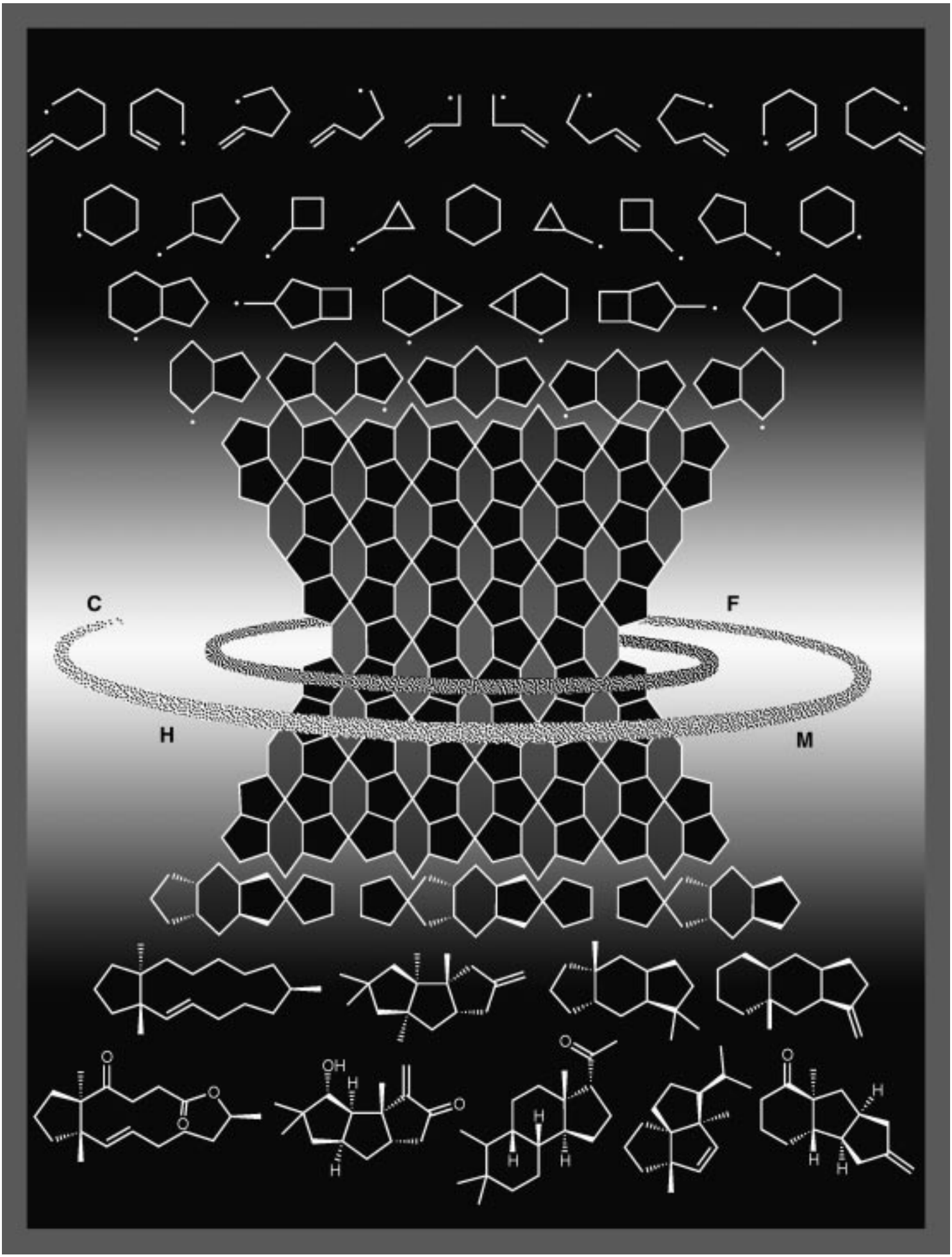

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Programming Organic Molecules: Design and Management of Organic Syntheses through Free-Radical Cascade Processes

Andrew J. McCarroll and John C. Walton*

Cascade, domino, or tandem processes, that link together two or more transformations in one pot, are increasing in popularity because they lead to improvements in synthetic efficiency and decreases in environmental impact. Not only do these cascades contain choice mechanistic gems but they also deliver compact and elegant syntheses of complex natural products. Longer cascades require more functional groups precisely configured within carefully designed initial molecular architectures. Such "purposeful" molecules can be thought of as chemical algorithms.This article surveys the phenomenal range of unimolecular free-radical cascades. A convenient system for classifying free-radical cascades is described that is useful for evaluating and comparing cascades and aids the design of synthetic routes to polycyclic structures.Double cyclization cascades lead to cyclopentylcyclopentane or bicyclo[3.3.0]octane derivatives. Precursors that contain a ring as a template have been used to control stereochemistry in syntheses of triquinanes and many related compounds. Of the cascades containing ring-cleavage steps, the most useful are the ring expansions which have opened up new synthetic routes to medium ring polycycles.The key design features of three-stage unimolecular free-radical cascades that yielded steroid structures, are linear arrays of radical acceptor units associated with methyl groups distributed every fifth C-atom in the precursor polyenes. Ring cleavage is the reverse of cyclization. In special, symmetrical structures, therefore, this led to sequences that were reversible, thus launching endlessly repeating cascades supported by delightfully fluxional structures. The science of "programming" organic molecules to achieve particular target structures is maturing rapidly. Coordination and classification of the welter of information in this area is intended to facilitate design and hence to extend the range and complexity of attainable structures.

Keywords: cyclizations · domino reactions · radical reactions · rearrangements · synthetic methods

1. Introduction

1.1. Description, Scope, and Uses of Cascade Reactions

Chemical processes in which two or more consecutive molecular transformations are intimately linked together in time and space, (that is, in "one pot"), have been variously dubbed cascade, domino, tandem, or sequential reactions. Perception and chemical understanding of such processes is still immature, but the pace of development has conspicuously quickened recently because of an emerging realization of the actual and potential advantages they possess. By means of cascade methodology, the number of discrete laboratory manipulations required for the construction of a complex target molecule can be reduced, with consequent savings in hardware, operator, and instrument time. Affiliated with this are reductions in the amounts of solvents and reagents needed and in the amounts of unwanted by-products. These factors can lead to significant improvements in synthetic efficiency and decreases in environmental impact. This potential to streamline laboratory and large-scale preparations guarantees a bright future for cascade processes.

The more steps there are in a cascade process the more functional groups must be precisely located within a carefully designed initial molecular architecture. This requirement may well offset some of the potential benefits of cascade methodology. The structure of the precursor molecule(s) must be carefully "programmed" to enable a complex, scripted, reaction coordinate to be followed, predictably bringing about a drastic configurational change, and ending in the target molecular design. Such pre-adapted precursor molecules can be described as "chemical algorithms" or, in more anthropomorphic terms, as "purposeful molecules". The precise structural information built into a precursor molecule

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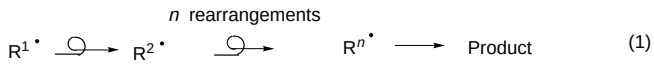
often leads to high stereoselectivity, a very desirable characteristic in synthetic organic chemistry. Well designed cascades are noted for their simplicity and elegance and have provided some of the most exquisite examples of synthetic art.

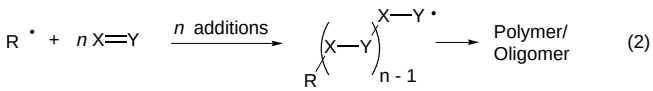
Choice cascades are also impressive specimens of complex mechanisms that test theories of bonding and reactivity to the limits. However, their main use has been in synthetic organic chemistry, particularly in the preparation of complex polycyclic molecules, including many natural products. Cascade processes occur in nature, particularly in the biosynthesis of alkaloids, terpenes, and steroids, and several illustrative examples were described by Tietze et al. in their valuable reviews of sequential transformations.[1] Cascade sequences may incorporate two or more cationic, anionic, radical, or pericyclic steps, as well as several more exotic reaction types. A broad framework for classifying these sequences in a systematic manner, based on the reaction type of the first two steps, was devised by Tietze and Beifuss.[1a] Several reviews and compilations of synthetic applications,[2] and other aspects of cascade processes,[3–5] have appeared in recent years.

This article focuses on the snowballing number of multistep processes that feature only free-radical reactions as individual steps. Cascades may, of course, encompass reactions that are intermolecular and/or intramolecular. In substitution and bond-forming processes, the latter type usually possess an inbuilt entropic advantage. Moreover, if more than one intermolecular step is incorporated into a cascade, additional reactants and/or reagents need to be introduced. Most likely this will lead to difficult if not insoluble problems of selectivity. Thus, the great majority of free-radical cascades involve sequences of intramolecular steps, the overall propagation coordinate being unimolecular (excluding initiation and termination steps) [Eq. (1)]. This review coordinates



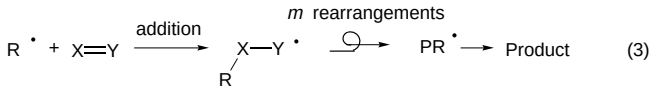
(1)

information on this particular unimolecular type of cascade. The most important alternative radical cascades are: first, comparatively unsophisticated oligomerizations and polymerizations in which many radical additions to a limited range of alkenes (or other acceptors) [Eq. (2)] take place and second,



(2)

processes for which one step, usually the first, is radical addition to a suitably functionalized acceptor [Eq. (3)]. Many instances of this latter type of radical cascade can be found in the recent literature, but for reasons of space they will not be systematically covered here.



(3)

For programming purposeful molecules, suitable for target syntheses, knowledge is needed of the allowed steps, their regio- and stereoselectivity, valid ways of coupling them together in a sequence, and preferably of individual rates. The propagation steps of a generalized intramolecular free-radical cascade process are illustrated in Scheme 1. The configured precursor molecule (S^b) is converted into the first free-radical intermediate ($R^{1\bullet}$) by the initiation step(s) (In), which may be abstraction(s) or substitution(s), as with organotin hydrides or tristrimethylsilylsilane (TTMSS), or redox processes, as with transition metal initiators. Radical intermediate $R^{1\bullet}$ then undergoes a unimolecular rearrangement that converts it into intermediate $R^{2\bullet}$ with or, better, without production of side-product B^1. The cascade can proceed through any number $(n-1)$ of unimolecular rearrangements until the final inter-

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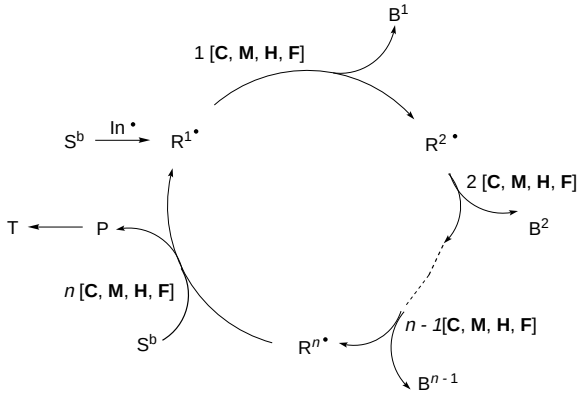


Scheme 1. Generalised intramolecular free-radical cascade. See Scheme 2 for an explanation of the abbreviations.

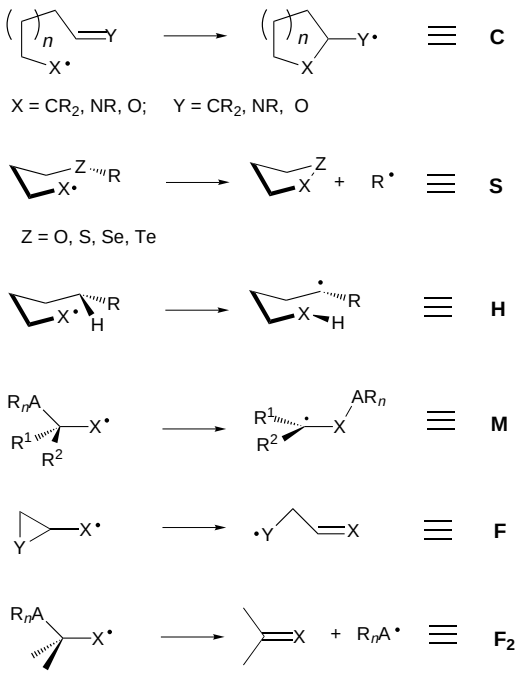
mediate $R^{n\bullet}$ converts into the desired product (P) that can itself be commuted into the target molecule (T) by means of extraneous functional group transformations which do not form part of the cascade. For many cascades the final step also regenerates the first intermediate, by reaction with more precursor, as shown in Scheme 1 (or otherwise), and the whole cascade is then a chain reaction. This chain character is not an absolute requirement for cascade status.

For a cascade to function efficiently, the rates of the individual rearrangements must be fast in comparison with termination reactions (combination, disproportionation, redox) of the $R^{x\bullet}$ intermediates and in comparison with their reactions with solvent, precursor S^b and initiator molecules. It is desirable that the final intermediate $R^{n\bullet}$ react selectively with S^b, while the rest of the intermediate radicals do not. To achieve this, the final rearrangement step needs to bring about a major change in polarity or reactivity of the propagating radical, for example, by generating an *O*-centered radical or perhaps a vinyl-type radical.

1.2. Classification of Unimolecular Homolytic Cascades

Radical rearrangements are comparatively well understood[6, 7] enabling the four major classes of unimolecular processes that take place at appropriate rates for incorporation into homolytic cascades ($k \geq 10^3\ s^{-1}$ at 25 °C) to be pinpointed. The main archetype cyclizations are summarized by the generalized equation in Scheme 2 where the symbol **C** is introduced to label them. Superscripts will be added to make individual rearrangement symbols more informative. For cyclizations, the size of ring formed, and whether ring closure is *exo* (**x**) or *endo* (**n**), will be included. The scope of this reaction is huge, but the most prevalent ring closure is 5-*exo-trig* (**C^{5x}**). Radical 6-*endo* (**C^{6n}**), and 6-*exo* cyclizations (**C^{6x}**) are not unusual and medium and macrocyclizations are also readily accomplished. Baldwin's rules give helpful guidance as to allowed and disfavored cyclization modes.[6, 8] The chain may contain many types of heteroatoms and be configured in many different ways.[9–11]

Intramolecular homolytic substitutions (S_Hi or **S**; Scheme 2) also result in cyclization.[12] The scope of this type

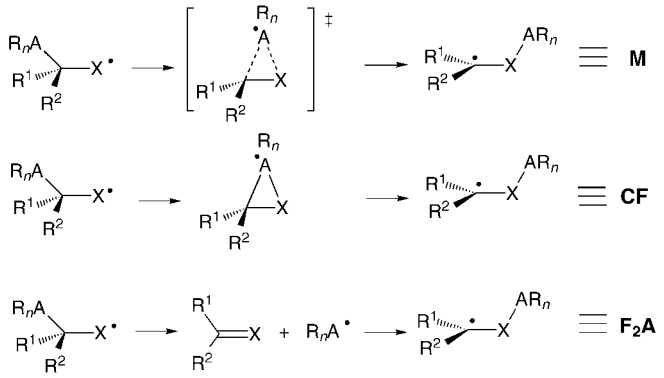


Scheme 2. Classes of unimolecular free-radical rearrangements. See text for full details.

of reaction is limited because, except for a few exotic cases, the attacked center Z cannot be carbon and is usually either oxygen or an element from the second or subsequent rows of the periodic table. Furthermore, the radical center does not remain with the main ring, but is ejected with the displaced radical. Hence these **S** type rearrangements can normally only be the final step in a cascade. The released radical $R^{\bullet}$ may lead to (deleterious) branching of the cascade. For these reasons very few cascade sequences incorporating **S** type processes are known.

The third type of process allowed in homolytic cascades is intramolecular hydrogen abstraction (**H** in Scheme 2). 1,5-Hydrogen migrations (**H^5**) are the most common, and 1,6-migrations (**H^6**) are also very well known. Occasional 1,4-shifts (**H^4**) can be found in the literature,[6, 13] but it should be noted that what may appear to be a single hydrogen shift, may in reality be two sequential shifts.

1,2-Group migrations (designated **M**) are mechanistically more enigmatic.[6] The process is akin to a homolytic substitution in which the attacked center is adjacent to the radical center. The distinction between **S** and **M** is appropriate, however, because conventional **S** reactions require "linear" transition states.[12] Carbon-centered groups, R_3C, with sp^3 hybridization do not usually undergo 1,2-migrations. Most migrations involve groups that contain some unsaturation such as in aryl, vinyl, or carbonyl, or are otherwise able to make available a low lying orbital to accept the unpaired electron during the migration. A 1,2-migration may take place as a single concerted step via a transition state (true **M** Scheme 3). It may also occur as a cyclization **C** to afford a discrete intermediate radical, followed by a fragmentation step (**CF**, Scheme 3). Another alternative is fragmentation followed by re-addition (**F_2A**, Scheme 3). This is favored by

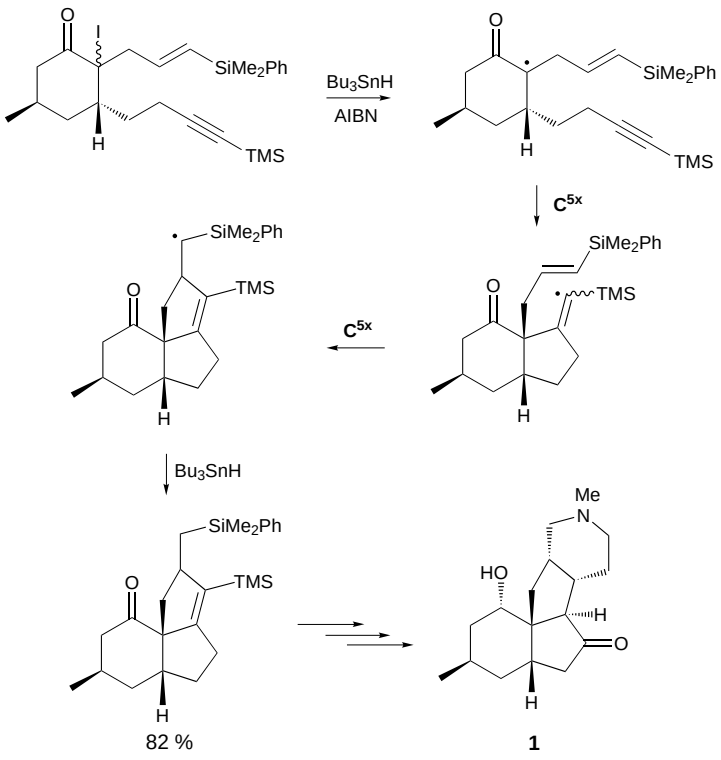


Scheme 3. Radical processes that result in overall 1,2-group migration.

halogen, sulfenyl (RS), organostannyl, and related groups. Often the exact mechanism of a "migration" will not be known, and informed guesswork may have to be used to arrive at a tentative classification for the process. In general, steps for which the overall result is group migration will be classified as **M**, unless evidence specifically points to one of the other mechanisms.

The final category of isomerization is fragmentation. Ring opening, in which a single unsaturated radical is produced (**F** in Scheme 2) is the most important manifestation of this type. This is the reverse of cyclization. Ring opening (i.e. fragmentation by β-scission) of cyclopropylmethyl and oxiranylmethyl radicals (**F**^{3}) is an extremely rapid process. Ring opening of cyclobutylmethyl and related radicals (**F**^{4}) is also rapid. However, for cycloalkylmethyl radicals containing larger rings β-scission is normally thermodynamically unfavorable and unimportant in solution. Alkoxyl radicals, however, fragment with ease at moderate temperatures and therefore ring-opening of cycloalkyloxyl radicals with small, and large ring sizes to yield carbonyl compounds is common. If an intermediate radical cleaves into two or more fragments this will usually start cascade branching. Such degradative fragmentation processes, for example, decarboxylations, can be useful in certain circumstances, and will be designated **F$_2$** (Scheme 2).

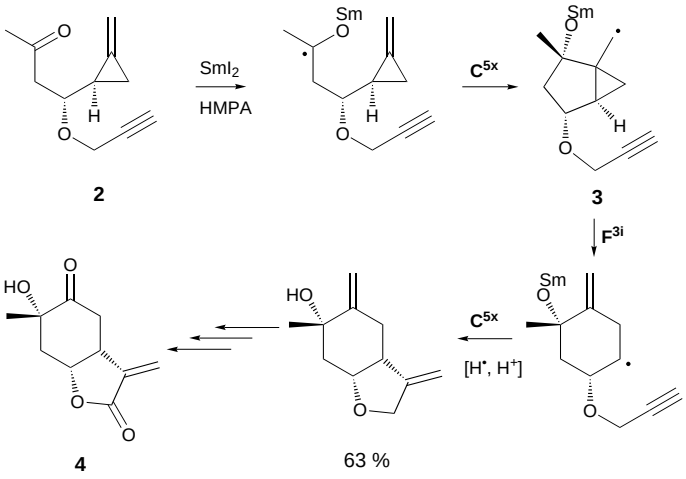
Various exotic rearrangements are known, such as Stevens-type radical-pair combinations, but these processes are not currently included in cascades and will not be examined here. Cascades are terminated by hydrogen or halogen transfer, by β-scission, by electron transfer, and in other ways. In classifying free-radical cascades only the propagation steps which form the cycle (see Scheme 1) will be considered as strict integral parts of the cascade. The initiation and termination steps do not form part of the central chain process; the same cascade can often be initiated in several different ways. In metal hydride mediated cascades the initial intermolecular halogen abstraction (or SePh displacement, etc.) that starts the sequence and the hydrogen abstraction from R$_n$MH that ends it, are not classed as part of the cascade. For example, the synthesis[14] of the (+)-paniculatine (**1**) precursor shown in Scheme 4 will be classified as a two stage, **C^{5x}C^{5x}**, cascade because propagation involves two cyclization steps. The initial iodine atom abstraction, and the final H abstraction from



Scheme 4. Double cyclization cascade route to a precursor of (+)-paniculatine **1**.

Bu$_3$SnH that terminates the cascade, are not included in the classification .

Consider also the partial synthesis[15] of paeonilactone B (**4**) (Scheme 5). This three-step cascade was launched by treatment of methylenecyclopropane derivative **2** with samarium



Scheme 5. Three-step cascade synthesis of the skeleton of paeonilactone B **4**.

diiodide. The first intermediate radical ring closed via a 5-*exo*-cyclization to generate (bicyclo[3.1.0]hexyl)methyl radical **3**. The latter selectively underwent β-scission of its inter-ring bond (**i**), rather than the outer cyclopropane bond (**o**), for stereoelectronic reasons[6, 7, 16] and was thus transformed into a substituted cyclohexyl radical. A further 5-*exo*-cyclization

assembled the 7-oxabicyclo[4.3.0]nonane skeleton, ready for conversion into lactone **4**. The designation $\mathbf{C^{5x}F^{3i}C^{5x}}$ is therefore appropriate for this cascade.

When a cascade does not proceed by a regular chain process it may be fitting to include the initial and final steps in the classification.

Matrices containing the codes of all 16 possible two-stage unimolecular cascade sequences and all 64 theoretical unimolecular three-stage cascade sequences, that can be obtained by combining the four rearrangement types **C**, **H**, **F**, and **M**, are shown in Schemes 6 and 7. Each individual two-letter code represents a range of possible cascades within a particular subtype. Further matrices could be constructed, based around the superscripts outlined above, to elaborate possibilities within each subtype. However, additional symbols to indicate heteroatoms, configurational details etc. would be needed for a thorough description. Such elaboration would probably stretch the classification beyond its limits of usefulness and will not be attempted here.

Initial step	Second step C	M	H	F
C	CC	CM	CH	CF
M	MC	MM	MH	MF
H	HC	HM	HH	HF
F	FC	FM	FH	FF

Scheme 6. The codes for two-step unimolecular free-radical cascades.

Initial step	Second step C	M	H	F	Final step
C	CCC	CMC	CHC	CFC	C
	CCM	CMM	CHM	CFM	M
	CCH	CMH	CHH	CFH	H
	CCF	CMF	CHF	CFF	F
M	MCC	MMC	MHC	MFC	C
	MCM	MMM	MHM	MFM	M
	MCH	MMH	MHH	MFH	H
	MCF	MMF	MHF	MFF	F
H	HCC	HMC	HHC	HFC	C
	HCM	HMM	HHM	HFM	M
	HCH	HMH	HHH	HFH	H
	HCF	HMF	HHF	HFF	F
F	FCC	FMC	FHC	FFC	C
	FCM	FMM	FHM	FFM	M
	FCH	FMH	FHH	FFH	H
	FCF	FMF	FHF	FFF	F

Scheme 7. The codes for three-step unimolecular free-radical cascades.

Cyclization processes are bond forming and are therefore the most significant for organic syntheses. Thus the **CC** and **CCC** cascade types in the top left-hand corners, together with types clustering in the top rows, and left-hand columns of the matrices are particularly important. The central areas of the matrices mainly represent cascades in which translocations of the radical center, and associated hydrogen atoms or functional groups, occur. Degradative cascades in which original programmed structure is largely lost by sequences of ring-opening β-scissions are represented by **FF**, **FFF**, and associated subtypes in the lower right-hand corners of the matrices. Several subtypes, particularly the multiple cyclizations, have been intensively studied, but some cascade subtypes remain unknown in reality.

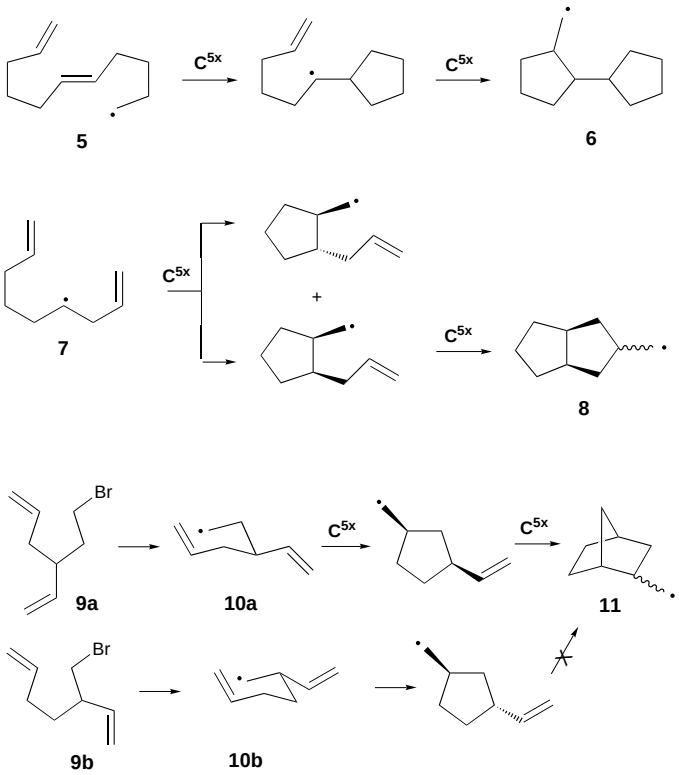
This system provides a short means of classifying the scattered and mixed array of cascade chemistry dispersed in the literature. It is intended to help in storing, displaying, evaluating, and comparing cascades. It should also assist in inferring the reaction mechanisms of radical cascades and in the design of target directed syntheses. The system is easily extendible to cascade types not included in this review, for example, to cascades containing intermolecular addition steps (**A**).

2. Two-Stage Unimolecular Free-Radical Cascades

2.1. The Acyclic Approach to Double Cyclizations

Starting structures may contain undeca-, nona-, or octadiene units, and the radical center may be generated within the diene chain, or in a branch attached to the diene chain. For example, if the radical is generated at the end of an undeca-5,10-dien-1-yl radical (**5**) the $\mathbf{C^{5x}C^{5x}}$ cascade produces a cyclopentylcyclopentane derivative **6** (Scheme 8). Heterocyclic and alkyne analogues are also known, as are the corresponding processes for double cyclizations via the $\mathbf{C^{6x}}$ and $\mathbf{C^{6n}}$ modes.

Alternatively, if the radical center is generated within the chain of a nonadiene **7** then the $\mathbf{C^{5x}C^{5x}}$ cascade leads to bicyclo[3.3.0]octane structures **8** (Scheme 8). Generally, the first cyclization produces a mixture of *cis* and *trans* cyclo-

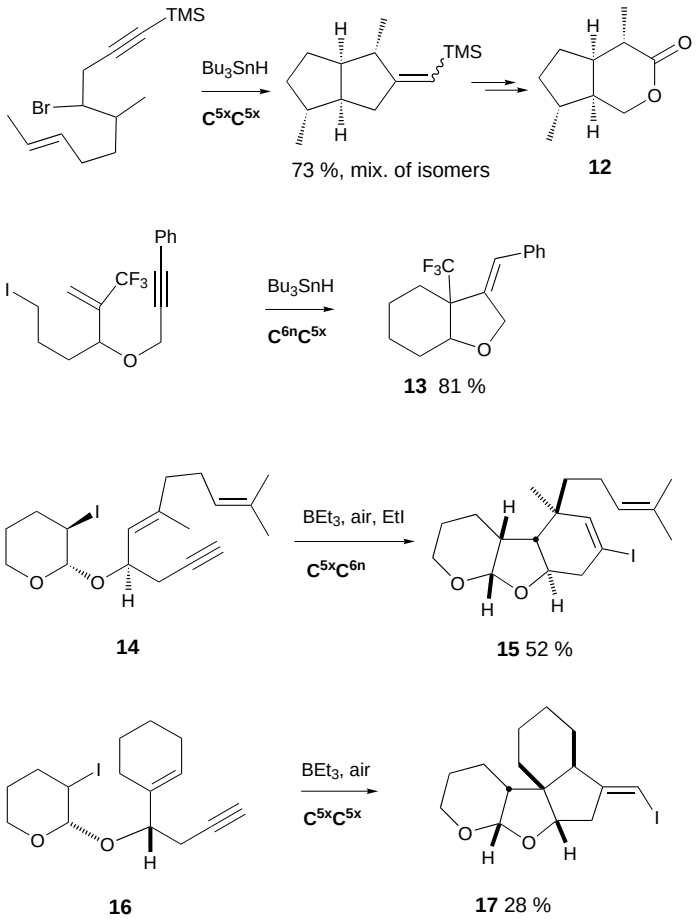


Scheme 8. Double 5-*exo* cyclizations of linear and branched dienyl radicals.

alkylalkyl radicals and only the *cis* radical can undergo a second ring closure. For efficient syntheses, therefore, it is necessary to include some substituent which will induce *cis* selectivity in the first step. This "acyclic approach"[17] to **CC** cascades, in which there are no rings already present to direct stereoselectivity, shows great diversity. Furthermore, stereoselectivity is often extremely good.[18] The first cyclization of branched octadieneyl radical **10a**, generated from bromodiene **9a**, was found to be *cis* selective permitting efficient occurrence of the second ring closure to a bicyclo[2.2.1]heptane skeleton **11** (Scheme 8). Radical **10b** on the other hand cyclized to give predominantly the cyclopentylmethyl radical with a *trans* configuration, which could not undergo a second cyclization to give bridged bicycle **11**.[19, 20]

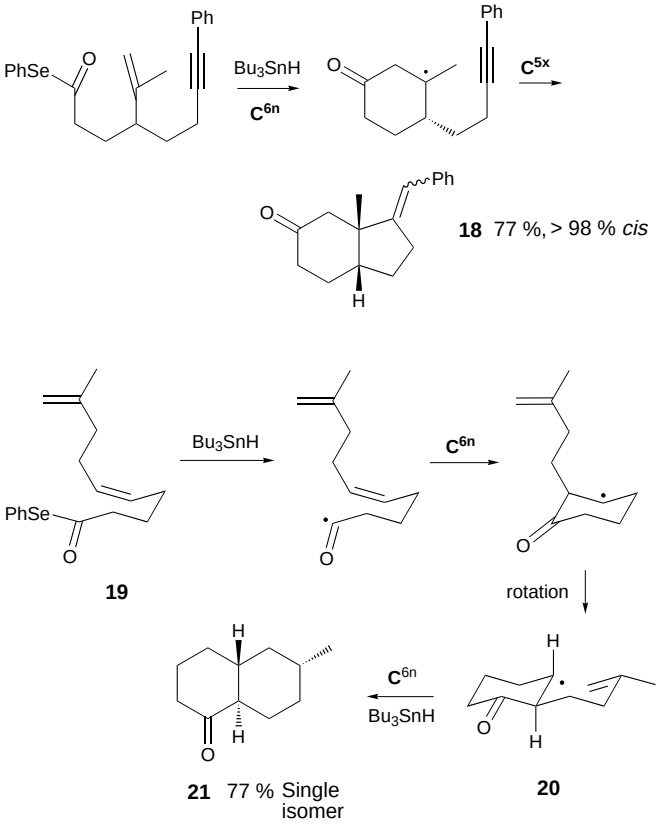
Parsons et al. provided an early example of an acyclic system being used in the synthesis of the natural product framework, avermectin A_{2b}.[21] Likewise, Kilburn used a **CC** cascade in a synthesis of isoiridomyrmecin (**12**) demonstrating the high degree of stereoselectivity that can be obtained (Scheme 9).[22] Morikawa et al. established that "awkward" angular trifluoromethyl substituted bicyclic systems such as **13** could be synthesized by a $\mathbf{C^{6n}C^{5x}}$ sequence that started with a 6-*endo* cyclization (Scheme 9).[23]

The synthesis of heteroannular acetals, for example, **15** and **17**, by radical double cyclization cascades starting from enynes was studied by Hoffmann et al.[24] Enyne **14**, and related precursors with the *R* configuration, underwent a $\mathbf{C^{5x}}$ cyclization, followed by a $\mathbf{C^{6n}}$ process that was dictated by ring strain. For the diastereomeric enyne containing the *S* configuration, and related precursors such as **16**, the cascade was largely diverted into the more normal $\mathbf{C^{5x}C^{5x}}$ mode, especially if a quaternary carbon center was established during the first cyclization (Scheme 9). These and related cascades were remarkable in that they allowed the construction of four or more chiral centers in a single convergent step. Another attractive feature was the avoidance of organotin compounds, because use of triethylborane/air as initiator worked well.



Scheme 9. Synthesis of oxapolycyclics by **CC** cascades.

The chemistry of acyl radicals, including cascade reactions, has recently been comprehensively reviewed[25] so only a couple of illustrative sequences will be described. Boger and Mathvink demonstrated an acyl-radical mediated $\mathbf{C^{6n}C^{5x}}$ cascade sequence that led to bicyclo[4.3.0]nonanone derivative **18** (Scheme 10).[26] Related reactions involving 6-*exo* cyclizations displayed much poorer stereoselectivity.



Scheme 10. Preparation of bicyclic ketones by double cyclizations of acyl radicals.

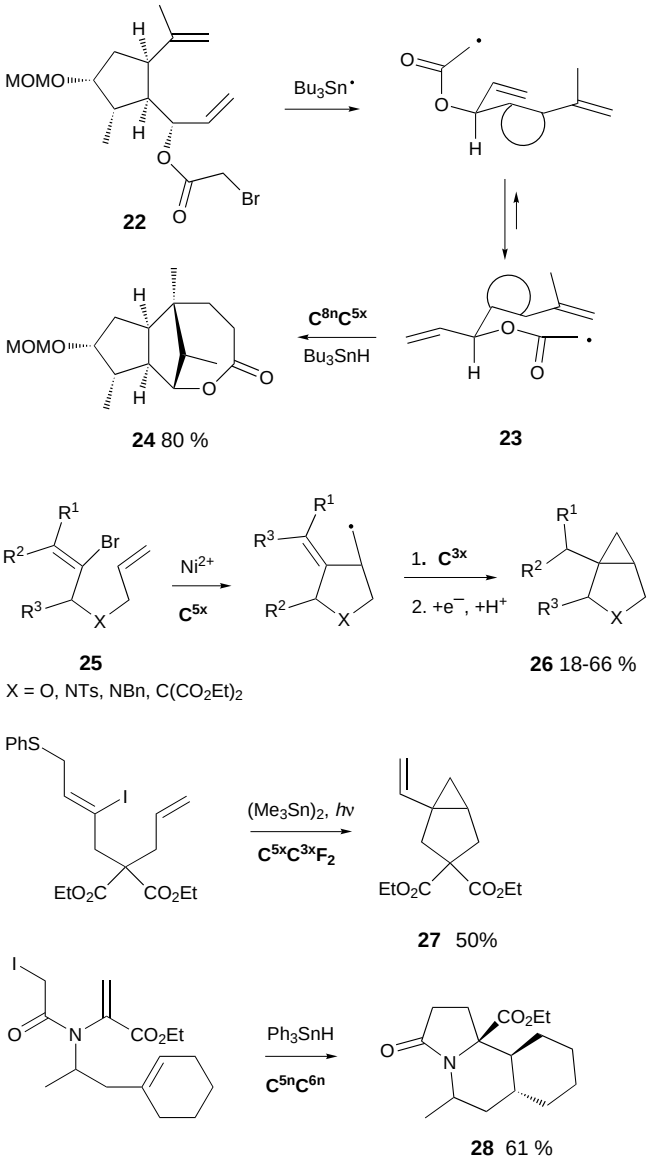
Many cascades starting from acyl radicals have featured consecutive 6-*endo* cyclizations ($\mathbf{C^{6n}C^{6n}}$) to afford decahydronaphthalen-1-ones, that is, generate the A and B steroid rings.[25]. The initial acyl radicals are more likely to cyclize in a 6-*endo* fashion, either directly or by ring expansion. The $\mathbf{C^{6n}C^{6n}}$ cascade shown in Scheme 10[27] was initiated by treatment of a selenoester **19** with tributyltin hydride. The starting acyl radical preferentially cyclized in the $\mathbf{C^{6n}}$ mode and the second cyclization was biased in favor of $\mathbf{C^{6n}}$ closure because the intermediate hex-5-enyl-type radical **20** contained a

methyl substituent at C(5). Overall this resulted in a good yield of *trans*-6-methyldecahydronaphthalen-1-one **21** as a single isomer. Other sequences, including cyclizations disfavored according to Baldwin's rules,[8] are possible.

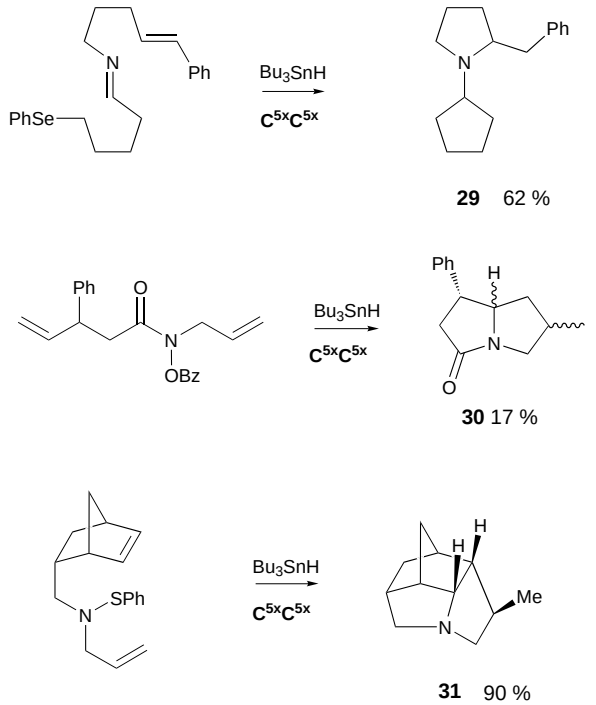
Having made guaianolide with a $\mathbf{C^{5x}C^{7n}}$ sequence,[28] Lee et al. were optimistic that tricyclic γ-lactone **24** could be synthesized by a similar sequence.[29] Instead, the initial (alkoxycarbonyl)methyl radical preferred to cyclize in an 8-*endo* fashion, and underwent a $\mathbf{C^{8n}C^{5x}}$ sequence (Scheme 11). The intermediate (alkoxycarbonyl)methyl radical preferred conformation **23** that favored closure to an eight-membered ring lactone in the first step. 3-*Exo* cyclizations may sometimes be rendered irreversible by stabilizing the product radical. This tactic was used to prepare bicyclo[3.1.0]hexane derivatives **26** in $\mathbf{C^{5x}C^{3x}}$ sequences starting from bromodienes **25**, initiated electrochemically, but mediated by a nickel complex (Scheme 11).[30] It was necessary for R^1 and R^2 to be radical stabilizing groups that also facilitated a rapid electron transfer (ET) reaction and the best yield (66%) was obtained when $R^1 = R^2 = R^3 = Ph$ and X = O.

Two different radical cascades were used to prepare bicyclo[3.1.0]hexane derivatives, both of which involved the initial cyclization of a vinyl radical.[31] In one of these sequences the three-membered ring was trapped by following the reversible 3-*exo* cyclization with an effectively irreversible fragmentation to yield **27** (Scheme 11).[31b] The presence of heteroatoms can sometimes enable "disfavored" 5-*endo* ring closures to take place. For example, appropriately substituted α-carbamoylmethyl radicals were used in cascade reactions to give indolizidinones such as **28** via $\mathbf{C^{5n}C^{6n}}$ sequences (Scheme 11).[32] Attempts at pyrrolizidine synthesis, from similar compounds with appropriately placed electron-withdrawing groups, failed. The presence of the carbonyl group in the precursor was vital. Analogous enamines merely underwent decomposition, presumably because the carbonyl group crucially affects the geometry of the α-carbamoylmethyl moiety.

Nitrogen-centered radicals cannot be easily generated by halogen abstraction. However, aminyl radicals have been produced by cyclization onto an imine (Scheme 12). The system was designed such that a further cyclization occurred to yield cyclopentylpyrrolidines **29**.[33] Sometimes a Lewis acid was beneficial, because this generated a much more nucleophilic aminium radical, but yields were variable.



Scheme 11. Double cyclizations embodying unusual steps, Ts = 4-methylphenylsulfonyl.



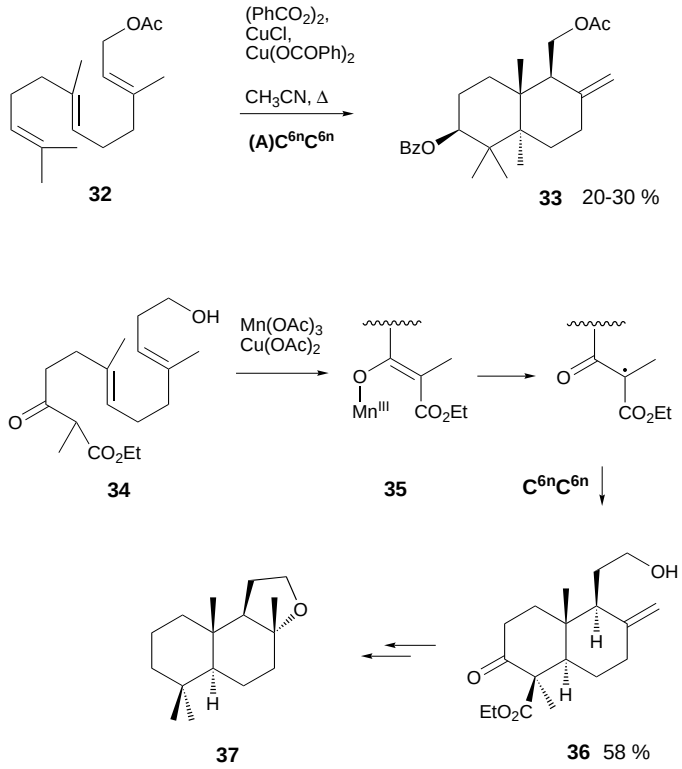
Scheme 12. Domino double cyclizations involving *N*-centered radicals. In **30** the isomer ratio is 3:2:1.

Apart from the above, the geminal donor/acceptor *N*-aziridinylimine method of Kim et al.,[34] and the synthesis of (±)-γ-lycorane by Zard et al. (Section 2.2) are additional examples of the exploitation of *N*-centered radicals. Amidyl radicals have been obtained from *N*-hydroxypyridine-2-thi-

one imidate esters (PTOC imidate esters)[35] and from *O*-acyl hydroxamic acid derivatives,[36] and used in $\mathbf{C^{5x}C^{5x}}$ cascade cyclizations resulting in hexahydropyrrolizin-3-ones such as **30** (Scheme 12), containing bridgehead nitrogen atoms.

Aminyl radicals are less electrophilic than amidyl radicals, and seem to be less well behaved, but can still undergo cascade cyclizations. They too can be generated from PTOC imidate esters, and have been used in a domino fashion.[37] Bowman et al. have described a series of syntheses in which aminyl radicals generated from phenylsulfenamides have undergone cascade cyclizations, (such as the formation of polycyclic amine **31**) though $\mathbf{C^{5x}C^{5x}}$ sequences in excellent yields.[38]

As long ago as 1968 Breslow reported an oxidative tandem cyclization (Scheme 13) that was initiated by the addition of a benzoyloxyl radical to triene **32** and consisted of a $\mathbf{C^{6n}C^{6n}}$ sequence followed by an oxidative termination step.[39] Although this method appears not to be generally applicable, it was followed by reports of numerous related oxidative annulations, mostly mediated by Mn^{III} acetate as one-electron oxidant.[40, 41]

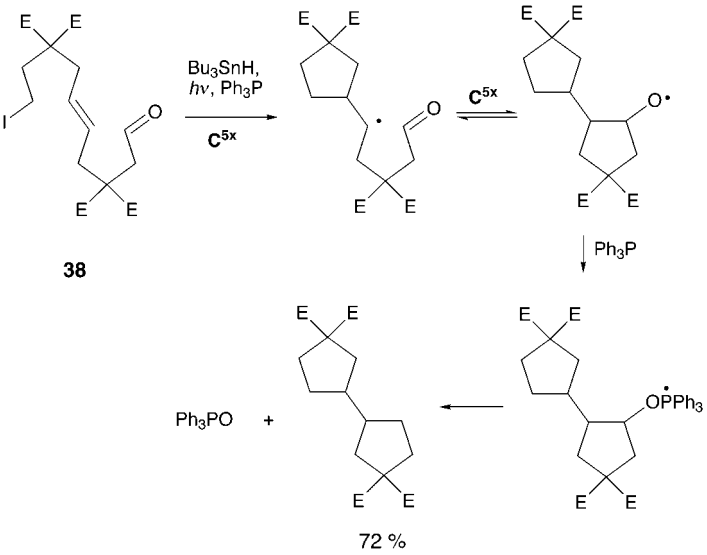


Scheme 13. Double cyclization cascades mediated by transition metal oxidants.

The synthesis of (−)-norlabdane oxide (**37**),[42] which is highly valued in the fragrance industry, serves to illustrate the use of the Mn^{III} acetate method (Scheme 13). The initial electrophilic carbon-centered radical was formed from β-keto ester **34** via enolate **35** and underwent a double cyclization ($\mathbf{C^{6n}C^{6n}}$) followed by oxidation,[43] in this, as in most other cases, by a Cu^{II} salt, to form the decalone derivative **36**. Natural products that have been synthesized utilizing Mn^{III} initiated two-step cascades include aloesaponol III and okicenone,[44] and the CD ring system of gibberellic acid.[45]

Unfortunately, the Mn^{III}/Cu^{II} ET system is not suitable as a general replacement for organotin hydrides, because only hydrogens on enolizable carbons are (effectively) abstracted, but it provides a neat, complementary method. Many of the **CC** cascades performed using Mn^{III} acetate were models for longer sequences (see Section 3).

Kim and Oh showed that cyclizations onto aldehydes could precede deoxygenation with organophosphorus compounds, and that this method was feasible for $\mathbf{C^{5x}C^{5x}}$ cascades as well (Scheme 14).[46, 47] This gambit facilitates the use of precursors **38** and others for which a terminal aldehyde may be easier to introduce than a terminal alkene.

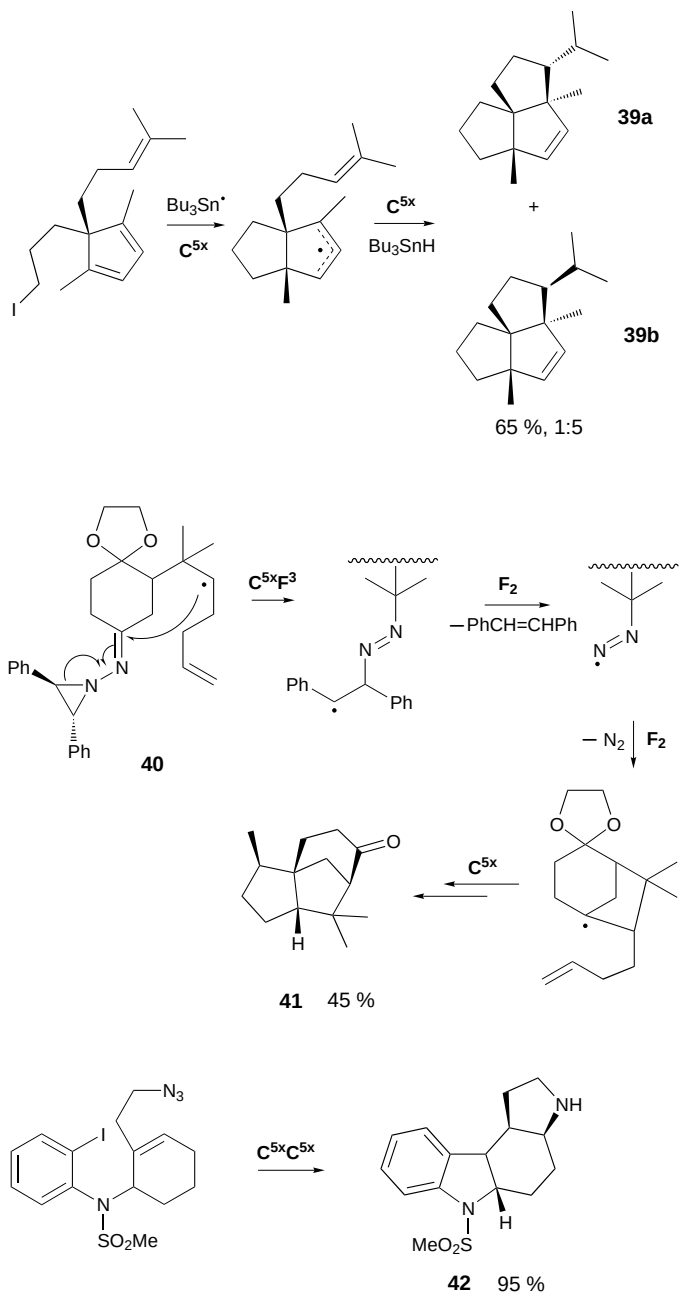


Scheme 14. Cascade featuring a cyclization onto a carbonyl group; E = CO_2Et.

2.2. The One-Ring Template Strategy for the Synthesis of Triquinanes and Related Tricyclics

This template strategy utilizes precursors that already contain a ring to control the stereochemistry of two subsequent cyclizations. The presence of a ring in the preadapted precursor, to which chains containing unsaturated centers and incipient radical centers are attached in a specific way, "bias(es) the stereochemical outcome of the cyclization."[17] Integration of a five-membered ring template with two $\mathbf{C^{5x}}$ steps leads to perhydrocyclopenta[*a*]pentalenes or perhydrocyclopenta[*c*]pentalenes (angular triquinanes). Six-membered ring templates have also been popular. The majority of these types of cascades have used organotin hydrides to mediate the reactions.

The one-ring template strategy was used by Curran and coworkers in admirable **CC** syntheses of (±)-silphiperfol-6-ene, (±)-9-episilphiperfol-6-ene,[48] (±)-modhephene, (±)-epimodhephene,[49] and the BCD ring section of crinipellin A (**39a**).[50] These preparations all required the cyclization of an allylic radical, which worked well, but gave the "wrong" isomer **39b** in a 5:1 ratio with **39a** (Scheme 15). The main



Scheme 15. One-ring template strategies for the stereocontrolled synthesis of triquinanes and related compounds.

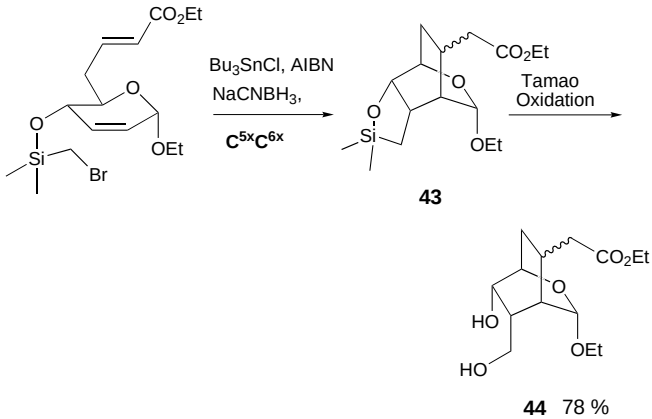
points of note were the 1,3-delocalization of the unpaired electron in the intermediate allylic radical and the preference for *cis* ring junctions in both cyclization steps. Curran's "PRT" method (see Section 2.5) was also used with acyl radicals generated from selenoesters. Unfortunately the unnatural isomer was always the major product.

The "one-ring template strategy", was combined with **CC** cascades in syntheses of lysergic acid derivatives,[51] a model for pseudocopsinine,[52, 53] and aspidosperma (6% yield).[53] Morphine,[54] (±)-α-cedrene,[55], α- and β-biotol,[56] and (+)-paniculatine[57] have also been targeted using these techniques.

The above rearrangements were all fairly standard organotin mediated $\mathbf{C^{5x}C^{5x}}$ sequences. Radical cascades can, however, be remarkably diverse, even within the limits of "one-ring template" **CC** sequences. One of the many syntheses of α-cedrene **41** provided an illustration of the potential value of *N*-aziridinylimines **40** in radical cascades (Scheme 15).[34] *N*-Aziridinylimines act as geminal radical donors/acceptors.[58] In effect, the carbon onto which addition has taken place will also be the carbon from which the subsequent addition will occur. The process that results in the radical center appearing on the same carbon as the radical acceptor is a triple $\mathbf{F^3F_2F_2}$ cascade accompanied by loss of stilbene and nitrogen (Scheme 15). The overall cascade is therefore a five-stage $\mathbf{C^{5x}F^3F_2F_2C^{5x}}$ process. Kim et al. used the same technique in syntheses of *dl*-pentalenene,[59] *dl*-zizaene, and *dl*-khusimone,[60] and a similar cascade was also used in the synthesis of (+)-7-deoxypancratistatin.[61]

Cyclization onto an azide moiety results, after a fragmentation, in the formation of a cyclic aminyl radical.[62] This sequence has been incorporated into an attractive **CC** cascade, which results in the formation of **42** (95%) containing the [6.5.6.5] ABCE ring system of aspidospermidine and related indole alkaloids (Scheme 15).[63]

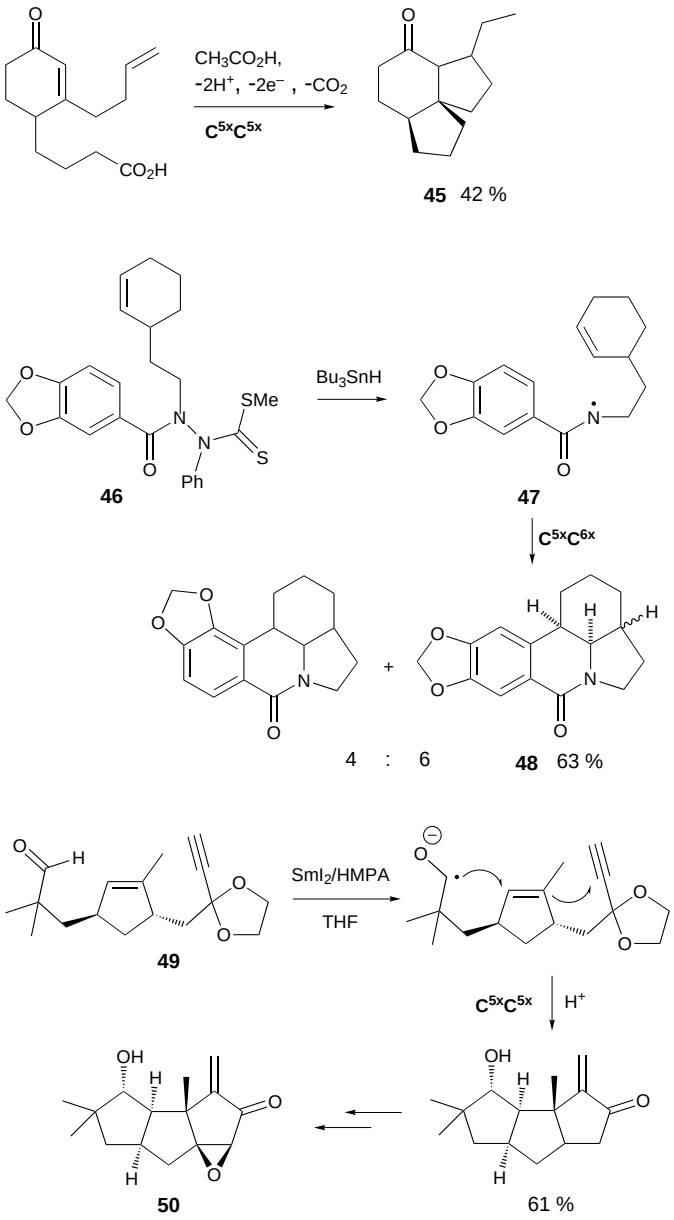
(Bromomethyl)dimethylsilyl allyl ethers have been the subject of extensive studies.[17, 64] The silicon is employed as a tether, enabling the increased stereocontrol inherent in cyclization reactions to be utilized. Tamao oxidation[65] of the 1,2-oxasiloles (**43**) formed in the first ring closure results in the production of 1,3-diols in a stereoselective manner. The technique, which originated from the work of Nishiyama et al.,[66] was used by the Fraser-Reid group in a $\mathbf{C^{5x}C^{6x}}$ cascade preparation of **44**, the precursor to reserpine in the total synthesis by Woodward, in enantiomerically pure form[67] (Scheme 16), and more recently by Belval et al. as a synthetic route to an isoprostanoid precursor.[68]



Scheme 16. Preparation by a double cyclization cascade of one of the intermediates employed by Woodward in the reserpine synthesis, AIBN = 2,2′azobis[(2-methyl)propanenitrile].

An electrochemically initiated sequence commenced from an unsaturated carboxylic acid and led by a $\mathbf{C^{5x}C^{5x}}$ cascade to the inden-4-one derivative **45** (Scheme 17).[69] Reaction conditions were crucial, with current density being the important factor.

The key step in the synthesis of (±)-γ-lycorane by Zard et al. involved generation of amidyl radical **47** from precursor



Scheme 17. Ring-templated cascade syntheses of **45**, the γ-lycorane precursor **48**, and (±)-hypnophilin **50**, HMPA = hexamethyl phosphoramide.

46. Subsequent $\mathbf{C^{5x}C^{6x}}$ double cyclization led to a 6:4 mixture of the desired **48** and undesired regioisomers (Scheme 17).[70] The major isomer **48** was reduced to (±)-γ-lycorane with lithium aluminum hydride.

Curran et al. employed SmI_2 to generate a ketyl radical in their cascade syntheses of (±)-hypnophilin **50** (total synthesis, Scheme 17) and the key intermediate in the formal synthesis of (±)-coriolin.[71]

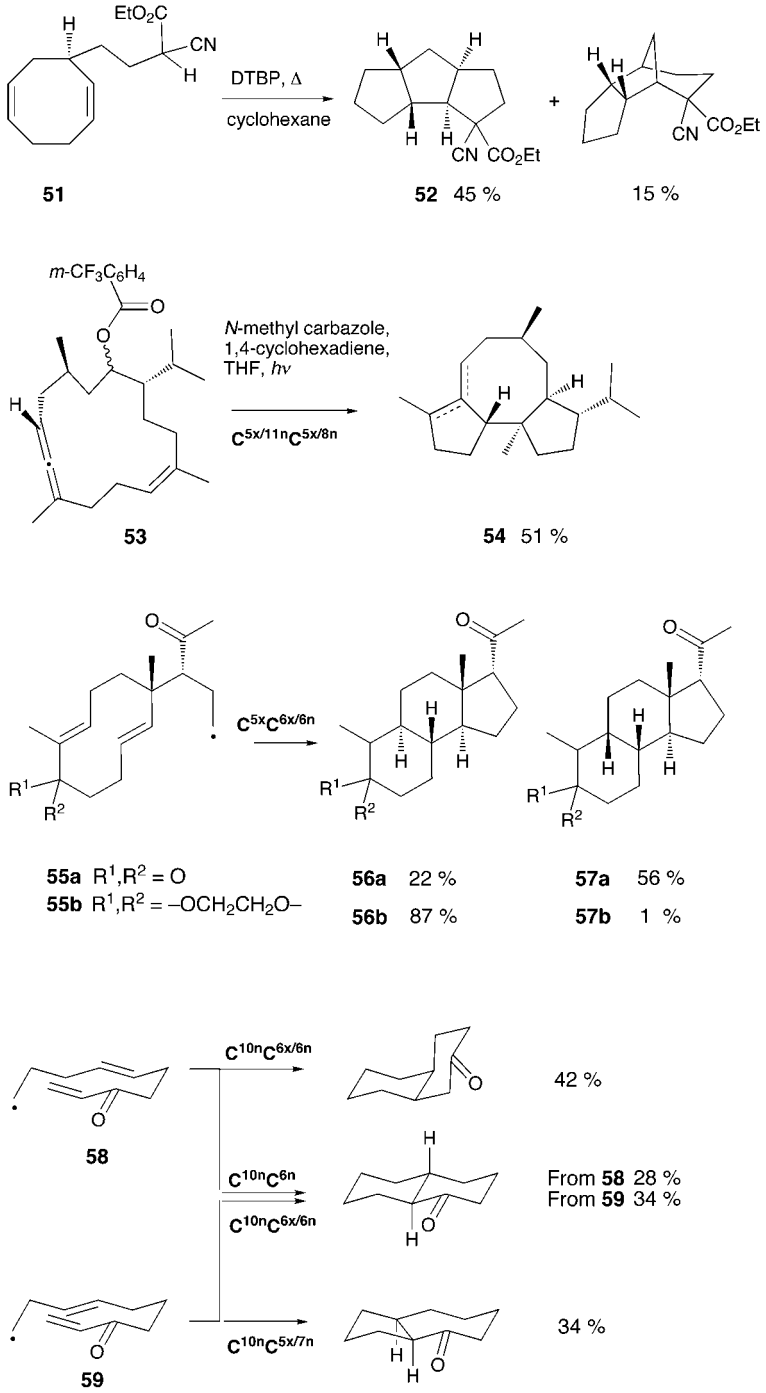
2.3. Transannular Double Cyclizations

Transannular cyclizations constitute a distinct type of rearrangement that is potentially very useful in cascade reactions,[72] but that has been neglected for some years because of perceived difficulties in syntheses of the medium and large rings of the precursors. Generally, the two rings that form in a transannular cyclization can be viewed as arising from two different modes. The superscript notation has therefore been expanded to display both possible modes, separated by a forward slash. A study by Winkler and Sridar on the formation of linear fused cyclopentanoids from double cyclization of 3-(cycloocta-2,6-dien-1-yl)propyl radicals revealed that the first cyclization occurred mainly in a *trans* fashion, which prevented a second cyclization from taking place. However, the presence of stabilizing groups at the radical center generated from the cyclooctadienyl precursor **51** rendered the cyclization reversible. Thermodynamic control encouraged formation of the more stable *cis* ring system, resulting in triquinane **52** as the major product from a $\mathbf{C^{5x}C^{5x/5n}}$ cascade (Scheme 18).[73] Conformational studies indicated that a substituent at the 4-position *trans* to the alkyl chain ought also to improve the proportion of *cis*-fusion, and this was found to be the case, although the effect was fairly small.[74]

In the $\mathbf{C^{5x/11n}C^{5x/8n}}$ cascade devised by Myers and Condroski as the key step in their synthesis of (±)-7,8-epoxy-4-basmen-6-one, both cyclizations were transannular.[75] Stannane-based radical-generation methods were unsuccessful, because of the tendency of tin-centered radicals to add to the allene moiety in the precursor (cf. **53**). The successful method (Scheme 18) involved illumination of the 14-membered ring trifluoromethylbenzoyl ester **53** in the presence of *N*-methylcarbazole and 1,4-cyclohexadiene in THF, and resulted in formation of the target tricyclic **54** in a 51 % yield.

Recently, the progesterone BCD ring system was synthesized using transannular cascade methodology.[76] MM2 transition-state models predicted that ketone **55a** would favor the undesired product **57**, whereas acetal **55b** would almost exclusively favor the desired stereoisomer **56**. Use of the acetal led, via a $\mathbf{C^{5x}C^{6x/6n}}$ cascade, to the expected product **56b** (Scheme 18).

Pattenden et al. have employed an impressive range of transannular cyclization cascades in their syntheses of steroids. They have taken the method a stage further by forming macrocycles in radical *endo* cyclizations as well, thus avoiding the difficulty of forming medium-sized rings in a separate step. Early applications were their syntheses of the taxane ring system in low yield by $\mathbf{C^{12n}C^{6x}}$,[77] and $\mathbf{C^{12n}C^{8n}}$ sequences,[78] (alternatives to the tin method, such as TTMSS, were tried, and found to be less successful) and the method was also used to make fused lactones and lactams.[79] A detailed investigation of the scope of the reaction has been published.[80] The macrocyclization needed to be onto an enone but it was shown that the reactions with **58** and **59** followed different pathways (Scheme 18), which were ascribed to the different conformations adopted by the two macrocyclic radicals. A variety of **CC** reactions were investigated,[80a] mainly with success, although it was noted that 5-*exo* cyclizations would occur "given half a chance" in preference to macrocyclization. Another surprising limitation was discovered when a 3-*exo* cyclization occurred instead of a macrocyclization, and was rendered irreversible by a sequential 5-*exo* cyclization to give a stabilized α-keto radical.[81]



Scheme 18. Two-step cascades involving transannular cyclizations, DTBP = di-*tert*-butylperoxide.

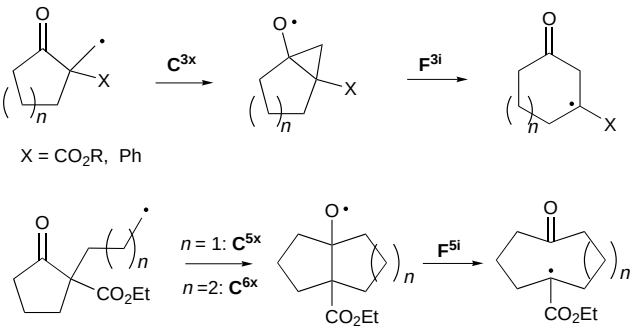
2.4. Cyclization/Ring Opening as a Versatile Ring-Expansion Methodology

"Dowd-type" ring expansions take place by **CF** cascades and hence this sequence has become common. Ring enlargements have, however, been reviewed[7, 82, 83] so only some illustrative and recent examples will be included. Recurring types are the one- ($\mathbf{C^{3x}F^{3i}}$), three- ($\mathbf{C^{5x}F^{5i}}$), and four-carbon ($\mathbf{C^{6x}F^{5i}}$) expansions shown in Scheme 19. Similar **CF** ring expansions have been reported for heterocyclic compounds containing O, S, and N atoms, various polycyclic compounds, medium-sized rings, and the method has been extended to **CCF** and similar cascades.[84] The ring expansion phenomenon may explain (or partly explain) other anomalous reactions, such as the preference of acyl radicals to cyclize in 6-*endo*, rather than 5-*exo* fashion.

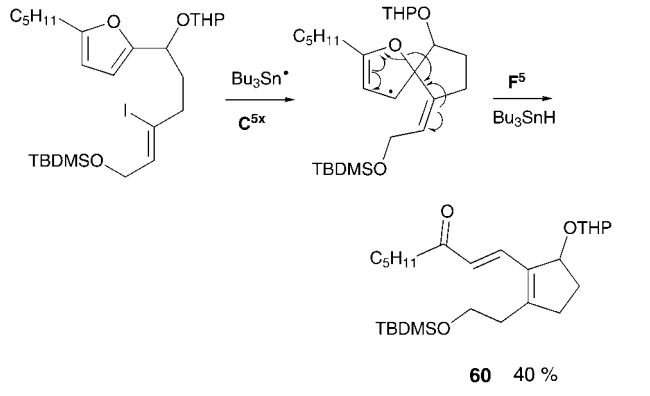
Parsons et al. utilized a different type of cascade ($\mathbf{C^{5x}F^{5}}$) for the formation of enone **60**.[85] Cyclization of a vinyl radical onto a furan ring (Scheme 20) produced an allylic radical that fragmented to an enone. This was another example of the allyl system being used to "translocate" a radical center. Replacement of the silyl protected alcohol with a phenylsulfanyl group (which could be eliminated in the final step) resulted in a product suitable for an in situ Cope-type rearrangement.

2.5. Sequences Containing Hydrogen Migrations; Protecting/Radical Translocating Reactions

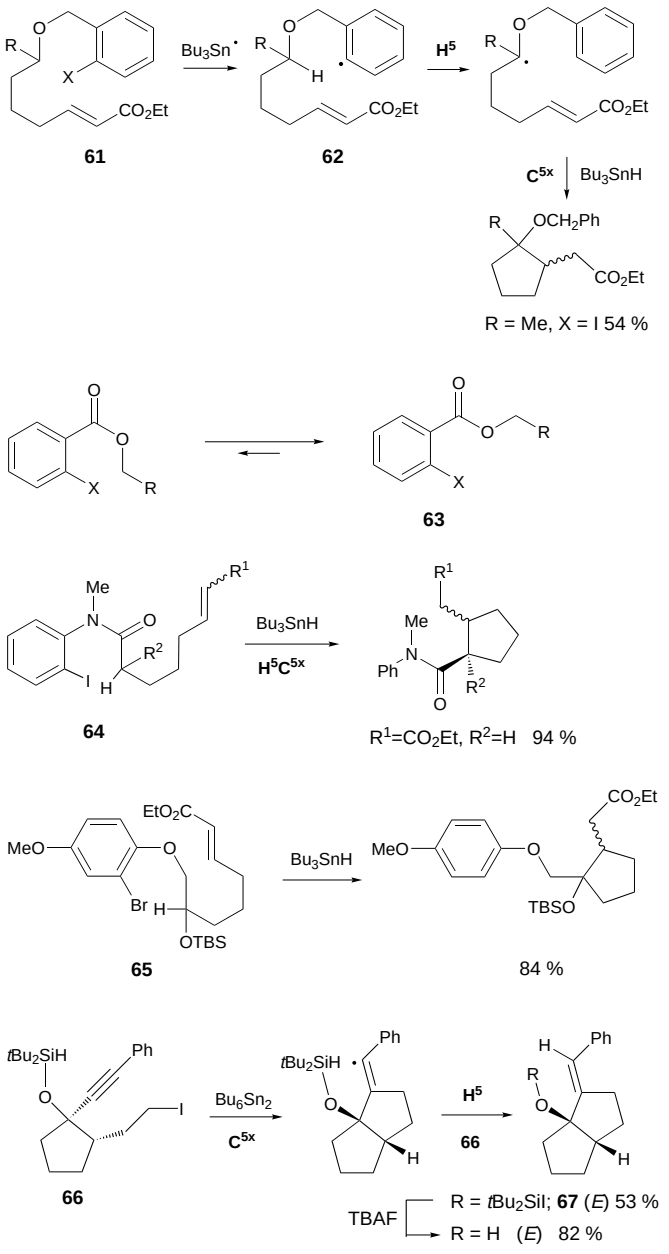
Sequences launched by a 1,5-hydrogen migration (**H**) generally include a cyclization as the second step. A special case, which automatically results in a radical lined up for a 5-*exo* cyclization, involves 1,5-H transfer to an initial vinyl (or aryl) radical. Such sequences have been extensively studied by the Curran group,[86] who described examples in which the initial species were aryl radicals.[87] The starting materials were benzyl ethers **61** prepared from alcohols containing hex-5-enyl-type chains (Scheme 21). These precursors contained C–H bonds, α to the oxygen atom, that were consequently weak and activated towards 1,5-hydrogen transfer. On generation of aryl radicals **62**, rapid 1,5-hydrogen transfer selectively generated α-alkoxyalkyl radicals[87, 88]. The resulting intermediates could ring close onto a suitably situated unsaturated group to yield cyclic benzyl ethers, that is, protected cycloalkanols, after the final hydrogen transfer from tin hydride. Curran dubbed these $\mathbf{H^5C^{5x}}$ sequences "Protecting/Radical Translocating Reactions" (PRT). He found that the (2-bromophenyl)dimethylsilyl group was often a more efficient hydroxyl protecting group.



Scheme 19. Ring enlargement by cyclization/fragmentation sequences.



Scheme 20. Preparation of enones by cyclization/fragmentation with furan-containing radicals.



Scheme 21. Radical cascades embodying 1,5-H shifts and cyclizations; TBSO = tri-*tert*-butylsiloxy, TBAF = *N*,*N*,*N*,-tributyl 1-butanaminium fluoride.

The PRT method enabled tin-centered radicals to be used for what was effectively a hydrogen abstraction.

The PRT method has been deployed with protected amides (or amines),[88a, 89] and carboxylates.[90] When an amide or ester group was present the preferred conformation of this functional group had to be taken into account. Esters exclusively adopted *syn* configurations **63** (Scheme 21), that precluded 1,5-H transfer, so esters could not be used as PRT groups for carboxylic acids.[90b] Anilides were predominantly in the desired configuration (for example **64**) especially in benzene, the normal reaction medium, and hence 2-iodoanilides functioned well as PRT groups and mediated cyclizations of unsaturated carboxylic acids (Scheme 21).[90a]

Curran deduced that the strength of the C–H bond was not as crucial to the success of 1,5-H migrations as was the geometry of the system.[86, 90b] He and J. Xu developed 2-bromo-4-methoxyphenyl ethers **65** as PRT groups that would generate radicals β to oxygen atoms in benzyl ether protected alcohols (Scheme 21).[91] 1,5-H Transfer was most efficient (80–85%) when a tertiary alkyl radical was generated. Deprotection was accomplished using ceric ammonium nitrate.

The rapidity of these H migrations enabled them to be coupled with intermolecular addition reactions, as was shown early on by Snieckus et al. [88a] The method has recently been used in stereoselective syntheses. For example, β-substituted β-amino acids were synthesized enantioselectively in this way,[92] stereoselective allylations were accomplished,[93] and *N*-(2-iodobenzyl) protected 1,3-oxazolidines were used to stereoselectively functionalize the 2-position of β-amino alcohols.[94]

HC sequences which do not involve the PRT process[95] have been used in the synthesis of bicyclic β-lactams,[96] and as routes to (±)-helistridane and (6*S*,7*S*)-dihydroxy-helistridane.[97] Acyl radical equivalents, derived from vinyl radicals, have also been used in **HC** processes.[98] 1,2-Group migration and 1,5-hydrogen migration steps also form parts of longer domino sequences (Section 3).

Sequences in which a cyclization is followed by a 1,5-hydrogen migration have also proved useful in preparations of bicyclo[3.3.0]octane derivatives and related polycyclics. For example, Curran et al. showed that silicon hydrides, functionalized as shown in **66**, on treatment with hexabutylditin, initially underwent an $\mathbf{C^{5x}}$ cyclization to generate a vinyl radical. This was followed by intramolecular hydrogen shift from the SiH group, that is, the $\mathbf{C^{5x}H^5}$ sequence amounted to a unimolecular chain transfer (UMCT) process.[99] This cascade specifically gave the *E* alkene **67** which was readily hydrolyzed with *N*,*N*,*N*-tributyl 1-butanaminium fluoride (TBAF) to the corresponding (*E*)-hexahydro-1*H*-pentalenol (Scheme 21). A similar principle involving homolytic substitutions was recently developed by Studer et al.[100]

2.6. Cascades Containing Ring-Opening Steps

Ring-opening processes result in the formation of double bonds and hence are often followed, at some point in a sequence, by a cyclization.

Motherwell et al. studied in detail $\mathbf{F^{3o}C^{5x}}$ sequences of butenyl- and butynylbicyclo[4.1.0]heptane derivatives (Scheme 22).[101] The ketyl radical that started the sequence was generated in four different ways but the best yield of spiro product **68** (79%) was obtained using SmI_2 with 1,3-dimethyl hexahydro-2-pyrimidinone (DMPU).

In a very similar system (containing a terminal rather than a silylated alkyne) the ketyl radical was generated by illuminating the initial bicyclo[*n*.1.0]alkanone in triethylamine and acetonitrile,[102] and a yield of 23% was obtained. Kim et al. uncovered a cascade of this general type in their investigations of cyclizations onto azide moieties (an $\mathbf{FCF_2}$ sequence).[62] Motherwell et al. also examined very similar reactions of C-centered radicals generated from thiocarbonylimidazoles **69** using tin hydride.[103] The reaction proceeded in an analogous manner ($\mathbf{F^{3o}C^{5x}}$), forming spiro[5.6]decene derivative **70** in 71% yield (Scheme 22). In both this, and the ketyl radical study, an **FCC** cascade was also described. Enholm and Jia put this type of **FC** cascade to good use in tin hydride mediated preparations of linear and angular triquinanes, which were obtained in excellent yields.[104]

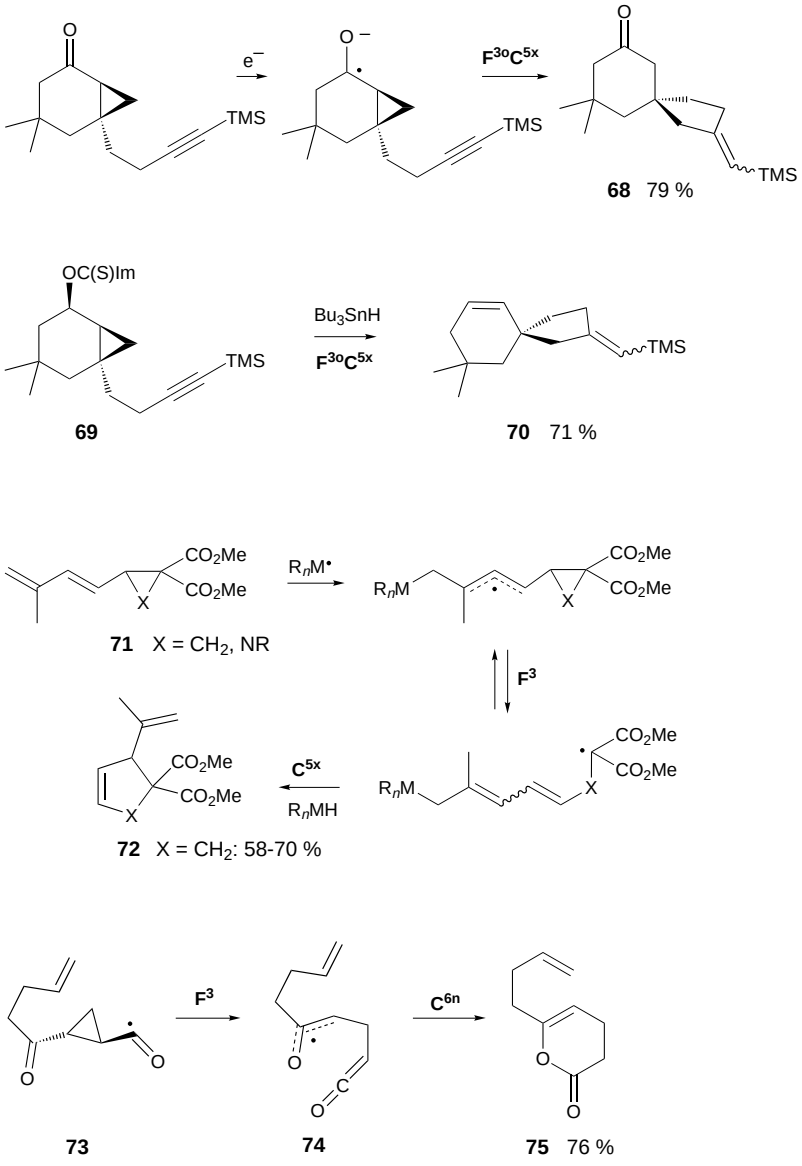
The "outer" mode cyclopropyl ring opening, giving primary radicals in the above sequences, resulted from stereoelectronic control. In contrast, the "Dowd type" ring expansions occurred in the "inner" mode because of the inclusion of substituent X (Section 2.4, Scheme 19) that stabilized the secondary radical.[105, 106]

Reactions started by fragmentations of three-membered rings that are not fused to another ring have also been reported. Bertrand et al. described **FCC** processes as routes to bicyclic lactones, lactams, and ketones.[107] Feldman et al. adapted their [3+2] cycloaddition strategy for intramolecular use in the synthesis of (±)-rocaglamide[108] and brefeldin.[108b] Miura et al. described an $\mathbf{F^3C^{5x}}$ sequence starting with dienylcyclopropane **71** ($X = CH_2$) and involving allyl radical translocation to yield functionalized allylcyclopentene **72** ($X = CH_2$; Scheme 22).[109] The design was such that the radical that added intermolecularly ($R_nM^{\bullet}$) was also the radical that was eliminated to terminate the sequence (and hence could hypothetically be used as a catalyst). Different radical sources were tested, and triphenyltin hydride generally gave the best results. The authors also applied the method with a dienylaziridine, thus forming a five-membered nitrogen heterocycle.[109]

Oxiranylmethyl and aziridinylmethyl radicals also ring open efficiently to yield heteroatom-centered radicals, except when phenyl or other product-stabilizing substituents, are present. A cascade consisting of ring opening of a butenyl epoxymethyl radical followed by cyclization of the resulting alkoxyl radical onto the butenyl bond ($\mathbf{F^3C^{5x}}$) has been used for the preparation of vinyl tetrahydrofurans.[110, 111] A second cyclization onto the vinyl group took place with the *cis*-isomer of the intermediate vinyl tetrahydrofuranylmethyl radical ($\mathbf{F^3C^{5x}C^{5x}}$) opening the way to 7-oxabicyclo[2.2.1]heptane derivatives. More recently, another **FC** reaction involving a homoallylic aminyl radical derived from an aziridinylmethyl radical has been described.[112]

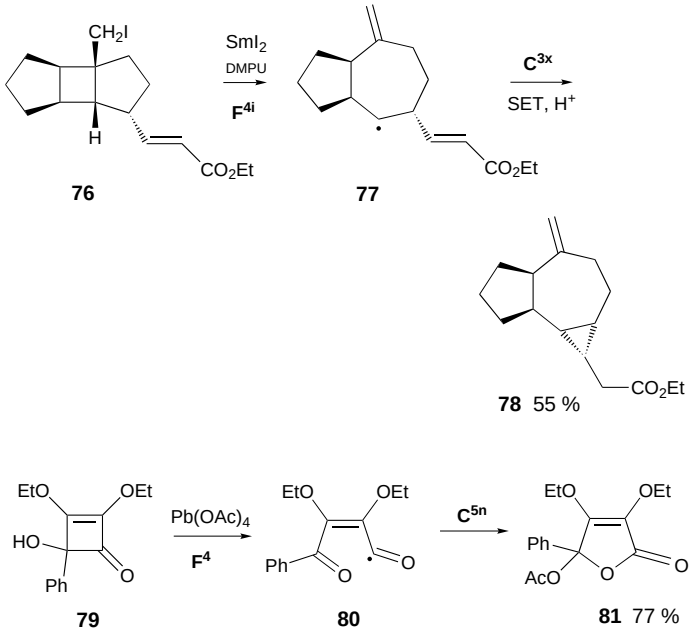
Pattenden et al. communicated a surprising and unusual sequence starting from cyclopropylacyl radical **73** (which was generated from a selenide) and leading to unsaturated lactone **75** by an $\mathbf{F^3C^{6n}}$ cascade (Scheme 22).[113] The ring-opening step produced ketenyl radical **74** which, after radical delocalization onto oxygen, underwent a 6-*endo* cyclization to afford lactone **75** in good yield.

Photochemical [2+2] cycloadditions have been widely applied for the preparation of functionalized bicyclo[3.2.0]heptanes that un-



Scheme 22. Cascades starting with three-membered-ring opening reactions; TMS = trimethyl silyl.

dergo radical-mediated opening of their four-membered rings to produce methylenecyclopentanes. For example, a cascade synthesis of the aromadendrane carbon skeleton was started by treatment of tricyclic iodide **76** with SmI_2 (Scheme 23).[114] Cleavage of the cyclobutylmethyl-type radical produced intermediate **77** which subsequently ring closed, underwent a rapid single electron tranfer (SET), and picked up a proton to a yield tricycle **78** containing the desired skeleton (Scheme 23). The cascade amounted to an $\mathbf{F^{4i}C^{3x}}$ process and cyclopropane ring formation was favored by the radical-stabilizing ester group.

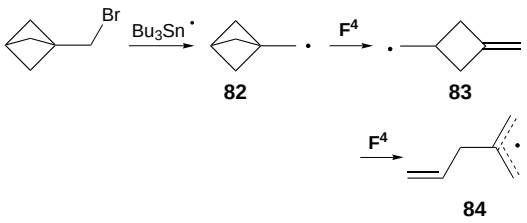


Scheme 23. Cleavage of four-membered rings followed by cyclization. DMPU = 1,3-dimethyl hexahydro-2-pyrimidinone.

An unusual series of reactions commencing with the squaric acid derivative **79** was described by Eguchi et al. (Scheme 23).[115] The alkoxyl radical, generated from alcohol **79** by lead tetraacetate, ring opened to give acyl radical **80**. Subsequent *endo* cyclization back onto the oxygen atom of the newly generated carbonyl group yielded unsaturated lactone **81** by an $\mathbf{F^4C^{5n}}$ sequence the overall effect of which was ring expansion. A similar sequence was also reported by O'Dell et al. for a reaction in which an alkoxyl radical was generated using mercuric oxide/iodine.[116]

Precursors programmed for successive ring opening of two three-membered rings must contain structures such that the but-3-enyl-type radical formed in the first $\mathbf{F^3}$ step will unmask a cyclopropylmethyl-type of radical. Several examples of $\mathbf{F^3F^3}$ sequences in, for example, quadricycl-3-yl radicals, dispiro-[2.2.2.2]decadiene-derived radicals and various biradicals have been reported in the older literature.[7] Most recent instances of $\mathbf{F^3F^3}$ types have formed parts of more complex cascades (Section 3.3).

The (bicyclo[1.1.1]pentyl)methyl radical **82** undergoes a unique double fragmentation involving two four-membered rings ($\mathbf{F^4F^4}$). The first β scission occurs at low temperatures transforming the molecule into the (3-methylenecyclobutyl)-methyl radical **83** that itself undergoes a second ring cleavage yielding the 2-allylallyl radical **84**[117, 118] (Scheme 24). This cascade is a rare instance where all three of the intermediates were individually characterized by EPR spectroscopy and the rate constants of both steps were determined.



Scheme 24. Double ring opening of (bicyclo[1.1.1]pentyl)methyl radicals.

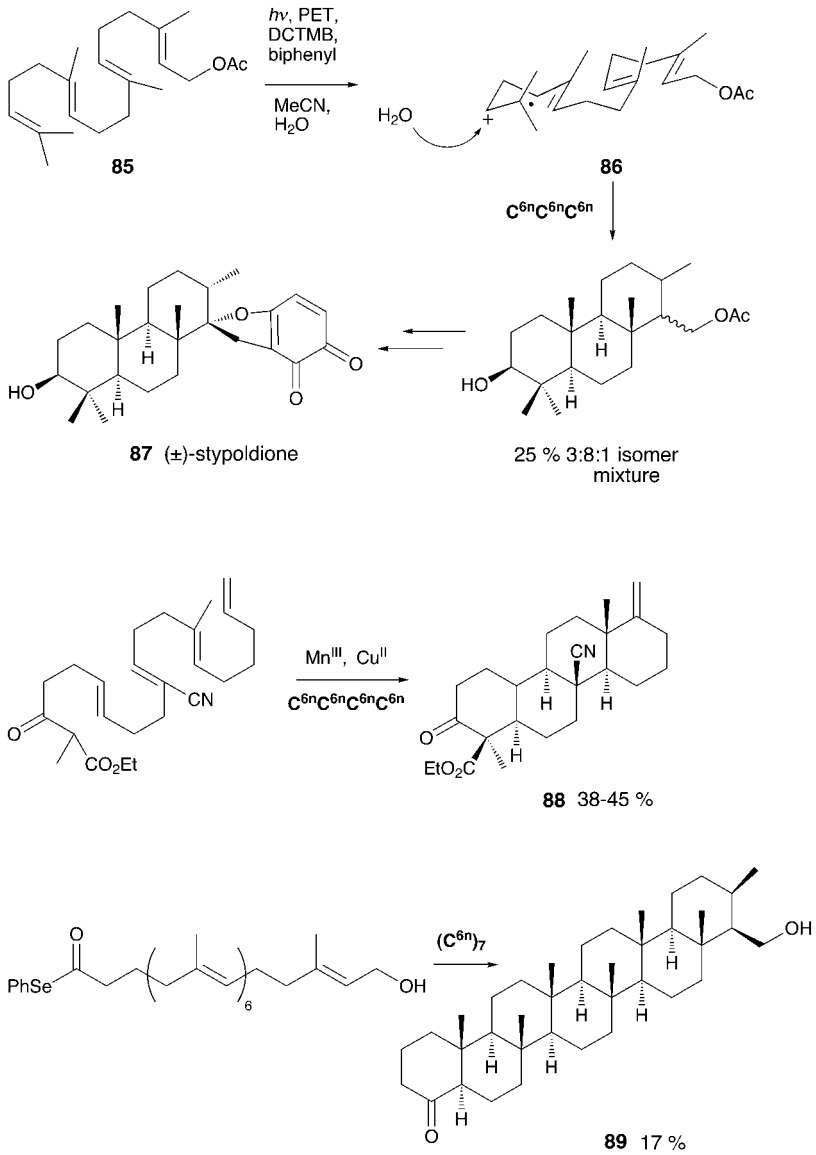
3. Three-Stage and Longer Unimolecular Cascades

3.1. Triple Cyclization Sequences

From the standpoint of organic synthesis, the triple cyclization (**CCC**) is the most important of the 64 sub-types of unimolecular three-stage cascades. Beginning with an initial acyclic radical, three $\mathbf{C^{5x}}$ steps lead to triquinane-type structures. However, many other polycyclic structures are accessible from initial designs that permit closures to different ring sizes. Longer cascades of cyclizations are more likely to involve precursors that contain repeating units, as exemplified by the cascade initiated by an unusual photoelectron transfer (PET) method (Scheme 25, top).[119] Although this cascade was started by initial formation of radical cation **86** from tetraene **85**, the domino cyclization was purely a radical process,[120] and was applied to the synthesis of (±)-stypoldione **87**. The three *endo* cyclizations were constrained by the three strategically placed methyl substituents in the original tetraene.

A large number of remarkable triple-**C** sequences mediated by Mn^{III} and Cu^{II} salts have been invented, and those in Scheme 25 are typical. The defining features were the linearity of the precursor polyene containing the radical acceptor units within the same chain, not branched or interrupted by the initial radical site, and the methyl groups, usually necessary to direct cyclizations *endo*, were distributed every fifth C-atom from the start of the polyene system. These cascades contributed to notable syntheses of *dl*-isopongiadiol,[121] *dl*-spongiatriol,[122] and to even more remarkable quadruple $\mathbf{C^{6n}C^{6n}C^{6n}C^{6n}}$ extensions in which complete homosteroid skeletons, for example, **88** were constructed (Scheme 25).[123]

Good use has been made of the preference shown by acyl radicals for the 6-*endo* mode of cyclization; the perhydrophenanthrone and -decalone ring systems were constructed[27, 124] and the method was extended to triple-**C** cascades and superb **CCCC** sequences leading to steroid ring systems. Yields were generally 60–80 % and just two D ring epimers



Scheme 25. Formation of steroidal structures by multiple *endo*-cyclizations; DCTMB = 1,4-dicyan-2,3,5,6-tetramethylbenzol, PET = poly(oxy-1,2-ethanediyloxycarbonyl-1,4-phenylenecarbonyl).

were formed. More recently this methodology was applied to the synthesis of spongian-16-one by a **CCC** sequence.[125] The range of cascade cyclizations was dramatically extended by the realization of a phenomenal seven-step all *endo* $\mathbf{C^{6n}C^{6n}C^{6n}C^{6n}C^{6n}C^{6n}C^{6n}}$ sequence (Scheme 25) that accomplished the one-pot synthesis of novel steroidal heptacycle **89** in a very acceptable yield of 17 %.[126]

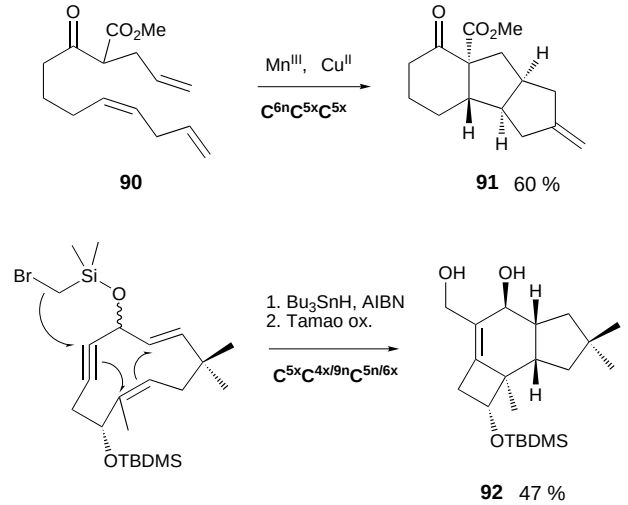
Pattenden et al. have also studied three-stage and longer macrocyclization – transannulation sequences;[80b] although unexpected or undesired reactions often served to highlight some of the drawbacks of these systems. For example, an ambitious attempt to assemble the steroid ring system by a macrocyclization – transannulation reaction consisting of a **CCCC** sequence failed.

The triple cyclization of "interrupted" polyene **90** produced the tricyclic ketone derivative **91** (Scheme 26) in good yield as a single diastereoisomer[127] by a $\mathbf{C^{6n}C^{5x}C^{5x}}$ cascade. The ester substituent stabilized the initial radical and promoted the first 6-*endo* cyclization. In the absence of additional directing substituents, however, the next two ring closures took place in the usual 5-*exo* mode (Scheme 26). Snider et al. recently synthesized a precursor of (±)-isosteviol and (±)-beyer-15-ene using this "interrupted" method which showed that it was more likely to suffer from lower yields because of alternative cyclizations taking place.[128]

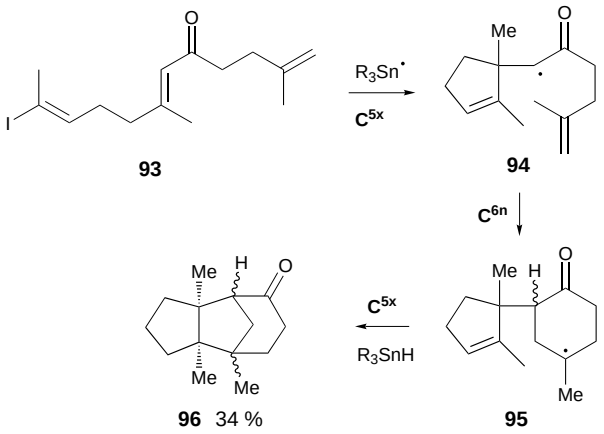
Of the few examples of triple and longer cyclizations, starting from structures that were very irregular in the disposition of radical acceptors, most involved silicon-tether methodology. One such cascade was a remarkable transannular $\mathbf{C^{5x}C^{4x/9n}C^{5n/6x}}$ sequence, that was used in the synthesis of *epi*-illudol (Scheme 26) which is shown in protected form (**92**).[129] Other **CCC** sequences have been described in a review.[17]

Triple cyclizations that amount to a "round trip", that is, are "isomerisations in which an intermediate radical ultimately adds back to the initial site of radical generation" have been investigated by several groups.[130] Treatment of the trione derivative **93** with tin hydride led to production of a mixture of isogymnomitrene (major) and gymnomitrene (minor) precursor ketones **96** (Scheme 27). An initial $\mathbf{C^{5x}}$ cyclization afforded radical **94**, which preferred to cyclize in the $\mathbf{C^{6n}}$ mode, as is normal for α-keto radicals, although considerable coaxing was needed.

Sugar-based dodeca-1,6-dien-11-ynes and dodeca-6-en-1,11-diynes sustained triple $\mathbf{C^{5x}C^{5x}C^{6n}}$ round-trip cascades to yield diastereomerically pure 1,6-dioxahydrindacenes on treatment with triphenyltin hydride.[131] These tetracycles were only minor products, because cascade propagation stopped after two cyclizations for the majority of intermediates.



Scheme 26. Triple cyclizations of interrupted and irregular triene and dieneyne units.



Scheme 27. "Round trip" triple cyclization leading to isogymnomitrene and gymnomitrene precursor ketones.

However, the reactions were noteworthy because of their stereospecificity and because the radical-promoted triple cyclization was equivalent to a [2+2+2] cycloaddition.

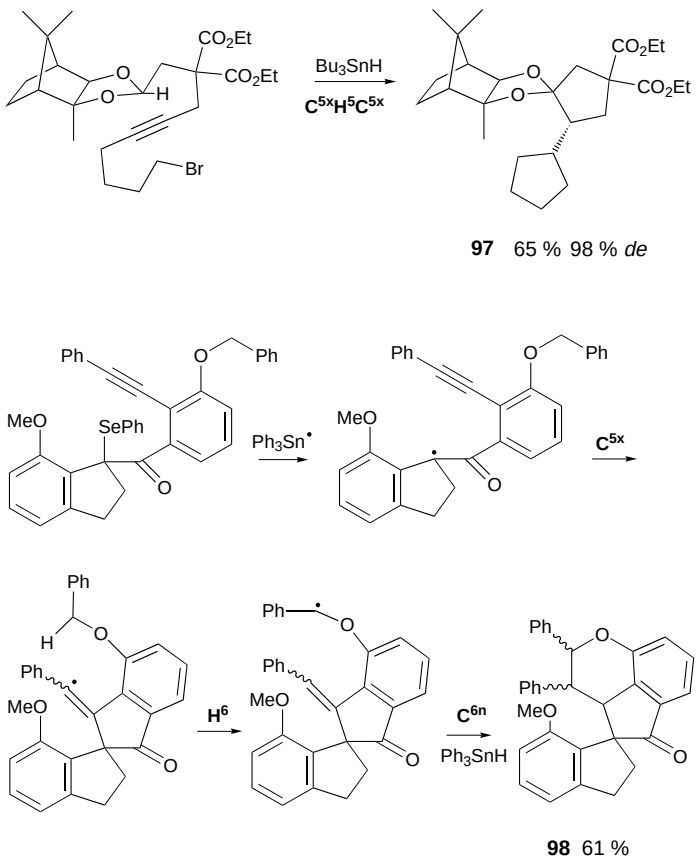
3.2. Other Multiple-Step Cascades Containing Cyclizations

Premature hydrogen transfers are one way that multiple-cyclization sequences can be diverted from their original design. For example, attempts by Malacria and co-workers to synthesize a steroid skeleton by means of a multiple-cyclization sequence was deflected into a **CCH** cascade,[132] and H migration from supposedly passive ether protecting groups may lead to the formation of dehydroxylated products.[133] However, hydrogen migrations can also be beneficial as in the **CCCCHC** process (followed by elimination of a trimethylsilyl radical) which aided the development of syntheses of linear triquinanes.[134]

CHC sequences are comparatively common, and have proved to be of some utility. Stien et al. published a report concerning a chiral acyl-radical equivalent that included the interesting $\mathbf{C^{5x}H^5C^{5x}}$ sequence shown in the top part of Scheme 28.[98] The same alkyne group was the acceptor for both cyclizations, and the product **97** was formed in good yield, and high diastereomeric excess. The large acyl-group equivalent was important for the stereoselectivity and for increasing the population of the conformer that promoted fast 1,5-H migration.

Radicals are useful for forming quaternary centers in spiro ring systems and this property was exploited in syntheses leading eventually to (±)-fredericamycin. Initially, spirocycle **98** was obtained by a $\mathbf{C^{5x}H^6C^{6n}}$ cascade (Scheme 28).[135]

Many **CHC** sequences involving [(bromomethyl)dimethylsilyl] allyl and propargyl ethers have been reported,[17, 136] including a $\mathbf{C^{5x}H^5C^{5n}}$ cascade terminating in a rare 5-*endo* cyclization involving no ring heteroatoms.[136b] More extended cascades were uncovered including various **CHCF** types,[136c] but the most impressive was probably the $\mathbf{C^{5x}H^6C^{6n}C^{4x}H^6}$ sequence sustained by diyne **99** (Scheme 29).[136e] The initial



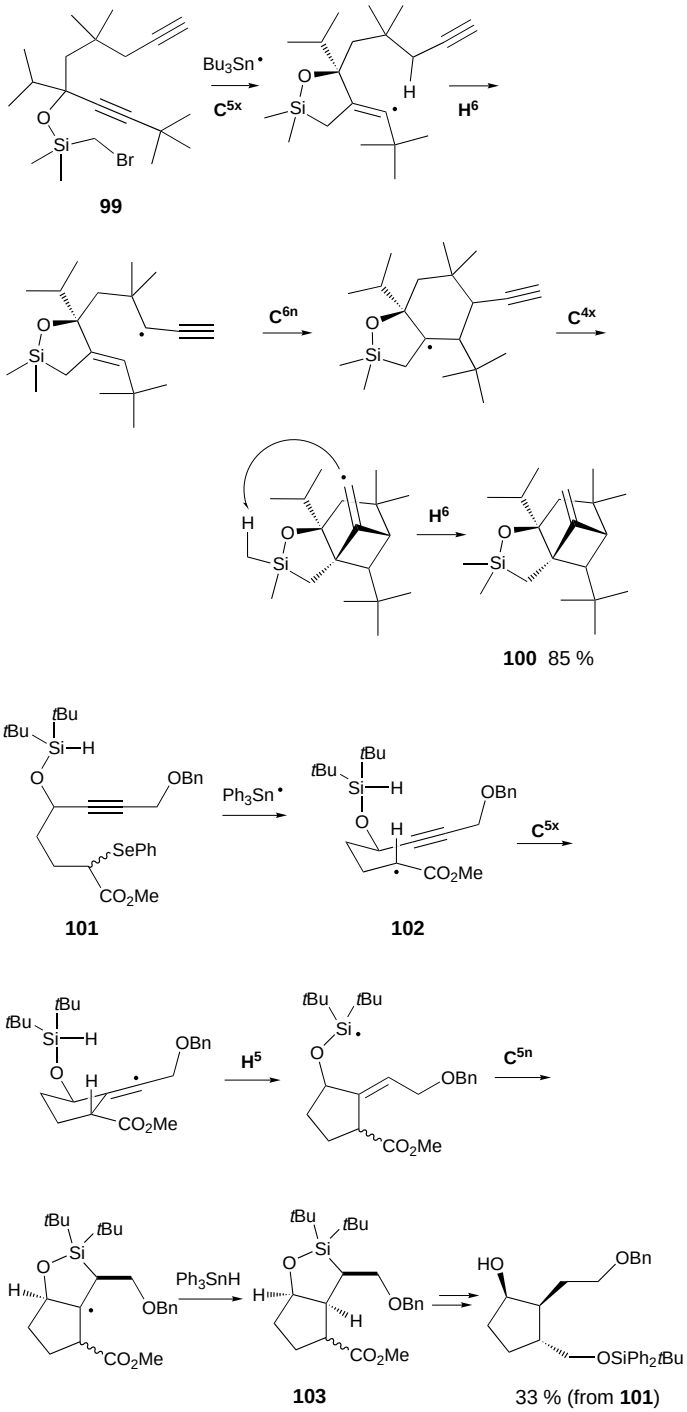
Scheme 28. Cascades starting with cyclization/H migration steps.

5-*exo* cyclization/1,6-H shift/6-*endo* cyclization sequence was not too surprising, but this was followed by an exceptional 4-*exo* cyclization, which was trapped by the sequential 1,6-H shift. The 85 % yield of tricyclic product **100** was also remarkable, and the reaction occurred with good stereoselectivity.

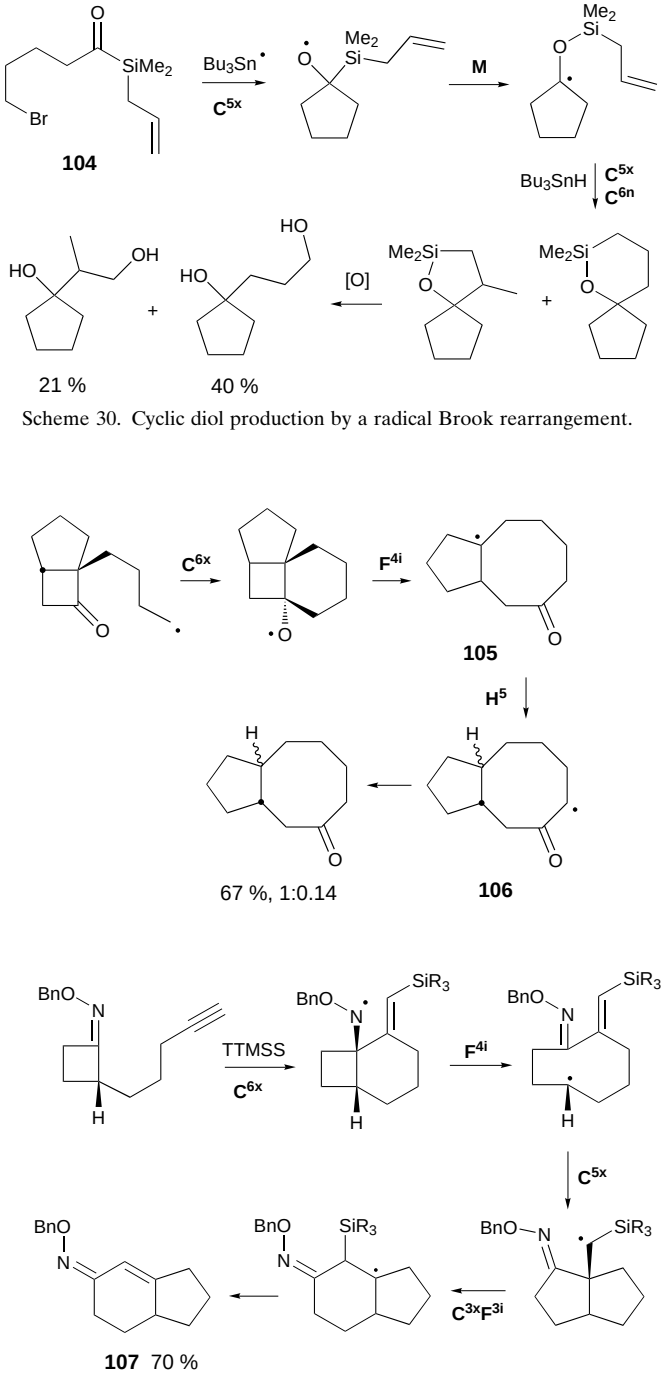
A $\mathbf{C^{5x}H^5C^{5n}}$ cascade starting from acetylenic selenide **101** and leading to a methyl *epi*-jasmonate precursor has also been reported (Scheme 29).[137] The first cyclization took place from the preferred conformer (**102**) of the initial radical in which the ester group was *trans* to the O–Si unit. The second cyclization to give **103** was a normally disfavored $\mathbf{C^{5n}}$ type, but presumably *endo* approach was permitted because of the longer Si–O and Si–C bonds associated with the Si-centered radical.

The radical Brook rearrangement involves a concerted 1,2-shift of a silicon group from a carbon atom to an oxygen centered radical. Tsai et al. developed this into an effective synthetic method, in which an acylsilane (e.g. **104**; Scheme 30) acts as a geminal radical acceptor/donor.[138] The basic process is a **CM** cascade, that transforms a cycloalkyloxyl radical to a cycloalkyl radical. The advantage occurs when further reactions take place such as a subsequent cyclization leading, after hydrolysis, to diol production (Scheme 30).

Extensions of the **CF** (Dowd) type of ring-expansion sequence take various directions including **CCF** processes,[139] and a rare $\mathbf{C^{6x}F^{4i}H^5}$ sequence (Scheme 31) resulting in the intermediate bicyclo[6.3.0]undecanone radical **106** (an α-acyl



Scheme 29. Cascade transformations of silyl ethers.



Scheme 31. Synthesis of bicyclic systems by sequences starting with cyclization/ring cleavage.

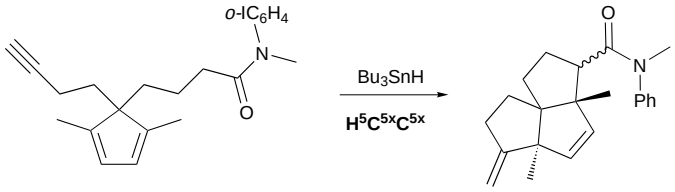
radical).[84c] The hydrogen shift in **105** is permitted because of the mainly *trans* configuration of the ring junction.

The scope of **CFC** sequences, including the effects of varying ring size and competing hydrogen transfers, have been studied,[139] and one was employed in a syntheses of *cis*-decalins.[140] Many permutations of an ingenious theme embodying cyclization onto a methylenecyclopropane unit, with subsequent ring opening, have been explored.[141] The consequent **CFC** cascades mediated by tin hydride have produced bicyclic systems [141c] and spirocycles,[141d] and the reaction has been extended to **CFCC** sequences for the synthesis of tricycles,[141e] and, notably, in the diastereoselective synthesis of paeonilactone B (see Scheme 5, Section 1.2).[141b]

Unusual cascades involving cyclization onto an oxime ether followed by fragmentation to a medium-sized ring and subsequent transannular cyclization, were investigated by Pattenden et al. The processes that occurred sequentially, depended on subtle structural differences in the systems used. A remarkably intricate $\mathbf{C^{6x}F^{4i}C^{5x}C^{3x}F^{3i}}$ sequence, that contained two separate ring expansions, ended in the formation of

bicyclic oxime ether **107** (Scheme 31).[142] Other syntheses involving **CF** sequences have been reported.[143, 144]

The usefulness of PRT sequences has been referred to (see Section 2.5), and an **HCC** sequence that afforded angular triquinane **108** based on this methodology has been reported (Scheme 32).[90a] The technique has been further developed: for example the method was used in the formation of γ-lactams.[132, 145]



108 75 %

Scheme 32. Triple cascade involving protection/translocation (PRT) methodology.

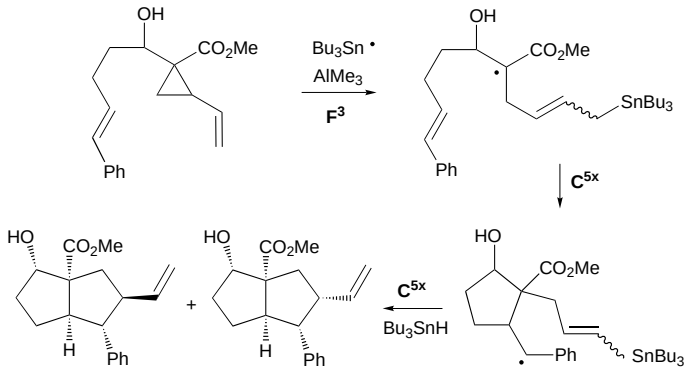
3.3. Multiple-Step Cascades Starting with Ring Cleavage

The butenyl unit, generated on cleavage of a cyclopropylmethyl radical, may eventually act as the acceptor in a subsequent cyclization. Consequently, cascades of the **FCC** type have been quite popular. A recent example demonstrated the excellent stereoselectivity that a Lewis acid can induce: Renaud et al. designed an $\mathbf{F^3C^{5x}C^{5x}}$ cascade that produced functionalized bicyclo[3.3.0]octanes **109a**, **b** (Scheme 33).[146] In the absence of trimethylaluminum at least eight stereoisomers were obtained, however, addition of this Lewis acid controlled the stereochemical outcome so that only two isomers were formed in a combined yield of 56 %.

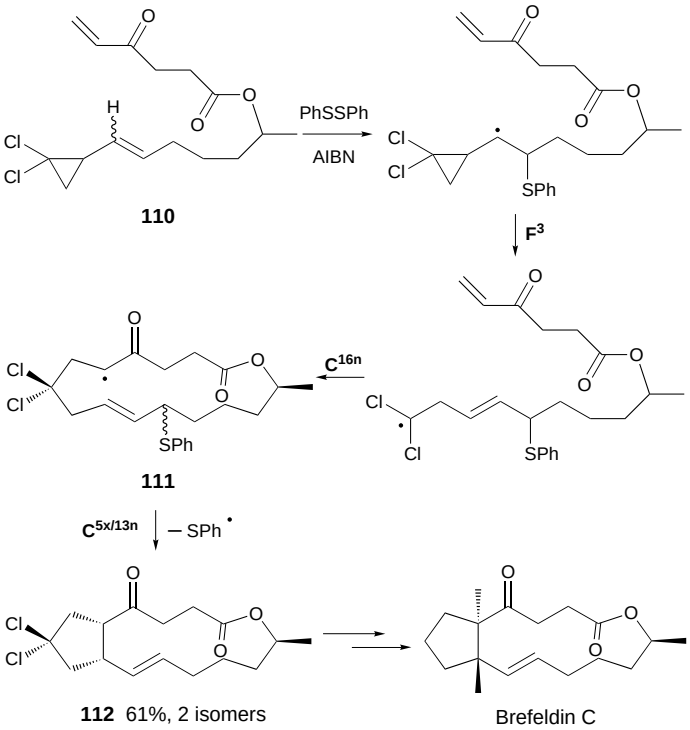
The brefeldin skeleton was obtained by addition of phenylsulfenyl radicals to the vinylcyclopropane **110**.[147] Ring opening was followed by an *endo* macrocyclization to intermediate **111** which underwent a further cyclization and final loss of a phenylthiyl radical. The complete $\mathbf{F^3C^{16n}C^{5x/13n}}$ sequence led to 13-membered cyclic lactone **112** (Scheme 33).

The tricyclic core structure (**113**) of laurenene was prepared using the $\mathbf{F^{6i}C^{5x}C^{5x}}$ process shown in Scheme 34.[148] Stereochemical control was critical to the success of this reaction; a *cis* arrangement of the allylic side chain and the hydroxyl group occasioned unwanted 1,5-migration of the allylic hydrogen. Axial substituents were also found to render the final cyclization unfavorable. Crimmins et al. described a series of cascades comprising a ring opening, followed by a ring expansion, that is, **FCF** sequences, as exemplified by the $\mathbf{F^{4o}C^{3x}F^{3i}}$ transformation leading to tricyclic ketone **114** (Scheme 34).[149]

Iminyl radicals were generated by treatment of polycyclic imines (such as **115**) with tributyltin radicals. Cleavage of the four-membered rings started cascades that, for certain stereochemical arrangements, promoted 1,5-hydrogen migrations.[150] For example, radical **116a** underwent a 1,5-H shift followed by rapid cleavage of the four-membered ring ($\mathbf{F^4H^5F^4}$) whereas isomeric radical **116b** underwent no further



109a,b 56 % (1:1.3)



110

111

112 61%, 2 isomers

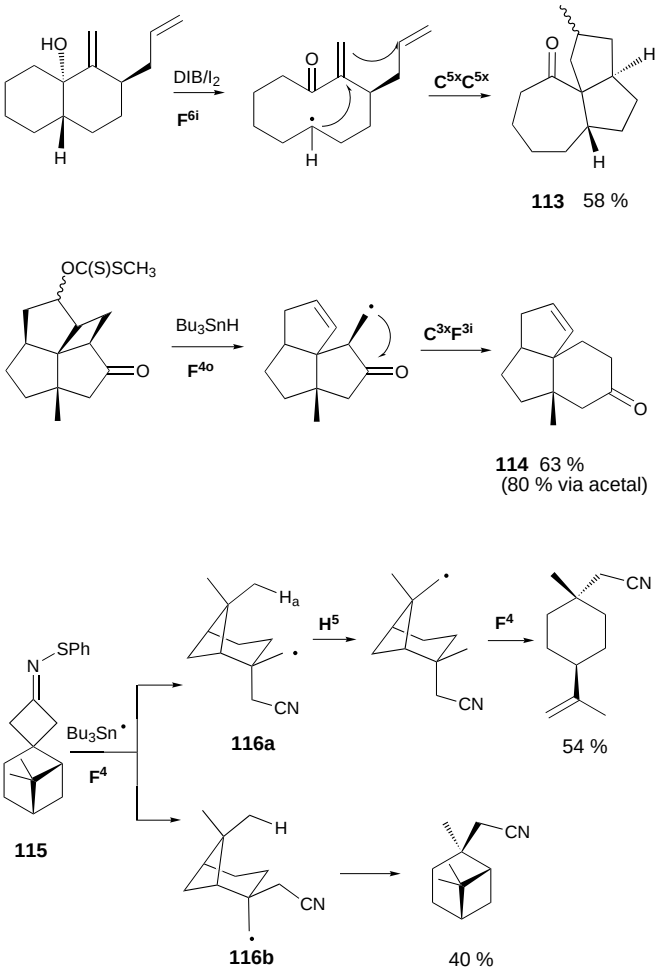
Brefeldin C

Scheme 33. Cascades involving ring cleavage followed by cyclization.

rearrangement (Scheme 34). Remarkably, abstraction of H_a in **116a** appeared to be facile, despite the fact that the resulting radical was primary.

Elegant **FHC** sequences were executed as routes from bicyclic epoxides to both linear and angular triquinanes (**117**, Scheme 35).[151, 152] Catalytic amounts of diphenyl disulfide were used to mediate the reactions.

Ziegler and Peterson described an unusual sequence starting with epoxide **118** and leading by an $\mathbf{F^{3o}F^3H^5}$ cascade to formation of the prostaglandin B_1 skeleton **120** (Scheme 35).[153] Two three-membered ring openings resulted in the formation of radicals **119a** and **119b**, which were in rapid equilibrium (presumably because of reversible closure/opening of the epoxide ring). Only the *cis* isomer **119b** could undergo the 1,5-H transfer. Synthesis of prostaglandin B_1 from **120** was straight forward.

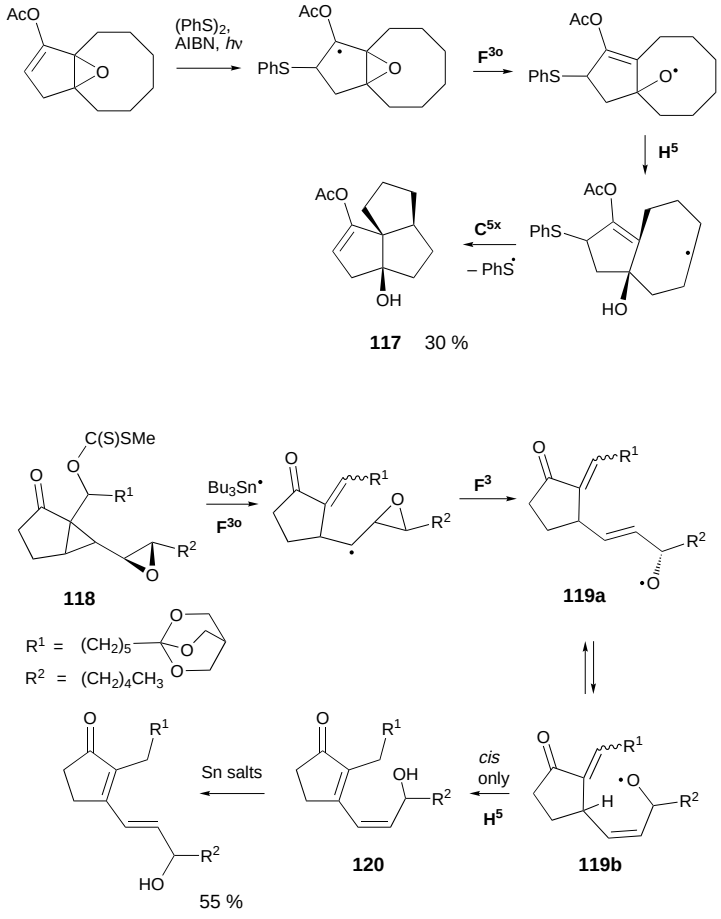


Scheme 34. Cascades involving ring cleavage, cyclization and H-migration; DIB = (diacetoxyiodo)benzene.

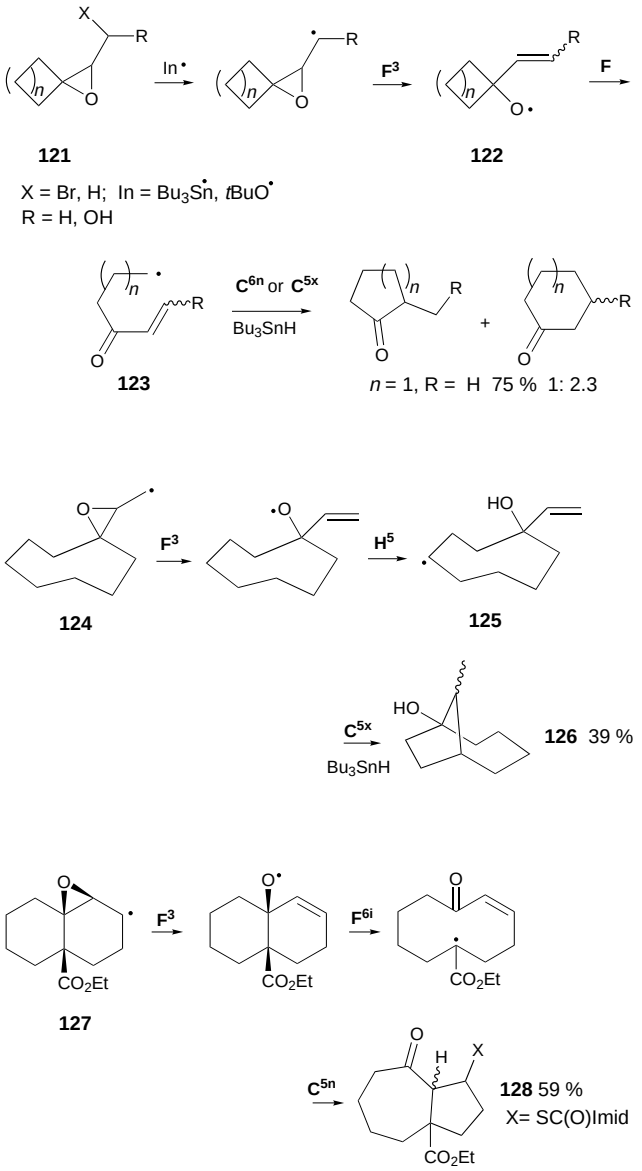
The potential for a short two-carbon ring expansion of cycloalkanones by **FFC**-cascade rearrangements of spiroepoxides **121** has been thoroughly examined (Scheme 36).[154, 155] The reactions all had the same premise; initial ring opening of the epoxide to generate an alkoxyl radical **122** that would ring open a second time to generate an alkyl radical **123**, ready for the final cyclization (Scheme 36). This cascade entails changes in hybridization at five of the original atoms yet the molecules were found to traverse this complex reaction coordinate with ease. The enone system in intermediate **123** was expected to enhance *endo*-cyclization but, although this predominated for most ring sizes, closure was not selective enough for the cascade to function as a general and efficient two-carbon ring expansion. Furthermore, it was found that for the larger rings, 1,5-H transfer was competitive with ring opening of the alkoxyl radicals.[154a] For example, radical **124** ($n = 5$) underwent ring opening and H migration to produce vinylcyclooctyl radical **125**, that took part in a final cyclization process to yield bicyclo[4.2.1]nonanol derivative **126**. Overall this amounted to an $\mathbf{F^3H^5C^{5x}}$ process.

Suárez et al. have taken advantage of the ready ring cleavage of cyclohexyloxyl radicals by means of a series of cascades in which an alkoxyl radical was generated from the corresponding alcohol using (diacetoxyiodo)benzene and iodine.[156] Most of these sequences incorporated intermolecular addition of oxygen, but an **FF** process in which the second fragmentation involved the ring opening of a cyclopropyl ring was described.[156] A combination of these rearrangements was utilized in syntheses of medium-sized, fused-ring polycyclics **128** (Scheme 36).[157] The overall sequences were $\mathbf{F^{3o}F^{6i}}$ or $\mathbf{F^{3o}F^{6i}C^{5n}}$, depending on conditions, which could be adjusted to favor either sequence.

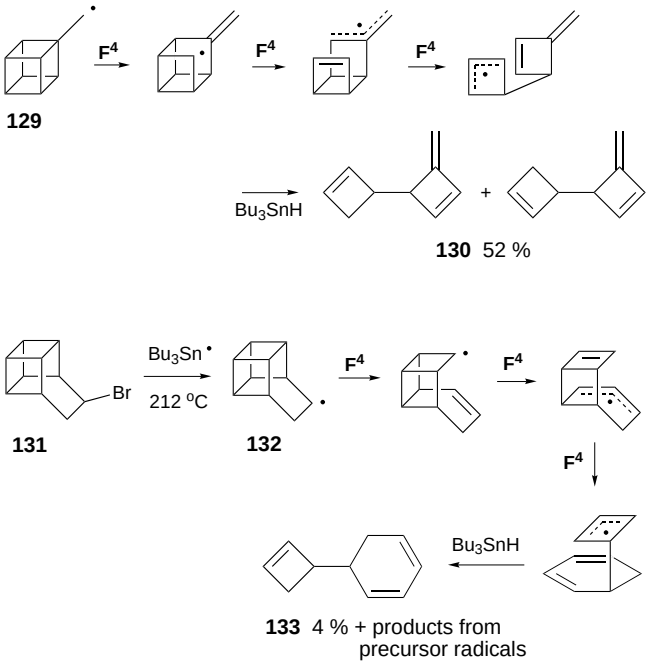
Most fragmentations found in cascade sequences embody cleavage of three- or four-membered rings. It follows that cascades of three or more fragmentations are rare because of severe problems in the preparation of precursors containing so much strain. Moreover, such cascades are essentially degradative, unraveling laboriously assembled structure and symmetry, and hence are usually of mechanistic interest only. Nevertheless, a few triple-fragmentation sequences have been investigated, notably those based around precursors with cubane and related structures. The cubylmethyl radical **129** was generated in several ways and found to rearrange very rapidly by a series of three **F**^{4} ring-opening steps (Scheme 37). Under appropriate conditions, just two isomeric methylenedicyclobutenes **130** were obtained as products, although by use of good hydrogen donors most of the intermediates radicals could be trapped,[158] and several were characterized by EPR spectroscopy.[159] The ring-opening steps were strictly



Scheme 35. Cascades starting with epoxide ring-cleavage processes.



Scheme 36. Cascade expansion/rearrangement of spiro and tricyclo epoxides.



Scheme 37. Triple-fragmentation cascades of cubylmethyl and basketyl radicals.

stereoelectronically controlled and rate constants were estimated for each.

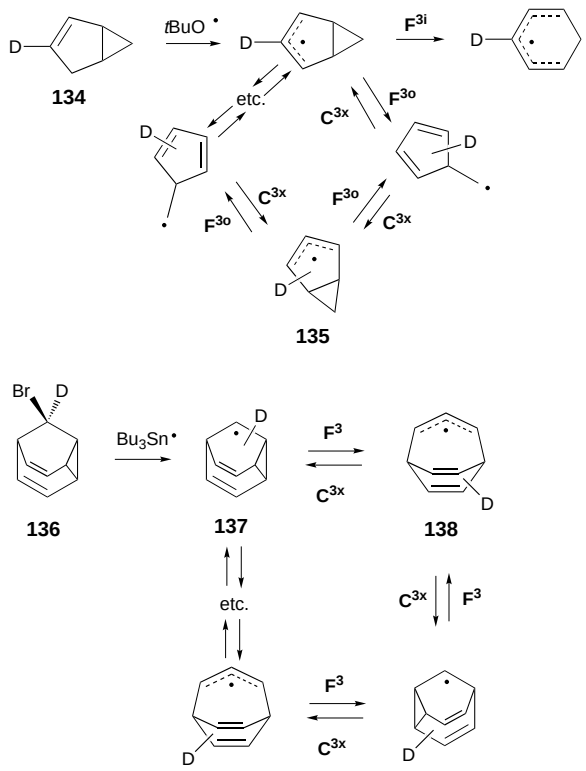
Remarkably, the 9-bishomocubyl (basketyl) radical **132** did not rearrange at 150 °C even though it contained approximately 470 kJ mol^{-1} strain. However, at 212 °C the tributyltin hydride mediated reaction of basketyl bromide **131** resulted in 5-(cyclobut-2-enyl)cyclohexa-1,3-diene **133** by a triple **F^{4}F^{4}F^4** cascade (Scheme 37) analogous to that sustained by radical **129**.[160] Impressively, considering its internal strain, the 9-homocubyl radical did not follow suit even at 220 °C.

4. Repeating and Infinite Free-Radical Cascades

In certain circumstances the rate of a **C**, **M**, **H**, or **F** rearrangement may be similar or even equal to that of its reverse rearrangement. As indicated in the introduction, ring opening is the reverse of cyclization and hence partial, or total, reversals of cascades containing **CF** sequences are permitted. In particular, the **F^3** ring opening is the reverse of the **C^3** cyclization and hence, in special cases that usually involve symmetric bi- and polycyclic species, cascades can occur that are degenerate, that is, return a radical to its original structure.

One such cascade is the "walk" or "circumambulation" established for the bicyclo[3.1.0]hexenyl radical (Scheme 38, top). Initial hydrogen abstraction from bicyclo[3.1.0]hex-2-ene gave the expected bicyclo[3.1.0]hexenyl radical, which rearranged by scission of its inter-ring bond (**F^{3i}**) to give a cyclohexadienyl radical and hence to the product benzene. Experiments with deuterium labeled precursors (**134**) showed that the label was statistically scrambled to every possible site in the intermediate cyclohexadienyl radical (**135**). This was rationalized by a cascade involving an infinite sequence of β scission (**F^{3o}**) and cyclization reactions (**C^{3x}**), the products being bled off by the competing **F^{3i}** ring cleavage (Scheme 38).[161, 162] Various substituted examples were studied spectroscopically.[162] Delicate balances of rearrangement possibilities can easily be redirected by structural changes. This was illustrated by the fact that the vinylogous bicyclo[5.1.0]octa-2,4-dienyl radical did not undergo an analogous walk.[163, 164]

A three dimensional analogue of the "walk" rearrangement has also been discovered. Tributyltin hydride reduction of 9-bromotricyclo[3.3.1.0^{2,8}]nona-3,6-diene (9-bromobarbaralane) gave bicyclo[3.2.2]nona-2,6,8-triene (83 %) together with unrearranged barbaralane (2 %).[165] Spectroscopic and deuterium-labeling (**136**) studies established that a remarkable series of ring-opening/cyclization steps rendered the structure fluxional and distributed the unpaired electron to



Scheme 38. Repeating cascades involving infinite sequences of ring-cleavage/cyclization steps.

every carbon (Scheme 38, bottom).[166] The tricyclo[3.3.1.$0^{2,8}$]-nona-3,6-dienyl radical **137** was transformed to the bicyclo[3.2.2]nona-2,6,8-trienyl radical **138** by an $\mathbf{F^3}$ ring cleavage. The process could be reversed by means of four possible $\mathbf{C^{3x}}$ cyclizations. However, radical **138** was stabilized by allyl-type electron delocalization and hence was the predominant partner in the equilibrium. Series of $(\mathbf{C^{3x}F^3})_n$ sequences (part shown in Scheme 38) scrambled deuterium to every site.

5. Summary and Outlook

The science of "programming" organic precursor molecules to achieve particular target structures by multiple step sequences of radical rearrangements is maturing steadily. A phenomenal variety of unimolecular radical cascades exist in which a single molecule undergoes a complete metamorphosis by means of combinations of four fundamental rearrangement types, with occasional assists from more exotic processes. These cascades are mainly responsible for dramatic skeletal reorganizations, rather than functional-group manipulations, although every cascade involves some functional-group alterations, usually in the initiation and/or termination stages. Multiple cyclization sequences build up polycyclic structures while hydrogen and group migrations transfer (translocate) radical centers. Ring cleavage processes undo prearranged structure but, because they usually introduce unsaturation, make subsequent cyclizations possible.

A convenient system for classifying free-radical cascades has been devised, based on combining the mechanisms of individual steps in such cascades. Every cascade can be represented by a multiletter that indexes the process. These codes display the component steps, give clues about the reaction course, and are useful for relating cascades to each other, for evaluating and comparing cascades and for inferring their mechanisms.

3-Step cascades of $\mathbf{C^{5x}}$ cyclizations typically produce linear and angular triquinanes and related polycycles. Many natural products containing all or parts of these skeletons, and analogues with one, two, or three six-membered rings, have been synthesized by this method. Acyl radicals preferentially cyclize in the $\mathbf{C^{6n}}$ mode to produce six-membered rings, and this mode can also be programmed by inclusion of methyl groups, five atoms away from incipient radical centers, at unsaturated bonds. By these means many partial and complete steroidal skeletons have been assembled. Stereoselectivity is often good even for acyclic precursors, but several strategies have been developed to facilitate closer stereochemical control. The one-ring template strategy starts with precursors containing five- or six-membered rings that then direct the stereochemistry of two or more cyclizations. Combinations of all these parameters have enabled impressive syntheses of many types of terpenoid, steroid, and alkaloid natural products.

Of the many intricate cascades containing ring-cleavage steps, the most useful synthetically are the ring expansions which have opened up synthetic routes to various types of medium-ring cycles and polycycles. Ring cleavage is the reverse of cyclization. In special, symmetrical structures, therefore, this can lead to sequences that are reversible, thus launching endlessly repeating cascades supported by delightfully fluxional structures.

Of the 64 possible three-stage cascades only about 16 have so far been investigated, with interest concentrating heavily on **CCC**, **CHC**, **CFC**, and **FCC** sequences. Cascades starting with hydrogen or group migrations have hardly been touched. The discovery field for four-stage and longer cascades is even more vast because fewer than 10 such sequence types have been examined to date. Of course, multiple cyclization cascades, particularly longer ones, are likely to maintain their priority of interest because they rank amongst the most powerful strategies for rapid syntheses of polycyclic structures. Cascades ending in heterocycle production currently represent quite a small proportion of the total and there is obviously major scope for expansion into, for example, nitrogen-containing heterocycles and alkaloids as well as oxygen-and sulfur-containing heterocycles. So far only a few cascades have been subject to detailed mechanistic and kinetic analysis. The unique structural distributions of rings, unsaturated bonds, and radical centers achievable in polycyclic intermediates invites disfavored steps and enhances favored ones. The doorway to kinetic and thermodynamic quantification of unusual and esoteric steps is therefore enticingly open.

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