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Computer-Assisted Mechanistic Evaluation of Organic Reactions. 14. Reactions of Sulfur and Phosphorus Ylides, Iminophosphoranes, and P=X-Activated Anions†

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CAMEO, an interactive computer program for the mechanistic evaluation of organic reactions, has been greatly extended in its treatment of sulfur and phosphorus ylides, iminophosphoranes, and P=X-activated anions. The incorporation of this chemistry required many modifications to the existing modules. This included development of rules governing competitions such as between proton transfer and addition, 1,2- and 1,4-addition, and the Peterson, Wittig, and Horner–Emmons olefination reactions. Issues including steric effects in conjugate addition, stereochemistry of olefination, and stability of σ-sulfuranes and σ-phosphoranes have also been addressed. The paper begins with a brief summary of the major preparations and reactions of these reagents and then outlines the changes required in CAMEO followed by analyses of sample sequences predicted by the program.

I. Introduction

CAMEO is a mechanistically based, interactive computer program designed to predict the products of organic reactions.[1] Starting materials and reaction conditions are entered via a graphics terminal and then processed by the program, after which the predicted products are output to the screen with accompanying comments informing the user of the mechanistic decisions that were made. The program differs from the pioneering efforts of Corey[2] in this field in two principal ways. The processing in CAMEO proceeds in the forward (synthetic) direction, while in Corey's program, LHASA, the emphasis is on designing complete synthetic routes to a target molecule through retrosynthetic analysis. Furthermore, the approach to reaction evaluation in CAMEO features the internal simulation of reaction mechanisms guided by rules for competing reactions and numerous structure/reactivity relations. LHASA, on the other hand, gauges the feasibility of the retro-reactions by using extensive data tables for many specific, known reactions.

Recently, the CAMEO program has been significantly extended in the area of nucleophilic chemistry. Specifically, the preparations and reactions of sulfur and phosphorus ylides, iminophosphoranes, and P=X-activated anions (e.g. Horner–Emmons reagents and phosphoramidates) have been rigorously reviewed and implemented in the program. These reagents are valuable synthetic tools which offer effective routes to epoxides, cyclopropanes, olefins, and compounds with C=N bonds. Although rudimentary capabilities existed in this area,[1c] the efforts discussed here have dramatically refined and broadened the treatment of this chemistry in CAMEO. For the present purposes, the general term "ylide" will be used to designate sulfur and phosphorus ylides, iminophosphoranes, and P=X-activated anions unless otherwise stated. A brief discussion highlighting the important aspects of the chemistry of these reagents is first presented followed by a section on the incorporation of the new reactivity rules in the program.

II. Key Aspects of Ylide Chemistry

Phosphorus and sulfur ylides along with P=X-activated anions have emerged as exceedingly useful reagents in organic synthesis. They are characteristically nucleophilic and generally react at electrophilic sites before participating in proton transfer, even when the proton transfer site is considerably more acidic. They are also quite selective. For instance, their reactivity toward carbonyl

† Dedicated to Professor E. J. Corey on the occasion of his 60th birthday.

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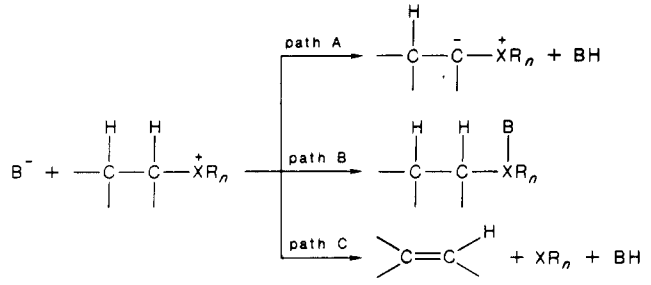
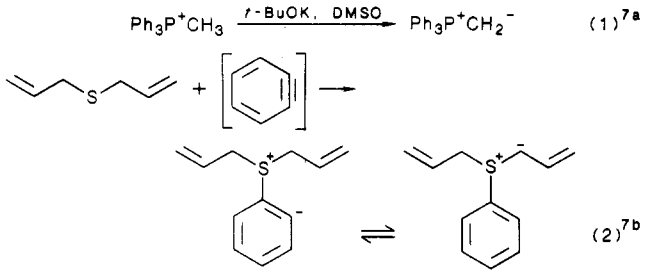
Scheme I[a]

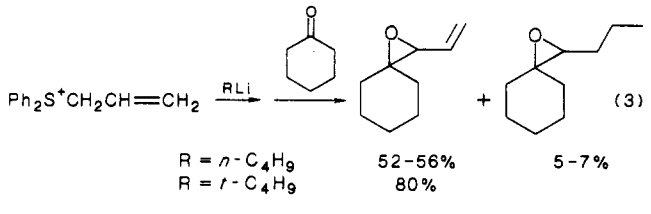


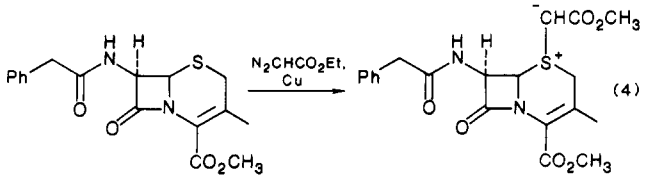
[a] XR_n = SR_2 or PR_3.

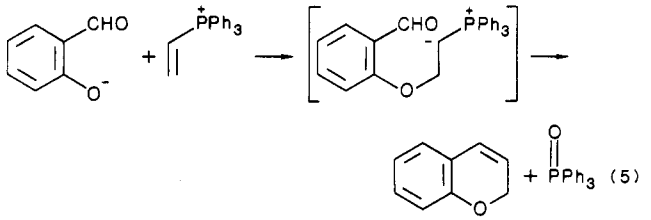
compounds is aldehydes > ketones > esters.[3] Moreover, they can usually be condensed with carbonyl compounds without displacing some generally reactive substitution groups, e.g. epoxides.[4] Their novel reactivity centers on their biphilic nature, which has been covered thoroughly in recent publications.[5,6] The brief summary presented here focuses on their applications in epoxidation, cyclopropanation, olefination, and C=N bond-forming reactions and forms a basis for the development of the requisite reactivity rules.

A. Ylide Preparation. Sulfur and phosphorus ylides are most commonly prepared by deprotonation of a salt that is either preformed or generated in situ as shown in eq 1 and 2. Higher homologues can be obtained by alkylation or acylation of simpler ylides. The choice of base is dependent on the ylide being generated. Use of nucleophilic organolithium bases, e.g. *n*-BuLi, MeLi, and PhLi, can give byproducts that result from direct coupling with the cationic sulfur or phosphorus center and from E2 elimination[8] (paths B and C in Scheme I), whereas the less nucleophilic but highly basic *t*-BuLi is less likely to give such side reactions as illustrated in eq 3.[9] Note that the propyloxirane arises from coupling with sulfur followed by ligand exchange to give diphenylsulfonium butylide. The best results are generally obtained by using *t*-BuLi, dialkylamides, NaH, or dimsylsodium. Two less common but quite useful approaches to ylides are reaction of a sulfide or a phosphine with a carbene and addition to a vinyl sulfonium or phosphonium ion (eq 4[10] and 5[11]). The carbene approach is particularly well suited for synthesizing stabilized oxosulfonium ylides which are not available by direct condensation with α-halocarbonyl compounds.[12]



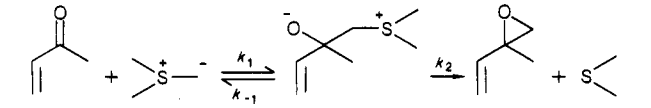






B. Sulfur Ylides. The major synthetic applications of sulfur ylides are the formation of epoxides from aldehydes and ketones and the cyclopropanation of α,β-unsaturated compounds. They are commonly divided into two distinct classes: sulfonium ylides, which are characteristically unstable at room temperature and therefore must be generated at low temperatures and used directly, and stabilized sulfonium ylides and oxosulfonium ylides, which are usually stable enough to be isolated and stored. Stabilized sulfonium ylides are defined here as compounds whose ylide carbon has an attached group that is at least as stabilizing as a vinyl or phenyl group.

1. Sulfonium Ylides. Sulfonium ylides react at addition sites by kinetic control. In general, the 1,3-elimination step is faster than reversion of the carbonyl addition ($k_2 > k_{-1}$); hence, epoxide formation is the normal course with α,β-unsaturated aldehydes and ketones. Esters, in contrast, undergo 1,2-elimination more readily than 1,3-elimination, presumably aided by the stability of the ylide that is ultimately formed. Despite the marked preference for reaction at the carbonyl group, conjugate addition has been observed in the following cases: with particularly activated Michael acceptors (eq 6[13]), with tertiary ylides as in eq 7[14] (1,3-elimination is hampered giving rise to thermodynamic control), and in an isolated case in which the methylene group was delivered intramolecularly (eq 8[15]). It should also be noted that tertiary ylides are sensitive to steric effects. Consequently, adding a methyl group to the conjugate addition site in eq 7 is sufficient



(3) For example, see: House, H. O.; Boots, S. G.; Jones, V. K. *J. Org. Chem.* **1965**, *30*, 2519. Kojima, K.; Sakai, K. *Tetrahedron Lett.* **1976**, 101. Anderson, R. J.; Henrick, C. A. *J. Am. Chem. Soc.* **1975**, *97*, 4327.

(4) For example, see: Kitamura, M.; Isobe, M.; Ichikawa, Y.; Goto, T. *J. Am. Chem. Soc.* **1984**, *106*, 3252. Trost, B. M.; Bogdanowicz, M. J. *J. Am. Chem. Soc.* **1972**, *94*, 4777.

(5) For reviews on sulfur ylides, see: (a) Trost, B. M.; Melvin, L. S., Jr. *Sulfur Ylides*; Academic Press: New York, 1975. (b) Johnson, A. W. *Ylide Chemistry*; Academic Press: New York, 1966.

(6) For reviews on phosphorus ylides, see: (a) Cadogan, J. I. G. *Organophosphorus Reagents in Organic Synthesis*; Academic Press: New York, 1979. (b) Emsley, J.; Hall, D. *The Chemistry of Phosphorus*; Harper and Row: London, 1976. (c) Reference 2b.

(7) (a) Drefahl, G.; Ponsold, K.; Schick, H. *Chem. Ber.* **1965**, *98*, 604. (b) Hellmann, H.; Eberle, D. *Ann.* **1963**, *662*, 188.

(8) (a) Corey, E. J.; Oppolzer, W. *J. Am. Chem. Soc.* **1964**, *86*, 1899. (b) Seyferth, D.; Heeren, J. K.; Hughes, W. B. *J. Am. Chem. Soc.* **1965**, *87*, 3467.

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(11) Schweizer, E. E. *J. Am. Chem. Soc.* **1964**, *86*, 2744.

(12) For example, see: (a) Dost, F.; Gosselck, J. *Tetrahedron Lett.* **1970**, 5091. (b) Ando, W.; Yagihara, T.; Tozune, S.; Nakaido, S.; Migita, T., *Tetrahedron Lett.* **1969**, 1979.

(13) Trost, B. M.; Hammen, R. F., unpublished results.

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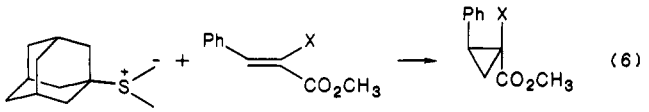
(15) Matthews, R. S.; Meteyer, T. E. *J. Chem. Soc., Chem. Commun.* **1971**, 1576.



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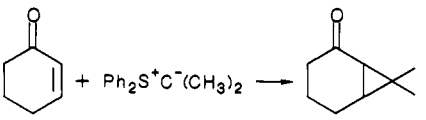

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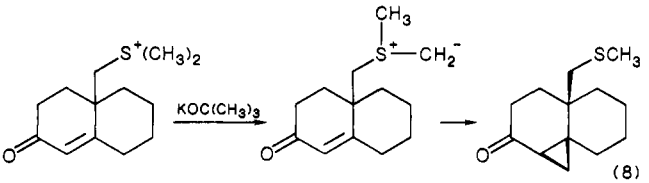
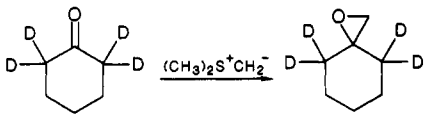


(8)

to give epoxidation rather than cyclopropanation.[14]

Finally, sulfonium ylides are highly nucleophilic. They typically undergo addition without complications from proton transfer unless there exists a site that is substantially more acidic than the ylide. Dimethylsulfonium methylide, for instance, condenses with tetradeuteriocyclohexanone with essentially no deuterium loss whereas it fails to react with deoxybenzoin, presumably because it acts as a base for enolization (eq 9[16] and 10[17]). The pK_a's for trimethylsulfonium ion, cyclohexanone, and deoxybenzoin in DMSO are roughly 23, 27, and 18.[1j]



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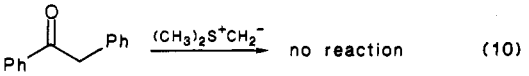
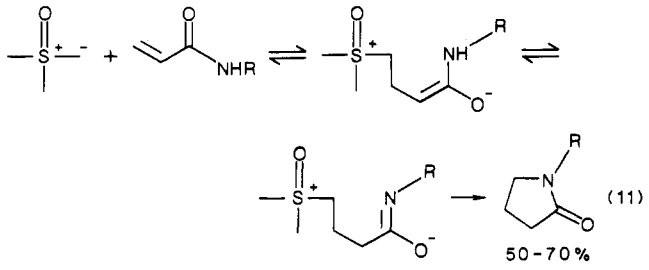


(10)

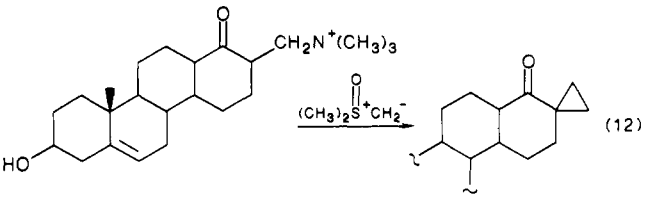
2. Stabilized and Oxosulfonium Ylides. Stabilized and oxosulfonium ylides react at addition sites by thermodynamic control. This is due to the greater stability imparted on the nucleophilic carbanion by the enhanced electron withdrawing character of the neighboring substituents, which subsequently increases the reversibility of the carbonyl addition. Consequently, cyclopropanation is the normal course of reaction with α,β-unsaturated carbonyl compounds. Esters give both cyclopropanation and acylation products since the back-elimination is competitive with reversion of carbonyl addition. α,β-Unsaturated amides, in contrast, typically do not yield products of cyclopropanation or acylation but instead give γ-lactams as illustrated below.[18] The facile tautomerization usually



(11)

precludes 1,3-elimination to form cyclopropanes. Epoxidation is possible with stabilized and oxosulfonium ylides for substrates that lack conjugate addition sites.

Masked Michael acceptor systems are also subject to cyclopropanation. For instance, the Mannich base in eq 12 eliminates trimethylamine in situ to form the corresponding enone which then undergoes cyclopropanation.[19] Following a related course of events, α-halo carbonyl compounds also consume multiple equivalents of ylides to yield cyclopropanes as in eq 13.[20] Substitution by the ylide and subsequent elimination of dimethyl sulfoxide generate the reactive Michael acceptor.



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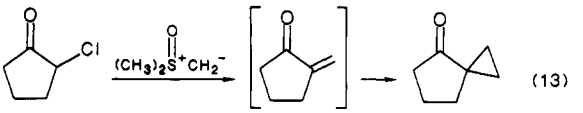
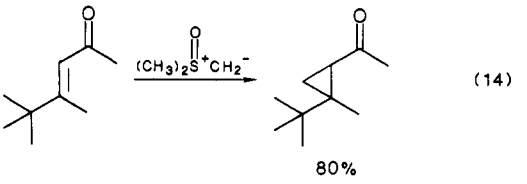


(13)

Stabilized and oxosulfonium ylides cyclopropanate even if the steric congestion at the conjugate addition site is great (eq 14).[21] In such cases, the yield is generally diminished, but the reaction pathway is not altered. However, steric effects can determine the position of cyclopropanation when there are multiple conjugate addition sites. Consequently, the less hindered double bonds are selectively attacked as illustrated in eq 15[17] and 16.[22]



(14)

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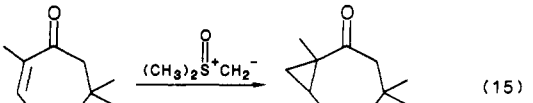

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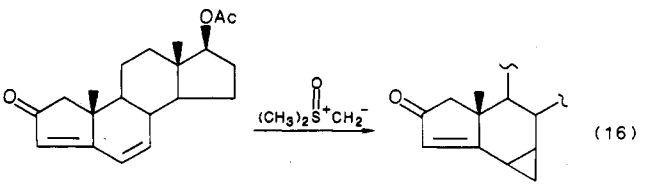

(16)

C. Phosphorus-Stabilized Anions. Phosphorus-stabilized anions, notably phosphorus ylides and P=O-activated carbanions, have gained widest application in the synthesis of olefins. The major advantage of this approach over other olefination methods is that the double bond can be introduced regiospecifically in almost every case. Moreover, investigations into the effect of changing the reaction conditions have led to effective ways of controlling the stereochemistry of the double bond. The olefination reaction is quite general and can be extended to the formation of C=N bonds as well. These reagents can also participate in alkylation and acylation reactions offering

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(17) Corey, E. J.; Chaykovsky, M. *J. Am. Chem. Soc.* **1965**, *87*, 1353.
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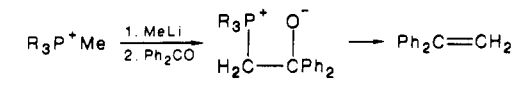
(21) Agami, C.; Aubouet, J. *Bull. Soc. Chim. Fr.* **1967**, *5*, 1391.
(22) Pfister, J.; Lehmann, C.; Wehrli, H. *Helv. Chim. Acta* **1968**, *51*, 1505.

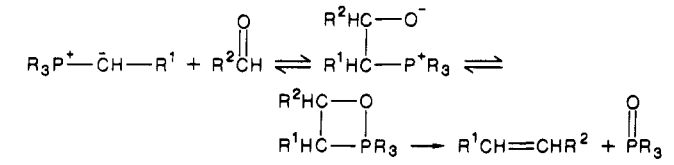
Table I. Conditions for Betaine Decomposition to Alkene



R	conditions	yield, %	ref
Ph	5–6 °C	84	25
Me	3 days (reflux) THF	40	26
	180 °C	0	27

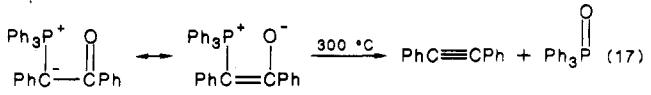
convenient routes to α-substituted derivatives.

1. Phosphorus Ylides and Iminophosphoranes. The most widely used application of phosphorus ylides is in the Wittig reaction. The generally accepted mechanism involves nucleophilic addition of the ylide to a carbonyl compound producing a betaine intermediate which subsequently decomposes via a four-membered cyclic intermediate (oxaphosphetane) to yield a phosphine oxide and



an olefin.[23] The stability of the ylide is key to the reaction. As the ylide becomes increasingly stabilized, the addition step becomes energetically less favorable and therefore more severe reaction conditions are required. In fact, the ylide can become so stabilized, e.g. cyclopentadienetriphenylphosphorane,[24] that no reaction is observed with carbonyl compounds. The neutralization and decomposition steps, in contrast, are more dependent on the nature of the groups attached to phosphorus. This is evident with unstabilized ylides where it has been shown that stabilization of the phosphonium center can slow down or completely retard the betaine decomposition step (Table I).

The decomposition step is also dependent on certain structural features. Generally, if the negative charge in the betaine can be resonated to the carbon adjacent to phosphorus as in eq 17,[28] high temperatures are required



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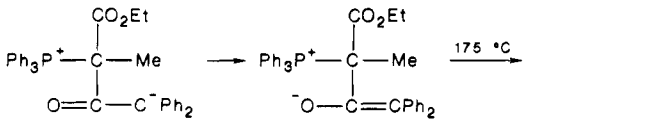
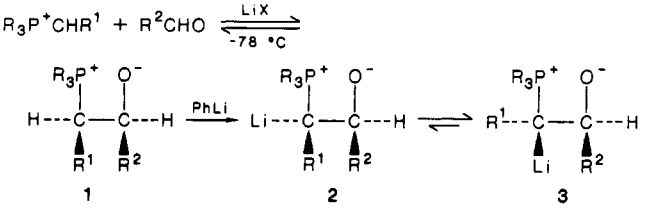


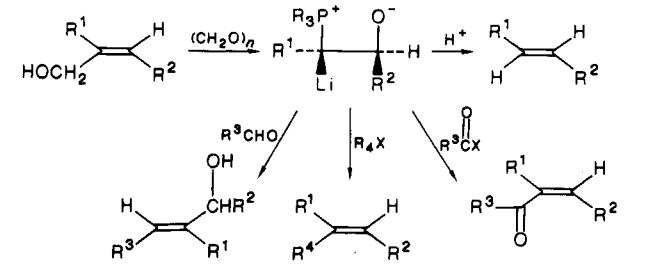
(18)

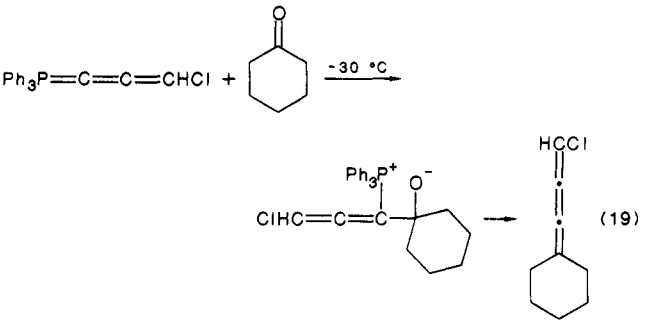
to effect the decomposition to the acetylene. However, if the resonance is with another carbon (exo to the oxaphosphetane) as in eq 18,[29] less severe conditions are required even though a cumulene is formed. Furthermore, unsaturation next to the ylide carbon (again corresponding to a double bond exo to the oxaphosphetane) creates no problems and decomposition occurs under normal Wittig conditions (e.g., eq 19[30]). Nitro-activated phosphorus ylides, however, are unstable and cannot be prepared due to subsequent decomposition to the phosphine oxide and fulminate ion.[28]

Scheme II



Scheme III





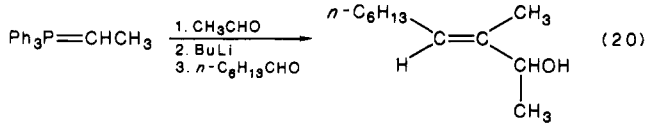
(19)

The stereochemistry of the alkene produced in the Wittig reaction is largely dependent on the stability of the phosphorus ylide. Typically, the product mixture of (*Z*)- and (*E*)-alkene shifts from predominantly (*Z*)-alkene to predominantly (*E*)-alkene as the phosphorus ylide becomes more stabilized. For example, propylenetriphenylphosphorane[31] and (carbethoxymethylene)tributylphosphorane[32] react with benzaldehyde to give 96:4 and 5:95 *Z* to *E* ratios, respectively. Alkyl substitutions on the ylide carbon and reactions with unsymmetrical ketones, however, can lead to a loss of stereoselectivity. The ratio of (*Z*)- to (*E*)-alkene is also sensitive to salt and solvent effects. Notably, unstabilized phosporus ylides generated free of lithium salts generally give greater percentages of (*Z*)-alkenes as do resonance-stabilized phosphorus ylides when run in protic solvents.[31,33]

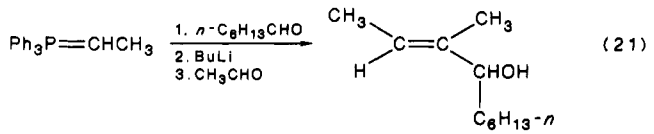
Stereoselective synthesis of (*E*)-alkenes can be afforded via β-oxido ylides.[6a] These ylides are formed by combining a phosphorus ylide with an aldehyde at low temperatures in the presence of a lithium salt to prevent decomposition of the betaine (Scheme II). The betaine–lithium complex 1 is then α-metalated with an organolithium base to form

(23) (a) Schlosser, M.; Piskala, A.; Tarchini, C.; Tuong, H. B. *Chimia* **1975**, *29*, 341. (b) Vedejs, E.; Snoble, K. A. J. *J. Am. Chem. Soc.* **1973**, *95*, 5778. (c) Vedejs, E.; Meier, G. P.; Snoble, K. A. J. *J. Am. Chem. Soc.* **1981**, *103*, 2823.
(24) Ramirez, F.; Levy, S. *J. Am. Chem. Soc.* **1957**, *79*, 6167.
(25) Wittig, G.; Geissler, G. *Ann.* **1953**, *580*, 44.
(26) (a) Trippett, S.; Walker, D. M. *Chem. Ind. (London)* **1960**, 933. (b) Trippett, S.; Walker, D. M. *J. Chem. Soc.* **1961**, 1266.
(27) Wittig, G.; Weigmann, H. D.; Schlosser, M. *Chem. Ber.* **1961**, *94*, 676.
(28) Trippett, S.; Walker, D. M. *J. Chem. Soc.* **1959**, 3874.
(29) Bestmann, H. J.; Hartung, H. *Chem. Ber.* **1966**, *99*, 1198.
(30) Arnold, R. D.; Baldwin, J. E.; Ziegler, C. B. *J. Chem. Soc., Chem. Commun.* **1984**, 152.
(31) Schlosser, M.; Christmann, K. F. *Ann.* **1967**, *708*, 1.
(32) Bissing, D. E. *J. Org. Chem.* **1965**, *30*, 1296.
(33) House, H. O.; Jones, V. K.; Frank, G. A. *J. Org. Chem.* **1964**, *29*, 3327.

the β-oxido ylide **2**. Equilibrium for the two diastereomeric betaines usually lies on the side of the more stable threo isomer **3**. Once formed, this new ylide can react with a variety of electrophiles including proton donors (Wittig–Schlosser reaction), alkyl halides, acid halides, and aldehydes (Scheme III). The most important application of β-oxide ylides is the stereospecific conversion of aldehydes into (*E*)-allylic alcohols. While addition of the second aldehyde component affords two possible routes for decomposition of the betaine, product formation is only observed from the oxaphosphetane originating from the second aldehyde as in eq 20 and 21[34]. Paraformaldehyde is an exception in that the product arises from loss of oxygen from the first carbonyl component.[34]

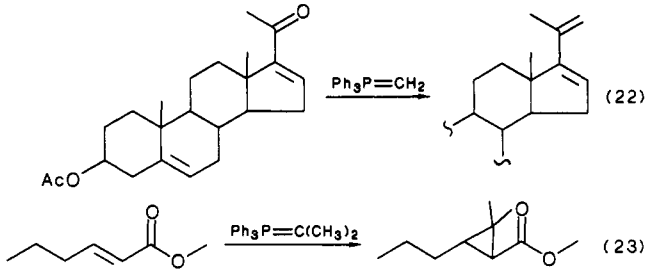


(20)



(21)

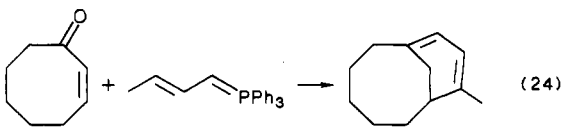
Selectivity has also been extensively studied for phosphorus ylides. Reaction generally occurs at the carbonyl carbon for α,β-unsaturated aldehydes and ketones, whereas conjugate addition is normally observed with α,β-unsaturated esters (e.g., eq 22[35] and 23[36]). Steric effects do not



(22)

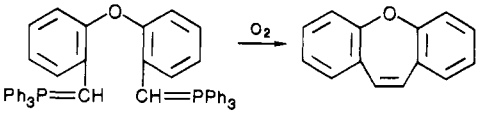
(23)

usually play a role unless the carbonyl site is particularly encumbered in which case conjugate addition occurs. Stabilized phosphorus ylides, in contrast, are less effective in the Wittig reaction with α,β-unsaturated ketones and esters (aldehydes do give attack at the carbonyl group) since products of Michael addition are commonly observed. Allylidenetriphenylphosphorane reagents are notable in that they give conjugate addition products with α,β-unsaturated aldehydes and ketones. This feature has been exploited in the synthesis of highly strained bicyclic alkenes as shown in eq 24.[37] Phosphorus ylides also react



(24)

with the C=O bonds of ketenes,[38] isocyanates,[39] and certain anhydrides and imides,[40] the C=N bonds of imines, and the N=O bonds of nitroso compounds.[41] Reactions with oxygen can lead to coupling products as illustrated with the bisylide below.[42] Phosphorus ylides have also



(25)

been acylated with a variety of reagents including acid chlorides,[43] chlorocarbonates,[44] esters,[45] and thioesters[46] to form stabilized ylides.

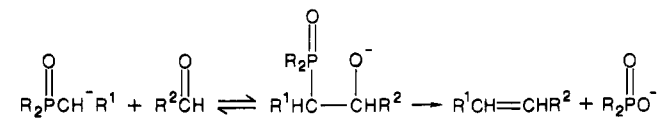
Iminophosphoranes are the nitrogen analogues of phosphorus ylides. Their chemistry parallels phosphorus

$$R_3^+ - N^-R' \leftrightarrow R_3P{=}NR'$$

ylides in that they are alkylated and acylated with the same reagents and that reactions with carbonyl compounds yield C=N rather than C=C bonds. Their major application is in the synthesis of heterocyclic compounds.[3a]

2. P=X-Activated Anions. The chemistry of P=X-activated anions is analogous in many ways to phosphorus ylides. In olefin synthesis, they offer several advantages over the Wittig reaction. First, P=X-activated anions are more nucleophilic than the corresponding phosphorus ylides and therefore react with a wider range of carbonyl compounds under milder conditions. Second, the alkene and phosphorus byproduct are more readily separated than with the Wittig reaction since the phosphinic, phosphonic, and phosphoric acid derivatives obtained from P=O-activated syntheses are all water soluble. Finally, many P=X-containing compounds can be cheaply and conveniently prepared via the Michaelis–Arbusov reaction (vide infra), while phosphorus ylides require relatively expensive phosphine starting materials. A limitation of these reagents is that unstabilized phosphine oxides, phosphonates, and related reagents do not decompose to alkenes except under very harsh conditions and instead give β-hydroxy compounds.

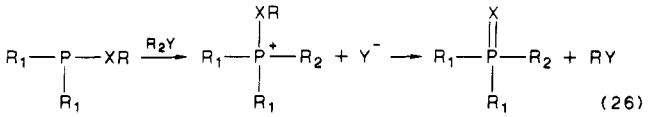
The accepted mechanism for P=X-activated anion olefin formation is similar to that proposed for the Wittig reaction. It features initial irrevesible addition to the carbonyl carbon producing an alkoxide intermediate followed by irreversible decomposition to an alkene and a phosphonate anion. Resonance-stabilizing substituents



are required on the carbanion adjacent to the phosphoryl group for the decomposition step which suggests that there is a build-up of negative charge in the transition state α to phosphorus. Horner published the first example of the reaction,[47] which was soon followed by a definitive paper by Wadsworth and Emmons[48] which outlined almost every future application. Today, the names of these early contributors are frequently used in various combinations to describe the reaction, although no one combination has been generally accepted.

(34) Corey, E. J.; Yamamota, H. *J. Am. Chem. Soc.* **1970**, *92*, 226.
(35) Sondheimer, F.; Mechoulan, R. *J. Am. Chem. Soc.* **1957**, *79*, 5029.
(36) Grieco, P. A.; Finkelhor, R. S. *Tetrahedron Lett.* **1972**, 3781.
(37) Dauben, W. G.; Ipaktschi, J. *J. Am. Chem. Soc.* **1973**, *95*, 5088.
(38) Aksnes, G. A.; Froyen, P. *Acta Chem. Scand.* **1968**, *22*, 2347.
(39) Froyen, P. *Acta Chem. Scand., Ser. B* **1974**, *28*, 586.
(40) (a) Flitsch, W.; Peters, H. *Tetrahedron Lett.* **1969**, 1161. (b) Flitsch, W.; Schindler, S. R. *Synthesis* **1975**, 685.
(41) Bestmann, H. J.; Denzel, T.; Salbaum, H. *Tetrahedron Lett.* **1974**, 1275.
(42) Bestmann, H. J.; Haberlein, H.; Kratzer, O. *Angew. Chem.* **1964**, *76*, 226.
(43) (a) Bestmann, H. J. *Tetrahedron Lett.* **1960**, *4*, 7. (b) Bestmann, H. J.; Arnason, B. *Tetrahedron Lett.* **1961**, 455.
(44) (a) Bestmann, H. J.; Schulz, H. *Angew. Chem.* **1961**, *73*, 27. (b) Speciale, A. J.; Ratts, K. W. *J. Org. Chem.* **1963**, *28*, 465.
(45) (a) Wittig, G.; Schollkopf, U. *Chem. Ber.* **1954**, *87*, 1318. (b) Trippett, S.; Walker, D. M. *Chem. Ind. (London)* **1960**, 202.
(46) Bestmann, H. J.; Arnason, B. *Chem. Ber.* **1962**, *95*, 1513.
(47) Horner, L.; Hoffmann, H.; Wippel, H. G. *Chem. Ber.* **1958**, *91*, 61.
(48) Wadsworth, W. S.; Emmons, W. D. *J. Am. Chem. Soc.* **1961**, *83*, 1733.

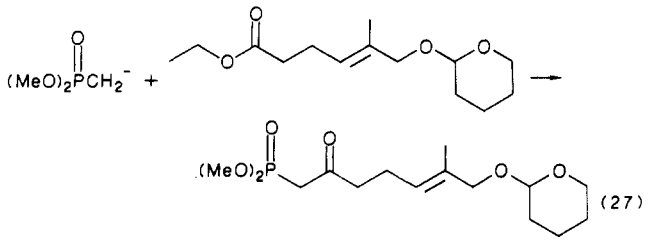
The most general route to reagents containing the P=X group is via the Michaelis–Arbusov reaction in which a tertiary phosphorus alkyl ester is treated with an alkylating agent to produce a phosphonium salt which subsequently decomposes to the corresponding P=X compound (eq 26).



R_1 = OR, NR_2, SR, alkyl, aryl
X = O, S, N

(26)

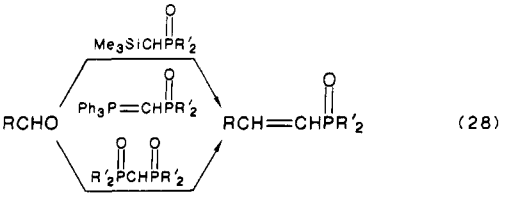
For mixed phosphorus alkyl esters, dealkylation occurs in the general order O > S > N such that P=O is formed in preference to P=S and P=S in preference to P=N.[49] This reaction is not suitable for making α-keto derivatives from α-halo ketones since the Perkow reaction occurs, giving enol phosphatess.[50] Thus, α-keto derivatives are best made by acylation as illustrated in eq 27.[51]



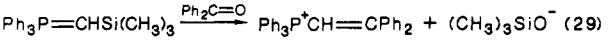
(27)

95%

The applications of P=X-activated reagents in alkene synthesis are numerous. They have been used in the preparation of a large variety of α,β-unsaturated compounds and have played a prominent role in prostaglandin and steroid synthesis. They react with α,β-unsaturated aldehydes and ketones to give conjugated alkenes but yields are diminished due to competing Michael addition.[52] An interesting selectivity arises when the P=X-activated anion is further activated by a silyl or phosphonium group. In each variation, there exist two potential olefination routes. The reactivity hierarchy is such that Peterson olefination is faster than the Wittig reaction which is in turn faster than olefination utilizing P=X-activated anions. This hierarchy is reflected in eq 28[53] and 29.[54] The



(28)



(29)

stereochemistry of the alkene obtained from the P=X-activated anion olefination reaction is generally *E*; however, there have been some reports of significant amounts of (*Z*)-alkene formation.[55] Most notably, Still has reported a stereoselective method for the formation of *Z*-trisubstituted alkenes using bis(trifluoroethyl) phosphonate esters.[55d] Finally, phosphoramidate anions, e.g. $(RO)_2P(O)N^-R'$, react with carbonyl compounds in an analogous way to iminophosphoranes and offer the same advantages over them that phosphonate carbanions offer over phosphonium ylides.

III. Implementation

The majority of changes that have been made in CAMEO to address the chemistry just discussed have been effected in the nucleophilic module. The general organization of the module has been presented recently;[1k] hence, only a brief outline of the logic followed will be presented here before addressing the specific changes.

Once the user has entered the starting materials and reaction conditions at a graphics terminal, the program proceeds to a general perception phase where rings, stereochemistry, and related structural features are recognized. Following general perception, the program branches to the mechanistic module selected by the user. The nucleophilic module, in particular, is basically divided into four phases: perception of nucleophilic sites, perception of electrophilic sites, mechanistic evaluation, and pathway evaluation. After the nucleophilic sites have been determined, the program cycles through each one and determines the valid electrophilic sites for that nucleophilic site. The electrophilic sites are then paired with the nucleophilic site one by one and evaluated for possible mechanisms. This process continues until all combinations are exhausted, usually giving rise to multiple reaction pathways. During pathway evaluation, the products may be rejected or designated major, minor, or disfavored. The remaining products are then sent on to general perception to decompose any unstable functionalities that may have formed before ultimately being displayed at the graphics terminal. The modifications that have been made in these areas are discussed next.

A. Perception of Nucleophilic Sites. Nucleophilic sites can be generated in CAMEO by proton transfer, halide–alkyllithium exchange, and metal insertion or they may be perceived directly in the starting material.[1c,k] The former processes, referred to as "mechanistic presteps", are typically faster than substitution, elimination, and addition reactions and are therefore considered first. The rate hierarchy for the mechanistic presteps is fast proton transfer (from heteroatoms) > halide–alkyllithium exchange > slow proton transfer (from carbon) ≫ metal insertion. For all mechanistic presteps, the most stable anion and any others within a 4 pK_a unit window are generated at room temperature. This window, however, is waived for ylides when considering slow proton transfer due to their observed tendency to act as nucleophiles rather than as bases. Consequently, *if an ylide is present, proton transfer is only considered for sites more acidic than the ylide.* For example, enolization is not performed for eq 9 since the predicted pK_a's in DMSO for the sulfonium ion and the ketone are 23 and 27, respectively. Also, *if an addition site is perceived, the ylide is stored as a potential nucleophile even when there are slow proton transfer sites that are greater than 4 pK_a units*

(49) For example, see: (a) Sheppard, W. A. *J. Org. Chem.* **1961**, *26*, 1460. (b) Harpp, D. N.; Orwig, B. A. *Tetrahedron Lett.* **1970**, 2691. (c) Chapleur, Y.; Castro, B.; Gross, B. *Synth. Commun.* **1977**, *7*, 143.

(50) Shahak, I. *Synthesis* **1969**, 170. Shahak, I.; Almog, J. *Synthesis* **1970**, 145.

(51) Dauben, W. G.; Beasley, G. H.; Broadhurst, M. D.; Muller, B.; Peppard, D. J.; Pesnelle, P.; Suter, C. *J. Am. Chem. Soc.* **1975**, *97*, 4973.

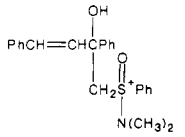
(52) (a) Michalski, J.; Musierowicz, S. *Tetrahedron Lett.* **1964**, 1187. (b) Landor, P. D.; Landor, S. R.; Odyek, O. *J. Chem. Soc., Perkin Trans. 1* **1977**, 93.

(53) (a) Corey, F. A.; Court, A. S. *J. Org. Chem.* **1972**, *37*, 939. (b) Peterson, D. J. *J. Org. Chem.*, **1968**, *33*, 780. (c) Paulsen, H.; Bartsch, W.; Thiem, J. *Chem. Ber.* **1971**, *104*, 2545.

(54) Gilman, H.; Tomasi, R. A. *J. Org. Chem.* **1962**, *27*, 3647.

(55) (a) McGreer, D. E.; Chiu, N. W. K. *Can. J. Chem.* **1968**, *46*, 2225. (b) Huff, R. K.; Moppett, C. E.; Sutherland, J. K. *J. Chem. Soc. C* **1968**, 2725. (c) Lavielle, G.; Reisdorf, D. *C. R. Hebd Seances Acad. Sci., Ser. C* **1971**, *272*, 100. (d) Still, W. C.; Gennari, C. *Tetrahedron Lett.* **1983**, *24*, 4405.

Table II. New Types of Electrophilic Sites Perceived in the Nucleophilic Package[a]

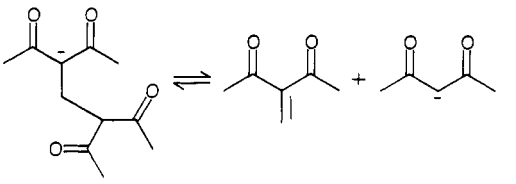
electrophilic site	example	directory	ref
CXP^+R_3	$CH_3OP^+(OCH_3)_2$-$CH_2CH_2CH_3$	All Path, E1	49
R_3S^+	$Ph_2S^+CH_2CH{=}CH_2$	All Path, E1	9
C-CZR_2, C-CY_2R, and C-CY_3		E1	56

[a] X = O, S, N, and Se. Z = cationic or multiply bonded group. Y = Z or heteroatom.

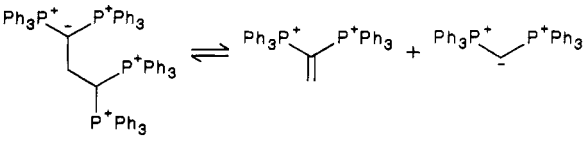
more acidic than the ylide; otherwise, only proton transfer is performed. This is illustrated in eq 19 where the phosphacumulene ylide condenses with the ketone despite the fact that cyclohexanone is predicted[1j] to be 21 pK_a units more acidic than the ylide. Enolization is predicted to be a side product.

The competition between proton transfer and ligand exchange in the preparation of ylides with organolithium bases (e.g. eq 3) is partly handled in nucleophile perception. If an organolithium base is submitted and a phosphonium or sulfonium center is perceived, the organolithium base is stored as a potential nucleophile in addition to the ylide formed by proton transfer. Later, in pathway evaluation, the coupling product is deemed minor with respect to the proton-transfer product. Additional modifications have been made to handle the chemistry of β-oxido ylides shown in Scheme III. Dianionic reagents normally react with electrophiles via the more basic anion.[1k] Since the alkoxide site was predicted to be more basic than the ylide carbon (pK_a's of 29 and 24, respectively), the program was unable to process these reactions. We have attributed the low basicity of the alkoxide site to aggregation and complexation with the lithium ion. Consequently, *the effective pK_a of alkoxides is dropped 7 units in the presence of lithium or magnesium counterions.* This enables the program to predict the reaction sequences given in Scheme III. One last note: a symmetry check has been implemented to eliminate the redundant nucleophilic sites perceived in simple compounds such as dimethylsulfonium methylide, hydrazine, and carboxylate ions.

B. Perception of Electrophilic Sites. In the nucleophilic package, electrophilic sites are grouped into two directories based on the chemistry that they typically undergo. The "All Path directory" is used to store electrophilic sites that can potentially react in any type of mechanism, whereas the "E1 directory" is used to store poorer electrophilic sites that are only able to participate in E1cb reactions. Three new types of electrophilic sites have been added as summarized in Table II. The first entry is the quasiphosphonium salt intermediate produced in the Arbusov reaction. Electrophilic sites are initially ranked according to the pK_a of the conjugate acid of the leaving group and are then modified to account for special effects such as steric hindrance and relief or ring strain. Since the program predicts R_3P^+–SH to be more acidic than R_3P^+–OH, −10 andd 7 where R is methyl,[1j] a special adjustment of 18 units is added to the initial ranking for C–SP^+R_3 and 5 units is substracted from the initial ranking for C–OP^+R_3 to give final rankings of 8 and 2, which provide for the appropriate selectivity observed with mixed alkyl esters as discussed above. The second entry has been established to account for the ligand exchange byproducts observed when sulfonium salts are treated with organolithium reagents, e.g. eq 3. These electrophilic sites are assigned a ranking of 4 (slightly less active than an alkyl halide), since they have no formal leaving group. The last entry allows for a greater variety of E1cb reactions involving C–C bonds. Previously, the E1cb process depicted in eq 30 was picked up as a 1,4-E1cb fragmentation by


(30)

virtue of the perception of the C=O bond in the All Path and E1 directories. The ranking for the electrophilic site corresponded to the leaving ability of the C=O bond, an alkoxide, rather than the more stabilized 1,3-dione. Moreover, the old perception did not allow the fragmentation in eq 31 since electrophilic sites of the type C–CY_2R,


(31)

where Y is a cationic group, were not perceived. Consequently, eq 30 and 31 are now processed as 1,2-E1cb reactions with the appropriate electrophilic site rankings. The addition of these electrophilic sites has greatly enhanced the treatment of E1cb fragmentations.

C. Mechanistic Evaluation. The mechanistic evaluation phase keys on the competitions between different mechanisms available for one nucleophilic site. The most general rule applied here is the ΔpK_a rule, which states that the pK_a of the conjugate acid of the nucleophilic site should be no more than 10 units below the ranking of the electrophilic site. This limit has been expanded to 20 units for ylides since these nucleophiles appear to yield intermediates far more basic than themselves. This is illustrated in eq 11 where the pK_a of the conjugate acid of dimethyloxosulfonium methylide is 18 and the ranking of the 1,4-addition site when R is alkyl is 34.

In general, the competitions between reactions of one nucleophilic site at different addition sites are handled by the ranking of the electrophilic sites. Only the best addition sites within a 6 "pK_a" unit window are considered by the program. Ylides, however, often favor either addition into the carbonyl moiety or conjugate addition and are therefore assigned designated pathways based on the nature of the ylide. Consequently, *if 1,2-addition is deemed the preferred pathway, only 1,2-addition sites that are within 6 "pK_a" units of the best 1,2-addition site are considered. However, if there is a conjugate addition site that is ranked more than 6 "pK_a" units lower than the best 1,2-addition site, both pathways are considered (recall eq 6). This treatment is also performed for the converse situation in which 1,4-addition is initially deemed preferable. In the event a 1,2- and a 1,4-addition pathway are deemed preferred, both pathways are evaluated collectively invoking the usual 6 "pK_a" unit window.* The rules governing the competition between 1,2- and 1,4- addition with ylides in CAMEO are summarized in Table III. The designated pathways are limited to intermolecular reactions only, since geometry constraints usually play the deciding role in intramolecular reactions as exemplified in eq 8.

The steric environment of the nucleophilic and electrophilic sites can also have an effect on the product outcome. As mentioned above, oxosulfonium ylides

Table III. Summary of the Reaction Pathways Predicted by CAMEO for the Intermolecular Addition of Ylides into α,β-Unsaturated Carbonyl Compounds[a]

α,β-unsaturated electrophile[b]	unstabilized sulfonium ylide	stabilized sulfonium ylide	oxosulfonium ylides	unstabilized phosphorus ylide	stabilized phosphorus ylide	P=X-activated anions
aldehyde	1,2	1,4	1,4	1,2	1,2	1,2/1,4
ketone	1,2/1,4[c]	1,4	1,4	1,2	1,2/1,4	1,2/1,4
ester	1,2/1,4[c]	1,2/1,4	1,2/1,4	1,2/1,4	1,2/1,4	1,2/1,4
amide	1,4[d]	1,4[d]	1,4[d]	1,4[d]	1,4[d]	1,4[d]

[a] 1,2 designates reaction at the carbonyl carbon, whereas 1,4 designates conjugate addition. [b] Assumes monoactivated alkenes, e.g. methyl vinyl ketone. [c] Unstabilized sulfonium ylides with a tertiary ylide carbon are predicted to add conjugatively to unhindered α,β-unsaturated ketones and esters. The normal case is 1,2-addition. [d] Carbonyls with activated nitrogen leaving groups, e.g. imides, are predicted to give 1,2- and conjugate addition.

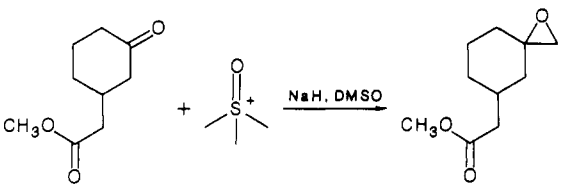
preferentially attack the least hindered conjugate addition sites (eq 15 and 16). A steric factor, S, has been developed to evaluate the hindrance of conjugate addition sites and is defined below. Congestion about the leaving atom is

$$S = \sum_{i}^{\text{levels}} \sum_{j}^{\text{atoms}} C_{ij}/i$$

assumed to have a negligible impact on the hindrance of the site; consequently only atoms branching from the electrophilic atom (not including the leaving atom) are considered in the calculation. The quantity i is the distance in atoms of the atom j from the electrophilic atom, while the constants C are weighting factors based on the hybridization of the atom j and are 1, 0.6, and 0.2 for sp^3, sp^2, and sp hybridized atoms, respectively. Only non-hydrogen atoms j are included in the sum. The factor $1/i$ is applied to atoms in the ith level to account for their diminishing contribution with increasing distance. A maximum of three levels is considered for any given site. Accordingly, a conjugate addition site is deemed unhindered if its steric factor is less than 2, mildly hindered if it is less than 2.5, moderately hindered if it is less than 4.5, and greatly hindered if it is greater than or equal to 4.5. For electrophilic sites with competitive rankings, the product designations for reactions at the first three types of hindered sites are major, minor, and disfavored. Products resulting from the greatly hindered class are only formed if a product could not be formed with a better designation. For example, in eq 15 reaction at the 1,4-addition site is deemed major while reaction at the 1,6-addition site is deemed disfavored; the corresponding S values are 1.23 and 2.7, respectively. This treatment can be summarized as follows.

S	hindrance	product
0–2	none	major
2–2.5	mild	minor
2.5–4.5	moderate	disfavored
≥4.5	high	only if no other

Additional modifications that were required in the mechanistic evaluation phase area are as follows. (1) The neutralization of betaines to form oxaphosphetanes is not permitted below 0 °C in the presence of lithium salts (Scheme II) and in cases where the cationic phosphorus atom in the betaine is particularly stabilized by electron-donating groups (Table I). (2) Reactions that produce intermediates that are greater than 30 pK_a units more basic than the most basic site in the entered materials are only permitted to do E1cb and proton-transfer reactions (e.g., eq 2). (3) With respect to *intermolecular* additions and substitutions, reactions of aldehydes are deemed faster than for ketones which in turn are deemed faster than for esters or weakly electrophilic substitution sites, ranking >5.[3,4] In a competitive case, the corresponding product designations would be major and minor for aldehydes and ketones, while the last class would not be displayed. For instance, in eq 32 selective epoxidation is predicted and



(32)

observed at the ketone with no addition to the ester group.[3] (4) With respect to olefination reactions, the following rate hierarchy is imposed: Peterson olefination > Wittig reaction > olefination utilizing P=X-activated carbanions (e.g., eq 28 and 29). (5) Finally, ylides add to esters to form a tetrahedral intermediate which can potentially undergo a variety of reactions. With sulfur ylides, 1,2-elimination ejecting alkoxide is deemed faster than intramolecular S_N2 producing an epoxy ether, whereas with phosphorus ylides, 1,2-elimination is deemed competitive with olefination (an example is provided below). Note, intramolecular S_N2 displacing a phosphine is only considered when the nucleophilic atom is carbon, e.g., for cyclopropanation following conjugate addition of a phosphonium ylide as in eq 23.

D. Pathway Evaluation. Pathway evaluation focuses on the competitions between the alternate reaction paths available for different nucleophilic sites. Two additions have been made in this area. First, with respect to the preparation of phosphorus and sulfur ylides with organolithium bases, proton transfer and any reactions arising therefrom are deemed faster than ligand exchange (e.g., eq 3). Ligand exchange is performed in CAMEO via a neutralization step followed by decomposition in general perception (vide infra). Second, when an ylide is submitted, intermediates generated by proton transfer to the ylide and the ylide itself might all be considered for further processing. In this case, products arising from proton-transfer intermediates generated by the starting ylide are designated minor with respect to reactions issued from the ylide. The phosphacumulene in eq 19, for example, is predicted to generate an enolate intermediate which subsequently adds into the neutralized cumulene. Accordingly, CAMEO deems this addition product minor with respect to the Wittig product.

E. Unstable Functionalities. The multiple-bond-forming reactions characteristic of phosphorus ylides, iminophosphoranes, and P=X-activated anions all proceed via a four-membered cyclic intermediate. In CAMEO, the

intermediate is treated as an unstable functionality and

subsequently decomposed in general perception. The program has been expanded to handle cases where Y, Z = C or N, and X = O, S, Se, or N. Decomposition is not performed when the cyclic intermediate bears one sp^2 center at atom Y and the user selected a temperature range below 150 °C (e.g., eq 18) or when the intermediate bears two sp^2 centers at atoms Z and Y and the user selected a temperature range below 300 °C (e.g., eq 17). In both cases, a comment is provided when the product is displayed to inform the user of the chemical decision. The only exception is for nitro-activated phosphorus ylides. These reagents are flagged in mechanistic evaluation and only permitted to undergo oxaphosphetane formation and subsequent decomposition in any temperature range.[28]

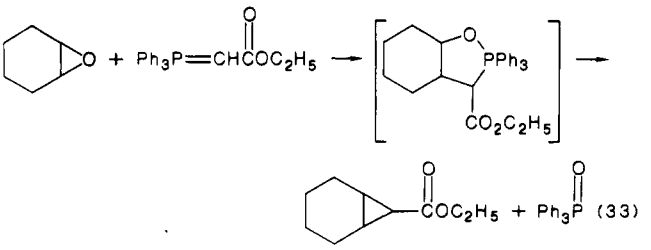
In addition to performing the decomposition step, general perception also imparts the appropriate stereochemistry to newly formed C=C bonds that result from the condensation of an aldehyde with an unsubstituted ylide. This is gauged for phosphorus ylides by the pK_a of the conjugate acid of the ylide undergoing the olefination process.[31,32] If the pK_a is less than 12, only the (*E*)-alkene is output, whereas only the (*Z*)-alkene is displayed if the pK_a is greater than 19. The stereochemistry is shown as *E* when the pK_a is between 12 and 19 and a "U" is placed next to the double bond, indicating a mixture of both *Z* and *E* products is likely. These cutoffs, below 12 and above 19, were chosen to show the stereochemistry of the product that is obtained in at least a 75:25 ratio with respect to its other stereoisomer. Horner–Emmons reagents are decomposed to (*E*)-alkenes since this is the stereochemistry most commonly observed.[6] For substituted ylides and reactions with unsymmetrical ketones, the stereochemistry is too difficult to predict systematically and so the alkenes produced by these reactions are output with a "U" next to the new C=C bond. Finally, the stereochemistry of the alkene for intramolecular cyclizations is defaulted to *Z*. Since the *E* isomer is observed to be more stable in medium and large rings, a "U" accompanies all newly formed C=C bonds in rings of size 10 or greater.[57]

A method of decomposing σ-sulfuranes and σ-phosphoranes has also been implemented in general perception

since many of these species are unstable and heterolytically dissociate, ejecting a formally anionic group and either a sulfonium or phosphonium ion. The anionic group is the one that corresponds to the most stable anion. However, since phosphorus has such a high affinity for oxygen, P–O bonds are ranked 10 pK_a units less favorable than the predicted acidity of the conjugate acid of the oxygen leaving group. Thus, the program is able to perform ligand exchange reactions via a neutralization reaction followed by a decomposition step. The conversion of epoxides into cyclopropanes[58] and aziridines[59] are similarly handled by this treatment (e.g., eq 33[58]).

IV. Sample Sequences

A principal goal of the CAMEO project is to provide a tool to aid in the evaluation of proposed reactions. Consequently, the following section is presented to illustrate the program's capabilities by comparing its predictions with observed experimental results for several reaction sequences. Each product is presented with the product designation and process output by CAMEO.



(33)

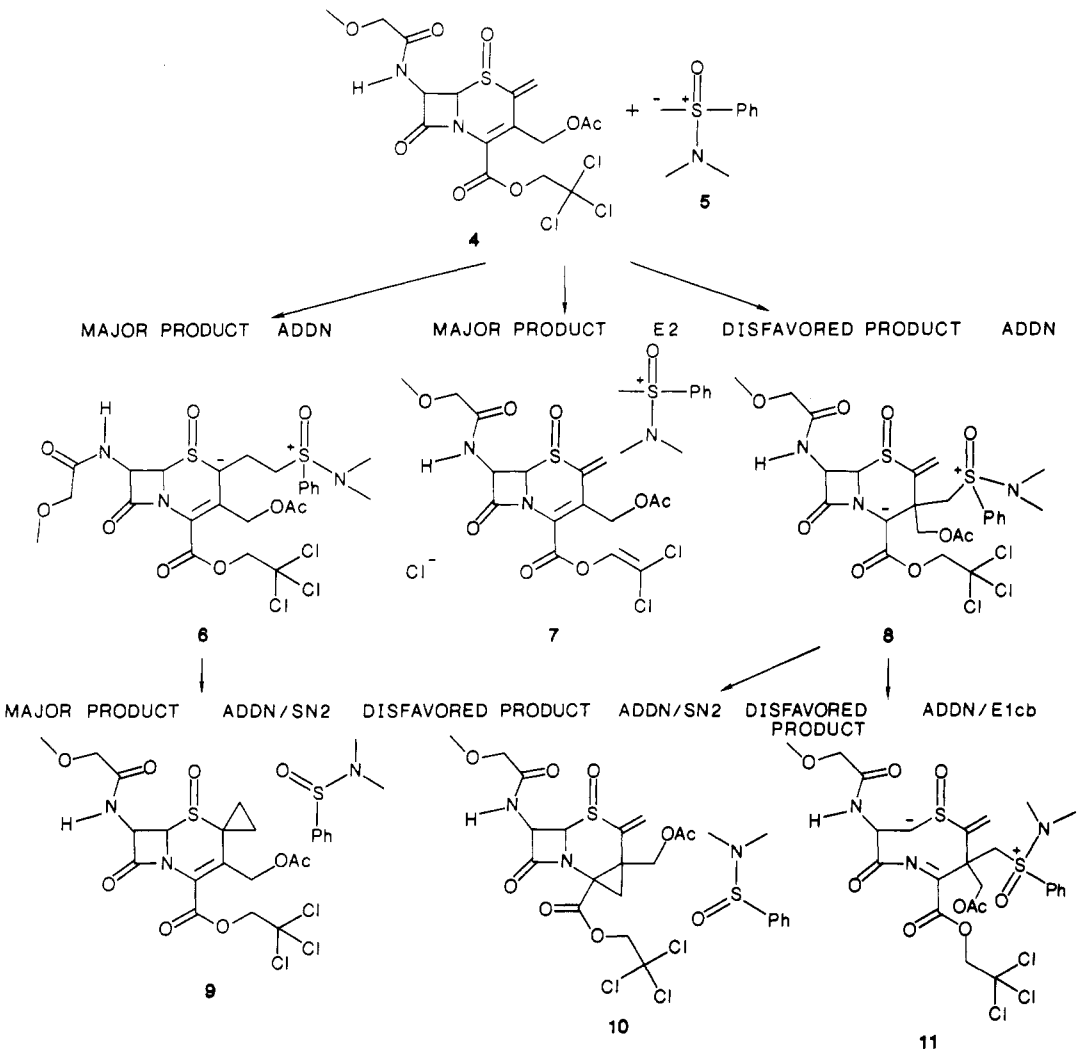
Scheme IV is an analysis of a cyclopropanation reaction utilizing (dimethylamino)phenylsulfoxonium methylide (**5**).[60] The program first identifies the ylide carbon as the most nucleophilic site and then determines the mechanisms it can undergo. The possibilities initially include 1,2-addition, conjugate addition, and E2 elimination. After further evaluation, the preferred addition pathways are deemed to be with the ester groups and conjugate addition sites (Table III). However, since the conjugate addition sites, the exo methylene group, and the cyclic C=C bond (rankings = 19 and 22, respectively), are ranked better than the ester groups (rankings = 26 and 30 for the acetate), all reactions at the ester groups are rejected. Attack at the cyclic C=C bond produces the addition intermediate **8** which is deemed disfavored due to the steric hindrance of the electrophilic site (steric factor = 3.43). The end products of this pathway, **10** and **11**, are also deemed disfavored since they emanate from **8**. The steric factor for the electrophilic site of the exo methylene group is 0, consequently the addition intermediate **6** and the resulting cyclopropane compound **9** are given as major products. The elimination product **7** is the only other one predicted to be competitive by CAMEO These results are consistent with the experimental findings where the highly functionalized cephalosporin nucleus **4** was cyclopropanated to give **9** in 85% yield.[60]

Scheme V summarizes the evaluation of two steps used in Still's recent synthesis of baccharin B5, a potent antileukemia agent.[61] In the first step, the stabilized ylide is predicted to selectively give the (*E*)-α,β-unsaturated aldehyde **13**. The ester groups and epoxide (ranking = 5) are not deemed competitive with the aldehyde on an intermolecular basis and are therefore rejected. Proton transfer to form the phosphonate carbanion is also ruled out since the program predicts the phosphonium ylide to be 7 pK_a units more acidic (pK_as = 15 and 8, respectively).[1j] Experimentally, **13** was obtained in 60–65% overall yield as a 4:1 *E*:*Z* mixture.[61]

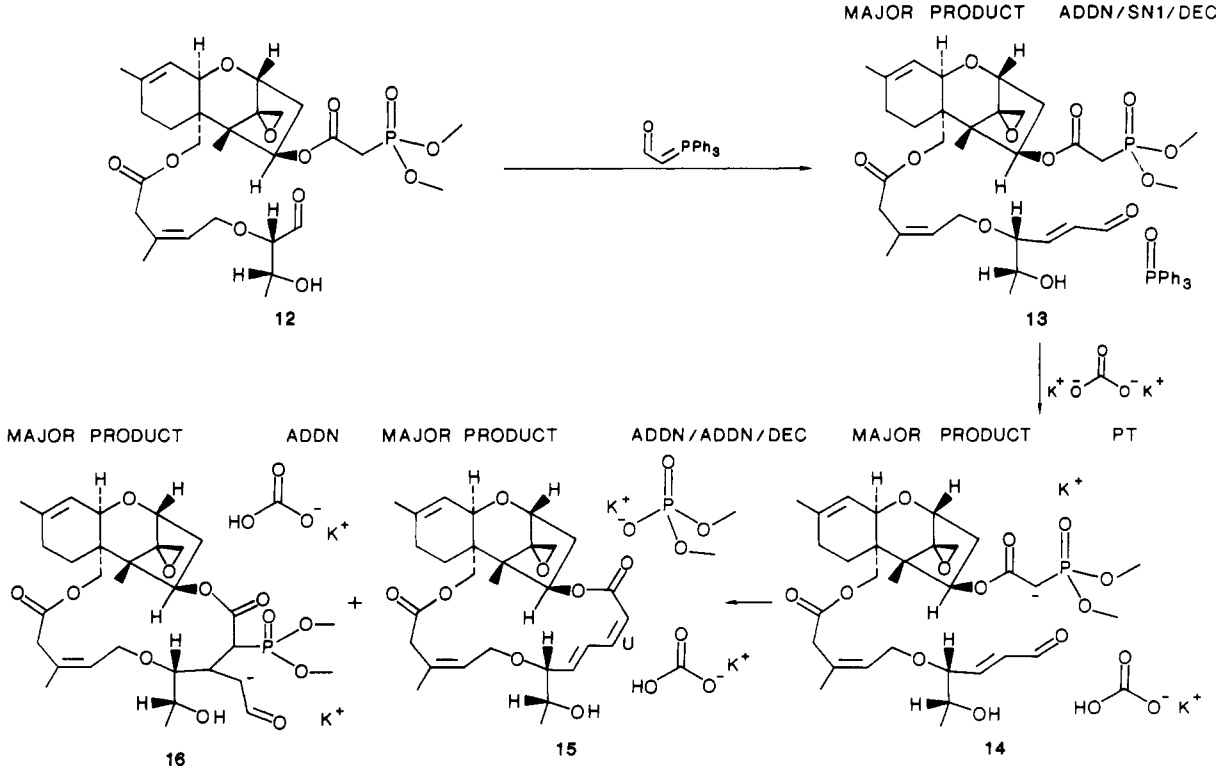
In the second step, the stabilized phosphonate carbanion **14** is generated by submitting **13** to CAMEO with potassium carbonate as the reagent (pK_a = 12).[1j] After further evaluation, the program forms the macrocycle **15** and the conjugate addition product **16**. The new double bond in **15** is displayed with a "U", indicating a mixture of *E* and *Z* products is likely. Addition to the ester group branching from the cis fusion and substitution at the epoxide are also considered but rejected on grounds of steric inaccessibility.[1k] Experimentally, **15** was produced in a 1.5:1 mixture of *E*,*Z* and *E*,*E* macrolides in 75% yield.[61] Although no

(56) Johnson, C. J.; Schroeck, C. W.; Shanklin, J. R. *J. Am. Chem. Soc.* **1973**, *95*, 7424.
(57) Cope, A. C.; Moore, P. T.; Moore, W. R. *J. Am. Chem. Soc.* **1959**, *81*, 3153.
(58) Denney, D. B.; Vill, J. J.; Boskin, M. J. *J. Am. Chem. Soc.* **1962**, *84*, 3944.
(59) Appel, R.; Halstenberg, M. *Chem. Ber.* **1976**, *109*, 814.
(60) Spry, D. O. *Tetrahedron Lett.* **1973**, 2413.
(61) The carboxylic acids were protected with PNB groups, but are shown in this scheme with benzyl groups for simplicity. Still, W. C.; Gennari, C.; Noguez, J. A.; Pearson, D. A. *J. Am. Chem. Soc.* **1984**, *106*, 260.

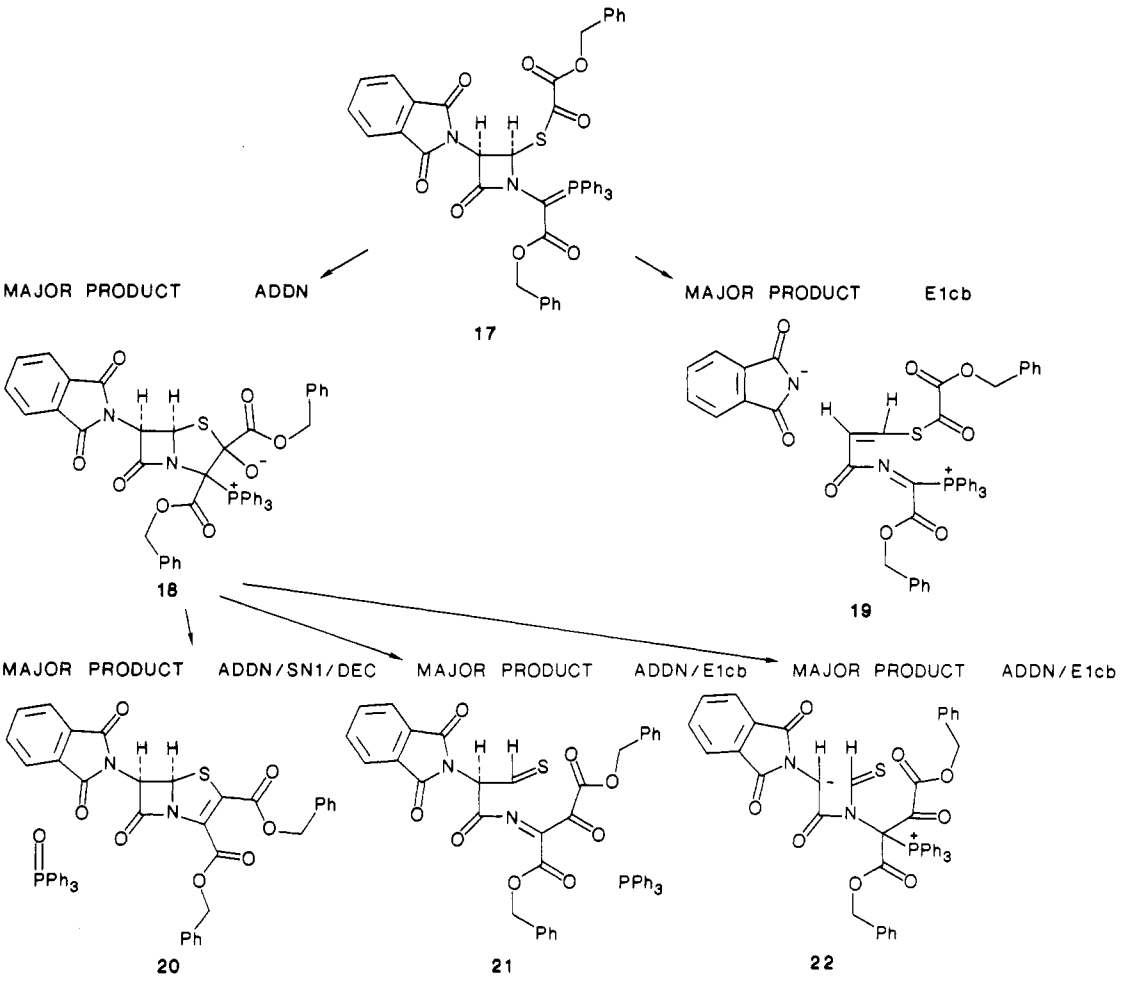
Scheme IV



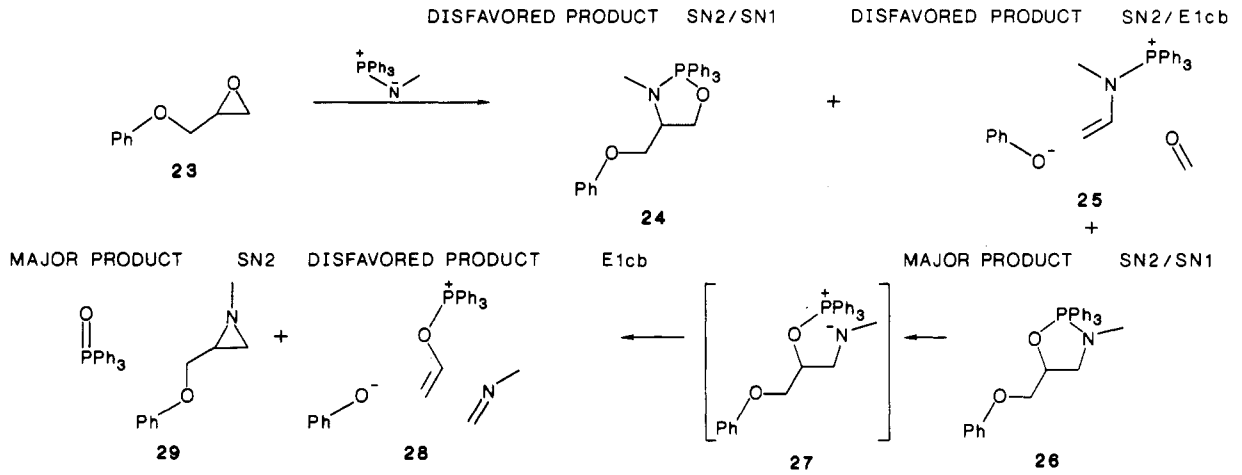
Scheme V



Scheme VI



Scheme VII



conjugate addition product was reported, the formation of **16** is predicted to be reversible by the program as well as energetically less favorable. Since no distinctions are made based on heats of reactions, **16** is also output as a major product.

Scheme VI suggests several competing pathways for an intramolecular Wittig cyclization used to synthesize the penem derivative **20**.[62] Addition into the most reactive electrophilic site, the thioester, is correctly predicted by the program and produces the betaine **18**. Since the olefination is deemed competitive with addition–elimination, the program generates the desired penem **20** as well as two elimination products **21** and **22**. An alternate elimination pathway is also recognized which ejects the stable phthalimide anion (pK_a = 10) to generate **19**. All elimination pathways are driven by the energy gained in opening the strained four-membered ring. These results are consistent with the modest 42% yield reported for the reaction.[62]

The final sequence, Scheme VII, illustrates how epoxides can be transformed into aziridines via imino-

(62) Kametani, T.; Kanaya, N.; Nakayama, A.; Mochizuki, T.; Yokohama, S.; Honda, T. *J. Org. Chem.* **1986**, *51*, 624.

phosphoranes.[59] In CAMEO, the treatment of the epoxide **23** with *N*-methyliminophosphorane produces three products. The first two, **24** and **25**, are deemed disfavored due to initial S_N2 attack at the more sterically hindered side of the epoxide. Resubmission of the major product, the oxazaphospholidine **26**, ultimately gives the aziridine **29** and an elimination product **28** via the intermediate **27**. The product **28** is deemed disfavored with respect to the S_N2 reaction since intramolecular cyclizations are typically faster than Grob fragmentations.[1k] Note that the weaker P–N bond in **26** is selectively cleaved to generate **27** despite the fact that cleavage of the P–O bond would result in a more stable base (amide vs alkoxide). Here, bond strength is considered to be the dominant factor for σ-phosphorane decomposition. Experimentally, **29** was obtained in 72% yield which is consistent with the predictions made by CAMEO.[59]

V. Conclusion

The capabilities of the nucleophilic module in CAMEO have been refined and extended in the treatment of ylide chemistry. Many new competitions have been addressed as well as steric effects for conjugate addition, stereochemistry of olefination, and the decomposition of unstable functionalities that are produced in many reactions of ylides. Through the continued recognition, refinement and implementation of such organizing principles, a better model is established, permitting the more accurate treatment of a broader range of chemistry.

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Thermal Cycloaddition Reactions of π-Delocalized Singlet Vinylcarbenes: Three-Carbon 1,1-/1,3-Dipoles. The Thermal Three-Carbon + Two-Carbon Cycloaddition

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Full details of investigations defining new aspects of the scope and mechanism of the three-carbon + two-carbon cycloaddition reaction of π-delocalized singlet vinylcarbenes (three-carbon 1,1-/1,3-dipoles generated in a reversible, thermal ring opening of cyclopropenone ketals) are detailed.

In recent efforts we have detailed the reversible, thermal generation of π-delocalized singlet vinylcarbenes (three-carbon 1,1-/1,3-dipoles) from cyclopropenone ketals[2,3] and have described their well-defined participation as 2π components of an endo-selective $[{}_{\omega}2_a + {}_{\pi}2_s]$ nonlinear, cheletropic cycloaddition with selected electron-deficient olefins and as 2π components of a thermal $[{}_{\pi}2_s + {}_{\pi}4_s]$ cycloaddition with selected α-pyrones (eq 1, Scheme I).[2] Concurrent with these observations we have detailed an effective, three-carbon + two-carbon cycloaddition of the thermally generated π-delocalized singlet vinylcarbenes with electron-deficient olefins and dienes bearing two geminal electron-withdrawing substituents and have detailed three plausible mechanistic pathways that might account for this observed cycloaddition reaction (eq 2, Scheme I).[2a] Of the *five* thermal, cycloaddition reactions available to the cyclopropenone ketal $\rightleftarrows$ π-delocalized singlet vinylcarbene, which include (1) a $[{}_{\pi}2_s + {}_{\pi}4_s]$ Diels–Alder reaction of the cyclopropenone ketal,[2a,e,3b] (2) a $[{}_{\pi}2_s + {}_{\pi}4_s]$ cycloaddition of the π-delocalized singlet vinylcarbene,[2a,d] (3) an $[{}_{\omega}2_a + {}_{\pi}2_s]$ cycloaddition of the π-delocalized singlet vinylcarbene,[2a,c] (4) a [2 + 2] (olefin–olefin/olefin–carbonyl)[2a,3] dimerization, (5) and a three-carbon + two-carbon [3 + 2] cycloaddition,[2a,b,f,3b] the three-carbon + two-carbon cycloaddition has been found to proceed with the greatest facility and constitutes the exclusive reaction course observed with *all* olefin *or* diene substrates bearing two geminal electron-withdrawing substituents that have been examined to date.[2] Herein, we detail additional studies of the [3 + 2] cycloaddition reaction of π-delocalized singlet vinylcarbenes conducted with the intention of more carefully defining the mechanism and scope of this reaction.

Stepwise Dipolar or Biradical Addition–Cyclization Reaction. The absolute rate of the [3 + 2] cycloaddition reaction was determined to be sensitive to the type and extent of olefin substitution and has been shown to be insensitive to the polarity of the reaction solvent [approximate relative rate for a given substrate:

(1) National Institutes of Health research career development award recipient, 1983–88 (Grant CA 00898/01134). Alfred P. Sloan research fellow, 1985–89.

(2) (a) Boger, D. L.; Brotherton, C. E. *J. Am. Chem. Soc.* **1986**, *108*, 6695, 6713. For preliminary studies, see: (b) [3 + 2] cycloaddition: Boger, D. L.; Brotherton, C. E. *J. Am. Chem. Soc.* **1984**, *106*, 805. Boger, D. L.; Brotherton, C. E.; Georg, G. I. *Org. Synth.* **1987**, *65*, 32. (c) [1 + 2] cycloaddition: Boger, D. L.; Brotherton, C. E. *Tetrahedron Lett.* **1984**, *25*, 5611. (d) [3 + 4] cycloaddition: Boger, D. L.; Brotherton, C. E. *J. Org. Chem.* **1985**, *50*, 3425. (e) [4 + 2] cycloaddition: Boger, D. L.; Brotherton, C. E. *Tetrahedron* **1986**, *42*, 2777. (f) [3 + 2] cycloaddition with carbonyls: Boger, D. L.; Brotherton, C. E; Georg, G. I. *Tetrahedron Lett.* **1984**, *25*, 5615. (g) Transition-metal-catalyzed [2 + 2] and [1 + 2] cycloaddition: Binger, P.; Biedenbach, B. *Chem. Ber.* **1987**, *120*, 601.

(3) For the preparation of 3,3-dimethoxycyclopropene, see: (a) Baucom, K. B.; Butler, G. B. *J. Org. Chem.* **1972**, *37*, 1730. Breslow, R.; Pecoraro, J.; Sugimoto, T. *Org. Synth.* **1977**, *57*, 41. For the first disclosure of the [4 + 2] Diels–Alder cycloaddition of cyclopropenone ketals, their participation in a single [3 + 2] and [2 + 2] cycloaddition with two, selected carbonyl compounds, and for the preparation of cyclopropenone 1,3-propanediyl ketal, see: (b) Albert, R. M.; Butler, G. B. *J. Org. Chem.* **1977**, *42*, 674. Butler, G. B.; Herring, K. H.; Lewis, P. L.; Sharpe, V. V., III; Veazey, R. L. *J. Org. Chem.* **1977**, *42*, 679.

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