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Computer-Assisted Mechanistic Evaluation of Organic Reactions. 24. Carbene Chemistry[†]

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A module that simulates carbene chemistry has been incorporated into the CAMEO program. It is mechanistically and thermodynamically based, allowing it to correctly predict the behavior of a wide range of compounds it has never encountered before. As with CAMEO generally, the Carbene Module not only predicts the major course of reaction but also the likely side products and gives insight into the mechanistic processes occurring in the system through messages issued when mechanistic decisions are made. The module encompasses five stages: (1) Optional carbene formation, incorporating all major preparative routes. (2) Perception of carbene philicity, selectivity, and spin multiplicity, as well as the steric and electronic activation of other atoms and bonds. (3) Mechanistic analysis, incorporating a simple kinetic model to address competing reactions. (4) Product evaluation and generation. (5) Product display.

I. Introduction

CAMEO, an interactive computer program which predicts the products of organic reactions given starting materials and conditions,[1] has been extended to treat the chemistry of carbenes. Whereas most programs in the field of computer-aided organic synthesis use databases of topological patterns and associated transforms, an approach which can make the assessment of competitions between reactions difficult, a more mechanistically based approach coupled with rules governing competing reactions is usually taken in the CAMEO program. Algorithms based on literature data have been developed that address specific chemical issues about fundamental reaction steps, including relative kinetics, environmental effects, and especially their competitions. In the case of carbene chemistry, for example, it is not enough to recognize a β-hydrogen and execute a 1,2-H shift. If the carbene is stabilized enough, then an intermolecular addition can compete; and if the carbene is in a three-membered ring, rupture to the allene will occur instead—but only if the ring has not been electronically deactivated. There are so many effects, and they are so interconnected, that the model used is crucial.

The mechanistic rule-based approach also makes the program's explanations more familiar and useful. Comments are generated when key decisions are made in order to illuminate the program's analysis and choices. Finally, since many transformations span more than one elementary reaction, consideration of the steps individually and independently facilitates the identification of side reactions.

Carbene chemistry is a field whose understanding has developed fairly recently and is still advancing in basic ways. The 1950's provided many fundamental advances.[2] However, many carbene reactions are still not understood well on a detailed mechanistic level, and predictive power is still incomplete as a result. Such understanding is being pieced together, especially in the area of metal carbene chemistry,[3] to provide the insight required for simulation by a mechanism-based program such as CAMEO.

Carbenes are interesting on three fronts:

(1) Carbenes are among the most reactive molecules known, and it is intriguing to identify and explain their elementary reactions. How structural factors (bond angle, electron-withdrawal by induction and electron-donation by resonance) influence the relative stabilities of these states is still under scrutiny.[4]

(2) The rapidity of carbene reactions, some of which are diffusion-limited, has challenged experimental techniques. The challenge is being met with picosecond instrumentation;[5] matrix isolation has also proven useful to probe reactivity and spin state.[6]

(3) Carbenes find application in organic synthesis and other areas, principally: the Arndt–Eistert chain homologation procedure, the Reimer–Tiemann reaction (formylation of phenols), cyclopropanation of alkenes[7] and subsequent rearrangements,[8] ketene and allene[9] preparation, synthesis of strained ring systems, ylide generation and subsequent rearrangements, *e.g.* 1,3-dipolar cycloaddition reactions,[10] and photoaffinity labeling.[11]

[†] Based on the Ph.D. dissertation of H. Helson (Purdue University, 1993).

[®] Abstract published in *Advance ACS Abstracts,* June 1, 1994.

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[2] For a brief history of carbene chemistry see: Skell, P. S. *Tetrahedron* **1985**, *41*, 1427–1428.

[3] (a) Doyle, M. P *Acc. Chem. Res.* **1986**, *19*, 348–356. (b) Bruce, M. I., *Chem. Rev.* **1991**, *91*, 197–257. (c) Doyle, M. P. *Ibid.* **1986**, *86*, 919–939.

[4] Irikura, K. K.; Goddard, W. A.; Beauchamp, J. L. *J. Am. Chem. Soc.* **1992**, *114*, 48–51.

[5] a) Eisenthal, K. B.; Moss, R. A.; Turro, N. J. *Science* **1984**, *225*, 1439–1445. (b) Griller, D.; Nazran, A. S.; Scaiano, J. C. *Acc. Chem. Res.* **1984**, *12*, 283–289. (c) *Kinetics and Spectroscopy of Carbenes and Biradicals*; Platz, M. S., Ed.; Plenum Press: New York, 1990.

[6] (a) Sander, W. W.; Patyk, A.; Bucher, G. *J. Mol. Struct.* **1990**, *222*, 21–31. (b) Platz, M. S. *Acc. Chem. Res.* **1988**, *21*, 236–242. (c) Wright, B. B. *Tetrahedron* **1985**, *41*, 1517–1523. (d) Tomioka, H.; Hirai, K.; Tabayashi, K.; Murata, S.; Izawa, Y.; Inagaki, S.; Okajima, T. *J. Am. Chem. Soc.* **1990**, *112*, 7692–7702.

[7] (a) Salaun, J. *Chem. Rev.* **1989**, *89*, 1247–1270. (b) Arlt, D.; Jautelat, M.; Lantzsch, R. *Angew. Chem. Intnl. Ed. Engl.* **1981**, *20*, 703–722. (c) Burke, S. D.; Grieco, P. A. *Org. React.* **1979**, *26*, 361. (d) Fritschi, H.; Leutenegger, U.; Pfaltz, A. *Helv. Chim. Acta* **1988**, *71*, 1553–1565.

[8] Brookhart, M.; Studabaker, W. B. *Chem. Rev.* **1987**, *87*, 411–432.

[9] For a stereospecific preparation, see : Walbrick, J. M.; Wilson, J. W., Jr.; Jones, W. M. *J. Am. Chem. Soc.* **1968**, *90*, 2895–2901.

[10] Padwa, A.; Hornbuckle, S. F. *Chem. Rev.* **1991**, *91*, 263–309.

[11] For a recent example, see: Baldwin, J. E.; Jesudason, C. D.; Moloney, M.; Morgan, D. R.; Pratt, A. J. *Tetrahedron* **1991**, *47*, 5603–5614.

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II. Essential Features of Carbene Chemistry

Before discussing the implementation, it is worthwhile to note the following salient points about carbene reactivity:

Singlet carbenes tend to involve both nonbonded electrons in their reactions. Triplet carbenes contribute only one electron at a time, resulting in a reactivity profile similar to that of ordinary radicals.[12] The remaining notes apply to the singlet state.

Carbenes exhibit variable selectivity with modest temperature dependence.[13,14] Substitution of methylene increases selectivity, mainly by stabilizing the carbene, but π-donating and σ-withdrawing substituents are the most effective.[15] Carbenes only become useful synthetically when they are heavily stabilized or have been tamed by the influence of metal catalysts.

Most carbenes are electrophilic, a state which metal catalysis preserves. Carbenes are also basic, protonation at the lone pair becoming an important reaction for nucleophilic carbenes.

Due to the carbene's unique electronic configuration it can insert into single bonds in a concerted fashion. Both the bond dissociation energy and the electron richness of the breaking bond are important. Probably due to steric factors, insertion is seen practically only with C—H and other bonds to hydrogen. Insertion into C—C bonds is rare,[16] but insertion into the Si—C bond is easier, no doubt due to easier steric access in addition to reduced bond strength.[17]

Carbenes also insert into polar single bonds, especially O—H and N—H, for which three mechanisms are widely proffered:

$$\mathrm{ROH} + \mathrm{R_2C{:}} \rightarrow \mathrm{ROCHR_2} \quad \text{concerted O−H insertion}$$

$$\mathrm{ROH} + \mathrm{R_2C{:}} \rightarrow \mathrm{RO^-} + \mathrm{R_2CH^+} \rightarrow \mathrm{ROCHR_2} \quad \text{proton transfer}$$

$$\mathrm{ROH} + \mathrm{R_2C{:}} \rightarrow \mathrm{ROH^{+}\text{-}{}^{-}CR_2} \rightarrow \mathrm{ROCHR_2} \quad \text{ylide formation}$$

The proton transfer mechanism is expected with acidic alcohols and secondary or nucleophilic carbenes, while ylide formation should predominate with less acidic alcohols and carbenes bearing electron-withdrawing groups. There is no experimental support for the concerted mechanism,[12] and the relative importance of the two ionic mechanisms is known in only a few cases.[18] Triplet carbenes, which react by an abstraction−recombination mechanism, do not insert into the strong O—H and N—H bonds, preferring to abstract hydrogen from the adjacent carbon, leading to C—H insertion.

There is a strong preference for five-membered ring formation, which undoubtedly results from a coincidence of kinetic and thermodynamic effects.[19,20] Three- and six-membered ring formation is also facile, but formation of four-membered rings is rare.

In accord with Hammond's postulate, carbene reactions being very exothermic tend to have early, loose transition states. Consequently, transition states are strongly affected by entropy, although by no means to the exclusion of enthalpy.[21]

The chief function of catalysts, besides unleashing the carbene from its precursor, is to stabilize the carbene and thus increase its selectivity. The term "carbenoid" is used to describe the liaison of carbene and transition metal ($\mathrm{R_2C{=}ML}_n$) or metal halide ($\mathrm{R_2CXML}_n$). The latter group comprises Zn (the Simmons−Smith reagent and its Conia modification) and LiX. The reactivity profile of a carbenoid is somewhat different from that of the free carbene, but not extremely so. Alkylidene (as opposed to dihalocarbene) carbenoids of LiX, however, are often plagued by ionic chemistry, and probably aggregation and chelation effects which are not easily predictable. These ionic pathways are ignored in the Carbene Module (CM), but the user may pursue them in the Basic/Nucleophilic Module.

III. Overview of the Implementation

The implementation focuses on practical synthetic carbene chemistry, but because the reactivity model was constructed as much as possible from general physical principles, the module will often "stretch" to cover more theoretical settings, particularly very high and low temperatures, and gas phase reactions.

The key ingredients of the simulation are the following:

Singlet vs Triplet Reactivity. Carbenes are assumed to react in the singlet state. If the CM determines that the triplet state is significantly populated, the reaction is shared with the Radical Module, which handles diradicals generally.[22] The two unpaired electrons of triplet carbenes reside in different orbitals and are assumed to react more or less independently, like free radicals.

Exhaustiveness. Every conceivable reaction, drawn from the small set of elementary reaction types that is possible with the ensemble of starting materials, is examined. This is inefficient in that the presence of some obviously faster pathways should obviate the need to explore the slower ones. However, because the analysis is so rapid, and because its duration is linear with the size of the system, this inefficiency is not tangible. Actual product formation, with its concomitant overhead, does not occur until all reactions have been rated.

Activation Model. Each possible reaction is rated by combining quasi-thermodynamic adjustments in a heu-

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[12] Kirmse, W.; Kund, K. *J. Org. Chem.* **1990**, *55*, 2325−2332.

[13] Houk, K. N.; Rondan, N. G.; Mareda, J. *Tetrahedron* **1985**, *41*, 1555−1563.

[14] *Reactive Intermediates*; Jones, M., Jr., Moss, R. A., Eds.; J. Wiley & Sons: New York, 1985; Vol. 3, Chapter 3.

[15] Part of the extraordinary reactivity and indiscriminacy of methylene is due to its freedom from steric interactions with potential reactants.

[16] For exceptions see: (a) Jackson, J. E.; Mock, G. B.; Tetef, M. L.; Zheng, G.-X; Jones, M., Jr. *Tetrahedron* **1985**, *41*, 1453−1464. (b) Xu, L. X.; Miebach, T.; Brinker, U. H. *Tetrahedron Lett.* **1991**, *32*, 4461−4464, and refs therein.

[17] For an example, see: Matsumoto, K.; Oshima, K.; Utimoto, K. *Tetrahedron Lett.* **1990**, *31*, 6055−6058.

[18] (a) Kirmse, W.; Sluma, H. D. *J. Org. Chem.* **1988**, *53*, 763−767. (b) Du, X.-M.; Fan, H.; Goodman, J. L.; Kesselmayer, M. A.; Krogh-Jespersen, K.; LaVilla, J. A.; Moss, R. A.; Shen, S.; Sheridan, R. S. *J. Am. Chem. Soc.* **1990**, *112*, 1920−1926. (c) Kirmse, W.; Loosen, K.; Sluma, H. D. *J. Am. Chem. Soc.* **1981**, *103*, 5935−5937. (d) Boate, D. R.; Johnston, L. J.; Kwong, P. C.; Lee-Ruff, E.; Scaiano, J. C. *J. Am. Chem. Soc.* **1990**, *112*, 8858−8863. (e) Kirmse, W.; Kilian, J. *J. Am. Chem. Soc.* **1990**, *112*, 6399−6400. (f) Moss, R. A.; Shen, S.; Wlostowski, M. *Tetrahedron Lett.* **1988**, *29*, 6417−6420.

[19] Gilbert, J. C.; Giamalva, D. H.; Weerasooriya, U. *J. Org. Chem.* **1983**, *48*, 5251−5256.

[20] See: Kirmse, W.; Kund, K. *J. Am. Chem. Soc.* **1989**, *111*, 1465−1473, and refs 22, 24, 34 therein.

[21] For general discussions of transition state thermodynamics see: (a) Moss, R. A. *Acc. Chem. Res.* **1989**, *22*, 15−21. (b) Reference 14, pp 74−78. (c) Skell, P. S.; Cholod, M.S. *J. Am. Chem. Soc.* **1969**, *91*, 7131−7137.

[22] Laird, E. R.; Jorgensen, W. L., *J. Chem. Inf. Comput. Sci.* **1990**, *30*, 458−466.

ristic rate equation related to transition state theory. The thermodynamic variables are referred to as activation enthalpy and entropy, because of their different dependencies on temperature, but should not be interpreted as quantitative assessments of the real variables. Thus, increasing temperature benefits the entropically favored γ C−H insertion at the expense of the enthalpically favored 1,2-alkyl shift.[23]

Selectivity. Carbene selectivity is a dominant factor influencing relative reaction rate. Stabilization of the carbene is equated to increasing its selectivity, which is in turn interpreted as increasing the importance of the enthalpic term for a given reaction. Thus γ C−H insertion, an entropically facile process, is an important pathway for unstabilized carbenes, while stabilized carbenes may survive long enough to undergo the more enthalpically satisfying ϵ C−H insertion or intermolecular addition.

Catalysis/Complexation. The major effect of catalysis is interpreted in this work as increasing selectivity, *i.e.* strengthening the role of enthalpy.

Program Flow. A reaction follows the basic sequence: input of starting materials,[24] specification of reaction conditions, perception of starting materials, the module-specific activity including generation of products, perception of products, duplicate product identification, and product display. The Carbene Module (CM) *per se* incorporates four units:

(1) Formation. If a carbene is not present in the starting materials, one is conjured out of them, if possible, by application of one of the standard preparative reactions.

(2) Perception. The carbene atom's electronic properties are estimated, as well as the reactivities of the other atoms and bonds in the system.

(3) Mechanistic Analysis. The carbene is paired with all potentially reactive atoms and bonds, and a ranking is assigned to each pairing reflecting the speed of reaction. Carbene chemistry is thus viewed as a contest between a large number of simultaneous, competing reaction channels.

(4) Product Generation. After all reactions have been evaluated, the best are selected and executed.

We now examine these stages in detail.

IV. Reaction Conditions

Because carbene reactions have their own characteristic reagents and conditions, a supplemental reagent menu is provided, containing the following options:

Spin Multiplicity (use only singlet or triplet). Normally the CM assesses the spin state properties of the carbene automatically, but this option focuses the simulation on one spin state or the other. Selecting triplet chemistry is equivalent to submitting the starting material directly to the Radical Module.

Spin Multiplicity (triplet sensitizer). A triplet sensitizer (*e.g.* Hg, Ph_2CO) results in the carbene appearing initially in the triplet state. This normally has the effect of suppressing singlet chemistry, but if the rate of intersystem crossing (ISC) is high, and the carbene is a ground state singlet, then the singlet carbene is expected to contribute. This interplay is considered during carbene perception and product generation.

Transition Metal Catalyst and Simmons−Smith/Conia Reagent. These options, nearly identical in effect, suppress triplet chemistry, and increase the importance of activation enthalpy and (to a lesser extent) sterics. Seemingly small differences in catalyst often translate into drastically different product distributions, but it is difficult to perceive simple, general trends. The diversity of catalysts, the difficulty of inferring their reactivity from their structure, and the complexity of entering polynuclear structures or maintaining them on a special menu, all make it impractical for CAMEO to consider catalyst structure.[25] When a metal catalyst option is selected, only the effects common to most are implied, *i.e.* the liberation of carbene from its diazo precursor, and increased selectivity, particularly promotion of addition and coordination reactions relative to C−H insertion. The principal distinction of the Simmons−Smith[26] and Conia[27] reagents is that their cyclopropanations are affected by directing groups like hydroxyl.

Solvent. Selection of solvent is optional, but if one or more are specified, then they will be considered as potential substrates for the carbene. Solvent dilution can be specified as *low, average, high,* or *gas phase*; dilution of the reactants has the primary effect of slowing intermolecular reactions not involving the solvent. At the *gas phase,* extreme intermolecular processes are suppressed altogether.

Temperature. The major effect of increasing temperature is to increase the importance of entropic factors. Additionally, in the absence of a catalyst or light, a higher temperature is necessary to liberate carbenes from diazirines and diazo compounds (50−100 °C) and tosylhydrazone salts (100−200 °C).

Form Trace Products. If this option is picked, then up to 15 of the next-best products will be generated. Ordinarily only major, minor, and third-tier products are created.

Other options provide for photolytic conditions and online help.

V. Carbene Formation

The carbene formation routine's task is to produce a carbene when none is present. Each carbene created is housed in a new structure in the synthesis tree. Because more than one carbene could conceivably be formed from the starting material, and because general perception is required for the new substance(s), program flow is simplest if each created carbene is processed independently. The carbenes formed are therefore queued for orderly submission back to the CM, and after it has pursued all formation pathways the formation routine relinquishes control to the mechanistic executive (Figure 1). If any carbene(s) have been created, the CM will be reentered for each one.

To some extent the CM can warn of possible side reactions, such as carbenium ion chemistry when a diazo precursor decomposes in a protic[28] system, but the nuances involved in predicting other ionic and pericyclic processes are best left to the modules equipped to treat them.

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[23] Moss, R. A.; Ho, G.-J. *J. Am. Chem. Soc.* **1990**, *112*, 5642−5644.

[24] Descriptions of the user interface may be found in ref 1.

[25] Collaboration with the developing Transition Organometallic Module might change this situation in the future.

[26] Simmons, H. E.; Smith, R. D. *J. Am. Chem. Soc.* **1958**, *80*, 5323. *Ibid.* **1959**, *81*, 4256.

[27] Conia, J. M. *Pure Appl. Chem.* **1975**, *43*, 317−326.

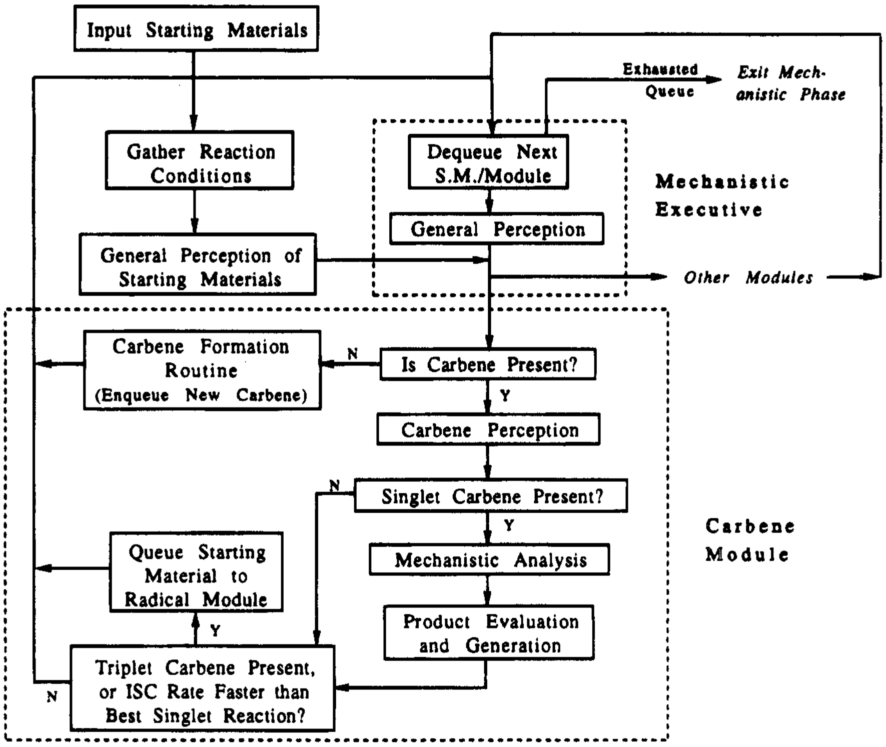
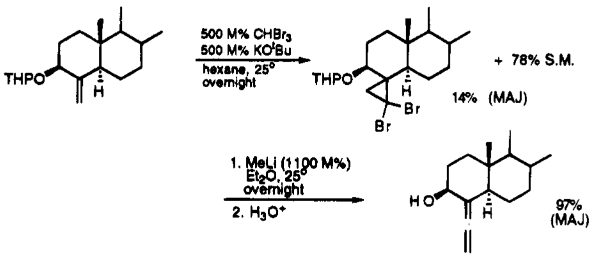


Figure 1. Program flow in and around the Carbene Module.

There are many routes to carbenes. Although it would be desirable to reproduce them all, this is not essential as the user can always submit a free carbene directly. Nonetheless, the major ones are implemented and are described briefly below. The carbene formation routine is not sophisticated about the relative rates of different formation reactions; in the unlikely event that more than one is possible, all will be executed.

Except as noted, all reactions that follow are handled by the CM as indicated. The designations MAJ, MIN, and DISF refer to the CAMEO-assessed yields: major, minor, and disfavored. Another third-tier category, TRACE, describes products considered but not ordinarily generated. Indicated numerical yields are experimental data and those in parentheses represent relative yields.

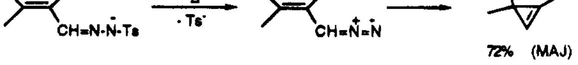
Ionic Processes. α-Elimination. α-Elimination, the consecutive loss of a proton and an anionic leaving group, is probably the commonest route to carbenes in synthetic chemistry. (Because of its importance, α-elimination has also been incorporated into the Basic/Nucleophilic Module to a limited extent.[29]) Often the object is cyclopropanation of an alkene, and the carbene is dichlorocarbene or dibromocarbene generated from the corresponding haloform.[30,31] The resulting dihalocyclopropane can be reduced or it can be ring-opened to an allene in a second carbene reaction (eq 1[32]), thereby constituting one of the best preparative routes to allenes free of acetylenic contaminants.[33]



(1)

The strength of the base required depends on the acidity of the halide. Haloforms eliminate easily under the influence of an oxide base, whereas dihaloalkanes require hydrogen−metal exchange. Epoxide oxygens may also serve as leaving groups.

An important preparation of free carbenes is the Bamford-Stevens reaction (eq 2[34]), which involves an elimination of tosylate followed by loss of N$_2$. The carbene is formed in one step by CAMEO even though the intermediate diazo compound is isolable in some cases.



(2)

Direct Elimination. If a carbanion with a suitable leaving group is already present, a carbene is generated

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(28) The system is considered protic if the solvent is protic or if one of the reactants has a carboxylic acid function or similarly acidic group.

(29) When an anion of low acidity that bears a leaving group is produced as an intermediate its structure is queued to the CM for possible carbene formation.

(30) For an excellent review of phase transfer catalysis see: Makosza, M. *Pure Appl. Chem.* **1975**, *43*, 439−463. For synthetic examples: (a) ref 14, pp 76−79. (b) Downing, W.; Latouche, R.; Pittol, C. A.; Pryce, R. J.; Roberts, S. M.; Ryback, G.; Williams, J. O. *J. Chem. Soc. Perkins Trans. 1*, **1990**, 2613−2615. (c) Dunkelblum, E.; Singer, B. *Synthesis* **1975**, 323. (d) Vogel, E.; Klug, W.; Breuer, A. *Org. Synth.* **1974**, *54*, 11−18.

(31) For a recent example using ultrasound see: Xu, L.; Smith, W. B.; Brinker, U. H. *J. Am. Chem. Soc.* **1992**, *114*, 783−784.

(32) Ekhato, V.; Robinson, C. H., *J. Org. Chem.* **1989**, *54*, 1327−1331. CAMEO predicts that most of the carbene in the first step is consumed by reaction with the solvent.

(33) Taylor, K. G. *Tetrahedron* **1982**, *38*, 2751−2772. See p 2755.

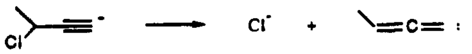
(34) (a) Jones, M., Jr.; Moss, R. A. *Carbenes*; John Wiley & Sons: New York, 1973; Vol. 1, p 27. (b) Closs, G. L.; Closs, L. E.; Boll, W. A. *J. Am. Chem. Soc.* **1963**, *85*, 3796−3800.

Chart 1

Algorithm I. Assignment of selectivity

- *IF* a catalyst is present or the carbene is otherwise active as a carbenoid, selectivity is ***HIGH***;
- *ELSE IF* the carbene is bonded to a nitrogen or oxygen atom, selectivity is ***HIGH***;
- *ELSE IF* the number of adjacent atoms with a lone pair to donate, plus the number of adjacent polarized multiple bonds (particularly keto, ester, cyano) is two, *i.e.* present on both sides, selectivity is ***HIGH***;
- *ELSE IF* this count is one, selectivity is ***MEDIUM***;
- *ELSE IF* the carbene is conjugated (particularly vinyl and aryl carbenes), selectivity is ***MEDIUM*** if conjugated on both sides, or ***LOW*** if on one side only;
- *ELSE* selectivity is ***VERY LOW***.

by ejection of the leaving group. This extends to the γ-elimination of propargyl halide anions (eq 3).[35]

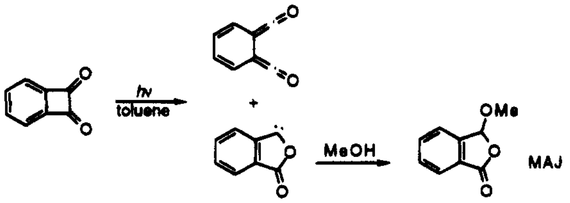


(3)

Halogen–Metal Exchange. Simple halogen–metal exchange is executed in tandem with the elimination step for di- and trihaloalkanes.

Homolytic Processes. Thermal or Photochemical Elimination of Small Molecules.[36] Nowadays the preeminent carbene precursors are the diazo compounds,[37] which lose inert nitrogen readily to give free carbenes. Others are trichloroacetate (loss of CO_2), oxiranes, oxirenes, and the diazirines (now generally available from the ketone using Graham's oxidation,[38] Moss's exchange reaction,[39] or other methods[40,41]). Many more exotic cycloelimination reactions are known, but are not normally convenient or reliable.

Valence Isomerizations. Photolytic Rearrangement. Two less-common carbene sources involving the triplet rearrangement of certain photoexcited ketones are implemented. Triplet acylsilanes are in equilibrium with siloxy carbenes,[42] although the path is not reliable or high-yielding. Once formed, the siloxy carbene quickly collapses to the ground state singlet.[43] A similar reaction befalls cyclobutanones (eq 4[44]) and ketones situated in certain bridged systems.[45] CAMEO-calculated bond dissociation energies are used to predict the regiochemistry of the rearrangement.



(4)

VI. Perception of Carbene and Substrate

The purpose of the carbene perception phase is to perform the physical evaluations of the reactants necessary to mechanistic evaluation. It exists as a discrete phase so as to simplify the conception, writing, and operation of the analysis phase.

Table 1. Selectivities of Representative Carbenes

carbene	CAMEO selectivity
MeO(Cl)C:	high
MeO(Me)C:	high
Cl_2C:	high
MeClC:	medium
$H(CO_2Et)C$:	medium
PhHC:	low
cyclopentadienylidene	low
Me_2C:	very low
H_2C:	very low

A. Carbene Perception. The qualities important to the carbene are its philicity, selectivity, and spin state. Note that "reactivity" is not needed: while a carbene may be more or less reactive, it is its relative reactivities toward a spectrum of reactants that is of interest. What determines these are its philicity, *i.e.* the enthalpic preference for electron-rich or -poor atoms and bonds, and its selectivity, which is defined in this work as the extent to which it prefers enthalpically superior reaction pathways.[46]

1. Selectivity. Doering conceived[47] and Moss has developed the "carbene selectivity index" for comparing the selectivities of different carbenes in their additions to alkenes. While all electrophilic carbenes tend to add faster to electron-rich alkenes than to electron-poor ones, more-selective carbenes show a larger spread in their rates of reaction and consequently give cleaner reactions. Moss found that many experimental selectivities are reproduced well by a linear equation involving σ_{R+} and σ_I,[21a] but a simpler, qualitative role for selectivity was considered more appropriate for CAMEO (Chart 1).[48] Table 1 lists representative carbenes and their assignments. The most unselective carbenes usually undergo intramolecular rearrangements faster than they can be trapped intermolecularly or can decay to the triplet

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[35] For examples of γ-elimination preparations, see: (a) Stang, P. J. *Acc. Chem. Res.* **1982**, *15*, 348–354; see p 349. (b) Sheu, J.-H.; Yen, C.-F.; Chan, Ya-L.; Chung, J.-F. *J. Org. Chem.* **1990**, *55*, 5232–5233. (c) Sheu, J. H.; Yen, C. F.; Huang, C. W.; Chan, Y. L. *Tetrahedron Lett.* **1991**, *32*, 5547–5550.

[36] For a review, see: Griffin, G. W.; Bertoniere, N. R., Chapt. 3 in ref 34a.

[37] *The Chemistry of Diazonium and Diazo Groups*; Patai, S., Ed.; J. Wiley & Sons: New York, 1978.

[38] See, for example: (a) Reference 21a, pp 15–16. (b) Ibata, T.; Liu, M. T. H.; Toyoda, J. *Tetrahedron Lett.* **1986**, *27*, 4383–4386.

[39] (a) Reference 21a, p 16. (b) Wlostowska, J.; Moss, R. A.; Guo, W.; Chang, M. J. *J. Chem. Soc., Chem. Comm.* **1982**, 432–433. (c) Cox, D. P.; Moss, R. A.; Terpinski, J. *J. Am. Chem. Soc.* **1983**, *105*, 6513–6514.

[40] For references, see: Baldwin, Jack E.; Pratt, A. J.; Moloney, M. G. *Tetrahedron* **1987**, *43*, 2565–2575.

[41] *Chemistry of Diazirines*; Liu, M. T. H., Ed.; CRC Press: Boca Raton, 1987.

[42] Reference 14, pp 69–71.

[43] Page, P. C. B.; Klair, S. S.; Rosenthal, S. *Chem. Soc. Rev.* **1990**, *19*, 147–195. The acylsilane rearrangement is discussed on pp 191–195.

[44] Boate, D. R.; Johnston, L. J.; Kwong, P. C.; Lee-Ruff, E.; Scaiano, J. C. *J. Am. Chem. Soc.* **1990**, *112*, 8858–8863.

[45] Kirmse, W. *Carbene Chemistry*, 2nd ed.; Academic Press: New York, 1971. See pp 47–51; 423.

[46] Some carbenes disobey the reactivity–selectivity principle, which holds that, within a related series, the more reactive species are less selective, and that selectivity decreases as temperature increases. See: (a) Reference 13, p 1556. (b) Reference 14, p 65.

[47] Doering, W. v. E.; Henderson, W. A. *J. Am. Chem. Soc.* **1958**, *80*, 5274.

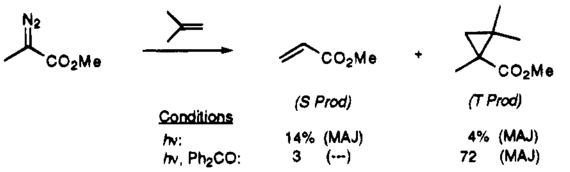
[48] In an earlier version of the program, m_{cxy}'s were calculated by Moss's equation. A routine was written that returns accurate substituent constants and m_{cxy} values for the common carbenes, but its method was *ad hoc*, making it unreliable for unusual carbenic structures. Algorithm I suffers from the same defect, but at least its simplism is apparent.

Table 2. Philicity of Carbenes, R = Alkyl, Aryl

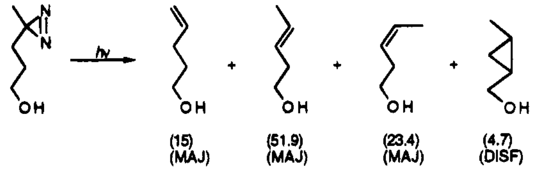
electrophilic	ambiphilic	nucleophilic
X_2C:	ROC:X	$Me_2N(Ph)C$:
$RO_2C(Br)C$:	RC:X[a]	$(RO)_2C$:
R(CN)C:	ROC:R[b]	cyclopropenylidene
cyclopentadienylidene		cycloheptatrienylidene

[a] Aryl halocarbenes, including the recently synthesized pyridinyl chlorocarbenes, are on the borderline between electrophiles and ambiphiles.[52] [b] Although ambiphilic, dominated by nucleophilic reactions with normal alkenes.

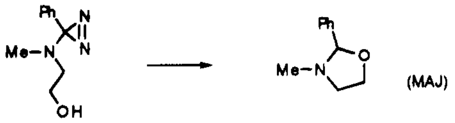
state.[49] Equation 5 illustrates this elusiveness and how a triplet sensitizer can increase yields of intermolecular reactions.[50] Likewise, the unstabilized carbene of eq 6 was estimated by the authors to undergo 1,2-hydrogen shift "three orders of magnitude faster than for any likely intermolecular capture reaction."[51] They contrast it with the stabilized analog in eq 7, which survives long enough to undergo the energetically preferred ring closure in "high yield".



(5)



(6)



(7)

2. Philicity. While the common carbenes are electrophilic, over the past 15 years it has become clear that there is a continuous spectrum of philicity (Table 2). Electrophilic carbenes react faster with electron-rich olefins, whereas nucleophilic carbenes shun all but electron-poor ones. An ambiphilic carbene reacts more rapidly with either electron-poor or -rich olefins, but sluggishly with average alkenes.[53] (In an absolute sense, all carbenes would display ambiphilic behavior were the alkene electron-rich or -poor enough, but we are interested in the normal spread of alkenes.)

It is fruitful to consider frontier molecular orbitals (FMO's) when trying to understand carbene philicity and selectivity,[54] particularly in addition reactions.[55] The interaction of an unexcited singlet carbene with an alkene can occur on two levels: the usual "electrophilic" one, where the empty p orbital (LUMO) of the carbene mixes with the π HOMO of the alkene; and the "nucleophilic" type, where the filled σ orbital (HOMO) of the carbene mixes with the π^* LUMO of the alkene. Both interactions occur simultaneously, but their contributions depend on the relative energies of the orbitals involved in each, and one interaction usually dominates.

It would be desirable to apply the FMO model quantitatively to addition reactions, especially since CAMEO has a good algorithm for predicting HOMO/LUMO energies of alkenes,[56] but it has not proved feasible to estimate FMO energies accurately for all of the diverse carbenes.[57] Furthermore, the FMO view may not be sufficient to explain relative rates of carbene–alkene additions. The role of entropy is clearly important, but the causes of even qualitative reactivity trends have been debated for over a decade.[58] Nonetheless, the FMO analysis rationalizes a great deal: carbenes are more or less selective according to the magnitude of their FMO gap with, in particular, alkenes; and are electrophilic, ambiphilic, or nucleophilic depending on which of the two FMO interactions prevails. These two dimensions can be predicted qualitatively, and as such can be applied to other processes besides cyclopropanation.

For CAMEO's purposes it is simplest to categorize carbenes based on the nature of their substituents (Chart 2). An exception is made for cyclopropenylidene and cycloheptatrienylidene, which are nucleophilic, due probably to the contribution of aromatic resonance forms (eq 8).

(8)

3. Spin Multiplicity. Assessing the effects of the carbene's spin state is difficult. Indeed, assigning this property can be difficult retrospectively when viewing published accounts of reactions in which the products are known. CAMEO distinguishes three types of multiplicity: initial, ground state, and effective. The initial spin state is the state in which the carbene is generated and is normally the singlet.[59] It will be the triplet if a triplet sensitizer (typically mercury vapor or benzophenone) has been used or if the carbene originated from the rearrangement of an acylsilane or similar triplet excited species.

A few simple rules are adequate to assign the ground state multiplicity, although not the magnitude of the

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(49) For many years it was noted in the literature that intermolecular reactions of dialkyl carbenes were unknown. Possibly the first dialkyl carbene discovered to be stable against intramolecular rearrangement is diadamantyl carbene, whose 1,2-shift would lead to a Bredt violation and whose γ C–H insertion is apparently difficult sterically: Myers, D. R.; Senthilnathan, V. P.; Platz, M. S.; Jones, M., Jr. *J. Am. Chem. Soc.* **1986**, *108*, 4232–4233.

(50) Sohn, M.; Jones, M. *J. Am. Chem. Soc.* **1972**, *94*, 8280–8281.

(51) Stevens, I. D. R.; Liu, M. T. H.; Soundararajan, N.; Paike, N. *Tetrahedron Lett.* **1989**, *30*, 481–484.

(52) Moss, R. A.; Jang, E. G.; Kim, H.-R.; Ho, G.-J.; Baird, M. S. *Tetrahedron Lett.* **1992**, *33*, 1427.

(53) Moss, R. A., Shen, S.; Hadel, L. M.; Kmiecik-Lawrynowicz, G., Wlostowska, J.; Krogh-Jespersen, K. *J. Am. Chem. Soc.* **1987**, *109*, 4341–4349.

(54) (a) See pp 62–64 in Moss, R. A. *Acc. Chem. Res.* **1980**, *13*, 58–64. (b) Jones, W. M.; Brinker, U. H. In *Pericyclic Reactions;* Marchand, A. P., Lehr, R. E., Eds.; Academic Press: New York, 1977; Vol. 1. See pp 109 ff.

(55) The "curve-crossing approach" has recently been applied to addition reactions: Pross, A.; Moss, R. A. *Tetrahedron Lett.* **1990**, *31*, 4553–4556.

(56) Burnier, J. S.; Jorgensen, W. L. *J. Org. Chem.* **1983**, *48*, 3923–3941.

(57) For some theoretically derived carbene FMO values, see: (a) Rondan, N. G.; Houk, K. N.; Moss, R. A. *J. Am. Chem. Soc.* **1980**, *102*, 1770. (b) Moss, R. A.; Perez, L. A.; Wlostowska, J.; Guo, W.; Krogh-Jespersen, K. *J. Org. Chem.* **1982**, *47*, 4177–4180. (c) Reference 53.

(58) Giese does not agree with the simple FMO analysis just presented and has proposed an intermediate carbene–alkene complex (ref a following), but computations have not supported this idea, at least for the carbenes studied (b, c). Still, anomalies persist that resist simple explanations (d). References: (a) Giese, B.; Lee, W. B. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 310. (b) Blake, J. F.; Wierschke, S. G.; Jorgensen, W. L. *J. Am. Chem. Soc.* **1989**, *111*, 1919–1920. (c) Referencde 13. (d) Soundararajan, N.; Platz, M. S.; Jackson, J. E.; Doyle, M. P.; Ooon, S.-M.; Liu, M. T. H.; Anand, S. M. *J. Am. Chem. Soc.* **1988**, *110*, 7143–7152.

(59) Wentrup, C, *Reactive Molecules: the Neutral Reactive Intermediates in Organic Chemistry*; John Wiley & Sons: New York, 1984; Chapter 4. See p 181 for a discussion.

Chart 2

Algorithm II. Assessment of philicity

- *IF* a conjugated cyclic system of size 4n+3, *viz.* cyclopropenylidene or cycloheptatrienylidene, philicity is ***Nucleophilic***;
- *ELSE IF* carbene has an oxygen or nitrogen substituent, and a halogen or polarized multiple bond substituent (C=O, C=N *etc.*) it is ***Ambiphilic***;
- *ELSE IF* carbene has an oxygen, nitrogen or sulfur substituent, it is ***Nucleophilic***;
- *ELSE* carbene is ***Electrophilic***.

Chart 3

Algorithm III. Assignment of ground state multiplicity. GS=Ground state multiplicity; *S*=singlet; *T*=triplet; *M*=triplet with low-lying singlet.

	Examples
• *IF* there is a substituent bearing a lone pair, GS=***S***;	Cl_2C:, MeO(H)C:, ArClC:
• *ELSE IF* carbene is doubly bonded, GS=***S***;	H_2C=C:
• *ELSE IF* carbene is part of an otherwise fully conjugated ring, then:	
• Cyclopropenylidene and cycloheptatrienylidene are ***S***;	
• Others are ***M***;	Cyclopentadienylidene
• *ELSE IF* carbene is conjugated, GS=***M***;	PhHC:, H_2C=CMe(H)C:, $(RO_2C)HC$:
• *ELSE* GS is ***T***.	CH_2:, Me_2C:[60]

singlet–triplet (S–T) splitting;[60] see Chart 3. Generally, resonance-donating substituents strongly stabilize the singlet, and adjacent unsaturation decreases the S–T gap to a lesser extent. The most prominent group in the latter category is the aryl carbenes, whose S–T splitting is small. Unusual features amend these trends: being situated in a quasi-aromatic ring tends to close the S–T gap by consolidating the carbene's electrons either into or out of the ring; and vinylidenes (R_2C=C:) are decidedly singlet, as might be expected from their geometry.[61] Cycloheptatrienylidene may be a transition state between two allenic enantiomers;[61d] however it is fruitful to assume, on the basis of the precursors' reactivity, a carbene intermediate. The ground states of few carbenes have been experimentally determined; although in accord with conventional thinking, it remains to be seen if CAMEO's predictions are true.

The effective spin state is a contrivance that determines which real spin state, or both, will be considered. If the ground and initial states are the same, then the effective spin state is also the same. Otherwise, the effective state is a function of the initial state, the ground state, the rate of intersystem crossing, and the speed of the carbene's reactions from the initial state.[5a,62] In general, chemistry from both states is anticipated. Singlet chemistry is first pursued; if it is found that the singlet has a very rapid reaction available and the rate of intersystem crossing is high, triplet chemistry is suppressed. Otherwise the carbene is queued to the Radical Module for processing after the CM completes all its processing. A mixture of spin states is characteristic of aryl carbenes, whose rate of intersystem crossing may be faster than the reactions of either individual spin state.[61b,63,64] An important and common exception to these rules is when a catalyst is present. All types of carbene complexes undergo exclusively singlet-like chemistry.

If the effective spin state is the triplet (*e.g.* the second reaction of eq 5), there is nothing for the CM to do, and, after queuing the starting material for submission to the Radical Module, program flow returns to the mechanistic executive routine (Figure 1).

4. Steric Hindrance. Steric effects are subtle in carbene chemistry[65] and have not been thoroughly studied and incorporated into the program. A crude measure of the hindrance offered by the carbene's environment is obtained from CAMEO's Taft E_s estimation procedure,[66] even though it was not designed for carbenic centers. The carbene's blockage is then classified as low, medium, or high. Transition metal carbenes are automatically assigned the "high" value, due to the bulk of the metal complex.[67] These rough steric assessments will contribute only slightly in the subsequent analysis phase.

B. Substrate Perception. 1. Symmetry Reduction. The Symmetry-Reduced Atom and Bond Table (SRAB), the subset of the atom and bond table remaining after symmetrically redundant entries have been stripped,[68] is constructed. The number of reactive sites that must be considered is minimized by restricting

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(60) A recent compilation lists ground state multiplicities and singlet–triplet energy gaps for many carbenes: Nefedov, O. M.; Egorov, M. P.; Ioffe, A. I.; Menchikov, L.G.; Zuev, P. S.; Minkin, V. I.; Simkin, B. Y.; Glukhovtsev, M. N. *Pure Appl. Chem.* **1992**, *64*, 265–314.

(61) (a) Stang, P. J. *Chem. Rev.* **1978**, *78*, 383–405. For other discussions of the effect of bond angle on spin state, see: (b) Schuster, G. B. *Adv. Phys. Org. Chem.* **1986**, *22*, 311–361. Although limited to arylcarbenes, this review offers an enlightening analysis of mechanisms, singlet vs triplet reactivity, intersystem crossing, and factors affecting ground state multiplicity. (c) Hoffmann, R.; Zeiss, G.D.; Van Dine, G. W. *J. Am. Chem. Soc.* **1968**, *90*, 1485. (d) Wentrup, C.; Mayor, C.; Becker, J.; Lindner, H. J. *Tetrahedron* **1985**, *41*, 1601–1612.

(62) The rate of intersystem crossing is also affected by carbene structure, the magnitude of its singlet–triplet gap, and the solvent's polarity: (a) Langan, J. B.; Sitzmann, E. V.; Eisenthal, K. B. *Chem. Phys. Lett.* **1984**, *110*, 521–527. (b) Eisenthal, K. B.; Turro, N. J.; Sitzmann, E. V.; Gould, I. R.; Hefferon, G.; Langan, J.; Cha, Y. *Tetrahedron* **1985**, *41*, 1543.

(63) (a) Bethell, D.; Stevens, G.; Tickle, P. *J. Chem. Soc., Chem. Commun.* **1970**, 792–794. (b) Reference 12, and refs therein.

(64) For a dissenting view see: Tomioka, H.; Tabayashi, K.; Ozaki, Y.; Izawa, Y. *Tetrahedron* **1985**, *41*, 1435–1440, and refs 4, 11, 12 therein.

(65) Regarding steric effects on carbene chemistry, see: (a) Reference 34a, pp 256–265. (b) Moss, R. A. In *Selective Organic Transformations*; Thyagarajan, B. S., Ed.; John Wiley & Sons: New York, 1970; Vol. 1. See pp 35–88.

(66) (a) Unger, S. H.; Hansch, C. *Progr. Phys. Org. Chem.* **1976**, *12*, 91. (b) Taft, R. W., Jr. In *Steric Effects in Organic Chemistry*; Newman, M. S., Ed.; J. Wiley & Sons: New York, 1956. See pp 556 ff. (c) A manuscript on CAMEO's estimation of E_s is in preparation by J. M. Fleischer.

(67) For example, see p 197 in: Maas, G. *Top. Curr. Chem.* **1987**, *137*, 75–253, a comprehensive survey of transition metal-catalyzed reactions from 1978 to 1985.

(68) Helson, H. E., Ph.D. Dissertation, Purdue University, 1993; Chapter 4.

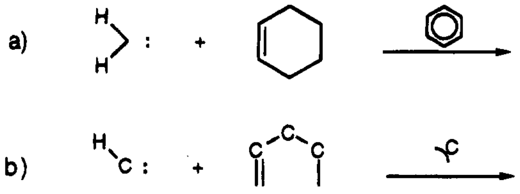

Figure 2. The Symmetry-Reduced Atom and Bond Table (SRAB, second reaction) results when redundant atoms and bonds are removed. Atoms present in the SRAB are lettered explicitly.

future attention to the SRAB. The starting materials shown in Figure 2a, for example, contain nine redundant atoms (one hydrogen in the carbene, three carbons in cyclohexene, five in benzene) and eight redundant bonds (one in the carbene, two in cyclohexene, five in benzene) that are removed from the SRAB in Figure 2b.

2. Multiple Bonds: Electronics and Sterics. For the analysis of addition reactions every nonaromatic multiple bond is rated for electron richness (ER) and steric accessibility. The ER value ranges from 0 (tetracyanoethylene) to 100 (tetraethylethylene), depending on the HOMO energy as calculated by CAMEO[66] (eq 9).

$$\mathrm{ER} = 100 \times \frac{\mathrm{HOMO} - \mathrm{HOMO}_{\mathrm{TCNE}}}{\mathrm{HOMO}_{\mathrm{TEE}} - \mathrm{HOMO}_{\mathrm{TCNE}}} \qquad (9)$$

ER's are tabulated in Table 3 for a variety of unsaturated compounds and generally correspond to expectations for the alkenes. The HOMO's of carbonyl compounds, however, would suggest a reactivity toward carbenes that they do not possess.[70] To inhibit additions to all polarized multiple bonds, 80 is deducted from their ratings.

The steric total of a multiple bond (Table 3) is the sum of the E_s of its (up to) four substituents. The result is scaled so that it ranges from 0 (ethylene) to 100 (tetra-*tert*-butylethylene). Because the carbene is free to approach the olefin by the less-congested route, the steric index is reduced by one-half if mono-substituted, one-quarter if geminally disubstituted, and one-third if *cis*-vicinally disubstituted.

3. Kinetic Accessibility and Cyclizations. Kinetic accessibility, the clearest manifestation of entropy, arises from three sources: (1) molecularity, *i.e.* whether the reaction is intra- or intermolecular; (2) symmetry; and (3) resultant ring size and intervening geometry, particularly hybridization, arising during intramolecular cyclization.[71] The normal kinetic order for forming N-membered rings is 3 ≫ 5 > 6 > 7 ≫ 4, 8, ... If there are two or more intervening sp^2 centers, the preference for five- over six-membered ring formation disappears.

Molecularity and symmetry are conveniently interpreted during mechanistic analysis as they are needed, but cyclization geometry requires considerable computation, and it is efficient to consider the collection of atoms in advance. A routine was written to assess the ease of cyclization with every other atom in the carbene's molecule. Paths are grown recursively from the carbene outwards, keeping track of the intermediate atoms' hybridization along each path. Each atom is assigned a value from −2 (precluded by path geometry) to 1 (rapid). Like the symmetrically redundant atoms and bonds, unreactive atoms and bonds will not be considered further. The value −1 is used for the four-membered ring formation in benzocyclobutene, which is appreciably slower than ordinary four-membered ring formation. Otherwise, atoms that would yield three-, five-, or six-membered rings are designated 1 (rapid) and other ring sizes are designated 0 (moderate reactivity).

Table 3. Multiple Bond Electron-Richness Derived from HOMO Energies (eV). Values in Parentheses are Experimental;[69] the Rest are Derived by CAMEO

substrate	HOMO		electron richness	steric value
ethylene	−10.5	(−10.5)	37	0
propene	−9.9	(−9.8)	57	2
2-methylpropene	−9.5		70	7
trans-2-butene	−9.5	(−9.1)	70	10
2-methyl-2-butene	−9.3	(−8.7)	77	15
tetramethylethylene	−9.2	(−8.3)	80	20
tetraethylethylene	−8.6		100	20
cyclohexene	−8.9	(−9.0)	90	6
fluoroethylene	−10.5	(−10.6)	37	0
cyanoethylene (C=C)	−11.0	(−10.9)	20	1
tetracyanoethylene (C=C)	−11.6	(−11.8)	0	8
methyl vinyl ether	−8.9	(−9.1)	90	1
1,3-butadiene	−9.0	(−9.0)	87	5
styrene	−8.4	(−8.4)	107	8
dimethyl fumarate (C=C)	−10.8	(−10.5)	27	32
maleic anhydride (C=C)	−11.0	(−11.1)	20	21
TMS-ethylene	−10.0	(−9.8)	53	6
methyl acrylate (C=C)	−10.7	(−10.7)	30	8
norbornene	−8.8	(−8.9)	93	15
acetone (C=O)	−12.3		−103*	7
ethyl acetate (C=O)	−9.9	(−11)	−23*	6
dimethyl fumarate (C=O)	−9.3		−3*	12
maleic anhydride (C=O)	−10.9		−57*	10
acetonitrile (C≡N)	−12.4		−107*	2
cyanoethylene (C≡N)	−10.9	(−10.9)	−57*	5

* Includes a reduction of 80 for a polarized multiple bond.

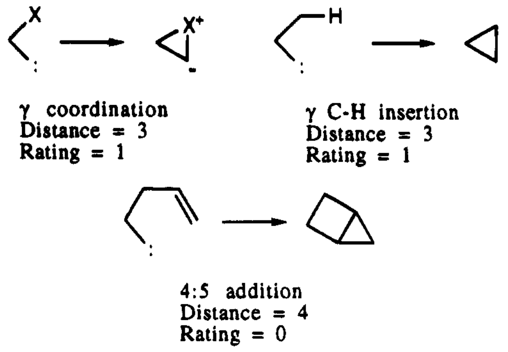

Figure 3. Kinetic accessibility of atoms and bonds.

It became evident that the kinetic accessibility of bonds is neatly determined by the distance from the carbene to the atom in the bond that is nearer the carbene before closure (Figure 3). The kinetic rating of the bond is given the value calculated for this nearer atom.

4. Aromatic Rings. The last action of the perception phase is to assess the reactivity of any aromatic rings present. To this end the ring reactivity number[72] of the most reactive arene is calculated.

VII. Mechanistic Analysis

Mechanistic analysis consists of applying the fundamental carbene reaction pathways to every nonredundant

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[69] Paderes, G. D.; Jorgensen, W. L. *J. Org. Chem.* **1992**, *57*, 1904–1916.

[70] Instances of formal addition to ketones are known, but these are more likely the result of ionic mechanisms, *i.e.* nucleophilic addition or ylide formation followed by rearrangement. The sole compelling example of carbonyl addition is the oxirene byproduct of the Wolff rearrangement, which is driven by proximity.

[71] For a recent discussion of intramolecularity and reaction rate, see: Menger, F. M. *Acc. Chem. Res.* **1993**, *26*, 206–212.

[72] Bures, M. G.; Roos-Kozel, B. L.; Jorgensen, W. L. *J. Org. Chem.* **1985**, *50*, 4490.

Table 4. The Carbene Reaction Pathways, Including Their Basic Rank and Standard Processing Category

base rate	category	pathway
		1,2-shifts
0	H	1,2-H shift
0	B	cyclopropylidene-to-allene rearr
1–4	B	ring contractions and expansions
1	O	cyclopropylcarbene fragmentation
6	B	other 1,2-shifts, incl the Wolff rearr
1	O	Skattebol rearr
6	A	addn to triple bonds
9	NA	cycloheptatrienylidene-to-arylcarbene rearr
10	A	addn to aromatic bonds, incl the arylcarbene rearr
3	A	addn to double bonds
5	H	C–H insertion (other than 1,2-H shifts)
7	H	X–H insertion (X = N, O, Si)
5	B	R–X insertion (R = C, Si; X = Cl, Br, I)
5	O	proton transfer
3	O	coordination (ylide formation)
15	NA	EAS Module
6	NA	alkoxy halo carbene fragmentation
10	O	dimerization/azine formation

[a] Legend: H, X–H insertion; A, addition to a π bond; B, insertion into a σ bond; O, other; NA, kinetic assessment not applicable.

and conformationally accessible atom and bond, and assigning a rating to every resulting "latent" product. After all conceivable products have been considered, the best will be queued for actual product generation. There are 18 discrete pathways recognized (Table 4). The order of the pathways is mostly arbitrary, as a result of there being little overlap between the atoms and bonds targeted by each.

A. Transition State Model. The model used to estimate reaction rate must account for carbene selectivity. Selectivity generally increases with increasing stabilization, which itself correlates with greater nucleophilicity and higher LUMO energy. These factors are electronic, leading to the expectation that selectivity is associated with the enthalpy of activation.

It was also desired for the rating system to incorporate the effects of temperature rationally. Thirdly, it was hoped that a kinetic framework might steer the many adjustment parameters toward physically meaningful values, *e.g.*, a differential enthalpy of activation in the 1,2-shift attributable to aryl substitution. This last goal has not been realized, but more research into the kinetics of real model systems could only help the situation.[73] The model was adapted from transition state theory and is quantified in eq 10.

$$\text{rate level} = \text{base\_level} + \frac{1}{\ln 5}\left(\ln T - \text{wt} \times \frac{\Delta H^{\ddagger}}{RT} + \frac{\Delta\Delta S^{\ddagger}}{R}\right) \quad (10)$$

Products are said to appear on different rate levels, with lower levels representing faster reactions. The term $^{1}/_{\ln(5)}$ implies that the products on a given level are formed about five times faster than those on the next higher level. This spacing is sufficient to place most product rate levels in a range of *ca.* 1 to 15, but is fine enough so that major, minor, and disfavored product distinctions can be made.

The weighting factor (wt) attached to the enthalpic term represents the carbene's selectivity. Selective carbenes feel the full force of this term, whereas unselective ones feel it very little and are left essentially with the entropic influence only (Table 5). Increasing the temperature has the effect of accelerating all reactions (provided $\Delta H^{\ddagger}$ is positive) and de-emphasizing the enthalpic barrier in particular.

Table 5. Enthalpic Weights for Different Selectivities

example	selectivity	enthalpic weight
Me_2C:	very low	0.20
PhHC:	low	0.30
$Me(CO_2Me)C$:	medium	1.0
Cl_2C:	high	1.5
$PhCH_2CCl{\cdot}LiCl$	*carbenoid*	3.0

$\Delta\Delta S^{\ddagger}$ is the difference in entropic activation relative to an undetermined standard value. The standard used is irrelevant; the goal is to develop a scale of differential entropic effects ($\Delta\Delta S^{\ddagger}$) relatable to structural features and absorb the general magnitude of the activation entropy into an empirical, pathway-specific constant (*i.e.* base_level in eq 10).

Reactions are rated by the following four-step sequence:

(1) Each pathway type has an empirical rating (Table 4, first column), ranging typically from 0 (fast) to 15 (slow). Base_level is initialized to this value.

(2) Adjustments are made to base_level reflecting the pathway's particular susceptibilities to its current structural environment. These are adjustments that are not easily categorized as enthalpic or entropic, although their mathematical treatment brands them as entropic. An example is the effect of stereochemistry on the Skattebol rearrangement.

(3) Entropic, enthalpic, and steric evaluations are made, based on functionality and structure about the reacting center. The steric activation is then evenly divided between the entropic and enthalpic variables just before the fourth step.

(4) The enthalpic component is weighted according to the carbene's selectivity. Application of eq 10 yields the final level rating.

The quantities in the first two steps are calibrated so as to sequence a variety of standard reactions correctly. The fourth step expresses the effects of temperature and selectivity. The third step should ideally be founded on relative reactivity data, experimental rate constants, and any other kinetic data at hand; however, in most cases numbers were developed that satisfied intuitive notions about carbene reactivity and tended to reproduce known carbene chemistry.

The enthalpic, entropic, and steric adjustments are represented internally as conveniently scaled integers, with ten units amounting to approximately one rate level at room temperature and medium carbene selectivity. They are defined to be positive when they speed rate of reaction and negative when they retard it. The sense of the base_level rating and the final level rating is opposite, with smaller meaning faster.

It is emphasized that eq 10 is used heuristically. The "enthalpic" and "entropic" adjustments detailed below are highly empirical and chosen solely to reproduce observed reactivity trends. Though connection to basic concepts such as bond energies is made, little significance can be attached to the specific values for the adjustments. As new experimental data become available, it may be necessary to change the heuristic approach fundamentally and/or make changes to the adjustments.

B. The General Structural Effects Package. The similarity in mechanism among certain pathways implies that their treatments should overlap. Electron-donating groups, for example, assist 1,2-shifts regardless of whether

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(73) A notable example of such a study has recently appeared: Nickon, A. *Acc. Chem. Res.* **1993**, *26*, 84–89.

it is hydrogen or alkyl migrating. Most of the common structural effects have been pooled into a standard procedure, the General Structural Effects Package. Indeed, the treatment for some of the pathways consists merely of initializing the base rating and invoking the package. We first explore the package before describing the pathways individually.

There are three distinct mechanistic entry points within the package: (1) addition to multiple bonds, (2) C–H and X–H insertion reactions, including 1,2-H shifts, (3) insertion into an X–Y σ bond, where X and Y are not hydrogen. This includes the remaining 1,2-shifts.

Which one is used by any given pathway is listed in the second column of Table 4. Additionally, there is a procedure to evaluate the 1,2-shifts common to 2 and 3 and a procedure to calculate the entropic consequences of molecularity, cyclization geometry, and symmetry.

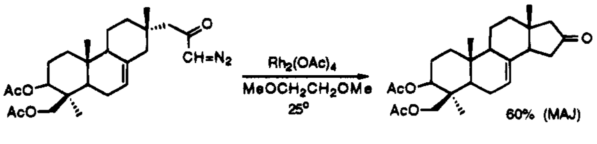
1. Addition to Multiple Bonds. The primary enthalpic adjustment in additions to nonaromatic multiple bonds is determined by the electron richness (ER) of the bond and the philicity of the carbene. Based on the relative reactivites of various alkenes with Cl_2C:,[74] a linear equation was derived to relate bond reactivity to ER:

$$\mathrm{Adj} = 0.2{*}A - 10 \tag{11}$$

where A depends on the carbene's philicity and for electrophilic carbenes is equal to the bond's ER (eq 9). A steric adjustment is also made consisting of the bond's steric hindrance calculated in perception (Table 3). Overall, it has proven difficult to fine-tune the reactivities of the alkenes, although assessing their competitions with other reaction types does not usually demand such accuracy.

Carbenes add to aromatic bonds, but for obvious thermodynamic reasons not as easily as to simple alkenes and alkynes. Consequently, the base rating for this process is higher, and an enthalpic adjustment ranging from −75 to −98 is made according to the ER of the ring, as represented by the EAS Module's ring reactivity number.[72]

2. Insertion into Single Bonds. This category comprises all insertions into σ bonds, principally C–H and X–H insertions, and 1,2 shifts, which can be viewed as insertions into the β bond. (1,2-shifts have an additional treatment; see below.) The order of reactivities frequently observed in carbon–hydrogen insertion reactions,[75] (tertiary > secondary benzylic > secondary ≫ primary > aryl), suggests that carbon–hydrogen bond strength is an important enthalpic variable.[76,77] In eq 12,[78] for example, C–H insertion at an allylic site is faster than similar non-allylic alternatives. The first enthalpic component is based on the bond dissociation energy, as calculated by CAMEO.[79] Dependence on BDE is different for X–H bonds and bonds not involving hydrogen (X–Y) (eqs 13, 14):



(12)

Table 6. Enthalpic Effect of Bond Dissociation Energy (kcal/mol) on Insertion into σ Bonds. BDE's (kcal/mol) are Calculated by CAMEO.[79] Type a Adjustments are C–H or X–H Insertions; Type b Processes are C–X or X–Y Insertions

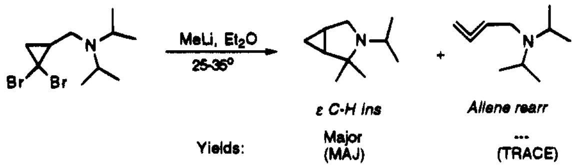
atom type	BDE	difference	type	adjustment
3-Me-pentane, primary H	98	0 (std)	a	−25
3-Me-pentane, secondary H	95	3	a	−18
3-Me-pentane, tertiary H	92	6	a	−10
toluene, sp^3-H	85	13	a	+7
toluene, aryl-H	111	−13	a	−57
TMS-H	61	37	a	+67
TMS-Br	74	24	b	+34
TMS-CH_3	63	35	b	+25
H-CH_2OMe	94	4	a	−15
MeCH=CH_2, C3-H (sp^3)	88	10	a	0
MeCH=CH_2, C2-H (sp^2)	108	−10	a	−45
MeCH=CH_2, C1-H (sp^2)	108	−10	a	−45

$$\mathrm{BDE(X{-}H)\colon\ adj} = 2.5{*}(\mathrm{BDE}^0 - \mathrm{BDE}') - 25 \tag{13}$$

$$\mathrm{BDE(X{-}Y)\colon\ adj} = (\mathrm{BDE}^0 - \mathrm{BDE}') - 10 \tag{14}$$

where BDE° is the BDE of the primary C–H bond of *n*-pentane (98 kcal/mol) and BDE′ is that of the bond broken. Table 6 contains some representative bonds and their adjustments. Judging from the large bond energy, it is likely that the products of formal aryl–hydrogen insertion actually arise from addition followed by rearrangement.

C–H insertion is promoted by alkoxy substituents[80] (enthalpic adjustment: +30), except for γ C–H insertions, wherein oxygen has a retarding influence (−24; −10 for nitrogen). C–H bonds are activated by in-path ether and amine functionality, presumably due to a directing effect, as it is lithium halide carbenoids in which the effect has been noted (eq 15).[81]



(15)

3. 1,2-Shifts. 1,2-Shifts, which are among the fastest carbene reactions, begin their treatment as either C–H insertions or C–C/C–X insertions depending on the type of the migrating atom. The unique aspects of the 1,2 geometry are then superimposed. One effect is that substitution of the intervening (β) atom by a heteroatom, particularly oxygen, facilitates the shift. This is attributed to stabilization of a partial positive charge at the β atom, which the oxygen can mitigate.[82] Conversely, a penalty is made for every β inductively electron-withdrawing substituent (carbonyl, ester, cyano, *etc.*).

The shift is suppressed if it would lead to a cyclic allene or a violation of Bredt's rule. The latter results when the intervening atom is a bridgehead (eq 16[83]) or fusion atom, although spiro sites are viable, and the migrating atom is hydrogen or is in any ring not containing the carbene.

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[74] Reference 34a, Chapt. 2.

[75] For example, Wolinsky, J; Clark, G. W.; Thorstenson, P. C. *J. Org. Chem.* **1976**, *41*, 745–750.

[76] Pascal, R. A; Mischke, S. *J. Org. Chem.* **1981**, *56*, 6954–6957.

[77] This order also corresponds to carbenium ion stabilities. It is conceivable that the transition state for concerted C–H insertion might harbor some polar character, although deuterium isotope effects indicate dependence on C–H bond strength.

[78] Reference 3c, p 933.

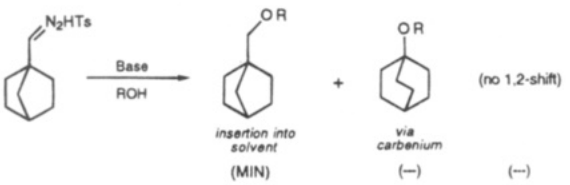
[79] Laird, E. R.; Jorgensen, W. L. *J. Org. Chem.* **1990**, *55*, 9–27.

[80] Adams, J.; Poupart, M.-A.; Grenier, L.; Schaller, C.; Ouimet, N.; Frenette, R. *Tetrahedron Lett.* **1989**, *30*, 1749–1752.

[81] Reference 33, p 2767.

[82] Reference 33, p 2752.

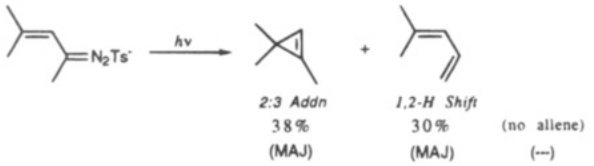
[83] Reference 34a, p 40.



(16)

Heteroatoms do not migrate as well as carbon or hydrogen, although sulfur is an exception.[84] Migratory aptitude in the acyclic 1,2-shift is generally H > Ar > alkyl > hetero, although exceptions to this order are easy to find, as is the case with carbenium ion rearrangements. Migratory aptitude is strongly affected by ring membership. Ring expansions, contractions, and the cyclopropylidene-to-allene rearrangement all have different intrinsic speeds, which are established with different initial base ratings (Table 4).

A severe entropic penalty (−80) was found necessary to inhibit shifts in β,γ-unsaturated carbenes and can be rationalized from a model of the transition state geometry. The carbene's vacant p orbital is geometrically locked into conjugation with the adjacent π bond, preventing it from adopting the necessary transition state (Figure 4). 1,2-alkyl shifts from β,γ-unsaturated carbenes are not observed because 2,3-cyclopropanation is faster (eq 17[85]). The Wolff reaction does constitute a slower 1,2-shift, presumably because oxirene formation is either slow or reversible.



(17)

4. Cyclization Effects. Intramolecular cyclizations receive the enthalpic and entropic adjustments listed in Table 7. The enthalpic values are not identical to the corresponding ring strain energies because they reflect strains in the transition state and in any case are approximate. The enthalpic values were developed by observing the influence of carbene selectivity on product distribution, as opposed to the effects of temperature. The entropic parameters were figured so as to sequence final products correctly. A slight preference is observed for forming fused junctions over spiro and bridged rings; enthalpic corrections of +2, −4, and −8 are made for formation of a fused, spiro, or bridged ring system, respectively.

5. Molecularity and Symmetry. The dominant entropic contribution pertains to the molecularity of the reaction (Table 8). Intermolecular reactions are more or less disfavored depending on how diluted the reactants are, but the penalty is mitigated when reaction is with a solvent.

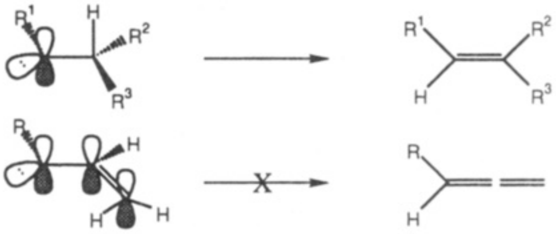


Figure 4. Reactant geometry for the 1,2-shift. Conjugated carbenes may have difficulty attaining the requisite geometry.

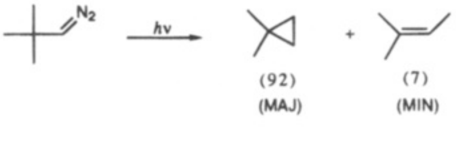
Table 7. Cyclization Parameters in Forming Saturated Rings. For Cyclopropanations, Ring Size Refers to the Larger Ring Formed Rather Than the Cyclopropane

ring size	enthalpic	entropic
1,2-shift	–	+50
3	−20	+30
4	−20	−40
5	+40	0
6	+15	−10
7	−5	−25
8+	−10	−30

Table 8. Effect of Molecularity on the Entropic Component

molecularity	reaction is with solvent	cyclization facility rating	result
intra	–	−2	precluded
intra	–	−1	−100
intra	–	0	−50
intra	–	+1	0
inter	yes	–	−20
inter	no		
	low dilution		−50
	av dilution		−100
	high dilution		−150
	gas phase		precluded

Since only one representative from every different type of atom and bond is examined, a secondary entropic consideration is the symmetric magnification resulting when there is more than one instance of a given reacting atom or bond. For example, γ C−H insertion yields increase as the β position becomes more substituted (eq 18[86]). Although electronics are important, part of the explanation is due to the statistically greater number of γ hydrogens available. Assuming that an N-fold symmetry increases the rate of reaction by N, it is simple to derive a symmetry adjustment of $-9.5 \ln(N)$ in the units used. For *tert*-butylcarbene, having nine equivalent hydrogens, this amounts to 21 entropic units, or 1.36 rate levels.



(18)

C. The Reaction Pathways. Unless otherwise noted, each pathway invokes the General Effects Package described in the previous section. Some pathways require no additional treatment and will not be discussed further. These include: simple 1,2-shifts, including ring contractions and expansions, the cyclopropylidene-to-allene rearrangement, C−H insertions, and additions to double and triple bonds. The other reactions are discussed now.

Wolff Rearrangement. It has long been an open question whether or not the photolytic Wolff rearrangement of α-diazo ketones involves the free carbene. It has been argued that a concerted rearrangement of the excited diazo compound, in which the alkyl group migrates as a molecule of nitrogen departs, accounts best for certain product distributions. Such a mechanism would require an *s-cis* conformation of the diazo and

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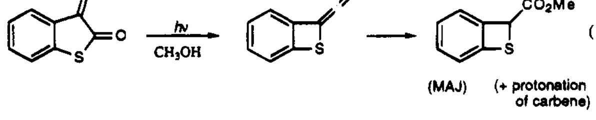
[84] Robson, J. H.; Shechter, H. *J. Am. Chem. Soc.* **1967**, *89*, 7112–7114. Involvement of a different mechanism (thiooxiranium cation) is thought to explain sulfur's anomalous behavior.

[85] Dürr, H. *Chem. Ber.* **1970**, *103*, 369.

[86] Reference 45, pg. 87.

carbonyl groups,[87] conforming well to the observation that the reaction proceeds poorly except in cyclic systems, wherein the requisite conformation is imposed (eq 19, a sulfur analog),[88] and diazomethylketones (eq 20, top route),[89] in which the absence of a second alkyl substituent would make the necessary conformation attainable.



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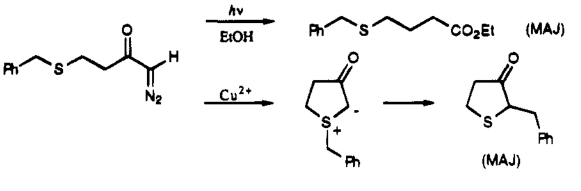
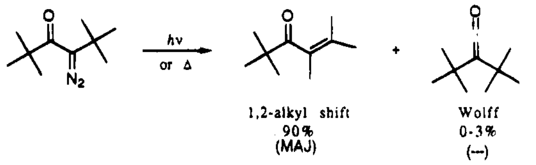


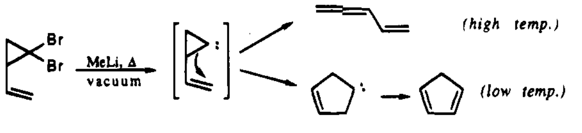
(20)

Recently some experiments and theoretical computations have cast doubt on the concerted mechanism.[90] Whether or not it is right, the experimental results are explained well and simply by a model in which there are two independent routes to the ketene: one fast but conformationally demanding and another slow but undemanding. The dual-mode model, in conjunction with the inherent sluggishness of the 1,2-shift through an unsaturated center (eq 21)[91] imposed by the General Effects Package, suffices to reproduce Wolff chemistry well; no additional corrections are required. The concerted reaction is executed by the carbene formation routine under photolytic conditions.

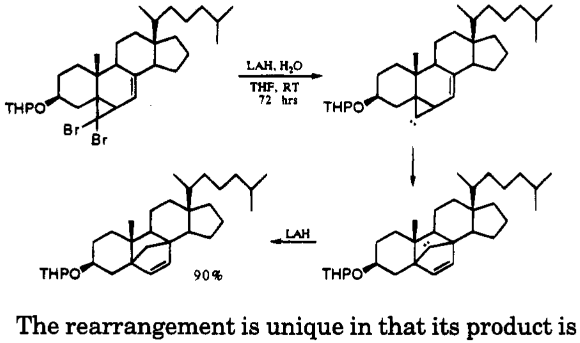


(21)

Skattebol Rearrangement. As might be expected from entropic considerations, the Skattebol rearrangement[54b,92,93] is favored at lower temperatures, while allene formation is preferred at higher ones, with a balance struck at *ca.* 30 °C for the parent reaction (eq 22). As a consequence of strong steric inhibition by *cis*-substitution, either at C3 or C5,[92] the Skattebol reaction becomes synthetically useful when the bonds involved are held in position in a fused ring system (eq 23).[94]



(22)



(23)

The rearrangement is unique in that its product is also a carbene, necessitating a technique to extend analysis. It would not be satisfactory to guess what the secondary product will be (*e.g.*, a cyclopentadiene) because of the influence of conditions and structural variations (*e.g.*, eq 23). Furthermore, it is conceivable that the intermediate cyclopentadienylidene might be diverted to triplet reactions, which the one-step analysis could not anticipate. The solution adopted is to queue the product for resubmission back to the CM. The entire regimen of perception, mechanistic analysis. and product formation ensues, unprejudiced by the carbene's history.

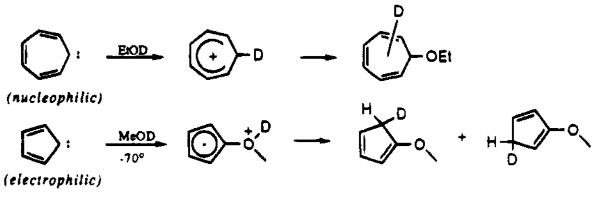
Concerted Insertions into Si–H, N–H, and O–H Bonds. This process is considered for electrophilic carbenes only. No special adjustments are made in addition to the General Effects Package. It is noteworthy that concerted insertions into N–H and O–H bonds based on BDE alone are always rated much slower than the two-step equivalent, ylide formation followed by rearrangement. As the true mechanism is uncertain, this provides a suggestion as to which it might be.

Proton Transfer. This process is considered only for nucleophilic and, to a lesser extent, ambiphilic, carbenes. Equations 25 and 26 contrast the reactivity of two carbenes toward a hydroxylic solvent.[18c] Stronger acids are naturally better for protonation,[18b,95] which is reflected by an adjustment to the base–level:

$$\text{proton transfer} \quad \text{adj} = (\mathrm{p}K_a' - \mathrm{p}K_a^\circ)/W \qquad (24)$$

where $\mathrm{p}K_a'$ is the strength of the acid under consideration, $\mathrm{p}K_a^\circ$ is the acidity of methanol, and *W* maps the different solvents onto the same scale (5 for DMSO, 8 for water).[96] For example, acetic acid, methanol, and dimethylamine have $\mathrm{p}K_a$'s of 12, 30, and 41 in DMSO and give adjustments of −3.6, 0.0, and +2.2, respectively.

The ease of protonation is strongly dependent on the ability of the carbene to stabilize a positive charge. This behavior is captured with an enthalpic contribution for each electron-donating group (+20 units: alkoxy, amino; eq 7 is an example) and electron-withdrawing group (−40 units: halogen, keto, cyano, *etc.*). The latter penalty effectively suppresses the reaction for Cl_2C: and other familiar carbenes.



(25)

(26)

Ylide Formation. Coordination to heteroatoms to form ylides is best viewed as a rapid equilibrium favoring the ylide and emerges when a secondary reaction of the ylide is faster than other reactions available to the

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[87] (a) Reference 59, pp 205–209. (b) Reference 14, pp 95–98.

[88] Voigt, E.; Meier, H. *Angew. Chem., Int. Ed. Engl.* **1976**, *15*, 117.

[89] Kondo, K.; Ojima, I. *J. Chem. Soc., Chem. Commun.* **1972**, 860.

[90] Bachmann, C.; N'Guessan, T. Y.; Debü, F.; Monnier, M.; Pourcin, J.; Aycard, J.-P.; Bodot, H. *J. Am. Chem. Soc.* **1990**, *112*, 7488–7497, and refs therein.

[91] Newman, M. S.; Arkell, A. *J. Org. Chem.* **1959**, *24*, 385.

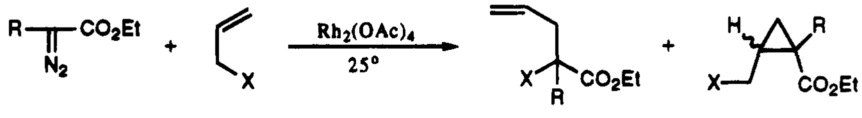
[92] Kirmse, W.; Chiem, P. V.; Henning, P. G. *Tetrahedron* **1985**, *41*, 1441–1451.

[93] (a) *Reactive Intermediates*; Jones, M.; Moss, R. A., Eds.; J. Wiley & Sons: New York, 1981; Vol. 2, Chapter 3. See pp 113–121. (b) Brinker, U. H.; Ritzer, J. *J. Am. Chem. Soc.* **1981**, *103*, 2116–2119.

[94] Yates, P.; Winnik, F. M. *Can. J. Chem.* **1985**, *63*, 2501–2506. The Redox Module is not yet equipped to reduce carbenes.

[95] Vasella, A.; Briner, K. *J. Org. Chem.* **1991**, *56*, 4741–4744.

[96] For CAMEO's $\mathrm{p}K_a$ prediction algorithm, see: Gushurst, A. J.; Jorgensen, W. L. *J. Org. Chem.* **1986**, *51*, 3513.



		Yield	Coordination		Addition
R = H	X = I	98%	100	:	0
H	Br	76	28	:	72
H	Cl	95	5	:	95
CO_2Et	Br	92	93	:	7

Figure 5. Competition between coordination and addition with various allyl halides. The ylide resulting from coordination undergoes a [2,3] sigmatropic rearrangement to give the products shown. Data from ref 97.

Table 9. Carbene Affinity for Various Heteroatoms. Larger Adjustments Reflect Higher Affinities

atom type	enthalpic adjustment
I	20
Br	10
R_2S	5
$R_2C{=}O$	−10
ester sp^2 O	−15
R_2O	−20
ester sp^3 O	−30
Cl	−30
R_3P	−30

carbene. To treat ylides effectively it was necessary to implement an equilibration model; it and the secondary reactions of ylides are taken up in Section IX.

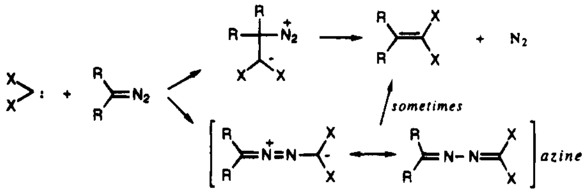
A series of experiments have established the relative affinities of carbenes for various heteroatoms, exemplified by Figure 5.[97] The corresponding enthalpic adjustments are presented in Table 9. Electron-withdrawing groups on the carbene stabilize the intermediate ylide and shift equilibrium in its favor (Figure 5, last entry); accordingly, a bonus of 10 enthalpic units per electron-withdrawing substituent, enough to invert the major/minor product yields of the two bromides in the figure, is assigned. Such groups are conveniently defined for this purpose as groups containing polarized multiple bonds, *e.g.* carbonyl, cyano, ester, and imino.

Electrophilic Aromatic Substitution. The detailed mechanism of reaction between carbenes and arenes is not known, in part because more than one may operate at different times. Formal insertion into aryl−hydrogen bonds, however, does not appear to occur directly. Instead, both free radicals and singlet carbenes react with unactivated rings beginning with attack on one of the aryl bonds. Radical and ionic mechanisms have been offered to rationalize the subsequent rearrangements to the products observed, normally cycloheptatriene and the formal products of aryl−hydrogen insertion.[98]

With unactivated arenes and carbenes the addition reaction appears to be concerted; a stepwise ionic mechanism is unlikely.[99] However, with activated arenes, and carbenes bearing electron-withdrawing groups, an EAS-like mechanism is plausible.[100,101]

Due to the uncertainty in mechanism, the treatment of arenes is rudimentary: the carbene is queued for submission to the EAS Module if the carbene has an electron-withdrawing group, and the ring is activated (ring reactivity number[90] > 1.0). The General Effects Package does not apply.

Dimerizations. Dimerization is a frequent undesired side reaction that is probably under-reported in literature accounts, especially where the dimer is volatile. Because singlet carbenes are highly reactive species, dimerization does not generally arise from the combination of two free carbenes. Rather, the usual genesis of dimers is reaction of a carbene with a molecule of its diazo precursor to yield an azine, which is apt to lose nitrogen under the thermal or photolytic conditions employed (eq 27).[102] This mechanism also applies to diazo and diazirine precursors, including tosylhydrazones, but dimerization from other sources such as LiX carbenoids must follow some other path. When metal catalysts are used, azines are less prevalent or not formed at all.[103] CAMEO does not generate the azine, but issues a comment regarding its concomitant formation. Nor does CAMEO attempt to predict the stereochemistry of the dimer, applying instead the "U" (unspecified) stereo label.



(27)

The factors considered by CAMEO are solvent dilution, carbene stability, and sterics. Dilution slows dimerization significantly, culminating in its complete suppression in the gas phase. Dimerization can only occur when the carbene is stable enough to survive until the requisite intermolecular collision occurs. An enthalpic adjustment between −30 and +30 is made depending on the carbene's perceived stabilization. That the steric surroundings of a carbene affect its rate of dimerization was utilized by Jones to increase yields from the arylcarbene rearrangement.[104] The steric adjustment, admittedly crude, is:

$$(\text{sterics})\text{adj} = {}^1/_2(3{*}S_1 + S_2)/4 \qquad (28)$$

where S_1 is the hindrance of the less sterically demanding flanking atom, and S_2 is that of the other. The scaling factor implies that the adjustment of the least-hindered carbene, methylene, will be nil, while that of the most congested (di-*tert*-butylcarbene has $S_1 = S_2 = 100$) will have an adjustment of *ca.* 50 units (three levels).

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[97] Doyle, M. P. *Acc. Chem. Res.* **1986**, *19*, 348−356, ref 15.

[98] Pusino, A.; Saba, A.; Rosnati, V. *Tetrahedron* **1986**, *42*, 4319−4324.

[99] Baldwin, J. E.; Smith, R. A. *J. Am. Chem. Soc.* **1967**, *89*, 1886−1890.

[100] Reference 45, pp 228−229.

[101] Gilbert, J. C.; Blackburn, B. K. *Tetrahedron Lett.* **1990**, *31*, 4727−4730. The authors propose addition as an alternative mechanism.

[102] Gilchrist, T. L.; Rees, C. W. *Carbenes, Nitrenes and Arynes*; Appleton-Century Crofts: New York, 1969. See p 82.

[103] Wulfman, D. S.; Poling, B. In *Reactive Intermediates*; Abramovitch, R. A., Ed.; Plenum Press: New York, 1980; Vol. 1, Chapter 5. See p 465.

[104] Jones, W. M. *Acc. Chem. Res.* **1977**, *10*, 353−359. See p 355.

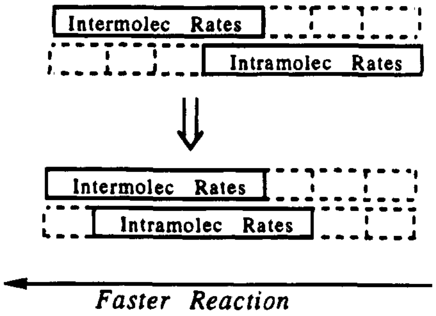

Figure 6. Equalization of rate by molecularity. Dashed boxes outline level units. The maximum equalization is two levels.

Table 10. Yield Assignments as a Function of Level Rating. Products Below the Cutoff are not Ordinarily Realized

level rating	product yield
best	Major
best + 1	Minor
best + 2	Disfavored
best + 3	Disfavored
– cutoff –	
>best + 3	trace

VIII. Product Evaluation and Generation

Once all reaction pathways have been explored for all applicable atoms and bonds, leading to a list of "latent" products, the relative rates of these products are examined, and the best are converted into real products.

Due to unpredictable variability in the behavior of real solvent systems, the relative quantities of inter- *vs* intramolecular reactions cannot be predicted exactly, especially if the two species comprising an intermolecular reaction are both at low concentration. Therefore, the levels of the best product from both groups are evened, with a maximum adjustment of two levels. If the intramolecular group of reactions is poorer, for example, then it will be helped by subtracting up to two levels from each of its members (Figure 6).

The latent products are next sorted by level rating such that better products appear before worse ones. All latent products whose level rating is within three levels of the best product's level are realized; equilibrium products are not considered when determining the best level. Yield assignments decrease with increasing level, as shown in Table 10. If the user has elected to see trace products then up to 15 of the next-best products are also generated. This feature is useful if the user is dissatisfied with CAMEO's competition assessment or wishes to probe what other chemistry might be occurring.

To accommodate the needs of ylides and the arylcarbene rearrangement, the concept of "equilibrium products", products in equilibrium with their precursors, was introduced. The implementation of this concept varies by module, but for the CM the effects of equilibration are reasoned not in the mechanistic phase at the time it is noted, but in the "debrief" phase before product display. At that point the rate levels and yields of products are adjusted so that a fast equilibrium with no compelling resolution is suppressed by a slower, nonreversible reaction.

IX. Further Reactions of Carbene Products

Certain elementary reactions of carbenes yield strained intermediates that easily generate new carbenes or other species so reactive that they would not be satisfying if presented as final products. Rather than require the user to resubmit these intermediates manually, they are automatically queued back to the CM for further reaction after the current cycle of activity is complete. The entire focus of perception and mechanistic analysis is then brought to bear on the intermediate. Reactions in this category are: the Skattebol rearrangement,[105] which generates a new carbene; the oxirene rearrangement, a side reaction of the Wolff rearrangement; and the arylcarbene rearrangement, which may give surprising products (Figure 7).[106] Like oxirene formation, it is thought[105d] to proceed by addition to a β-double bond, generating a strained cyclopropene intermediate. The number of intermediates required to arrive at final products in the arylcarbene rearrangement would often be uncomfortably large. To expedite this chemistry an "extended mechanistic step" links the arylcarbene and the cycloheptatrienylidene in both directions.

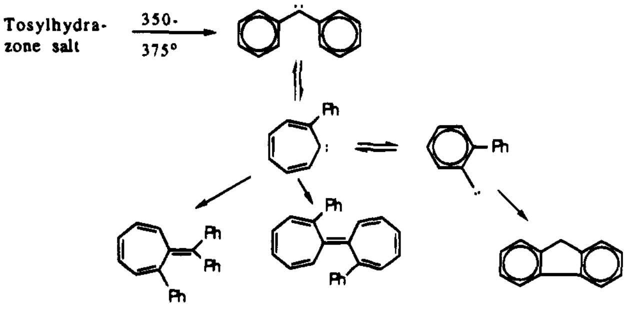

Figure 7. The arylcarbene-to-cycloheptatrienylidene rearrangement.

In order to avoid backtracking along a reversible pathway, the set of atoms that have appeared as the divalent carbon in cycloheptatrienylidenes and ketocarbenes is maintained, and such structures are not recreated.

A fourth class of unstable products handled by resubmission is the ylides. Quite a few avenues are available for their decomposition,[10] shown in Figure 8. The first five pathways in the flowchart are each much faster than the ones that follow them; the last two mechanisms are slower. The Stevens rearrangement[107] is strongly dependent on structure and is only rapid when the migrating group is benzyl or tertiary alkyl (eq 20, bottom). The customary rearrangements of ketone ylides, *viz.* proton transfer, 1,3-dipolar cycloaddition, and epoxide formation, are not implemented.

Two other types of secondary reaction do not require resubmission and are addressed during postmechanistic perception. The first is the solvolysis of ketenes formed by Wolff reactions in a hydroxylic (or amino-bearing) solvent to yield carboxylic acids, esters, and amides. The final solvolysis products are housed in additional ("perception time-derived") structures. The second common alteration is the electrocyclic rearrangement of norcaradienes (which result from additions to arenes) to cycloheptatrienes. Not all norcaradienes undergo the rear-

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(105) For reviews of the arylcarbene rearrangement see: (a) Wentrup, C. In *Reactive Intermediates*; Abramovitch, R. A., Ed.; Plenum Press: New York, 1980; Vol. 1, Chapter 4. (b) Gaspar, P. P.; Hsu, J. P.; Chari, S.; Jones, M. *Tetrahedron* **1985**, *41*, 1479–1507. (c) Reference 104. For other recent papers see: (d) Miller, P. C.; Gaspar, P. P. *J. Org. Chem.* **1991**, *56*, 5101–5107. (e) Tomioka, H.; Kobayashi, N.; Murata, S.; Ohtawa, Y. *J. Am. Chem. Soc.* **1991**, *113*, 8771–8778.

(106) Reference 105b, p 1483.

(107) For reviews see: (a) Pine, S. H. *Org. React.* **1970**, *18*, 403–464. (b) Stevens, T. S. *Prog. Org. Chem.* **1968**, *7*, 48–74. (c) March, J. *Advanced Organic Chemistry*, 3rd ed.; J. Wiley & Sons: New York, 1985. See pp 992–994.

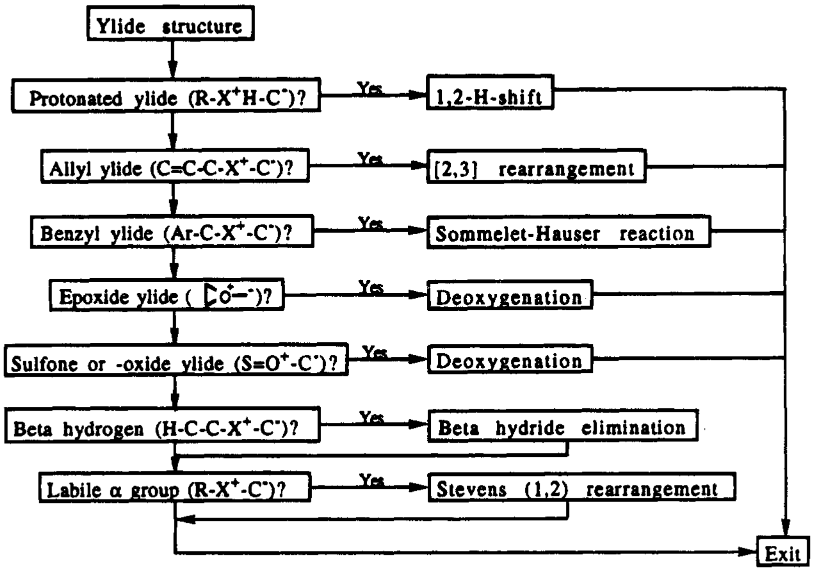
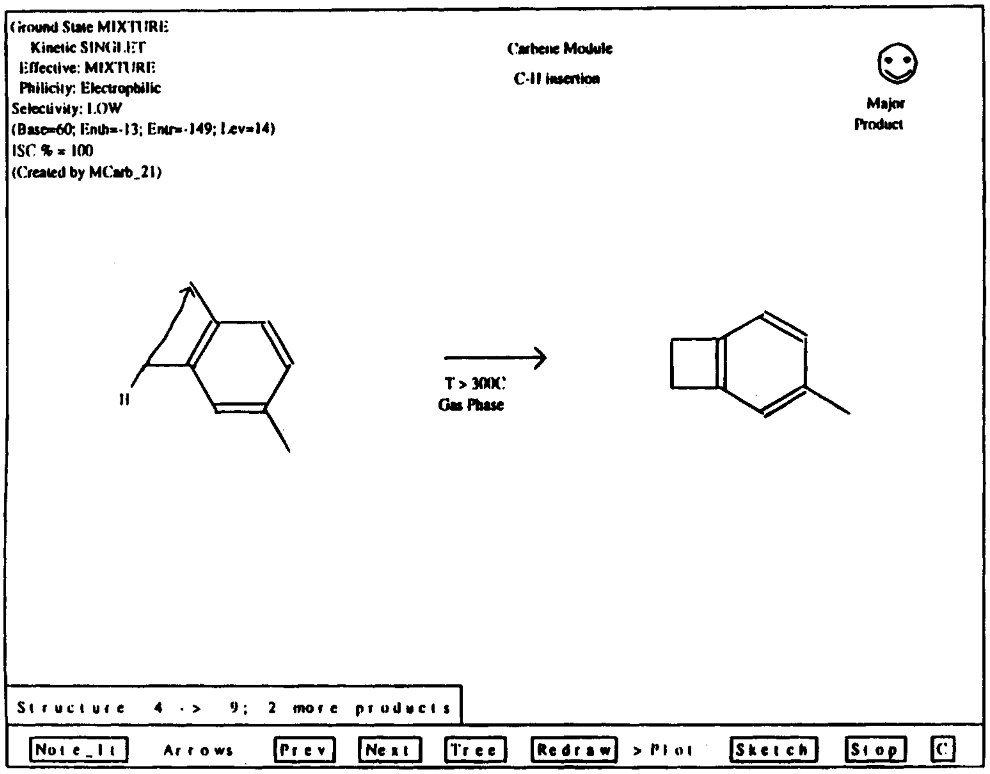


Figure 8. Ylide rearrangements.


Ground State MIXTURE
Kinetic SINGLET
Effective: MIXTURE
Philicity: Electrophilic
Selectivity: LOW
(Base=60; Enth=-13; Entr=-149; Lev=14)
ISC % = 100
(Created by MCarb_21)

Carbene Module
C-H insertion

Major
Product

T > 300C
Gas Phase

Structure 4 -> 9; 2 more products

Figure 9. Product display.

rangement, however. A simple heuristic is that the rearrangement occurs as long as the aromaticity of the adjacent ring(s) is not sacrificed.[108]

X. Product Display

An example of product display is given in Figure 9. At the top center is a caption declaring where the product was conceived, *viz.* the carbene formation package, the CM proper, or postmechanistic perception. Any special conditions, *e.g.* photolysis, transition metal catalysis, triplet sensitizer, and solvents, are displayed about the reaction arrow. In the top left corner is presented the physical profile of the carbene that influenced mechanistic decision-making, including spin state multiplicity, philicity, and selectivity. In program development mode additional information appears: activation enthalpy, entropy, base level, and rate of intersystem crossing.

A mechanistic overview of the reaction is presented in the new trace menu (Figure 10). It not only summarizes the types of mechanism that occurred, their molecularity, and relative rate, but also provides quick location and access to particular steps of interest. Selecting the "arylcarbene rearr." caption, for example, would highlight the structure formed by that mechanism. The START button would initiate its display.

XI. Future Improvements

Despite its strengths the CM, and the general ability of the program to present the user with carbene chem-

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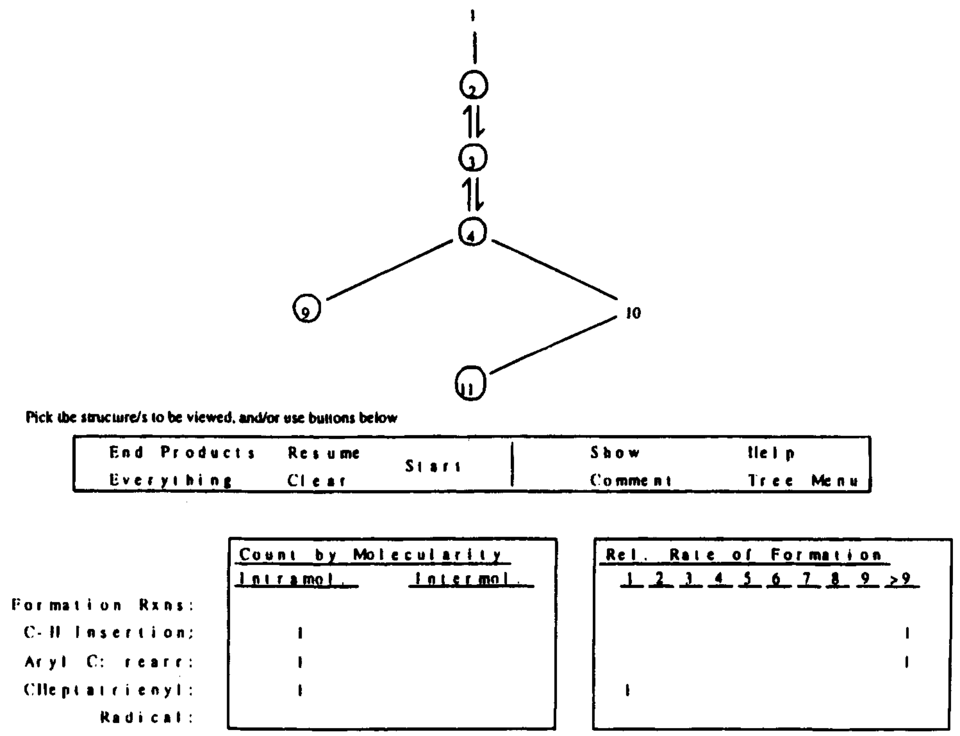
[108] Based on Wulfman & Poling's rule: ref 103, p 400.



Pick the structure/s to be viewed, and/or use buttons below

	Count by Molecularity		Rel. Rate of Formation									
	Intramol.	Intermol.	1	2	3	4	5	6	7	8	9	>9
Formation Rxns:												
C-H Insertion:	1											1
Aryl C: rearr:	1											1
CHeptatrienyl:	1		1									
Radical:												

Figure 10. The Trace Menu.

istry clearly, accurately, and conveniently, have some shortcomings. (1) The side reactions characteristic of transition metal catalysis, such as double bond migration, are not implemented. (2) The competing ionic chemistry of LiX carbenoids is not pursued. (3) Certain rarer reactions of carbenes are not recognized, as 1,4- and other cycloadditions,[109,110] and the commoner 1,3-dipolar cycloadditions of carboalkoxycarbenes. (4) Of the five types of stereoselectivity frequently encountered with carbenes,[111] only the Skell type (*i.e. syn* addition)[112] is implemented. (5) Reaction with arenes is crude; there is currently no distinction in the reactivity between different aromatic bonds.

XII. Conclusions

The simulation of carbene reactions has been incorporated into the CAMEO program as an independent module. Noteworthy is its grounding in a physical model of carbene reactivity (spin state, philicity, and selectivity) and substrate reactivity (electron-richness, concentration, geometric accessibility, symmetry effects, and sterics). It is mechanistically constructed such that chemical reactions emerge as the fastest competitors in a contest among a spectrum of competing elementary pathways. Particular structural features do not blindly trigger particular mechanisms; instead every mechanism is evaluated independently, and its absolute viability rated.

The module treats singlet carbene chemistry only, but coordinates strategy with the Radical Module in order to present both chemistries where appropriate. Carbene formation is available as a prestep through recognition of common precursors and conditions. Techniques such as kinetic equilibration and resubmission of reactive intermediates permit the accurate prediction of multistep reactions.

Acknowledgment. Michael Hughey deserves credit for beginning this project *ca.* 1985. The authors are grateful to the National Science Foundation for financial support.

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(109) 1,4-Addition to butadienes and norbornadienes: ref 59 has a brief discussion (pp 191–192), as do ref 14 (pp 62–63), ref 103 (pp 92–95), and ref 93a (pp 83–86). For recent papers see: (a) *Izv. Akad. Nauk SSSR, Ser. Khim.* **1990**, 1430 (butadiene). (b) Dolbier, W. R., Jr.; Wojtowicz, H.; Burkholder, C. R. *J. Org. Chem.* **1990**, *55*, 5420–5422 (norbornadiene).

(110) 1,4-Addition to a σ bond network: Jackson, J. E.; Mock, G. B.; Tetef, Merry L.; Zheng, G. X.; Jones, M. *Tetrahedron* **1985**, *41*, 1453–1464.

(111) Syn *vs* anti addition; endo/exo addition; asymmetric induction in additions; *cis vs trans* enes from the 1,2-shift; asymmetric induction in R–H insertions.

(112) (a) Skell, P. S.; Garner, A. Y. *J. Am. Chem. Soc.* **1956**, *78*, 3409. See also: (b) Skell, P. S., Woodworth, R. C. *Ibid.* **1956**, *78*, 4496. (c) Doering, W. v. E.; LaFlamme, P. *Ibid.* **1956**, *78*, 5447. (d) Griller, D.; Nazran, A. S.; Scaiano, J. C. *Tetrahedron* **1985**, *41*, 1525–1530.