and 2,4,6-trichlorobenzoic acid at room temperature, the lactonization proceeded quite rapidly and was completed within 8 min to give the lactone (**20**) in almost quantitative yield.[13,15] This excellent lactonization can be explained in terms of reflection of both the suitable conformation of **7**[17] and the efficient formation of the highly reactive acylpyridinium salt.[13]

Finally, removal of the protecting groups gave 9-dihydroerythronolide A (**2**), which was readily converted to the title compound (**1**).[2c]

Acknowledgment. We thank Dr. A. Kinumaki, Tanabe Seiyaku Co., Ltd., for cooperation in obtaining NMR (NOESY) spectra.

Supplementary Material Available: Physical data for compounds **7**, **10**, **11**, **14**, **15**, **16**, **18**, **19**, and **20** (4 pages). Ordering information is given on any current masthead page.

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[13] The activation effect of DMAP may be explained in terms of formation of a more reactive acyl pyridinium salt as already proposed by Steglich et al.[14] Although attempts to detect the acylpyridinium salt by NMR spectroscopy were unsuccessful, an indirect proof was obtained by the silica gel TLC analysis of the reaction mixture at regular time intervals, i.e., after 1 min, the seco-acid (**7**) and the mixed anhydride were mainly detected probably because the acylpyridinium salt was too labile to exist under the TLC conditions. However, the two compounds disappeared with time, and after 8 min the lactone (**20**) was detected as a single spot. The difference in reactivity between the Yamaguchi mixed anhydride and the Corey active ester is presumably due to the difference in rate and efficiency of the formation of the acylpyridinium salt.

[14] Höfle, G.; Steglich, W.; Vorbruggen, H. *Ang. Chem., Int. Ed. Engl.* **1978**, *17*, 569.

[15] DCC was also effective for the lactonization as reported by Keck et al.,[2d,16] but a longer time was required [**7** (17 mM), DCC (50 mM), DMAP (31 mM), CSA (17 mM), in CH_2Cl_2, room temperature, 8 h, 85%].

[16] Boden, E. P.; Keck, G. E. *J. Org. Chem.* **1985**, *50*, 2394.

[17] Comparison of J values (^1H NMR) of the seco-acid (**7**) ($J_{10,11}$ = 2.0 Hz, $J_{9,10}$ = 0 Hz, $J_{8,9}$ = 11.5 Hz, $J_{7,8}$ = 0, 7.0 Hz, $J_{4,5}$ = 1.5 Hz, $J_{3,4}$ = 1.5 Hz, $J_{2,3}$ = 10.0 Hz) with those of the lactone (**20**) ($J_{10,11}$ = 1.5 Hz, $J_{9,10}$ = 0 Hz, $J_{8,9}$ = 11.0 Hz, $J_{7,8}$ = 0, 11.5 Hz, $J_{4,5}$ = 1.0 Hz, $J_{3,4}$ = 1.0 Hz, $J_{2,3}$ = 11.0 Hz) revealed that rotation of only the C7–C8 bond (the least substituted bond) was presumably required for the lactonization of **7** into **20**, although accurate NOE and NOESY measurements are required for unequivocal determination of the C5–C7 conformation of **7**.

Articles

Computer-Assisted Mechanistic Evaluation of Organic Reactions. 17. Free Radical Chain Reactions

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A mechanistic model for free radical chain reactions has been developed for the computer program CAMEO. The controlling algorithm treats all reactions as a series of fundamental radical processes, i.e., abstractions, additions, and fragmentations. Chain-propagating steps are mimicked by automatic resubmission of selected intermediates. This paper provides an overview of radical chain processes and descriptions of the rules implemented for the logical prediction of chain reaction sequences. Several prominent examples that demonstrate the synthetic utility of free radical reactions and the success of the CAMEO program in predicting complex sequences are presented. An appendix which describes the algorithm for estimating homolytic bond dissociation energies is included.

I. Introduction

CAMEO is an interactive computer program for the logical prediction of organic reaction products. Given graphical input of starting materials and conditions, the program arrives at its conclusions by application of mechanistic rules. The approach is unique in that large databases and topological simplifications are avoided; reaction modules correspond to and are designed for the evaluation of reactions by the type of intermediate involved. The program is presently capable of analyzing base-catalyzed and nucleophilic,[1] acid-catalyzed and electrophilic,[2,3] electrophilic aromatic,[4] pericylic,[5] oxidative,[6] and reductive[7] reactions. The program has now been expanded to include analysis of organic free radical chain reaction sequences. Mechanistically, the program treats the intermediates of chain reactions by iterative consideration of three fundamental processes, i.e., abstractions, additions, and fragmentations. This paper opens with an overview of these fundamental processes and their controlling physical aspects, which provide a basis for the organization and implementation of the chemistry in the CAMEO program. The competitions between the fundamental processes and the rules implemented for their treatment are then specifically considered in Section III. The paper concludes with several chain reaction sequences for illustration of the program's capabilities as well as the emerging recognition of free radical

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[1] (a) Salatin, T. D.; Jorgensen, W. L. *J. Org. Chem.* **1980**, *45*, 2043. (b) Salatin, T. D.; McLaughlin, D.; Jorgensen, W. L. *J. Org. Chem.* **1981**, *46*, 5284. (c) Peishoff, C. E.; Jorgensen, W. L. *J. Org. Chem.* **1985**, *50*, 1056. (d) Gushurst, A. J.; Jorgensen, W. L. *J. Org. Chem.* **1986**, *51*, 3513. (e) Metivier, P.; Gushurst, A. J.; Jorgensen, W. L. *J. Org. Chem.* **1987**, *52*, 3724. (f) Gushurst, A. J.; Jorgensen, W. L. *J. Org. Chem.* **1988**, *53*, 3397.

[2] McLaughlin, D. R. Ph.D. Thesis, 1983, Purdue University.

[3] Bures, M. G.; Jorgensen, W. L. *J. Org. Chem.* **1988**, *53*, 2504.

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

[5] (a) Burnier, J. S.; Jorgensen, W. L. *J. Org. Chem.* **1983**, *48*, 3923. (b) Burnier, J. S.; Jorgensen, W. L. *J. Org. Chem.* **1984**, *49*, 3001.

[6] Paderes, G. D.; Jorgensen, W. L. *J. Org. Chem.* **1989**, *54*, 2058.

[7] Metivier, P.; Paderes, G. D.; Jorgensen, W. L., manuscript in preparation.

0022-3263/90/1955-0009$02.50/0

reactions as important synthetic tools.

Several aspects of free radical reactions rely upon the strength of bonds being broken and formed. Consequently, accurate prediction of reactive sites for abstractions and fragmentations requires access to relative bond dissociation energies (BDEs). An appendix has been included to describe the algorithm developed for the estimation of homolytic BDEs.

II. Key Aspects of Organic Free Radical Chemistry

Free radical reactions have recently achieved enhanced prominence in organic synthesis. The mildness of reaction conditions and the (normally) high levels of their chemo-, regio-, and often stereoselectivity allow radical reactions to serve as powerful synthetic tools whose applications often complement those of their ionic counterparts. This section briefly reviews the fundamentals of neutral organic monoradical reactions with emphasis on the considerations needed for the automated prediction of products.[8] Several current monographs and reviews are available for more thorough discussions.[9-13]

All monoradical chain processes may be divided into three discrete mechanistic phases, as outlined below.

1. **Initiation: Neutral → Radical + Radical.** Generation of free radicals from a neutral species typically occurs via homolytic cleavage of a weak σ bond. Initiators generally possess at least one bond with a homolytic bond dissociation energy of ca. 75 kcal/mol or lower. The requisite energy for bond breaking is supplied thermally (less than 100 °C is sufficient) or photolytically.[14] With few exceptions, initiation results in heteroatom-centered radicals; the more synthetically interesting carbon radicals are usually generated during chain propagations.

2. **Propagation(s): Radical (+ Neutral) → New Radical (+ Neutral).** Propagation steps involve relocation of the unpaired electron, either by rearrangement or by reaction with a neutral molecule. Note that a new radical is always produced by these propagations; thus, they comprise the main body of the chain reaction. This phase may include any combination of intra- or intermolecular abstractions, additions, or fragmentations of bonds.

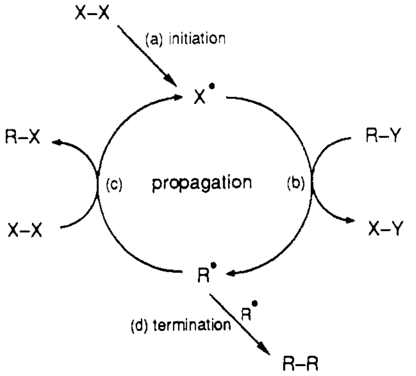
3. **Termination: Radical + Radical → Neutral.** These reactions end the chain process by failing to produce another radical fragment. Termination occurs by recombination of two radicals or by disproportionation between them. Such reactions occur at diffusion-controlled rates; since the concentration of radical species is low, termination steps do not compete effectively with reactions involving nonradicals and will not be discussed at length.

The variety of mechanistic steps is portrayed in Figure 1, while a representation showing a combination of steps that produce a simple chain reaction is provided below. Here, steps b and c constitute the propagating phase of the reaction; iterative abstractions assure regeneration of $X^\bullet$ and $R^\bullet$. It is also evident from this figure that efficient propagation requires $X^\bullet$ to react preferentially with R–Y; likewise $R^\bullet$ must prefer reaction with X–X.[15] Such selectivities lead to a continuous but small supply of free radicals such that (1) only catalytic amounts of initiators are required and (2) diffusion-controlled recombination reactions are avoided.[15] Any other desired reactions possible for $R^\bullet$ (e.g., addition, fragmentation) must be faster than the "chain transfer" step c. Adjusting the relative selectivities of intermediates in the presence of several potentially reactive components requires control by substituent effects. Details and examples of these effects in the propagation phase of radical reactions are given in the sections that follow. The combination of radical steps and the competition among possible propagations are discussed in Section III and illustrated in Section IV.

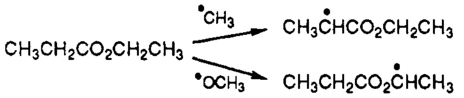
Table I. Electronic Assignments for Heteroatom Radicals

radical	χ^a	
$RO^\bullet$	3.44	
$R_2N^\bullet$	3.04	
$Cl^\bullet$	3.16	electrophilic
$Br^\bullet$	2.96	
$RS^\bullet$	2.58	
$R_3C^\bullet$	2.55	
$R_3Ge^\bullet$	2.01	
$R_3Sn^\bullet$	1.96	nucleophilic
$R_3Si^\bullet$	1.90	

[a] Electronegativity of the radical center from ref 18.



A. Radical Philicity. The electronic nature of a free radical controls its subsequent reaction(s). Nucleophilic radicals seek electron-poor addition or abstraction sites, while electrophilic radicals react at sites of higher electron density,[16,17] e.g.,



$$CH_3CH_2CO_2CH_2CH_3 \begin{array}{l} \xrightarrow{{}^\bullet CH_3} CH_3\overset{\bullet}{C}HCO_2CH_2CH_3 \\ \xrightarrow[{}^\bullet OCH_3]{} CH_3CH_2CO_2\overset{\bullet}{C}HCH_3 \end{array} \qquad (1)$$

The interplay between polarity of the radical and substituents on the neutral partner will be discussed subsequently. For ease of the discussions, it is convenient to assign radical philicity at this point.

Radicals centered on atoms significantly more electronegative than carbon are considered electrophilic; conversely, atoms less electronegative than carbon form nucleophilic radicals.[15] Table I provides examples. The philicity of carbon-centered radicals depends upon substitution. Positive ρ values for Hammett plots of cyclohexyl radical addition to substituted olefins indicate that alkyl and σ radicals (i.e., acyl, aryl, and vinyl) and those

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[8] For clarity, the phrase "neutral monoradical" refers to those reactions that are thermally or photochemically induced *chain* processes involving *one* radical atom per mechanistic step. This excludes "formal" photochemistry, i.e., photolysis to form biradical species which do not propagate chains.

[9] Giese, B. *Radicals in Organic Synthesis: Formation of Carbon–Carbon Bonds*; Pergamon: New York, 1986.

[10] Selectivity and Synthetic Applications of Radical Reactions, Tetrahedron Symposia-in-Print Number 22, Giese, B., Ed. *Tetrahedron* **1985**, *41*, No. 19.

[11] Curran, D. P. *Synthesis* **1988**, 417, 489.

[12] Hart, D. J. *Science* **1984**, *223*, 883.

[13] Ramaiah, M. *Tetrahedron* **1987**, *43*, 3541.

[14] Mercury discharge lamps with significant emission at 253.7 nm are frequently used for initiations. *Reactive Intermediates in Organic Chemistry*; Isaacs, N. S., Ed.; John Wiley & Sons: New York, 1974; p 294.

[15] Reference 9, Chapter 2, p 4.

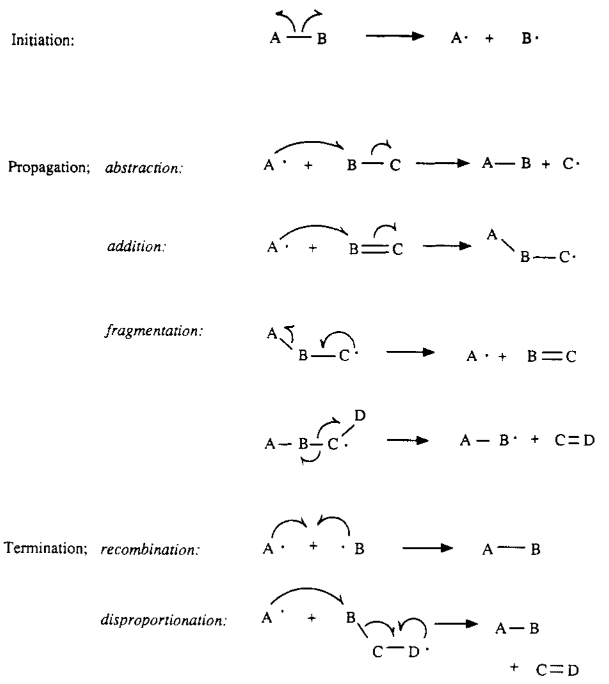


Figure 1. Possible modes of reaction for organic free radicals.

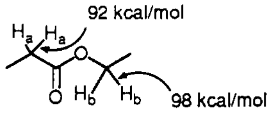
substituted with electron-releasing groups are nucleophilic,[16] while carbon radicals with electron-withdrawing groups are electrophilic,[19] e.g., $F_3C^\bullet$, $(NC)_2HC^\bullet$.

B. Radical Propagations. Current synthetic interest is focused on useful bond formations that occur during propagation reactions. Propagation steps may be controlled by utilizing the subtle balance between electronic, steric, and bond strength effects. These factors will be considered for each of the possible propagation modes represented in Figure 1. Also, many of the numbered points below provide the basis for rules for the implementation of free radical chemistry in CAMEO.

1. Abstractions. While it is occasionally adequate to assume that homolytic substitution (S_H2) involves cleavage of the weakest bond, consideration of electronic and steric effects permits more accurate predictions.

a. Physical Aspects. Groups available for abstraction are observed to be limited to mono- or divalent atoms, undoubtedly due in part to their steric accessibility. Sites of reaction are therefore exclusively hydrogen, the halogens,[11] and occasionally sulfides, selenides, and tellurides.[20]

As eq 1 indicated, regioselectivity of abstraction is dependent upon the attacking radical. Despite the lower bond energy of the C–H_a bonds,[21] the electrophilic alkoxy radical preferentially attacks the alkyl C–H_b bonds.[17]



Such regioselectivities can be attributed to polar transition states. In reactions involving a radical with a series of similar substrates, an Evans–Polanyi relationship does exist between the activation energy for abstraction and the strength of the bond being broken. For example, the activation energy for hydrogen abstraction by methyl radical from a series of alkanes decreases linearly in the order methyl > primary > secondary > tertiary C–H bonds.[22] This bond-energy dependence is only applicable when the electronic features of the reactions being compared do not differ significantly. Electrophilic radicals such as the halogens and alkoxy prefer to attack C–H bonds at sites of higher electron density, e.g., the α C–H bonds of ethers and amines which have high σ_{CH} orbital energies.[17] Nucleophilic radicals prefer interaction with the low-lying unoccupied orbitals of electron-deficient species.[15]

b. Synthetic Considerations. From a synthetic standpoint, rules governing abstractions must accommodate complex systems where several low valency atoms may be available:

1. Nucleophilic heteroatom radicals do not abstract hydrogen, due to the unfavorable enthalpy relative to that of heteroatom abstraction:[23,24]

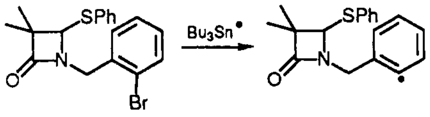
$$BrH_2C\text{-}H + Me_3Sn^\bullet \rightarrow {}^\bullet CH_2Br + Me_3SnH \qquad \Delta H \cong 32\ \text{kcal/mol} \tag{2}$$

$$CH_3\text{-}Br + Me_3Sn^\bullet \rightarrow {}^\bullet CH_3 + Me_3SnBr \qquad \Delta H \cong -14\ \text{kcal/mol} \tag{3}$$

The mildness and selectivity of nucleophilic stannyl radicals have made them the premier vehicle for driving free radical reactions.[25] In general, the reactivity of competing atoms toward abstraction by tributyltin radical reflects the bond energy at the possible abstraction sites, as in eq 4.[26]

(4)

2. Monovalent atoms are preferred over divalent ones, even if the bond to the monovalent atom is much stronger, e.g.,[27]



(5)

In this example, the BDE for the aryl–Br bond is at least 20 kcal/mol greater than for the C–SPh bond.[28] Orientational freedom in the approach to the divalent atom is clearly more restricted.

3. Electrophilic heteroatom radicals prefer hydrogen abstraction, again due to the large enthalpy differences:[29]

$$(CH_3)_3C\text{-}O^\bullet + Br\text{-}CH_3 \rightarrow (CH_3)_3COBr + {}^\bullet CH_3 \qquad \Delta H \cong 13\ \text{kcal/mol} \tag{6}$$

$$(CH_3)_3C\text{-}O^\bullet + H\text{-}CH_2Br \rightarrow (CH_3)_3COH + {}^\bullet CH_2Br \qquad \Delta H \cong -2\ \text{kcal/mol} \tag{7}$$

4. Tedder states that polar transition-state effects override bond-energy differences for exothermic reactions,[17]

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(16) Giese, B. *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 753.

(17) Tedder, J. M. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 401.

(18) Allred, A. L. *J. Inorg. Nucl. Chem.* **1961**, *17*, 215.

(19) Tedder, J. M. *Tetrahedron* **1980**, *36*, 701.

(20) Back, T. G. *Organoselenium Chemistry*; Liotta, D., Ed.; John Wiley & Sons: New York, 1987; p 338.

(21) Egger, K. W.; Cocks, A. T. *Helv. Chim. Acta* **1973**, *56*, 1516.

(22) Grey, P. A.; Herod, A. A.; Jones, A. *Chem. Rev.* **1971**, *71*, 247.

(23) Beckwith, A. L. J.; Pigou, P. E. *Aust. J. Chem.* **1986**, *39*, 77.

(24) Bond energy data for BrH_2C–H taken from ref 21.

(25) Neumann, W. P. *Synthesis* **1987**, *8*, 665.

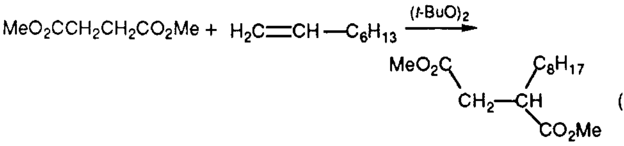
(26) Nagashimo, H.; Wakamatsu, H.; Itoh, K. *J. Chem. Soc., Chem. Commun.* **1984**, 652.

(27) Beckwith, A. L. J.; Boate, D. R. *Tetrahedron Lett.* **1985**, *26*, 1761.

(28) Bond energy data for Ph–Br from ref 21; data for C–SPh from Kerr, J. A. *Chem. Rev.* **1966**, *66*, 465.

(29) Bond energy data for RO–Br from Kerr (ref 28); remaining values from ref 21.

although alkylation reactions of esters suggest that carboxyl C–H bonds may be preferred over alkyl C–H bonds if the BDE difference is sufficient.[30,31]

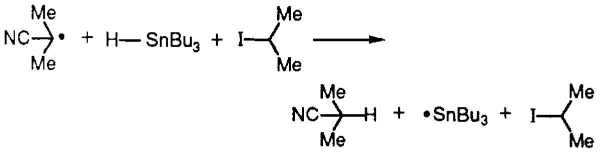


$$\mathrm{MeO_2CCH_2CH_2CO_2Me + H_2C{=}CH{-}C_6H_{13}} \xrightarrow{(t\text{-BuO})_2} \mathrm{MeO_2C{-}CH_2{-}CH(C_8H_{17})(CO_2Me)} \quad (8)$$

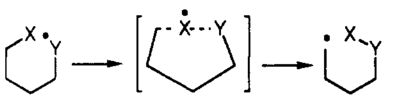
$$\mathrm{NC\text{-}CH_2\text{-}CO_2Et} \xrightarrow{t\text{-BuO}^\bullet} \mathrm{NC\text{-}\dot{C}H\text{-}CO_2Et} \qquad (9)$$

Abstraction from the methyl group in eq 8 would result in a primary radical stabilized only by the oxygen, while the additional stabilization afforded by the cyano group in eq 9 prevents abstraction from the ethyl group.

5. Carbon-centered radicals may abstract hydrogen or heteroatoms, the hierarchy being determined by relative bond strength. Weak bonds to hydrogen (i.e., bond energy less than ca. 75 kcal/mol) are cleaved in preference to bonds to heteroatoms, e.g.,

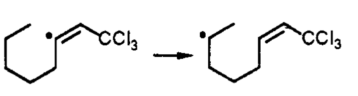


c. Intramolecular Abstractions: Atom Migrations. Intramolecular abstractions (S_Hi) occur when a favorable geometry places the radical center in close proximity to an abstractable atom, allowing a collinear transition state:[32]



Such rearrangements include migration of hydrogen or atoms bearing lone pairs or vacant d orbitals.[33] Hydrogen shifts are the most common and are driven by favorable enthalpies. Examples of 1,2- and 1,4-shifts are exceedingly rare; some 1,3-hydrogen shifts have been reported[34] but are suspected to be *inter*molecular.[32]

Both 1,5- and 1,6-hydrogen migrations are facile when exothermic, with 1,5-abstractions generally favored, as in eq 12.[32,35]



Hydrogen transfers to oxygen and nitrogen radicals are exothermic and rapid, with rate constants of ca. 10^6–10^8 s^{-1}.[36] Such migrations comprise the Barton and Hofmann–Löffler–Freytag reactions permitting remote functionalization of unactivated C–H bonds, e.g.,[37]

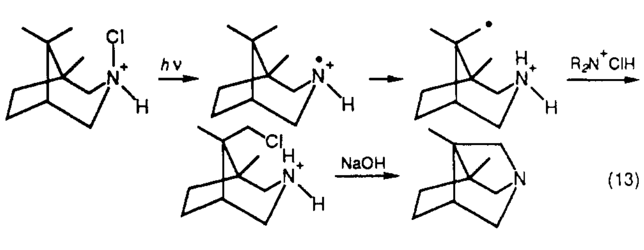
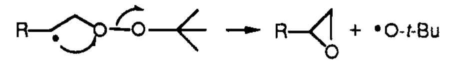


Table II. Effect of Olefin β Substituents: Relative Addition Rates for Cyclohexyl Radical + Olefins $H_2C{=}CHR$ and Comparison to Hammett σ Values[a]

	R =						
	C_4H_9	H	Cl	Ph	CO_2CH_3	CN	CHO
k_{rel}	1	3.75	30	250	1675	6000	8500
σ	−0.16	0	0.23	0.01	0.52	0.63	0.45

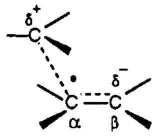
[a] Data from ref 46 and 47.

Intramolecular heteroatom abstractions include ring formation by organothiyl migrations[27] and attack upon oxygen when peroxide or perester bonds are available, as in eq 14.[38]



2. Additions. Free radical addition reactions are recognized as powerful means for inter- and intramolecular carbon–carbon bond formation. Although addition to carbon–heteroatom multiple bonds is known, addition to carbon–carbon multiple bonds is more favorable energetically since a carbon–carbon σ bond (ca. 88 kcal/mol) is formed at the expense of a carbon–carbon π bond (π_{CC} = 54–59 kcal/mol vs π_{CO} = 73–78 kcal/mol).[39] Radical additions are subject to electronic and steric effects; the relative impact of these factors is dependent upon whether the addition is inter- or intramolecular.

a. Intermolecular Additions: Physical Aspects. Substituent effects on intermolecular free radical addition reactions have been addressed in recent publications.[16,17,19,30,40] The rate and regioselectivity are affected by substituents on both the attacking radical and on the α- and β-positions of the multiple bond. According to the Hammond postulate, the exothermic addition of alkyl radicals to alkenes is expected to have an early transition state; calculations have suggested a dipolar complex:[41,42]



This charge distribution is in accord with the concept that alkyl radicals behave as nucleophiles. The existence of an early transition state has led to the use of frontier molecular orbital (FMO) theory to explain electronic effects on free radical addition reactions.[16] The addition rates are proposed to be determined by the relative energy gaps between the singly occupied molecular orbital (SOMO) of

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(30) Reference 9, Chapter 3, p 36.

(31) Cazaux, M.; Lalande, R. *Bull. Soc. Chim. Fr.* **1971**, *2*, 461.

(32) Beckwith, A. L. J.; Ingold, K. U. *Rearrangements in Ground and Excited States*; de Mayo, P., Ed.; Academic Press: New York, 1980; Vol. I, Chapter 4, p 181.

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(35) Heiba, E. I.; Dessau, R. M. *J. Am. Chem. Soc.* **1967**, *89*, 3772.

(36) Gilbert, B. C.; Holmes, R. G. G.; Laue, H. A. H.; Norman, R. O. C. *J. Chem. Soc., Perkin Trans. 2* **1976**, 1047.

(37) Wolff, M. E. *Chem. Rev.* **1963**, *63*, 55.

(38) Maillard, B.; Kharrat, A.; Rakotomanana, F.; Montaudon, E.; Gardrat, C. *Tetrahedron* **1985**, *41*, 4047.

(39) Bond energy data from ref 21.

(40) Giese, B. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 553.

(41) Hoyland, J. R. *Theor. Chim. Acta* **1971**, *22*, 229.

(42) Fujimoto, H.; Yamabe, S.; Minato, T.; Fukui, K. *J. Am. Chem. Soc.* **1972**, *94*, 9205.

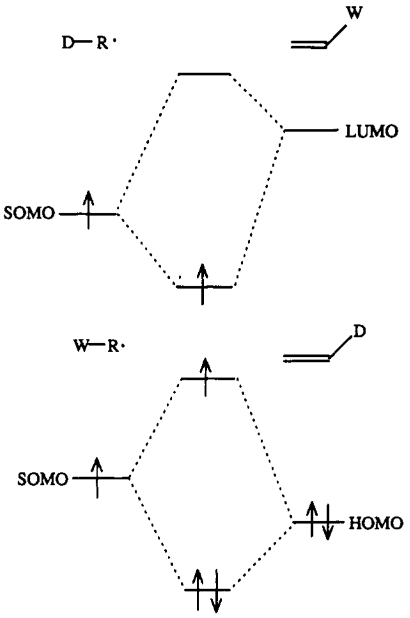


Figure 2. (a, top) Dominant orbital interactions for nucleophilic radicals (D ≡ electron donor) and electron-deficient alkenes (W ≡ electron acceptor). (b, bottom) Dominant orbital interactions for electrophilic radicals and electron-rich alkenes.

the attacking radical and the highest occupied or lowest unoccupied molecular orbitals (HOMO and LUMO, respectively) of the olefin. Figures 2a and 2b reproduce Giese's interpretation of these interactions.[15,16]

The factors that govern addition rates and regiochemistry have been extensively studied and are summarized by Tedder:[17]

1. The preferred orientation for addition to a terminal alkene is always toward the unsubstituted terminus.

2. The early transition state of exothermic additions suggests that delocalization of the developing radical is of minor importance in determining addition rates unless substituents contain carbon–carbon π bonds.

3. Nucleophilic radicals prefer addition to electron-poor olefins; electrophilic radicals preferably interact with electron-rich olefins:

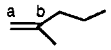
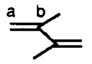
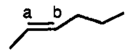
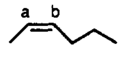
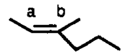
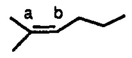
(a) Increasing radical nucleophilicity with alkyl substituents causes enhanced rates of addition to electron-deficient olefins, as shown by the following data for additions to $H_2C{=}CHPO(OEt)_2$:[43,44]

	$CH_3^\bullet$	$CH_3CH_2^\bullet$	$CH_3OCH_2^\bullet$	$(CH_3)_2CH^\bullet$	$(CH_3)_3C^\bullet$
k_{rel}:	1	1	2.7	4.8	24

These polar effects must offset both the increased stability of the attacking radical and any steric hindrance to addition,[16] since increasing steric bulk of the radical in additions to *unactivated* alkenes leads to reduced rates.[45] For addition to electron-poor alkenes, only very powerful stabilizing functionalities (e.g., phenyl) on the attacking radical reduce the rate to any significant extent.[16]

(b) The relative rate data of Table II demonstrate the significance of electron withdrawal by β groups.[46] Similar trends exist between relative rate and Hammett σ constant for each substituent.[45,47] Stabilization of the forming radical by β substituents is of minor importance; the stabilizing effect of a phenyl group is considerably greater than that of an acyl group,[21,23] yet addition to acrolein is 34 times faster than addition to styrene.

Table III. Steric Effects on Addition Regioselectivities: Addition of Dicyanomethyl Radicals[a]

olefin	% addition to C$_a$	% addition to C$_b$	k_{rel}
	≥95	≤5	1.16
	≥95	≤5	18.4
	≥95	≤5	2 × 136.6
	ca. 50	ca. 50	2 × 0.50
	ca. 50	ca. 50	2 × 0.63
	≥95	≤5	15.0
	≤5	≥95	13.9

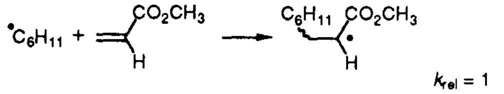
[a] Data from ref 32.

(c) Electrophilic radicals prefer addition to electron-rich olefins. However, substituent effects are modest in this case. For the dominant three-electron interaction (cf. Figure 2b) to be particularly rate-enhancing, the stabilization from the doubly occupied, mixed orbital would have to be greater than the destabilization from elevation of the singly occupied mixed orbital.[15]

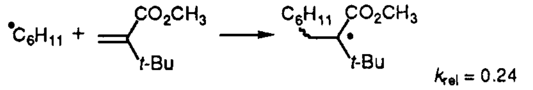
4. For addition to unsymmetrical polysubstituted olefins, regioselectivity is under steric control; in isosteric situations, the site of addition is determined by polarity.

(a) Examples of additions to acyclic olefins are given in Table III.[48] Though addition to the less hindered site is preferred, stability of the forming radical contributes to the rates, e.g., the first three entries of Table III.

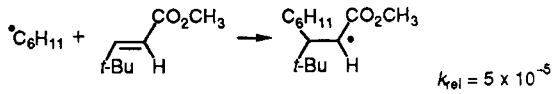
(b) Steric effects are significantly larger at the α-position than at the β-position. A β *tert*-butyl group slows addition by a factor of 4, while in the α-position the same group decreases the rate by a factor of ca. 20 000:[49]



(15)

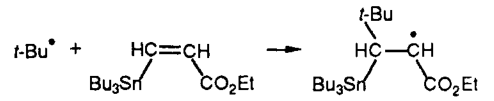


(16)



(17)

These generalities have been confirmed by Giese and Münger,[16,50] although the competition between steric and electronic effects is difficult to predict a priori, e.g., eq 18.[51]



(18)

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(43) Caronna, T.; Citterio, A.; Ghirardini, M.; Minisci, F. *Tetrahedron* **1977**, *33*, 793.

(44) Baban, J. A.; Roberts, B. P. *J. Chem. Soc., Perkin Trans. 2* **1981**, 161.

(45) Tedder, J. M.; Walton, J. C. *Adv. Free Radical Chem.* **1980**, *6*, 155.

(46) See ref 16 and references cited therein.

(47) Hammett σ values from Jaffé, H. H. *Chem. Rev.* **1953**, *53*, 191.

(48) Riemenschneider, K.; Drechsel-Grau, E.; Boldt, P. *Tetrahedron Lett.* **1979**, 185.

(49) Giese, B.; Lachein, S. *Angew. Chem., Int. Ed. Engl.* **1981**, *20*, 967.

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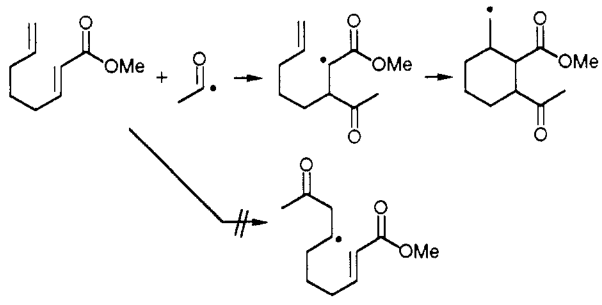
(51) Baldwin, J. E.; Kelly, D. R.; Ziegler, C. B. *J. Chem. Soc., Chem. Commun.* **1984**, 133.

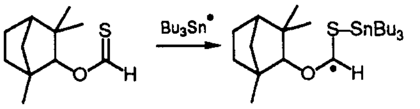
The tributyltin functionality is clearly more bulky than the ester group; control of regiochemistry appears to be electronic in origin. Indeed, addition to electronically activated bonds dominates even when unhindered, unactivated alkenes are available:[52]



(19)

Equations 17–19 clearly suggest that electronic effects actually outweigh steric considerations.

Nucleophilic radicals may also add to carbon–heteroatom multiple bonds, generally as part of addition/β-scission sequences (cf. Section IV). Functionalities available for facile addition include xanthates and other thione derivatives,[53] isonitriles, and nitro groups,[54,55] e.g., eq 20 and 21.[56,57]



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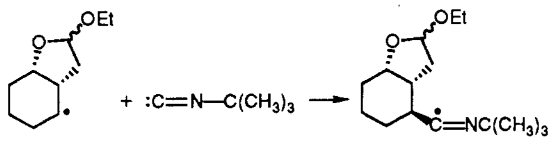
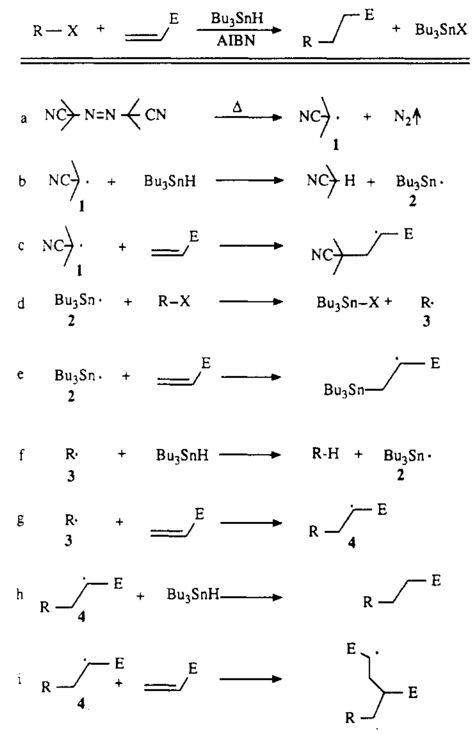


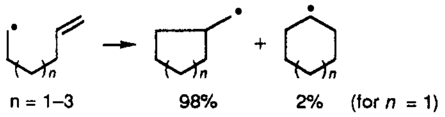
(21)

For synthetic utility, free radical additions must be controlled by alternating the electronic nature of the attacking and adduct radicals. Scheme I presents the possible steps that must be considered in a tin hydride mediated reaction. Several paths of reaction are possible for each radical propagated. The initiated 2-cyanopropyl radical 1 may abstract hydrogen from Bu_3SnH or it may add to the available alkene (path c). If E is an electron-withdrawing substituent, the addition rate for electrophilic 1 is unlikely to compete with the path b abstraction (k_H ca. 2×10^6 M^{-1} s^{-1}).[11] The resultant nucleophilic stannyl radical may abstract X (path d) or follow addition path e. Here, if E is electron-withdrawing, the addition should be facile. However, such additions are reversible due to the weak Sn–C bond, so that competition with path d depends upon the rate of abstraction of X. Stannyl additions typically compete to only a minor extent even when abstraction is slow, i.e., X = unactivated chlorine or sulfuryl groups.[23] Therefore, formation of R$^\bullet$ (3) should prevail. If 3 is nucleophilic, addition path g produces the electrophilic adduct 4. This reversal of polarity in the adduct controls the chain sequence, i.e., since 4 is electrophilic it cannot compete with nucleophilic 3 for the electron-poor alkene. Telomerization (path i) is avoided, and the trapping sequence h becomes the preferred option for 4.

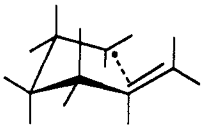
Scheme I



b. Intramolecular Additions. Ring closure reactions have received much synthetic attention. A marked preference for exo ring closure exists, i.e., 5-hexenyl, 6-heptenyl, and 7-octenyl radicals predominantly close to form cycloalkylcarbinyl radicals:[58]



The preferred formation of a less stable primary radical is due to a chairlike transition state[59] and indicates that radical ring closures are subject to stereoelectronic and kinetic rather than thermodynamic control.[32] This transition state permits favorable overlap between the radical SOMO and the π^* orbital of the alkenyl terminus without submitting to the strain required for sufficient overlap in an endo approach.[60,61] Similar control is exerted over intramolecular additions to alkynes, allenes, and closures involving analogous heteroatom radicals.[62] Unlike intermolecular additions, closure onto unactivated carbon–carbon bonds is facile (ca. 10^5 s^{-1}),[63] and cyclization involving polarized multiple bonds (e.g., C≡N, C=O) is possible.



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[53] Barton, D. H. R. *Substituent Effects in Radical Chemistry*; Viehe, H. G., Janousek, Z., Merenyi, R., Eds.; Riedel: Dordrecht, Holland, 1986; p 443.

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[61] Beckwith, A. L. J.; Schiesser, C. H. *Tetrahedron* **1985**, *41*, 3925.

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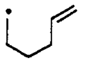
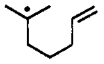
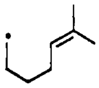
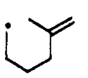
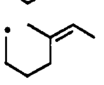
[63] Carlsson, D. J.; Ingold, K. U. *J. Am. Chem. Soc.* **1968**, *90*, 7047.

Table IV. Relative Cyclization Rates for Substituted Hexenyl Radicals[a]

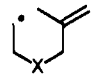
radical	k_{rel} exo	k_{rel} endo
	1.0	0.02
	1.4	0.02
	2.4	<0.01
	.022	0.04
	0.16	<0.002

[a] Data from ref 32.

The preference for exo over endo closure may be inverted sterically or by inducing reversibility. The following rules apply:

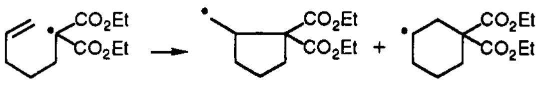
1. For the 5-hexenyl radical, alkyl substituents at the 1- or 6-position have little effect on rate or regiochemistry; however, substitution at the 5-position can cause a preference for endo closure.[62] Table IV provides examples and relative rate data. Substituents at the 2-, 3-, or 4-positions are also found to enhance the cyclization rate; for example, 2,2-dimethylhex-5-enyl radical cyclizes 10 times faster than its unsubstituted analogue.[32]

2. If the ring closure path contains a first-row heteroatom, the decreased path length emphasizes the strain differences in exo/endo transition states such that 5-substituted hexenyl radicals revert to exo dominance, e.g.,[32]



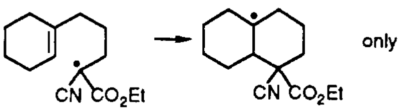
X	k_{exo}/k_{endo}
CH_2	0.55
O	38.6

3. Closure of stabilized radicals is reversible, allowing thermodynamically favored products to compete or even dominate, as in eq 22 and 23.[60,64]



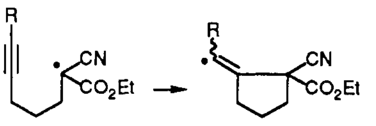
(22)

3 : 2



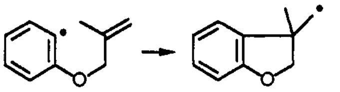
(23)

4. Alkynyl radicals are even more subject to stereoelectronic control, and even stabilized hexynyl radicals undergo exclusive exo closure:[65]

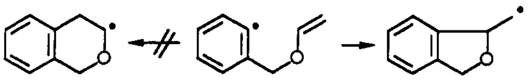


(24)

5. Aryl radicals also undergo specific exo closure. Equations 25 and 26[66,67] demonstrate that this preference is not overwhelmed by steric hindrance at the site of attack nor by the alternative formation of an oxygen-stabilized radical.

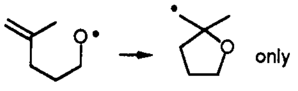


(25)



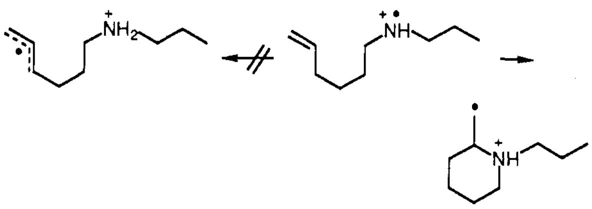
(26)

6. Heteroatom radicals prefer exo cyclization to varying degrees. Oxy radicals cyclize rapidly (ca. 10^8 s^{-1}) and specifically to give exo products, despite varied substitution,[68] e.g., eq 27, which can be compared with the fourth entry of Table IV.[32]



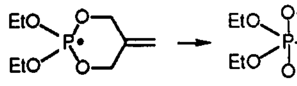
(27)

7. Aminyl radicals cyclize slowly, but closure of aminium radicals can thwart Hofmann–Löffler–Freytag reactions:[69]



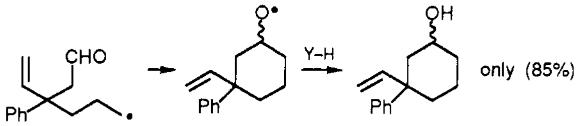
(28)

8. Second-row atoms also undergo ring closures. Sulfuryl radical cyclizations are reversible, however, and lack regioselectivity.[70] Silyl radicals with bulky or stabilizing substituents may prefer endo closure.[32] Phosphoranyl radicals are unique in that 1,4-exo cyclizations can be favorable, as in eq 29.[32]



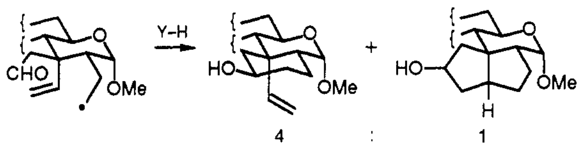
(29)

9. It has become apparent that intramolecular addition to carbonyl and nitrile π bonds can be facile.[71,72] Tsang et al. reported that closure onto aldehydes to form cyclohexanols can dominate in the presence of hexenyl systems:[73,74]



(30)

Similarly, attempts to form bis-annulated sugars (eq 31) were foiled by formation of the cyclohexanol as the major product:[71]



(31)

4 : 1

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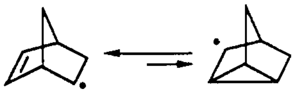
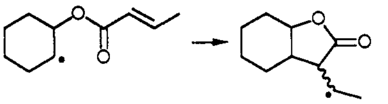
10. Cyclization of 3-butenyl radicals occurs, but is subject to rapid reopening due to the ring strain. However, in constrained systems, cyclized products can be isolated, e.g., eq 32.[75]


(32)

11. Closure of 4-pentenyl systems are unknown.[32] Exo closure to give a cyclobutylcarbinyl radical is thermally disfavored due to the impending ring strain, while the stereoelectronics necessary for an endo closure are also prohibitive.

12. Heptenyl and octenyl radicals prefer to cyclize in the exo mode, albeit more slowly than hexenyl radicals (ca. 10^4 and 10^2 vs 10^5 s^{-1}).[58]

13. Radical cyclizations forming 5–7-membered rings clearly are not subject to the polar effects which can dominate intermolecular additions, e.g., eq 33.[76] Nevertheless, the effect of activating substituents cannot be discounted entirely; yields can be improved by an advantageous combination of stereoelectronic and polar features.[77] However, deactivating groups have little directing effect, as in eq 34.[78,79]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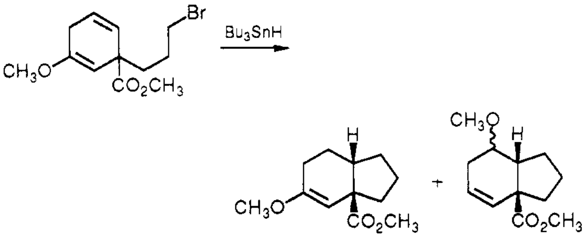
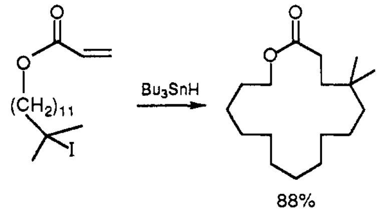


(34)

1 : 1

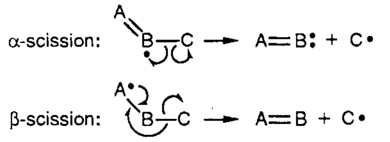
14. Although radical cyclizations creating rings of 8–10 members have not been reported, Porter and Chang have described radical closures forming macrolides of 11–20 atoms.[80] At these chain lengths the systems behave like intermolecular reactions, with control reverting to steric and polar effects, as in eq 35.[80]



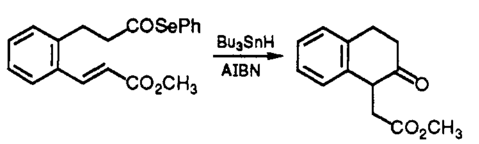
(35)

88%

3. **Fragmentations.** Homolytic cleavage of appropriately constituted bonds may occur at positions α or β to the free spin. The driving force for these cleavages is often the formation of small, stable molecules (e.g., CO, CO_2, SO_2), relief of ring strain, or generation of a π bond at the expense of a weaker σ bond.

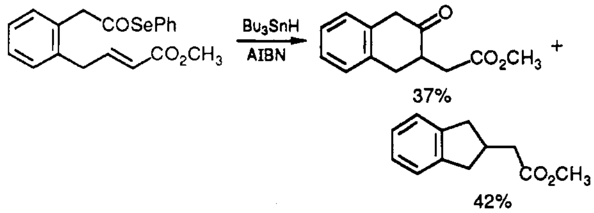


a. **α-Fragmentations.** Loss of CO, SO_2, etc. from acyl and sulfonyl radicals does not generally have synthetic utility, but must be considered a phenomenon competitive with other processes. Loss of CO from acyl radicals can be avoided by use of a fast trapping agent such as a stannane, so aldehydes can be isolated from acyl halides in good yield.[81] Even intramolecular additions can compete well with decarbonylation, as in eq 36 and 37.[82] The decarbonylated product of eq 37 is presumed to arise because fragmentation produces a stabilized benzylic radical.[82,83]



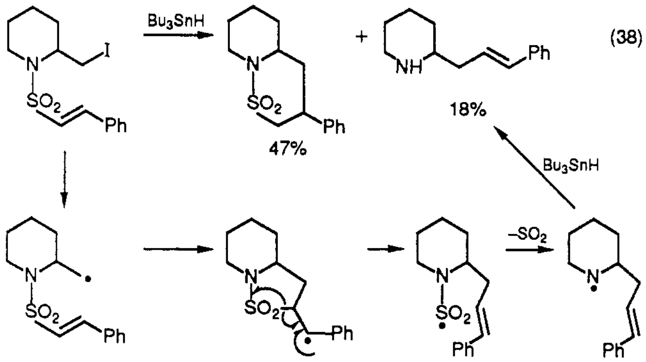
(36)

83%



(37)

Sulfonyl radicals lose SO_2 rapidly, as in the sulfonamide rearrangement suspected to preclude simple exo cyclization in eq 38.[84]



(38)

b. **β-Fragmentations.** β-Fragmentation reactions have not received cohesive treatment in the literature. Generalities may be determined from primary synthetic sources. Driving forces include:

1. **Relief of Ring Strain.** Fragmentations of cyclopropyl, cyclopropylcarbinyl, and cyclobutylcarbinyl radicals can compete with such facile processes as ring closures.[32]

(a) Cleavage of cyclopropyl rings is highly exothermic due to ring strain relief and formation of allylic radicals.[32] The rate of ring opening is actually low, since fragmen-

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[75] Warner, C. J.; Strunk, R. J.; Kuivila, H. G. *J. Org. Chem.* **1966**, *31*, 3381.

[76] Clive, D. L. J.; Beaulieu, P. L. *J. Chem. Soc., Chem. Commun.* **1983**, 307.

[77] Stork, G.; Mook, R.; Biller, S. A.; Rychnovsky, S. D. *J. Am. Chem. Soc.* **1983**, *105*, 3741.

[78] Beckwith, A. L. J.; Roberts, D. H. *J. Am. Chem. Soc.* **1986**, *108*, 5893.

[79] Park, S.-U.; Chung, S.-K.; Newcomb, M. *J. Am. Chem. Soc.* **1986**, *108*, 240.

[80] Porter, N. A.; Chang, V. H.-T. *J. Am. Chem. Soc.* **1987**, *109*, 4976.

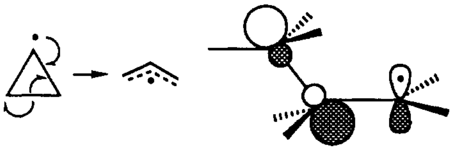
[81] Kuivila, H. G.; Walsh, E. J. *J. Am. Chem. Soc.* **1966**, *88*, 571.

[82] Boger, D. L.; Mathvink, R. J. *J. Org. Chem.* **1988**, 3377.

[83] Brunton, G.; McBay, H. C.; Ingold, K. U. *J. Am. Chem. Soc.* **1977**, *99*, 4447.

[84] Köhler, J. J.; Speckamp, W. N. *Tetrahedron Lett.* **1977**, 635.

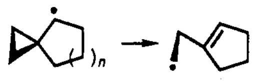
tation is favored when the semi-occupied orbital eclipses the σ^* orbital of the cleaving bond:[32]



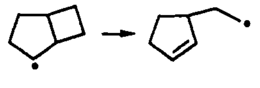
(b) Appropriate substitution can enhance the rate, and eq 39 suggests that the rate of ring opening must exceed 10^5 s^{-1}, since fragmentation competes with cyclization.[85]

(39)

(c) β-Fragmentation of cyclopropylcarbinyl and cyclobutylcarbinyl radicals is a comparatively facile process (ca. 10^8 and 10^2 s^{-1}, respectively, at 25 °C).[32] The large rate differences indicate stronger mixing between the radical p orbital and unoccupied Walsh orbitals for the three-membered ring. Furthermore, the results of eq 40 and 41 suggest that the requirement that the cleaving bond eclipse the singly occupied orbital is probably less important for cyclopropylcarbinyl systems than for cyclobutylcarbinyl analogues. The spiro cyclopropylcarbinyl radical (eq 40) undergoes fragmentation despite the fixed bisected conformation.[86] Formation of the less stable primary radical in eq 41 suggests that for cyclobutyl fragmentation, the conformational requirement exceeds the propensity for maximizing stability.[87]

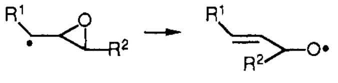


(40)

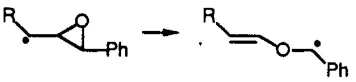


(41)

(d) If an epoxide ring resides α to the radical center, the C–O bond cleaves in preference to the C–C bond unless the latter is stabilized by aryl or vinyl groups:[88,89]

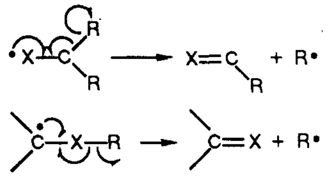


(42)

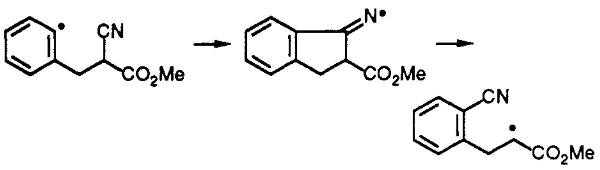


(43)

2. Formation of Strong π Bonds. Fragmentations involving formation of C=O and C≡N π bonds are ubiquitous. These may occur via heteroatom-centered radicals or α-hetero carbon-centered radicals:

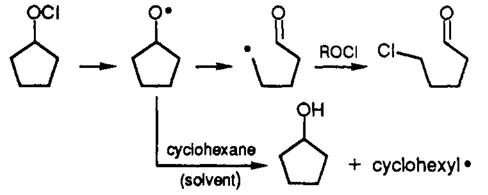


(a) Rate constants for β-scission of cycloalkyloxy radicals are expected to exceed 10^6 s^{-1}.[32] Fragmentation of iminyl radicals is significantly slower, but is known to participate in cyano group migrations (eq 44).[72,90]

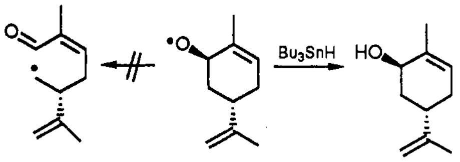


(44)

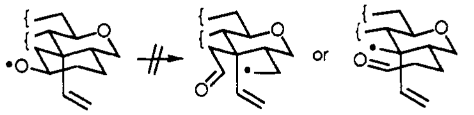
(b) Heteroradical fragmentations must produce stabilized radicals in order to occur in the presence of fast trapping agents, as in eq 45[91] and 46.[88] Formed in the absence of a fast atom transfer agent, the cyclopentyloxy radical of eq 45 has ample opportunity for fragmentation to a primary radical. Barton's carveol production (eq 46) is successful because the rate of hydrogen abstraction from the trapping agent Bu_3SnH exceeds the rate of fragmentation to a primary alkyl radical. Moreover, the results of Tsang and Fraser-Reid suggest that in the presence of fast trapping agents, fragmentation from oxy radicals only occurs if the resultant radical is at least secondary:[74,92]



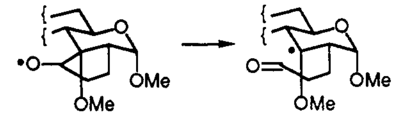
(45)



(46)

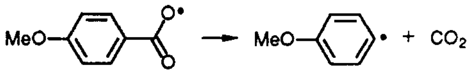


(47)



(48)

(c) Conversely, when CO_2 loss is possible, even unstable aryl radicals can be formed readily:[93]



(49)

(d) Observation of iminyl radicals suggests a similar minimum stabilization requirement.[32,94] Reported fragmentations of aminyl radicals have been limited to those involving cyclopropyl- and cyclobutylaminyl systems[95] and

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[85] Descoins, C.; Julia, M.; van. Sang, H. *Bull. Soc. Chim. Fr.* **1971**, *11*, 4087.

[86] Suzuki, M.; Murahashi, S.-I.; Sonoda, A.; Moritani, I. *Chem. Lett.* **1974**, 267.

[87] Hill, E. A.; Theisen, R. J.; Cannon, C. E.; Miller, R.; Guthrie, R. B. Chen, A. T. *J. Org. Chem.* **1976**, *41*, 1191.

[88] Barton, D. H. R.; Motherwell, R. S. H.; Motherwell, W. B. *J. Chem. Soc., Perkin Trans. 1* **1981**, 2363.

[89] Johns, A.; Murphy, J. A.; Patterson, C. W.; Wooster, N. F. *J. Chem. Soc., Chem. Commun.* **1987**, 1238.

[90] Beckwith, A. L. J.; O'Shea, D. M.; Westwood, S. W. *J. Am. Chem. Soc.* **1988**, *110*, 2565.

[91] Walling, C.; Clark, R. T. *J. Am. Chem. Soc.* **1974**, *96*, 4530.

[92] Tsang, R.; Fraser-Reid, B. *J. Am. Chem. Soc.* **1986**, *108*, 8102.

[93] Barton, D. H. R.; Lacher, B.; Zard, S. Z. *Tetrahedron Lett.* **1985**, *26*, 5939.

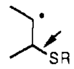
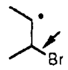
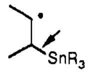
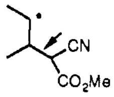
[94] Tanner, D. D.; Rahimi, P. M. *J. Org. Chem.* **1979**, *44*, 1674.

[95] Maeda, Y.; Ingold, K. U. *J. Am. Chem. Soc.* **1980**, *102*, 328.

[96] Sanderson, R. T. *Chemical Bonds in Organic Compounds*; Sun & Sand: Scottsdale, AZ, 1976; p 53.

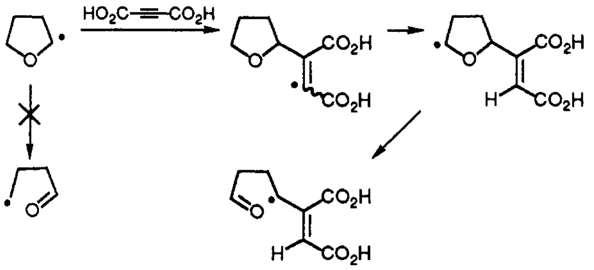
[97] Jackson, R. A. *J. Organomet. Chem.* **1979**, *166*, 17.

Table V. β-Scission Precursors

radical	BDE, kcal/mol	ref
	70	96
	68	21
	65	97
	53	21
	66	98

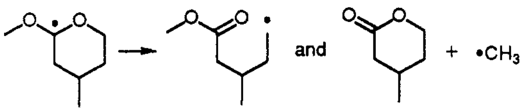
are probably driven by ring strain relief. β-Scissions of sulfuryl radicals have not been reported; indeed, the driving force behind several of Barton's decarboxylation reactions is the overall exchange of a C=S π bond for a C=O π bond (cf. Section IV).[53]

(e) β-Scissions generating carbon–heteroatom π bonds may also occur from appropriate carbon radicals. For simple α-alkoxyalkyl radicals, fragmentation is too slow to compete with other possible processes, e.g., eq 50.[34]



(50)

(f) Cleavage generally occurs in the direction forming the most stable radical. However, exocyclic C–O bonds are often cleaved competitively due to better overlap with the semi-occupied orbital, despite formation of a less stable radical (eq 51).[32]



(51)

3. **Fragmentation of Weak σ Bonds.** β-Fragmentations driven by cleavage of weak carbon–hetero or hetero–hetero single bonds comprise the final class of neutral radical propagation steps. Table V provides a series of candidates for fragmentation and indicates that the bond dissociation energy of the cleaving bond does not exceed ca. 70 kcal/mol.

III. Implementation of Free Radical Chemistry in CAMEO

Treatment of modern free radical chemistry is essential to any synthetic analysis program; however, the chain propagating nature of free radical reactions poses significant challenges. Several intermediate radical species must be formed and evaluated even for reactions resulting in relatively simple overall transformations.

The operational premise for this module is that complex interconversions may be explained and predicted by reducing processes to a series of fundamental steps. Successful predictions are made because each radical intermediate is explicitly generated and submitted to a series of mechanistic algorithms. This iterative resubmission process mimics the self-propagating nature of chain reactions. The success of the approach is demonstrated in Section IV.

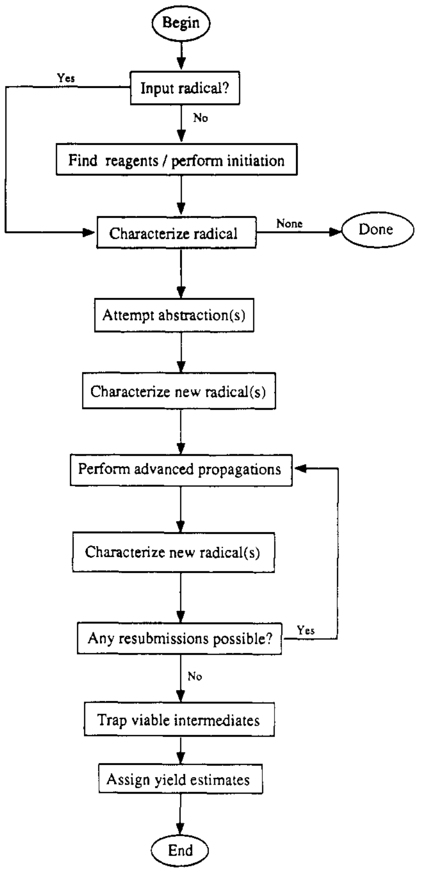


Figure 3. Flowchart for free radical processing.

A. General Program Flow. The usual format in CAMEO is that the only molecules available for reaction are those explicitly entered at the graphics terminal, e.g., self-condensation of acetone requires the entry of *two* molecules of acetone and a base. Modifications to this procedure were clearly required to accommodate the initiation and propagation of radical chain reactions. Overall transformations give the illusion of 1:1 stoichiometry of reactants; however, analysis of chain mechanisms illustrates that proper treatment requires the *implicit* presence of duplicate molecules. Initiator species are also usually present only in trace amounts and must be formally identified and removed from processing beyond the first homolysis. Since free radicals are not isolable species, it is desirable to display only trapped products. Furthermore, termination steps typically result in trace products which should not be displayed. Despite these complications, it is possible to treat free radical reactions in a mechanistic fashion with few artificial constructions.

An overview of the processing is presented in Figure 3, encompassing the four key reaction phases, i.e., initiation, primary propagation (intermolecular abstractions), advanced propagations (rearrangements and additions), and radical trapping (implicit chain transfer). The module follows straightforward mechanistic logic. Note, however, that termination steps are excluded.

The program first determines whether a radical intermediate has been entered. If so, pertinent information is

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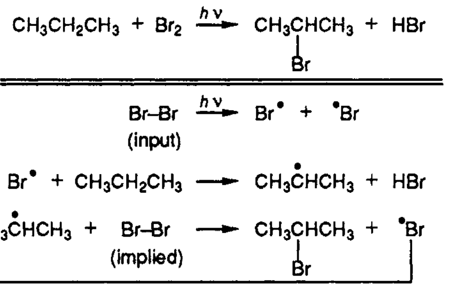
[98] Bond dissociation energy estimated as described in the Appendix.

garnered such as location and philicity of the radical site. If only closed-shell reactants are present, the program seeks an initiator molecule for homolysis. Initiators are sought according to a decomposition rate hierarchy, and cleavage is performed to generate the initial radical. The mode of eventual radical trapping is noted at this stage, i.e., the appropriate atom or fragment type is determined by the initiator species.

Following radical characterization, intermolecular abstractions are attempted. This "primary propagation" phase is isolated from remaining propagations to prevent indiscriminant abstraction by resubmitted intermediates (vide infra).

Radicals formed by abstraction are characterized and evaluated for the possibility of additional propagations. Fragmentations, ring closures, additions, and intramolecular abstractions are performed at this point. Any new intermediates generated are tested for resubmission, i.e., if brief inspection reveals the possibility for favored processes, the selected structures are issued to the propagation phase for thorough analysis and intermediate formation. This resubmission process continues until no new intermediates result. All viable intermediates are then converted to trapped products during the last phase of processing by enacting the implied chain-transferring abstraction.

The separation of abstraction steps from the propagation phase is addressed by consideration of eq 52. To perform



(52)

this simple halogenation, a program user would input reagents with 1:1 stoichiometry as indicated in the overall reaction. As noted above, the program usually operates only on the molecules that are input; however, the mechanism makes it clear that *two* molecules of Br_2 are required to complete the halogenation. Br_2 is the only reasonable candidate for abstraction by the isopropyl radical, but would no longer be explicitly available due to its decomposition in the first step. The situation is recognized during the initiation phase, and a second implicit Br_2 is provided so that abstraction can occur from it. Details for each of the major phases of chain reaction processing are provided in the following sections.

B. Radical Initiation. Initiator molecules are sought according to relative decomposition rates.[99] Simple cleavage of the weakest available bond is insufficient for subsequent processing. Furthermore, many initiators are asymmetric, and only one fragment may be appropriate for chain propagation. Therefore, initiators are identified according to bond type and assigned a rate level that categorizes the ease of fragmentation. Homolysis is subsequently performed, and only the fragments necessary for clarity are retained, e.g., only one alkyl radical and N_2 result from RN=NR.

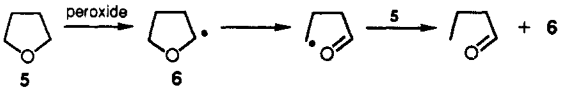
It is also convenient to determine the mode of radical trapping at this point. For example, if the initiating species is Br_2, the trapping atom type will necessarily be Br. Also, control of subsequent radical reactions depends upon the trapping step. For example, α-fragmentation of acyl radicals can be minimized by use of a fast trapping agent such as Bu_3SnH.[81,82] Thus, it is necessary to assign trapping rate levels for appropriate assessment of subsequent propagation and trapping competitions. The trapping level (TLVL) is simply assigned the value 1 for rapid product trapping or 2 for moderate to slow trapping.

Table VI. Categorization of Rate Levels for Initiators and Trapping Agents. Level 1 Reagents Decompose at the Highest Rate; Level 6, the Lowest

reagent	initiation result	trapping level	trapping fragment
Level 1			
RHgH	R• + Hg	1	H
RHgX/H^-	R• + Hg	1	H
(X = Cl, Br, OAc, etc.)			
RN=NR	R• + N_2	2	?
Level 2			
R_3SnH	R_3Sn•	1	H
RSH	RS•	2	H
Level 3			
R_3GeH	R_3Ge•	2	H
R_3Sn–SnR_3	R_3Sn•	2	?
allyl-$SnBu_3$	Bu_3Sn• + allyl-$SnBu_3$	2	?
Level 4			
RCO_2–O_2CR	RCO_2•	2	H
RCO_2–OR	RCO_2•	2	H
Level 5			
RO–OR	RO•	2	H
RS–SR	RS•	2	H
Level 6[a]			
CHX_3	X_3C•	2	H
CX_3Y	X_3C•	2	Y
X_2	X•	2	X
R_2NX	R_2N•	2	X
RON=O	RO•	2	NO
ROX	RO•	2	X

[a] X/Y = Cl, Br, I.

Table VI summarizes the rate hierarchy of the initiation phase for all reagent types recognized by the CAMEO program. Only one initiator from the highest available rate level is permitted. If, for example, both a mercury hydride *and* an azo compound are identified, complex mixtures are expected, and the user is requested to limit input to one initiator. However, agents from different levels are permitted. Thus, a mixture of AIBN, Bu_3SnH, and Cl_3CBr would result only in decomposition of AIBN. For most reagents, the trapping molecule is an implied duplicate of the reagent. However, when reactions are initiated from peroxides, the products are trapped by hydrogen abstraction from another substrate molecule, as in eq 53.[100]



5 6 (53)

The additional substrate is implicit, and the trapping atom is assumed to be hydrogen. For carbon-centered radicals or tin radicals arising from sources other than stannyl hydrides, the trapping step also involves a substrate molecule, as in eq 54.[101] Since the first abstraction may

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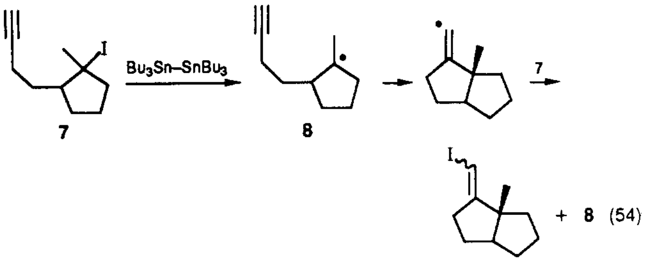
[99] Based upon rate data where available and literature precedent where more than one potential initiator is present.

[100] Huyser, E. S. *J. Org. Chem.* **1960**, *25*, 1820.

[101] Curran, D. P.; Chen, M. H.; Kim, D. *J. Am. Chem. Soc.* **1986**, *108*, 2489.



(54)

involve a variety of heteroatoms, the trapping fragment is not assigned until the possible competitive abstractions are fully analyzed. Initiators in this class lack a "trapping fragment" designation in Table VI.

C. Radical Characterization. All generated radicals are submitted for brief characterization prior to subsequent processing. Pertinent information determined and stored includes:

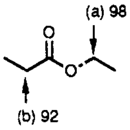
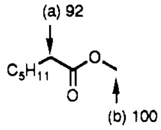
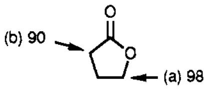
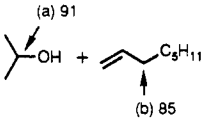
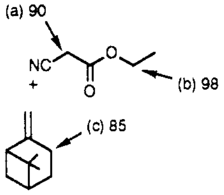
1. Location of the radical atom.
2. Determination of whether the radical is isolated or if potentially reactive partners are present. Such information is important in assessing competitions, such as in eq 50.[34,102] Ring openings that form primary alkyl radicals are generally disfavored unless no other options exist.[32]
3. Determination of radical philicity. The electronic nature of each intermediate is a primary determinant of subsequent reactions. As discussed in Section IIA, when the atom bearing the lone electron is more electronegative than carbon, the radical is designated as electrophilic, while radicals of atoms less electronegative than carbon are deemed nucleophilic. For carbon-centered radicals, substituent effects are assessed. Electron-releasing and alkyl groups attached to the radical center enhance the inherent nucleophilicity. Any α electron-withdrawing groups cause an electrophilic designation.
4. The thermodynamic stability of the radical is estimated from the bond dissociation energy for the corresponding bond to hydrogen. The algorithm for predicting BDEs is presented in the Appendix.

D. Primary Propagations: Intermolecular Abstractions. Primary propagations are those reactions directly involving the initially input or generated radical and a closed-shell molecule. For reasons discussed previously (cf. Section IIIA), the primary propagation phase is limited to intermolecular abstraction (S_H2) reactions. Note that abstractions are not forced if more favorable reactions exist; *all* propagation processes are considered in order of relative favorability.

The flowchart for the abstraction phase presented in Figure 4 describes the rules for intermolecular S_H2 reactions. The general rules are: (1) Abstraction is always limited to mono- and divalent atoms. (2) Monovalent atoms are abstracted in preference to divalent atoms. (3) Within this division, abstraction is always somewhat dependent upon the strength (BDE) of the bond being broken. Specific rules for abstraction are dependent upon the attacking radical, as discussed next.

1. Electrophilic Heteroatom Radicals. Non-carbon electrophilic radicals (cf. Table I) are limited to abstraction of hydrogen atoms (Section IIB-1b, point 3). As indicated in Figure 4, abstractions are dependent upon a balance of bond energy and polar effects. Electrophilic radicals prefer abstraction from relatively electron-rich sites, even if slightly weaker bonds are available. The set of weakest Y–H bonds plus those within a 7 kcal/mol window are located first. Among these, the set of bonds α to π donors are preferred, and those α to withdrawing groups are considered second. If only unactivated hydrogens are available, abstraction is permitted, but the initial radical is retained as a candidate for advanced propagations (vide infra). Table VII contains several illustrative examples of this abstraction hierarchy. Note that polar control dominates when the electron-rich bond is within 7 kcal/mol of the weakest available C–H bond.

Table VII. Polar vs Bond Energy Effects in Hydrogen Abstractions by t-BuO$^{\bullet}$[a]

structure	site of H abstraction	ref
	a	17 (21)
	a	9 (21)
	b	103 (98)
	a	104 (105)
	a	31 (98)

[a] BDE values in kilocalories/mole; references for BDEs in parentheses.

2. Nucleophilic Heteroatom Radicals. The rate hierarchy for stannyl and germyl abstractions is well established. The general order for attack, assuming the same alkyl groups, is I > Br > PhSe > Cl > ArS > RS.[23] With the exception of sulfur, the order correlates directly with relative bond dissociation energies. The abstraction algorithm relies upon estimated bond dissociation energies to locate the appropriate site, e.g., benzyl chloride (BDE = 69 kcal/mol) is as reactive as an alkyl bromide (BDE = 68 kcal/mol).[23,39] The relatively low reactivity of sulfides is not well explained,[23] and if any other monovalent or divalent atoms having a BDE within 35 kcal/mol of the sulfide bond are available, these are selected regardless of bond energy, e.g., eq 55 and 56.[106,107,28] If attack upon a sulfide group is the sole possibility, abstraction is executed, but the attacking radical is also submitted for analysis of propagation, as in eq 57.[108]

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(102) Wilt, J. W. In *Free Radicals*; Kochi, J. K., Ed.; Wiley: New York, 1973; Vol. 1, Chapter 8.

(103) Elad, D.; Youssefyeh, R. D. *J. Chem. Soc., Chem. Commun.* **1965**, 7.

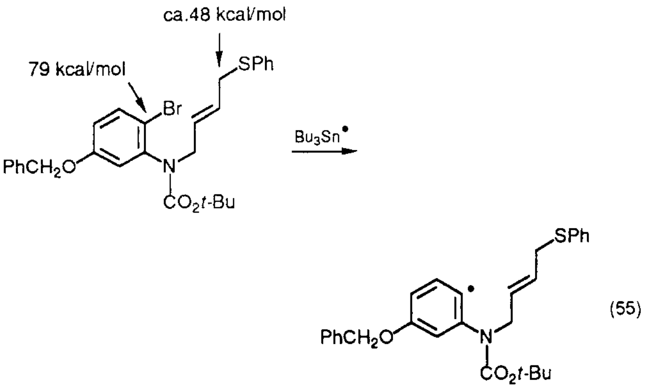
(104) Urry, W. H.; Stacey, F. W.; Huyser, E. S.; Juveland, O. O. *J. Am. Chem. Soc.* **1954**, *76*, 450.

(105) *Handbook of Chemistry and Physics*, 60th ed.; CRC Press: Boca Raton, FL, 1979; F231–235.

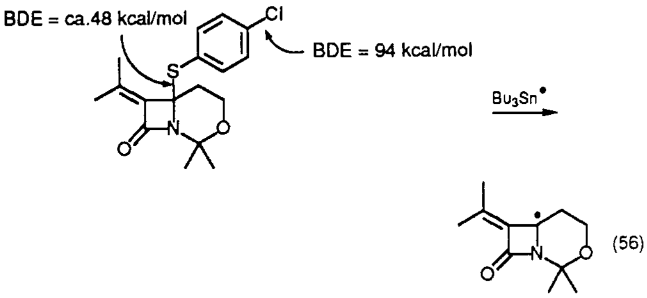
(106) Boger, D. L.; Wysocki, R., personal communication.

(107) Buynak, J. D.; Rao, M. N. *J. Org. Chem.* **1986**, *51*, 1571.

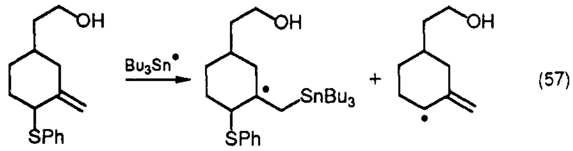
(108) Denmark, S. E.; Weber, E. J. *J. Am. Chem. Soc.* **1984**, *106*, 7970.



(55)



(56)



(57)

3. **Carbon Radicals.** Carbon-centered radicals may abstract hydrogen or heteroatoms according to the following hierarchy: (1) Very weakly bound hydrogen (BDE $\leq$ 75 kcal/mol, e.g., Sn–H and S–H).[109] (2) Bonds to mono- and divalent heteroatoms, echoing the rules for nucleophilic radicals. (3) Thermodynamically favorable C–H bonds. Although C–H bonds are not usually attacked,[109] abstraction is permitted if no other options are available. Equations 10 and 11 provide generic examples of rules 1 and 2; it is well established that most tin hydride mediated reactions are actually launched by AIBN homolysis and abstraction of hydrogen from the stannane, while direct heteroatom abstraction by 2-cyanopropyl radical is also well known.[110]

Any radicals emerging from the abstraction phase are labeled as intermediates of primary propagation (RADIN1) and are considered for advanced propagations. An important exception exists when abstraction results in a metal radical. For reactions involving the AIBN/R_3MH pair, the resultant metal radical is typically involved in a second abstraction. Thus, when stannyl or germyl radicals are formed, the primary propagation phase is immediately repeated.

E. Advanced Propagations. In this phase of processing, the most synthetically significant transformations, such as fragmentations, additions, ring closures, and intramolecular S_H2 reactions, are executed. The implemented algorithm is fully linear, is based on experimental kinetic data and product distributions,[111] and is organized into the following four subphases.

Subphase I: intramolecular processes with rate constants $\geq 10^5$. (1) α-scissions (rates approach 10^7 s^{-1}).[83] (2) Hydrogen migrations to electrophilic heteroradicals (rates of ca. 10^6–10^8 s^{-1}).[36] (3) 1,6-C=O and 1,5-C=C closures (rates $\geq 10^5$ s^{-1}).[32,71,73,74] (4) β-Scissions (10^5–10^8 s^{-1}).[32] (5) 1,5-C=O closures.

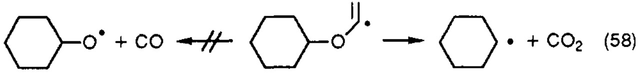
Subphase II: intramolecular processes with rate constants $\geq 10^3$. (1) 1,6-C=C, and 1,5- and 1,6-C≡N closures (rates of ca. 10^4 and 10^3 s^{-1}, respectively).[32] (2) 1,5 and 1,6 hydrogen shifts to carbon.

Subphase III: (1) 1,7-C=C closures (ca. 10^2 s^{-1})[32] and 1,3-C=O or C≡N closures. (2) Intermolecular additions and large (>10-membered) ring closures.

Subphase IV: 1,3-C=C closures.

Exit points exist between each subphase to avoid formation of spurious products, e.g., intermolecular additions are not considered if 5- or 6-membered ring closures are possible. The competitions within a subphase are considered in greater detail within the appropriate context; some rules applied by the program are provided below.

1. **α-Fragmentations.** α-Scissions of sulfonyl and acyl radicals are always permitted, although decarbonylation is considered a minor process if the trapping rate level (TLVL) is 1 or other subphase I processes are available (recall Section IIB-3). Furthermore, when competition exists between decarbonylation and decarboxylation, the latter is preferred, as in eq 58.[112]

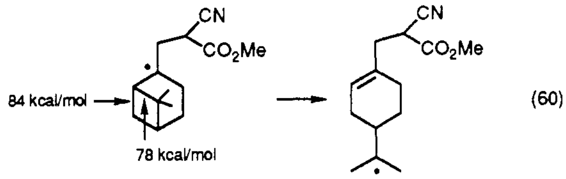


(58)

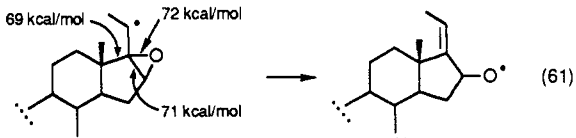
2. **β-Fragmentations.** Cleavage of bonds β to the radical atom is considered according to the criteria discussed in Section IIB-3b, i.e., possibilities for (1) ring strain relief, (2) formation of C=O or C≡N π bonds, and (3) fragmentation of σ bonds with BDE $\leq$ 70 kcal/mol.

1. Small ring cleavages: (a) Cyclopropyl radicals contain only one eligible β bond and yield an allyl radical, as in eq 59.[113] (b) If the radical atom is α to a 3- or 4-membered ring, β bonds considered for fragmentation are limited to those within that ring and the weakest of these is selected for cleavage. (c) If the radical atom is α to an epoxide ring, the β C–O bond fragments unless the β C–C bond possesses a bond dissociation energy of $\leq$65 kcal/mol. Equations 60–62 provide examples.[31,88,89,98]

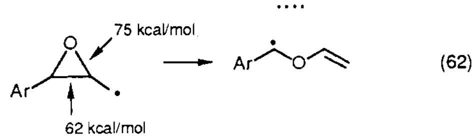
(59)



(60)



(61)



(62)

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[109] Walling, C. *Tetrahedron* **1985**, *41*, 3887.

[110] for examples, see: (a) reference 9, p 79. (b) Krause, G. A.; Landgrebe, K. *Tetrahedron* **1985**, *41*, 4039. (c) Keck, G. E.; Enholm, E. J.; Yates, J. B.; Wiley, M. R. *Tetrahedron* **1985**, *41*, 4079. (d) Keck, G. E.; Byers, J. H.; Tafesh, A. M. *J. Org. Chem.* **1988**, *53*, 1127.

[111] Based upon rate data where available; otherwise empirical rules are derived from numerous examples where competition is possible.

[112] Hartwig, W. *Tetrahedron* **1983**, *39*, 2609.

[113] Sustman, R.; Gellert, R. W. *Chem. Ber.* **1976**, *109*, 345.

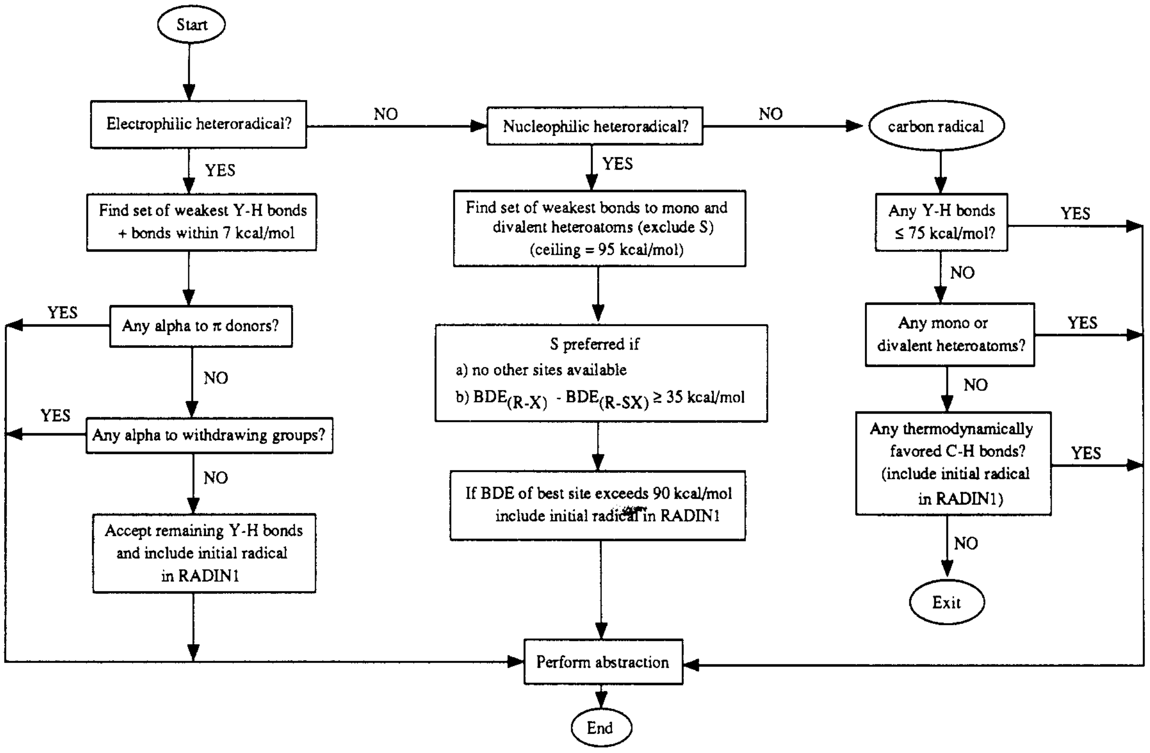
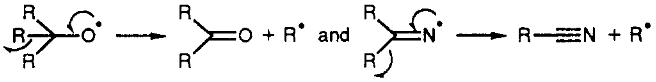


Figure 4. Flowchart for intermolecular abstraction (S_H2) reactions.

2. Fragmentations forming π bonds: Fragmentations of oxy and iminyl radicals, i.e.,

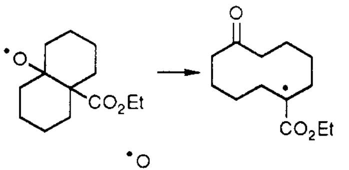


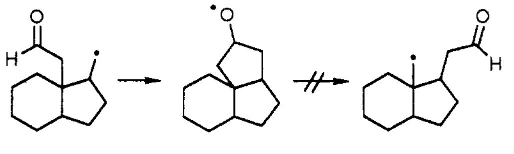
occur with the following restrictions:

(a) The weakest β bond is selected for cleavage. The upper BDE limit is 78 kcal/mol; if other subphase I processes are available, formation of simple primary radicals is prohibited.

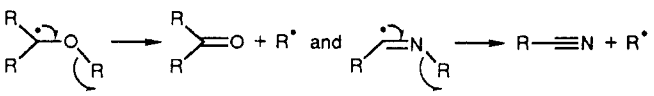
(b) If loss of CO_2 or CSO is possible, the upper limit is 106 kcal/mol.

These BDE ceilings are implemented to avoid fragmentation to primary alkyl or unstabilized radicals if other possible reactions exist. In fact, all accounts of radical ring expansion by addition/oxy radical elimination involve fragmentation of activated bonds, as in eq 63.[90,114] Consistently, aldehyde migration is not observed in eq 64.[73] However, CO_2 or CSO loss permits even aryl radical formation, as in eq 49.


(63)


(64)

(c) Fragmentation from carbon radicals to form polarized π bonds, i.e.,

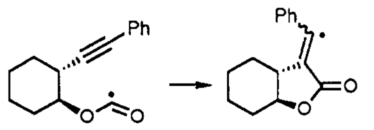


also requires that R$^\bullet$ is not primary or otherwise unstable unless no subphase I–III alternatives exist, as in eq 50 and 53.

3. β-Cleavage of simple σ bonds is considered last and occurs only when the estimated BDE does not exceed 70 kcal/mol, e.g., for systems such as those found in Table V. The weakest candidate bond plus others with a BDE within 2 kcal/mol are permitted to fragment.

3. Ring Closures. Radical cyclization reactions are complex enough to warrant special treatment. Eligible sets of bonds are found according to the reactivity hierarchy outlined above. The selected bonds are then analyzed individually with a specialized algorithm that determines the relative feasibility of exo and endo ring closure. Structural information is accumulated such as the size of the new ring, the cis/trans relationship of the joining termini, and the types of atoms and bonds residing in the path between the radical atom and the bond in question. The following restrictive rules apply to formation of 7-membered or smaller rings:

1. Ring closure is prohibited, if (a) a triple bond or trans double bond resides in the path, (b) a 1,3-closure is not promoted by a bridgehead atom in the path (simple cyclopropyl formation *is* permitted if *no* other possibilities exist), or (c) the termini bear a trans relationship about a ring and are nonvicinal. For example, the closure in eq 65 occurs because the substituents are on adjacent ring atoms, so they may become proximal via a diequatorial conformation.[115]


(65)

2. Endo ring closure is excluded (a) for simple 5-hexynyl radicals, (b) when formation of a bridged ring would occur for a 5-hexenyl system, (c) when closure involves a terminal

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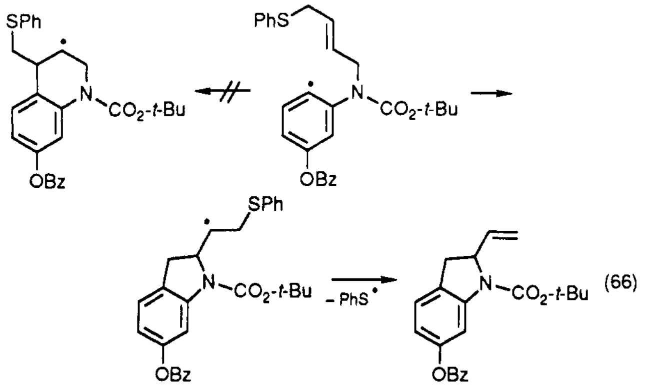
(114) Dowd, P.; Choi, S.-C. *J. Am. Chem. Soc.* **1987**, *109*, 3493, 6548.

(115) Bachi, M. D.; Bosch, E. *Tetrahedron Lett.* **1986**, *27*, 641.

Table VIII. Ranking of Ring Closure Products

condition	exo closure	endo closure
uncyclized radical is stabilized	minor	major
crowded exo atom	disfavored	major
1,6-C=O closure is available	minor	disfavored
amidyl radical/terminal bond	disfavored	major
amidyl radical/nonterminal bond	major	minor
row-1 heteroatom resides in the path	major	disfavored
Si atom in path	minor	major
default condition	major	disfavored

$C\overset{\cdot\cdot\cdot}{=}X$ bond, or (d) when the corresponding exo closure product would subsequently undergo rapid fragmentation, e.g.,[106]



3. Formation of a bridged ring system is not allowed, if (a) the radical can fragment rapidly, (b) the closure involves a $C\overset{\cdot\cdot\cdot}{=}X$ bond, (c) the closure is strained by ring fusions or bridges already residing in the path, or (d) closure to form a fused ring system is possible.[116]

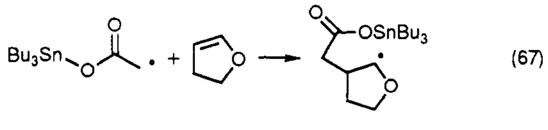
4. Cis double bonds in the path yield only endo closure for additions to double (not triple) bonds.

If both exo and endo closures are permitted, the cyclization program ranks the products as "major", "minor", or "disfavored" according to the criteria in Table VIII. These designations appear when the product is displayed at the graphics terminal.

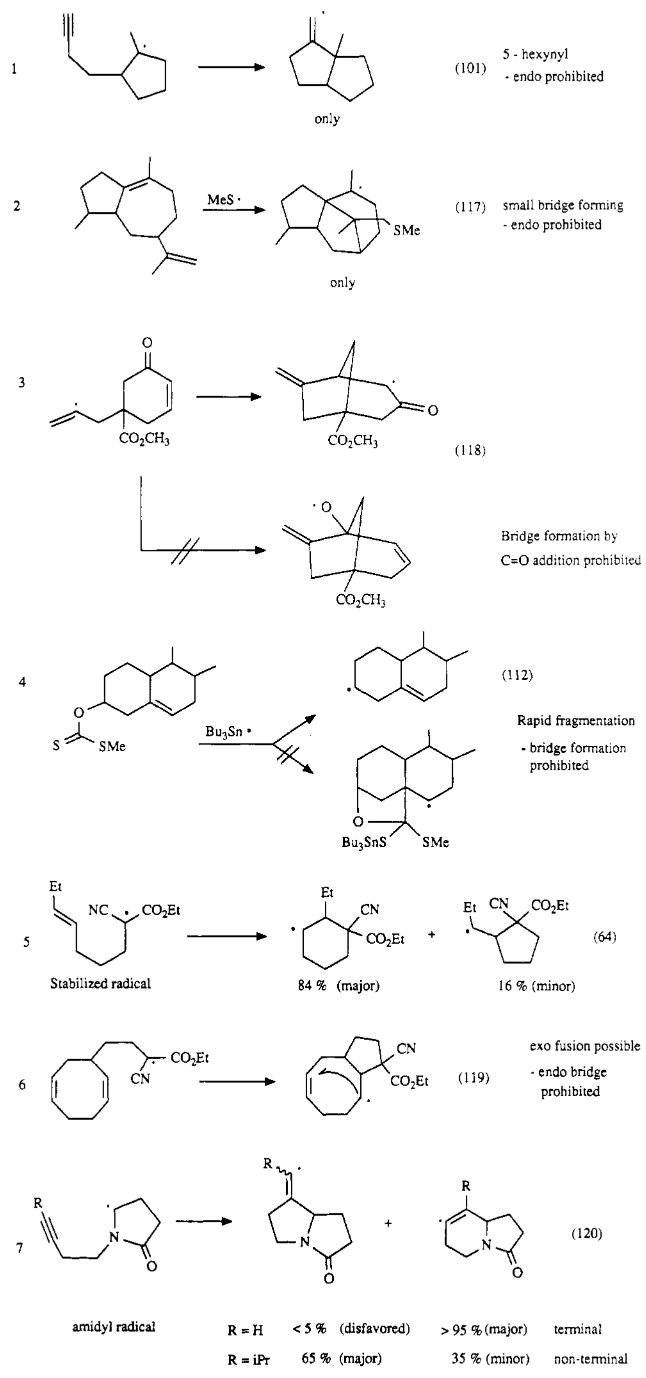
Examples illustrating these restrictions and rankings are considered in Scheme II and the schemes that end this paper. Note that the restrictive rules have precedence over the ranking rules of Table VIII. For example, comparison of entries 5 and 6 of Scheme II indicates that bridge prevention has priority over the usual favoring of endo closure for a stabilized radical.

4. Intermolecular Additions. The rules for intermolecular addition are straightforward and are also used for closures of large rings (>10 atoms).

1. For electrophilic radicals, multiple bonds with attached electron-donating groups are preferred for attack, as in eq 67.[121]

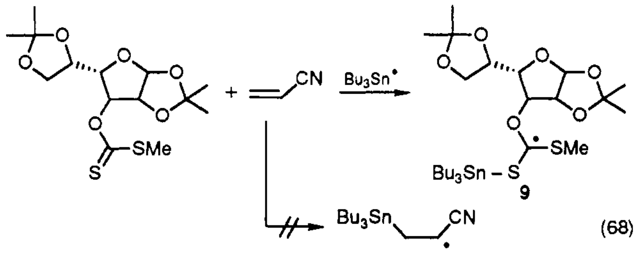


Scheme II[a]



[a] References in parentheses.

2. If the radical is nucleophilic, addition to reactive polarized multiple bonds is considered first (e.g., eq 68).[122] The order of selection is: $R_2C{=}S > NO_2$, N=C:.



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(116) Peishoff, C. E.; Jorgensen, W. L. *J. Org. Chem.* **1985**, *50*, 3174.

(117) Kuehne, M. E.; Damon, R. E. *J. Org. Chem.* **1977**, *42*, 1825.

(118) Marinovic, N. N.; Ramanathan, H. *Tetrahedron Lett.* **1983**, *24*, 1871.

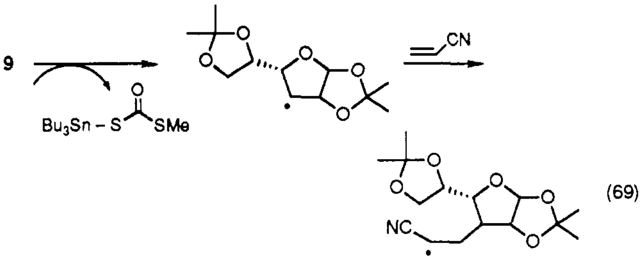
(119) Winkler, J. D.; Sridar, V. *J. Am. Chem. Soc.* **1986**, *108*, 1708.

(120) Burnett, D. A.; Choi, J. K.; Hart, D. J. *J. Am. Chem. Soc.* **1984**, *106*, 8201.

(121) Ref 110b.

(122) Giese, B.; Gonzâlez-Gômez, J. A.; Witzel, T. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 69.

3. If the radical is nucleophilic and no reactive polarized bonds are available, multiple bonds with attached electron-withdrawing groups are selected, as in the continuation of eq 68:

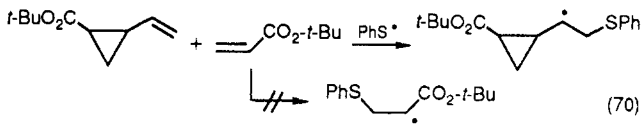


(69)

4. For the chosen bond(s), the atom β to the origin atom of the polar group is designated as the site of attack (cf. eq 67).

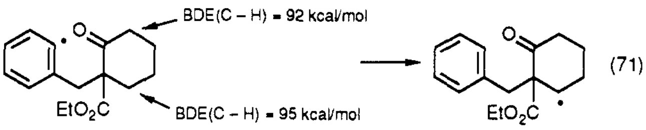
5. Among electronically competitive attack sites, the least hindered is preferred.[123]

6. If no bonds of appropriate polarity are located, steric hindrance becomes the sole criterion, i.e., the olefinic atoms with the fewest attachments become the sites of attack. Among sterically similar sites, those involving bonds of less desirable polarity are avoided, as in eq 70.[124,125]



(70)

5. Intramolecular Abstractions. Intramolecular abstractions are presently limited to 1,5- and 1,6-hydrogen migrations and occur only when the abstraction is thermodynamically favored by a minimum of 10 kcal/mol.[126] Geometrically accessible 1,5- and 1,6-abstraction sites of appropriate BDE are located; 1,5 sites are preferred even when the BDE exceeds that of available 1,6 sites by up to 3 kcal/mol, as in eq 71.[90]



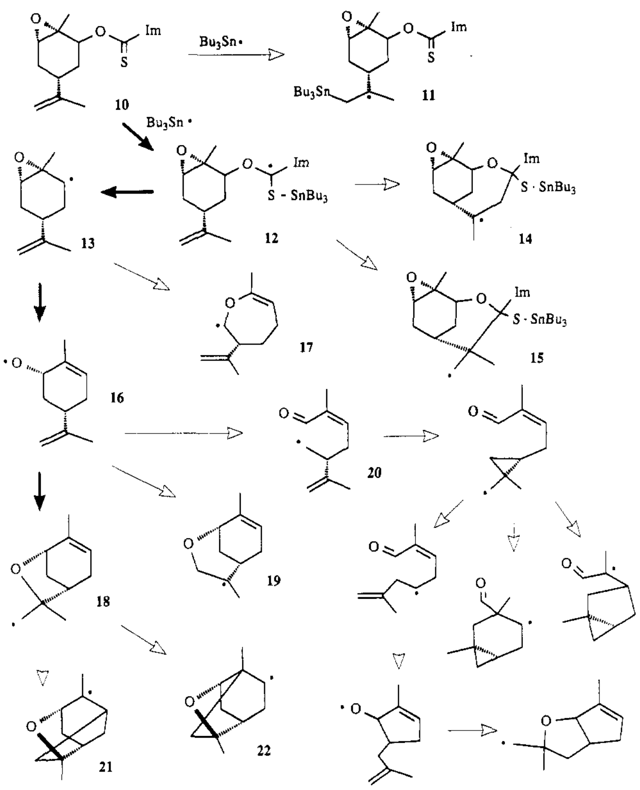
(71)

F. Resubmission of Intermediates. The preceding discussions concentrate on isolated steps of radical chain reactions. Each intermediate generated during the advanced propagation phase is considered for resubmission and analysis for subsequent reactions. Intermediates are briefly scanned for (1) fast ring closure sites (i.e., 1,5- and 1,6-, and certain 1,3- closures), (2) rapid fragmentations, (3) intermolecular additions, and (4) 1,5- and 1,6-hydrogen migration sites. If any of these possibilities exist, the radical is resubmitted and subjected to the detailed analysis discussed above.

Another consideration deals with avoidance of repeated addition and fragmentation of the same atoms during product formation sequences. For example, the atom which has been expelled during a fragmentation process is not permitted to add to the same site; likewise scission of a bond formed by addition is prohibited.

G. Radical Trapping. The fourth phase of the free radical module involves product formation in an implied chain-transfer step. The atom or fragment designated during the initiation or abstraction phase is created and bonded to the radical species. This simulated abstraction step circumvents the need to recreate an explicit chain transfer agent.

Scheme III[a]



[a] Faint arrows indicate spurious paths that are considered and rejected.

Certain intermediates are prevented from trapping, e.g., closures forming 3-membered rings are not trapped unless no other reactions can occur and the subsequent ring opening is redundant, or the uncyclized radical contains an intervening bridgehead atom (e.g., eq 32). Likewise, structures capable of rapid fragmentation of weak σ bonds are not trapped. The initial radical of the chain is also ignored in the trapping phase to prevent trivial production of the starting material.

IV. Example Reaction Sequences

The hallmark of the free radical module in CAMEO is its simulation of chain processes with full mechanistic detail. The philosophy dictates that each radical be submitted to each of the simple algorithms described in the preceding sections. Allowing the simulated chain to self-propagate provides ample opportunity for potential side reactions as well as known major pathways. Several schemes from the synthetic literature are presented here to emphasize the complexity of free radical reactions and the ability of CAMEO to recreate multistep transformations while avoiding a plethora of undesirable products. In the accompanying discussions, rules affecting propagation decisions are described fully in Section IIIE and are referred to by the notation *subsection number-rule number.*

The repetitive nature of the free radical module suggests that an excessive number of intermediates could be generated. Scheme III illustrates this problem in detail. In this attempt to form *cis*-carveol (**16**-H),[88] the nucleophilic stannyl radical locates no abstractable atoms and is thus submitted directly to the advanced propagation phase.

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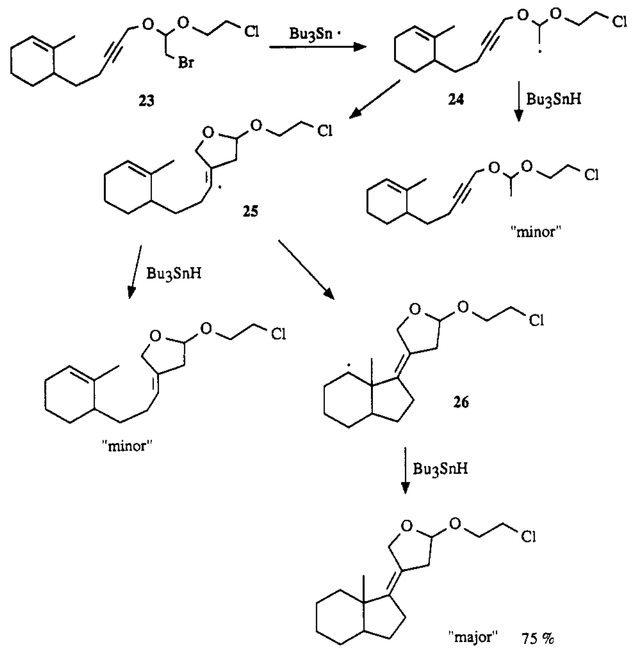
[123] Giese, B. *Chem. Ber.* **1984**, *117*, 3175.

[124] Feldman, K. S.; Romanelli, A. L.; Ruckle, R. E.; Miller, R. F. *J. Am. Chem. Soc.* **1988**, *110*, 3300.

[125] Bonds of inappropriate polarity are accepted if no other options exist. The products of such additions are labeled as disfavored, and an explanatory comment is issued.

[126] Based upon comparison of known migration reactions.

Scheme IV

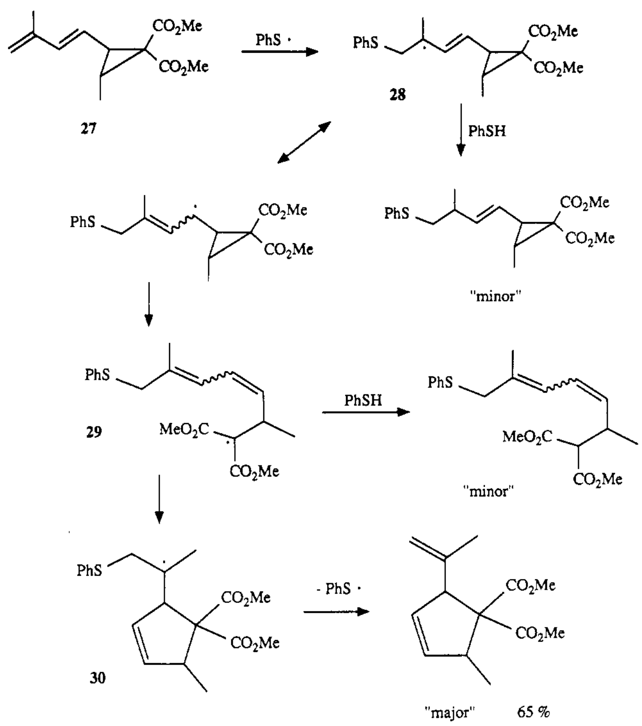


Intermolecular addition to the polarized multiple bond of thiocarbonyl imidazolide **10** is considered first (rule 4-2), and formation of adduct **11** is avoided. Adduct **12** is formed and undergoes β scission to form a C=O π bond in preference to the exo and endo closures to give **14** and **15** (subphase I vs subphase II). A second β-fragmentation is the only possible process for radical **13**; the β C–C BDE estimate exceeds 65 kcal/mol, and rule 2-1c indicates that fragmentation to **16** is the sole process. Oxy radical **16** has several subphase I options: exo/endo closures, 1,5- and 1,6-hydrogen migrations at the allylic sites (not shown), as well as a third fragmentation. However, formation of primary radical **20** is not competitive with the possible ring closure (rule 2-2a), and the hydrogen shifts are geometrically poor. In addition, only the exo closure to form bridged **18** is permitted; endo closure is inhibited when small bridge formations are involved (rule 3-2b).

A second 1,5-ring closure site exists for **18**. Formation of **21** and **22** are considered and rejected (rule 3-3c). The reaction analysis ends with trapping of **12** as a minor component[127] and **16**-H and **18**-H as the major products, carveol and pinol, respectively. Experimentally, normal addition of Bu_3SnH/AIBN to **10** produced 16% carveol and 18% pinol.[88] The remaining intermediates of Scheme III would result from further propagation of **20**; these are *not* considered, due to the previous rejection of **20** itself. Their inclusion in the scheme emphasizes the need for selectivity at all stages of processing. Similarly, **17** would promote another series of inappropriate addition/elimination products.

Scheme IV presents Stork's well-known tandem cyclization.[128] Several features of radical control are evidenced here: (1) Bromine abstraction is specific. Abstraction of either Br or Cl results in a primary radical; control is via the relative bond dissociation energies (68 vs 81 kcal/mol).[98] (2) The first cyclization shows alkynyl radical closure specificity (rule 3-2a). (3) Vinyl radical **25** possesses several thermodynamically favorable hydrogen migration sites. For carbon radicals, these subphase II reactions cannot compete with the ensuing subphase I ring closure. (4) The second radical addition is also limited to the exo mode. Endo addition would lead to a bridged ring system and is uncompetitive with formation of fused **26** (rule 3-3d). (5) Further cyclization of **26** to a cyclopropylcarbinyl radical is rejected (rule 3-1b).

Scheme V



All three intermediates are trapped by CAMEO, although products from **24** and **25** are not reported in the literature.[128] Acyclic and monocyclic products *are* isolable with sufficient stannane concentrations;[129] thus, trapping of viable intermediates is considered competitive when rapid chain-transfer agents are involved. Such products are designated as minor, however, when the parent radical is capable of subsequent reactions, as in this example.

Miura et al. have reported a vinylcyclopropane-cyclopentene rearrangement.[130] This novel sequence is portrayed in Scheme V. No hydrogens α to appropriate polar groups are available for abstraction by the electrophilic sulfuryl radical, and the lack of polar groups also results in steric control of addition to **27**. Attack of the initial radical at the least hindered olefinic site provides allylic radical **28**, whose resonant form is recognized as a cyclopropylcarbinyl radical with an activated β bond. Ring opening generates dicarboxylate radical **29**, with one bond eligible for ring closure and a double bond of undefined stereochemistry in the closure path. The program recognizes a cis component in intermediates of mixed stereochemistry and permits resubmission as well as trapping of intermediate **29**. Endo closure is generally favored for such stabilized radicals (cf. Table VIII) and is *exclusive* for radicals with cis double bonds in the reaction path (rule 3-4). The imminent weak bond fragmentation of exo closure intermediate **30** has priority, however, and endo closure does not compete (rule 3-2d). Expulsion of the

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[127] Yields of trapped thiocarbonyl adducts are not commonly reported, but their trapping is possible at lower temperatures and high hydride concentrations. See: Barton, D. H. R.; Subramanian, R. *J. Chem. Soc., Perkin Trans. 1* **1977**, 1718. Barton, D. H. R.; McCombie, S. W. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1574 and reference 53.

[128] Stork, G.; Mook, R. *J. Am. Chem. Soc.* **1983**, *105*, 3720.

[129] Beckwith, A. L. J.; Moad, G. *J. Chem. Soc., Perkin Trans. 2* **1975**, 1726.

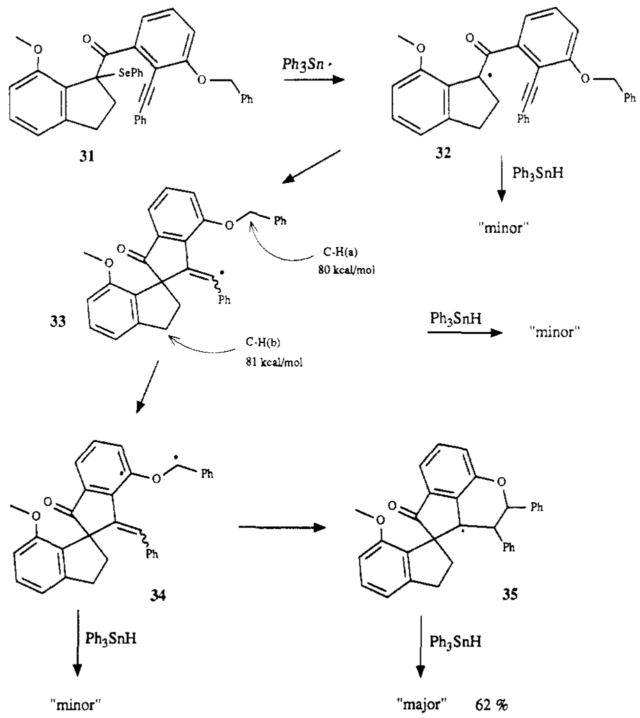
[130] Miura, K.; Fugami, K.; Oshima, K.; Utimoto, K. *Tetrahedron Lett.* **1988**, *29*, 1543.

Table IX. Representative CBE Values in CAMEO (kcal/mol)[a]

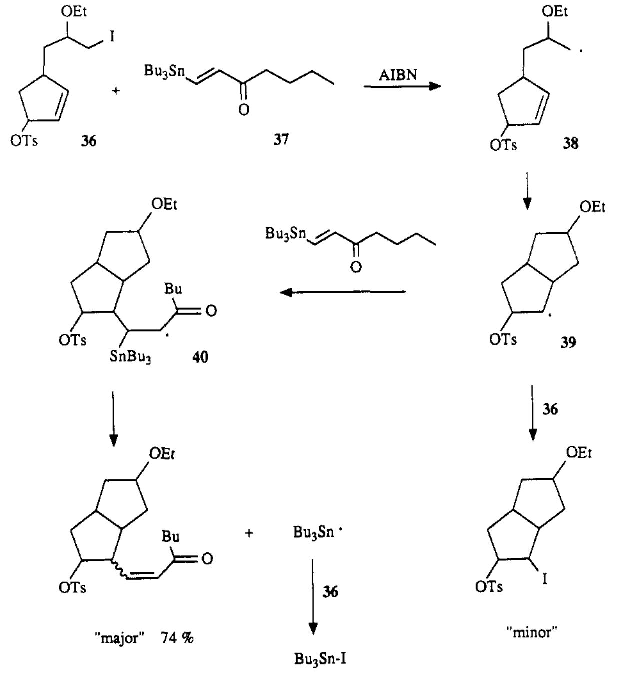
H	O	N	C	Cl	Br	I	Si	S	Sn	
104	104	110	98	103	87	71	99	88	65	H
	51	53	91	52	48	56	108	–	98	O
		39	84	46	40	–	–	–	70	N
			88	81	68	53	72	73	69	C
				58	–	–	87	61	94	Cl
					46	–	74	52	83	Br
						36	56	–	62	I
							81	–	–	Si
								60	70	S
									50	Sn

[a] Data from ref 135.

Scheme VI



Scheme VII



weakly bound Ph–S group (BDE estimate: 58 kcal/mol[98]) results in the major product.

During their syntheses of spiro compounds related to fredericamycin A, Bennett and Clive[131] found that hydrogen migration can result in an "interrupted" tandem cyclization, as in Scheme VI. The phenylselenyl group provides the sole abstraction site, and only exo closure is permitted for alkynyl radical **32** (rule 3-2a). Reactive vinyl radical **33** contains two possible intramolecular abstraction sites: 1,5-C-H_b is thermodynamically favored, but is geometrically inaccessible, so 1,6-C-H_a is preferred. The resultant **34** cannot fragment to give benzaldehyde and an aryl radical (the O-aryl BDE estimate exceeds 78 kcal/mol), as per rule 2-2c. Propagation is thus limited to a second cyclization and further restricted to endo ring closure (giving **35**) due to the "cis" double bond in the path provided by the aryl ring (rule 3-4).

This section concludes with Keck's elegant free-radical allylation reaction applied in a concise total synthesis of $PGF_{2\alpha}$ (Scheme VII).[132] This key step in the synthesis begins with AIBN homolysis and abstraction of iodine from **36**. The ring closure has priority over any intermolecular addition (subphase I vs subphase III). Closure of **38** gives only the fused intermediate **39** (rule 3-3d). Addition to the vinyl tin agent **37** is under electronic control to form **40** (rules 4-3 and 4-4). The allylation product results from β-fragmentation of **40**, generating $Bu_3Sn^\bullet$ as the chain carrier.

Table X. Representative Correction Factors (E_c) for Hybridization and Ring Strain of Atoms A and B in Bond A–B (kcal/mol)

type	E_c, kcal/mol	comments
3-ring[a]	+6	(+4 for C–halogen bonds)
4-ring[a]	+3	
5- or 7-ring[a]	−2	
vinyl	+10	
aryl	+13	(+18 for Ar–OR and Ar–NR_2)
propargyl	+27	
polarized double bond	−10	(for C–C)
	−5	(for C–H)
	+17	(for C–heteroatom)
polarized triple bond	+36	(+27 for C–H)

[a] Ring contributions apply when the A–B bond is exo only.

V. Conclusion

The CAMEO program has been expanded to include the analysis of free radical chain reactions. The module follows mechanistic logic and mimics chain processes by iterative treatment of viable intermediates. Evaluation requires segregation of processes into discrete phases for initiation, propagation, and termination steps. In addition, proper gauging of competitions for important propagation steps

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(131) Bennett, S. M.; Clive, D. L. J. *J. Chem. Soc., Chem. Commun.* **1986**, 878.

(132) Keck, G.; Burnett, D. A. *J. Org. Chem.* **1987**, *52*, 2958.

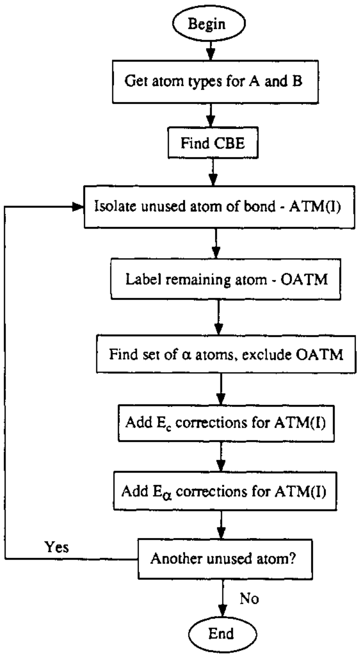
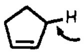
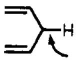
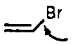
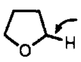
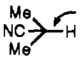
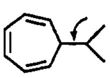
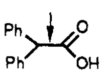


Figure 5. Flowchart for BDE estimates.

Table XI. Representative Contributions (E_α) to BDE by α-Substituents

α group	E_α, kcal/mol	comments
alkyl, silyl	-3	
aryl	-15	(some bond type dependence)
vinyl	-10	(some bond type dependence)
propargyl	-4	
polarized triple bonds	-5	(-10 for C-C bonds)
polarized double bonds	-3 → -6	(considerable bond type dependence)
heteroatoms (O, N, S)	-4	(+2 if acid derivative)

Table XII. Example BDE Estimates

bond	CAMEO estimate, kcal/mol	lit. value[a]
	$98-10_{\text{allyl}} - 3_{\text{alkyl}} - 2_{\text{ring}} = 83$	82 (105)
	$98 - 2(10)_{\text{allyl}} = 78$	80 (105)
	$68 + 10_{\text{vinyl}} = 78$	76 (21, 96)
	$98 - 4_{\text{hetero}} - 2_{\text{ring}} = 92$	92 (21)
	$98 - 2(3)_{\text{alkyl}} - 5_{\text{C=X}} = 87$	87 (105)
	$88 - 2(10)_{\text{allyl}} - 5_{\text{conj}} - 2(3)_{\text{alkyl}} = 57$	57 (21)
	$88 - 2(15)_{\text{benzyl}} - 3_{\text{C=X}} = 55$	52 (28)

[a] References for BDE values in parentheses.

is aided by the development of rules based on kinetic observations. The reaction schemes that close this paper demonstrate (1) the synthetic utility of free radical reactions in accomplishing complex transformations with a single reaction chain, (2) the importance of evaluating these multistep reactions in the stepwise fashion presented, and (3) the ability of the program to predict both major and important side products of free radical reactions.

Acknowledgment. Gratitude is expressed to the National Science Foundation for support of this work and to Dr. Roberto Rozas for assistance at the outset of the project.

Appendix: Estimation of Bond Dissociation Energies

From the preceding discussions, it is clear that analysis of free radical reactions requires that the homolytic bond dissociation energies (BDEs) of reactants be known or calculated. An algorithm has been implemented in CAMEO that allows estimation of BDEs for σ bonds. The method is patterned after Sanderson's radical "reorganization" energies.[133]

Sanderson's concept defines the BDE of bond A-B as

$$\text{BDE} = \text{CBE} + E_{\text{R}}(\text{A}) + E_{\text{R}}(\text{B}) \qquad (72)$$

where CBE = the contributing bond energy, i.e., that part of total atomization energy that bond A-B contributes, and E_{R} = the energy consumed or released by reorganization of the bonding in the resultant radicals. If the liberated bonding electron influences the remaining bonding such that it becomes stronger, energy is released that decreases the energy required for bond dissociation. If the remaining bonding is weakened, energy is absorbed in the reorganization and the BDE is increased correspondingly. A negative reorganization energy thus corresponds to a relatively stabilized radical; such values are a convenient measure of substituent influence upon radicals and bond energies.

Equation 72 has been modified for CAMEO as

$$\text{BDE(A-B)} = \text{CBE(A-B)} + E_{\text{c}}(\text{A}) + E_{\text{c}}(\text{B}) + \sum E_\alpha \qquad (73)$$

where CBE(A-B) = BDE for the simplest organic molecule containing the bond A-B, E_{c} = correction factors for the hybridization, ring strain, etc., of atoms A and B, and E_α = contribution by groups attached to atoms A and B. The calculation is convenient in that consideration of only the groups directly attached to atoms A and B is sufficient,[21] and that the effects are generally additive.

A flowchart for the program is given in Figure 5. Once atoms A and B have been identified, the CBE is retrieved from a small database containing bond energies for the simplest organic molecules containing the bond under consideration.[134] For example, CBE for carbon-carbon bonds is 88 kcal/mol, corresponding to the bond energy in ethane.[39] Table IX provides representative values.[135] The CBE value is then augmented by corrections for the bonded atoms and the influence of any α substituents. As an example, the C-C σ bond of propene is evaluated by considering a CBE of 88 kcal/mol plus an additional E_{c} of 10 kcal/mol for the vinylogous nature of one atom. Representative values for these E_{c} and E_α contributions are found in Tables X and XI, respectively, and example BDE estimates are given in Table XII. The correction factors were developed by considering reported bond dissociation energies for over 550 bonds,[135] and estimates are generally within reported experimental errors (2-4 kcal/mol).

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(133) Sanderson, R. T. *J. Org. Chem.* **1982**, *47*, 3835.

(134) The exception is C-H, for which the base value of 98 kcal/mol is taken from ethane.

(135) Data and examples for bond dissociation energies obtained from ref 21, 28, 96, 97, and 105. See also: Wentrup, C. *Reactive Molecules*; John Wiley & Sons: New York, 1984. McMillen, D. F.; Golden, D. M. *Ann. Rev. Phys. Chem.* **1982**, *33*, 493. Benson, S. W. *J. Chem. Ed.* **1965**, *42*, 502. Neumann, W. P. *The Organic Chemistry of Tin*; John Wiley & Sons: New York, 1970.