Saturated nitrogen heterocycles

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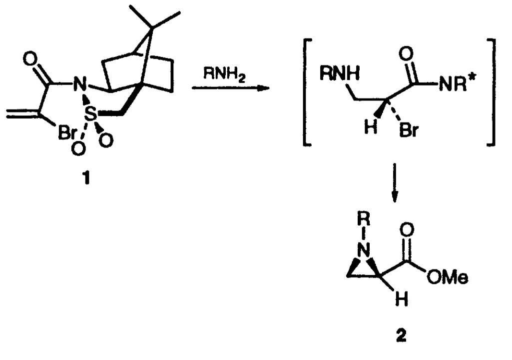
Reviewing the literature published between June 1993 and December 1994

1 Three- and four-membered rings

1.1 Aziridines

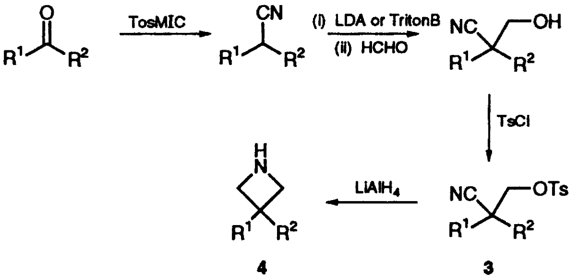
A review detailing the synthesis of chiral aziridines and their uses in stereoselective transformations has recently appeared.[1] An improved procedure for the generation of the useful nitrene $\ddot{N}CO_2Et$ has been described which proceeds via α-elimination from $NsONHCO_2Et$ using an inorganic base without a catalyst; this nitrene is a convenient aziridine precursor.[2] Homochiral aziridine-2-carboxylates, which are useful building blocks for the syntheses of modified amino acids, can be prepared by the Michael addition of amines to the bromo-acrylate **1** using the Oppolzer sultam as a chiral auxiliary. The enantio-differentiating step is asymmetric *si*-face protonation of the Michael adduct, leading to (*S*)-aziridine carboxylates **2**, after removal of the auxiliary using $Mg(OMe)_2$ in MeOH.[3]



Two reports detailing the asymmetric aziridination of olefins using PhI=NTs and a chiral catalyst have appeared. Katsuki *et al.* have used optically active (salen) manganese(III) complexes for the aziridination of styrene derivatives; however, at present the levels of asymmetric induction and chemical yields are low.[4] Evans *et al.* have reported that cinnamate derivatives undergo highly enantioselective aziridination using PhI=NTs and a chiral bis(oxazoline)-copper complex.[5] At this time, however, the optimal conditions identified for the aziridination of cinnamate esters cannot be extrapolated reliably to other olefinic substrates.

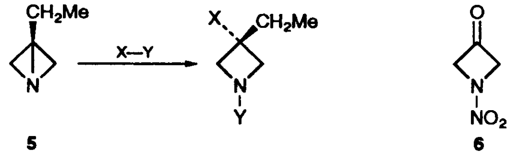
1.2 Azetidines

A straightforward but extremely useful synthesis of 3,3-disubstituted azetidines **4** starting from an appropriate ketone is outlined in **Scheme 1**; the one-pot reduction–cyclization of the cyano-tosylate intermediate **3** is noteworthy.[6] Both cyclic and acyclic ketones have been used in this sequence.



Scheme 1

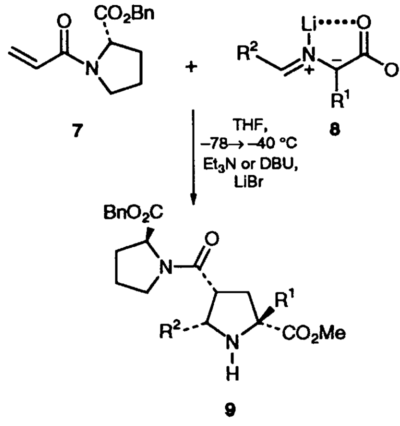
A novel route to 3-substituted azetidines involving the addition of a reagent X–Y across the highly strained σ-bond of the unusual bicyclic amine **5** has been described.[7] The presence of the ethyl group limits the generality of this procedure at this time, but the methodology can be used to prepare potentially useful azetidin-3-one derivatives such as **6**.



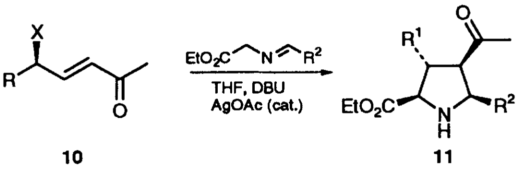
2 Five-membered rings

2.1.1 Pyrrolidines via 1,3-dipolar cycloaddition reactions

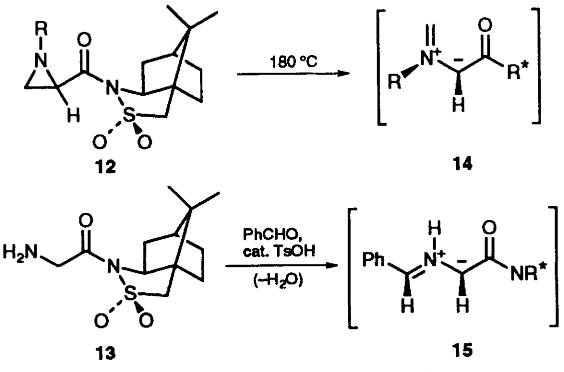
The 1,3-dipolar cycloaddition of azomethine ylides with olefins continues to be one of the most effective and useful methods for the construction of the pyrrolidine ring. Since these reactions are highly stereospecific the identification of chiral controller groups would allow the preparation of enantiopure pyrrolidine derivatives. *N*-Acryloyl proline benzyl ester **7** functions as an excellent chiral auxiliary in the cycloaddition with azomethine ylides **8** (readily derived from amino acids). In all of the examples studied the cycloaddition proceeds with almost exclusive *endo*-selectivity and also with excellent facial discrimination, providing highly functionalized pyrrolidine derivatives **9** via a highly ordered, chelated transition state.[8]



An alternative approach to obtaining asymmetric induction in these cyclizations is to use an enone bearing a chiral alkoxy or amino substituent in the γ-position, *e.g.* **10**, as the dipolarophile. In this way Pätzel and co-workers[9] observed extremely high regio- and diastereo-selectivity in cycloaddition reactions with azomethine ylides, providing pyrrolidines **11** as single diastereoisomers.

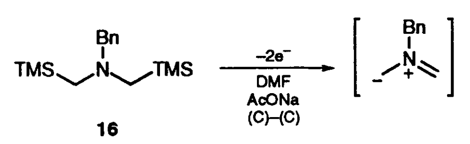


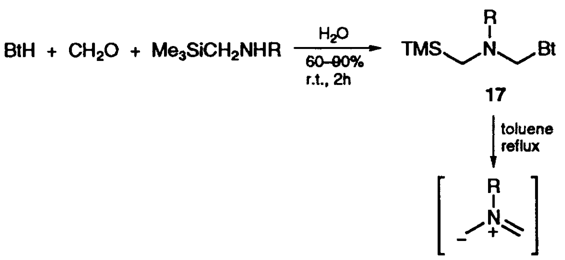
Garner and Dogan have investigated the Oppolzer sultam as a dipole based chiral auxiliary in cycloaddition reactions with achiral dipolaraphiles.[10] The desired carbonyl stabilized azomethine ylides **14** and **15** were generated by thermolytic ring-opening of the aziridine derivatives **12** or by condensation of the glycine derivative **13** with an aldehyde followed by tautomerization. The *endo–exo* selectivity and regioselectivity were found to be somewhat dependent on the structure of the dipolarophile; however, moderate to good face selectivity (5:1 to 11:1) was achieved (**Scheme 2**).



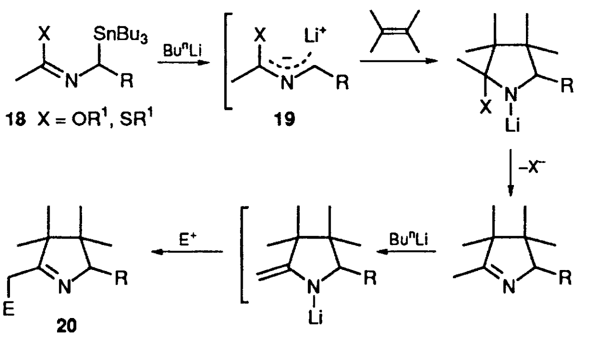
Scheme 2

The dipolar cycloaddition reactions of non-stabilized azomethine ylides are generally restricted to reactions with electron-deficient alkenes. However, ethylenic compounds bearing a trifluoromethyl group are sufficiently activated to allow the formation of 3-trifluoromethylated pyrrolidines in good yield.[11] A new method for the generation of non-stabilized azomethine ylides involves electrochemical oxidation of *N*,*N*-bis(trimethylsilylmethyl) benzylamine **16**. Electrochemical reduction of enone receptors is a competing side-reaction.[12] Alternatively, azomethine ylides can be generated under thermal conditions without using a catalyst starting from a benzotriazole derivative such as **17**.[13]



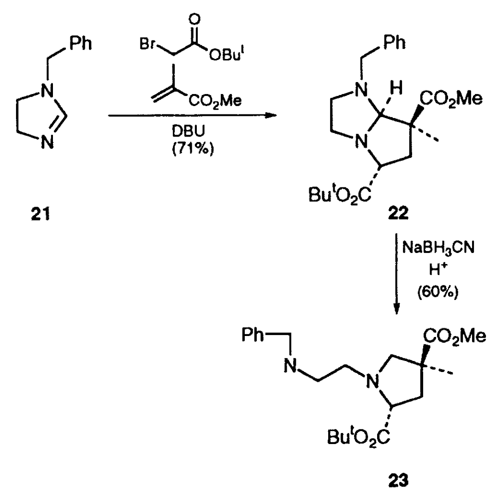


The synthesis of pyrrolidines by the $[\pi 4s + \pi 2s]$ cycloaddition between highly reactive non-stabilized 2-aza-allyl anions and electron-rich alkenes complements azomethine ylide chemistry, where an electron deficient alkene is normally used. In an extension of earlier work, Pearson *et al.* have described the generation and cycloaddition reactions of heteroatom-substituted 2-aza-allyl anions **19** with alkenes and alkynes leading to 1-pyrrolines **20**.[14] The aza allyl anions are generated by tin–lithium exchange starting from stannyl imidates or thioimidates **18** (**Scheme 3**).

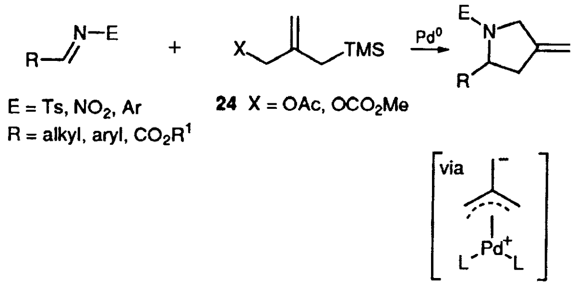


Scheme 3

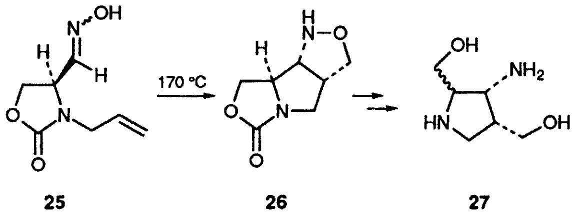
Jones *et al.* have reported an improvement to their earlier procedure for the preparation of pyrrolidines **23** by the 1,3-dipolar cycloaddition of 4,5-dihydroimidazolium ylides (**21**) with alkenes, followed by reduction of the resulting adduct **22**.[15] This one-pot procedure utilizing a t-butyl ester as quarternizing agent provides experimental simplification and improved stability of the products **23**.



Trost and Marrs have described a [3+2] cycloaddition approach to the synthesis of pyrrolidines via reaction of the extremely versatile all carbon 1,3-dipole synthon **24** with imines under Pd-catalysis.[16] Whereas simple imines fail to react, incorporation of electron-withdrawing groups at either the nitrogen or carbon centres enhance the electrophilicity of the imine sufficiently to make it an excellent acceptor. The results are consistent with a two-step addition process.

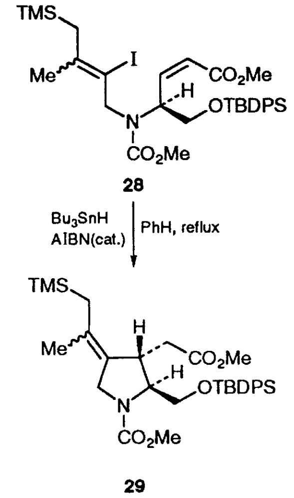


The intramolecular oxime-olefin cycloaddition of the unsaturated oxime **25** derived from L-serine provides the unusual tricyclic intermediate **26** in a highly stereoselective cyclization.[17] The tricycle **26** was then converted into the highly functionalized pyrrolidine **27**, following reduction and hydrolysis. The reason for epimerization at C-2 during the hydrolysis is being investigated.

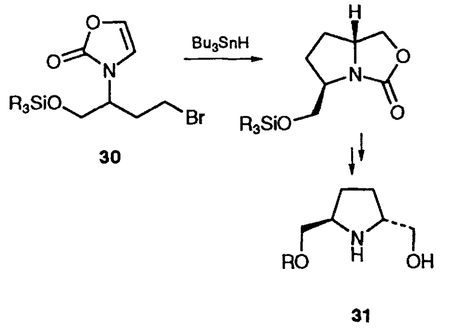


2.1.2 Pyrrolidines via intramolecular cyclization

The propensity of radicals to undergo 5-*exo* cyclizations onto proximate alkene bonds has made this an attractive method for pyrrolidine synthesis. Thus Takano *et al.* have reported a highly diastereoselective radical cyclization of the densely functionalized precursor **28** leading to the pyrrolidine **29** *en route* to an enantiospecific synthesis of (−)-kainic acid.[18]



Shibuya *et al.* have described an approach to the *trans*-2,5-disubstituted pyrrolidine derivatives **31** via radical cyclization involving $\Delta^{4,5}$-oxazolidin-2-one precursors **30**. The high diastereoselectivity is attributable to minimization of $A^{1,3}$ strain in the preferred transition state **32**.[19] Shibuya has used an extension of this methodology in a useful synthesis of (+)-bulgecinine **36** (**Scheme 4**).[20] Thus, cyclization of the O-stannyl ketyl radical **34** derived from the aldehyde **33** proceeded with high face selectivity, but without diastereoselectivity at the alcohol bearing centre, to provide a 1:1 mixture of the alcohols **35**. These two alcohols subsequently converged following oxidation – reduction of the unwanted epimer.[20]



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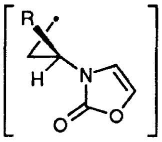

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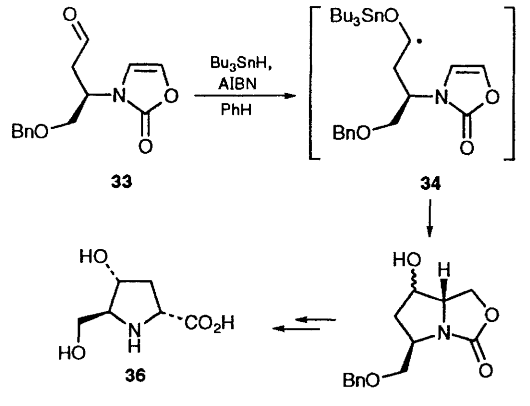
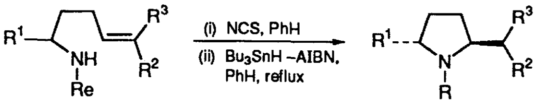


33 **34** **35** **36**

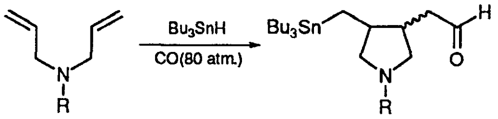
Scheme 4

An alternative approach to the stereoselective synthesis of *trans*-2,5-disubstituted pyrrolidines **38** involves cyclization of aminyl radicals generated from unsaturated amines **37**. The high stereoselectivity is noteworthy and contrasts with the results obtained when aminyl radicals are generated by other means.[21] Rate constants for the cyclization of aminyl radicals have been determined.[22]



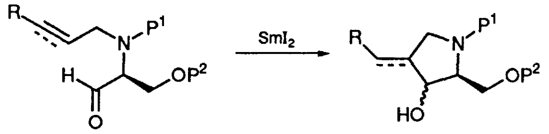
37 **38**

Treatment of 1,6-dienes **39** with tributyltin hydride under CO pressure leads to stannylformylation with concomitant ring closure, leading to the substituted pyrrolidines **40** in moderate yield.[23]



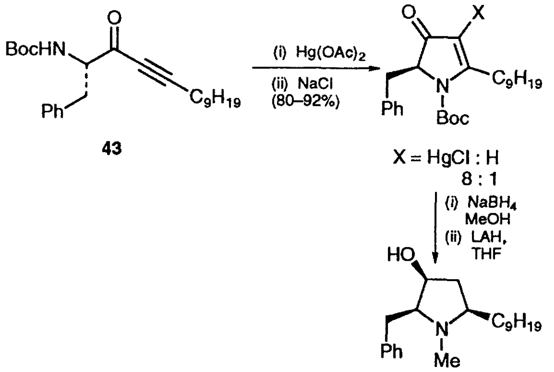
39 **40**

The samarium(II) iodide mediated ring closure of N-allyl and N-propargyl substrates **41** derived from L-serine has been investigated by Baldwin *et al.*, leading to 2,3,4-trisubstituted pyrrolidine derivatives **42**. However, in general the reactions are not diastereoselective.[24]



41 **42**

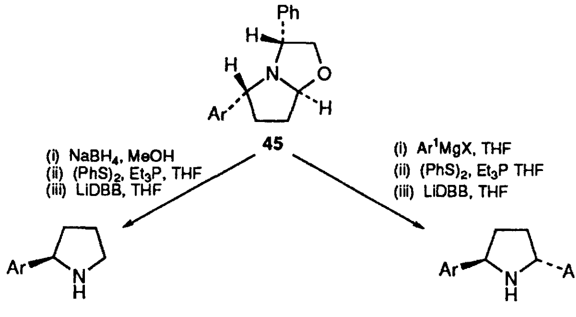
Hecht *et al.* have reported a concise synthesis of (+)-preussin **44** utilizing a mercury mediated 5-*endo-dig* cyclization of the ynone **43**, prepared in two steps from *N*-Boc-(*S*)-phenylalanine. The overall synthesis is complete in five steps.[25]



43 **44**

2.1.3 Pyrrolidines via miscellaneous methods

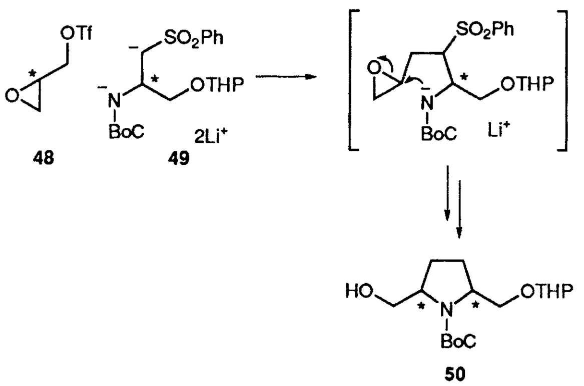
A number of alternative methods for the stereoselective synthesis of 2,5-disubstituted pyrrolidines have appeared during the period covered by this report. Thus, the bicycle **45**, which is



45 **46** **47**

readily prepared by addition of Grignard reagents to phenylglycinol-derived imines, functions as a precursor to either (*R*)-2-aryl **46** or (*R*,*R*) 2,5-bis(aryl) pyrrolidines **47**.[26]

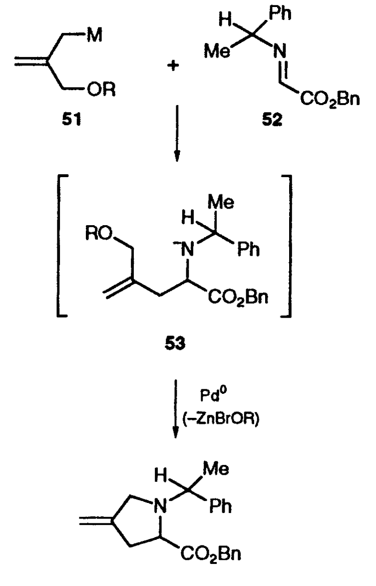
Saski *et al.* have reported a general method for the chirospecific synthesis of any enantiomer of the 2,5-disubstituted pyrrolidine derivatives **50**, by appropriate choice of the desired enantiomers of the starting glycidyl triflate **48** and the sulfone **49**. The reactioin proceeds via regioselective (>92%) attack of the sulfonyl carbanion of **49** at C-1 of the glycidyl triflate, followed by 5-*exo* cyclization onto the adjacent epoxide.[27]



48 **49**

50

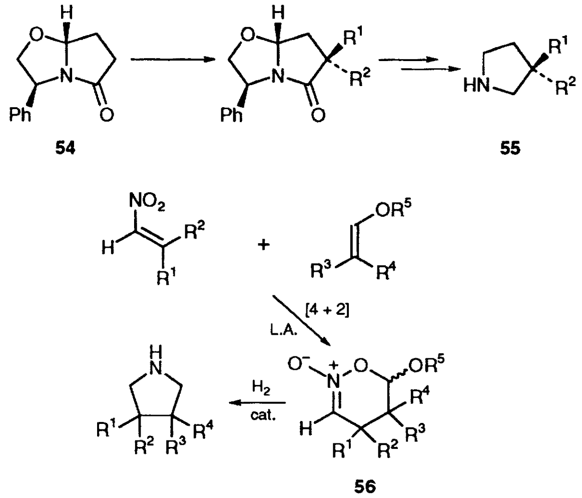
Two reports describing the synthesis of optically active 2,5-*trans*-disubstituted pyrrolidines by reaction of amines with 1,4-dibromo and 1,4-mesyloxy derivatives have appeared.[28,29] The synthesis of 3-methylenepyrrolidines by [3+2] cycloaddition reactions involving activated imines has already been described.[16] In a conceptually similar approach, the addition of the allyzinc reagent **51** to activated imines **52** bearing a chiral group on nitrogen, followed by Pd^0-catalysed cyclization of the adduct **53**, allows the one-pot preparation of 3-methylene pyrrolidines with good to excellent diastereoselectivity.[30]



51 **52**

53

Enantiomerically pure 3- and 3,3-disubstituted pyrrolidines **55** can be prepared by alkylation of the phenyl-glycinol derived bicyclic lactam **54**, followed by reduction (**Scheme 5**).[31] An alternative approach to 3,3- and 3,4-disubstituted pyrrolidines, reported by Denmark *et al.*, involves the Lewis-acid promoted [4+2] cycloaddition of nitroalkenes with vinyl ethers to afford cyclic nitronates **56** in good yield, followed by reduction (**Scheme 5**).[32]

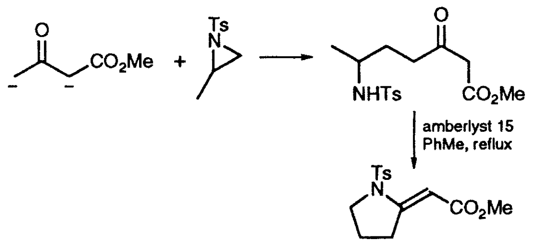


54 **55**

56

Scheme 5

N-Tosyl aziridines can be ring-opened with the dianion derived from a β-keto ester to provide pyrrolidine derivatives **57** after acid-mediated cyclization. In general the less-hindered (*E*)-isomers of **57** are formed.[33]



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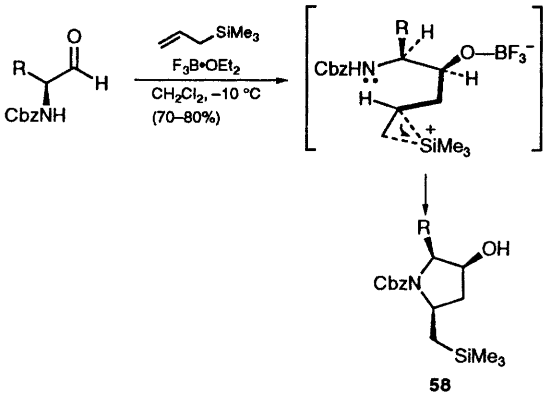
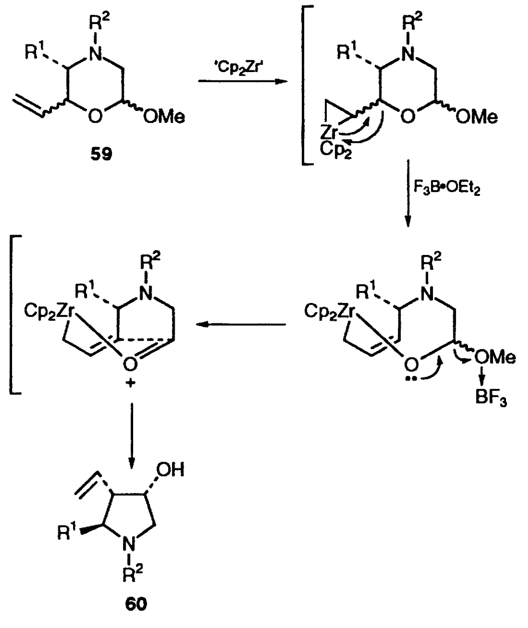
An interesting annulation reaction of N-Cbz-α-amino aldehydes with allyltrimethylsilane has been reported by Kiyooka *et al.*, leading to all-*cis* 2,3,5-trisubstituted pyrrolidines **58**. It is interesting that the *si*-face selection with $F_3B \cdot OEt_2$ results in



58

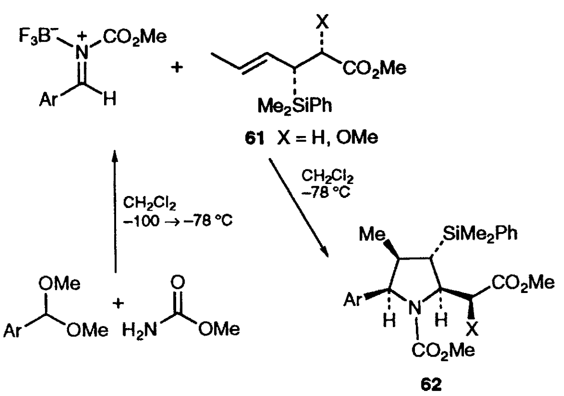
the 'chelation controlled' stereochemistry; cyclization of the resulting silicon cationic intermediate then provides the product.[34]

Taguchi *et al.*[35] have described a highly stereoselective zirconium-mediated ring contraction reaction of vinyl morpholine derivatives **59** (readily prepared from amino acids) leading to 2,3,4-trisubstituted pyrrolidines **60**. The stereochemistry of the final product is independent of diastereoisomers generated at any step in the synthesis of the starting vinyl morpholines **59**, and depends only on the absolute configuration of the starting amino acid (**Scheme 6**).[35]



Scheme 6

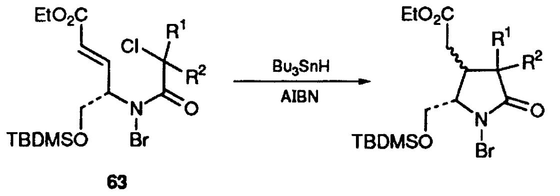
Panek *et al.* have described an asymmetric synthesis of the highly functionalized pyrrolidines **62** by low temperature condensation of chiral (*E*)-crotyl silanes **61** with *in situ* generated achiral N-acyl imines derived from aromatic aldehydes.[36] This study represents the first asymmetric addition of a chiral allyl silane to *in situ* generated imines.



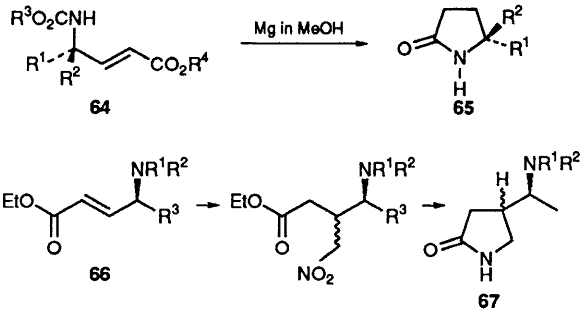
Finally, a review detailing the hetero Diels–Alder reaction with nitroso dienophiles has been published.[37] The adducts can be easily transformed into pyrrolidines via stereospecific reactions.

2.2 Pyrrolidinones

The use of radical chemistry for the preparation of lactams is currently undergoing a resurgence. In studies directed toward synthesis of the kainoids, Taylor *et al.* have investigated the radical cyclization of the serine-derived α-chloroamides **63**. In general, radicals substituted at the α-position (R^1, R^2 = Me, H; Ph, H; Cl_2) were found to cyclize more efficiently than the unsubstituted derivatives.[38] Zard *et al.* have reported the remarkable reagent system of nickel powder and acetic acid for effecting a similar cyclization. This particularly mild and selective method extends the scope of radical cyclizations of α-halo amides by allowing atom transfer cyclizations and intermolecular trapping of the cyclized radicals with radical traps, *i.e.* cyanide, TEMPO, O_2.[39]



Magnesium–methanol is a simple, yet selective, reagent for the reduction of α,β-unsaturated esters. This method has been used in a one-pot synthesis of 5-substituted 2-pyrrolidinones **65** from the N-alkoxycarbonyl γ-amino α,β-unsaturated carboxylates **64** without racemization.[40] An alternative approach to pyrrolidinones starting from γ-amino α,β-unsaturated carboxylates **66**, involves Michael addition of nitromethane followed by reduction of the nitro group with Raney nickel. Reasonable diastereoselectivity is observed in the addition leading to 3-aminoethyl substituted pyrrolidines **67** after spontaneous ring closure (**Scheme 7**).[41(a)]



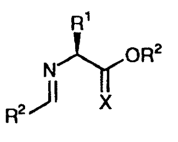
Scheme 7

Finally, pyrrolidines can be prepared in good yield by cyclization of β,γ-unsaturated amides using trifluoromethanesulfonic acid.[41(b)]

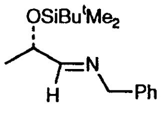
3 Six-membered rings

3.1.1 Piperidines via [4+2] cycloaddition reactions

The asymmetric hetero Diels–Alder reaction has recently been reviewed.[42] For the construction of piperidine rings, either hetero-dienes or hetero-dienophiles (imines) can be employed. A number of papers have appeared describing chiral aldimines derived from amino acids, *e.g.* **68**,[43] from ethyl lactate, *e.g.* **69**,[44] and from chiral iron-tricarbonyl complexes, *e.g.* **70**.[45] These chiral dienophiles react with electron rich dienes, *e.g.* Danishefsky's diene, under Lewis acid catalysis to afford 4-piperidinone derivatives with good selectivity.



68 X = O, H$_2$



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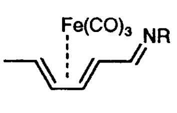

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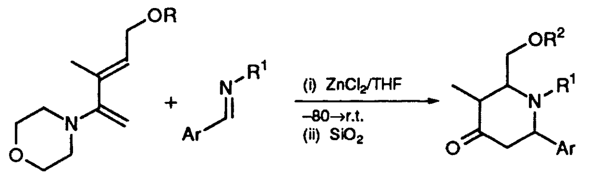
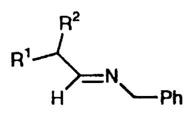
2-Amino-1,3-butadienes such as **71** react with non-activated achiral aldimines derived from aromatic aldehydes under the aegis of ZnCl$_2$ to afford 4-piperidinone derivatives **72** after hydrolysis. The stereoselectivity of the reaction is very high but strongly dependent on the nature of the imine.[46] Amino-dienes, such as **71** but bearing a proline-derived chiral amine, have been shown to undergo stereoselective aza-Diels–Alder cycloaddition with N-silyl aldimines to provide 4-piperidinone derivatives with high enantiomeric excess.[47]

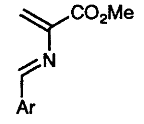


71 **72**

Unactivated imines, such as **73**, derived from alkyl aldehydes and bearing α-hydrogens, react smoothly with 2-siloxy-1,3-butadienes using TMSOTf as catalyst.[48] Gilchrist *et al.* have reported that the 2-azadiene **74** undergoes [4 + 2] cycloaddition with both electron rich (*e.g.* enamines) and electron poor dienophiles (*e.g.* methyl vinyl ketone). In general yields are moderate to poor, and in all cases the cycloadditions were highly regioselective but not stereoselective.[49]



73 R^1, R^2 = alkyl, H



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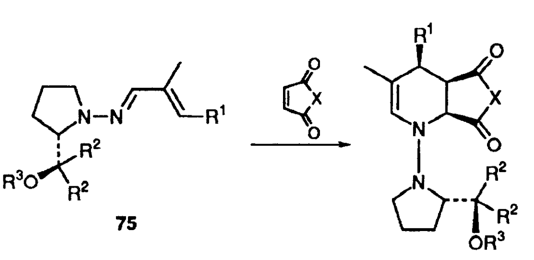
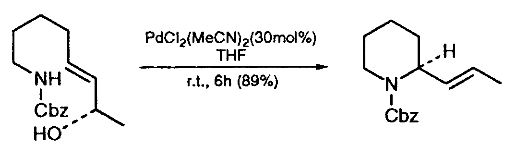
In an extension of his earlier work, Ghosez has reported that chiral aza-dienes **75** derived from α,β-unsaturated aldehydes and Enders' hydrazines cycloadd to cyclic dienophiles with high facial selectivities. The adducts can be readily converted into enantiopure piperidine derivatives.[50] To date, efforts to employ less reactive dienophiles, such as methyl acrylate or dimethyl fumarate, have proved unsuccessful.



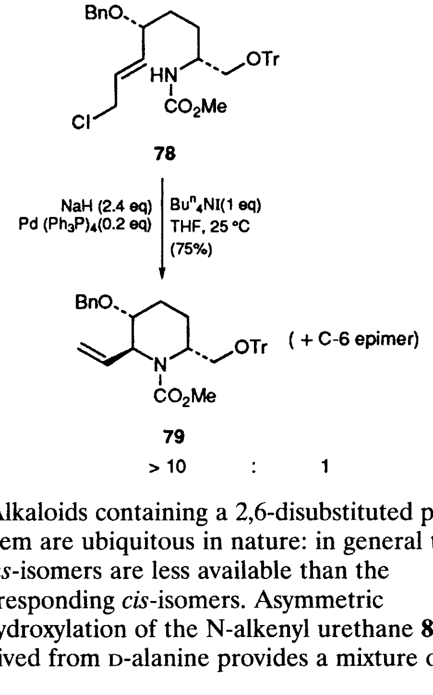
75

3.1.2 Piperidines via intramolecular cyclization

Cyclization of the homochiral urethane **76** under palladium catalysis occurs with efficient chirality transfer, affording the homochiral piperidine **77** in good yield.[51] A Pd^0-catalysed intramolecular N-alkylation forms the key step in a synthesis of piperidine alkaloids described by Tadano *et al.* Thus, treatment of the allylic chloride **78** with NaH in the presence of catalytic Pd^0 led to the piperidine derivative **79** with high diastereoselectivity.[52]

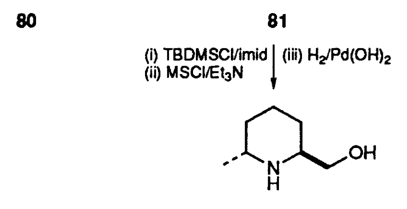


76 **77**



78 **79**

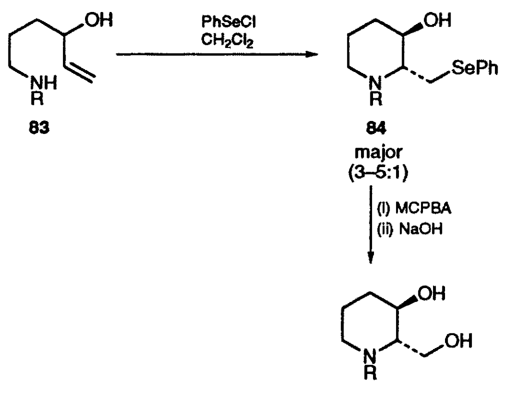
Alkaloids containing a 2,6-disubstituted piperidine system are ubiquitous in nature: in general the *trans*-isomers are less available than the corresponding *cis*-isomers. Asymmetric dihydroxylation of the N-alkenyl urethane **80** derived from D-alanine provides a mixture of



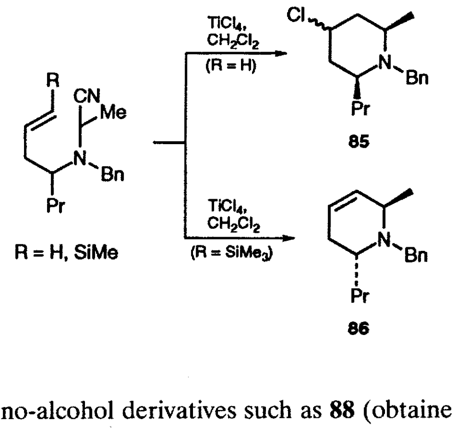
80 **81** **82**

diastereoisomeric alcohols **81** which, after protection of the primary alcohol and activation of the secondary alcohol, undergo ring closure to afford the *trans*-2,6-disubstituted piperidine **82** as the major (3:1) isomer.[53]

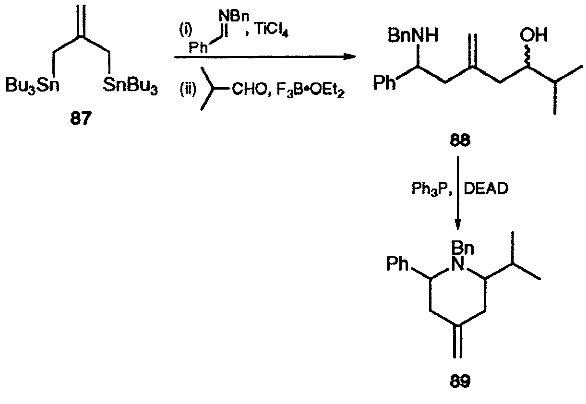
4-Hydroxy-5-hexenylamines such as **83** have hitherto proved fairly unreactive toward electrophilic cyclization. However, carbamates, sulfonamides, and amides of these precursors undergo efficient selenium-induced cyclization in the presence of silica gel and anhydrous K_2CO_3 to give predominantly *trans*-2-(phenylselenomethyl)-3-hydroxypiperidines **84** in moderate yield. The selenium moiety can be replaced by a hydroxyl group, following oxidation to the selenone and nucleophilic displacement with NaOH.[54]



An extremely versatile approach to either *cis*- or *trans*-2,6-disubstituted piperidines involves the stereoselective cyclization of an α-cyanoamine containing a vinyl group induced by $TiCl_4$. When the vinyl group is unsubstituted, the *cis*-diastereoisomer **85** is formed whereas when the vinyl group contains a silyl substituent the *trans*-isomer **86** is the exclusive product.[55]

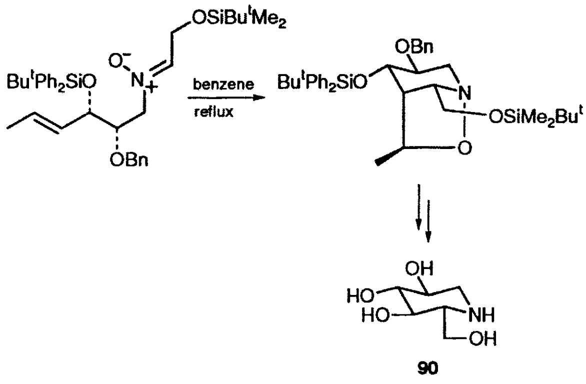


Amino-alcohol derivatives such as **88** (obtained by sequential addition of the bis-metallic reagent **87** to an imine, then an aldehyde under Lewis acid catalysis) can be cyclized under Mitsunobu conditions to provide piperidines, *e.g.* **89** although diastereoselectivity is low.[56]

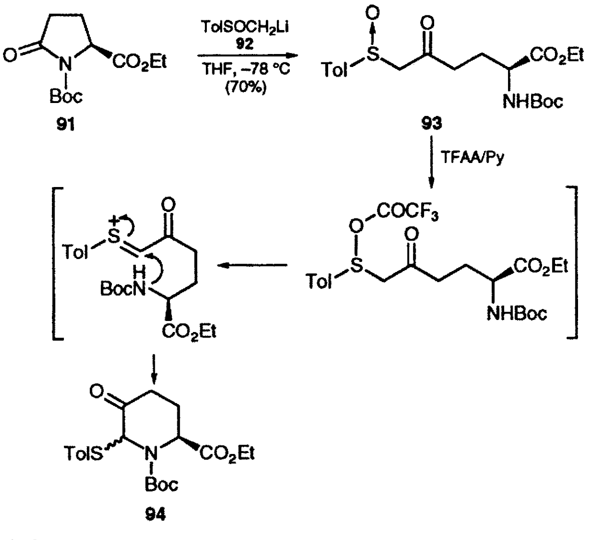


3.1.3 Piperidines via miscellaneous methods

Homes *et al.* have utilized an intramolecular nitrone cycloaddition to assemble the key piperidine ring in an enantioselective synthesis of the azasugar deoxynojirimycin **90**.[57] The aza-sugar skeleton is secured by the kinetic preference for a six-membered ring over a seven-membered ring during the initial carbon–carbon bond formation.



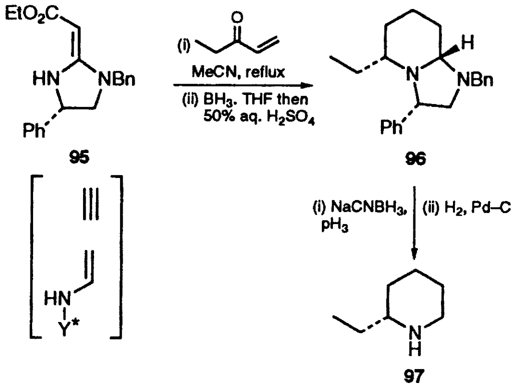
The use of pyroglutamic acid as a starting material for natural product synthesis is well established. Thus, *N*-Boc pyroglutamate ethyl ester **91** can be ring-opened with the lithiated sulfoxide **92**



Scheme 8

to first provide the adduct **93**. This material then undergoes Pummerer rearrangement with concomitant intramolecular cyclization leading to the 5-oxo pipecolic acid derivative **94** in near quantitative yield (**Scheme 8**). This route provides a new synthetic approach to this important class of natural products.[58]

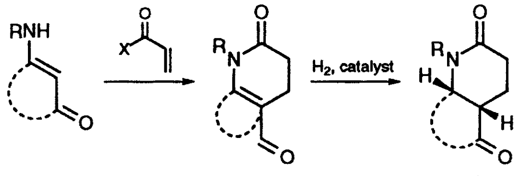
Jones *et al.* have reported a new route to homochiral piperidines such as **97** starting from the optically active enaminoester **95**. The route involves conjugate addition of **95** to an α,β-enone, followed by reductive cyclization–fragmentation to octahydroimidazopyridines **96**, and finally further reduction to remove the auxiliary atoms.[59] In this sequence **95** functions as a homochiral 'ethanol enamine' equivalent.



95 **96** **97**

3.2 Piperidones

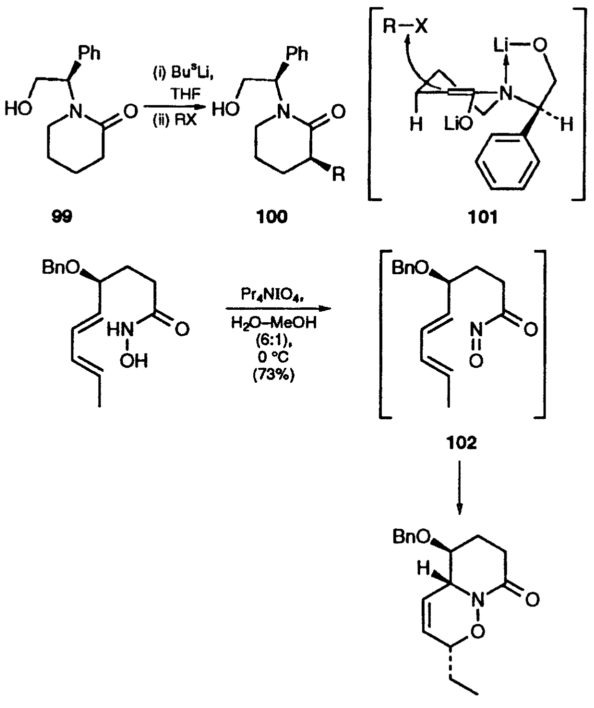
In a series of publications, Stille *et al.* have described a synthetic approach to the 2-piperidone derivatives **98** utilizing the aza-annulation of enamines with acryloyl chloride (**Scheme 9**). This strategy provides a convergent route for the construction of six-membered nitrogen heterocycles, and has been illustrated by the total synthesis of a range of alkaloids.[60–63]



98

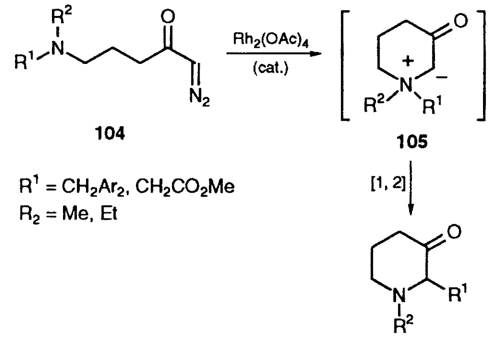
Scheme 9

Homochiral 3-substituted-2-piperidinone derivatives such as **100** are obtained by alkylation of the corresponding hydroxy lactam **99**; the excellent diastereoselection observed can be rationalized via the chelated amide enolate intermediate **101**.[64] An interesting approach to 2-piperidinone derivatives utilizes an intramolecular hetero Diels–Alder reaction from the chiral acylnitroso compound **102**. The diastereoselectivity of the process is significantly enhanced when the reaction is carried out in a aqueous solvent system, producing the major *trans*-isomer **103** in a 4.5:1 ratio. The lactam **103** was subsequently converted into (−)-pumiliotoxin C.[65]



99 **100** **101** **102** **103**

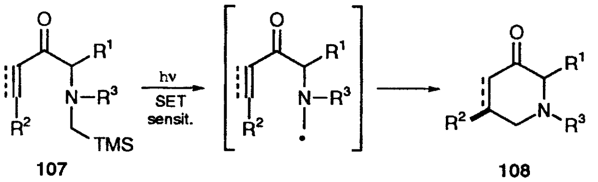
Two reports detailing novel approaches to 3-piperidinones have appeared. In the first of these, West *et al.* have utilized the Stevens rearrangement of ammonium ylides **105** to generate 2-substituted-3-piperidinones **106**. The ylides **105** can be generated by rhodium(II)-catalysed decomposition of amino-bearing diazo-carbonyl compounds **104**. In all the cases studied the carbon with the best radical stabilizing substituent was found to undergo migration.[66]



104 **105** **106**

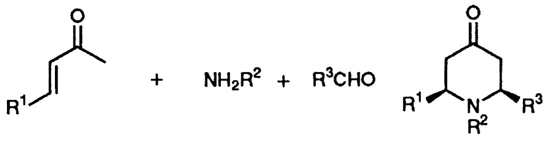
$R^1 = CH_2Ar_2, CH_2CO_2Me$
$R_2 = Me, Et$

Alternatively, α-silylamino-enones and ynones **107**, which are readily prepared from amino acids, undergo photoinduced radical cyclization under SET conditions to provide 3-piperidinone derivatives **108**. This 6-*endo* cyclization has been shown to proceed with high levels of diastereoselectivity.[67]



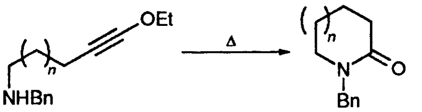
107 **108**

A particularly facile synthesis of 2,6-disubstituted 4-piperidinones **109** has been described by Edwards *et al.* where the condensation between an α,β-unsaturated ketone, an aldehyde, and an amine gives the products **109** with generally high *cis*-selectivity.[68] The yields are poor (20–35%), but the operational simplicity of a one-pot reaction should make this a useful synthetic method.



109

Thermolyses of amino ethylalkynyl ether derivatives **110** at 150°C produce the corresponding ketenes which can be trapped intramolecularly, leading to the lactams **111**. This methodology can be used to produce 6–15 membered lactams in good to excellent yield.[69]

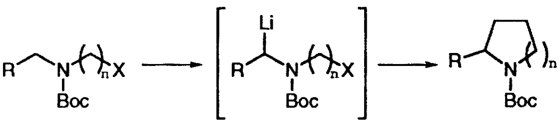


110 (n = 1–10) **111**

4 General methods for the construction of nitrogen heterocycles of varying ring sizes

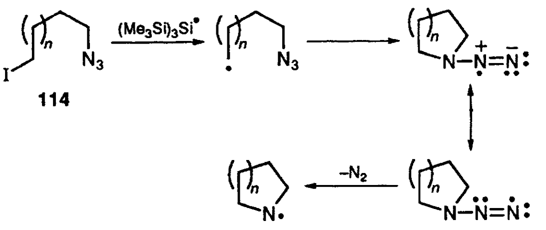
4.1 Monocyclic heterocycles

A review detailing the synthesis of medium-sized rings by ring expansion reactions has been published.[70] The use of iminophosphoranes as useful building blocks for the preparation of nitrogen heterocycles (aza-Wittig reaction) has also been reviewed.[71] Beak *et al.* have reported a general approach to nitrogen heterocycles via a lithiation/intramolecular cyclization sequence. Using this methodology a variety of easily prepared acyclic N-Boc amines **112** are transformed to the cyclic products **113**.[72] Epoxides as well as halides have been used as the leaving group X.



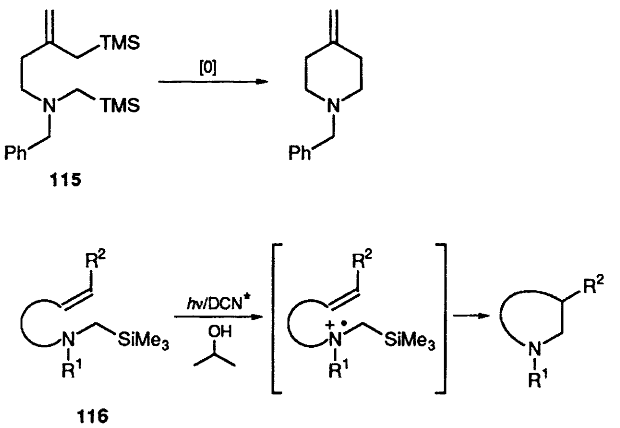
112 **113**

Kim *et al.* have reported novel cyclizations involving alkyl azides leading to nitrogen heterocycles.[73] In this approach, the heterocycle is generated by direct carbon–nitrogen bond formation via addition of an alkyl radical to an azide (**Scheme 10**). Of key importance to the success of this approach was the finding that azides are relatively inert to tris(trimethylsilyl)silyl radical, thus allowing chemoselective alkyl radical generation from an iodo azide **114** without concomitant azide reduction.



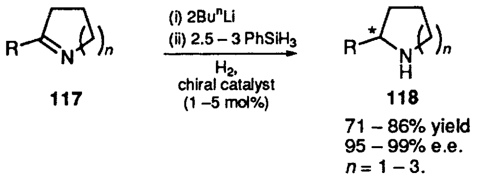
Scheme 10

The intramolecular cyclization of alkenes onto iminium ions provides a versatile method for the construction of nitrogen heterocycles. Mariano *et al.* have described the oxidation of α-silyl amines **115** as a mild, regioselective method of iminium ion generation. Both photoinduced single-electron transfer and metal-based oxidants can be used.[74] In related work, Pandey *et al.* have demonstrated that α-silyl amines such as **116** undergo efficient cyclization upon photoinduced electron transfer leading to pyrrolidines and piperidines. These authors invoke a delocalizaed α-silylmethylamine radical cation as an intermediate (**Scheme 11**).[75]

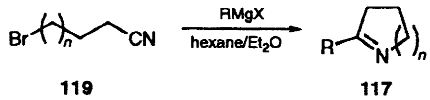


Scheme 11

Buchwald *et al.* have reported that cyclic amines **118** can be produced with very high e.e.'s by catalytic asymmetric hydrogenation of the corresponding cyclic imines **117** using a chiral titanocene catalyst. The reaction is general for cyclic imines of ring size 5–7 and exhibits a high degree of functional group compatibility.[76]

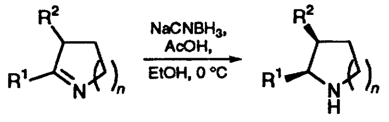


Cyclic imines such as **117** are conveniently prepared by the tandem addition–cyclization of Grignard reagents to ω-bromonitriles **119**. The use of hydrocarbon/ether solvent mixtures to suppress enolization of the nitrile is critical to the success of this reaction.[77]



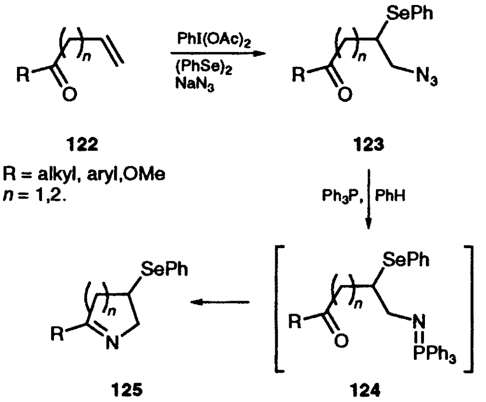
119 **117**

Cyclic imines bearing both C-2 and C-3 substituents such as **120** are useful precursors for the generation of *cis*-2,3-disubstituted pyrrolidines and piperidines **121**. These imines undergo stereoselective reduction (NaCNBH$_3$, AcOH, EtOH, 0°C) from the less-hindered face of the heterocycle, leading to the *cis*-products **121** with high selectivity.[78]



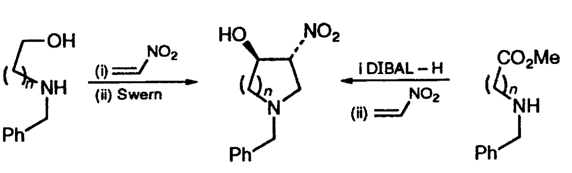
120 n = 1, 2 **121**

Terminal alkenes containing a remote carbonyl group, *e.g.* **122**, react with iodobenzene diacetate, diphenyl diselenide, and sodium azide to afford the products of *anti*-Markovnikov azidophenylselenenylation of the double bond, *e.g.* **123**. Addition of triphenylphosphine to these products produces the corresponding imines **125** bearing a pendant phenylselenyl moiety via the iminophosphorane intermediate **124** (Scheme 12).[79]



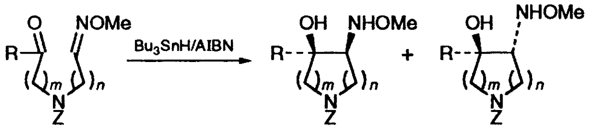
Scheme 12

Nitrohydroxylated pyrrolidines and piperidines **127** are conveniently prepared through a one-pot procedure involving initial Michael addition of a nitrogen nucleophile bearing a latent aldehyde to nitroethylene. The latent aldehyde is directly trapped in a subsequent nitroaldolization step. Both the amino alcohols **126** and the amino esters **128** can function as the nitrogen nucleophile.[80] The products can be transformed into a range of useful products, including amino alcohols.



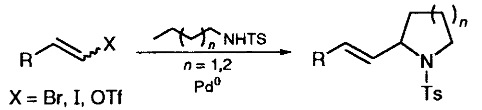
126 n = 1, 2 **127** **128**

Naito *et al.* have reported an alternative route to amino alcohols which involves intramolecular radical cyclization of oxime ethers which are tethered to an aldehyde or ketone **129**. The reaction is mediated by tributyltin hydride, and in general the *trans*-isomers predominate. Yields are moderate.[81]



129 m = 1,2,3
n = 1,2

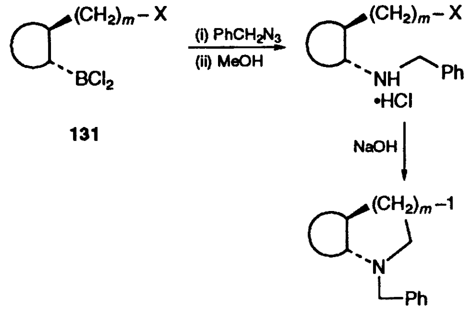
In a useful extension to earlier work, Larock and Weinreb have described a versatile synthesis of the 2-(1-alkenyl)pyrrolidine sulfonamides **130** starting from simple vinylic halides and unactivated olefinic sulfonamides.[82] The sequence proceeds via vinyl palladium addition to the olefin, followed by regioselective rearrangement to a π-allylpalladium intermediate, and subsequent intramolecular nucleophilic displacement of palladium.



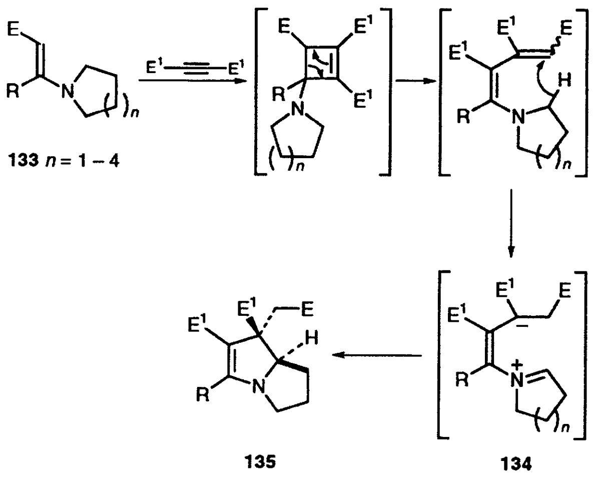
X = Br, I, OTf **130**

4.2 Bicyclic and polycyclic heterocycles

trans-Fused bicyclic pyrrolidines and piperidines such as **132** can be prepared from ω-halogenoalkyldichloroboranes **131**, following amination with benzylazide and intramolecular nucleophilic substitution; the precursors **131** are readily prepared either by hydroboration or Diels–Alder reaction.[83]



Viehe *et al.* have described a general, diastereoselective synthesis of the fused heterocycles **135** based on the 'α-cyclization of tertiary amines.'[84] The reaction is thought to proceed via initial [2 + 2] cycloaddition of DEAD to the enamine **133**, followed by ring-opening and hydrogen shift to generate the cyclization precursor **134** (Scheme 13).



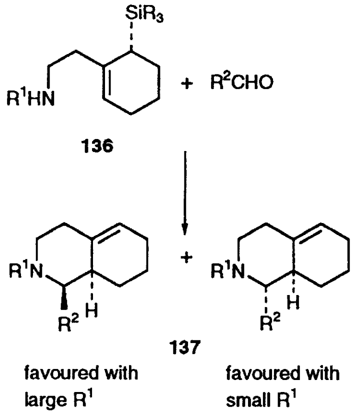
133 $n = 1-4$

135

134

Scheme 13

The intramolecular cyclization of a tethered nucleophile onto an iminium ion provides one of the most useful methods for the synthesis of nitrogen heterocycles. By careful choice of the group on nitrogen, Overman *et al.* were able to selectively prepare either stereoisomer of the 1-substituted octahydroisoquinoline **137** by reaction of the allylsilane **136** with an aldehyde.[85] The reversal of selectivity is attributed to non-bonded interactions between R^1 and R^2 in the cyclization transition state when R^1 is large.



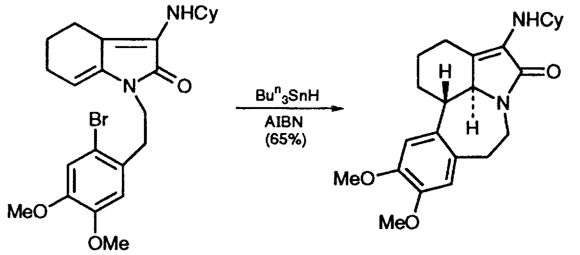
136

137

favoured with large R^1

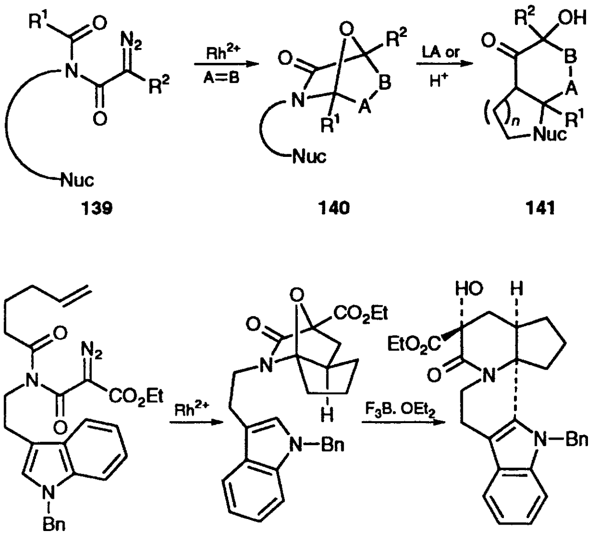
favoured with small R^1

Rigby *et al.* have utilized a relatively uncommon 7-*endo* radical cyclization process for construction of the hydroapoerysopine ring system **138**. None of the corresponding product derived from a 6-*exo* pathway was detected, and the formation of the *trans*-fused product is noteworthy.[86] The cyclization was unsuccessful under palladium-mediated cyclization conditions.



138

Finally, Padwa *et al.* have described a powerful approach to polyheterocyclic ring synthesis based on a tandem cyclization–(dipolar cycloaddition)–cationic cyclization sequence.[87] Thus the α-diazoimides **139** undergo cyclization–cycloaddition under the aegis of Rh^{2+} to provide oxabicyclic amides **140**. These useful cycloadducts contain a 'masked' N-acyliminium ion which is able to further react with an internal tethered nucleophile leading to more-complex heterocyclic systems (**141**). The approach is specifically illustrated by conversion of the α-diazoimide **142** into the tricycle **143** (**Scheme 14**).



139 **140** **141**

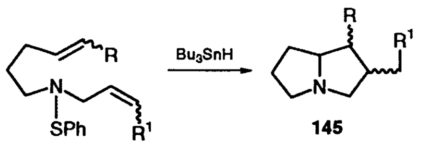
142 **143**

Scheme 14

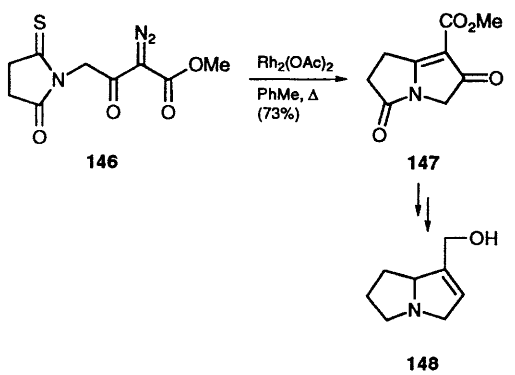
5 Pyrrolizidine, indolizidine, and quinolizidine ring systems

5.1 Pyrrolizidines

Aminyl radicals generated from sulfenamide precursors, *e.g.* **144**, undergo tandem radical cyclization in the presence of low concentrations of



144 **145**

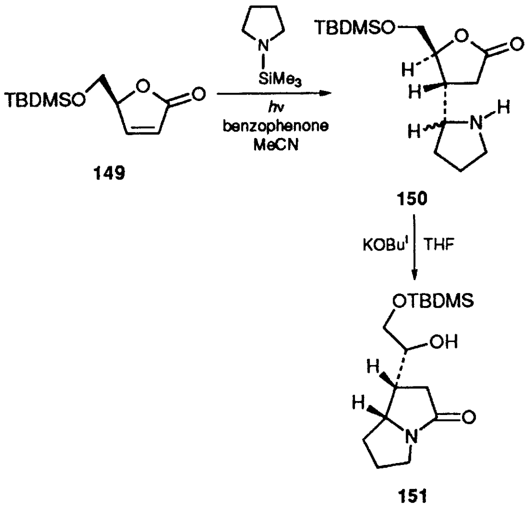


146 **147**

148

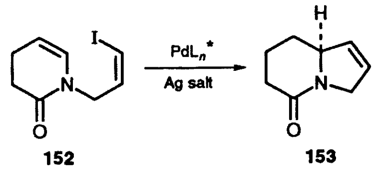
Bu_3SnH to provide the pyrrolizidine skeleton **145**.[88] Kim *et al.* have utilized a diazoketo ester-thioimide cyclization of the precursor **146** to generate the bicyclic lactam **147**, which was readily converted into (±)-supinidine **148**.[89]

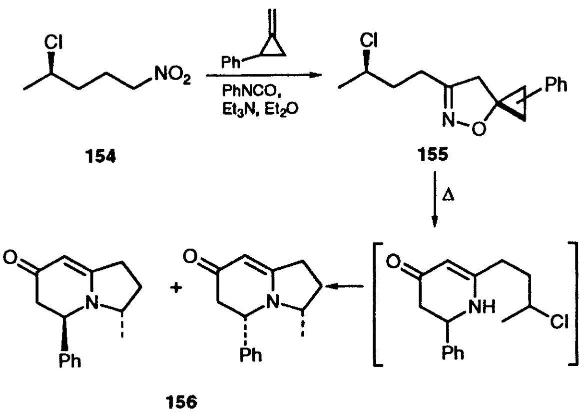
An unusual approach to the pyrrolizidine skeleton involves the photocatalysed addition of N-substituted pyrrolidines to the butenolide **149**. The adduct **150** undergoes cyclization in the presence of $KOBu^t$ to provide the lactam **151**, which has the ring skeleton and stereochemistry of the pyrrolizidine alkaloid lindelofidine.[90]



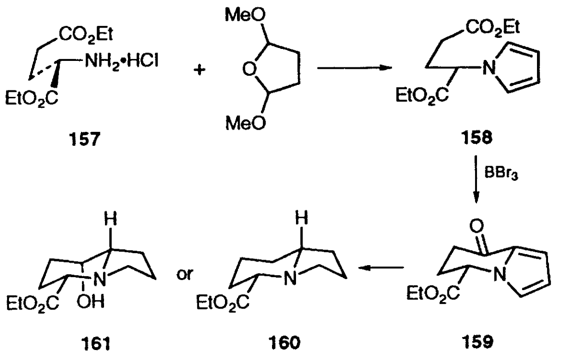
5.2 Indolizidines

Shibasaki *et al.* have used a catalytic asymmetric Heck reaction for the synthesis of the indolizidine derivative **153** starting from the prochiral alkenyl iodide **152**. Enantiomeric efficiencies of up to 86% have been obtained.[91] An alternative approach to homochiral indolizidine derivatives involves thermal rearrangement of isoxazolines, *e.g.* **155**, which are prepared from homochiral (*R*)-(−)-2-chloro-5-nitropentane **154**, via nitrile oxide cycloaddition.[92] The diastereoisomeric indolizidines **156** are obtained with 96% e.e. The enantioselectivity of the thermal rearrangement is dependent on the experimental conditions and on the structures of the chiral isoxazolines.



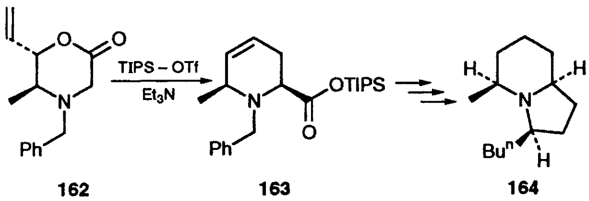


A number of synthetic approaches to the indolizidine skeleton involve substituted pyrroles as precursors. Thus, diethyl-L-glutamate. HCl (**157**) undergoes reaction with 2,5-dimethoxy tetrahydrofuran to provide the pyrrole **158** without racemization. Following Friedel–Crafts acylation (BBr_3), the homochiral keto-pyrrole **159** can be reduced to either the indolizidine **160** or the hydroxy derivative **161** depending on the catalyst used (**Scheme 15**).[93] A similar approach using L-glutamic acid and HCl/MeOH for the Friedel–Crafts step has previously been described by Taylor *et al.*[94]

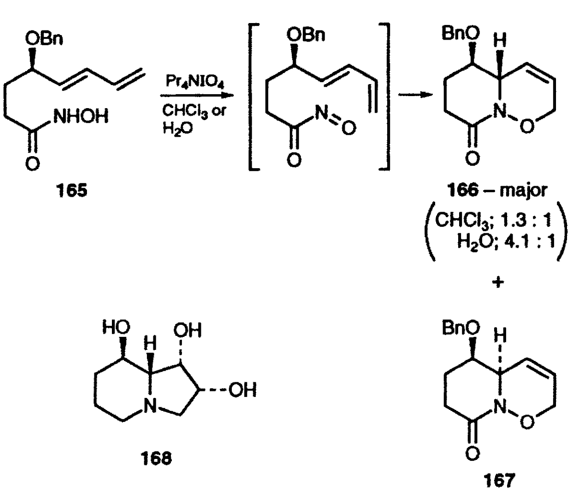


Scheme 15

Pipecolic acid derivatives contain useful functionality for further elaboration to the indolizidine skeleton. As the key step in a total synthesis of (+)-monomorine (**164**) Angle *et al.* have used the conformationally restricted Claisen rearrangement of the lactone **162** to produce the pipecolic acid derivative **163**. This intermediate was transformed into the natural product in just three operations.[95]

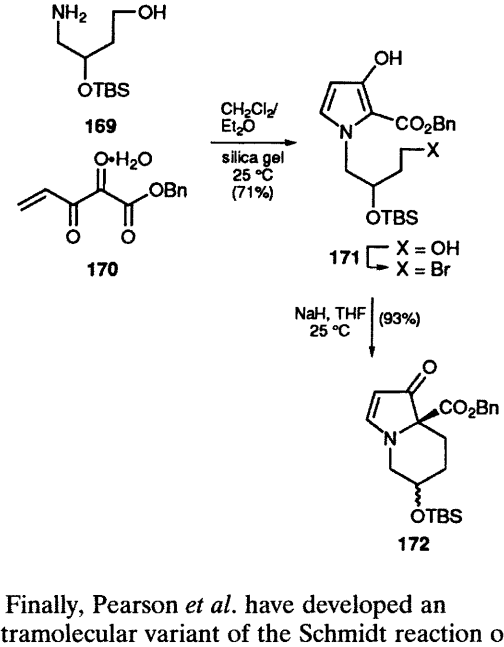


Both Keck[96] and Kibayashi[97] have described a new chiral route to (−)-swainsonine (**168**) and related compounds based on an intramolecular acylnitroso cycloaddition. The Kibayashi approach is summarized in **Scheme 16**. In both cases the diastereomeric ratio of the product 1,2-oxazines **166** and **167** was low when CH_2Cl_2 or $CHCl_3$ was used as solvent. However, some improvement in diastereoselectivity and yield was achieved when the reaction was conducted under aqueous conditions.[97]

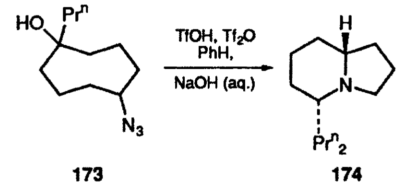


Scheme 16

Wasserman *et al.* have further extended the use of vicinal tricarbonyls to the synthesis of the indolizidine alkaloid (±)-slaframine. The key step in the synthesis is the intramolecular alkylation of the N-substituted 3-hydroxypyrrole derivative **171** to provide the indolizidine skeleton **172**. The hydroxy pyrrole **171** was itself prepared in a single step by reaction of the primary amine **169** with the vicinal tricarbonyl **170**.[98]

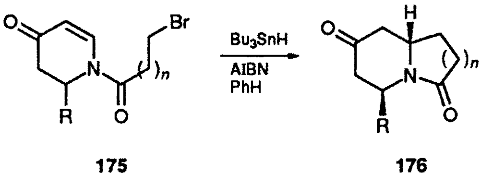


Finally, Pearson *et al.* have developed an intramolecular variant of the Schmidt reaction of azides with carbocations for the construction of nitrogen heterocycles. Thus, upon treatment with triflic acid the alcohol **173** undergoes ionization and the resulting carbocation is captured intramolecularly to produce an aminodiazonium ion intermediate. Carbon-to-nitrogen bond rearrangement then occurs providing the indolizidine **174** in 47% yield.[99] By appropriate choice of starting material a range of interesting bridged or fused nitrogen heterocycles (*e.g.* quinuclidines) can be prepared with reasonable efficiency.

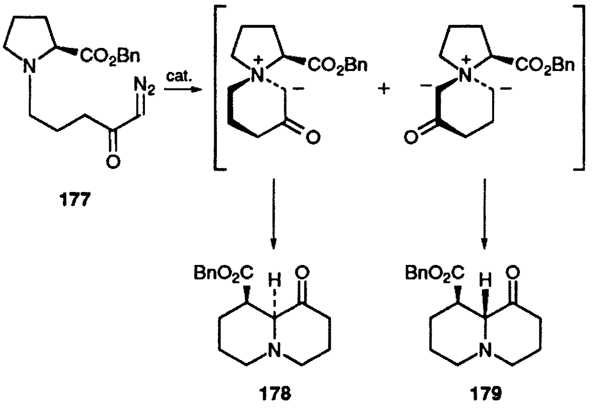


5.3 Quinolizidines

Beckwith *et al.* have described the highly diastereoselective formation of substituted indolizidines and quinolizidines **176** by intramolecular radical cyclization starting from the bromides **175**. In all cases studied the radical intermediate approaches the side of the double bond *anti*-to the substituent at C-2 with high selectivity.[100]

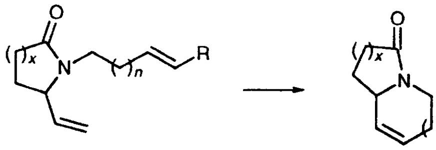


In an extension of earlier work. West *et al.* have utilized the Stevens [1, 2]-shift of cyclic ammonium ylides in an enantioselective route to the quinolizidine (−)-epilupinine. Thus, treatment of the diazo ketone **177** with $Cu(acac)_2$ provided the bicyclic ketone **179** with high diastereoselectivity (**178**:**179** = 5:95) and 65–75% e.e. (**Scheme 17**). Much lower diastereoselectivity (**178**:**179** = 1:3) was obtained using $Rh_2(OAc)_4$ as the catalyst.[101]



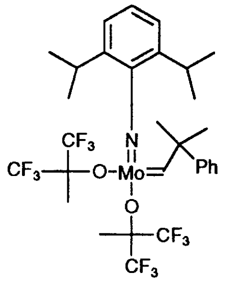
Scheme 17

Finally, Martin *et al.* have disclosed a novel technique for the efficient synthesis of fused nitrogen heterocycles based on the molybdenum alkylidene-catalysed metathesis of the α,ω-dienes **180**. These precursors are readily prepared from succinimide and glutarimide in three steps, and they undergo efficient ring-closing methathesis in the presence of the catalyst **182** to provide the corresponding bicycles **181** in 65–90% yields.[102]



180 $x = 1,2$
$n = 0-3$

181



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Thus, using this methodology the feasibility of constructing the pyrrolizidine, indolizidine, quinolizidine, pyrrolidinoazocine, and piperidinoazocine ring skeletons has been demonstrated.

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