was irradiated for 5 h. The ratios of the slopes extrapolated to zero conversions of each pair (i.e., α-, β-, or δ-BHC to γ-BHC) gave their initial relative rates for the dechlorination, from which the corresponding quantum yields were obtained and summarized in Table I. Similarly, initial relative rates of *t*- and *c*-DCC to the standard γ-BHC were measured (*t*-DCC/*c*-DCC/γ-BHC ratio of 4.8:1:37), from which quantum yields for *t*- and *c*-DCC were obtained.

Polarography. Polarographic analysis was carried out on a Yanagimoto polarograph, Model P8. A solution of ca. 10^{-4} M samples in dimethylformamide (DMF) with 0.1 M tetraethylammonium perchlorate (TEAP) as a supporting electrolyte was bubbled with N_2 prior to the measurement. Typical polarograms for *t*- and *c*-DCC were not obtainable, which shows that they possess reduction potentials at least lower than −2.30 V, as control experiments without the sample enable one to sweep to potentials of −2.30 V in DMF. The results are compiled in Table I.

Acknowledgment. This research was supported by the Ministry of Education of Japan (Grant in Aid No. 543024).

Registry No. *c*-DCC, 10498-35-8; *t*-DCC, 822-86-6; α-BHC, 319-84-6; β-BHC, 319-85-7; γ-BHC, 58-89-9; δ-BHC, 319-86-8; TEA, 121-44-8.

Computer-Assisted Mechanistic Evaluation of Organic Reactions. 4. Organosilicon Chemistry

Catherine E. Peishoff and William L. Jorgensen*

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

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CAMEO, an interactive computer program which predicts the products of organic reactions using mechanistic reasoning, has been enhanced to encompass nucleophilic and electrophilic processes involving organosilicon compounds. The existing modules for such reactions were modified to accommodate the special reactivity of silanes. This includes considerations such as the high affinity of silicon for oxy and halide anions, directing effects for electrophilic additions to allyl and vinyl silanes, stabilization of carbanions and of S_N2 transition states by adjacent silicon, stereochemistry of β-elimination reactions, and steric effects in the formation and removal of silyl protecting groups. Consequently, changes were required in several parts of the program, particularly in the perception of acidity levels and of the reactivity of nucleophiles and electrophiles. General procedures for handling the stereochemistry of β-elimination reactions have also been implemented and are described. The paper begins with a short summary highlighting examples of the novel nature of organosilicon chemistry. The modifications to CAMEO are then presented followed by analyses of sample reaction sequences predicted by the program.

A computer program, CAMEO, which predicts the products of organic reactions given starting materials and conditions, is under continued development.[1-3] Two important features of the program are that it is highly interactive, with structures being input and output on a computer graphics terminal, and that the program arrives at its predictions by mimicking traditional mechanistic reasoning.[1,3] In 1978, the first class of reactions to be implemented was base-catalyzed and nucleophilic processes that could include proton transfer, S_N2, E2, E1cB, and addition steps.[1] This followed extensive work on the parts of the program controlling structure entry and display (graphics) and the recognition of structural features such as functional groups, rings,[2] and stereochemistry (perception).[1] The mechanistic capabilities were subsequently enhanced to cover ylide chemistry and reactions of organolithium, magnesium, and lithium cuprate reagents.[3] This involved the implementation of halogen–metal exchange and detailed consideration of the competitions between exchange, proton transfer, and organometallic addition.[3]

During the last 2 years, the scope and sophistication of the program have increased substantially. Modules have now been added for acid-catalyzed and electrophilic reactions[4] including electrophilic aromatic substitution[5] and for six-electron cycloadditions including reactions with 1,3-dipoles.[6] The nucleophilic and electrophilic routines have also been enhanced to treat the special reactivity associated with organosilicon compounds. This addition, which is the topic of the present report, is clearly important since transformations involving organosilicon intermediates are now commonplace in syntheses of natural products. Silyl protecting groups and the directing ability of silicon have become powerful tools of synthetic organic chemists.[7]

Besides enhancing the capabilities of the program, the implementation of a new area of chemistry in CAMEO is intrinsically valuable since it requires the analysis and organization of literature data on reactivity. In the present case, the similarities and differences in behavior of carbon and silicon compounds must be clearly delineated so that the organosilicon chemistry can be efficiently merged into the existing routines for nucleophilic and electrophilic reactions. Thus, a short review of the special properties and reactivity of organosilanes is presented first. The incorporation of these characteristics into the CAMEO program is then described. The paper concludes with the presentation and analyses of sample synthetic sequences predicted by the program.

Key Aspects of Organosilicon Chemistry

The many facets of organosilicon chemistry and its applications in organic synthesis have been covered thoroughly in recent reviews.[7-10] The brief summary presented here focuses on the novel reactivity of organosilanes that is distinct from the behavior of corresponding carbon

(1) T. D. Salatin and W. L. Jorgensen, *J. Org. Chem.*, **45**, 2043 (1980).
(2) B. L. Roos-Kozel and W. L. Jorgensen, *J. Chem. Inf. Comp. Sci.*, **21**, 101 (1981).
(3) T. D. Salatin, D. McLaughlin, and W. L. Jorgensen, *J. Org. Chem.*, **46**, 5284 (1981).
(4) D. McLaughlin and W. L. Jorgensen, to be submitted for publication in *J. Org. Chem.*
(5) B. L. Roos-Kozel, Ph.D. Thesis, Purdue University, 1981.
(6) J. A. Schmidt and W. L. Jorgensen, submitted for publication in *J. Org. Chem.*
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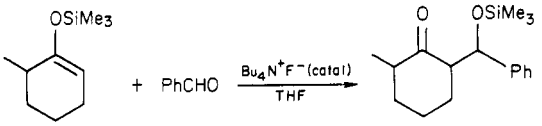
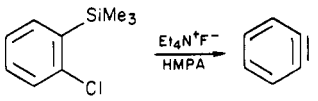
compounds and that consequently requires explicit consideration in CAMEO.

(A) Substitution at Silicon. Since silicon is more electropositive than carbon or hydrogen, it is highly susceptible to nucleophilic attack. Fluoride and oxy anions are particularly effective due to the unusually strong bonds between these elements and silicon. In fact, the following reactivity series has been established for trialkylsilanes (R_3SiX): X = I < SR < Br < H < NC < Cl < NCS < NCO < OR, F, such that sulfide can displace iodide, etc.[11] Thus, fluoride ion is a very commonly used desilylating agent as in eq 1 and 2.[12,13] These processes illustrate the driving



(1)



(2)

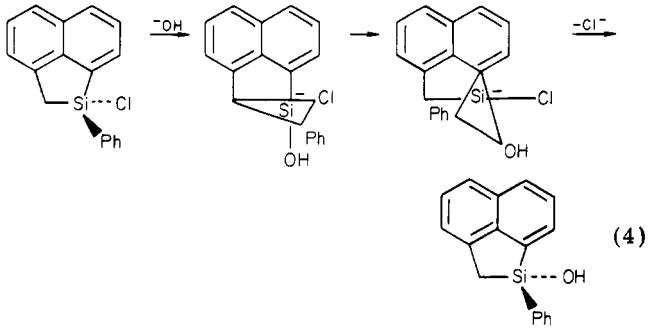
force of creating an Si–F bond. The weakly basic fluoride ion essentially generates a much stronger base, the enolate ion, in the first case, and the strained benzyne is produced in the second example. Fluoride or alkoxide ions can also be used to release acetylide ions from alkynylsilanes.[14]

Another point is the strong preference for substitution at silicon rather than elimination to yield silenes (eq 3).[8]

$$H_2C{=}SiMe_2 \xleftarrow{MeO^-} Me_3SiCl \xrightarrow{MeO^-} MeOSiMe_3 \qquad (3)$$

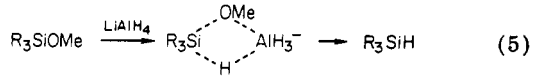
This reflects the relative weakness of the 2p–3p π bond between carbon and silicon. The facile substitution on trialkylsilanes also indicates there is little steric hindrance in approaching such electrophiles which can be attributed to the long Si-C bonds (ca. 1.85 Å). In contrast, *t*-BuCl when treated with methoxide yields only isobutylene.

The predominant process occurring at silicon is S_N2 displacement via a trigonal-bipyramidal intermediate.[8] In acyclic cases, inversion of configuration is the norm particularly with good leaving groups and strong nucleophiles. However, with poorer leaving groups and in hindered systems retention may be observed and can involve pseudorotation of the pentacoordinate intermediate as in eq 4.[8,15] A second retention mechanism (S_Ni-Si) features



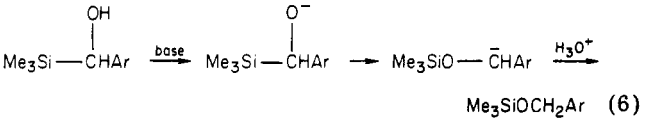
(4)

front-side attack. It is proposed for some intramolecular migrations and for intermolecular cases such as lithium aluminum hydride reduction of trialkylsilyl methyl ethers (eq 5).[16] An important intramolecular migration is the



(5)

Brook rearrangement of α-(trialkylsilyl)alkoxides (eq 6)



(6)

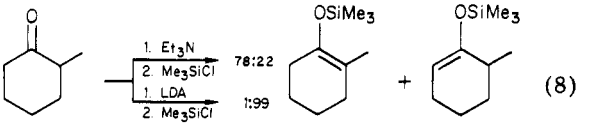
which yields retention at silicon.[17] The pseudorotation mechanism is believed to be operative in this case. Furthermore, the affinity of oxygen for silicon is again apparent.

(B) Steric Effects and Protecting Groups. Silyl functional groups are best known for their use as protecting groups for compounds with labile hydrogens. Alcohols, ketones, and aldehydes are the most commonly guarded; however, carboxylic acids and esters, sulfenic acids, alkynes, and ketenes have been protected via silyl derivatives as well. Silylation is often achieved by deprotonation followed by displacement on trialkylhalosilanes (eq 7). In

$$ROH + R'_3SiX \xrightarrow{base} ROSiR'_3 \qquad (7)$$

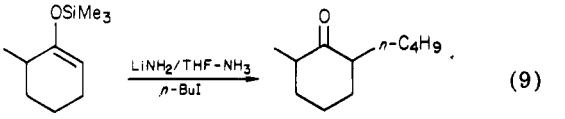
addition, there are numerous other silylating reagents including silylamides such as *N*-(trimethylsilyl)diethylamide (TMSDEA) and *N*-(trimethylsilyl)imidazole (TMSI). Substantial variations in reactivity and sensitivity to the steric environment of the group being protected can be obtained with these reagents. Consequently, the selective protection of less hindered alcohols has been used advantageously in prostaglandin syntheses.[18]

Ketones and aldehydes are readily converted to silyl enol ethers; the predominance of O- rather than C-silylation is consistent with the relative strengths of Si–O (90 kcal/mol) and Si–C (70 kcal/mol) bonds. Nitrogen also has a lower affinity for silicon than oxygen; so, for example, amides and amines generally eliminate (β-haloalkyl)silanes to vinylsilanes, while alkoxides yield the alkenes.[7,19] An important aspect of the production of silyl enol ethers is the regioselectivity that can be obtained by generating the enolates under conditions of kinetic or thermodynamic control (eq 8).[20,21] Furthermore, regeneration of the



(8)

enolate under aprotic conditions occurs without equilibration (eq 1 and 9).[21,22]



(9)

A nice example of the protection of a terminal acetylene may be found in Corey's use of the reagent 3-lithio-1-

(8) I. Fleming in "Comprehensive Organic Chemistry", Vol. 3, D. Barton and W. D. Ollis, Eds., Pergamon Press, Oxford, 1979, p 541.
(9) I. Fleming, *Chem. Soc. Rev.*, **10**, 83 (1981).
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(11) (a) C. Eaborn, *J. Chem. Soc.*, 3077 (1950); (b) H. H. Anderson and M. Fischer, *J. Org. Chem.*, **19**, 1296 (1954).
(12) R. Noyori, K. Yokoyama, J. Sakata, I. Kuwajima, E. Nakamura, and M. Schimuzu, *J. Am. Chem. Soc.*, **99**, 1265 (1977); I. Kuwajima, E. Nakamura, and M. Shimizu, *ibid.*, **104**, 1025 (1982).
(13) R. F. Cunico and E. M. Dexheimer, *J. Organomet. Chem.*, **59**, 153 (1973).
(14) C. Eaborn and D. R. M. Walton, *J. Organomet. Chem.* **4**, 217 (1966).
(15) M. Mislow, *Acc. Chem. Res.*, **3**, 321 (1970).
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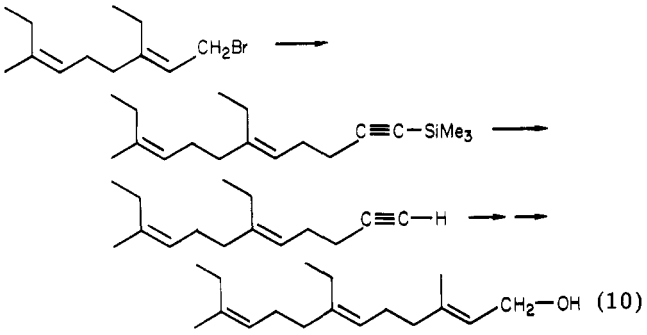
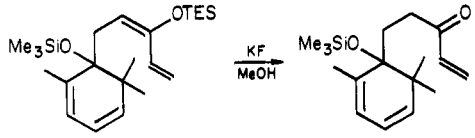
(18) E. W. Yankee, U. Axen, and G. L. Bundy, *J. Am. Chem. Soc.*, **96**, 5865 (1974).
(19) A. Ottolenghi, M. Fridkin, and A. Zilkha, *Can. J. Chem.*, **41**, 2977 (1963).

(trimethylsilyl)propyne,[23] as in a juvenile hormone synthesis (eq 10).[24] After deprotection and elaboration, stereoselective syntheses of 1,5-dienes are obtained.



(10)

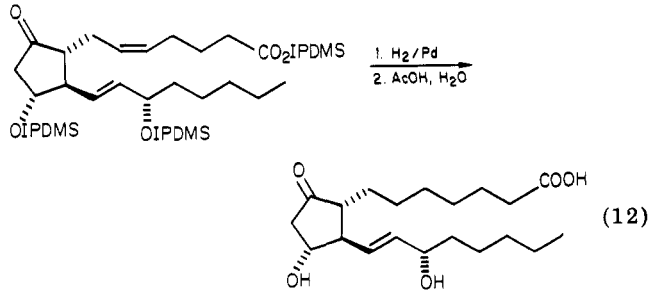
Variation of the alkyl groups on silicon is an important factor in rates of desilylation. Thus, the utility of trimethylsilyl protecting groups is restricted by their sensitivity to hydrolysis and to attack by other nucleophiles. Consequently, larger alkyl groups have been used to afford greater protection. Some popular alternatives are triethylsilyl (TES), isopropyldimethylsilyl (IPDMS), *tert*-butyldimethylsilyl (TBDMS),[25] and *tert*-butyldiphenylsilyl (TBDPS).[26] The enhancement of stability relative to trimethylsilyl ethers varies significantly with the cleavage conditions and leaving group; however, some rough rate factors are 10^{-1}–10^{-2} for TES, 10^{-2}–10^{-3} for IPDMS, 10^{-4} for TBDMS, and 10^{-5} for TBDPS.[7,8] Selective cleavage of one silyl group in the presence of another can then be controlled by manipulation of the steric environments. Furthermore, selective cleavage of similar protecting groups is governed by relative leaving group abilities as illustrated in eq 11.[27] This is the usual situation for CAMEO



(11)

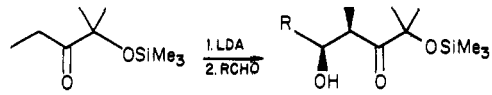
and is treated by assigning "effective pK_a's" to the leaving groups.[1,3]

Trialkylsilyloxy groups may also be used effectively as steric protecting groups for proximate functionality. For example, Corey has used two OIPDMS groups to shield the C13–C14 double bond in a PGE_2 derivative which then leads to PGE_1 (eq 12).[28] And Heathcock has found the



(12)

OSiMe$_3$ group to be conjesting enough to promote (*Z*) enolate formation and stereoselectivity in acyclic aldol condensations as in eq 13.[29]



(13)

(C) Directing Effects of Silicon. Trialkylsilyl groups are the source of several interesting and synthetically useful directing effects. The key generalizations are that relative to hydrogen silicon stabilizes an adjacent negative charge or S_N2 transition state and a β positive charge, while it has essentially no effect on an adjacent positive charge.

The stabilization of an adjacent negative charge permits α-metallosilanes to be generated from otherwise quite inert acids via proton transfer, halogen–metal exchange or organometallic addition as shown in eq 14–17.[7,30] Substi-

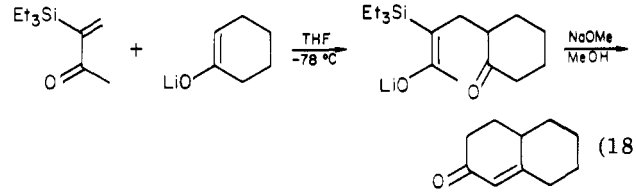
$$(CH_3)_3SiCH_2Cl \xrightarrow[THF,\ -78\ ^\circ C]{sec\text{-}BuLi} (CH_3)_3SiCHLiCl \quad (14)$$

$$(CH_3)_3SiCl \xrightarrow[THF,\ -78\ ^\circ C]{t\text{-}BuLi} LiCH_2Si(CH_3)_2Cl \quad (15)$$

$$(CH_3)_3SiCH_2Br \xrightarrow[Et_2O]{n\text{-}BuLi} (CH_3)_3SiCH_2Li \quad (16)$$

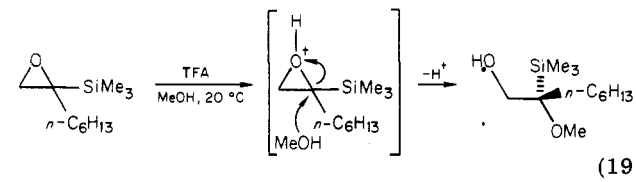
$$(CH_3)_3SiCH{=}CH_2 \xrightarrow[THF]{n\text{-}BuLi} (CH_3)_3SiCHLi(CH_2)_4CH_3 \quad (17)$$

tution at silicon is avoided by using carbon and nitrogen bases which have a much lower affinity than oxygen for silicon. In general, *sec*-butyllithium is the reagent of choice to deprotonate a center activated only by silicon. Consistently, the pK_a of alkylsilanes appears to be about 35. The stabilization of an anion α to silicon involves a combination of polarization, inductive effects, and anionic hyperconjugation with the σ^*_{SiC} bond orbitals which are relatively low in energy. Some mixing between the filled 2p orbital of the anion and 3d orbitals on silicon is also possible, though this idea is controversial.[31] In any event, the stabilization has been used to reduce the reversibility of Michael reactions, so the annelation in eq 18 proceeds in 80% yield, while the corresponding process with methyl vinyl ketone yields almost no Michael product.[32]



(18)

A related observation is that silyl groups direct S_N2 attack to adjacent carbons, if displacement is unfavorable at silicon. Thus, α,β-epoxysilanes usually give products of α cleavage even in hindered cases like eq 19.[7]



(19)

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(21) H. O. House, L. J. Czuba, M. Gall, and H. O. Olmstead, *J. Org. Chem.*, **34**, 2324 (1969).
(22) E. S. Binkley and C. H. Heathcock, *J. Org. Chem.*, **40**, 2156 (1975).
(23) E. J. Corey and H. A. Kirst, *Tetrahedron Lett.*, 5041 (1968).
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(25) E. J. Corey and A. Venkateswarlu, *J. Am. Chem. Soc.*, **94**, 6190 (1972).
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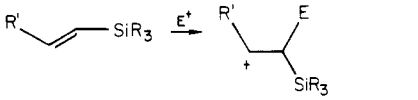
(31) H. Kwart and K. King, "d-Orbital Involvement in the Organic Chemistry of Silicon, Phosphorus, and Sulfur", Springer-Verlag, West Berlin, 1977.

The directing effect that is at the heart of the chemistry of vinyl-, alkynyl-, and allylsilanes stems from the ability of silyl groups to stabilize a β carbonium ion site. Thus, electrophilic additions to these unsaturated species show a preference for forming β-silyl carbonium ions (eq 20).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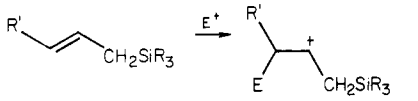
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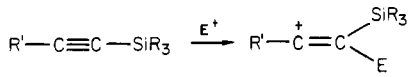
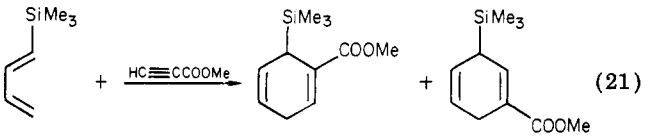

(20c)

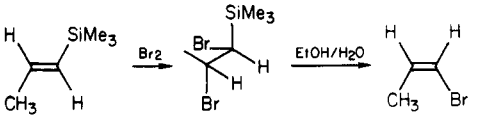
The β effect is due to the enhanced hyperconjugating ability of C–Si bonds; the C–Si bond orbital is relatively high in energy which follows from the electropositive nature of silicon and the long bond length. From σ_p^+ values a CH_2SiR_3 group may be placed between simple alkyl groups and ethers at about the level of a NHCOR group in its ability to stabilize a positive charge.[7,8] In contrast, silyl groups have little effect on an α positive charge in comparison to hydrogen. This is apparent from solvolysis data,[33] from the lack of regioselectivity in Diels–Alder reactions such as eq 21,[34] and from the regioselectivity of electrophilic additions to vinylsilanes.


(21)

40:37

The electrophilic additions are often followed by facile displacement of the silyl group to give net addition/elimination as in eq 22–26. These examples illustrate several important points. (1) The elimination may occur with retention or inversion of configuration at the double bond of a vinylsilane. In general, halogens give anti addition and anti elimination for net inversion, while most other electrophiles yield retention.[7,8] (2) Lewis acid catalysis is often used to enhance the rate of electrophilic additions to unsaturated silanes as in eq 24 and 25. The latter example also illustrates that the silyl group can be used to direct the elimination; without it a mixture of olefins is obtained.[38] (3) The β effect is again apparent in eq 26, since if the Me_3Si group is replaced by methyl, the product has a five-membered D ring.[39]

(D) Stereochemistry of β Eliminations. Eliminations of (β-haloalkyl)silanes can be effected under mild conditions to produce even benzynes (eq 2) and allenes (eq 27).[40] The elimination to form olefins strongly prefers to be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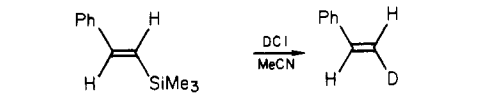
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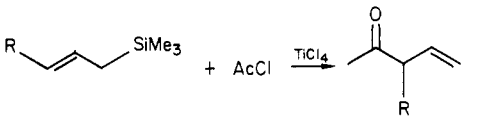
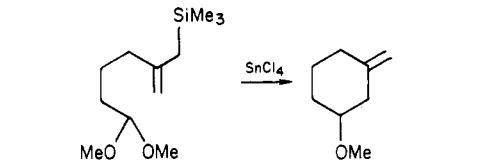
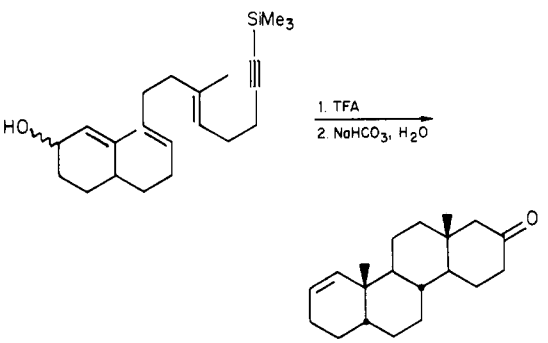
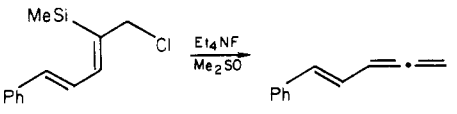
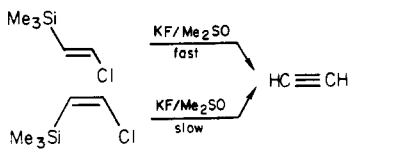

(24)[37]


(25)[38]

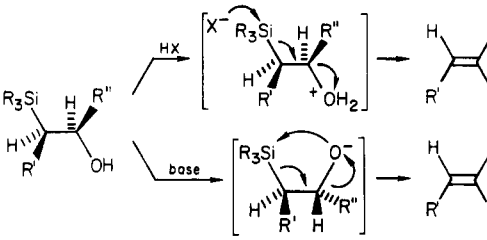

(26)[39]

stereospecifically anti as in eq 22, although syn eliminations can occur at a much slower rate. This is also true for vinylic systems (eq 28).[41]

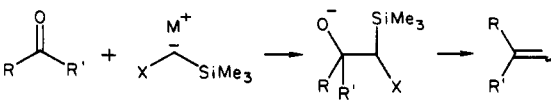

(27)


(28)

β-Hydroxysilanes also undergo stereospecific elimination: acidic and basic conditions lead to anti and syn eliminations, respectively (eq 29). The β-alkoxysilane


(29)

intermediates can be generated directly by addition of α-metallosilanes to carbonyl compounds (eq 30). The

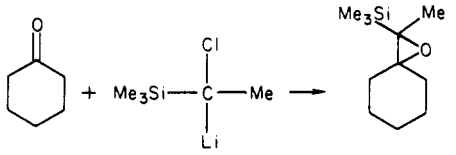

(30)

overall addition/elimination is referred to as Peterson olefination.[42] It has obvious similarities to the Wittig

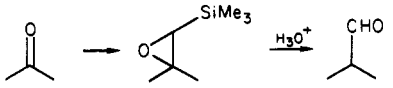
(32) G. Stork and B. Ganem, *J. Am. Chem. Soc.*, **95**, 6152 (1973); R. K. Boeckman, *ibid.*, *96*, 6179 (1974); G. Stork and J. Singh, *ibid.*, *96*, 6181 (1974).
(33) M. A. Cook, C. Eaborn, and D. R. M. Walton, *J. Organomet. Chem.*, **29**, 389 (1971).
(34) I. Fleming and A. Percival, *J. Chem. Soc., Chem. Commun.*, 681 (1976); *ibid.*, 178 (1978).
(35) A. W. P. Jarvie, A. Holt, and J. Thompson, *J. Chem. Soc. B*, 852 (1969).
(36) K. E. Koenig and W. P. Weber, *J. Am. Chem. Soc.*, **95**, 3416 (1973).
(37) See ref 7, pp 109–111, for numerous examples.
(38) I. Fleming, A. Pearce, and R. L. Snowden, *J. Chem. Soc., Chem. Commun.* 182 (1976).
(39) W. S. Johnson, T. M. Yarnell, R. F. Myers, D. R. Morton, and S. G. Boots, *J. Org. Chem.*, **45**, 1254 (1980).
(40) T. H. Chan and W. Mychajlowskij, *Tetrahedron Lett.*, 171 (1974).
(41) R. F. Cunico and E. M. Dexheimer, *J. Am. Chem. Soc.*, **94**, 2868 (1972).

reaction with some advantages for stereochemical control and ease of workup. The choice of metal counterion affects whether the reaction stops at the hydroxysilane stage or proceeds to olefin. Sodium and potassium promote the elimination, Grignard reagents allow isolation of hydroxysilanes, and lithium can give either product, depending on the nature of the X group. In particular, electron-withdrawing groups favor the elimination.

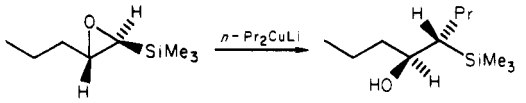
An offshoot of the Peterson reaction which is reminiscent of Darzen's condensation yields epoxysilanes (eq 31).[43]


(31)

It is advisable to use chlorine as the leaving group, since, for example, bromine often yields primarily vinyl bromide products. The epoxysilanes are important intermediates since they are easily hydrolyzed to aldehydes or ketones, yielding an acyl anion equivalent overall (eq 32). They


(32)

also undergo stereospecific α cleavage as in eq 19 and 33.[44]


(33)

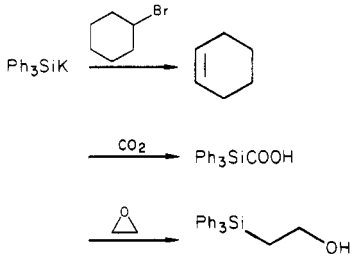
(E) Organosilyl Anions. One final topic that must be considered by CAMEO is the formation and reactivity of organosilyl anions. The preferred route to silicon–metal bonds is by cleavage of disilanes (eq 34).[45] Alternatives

$$Me_3SiSiMe_3 \xrightarrow{\text{MeLi, HMPA}} Me_3SiLi + Me_4Si$$
$$\xrightarrow{\text{KOMe, HMPA}} Me_3SiK + Me_3SiOMe \quad (34)$$

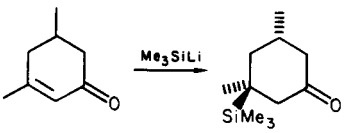
are the deprotonation of hydrosilanes with potassium hydride and reduction of arylalkylhalosilanes (eq 35).[46]

$$PhMe_2SiCl \xrightarrow{\text{Li, THF}} PhMe_2SiLi \quad (35)$$

The metallosilanes are strong bases and good nucleophiles that will react with a variety of electrophiles as in eq 36.[8]


(36)

Their behavior in additions to α,β-unsaturated ketones parallels that of organocuprate reagents. Addition is predominantly 1,4 with a strong preference for axial attack (eq 37).[45] Addition of cuprous iodide allows for higher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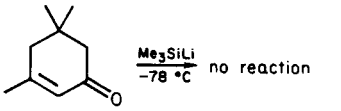
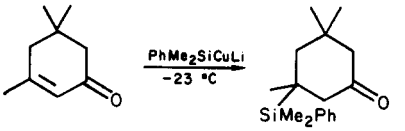
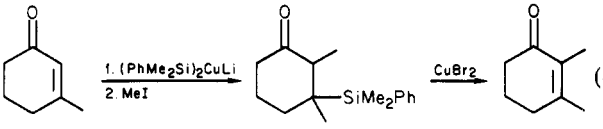

(38)


(39)

reaction temperatures which can help overcome steric barriers (eq 38 and 39).[47] The utility of this reaction is increased due to its role in the synthesis of α-substituted enones by trapping the enolate, halogenation, and elimination (eq 40).[47]


(40)

Implementation in Cameo

The majority of changes needed to properly treat organosilicon chemistry in CAMEO were in the routines that handle base-catalyzed and nucleophilic processes. These modifications will be discussed first, and then a short summary of the considerations for electrophilic reactions will be given. It should be realized that CAMEO is a large, complex program consisting of over 20 000 lines of FORTRAN code. Consequently, although great detail could be provided, effort has been made to keep the presentation general and concise.

The logic followed for base-catalyzed and nucleophilic chemistry has been presented previously.[1,3] Only a very brief review is presented here with the aid of the flow chart in Figure 1. After the reactants and conditions are input via the graphics terminal, the perception phase is entered, during which structural features such as functional groups, rings, and stereochemical relationships are recognized. The functional group data are used to determine the acidities for any sites with labile hydrogens and the basicity of the initial base if one has been input. This information is then used to decide if any proton transfer, halogen–metal exchange, or organometallic addition reactions should be performed. These are the fastest processes, and appropriate proton transfers or halogen–metal exchanges are performed at this point. Organometallic additions are performed later; however, if they are deemed dominant, they will suppress possible competing proton transfers or halogen–metal exchanges.[3] If these latter two processes occur, the resulting anionic sites are then designated as nucleophiles. Otherwise the initial base is the nucleophile.

The electrophilic sites are then recognized; possibilities for leaving group bonds include most bonds to heteroatoms and multiple bonds. Next, the nucleophiles are processed one at a time. If a nucleophile can participate in an ElcB elimination, e.g., decomposition of an α-halo alkoxide, this is the only pathway for the nucleophile since it is a very fast process. Otherwise, the nucleophile is paired with all electrophiles to consider conjugate ElcB (Grob fragmentations), S_N2, E2, and addition reactions. The competitions

(42) D. J. Peterson, *J. Org. Chem.*, **33**, 780 (1968).
(43) F. Cooke and P. Magnus, *J. Chem. Soc. Chem. Commun.*, 513 (1977).
(44) P. F. Hudrlik, D. Peterson, and R. J. Rona, *J. Org. Chem.*, **40**, 2263 (1975).
(45) W. C. Still, *J. Org. Chem.*, **41**, 3063 (1976); P. B. Dervan and M. A. Shippey, *J. Am. Chem. Soc.*, **98**, 1265 (1976).
(46) M. V. George, D. J. Peterson, and H. Gilman, *J. Am. Chem. Soc.*, **82**, 403 (1960).
(47) D. J. Ager and I. Fleming, *J. Chem. Soc., Chem. Commun.*, 177 (1978).

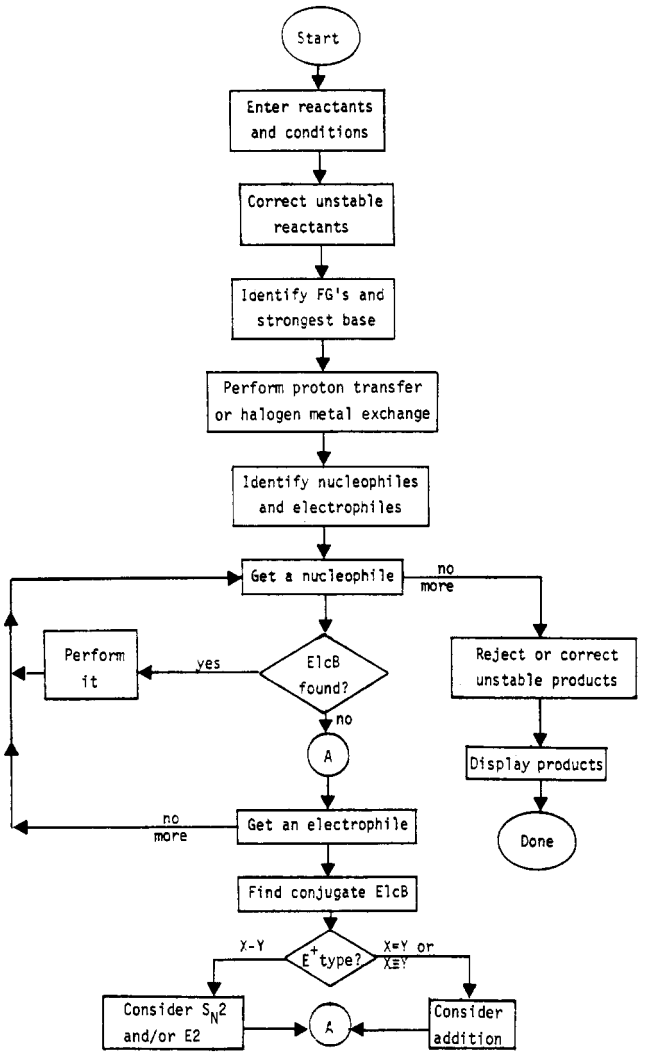


Figure 1. Simplified flow chart for processing base-catalyzed and nucleophilic reactions in CAMEO.

between these processes are handled by heuristics based on literature precedents that are described elsewhere.[1,3] A key point in choosing electrophiles is the use of the "ΔpK_a rule". It is thermodynamically beneficial for the leaving groups to be weaker bases than the nucleophile. So, unless a protic solvent is used, the conjugate acid of the leaving group is not allowed to be more than about 5 pK_a units above the conjugate acid of the nucleophile.[1] For this purpose, the leaving groups are assigned "effective pK_a's" which take into account their intrinsic acidities and other factors such as strain relief for epoxides and bond strengths for hetero–hetero vs. carbon–hetero leaving bonds. Only the leaving groups with the lowest effective pK_a and those others no more than one level (3–5 pK_a units) higher may be displaced.

The changes needed to incorporate organosilicon chemistry into this scheme may now be considered.

(A) pK_a Perception. α-Metallosilanes can be generated by proton transfer, halogen–metal exchange, or addition of organometallics to vinyl silanes (eq 14–17). Simple hydro- and alkylsilanes are classed in level 15 of the 18-level pK_a scale used in CAMEO which allows deprotonation by secondary alkyl anions.[3] Vinylsilanes are recognized as additive groups for organometallic reagents at least as basic as *n*-alkyllithiums. Moreover, the ability of silicon to further activate an adjacent proton-transfer site is handled by lowering the pK_a value one level in such cases. For example, a ketone normally in level 9 (pK_a ca. 20) is

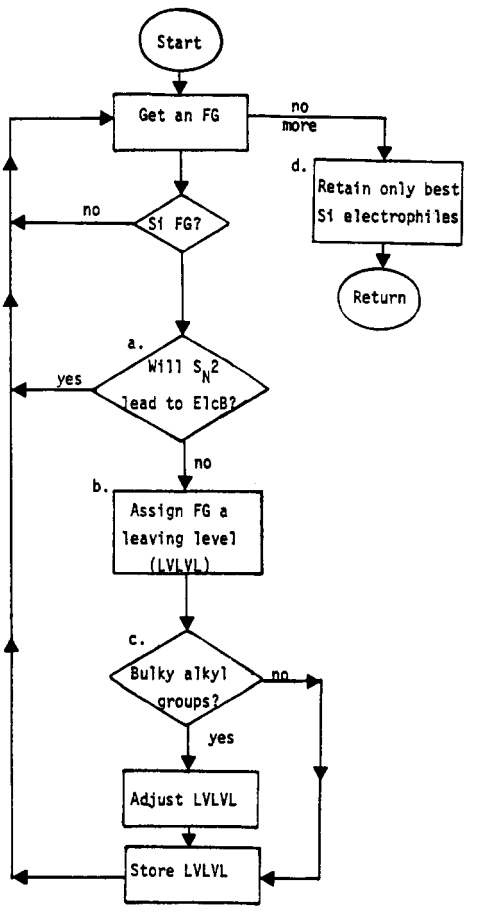


Figure 2. Flow chart for processing silyl electrophiles.

lowered to level 8 by an α-trialkylsilyl group as long as there is still an α hydrogen. With these assignments the normal rules for proton transfer are then followed.[1] Specifically, proton transfer generates the weakest base and others no more than one level more basic. The competitions between proton transfer, halogen–metal exchange, and organometallic addition are handled as before; in general, the processes yielding the weakest bases dominate, though competition between addition and exchange must always be considered.[3] Also, exchange usually takes place only between an organolithium reagent and an iodide or bromide.

(B) Perception of Electrophiles. Electrophiles are perceived and rated by CAMEO through an evaluation of their leaving groups. The associated leaving group level (LVLVL) reflects the pK_a of the conjugate acid of the leaving group and other factors as noted above. In particular, cleavage of hetero–hetero bonds is more facile than that of the corresponding carbon–hetero bonds; therefore, an adjustment of the LVLVL's is made. For example, $PhOC(CH_3)_3$ has a LVLVL of 11, while $PhOSi(CH_3)_3$ is initially assigned a LVLVL of 7. Thus, treatment with an alkoxide (pK_a level 8) would not be allowed to eliminate phenoxide from *tert*-butyl phenyl ether; however, substitution at silicon in the silyl analogue would be permitted.

The adjustment of leaving levels also provides an efficient means for handling the steric effects for bulky trialkylsilyl groups. For example the initial LVLVL's for $PhOSiMe_3$, $PhOSiEt_3$, $PhOS(i\text{-}Pr)_3$, and $PhOSiMe_2t\text{-}Bu$ are taken as 7, 8, 9, and 10, respectively, which reflects the change in rates of ca. 10^{-4} for hydrolysis along the series. By use of the ΔpK_a rule only the $SiMe_3$ and $SiEt_3$ groups would be attacked if all four groups were present.

A summary of the processing for silyl leaving groups is given in Figure 2. The following points correspond to the

lettered boxes on the flow chart. (a) Substitution on silicon γ to a leaving group would lead to subsequent elimination. Such reactions are handled as E2 eliminations to obtain proper stereochemistry for the product, and the silicon is not considered an electrophile for S_N2 reactions. (b) Leaving groups associated with a functional group (halides, sulfonates, enolates, etc.) as well as those not part of a functional group such as allylic or benzylic anions are ranked according to the nucleophile's ability to displace them. (c) If bulky alkyl groups are present on the silicon, the leaving level is adjusted appropriately. (d) Only the best silicon electrophile and those others with leaving groups within one leaving level are retained. After this screening one final adjustment of the leaving levels may be made. This is necessary to reflect the high affinity of silicon for fluoride, chloride, and oxy anions. Since fluoride and chloride are in pK_a level 1, valid leaving groups on silicon are given a final LVLVL of 1 in the presence of these ions or oxy anions. Consequently, about the only groups that will not be displaced directly from silicon by these ions are simple alkyl, vinyl, or aryl groups. Also, silicon–hetero bonds will be cleaved in preference to silicon–carbon bonds, if both are present and part of valid leaving groups (cf. eq 2).

(C) Silyl Anions and Addition Reactions. Nucleophiles are also classified in CAMEO with nucleophile qualification values (NQV's).[1] The NQV's are used to help treat the competitions between S_N2, E2, and addition reactions; proton transfer or halogen–metal exchange has occurred previously if appropriate. Since silyl anions are strong bases and good nucleophiles that may participate in substitution, elimination, or addition reactions, they are placed in the same category (NQV = 4) as nucleophiles such as enolates and unhindered alkoxides. Weaker, unhindered bases like RS^- or Cl^- are in class 3 and generally do not participate in eliminations. Classes 1 (LDA, DBU) and 2 (t-BuO^-) are for strong, hindered bases that completely (NQV = 1) or generally (NQV = 2) prefer elimination. It may also be noted that formerly the product of addition of a silyl anion to an unsaturated system would have been treated as unstable along the lines of a hemiacetal. They are now recognized as valid nucleophiles for additions, and their preference for conjugate over 1,2-addition is taken into account.

(D) E2 Eliminations. Antiperiplanar eliminations are being handled as E2 reactions with silicon acting as the proton substitute. Normally, substitution at silicon in such cases is faster than removal of a proton when the base is nucleophilic.[8,48] In CAMEO, bases with an NQV of 3 or 4 perform the silicon elimination, while the hindered bases like LDA yield the normal E2 elimination. Several other modifications were needed to accommodate the silicon eliminations. First, primary electrophiles which could formerly only undergo substitution reactions with good nucleophiles may now participate in substitutions and silicon eliminations, but still not in simple E2 reactions. Second, aromatic halides can now yield benzynes both through silicon elimination (eq 2) and proton removal by strong bases such as sodium amide. Third, stereo arrangements are considered when gauging relative rates of eliminations, with anti orientations given preference over syn. The synperiplanar eliminations in the Peterson reaction are handled by treating the β-alkoxysilanes as unstable functional groups (depending on the counterion) in the same way that betaines from Wittig reactions are decomposed in post-mechanism perception.[1,3]

(48) E. J. Corey, W. J. Howe, and D. A. Pensak, *J. Am. Chem. Soc.*, **96**, 7724 (1974).

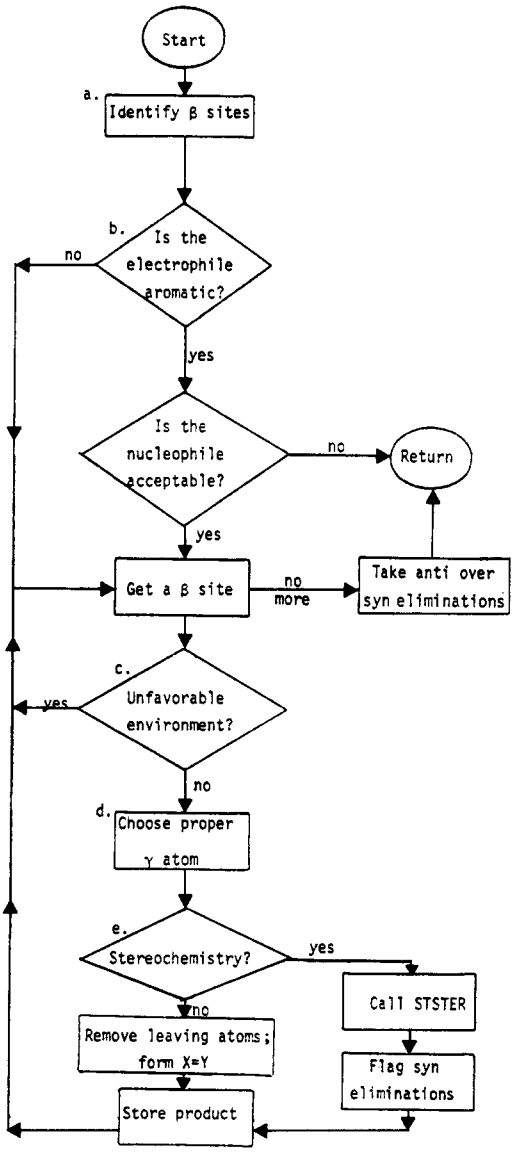
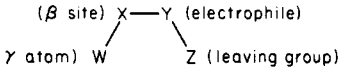


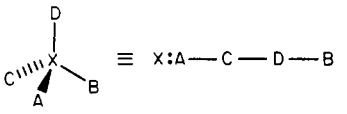
Figure 3. Flow chart for selecting leaving groups for E2 eliminations.

Following this discussion, the summary of the processing of a leaving group for E2 reactions shown in Figure 3 is relatively self-explanatory. However, a few lettered points should again be noted. The environment of a leaving group is defined by the digram below. (a) The β sites are those



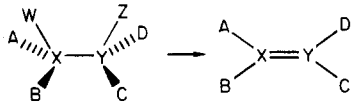
atoms β to the leaving group that are bonded to a removable proton or silyl group. The proton(s) or silicon(s) is designated as the γ atom. (b) Formation of benzynes requires a strong base for proton removal or a strong nucleophile for silicon elimination. (c) The formation of 2p–3p π bonds or γ atoms that are inaccessible due to steric hindrance rule out possible eliminations. (d) In the presence of a good nucleophile γ silicon atoms are chosen for elimination rather than hydrogens. (e) If the β site (X) and the electrophilic atom (Y) are both stereocenters, the configuration of the double bond in the product will be drawn to reflect anti or syn elimination as appropriate. The necessary processing is described in the next section. It should be noted that the products of any reaction always go through post-mechanism screening for unstable functional groups and for overly strained rings.

(E) Stereochemical Manipulations. Routines have been implemented in CAMEO that allow the proper stereochemistry to be displayed for products of substitution and elimination reactions. The same linear representation is used to define a stereocenter as employed by Corey and Wipke in their programs.[48,49] Briefly, it is the clockwise ordering of the atoms about a stereocenter sighting down a wedged or dotted bond. There are 12 equivalent linear



representations for a tetrahedral center that can be interconverted by double permutations of the indices for the four attachments. A single permutation corresponds to inverting the stereocenter. Manipulations of such stereorepresentations can then be used to perceive structural data including cis and trans relationships of substituents on rings or around double bonds, cis and trans fusion bonds, the identicality of appendages, and *R* and *S* designations.[48-50]

For the purpose of performing E2 eliminations stereospecifically in CAMEO, it was necessary to solve the following problem. If a structure is entered as shown below, the



leaving atoms are removed, and the positions of the other atoms are unchanged, will the resultant stereochemistry for the double bond correspond to a syn or anti elimination? If an anti elimination is appropriate and the geometry of the double bond is consistent, no redrawing would be necessary. On the other hand, if, for example, anti elimination was desired and the direct removal of the leaving atoms generates the wrong configuration for the double bond, then the coordinates for the substituents on one end of the double bond must be interchanged. Naturally, the problem must be solved in a completely general way that only uses the stereorepresentations.

Four steps are needed to find out if the orientation as entered would correspond to a syn or anti elimination. In step 1, the original stereorepresentations (STEREP) are reordered for X and Y such that STEREP(1) is the other

$$\text{STEREP for X: } \overset{\text{original}}{\text{B-A-W-Y}} \rightarrow \overset{\text{reordered}}{\text{Y-W-A-B}}$$

$$\text{STEREP for Y: C-X-Z-D} \rightarrow \text{X-Z-C-D}$$

atom in the incipient double bond, STEREP(2) is the leaving atom, and the remaining elements in STEREP are the other substituents in the clockwise ordering. In step 2, the leaving groups are removed, and the double bond is formed, while the other atoms retain their original positions. Step 3 involves generating a second set of representations (REP) for the now trigonal X and Y. REP(1)

$$\text{REP for X: Y-B-A}$$

$$\text{REP for Y: X-D-C}$$

is the other atom in the double bond, and REP(2) and REP(3) give the clockwise ordering for the substituents. The final step is a comparison of the STEREPs and REPs. There are four possibilities. If STEREP(3) and REP(3)

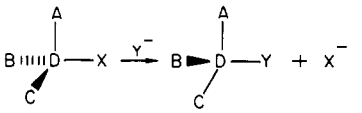
$$\text{STEREP for X: Y-W-A-B} \quad \text{STEREP for Y: X-Z-C-D}$$

$$\text{REP for X: Y-B-A} \quad \text{REP for Y: X-D-C}$$

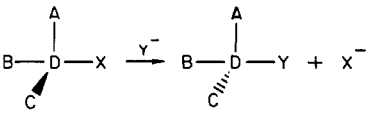
both match for both X and Y (as in the example) or if they *both* do not match, then the elimination as drawn would be syn. On the other hand, if STEREP(3) and REP(3) match for either X or Y but not for both, the elimination would be anti. Of course, only one case, the syn, is checked in the program because there is only one alternative, anti elimination.

The inversion of a stereocenter in a substitution reaction is less complicated. Only one stereobond is required in CAMEO to define a stereocenter; it is assumed that the bond opposing the stereo bond has the same stereotype (wedged or dotted) as illustrated below. However, a stereocenter

will not be recognized if all four attachments are not explicit. Furthermore, dotted bonds are directional in CAMEO and are equivalent to an inverted wedge. In the drawing of the product of a substitution reaction, the bond between the electrophile and the leaving atom is severed, and the fragments are separated. The nucleophilic atom is then positioned so that it occupies the original coordinates of the leaving atom. Then, if there was a dotted bond, it is redrawn as a wedge, and all other stereochemistry is re-



moved from the center. If there was only a wedged bond, it is dotted. Minor adjustments are necessary when the



electrophile and leaving atom are in a ring, e.g., an epoxide, so that the product is drawn in an acceptable manner.

(F) Electrophilic Chemistry. The treatment of electrophilic reactions in CAMEO will be described in detail elsewhere.[4] The key processes are the generation of carbonium ions and their subsequent elimination, rearrangement, or quenching. The generation may occur by adding an electrophile to an unsaturated bond or by S_N1 reactions that may be catalyzed by an electrophile. Prediction of the relative stabilities of carbonium ions is critical in assessing competitive processes. Along these lines, the effects of silyl groups α and β to a carbonium ion site described in the section on Directing Effects of Silicon are taken into account. In addition, the effect of bulky alkyl groups on rates of solvolysis for trialkylsilyl ethers is considered.

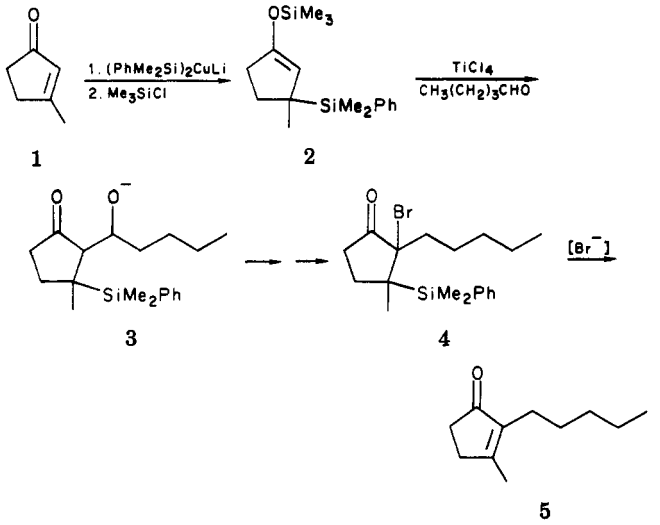
Sample Sequences

Before closing, a few comparisons of reaction sequences observed experimentally and predicted by CAMEO may be presented. The results of the analyses are shown in Schemes I–V.

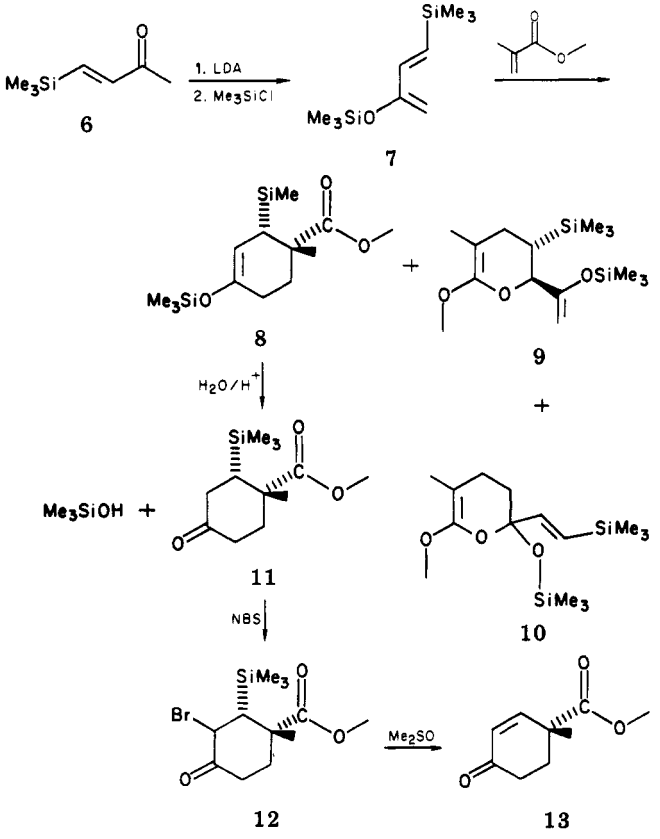
Scheme I presents several steps from a synthesis of dihydrojasmone (**5**).[51] For the first reaction, CAMEO correctly predicts the 1,4-addition of the silyl cuprate and the subsequent O-silylation to give **2** which was reported in

(49) W. T. Wipke and T. M. Dyott, *J. Am. Chem. Soc.*, **96**, 4825 (1974).
(50) E. J. Corey and W. L. Jorgensen, *J. Am. Chem. Soc.*, **98**, 189 (1976).
(51) D. A. Ager, I. Fleming, and S. K. Patel, *J. Chem. Soc., Perkin Trans. 1*, 2520 (1981).

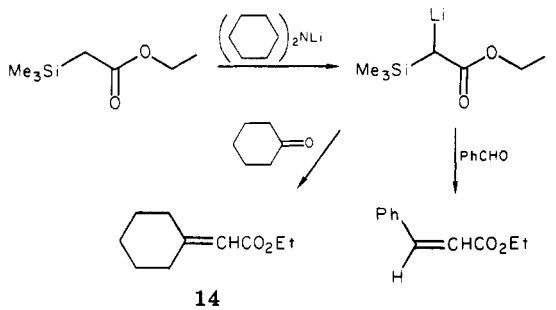
Scheme I



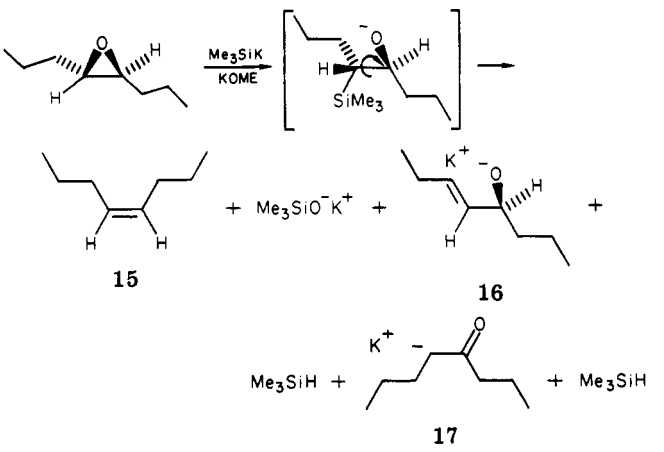
Scheme II



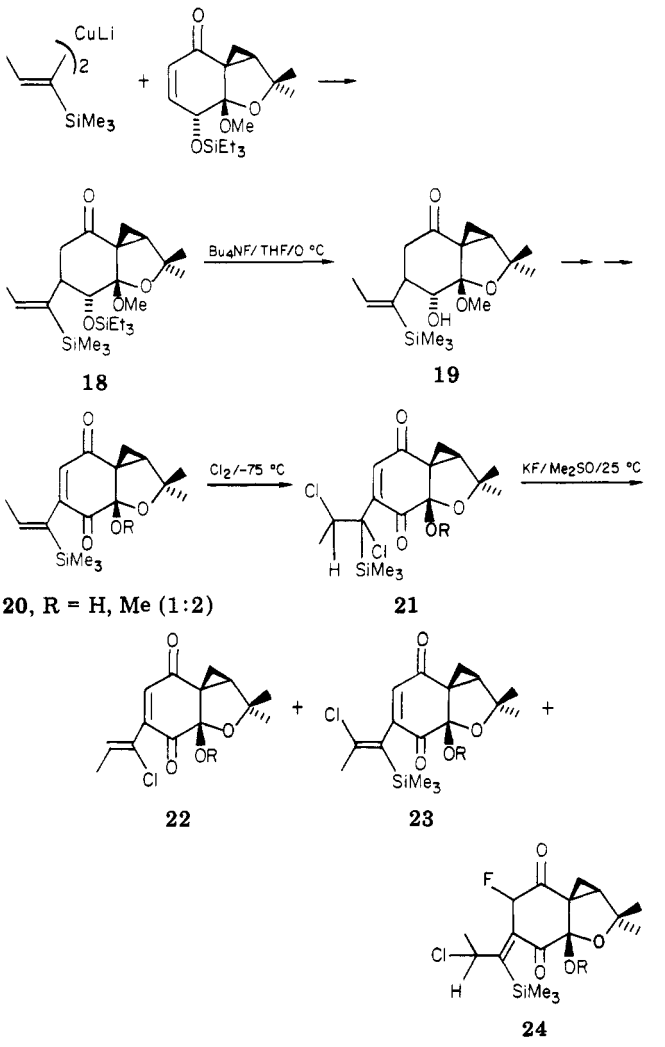
Scheme III



Scheme IV



Scheme V



82% yield.[51] A key reaction in this sequence is the regeneration of the α,β-unsaturation under mild conditions (**4** → **5**). This reaction proceeds in 91% yield, and the observed product is the only one predicted by CAMEO. Substitution on the tertiary bromide and elimination with the β hydrogen were considered but rejected as improbable by the program.

Scheme II[52] begins with silyl enol ether formation and a Diels–Alder reaction. Two additional products, **9** and **10**, are suggested by CAMEO.[6] However, the program also computes and displays ΔH's for each reaction,[5] and **9** and **10** are found to be at least 30 kcal/mol less thermodynamically favorable than **8**. The sequence is completed

(52) I. Fleming and A. Percival, *J. Chem. Soc., Chem. Commun.*, 178 (1978).

by hydrolysis of 8, bromination, and elimination. At this time, CAMEO does not perform the NBS bromination since it is a radical process. However, electrophilic bromination of 11 is predicted by the program to yield 12.

Examples of the Peterson reaction are shown in Scheme III.[53] The process rivals the Wadsworth–Emmons reaction of carbethoxymethylphosphonate anion with carbonyl compounds to form α,β-unsaturated esters.[54] The Wadsworth–Emmons reaction produces low yields of product with readily enolized ketones. However, a 95% yield of 14 from cyclohexanone is reported on using the Peterson reaction.[53]

Scheme IV is part of an olefin inversion[45b] similar to that obtained by using lithium diphenylphosphide.[55] To obtain the reported product, 15 (96%, >99% *Z*), CAMEO performed an S_N2 reaction with inversion and recognized the need for rotation to carry out the synperiplanar elimination of the trimethylsilyloxy anion. 16 and 17 are predicted by the program as possible side products arising from E2 eliminations of the epoxide.

The final sequence, Scheme IV, is composed of selected steps from the recent synthesis of mycorrhizin A (22, R = H).[56] The sequence begins with a cuprate reaction that yields product 18 which then undergoes selective cleavage of the silyl ether in the presence of tetrabutylammonium fluoride. Two oxidation steps, which CAMEO does not handle currently, lead to 20. Electrophilic addition of chlorine yields 21 with no implied stereochemistry according to CAMEO. Chlorine is known to add in both the syn and anti manner to olefins.[4] Next, E2 reactions are predicted by CAMEO to yield both 22 (reported in 73% yield) and the *E* isomer. The program also yields 23 through another possible E2 reaction and two products arising from S_N2 displacement of the chlorines which have not been shown. The last product, 24, is the result of an S_N2' chlorine displacement which by electronic arguments should not be favorable.

(53) K. Shimosi, H. Taguchi, K. Oshima, H. Yamamoto, and H. Nozaki, *J. Am. Chem. Soc.*, **96**, 1620 (1974).
(54) W. S. Wadsworth and W. D. Emmons, *J. Am. Chem. Soc.*, **83**, 1733 (1961).
(55) E. Vedejs and P. L. Fuchs, *J. Am. Chem. Soc.*, **95**, 822 (1973).
(56) E. R. Koft and A. B. Smith III, *J. Am. Chem. Soc.*, **104**, 2659 (1982).

Conclusion

The capabilities of the CAMEO program have been extended to include electrophilic and nucleophilic processes involving organosilicon intermediates. The unique reactivity and directing ability of silyl groups required modification to several parts of the program, including the perception of acidities, electrophiles, nucleophiles, and carbonium ion stabilities. In addition, the stereochemical sophistication of the program has been enhanced to provide correct stereochemistry for products of substitution and β-elimination reactions.

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Reactivity of the Perhaloalkanes CF_2X_2 (X = Cl, Br) with Nucleophiles. 6.[1] Coexistence of Carbene and Radical Processes Initiated by Single-Electron Transfer

I. Rico, D. Cantacuzene, and C. Wakselman*

CNRS-Cercoa, 94320 Thiais, France

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In the condensation of sodium thiophenoxide with CF_2BrCl in DMF at −40 °C, two mechanisms are involved simultaneously. A carbene chain process is postulated for the formation of $C_6H_5SCF_2Br$ and $C_6H_5SCF_2H$. A radical chain process is implicated for the formation of $C_6H_5SCF_2Cl$ and $C_6H_5SCF_2SC_6H_5$. These competitive chain processes could occur after an initial one-electron transfer from the thiophenoxide to CF_2BrCl, giving a caged intimate radical/anion radical pair (RARP).

Recently we showed that perhaloalkanes CF_2BrX (X = Cl, Br) can react by two types of mechanisms when opposed to nucleophiles. In the condensation with phenoxides, thiophenoxides,[2,3] and carbanions,[4] we postulated a chain mechanism involving the difluorocarbene (Scheme I). The fact that hydrogenated byproducts $NuCF_2H$ and bromo derivatives $NuCF_2Br$ were obtained with CF_2BrCl was in favor of this mechanism. Furthermore, the condensation of CF_2Br_2 with potassium 2-allylphenoxide shows evidence for difluorocarbene formation since two CF_2 units are incorporated in the molecule.[1] Other reports are in agreement with the carbene process.[5,6]

Scheme I (Path A)

$$Nu^- + BrCF_2X \rightarrow NuBr + CF_2X^-$$

$$CF_2X^- \rightarrow :CF_2 + X^-$$

$$Nu^- + :CF_2 \rightarrow NuCF_2^-$$

$$NuCF_2^- + BrCF_2X \rightarrow NuCF_2Br + CF_2X^-$$

$$NuCF_2^- + \text{"H"} \rightarrow NuCF_2H$$

(1) Part 5: I. Rico and C. Wakselman, *J. Fluorine Chem.*, **20**, 765 (1982).
(2) I. Rico and C. Wakselman, *Tetrahedron Lett.*, **22**, 323 (1981).
(3) I. Rico and C. Wakselman, *Tetrahedron*, **37**, 4209 (1981).
(4) I. Rico, D. Cantacuzene, and C. Wakselman, *J. Chem. Soc., Perkin Trans. 1*, 1063 (1982).

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