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Addition of carbon-centered radicals to imines and related compounds

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1. Introduction

Imines (azomethines), iminium salts, and related compounds have been used as electrophiles for ionic bond constructions (e.g. in the Mannich reaction) for many years, but the ongoing demand for more efficient, mild and general synthetic methodology makes radical addition to imine derivatives an increasingly important alternative. Although industrially important radical addition to alkenes has long attracted research efforts, radical addition to imines and

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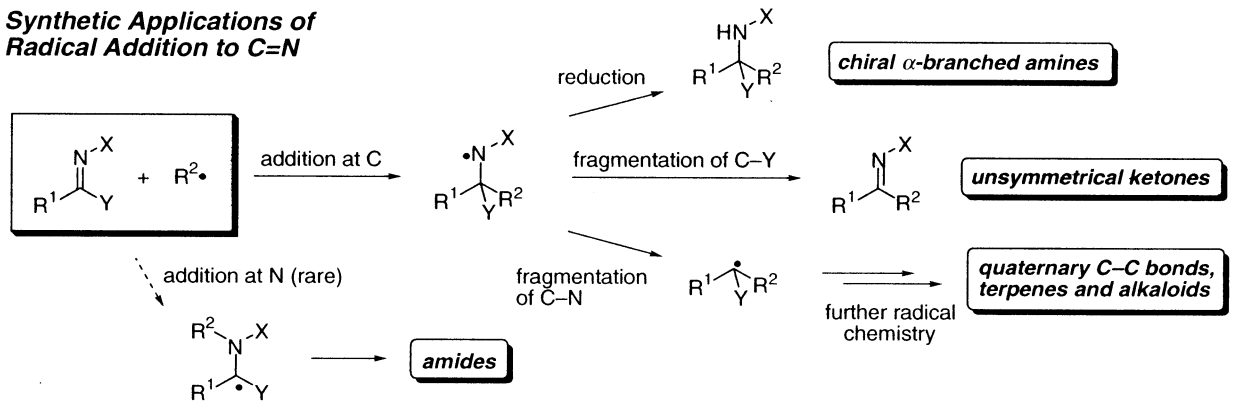


Scheme 1.

related compounds began to emerge as a useful synthetic process only since the 1980s. This is rather surprising in retrospect, given that these functional groups can exhibit up to three orders of magnitude higher radical addition rates relative to analogous alkene acceptors. Furthermore, a useful functional group remains available for subsequent synthetic elaboration, either via fragmentation and further radical chemistry, or by traditional transformations of closed-shell products. In contrast to alkenes, the Lewis basic nitrogen of imines offers an inherent site within the acceptor for Lewis acid complexation, which has ramifications for rate enhancement and stereochemical control.

Synthetic applications of radical addition to C=N bonds are summarized in Scheme 1. By far the most common application is reductive addition to obtain amines. Interest in these reductive radical addition reactions has been building since the first pinacol-type radical cyclization of an oxime ether appeared in 1983. Subsequently, seminal studies in 1988 explored the radical acceptor behavior of oxime ether carbon–nitrogen π bonds in reductive additions (see Section 2.1). Non-reductive radical additions to oximes and nitronates had previously been known but largely neglected and underdeveloped from the synthetic perspective; this has begun to change within the last decade, leading to new routes to ketones and nitro compounds (see Section 3.1). Meanwhile, specialized functional groups have been developed as radical acceptors for tandem processes involving addition followed by fragmentation of bonds at either the N-terminus or C-terminus of the original C=N bond. In such fragmentation processes the strategic construction of a carbon–carbon bond via radical addition to C=N has been used in syntheses even when the final target contains no nitrogen. Currently, radical addition to imines and related compounds is rapidly developing into a general and reliable synthetic strategy: applications to complex natural product targets have appeared, adaptations to solid-phase synthesis are available, and methods for achieving acyclic stereocontrol have recently emerged.

1.1. Literature coverage

This review focuses on carbon-centered free radical additions to carbon–nitrogen π bonds (hereafter referred to as 'C=N bonds') with literature coverage through mid-2000 and an emphasis on applications to organic synthesis. Radical additions to nitriles, isonitriles and nitrogen-containing heteroaromatic ring systems are not covered in this review, nor are various cycloaddition reactions with potential implications of diradical character. Section 2 is essentially a continuation of a previous *Tetrahedron Report* by Fallis and Brinza,[1] and therefore examines mostly the more recent (1997–2000) intramolecular reactions involving radical additions to C=N bonds. Throughout Section 2 carbon numbering in cyclizations is based on the parent hydrocarbon radical, e.g. 5-hexenyl, for consistency. The intermolecular version of this reaction has also seen dramatic new developments, and is reviewed here for the first time in Section 3, organized according to stereocontrol considerations. Although the available data are limited, some kinetic and thermodynamic parameters associated with the reactions discussed herein are available in the previous review by Fallis; more recent data will be included here where available.

It is assumed the reader has an elementary working knowledge of radical reactions and the common reagent systems used in these transformations. Readers seeking such information may wish to consult an excellent synopsis by Curran, Porter, and Giese in *Stereochemistry of Radical Reactions*;[2] more thorough discussion is available in pertinent books and reviews.[3] In addition, several more specialized reviews have appeared which focus on various mechanistic viewpoints or synthetic objectives with respect to radical reactions.[4]

1.2. Practical considerations among common C=N acceptors

1.2.1. Comparisons of imino functional groups. Oxime ethers and hydrazones are by far the most commonly used radical receptors among the various C=N-containing functional groups. Imines can be used, but they are more difficult to handle since they are more prone to hydrolysis and tautomerization than the oximes and hydrazones. For example, *O*-alkylformaldoximes can be purified and stored normally, while formaldimines are rather unstable. More importantly, imines have slower radical addition rates. Selected rate constants for intramolecular radical addition reactions are compiled in Fig. 1.[1]

Kim has rationalized the rate differences by considering semi-empirical calculations (MOPAC) of electron densities

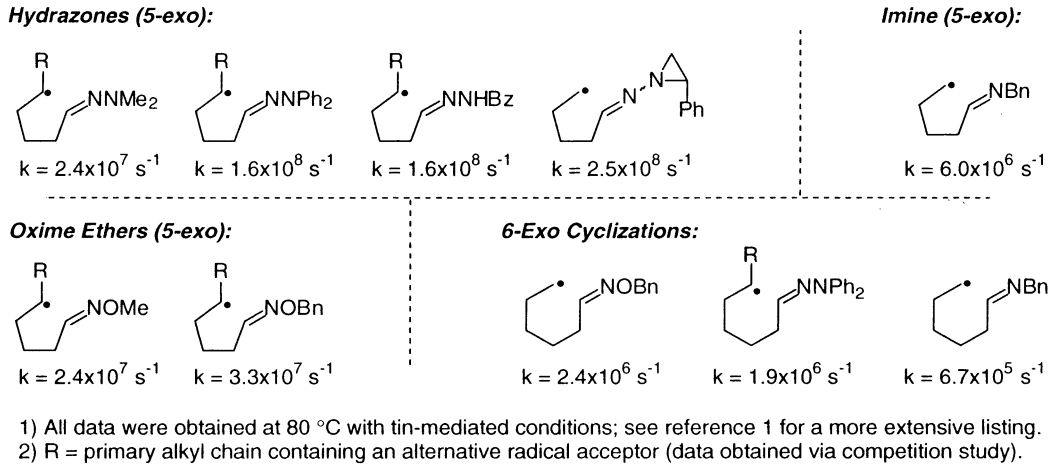


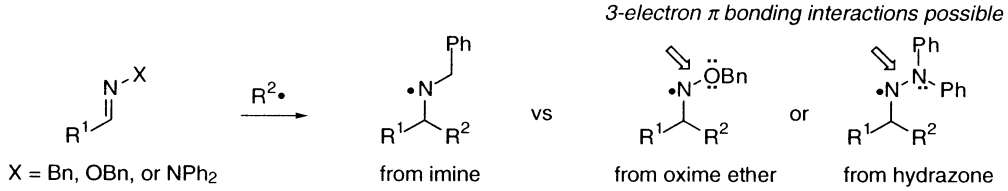
Figure 1. Selected radical cyclizations for rate comparisons among imino acceptors.

on the C=N carbon, which are in the order hydrazone>oxime ether>imine.[12] Also, imines lack the potential for a stabilizing three-electron π-bond in the adduct aminyl radical (Scheme 2); this developing interaction could effect stabilization of the transition state.

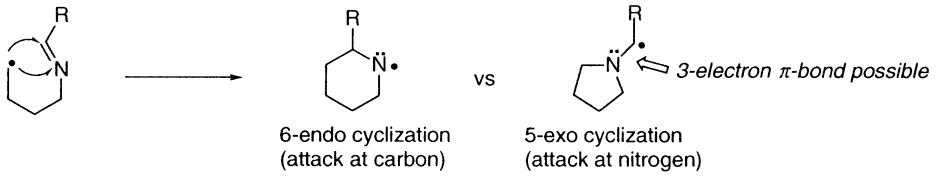
Unfortunately, since the relevant kinetic data are mostly unavailable, direct comparisons of the rates of intermolecular radical addition to various C=N-containing functional groups cannot presently be made. Rates of intermolecular 5-hexenyl addition to $Me_2C{=}NO_2{}^-Li^+$ ($3{\times}10^4\ M^{-1}\ s^{-1}$, 40°C in DMSO)[5] and 4-phenoxybutyl addition to PhO_2S-CH=NOBn ($9.6{\times}10^5\ M^{-1}\ s^{-1}$, 25°C in PhH)[6] have been determined, though comparisons require caution since these were independently obtained under quite different conditions.

1.2.2. Regioselectivity. Attack at carbon of the C=N bond is almost exclusively observed, except in unusual cases (see Section 2.3). One might envision that radical addition to the C=N bond could occur with attack at nitrogen to give an α-amino radical (Scheme 3), which should be stabilized by the adjacent nitrogen. The competition between 5-*exo* and 6-*endo* cyclizations has been used to examine this issue. Favored attack at carbon is illustrated nicely by Warkentin's competition studies with aryl radical cyclizations, wherein 6-*endo* attack at carbon was preferred over 5-*exo* attack at nitrogen.[7] This is in contrast with the radical cyclizations of alkenes wherein 5-*exo* cyclization rates are higher. Warkentin's calculations of aldimines exhibit higher LUMO coefficients on carbon, consistent with the kinetically preferred attack at this site. Ryu and Komatsu have conducted ab initio (UHF/3-21G) MO calculations of the alternative 5-*exo* (attack on N) and 6-*endo* (attack on C) cyclizations of a vinyl radical, finding that the latter transition state is preferred by 3.4 kcal mol^{-1}.[8] There was virtually no thermodynamic preference for 6-*endo* cyclization, so attack at the C-terminus of C=N bonds appears kinetically favored, consistent with their experimental results.

1.2.3. Reversibility. A generalization can be made that, from a practical viewpoint, alkyl radical additions to alkenes are irreversible in the absence of ring strain, while additions to carbonyl groups are reversible. In this simplified view, additions to C=N bonds fall between the former two functional groups; reversibility appears to be more dependent on the nature of the adduct radical. Bowman has reported that generation of a cyclopentylaminyl radical by an alternative method from **1** (Fig. 2) gave no ring-opened product, but the



Scheme 2.



Scheme 3.

Figure 2. Precursors for alternative generation of aminyl radicals by N–S homolysis to test reversibility.

aminyl radical from **2** eliminated diphenylmethyl radical, affording diphenylmethane in 67% yield.[9] Kinetic data[12] and MO calculations[8] suggest that 5-*exo* and 6-*exo* cyclizations of both imines and oxime ethers are essentially irreversible.

1.2.4. Other considerations for synthetic planning. The presence of a basic nitrogen, either after a reductive radical addition or during earlier synthetic transformations, may conflict with radical precursor functionality such as carbonyl or halide functional groups. Although apparently a rare problem (and even sometimes desirable), products of *N*-alkylation have been observed.[10,11] Many radical precursor groups other than electrophilic halides are available, however, and among these the selenides are a useful alternative when such situations are problematic.[12]

Oxime ethers are usually formed as inseparable *E*/*Z* isomeric mixtures with respect to the C=N bond. This ambiguity may interfere with design of asymmetric processes and can complicate purifications and characterizations during multistep sequences. In contrast, aldehyde hydrazones are generally obtained as *E* isomers.[13]

A practical advantage of oximes and hydrazones over simple imines is the variety of methods available for removal of the *N*-substituent from the hydroxylamine or hydrazine product in reductive radical additions. Complete discussion is beyond the scope of this review, but a few successful methods are compiled here. Reduction with H_2/Pd–C,[14] H_2/Raney nickel,[15] Zn/HOAc,[16] and molybdenum hexacarbonyl[17] have all been used for the N–O bond cleavage in hydroxylamines. One-electron reductants are also effective; Na(Hg), Al(Hg),[18] and $TiCl_3$ [19] have been used, and recently Keck has evaluated in some detail the use of SmI_2 for N–O bond cleavage.[20] For hydrazines, hydrogenolysis methods may be used (H_2 with Pd–C,[21] $Pd(OH)_2$,[22] PtO_2,[23] or Raney nickel[24] catalysts) along with dissolving metal reduction,[25] SmI_2,[26] BH_3·THF,[27] and other reagents.[28] In addition to the selected citations found here, many examples of these methods for N–O and N–N bond cleavage can be found in the literature referenced throughout this review. Thus, a number of complementary methods are available for the N–O or N–N bond cleavage to allow compatibility with a variety of functionalized molecular environments.

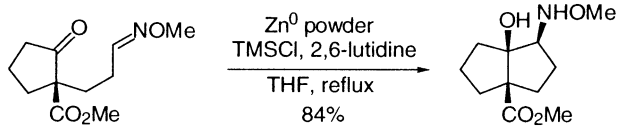
2. Radical cyclizations of C=N acceptors

This section covers mainly the literature from 1997 to 2000 and is a continuation of the literature coverage in the previous review by Fallis and Brinza.[1] However, for perspective on the development of the field, a few selected examples from the earlier literature are included.

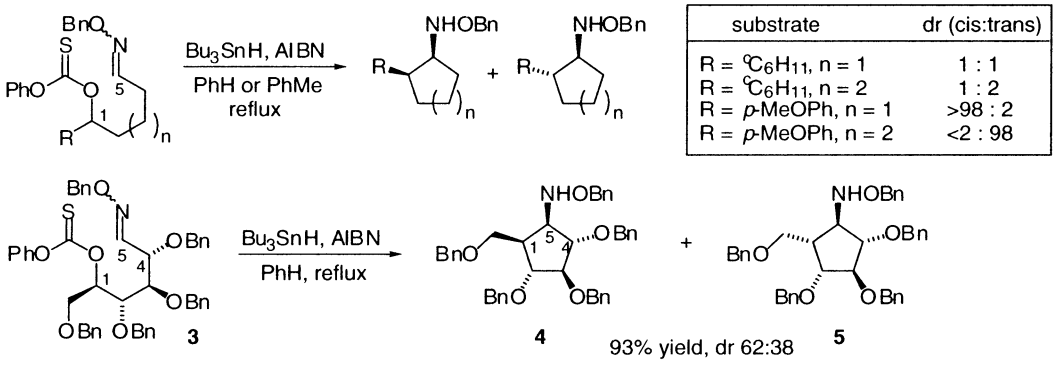
2.1. Reductive addition to the C-terminus of C=N

The first radical cyclization involving an oxime ether acceptor was reported by Corey in 1983.[29] Reduction of various cyclic ketones with zinc powder in the presence of trimethylsilyl chloride and 2,6-lutidine generated ketyl radicals which underwent addition to various pendant multiple bonds. Under these conditions, a ketomethoxime (Scheme 4) cyclized to afford a bicyclo[3.3.0]octane hydroxylamine.

Bartlett showed in 1988 that carbocyclic hydroxylamines could be prepared by reductive cyclization of phenyl thionocarbonates or bromides onto oxime C=N bonds (Scheme 5).[30] Although simple diastereoselectivity was low in most cases, methoxyphenyl substitution at the radical site led to excellent stereocontrol. Carbohydrate-derived substrate **3** led only to diastereomers **4** and **5** (among four possible). These observations are consistent with the Beckwith–Houk transition state model (Fig. 3), wherein 1,3-diaxial steric effects and allylic strain are minimized within chairlike structures having most substituents in pseudoequatorial orientations.[31] Complete 4,5-*trans* selectivity (5-hexenyl numbering) is observed from the effect of the substituent at the 4-position due to additional contributions from allylic



Scheme 4.



Scheme 5.

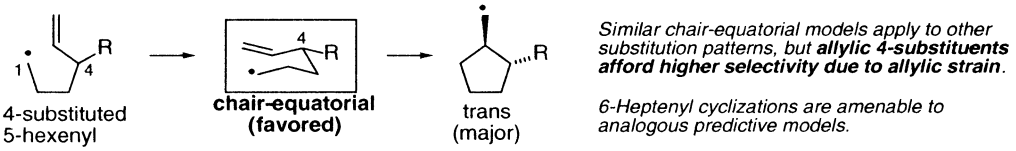
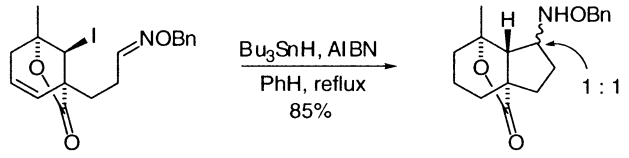
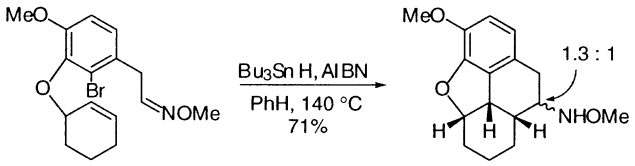


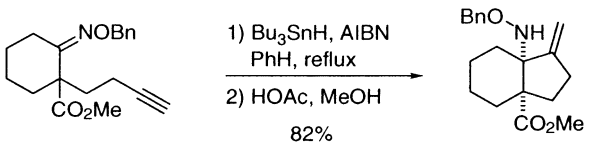
Figure 3. The Beckwith–Houk predictive model for stereocontrol in 5-hexenyl radical cyclizations.



Scheme 6.



Scheme 7.



Scheme 8.

strain, but the two diastereomers **4** and **5** are epimeric at the 1-position due to less effective conformational control of the substituent at the radical site.

Hart reported in 1988 the cyclization of a bicyclic iodolactone to a pendant oxime (Scheme 6) as a footnote in the seminal paper on intermolecular addition of radicals to formaldehyde oxime ethers[32] (vide infra, Section 3). In contrast to Corey's ketyl cyclization, here a 1:1 mixture was obtained.

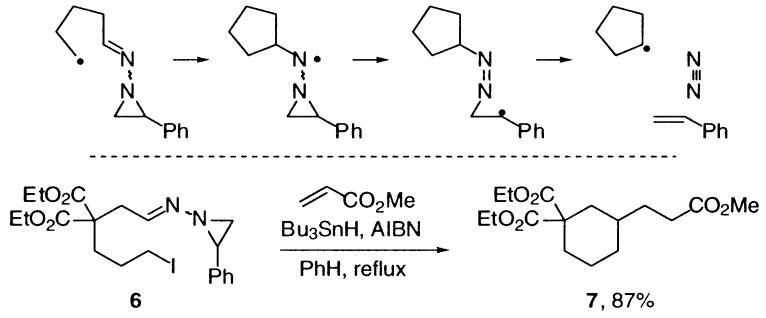
During synthetic studies toward morphine, Parker reported in 1988 a dramatic tandem cyclization process via aryl radical cyclization to an alkene followed by a second cyclization to afford a fused tetracycle (Scheme 7).[33] Conformational constraints enforced complete control of the ring fusion diastereoselectivity, though control at the prochiral oxime was minimal.

The first example of the use of a C=N bond as an acceptor for a radical generated by heteroatom addition to another multiple bond was an addition/cyclization tandem reaction reported by Enholm in 1990.[34] Stannyl radical addition to the terminal alkyne initiated a vinyl radical cyclization onto an oxime (Scheme 8); protodestannylation with acetic acid completed the process to afford the *cis*-bicyclo[4.3.0]-nonane ring system in 82% yield.

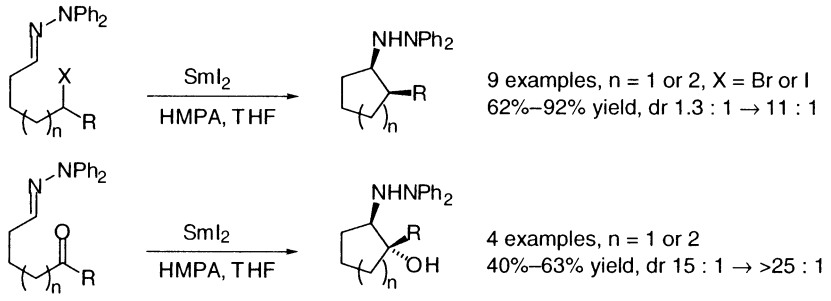
In 1991, Kim reported the first use of a hydrazone as a radical acceptor.[35] The *N*-aziridinylimine group[36] also was found to have the unusual capability to promote two carbon–carbon bond constructions at the same carbon by exploiting ring strain in a tandem addition/fragmentation process (Scheme 9). The initial radical cyclization to form an aminyl radical was followed by aziridine opening and fragmentation, releasing dinitrogen and styrene, and returning the radical character to the original acceptor carbon for subsequent reaction. For example, 6-*exo*-trig cyclization of iodide **6** and fragmentation gave a cyclohexyl radical which underwent Giese-type intermolecular trapping with methyl acrylate in high yield. A series of elegant applications of this chemistry have since appeared, leading to syntheses of modhephene, cedrene, zizaene, and pentalenene (vide infra).

Although, it had been shown that specialized hydrazones endowed with unusual ring strain could undergo radical addition followed by loss of nitrogen, Fallis first documented that simple *N*,*N*-diphenylhydrazones lacking this strain feature were useful radical acceptors. Reductive cyclizations of halohydrazones or carbonylhydrazones induced by SmI_2 (Scheme 10) preserved the C–N linkage and gave potential for chiral amine synthesis.

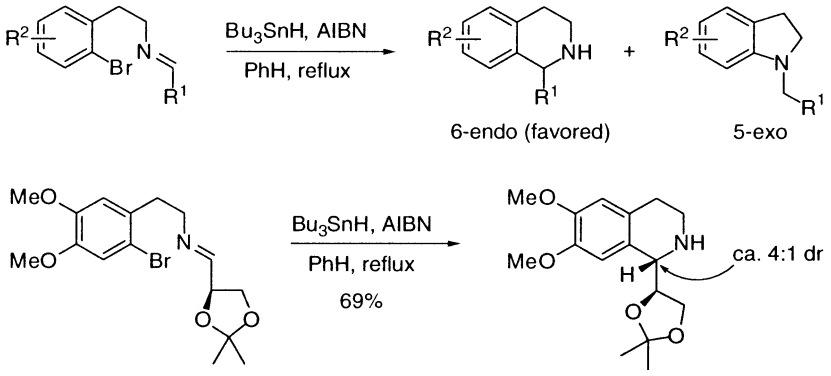
Radical addition to simple aldimine functional groups made sporadic appearances beginning in 1975 as proposed mechanistic steps in various unusual reactions.[37] The first



Scheme 9.



Scheme 10.

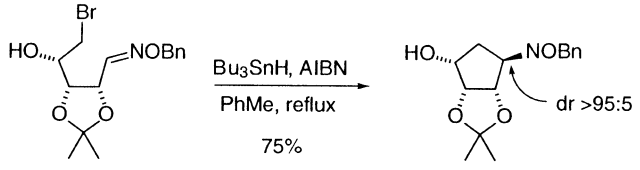


Scheme 11.

synthetic utility of an imine as a radical acceptor was reported by Takano in 1990 in a synthesis of cryptostyline alkaloids.[38] Warkentin subsequently contributed detailed studies, including kinetic analyses, of related reactions to access tetrahydroisoquinoline structures (Scheme 11).[7] Here 6-*endo*-trig cyclization is favored; this was rationalized by considering the larger calculated LUMO coefficients on carbon and a smaller C–N=C bond angle relative to the corresponding alkene leading to better orbital overlap of the aryl radical with the C=N LUMO. Substrate-induced diastereocontrol was observed using a glyceraldehyde-derived imine, which led to a 4:1 diastereomeric mixture (favoring the epimer of the major product in the corresponding Pictet–Spengler reaction).

This section has highlighted some selected early studies of reductive radical cyclizations to various C=N acceptors to give a perspective on the development of the field. With these precedents, novel cyclization chemistry developed rapidly during the 1990s. As noted above, this progress has previously been reviewed, and the remainder of Section 2 will therefore focus on work published from 1997 to 2000.

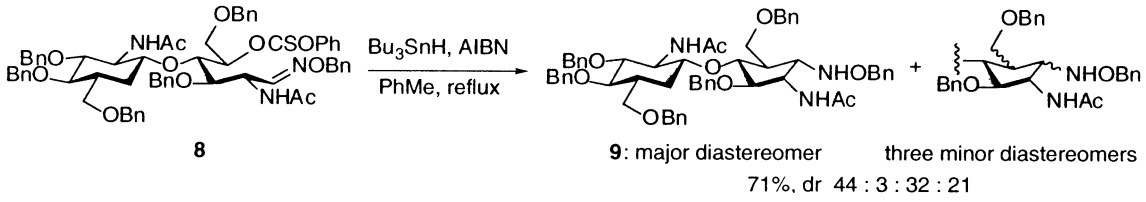
2.1.1. Reductive cyclization initiated by atom or group homolysis. Following the seminal findings of Bartlett, Hart, and Parker, a large body of work has now accumulated wherein atom abstraction or other homolytic processes lead to reductive cyclizations onto the C-terminus of a C=N bond in 5-*exo* or 6-*exo* modes.



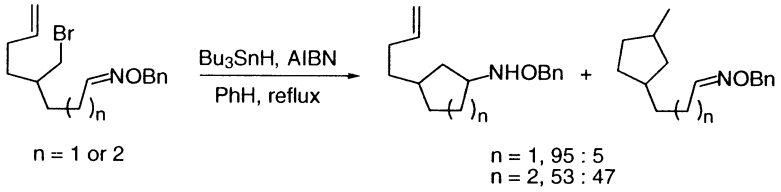
Scheme 12.

Extensive studies of carbocyclizations of carbohydrate precursors by Marco-Contelles et al. have been recently summarized.[39a] A series of Bu_3SnH- and SmI_2-promoted reactions involving homolytic formation of radicals from halides afforded various aminocyclitols (e.g. Scheme 12).[39b,39c] This and related 6-*exo* cyclizations[40] have stereochemical outcomes consistent with the Beckwith–Houk chairlike transition state model (Fig. 3). The same transformation attempted with SmI_2 led to low yields accompanied by premature reduction, β-elimination and epoxide formation; the potential for base-induced side reactions and possible formation of organosamarium (III) intermediates should be considered when planning the use of SmI_2 with such highly functionalized halides.

An extension of this carbohydrate carbocyclization strategy to a disaccharide has been reported by Takahashi et al.[41] Beginning with an *S*-glycoside, conversion to the anomeric oxime ether and installation of a thiocarbonate radical precursor enabled tin-mediated cyclization studies of **8** (Scheme 13) with AIBN or Et_3B initiation and comparison of stereoselectivity at various temperatures. Optimal results were obtained in this case using AIBN in refluxing toluene, giving a 31% isolated yield of **9**, which was used to prepare a truncated disaccharide analog of the chitinase inhibitor allosamidin. A small effect on the diastereomer ratios was observed upon cyclization in the presence of Et_3B, suggesting coordinative restriction of conformer populations. There



Scheme 13.



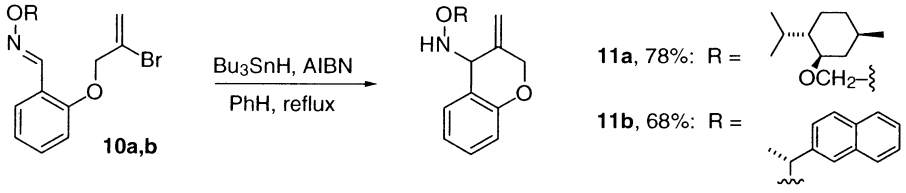
Scheme 14.

was no significant difference between *O*-methyl and *O*-benzyl oxime ethers.

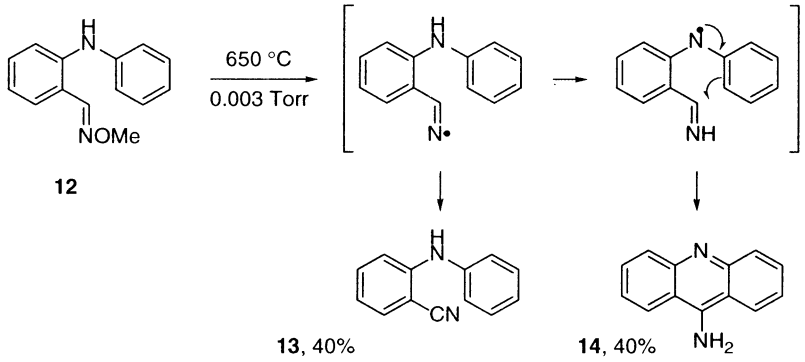
Simple imines and oxime ethers have been exploited by Kim et al. for kinetic studies of 6-aza-5-hexenyl and 7-aza-6-heptenyl cyclizations.[12] Using the known rate of H-atom transfer from Bu_3SnH, product ratios from the competition between cyclization and premature reduction gave cyclization rate constants (80°C) for benzyl oxime ethers of 4.2×10^7 s^{-1} (5-*exo*) and 2.4×10^6 s^{-1} (6-*exo*) and for imines 6.0×10^6 s^{-1} (5-*exo*) and 6.7×10^5 s^{-1} (6-*exo*) (see Fig. 1 for structures). An independent method involving intramolecular competition between oxime ether and alkene functionality in more complex substrates (Scheme 14) gave similar but slightly higher rate constants.

Jenkins and coworkers reported vinyl and aryl radical cyclizations of oxime ethers in the early 1990s.[42] More recently, these efforts have been followed up by attempts to achieve transfer of stereochemical information through the oxime ether linkage.[43] Thus, *O*-alkylation of the simple oxime with chloromethyl-(1*R*)-menthyl ether and condensation of *O*-(*R*-naphthylethyl)hydroxylamine with the corresponding aldehyde gave chiral oxime ethers **10a** and **10b**, respectively (Scheme 15). Tin-mediated cyclizations gave the desired products **11** in good yield, but unfortunately no stereocontrol was observed. The authors attributed this to the lack of conformational restriction in the oxime ether linkage. Use of a related chiral oxime ester prepared from camphanic chloride did not yield identifiable cyclization products.

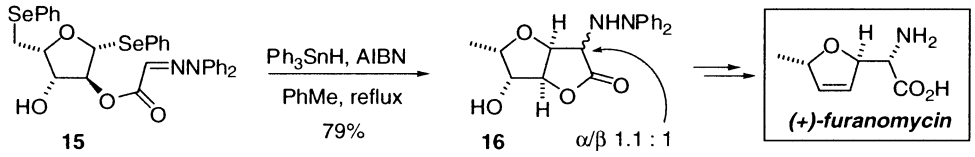
McNab and collaborators reported that flash vacuum pyrolysis of oxime ethers gave iminyl radicals which underwent various secondary processes including addition to the C=N bond.[44] Formation of **14** from aldoxime **12**



Scheme 15.



Scheme 16.



Scheme 17.

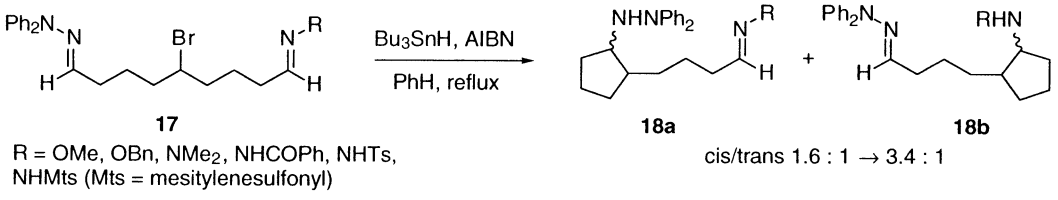
(Scheme 16) was attributed to tandem reactions involving N–O homolysis, radical translocation, and 6-*exo* cyclization onto the C=N bond. The related acetophenone ketoxime (not shown) gave a complex mixture of products.

Following preliminary studies of cyclizations using ester-linked radical addition to glyoxylic acid imino derivatives,[45] Clive has applied this methodology to preparation of furanomycin[46] (Scheme 17) and of a *C*-glycosyl amino acid.[47] Cyclization of xylose-derived anomeric selenide **15**, for example, led to a mixture of diastereomeric hydrazinolactones **16** en route to a synthesis of furanomycin. In this and several other carbohydrate-based examples, the anomeric C–C bond was constructed stereoselectively and in good yield (48–82%), although the configuration of the hydrazino substituent was uncontrolled.

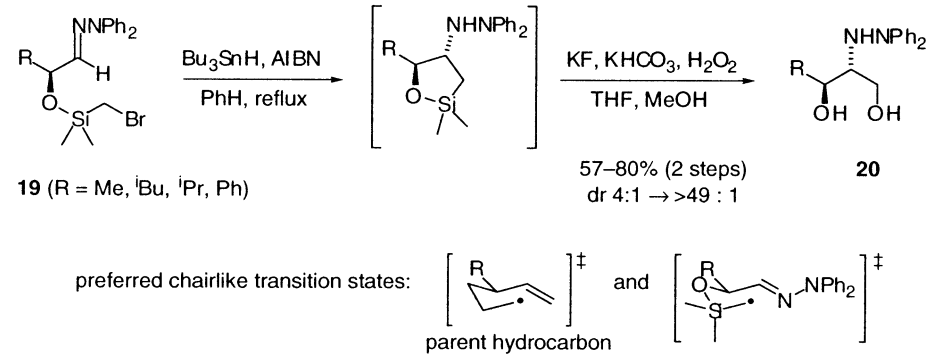
Fallis has used secondary radicals with two different C=N acceptors for 5-*exo*-trig cyclization competition studies.[48] With varying functional groups at the second C=N acceptor, tin-mediated cyclization of δ-halodiphenylhydrazones **17** (Scheme 18) enabled relative rate constants for formation of both *cis* and *trans* products to be extracted from product ratios **18a/18b** based on the previously known rate of 5-*exo* cyclization to diphenylhydrazones. The benzoylhydrazone (R=NHCOPh) gave the fastest cyclization among those analyzed (1.6×10^8 s^{-1}, 80°C) and was also more *cis*-selective (*cis*/*trans*=3.4:1). Product analysis in cyclizations of arenesulfonylhydrazones (R=NHTs, NHMts) was complicated by fragmentation of the N–S bond; accurate data for these substrates were not obtained.

We have recently begun to explore cyclizations of silicon-tethered radicals after which the tether may be removed to afford acyclic products with useful and predictable stereocontrol.[49] In the first example of this approach, we utilized α-hydroxyacids as precursors of chiral hydrazones **19** (Scheme 19). By design, the stereogenic center is in the 4-position of the aza-5-hexenyl system, where allylic strain effects can enhance stereocontrol. Tin-mediated cyclization and Tamao oxidation afforded *anti* 2-hydrazino-1,3-diols **20** with good-to-excellent stereocontrol. Diastereomer ratios were observed to correlate well with steric demand of the substituents R (as estimated by A values: Me<^{i}Bu<^{i}Pr<Ph), in accord with the Beckwith–Houk model (Fig. 3).

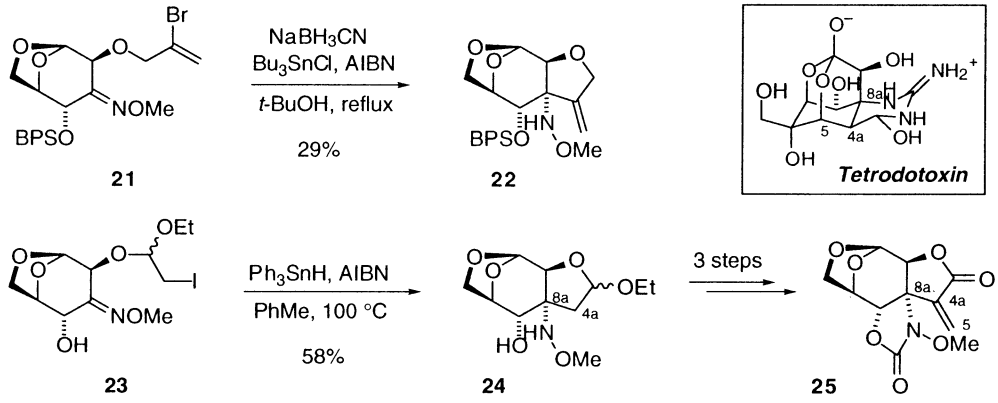
The considerable synthetic challenge posed by tetrodotoxin (Scheme 20) has prompted the development of radical cyclization approaches to constructing its C8a amine stereogenic center. Following the initial report,[50a] Alonso has now published full details with useful comparisons of different cyclization methods.[50b] Initial efforts focused on haloacetal radical cyclization, but only the premature reduction product (non-cyclized) was observed under tin-mediated conditions (not shown). Under Stork's catalytic tin conditions (Bu_3SnCl, $NaBH_3CN$) there was no desired cyclization; instead a non-radical N-alkylation/iminium



Scheme 18.



Scheme 19.



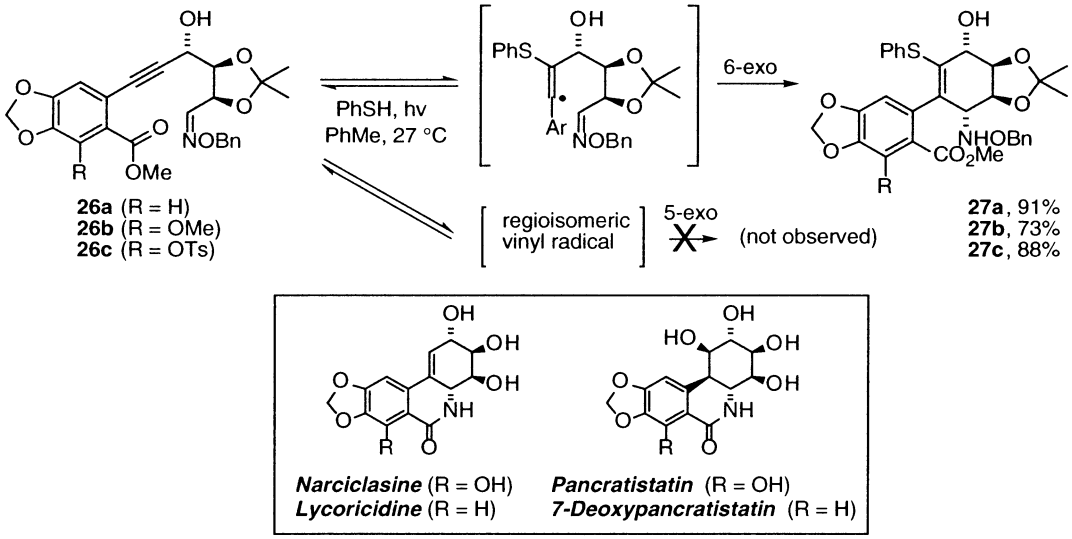
Scheme 20.

ion reduction process occurred. To prevent this, the vinyl radical derived from **21** was employed, providing 5-*exo* cyclization product **22** in 29% yield, accompanied by premature reduction (29%). Interestingly, there was no direct hydride reduction of the C=N bond by $NaBH_3CN$. Fortuitously, it was finally found that the silyl protecting group was not necessary, and in fact had detrimental effects on the radical cyclizations. Thus, **23** cyclized in reasonable yield using syringe pump addition of triphenyltin hydride and AIBN, constructing the C8a–C4a bond of the tetrodotoxin skeleton with complete diastereoselectivity. A subsequent three-step sequence converted the acetal to *exo*-methylene lactone **25**, envisioned as a key intermediate for completion of the total synthesis of tetrodotoxin.

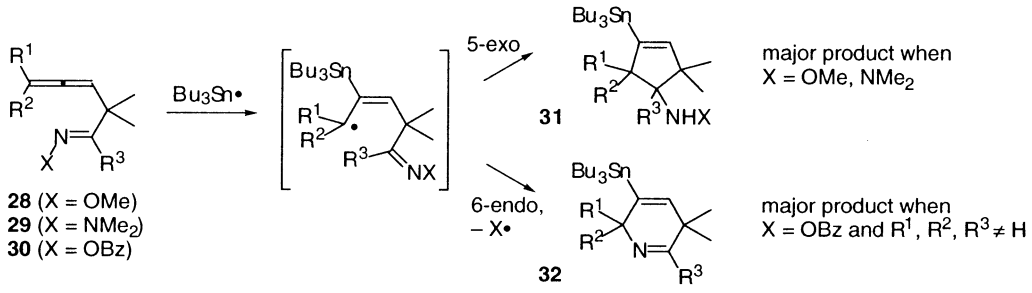
2.1.2. Cyclization initiated by intermolecular radical addition to alkenes or alkynes. Because free radical addition generates a new reactive radical, much effort has been expended to incorporate such reactions in controlled tandem sequences involving two or more different radical acceptors. Applying this general premise, reversible intermolecular addition of tin- or sulfur-centered radicals to multiple bonds has been used in a variety of circumstances to induce subsequent cyclizations to C=N acceptors. Most of these examples involve alkynyl oxime ethers, according to the seminal precedent of Enholm (Scheme 8), although alkenes and allenes have also been used.

Keck and coworkers have exploited tandem addition/cyclization in their approaches to (+)- and (−)-lycoricidine and (+)-narciclasine (Scheme 21). Conveniently accessed through Sonogashira coupling, the aryl alkynes **26a–26c** each underwent intermolecular thiyl radical addition and subsequent 6-*exo* vinyl radical cyclization to the oxime ether to afford **27a–27c** as single diastereomers. Alternative regioisomers were not obtained; 5-*exo* cyclization may be slowed in this case by steric hindrance of oxime approach to the p-type vinylic radical due to the neighboring coplanar vinyl substituents. Thus, although thiyl addition was presumed to give both regioisomeric vinyl radicals, the reversibility of this initial process facilitated 6-*exo* cyclization. The corresponding Bu_3SnH-mediated process gave alkyne hydrostannylation without cyclization.

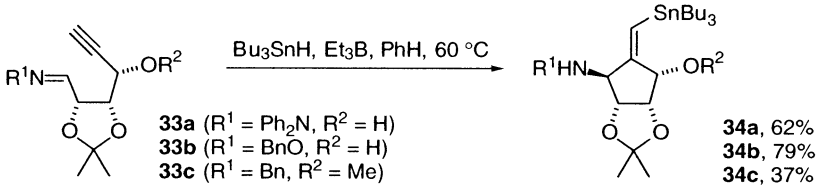
Using C=N bonds as acceptors for allylic radicals generated by intermolecular stannyl addition to allenes, Hatem et al. have explored the formation of 5- and 6-membered rings by 5-*exo* and 6-*exo* cyclizations.[51] With oxime ether **28** and



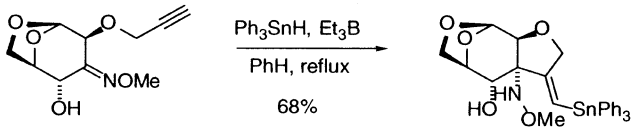
Scheme 21.



Scheme 22.



Scheme 23.



Scheme 24.

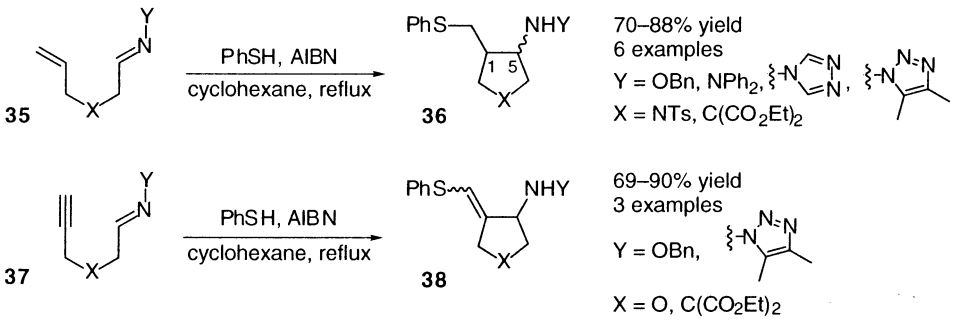
hydrazone **29** (Scheme 22), cyclization onto the C-terminus of the C=N bond gave products of type **31**; employing a SAMP hydrazone led only to modest stereocontrol (3:1). Recently, the use of related allenyl *O*-benzoyloximes **30** has uncovered an unusual 'nitrogen-philic' reaction manifold depending on substitution.[52] With heavily substituted systems, addition to the N-terminus of the C=N bond occurred, followed by benzoate radical elimination to afford dihydropyridines **32**. More examples of addition to the N-terminus are discussed in Section 2.3.

Marco-Contelles has studied addition/cyclization processes with alkynyl imine derivatives from carbohydrate precursors.[39d] Stannyl addition and cyclization of oxime ethers, hydrazones, and imines **33** furnished the corresponding cyclic vinylstannanes **34**. Imine **33a** gave only a modest yield, but oximes and hydrazones (e.g. **33b** and **33c**) were quite effective (Scheme 23).

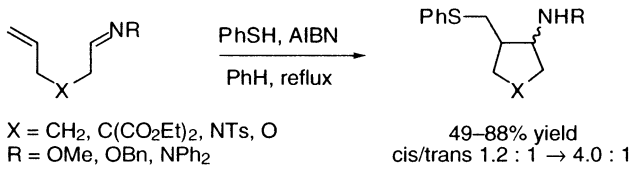
Alonso et al. have also examined stannyl addition/cyclization during their tetrodotoxin synthetic studies.[50] An alkyne (Scheme 24), upon addition of triphenyltin hydride and triethylborane via syringe-pump, furnished a cyclized vinylstannane in good yield, accompanied by small amounts of both regioisomeric alkyne hydrostannylation products (3% each). However, subsequent transformations toward tetrodotoxin were best achieved using the haloacetal radical cyclization product described above (Scheme 20).

El Kaim and coworkers reported a study of thiyl addition to alkenes or alkynes as a means of inducing radical cyclization to a variety of C=N acceptors.[53] Upon treatment of alkenes **35** with PhSH and AIBN, good yields of 5-*exo* cyclization products **36** were generally obtained with modest *cis* diastereoselectivity (2:1→4:1) as expected for a 1-substituted aza-5-hexenyl cyclization. Alkynes **37** also cyclized efficiently to afford predominantly the *cis* alkenylsulfides **38**. Though not general, 6-*exo* cyclization was successful with 2-(propargyloxy)benzaldehyde hydrazones (Scheme 25).

Naito has explored a similar reaction with an alkene as the initial thiyl (sulfanyl) radical acceptor.[54] With a series of substrates, varying the linker and the C=N acceptor, thiyl radical addition led to diastereomeric mixtures of



Scheme 25.

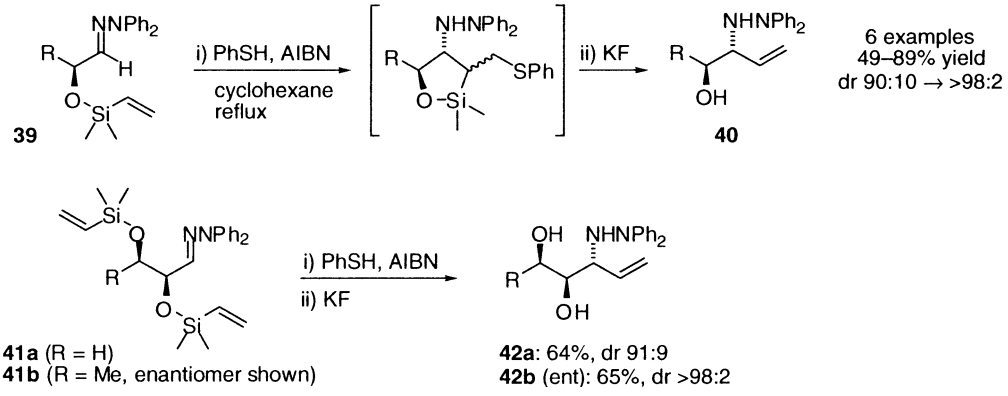


Scheme 26.

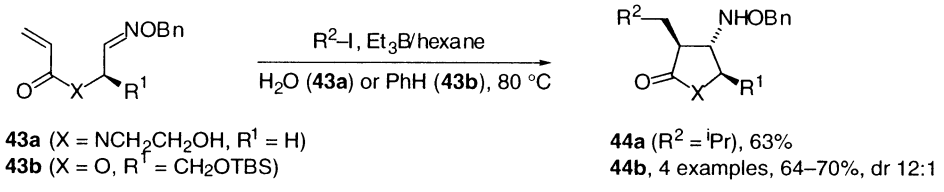
cyclization products in good yields. The *cis* products were favored in all cases, with higher selectivity obtained using oxime ethers (Scheme 26).

This reaction has recently been studied in our laboratory from the perspective of developing predictably high stereocontrol in radical additions to C=N bonds.[55] We have exploited the silicon tether (Scheme 19) to transmit stereochemical information to the new C–C bond through conformational constraints within the Beckwith–Houk model (Fig. 3). To apply the tandem addition/cyclization approach, silyl ether-linked vinylsilanes **39** (Scheme 27) were prepared from chiral α-hydroxyhydrazones and chlorodimethylvinylsilane. Using thiophenol and AIBN, 5-*exo* cyclization occurred readily and the silicon tether was removed in the same pot by fluorodesilylation and concomitant β-elimination of benzenethiolate, furnishing chiral substituted vinylglycinol building blocks **40**. Thus a neutral vinyl addition to a C=N bond was achieved via a tandem radical addition process, and in all cases, diastereomer ratios were 9:1 or higher. Bis-silyl ethers **41a** and **41b** prepared from chiral diols were processed similarly to afford highly functionalized vinyl adducts **42a** and **42b** in good yield.[56]

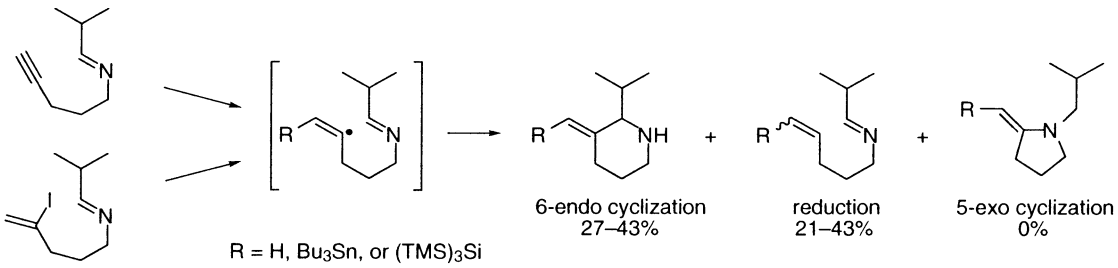
Recently, Naito has reported a tandem addition cyclization reaction which uses intermolecular addition of a carbon-centered free radical, then cyclization.[57] Acrylamide **43a** (Scheme 28) underwent tandem C–C bond constructions in aqueous solution to afford lactam **44a** in 63% yield as a mixture of diastereomers, wherein intermolecular isopropyl radical addition was followed by cyclization. A more in-depth study of this approach using glyceraldoxime acrylate **43b** has appeared recently.[58] Using either aqueous or non-aqueous solvents, it was found that ethyl radical (from Et_3B) and several secondary radicals (from Et_3B/RI) underwent addition to the acrylate alkene bond, followed by cyclization. Interestingly, high *trans* selectivity across the new C–C bond was observed, an apparent departure from



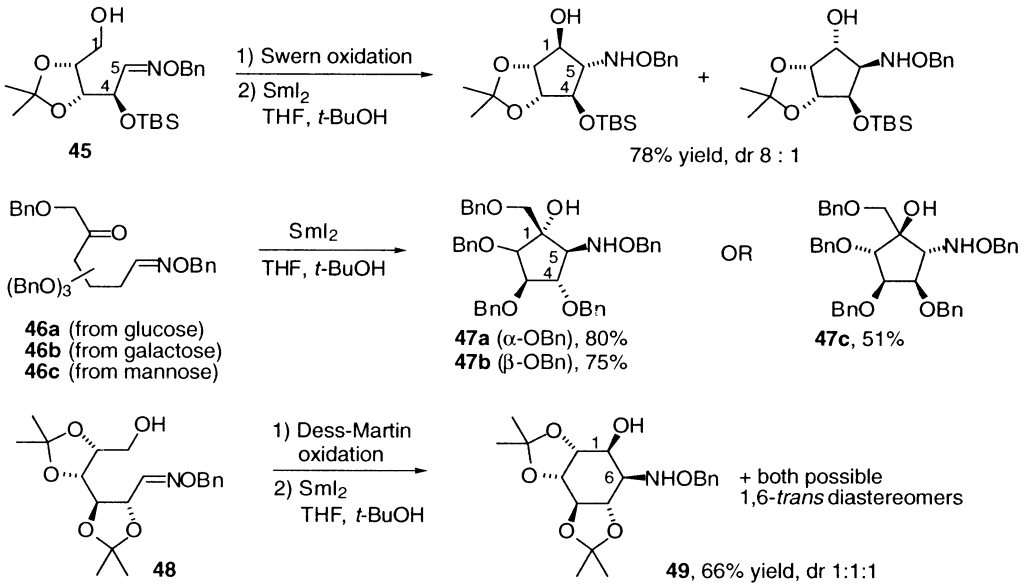
Scheme 27.



Scheme 28.



Scheme 29.



Scheme 30.

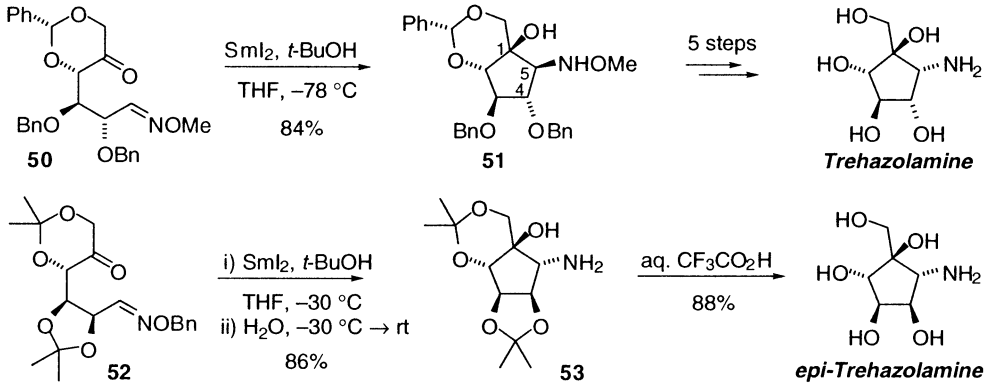
the Beckwith–Houk model (Fig. 3); a boat transition state was proposed in this case. The resulting β-aminolactones **44b** have structural connectivity corresponding to Mannich products.

Ryu and Komatsu et al. have critically examined regioselectivity with both experimental and computational approaches using the competition between 5-*exo* cyclization and 6-*endo* cyclization of vinyl radicals generated by heteroatom radical addition.[8] Addition of tributyltin or tris(trimethylsilyl)silyl radical to an alkyne established a competition between the two modes of radical addition (Scheme 29), and in fact no 5-*exo* cyclization was observed, even at higher concentrations. Atom abstraction from a vinyl iodide led to the same result. Even a sterically hindered ketimine gave no 5-*exo* cyclization; in this case only reduction was observed. As noted above (Section 1.2), MO calculations concurred with the experimental finding of kinetically preferred attack at the C-terminus of C=N bonds.

2.1.3. Cyclization of ketyl-type radicals. Due to the importance of cyclic amino alcohols in a variety of natural products and asymmetric synthesis applications, there has been extensive study of C–C bond constructions via pinacol-type reductive coupling of aldehyde or ketone groups with C=N radical acceptors. Indeed, as noted in Section 2.1, the first radical addition to a C=N bond by Corey was of this type, involving ketyl radical generation under reductive conditions. In recent years the advent of SmI_2 as a convenient one-electron reductant in organic synthesis has led to its frequent application to amino alcohol synthesis. Early on, control experiments by Shono (electrochemical reduction)[59] and Fallis (SmI_2)[60] independently established the C=N bond was not reduced under their respective coupling conditions, but rather the coupling was initiated by chemoselective one-electron reduction of C=O. Therefore these reactions are regarded as ketyl radical cyclizations onto the C=N bond. These Sm-mediated cyclizations are not as readily rationalized by the Beckwith–Houk model, probably due in part to the coordination chemistry of Sm(III) and the Lewis basic functionality in the intermediates involved. A related *O*-stannyl ketyl radical is generated by reversible stannyl radical addition to the O-terminus of a C=O bond, leading also to reductive cyclizations with C=N acceptors. Thus two general methods, involving either SmI_2 or Bu_3SnH for generation of ketyl-type radicals, have found numerous applications in recent years and are the subject of this section, which focuses on literature published since 1997.

Samarium(II)-induced ketyl cyclizations. Marco-Contelles has explored reductive cyclization of carbohydrate-derived oxime ethers containing δ- or ϵ-carbonyl groups.[61] A variety of highly functionalized oxime ethers obtained by condensation with reducing sugars led to cyclization substrates with either ketone or aldehyde ketyl precursors (Scheme 30). Aldehydes cyclized with variable 1,5-diastereoselectivity (5-hexenyl numbering); depending on the carbohydrate stereochemistry the major products had either *cis* or *trans* relative configurations with respect to the new C–C bond. In a favorable case, Swern oxidation of alcohol **45** and treatment with SmI_2 led to 5-*exo* cyclization with good 1,5-*trans* and 4,5-*trans* selectivity. Ketones **46** provided 1,5-*trans* amino alcohols **47a**–**47c**. Regardless of the starting carbohydrate, the favored diastereomers all had 1,5-*trans* and 4,5-*trans* relationships. A less selective 6-*exo* cyclization of **48** provided three diastereomeric products in equal quantities. These cyclizations could be successfully conducted in a one-pot protocol together with the prior oxidations.

Giese[62] and Chiara[63] independently approached aminocyclitols of relevance to glycosidase inhibition from the ketyl radical cyclization perspective (Scheme 31). Samarium ketyl cyclization of a glucose tetra-*O*-benzyl derivative (i.e. acyclic analog of **50**, not shown) led to the desired 1,5-*trans* (5-hexenyl numbering) relationship, but both the OH and NHOMe groups were epimeric to trehazolamine. In contrast, cyclization of constrained 4,6-*O*-benzylidene derivative **50** gave a single diastereomer

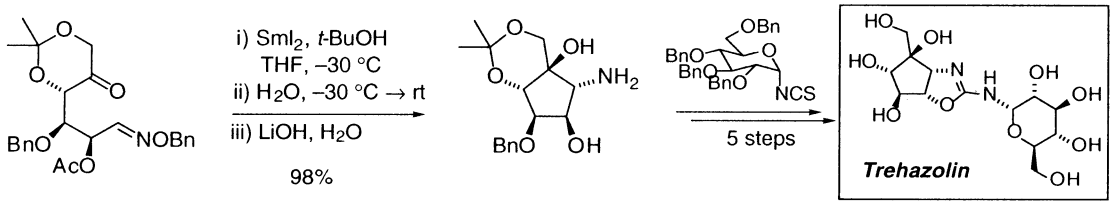


Scheme 31.

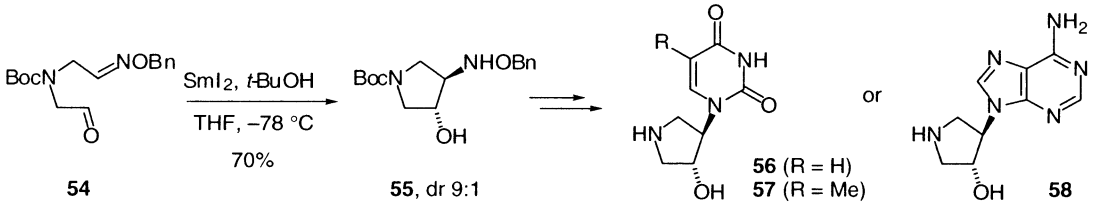
with the correct β-OH configuration. The β-amino group was epimerized via an oxidation/reduction of **51** leading to trehazolamine.[62] Meanwhile, bis-acetonide **52** derived from D-mannose cyclized in high yield to afford exclusively **53** with complete diastereocontrol to afford a trehazolamine epimer.[63] Introduction of 30 equiv. water to the ketyl cyclization reaction mixture led conveniently to in situ N–O bond cleavage.

Subsequently, Chiara et al. exploited the cyclic acetal constraints shown above for configurational control at the amine and quaternary centers of trehazolamine together with monoacetate diol differentiation.[64] After samarium ketyl cyclization (Scheme 32), the configuration of the epimeric secondary alcohol was corrected during construction of the oxazoline ring to achieve a highly efficient route to trehazolin from D-mannose (34% overall yield, 14 steps).

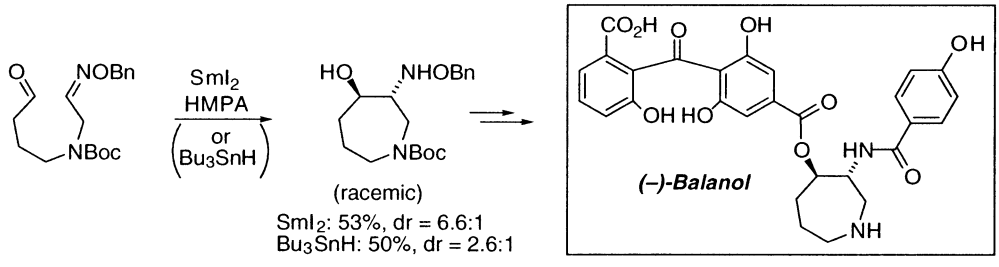
Pyrrolidine nucleoside analogs have been prepared through SmI_2-induced ketyl cyclization to C=N bonds.[65] The 5-*exo* cyclization of aldehydo-oxime ether **54** (Scheme 33) occurred upon treatment with SmI_2 in the presence of *t*-BuOH without HMPA to provide a good yield of *trans* amino alcohol **55**, although HMPA was necessary in 7-*exo* cyclization. Cyclization via the *O*-stannyl ketyl radical gave lower diastereoselectivity (dr 3:1). Hydrogenolysis of the N–O bond and construction of pyrimidine and purine rings led to unusual nucleosides **56**–**58**.



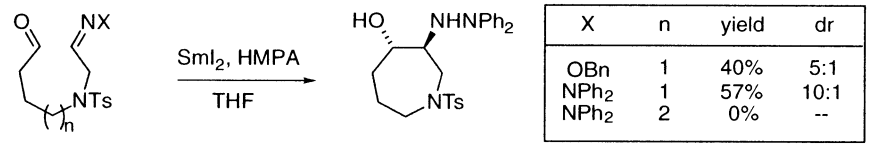
Scheme 32.



Scheme 33.

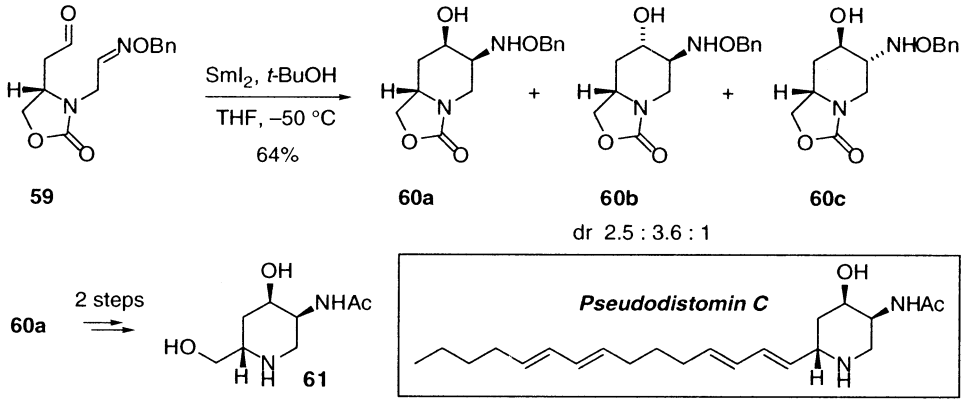


Scheme 34.



X	n	yield	dr
OBn	1	40%	5:1
NPh_2	1	57%	10:1
NPh_2	2	0%	--

Scheme 35.



Scheme 36.

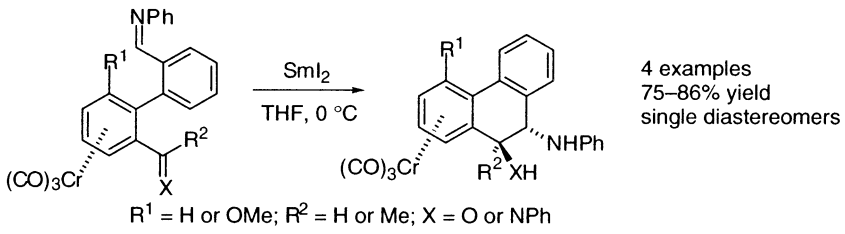
Application of samarium ketyl cyclization to total synthesis of (−)-balanol demonstrated 7-membered ring construction by this strategy.[66] Thus, an aldehydo-oxime was cyclized to afford predominantly the *trans* amino alcohol (Scheme 34). Using *E*/*Z* oxime isomer mixtures, higher selectivity was obtained with SmI_2/HMPA (6.6:1) than Bu_3SnH (2.6:1), while separate cyclizations of pure *E* and *Z* oxime isomers showed no significant effect of C=N isomerism on selectivity. The racemic *trans* amino alcohol product was converted in several steps to (−)-balanol, a potent protein kinase inhibitor.

Balanol synthetic studies by Skrydstrup et al. include mechanistic discussion of the SmI_2/HMPA reagent system and comparisons with related reducing agents for ketyl formation, including SmI_2 alone, $SmBr_2$, $SmCl_2$, Cp_2TiCl and Cp_2TiPh.[67] Using SmI_2 with HMPA, side products of intermolecular pinacol coupling or simple C=O reduction are avoided, and the cyclic *trans* amino alcohol is obtained (Scheme 35). To explain both the effect of HMPA and the higher *trans* selectivity of hydrazones (dr 10:1) relative to the corresponding oxime ether (dr 5:1), a non-chelation model was proposed which involves a simple vicinal steric interaction between the bulky Sm(III)/HMPA coordination complex and the diphenylamino group. Attempts to take advantage of the proposed model to achieve reagent control with various chiral ligand additives unfortunately gave no significant enantiomeric excess.

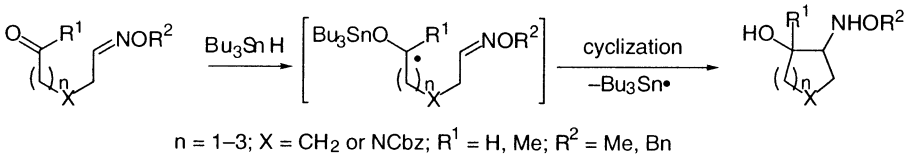
The use of pre-existing chirality allows access to enantiomerically pure 2-substituted piperidines. Thus, Naito et al. have employed L-aspartic acid as a precursor to prepare cyclization substrate **59** (Scheme 36), wherein the two reactive centers are tethered via a chiral oxazolidinone.[68] Samarium ketyl cyclization afforded mixtures of three diastereomers in variable ratios depending on temperature and additives. The separated diastereomers were further transformed into protected hydroxymethyl piperidines potentially useful for synthesis of diastereomeric pseudodistomin natural products; as exemplified by conversion of **60a** to diol **61** related to pseudodistomin C.

Enantiomerically pure *trans* amino alcohols, diamines, and diols have been prepared by Uemura et al. via samarium ketyl cyclizations of reactive functionality tethered through a planar chiral biphenyl–$Cr(CO)_3$ complex (Scheme 37).[69] In all cases, the observed product was a single diastereomer with NHPh and XH (X=O or NPh) in a *trans* relationship. Ready photolytic decomplexation from the chromium tricarbonyl afforded arenes of potential utility in asymmetric catalysis.

Stannane-induced ketyl cyclizations. In a series of papers, Naito et al. have examined the application of Bu_3SnH to ketyl radical cyclizations of oxime ethers tethered to a carbonyl group, processes useful for synthesis of biologically important 5-, 6-, and 7-membered heterocyclic *trans*



Scheme 37.



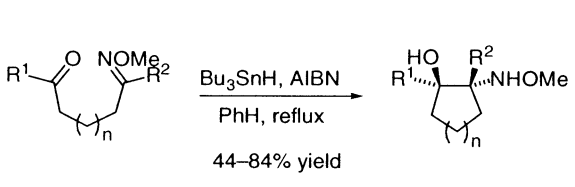
Scheme 38.

1,2-amino alcohols.[70] Reversible *O*-stannyl ketyl generation by addition of $Bu_3Sn^{\cdot}$ to C=O bonds (Scheme 38) leads to reliable 5-*exo* and 6-*exo* cyclizations to C=N bonds in moderate to good yield. The *trans* amino alcohol is generally favored, with selectivities ranging from 1.3:1 to 4:1, although a ratio of 14:1 was observed in one example.[71]

Related studies also explored this *O*-stannyl ketyl radical strategy to make *trans* carbocyclic amino alcohols.[72] As shown by a table of selected examples (Scheme 39), higher diastereomer ratios were obtained with 5-*exo* cyclizations (n=1) and with ketoximes (R^2=Me).

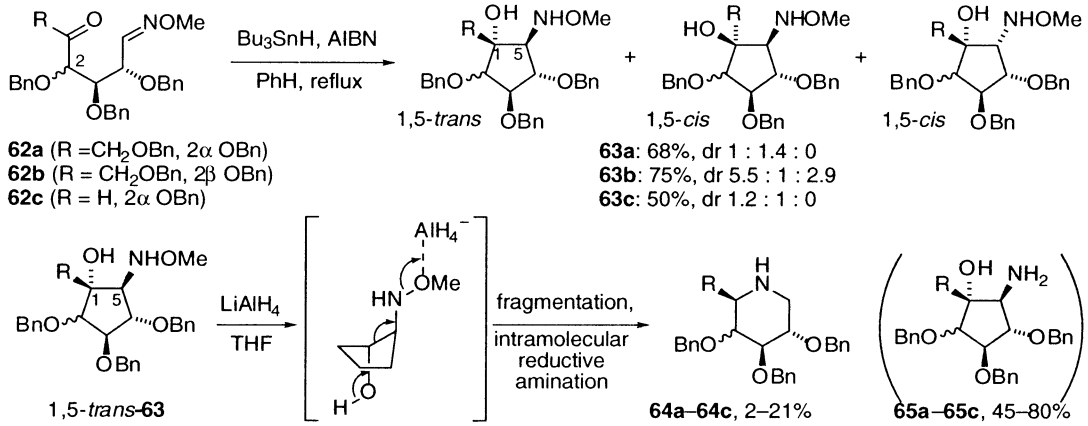
In studies of relevance to glycosidase inhibitors, stannyl ketyl cyclizations of per-*O*-benzylated substrates **62** derived from D-glucose, D-galactose, and D-xylose were examined (Scheme 40).[73] In contrast to the related SmI_2-induced cyclizations described above (see Scheme 30), here mixtures of two or three products were obtained depending on the starting material. Interestingly, when N–O cleavage of *trans*-**63** was attempted with $LiAlH_4$, a fragmentation/reductive cyclization led to ring expansion side products **64** in modest yield, along with the desired **65**. *cis* Amino alcohols did not undergo the reductive ring expansion, suggesting an antiperiplanar stereoelectronic requirement.

In related cyclizations of vinylogous carbonyl systems (Scheme 41), the *trans* product was exclusively formed in 5-*exo* cyclizations.[74] Equilibration via reversible cyclization of a stabilized allylic *O*-stannyl ketyl radical was proposed to account for the complete selectivity for the more stable *trans*-disubstituted pyrrolidine ring. However, when the vinylogous relationship was applied to the oxime acceptor instead (not shown), a nearly 1:1 mixture of *cis*/*trans* products was obtained via ketyl or vinylogous ketyl addition to the C=C bond of the unsaturated oxime ether.

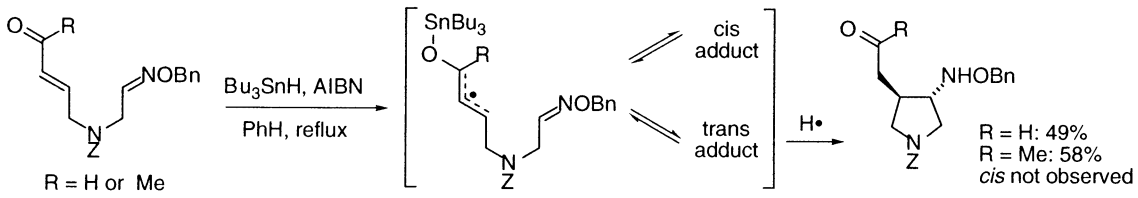


R^1	R^2	n	dr
H	H	1	18:1
H	Me	1	>180:1
H	H	2	3:1
H	Me	2	7:1
Me	Me	1 or 2	no reaction

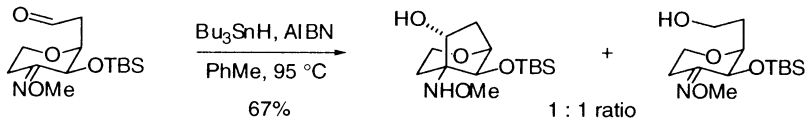
Scheme 39.



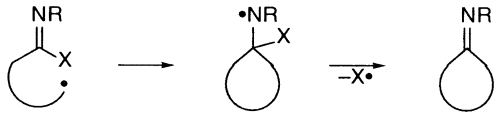
Scheme 40.



Scheme 41.



Scheme 42.



Scheme 43.

In preparation of constrained bicyclic amino alcohols for use in oligonucleotide analogs, Leumann et al. tested various conditions for ketyl cyclization of an oxime ether for the key C–C bond construction (Scheme 42).[75] Neither Ti(III) nor Zn/TMSCl were successful, but treatment with Bu_3SnH/AIBN in hot toluene gave a moderate yield of the bicyclic adduct along with the uncyclized reduction product. High diastereoselectivity was attributed to steric direction by the proximal silyloxy substituent.

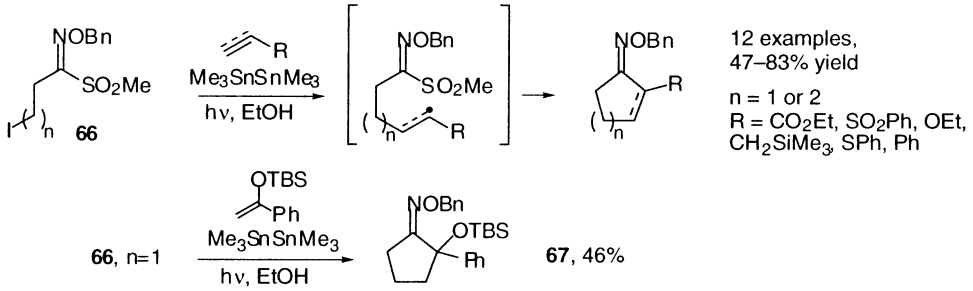
2.2. Cyclization to the C-terminus of C=N followed by fragmentation

Radical addition to C=N bonds can lead to N-centered radicals prone to fragmentation by β-elimination if weak bonds are appropriately located. Fragmentation can be encouraged by the presence of ring strain or groups that afford stable free radicals upon homolysis. Three general modes of this process are observed: cleavage of a weak C–X bond to the C-terminus of the original C=N bond, cleavage of a C–C bond at the C-terminus aided by relief of ring strain, or fragmentation of a bond within the group linked to the N-terminus of C=N.

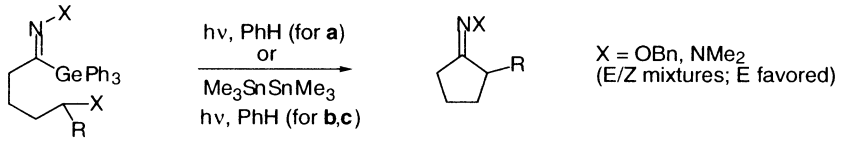
2.2.1. Cleavage of C–X bonds at the C-terminus. Addition and fragmentation of bonds to the same C=N carbon effects a formal aza-acyl substitution reaction, and the net result is a non-reductive radical addition to C=N. The regeneration of the C=N bond makes this strategy useful for ketone synthesis by acylation of radicals. The general features are shown in Scheme 43 for various weak C–X bonds; although most cases involve cyclization, intermolecular examples are known (see Section 3.1.1). A relative reactivity scale corresponding to the rates of elimination of various radicals has been constructed; the results (determined with intermolecular examples) indicate that relative rates of β-eliminations from N-centered aminyl radicals (X=PhSe>$PhSO_2$>PhS~Br) are in a reactivity order different from the corresponding alkyl radicals (X=Br≧PhSe>PhS>$PhSO_2$>Cl) resulting from initial addition to a C=C bond.[76]

Kim has developed the use of C-sulfonyl oxime ethers in intermolecular reactions (Section 3.1.1).[77] These reactions have been adapted to a general tandem radical annulation procedure, wherein an initial intermolecular addition of iodide **66** to an alkene or alkyne led to a radical which then underwent non-reductive cyclization via fragmentation of the C–S bond. The regenerated C=N bonds enabled hydrolysis to cyclic ketones. The silyl enol ether from acetophenone also participated in this annulation, giving 1,2-difunctional product **67** (Scheme 44).

Curran and Iserloh have utilized C-germyl C=N radical acceptors **68a**–**68c** for preparation of cyclic hydrazones and oxime ethers (Scheme 45).[78] These acylgermane C=N



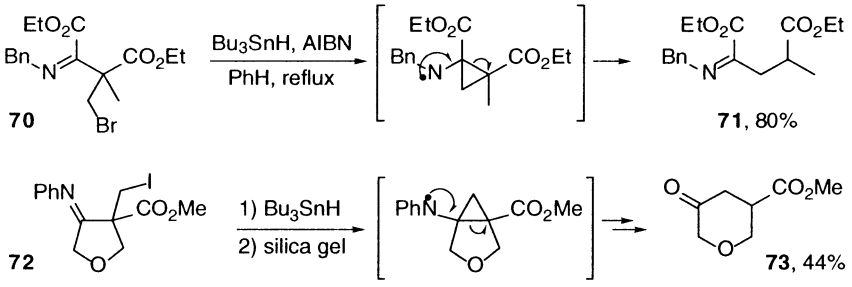
Scheme 44.



68a (R = H, X = Br or SePh)
68b (R = Me, X = SePh)
68c (R,X = CH_2)

69a (R = H), 95%
69b (R = Me), 66%
69c (R = CH_2GePh_3), 74%

Scheme 45.



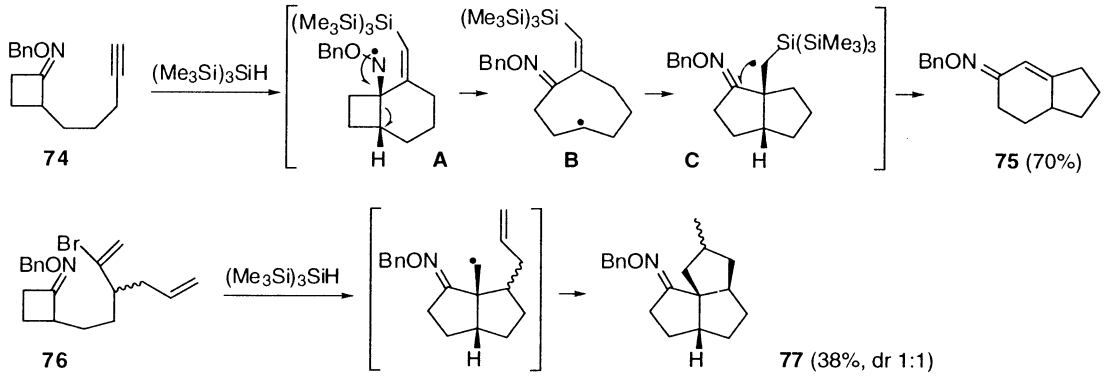
Scheme 46.

derivatives (X=NMe_2 or OBn) had radical cyclization rate constants of ca. $10^7\ s^{-1}$, about 2–3 times faster than the corresponding acylgermanes. Bromide or selenide precursors could be used, though bromide **68a** cyclized efficiently without hexamethylditin. Cyclopentanone hydrazones and oxime ethers **69** were obtained predominantly as *E*-isomers with respect to the C=N bond. The olefinic substrate **68c** provided the group transfer addition/cyclization product **69c**.

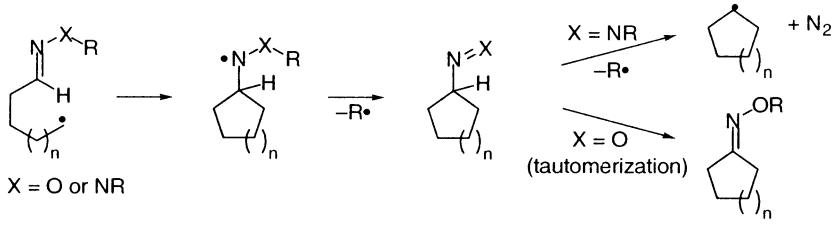
2.2.2. Cleavage of C–C bonds at the C-terminus. Among the many ring expansion and related rearrangements[79] explored by Dowd and coworkers are some which involve cyclization onto C=N bonds. Treatment of α-iminoester **70** (Scheme 46) with tin hydride led to methylene-inserted rearrangement product **71** in 80% yield.[80] Analogously, cyclic imine **72** undergoes ring expansion to afford ketone **73** after imine hydrolysis.[81] Both processes involve formation of a strained cyclopropylaminyl radical which rapidly fragments to a carboxylate-stabilized radical prior to H-atom abstraction.

In remarkable tandem sequences, this strain-induced C–C cleavage strategy has been exploited by Pattenden et al. for fragmentation and transannular cyclization followed by either ring expansion or additional C–C bond construction.[82] Treatment of cyclobutanone **74** (Scheme 47) with tris(trimethylsilyl)silane afforded 6,5 fused ring oxime **75**. The proposed mechanism involves silyl radical addition to the acetylene and 6-*exo* cyclization to give aminyl radical **A**, which then fragments to regenerate the C=N bond in radical **B**. Transannular 5-*exo* cyclization gives radical **C**, Dowd-type ring expansion via 3-*exo* cyclization onto the C=N bond and fragmentation, and finally β-elimination of the silyl radical then leads to unsaturated oxime **75**. Hydrolysis gave the corresponding ketone, which may also be obtained by Robinson annulation. A synthetically challenging triquinane structure was obtained by intramolecular trapping prior to ring expansion; the pendant allyl group of substrate **76** enabled cyclization to give triquinane **77** in 38% yield as a mixture of diastereomers.

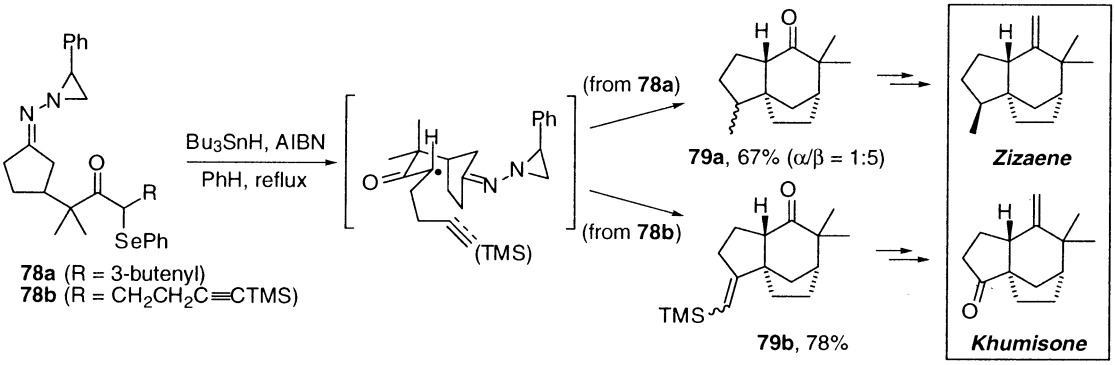
2.2.3. Fragmentation of N-linked groups. Oxime ethers and hydrazones have O–C and N–C bonds in a β-position relative to the aminyl radical formed upon radical addition to C=N. Such bonds are prone to fragmentation, as shown



Scheme 47.



Scheme 48.



Scheme 49.

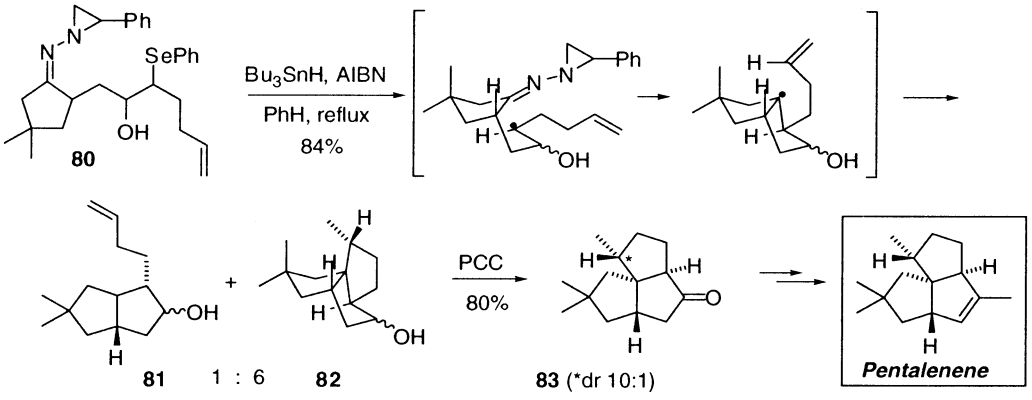
schematically in Scheme 48, if formation of a stable radical or relief of ring strain results. Certain hydrazones can further fragment to lose nitrogen, while oxime ethers give nitroso compounds that may tautomerize to the corresponding oxime.

Kim has extensively developed the use of *N*-aziridinylimines, which fragment with loss of nitrogen and styrene (or stilbene) to return the unpaired spin to the carbon of the original C=N acceptor (see Scheme 9, Section 2.1). Thus, this class of compounds can serve as geminal radical donor and acceptor, and consecutive C–C bond constructions occur at the same carbon. This novel strategy has been applied to a number of problems in sesquiterpene synthesis.

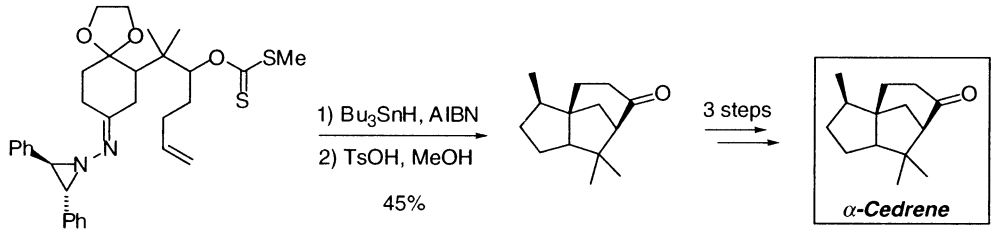
Formal syntheses of the sesquiterpenes zizaene and khusimone have been devised using *N*-aziridinylimine approach (Scheme 49).[83] Relative configurations of three carbons were established in a single transformation involving radical cyclization of α-selenoketone **78** via a chairlike conformation, then fragmentation and loss of styrene and nitrogen to generate a new carbon-centered radical. Tandem cyclization onto the alkene side chain led to **79a**, which completed a formal synthesis of zizaene. Alternatively, the alkyne side chain provided the *exo*-methylene analog **79b** as part of a formal synthesis of khumisone.

This tandem strategy for construction of tricyclic compounds has also been applied to a synthesis of pentalenene (Scheme 50).[84] Here β-hydroxyselenide **80** was used as a radical precursor, leading to tricyclic alcohol **82** in a 6:1 ratio with minor bicyclic product **81**. Oxidation completed a formal synthesis of pentalenene and revealed the diastereomer ratio at the methyl-substituted stereocenter; the major ketone **83** had the required α configuration (dr 10:1).

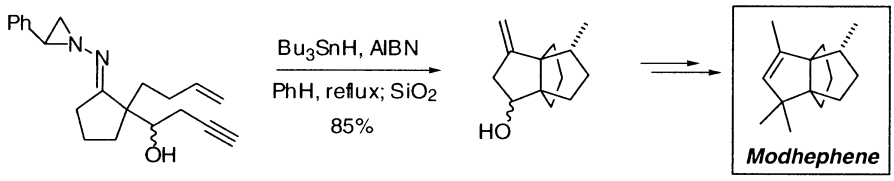
The *N*-aziridinylimine process has also been used for the synthesis of α-cedrene.[85] Thus, a xanthate (Scheme 51)



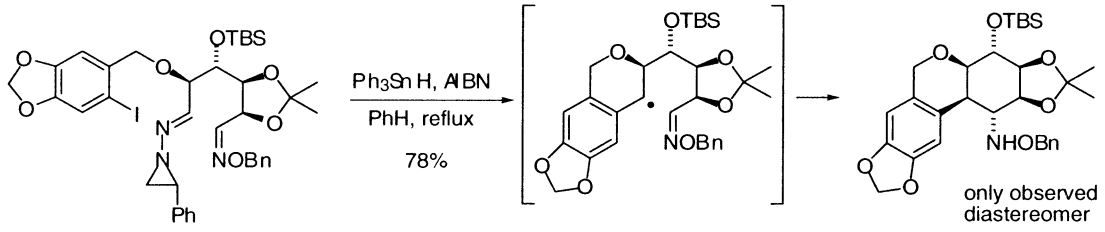
Scheme 50.



Scheme 51.



Scheme 52.



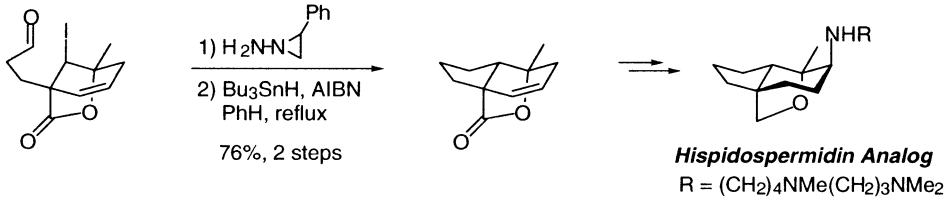
Scheme 53.

underwent group homolysis and 5-*exo* cyclization to the C=N acceptor. Fragmentation with loss of stilbene, then a second 5-*exo* cyclization to the pendant alkene gave the desired cedrene framework after ketone deprotection. A side product of 5-*exo*/6-*endo* tandem cyclization was also formed in 15% yield. Three additional steps completed an inventive and elegant synthesis of α-cedrene.

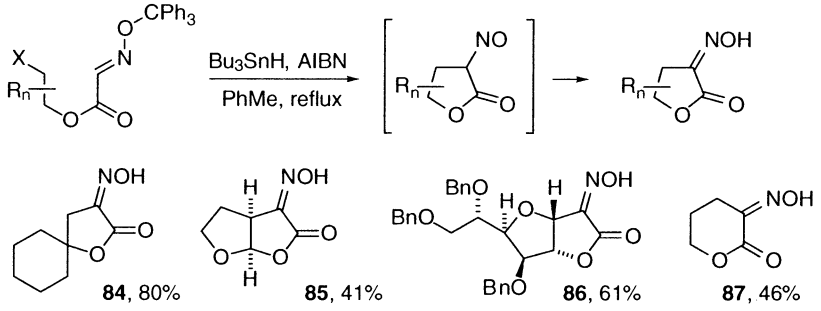
Kim has used an addition/cyclization strategy (see Section 2.1.2) in combination with his *N*-aziridinylimine method to form two C–C bonds of one of the quaternary carbons of modhephene.[86] Thus, treatment of an aziridinylimine containing a pendant alkyne with Bu_3SnH (Scheme 52) initiated a tandem process of stannyl addition to the alkyne, cyclization and fragmentation, and a second cyclization to forge the propellane skeleton. Silica-induced destannylation gave the isolated product in excellent yield, which was a single diastereomer with respect to the C-methyl stereogenic center. Subsequent transformation to modhephene (2 steps) was substantially more efficient in this second-generation route than in a previous synthesis using *N*-aziridinylimines.[87]

In development of synthetic routes to Amaryllidaceae phenanthridone alkaloids shown in Scheme 21, Keck and coworkers have exploited several approaches involving radical addition to C=N bonds to construct the aminocyclitol C-ring.[88] Applying Kim's *N*-aziridinylimine methodology, cyclization of an aryl iodide (Scheme 53) followed by fragmentation and a second cyclization onto the C=N of an oxime ether generated two C–C bonds to the same carbon in a single operation with complete stereocontrol. The stereochemical course of this aza-6-heptenyl cyclization is nicely accommodated by the usual requirement for a *cis* ring junction, together with a chairlike transition state with the alkoxy group α to the oxime in an equatorial orientation (minimized allylic strain).

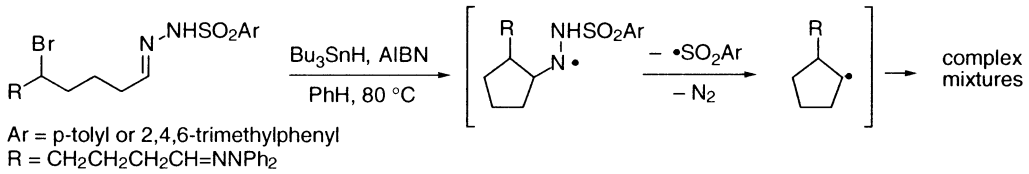
Hart has recently disclosed the use of Kim's *N*-aziridinyl



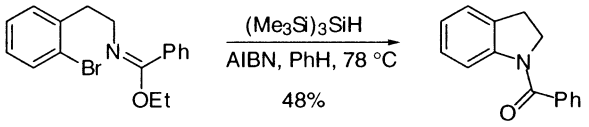
Scheme 54.



Scheme 55.



Scheme 56.



Scheme 57.

imine methodology in a strategy for synthesis of a *trans*-fused perhydroindan related to hispidospermidin (Scheme 54).[89] In this instance the approach was used only for one C–C bond construction; radical cyclization and loss of nitrogen was followed by quenching by tin hydride.

Clive has developed the use of *O*-trityl oximes to achieve ring closure with regeneration of the oxime function.[90] Attachment of crystalline *O*-trityloximino glyoxylic acid to various radical precursors through DCC-mediated esterification enabled cyclizations shown generically at the top of Scheme 55, which provided cyclic oximes in 41–80% yield for several cases. The putative C-nitroso intermediate generated upon loss of trityl radical was not observed directly; apparently rapid tautomerization occurs. Specifically, highly functionalized 5-*exo* cyclization products including spirolactone **84**, fused acetal **85**, and *C*-glycoside **86** were obtained, and in one case a 6-*exo* cyclization also was effective to give **87**.

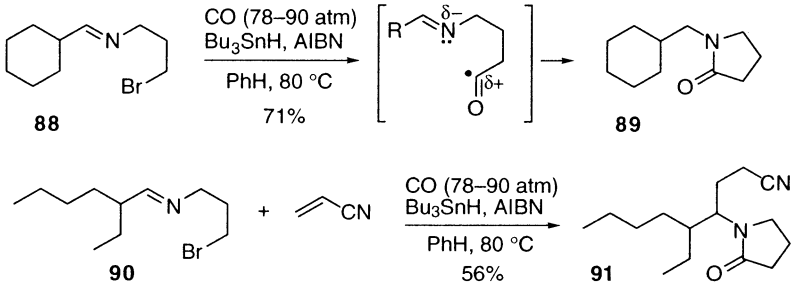
Finally, it should be noted that one example of the fragmentation with loss of nitrogen may be responsible for decomposition in attempted radical cyclizations to sulfonylhydrazones (Scheme 56).[48] Fallis proposed decomposition pathways involving sequential loss of a sulfonyl radical and nitrogen to explain complex mixtures obtained in these cyclizations.

2.3. Addition to the N-terminus of C=N ('nitrogen-philic' addition)

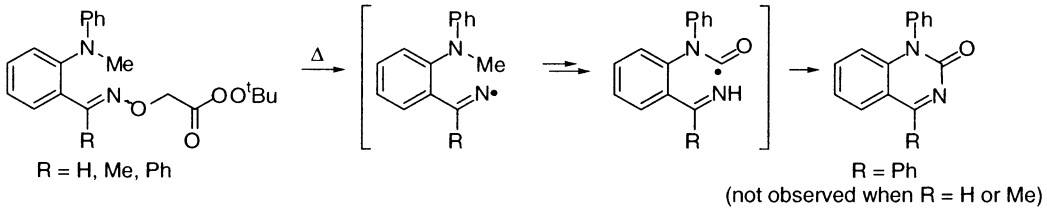
Despite numerous examples of radical addition to C=N bonds, there have been only sporadic cases wherein addition occurs at the nitrogen. A stabilizing 3-electron interaction of the forming aminyl radical with non-bonding electrons on either oxygen or nitrogen is generally invoked to explain the facility of radical addition to oxime ethers and hydrazones. In the case of imines, this 'radical α-effect' is not possible; thus it is rather surprising that addition does not often occur at nitrogen given the stabilization available through interaction of the adduct α-aminyl radical with the non-bonding electron pair on nitrogen. In the cases of addition at nitrogen known to date, additional stabilizing groups (e.g. benzylic), conformational restriction, severe steric hindrance, or polar effects are present to further promote attack at nitrogen. Early examples by Takano[38] and Warkentin[7] involved aryl radical cyclizations onto aryl aldimine C=N bonds to afford benzylic radicals. Even in these favorable cases, the selectivity was not optimal. More recently, an example mentioned above involving an oxime ester has appeared (see Scheme 22), and some success has been gained by using acyl radicals or imidate radical acceptors.

McClure and coworkers explored the possibility of addition to the N-terminus of the imidate functional group (Scheme 57), wherein the adduct C-centered radical would benefit from stabilizing effects of both nitrogen and oxygen substituents.[91] An aryl bromide cyclized upon treatment with Bu_3SnH in refluxing benzene, but the uncyclized reduction product predominated. With tris(trimethylsilyl)silane, 'nitrogen-philic' cyclization occurred in 48% yield. Oxidation of the product radical by oxygen or by loss of ethyl radical were proposed to explain the observed amide functionality. The product of 6-*endo* cyclization (addition to the C-terminus of C=N) was not observed.

Ryu and Komatsu et al. have found that carbonylation of alkyl radicals containing γ-imino groups gives lactams (Scheme 58).[92] The intermediate acyl radical and the imine group have matched polarity with respect to the carbonyl carbon and the imine nitrogen, and this was proposed to allow novel selective attack of the acyl radical at nitrogen. Indeed, in 12 examples there was no evidence for radical attack at the C-terminus (6-*endo*), instead



Scheme 58.



Scheme 59.

'nitrogen-philic' cyclization occurred exclusively. Bromide **88** exemplifies the process, yielding pyrrolidinone **89** upon treatment with Bu_3SnH under CO. Introduction of acrylonitrile (4 equiv) enabled a second C–C bond construction from bromide **90** by intermolecular trapping of the cyclized radical to afford **91**. In addition to a polar effect, steric hindrance also may contribute to regioselectivity, as all reported examples were branched aldimines or ketimines. More recently, this reaction has been viewed as a nucleophilic addition of the imine nitrogen to the carbonyl group rather than a radical addition reaction.[8]

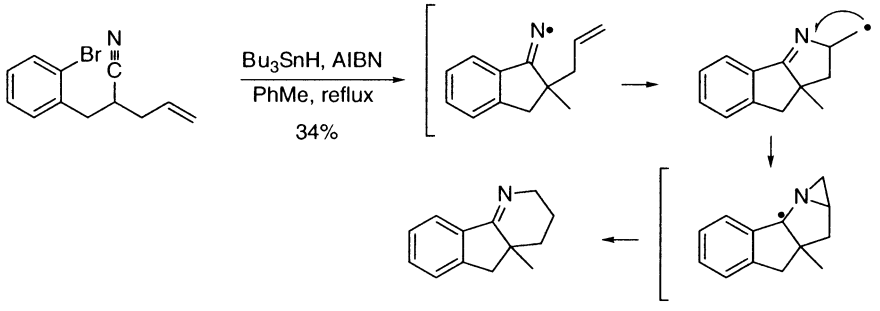
Thermal decomposition experiments have been proposed to generate acyl radicals which similarly cyclize onto nitrogen, aided by the formation of a doubly benzylic radical.[93] From peroxide precursors (Scheme 59, R=Ph), Leardini et al. thus observed small amounts (7–8%) of cyclized product, but this pathway was not observed when R=H or Me.

Very recently, Bowman et al. described a ring expansion via radical cyclization to the N-terminus of an imine acceptor.[94] Aryl radical cyclization of a nitrile (Scheme 60) generated an iminyl radical, which subsequently cyclized to the apparent 6-*endo* product. This was proposed to occur through 5-*exo* cyclization followed by Dowd-type ring expansion involving 3-*exo* cyclization to the imine nitrogen to give a relatively stable benzylic radical, followed by fragmentation to the expanded ring.

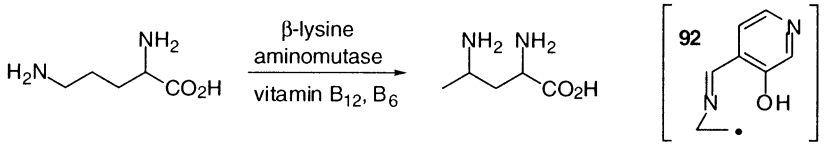
The viability of such rearrangements within a biosynthetic pathway has been recently evaluated computationally by Radom and coworkers. A 3-*exo* radical cyclization onto the N-terminus of imine bonds may be involved in coenzyme B_{12}-dependent lysine aminomutase activity (Scheme 61).[95] Cyclization of a radical such as **92** to generate an aziridinylcarbinyl radical was proposed to lead to net 1,2-amino group migration after C–N bond fragmentation and imine hydrolysis. Interestingly, the calculations showed protonation of the pyridine ring nitrogen reduced the barrier for ring closure of **92** by 24 kJ mol^{-1} in a degenerate rearrangement model.

3. Intermolecular radical addition to C=N acceptors

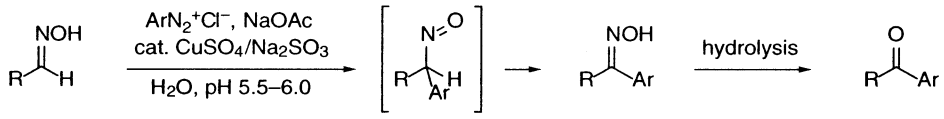
There are few applications of intermolecular radical addition to C=N bonds in organic synthesis due to a paucity of general synthetic methods. In contrast to cyclizations, relatively little is known about intermolecular radical additions to C=N bonds. Furthermore, cyclizations are generally rendered stereoselective in a straightforward way by exploiting endocyclic conformational control elements for internal diastereoselectivity, while intermolecular reactions require somewhat underdeveloped acyclic stereocontrol of radical reactions. Because there is a prominent current focus on the challenge of understanding and developing predictable stereoselective intermolecular radical additions, the literature on this topic reviewed here is organized with respect to stereocontrol strategies.



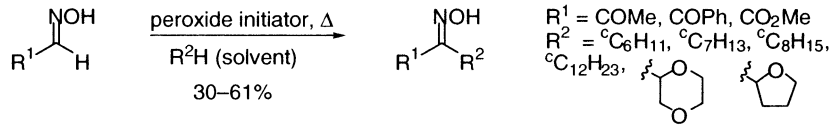
Scheme 60.



Scheme 61.



Scheme 62.



Scheme 63.

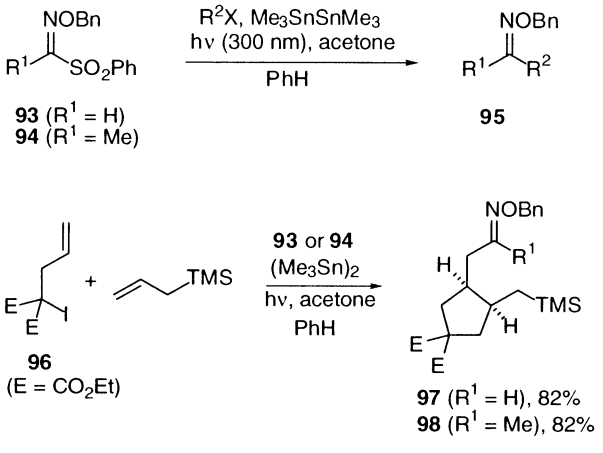
3.1. Nonstereocontrolled intermolecular radical addition

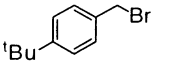
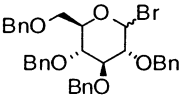
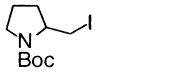
3.1.1. Non-reductive addition. *Oxime ethers*. As early as 1907, the use of diazonium salts in arylation of oximes was reported.[96] It was later found that copper salts efficiently catalyze similar reactions at nearly neutral pH (Scheme 62),[97] suggesting a radical mechanism may be involved. A speculative radical addition mechanism for these non-reductive reactions may involve stepwise electron transfer and proton loss from the adduct aminyl radical; the one-electron oxidant could be either arenediazonium ion or copper (II) salt, reduction of which could serve as a propagation step. Tautomerization of a nitrosoalkane would then restore the oxime functional group.

Citterio and Filippini, following the precedent involving aldoxime *C*-arylation by diazonium salts, developed a *C*-alkylation of aldoximes with various cycloalkyl radicals generated by H-atom abstraction from cycloalkane or cyclic ether solvents (Scheme 63).[98] Aldoximes with a vicinal carbonyl group (R^1=$COCH_3$, COPh, or CO_2CH_3) gave moderate yields of ketoximes, while acetaldehyde or benzaldehyde oximes gave only 10% and 16% yields, respectively, of cyclohexyl ketoximes.

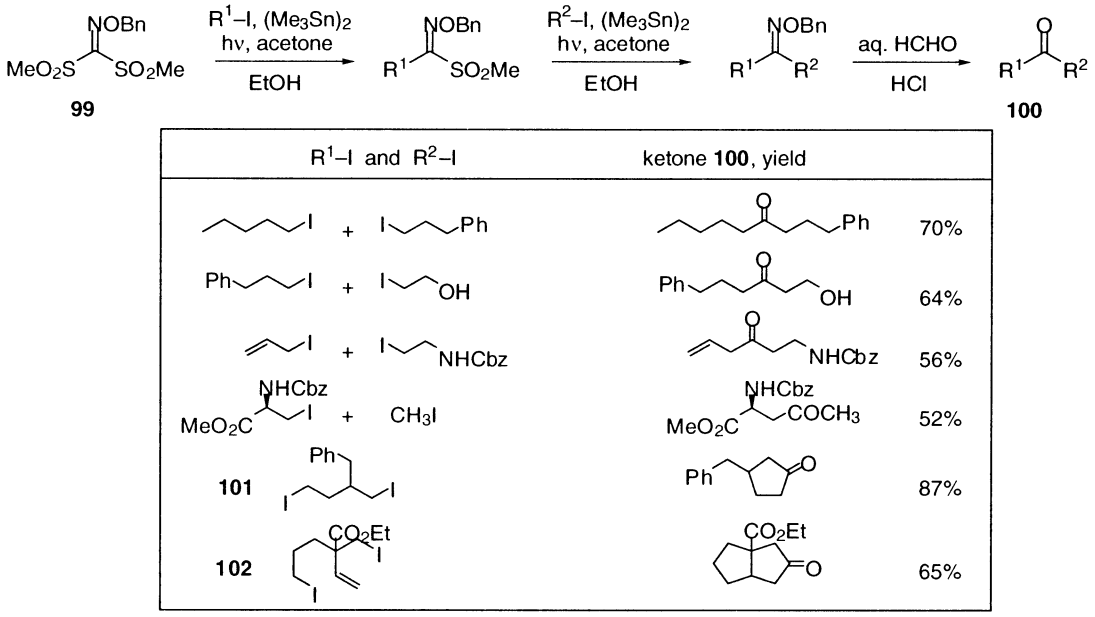
In contrast to the tautomerizations noted above, radical fragmentation of a bond to the C-terminus of the C=N bond would also regenerate the oxime ether functionality (see Section 2.2.1). Intermolecular radical addition via such an approach has been smoothly implemented by Kim and coworkers using C-phenylsulfonyl oxime ethers for radical acylation (Scheme 64).[99] Irradiation of a wide variety of simple and functionalized alkyl iodides in the presence of oxime ethers **93** and **94** and hexamethylditin led to addition/elimination products **95** in good yield. Tandem reactions involving both cyclization and intermolecular addition were also successful, as exemplified by the annulation of iodide **96**. Kinetic data revealed that rates of 4-phenoxybutyl radical addition to **93** ($9.6\times10^5\ M^{-1}\ s^{-1}$, 25°C) are an order of magnitude faster than addition to **94** ($7.3\times10^4\ M^{-1}\ s^{-1}$, 25°C), although both are fast and efficient processes. According to competition studies, the rates of addition to **93** and **94** are at least three times faster than to allyltributylstannane and roughly twice that of addition to acrylonitrile.[6]

The distinctions in rates of addition can be exploited in related reactions for selectivity purposes. Sequential intermolecular acylation of two different alkyl iodides or diiodides has been explored by Kim et al. in an elegant method for unsymmetrical ketone synthesis (Scheme 65).[100] Using bis-methanesulfonyl oxime ether **99** as a carbonyl equivalent, two C–C bonds were formed at the same carbon via the addition/elimination process described above. A one-pot three-step method involved photoinitiated acylation of one alkyl iodide with **99** in the presence of



R^2X	yield of **95**
$^cC_6H_{11}I$	91% (R^1 = H)
	87% (R^1 = Me)
^tBuI	85% (R^1 = H)
	15% (R^1 = Me)
$THPOCH_2CH_2I$	93% (R^1 = H)
$HOCH_2CH_2Br$	61% (R^1 = H)
$CH_3(CH_2)_8O_2CCH_2I$	72% (R^1 = H)
	40% (R^1 = H)
	64% (R^1 = H)
	53% (R^1 = Me)
	95% (R^1 = H)

Scheme 64.



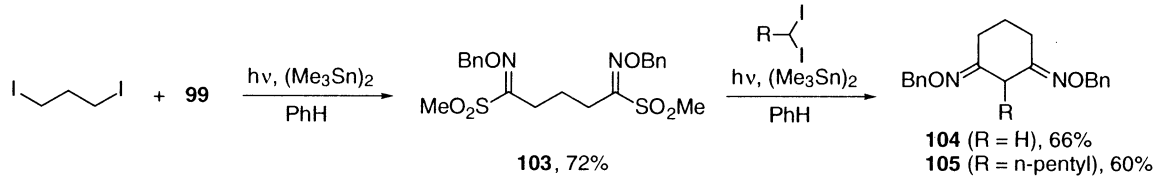
Scheme 65.

hexamethylditin, followed by introduction of a different iodide and additional tin reagent for the second radical addition, and finally hydrolysis of the oxime ether to obtain ketones **100** from a wide variety of functionalized iodides. Diiodides such as **101** and **102** gave cyclic ketones via tandem reaction sequences.

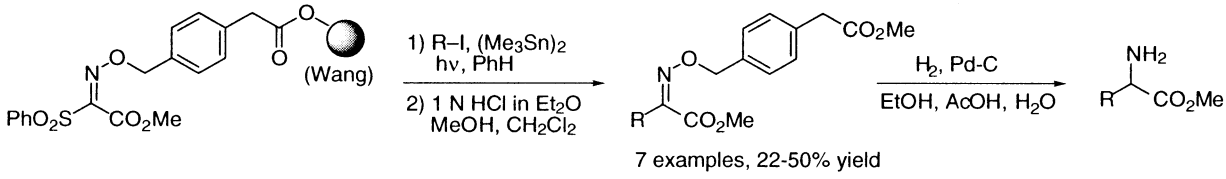
An interesting variation on this theme is seen in the use of 1,3-diiodopropane, which does not give the cyclobutanone oxime, but rather is homologated at both termini to afford bis-oxime **103** (Scheme 66). Subsequent tandem radical addition/cyclization using a geminal diiodide completes a [3+1+1+1] annulation sequence to furnish **104** or **105** in good yield.[77]

The radical addition reactions of these C-sulfonyl oxime ethers have been examined on solid support.[101] Using Wang resin and attachment through a modified *O*-benzyl group on the oxime (Scheme 67), a series of radical additions of alkyl halides to the resin-linked acceptor gave the corresponding *C*-alkylated oxime ethers after detachment from the resin. Isolated yields were in the range of 22–50%, and the products were further transformed to α-amino esters. Primary and secondary iodides worked best, while iodoacetates did not give the acylated products.

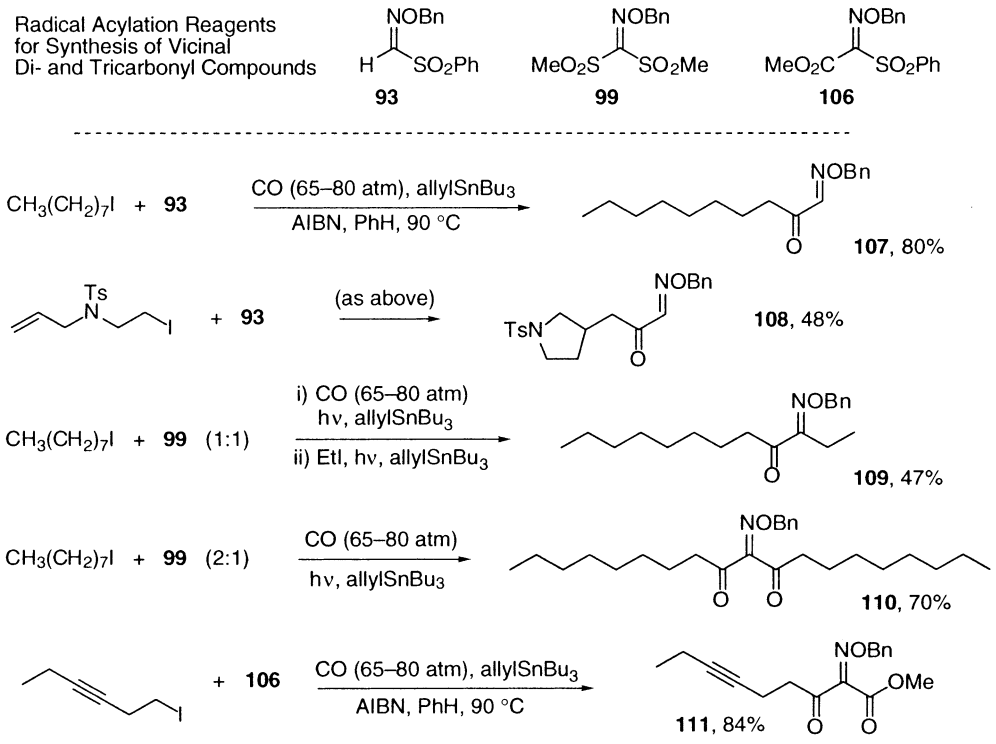
Impressive cascade reactions involving up to five components have been developed by Ryu and Kim and coworkers using one-carbon radical synthons.[102] To circumvent difficult acyl radical addition to CO, Kim's C-sulfonyl oxime ethers **93**, **99** and **106** (Scheme 68) were employed as CO surrogates for assembly of diverse vicinal di- and tricarbonyl compounds via single or double acyl radical addition. Alkyl halides were homologated via thermally or photochemically initiated radical addition to CO (65–80 atm), then addition of the resulting acyl radicals to the indicated C=N acceptors gave multicomponent coupling products as exemplified in preparations of **107**–**111**. Allyltributyltin was used in these reactions as both a chain propagation reagent and as a trap for sulfonyl radicals.



Scheme 66.



Scheme 67.

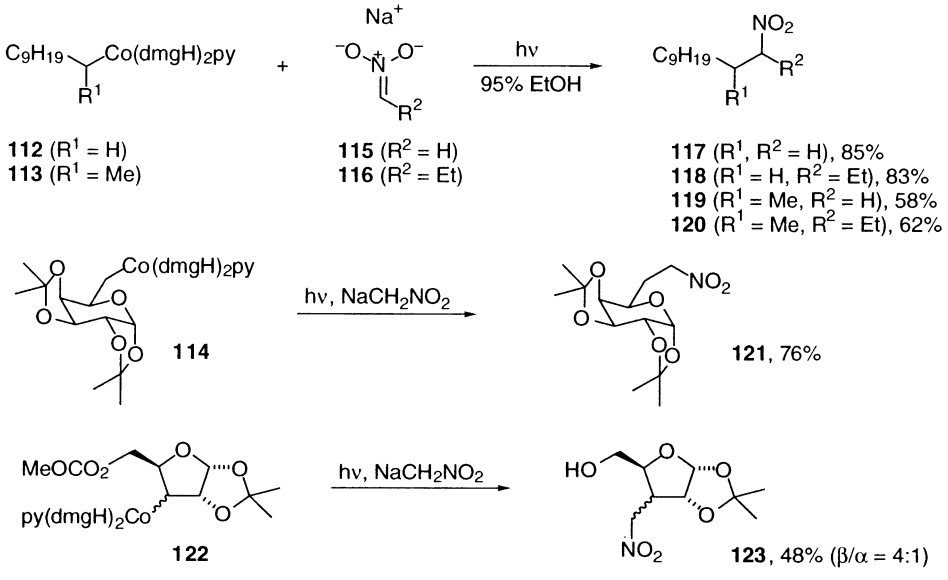


Scheme 68.

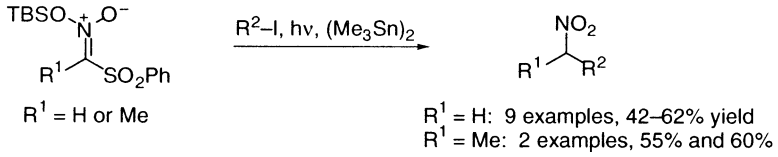
Reductive deoximation with zinc and acetic acid was found to release the latent carbonyl group. Also, direct additions to glyoxylate-type acceptor **106** without the presence of CO provide a versatile route to α-ketoesters[103] (not shown). Thus a variety of simple and functionalized α-oximinoesters were prepared by photolysis of alkyl iodides in the presence of **106** and hexamethylditin in good-to-excellent yields.

Nitronates. Nitroalkyl anions (nitronates) undergo non-reductive radical coupling reactions, as has been extensively studied by Kornblum and Russell.[104] These reactions fall within the broader class of $S_{RN}1$ radical anion chain coupling reactions, and these have been previously reviewed.[105] Although the extensive mechanistic studies of these reactions are beyond the scope of this review, some more recent synthetic developments are included below.

Branchaud and Yu have exploited non-chain versions of radical addition to nitroalkyl anions using homolytic chemistry of the carbon–cobalt bond.[106] Visible-light photolysis of cobaloximes **112–114** (Scheme 69) in the



Scheme 69.



Scheme 70.

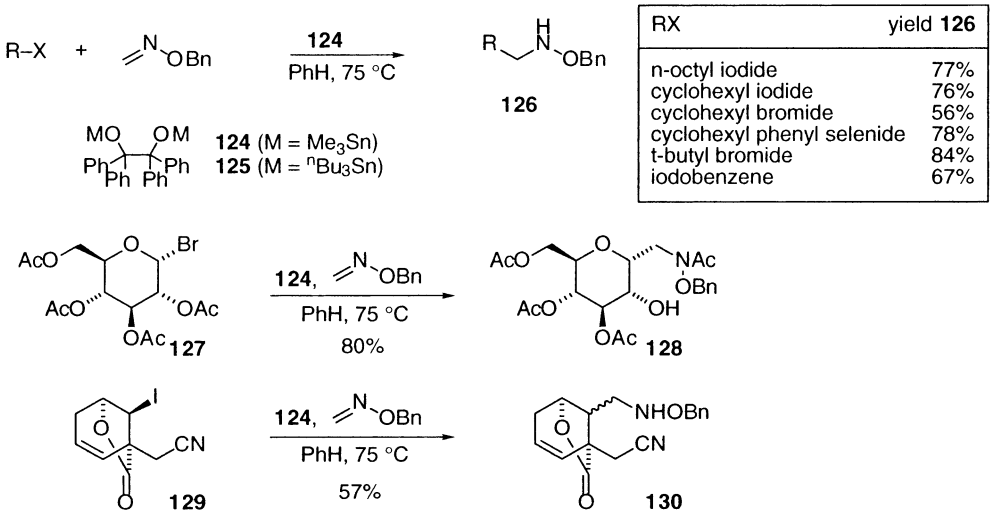
presence of the sodium nitronate from either nitromethane (**115**) or 1-nitropropane (**116**) gave cross-coupling products **117**–**121**. After radical addition to the C=N bond, hydrogen atom abstraction from the adduct radical regenerated the nitronate C=N bond, which was then protonated to return the nitroalkane functionality for further elaboration. Although the base-sensitive carbonate ester was hydrolyzed during the reaction of **122**, the coupling still proceeded in modest yield to give **123**. Nitropropane gave the corresponding coupling products as diastereomeric mixtures.

The extensive studies of C-sulfonyl imino compounds by Kim's group (vide supra) have also extended into similar addition–fragmentation reactions of silyl nitronates (Scheme 70).[107] Primary, secondary, tertiary, and benzylic iodides, including methyl iodoacetate, underwent photolytic tin-mediated coupling with *O*-silyl nitronates derived from nitromethane and nitroethane, respectively.

3.1.2. Addition to non-prochiral formaldoximes. Formaldehyde imino derivatives, by virtue of their terminal methylene unit, are free from stereocontrol considerations. Because of the sterically unhindered carbon, it is not surprising that these were among the first C=N radical acceptors to be exploited for useful synthetic methodology.

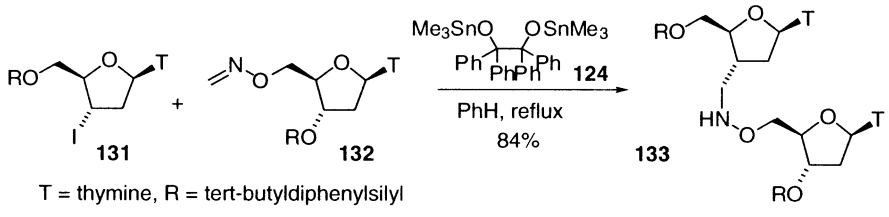
Hart and Seely reported the first reductive intermolecular addition to C=N bonds in 1988, using *O*-benzylformaldoxime for one-carbon homologation of alkyl halides to amines (Scheme 71).[32a] Tributyltin hydride or photolytic hexamethylditin conditions were not useful due to premature reduction or unwanted photochemical side reactions. However, in the presence of **124**, a non-reducing tin radical source, a series of simple halides gave the corresponding homologated hydroxylamines **126** in 56–84% yield, using equimolar amounts of halide and C=N acceptor. Not only halides, but also cyclohexyl phenyl selenide was used successfully. More complex radical precursors **127** and **129** also furnished good yields of homologated products **128** and **130**, respectively. More recently, the alternative tributyltin reagent **125** has been introduced as a less toxic alternative.[32b] The reactions are believed to occur through a non-chain process enabled by the persistent radical effect.[108]

Bhat and coworkers employed Hart's method for reductive aminomethylation for intermolecular coupling of 2-deoxy nucleosides (Scheme 72).[109] With one nucleoside attached

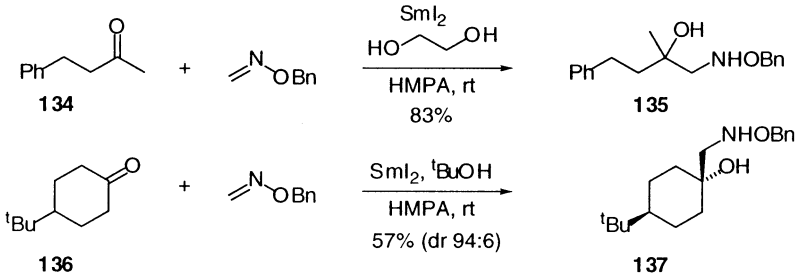


RX	yield **126**
n-octyl iodide	77%
cyclohexyl iodide	76%
cyclohexyl bromide	56%
cyclohexyl phenyl selenide	78%
t-butyl bromide	84%
iodobenzene	67%

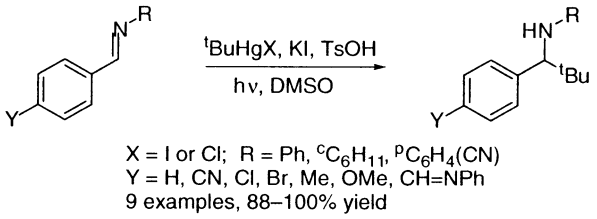
Scheme 71.



Scheme 72.



Scheme 73.



Scheme 74.

through an ether linkage to formaldehyde oxime, the other was introduced as the 3′-alkyl radical. In the optimized procedure, heating a 1:3:2 molar ratio of **131**, **132**, and tin reagent **124** in benzene gave an excellent yield of addition product **133** (T=thymine). A series of nucleosidic dimers were then prepared using this method, with yields ranging from 30 to 84% depending on protecting groups used.

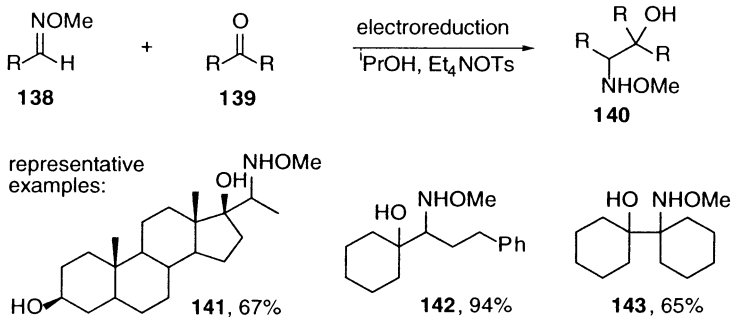
Inanaga reported the use of *O*-benzyl formaldoxime in intermolecular samarium-mediated pinacol-type addition reactions (Scheme 73).[110] Thus, various ketones and cyclohexane carboxaldehyde each produced the homologated amine in a ketyl radical analogy with Hart's work. Representative examples are the aminomethylation of 4-phenyl-2-butanone (**134**) to provide amino alcohol **135** in high yield and *t*-butyl cyclohexanone (**136**) to afford the axial aminomethyl group in **137**. Several other difunctional 1,2-amino alcohols were formed in moderate yields.

3.1.3. Non-stereocontrolled addition to prochiral C=N bonds. Early examples of intermolecular addition to prochiral imine derivatives uncovered useful reaction features, though stereoselectivity was not addressed until the late 1990s.

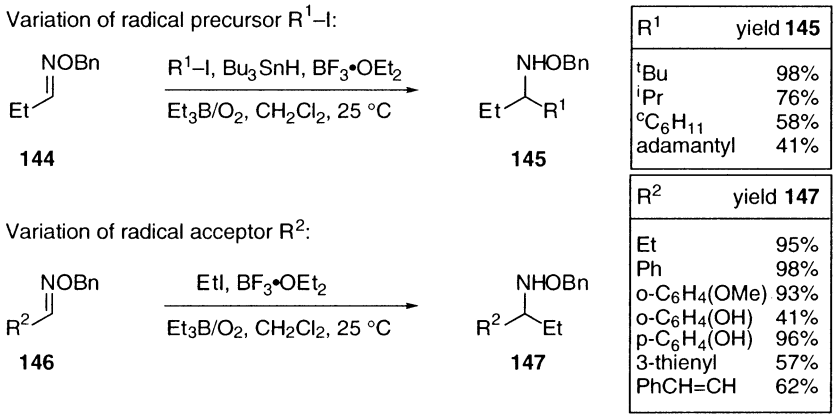
Russell reported intermolecular additions of radicals generated from *tert*-butylmercuric halide to benzaldehyde and formaldehyde imines (Scheme 74), with reactivity increasing in the presence of acid.[111] Virtually quantitative yields of adducts were obtained for a series of aryl aldimines in the presence of *p*-toluenesulfonic acid (TsOH), without detrimental effects from either electron-donating or -withdrawing aryl substituents. Benzophenone and cyclohexanone *N*-phenyl ketimines did not react. The use of ammonium ion instead of TsOH resulted in lower yields (68–86%) from the same substrates; this fact, together with the pK_a differential, suggested different roles for the two acids. While NH_4^+ can protonate the adduct aminyl radical to facilitate chain propagation (by electron transfer from $^tBuHgI_2^-$), TsOH is a strong enough acid to protonate the imine substrate, which facilitates both radical addition and chain propagation.

A quite general electroreductive coupling procedure affording 1,2-amino alcohols from ketones and oxime ethers was reported by Shono in 1991.[59] At constant current (0.2 A) using a tin cathode and a carbon anode, a mixture of oxime ether **138** (Scheme 75) and ketone **139** in Et_4NOTs/2-propanol was converted selectively to the cross-coupled product **140**. In 16 examples, yields of 43–98% were obtained, and a notable feature of the reaction was the tolerance for steric hindrance. Thus, a hindered steroidal ketone was coupled to form **141** in good yield, and cyclohexanone also underwent cross coupling to give hydroxylamines **142** and **143**. Since the oxime ethers were inert under these conditions, the selective reaction was proposed to involve initial one electron reduction of ketones, followed by intermolecular ketyl radical anion addition to the closed-shell oxime ether function.

Naito and coworkers reported the first general method



Scheme 75.



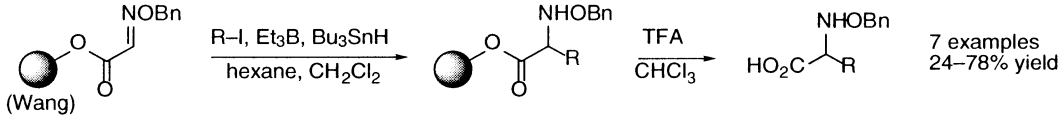
Scheme 76.

for achieving addition of neutral radicals to prochiral aldoximes. Although unhindered formaldoximes and activated glyoxylic oxime ethers did not require Lewis acid activation, the beneficial effect of $BF_3{\cdot}OEt_2$ allowed general application to various oxime ethers.[11,112] Using triethylborane/oxygen initiation, propionaldehyde oxime ether **144** (Scheme 76) served as a radical acceptor for various secondary and tertiary radicals to afford 41–98% yields of addition products **145**. Primary radical addition using alkyl iodides with this method was problematic due to side reactions or inefficient initiation by the triethylborane initiating system, which is not well-suited to selective iodine atom transfer to generate energetically similar primary radicals from ethyl radicals. However, ethyl radicals themselves afforded good yields of addition products with various oxime ethers **146**. Interestingly, selective 1,2-addition to the C=N bond occurred with an unsaturated oxime ether (R^2=PhCH=CH).

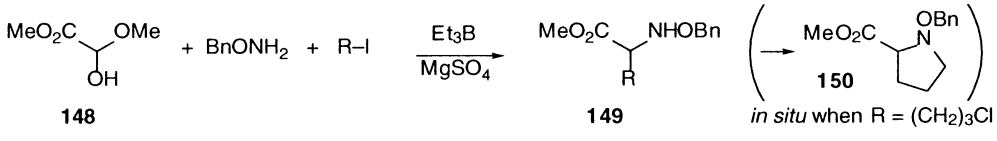
Glyoxylic oxime ethers are valuable as radical acceptors in a variety of applications (vide infra). The vicinal carboxylate group activates the imine group toward radical addition, and this has enabled synthesis of amino acids by radical addition to the C=N bond of these oximes.[11,112] In addition to auxiliary controlled asymmetric synthesis results described below (Section 3.3), these reactions have been successfully applied to solid phase synthesis.[113] Using Wang resin with the radical acceptor attached through the carboxylate group (Scheme 77), addition of several alkyl iodides gave the corresponding hydroxylamino acids after cleavage from the resin. Isopropyl, cyclohexyl, *sec*-butyl, and *tert*-butyl iodides performed well (61–78%). Use of Tentagel resin was also successful in one case, albeit with lower yield.

Oxime ethers can be formed under conditions compatible with the radical addition. Naito took advantage of this situation to establish a one-pot three-component coupling reaction to generate amino acids via radical addition to an in situ-generated C=N bond (Scheme 78).[114] Combination of *O*-benzylhydroxylamine, methyl 2-hydroxy-2-methoxyacetate (**148**) and a typical series of secondary and tertiary alkyl halides in the presence of triethylborane and tributyltin hydride gave good yields of *N*-benzyloxyamino esters **149**. Primary radicals were not generated efficiently using triethylborane initiation, so competitive ethyl addition was a significant side reaction in such cases (10–25% yield). Nevertheless, 3-chloropropyl iodide underwent tandem radical addition and nucleophilic cyclization to generate proline derivative **150** in 46% yield.

Avoiding the use of toxic and difficult-to-remove tin



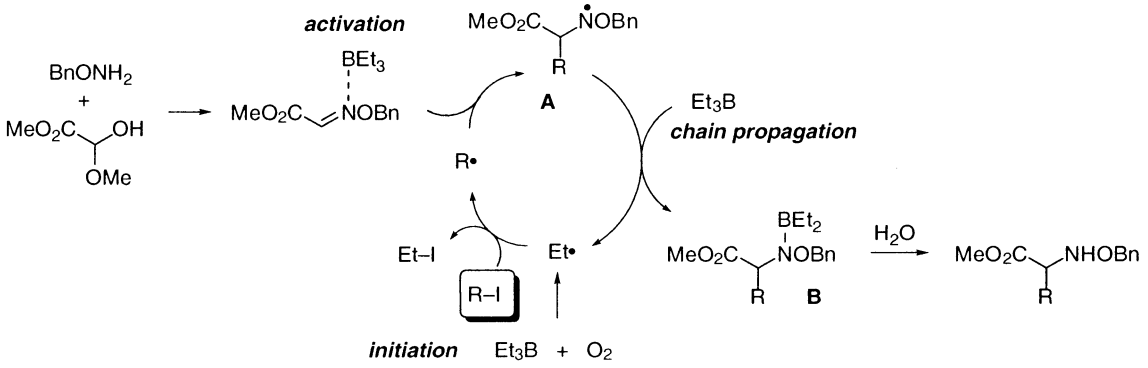
Scheme 77.



Conditions A: Bu_3SnH, 5 equiv RI (1°, 2°, or 3°), CH_2Cl_2, rt: 46–86%
Conditions B: 30 equiv RI (2°), PhMe, reflux: 76–94%

Scheme 78.

Multiple roles of triethylborane in the absence of tin hydride:



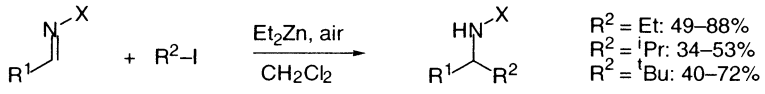
Scheme 79.

reagents is attractive from a practical perspective. Optimized tin-free conditions for secondary alkyl iodides led to improved yields (76–94%) in refluxing toluene using 30 equiv. of the iodide.[115] These conditions exploited multiple roles of triethylborane[116] for Lewis acid activation, radical initiation, and chain propagation (Scheme 79). The latter behavior was attributed to its reaction with aminyl radical **A** to release ethyl radical, generating a closed-shell aminoborane **B**. Excess triethylborane was required in the optimized procedure. It is worth noting that any amino acid synthesis by a one-pot condensation/addition method would require care to ensure tolerance for the water generated during formation of the C=N acceptor; these radical addition conditions meet this requirement.

A similar procedure has also been developed for use with aryl and alkyl aldehydes, which require a stronger Lewis acid for C=N acceptor activation. Thus, when $BF_3{\cdot}OEt_2$ was included in the reaction mixtures, pentanal, benzaldehyde, and several other aromatic aldehydes gave successful reactions (13 examples, 54–92% yield) analogous to those described above, extending the three-component coupling beyond the amino acids.[117]

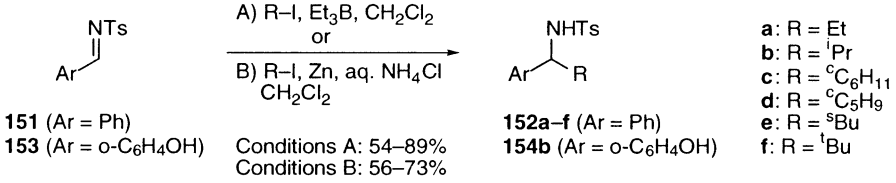
Diethylzinc has been used by Bertrand and coworkers as a chain-transfer reagent in related radical additions to imines as well as methyl glyoxylate oxime ether and hydrazone derivatives (Scheme 80).[118] Several substrates each gave remarkably similar results upon controlled comparison of the Et_3B or Et_2Zn conditions, establishing a parallel between the two radical initiation systems. This parallel did not extend to C=C or N=N radical acceptors, however. An essentially similar mechanism to that presented above for triethylborane was presumed responsible.

Sulfonylimines can be used as acceptors in intermolecular radical addition reactions (Scheme 81), as recently reported by the Naito group.[119] In contrast to the *O*-benzyloximes, no Lewis acid was required for efficient reaction. Thus, benzaldimine **151** provided 84% yield of ethyl adduct **152a** using Et_3B in CH_2Cl_2, while iodine atom-transfer occurred using Et_3B and secondary alkyl iodides to provide

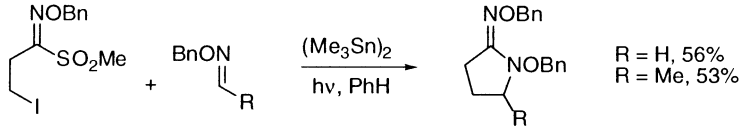


R^1 = CO_2Me or p-C_6H_4Cl; X = CH(Me)Ph), OBn, NPh_2, or Ph)

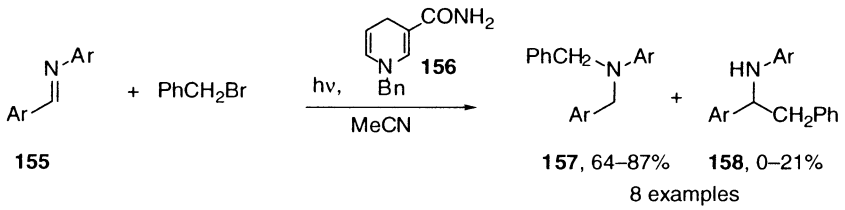
Scheme 80.



Scheme 81.



Scheme 82.



Scheme 83.

addition products **152b–d** and **154b** in 54–89% yield. Interestingly, addition to sulfonylimines also occurred under aqueous conditions using Zn-mediated addition. Treatment of a mixture of the sulfonylimines **151** or **153** and secondary or tertiary alkyl iodides with zinc and aqueous ammonium chloride (CH_2Cl_2 cosolvent) gave the desired adducts in 56–73% yield, accompanied by 8–20% of C=N reduction product. Without NH_4Cl, the Zn-mediated addition did not occur.

Kim has reported a tandem sequence involving an intermolecular addition to *O*-benzylformaldoxime or -acetaldoxime followed by cyclization of the resulting aminyl radical onto a C-sulfonyloxime ether, providing iminolactam heterocycles in reasonable yields (Scheme 82).[77]

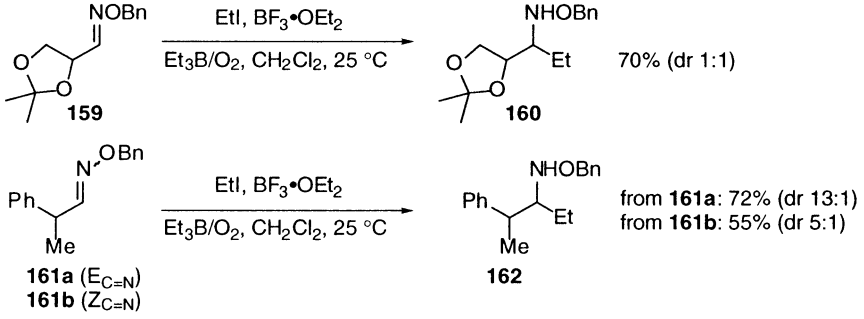
Photoinduced electron transfer-mediated addition involving imines has been reported by Liu et al.[120] Irradiation of a series of aromatic imines **155** (Scheme 83) with benzyl bromide in the presence of **156** led to addition products **157** and **158**. Addition to the N-terminus of the imines was favored, with small amounts of the alternative isomer **158** observed only in two cases. The rather unusual selectivity of the reaction was suggested to be controlled by polar effects.

3.2. Simple diastereoselectivity in addition to chiral imine derivatives

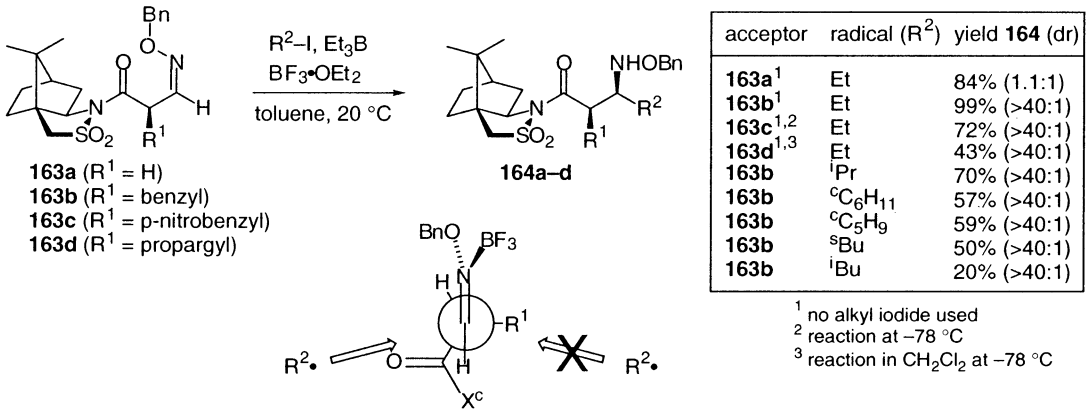
3.2.1. α-Chiral C=N acceptors. Very few examples of the effects of a neighboring chiral center on addition to C=N bonds have been reported for intermolecular reactions. Thus any conclusions about the general utility of such a mode of stereocontrol are quite premature at this time.

Naito has reported additions to chiral oxime ethers with α-substituents.[11] Glyceraldoxime acetonide **159** (Scheme 84) gave no stereocontrol, although **161a** and **161b** gave the same product **162** with dr 13:1 and 5:1, respectively (configurations not reported), showing an interesting dependence on C=N isomerism.

More recently Naito has exploited malonate-derived substrates **163** (Scheme 85), prepared by stereoselective



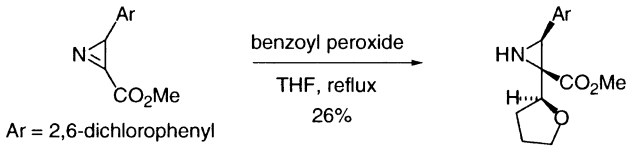
Scheme 84.



acceptor	radical (R^2)	yield **164** (dr)
163a[1]	Et	84% (1.1:1)
163b[1]	Et	99% (>40:1)
163c[1,2]	Et	72% (>40:1)
163d[1,3]	Et	43% (>40:1)
163b	^{i}Pr	70% (>40:1)
163b	$^{c}C_6H_{11}$	57% (>40:1)
163b	$^{c}C_5H_9$	59% (>40:1)
163b	^{s}Bu	50% (>40:1)
163b	^{i}Bu	20% (>40:1)

[1] no alkyl iodide used
[2] reaction at –78 °C
[3] reaction in CH_2Cl_2 at –78 °C

Scheme 85.



Scheme 86.

alkylation of the chiral camphorsultams, for 1,2-asymmetric induction in radical addition.[121] For three different oxime acceptors **163b–163d**, diastereoselectivity was extremely high (dr >40:1) in ethyl radical addition utilizing $BF_3{\cdot}OEt_2$ and Et_3B. The camphorsultam itself was not the major stereocontrol element, as **163a** led to essentially no stereocontrol, consistent with precedent involving radical addition to acrylamides using this auxiliary.[2] Next, using 30 equiv alkyl iodide, secondary alkyl radical addition to **163b** was conducted using 9 equiv each of $BF_3{\cdot}OEt_2$ and Et_3B. In all cases, very high selectivity (dr >40:1) was obtained. In these cases, minimization of allylic strain was presumed to favor the transition state shown, wherein the α-substituent R^1 blocked one face of the C=N acceptor. The primary isobutyl radical addition gave a low yield due to competitive ethyl radical addition.

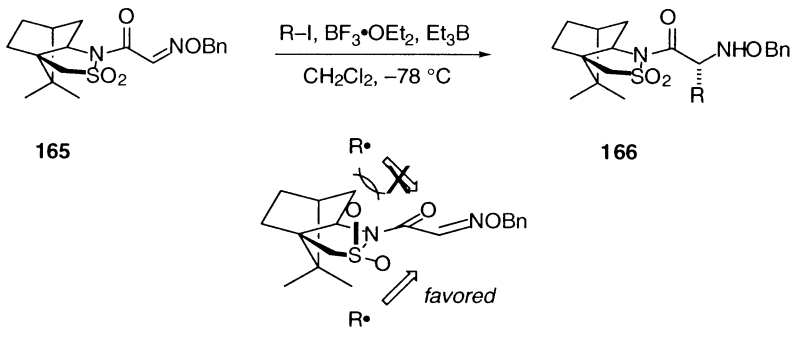
3.2.2. Prochiral radicals. Although several examples of additions of *sec*-butyl radicals to C=N acceptors have been reported (see Sections 3.2.1 and 3.3.1), none have exhibited control over the resulting stereogenic center at the methyl substituent. This remains a significant problem to be solved, particularly if radical additions are to have applications in target-directed synthesis.

In one isolated example, Gilchrist et al. fortuitously found high diastereoselectivity in a radical addition of tetrahydrofuran to an azirine (Scheme 86).[122] After the adduct was first obtained as an unexpected side product in an attempted malonate addition to the azirine, a subsequent intentional preparation using benzoyl peroxide in refluxing THF also gave the same aziridine product in modest yield. Only a single diastereomer was detected, indicating that the aryl group controlled the face of attack on the azirine. More surprisingly, the configuration generated at the prochiral radical center was also controlled in this reaction.

3.3. Auxiliary-directed stereocontrol

For general utility in target-directed synthesis, asymmetric induction via a temporarily linked external stereocontrol element, i.e., an auxiliary, is an important objective. Currently only three approaches to auxiliary stereocontrol have been disclosed; auxiliary linkage through both carbon and nitrogen termini of C=N have been examined.

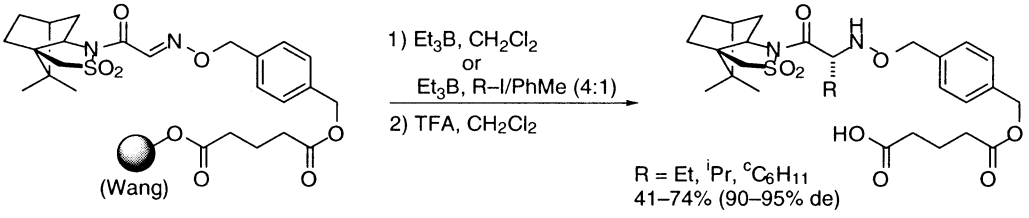
3.3.1. Camphorsultam derivatives. Naito and coworkers first reported intermolecular stereoselective radical addition to C=N bonds in 1997.[123] In this seminal paper, Oppolzer's camphorsultam auxiliary (Scheme 87) was linked through an amide bond to the *O*-benzyloxime derivative of glyoxylic acid. Substrate **165** was submitted to radical addition conditions using a variety of Lewis acid promoters and alkyl iodides along with triethylborane initiation. Optimal yields and selectivities were obtained using $BF_3{\cdot}OEt_2$ in CH_2Cl_2; under these conditions addition of ethyl, isopropyl, cyclohexyl and *tert*-butyl radicals gave amino acid derivatives **166** in 80–86% yield with very high stereoselectivity. Separate steps cleaved the N–O bond ($Mo(CO)_6$) and removed the auxiliary, which led in one case to D-valine and an absolute configurational assignment. A stereocontrol model consistent with the observed product configuration was proposed, suggesting that the sulfonamide oxygen was critical for blocking one of the approach trajectories.[124] In a subsequent detailed account, the addition reactions were reported to be effective with isobutyl and *sec*-butyl radicals.[125] Although ω-functionalized *n*-butyl radicals



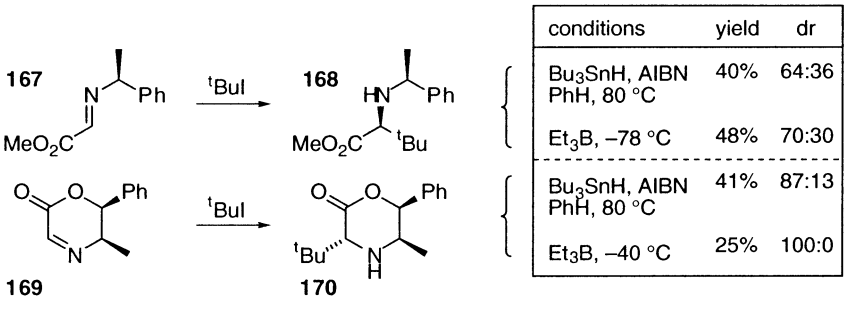
R	yield **166**	dr
Et	80%	95:5
^{i}Bu	83%	97:3
^{i}Pr	80%	96:4
^{s}Bu	69%*	>98:2
$^{c}C_6H_{11}$	86%	96:4
^{t}Bu	83%	>98:2
$AcO(CH_2)_4$	41%**	>98:2
$Cl(CH_2)_4$	15%**	>98:2

*Obtained with dr = 1:1 at the methyl substituent. **Major product was from ethyl addition.

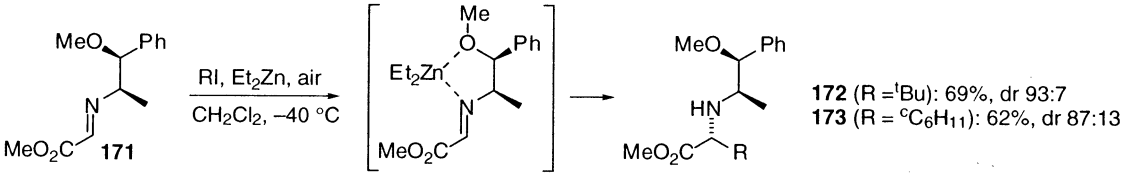
Scheme 87.



Scheme 88.



Scheme 89.



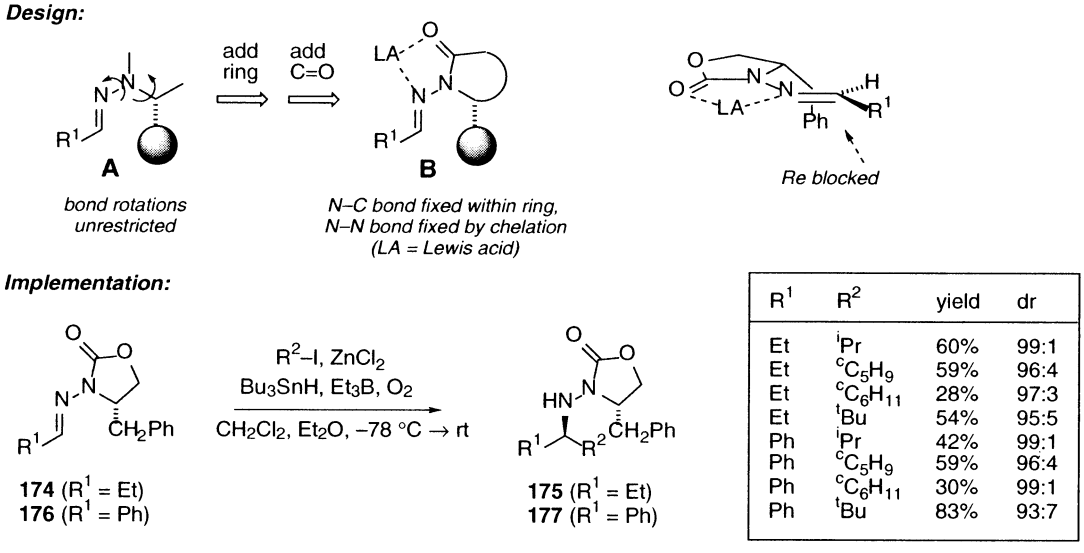
Scheme 90.

added with very high stereocontrol, the yields were handicapped by competitive ethyl radical addition (from triethylborane).

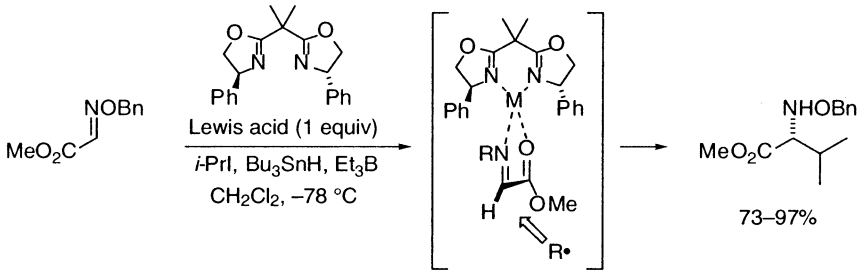
By including a resin attachment point in the benzylic group of the *O*-benzyloxime, this asymmetric amino acid synthesis was adapted to the solid phase.[126] Reaction of Wang resin-bound oxime ether (Scheme 88) with triethylborane in CH_2Cl_2 or in a 4:1 mixture of alkyl halide/toluene as solvent afforded radical addition products which were released from the solid phase to afford amino acid derivatives in >90% de in all cases.

3.3.2. Chiral imines. In 1998, Bertrand and coworkers reported the radical addition of various alkyl iodides to cyclic and acyclic chiral glyoxylate imines.[127] Selected examples employing *tert*-butyl iodide facilitate comparisons of the source of asymmetry and of initiation conditions. The acyclic imine **167** (Scheme 89) gave modest stereocontrol, and employing a Lewis acid ($MgBr_2$) led to a side reaction involving reduction of the C=N bond. In contrast, the cyclic chiral imine **169** led to much higher selectivities, presumably due to conformational constraints. In both cases, low-temperature initiation with Et_3B led to higher selectivity.

More recently, Bertrand et al. have described the use of diethylzinc to promote radical addition to similar chiral imines (Scheme 90).[128] Stereoselectivity was poor in additions to phenethylamine derivative **167**, but the use of imines capable of an additional binding interaction with Lewis acidic Zn(II), such as norephedrine-derived imine **171** and a valine-derived analog, led to improved diastereomer ratios in *tert*-butyl or cyclohexyl radical adducts **172** and **173**, presumably via a chelated acceptor.



Scheme 91.



Lewis acids: $Zn(OTf)_2$ (10% ee), $Yb(OTf)_3$ (24% ee), $Mg(OTf)_2$ (2% ee), $MgBr_2$ (52% ee)

Scheme 92.

3.3.3. Chiral *N*-acylhydrazones. We have recently reported the design and implementation of a novel chiral *N*-acylhydrazone approach to auxiliary stereocontrol in intermolecular radical addition to C=N bonds.[129] In our design, we envisioned that stereochemical information could be delivered through the nitrogen of a hydrazone **A** (Scheme 91) for maximum structural variability in the branches of the chiral α-branched amine product. Restricting conformational freedom by templating the stereocontrol element within a ring and including a carbonyl for two-point Lewis acid binding, an activated and rigidified acceptor **B** was conceived. To test this, radical addition of secondary and tertiary alkyl radicals to hydrazones **174** and **176** prepared from 3-amino-2-benzyloxazolidinone were conducted in the presence of $ZnCl_2$ and Bu_3SnH with triethylborane initiation. Yields of adducts **175** and **177** ranged from 28 to 83%, and in all cases, high diastereoselectivity was observed. Because the hydrazones are more effective radical acceptors than imines, there is no restriction to glyoxylate derivatives with an activating carboxylate group. Primary alkyl halides do not undergo radical addition under these conditions, probably due in part to premature reduction of the primary radical by tin hydride, and/or less favorable initiation by triethylborane. More recently, we have found that non-reductive photolytic initiation conditions significantly extend the scope and improve the yield of the reaction.[130]

3.4. Asymmetric catalysis

The prospect of achieving asymmetric catalysis in radical addition to C=N bonds is an open question. While Lewis acids have been shown to promote radical addition to C=N acceptors, a major problem remains in encouraging product release for catalytic turnover, since the imine reactants may be weaker ligands than the amine products. Using substoichiometric amounts of Lewis acid, i.e. true catalysis, may therefore require some creative alternative strategies.

So far only one reported attempt of the use of chiral Lewis acids to promote radical addition to C=N bonds has appeared in the literature.[126] In the presence of equimolar amounts of Zn(II), Yb(III), or Mg(II) Lewis acids modified by a chiral bisoxazoline ligand (Scheme 92), Naito found that isopropyl radical addition proceeded in excellent yield under tin-mediated conditions. The most promising Lewis acid was that derived from $MgBr_2$, which gave the desired product in 97% yield and 52% ee.

4. Concluding remarks

A large body of research has accumulated to support the notion that radical addition to C=N bonds is a synthetically useful process. Although the primary focus of this review is synthetic organic chemistry, these radical additions also have applications in organometallic chemistry,[131] bioorganic and medicinal chemistry,[132] and polymer chemistry.[133] This review will hopefully stimulate continued development and applications of these reactions, not only for organic synthesis but also various avenues of interdisciplinary research.

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Biographical sketch

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