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Homolytic Substitution: A Molecular Ménage à Trois

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Nucleophilic versus Homolytic Substitution

The concept of nucleophilic aliphatic substitution has been a key organizing principle in organic chemistry ever since it was first clearly defined by C. K. Ingold and coworkers.[1] The phenomenal importance of nucleophilic substitution as a means of rationalizing the behavior of smaller molecules in chemical transformations and of larger species in enzyme-mediated processes can hardly be over emphasized. It is also of enormous practical value in functional group manipulations, in the stereocontrol of bond-forming reactions, and in numerous annulations. In the limiting bimolecular version of nucleophilic substitution (S_N2), a nucleophile with a nonbonding pair of electrons (R^-) forms a bond to molecule AL, which loses group L^- complete with its pair of nonbonding electrons:

$$R^- + A{-}L \rightarrow [R\text{- - -}A\text{- - -}L]^{-\ddagger} \rightarrow R{-}A + L^- \qquad (1)$$

In the limiting unimolecular version (S_N1), the bond between A and L breaks before approach of the nucleophile.

There exists an analogous free radical process with many mechanistic similarities to eq 1, but with a very different range of applicability, notably in that the attacked atom A can rarely be carbon. Bimolecular homolytic substitution (S_H2) may be a concerted process in which a free radical forms a bond to A, with simultaneous homolytic scission of the A−L bond and loss of the group L complete with one electron:

$$R^\bullet + A{-}L \rightarrow [R\text{- - -}A\text{- - -}L]^{\bullet\ddagger} \rightarrow R{-}A + L^\bullet \qquad (2)$$

Stepwise versions are also known in which radical $R^\bullet$ attaches itself to AL, giving an intermediate $(RAL)^\bullet$ which subsequently undergoes unimolecular decomposition. This fleeting or prolonged molecular "ménage à trois", i.e. $[RAL]^\bullet$, may be likened to a threesome relationship familiar from human society in the round. A large special category of S_H2 reactions contains processes in which atom A is univalent (hydrogen or halogen). These reactions are generally called atom abstractions and are not the focus of this review.

The steric requirements of nucleophilic and homolytic substitutions at a given atom A are obviously very similar. Electronically, the same frontier orbitals will be populated, doubly and singly occupied in the two cases. Reactants, the transition state, and products may (or may not) be charged in (1), and hence, solvation will play a more important role than in the electronically neutral homolytic substitution. In individual cases this may decisively favor nucleophilic displacement, but the reverse will also occur. There are, therefore, no global kinetic or thermodynamic factors which would disfavor (2) in comparison with (1). Broadly speaking then, S_H2 reactions are expected to be as common as S_N2 reactions. Taking the periodic table as a whole this may eventually prove to be true. However, organic and biological chemistry revolve largely around carbon, other first-row elements, and comparatively few elements with higher atomic numbers. The S_H2 reaction is favored when the A−L bond is both weak and nonpolar. When A is a first-row element, bonds are either strong so that homolysis is difficult or polar so that heterolysis is preferred. A second adverse factor in homolytic substitution is that the attacking radical $R^\bullet$ has available fast alternative pathways which energetically compete with the displacement process. For example, coupling reactions,

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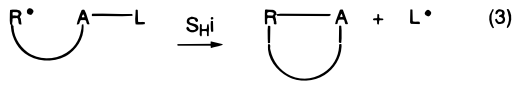
$2R^{\bullet} \rightarrow R_2$, are extremely rapid for neutral radicals (unlike charged nucleophiles), as are hydrogen abstraction reactions from alkyl chains of the reactants. For these reasons, S_H2 reactions at carbon are only common for molecules where the C−L bond is notably weak, as in small strained rings and in certain organometallics with C−Co or similar bonds.

Homolytic substitution is a far less mature area of chemistry than nucleophilic substitution. A thorough review of work up to the early 1970s gave a useful map of the main features.[2] The immense success of free radical methodology in organic synthesis over the past decade has led to a corresponding exponential growth in the discovery and exploitation of homolytic substitutions. Of particular note are intramolecular homolytic substitutions (S_Hi) in which the attacking radical is tethered to the A−L part of the molecule so that expulsion of radical $L^{\bullet}$ is accompanied by ring formation:

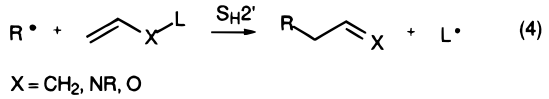


(3)

Atom A can only be carbon in exceptional circumstances, and in the majority of examples studied to date, it is oxygen, sulfur, or selenium. In practice, the number of known variants of this new annulation is climbing, and a diverse range of heterocycles is being prepared.[3]

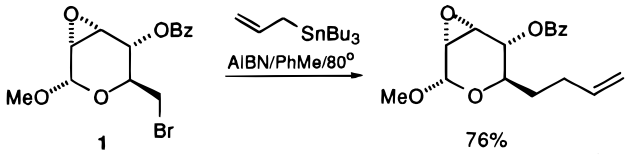
Homolytic Allylations

The vinylog of the homolytic substitution reaction comprises addition of an initial radical to an allyl compound, concerted with, or followed by, loss of an outgoing radical, and is known as the S_H2' process:

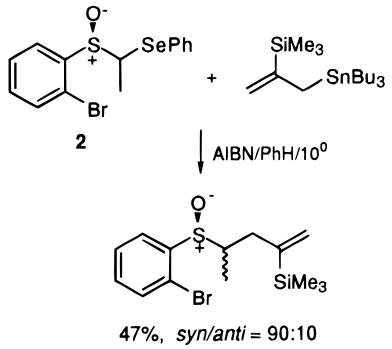


(4)

The outgoing radical $L^{\bullet}$ may be a halogen atom or a thiyl radical $RS^{\bullet}$, but is most frequently $R_3Sn^{\bullet}$, and allyltrialkylstannanes have found considerable use as reagents for allylations.[4] Ketal, lactone, ester, epoxide (**1**), and free



hydroxyl functional groups are tolerated. Best yields are obtained when the initial radical $R^{\bullet}$ is electrophilic. Significant stereoselectivity in the addition stage has been observed with initial radicals containing chiral elements, for example, with radicals derived from carbohydrates[4] and with ortho-substituted aryl sulfoxides such as[5] **2**. Analogous substitutions have been observed with alkynylstannanes, which give the corresponding allenes, and with (alkenyloxy)stannanes, which introduce a 2-oxoalkyl unit into an alkyl halide.[6]



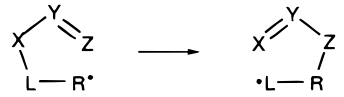
47%, *syn/anti* = 90:10

S-(Tris(trimethylsilyl)silyl)thiopropene (**3**) is a sophisticated alternative for allylation of alkyl halides.[7] The mechanism embodies a 1,2 migration of a silyl group from silicon to sulfur in the intermediate thiyl radical **4**, which unmasks the silicon-centered radical **5** for selective generation of $R^{\bullet}$ from the alkyl halide (or selenide) (Scheme 1). Note the analogy with the $(Me_3Si)_2Si(Me)SH$-mediated reductions of alkyl halides.[8]

A further development of this process deploys allyl, allenyl, or alkynyl cobaloximes,[9,10] The most successful reagents are organobis(dimethylglyoximato)pyridines (**6**) (Scheme 2), which react with electrophilic radicals to afford allyl compounds together with $Co^{II}(dmgH)_2py$ (**7**). The displaced cobalt complex **7** is instrumental in generation of the initial radical in the second stage of chain propagation. Analogous displacement reactions have been observed with allyl complexes of other transition metals specifically[10,11] Fe, Rh, Ir, and Cr.

Free Radical [2,3]-Migrations

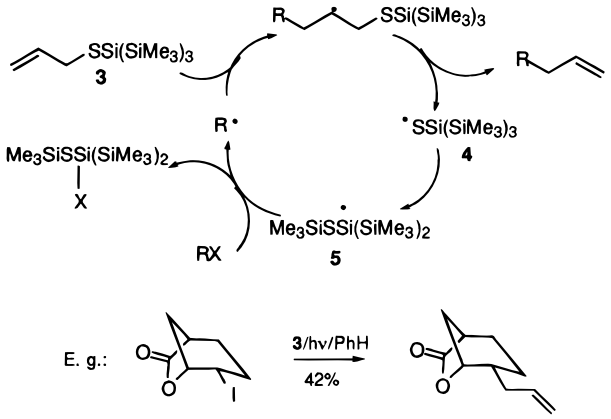
The allylation has several informative intramolecular analogues in which an allyl type unit (the three component) is transferred to an adjacent radical center of the two component, i.e. **8** to **9**. The best known involves



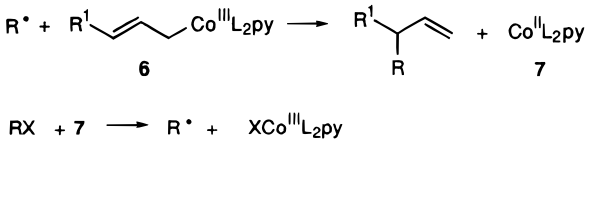
migration of an acyloxy group from C_β to the adjacent radical center[12] in a suitably constituted β-(acyloxy)alkyl radical (**10**) (Scheme 3). Dissociative mechanisms, i.e. elimination followed by re-addition, were ruled out because the intermediate acyloxyl radical [RC(O)O•] would decarboxylate too readily. 2,5-Dioxacyclopentyl radicals were shown not to be intermediates by EPR spectroscopic studies and by independent generation. Experiments with ^{18}O-labeled radicals demonstrated that migration of the acyloxy group involved complete transposition of the ether and carbonyl labels, except in the 5-α-(acetyloxy)cholestan-7-yl radical.[13] The evidence favors a concerted mechanism via a cyclic 5-center−5-electron transition state (**11**) but suggests that the 3-center−3-electron transition state (**12**), and possibly a solvent caged radical-cation/anion pair, may contribute in some circumstances.[14]

Rate constants for acetyloxy migration are on the low side for preparative purposes, but 2-deoxy sugars **14**,

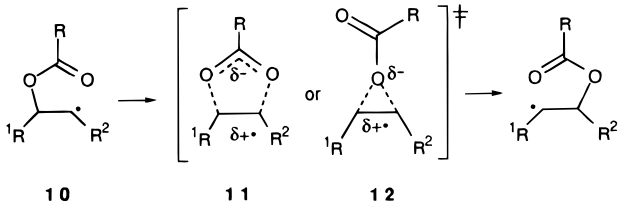
Scheme 1



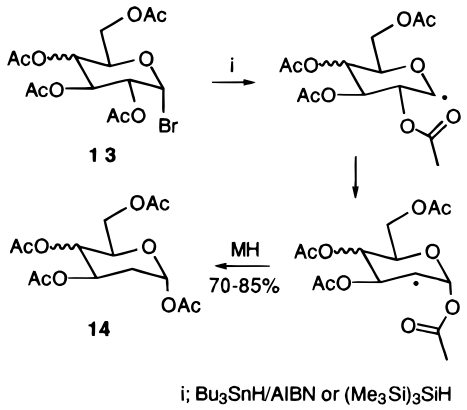
Scheme 2



Scheme 3

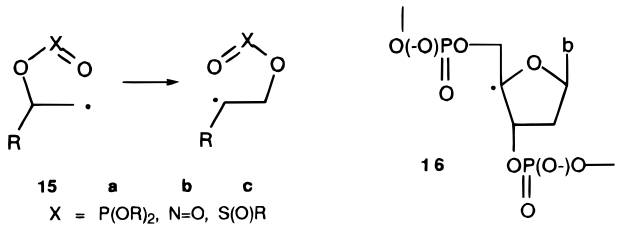


Scheme 4

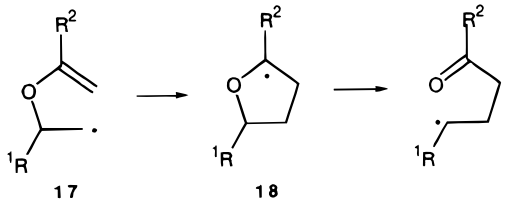


which are needed as precursors of compactin, olivomycin, and other natural products, were prepared in good yields by slow addition of a metal hydride to glucosyl or galactosyl bromides[15,16] (**13**, Scheme 4). The acyloxy migration has also found use as a method for contraction of seven-membered- to six-membered-ring lactones.[17]

The β-(phosphatoxy)alkyl rearrangement[18,19] (**15a**) takes place via transition states analogous to **11** and **12**, although in polar solvents, elimination/re-addition competes.[14] This migration has provoked considerable interest because radicals derived from antibiotics such as bleomycin and neocarzinostatin[14,20] attack DNA with, among other things, the formation of deoxyribonucleosyl radicals centered at the 4′-position, i.e. β-(phosphatoxy)alkyl radicals **16**. Migration of phosphatoxy groups occurs faster than that of acyloxy groups and has been utilized in an alternative synthesis of 2-deoxy sugars.[19]

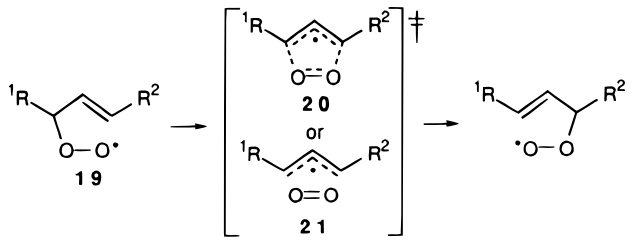


The analogous rearrangements of β-(nitroxy)alkyl[21] **15b** and β-(sulfonaloxy)alkyl radicals[21] **15c** occur efficiently but have been little studied. Isolation of tetrahydrofuran derivatives suggested that rearrangements of β-(vinyloxy)-alkyl radicals **17** proceed in two steps via tetrahydrofuranyl radicals **18** which fragment to the final product.[22]

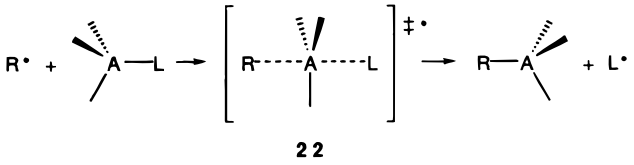


In the much-studied [2,3]-allylperoxyl rearrangement (Schenck rearrangement), a peroxyl unit is transferred from one end of an allyl group to the other. The main practical importance of this process lies in its effect on the composition ratio of hydroperoxides formed in the autoxidation of unsaturated lipids.[23,24] For instance, the proportions of the six hydroperoxides formed in the autoxidation of methyl oleate were shown to depend on competition between hydrogen abstraction and [2,3]-rearrangement of the intermediate allylperoxyl radicals.[24] That the migration does not occur in a two-step process by endo-cyclization of **19** to produce a localized dioxolanyl radical, which subsequently undergoes β-scission, was demonstrated by product studies with designer hydroperoxides[25] and by separate generation of authentic dioxolanyl radicals. The rearrangement is highly stereoselective and, for example, (*S*)-methyl-9-peroxyloctadec-10(*E*)-enoate (**19**-H, $R^1 = n\text{-}C_7H_{15}$, $R^2 = (CH_2)_7CO_2Me$) rearranges with inversion to give (*R*)-methyl-11-peroxyloctadec-10(*E*)-enoate.[26] This is consistent with a concerted mechanism via a five-membered-ring transition state **20** or with a caged allyl−oxygen pair **21**, which undergoes re-addition without stereochemical degradation[25,27,28] (Scheme 5). Data on oxygen uptake during the autoxidations of methyl oleate[29] and 7α-hydroperoxy-3β-hydroxycholest-5-ene[27] implied that the most probable transition state was **21**, which may have substantial charge-transfer character.[24]

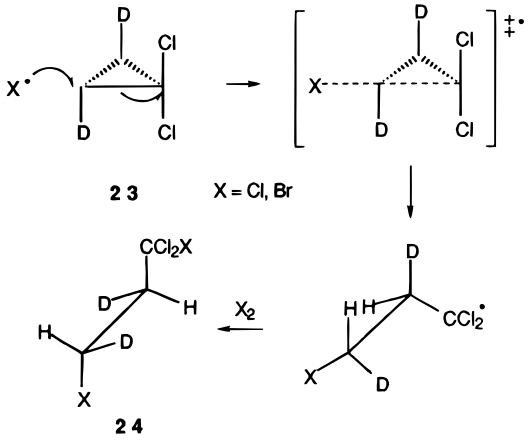
Scheme 5



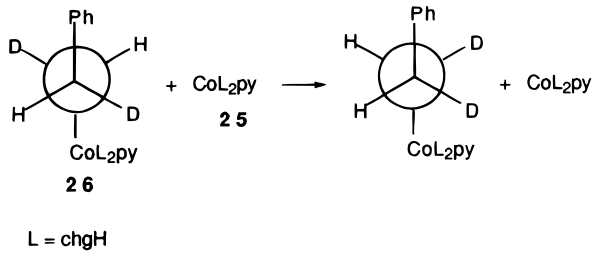
Scheme 6



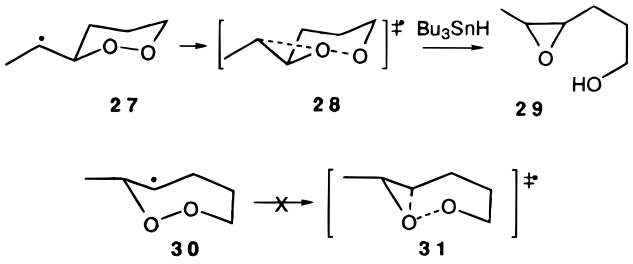
Scheme 7



Scheme 8



Scheme 9



Stereochemistry of Homolytic Substitutions

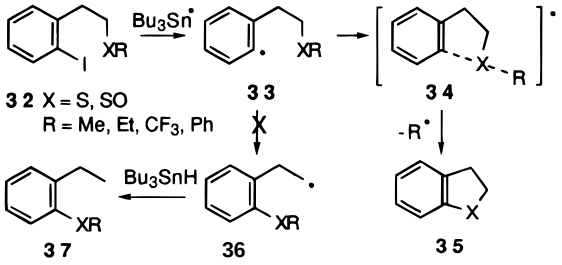
A notable feature of orthodox S_N2 reactions is that substitution is accompanied by complete inversion at the attacked center. This property is the foundation of the leading role played by nucleophilic substitutions in asymmetric syntheses. In the interests of realizing the full synthetic potential of homolytic substitutions, it is essential that their stereochemical path be equally well understood. Standard VSEPR considerations suggest that the lowest energy transition state for homolytic attack at an sp^3 center will be trigonal bipyramidal **22**, which implies "backside" approach by the incoming radical, a collinear arrangement of the three central atoms, and inversion of the original configuration, exactly as in an S_N2 process.

Applications of the classical stereochemical tests to this scheme have been hindered by the scarcity of S_H2 reactions at potentially chiral centers. Heroic experiments were carried out in the 1970s with chiral cyclopropanes such as 1,1-dichloro-2,3-*trans*-dideuteriocyclopropane (**23**), ring opening of which by both chlorine and bromine atoms[30] gave >96% of the erythro isomer of product **24** (Scheme 7). This, together with other halogenation studies,[31] established that the displacement step occurred with complete inversion at the attacked center.

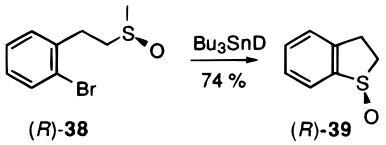
A disturbing possibility was that this high stereoselectivity might not be representative of S_H2 reactions unfettered by strained cages. The discovery of homolytic displacements at the α-carbon atom of alkylcobaloximes enabled classical methods to be deployed.[32] Complete inversion of configuration was observed in the reaction of bis(cyclohexanedionedioximato)pyridinylcobalt (**26**) with the corresponding dideuterated *β*-phenylethyl cobaloxime **25** (Scheme 8).[32,33] The intramolecular substitution reaction of sulfonyl radicals at the α-carbon atom of cobaloximes was also shown to occur with significant steroselectivity.[10] Several studies of the stereochemistry of halogen displacement at chiral sp^3-hybridized carbon atoms, by recoil halogen atoms in the gas phase, e.g. in diastereomeric 3-bromo-4-fluorohexanes, have demonstrated extensive inversion.[34,35] The evidence is therefore virtually unanimous that homolytic substitutions at C atoms proceed with inversion as depicted in **22**. Carbon-centered radicals displace alkoxyl radicals from a variety of cyclic and acyclic peroxides. Although oxygen atoms cannot display chirality, indirect probes of the geometry of the substitution step were designed around cyclic peroxides in which the O−O bond and the radical center were structurally constrained. For example, dioxolanylalkyl radical **27** was generated from the corresponding bromide and rapid intramolecular attack at the O−O bond afforded epoxyalcohol **29**, after hydrogen abstraction.[36] In the transition state of this S_Hi process, C• and the two oxygens can easily attain a collinear arrangement **28** in which the C•−C−O−O dihedral angle is ca. 180°. In dramatic contrast, the rate constant for epoxidation of **30** was nearly 6 orders of magnitude less. In the dioxepan-4-yl structure collinear approach is prevented so that S_Hi access is side-on only (**31**) with a C•−C−O−O dihedral of ca. 60°. Several additional examples[36,37] established that the collinear configuration must be attainable for successful epoxide production.

Atoms from the second and subsequent rows of the periodic table expand their valence shells with comparative ease, and hence, stepwise mechanisms via intermedi-

Scheme 10

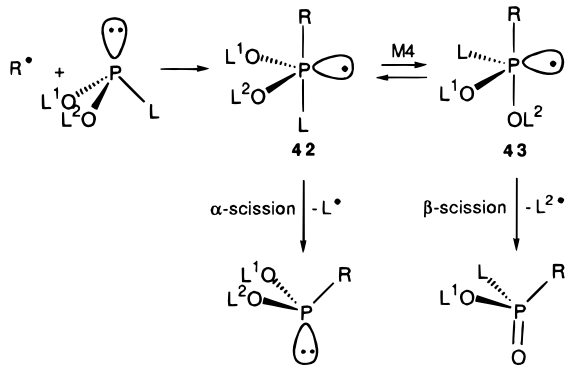


ates with appreciable lifetimes become real possibilities.[38] Displacements at sulfur take place efficiently in sulfides, sulfoxides, disulfides, etc., thus providing ample scope for study of the stereochemistry. As with oxygen, radicals specially designed for competition of differing S_Hi (and other) processes were examined. Aryl radicals **33** generated from the corresponding alkyl 2-(2-iodophenyl)ethyl sulfides or sulfoxides **32** afforded dihydrobenzothiophene (or the corresponding oxide) **35** along with minor amounts of the direct reduction products.[39] None of the 2-ethylphenyl sulfides **37**, derived from the alternative displacement yielding radical **36**, were observed, even when the radical displaced in forming **35** was thermodynamically less stable (Me$^\bullet$, $CF_3^\bullet$, Ph$^\bullet$). The preference for formation of **35** cannot, therefore, be ascribed to differences in leaving group ability but depends instead on the fact that a collinear arrangement of the three centers (**34**) can easily be attained during displacement of R$^\bullet$, whereas the cyclic structure prevents collinearity in the formation of **36**. Definitive evidence of a linear "backside" inversion pathway was provided by a study of the reaction of chiral sulfoxide (*R*)-**38** with tributyltin deuteride,[40] which afforded (*R*)-2,3-dihydrobenzothiophene 1-oxide [(*R*)-**39**] in an ee ≥ 98%. Thus, the exo ring closure proceeded with complete inversion of configuration[41] through a quasi-trigonal bipyramidal structure in which the entering and leaving groups occupied apical sites.

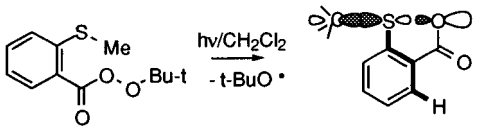


The evidence from product studies did not enable a distinction to be made between a two-step mechanism via an intermediate in which pseudorotation was slow compared to scission and a concerted substitution in which structures such as **34** were transition states. A fair number of sulfuranyl radicals $X_3S^\bullet$ [9-S-3 species, i.e. 9-electron, 3-valent], with one or more strongly electronegative ligands, have sufficient lifetimes for observation in solution by EPR spectroscopy and have been assigned quasi-trigonal bipyramidal structures.[42] That these sulfuranyls can be intermediates in homolytic substitutions was neatly demonstrated by an EPR spectroscopic study[43] of the photolytic decomposition of perester **40**. The spectrum of **41** showed hyperfine splittings from the methyl hydrogens and a single aromatic hydrogen. Together with other data, this led to the conclusion that **41**

Scheme 11



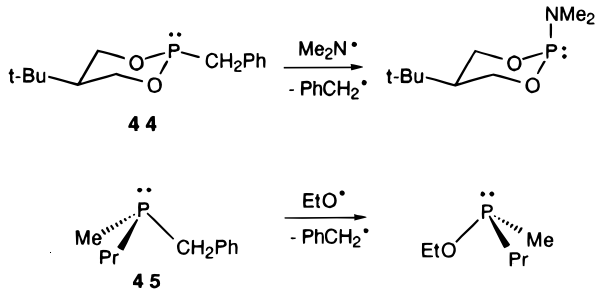
contained a 3-center−3-electron σ-bond. Note the single aromatic hydrogen which is all-trans with respect to the σ-orbital containing the unpaired electron (W-plan).



$R_3S^\bullet$ radicals *without* electronegative substituents have not been detected spectroscopically,[44] and their lifetimes have been the subject of much speculation. Kinetic data for S_Hi ring closure of 4-(alkylthiyl)butan-1-yl radicals suggested a product-like transition state, i.e. no discrete sulfuranyl intermediates.[45] Selenuranyl radicals $R_2Se^\bullet-X$ with electronegative ligands have also been observed in solution by EPR spectroscopy and ascribed quasi-trigonal bipyramidal structures.[46]

Free radical attack on trivalent phosphorus (and arsenic) compounds results in *addition*, affording 9-P-4 species, i.e. phosphoranyl radicals (and 9-As-4 arsoranyl radicals) with appreciable lifetimes. The structures, reactivities, and stereochemistries of their reactions have been assiduously investigated by EPR spectroscopy and by chemical means.[47−49] Phosphoranyls of type $RP^\bullet L(XL)_2$ fragment in two main ways: cleavage of the P−L bond (α-scission) and cleavage of an X−L bond (β-scission). α-Scission corresponds to overall homolytic substitution at P (Scheme 11). Frequently this is a two-stage process, but it may be concerted if the displaced radical is stablized. In general, β-scission is considerably more exothermic than α-scission, but this is offset by faster rates for α-scission, and hence, products from both processes are often isolated. For reaction of *t*-BuO$^\bullet$ with $ZP(OEt)_2$, α-cleavage predominates for Z = $PhCH_2$, *t*-Bu, Et, PhO, and Bu_2N, whereas β-scission predominates for Z = Ph and RO.[47] Overall inversion during substitution at P has been demonstrated[50] for several cyclic phosphites such as **44** and for phosphines such as **45**.

The overall stereochemistry can be deceptive because of rapid ligand permutational isomerization. EPR spectral studies of the intermediate phosphoranyl radicals[47] demonstrated that their structures are usually quasi-trigonal bipyramidal (TBP) with the unpaired electron considered



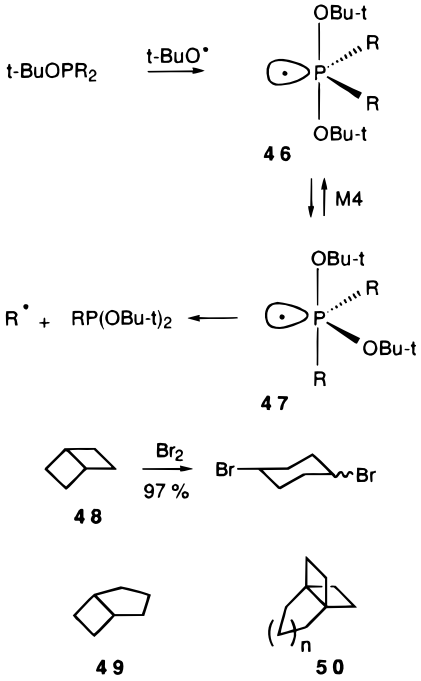
as a phantom ligand, e.g. **42**. In these species, the unpaired electron occupies a 3-center σ^*-molecular orbital composed of P σ-orbitals in an antibonding combination with appropriate orbitals from two apical ligands. Most arylphosphoranyls are exceptions, having structures resembling phosphonium-substituted aromatic radical anions. A wealth of EPR spectroscopic evidence established that acyclic and cyclic TBP phosphoranyls undergo rapid apical−equatorial ligand exchange,[47] which was corroborated by stereochemical studies with a range of cyclic phosphites.[47−49] Generally, ligand apicophilicity increases with electronegativity. Five "modes" of ligand exchange have been described (M1 to M5) and have aroused considerable theoretical interest.[47] The majority of evidence favors the M4 mode, an example of which is shown above (**42** → **43**). The mechanism is probably intramolecular and may proceed via species with quasi-tetrahedral P atoms. Kinetic studies of the decay of phosphoranyl radicals with a range of apical and equatorial ligands gave strong evidence that the radical loss in α-scission occurs preferentially from an apical site.[50,51] For example, when *tert*-butoxyl radicals added to dialkylisobutoxyphosphines, the only detectable phosphoranyl radical was **46** with two apical *tert*-butoxy ligands. However, it was inferred from the relative rates of alkyl radical loss that an M4 isomerization to **47**, containing an apical alkyl ligand, preceded α-scission.[50,51] Equilibrium was established between **46** and a minor amount of isomer **47** from which loss of the apical alkyl group occurred.

Firm experimental evidence is lacking about the direction of approach of the attacking radical in the addition step. It is usually assumed, however, that R• enters apically because addition is the microscopic reverse of α-scission and because MO calculations favor this.

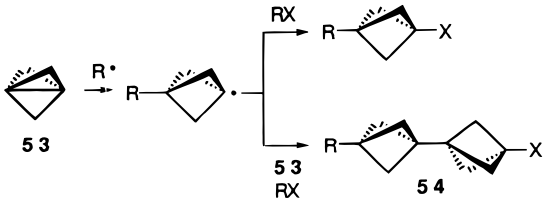
New Homolytic Displacements at Carbon

The notion that homolytic substitution at carbon is confined to halogenation of cyclopropanes has now been thoroughly laid to rest. Trifluoromethyl radicals displace methyl radicals from 2,2-dimethylpropane,[52] and although radical attack on monocyclobutanes occurs exclusively by hydrogen abstraction,[53] ring cleavage supervenes for C−C bonds shared by two four-membered rings. For example, the brominations of bicyclo[2.2.0]hexane[54] (**48**) and [*n*.2.2]-propellanes[55] **(50)** (but, interestingly, *not* bicyclo[3.2.0]-heptane (**49**)) cleanly gave the corresponding dibromides. Photobromination of cubane **51** launched a cascade which produced a single stereoisomer of tricyclo tetrabromide

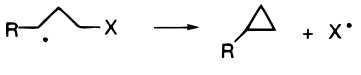
Scheme 12



52 as the sole product[56] (Scheme 13). The cross-cage "bond" in [1.1.1]propellane **53** is certainly rather special, but it is cleaved[57−60] to afford bicyclo[1.1.1]pentane derivatives and oligomeric "staffanes" (**54**) by alkyl, acyl, thiyl, phosphorus-centered,[61] and other radicals. [1.1.1]Propellane is easily made,[62] thus affording a practical entry to many bridgehead substituted bicyclo[1.1.1]pentanes.



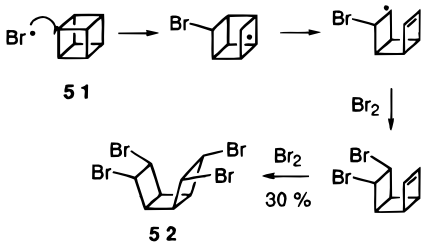
Homolytic cleavage of three-membered rings has been probed in many mono- and polycyclic compounds; it is less well-known that the reverse displacement with formation of cyclopropane derivatives occurs in propyl radicals containing suitable 3-substituents (**55**). Displace-



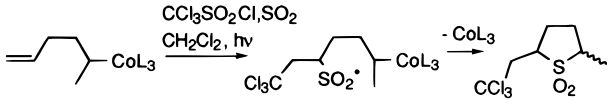
55 R = alkyl, alkoxy.
X = Cl, Br, Me_3Sn, Co(III), Fe(II)

ments of halogen atoms,[63−65] trimethyltin radicals,[66] and cobalt and iron species[67] all afford cyclopropanes. Photoaddition of electrophilic radicals to the double bond of but-3-enylcobaloximes generated substituted propyl radicals which closed to three-membered rings in yields as high as 75% by S_Hi reaction at the carbon atom α to cobalt.[68,69] Furthermore, radical addition to hex-5-enylcobaloximes afforded pentyl radicals which cyclized to produce cyclopentane derivatives by displacement of a Co(II) group.[70] Functionalized sulfolanes **56** were made

Scheme 13



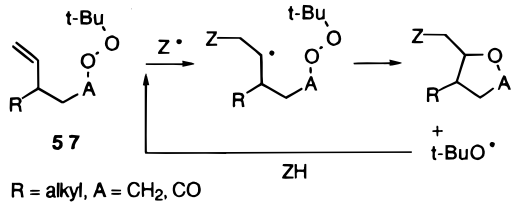
in good yields, and with significant enantiomeric purity, by reaction of trichloromethanesulfonyl chloride with pent-4-enylcobaloximes[71] or by use[68] of CCl_4 under an atmosphere of SO_2.



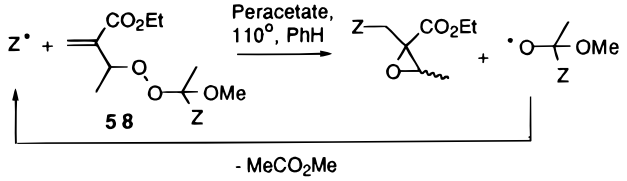
CoL_3 = Co(dmgH)$_2$py **56** 70 %, 65 % ee

Applications in Organic Synthesis

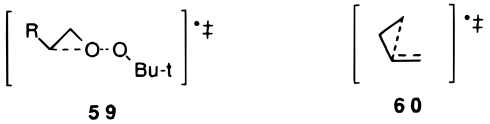
Bimolecular homolytic substitutions involving organotin compounds, aryl selenides, and aryl sulfides are routinely used for radical generation in preparative work. Synthetic possibilities of homolytic allylations and of 2,3-migrations have been outlined above, as well as the uses of cobaloximes and [1.1.1]propellane. Recent research has identified a range of S_Hi ring closures (eq 3) suitable for the preparation of heterocycles. Radical additions to alkenyl peroxides **57** initiate chain processes which culminate in



the formation of cyclic ethers or lactones. The chain-propagating radical Z• may be obtained by hydrogen abstraction from a cosubstrate (or solvent) ZH by the displaced alkoxyl radical. Good yields of oxacycloalkanes were obtained with solvents containing a single type of hydrogen, e.g. cyclohexane, CH_2Cl_2, or 1,4-dioxane.[72] The cyclic ethers were produced as mixtures of stereoisomers, but some selectivity was achieved with larger substituents R attached to the rings.[73] Depending on the length of the alkenyl chain, ring sizes from three- to six-membered were accessible but yields were best for epoxides and tetrahydrofurans. The method also gave spiranic heterocycles with oxirane, oxetane, or THF rings.[74] The rate of the S_Hi reaction increased for weaker O−O bonds, and hence, *tert*-butoxyl was preferred as the radical displaced from the peroxide or perester. An ingenious alternative embodied the displacement of an alkoxyl radical designed to immediately convert to a carbon-centered radical by cyclization, 1,5-hydrogen transfer, or fragmentation.[75,76] For example, peroxyketals **58** afforded oxiranes (45−90%) plus an alkoxyl radical which ejected a new carbon-centered radical ready to add to the double bond of **58**.



A remarkable feature of these substitutions is the ease of formation of three-membered oxirane rings. Thiirane formation has not been reported for analogous disulfide-containing radicals. Cyclization of but-3-enyl-type radicals by intramolecular addition is normally much too slow for cyclopropanes to be isolated. The transition-state geometries of the S_Hi and intramolecular addition reactions are very different (**59**, **60**), but the decisive factor



59 **60**

appears to be thermodynamic. S_Hi oxirane formation is strongly exothermic because of the weak O−O bond (37 kcal mol^{-1} in di-*tert*-butyl peroxide) compared to the S−S bond (ca. 70 kcal mol^{-1}) or the C=C π-bond in intramolecular addition (ca. 60 kcal mol^{-1}). In agreement with this conclusion, S_Hi cyclopropane formation *does* occur in propyl radicals containing weakly bound metal groups, e.g. DH°(C−Co) ~ 20 kcal mol^{-1}, or halogen atoms, vide supra. By starting with substituted allyl peroxides, the method has been used to introduce an oxiranylcarbinyl group into a range of substrates ZH.[77] The oxiranes are formed as a mixture of diastereoisomers, generally with a predominance of the *E*-isomer. If ZH contains several abstractable H atoms regioselectivity may be low. However, for H atoms flanked by ester groups, polarity reversal catalysis with an amine−borane leads to good isolated yields, at low temperatures, with high regiospecificity.[78]

A large number of successful S_Hi ring closures to heterocycles, particularly heteracyclopentanes, have been achieved recently starting from sulfides or selenides containing a good homolytic leaving groups such as benzyl, and even from compounds containing Si−Si bonds. This subject has been reviewed recently.[3]

Social Peculiarities of Free Radicals

The foregoing disclosures of the social habits of free radicals reveal that they fully live up to their name and interpret their vows of valence in the most liberal manner; especially denizens from the lower social strata of the periodic table. However, their frequently changing relationships are always preceded by a stylized courtship ritual in which spectators circulate around a linear pulsation of the principal ménage. The linear theme is rigidly adhered to, and radicals exhibiting bent or kinky tendencies are adamantly excluded from the action. This straight-laced veneer considerably curbs the conduct during intramo-

lecular liaisons. Approach of the radical center to the distal heteroatom in an ω-dichalconogenidoalkyl radical (endo approach) is effectively forbidden, except for very long chains, and hence, the exo approach to the proximate heteroatom is strongly preferred. Transannular encounters are sterile, as are approaches by axial (but not equatorial) radical centers to heteroatoms within rings. Ability to beget bi- and polycyclics is thus severely restricted. In an S_Hi annulation, the radical center becomes displaced from the ring and consequently this process can only be utilized as the final step of a cascade sequence. Many intriguing particulars of the alternative lifestyles of Bohemian radicals dwelling in the depths of the periodic table will undoubtedly emerge soon, 1,2-migrations (radical Brook rearrangements) for example. There is obvious scope for growth in the use of [2.3]-migrations, and particularly organometallics (e.g., C−Co), in homolytic substitutions because these lead to C−C bond formation with excellent possibilities for stereocontrol.

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