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Free Radical Cyclizations Involving Nitrogen

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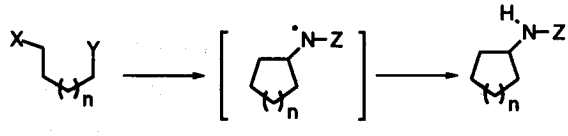
INTRODUCTION

Free radical reactions have stimulated the research interests of organic chemists for nearly a century.[1] However, it is only in the last two decades that this knowledge has been widely utilized in diverse areas of organic chemistry. Thus free radical reactions have evolved to join their counterparts, electrophilic, nucleophilic, and pericyclic processes in the arsenal of the synthetic organic chemist. This explosive growth has resulted in both increased understanding of the basic chemistry and the application of various intramolecular sequences to the synthesis of a vast array of carbocyclic and heterocyclic systems (Scheme 1). Several books and review articles have documented these achievements, including the synthesis of diverse

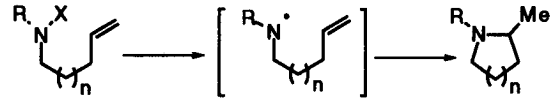


n = 1, 2, 3

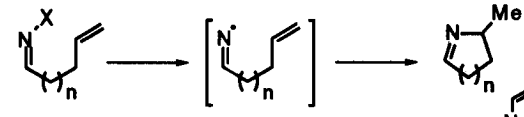
X = Br, I, SR, SePh, O(C=S)OPh, O(C=S)Im, also C-X = C=O, $CBr=CH_2$, C≡C−H, $CH=C=CR_2$

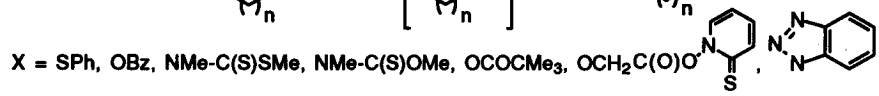
Y = C=N-OR, $C=N-NR_2$, C=N-R, C≡N, N_3

Z = OR, NR_2 , R, H, NR, N_2

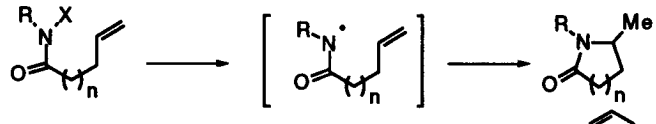


X = N=NR, Li, N_2, SPh, Cl, SePh, $C(O)O$





X = SPh, OBz, NMe-C(S)SMe, NMe-C(S)OMe, $OCOCMe_3$, $OCH_2C(O)O$,



X = Cl, NO, NMe-C(S)SMe, NMe-C(S)OMe, $OCOCMe_3$, $C(O)O$

Scheme 1

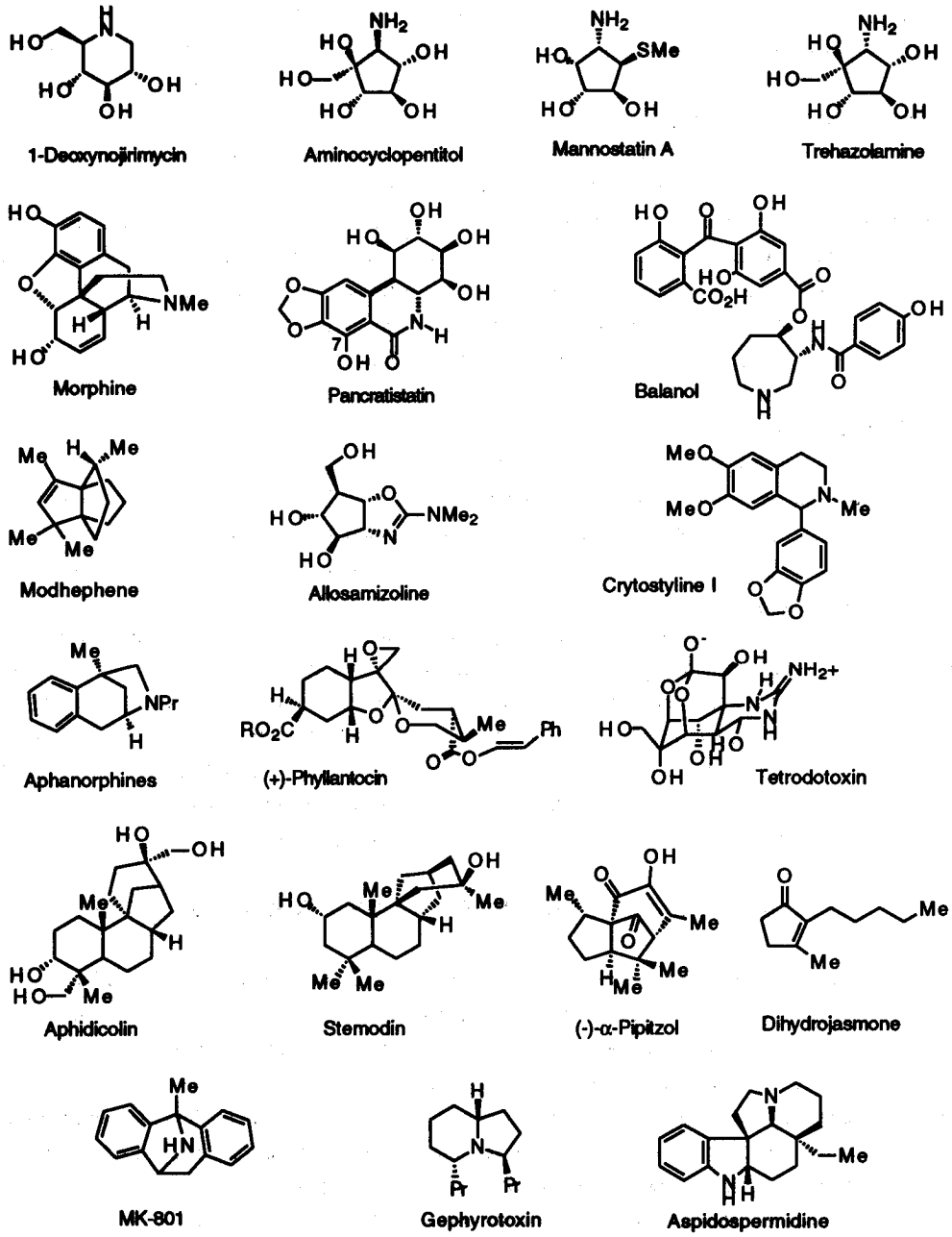


Figure 1. Natural Product Targets

natural products (Figure 1).[2] This is a consequence of the mild, neutral reaction conditions, the compatibility of these conditions with various functional groups, the body of kinetic data that is available and the level of regio- and stereoselectivity that can now be achieved. Future developments will undoubtedly lead to even greater progress and understanding.

The majority of these studies have concentrated on the examination and utilization of carbon based radicals interacting with alkenes and related carbon based unsaturated systems. Heteroatom acceptors such as carbonyl groups, imines, nitriles, and related systems have received much less scrutiny. This is rapidly changing. The initial sections of this review summarize a cross section of intramolecular reactions of carbon based radicals onto unsaturated acceptors in which part of the π component is nitrogen. In addition to these examples, the cyclization reactions of nitrogen centered radicals onto various acceptors are also discussed. These features are highlighted in simplified form in Scheme 1. Radical intermediates are displayed in brackets but other intermediates are not.

The emphasis has been placed on intramolecular cyclizations as these reactions have received the most study. In addition they are among the most useful for the synthesis of the multitude of five-, six-, and seven-membered ring systems, as well as the more complex fused and bridged ring skeletons found in nature. A cross section of the natural product skeletons, aglycones and related targets that are of current interest are compiled in Figure 1. In several cases total syntheses have not been completed but closely related intermediates and analogs have been synthesized. The near future will likely see the number of these targets expanded significantly. In order to avoid large tables of data, representative examples from various publications have been selected so the interested reader can accumulate the important features by "reading structures" and consult the primary literature for more details. To aid comparisons product ratios have been converted to percentages where feasible. Kinetic measurements and rate constants are mentioned in passing where appropriate. To avoid unnecessary duplication a separate section is devoted to a brief discussion of rate constants for reductions (quenching) and cyclizations for nitrogen and relevant carbon centered systems. To facilitate comparison and synthetic planning these values are tabulated in structural form in a Petite Horlogerie.

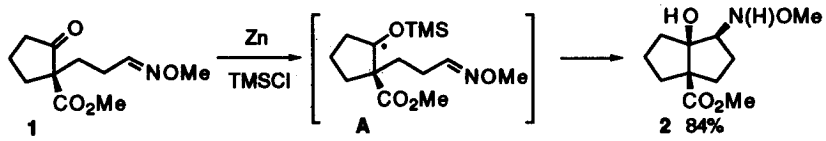
CYCLIZATIONS onto CARBON-NITROGEN UNSATURATED SYSTEMS

Historically the oxime ethers were the first of the important unsaturated nitrogen functional groups to be employed in synthesis. Nitriles also have been recognized and exploited as useful, but capricious, radical acceptors for many years. However, detailed examination of the hydrazones and imines are of more recent vintage. In practice the use of an imine functional group (oxime ether, hydrazone, imine, etc.) alters the normal electronic character of the carbonyl group. Generally carbonyl acceptors are less satisfactory as radical acceptors than either alkene or imine systems. This is a consequence of the fact that the rate of ring opening of the oxygen radical is similar to the cyclization rate. As discussed below, the 5-*exo* cyclization rate onto carbon-nitrogen double bonds is usually more rapid than the rate for simple alkenes. These reactions also illustrate several of the desirable features that accrue from addition to a functionalized acceptor. A liability inherent in classical radical cyclization precursors, such as unsaturated organic halides, is the net loss of the two participating functional groups. This does not arise with heteroatom acceptors but instead generates

products that retain synthetically useful functionality for subsequent manipulation, particularly when ketyl or stannyl substituted radicals are employed. If desired, the nitrogen may be extruded to afford carbocyclic systems. Consequently, the study and application of oxime ethers and related acceptors has expanded greatly in recent years.

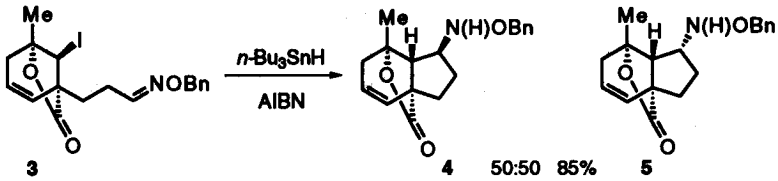
Oxime Ether Acceptors

One of the first examples of the cyclization of a carbon centered radical onto a C=N π system was reported by Corey and Pyne[3] in 1983. This early study involved the cyclization of the trimethylsilyl protected ketyl radical **A**, generated *in situ* by treatment of a suitable cyclopentanone, such as **1**, with zinc-trimethylchlorosilane to afford the diquinane amino-alcohol **2** in 84% yield as a single diastereomer (Scheme 2). Oxime ethers are thus efficient radical traps.



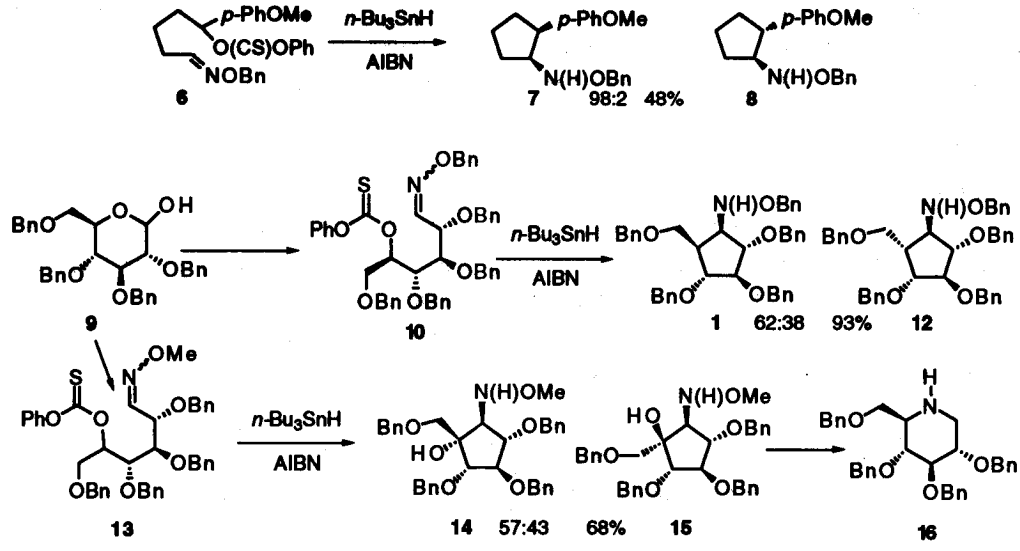
Scheme 2

In 1988 Hart and Seely[4a] demonstrated that the radicals generated from halo or seleno precursors with bis(trimethylstannyl)benzopinacolate (Me_3SnOPh_2C-CPh_2OSnMe_3) added readily to *O*-benzylformaldoxime. They also reported that the bicyclo iodo-lactone **3** cyclized in the presence of tributyltin hydride to afford a 50:50 diastereomeric mixture of the perhydroindans **4** and **5** in 85% yield (Scheme 3).



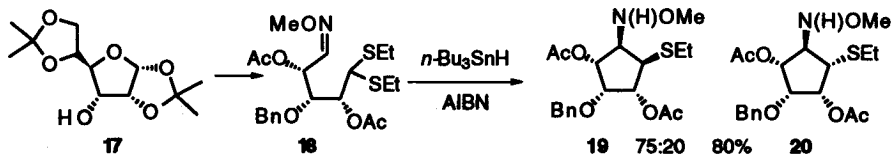
Scheme 3

In the following paper, Bartlett and coworkers[5] described the synthesis of both cyclopentane and cyclohexanes. They employed *O*-benzyloxime ether acceptors for the capture of radicals formed from bromide or phenyl thionocarbonate precursors. As expected the yield varied with the substitution pattern and ring size. The yields ranged from 42-89% for five membered rings and from 18-71% for the cyclohexanes. With the *p*-methoxyphenyl substituent contained in **6** the yield of **7** and **8** was 48% with a *cis:trans* ratio of 98:2. This ratio decreased to ~50:50 in other less hindered cases. However, because of the bulky substituent and the increased radical stability, the cyclization rate was diminished and a significant amount of the initial radical was captured as the phenyl ether, reducing the yield of cyclized material. This chemistry was extended further to an interesting carbohydrate to carbocycle conversion. Related sequences have become very popular. Thus the benzyl protected D-glucose **9** afforded a 62:38 ratio of **11** and **12** in 93% yield (Scheme 4).



Scheme 4

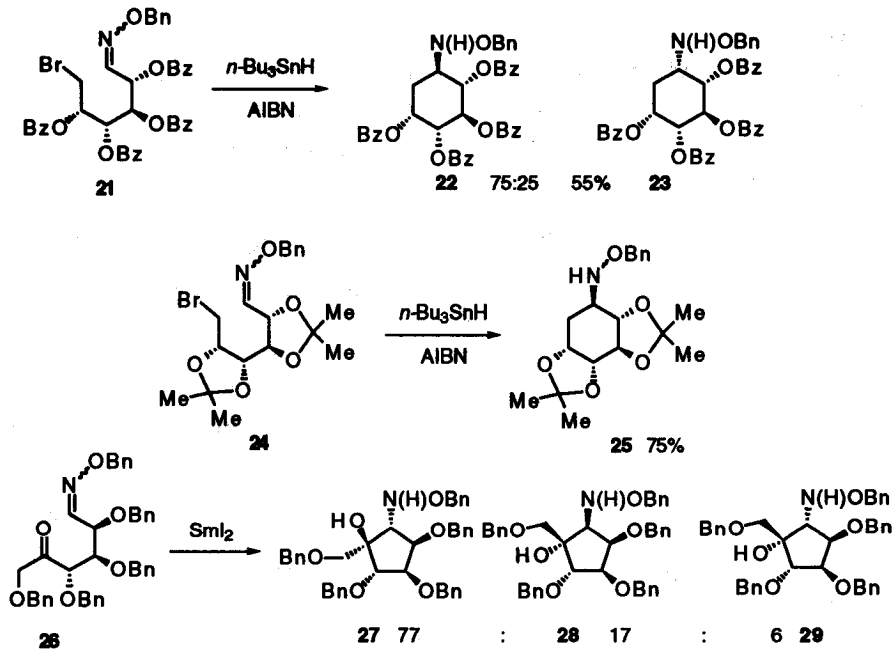
In recent years a number of glycosidase and chitinase inhibitors have received attention due to their potential to treat various metabolic disorders, as well as viral and yeast infections. The investigations of Naito and coworkers[6a] also commenced with the tetrabenzyl hemi-acetal **9** (Scheme 4). The resulting keto-oxime ether **13** cyclized to the *cis* and *trans* mixture of **14** and **15** in 68% yield in a 57:43 ratio. Further manipulation of **14** afforded the tetrabenzyl ether **16**, an intermediate for the synthesis of 1-deoxynojirimycin (Figure 1). Moore and coworkers[7] commenced with D-allofuranose and synthesized a derivative of the sugar hydrolase inhibitor mannostatin A (Figure 1) from the bisisopropylidene derivative **17**. In this instance the radical intermediate was derived from the dithioacetal **18**,[8a-c] which under tributyltin hydride conditions afforded **19** and **20** in a ratio of 75:25 (80%) (Scheme 5).



Scheme 5

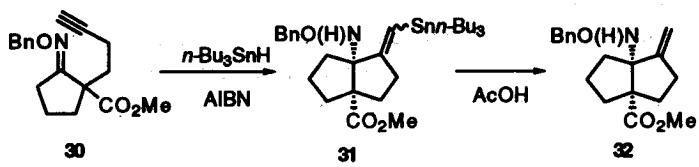
Similar chemistry, developed by Marco-Contelles and coworkers[9a] from D-ribose precursors afforded mannostatin A analogs. They have also synthesized cyclohexyl amino alcohols via 6-*exo* cyclizations of the acyclic carbohydrate derived benzyl oxime **21**.[9b] Cyclization proceeded in 55% yield to provide a 75:25 mixture of **22** and **23**. The stereoselectivity is improved significantly when the number of conformers is restricted due to the presence of isopropylidene acetals. Thus the oxime ether **24** in the *gluco* series cyclized in 75% yield to the carbocycle **25** with a diastereomeric excess of 82%. Similar results have been achieved from

5-*exo* cyclizations to give homochiral cyclopentanols.[9c] In related recent studies,[9d] samarium diiodide has been used for the reductive coupling of the carbonyl and oxime functions in **26** to give the three cyclic alcohols **27**, **28**, and **29** in a 77:17:6 ratio (Scheme 6). The major isomer was converted to trehazolamine (Figure 1), the aminocyclopentitol aglycon of the trehalaze inhibitor trehazoline.



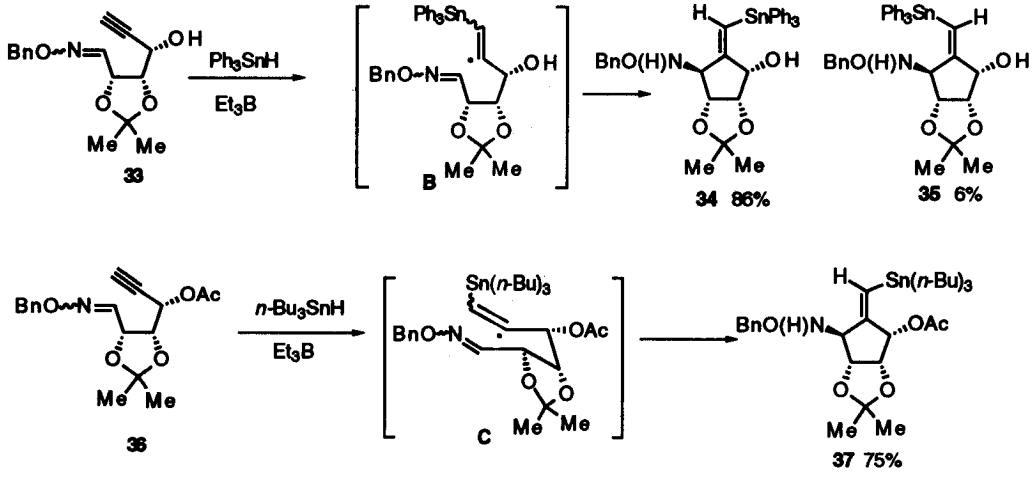
Scheme 6

Vinyl radicals also add readily to oxime ethers in an intramolecular manner in both the 5-*exo* and 6-*exo* modes. Terminal alkynes undergo free radical hydrostannylation to generate a vinyl stannane radical that cyclizes readily onto an attached benzyloxime ether. The utility of the direct cyclization from a vinyl radical onto an oxime ether was investigated by Enholm and coworkers.[10] The addition of the tributylstannane radical to the triple bond in **30** (*cf.*, **B**, Scheme 8) was followed by cyclization to **31** which contained a vinyl tin substituent and a protected amine. Subsequent protodestannylation with acetic acid afforded cyclopentanes related to **32** bearing an exocyclic methylene and a protected primary amine (56-90%). This has been followed by more sophisticated examples.



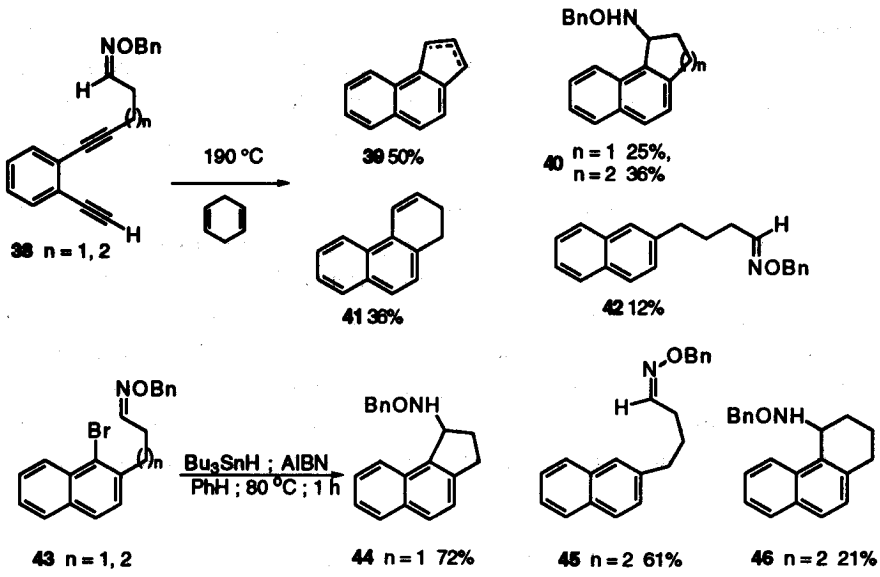
Scheme 7

Related studies by Marco-Contelles and coworkers[9e] have examined the reactions of vinyl radical cyclizations based on carbohydrate substrates (Scheme 8). A representative example commenced with 2,3-*O*-isopropylidene-D-ribose. The addition of triphenyltin hydride to the alkyne **33** in the presence of triethylborane[11] initially afforded the vinyl radical intermediate **B**, which added to the oxime in a 5-*exo* manner to give the cyclopentanols **34** and **35** in 91% yield as a 85%:6% *Z/E* mixture, from which the pure *S* isomer at the new stereocenter was isolated. The high level of stereochemical control for the *trans* product is a consequence of a chair-like early transition state (**C**) in which the majority of substituents adopt a preferred pseudoequatorial orientation. Thus cyclization of **36** afforded **37** in 75% yield as the pure *Z*-isomer. Similar results have been achieved in the D-mannofuranose series to give the other enantiomer and appropriate products have been transformed into various aminocyclopentitols.



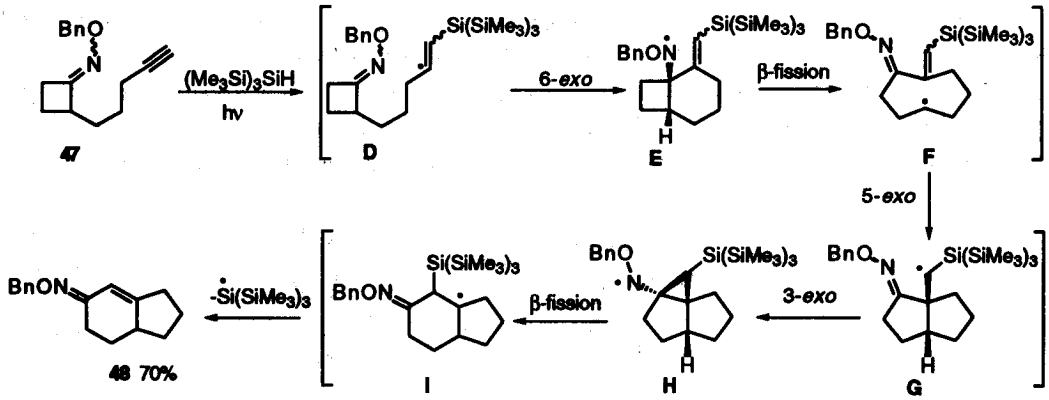
Scheme 8

Benzyloxime ethers are disappointing traps for the tandem cyclization of benzyne radicals generated by cycloaromatization of suitable enediynes. In part, this is a consequence of the high temperatures required for the cycloaromatization which results in elimination of the amino function. Grissom and Klingberg[12a] discovered that at 190 °C, in the presence of 1,4-cyclohexadiene as a hydrogen atom source, the benzyloxy amine **40** was the minor product (25%) from thermolysis of **38** (n = 1). This material was accompanied by the hydrocarbons **39** (50%) due to the elimination of the *O*-benzylhydroxylamine (Scheme 9). Similar complications were encountered in the preparation of cyclohexyl systems from a 6-*exo* addition. Equal amounts of **41** and **40** (n = 2) were formed accompanied by 12% of the quenched naphthalene **42**. In contrast, due to the greater reactivity of phenyl radicals and a lower temperature requirement (80°C), the bromonapthalene **43** (n = 1) afforded a 72% yield of **44** from 5-*exo* cyclization, although the yield was reduced to 21% for 6-*exo* cyclization product **46**, accompanied by the uncyclized naphthalene **45** (61%)[12b].



Scheme 9

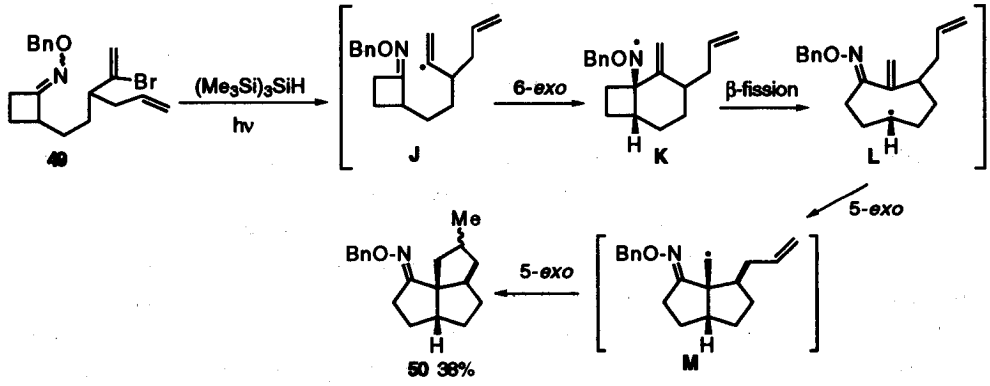
Pattenden and coworkers[13a] have examined an interesting radical cascade sequence for the synthesis of bi- and tricyclic ring systems in which an oxime ether plays a key role. This cascade commenced with the cyclobutanone oxime **47** in which the reaction was initiated by the formation of the vinyl tris(trimethylsilyl)silyl radical **D**. As illustrated in Scheme 10, 6-*exo* cyclization onto the oxime ether, afforded **E**. A β-fission led, in sequence, to the intermediate **F** and then **G** from a second cyclization. A third ring closure afforded the α-cyclopropylaminyl radical **H**. Regeneration of the oxime from a second β-fission to afford **I**, was followed by the final elimination of the tris(trimethylsilyl)silyl radical to continue the chain. Thus the bicyclic product **48** of this novel "one pot" cascade arose via a double ring expansion-cyclization



Scheme 10

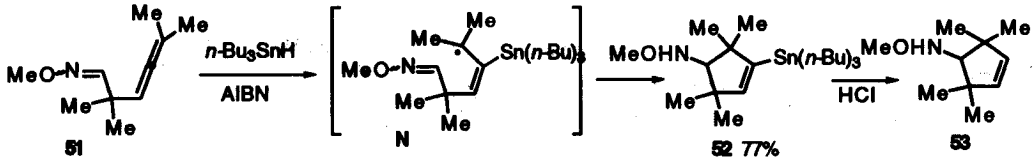
process involving aminyl radicals **E** and **H**. The oxime functionality is thus preserved and the *Z*- and *E*-isomers (93:7) of **48** may be separated. Subsequent hydrolysis generated the corresponding enone. Attempts to prepare a tricyclic nucleus failed, possibly due to the bulk of the trimethylsilyl groups and their rapid elimination at the end of the reaction. The use of a vinyl bromide substrate circumvented this difficulty (Scheme 11).

Thus subsequent studies,[13b] with the appropriate allyl side chain attached, permitted a third cyclization in order to generate a triquinane. Irradiation of **49** in the presence of tris(trimethylsilyl)silane afforded the triquinane **50** as a 1:1 mixture of α- and β-methyl diastereomers in 38% yield (Scheme 11). The product resulted from a cascade radical sequence that utilized a 6-*exo* cyclization, (**J** to **K**), an aminyl radical fragmentation (**K** to **L**), a 5-*exo* radical transannulation (**L** to **M**), and finally a further 5-*exo* ring closure to the tricyclic nucleus. As before the initial functional group was not transformed into an *O*-alkylhydroxylamine as in previous cyclizations above. The retention of the oxime ether in the final product provides a synthetic bonus as it may be hydrolyzed to a ketone, reduced to an amine or alcohol, or eliminated to form an olefin.



Scheme 11

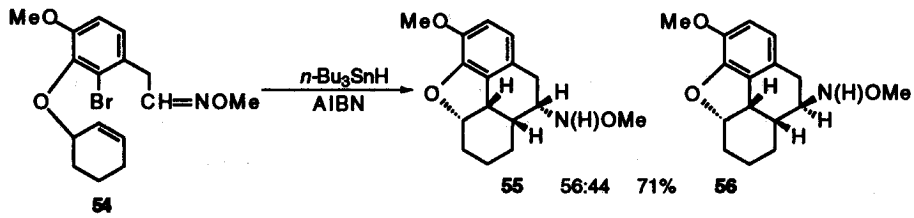
Allenes have received less attention than acetylenes as radical precursors, but Hatem and coworkers[14a] showed that β-allenic *O*-methyloximes underwent a facile free radical hydrostannylation to afford cyclopentenes bearing a protected amine group and a vinyl stannyl functionality in 37-91% yield. Tributyltin hydride added to the middle carbon of the allene **51** to form the allyl radical **N** which cyclized to the cyclopentenyl stannane **52**. Isolation of this material provided a vinyl tin species for further synthetic



Scheme 12

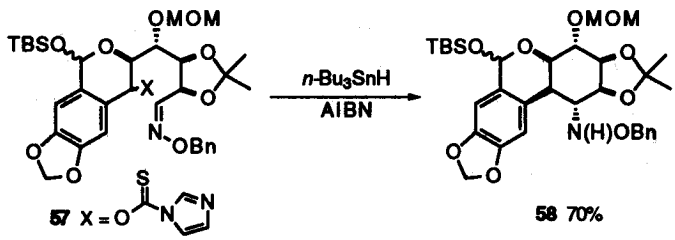
manipulation by exchange reactions. Alternatively these compounds underwent hydrodestannylation with acid to yield amino-cyclopentenes related to **53** (Scheme 12).

The analgesic and addictive properties of the opium alkaloids, plus the widespread use of morphine and its derivatives in medicine, have stimulated considerable research into better analogs with fewer side effects. Progress in this area requires access to the pentacyclic ring system in a direct manner. In a radical based approach to the morphine skeleton Parker and coworkers[15] employed the oxime ether in **54** as the final acceptor in an intramolecular, tandem aryl radical addition to a cyclohexene. This 5-*exo*-6-*exo* cyclization sequence cleanly established the required *cis* ring fusion in the decalin portion but an epimeric mixture at the amino ether center was generated. Unfortunately the required intermediate **56** was the minor isomer, accompanied by the amino epimer **55** in a total yield of 71% (Scheme 13).



Scheme 13

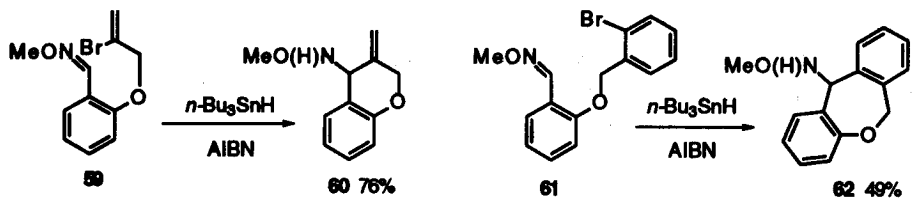
Pancratistatin (Figure 1) is a polyoxygenated tetracyclic alkaloid isolated from *Amaryllidaceae* that displays promising antineoplastic and antiviral activity. The 7-deoxy compound exhibits both better therapeutic properties and decreased toxicity. In their total synthesis of (+)-7-deoxypancratistatin (Figure 1) Keck and coworkers[16] employed a 6-*exo* cyclization of a benzylic radical, generated by deoxygenation of **57**, onto a oxime ether to construct the highly functionalized cyclohexane nucleus. The desired material **58** was isolated in 70% yield as a single stereoisomer at the newly formed centers (Scheme 14).



Scheme 14

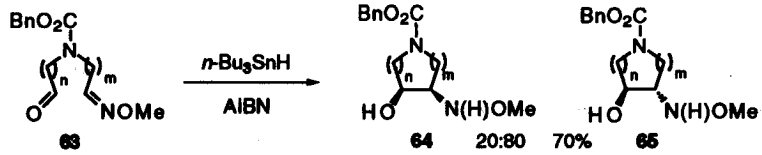
Heteroatoms in the connecting chain between the reactive partners provide access to various heterocycles. Jenkins and coworkers[17] have prepared six and seven membered ring cyclic ethers by cyclization onto aldehyde or methyl ketone derived oxime ethers. These reactions start with either a vinyl or aryl bromide, or, in parallel with the examples above, from tributyltin hydride addition to an acetylenic precursor. Thus treatment of the bromide **59** with tributyltin hydride afforded the heterocyclic olefin **60** in

76% yield. In contrast, the yield of **60** dropped to 52% when a terminal acetylene was used as the substrate. Related five membered ring fused carbocycles were also prepared by this route in yields of 68-90%. The reaction of **61** afforded the oxacycloheptane **62** in 49% yield accompanied by 29% of the reduced starting material (Scheme 15).



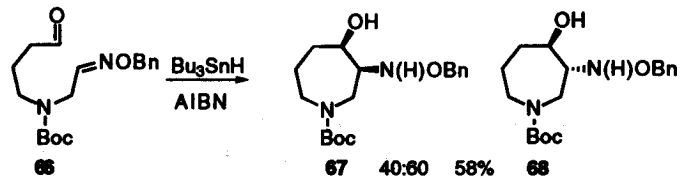
Scheme 15

Naito and coworkers[6b] have examined the synthesis of five, six and seven membered ring nitrogen heterocycles. Thus α-amino cyclic alcohols **64** and **65** were formed from the ketyl radical generated upon treatment of the keto or aldehyde oxime ethers, represented by **63**, with tributyltin hydride in the presence of AIBN. In all cases the *trans* isomer dominated in a range of *cis:trans* ratios from 20:80 to 40:60 in yields of 44 to 70%. The best yield (70%) was obtained for the azacyclohexanol (n = 2, m = 1) (Scheme 16).



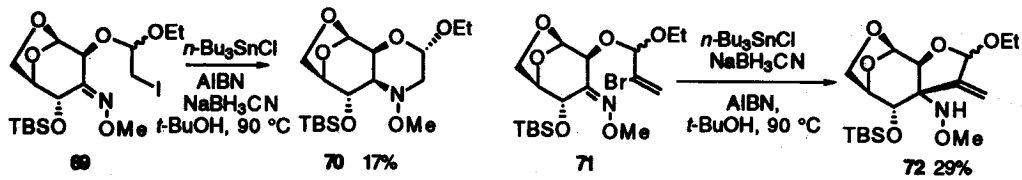
Scheme 16

(-)-Balanol (Figure 1), and its enantiomer, are potent inhibitors of protein kinase C enzymes. It is thus an attractive synthetic target. The hexahydroazepine ring system in balanol contains adjacent amino-alcohol groups in a *trans* relationship which is the predominant stereoisomer in the above examples. Both the *cis* and *trans* isomers **67** and **68** have been synthesized by Naito and coworkers[6c] by cyclization of the ketyl radical derived from aldehyde **66** onto a benzyloxime ether. The products were formed in 58% yield as a 40:60 mixture (Scheme 17). The major isomer was resolved for conversion to (-)-balanol.



Scheme 17

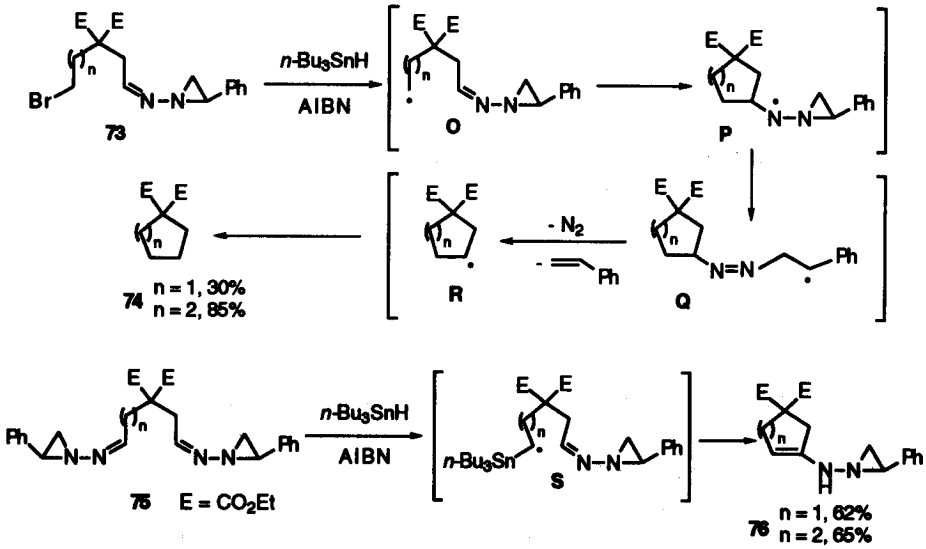
The puffer fish poison tetrodotoxin (Figure 1) is of fundamental interest due to its interaction with various sodium channels. Alonso and Noya[18] have employed an oxime ether as a receptor in a 1,6-anhydromannose derivative to construct an ether bridge. Standard conditions with tributyltin hydride gave only reduced material with either the iodide **69** or the corresponding bromide. Unexpectedly, under modified conditions (tributyltin chloride and sodium cyanoborohydride), the cyclization of the iodo compound **69** did not proceed in the expected 5-*exo* fashion, but instead the only cyclic product, in modest yield (17%), was the amine **70** from 6-*endo* addition to the nitrogen center of the oxime. However, the use of a vinyl bromide precursor **71**, or the corresponding acetylene, afforded the desired product **72** in 29% yield (Scheme 18).



Scheme 18

Hydrazone Acceptors

In contrast to their chemical cousins, the oximes, the hydrazones have received less scrutiny as participants in radical reactions until recently. The first example of a radical cyclization onto a hydrazone was published in 1991 by Kim and coworkers.[19a] This interesting example employed a unique hydrazone, a 2-phenyl-*N*-aziridinyl imine, as the radical acceptor. Upon treatment of the bromide **73** with tributyltin hydride

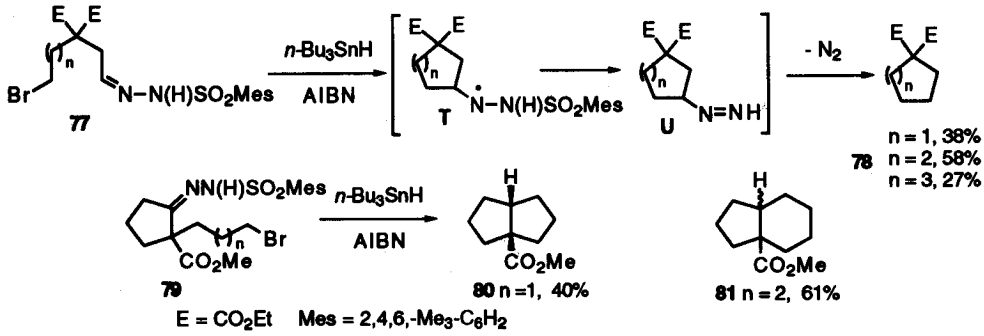


Scheme 19

the initial radical **O** added to the imine bond to generate an α-aziridinyl aminyl radical **P**. By analogy to the corresponding α-cyclopropyl systems, this intermediate **P** underwent rapid ring opening to the benzyl radical **Q**

with subsequent formation of styrene and expulsion of nitrogen to form the carbocycle **74** from quenching of **R**. For the 5-*exo* cyclization (n = 1) the yield was a modest 30% but this increased to 85% for the 6-*exo* addition to give the cyclohexane product **74** (n = 2). If desired, the intermediate cyclohexyl radical **R** (n = 2) may be trapped with methyl acrylate or acrylonitrile in yields of 87% and 86% respectively. The reaction also proceeded smoothly with keto-hydrazones and with alternative radical precursors such as phenyl selenides and acetylenes. Of additional interest is the ability of aziridinyl imines to function as radical precursors. Exposure of the bisaziridinyl substrate **75** to 0.3 equivalents of tributyltin hydride and AIBN in refluxing toluene afforded, via the α-stannyl radical **S** the expected cyclopentene and cyclohexene **76** in yields of 62% and 65% respectively (Scheme 19).

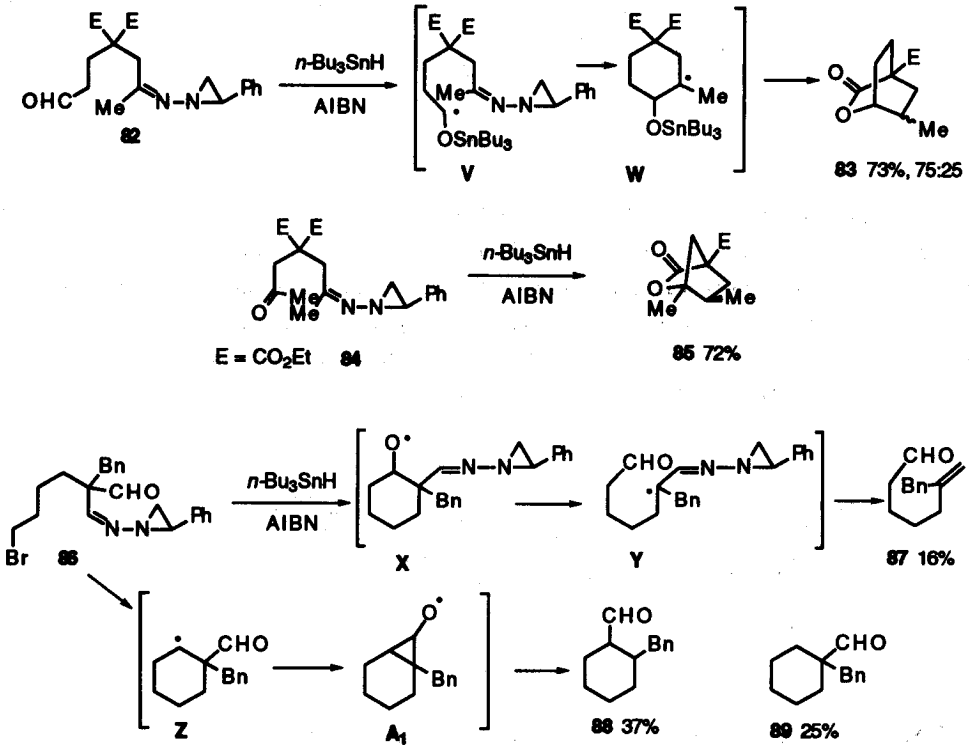
In an extension of their initial investigations Kim and coworkers[19b] examined the use of arenesulfonylhydrazones as radical acceptors. Initial addition was followed by β-elimination of the arenesulfonyl radical **T** and the extrusion of nitrogen from the diazene **U**. For these reactions to work efficiently, it was necessary to use mesitylenesulfonylhydrazones of type **77**. Thus, depending upon the chain length, 5, 6, and 7 membered rings (**78**) could be synthesized by this procedure. Appropriately substituted cyclopentanes (**79**) can be converted to the corresponding diquinane **80** and hydrindane **81** in yields of 40% and 61% respectively (Scheme 20). These techniques have provided general routes to carbocycles in a novel manner. However, these reactions incorporate a very special driving force and initially it was not clear if these features were essential for successful addition onto hydrazones. Fallis and Sturino[8d] as well as Bowman and coworkers[20a] have established that this is not the case, as discussed below, and that standard hydrazones are useful radical acceptors in which the nitrogen radical can be trapped to develop further chemistry.



Scheme 20

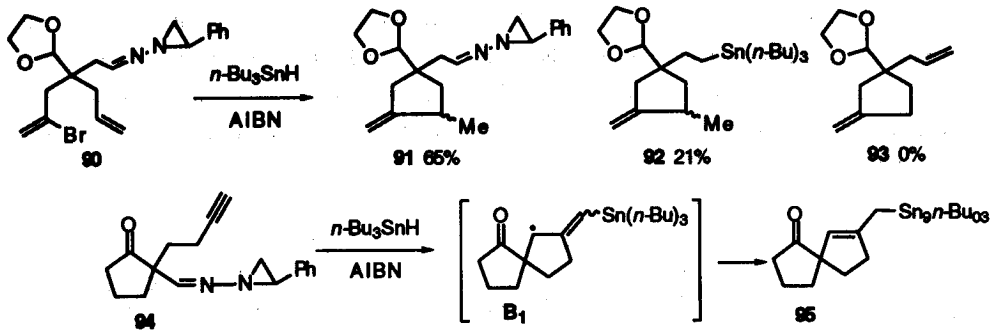
In order to expand the potential of the *N*-aziridinyl amino group as radical acceptors, Kim and coworkers[19c] examined the competition between carbonyl and alkene groups as radical acceptors. The preferred pathway for **82**, in the competition between a keto-hydrazone and an aldehyde carbonyl, involved initial attack at the aldehyde. The stannyloxy radical **V** generated from this addition cyclized onto the hydrazone to form the secondary radical **W** after loss of nitrogen and styrene. Subsequent reduction and lactonization afforded **83**. A similar preference was observed in the methyl ketone series in which clean conversion of **84** to **85** was observed. This situation was reversed when the choice was between a formyl

group and an imino group. Thus **86** afforded 16% of the aldehyde **87** from initial attack of the tributyltin hydride on the bromide followed by addition to the aldehyde to form **X**. This was followed by ring opening to **Y** and the elimination of the *N*-aziridinyl moiety. It was interesting that no epoxide was detected. The competing pathway for addition to the imine dominated and afforded 37% of **88** from rearrangement of $\mathbf{A_1}$ and 25% of **89** from the quenching of **Z** (Scheme 21).



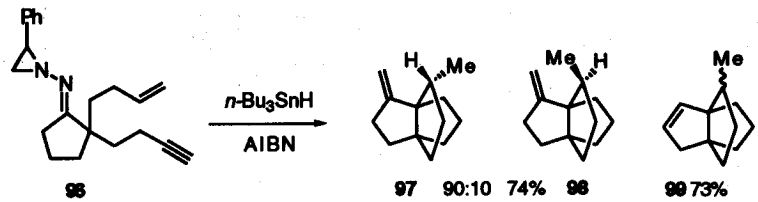
Scheme 21

The competition between an alkenyl double bond and an imino group in this series has also been studied.[19c] In this case the alkene proved to be a better acceptor than the *N*-aziridinyl imino function. With 1.1 equivalents of tributyltin hydride a mixture of **91** and **92** was generated in 65% and 21% yield, respectively, and there was no evidence for any of the diene **93**. When the quantity of tributyltin hydride was increased to 2.2 equivalents the stannane **92** was produced in 80% yield as the only product as a consequence of the addition of tributyltin hydride to the imino group in **90**. The situation was altered again with the competition between a cyclopentanone and the imino group. The reactive vinyl radical derived from acetylene **94** added preferentially to the hydrazone to afford the spiro diquinane **95** in 85% yield as a result of the ease of oxygen radical reversal when attack occurs on the ketone. Therefore the reaction funneled through the secondary radical $\mathbf{B_1}$ (Scheme 22).



Scheme 22

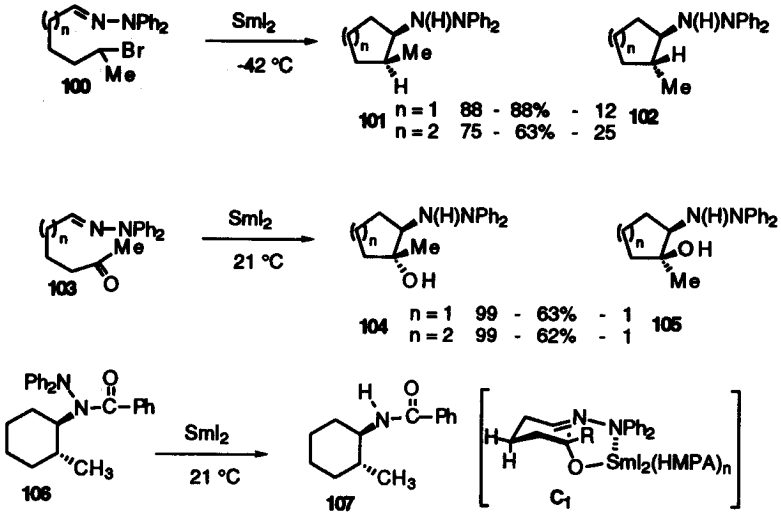
An extension of this chemistry[19d] employed *N*-aziridinyl imines in a tandem radical cyclization to produce the [3.3.3] propellane skeleton of modhephene (Figure 1). Upon tributyltin hydride addition to the acetylene **96** the vinyl stannyl radical cyclized efficiently (74%), in a selective manner, to the dominant isomer **97** (90:10, after destannylation) required for the sesquiterpene synthesis. Preparation of the initial radical from a vinyl bromide gave the endocyclic olefin isomer **99** in 73% yield but in a less satisfactory diastereomeric mixture. Further manipulation of **97** completed a formal total synthesis of *dl*-modhephene (Scheme 23).



Scheme 23

Clearly, the radical cyclizations of *N*-aziridinyl imines have introduced a versatile new approach for the formation of five and six-membered rings. However, this strategy does not retain the nitrogen functionality due to its expulsion as nitrogen. Fallis and Sturino[8d] established that *N,N*-diphenylhydrazones are excellent radical acceptors and thus can be gainfully employed in the synthesis of nitrogen functionalized cyclopentanes and cyclohexanes. In contrast to the inseparable *syn/anti* mixture that usually results from oxime ethers, hydrazones can be prepared as (*E*)-hydrazones exclusively. The reaction temperature significantly affected the *cis:trans* ratio of the cyclic products. Treatment of the bromomethyl ketone **100** with tributyltin hydride at 80 °C afforded **101** and **102** (n = 1) in 95% yield, in a 67:33 ratio. The same ratio was obtained with samarium diiodide under radical conditions with added HMPA, at 21 °C in 91% yield. However, with SmI_2/HMPA the diastereoselectivity increased as the temperature was lowered. Under more favorable conditions with samarium diiodide at -42 °C the cyclic hydrazines were isolated in 88% yield and consisted of **101** and **102** (n = 1) in a ratio of 88:12. A further improvement in selectivity was achieved by the use of an alkyl iodide as the radical precursor. The ratio was increased to 92:8 when the reaction was conducted at -78 °C. For 6-*exo*

cyclizations under the same conditions (-42 °C) the overall yield was 63% and the *cis:trans* ratio of **101** to **102** (n = 2) was 75:25 (Scheme 24).

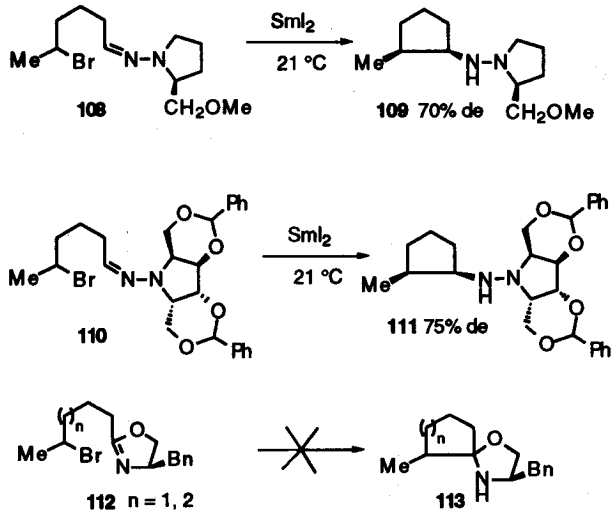


Scheme 24

In contrast to the temperature trends in the halide examples, the reductive cyclization of carbonylhydrazone systems were more selective at higher temperature. In addition, they provided *trans* cyclic hydrazino alcohols that retain useful functionality for further synthetic manipulation. For example, cyclization of **103** afforded **104** and **105** in 63% yield as a 99:1 ratio. This high level of selectivity was achieved for both the 5-*exo* cyclopentanol and 6-*exo* cyclohexanol series when the reaction was conducted at room temperature (21 °C). These products arose from a nine-membered ring chelate of type $\mathbf{C_1}$. This allowed the large *N,N*-diphenylamino substituent to adopt a pseudoaxial orientation, and the oxygen helped reduce the gauche interactions on route to the observed products. Hydrogenolysis may be effected with hydrogen and platinum oxide catalyst to prepare the amine, but a superior method[21] was to convert the products to their *N*-benzoylhydrazides such as **106**. Subsequent treatment with SmI_2 provided the corresponding benzyl amine **107** in five minutes at 21 °C in 85% yield (Scheme 24).

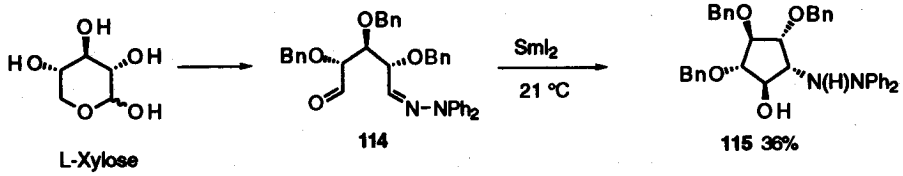
In view of the respectable levels of diastereocontrol observed with the diphenylhydrazone cyclizations, these studies were extended by Fallis and Sturino[8e] to hydrazones containing chiral auxiliaries. The SAMP hydrazone **108** afforded the cyclopentane **109** with a diastereomeric excess of approximately 70%. This result suggested that a C_2 hydrazone would be even more selective, but unfortunately this was not the case. The hydrazone system **110** was synthesized from D-mannose and subjected to cyclization under standard conditions to give **111**, but the improvement was marginal as the diastereomeric excess was only 75% (Scheme 25). The geometric relationships of these chiral systems place the key asymmetric centers a large distance from the site of addition of the radical to the imine carbon. Consequently, to achieve the required 90% plus diastereomeric excess for modern chemistry a different system will be required. Homochiral oxazolines

derived from amino acids such as **112** appeared attractive in this regard due to the placement of the chiral center adjacent to the nitrogen center. Unfortunately the oxazolines are inert as radical acceptors and none of the 5-*exo* cyclization product **113** (n = 1) was generated under the conditions examined. Similarly **113** (n = 2) was not detected as [1,5] hydrogen transfer was the exclusive pathway from the attempted cyclization of **112** (n = 2). This result was confirmed by labeling studies with tributyltin deuteride. Calculations discussed below indicated that the desired cyclization process was thermoneutral and lacked the favorable energy requirements for addition to proceed.



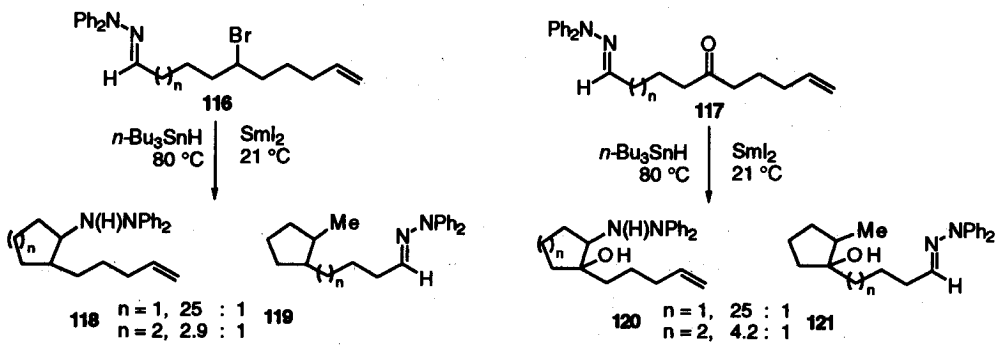
Scheme 25

As mentioned above, the synthesis of cyclic β–amino alcohols is of considerable current interest. Allosamizoline (Figure 1) is the aglycone portion of the natural product allosamidin which possesses potent chitinase activity. This highly functionalized cyclopentane ring with five stereogenic centers also bears a *trans* relationship between the adjacent hydroxyl and nitrogen substituents. In a model system L-xylose was converted to the benzyl protected hydrazone **114** and treated with samarium diiodide in the presence of HMPA to afford a 57% yield of three diastereomers (Scheme 26). The major diastereomer **115** was isolated in 36% yield and tentatively assigned the stereochemistry illustrated.[8f] For the future it is anticipated that a more rigid system containing isopropylidene groups will improve the stereoselectivity of the cyclization.



Scheme 26

Collectively the experiments above suggested that intramolecular addition to *N,N*-diphenylhydrazones was a reasonably fast reaction and clearly of synthetic utility. Fallis and Sturino[8g] designed an intramolecular, competitive "radical clock" cyclization of hydrazones and alkenes from both halo and carbonyl precursors in order to establish the rate constants for the 5-*exo* and 6-*exo* cyclizations. The structures employed are represented by the family of compounds **116** and **117** with n =1 or 2 (Scheme 27). Individual reactions conducted under standard conditions with tributyltin hydride or samarium diiodide/HMPA established that the rate constants for 5-*exo* cyclizations onto *N,N*-diphenylhydrazones were 1.1 x 10^8 s^{-1} and 4.6 x 10^7 s^{-1} at 80 °C for the *cis* and *trans* cyclopentylhydrazines respectively. The 6-*exo* hydrazone rate constant was 9.4 x 10^5 s^{-1} at 80 °C for both *cis* and *trans* isomers with activation barriers of 5.6 and 6.2 kcal/mol respectively. The important conclusion from this study was the finding that the 5-*exo* cyclization rate constant for addition to these hydrazones was approximately 200 times larger than the corresponding cyclization rate constant for 5-*exo* alkenes, while the advantage for 6-*exo* addition onto *N,N*-diphenylhydrazones was ~100 fold.

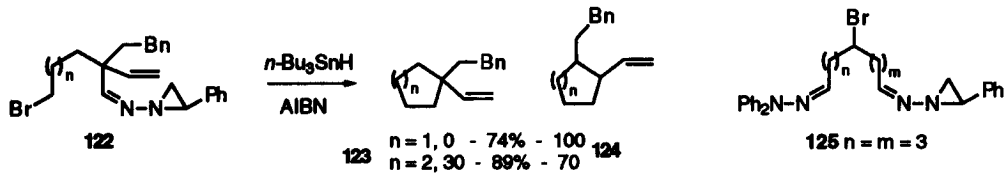


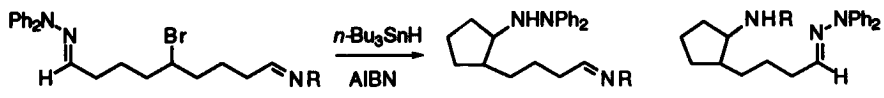
Scheme 27

Kim and coworkers[19e] have also utilized competition experiments to establish the rate constants for the 5-*exo* and 6-*exo* cyclizations of primary alkyl radicals onto *N*-aziridinyl imines The 5-*exo* rate constant is approximately 2.5 x 10^8 s^{-1} at 20 °C and the 6-exo rate constant is 4.7 x 10^6 s^{-1} at 80 °C. Scheme 28 illustrates some of the experiments conducted for these studies. Thus cyclization of **122** (n =1) provided only the rearranged product **124**, from addition of the cyclopentanyl radical to the double bond and cleavage of the α-cyclopropyl intermediate. In the cyclohexane series, a 30:70 mixture resulted (Scheme 28). Fragmentation of the aziridinyl ring depended on the reaction temperature and concentration of tributyltin hydride. Possibly as a consequence of the *gem*-dialkyl effect these cyclization rates were slightly faster than that for the *N,N*-diphenylhydrazones, although in these cases a primary radical was measured compared to a secondary radical.

In an attempt to obtain additional data in this area the bis hydrazone **125** (n = m = 3) was synthesized and studied by Fallis and Tauh,[8e] but unfortunately the complex mixtures obtained did not permit an accurate analysis. However, related investigations have provided rate constants and insight into the competitions of various imines illustrated in Scheme 28. The *N,N*-diphenylhydrazone group was a slightly better acceptor than the corresponding *N,N*-dimethylhydrazone as reflected in the cyclization of **126** to afford **127** and **128** in a ratio

of 75:25. The corresponding rate constant at 80 °C for the 5-*exo*-cyclization onto *N,N*-dimethylhydrazones was 2.4 x 10^7 s^{-1}. For these secondary radicals the cyclization rate constants for **135** and **129** onto the benzyl oxime **135** and the carbazone**129** are very similar, ~ 3 x 10^7 s^{-1}.

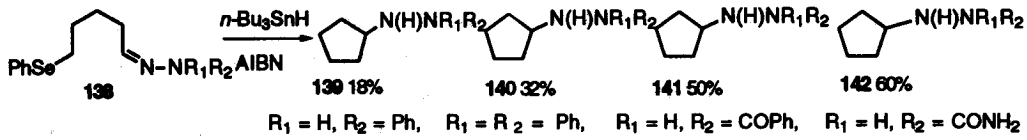




126 R = NMe_2	**127** R = NMe_2	75	25 **128**
129 R = NCOPh	**130** R = NCOPh	70	30 **131**
132 R = OMe	**133** R = OMe	76	24 **134**
135 R = OBn	**136** R = OBn	70	30 **137**

Scheme 28

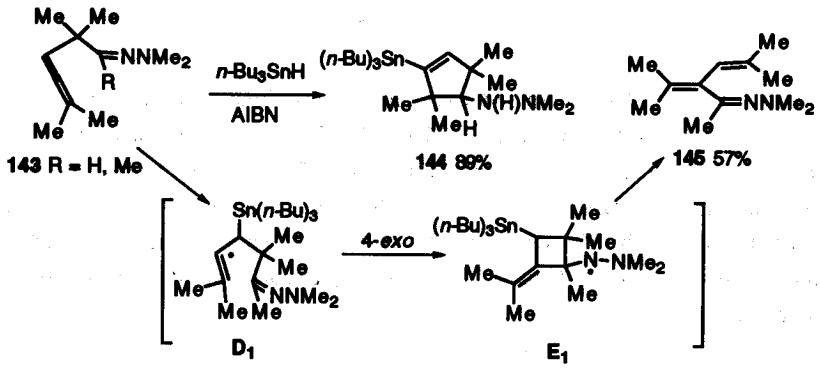
Bowman and coworkers[20a] examined the effect of different substituents on the hydrazone acceptor. The yield was increased as electron withdrawing groups were added to the hydrazone nitrogen thus rendering the imine nitrogen more electropositive and raising the rate of the reaction. The *N*-phenylhydrazone **138** gave **139** in 18% yield but this increased to 60% with the urea system **142** (Scheme 29). The lower yield of the *N,N*-diphenylhydrazone cyclization product (32% vs 95%) compared to Scheme 24 above may reflect the slightly different reaction conditions, primary versus secondary radicals, and the use of a selenide precursor. The extension of these studies to 5-*exo* cyclizations with SAMP and RAMP hydrazones did not result in significant asymmetric induction as a 50:50 mixture of diastereomers was obtained.[20b]



Scheme 29

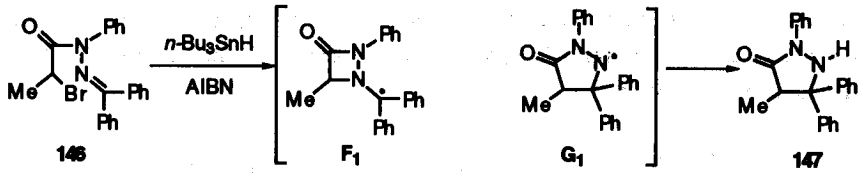
Hatem and coworkers[14b,c] have extended their oxime studies to β-allenic *N,N*-dimethylhydrazones. With aldehyde hydrazones such as **143** (R = H) hydrostannylation afforded the expected tertiary radical due to addition to the digonal center which cyclized to the cyclopentene **144** via a 5-*exo* mode in 89% yield. Methyl ketone derived hydrazones (**143**, R = Me) were not as reactive and an alternative pathway became competitive. Thus the vinyl radical D_1, formed from addition of the tributylstannyl radical to the trigonal carbon, underwent a rare 4-*exo* cyclization to form the aminyl radical E_1. Subsequent fragmentation with elimination of the

tributyltin radical afforded the diene **145** in 57% yield. The cyclopentene formed via the other 5-*exo* pathway was also isolated in 16% yield (Scheme 30). An attempt to use the SAMP hydrazone did not display useful selectivity as the diastereomeric excess was only 50%.



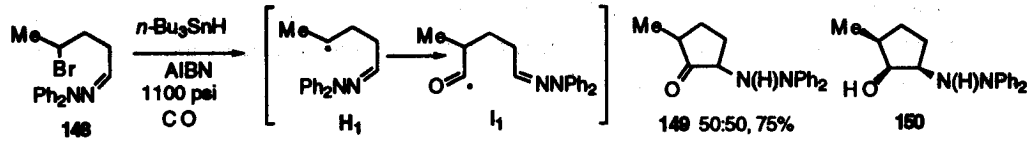
Scheme 30

Belletire and coworkers[22] synthesized a series of α-bromoacyl phenyl hydrazones containing various groups on the imine terminus. With aryl substituents, the anticipated product from 4-*exo* cyclization of **146** to the β-lactam product from quenching of intermediate $\mathbf{F_1}$ was not isolated. Instead the pyrazolidinone **147** was the only product formed in 92% yield. This compound could be the result of a 5-*endo* cyclization (*cf.* Scheme 49) to form the aminyl radical intermediate $\mathbf{G_1}$ followed by hydrogen atom transfer. However, the authors also suggested an alternative mechanism which involved initial cyclization to the benzyl radical $\mathbf{F_1}$ followed by rearrangement to $\mathbf{G_1}$ (Scheme 31).



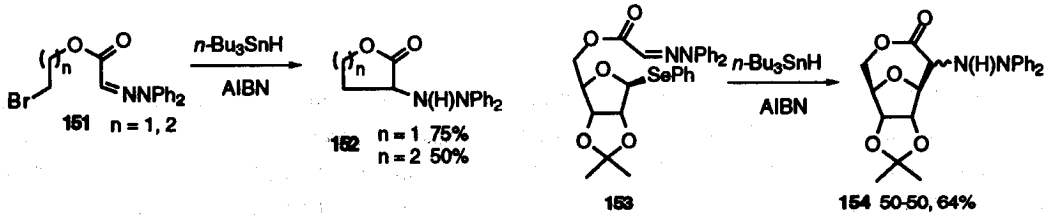
Scheme 31

In general the 4-*exo* cyclization is slow relative to other pathways. Fallis and Brinza[8h] have taken advantage of this to capture the initial alkyl radical with carbon monoxide prior to the cyclization step. The resulting acyl radical then added to *N,N*-diphenylhydrazones in a 5-*exo* manner. Thus treatment of the secondary bromide **148** with tributyltin hydride afforded $\mathbf{H_1}$ which added to carbon monoxide under pressure (1100 psi) to form the acyl radical $\mathbf{I_1}$. Cyclization gave the α-hydrazinocyclopentanone **149** in 75% yield as a 50:50 *cis/trans* mixture (Scheme 32). Reduction of the *cis* cyclopentanone with L-Selectride® gave exclusively the *cis* alcohol **150** in 90% yield, while hydrogenation in the presence of tris(triphenylphosphine)ruthenium(II) chloride catalyst in the nor-methyl series afforded the *trans*-β-hydrazinoalcohol in 72% yield.



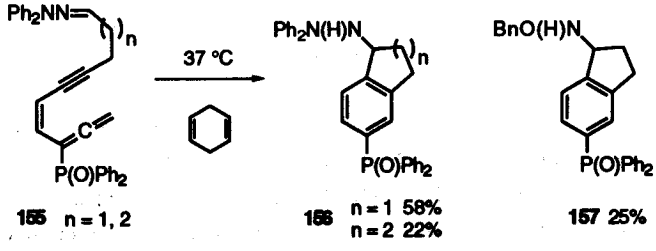
Scheme 32

Clive and Zhang[23a] have prepared α-aminolactones from appropriately substituted *N,N*-diphenylhydrazone and *O*-benzyloxime esters. A 75% yield of **152** (n =1) was obtained from **151**, although the yield from the corresponding oxime ether dropped to 51%. For the 6-*exo* cyclization of **151** (n = 2) the yield of the δ-lactone **152** was also reduced (50%) (Scheme 33). An interesting example of a 7-*exo* ring closure (also Schemes 15, 17, 20, 57) was provided by the cyclization of the ribose derived selenide **153** to generate the tricyclic system **154** in 64% yield. This facile ring closure was aided by the geometry constraints of the trioxaquinane nucleus.



Scheme 33

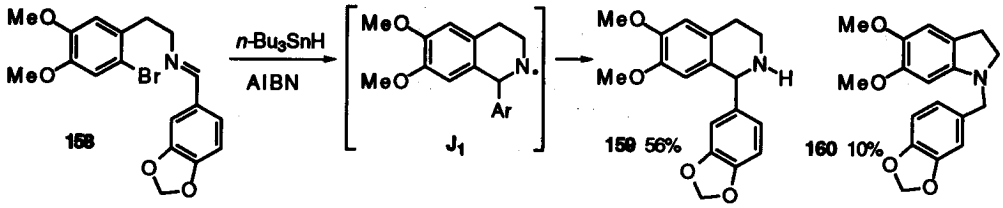
Grissom and coworkers[12c] have also examined the use of *N,N*-diphenylhydrazones as acceptors for tandem enyne-allene radical cyclizations. As observed previously, the 5-*exo* cyclization product **156** (n = 1) was formed in better yield (58%) than the cyclohexane system **156** (n = 2) (Scheme 34). Consistent with the example above (Scheme 33), the benzyloxime product **157** was generated with less than half the efficiency of the corresponding hydrazone **156** (n = 1).



Scheme 34

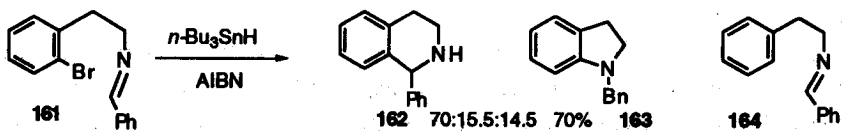
Imine Acceptors

An early example of an intramolecular radical addition onto an imine bond was reported by Takano and coworkers[24a] in 1990 as a key step in their synthesis of the Cryptostyline alkaloids (Figure 1), isolated from the *Orchidaceae*. Cyclization of the aryl bromide **158** gave as the major product the isoquinoline skeleton **159** (56%) from a 6-*endo* addition to form the aminyl radical J_1 from addition to the carbon center of the imine bond. The alternative pathway, the 5-*endo* cyclization, was the minor route and afforded the dihydroindole **160** in 10% yield (Scheme 35).



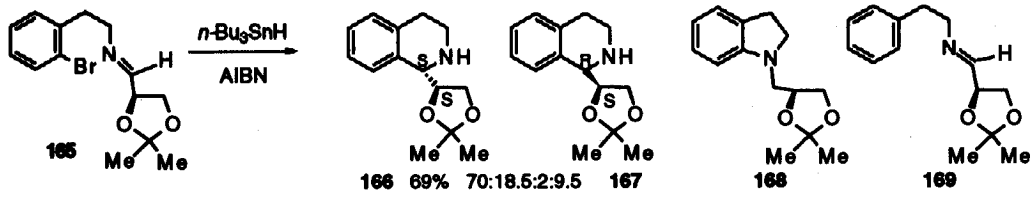
Scheme 35

This pattern of reactivity has also been noted in studies by Warkentin and Tomaszewski[25a] who reported a large 6-*endo* preference for the cyclization of an aryl radical onto an aldimine acceptor. Cyclization of the bromide **161** is a typical example and afforded a 70% yield of **162** accompanied by lesser amounts of the 5-*exo* product **163** and the reduced starting material **164** in an approximate ratio of 70:15.5:14.5 (Scheme 36). Lower concentrations of tributyltin hydride favored the 6-*endo* pathway (onto carbon), a route that was the opposite to that followed by the cyclization of aryl radicals onto alkenes. This was a consequence of the fact that formation of a carbon-carbon single bond is favored over the corresponding carbon-nitrogen bond by approximately 10 kcal/mol. In addition the geometry inherent in the imine functional group, with a C-C=N angle of approximately 119°, is more suited to *endo* addition than an alkene with a larger angle of approximately 125°. As a result, the transition state interorbital alignment between the SOMO of the radical center and the π^*-orbital of the imine was more favorable. The rate constant for the 6-*endo* cyclization in this reaction was measured as 1.6 x 10^8 s^{-1}. The 5-*exo* cyclization rate constant was slower with a value of 3.8 x 10^7 s^{-1}.[25b] Subsequent investigations with 1.3 equivalents of tributyltin hydride and 15% AIBN led to suppression of the 6-*endo* route and exclusive formation of **163** in 64% yield with a rate constant of 3.9 x10^8 s^{-1} at 80 °C (Scheme 36). Aryl radicals bearing an aldimine group as part of an *ortho* substituent preferred 5-*exo* closure to carbon over 6-*endo* addition to nitrogen.[25c] In contrast, 6-*endo* closure to carbon dominated in the isomeric imine series. A combination of both kinetic and thermodynamic factors coupled with relative radical stabilities, bond lengths, and bond angles account for this behavior.



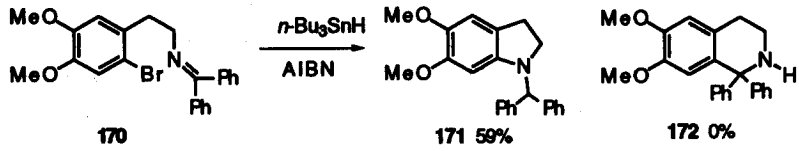
Scheme 36

In contrast to the hydrazone examples, a chiral auxiliary attached to an imine would be expected to confer greater asymmetry especially if it is adjacent to the new bond in an *endo* cyclization. However a modest diastereomeric excess of 58% was achieved from cyclization of the isopropylidene imine system **165**.[25b] The major product **166** was part of a mixture consisting of a 70:18.5:2:9.5 ratio of compounds as illustrated, in which the 6-*endo* product **166** exceeds the 5-*exo* product **168** by a ratio of 47:1 (Scheme 37).



Scheme 37

Takano and coworkers[24b] discovered that in the ketimines derived from acetophenone and benzophenone, contrary to the examples above, the free radical center added exclusively to the nitrogen terminus of the azomethine bond in a 5-*exo* fashion. Usually this pathway is kinetically disfavored but the extra steric hindrance present in **170** led to the exclusive formation of the indoline **171** (59%) at the expense of the isoquinoline **172** (Scheme 38). Thus fine tuning of the substituents allowed control of the competition between the 5-*exo* and the 6-*exo* cyclization modes (Scheme 38).

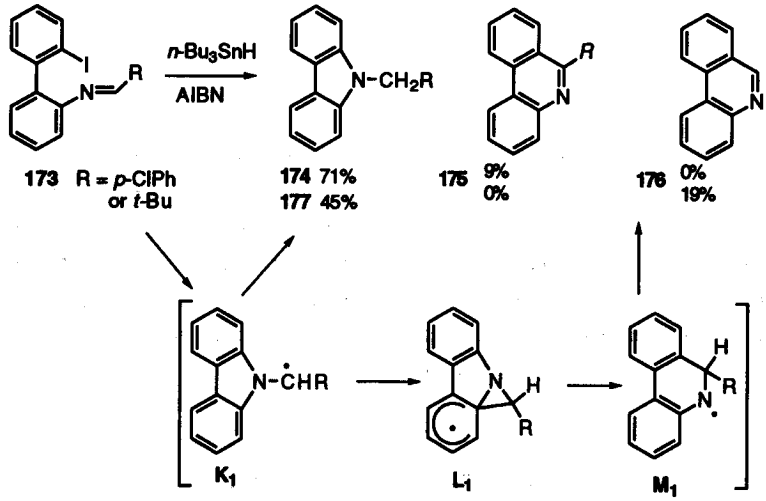


Scheme 38

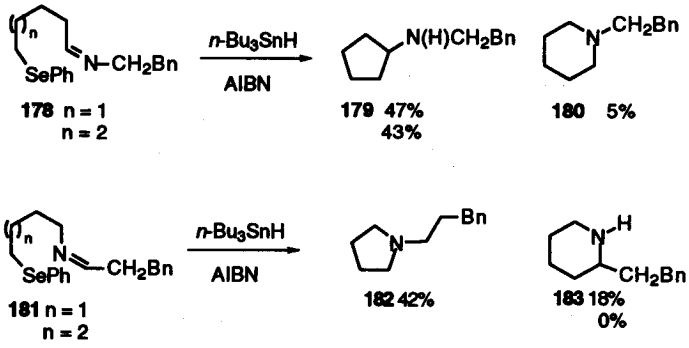
Leardini and Zanardi and coworkers[26a] reported related competitions between the 5-*exo* and 6-*endo* pathways that were dependent upon the imine substituent. With the *p*-chlorophenyl group the major product was the 5-*exo* product **174** in 71% yield accompanied by 9% of **175**. The mixture was altered when a *t*-butyl substituent was present. The *t*-butyl radical was eliminated in the final step to give **176** in 19% yield plus **177** (R = *t*-Bu) in 45% yield. These products may have arisen directly from the radical intermediates $\mathbf{K_1}$ and $\mathbf{M_1}$, respectively, but in view of the potential stabilization of the α-aziridinyl radical $\mathbf{L_1}$ an alternative pathway may also be involved (Scheme 39). Replacement of the iodo function in **173** by bromine gave rise to other products including those from a 1,5-hydrogen transfer. Imines derived from *o*-iodoaniline gave rise to indoles from 5-*exo* cyclizations with vinyl radicals.

Bowman and coworkers[20a] have investigated the cyclization of various primary radicals generated from phenyl selenides onto diverse imines. Representative examples included the cyclization of **178** (n = 1) to give the 5-*exo* product **179** (47%) and the 6-*endo* heterocycle **180** in 5% yield. In the case of **178** with n = 2, the only product arose from 6-*exo* cyclization to give **180** in 43% yield. Reversal of the regiochemistry of the

imine bond led to the investigation of **181**. In the case for n = 1 the major 5-*exo* cyclization product **182** was formed in 42% yield compared to 18% for the 6-*endo* product. With the longer chain (n = 2) none of **183** was formed (Scheme 40). No seven membered rings were found in these experiments.

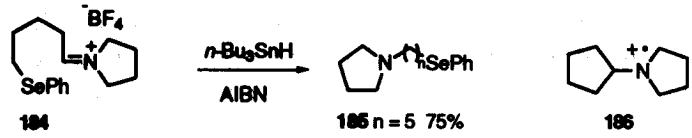


Scheme 39



Scheme 40

Cyclization onto iminium salts has also been examined by Bowman and coworkers[20b] in an attempt to improve the initial cyclization rate and provide the opportunity for a second cyclization of the radical cation **186** onto an alkene. However, the reaction of the iminium salt **184** gave only the uncyclized *N*-pentylpyrrolidine **185** (75%) indicating that addition to the imine salt was faster than stannyl radical abstraction of the benzeneselenyl moiety (Scheme 41).

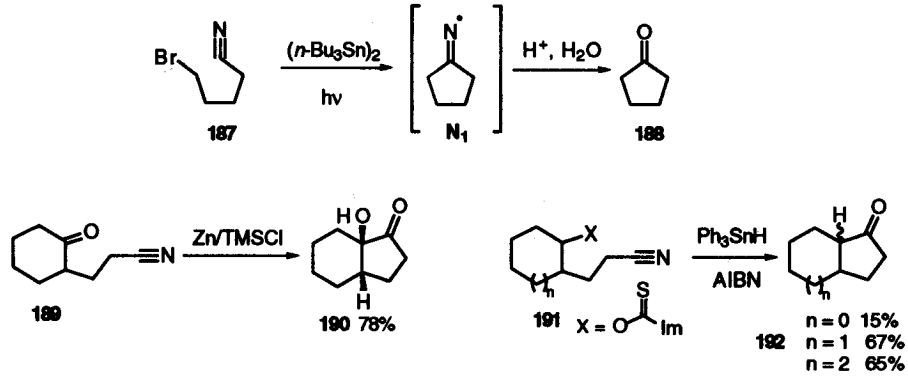


184 185 186

Scheme 41

Nitrile Acceptors

In 1975 Ogibin and coworkers[27] prepared cyclopentanone (**188**) via cyclization of 5-bromocyanopentane to generate the iminyl radical N_1 and subsequently the rate constant was determined by Ingold and coworkers[28a] to be 4 x 10^4 s^{-1} at 80 °C. Corey and Pyne[3] employed their zinc/trimethylchlorosilane method (Scheme 2) for the cyclization of the keto-nitrile **189** and isolated, after hydrolytic work up, the anticipated bicyclic ketone **190** in 78% yield. Clive and coworkers[23b] used triphenyltin hydride to generate the secondary radicals from the thiocarbamate precursors **191** to form the fused ring systems **192** in yields from 15-67% (Scheme 42).



187 N_1 188 189 190 78% 191 192

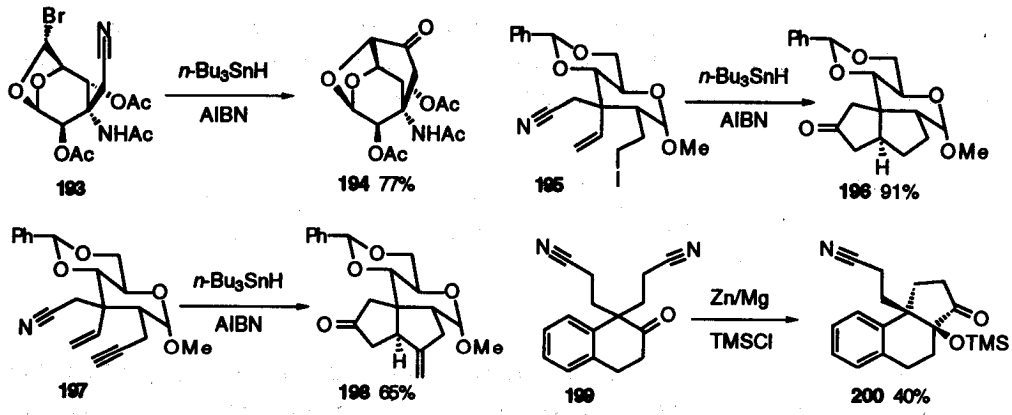
Scheme 42

The rate of 6-*exo* cyclization onto nitriles is quite slow and thus these reactions often fail[29,30] or succumb to competition from faster 1,5 hydrogen transfer processes.[4b] In an approach to the nucleus of (+)-phyllantocin (Figure 1) a 2% yield was observed from a 6-*exo* addition to a nitrile from a *cis* substituted tetrahydrofuran.[31a] However, good yields were achieved when the reactive centers were part of a more rigid system in which the unfavorable conformations were minimized. In an approach to the core of the puffer fish toxin tetrodotoxin (Figure 1) Fraser-Reid and coworkers[31b] used the constrained geometry of a 1,6-anhydro carbohydrate to prepare **194** from the bromonitrile **193** in 77% yield by a 6-*exo* cyclization.

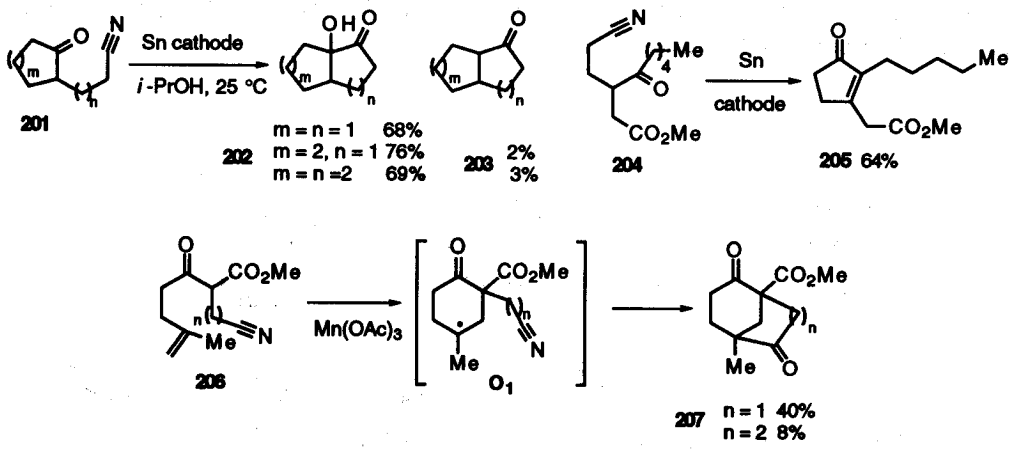
An even better result was achieved with a different carbohydrate framework in a tandem cyclization involving consecutive 5-*exo* additions.[31c] Thus treatment of **195** with tributyltin hydride followed by silica gel chromatography afforded the diquinane system **196** in 91% yield (Scheme 43). A related cyclization, the

conversion of **197** to **198**, proceeded in 65% yield on route to a total synthesis of the tricyclic cedrenoid sesquiterpene (-)-α-pipitzol (Figure 1).[31d]

Aphidicolin (Figure 1), isolated from the fungus *Cephalosporium ophidicola* Petch, is an inhibitor of DNA polymerase and has potential as both an anticancer and antiherpes agent. Stemodin (Figure 1) is a related diterpene isolated from *Stemodia maritima* L, a plant used for the treatment of venereal disease. Mann and Hegarty[32] have developed a radical addition to a nitrile as the key step in a general strategy for these ring systems. Thus treatment of **199** with zinc and magnesium in the presence of trimethylsilylchloride afforded a 40% yield of **200** accompanied by an additional 20% of the olefins from hydrolysis and elimination of the silyl ether functionality (Scheme 43).



Scheme 43



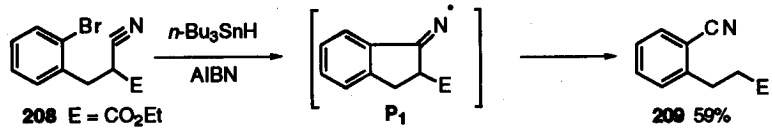
Scheme 44

Shono and Kise[33] developed electrochemical methods to generate ketyl radicals for the preparation of a series of fused ring systems. Exposure of ketone **201** to a tin cathode afforded the diquinane **202** (n = m = 1) in

68% yield, and when m = n = 2 the decalin was produced in 69% yield. Trace amounts of the saturated ketones **203** were also detected. This chemistry has been utilized for the synthesis of dihydrojasmone, a rose petal perfume constituent. Cyclization onto the nitrile function of **204** afforded the ketone **205** in 64% yield after work up (Scheme 44).

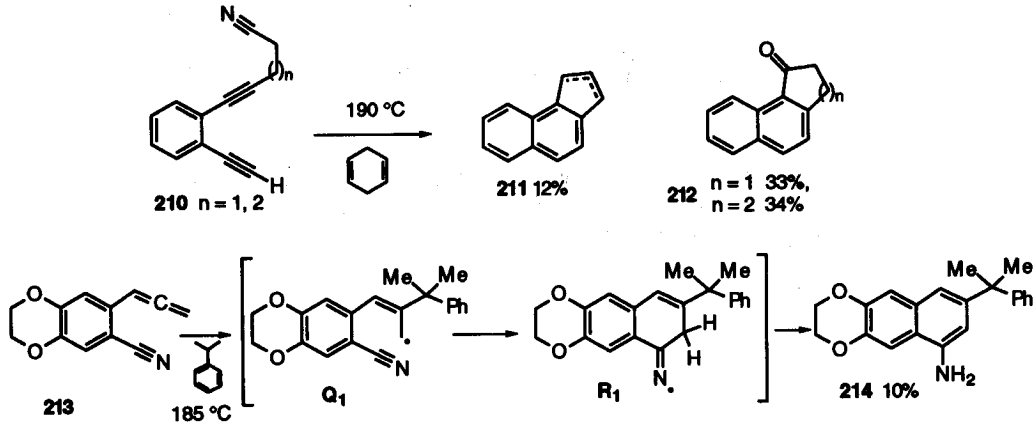
Snider and Buckman[34] established that manganese(III) based oxidative free radical tandem cyclizations may be terminated by addition to nitriles. Thus cyclization of **206** generated the cyclohexyl radical $\mathbf{O_1}$ initially, followed by further cyclization to the bicyclic ketone **207** (n = 1). This product from 5-*exo* ring closure was formed in 40% yield after aqueous work up. In comparison, the yield dropped to 8% for the preparation of the cyclohexanone system (Scheme 44).

The fact that aryl radicals cyclize more rapidly than their alkyl counterparts suggested that cyclization of **208** should readily generate intermediate $\mathbf{P_1}$ followed by hydrogen atom abstraction. However, Beckwith and coworkers[35a] observed that the cyclic imine was not isolated, but rather ring opening occurred faster than hydrogen atom transfer to afford the nitrile **209** in 59% yield (Scheme 45).



Scheme 45

Cycloaromatization studies[12b] revealed that **211** was formed in 12% yield accompanied by 33% of the cyclopentanone **212** (n = 1). These results were similar to those observed above for oxime ether terminators. In these systems the yields also improved when an aryl bromide was used as the radical precursor. Thus the expected cyclopentane annulation product was formed in an increased yield of 91%. The cyclization of **210** (n = 2) afforded the expected cyclohexanone in 34% yield.



Scheme 46

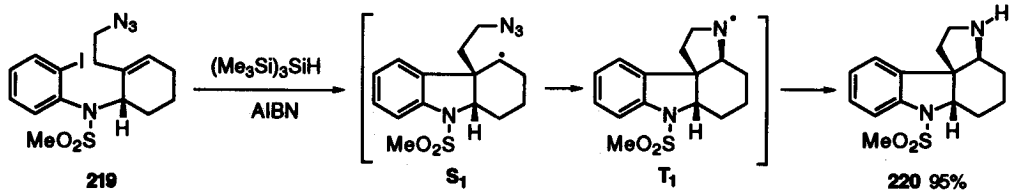
In a different pyrolysis study Gillmann and Heckhoff[36] noted that the cumyl radical added to the allene **213** and the resulting allylic radical $\mathbf{Q_1}$ cyclized onto the neighboring nitrile center. The iminyl radical $\mathbf{R_1}$ generated in this process formed the naphthyl amine in 10% yield (Scheme 46).

Azide Acceptors

A limited number of reports of azides as radical acceptors have appeared. However, under appropriate conditions they may be employed successfully to prepare a variety of heterocyclic rings. Kim and coworkers[19f] used tris(trimethylsilyl)silane with bromoalkanes and tributyltin hydride with the more reactive iodo systems. Thus **215** cyclized to **216** in 88% yield after tosylation on work up. The silyl hydride method afforded the 6-*exo* product **216** (n = 2) in 50% yield from the related starting material. In a related study, Kilburn and Santagostino[37] converted the methylene cyclopropane system **217** into a spiro-heterocycle **218** in 53% yield after tosylation (Scheme 47).

Scheme 47

Murphy and coworkers[38] have demonstrated the additional utility and efficiency of azides in an interesting tandem approach to the pentacyclic ring system of aspidospermidine (Figure 1). The aryl radical generated from iodide **219** in the presence of tris(trimethylsilyl)silane and AIBN afforded **220** in 95% yield as a single stereoisomer via the cyclohexyl radical $\mathbf{S_1}$ and the aminyl species $\mathbf{T_1}$ (Scheme 48).

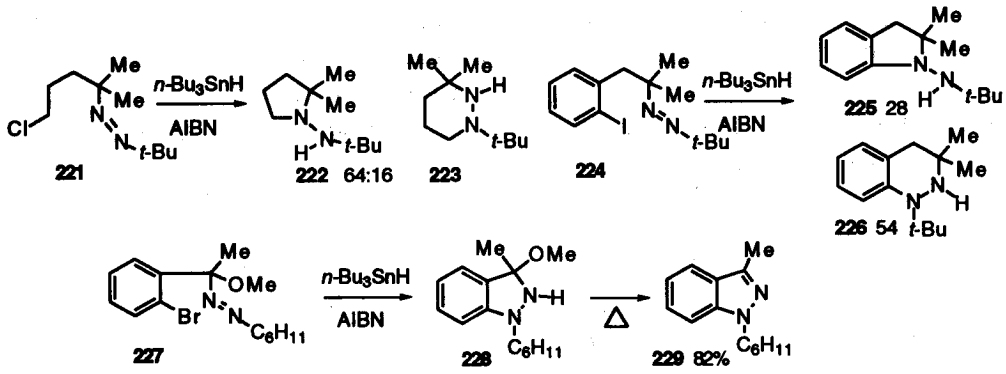


Scheme 48

Azo Acceptors

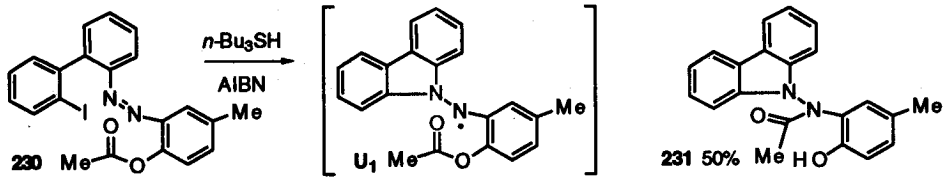
Warkentin and coworkers[25d] have investigated the 5-*exo* and 6-*endo* cyclizations of alkyl and aryl radicals onto azo acceptors and determined the rate constants. Cyclization of **221** afforded a mixture consisting of **222** and **223** and reduced starting material in an approximate ratio of 64:16:20 in an overall yield of 90%. Related aryl systems preferred the 6-*endo* pathway and product **226** was the major heterocycle from cyclization of **224**. Approximately 17% of the reduced starting material was also obtained along with 28% of **225**. The reactions involving the phenyl radical were quite rapid and the rate constants for the 5-*exo* process were 1.5 x 10^9 s^{-1} and 2.3 x 10^9 s^{-1} for the 6-*endo* cyclization at 82 °C. The latter number was approximately two orders

of magnitude larger than the corresponding rate constant for the cyclization of aryl radicals onto alkenes. The key factors that contribute to this difference appear to be the shortening of the azo double bond compared to the alkene, the tighter angle of approximately 115° compared to 120°, and a contribution from the geminal dimethyl effect. This work has been extended to the synthesis of indazoles.[25e] An 82% yield of **229** was achieved from cyclization of **227** in an efficient and fast (5.2×10^9 s^{-1} at 80 °C) 5-*endo* fashion to give the initial product **228** followed by elimination upon distillation to form **229** (Scheme 49).



Scheme 49

Zanardi, Leardini and coworkers[26b] have also examined an interesting example of a cyclization of an aryl radical onto an azo acceptor, but in this instance the initial addition proceeded in a 5-*exo* manner. Thus **230** gave rise to the new aminyl radical intermediate U_1, approximately 30% of which was quenched, and a portion of the hydrazine underwent ionic cyclization and rearrangement to generate the phenolic product **231** (Scheme 50).



Scheme 50

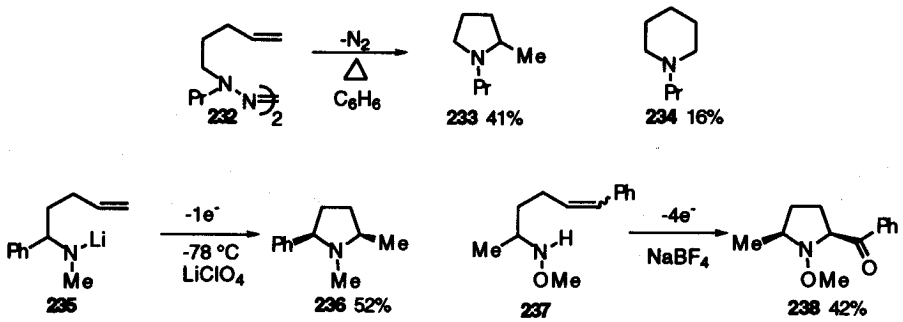
CYCLIZATIONS of NITROGEN RADICALS onto UNSATURATED SYSTEMS

Aminyl Radicals

The chemistry of nitrogen centered radicals has received considerably less attention than the corresponding carbon centered species, but their generation and reactions have been reviewed briefly by Esker and Newcomb.[39a] Nitrogen systems have their own attractions due to the fact that they incorporate a heteroatom in the cyclization step, and thus have considerable promise for the synthesis of pyrrolidines, alkaloids and related nitrogen containing structures, particularly those with medicinal potential. Neutral

aminyl radicals are nucleophilic, in contrast to amidyl radicals, various complexed aminyl radicals and aminium cation radicals, which are electrophilic to varying degrees depending upon the substitution pattern and complexing agent. Often higher yields are obtained with these species.

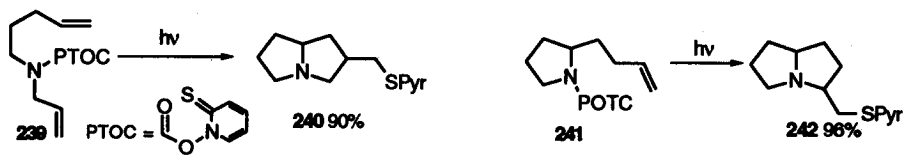
Early investigations of aminyl radicals utilized the thermal extrusion of nitrogen from azenes. Under these circumstances **232** cyclized predominantly in a 5-*exo* manner, to afford the pyrrolidine **233** in 41% yield, accompanied by 16% of **234** as a consequence of 6-*endo* cyclization (Scheme 51).[40] An extension of these studies examined the potential of 6-*exo* cyclizations to piperidines but only tiny amounts of the desired material were detected due to competing hydrogen atom abstraction from the solvent.



Scheme 51

Electrochemical oxidation of amide bases, particularly lithium salts, provided an alternative preparation of aminyl radicals. In a case such as **235**, the lithium salt was readily converted to **236**.[41a] These cyclizations gave the 5-*exo* products in which only the *cis* isomers were present. As illustrated by the conversion of **237** to **238**, the initial heterocycle was oxidized further to the ketone in 42% yield. This required a mixed solvent containing tetrahydrofuran, methanol, and water (Scheme 51).[41b]

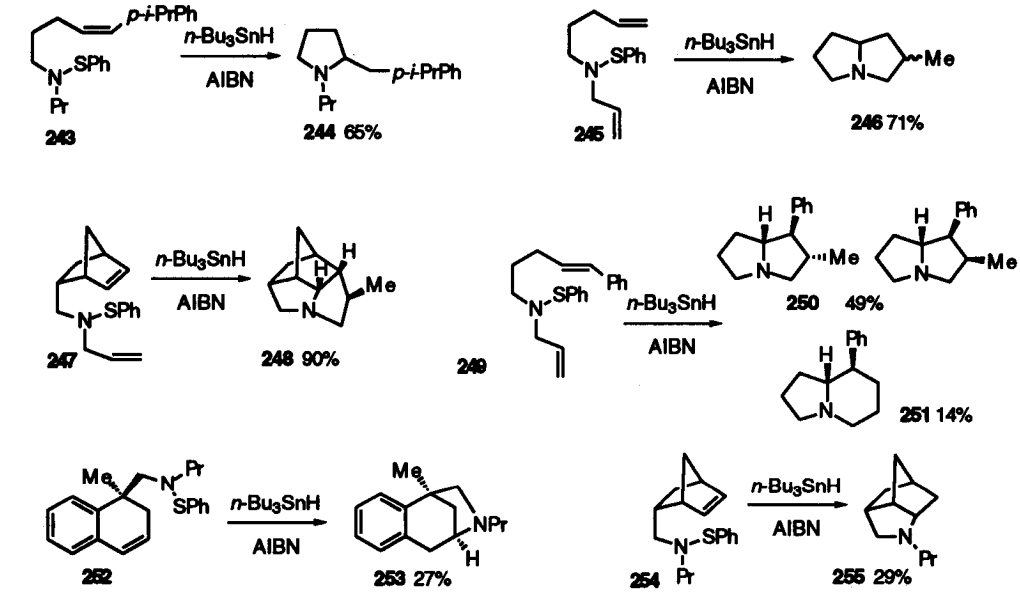
Barton esters (*N*-hydroxypyridine-2-(1H)thione acyl esters, PTOC esters) are another useful source of aminyl radicals that are generated upon irradiation.[39b] The tandem cyclization of **239** afforded the bicyclic skeleton in which the final primary radical was trapped as the sulfide to furnish the product **240** in 90% yield. A related example provided an alternative route to the same ring system when **241** was irradiated to give **242** in 96% yield (Scheme 52).



Scheme 52

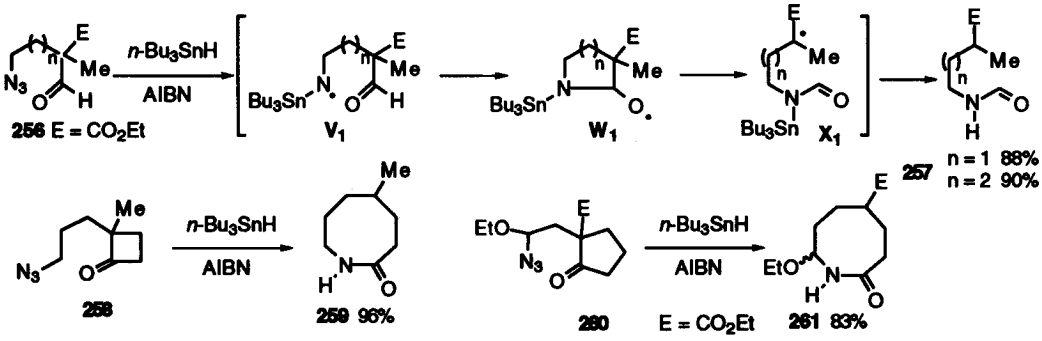
Bowman and coworkers[20c,d,g] have demonstrated the generality of arylsulfenamides for the generation of nitrogen centered radicals. Under standard tributyltin hydride conditions a variety of heterocyclic systems

have been synthesized (Scheme 53). The best cases were the tandem cyclizations represented by **245**, **247**, and **249** in which a polycyclic system was the final product. Cyclization of **249** afforded the major products **250** in 49% yield from a 5-*exo*-5-*exo* double cyclization, accompanied by 14% of the 5-*exo*-6-*endo* skeleton **251** (Scheme 53). A variety of other bridged ring heterocycles represented by **248**, **253**, and **255** were also synthesized.



Scheme 53

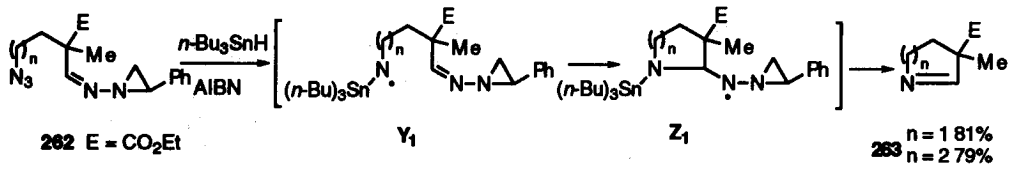
Kim and coworkers[19g] have developed an intramolecular addition of aminyl radicals to carbonyl groups to form amides after rearrangement of the initial oxygen radical intermediate. Thus treatment of the azide **256** with tributyltin hydride afforded the aminyl radical V_1, which after addition to the carbonyl group,



Scheme 54

gave the oxygen radical W_1. This intermediate underwent ring cleavage to generate the tertiary radical X_1 and provided the amides **257** in high yield. The application of this chemistry to cycloalkanones led directly to ring expanded lactams. Thus, ring expansion of the cyclobutanone **258** provided the cyclooctane lactam **259** in 96% yield. The eight membered ring system was also formed by intramolecular aminyl radical addition to the cyclopentanone **260** to give the lactam-ester **261** in 83% yield (Scheme 54).

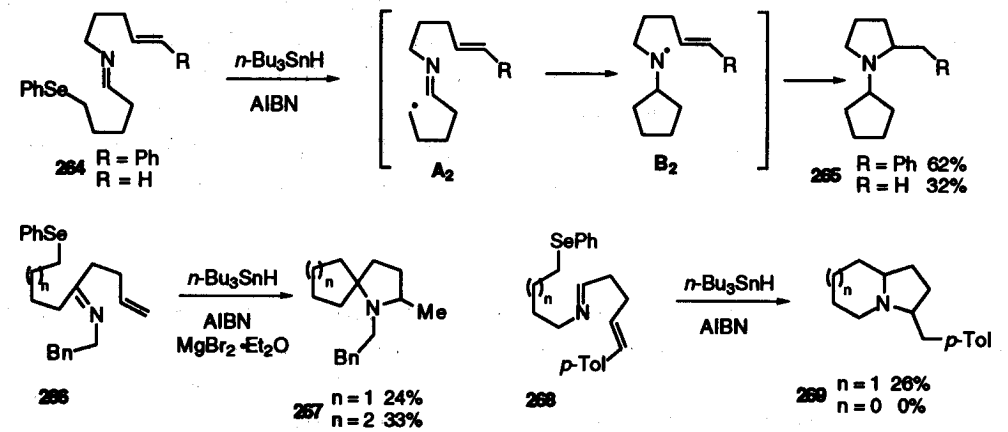
Related studies[19f] have focused on the use of azides such as **262**. Generation of an aminyl-stannane radical intermediate Y_1, led smoothly to a second nitrogen centered radical Z_1. This species provided the cyclic imines **263** in yields of ~ 80% after rearrangement by expulsion of nitrogen, styrene, and elimination of the tin radical (Scheme 55).



262 E = CO_2Et Y_1 Z_1 **263**

Scheme 55

Bowman and coworkers[20e] have also examined a series of tandem reactions in which the second step involved the addition of an aminyl radical to an alkene to provide various bicyclic nitrogen heterocycles. Treatment of **264** (R = Ph) with tributyltin hydride afforded a 62% yield of **265** (R = Ph) via the intermediate radicals A_2 and B_2. The yield of **265** (R = H) was reduced to 32% when the vinyl phenyl group was absent. In the related series of spiro precursors represented by **266** no tandem cyclization was observed with an unsubstituted alkene. However, the addition of a Lewis acid such as magnesium dibromide etherate had a



264 A_2 B_2 **265**

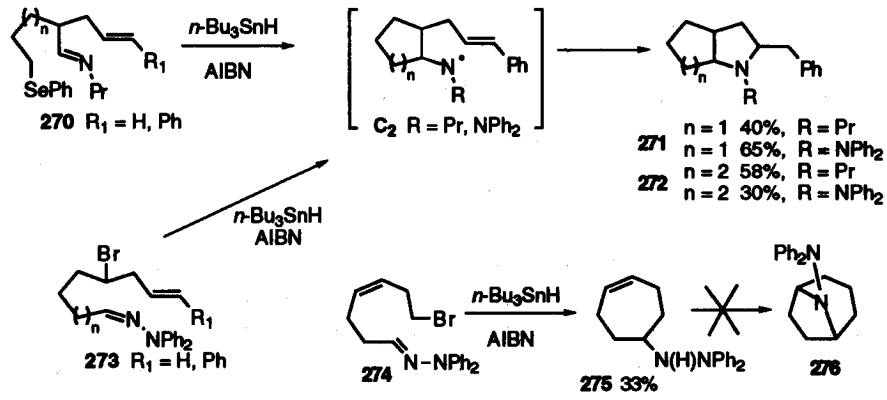
266 **267** **268** **269**

Scheme 56

dramatic effect and the yields of **267** increased from 0% to 24% and 33% for the 5-*exo* and 6-*exo* products **267** (n = 1, 2) in this series. These yields were similar to those in the vinyl phenyl series without Lewis acid

present. Indolizidines and pyrrolizidines arose from cyclization of **268**. In this series the 6-*endo* cyclization onto the electrophilic carbon of the imine might be expected to be competitive with the 5-*exo* addition onto the imine nitrogen. Thus with a *p*-tolyl substituent **268** (n = 1) a 26% yield of the heterocycle **269** (50:50 diastereomer ratio) was obtained from a 6-*endo* addition. The attempted cyclization of **268** (n = 0) required an unfavorable 5-*endo* cyclization and no tandem product was detected (Scheme 56).

For the series represented by **270** (R_1 = H) Lewis acid ($MgBr_2{\cdot}Et_2O$) was required to obtain a 35% yield of the tandem 5-*exo* product, otherwise only monocyclized material from reduction of the aminyl radical was detected. With a phenyl group present in **270** (R_1 = Ph) the major products were **271** (R = Pr) in 40% yield for n =1 and **272** in 58% yield for the 6-*exo* n = 2 series (R = Pr) (Scheme 57).



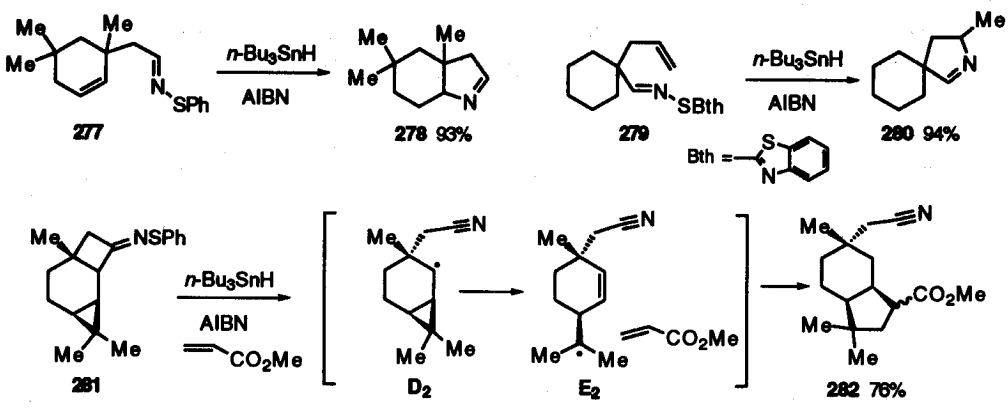
Scheme 57

Fallis and Gravelle[8e,i] encountered similar results in their hydrazone studies from different precursors. Commencing with **273** (R = H, n = 2), the tandem product was only formed in 12% yield but this yield was increased for the cyclization of **273** (R = Ph) to 30% of **272** (n = 2, R = NPh_2). For the double 5-*exo* closure the yield of **272** (n = 1, R = NPh_2) increased to 65%. In an attempt to prepare the tropane alkaloid skeleton **276** the cyclization of **274** was also examined. The cycloheptene **275** was generated in 33% yield along with reduced starting material. The addition of tin oxide did not improve the yield, and no bicyclic material was detected in either case.

Iminyl Radicals

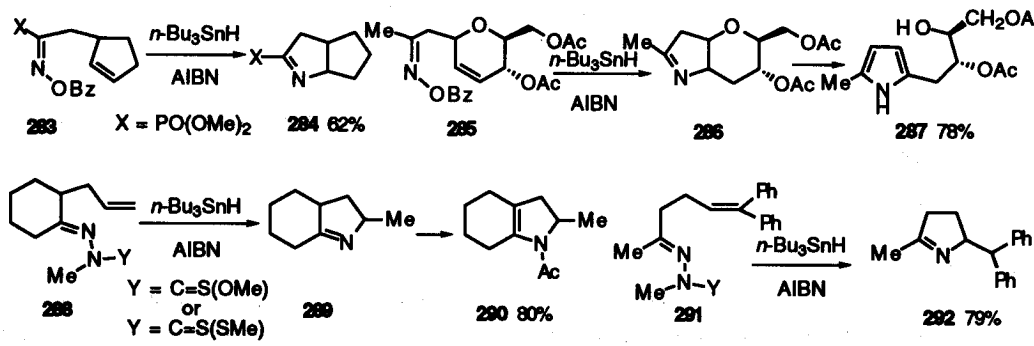
Iminyl radicals were encountered above as intermediates in the nitrile additions in Schemes 42-46. Early investigations of their behavior were reported by Forrester and coworkers,[42] mainly under acidic conditions, and more recently a summary of the current work by Zard and coworkers[43a] has appeared. Together with Newcomb and coworkers they have measured rate constants for iminyl systems.[39c] The generation and behavior of iminyl radicals generated from *S*-aryl, oxime benzoates, xanthyl hydrazones, *S*-benzothiazole sulphenylimines and *N*-benzotriazolimines for the synthesis of diverse pyrrolidine systems have been reported. Thus cyclization of **277** and **279**[43b,c] afforded the bicyclic products **278** and **280** in excellent yields. In addition, Zard and coworkers[43d,e] have investigated the ring opening of iminyl radicals derived from

cyclobutanones. For example, the ring cleavage of **281** generated the cyclohexyl radical **D_2** followed by rearrangement of this α-cyclopropyl radical to provide **E_2**. Conjugate addition of this species to methyl acrylate followed by a 5-*exo* cyclization provided the hydrindane **282** in 76% yield (Scheme 58).



Scheme 58

Oxime benzoates[43f-h] have provided another useful source of iminyl radicals although less reactive than the sulfur based systems. The best conditions employed cyclohexane as the solvent in the presence of tributyltin hydride and AIBN. Cyclization of **283** provided the bicyclic imine **284** in 62% yield. In a similar fashion **286** was prepared from **285** in 78% yield. The actual product in the latter case was **287** from treatment with silica gel. Zard and coworkers[43i] have also developed routes to iminyl radicals from xanthyl hydrazones. With this procedure cyclic imines **289** (isolated as **290**) and **292** were prepared from hydrazones **288** and **291** in a direct manner in approximately 80% yield (Scheme 59).

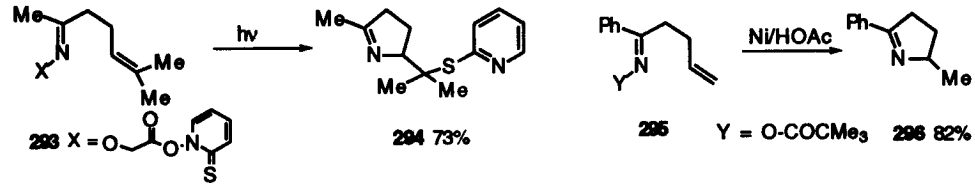


Scheme 59

Further investigations from the Zard group[43j] have capitalized on a modified Barton ester in which formaldehyde is expelled on route to the desired radical. Irradiation of **293** with visible light in refluxing

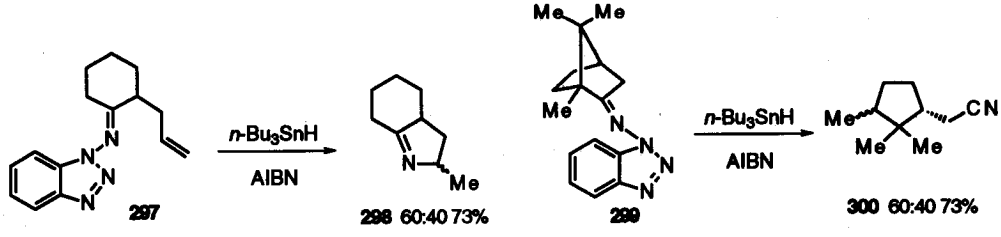
dichloromethane resulted in the facile cyclization of **293** and trapping of the resultant tertiary radical to give the sulfide **294** in 73% yield.

A new nickel/acetic acid system has also been developed as a mild single electron reducing agent.[43a] Heating pivaloyl oximes with this reagent in 2-propanol afforded the expected heterocycle **296** in 82% yield from **295** (Scheme 60). Introduction of a radical trap such as diphenyldiselenide to the reaction media resulted in primary radical capture with the introduction of a phenyl selenide moiety.



Scheme 60

Kaim and Meyer[44] have developed a route to iminyl radicals from benzotriazoles in which the initial attack by tin radical occurred at nitrogen. In this way the imine **297** was generated *in situ* from the corresponding cyclohexanone and afforded **298** in 73% yield. In a related fashion ring cleavage of the camphor derivative **299** provided the nitrile **300** (Scheme 61).



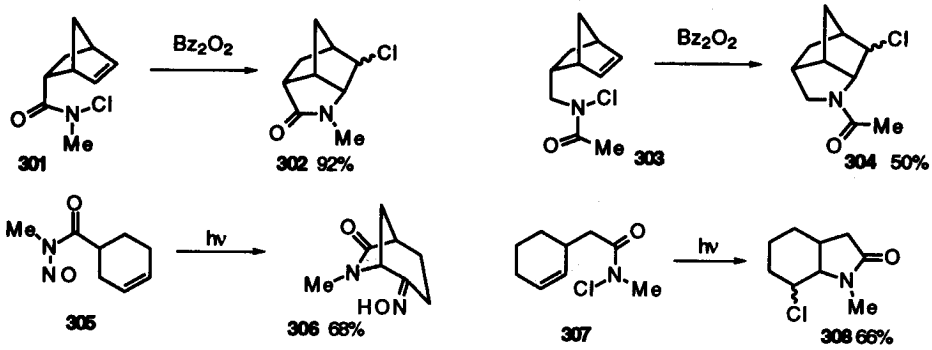
Scheme 61

The 5-*exo* cyclization rate constants for iminyl radicals are approximately one order of magnitude larger than those of aminyl radicals in structurally related systems with rate constants of 2×10^6 s^{-1} and 3×10^5 s^{-1} respectively at 25 °C.[39c,h]

Amidyl Radicals

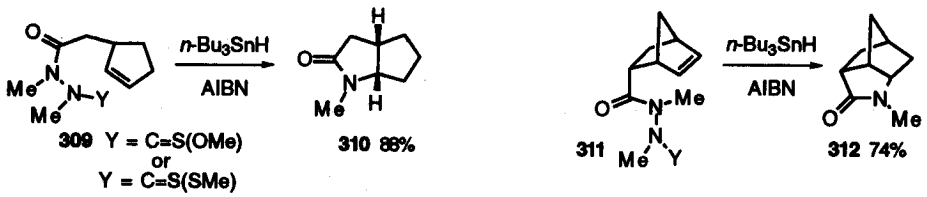
Amidyl radicals may be derived from *N* substituted amides in which the group cleaved is a halogen, a nitroso group, a hydrazine, a benzoate, or a *N*-hydroxypyridine-2-thione imidate. Lessard and coworkers[45] prepared the tricyclic systems **302** and **304** using benzoylperoxide as an initiator. Thus the tricyclic lactam **302** was produced from **301** in 92% yield. Placement of the carbonyl group outside the ring allowed greater flexibility and reduced the ease of cyclization. Thus the same nucleus **304** was generated from **303** but with a reduced yield of 50%. These reactions can also be conducted under photolytic conditions as illustrated by the

conversion of the nitroso system **305** to the oxime **306**[46] and the preparation of **308** in 66% yield from **307** (Scheme 62).[47]



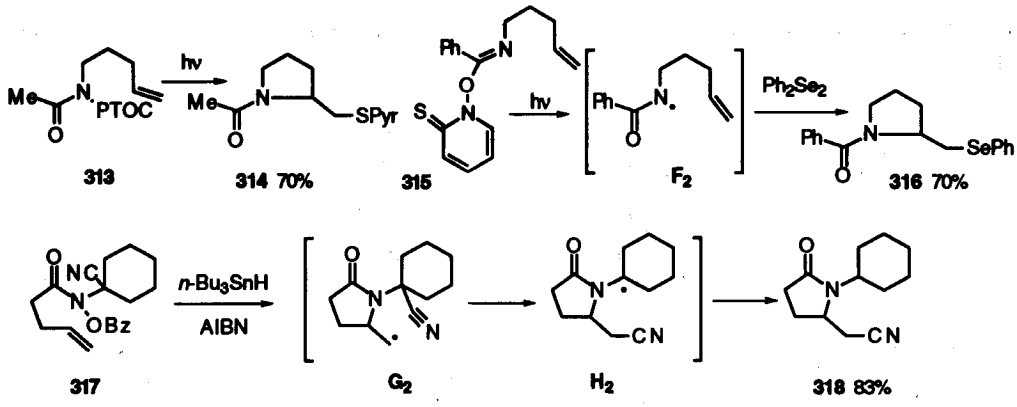
Scheme 62

Modification of the hydrazone concept in Scheme 59 permitted the development of a hydrazine route to amidyl radicals.[43i] These examples cyclized cleanly to lactams in yields that were similar to the related structural cases above. Thus hydrazines **309** and **311** afforded α-amino-acyl radicals (amidyl radicals) upon treatment with tributyltin hydride from which the heterocyclic systems **310** and **312** were isolated in yields of 88% and 74% respectively (Scheme 63).



Scheme 63

N-Hydroxypyridine-2-thione imidate esters have also been employed to generate amidyl radicals in systems such as **313**.[39d] The radical intermediate from **313** reacted cleanly to afford **314** in 70% yield. The yields were increased in related cases when an efficient trapping agent such diphenyldiselenide was added. In an extension of these investigations Newcomb and Esker[39d] have employed the thione unit in a different fashion to generate **316**. The initial oxygen radical from **315** afforded the radical $\mathbf{F_2}$ which cyclized and reacted with diphenyldiselenide to provide **316** in 70% yield. Benzoates[43g] have also been used to prepare amidyl radical intermediates. Under tributyltin hydride conditions the radical $\mathbf{G_2}$, derived from **317**, added to the nitrile. However, as observed above, the iminium radical was not reduced but rather rearranged with concomitant ring cleavage resulting in nitrile transfer to give $\mathbf{H_2}$. Subsequently the final product **318** was formed in 83% yield (Scheme 64).

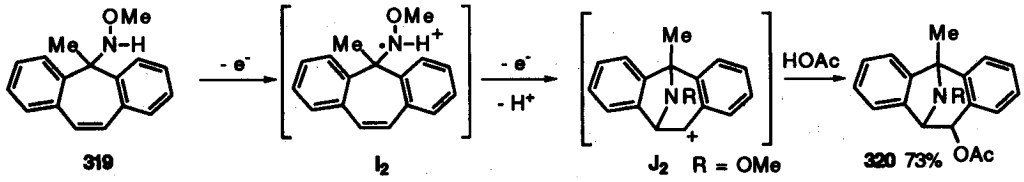


Scheme 64

Aminium Cation Radicals

Aminium cation radicals and metal or Lewis acid complexed aminyl radicals render the nitrogen center more electrophilic, and consequently these intermediates usually participate more readily in additions to unsaturated centers. The generation of these species has been reviewed.[39a] Brendan and Tsanaktsidis[48] suggested that the cyclization of the *N*-butyl-4-pentenylaminyl radical was not reversible and that the reaction was accelerated significantly by the addition of bis(tributyltin)oxide. However, a recent re-examination of this conclusion has established that there was no rate increase with added tin oxide. Thus for the uncomplexed aminyl system the cyclization rate constant was 14.6 x 10^4 s^{-1} and the ring opening value was 5.1 x 10^4 s^{-1} at 80 °C.[39e] As mentioned above the addition of magnesium salts to reactions involving the tandem cyclizations of imines (Scheme 56) generated an aminium complexed system and resulted in a beneficial increase in yield.

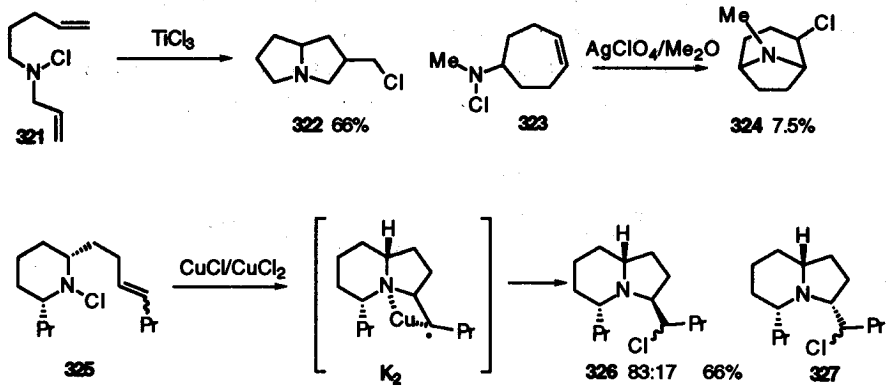
Weinstock and coworkers[49] have utilized the electrochemical procedure in Scheme 65 for the synthesis of an 11-hydroxy metabolite from MK-801, a *N*-methyl-D-asparate receptor antagonist. Initially the reaction of **319** afforded an aminyl radical that became the aminium radical $\mathbf{I_2}$. This intermediate cyclized to the benzylic species $\mathbf{J_2}$ from which the tropane skeleton **320** was formed in 73% yield.



Scheme 65

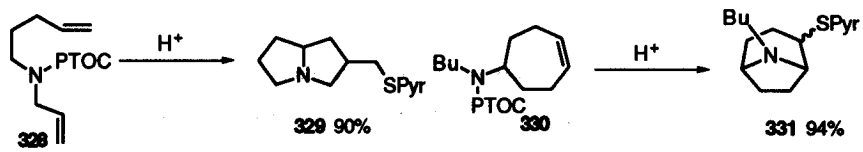
N-Alkyl-*N*-chloroamines in the presence of metal salts, such as copper, iron, or titanium or alternatively protic acids cyclize readily to heterocyclic systems. Scheme 66 illustrates some efficient examples in which the products incorporate a chlorine substituent from atom transfer. Thus Surzur and Stella[50] have prepared **322** from **321** in a tandem cyclization in 66% yield and the tropane skeleton **324** was synthesized in a modest 7.5%

yield from **323**.[51] Broka and Eng[52] applied these same conditions to the 5-*exo* cyclization of the chloroamine **325** to construct the indolizidine ring system for the total synthesis of gephyrotoxin (Figure 1). These cyclizations are believed to involve intermediates of type K_2 in which chlorine atom transfer completes the sequence. Cyclization afforded a 66% yield of an 83:17 mixture of **326** and **327** from **325** (Scheme 66).



Scheme 66

The use of PTOC carbamates for the generation and cyclization of aminium cation radicals in the presence of acid in acetonitrile is a very efficient process and leads to excellent yields of the desired heterocyclic ring systems. The best conditions employed malonic acid in acetonitrile. Comparison of the Schemes above illustrates the benefits of these substrates developed by Newcomb and coworkers.[39b] Yields of cyclized products exceeded 90% as illustrated by the reaction of **328** and the synthesis of the tropane system **331** from **330** (Scheme 67). This efficiency may be further improved under mild conditions with Lewis acids.[39f] Consequently the use of *i*-propyloxytitanium trichloride (0.5 equiv) at -78 °C resulted in yields of 98% of cyclized material in simple cases. Related studies have revealed that boron trifluoride was also an excellent additive although the degree of kinetic activation was less than with protic acids.

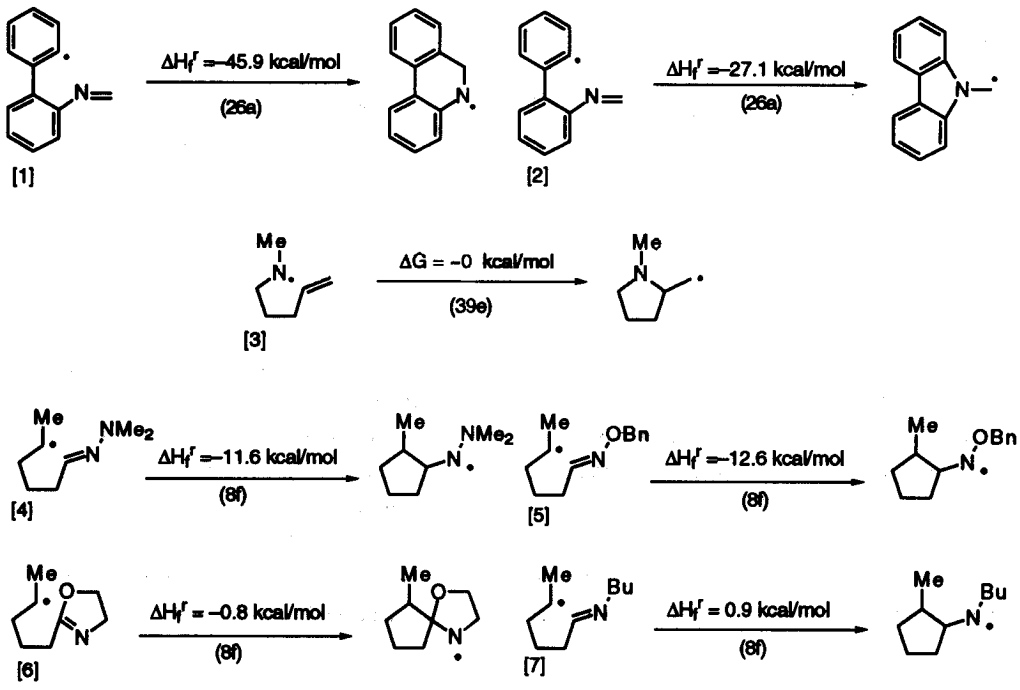


Scheme 67

CALCULATIONS and KINETIC DATA

At present limited thermochemical data are available for nitrogen related radical cyclizations. Figure 2 summarizes a combination of some of the available information. Entries 1-4 were derived experimentally and the remaining heats of formation were calculated at the AM1-UHF level. For Entries 1 and 2 the activation barriers were determined to be 14.7 kcal/mol for the 6-*endo* and 5.5 kcal/mol for the 5-*exo* cyclizations of aryl

radicals onto the nitrogen atom of the imines. For reasonable yields most synthetically useful radical cyclizations require the addition step to be exothermic. High level computations suggested that ΔG for Entry 3 is close to zero,[39e] although other values have also been reported. The failure of oxazolines to act as radical acceptors is apparent from the fact that for Entry 6 the cyclization reaction is thermoneutral in contrast to the *N,N*-dimethylhydrazone acceptors of Entry 4. This reaction afforded a value of -11.6 kcal/mol, slightly, less than the value obtained for the benzyloxime in Entry 5. Some of the radical character on nitrogen at the transition state will be stabilized by interaction with the attached heteroatom. This may explain why the 5- and 6-*exo* hydrazone cyclizations were found to have lower activation barriers than the corresponding alkene



Carbon Electron Densities

	MeHC=N-Me	MeHC=N-OMe	MeHC=N-NMe$_2$	
AM1-UHF	-4.075	-4.141	-4.177	(19h)
PM3-UHF	-4.092	-4.096	-4.127	

Figure 2. Thermochemical Data

cyclizations. The activation barriers for a secondary radical in 5-hexenyl type 6-*exo* cyclizations are 6.5 kcal/mol for the *cis* product and 7.4 kcal/mol for the *trans* carbocycle. For comparison, the corresponding values for 6-*exo* cyclizations onto N,N-diphenylhydrazones are 5.6 kcal/mol (*cis*) and 6.2 kcal/mol for the *trans* product, lower than the values for the corresponding carbocycles.[8g] The low endothermic value for the imine system in Entry 8 indicated that this step will be sluggish, consistent with the rate data below. The best

yields resulted from tandem examples or involved more reactive aryl radicals. The second nitrogen present in the hydrazones and the oxygen in oximes are likely involved in a 2-center, three-electron bond with the developing radical on the nitrogen of the imine. This three electron bond will help stabilize the developing nitrogen radical during cyclization. This is reflected in the positive influence of the R_2N and RO substituents on the reaction exothermicity for of these radical cyclizations compared to cyclizations onto alkenes.

The carbon electron densities of the different C=N bonds present in imines, oximes and hydrazones have been calculated at both the AM1-UHF and PM3-UHF level.[19h] As expected, these values increased when heteroatoms were attached to the nitrogen center.

Une Petite Horlogerie

In the Figures below a variety of rate constants are compiled. These include ring openings of cyclopropyl and cyclobutyl systems, cyclizations and reversions onto aldehyde carbonyl acceptors for both carbon and nitrogen centered radicals, cyclizations for carbocyclic systems onto alkenes, cyclizations for carbocyclic systems in which nitrogen substituents are retained, and cyclizations of various nitrogen radicals to

	n-Bu_3SnH	*t*-BuSH	PhSH	PhSeH
$RCH_2^{\bullet}$	$k_{25} = 2.4 \times 10^6\ M^{-1}\ s^{-1}$	$k_{25} = 8 \times 10^6\ M^{-1}\ s^{-1}$	$k_{25} = 1.4 \times 10^8\ M^{-1}\ s^{-1}$	$k_{25} = 2.1 \times 10^9\ M^{-1}\ s^{-1}$
$R_2N^{\bullet}$	$k_{25} = 4.9 \times 10^5\ M^{-1}\ s^{-1}$	$k_{25} = 6 \times 10^6\ M^{-1}\ s^{-1}$	$k_{25} = 1.2 \times 10^8\ M^{-1}s^{-1}$	$k_{25} = 2.2 \times 10^9\ M^{-1}\ s^{-1}$

Figure 3. Reduction Rate Constants

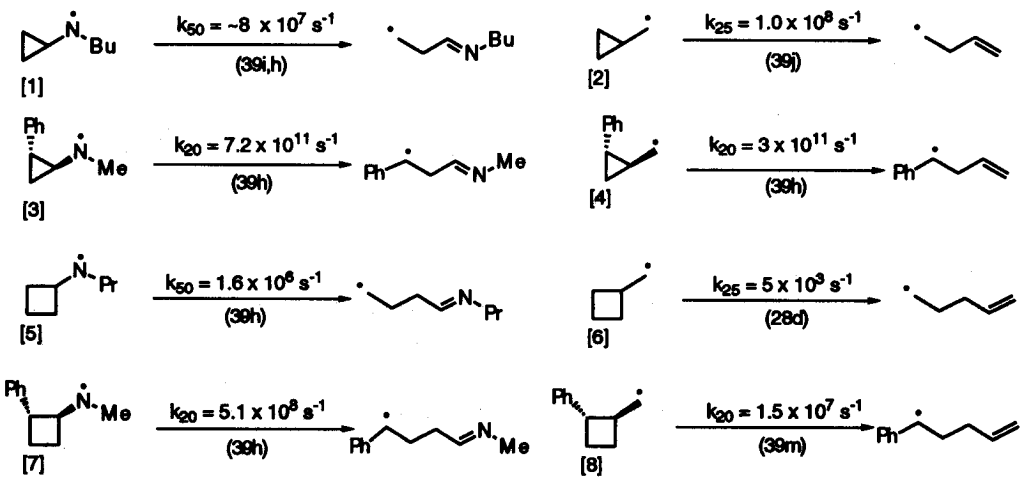


Figure 4. Ring Opening Rate Constants for Cyclopropyl and Cyclobutyl Systems

afford heterocyclic skeletons. It is anticipated that these equations will provide a useful framework for comparisons and to aid synthetic planning. The reader is referred to additional sources for further data.[39g,53] The reduction rate constants with tributyltin hydride and related hydrogen transfer agents for carbon and

nitrogen radicals are summarized in Figure 3.[39h] Clearly, phenylselenol is the most efficient hydrogen atom donor in the list. The hydrogen atom transfer rate from tributyltin hydride to oxygen radicals is 2 x 10^8 M^{-1} s^{-1} at 22 °C.[54]

The ring opening rates for α-cyclopropyl radicals are quite similar, and independent of their location on either a nitrogen or carbon center. However for the cyclobutyl series, Entries 5 and 6, the nitrogen system displays a modest advantage as the aminyl radical induces faster ring opening at similar temperatures. The oxygen values in Figure 5 indicate the close competition that exists between the cyclization rates and the rates for ring opening. In the case of the aminyl-stannane systems in Entries 3 and 4 the rate constants for ring opening are significantly larger than the cyclization rate constants. This requires that carefully designed experiments must be selected to achieve synthetically useful results. In the case of Entry 4, the conformation of the oxygen radical attached to the cyclohexyl ring will be favorably oriented for facile ring cleavage. In addition, the resulting radical is stabilized by the ester substituent.

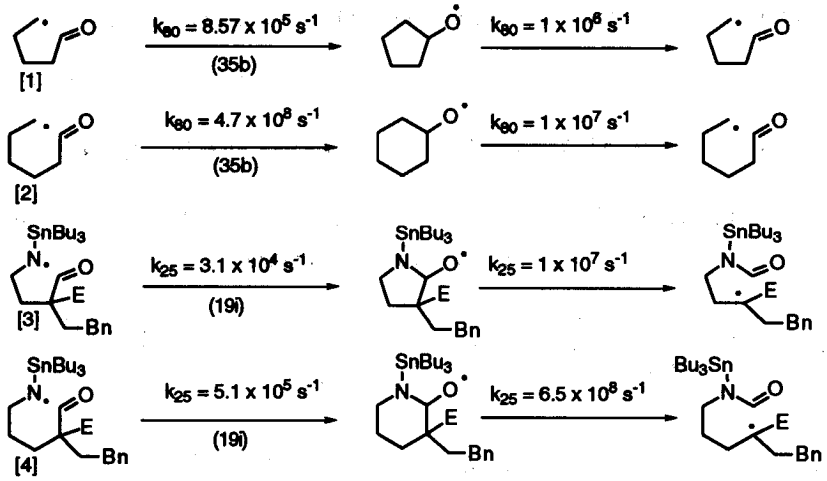


Figure 5. Cyclization and Ring Opening Rate Constants for Aldehydes

Comparison of appropriate entries in Figures 6 and 7 indicates that for 5-*exo* systems most rate constants are larger for cyclizations onto C=N systems. Compared to alkenes, one gains approximately one order of magnitude with simple imines as illustrated by the carbocyclic examples Entries 1 and 3 in Figure 6 versus the imine Entries 7 and 13 in Figure 7. A similar rate constant increase is apparent with the oximes, (Figure 7 Entries 11, 17, and 19). Hydrazone acceptors provide an additional gain as reflected in Entries 1, 3, 5, and 9 in Figure 7. Other interesting features of this table include the behavior of various aryl radicals. The rate constants of both the 5-*exo* and 6-*endo* cyclizations are large for both imine (Entries 10 and 12) and azo acceptors (Entries 14 and 16). The 5-*endo* rate constant (5.2 x 10^9 s^{-1}) for an aryl radical onto an azo systems is also large.[25e] The rate constants vary slightly with the experimental method. Thus the rate constants derived from intramolecular competition experiments in which the R substituent contains a different

unsaturated functional group tend to be slightly higher than those derived from standard kinetic measurements (Entries 17 vs. 19, 18 vs 20).

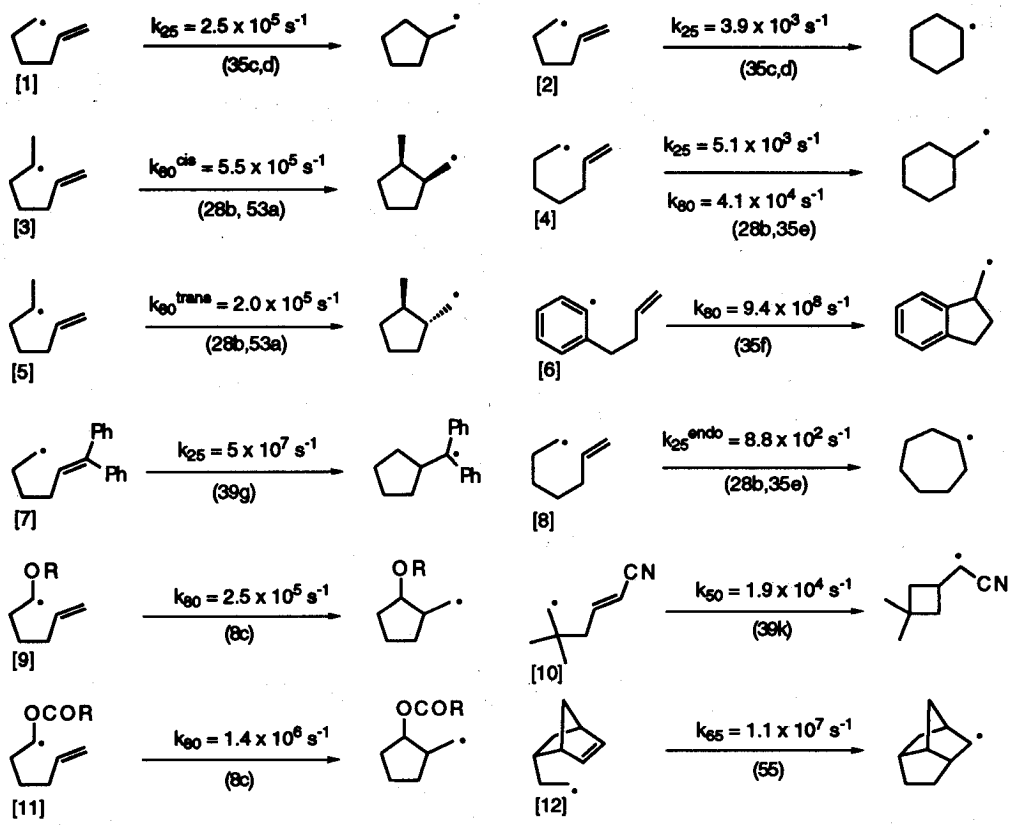


Figure 6. Cyclization Rate Constants for Carbocyclic Systems

Figure 8 allows an interesting comparison of nitrogen centered radical cyclizations. In the simplest case of Entry 1 for a 5-*exo* cyclization, the rate constants for cyclization and ring opening are nearly equal and thus there is a delicate balance between the two pathways. Other entries indicate various combinations that improve the rate of this type of cyclization. Activation of the double bond with a single phenyl group (Entry 3) increased the rate constant by a factor of 10. A slight further improvement is achieved with geminal phenyl groups (Entry 5). An additional 10 fold increase was achieved by the use of the iminyl radical in Entry 2.

The final comparisons of note demonstrate the use of a proton source to form aminium cation radicals *in situ* causing the nitrogen centers to react more rapidly with olefinic acceptors. Treatment with a Lewis acid such as magnesium dibromide etherate resulted in a modest increase in the rate constant for Entry 7 *versus* Entry 5. The rate constants for the 5-*exo* cyclizations, Entry 11 compared to Entry 12 illustrate the large rate increase due to complexation with a trace of protic acid such as CF_3CO_2H. A similar improvement is evident between Entries 6 and 8.

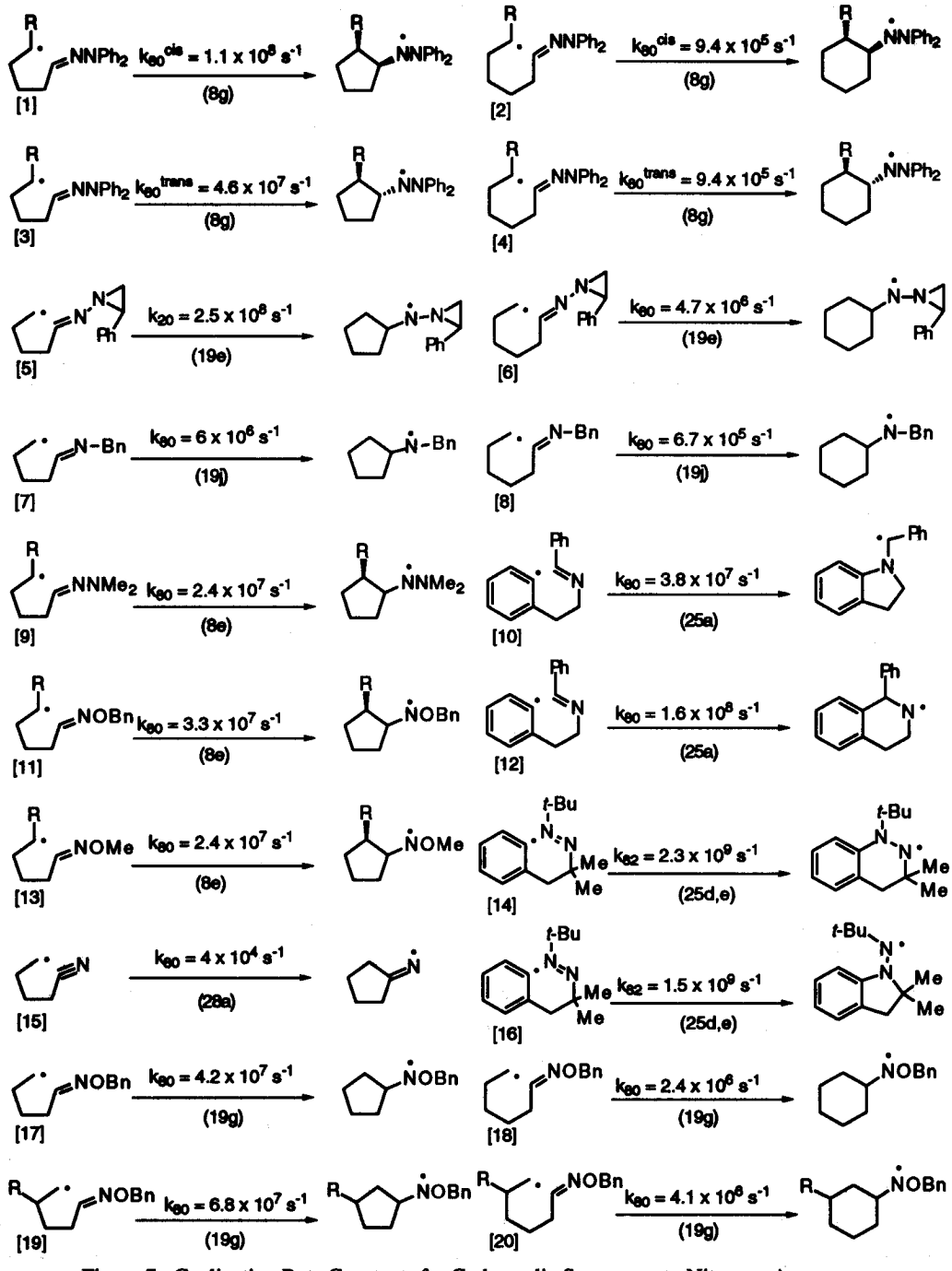


Figure 7. Cyclization Rate Constants for Carbocyclic Systems onto Nitrogen Acceptors

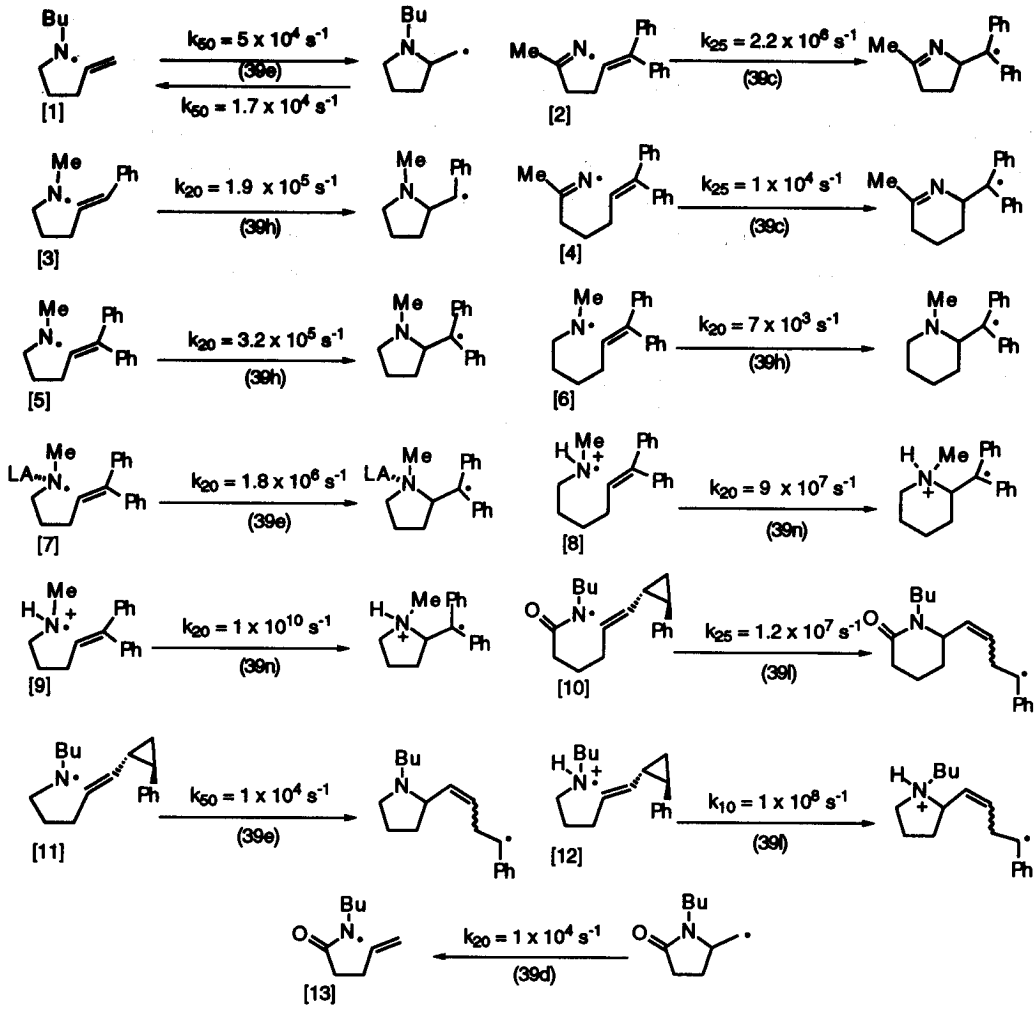


Figure 8. Cyclization Rate Constants for Aza Heterocyclic Systems from Nitrogen Radicals

Conclusions

The behavior of carbon and aminyl radicals in ring-closure and ring-opening reactions depends on the interplay of several factors. These include the fact that a carbon-nitrogen single bond in a tertiary amine is weaker than the corresponding carbon-carbon single bond of a tertiary hydrocarbon. However, the π-bond of an imine is stronger than the π-bond of an alkene. Thus cyclizations with aminyl radicals to form single bonds will result in slower reactions than for their carbon radical analogs. These features are reversed with fragmentation reactions to generate double bonds as aminyl radicals usually react faster.

It is clear that the radical chemistry discussed above has improved our basic understanding and knowledge of nitrogen containing systems. The future will undoubtedly see many further advances as new insights into the basic reactions are discovered. This will lead to increasingly more sophisticated synthetic applications including asymmetric methods. The data above illustrate that subtle changes can have a significant effect on cyclization rates and product distributions. Hydrazones and oximes are versatile acceptors for a variety of situations. As noted, protonation of neutral aminyl radicals has a major impact on the reactivity. Consequently aminium cation radicals will likely become more attractive and versatile for certain synthetic applications than the neutral aminyl radicals from which they are commonly derived.

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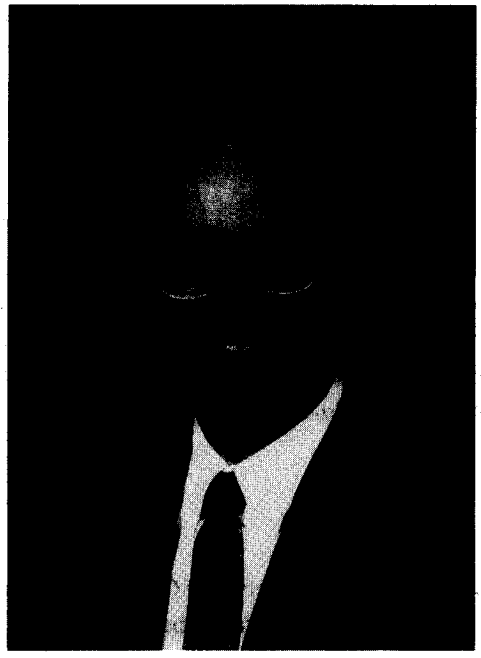
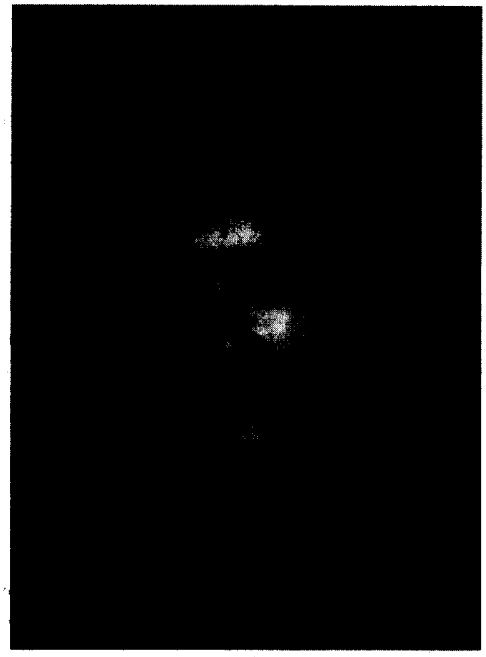
Biographical Sketch



Alex Fallis



Irina Brinza

Alex Fallis was born in Toronto and received his B.Sc. Hon. (1963), M.A. (1964), and Ph.D. (1967) degrees from the University of Toronto with the late Professor Peter Yates. After an NRC Postdoctoral Fellowship at Oxford University with Professor E.R.H. Jones he joined the Department of Chemistry at Memorial University of Newfoundland in 1969. In 1988 he was appointed Professor in the Department of Chemistry at the University of Ottawa and was Director of the Ottawa-Carleton Chemistry Institute from 1990-93. He has been Chairman, Board of Directors, Chemical Institute of Canada, 1984-86, an Editor of the Canadian Journal of Chemistry, 1992-95 and served on NSERC and NCI grant selection committees. He was a Visiting Professor at the California Institute of Technology and the Institute de Chimie des Substances Naturelles. In 1996 he was awarded the Basic Science Research Award of the Ottawa Life Sciences Council, for 1997-2000 he received the Saunders-Matthey Foundation award for Breast Cancer Research, and is the recipient of the Alfred Bader Award of the Canadian Society for Chemistry for 1998.

Alex Fallis' research encompasses synthetic and medicinal organic chemistry, particularly intramolecular pericyclic reactions, free radical cyclizations involving nitrogen, studies in π-facial diastereoselectivity, and the use of chiral control elements. Sequential intramolecular Diels-Alder reactions are being developed for taxoids using a chiral isopropylidene acetal tether control group. Additional studies include enediynes as taxoid hybrids (Taxamycins), eneyne cyclophanes (Revolvenynes) and related multibridged systems with helical chirality for carbon networks including C_{60} (Buckminsterfullerene).

Irina Brinza is currently in the fourth year of her Ph.D. program at the University of Ottawa working in the research group of Professor Alex G. Fallis where she is focusing on the study of free radical reactions of hydrazones. In 1993 she received a Masters (Diplom) degree in Chemical Engineering from the "Gh. Asachi" Technical University of Jassy, Romania working on the synthesis of semiconducting polyacetylenes. She is the recipient of an Ontario Graduate Scholarship and a University of Ottawa Excellence Scholarship.