3) Peishoff, C. E.; Jorgensen, W. L. *J. Org. Chem.* **1983**, *48*, 1970.
(4) McLaughlin, D. Ph.D. Thesis, 1983, Purdue University.
(5) Roos-Kozel, B. L. Ph.D. Thesis, 1981, Purdue University.
(6) Burnier, J. S.; Jorgensen, W. L. *J. Org. Chem.* **1983**, *48*, 3923.
(7) Burnier, J. S.; Jorgensen, W. L. *J. Org. Chem.* **1984**, *49*, 3001.
(8) Miller, J. "Reaction Mechanisms in Organic Chemistry. 8. Aromatic Nucleophilic Substitution"; Elsevier: London, 1968.
(9) Bunnett, J. F.; Zahler, R. E. *Chem. Rev.* **1951**, *49*, 273.
(10) Bunnett, J. F. *Q. Rev. Chem. Soc. (London)* **1958**, *12*, 1.
(11) Ross, S. D. In "Progress in Physical Organic Chemistry"; Cohen, S. G., Streitwieser, A., Taft, R. W., Eds.; Interscience: New York, 1963; Vol. 1, p 31 ff.
(12) Miller, J. *Rev. Pure Appl. Chem.* **1951**, *1*, 171.
(13) Jaffe, H. H. *Chem. Rev.* **1953**, *53*, 191.
(14) Millard, A. A.; Rathke, M. W. *J. Am. Chem. Soc.* **1977**, *99*, 4833. Tamas, K.; Sumitani, K.; Kumada, M. *J. Am. Chem. Soc.* **1972**, *94*, 4374. Bruggink, A.; McKillop, A. *Tetrahedron* **1975**, *31*, 2607.
(15) Kim, J. K.; Bunnett, J. F. *J. Am. Chem. Soc.* **1970**, *92*, 7463, 7464.

0022-3263/85/1950-1056$01.50/0

enheimer complexes, includes electrochemical[16] and spectral data[17] and, in some cases, the intermediate salt may be isolated.[18] There are several factors influencing the ability of an aromatic compound to react via this mechanism, the foremost among them being activation by electron-withdrawing substituents. However, leaving-group and nucleophile effects are also apparent. Because electronic influences are so important, this mechanism is also referred to as an activated aromatic substitution process. Kinetic studies of nucleophilic substitution via the addition–elimination mechanism[19] indicate generally consistent second-order kinetics for the reactions with anionic nucleophiles.[10] Reactions with neutral nucleophiles while typically also second order may be subject to acid, base, or autocatalysis as are the reactions of heteroaromatic substrates.[8] A recent review summarizes the kinetics and thermodynamics for the formation of Meisenheimer complexes.[20]

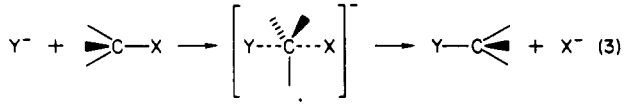
2. Substitution via the Elimination–Addition Mechanism. Aromatic compounds which are not readily susceptible to nucleophilic attack can in the presence of a strong base undergo a substitution reaction through an elimination–addition mechanism as outlined in eq 2. A



(2)

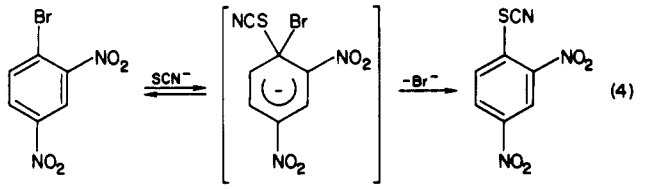
notable feature of this mechanism is the possibility of producing both the direct substitution product as well as a cine-substitution (substitution with rearrangement) product. Support for this mechanism includes labeling studies[21] and the unreactivity of compounds without hydrogen adjacent to the leaving group.[22] As with the addition–elimination mechanism, the overall reaction involving the aryne intermediate follows second-order kinetics. Evidence exists, however, to support both the E1cb and E2 mechanisms for formation of the aryne.[8]

B. Leaving Group and Nucleophile Effects. Comparison of the reaction paths for substitution at a saturated vs. an aromatic carbon atom illustrates the differing importance of leaving-group ability to these reactions. In the former, eq 3, attainment of the transition state involves



(3)

both nucleophile–electrophile bond formation and electrophile–leaving-group bond cleavage. Ease of bond breakage thus directly affects the rate of the reaction. In the activated aromatic reaction, eq 1, there are two transition states, the rate of one dependent on nucleophile–electrophile bond formation and of the other dependent on electrophile–leaving-group bond cleavage. Attainment of either transition state may be rate limiting, but the strength of the bond to the leaving group primarily affects only the second. An example of this is the reaction of thiocyanate with 2,4-dinitrofluorobenzene, eq 4, in which the first step is highly reversible.[24]



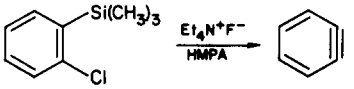
(4)

With the exception of halogen leaving groups, quantitative data on leaving-group ability for aromatic substitution is lacking. The qualitative order $F^- > NO_2^- > Cl^-$, $Br^-, I^- > N_3^- > OSO_2R^- > NR_3 > OAr^- > OR^- > SR^-, SAr^- > SO_2R^- > NR_2^-$ has been suggested,[10] however, there is evidence[23,24] that for a given atom the order should be $X^+ > X^+Y^- > X^0$, e.g., $NMe_3 > NO_2^- > NR_2^-$. A series of semiempirical theoretical calculations was performed[8] in order to study the potential energy surfaces for the reaction of anionic reagents with activated aromatic substrates. From this, it appears evident that leaving-group ability is connected to the nucleophilicity of the base and hence no single order of leaving-group abilities is universally valid. In general, however, the following series may be suggested.

$$NR_3, SR_2 > F^-, NO_2^- > Cl^-, Br^-, I^- > N_3^-, OSO_2R^- > OAr^-, OR^-, SAr^-, SR^-, SO_2R^- > NR_2^-$$

In contrast to the leaving-group comparison, the reactivity of nucleophiles toward saturated and aromatic electrophiles is quite similar. Both empirical and theoretical[8] evidence suggests that strong, hindered bases (e.g., Ph_3CK) will participate only in the elimination mechanism, while weaker, more nucleophilic bases (e.g., PhSK) participate only in the addition mechanism. Strong, nucleophilic bases such as sodium amide or *n*-butyllithium may participate in both processes. These trends are the normal pattern in CAMEO as applied to base-catalyzed aliphatic reactions.[1]

The choices for leaving group and nucleophile for the elimination–addition mechanism, in contrast to those of the addition–elimination mechanism, are quite limited. Chloride, bromide, and iodide leaving groups are typical; fluoride may also participate if the elimination mechanism is more E1cb than E2.[25] Strong bases such as sodium amide and lithium piperidide are common, but a notable exception is benzene formation from *o*-(trimethylsilyl)-chlorobenzene under mild conditions, eq 5.[26]



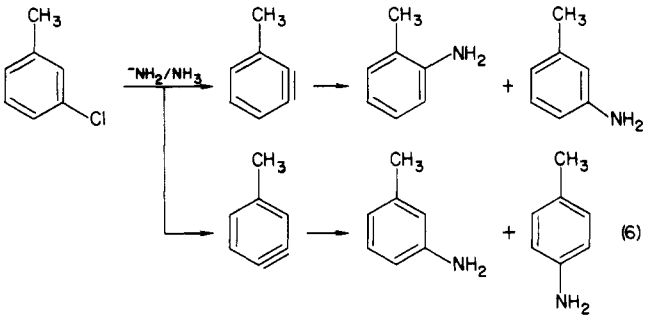
(5)

C. Substituent Effects. 1. Activated Aromatic Substrates. Reactivity in the addition–elimination mechanism is influenced primarily by electronic factors, i.e., the interaction of ring substituents with the developing negative charge. The Hammett equation was shown to be applicable to this type of aromatic substitution reaction.[27]

(16) Farr, J. D.; Bard, C. C.; Wheland, G. W. *J. Am. Chem. Soc.* **1949**, *71*, 2013.
(17) Foster, R.; Hammick, D. L. *J. Chem. Soc.* **1954**, 2153. Foster, R. *Nature (London)* **1955**, *176*, 746.
(18) Meisenheimer, J. *Liebigs Ann. Chem.* **1902**, *323*, 205.
(19) Strauss, M. J. *Chem. Rev.* **1970**, *70*, 667; *Acc. Chem. Res.* **1974**, *7*, 181. Bernasconi, C. F. *Acc. Chem. Res.* **1978**, *11*, 147. Crampton, M. R. *Adv. Phys. Org. Chem.* **1969**, *7*, 211.
(20) Terrier, F. *Chem. Rev.* **1982**, *82*, 77.
(21) (a) Roberts, J. D.; Simmons, H. E.; Carlsmith, L. A.; Vaughan, C. W. *J. Am. Chem. Soc.* **1953**, *75*, 3290. (b) Roberts, J. D.; Semenov, D. A.; Simmons, H. E.; Carlsmith, L. A. *J. Am. Chem. Soc.* **1956**, *78*, 601, 611. (c) Jenny, E. F.; Roberts, J. D. *Helv. Chim. Acta* **1955**, *38*, 1248.
(22) Benkeser, R. A.; Buting, W. E. *J. Am. Chem. Soc.* **1952**, *64*, 3011.
(23) Miller, J. *J. Am. Chem. Soc.* **1963**, *85*, 1628. Hill, D. L.; Ho, K. C.; Miller, J. *J. Chem. Soc. B* **1966**, 299. Ho, K. C.; Miller, J.; Wong, K. W. *J. Chem. Soc. B* **1966**, *310*.
(24) Miller, J.; Wong, K. W. *Aust. J. Chem.* **1965**, *18*, 117; *J. Chem. Soc.* **1965**, 5454. Bolto, B. A.; Miller, J. *Aust. J. Chem.* **1956**, *9*, 74, 304.
(25) Coe, P. L.; Stephens, R.; Tatlow, J. C. *J. Chem. Soc.* **1962**, 3227.
(26) Cunico, R. F.; Dexheimer, E. M. *J. Organomet. Chem.* **1973**, *59*, 153.

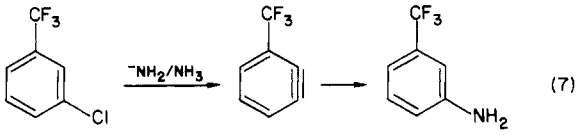
The use of σ^- values, which include resonance effects, gives a better estimate of reactivity for all but conjugatively electron-releasing substituents.[28,29] Using such data, a good relative ordering of substituent influence has been obtained. Since the majority of data is from para-substituted compounds, positional effects must be considered. In general, ortho substituents are less effective than their para counterparts when the effect is more conjugative than inductive. A relative value of 3:4 has been suggested and the effect is particularly noticeable with such groups as ketones, esters, and amides. Substituents such as OR and NR_2, however, exert a more inductive influence from the ortho position, causing less destabilization of the anion; these reactions are roughly 1–2 orders of magnitude faster than their para counterparts.[8] Meta substituent effects are purely inductive, thus each group will have a lesser net effect than when in the para position.[29] The effects of multiple substituents are generally considered to be additive for nucleophilic aromatic substitution reactions; however, less than additive effects have been found with multiple groups exerting the same electronic influence and when steric effects interfere with the planarity of the intermediate.

2. Unactivated Aromatic Substrates. There are three types of substituent effects operating during the elimination–addition mechanism. Most important are those destabilizing influences which lessen the aromatic substrate's ability to support the incipient negative charge in the Meisenheimer complex. The second type is a purely inductive effect which may affect both the proton acidity and the regiochemistry of nucleophile addition. A 1:2:1 ratio of ortho:meta:para products, eq 6, is expected when



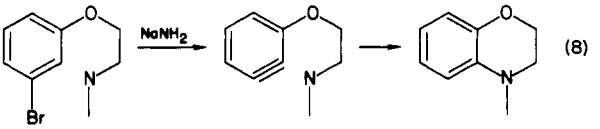
(6)

the substituent has little or no inductive electron-withdrawing ability (e.g., the methyl group), implying the formation of two benzyne intermediates and statistical product distribution in the subsequent addition reactions. The presence of the trifluoromethyl group, eq 7, sufficiently increases the acidity of the ortho proton such that the 2,3-benzyne is the only intermediate formed. The same electron-withdrawing effect governs the regiochemistry of amide addition to produce the more stable phenyl anion exclusively in this case.[30]



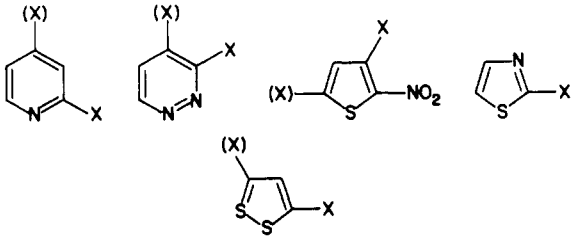
(7)

The third effect is found in intramolecular aryne reactions in which steric constraints dictate the regiochemistry of addition. In eq 8,[8,31] the 2,3-benzyne is formed as expected. However, addition of the amide ion proceeds to form the fused rather than the bridged product. When the side chain is long, formation of bridged aromatics is possible.[32]

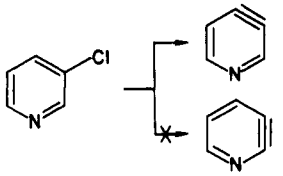


(8)

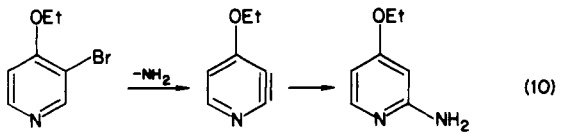
D. Heteroaromatic Substrates. Aromatic heterocycles, like their benzene counterparts, participate in both the addition–elimination[8] and elimination–addition[33] mechanisms. Activation of the π-deficient[34] heteroaromatics such as pyridine is comparable to that of the benzenoid systems where the ring nitrogen exerts approximately the same effect as a nitro group. Reactivity, then, is a function of the position of the leaving group relative to the heteroatom as well as a function of substituent effects. π-Excessive heteroaromatics which contain a five-membered ring and only one heteroatom are much less reactive toward the addition–elimination mechanism. One estimate places the unsubstituted substrates at approximately the activity of benzene so that reactivity toward this mechanism is supplied by electron-withdrawing substituents.[35] Sample substrates that react via the addition–elimination mechanism are shown below where X may be any leaving group. Parenthesized X indicates sites of equivalent reactivity.



Both five- and six-membered-ring heteroaromatics may react to form hetarynes under the same conditions as for benzyne formation, i.e. strong base and good leaving group. Again, selective formation of the new π bond may result; for example, 3-chloropyridine reacts with lithium piperidide in piperidine to give only the 3,4-pyridyne, eq 9.[36]



(9)



(10)

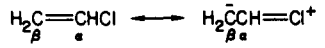
(27) Bunnett, J. F.; Draper, F., Jr.; Ryason, P. R.; Noble, P., Jr.; Tonkyn, R. G.; Zahler, R. E. *J. Am. Chem. Soc.* **1953**, *75*, 642. Hammett, L. P. *J. Am. Chem. Soc.* **1937**, *59*, 96.
(28) Miller, J. *Aust. J. Chem.* **1956**, *9*, 61.
(29) Greizerstein, W.; Bonelli, R. A.; Brieux, J. A. *J. Am. Chem. Soc.* **1962**, *84*, 1026.
(30) Heaney, H. *Chem. Rev.* **1962**, *62*, 81.
(31) Huisgen, R.; König, H. *Angew. Chem.* **1952**, *69*, 268.
(32) Hrutfiord, B. F.; Bunnett, J. F. *J. Am. Chem. Soc.* **1958**, *80*, 2021, 4749, and references following.
(33) den Hertog, H. J.; van der Plas, H. C. *Adv. Heterocycl. Chem.* **1965**, *4*, 121.
(34) Albert, A. "Heterocyclic Chemistry"; Athlone Press: London, 1959.
(35) Manly, D. G.; Amstutz, E. D. *J. Org. Chem.* **1957**, *22*, 133. Petfield, R. J.; Amstutz, E. D. *J. Org. Chem.* **1954**, *19*, 1944.
(36) Kauffmann, T. H.; Buettcher, F. P. *Angew. Chem.* **1961**, *73*, 65; *Chem. Ber.* **1962**, *95*, 949, 1528. Kauffmann, T. H. *Angew. Chem.* **1965**, *77*, 557; *Angew. Chem., Int. Ed. Engl.* **1965**, *4*, 543.

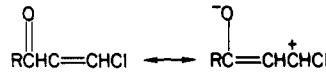
The 2,3-pyridyne is formed when there is no possibility of the other hetaryne, eq 10.[37] Nucleophilic addition to the triple bond may also be regioselective. Molecular orbital calculations suggest that the 2,3-pyridyne should yield only the 2-substituted product.[38] This is also seen in eq 10; however, the presence of the ethoxy group must certainly influence the regiochemistry.

III. Nucleophilic Reactions of Vinylic and Acetylenic Leaving Groups

Nucleophilic reactions of unsaturated aliphatic electrophiles, like those of their aromatic counterparts, fall into two main reaction types, substitution and elimination. Mechanisms abound to explain the results with as many as 16 suggested for the substitution process.[39] The focus of this section is to review the reactivity for the two mechanisms operative for the majority of substrates: substitution via addition–elimination and β-elimination.

A. Substitution via the Addition–Elimination Mechanism.[39-44] **1. Activation.** Nucleophilic vinylic substitution reactions were long thought to be difficult due to the strength of the electrophile–leaving-group bond which is enhanced by the sp^2 hybridization of the carbon and through resonance (eq 11). Addition of electron-

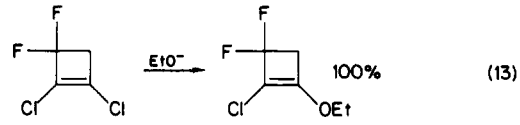

(11)


(12)

withdrawing groups to the β-carbon, however, may increase reactivity by increasing the electrophilicity of the α-carbon, eq 12, though this should also enhance the double-bond character for the bond to the leaving group. The withdrawing effect is similar to that for ortho- and para-activating groups in nucleophilic aromatic substitution although the quantitative result is not always the same.[40] With the assumption that bond making is the rate-determining step, the following activation series based on rate data has been suggested.[39,45]

$$2,4\text{-}(NO_2)_2C_6H_3 > PhCO > EtCO > PhSO_2 > CN > CO_2Et, PhSO > p\text{-}NO_2C_6H_4 > PhS > Cl$$

Geometric arrangement appears to have little importance as only small rate differences were found between cis and trans isomers. The addition of the nucleophile gives the most stable carbanion, i.e., the carbanion with the best electron-withdrawing substituents α to the negative charge.[46] Given two sites with identical stabilization, the one with the better β-stabilizing groups would form preferentially, eq 13.[47]



(13)

(37) Pieterese, M. J.; den Hertog, H. J. *Recl. Trav. Chim. Pays-Bas* **1961**, *80*, 1376.
(38) Jones, H. L.; Beueridge, D. L. *Tetrahedron Lett.* **1964**, 1577.
(39) Rappoport, Z. in "Advances in Physical Organic Chemistry"; Gold, V., Ed.; Academic Press: London, 1969; p 1 ff.
(40) Modena, G. *Acc. Chem. Res.* **1971**, *4*, 73.
(41) Miller, S. I.; Dickstein, J. I. *Acc. Chem. Res.* **1976**, *9*, 358.
(42) Rappoport, Z. *Acc. Chem. Res.* **1981**, *14*, 7.
(43) Patai, S.; Rappoport, Z. In "The Chemistry of Alkenes"; Patai, S., Ed.; Interscience: London, 1964; p 469 ff.
(44) Dickstein, J. I.; Miller, S. I. In "The Chemistry of the Carbon–Carbon Triple Bond", Part 2; Patai, S., Ed.; Wiley: Chichester, 1978; p 813 ff.
(45) In no case was the same nucleophile studied with all the substrates, thus the comparisons are indirect.
(46) Park, J. D.; Lacher, J. R.; Dick, J. R. *J. Org. Chem.* **1966**, *31*, 1116.

Table I. Leaving-Group Ranks for Selected $(E1cb)_R$ Reactions[a]

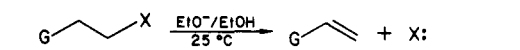
X	leaving-group ranks G = PhSO	G = CN
PhSe	10.4	10.0
p-tosyl-$^+$SMe	9.8	
$PhNMe_2^+$	9.2	10.7
$PO(OEt)_2$		8.0
PhO	8.9	8.2
PhS	8.7	7.9
$PhSO_2$	8.7	9.6
PhSO	7.1	
MeO	6.1	6.3
NMeTs	5.4	
NMeAc	5.0	6.6
$C(Me)_2NO_2$	2.6	
CN		<0.5

[a] Data from ref 50.

Alkynyl electrophiles have been found to be generally more reactive to nucleophiles than their vinyl and aryl counterparts. Seven mechanisms have been proposed for these systems,[39] with firm evidence available for two: addition–elimination and nucleophilic substitution on the leaving group (particularly if it is a halogen). Like the vinylic substrates, electron-withdrawing activation at the β-position increases the likelihood of the addition–elimination mechanism; however, substitution will occur even for unactivated alkynes, eq 14.[49]

$$HC{\equiv}CBr + NEt_3 \xrightarrow[81\ ^\circ C]{DMF} HC{\equiv}CN^+Et_3Br^- \quad (14)$$

2. Leaving-Group and Nucleophile Effects. The variety of leaving groups that may participate in a nucleophilic vinylic substitution as opposed to substitution at a saturated carbon center is quite large. Leaving-group ability in these reactions can be estimated by the rate of elimination in the corresponding $(E1cb)_R$ reactions where expulsion of the leaving group is the rate-determining step. Leaving-group ranks for the reaction in eq 15 are given in Table I.[50] As expected, neutral leaving groups are highly



(15)

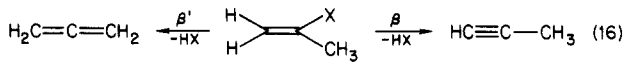
ranked; however, there is no general correlation of leaving-group rank with the pK_a of the conjugate acid of the leaving group. Me_3N, PhO^-, $NMeTs^-$, and CN^-, all with conjugate acid pK_a's of approximately ten, differ in leaving-group rank by as much as 10 (log) units. The more typical leaving groups (i.e., Cl, Br, I, and TsO) are not represented as these substrates react via either the $(E1cb)_I$ or E2 mechanism. In general, these rankings are consistent with leaving-group abilities in nucleophilic aromatic substitution reactions.

Little systematic study of nucleophilicity has been done for these reactions; however, one investigation[39] yielded the general order $RS^- > RO^- > R_3N > N_3^- > F^-, Cl^-, Br^-, I^-$ for the reaction with *trans*-*p*-$MeC_6H_4SO_2CH{=}CHCl$ at 0 °C in MeOH. Approximately half the nucleophiles were also found to be reactive toward elimination. This is consistent with the data for nucleophilic aromatic substitution reactions and with the current nucleophilicity evaluation in CAMEO.

(47) Park, J. D.; Groppeli, G.; Adams, J. H. *Tetrahedron Lett.* **1967**, *2*, 103.
(48) Delavarenne, S. Y.; Viehe, H. G. In "The Chemistry of Acetylenes"; Viehe, H. G., Ed.; Marcel Dekker: New York, 1969; Chapter 10.
(49) Tanaka, R.; Miller, S. I. *J. Org. Chem.* **1971**, *36*, 3856.
(50) Sterling, C. J. M. *Acc. Chem. Res.* **1979**, *12*, 198.

3. Stereochemistry.[39,42,51] The predominant stereochemical course for nucleophilic vinylic substitution reactions is retention of configuration. While stereoconvergence is also common, full inversion is rarely seen. The stereochemistry of the product is felt to be indicative of the addition–elimination mechanism; i.e., the adduct may be either a transition state (leading to retention) or an intermediate (leading to convergence). It has been suggested that the reaction path is variable, depending on the anion-stabilizing ability of the α-substituents and on the leaving group.[42] The single-step mechanism is proposed for slightly activated substrates with good leaving groups such as the β-bromostyrenes while highly activated systems (in which the pK_a of the conjugate acid of the intermediate carbanion is less than ten) are expected to proceed by the multistep mechanism. In general, retention is seen with good leaving groups until the carbanion is highly stabilized. For poor leaving groups, convergence is typical except in slightly or unactivated systems in which case retention is more common.

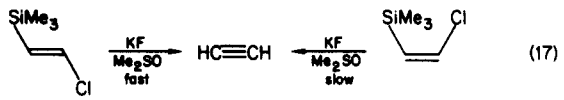
B. β-Elimination.[39,40,52] β- and β'-Elimination reactions to produce alkynes and allenes, eq 16, are common



(16)

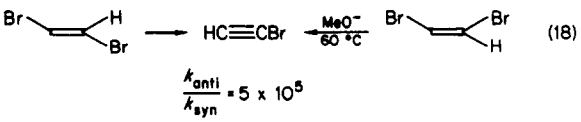
with vinylic electrophiles, even those that are not activated. The mechanistic possibilities are very similar to those for saturated substrates, with E1cb and E2 the most common in basic media. Addition of anion-stabilizing groups which increase the acidity of the β or β' hydrogen increases the rate of reaction. In some cases, the rate may equal or surpass that of the saturated compound; for instance, the reactivity ratio of β-bromoethylbenzene to β-bromostyrene is 10^{-2}–10^{-3} at 55 °C.[53]

The selection of leaving groups and bases is more constrained here than for the substitution reaction. Good leaving groups such as the halogens are generally required which parallels reactivity of the aromatic substrates toward this mechanism. As for most elimination reactions, the nucleophile must have a high hydrogen basicity; alkoxides and amines are the most common. However, when the proton is replaced by silicon, eq 17,[54] fluoride ion may be used to effect the elimination.



(17)

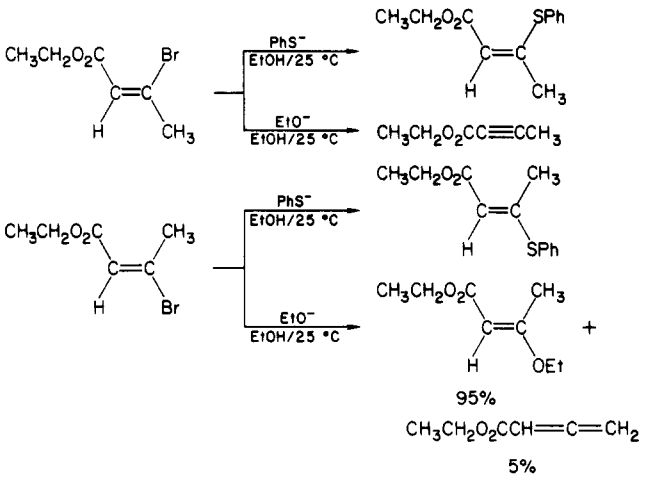
Since many of these reactions proceed via the E2 mechanism, substrate configuration is expected to affect the rate of the elimination. This is seen in the reaction of the unactivated 1,2-dibromoethenes, eq 18.[55] Much



(18)

smaller k_{anti}/k_{syn} ratios have been measured such as for the 1,2-diphenylchloroethenes which show a ratio of 200 in NaOH/aqueous EtOH and 6 with *t*-BuOK/*t*-BuOH.[56]

Scheme I



The selectivity for anti over syn eliminations appears to decrease as the base strength increases.

C. Competition between Substitution and Elimination. While substitution and elimination reactions are relatively well defined for nucleophilic aromatic reactions, nucleophilic vinylic substrates show a range of reactivities from exclusive substitution through to exclusive elimination. In general, substitution predominates for most leaving groups on activated olefins when the base is nucleophilic. Nonnucleophilic bases favor elimination, but only for the better leaving groups. Nucleophiles that are both strong bases and good nucleophiles may react by either mechanism. The reactions of (*E*)- and (*Z*)-β-bromoethylcrotonate in Scheme I illustrate these competitions.[57] With benzenethiolate ion, the ester group is sufficiently activating and the thiolate ion sufficiently nonbasic to yield the substitution product from both isomers with no elimination. Reaction of the *Z* substrate with ethoxide yields the alkyne elimination product while the *E* isomer produces the vinyl ether. Hence, a general order for anions that are both basic and nucleophilic is activated anti eliminations > activated nucleophilic addition > unactivated anti elimination > syn elimination.

IV. Implementation

A. Modifications to the Existing Program. In order to implement this new section of chemistry in CAMEO, it was necessary to modify the existing code to allow for the recognition of unsaturated electrophiles and their different reactivity. Before discussing these changes, a review of the original processing is necessary.[1,58] Figure 1 contains an overview of the original electrophile perception. Several points must be noted: First, aromatic electrophiles were not considered until recently when they became a special case for aryne formation;[3] second, with the exception of some organosilicon reactions, leaving-group ability (hence, electrophilicity) was assigned solely on the basis of the effective pK_a of the leaving group; third, the ΔpK_a rule[1] was invoked for all electrophiles, i.e., only the best electrophiles plus those with leaving groups one level (ca. 1–3 pK_a units) higher were considered for reaction. Two directories were used to store this information. ALPDIR (All Path DIRectory) contained those electrophiles which passed the pK_a screen and which were considered to have the potential for S_N2, addition of E2 reactions. The second directory, E1DIR (El DIRectory), contained all the elec-

(51) Miller, S. I. *Tetrahedron* **1977**, *33*, 1211.
(52) Saunders, W. H., Jr.; Cockerill, A. F. "Mechanisms of Eliminations"; Wiley: New York, 1973.
(53) Miller, S. I. *J. Org. Chem.* **1961**, *26*, 2619.
(54) Cunico, R. F.; Dexheimer, E. M. *J. Am. Chem. Soc.* **1972**, *94*, 2868.
(55) Miller, S. I.; Noyes, R. M. *J. Am. Chem. Soc.* **1952**, *74*, 629.
(56) Cristol, S. J.; Whittemore, C. A. *J. Org. Chem.* **1969**, *34*, 705.
(57) Theron, F. *Bull. Soc. Chim. Fr.* **1969**, 278.
(58) Salatin, T. D. Ph.D. Thesis, 1981, Purdue University.

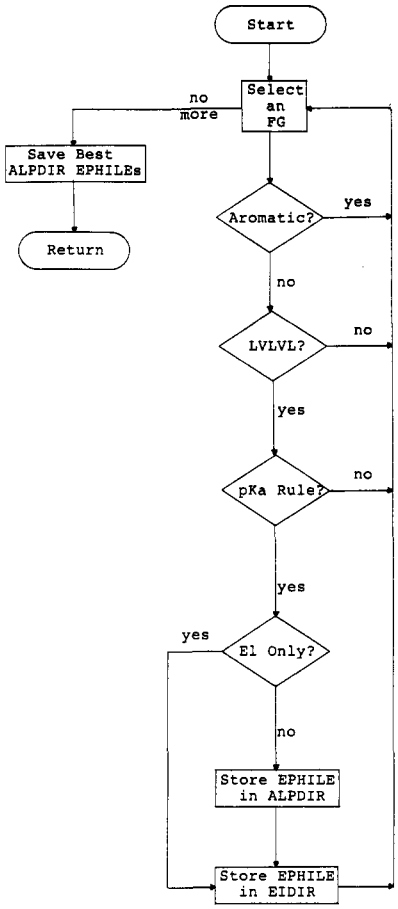
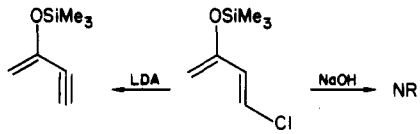


Figure 1. Flow chart of original electrophile perception.

trophiles in ALPDIR plus any poorer electrophiles which could only undergo E1cb reactions. These were stored for consideration in E1 reactions. The processing of these electrophiles, Figure 2, was primarily based on the electrophile type, i.e., primary, secondary or tertiary, and on the strength and hindrance of the base. In general, strong bases (NQV = 1, 2) or tertiary electrophiles predominantly give elimination; weak bases (NQV = 3) or primary electrophiles yield addition or substitution, and intermediate bases (NQV = 4) or secondary electrophiles give mixtures.

In addition to not handling aromatic electrophiles, the storage (in one directory) of all electrophiles whose leaving groups could undergo multiple reactions produced some inconsistent analyses. As illustrated, the presence of the



unsaturated chloride (which would rate a leaving level = 1) caused the deletion of the silyl enol ether (leaving level = 4) from ALPDIR. In the presence of a strong, nonnucleophilic base, the elimination reaction is currently predicted. The weaker base, OH^-, is considered for substitution or addition reactions. Since neither is viable for this electrophile, no reaction would be predicted, although cleavage of the silyl enol ether is certainly likely.

The initial changes to the program involved the creation of a third electrophile directory, UNSDIR (Unsaturated Directory), for the storage of multiply bonded electrophiles having singly bonded leaving groups. These include aromatic, vinylic, and acetylenic electrophiles. ALPDIR now contains only saturated or simple additive electrophiles and E1DIR includes ALPDIR, UNSDIR, and electrophiles which

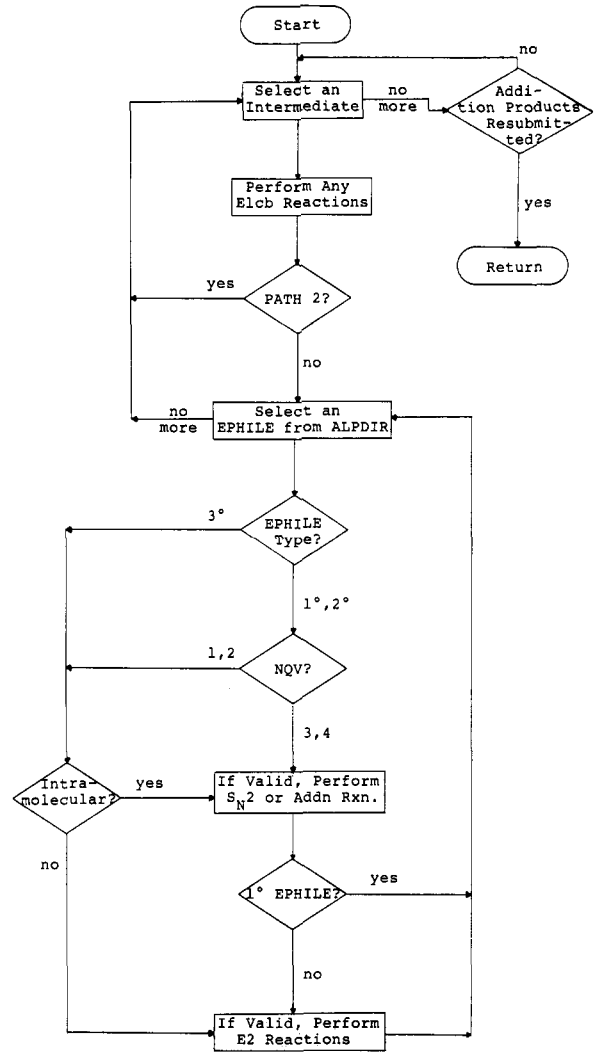
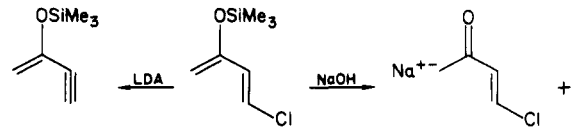


Figure 2. Flow chart for mechanism processing—original version.

can only undergo E1cb reactions. Figure 3 contains a flow chart of the current electrophile perception. LEAV2 contains the selection (by functional group number) of leaving groups which are valid in nucleophilic aromatic or vinylic/acetylenic substitution reactions. The Δ pK_a rule is still valid for ALPDIR electrophiles and is used as before to select the best set. Since reactions occurring at saturated electrophiles are generally faster than those at their unsaturated counterparts, the mechanistic executive, Figure 4, was altered to first consider ALPDIR electrophiles as well as unsaturated aliphatic electrophiles that may be competitive. In the event that there are no good leaving groups in ALPDIR (i.e., pK_a > 8, level > 4) or no reactions were performed with ALPDIR electrophiles, any aromatic electrophiles will also be processed and evaluated mechanistically. With these changes, the proper products are now formed for the reactions in eq 19.



Me_3SiOH (19)

B. Electrophile Perception in Unsaturated Systems. Recognition of reactivity in unsaturated systems is accomplished in two phases. Initially, all electrophiles must be found through their association with a leaving group. Since activation of the electrophile by electron-

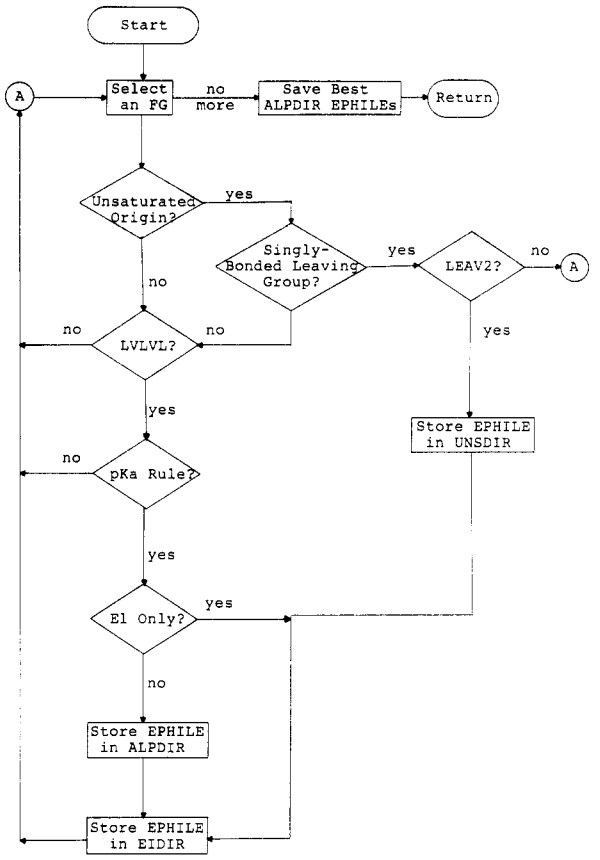


Figure 3. Flow chart for electrophile perception—current version.

Table II. Reactivity Levels and Allowed Mechanisms for Singly Bonded Leaving Groups on Unsaturated Electrophiles

level	leaving groups	allowed mechanisms
1	NR_3, SR_2, SeR_2, PR_3, N_2	addn/elim, elim/addn
2	F^-, NO_2^-	addn/elim
3	Cl^-, Br^-, I^-, OTs^-, $OPNB^-$, OBs^-, OMs^-, OTf^-	addn/elim, elim/addn
4	N_3^-, $OCOR^-$, $OSOR^-$, OSO_2R^-, SeR^-	addn/elim
5	OR^-, SR^-, CN^-, SO_2R^-, SOR^-, $P(O)(OR)_2^-$	addn/elim
6	NR_2^-, $NCOR^-$	addn/elim

withdrawing groups is the major factor in determining reactivity, leaving-group ability cannot be used alone to rate electrophilicity. Table II contains a list of possible leaving groups which are ranked by their relative ability to be displaced in a nucleophilic aromatic substitution reaction, all else being equal. Since these rankings reflect leaving-group ability in an E1cb reaction and are generally consistent with those in Table I for vinylic leaving groups, they are used for both aliphatic and aromatic systems. Additionally, the rankings indicate the mechanisms each group may undergo with the following exceptions: Fluorine, except after halogen–metal exchange is not involved in aryne formation; amines and amides do not react in aliphatic systems. These rankings are accessed from an array (LEAV2) by functional group number and are stored as UNRANK (EPHILE) where EPHILE equals 1 for the first electrophile found in the molecule, etc. Collectively, these electrophiles make up UNSDIR.

In the second phase, each electrophile is assigned a reactivity number which reflects the electronic characteristics of the molecule's substituents and their effect on the rate of reaction, i.e., the Hammett $\sigma\rho$ correlation.[27] The use of σ^- values is appropriate here; however, these data are

Table III. Rate Constants (log k_2) and CODE Values for the Reaction of 2-Nitro-4-X-chlorobenzenes with Sodium Methoxide at 50 °C

X	rate const[a] (log k_2)	CODE	X	rate const[a] (log k_2)	CODE
CH_3	−6.52	−8	CF_3	−2.69	25
F	−5.65	−1	CO_2Me	−2.41	25
H	−5.60	0	COMe	−2.30	28
CH_2OMe	−5.48	1	COPh	−2.18	29
N_3	−5.15	3	SO_2NMe_2	−1.72	32
CO_2^-	−5.07	5	SO_2NMePh	−1.69	30
Cl	−4.45	9	SO_2Me	−1.49	35
Br	−4.41	10	SO_2Ph	−1.33	36
I	−4.36	10	NMe_3^+	−1.27	36
SMe	−4.26	11	NO_2	−0.54	42
$CONH_2$	−3.18	23	SMe_2	−0.10	46
N=NPh	−2.85	23	NO	0.20	50

[a] Data from ref 8.

Table IV. Rate Constants (log k_2) and CODE Values for the Reaction of 2-Nitro-4-X-chlorobenzenes with Piperidine at 45 °C

X	rate const[a] (log k_2)	CODE	X	rate const[a] (log k_2)	CODE
NH_2	−8.52	−27	Br	−4.46	10
OEt	−7.12	−15	I	−4.36	10
OMe	−7.04	−15	CO_2^-	−4.28	5
CH_3	−6.28	−8	N=NPh	−2.74	23
CMe_3	−6.21	−11	CF_3	−2.72	25
H	−5.44	0	CO_2Et	−2.47	25
Ph	−5.12	4	CN	−1.67	30
Cl	−4.64	9	NO_2	−0.26	42

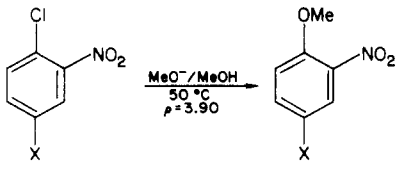
[a] Data from ref 29.

Table V. Rate Constants (log k_2) and CODE Values for the Reaction of 2-Nitro-5-X-chlorobenzenes with Piperidine at 45 °C

X	rate const[a] (log k_2)	CODE	X	rate const[a] (log k_2)	CODE
CMe_3	−5.77	−6	OMe	−4.82	5
CO_2^-	−5.71	−10	CO_2Et	−4.72	10
NH_2	−5.51	−3	I	−4.04	15
CH_3	−5.51	−3	Cl	−3.93	14
H	−5.44	0	Br	−3.90	15
Ph	−5.42	2	CN	−3.67	17
OEt	−4.87	5			

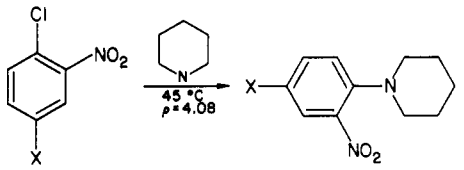
[a] Data from reference 29.

limited and it is preferable to calculate an index that represents the relative effect of any given substituent on a negatively charged transition state. The approach taken is similar to that reported for the calculation of substituent effects (τ) on frontier orbital energies for six-electron cycloadditions.[6] That procedure has been modified so that the τ values (referred to from this point as CODE values) reflect the logarithms of rate constants for the reaction in eq 20.[8] Rate constant data for various substituents along



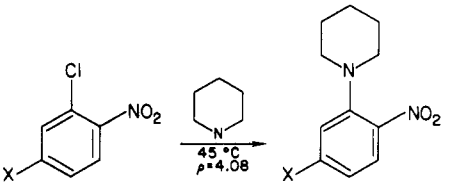
(20)

with the calculated CODE values are listed in Table III and plotted in Figure 5. To further demonstrate the applicability of the approach, the CODE values for reaction 21 are shown plotted against rate constants in Figure 6 and



(21)

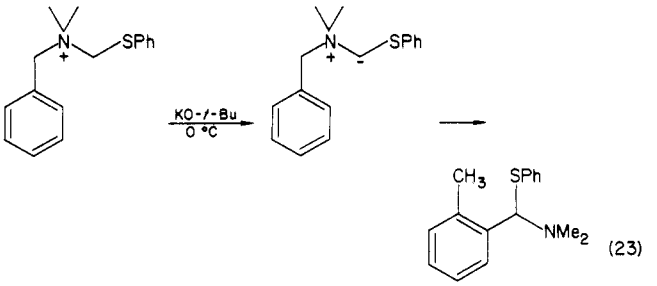
the data are listed in Table IV.[29] Since substituents in the meta position cannot be expected to exert the same influence, some adjustments to the CODE values are necessary. For electron-releasing substituents, the loss of unfavorable resonance interactions leads to approximately a hundredfold (thousandfold for nitrogen) increase in rate while for electron-withdrawing substituents the rate is decreased by a similar amount for the loss of favorable resonance interactions. Carbon and halogen rates are up to 10 times faster while aromatic substituents show a slight rate decrease. Table V contains the rate data[29] and adjusted CODE values for eq 22, which are plotted in Figure



(22)

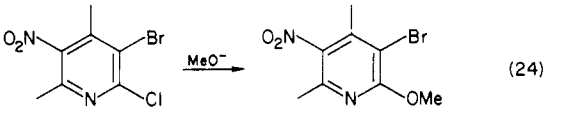
7. When heteroatoms are contained in the aromatic system, further adjustments to the CODE values are made according to the number of heteroatoms and their position relative to the leaving group. The rate constants for the reactions of heteroaromatic chlorides with sodium *p*-nitrophenoxide (listed in Table VI and plotted in Figure 8) were used as the reference.[8]

C. Mechanistic Evaluation for Unsaturated Electrophiles. 1. Overview. UNSDIR electrophiles are divided into three reactivity classes on the basis of the nucleophilicity of the anion, the electronic activation of the electrophile, and the leaving ability of the leaving group. The classes are substitution, elimination of HX, and X_2, or XY elimination such as in the reactions of dihalides (X = Br, I) or β-haloalkylsilanes (X = F, Cl, Br, I) with base. Figure 9 contains an overview of the processing. Initially, the qualification value (NQV) of the nucleophile, which is a gauge of its nucleophilicity and base strength, is used to differentiate substitution from elimination. Strong, hindered bases (NQV = 1, 2) only perform HX eliminations unless the anion is an oxygen in which case XY eliminations are also considered. Additionally, the leaving groups involved must have a high ranking (1 or 3, Table II) for the reaction to be viable. Weak bases which are also good nucleophiles (NQV = 3) may only eliminate in XY or X_2 systems. In the absence of these, substitution may be possible which is the predominant mechanism with strong bases which are also good nucleophiles (NQV = 4). To differentiate substitution from elimination, the electronic activation of the electrophile is gauged (vida infra). If substitution is not viable, good aromatic leaving groups are considered for elimination in the presence of a carbon or nitrogen anion; good aliphatic leaving groups may eliminate with any carbon or nitrogen base or with any NQV = 4 nucleophile if the proton is activated by electron-withdrawing groups. As a special case, the last reaction to be considered is an aromatic rearrangement such as the Hauser reaction, eq 23,[59] in which the leaving group is not directly bonded to the ring and the rearrangement proceeds through the aromatic π system.



(23)

2. Substitution. For any electrophile to be considered for aromatic substitutions, the activation indicator CODE must be at least 39 which is roughly equivalent to having one nitro group or two lesser activating groups ortho or para to the leaving group. In vinylic systems, the CODE must equal at least 20 which corresponds to activation by an amide or better. Alkynyl systems need only be activated to CODE = 0 before nucleophilic substitution can occur. This corresponds to the reactions of unsubstituted alkynyl halides. To gauge electrophilicity, the substituent CODE values are summed for each electrophile and the totals compared for the selection of the best electrophile. In the event the total contribution is equivalent for two or more electrophiles, the leaving-group rankings (Table II) determine the better electrophile(s). Sample calculations are shown in Figure 10 for the reactions in eq 24[29]

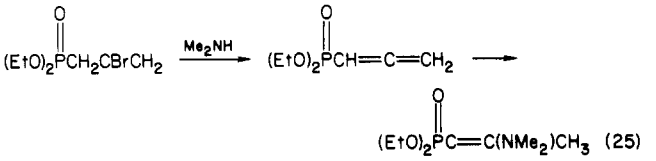


(24)

and 13.[47] Electrophiles involved in intramolecular aromatic reactions such as the Smiles rearrangement,[60] which form either fused or spiro intermediates are given an additional 30 units to reflect favorable entropic factors.

3. Elimination. The elimination reactions performed here are of two types: X_2 or XY and HX. XY eliminations currently include only β-halosilane systems as in eq 5 and 17. In the presence of weak, nucleophilic bases or good silicon nucleophiles such as fluoride and oxyanions, XY eliminations are preferred to HX. Aliphatic dihalides (X = Br, I) are the only X_2 substrates currently handled. They may react with weak, nucleophilic bases such as I^- or RS^-. For both XY and X_2 substrates, the reactivity heirarchy used is silyl > halo > H.

In H–X eliminations, there is often more than one proton available for reaction (e.g., eq 25[61] and 7). In both



(25)

cases, the acidity of the protons will influence formation of the intermediates. This is gauged in the same manner as electrophilicity by using the CODE values of the appropriate substituent groups. For aliphatic examples such as eq 25, the group(s) checked is that on the same carbon as the proton being considered but not the piece containing the electrophile. On aromatic systems, the substituent groups are one carbon removed from the atom carrying the

(59) Huyn, C.; Julia, S.; Lorne, R.; Michelot, D. *Bull. Soc. Chim. Fr.* **1972**, 4057.

(60) Warren, L. A.; Smiles, S. *J. Chem. Soc.* **1931**, 914, and subsequent papers.

(61) Sturtz, G. *Bull. Soc. Chim. Fr.* **1967**, 1345.

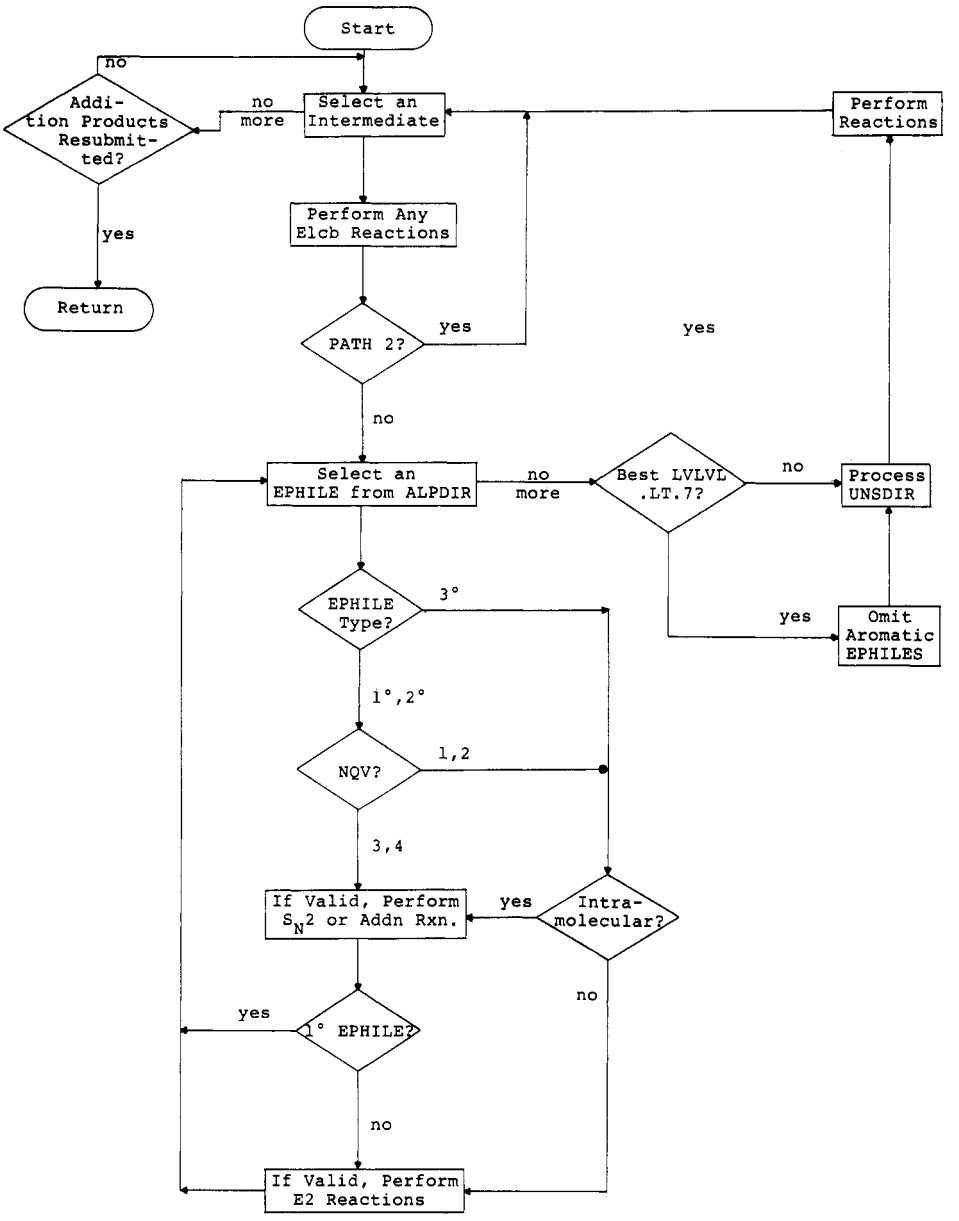


Figure 4. Flow chart for mechanism processing—revised version.

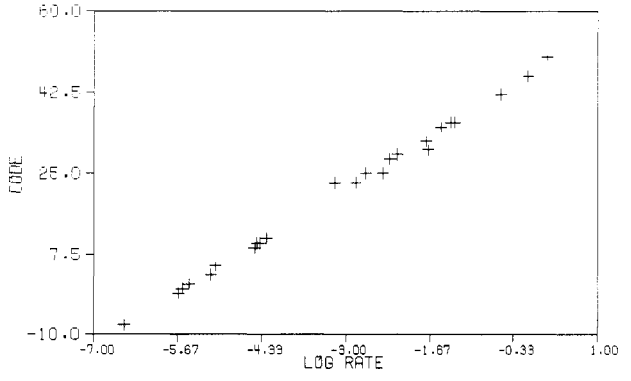


Figure 5. CODE vs. log k_2 for the reaction of 2-nitro-4-X-chlorobenzene with methoxide at 45 °C.

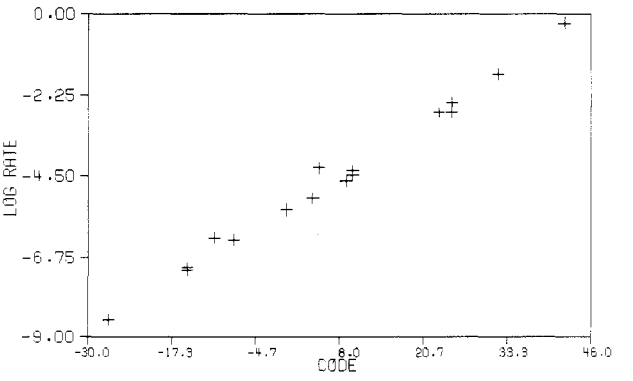


Figure 6. log k_2 vs. CODE for the reaction of 2-nitro-4-X-chlorobenzene with piperidine at 45 °C.

proton; again, the electrophile is not considered. Sample calculations for eq 25 and 6 are given in Figure 11. Standard CODE values are used for aliphatic systems since the effects here will be a combination of both resonance and induction, but the effects of the aromatic compound will only be inductive and thus a modification is necessary. Groups such as OR and NR_2 which are considered electron donating for substitution reactions are electron withdrawing in this situation. A good predictive gauge is use of the absolute CODE values and selection for one proton over the other if the difference between the values is greater than 14. Thus for eq 6, where ΔCODE is 8, both benzynes are produced as evidenced in the product ratios. On the other hand, the ΔCODE for eq 7 is 25 so only the

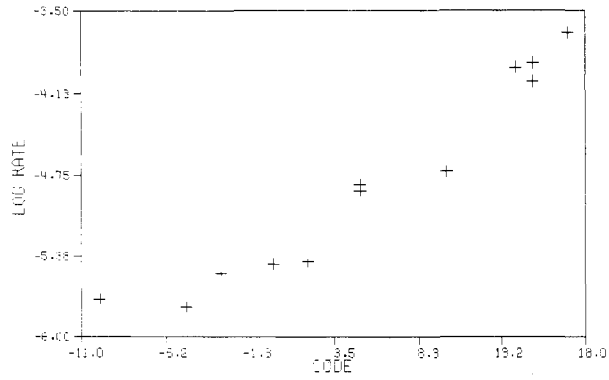


Figure 7. log k_2 vs. CODE for the reaction of 2-nitro-5-X-chlorobenzene with piperidine at 45 °C.

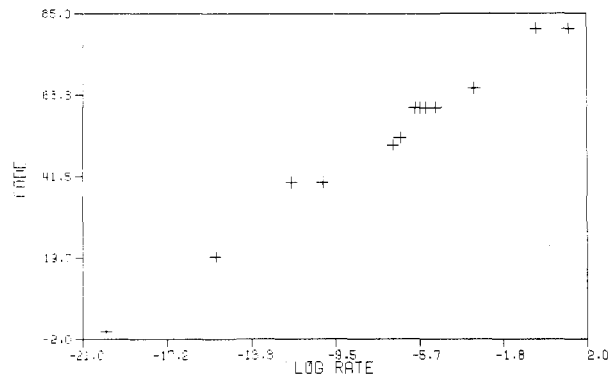


Figure 8. CODE vs. log k_2 for the reaction of heteroaromatic chlorides with sodium *p*-nitrophenoxide in MeOH at 50 °C.

Table VI. Rate Constants (log k_2) and CODE Values for the Reaction of Heteroaromatic Chlorides with Sodium *p*-Nitrophenoxide in MeOH at 50 °C

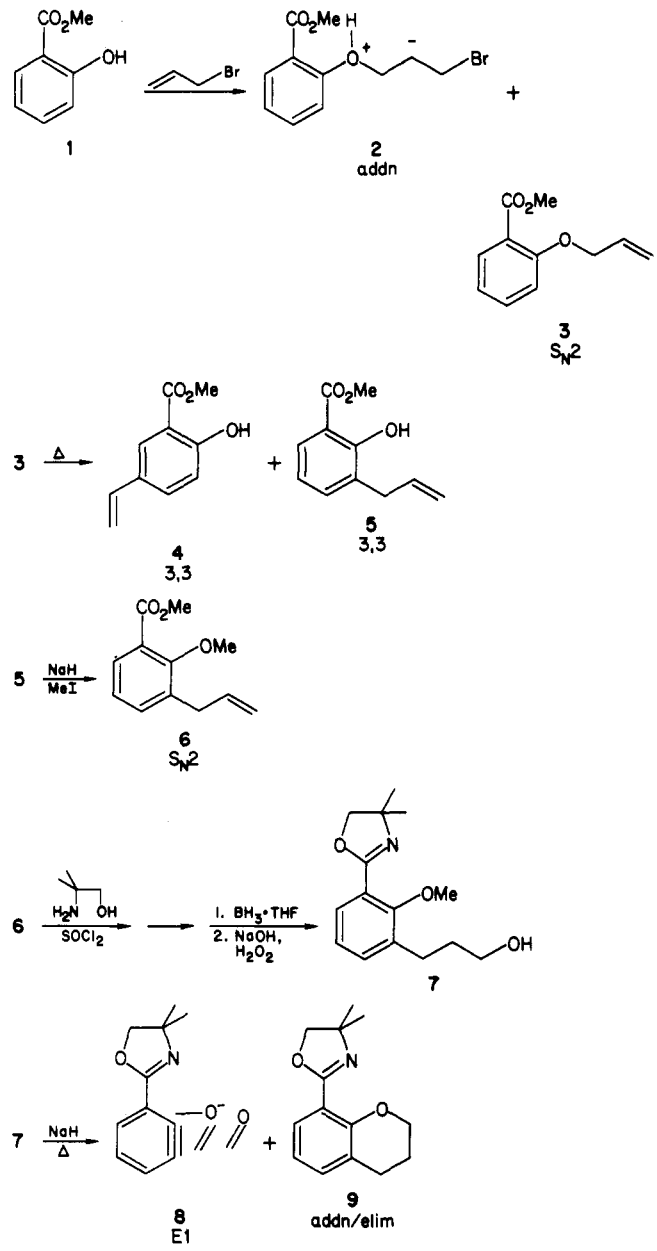
heteroaromatic chloride	rate const[a] (log k_2)	CODE
chlorobenzene	−19.96	0
3-chloropyridine	−15.00	20
2-chloropyridine	−11.52	40
4-chloropyridine	−10.09	40
5-chloropyrimidine	−6.89	50
N-methyl-3-chloropyridinium salts	−6.55	52
3-chloropyridazine	−5.89	60
4-chloropyridazine	−5.68	60
2-chloropyridazine	−5.35	60
4-chloropyrimidine	−4.92	60
2-chloropyrimidine	−3.16	65
N-methyl-4-chloropyridinium salts	−0.34	81
N-methyl-2-chloropyridinium salts	1.15	81

[a] Data from ref 8.

meta product is predicted and observed.[30]

At this point, the treatment of unsaturated aliphatic and aromatic elimination reactions diverges. Since the products of aliphatic eliminations are generally stable, subsequent addition to the multiple bond is not considered. This is left to the user since resubmission of the product and the nucleophile will yield any addition products via other sections of the program. The only further evaluation for aliphatic eliminations is stereochemical. Whenever possible, anti eliminations are given preference over syn. Arynes, however, are unstable, and the product(s) resulting from subsequent addition of the nucleophile is also generated by the program. (This is restricted to nucleophiles which are also strong bases [e.g., sodium amide] since

Scheme II



arynes produced from halosilane elimination generally do not show addition products.) There are, of course, two possible products, yields of which are governed by the same substituent influences that led to aryne formation. Thus, the same evaluation is used. If either anion produced by the addition is 14 or more CODE units more stable, then that product is the only one predicted. If the reaction is intramolecular, the formation of fused systems is given preference over bridged systems despite the electronics, eq 8. Since arynes are often generated for cycloaddition reactions, they are displayed as products to facilitate usage by the module for pericyclic chemistry.

4. Competition between Saturated and Unsaturated Electrophiles. The general reactivity hierarchy for addition, substitution and elimination mechanisms is E1cb > 1,2-addition, S_N2, $E2_{sat}$ > addition/elimination, $E2_{vinylic}$ > ArS_N2, ArE2. With the addition of activating functionality or the use of strong base, it is possible to increase the reactivity such that competition between the mechanisms may exist. To allow for this, the following reactivity rules have been incorporated into CAMEO: (1) 1,2-E1cb reactions are faster than all other processes unless the

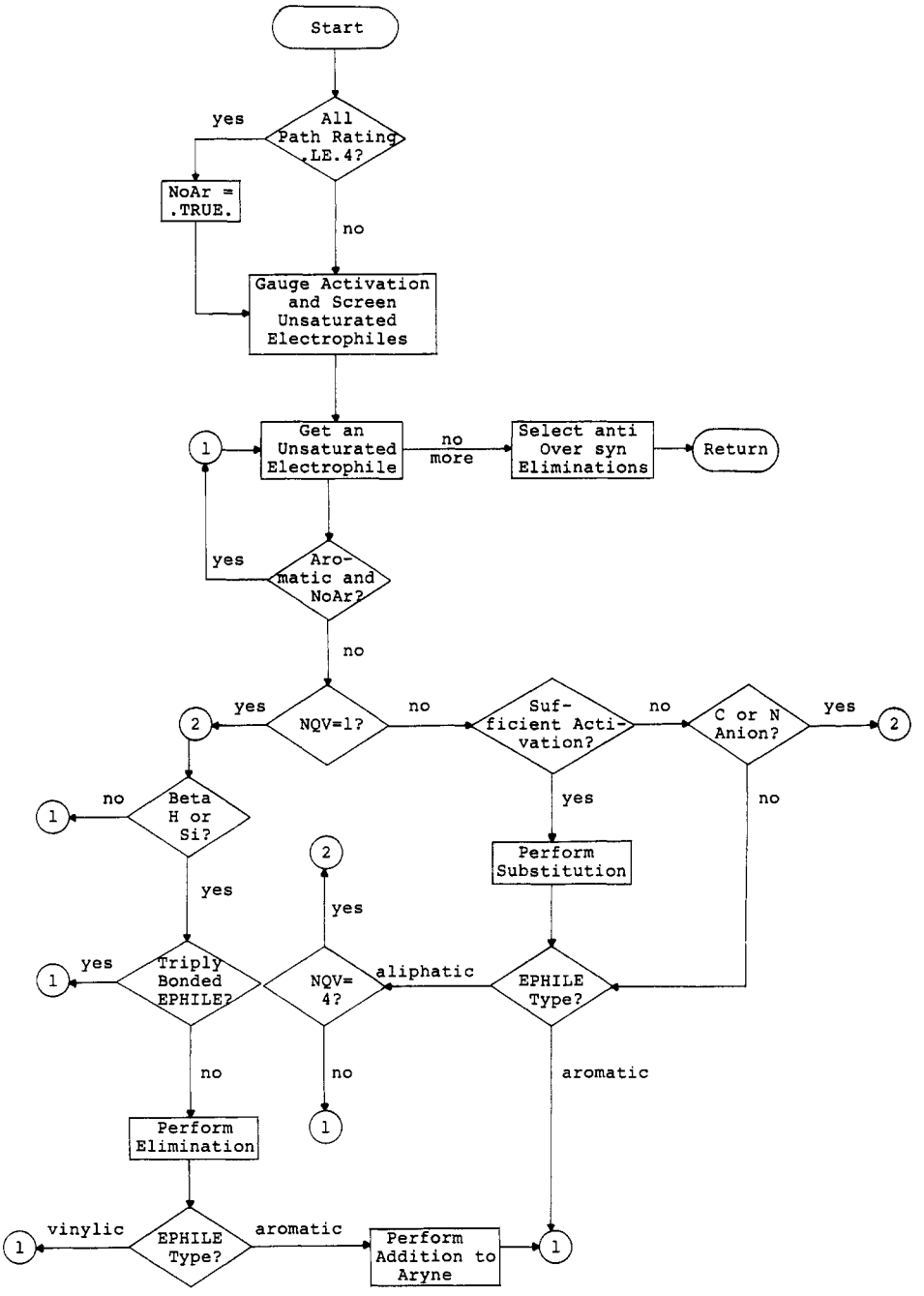


Figure 9. Flow chart for processing unsaturated electrophiles.

electrophile is aromatic. (2) Aromatic reactions do not compete with the reactions of saturated electrophiles if the saturated leaving group has a rating less than 5 (pK_a <8). (3) Activated vinylic or acetylenic reactions may compete with any saturated reaction for any base. (4) Unactivated vinylic reactions may compete with saturated reactions for strong bases. (5) Aromatic reactions may compete with vinylic and acetylenic reactions within the limits of their own reactivity.

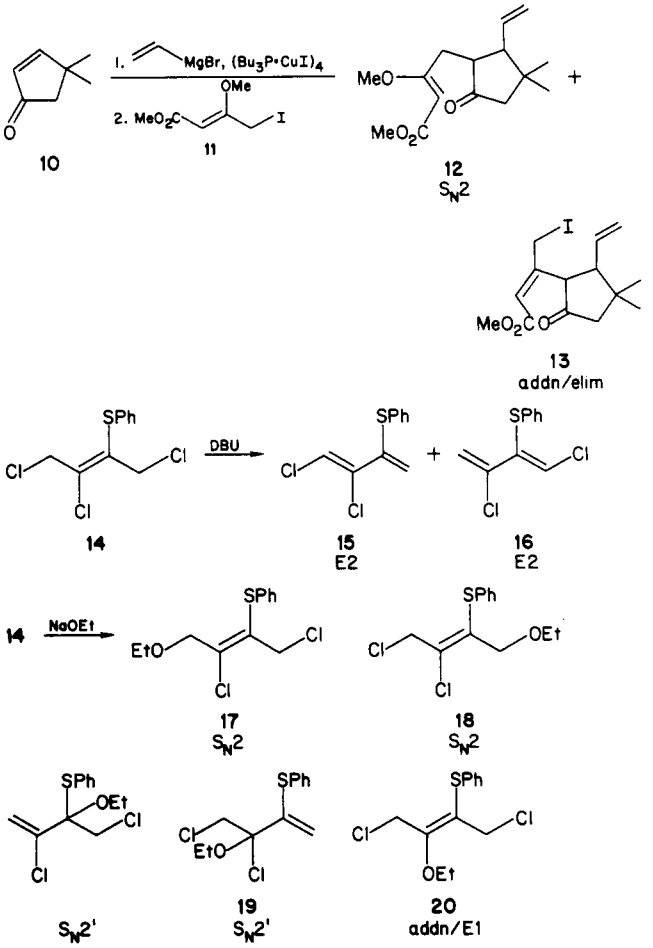
V. Sample Sequences

The integration of nucleophilic aromatic, vinylic, and acetylenic reactions into the existing nucleophilic module of CAMEO significantly broadens the program's scope. Predictions now made by the program are shown in the following schemes and include analyses by several mechanstic modules.

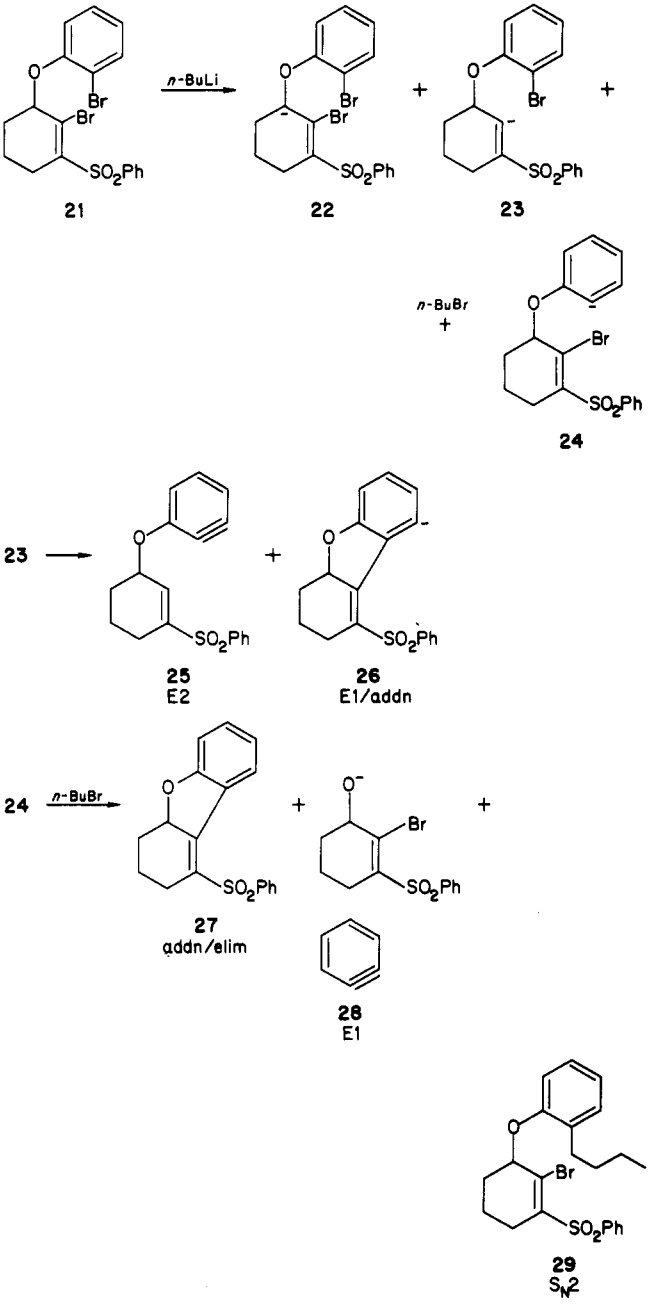
Scheme II contains a sequence from a study of aryloxazolines; specifically, the generation of benzo-fused ring systems from the trisubstituted compounds.[62] In the first step, phenolic ester 1 is reacted with allyl bromide to provide the allylic ether 3 in 70% yield experimentally. This product arises in CAMEO from both the S_N2 and S_N2' mechanisms. In CAMEO, the latter is perceived as the combination of an addition and an E1cb elimination. For each product, the pathway through which the product arose is displayed. In the first step, lactone formation was also considered but was rejected because the nucleophile and electrophile belong to the same resonance system. Product 3, in the second step, undergoes a Claisen rearrangement to produce compound 5 (99% yield[62]). This reaction is predicted by the pericyclic phase of CAMEO which also suggests that further rearrangement to the 1,2,4-substituted compound 4 is feasible. Compound 5

(62) Meyers, A. I.; Gabel, R.; Mihelich, E. D. *J. Org. Chem.* **1978**, *43*, 1372. Meyers, A. I.; Reuman, M.; Gabel, R. A. *J. Org. Chem.* **1981**, *46*, 783.

Scheme III



Scheme IV

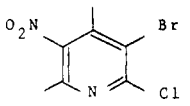


under basic conditions reacts with methyl iodide to produce the ether **6** (75% yield[62]). This is the only product predicted by the program. In a sequence of addition and elimination steps, compound **6** yields the oxazoline which is then hydroborated to produce compound **7**. Currently, CAMEO does not handle boron chemistry; however, its inclusion is planned. In the last step, compound **7** is heated in the presence of sodium hydride to produce the benzofused aryloxazoline **9** in 72% yield. This product is predicted along with a conjugate elimination product, **8**. The predicted ΔH value of 139.5 kcal/mol indicates that formation of the benzyne would be unfavorable and its output could be avoided by using the ΔH screening feature in the program.[63]

The reactions in Scheme III illustrate the reactivities of saturated and vinylic electrophiles. In the first reaction, cyclopentenone **10** is treated with vinyl magnesium bromide to yield a 1,4-addition product which in the presence of iodide **11** reacts to give **12** in moderate yield.[64] This substitution product is predicted by CAMEO along with a product, **13**, which arises from vinylic substitution of the activated methoxy group. Although **13** is competitive mechanistically, product **12** is favored thermodynamically. Products from reaction of **11** at the enolate oxygen are also predicted, but for simplicity, not shown. In the second reaction, olefin **14** is reacted with 1,8-diazabicyclo[5.4.0]-undec-7-ene (DBU) to provide diene **15** in 85% yield.[65] The alternate conjugate elimination product **16** is also predicted by the program; however, elimination of the vinylic chloride to give an allene is not predicted to be competitive. For contrast, **14** was submitted to CAMEO with sodium ethoxide as the base. Here, S_N2 reactions yielding **17** and **18** are predicted as well as two S_N2' products. Vinylic substitutions of the chloride and sulfide groups were also considered but deemed noncompetitive due to the lack of electron-withdrawing activation. A predicted product consistent with this mechanism, **20**, actually arises from the S_N2' reaction intermediate which also produced **19**. As mentioned previously, CAMEO views an S_N2' as the combination of an addition and an E1cb elimination. Here, two eliminations are possible.

The reaction in Scheme IV from a model study for a synthesis of morphine[66] is interesting in that many of the mechanisms considered by the nucleophilic chemistry module are operative. Vinyl sulfone **21** in the presence of *n*-butyllithium is predicted to undergo both halogen–metal

(63) Gao, J.; McLaughlin, D.; Jorgensen, W. L., to be published.
(64) Danishefsky, S.; Vaughan, K.; Gadwood, R.; Tsuzuki, K. *J. Am. Chem. Soc.* **1981**, *103*, 4136.
(65) Bridges, A. J.; Fischer, J. W. *J. Org. Chem.* **1984**, *49*, 2954.
(66) Fuchs, P. L.; Toth, J. E., personal communications.



1. Cl $\Omega_{ortho} = \Omega_{Br} + \Omega_{ring\text{-}N} = 10 + 40 = 50$

$\Omega_{para} = \Omega_{NO_2} = 42$

$\Omega_{meta} = 2\Omega_{CH_3} = 2(-3) = -6$

total 86

2. Br $\Omega_{ortho} = \Omega_{Cl} + \Omega_{CH_3} = 9 + (-8) = 1$

$\Omega_{para} = \Omega_{CH_3} = -8$

$\Omega_{meta} = \Omega_{NO_2} + \Omega_{ring\text{-}N} = 24 + 20 = 44$

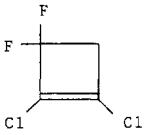
total 37

3. NO_2 $\Omega_{ortho} = 2\Omega_{CH_3} = 2(-8) = -16$

$\Omega_{para} = \Omega_{Cl} = 9$

$\Omega_{meta} = \Omega_{Br} + \Omega_{ring\text{-}N} = 15 + 20 = 35$

total 28



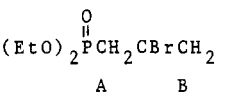
1. $Cl_{(1)}$ $= \Omega_{CH_2} + \Omega_{Cl} = 0 + 9 = 9$

2. $Cl_{(2)}$ $= \Omega_{CF_2} + \Omega_{Cl} = 13 + 9 = 22$

Figure 10. Sample CODE calculations ($\Omega \equiv$ CODE).

exchange (to intermediates **23** and **24**) and proton transfer (to intermediate **22**). Subsequent reaction of **23** yields the benzyne intermediate **25** and the tricyclic product **26** which is derived from **25**.[67] Intermediate **24** reacts through the addition/elimination, E1, and S_N2 mechanisms to give products **27**, **28**, and **29**, respectively. Additional products for this reaction were predicted but are not shown for simplicity. Although the desired product **26** was not formed, evidence for the formation of the three intermediates **22–24** was found.[66]

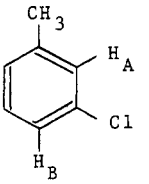
(67) It should be noted that in the presence of a strong initial base such as *n*-butyllithium, arynes may be formed for reaction with intermediate carbon or nitrogen anions. This is a pseudodianion reaction in that excess base is assumed to be present. Precedence for this may be found in a cephalotaxine synthesis: Semmelhack, M. F.; Chong, B. P.; Jones, L. D. *J. Am. Chem. Soc.* **1972**, *94*, 8629. Semmelhack, M. F.; Stauffer, R. D.; Rogerson, T. D. *Tetrahedron Lett.* **1973**, 4519.



$\Omega_{CH_2(A)} = \Omega_{phos} + \Omega_{H} = 26 + 0 = 26$

$\Omega_{CH_2(B)} = \Omega_{H} = 0$

Δcode 26



$\Omega_{H_A} = \Omega_{CH_3} = 8$

$\Omega_{H_B} = \Omega_{H} = 0$

Δcode 8

Figure 11. Sample CODE calculations for gauging proton acidity ($\Omega \equiv$ CODE).

VI. Conclusion

The module for base-catalyzed and nucleophilic reactions in the computer synthesis program CAMEO has been expanded to incorporate the reactions of vinylic, acetylenic, and aryl electrophiles. Included is the expansion, in general, of electrophile perception and the delineation of reactivity in the unsaturated substrates. The competition between the various mechanisms as well as the relative reactivity of the unsaturated and saturated electrophiles has also been addressed.

Acknowledgment. Gratitude is expressed to the National Science Foundation for support of this work. The assistance of Dr. J. S. Burnier is also greatly appreciated.