REVIEW

Saturated nitrogen heterocycles

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Reviewing the literature published in 1999. Continuing the coverage in *J. Chem. Soc.*, *Perkin Trans. 1*, 1999, 2553.

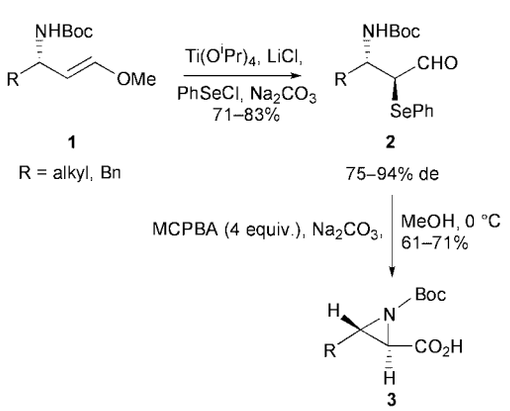
1 Introduction

This review covers the literature relating to saturated nitrogen heterocycles published in 1999. The classification of the chemistry described is similar to that found in the previous survey in ref. 1.

2 Three-membered rings

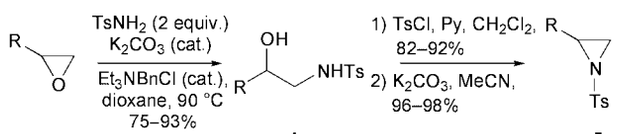
A new method for the deprotection of *N*-tosylaziridines has been described, using sodium naphthalenide to afford the corresponding N–H compounds.[2] The conditions were compatible with aromatic groups and benzyl ethers, but decomposition of the substrate was seen when a *tert*-butyl ester or benzoate group was present at the C-2 position.

Phenylselenyl chloride has been added stereoselectively to methoxyalkenes **1** derived from *N*-protected chiral amino acids (Scheme 1).[3] The aldehydes **2** thus obtained could be transformed into aziridinecarboxylic acids **3** in good yield by treatment with MCPBA in the presence of sodium carbonate.



Scheme 1

A simple but effective approach to the synthesis of *N*-tosylaziridines has been reported,[4] in which toluene-4-sulfonamide was added to epoxides under phase transfer conditions (Scheme 2). The ring-opened intermediates **4** were converted to the desired products **5** using standard methods.



R = CH_2OPh, n-C_6H_{13}, CH_2OBn

Scheme 2

Davis and co-workers have published a full account of their asymmetric aza-Darzens approach to aziridine-2-carboxylate esters **8** and **9**, starting from *N*-sulfinylimines **6** (Scheme 3).[5] In reactions with the lithium enolate of methyl α-bromoacetate, a range of *cis*-aziridines **7** was prepared in good yields and diastereomeric excesses. The configuration of the products was controlled by the sulfur stereogenic center. Oxidation of the *N*-sulfinylaziridines **7** with MCPBA readily afforded the *N*-tosyl analogues **8**. Alternatively, the sulfinyl group could be removed under acidic or basic conditions, yielding N–H aziridines **9**. Davis and M^{c}Coull have used the same approach in a synthesis of aziridine-2-phosphonates and azirinyl phosphonates.[6]

Atkinson's reagent has been used for the regioselective aziridination of polyenes (Scheme 4).[7] Ring formation occurred preferentially at the 2,3-double bond of geraniol, directed by the hydroxy group; geranyl acetate was predominantly aziridinated at the 6,7-double bond. Reduction of the *N*-quinazolinylaziridines **10** and **11** to their N–H analogues **12** and **13** was effected with dissolving metals or lithium naphthalenide. This methodology has been exploited in the synthesis of squalene synthase inhibitors.[8] Atkinson himself has recently written an excellent review on the use of 3-acetoxyaminoquinazolinones as aziridinating agents.[9]

3,3-Pentamethylenediaziridine **14** has been shown to aziridinate α,β-unsaturated amides **15** upon pre-treatment with *n*-butyllithium (Scheme 5).[10] Interestingly, the *cis*-aziridines **16** were isolated as the only products.

Pyridinium tribromide was reported as a new entry to the list of catalysts for the aziridination of alkenes with Chloramine-T (Scheme 6).[11] A potential advantage of this reagent is that it allows the aziridination of electron-deficient alkenes to proceed, which had not been reported for the previously described systems. Shortly afterwards, Sharpless suggested that the *N*-chloramine salt of *tert*-butylsulfonamide **17** could serve as an alternative for Chloramine-T in these reactions (Scheme 7).[12] Removal of the *tert*-butylsulfonyl group from derivatives of the products **18** could be easily achieved with triflic acid in dichloromethane in the presence of anisole.

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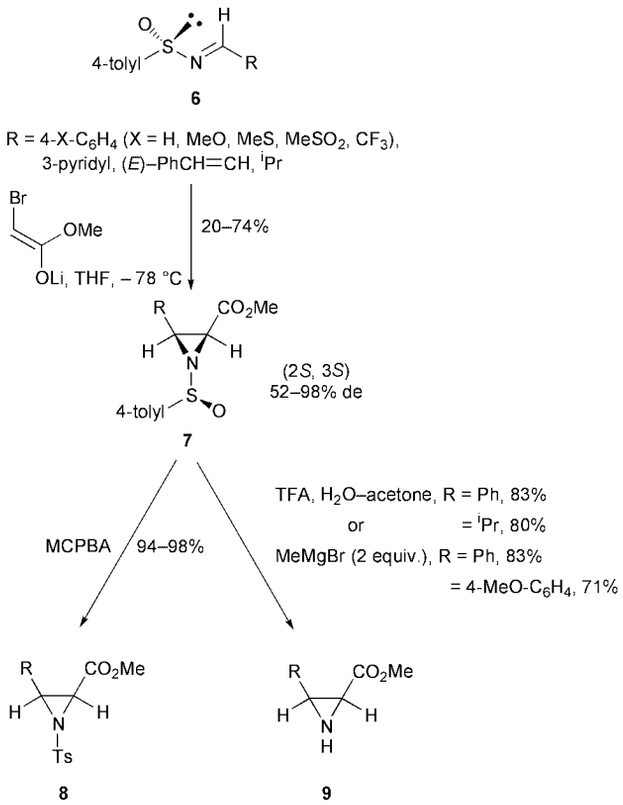
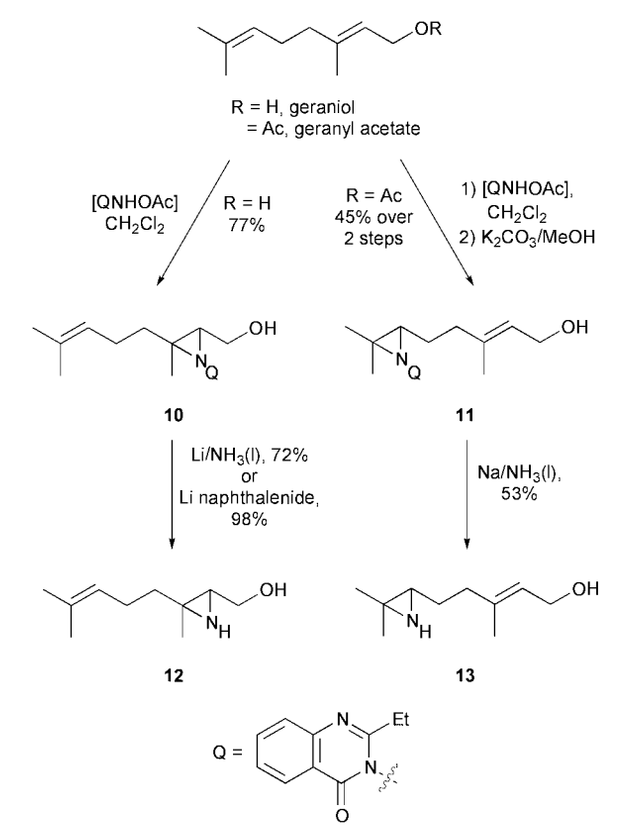
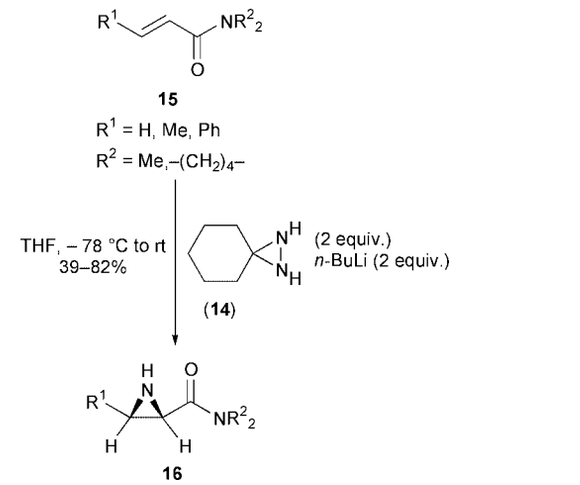


Scheme 3

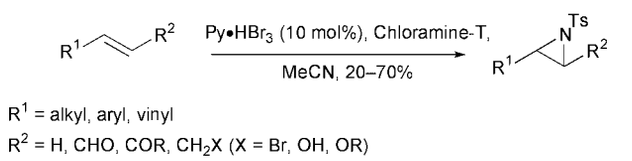


Scheme 4

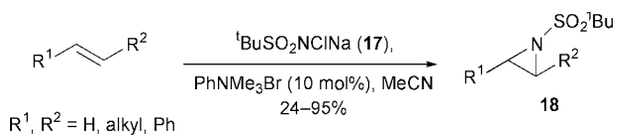
A variety of potential replacements for the well-known nitrogen-transfer reagent (tosyliminoiodo)benzene (PhINTs) have been described. Replacement of the tosyl group with imidazolyl- or pyridylsulfonyl yielded **19** and **20** respectively.[13] These reagents offer scope for chelation to metal catalysts, thus leading to the possibility of enantioselective nitrogen transfer. Iodonium ylide **21** was designed to contain an intramolecular



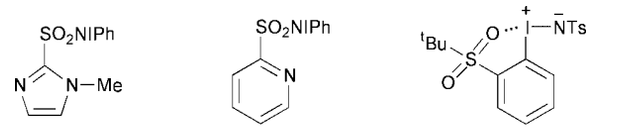
Scheme 5



Scheme 6



Scheme 7

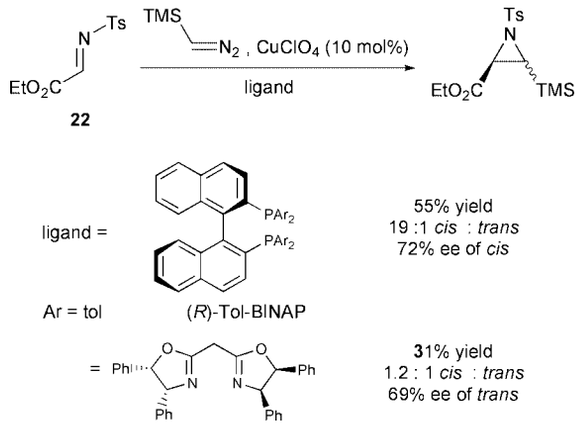


secondary bond, in order to prevent formation of the extended polymeric aggregates seen with PhINTs due to intermolecular secondary bonds.[14] Ylide **21** was found to be more soluble than PhINTs in common organic solvents, so homogeneous conditions were possible for its reactions with alkenes. Lower reaction temperatures could also now be explored.

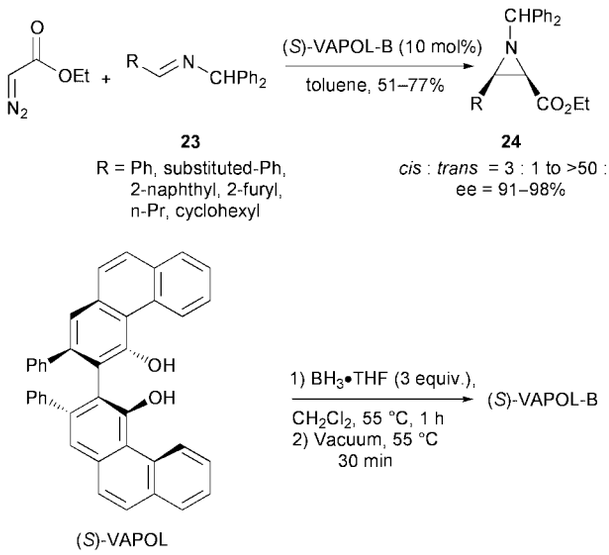
N-Tosylimino ester **22** has been reacted with trimethylsilyldiazomethane in the presence of catalytic BINAP– and bisoxazoline–copper salts, giving *cis*- and *trans*-aziridines with moderate enantiomeric excesses.[15] The best results are shown in Scheme 8. It was thought that nucleophilic attack of trimethylsilyldiazomethane onto the Lewis acid-activated imine was involved, rather than a carbene based mechanism.

A range of *N*-benzhydryl imines **23** was tested in reactions with ethyl diazoacetate in the presence of a chiral VAPOL-boron Lewis acid (Scheme 9).[16] Good to excellent diastereoselectivity and excellent enantiomeric excesses for the *cis*-aziridines **24** were observed, thus providing the first generally applicable method for catalytic asymmetric aziridination.

Lanthanide triflates have been demonstrated to catalyze the aziridination of imines with diazo compounds in various protic solvents.[17] The products were predominantly or exclusively *cis*-isomers. Ochiai and Kitagawa have published full details on the stereoselective synthesis of 2-acylaziridines from activated imines and monocarbonyl iodonium ylides.[18] The reaction of zincioallene **25** with *N*-benzyl imines **26** has been described, affording *trans*-propargylic aziridines **27** in moderate to good yields (Scheme 10).[19] Conversely, the reaction of **25** with an



Scheme 8

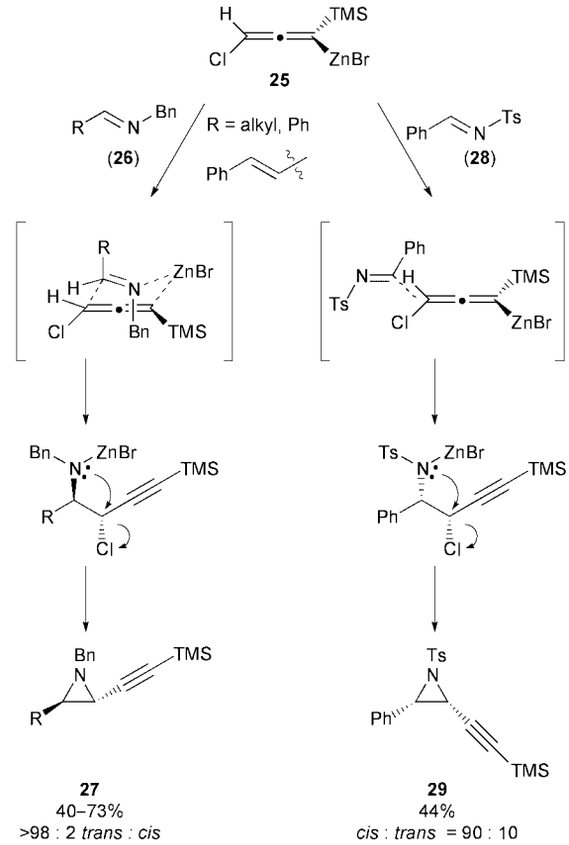


Scheme 9

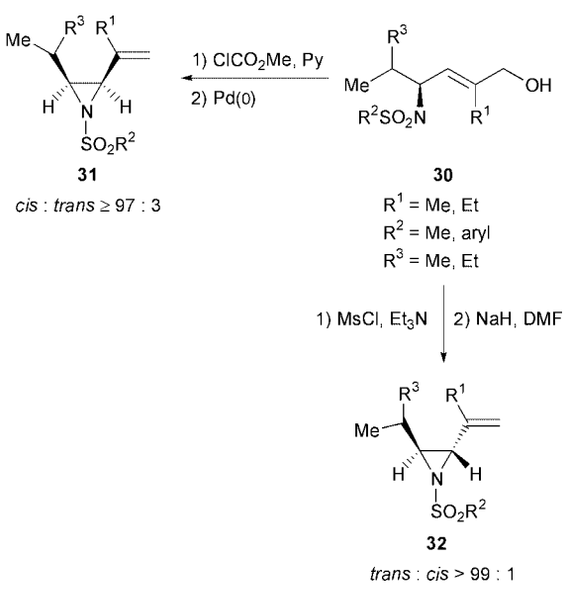
N-tosyl imine **28** yielded a *cis*-aziridine product **29**. Chelated and non-chelated transition states were suggested to explain the divergent stereochemistry for the non-activated and activated imines.

Expanding upon work published in 1998, Ibuka and co-workers have now shown that sterically congested 2,3-*cis*- (**31**) and 2,3-*trans*-2-alkenyl-3-alkylaziridines (**32**) can be prepared from *N*-protected (*E*)-alkyl-4-aminoalk-2-en-1-ols **30** (Scheme 11).[20] Yields for the ring closures were good to excellent (68–95%). It was noted in another communication that (*Z*)-amino allylic alcohol derivatives yielded 2,3-*cis*-2-vinylaziridines (palladium route) or 3-pyrrolines (mesylate route).[21] The same group has reacted enantiopure 3-substituted 2-ethynylaziridines **33** and **36**, prepared by standard methods,[22] with organocuprates, yielding chiral amino allenes **34** and **37** (Scheme 12).[23] In an unprecedented reaction, the amino allenes could be treated with aryl iodides in the presence of a palladium(0) catalyst to yield congested 2-alkenylaziridines **35**.[24] The ring closures were suggested to proceed through η^3-allylpalladium complexes **38** and **39**, which would be sufficiently electrophilic to suffer nucleophilic attack from the nitrogen (Scheme 13).

A number of cyclic diazoamides **40** have been reported to form the diazabicyclo[3.1.0]hexane core **41** upon treatment with rhodium(II) acetate (Scheme 14).[25] The piperidine-containing diazoamide was found to be so reactive that it could not be isolated, and afforded the product **41** without the need for catalysis. Three possible mechanisms were postulated, as shown in Scheme 15, including metal catalyst-induced cyclic ylide (**42**) formation, or triazole (**43**) formation (a non-catalyzed route).



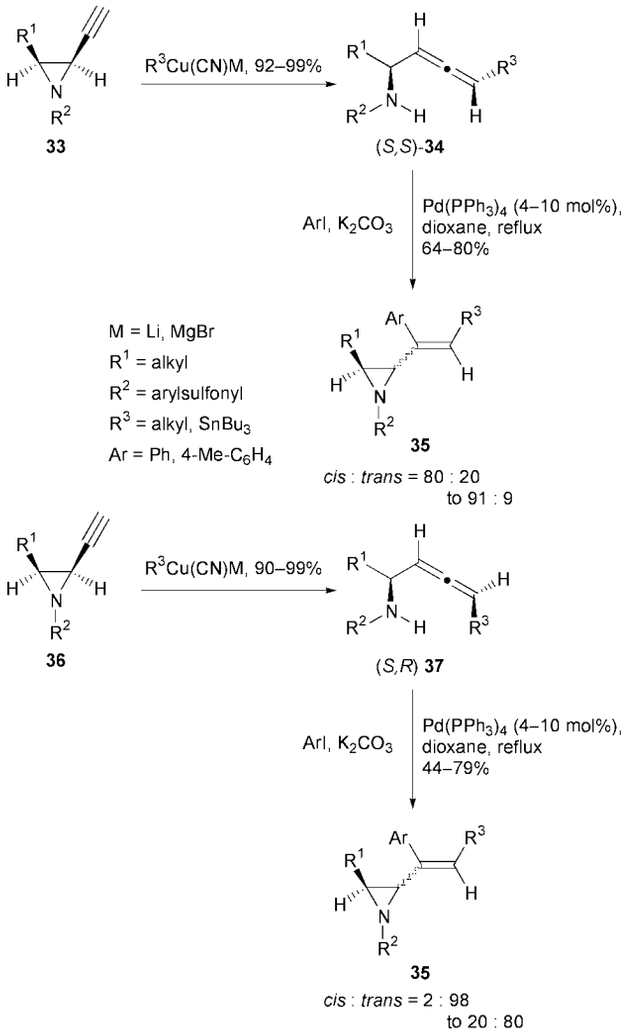
Scheme 10



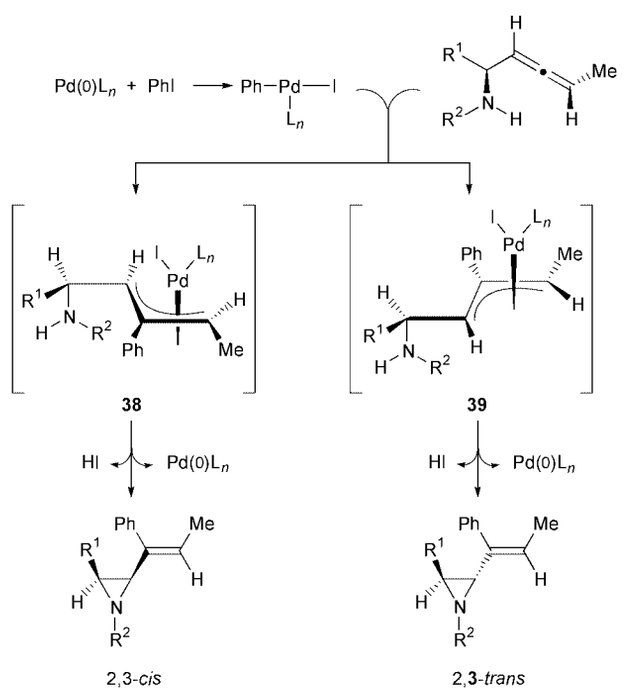
Scheme 11

A number of papers concerning azirines have appeared in the literature. Full details of the asymmetric synthesis of 2*H*-azirine-2-carboxylate esters have been published by Davis and co-workers.[26] A new general synthesis of 2-halo-2*H*-azirines **46** from phosphorus ylides **44** was reported (Scheme 16).[27] Intermediate alkenes **45** were prepared from **44** in good yield, *via* a halonium ion mechanism. Upon heating in heptane, the alkenes were completely converted into azirines **46**. The final products were isolable, but unstable.

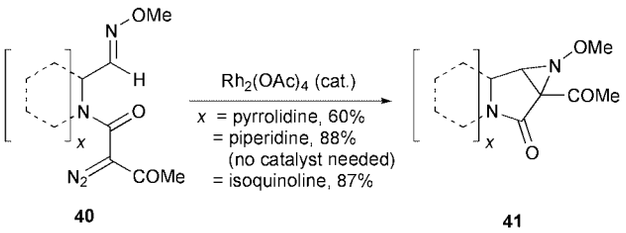
A systematic study of the reactions of methyl 2-aryl-2*H*-azirinecarboxylates **47** with nucleophiles has been described.[28] Of the nucleophiles tested, only reactions with thiols and secondary amines consistently gave the same products (**48** or **49** in Scheme 17). Nucleophilic attack occurred at the C=N bond



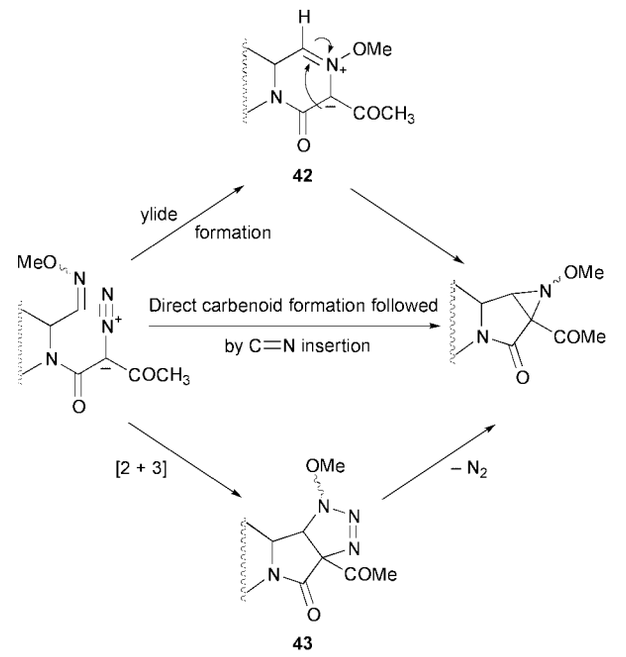
Scheme 12



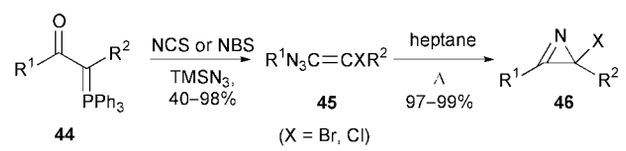
Scheme 13



Scheme 14

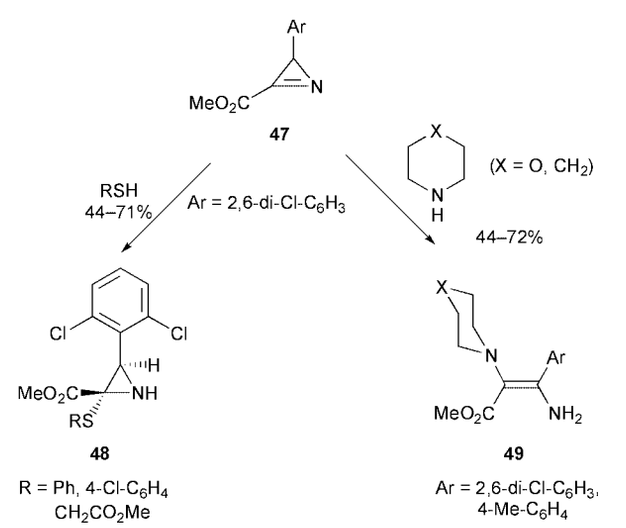


Scheme 15



R^1 = CO_2Me, CO_2Et, Ph, COPh, Me
R^2 = CO_2Me, CO_2Et

Scheme 16



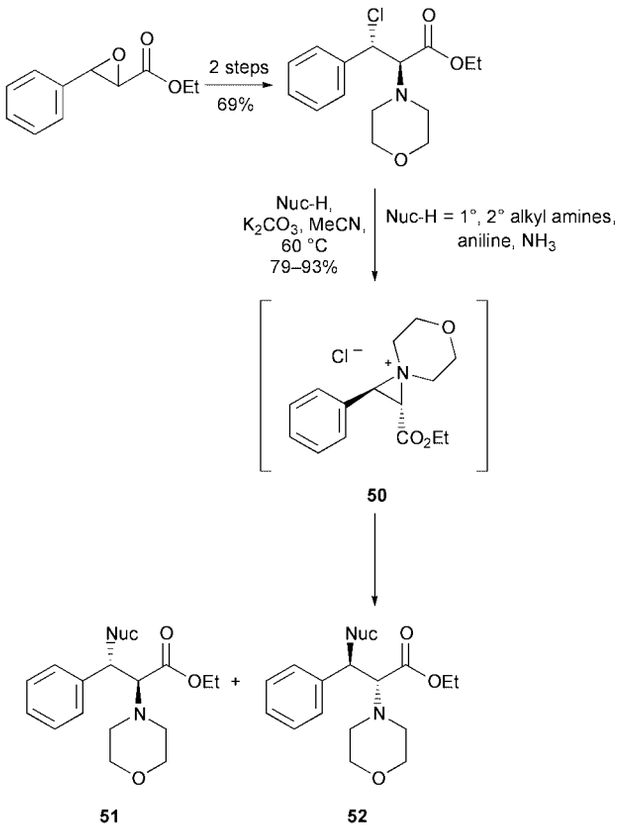
R = Ph, 4-Cl-C_6H_4
CH_2CO_2Me

Ar = 2,6-di-Cl-C_6H_3, 4-Me-C_6H_4

Scheme 17

of the azirine. Reactions with alcohols, enamines and activated methylene compounds were unpredictable.

Sharpless and Chuang have demonstrated stereospecific and regioselective ring-opening of an aziridinium ion **50** with various amines, generating α,β-diamino esters **51** and **52** (Scheme 18).[29] A potential advantage of aziridinium ions over aziridines is that they may be opened at moderate temperatures under



Scheme 18

neutral or basic conditions; aziridines need activation by an acidic agent, often precluding the use of many useful nucleophiles.

3 Four-membered rings

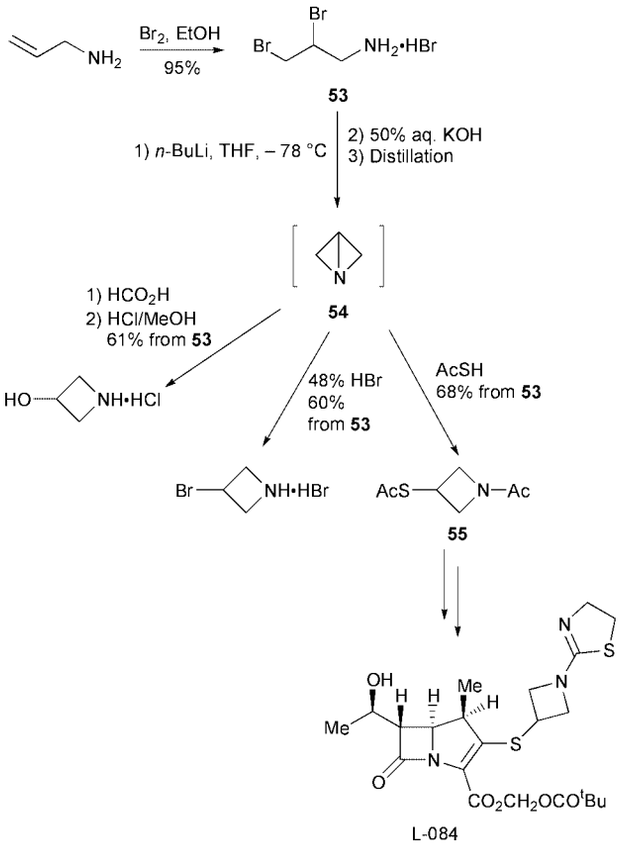
A novel, short synthetic route to the remarkably strained molecule 1-azabicyclo[1.1.0]butane **54** has been reported (Scheme 19).[30] This was then used as a versatile intermediate for the preparation of various azetidines, including **55**, which is a fragment of the new oral antibiotic 1β-methylcarbapenem L-084.

Chiral amino allenes **56** have been converted into 2,4-*cis*-azetidines **57** in a palladium(0)-catalyzed reaction (Scheme 20).[31] In contrast to the aziridinations of amino allenes described earlier (see Scheme 12), the best stereoselectivities were obtained using DMF as the solvent.

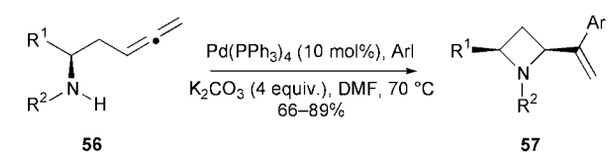
4 Five-membered rings

A chiral synthesis of 2,3,5,5-tetrasubstituted pyrrolidines **61** has been reported, in which an allylsilyllithium species **58** reacts with enantiopure aziridines **59**, yielding predominantly the *syn*-intermediates **60** (Scheme 21).[32] Silicon-directed cyclization of **60** occurred upon treatment with toluene-4-sulfonic acid, affording enantiopure products **61**. The silyl group could then be oxidatively cleaved to a hydroxy group, or the tosyl group could be removed with sodium naphthalenide.

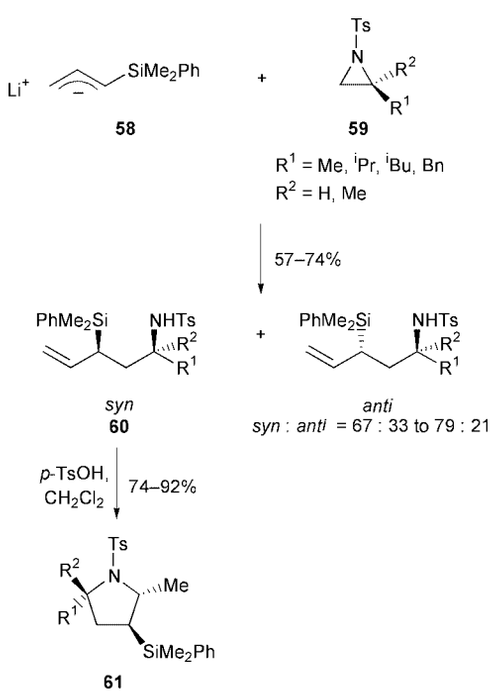
Proline has been elaborated to enantiomerically pure α-alkylprolines *via* 2-trichloromethyloxazolidin-5-one **62** (Scheme 22).[33] This intermediate was produced as a single diastereomer from L-proline by treatment of the amino acid with trichloroacetaldehyde. Alkylation at the 4-position was highly diastereoselective, and the products **63** were found to yield *N*-formyl-2-alkylproline methyl esters **64** upon treatment with sodium methoxide. Alternatively, free amino acids could be formed by standard hydrolysis of **63**.



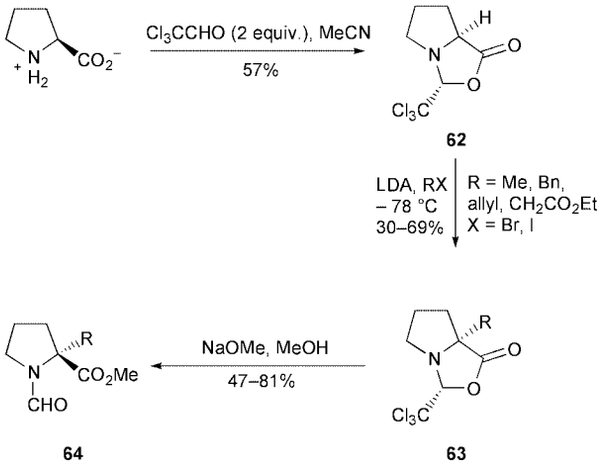
Scheme 19



Scheme 20



Scheme 21

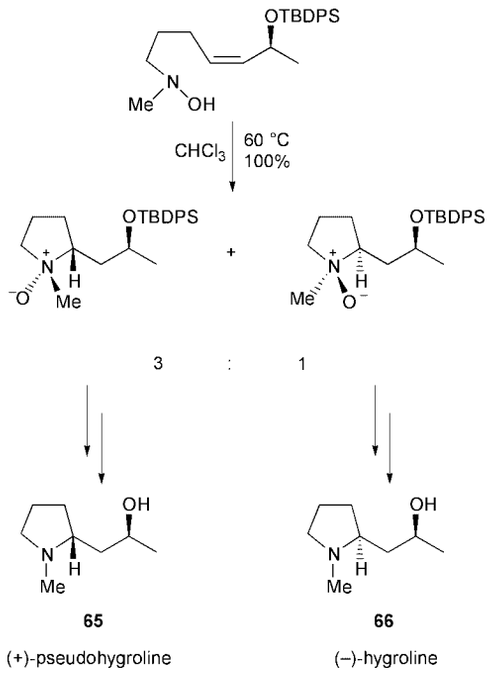


Scheme 22

A reverse-Cope elimination has been employed in the synthesis of (−)-hygroline **66** and (+)-pseudohygroline **65** (Scheme 23).[34] Contrary to earlier studies, which suggested that substituents at the distal end of the participating alkene precluded reaction, allylic oxygen groups were found to facilitate the cyclization. The stereoselectivity however, was found to be curiously low.

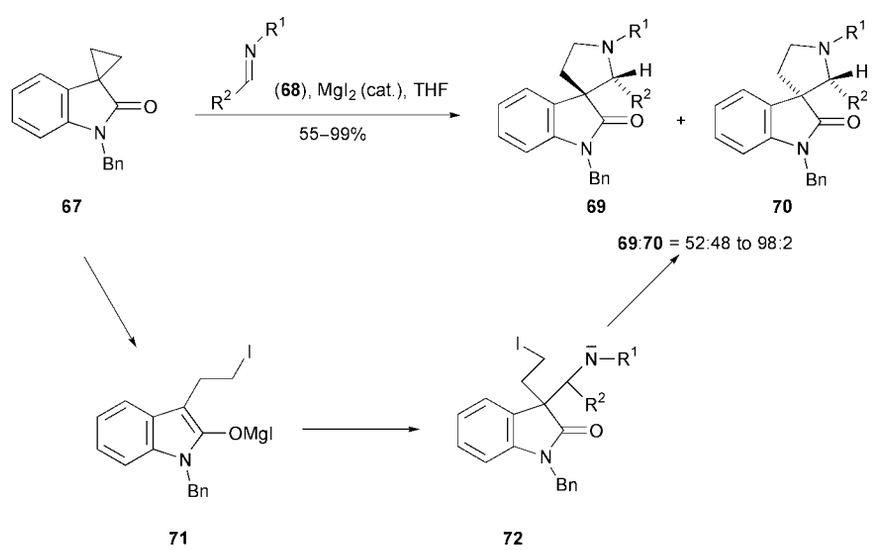
Ring expansion of cyclopropanes **67** by aldimines **68** has allowed the preparation of spiro[pyrrolidine-3,3′-indolin-2-one] **69** (Scheme 24).[35] Magnesium iodide was found to be the optimal catalyst for the transformation. It was suggested that ring-opening of the cyclopropane was first effected, generating enolate **71**, which could then react with imine **68** to give anion **72**. This could finally undergo alkylative cyclization, affording pyrrolidines **69** and **70**. Preliminary observations suggested that the ring expansion could be applicable to a much wider range of substrates.

Diastereoselective iodoaminations of 3-acetyloxybut-1-enylamines **73** and **75** have been performed, yielding pyrrolidines **74** and **76**.[36] The biphasic conditions shown in Scheme 25 were essential for high yields in short reaction times. Selenocyclizations of homoallylic sulfonamides have also been reported, but the stereochemical outcome of the pyrrolidine products was somewhat unpredictable.[37]



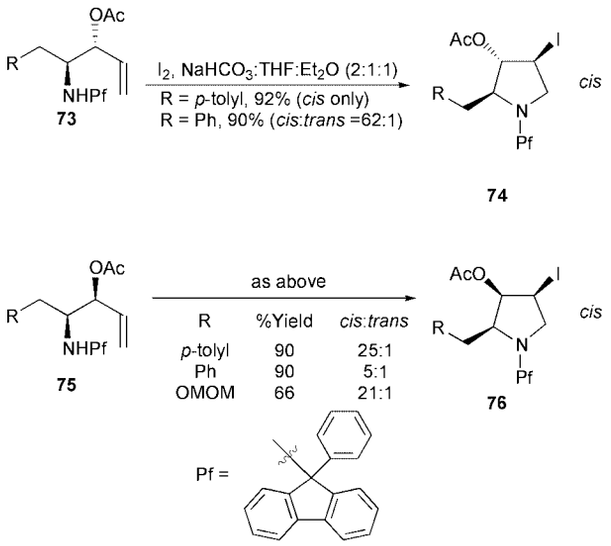
Scheme 23

Lithiated methoxyallene **77** has been used in the preparation of enantiopure 3-pyrrolines (Scheme 26).[38] Upon reaction of **77** with the SAMP-hydrazones [SAMP = (*S*)-1-amino-2-methoxymethylpyrrolidine] of aromatic aldehydes **78** in THF, pyrrolines **79** were produced with complete diastereoselectivity. The same reaction performed in diethyl ether yielded only hydrazine intermediates. Cleavage of the N–N bond in products **79** was effected by quaternization of a nitrogen in the hydrazino group with methyl chloroformate, and then catalytic hydrogenation, affording pyrrolines **80**. The replacement of the SAMP portion of **78** with other groups, such as *N,N*-dimethyl or piperidinyl, generally gave less satisfactory reactions, although morpholinyl was quite effective.[39] A similar procedure has also been reported, in which lithiated methoxyallene **77** reacts with imines to afford allenylamines, which could then be cyclized to pyrrolines with silver nitrate.[40]

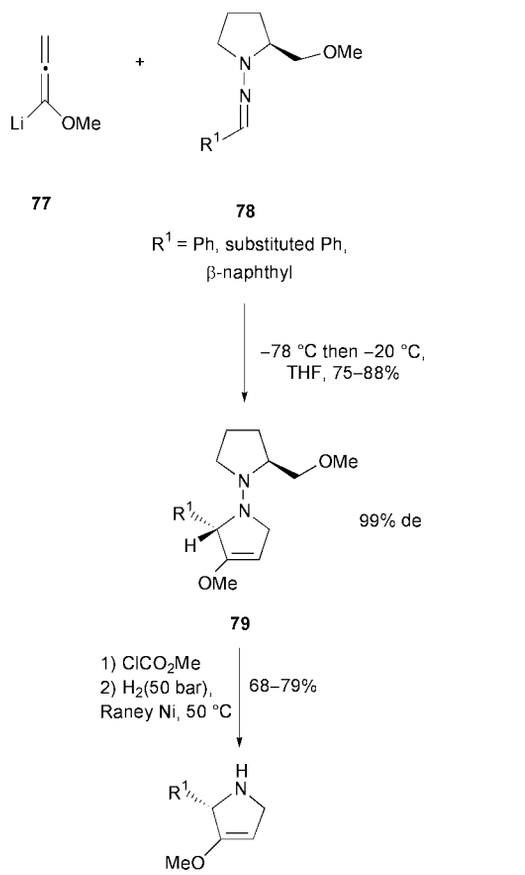


R^1 = allyl, Bu, Ts
R^2 = Et, ^{i}Pr, Ph, substituted Ph, furyl, PhCH=CH, PhCH=C(Me), ^{i}Pr$_3$SiC≡C

Scheme 24



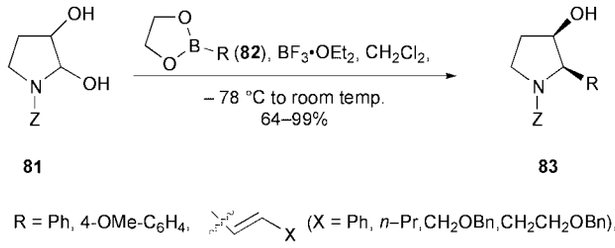
Scheme 25

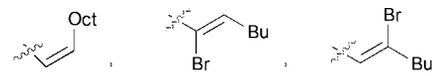


Scheme 26

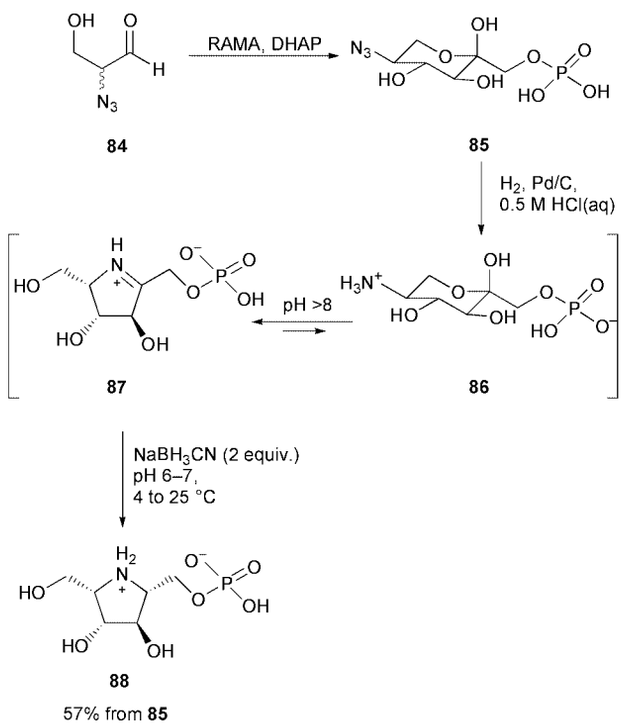
Alkenyl boronates **82** have been used in the stereoselective functionalization of pyrrolidine **81**, yielding exclusively *cis*-2,3-products **83** (Scheme 27).[41] The alkene stereochemistry was maintained in the reaction. Simple aryl boronates were also found to add, and preliminary results showed that piperidine substrates could also be functionalized.

A concise synthesis of phosphoryl azasugars has been reported, as shown in Scheme 28.[42] Reaction of the azidoaldehyde **84** with dihydroxyacetone phosphate (DHAP) in the presence of rabbit muscle aldolase (RAMA) yielded product **85** exclusively. Hydrogenation of **85** in 0.5 M hydrochloric acid allowed the ammonium hemiacetal **86** to be trapped. Adjusting the pH of the solution to > 8 established an equilibrium





Scheme 27



Scheme 28

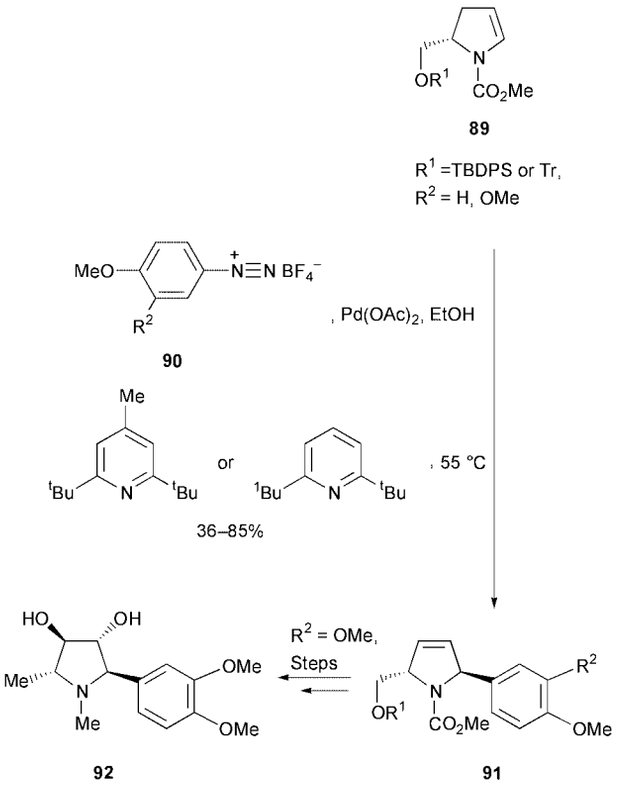
between **86** and the cyclic phosphoryl imine **87**, in which the latter predominated. Sodium cyanoborohydride reduction of **87** furnished the phosphoryl azasugar **88** with high diastereoselectivity. It was suggested that a range of stereoisomers would be accessible by choosing the appropriate aldolases.

A Heck reaction on enecarbamate **89** was the key step in a new formal synthesis of (−)-codonopsine **92** (Scheme 29).[43] It was necessary to use diazonium salts **90** as the aryl partner, in the presence of 2,6-di-*tert*-butylpyridine or 2,6-di-*tert*-butyl-4-methylpyridine as base. Products **91** were obtained with excellent regio- and stereoselectivity.

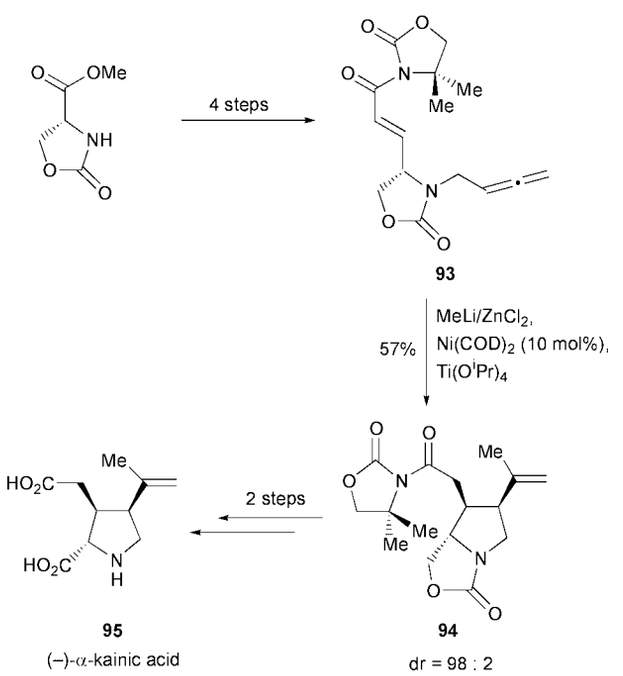
A novel nickel-catalyzed allene cyclization has been employed in a new synthesis of kainic acid **95** (Scheme 30).[44] Treatment of allene **93** with methyllithium and zinc chloride in the presence of nickel catalyst and a titanium Lewis acid yielded product **94** in good yield and excellent diastereoselectivity. The reaction mechanism was proposed to be the same as for the extensively studied nickel-catalyzed cyclization of alkynes.

A one-pot synthesis of pyrrolidines *via* a tandem Michael addition–cyclization reaction has been described (Scheme 31).[45] Copper(I) iodide was found to catalyze the formation of products **98** from propargylamines **96** and Michael acceptors **97**. Boc-Protected propargylamine was found not to be a suitable substrate for the reaction.

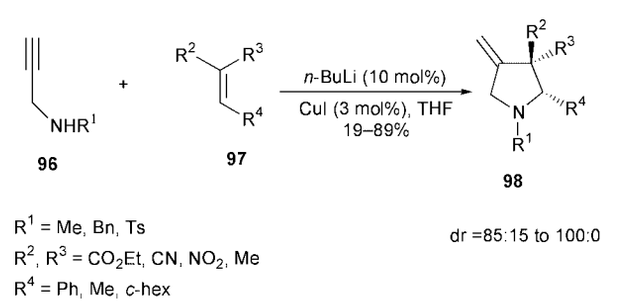
The synthesis of corrin precursors has been reported in a series of papers, using the iterative palladium(0)-catalyzed



Scheme 29

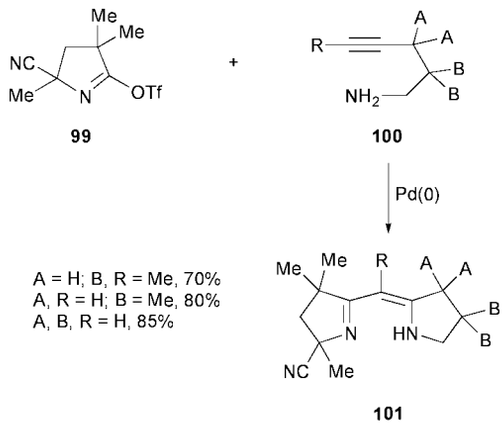


Scheme 30



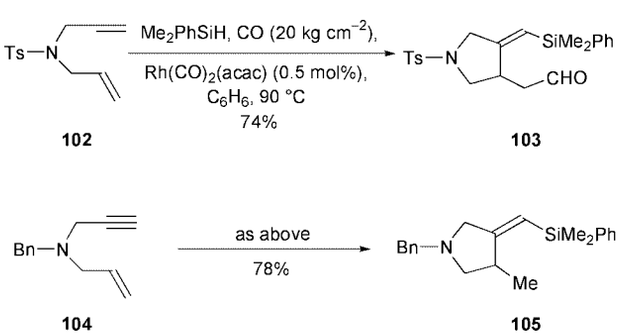
Scheme 31

addition of alkynes to iminoyl derivatives as the key feature.[46–48] An example is shown in Scheme 32, in which (H_6)-dipyrrins **101** are synthesized by the addition of alkyne amine **100** to iminoyl triflate **99** with concomitant ring closure.[48] The geminal dimethyl groups of **99** were found to protect the triflate from direct nucleophilic displacement by the amine.



Scheme 32

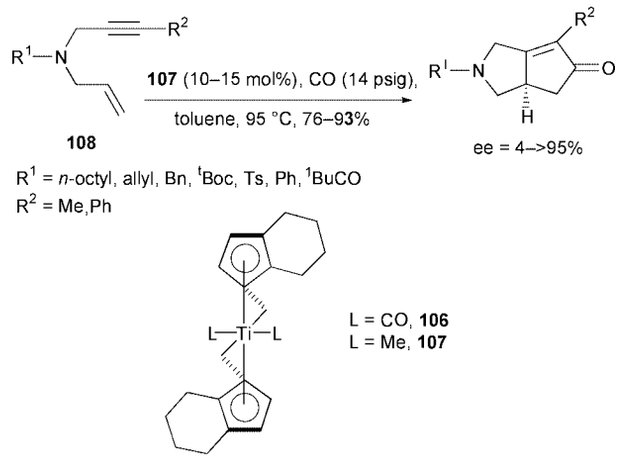
Pyrrolidines were prepared as part of a study on the rhodium-catalyzed domino silylformylation of enynes.[49] The nature of the *N*-substituent was found to greatly affect the outcome of the reaction (Scheme 33). The *N*-tosylenyne **102** yielded the expected product **103**, as seen for analogous carbocyclizations. The *N*-benzylenyne **104** however yielded pyrrolidine **105**, where carbon monoxide had not been incorporated into the product. Meanwhile, Buchwald and Sturla have reported an asymmetric cyclocarbonylation of enynes, catalyzed by an enantiomerically pure titanocene complex **106** (formed *in situ* from the precursor **107**).[50] For the best enantioselectivity, an electron-rich nitrogen center was required in the starting enyne **108** (Scheme 34). During the course of these studies, Buchwald and co-workers also discovered a titanocene-catalyzed cycloisomerization of enynes, one example of which yielded a pyrrolidine.[51]



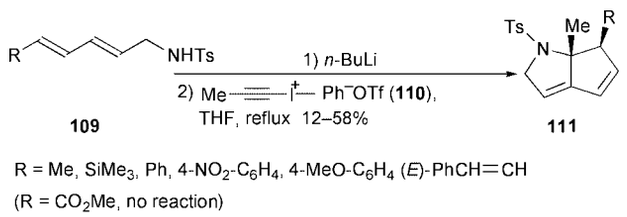
Scheme 33

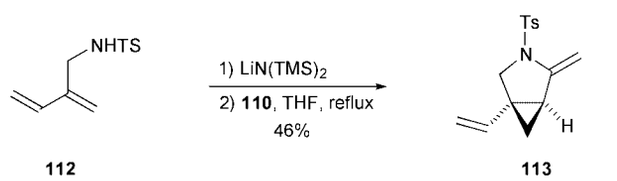
Annelated dihydropyrroles **111** have been prepared from the cascade addition–bicyclization reactions of dienyltosylamide anions with phenyl(propynyl)iodonium triflate **110** (Scheme 35).[52] The best yields were obtained when **110** was added to a solution of diene **109** and base. Azabicyclo[3.1.0]hexane **113** was isolated when a 2-substituted dienyltosylamide **112** was subjected to the reaction conditions.

A formal [5 + 2] cycloaddition has been observed between the chromium complex **114** and bulky terminal alkynes **115**, ultimately yielding pyrrolidines **116** as the products (Scheme 36).[53] The reaction was shown to proceed *via* the cycloadduct **117**, which decomplexed in pyridine yielding dione **118** upon hydrolytic work-up. Cyclization of **118** and elimination of water finally yielded the pyrrolidines **116**.



Scheme 34



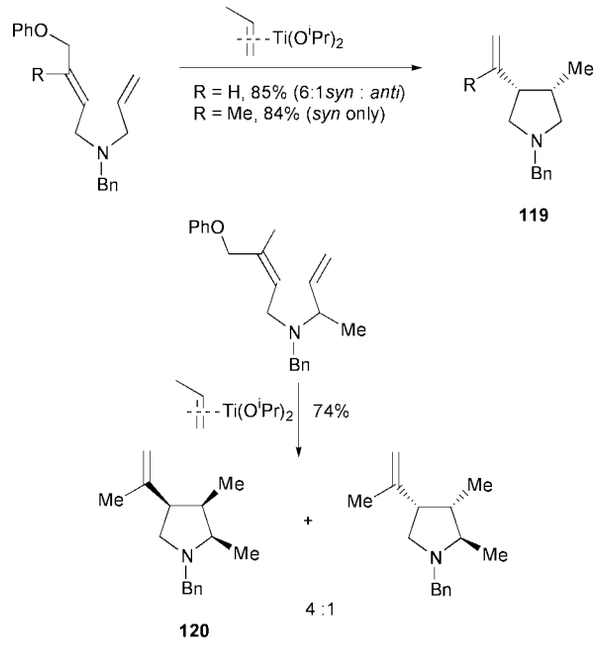


Scheme 35

Titanium-mediated diene metallabicyclization methodology has been used for the stereoselective preparation of *syn*-3,4-disubstituted (**119**) and *syn*,*syn*-2,3,4-trisubstituted pyrrolidine **120** (Scheme 37).[54] This was exploited in a new total synthesis of (−)-α-kainic acid.

Ring-closing metathesis has again been employed for the synthesis of pyrrolines. Recent substrates have included anilines,[55] phenyl-substituted dienes[56] and the products from enantioselective allylic aminations of allylic carbonates.[57]

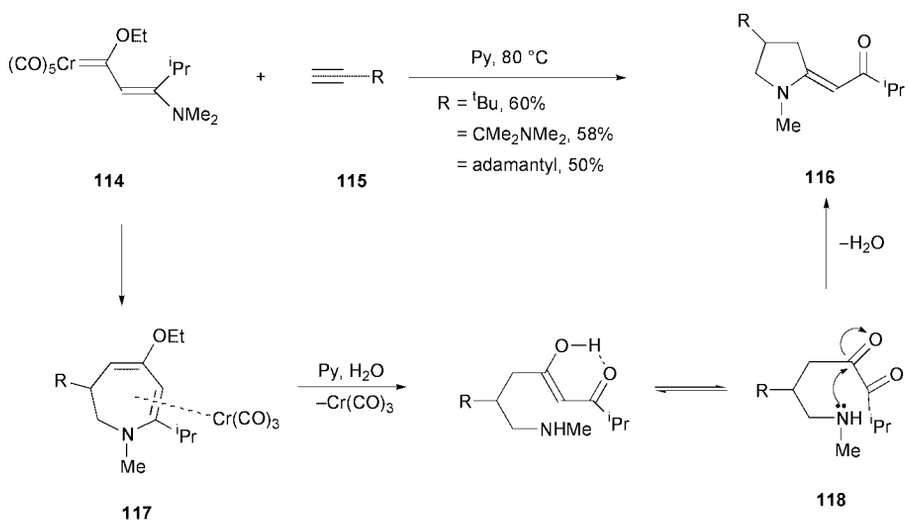
A number of papers concerning the stereoselective Birch reduction of pyrroles have appeared. Pyrrole **121** was found to undergo a double reductive alkylation, yielding *cis*-3,4-disubstituted pyrrolidines **122** (Scheme 38).[58] Bulky electrophiles were found to react slowly, thus allowing sequential dialkylations with different electrophiles in some cases. Pyrroles substituted at the 2-position with chiral auxiliaries have also been shown to undergo diastereoselective protonation[59] or alkylations[60] under Birch reduction conditions.



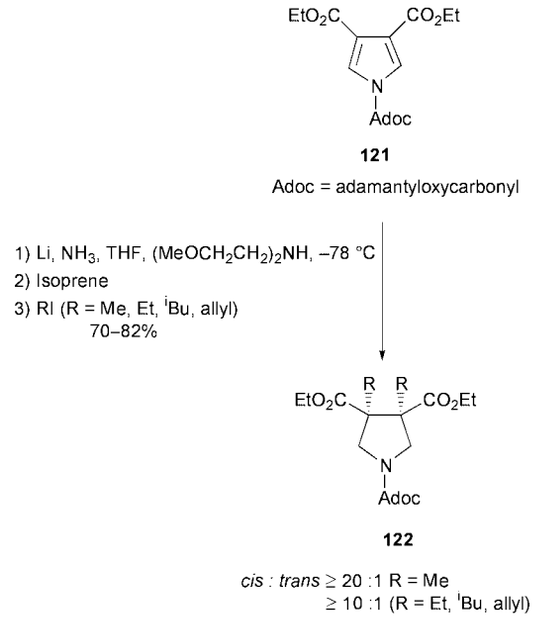
Scheme 37

New methods of iminyl radical formation have been described for the preparation of dihydropyrroles. Ketoxime xanthates,[61] *O*-2,4-dinitrophenyloximes[62] and transient sulfinate esters (generated from the Hudson reaction of oximes with 2,6-dimethylbenzenesulfinyl chloride)[63] have all been employed as iminyl radical precursors.

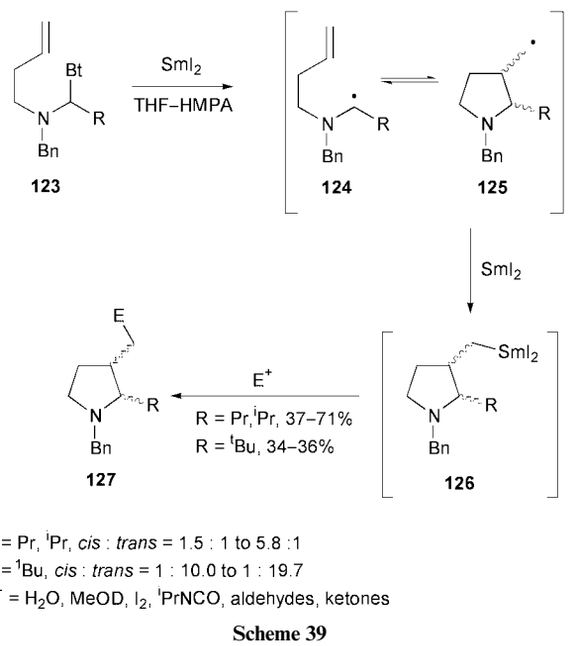
Samarium iodide has been used in two procedures to facilitate pyrrolidine formation by the addition of α-aminoalkyl radicals to alkenes. Radicals **124** generated from α-aminobenzotriazoles **123** exist in equilibrium with cyclized radicals **125** (Scheme 39).[64] The equilibrium could be driven towards **125** by rapidly reducing the cyclized radicals to organosamarium compounds **126**, which could finally be trapped by electrophiles yielding products **127**. The same procedure, applied to intramolecular radical addition to electron-deficient alkenes, was also reported.[65]



Scheme 36



Scheme 38

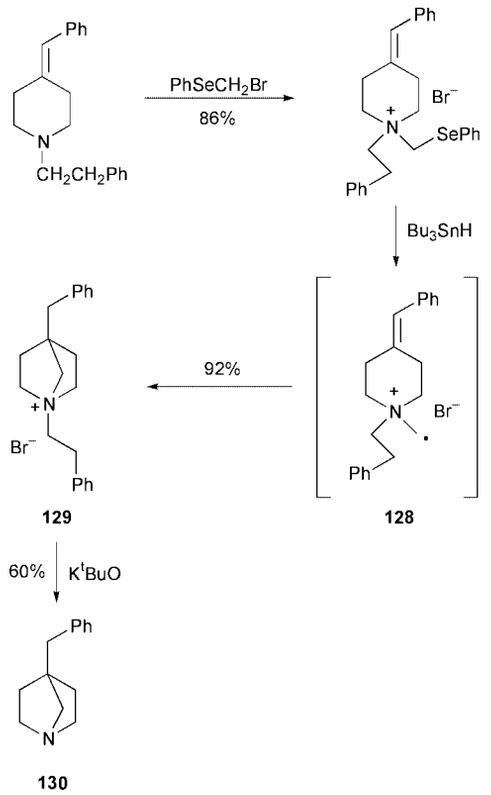


Scheme 39

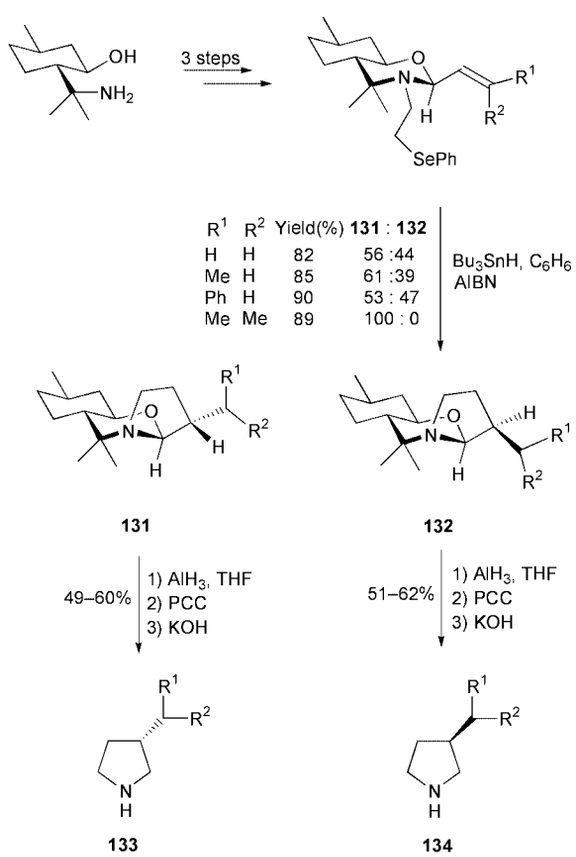
Bridgehead nitrogen heterocycles such as **130** have been synthesized by the cyclization of ammoniomethyl radicals **128** (Scheme 40).[66] To de-quaternize **129** at the end of the sequence, an *N*-phenethyl group was required, thus allowing Hofmann elimination to occur.

Modest diastereoselectivity was generally observed in radical pyrrolidine cyclizations, induced by a chiral perhydro-1,3-benzoxazine moiety (Scheme 41).[67] The major diastereomer from the reaction shown was product **131**. Separation of the isomers **131** and **132**, cleavage of the *N*,*O*-acetal moiety with aluminium hydride, and two-step removal of the chiral auxiliary, resulted in enantiopure 3-substituted pyrrolidines **133** and **134**. Changing the substituents at the nitrogen atom and at C-2 of the starting perhydro-1,3-benzoxazine allowed **134** to be produced as the major enantiomer from the sequence.

Pyrroloquinoline skeletons have been assembled using an azomethine ylide approach,[68] and non-stabilized azomethine ylides have been generated from *N*,*N*-bis(sulfonylmethyl)alkylamines with samarium iodide for pyrrolidine formation.[69] Following on from previous work, dipolar trimethylene-



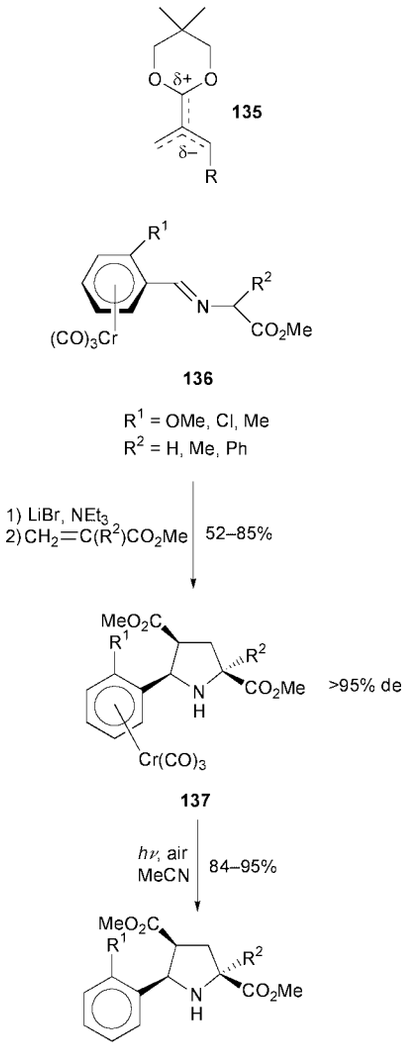
Scheme 40



Scheme 41

methane **135** has now been reacted with *N*-methoxycarbonyl- and *N*-tosylimines, yielding pyrrolidines.[70]

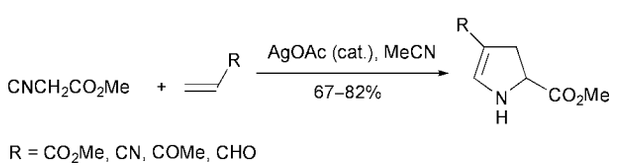
Highly diastereoselective [3 + 2] cycloadditions of azomethine ylides linked to a planar chiral arene chromium complex (**136**) and methyl acrylates have been described (Scheme 42).[71] Only one diastereomer was detected for the products **137**,



Scheme 42

which were then oxidatively decomplexed to yield pyrrolidines **138**. The use of a titanium Lewis acid resulted in reversed product regiochemistry.

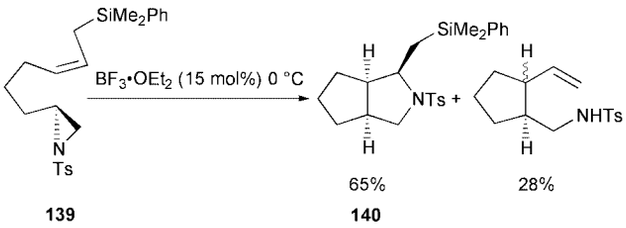
Silver acetate has been used as a catalyst for the cycloaddition of methyl isocyanoacetate with activated alkenes, yielding Δ^2-pyrrolines (Scheme 43).[72] A stepwise mechanism was proposed, explaining the partial loss of stereochemistry observed when disubstituted alkenes were used.



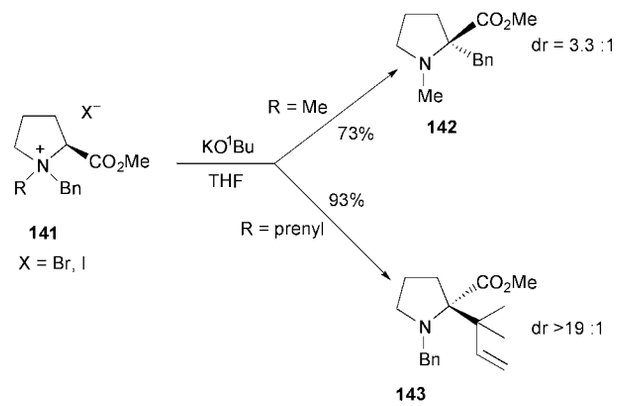
Scheme 43

A formal [3 + 2] intramolecular aziridine–allylsilane cycloaddition has been used as the key step in the synthesis of bicyclic proline analogues (Scheme 44).[73] Cyclization of precursor **139** with catalytic boron trifluoride–diethyl ether yielded diastereomerically pure product **140** in good yield; as expected, *ent*-**139** afforded *ent*-**140** in similar yield (62%). The analogous reaction to yield pyrrolidines fused to cyclohexane gave predominantly *trans*-fused products, with significant loss of diastereoselectivity.

Chirality transfer from nitrogen to carbon has been reported in proline derivatives (Scheme 45).[74] Salts **141** furnished [1,2]- and [2,3]-shift products **142** and **143** respectively, when treated with potassium *tert*-butoxide in THF. These products were converted into known proline derivatives to establish their diastereomeric purity. The benzyl shift yielding **142** was not completely stereospecific, confirming a radical reaction mechanism, whilst **143** was obtained as a single diastereomer.



Scheme 44



Scheme 45

5 Six-membered rings

Kobayashi and co-workers have described further progress in the catalytic asymmetric aza Diels–Alder reaction (Scheme 46).[75,76] Treatment of a mixture of imine **144** and Danishefsky's diene in benzene at 23 °C in the presence of molecular sieves, *N*-methylimidazole, zirconium *tert*-butoxide and 3,3′-diphenyl-BINOL (*R*)-**146** gave the piperidone derivatives **145** in reasonable yields and enantioselectivities. It was found that (*R*)-**146** gave asymmetric induction in the opposite sense to that obtained with the corresponding 3,3′-unsubstituted BINOL.

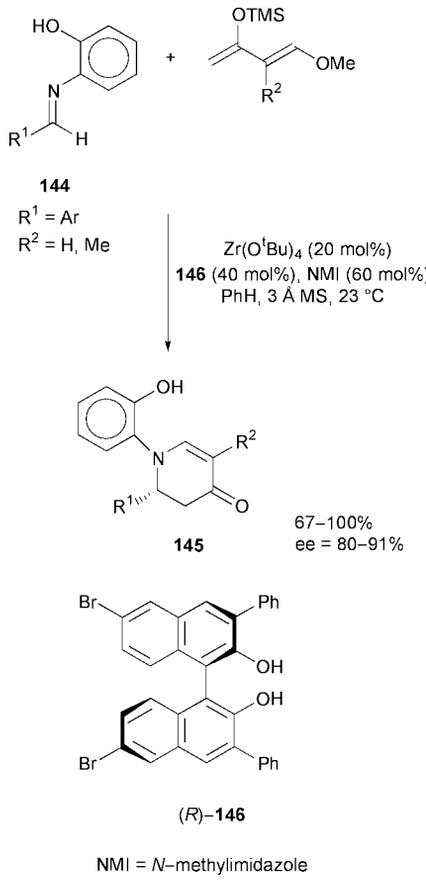
The use of indium(III) triflate (0.5 mol%),[77] aqueous tetrafluoroboric acid (10 mol%)[78] and zinc iodide (20 mol%)[79] to catalyze the aza Diels–Alder reaction of imines with Danishefsky's diene has been reported.

Wang and co-workers have described the solid phase aza Diels–Alder reaction of a 1,3-diene and an imine, generated *in situ* from an immobilized benzylamine and an aldehyde (**147**→**148**, Scheme 47).[80] The reaction was promoted by ytterbium(III) triflate in dichloromethane, (other lanthanide triflates were also effective), and following cleavage from the resin with ACE-Cl, substituted piperidines **148** were formed in reasonable yields and purities.

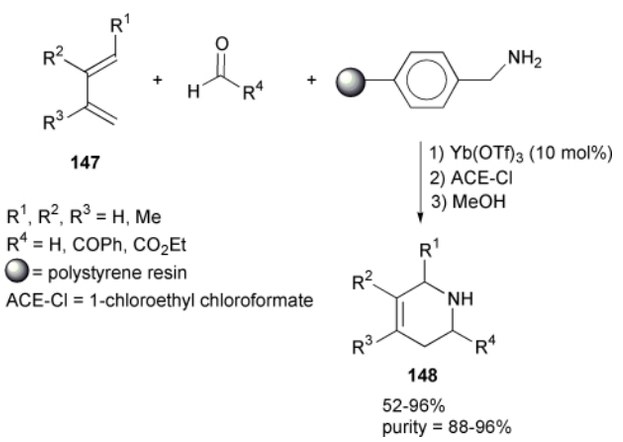
Barluenga and co-workers have described the application of a zinc chloride-catalyzed diastereoselective imine Diels–Alder reaction in the synthesis of (−)-nupharamine and related alkaloids (Scheme 48).[81]

Ghosez and Jnoff[82] have described the aza Diels–Alder reaction of the 2-azadiene **149** with dienophile **150** catalyzed by the Lewis acid derived from Evans' bis(oxazoline) **152** and copper(II) triflate (Scheme 49). With only one exception ($R^1 = R^2 = H$), the 2-piperidones **151** were obtained with extremely high *exo*:*endo* ratios, enantioselectivities and yields. Stronger Lewis acids were not compatible with the sensitive 2-azadienes.

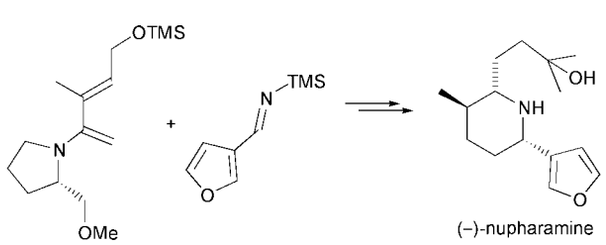
The intramolecular 1-azadiene Diels–Alder reaction (**153**→**154**, Scheme 50) can be accomplished either thermally or



Scheme 46



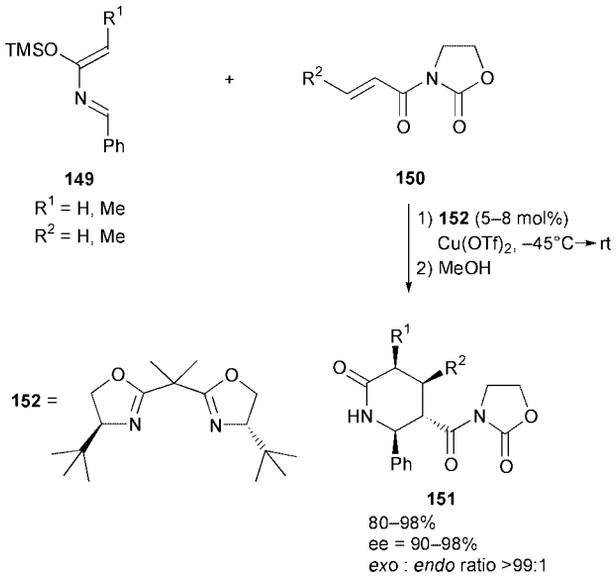
Scheme 47



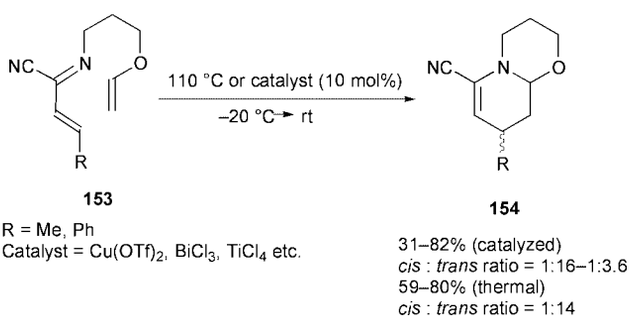
Scheme 48

by addition of a Lewis acid.[83,84] Although the thermal reaction gave higher *trans*:*cis* selectivities than in those catalyzed by a Lewis acid, the yields were generally lower, owing to partial degradation of the product at high temperatures. Royer and co-workers have reported the functionalization of derivatives similar to these.[85]

The selective functionalization of Boc-pyrrolidine by a rhodium-catalyzed carbene insertion reaction has been



Scheme 49

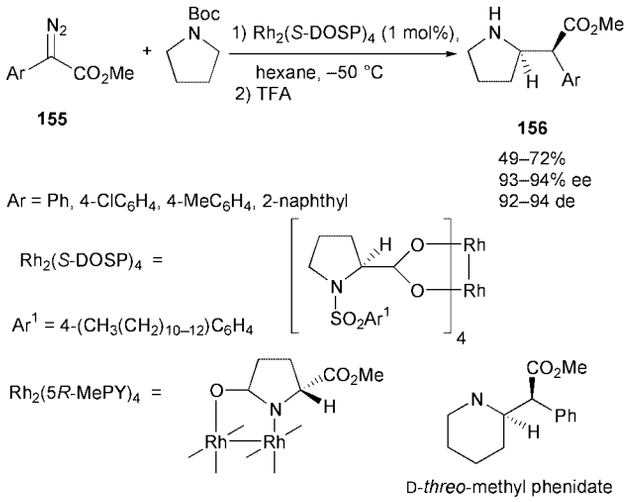


Scheme 50

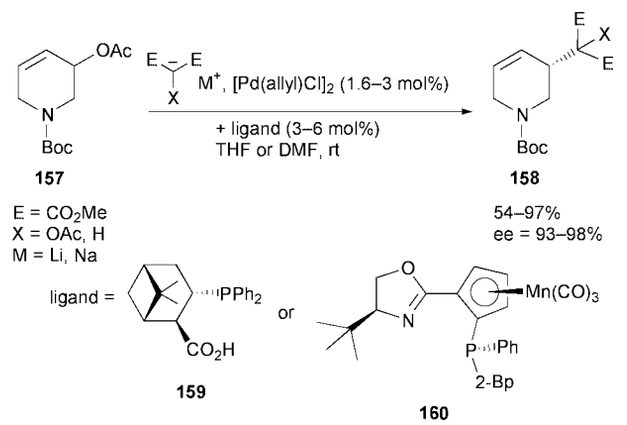
reported by Davies and co-workers (**155**→**156**, Scheme 51).[86,87] This useful reaction, which is highly regio-, stereo- and enantioselective proceeds with only 1% of the catalyst Rh_2(*S*-DOSP)$_4$, yielding **156** after deprotection with TFA. Furthermore, by increasing the quantity of the diazoacetate reagent and by performing the reaction at reflux, C_2-symmetric 2,5-disubstituted pyrrolidines were formed in good yield and enantioselectivity. With a slight change of reaction conditions and catalyst, *N*-Boc-piperidine could be analogously converted into methylphenidate (Ritalin) by reaction with methyl phenyldiazoacetate, although with reduced levels of stereocontrol. Winkler and co-workers[88] have reported similar results, discovering that Doyle's catalyst, Rh_2(5*R*-MEPY)$_4$ (1 mol%) catalyzes the same transformation with higher diastereoselectivity (94% de), but reduced enantioselectivity (69% ee). Chiral auxiliary- and resolution-based approaches to the synthesis of methylphenidate have also been disclosed.[89–92]

Helmchen and Schleich[93] have described the enantioselective allylic alkylation of tetrahydropyridines (obtained conveniently by a ring-closing metathesis reaction) with dialkyl malonates, catalyzed by a complex created from [Pd(allyl)Cl]$_2$ and phosphine ligand **159** or **160** (Scheme 52). Evans has described a similar reaction (**161**→**162**, Scheme 53),[94] involving an allylic carbonate and a mixed phosphorus–sulfur ligand **163**. In addition to a dialkyl malonate as the nucleophile, benzylamine was also reported to react with high enantioselectivity.

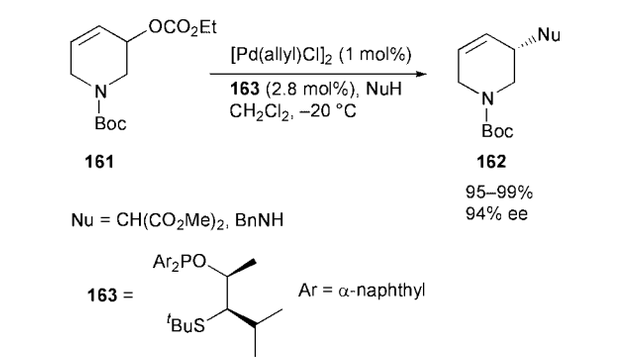
Simpkins and co-workers have described the desymmetrizing deprotonation of *meso*-piperidine diester **164** (readily obtained by hydrogenation of pyridine-2,6-dicarboxylic acid) with a chiral lithium amide base (Scheme 54).[95] Trapping of the resulting organolithium with a range of reactive electrophiles gave piperidines **165** in excellent yields, with near perfect stereocontrol (single diastereomer, ⩾ 98% ee).



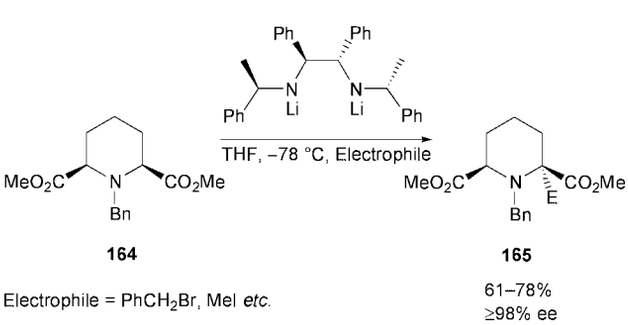
Scheme 51



Scheme 52



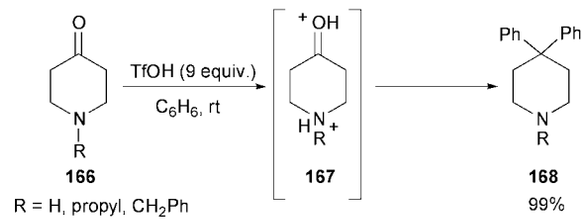
Scheme 53



Scheme 54

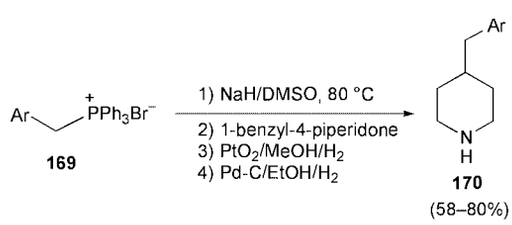
Treatment of **166** (Scheme 55) with an excess of triflic acid and benzene gave the disubstituted piperidines **168** in excellent yield, through the dicationic intermediate **167**.[96] Certain 3-piperidones and tropinones react analogously.

Zhou and Keana have described a practical synthesis of



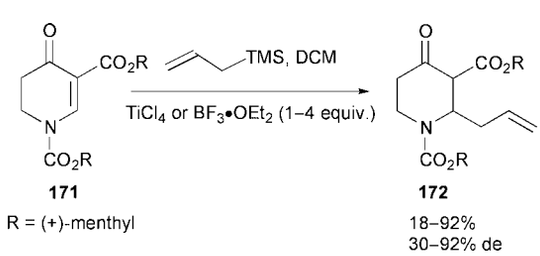
Scheme 55

4-substituted benzylpiperidines (and one 3-substituted benzylpyrrolidine) by a Wittig reaction (**169**→**170**, Scheme 56).[97] Treatment of the phosphonium salt of a benzyl bromide with sodium dimethylsulfinate at 80 °C and reaction with 1-benzyl-4-piperidone effected the Wittig reaction. Hydrogenation (firstly with PtO_2, then Pd/C) resulted in reduction of the alkene and deprotection to furnish the piperidines. Other bases commonly used for Wittig reactions were unsuccessful, as were attempts to simultaneously reduce the double bond and effect deprotection. The products of this reaction possess a wide range of biological activities, including affinity for 5HT receptors.



Scheme 56

The diastereoselective allylation of 3-menthyloxycarbonyl-5,6-dihydropyridin-4-ones has been reported (**171**→**172**, Scheme 57).[98] The highest diastereoselectivity was obtained with menthyl moieties on both the carbamate and ester groups. The resulting adduct was converted into the natural product (−)-*N*-methylconiine.

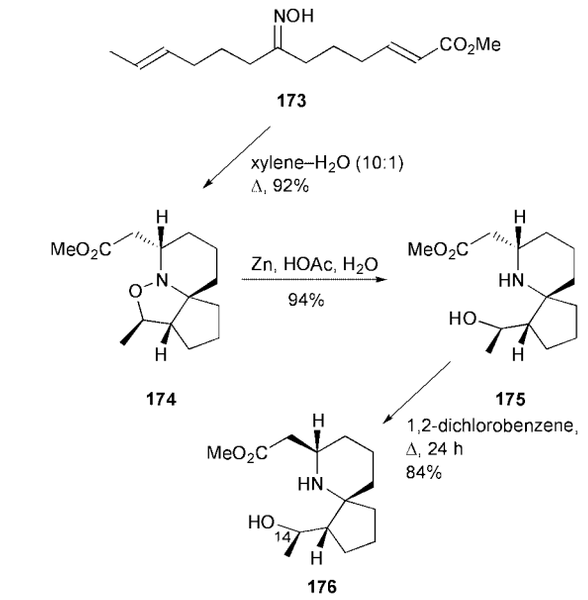


Scheme 57

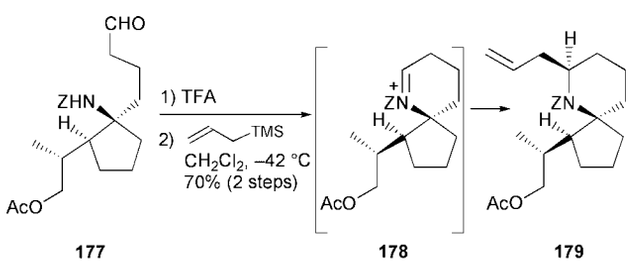
The structurally related alkaloids halichlorine and pinnaic acid have recently become important synthetic targets, owing in part to their potential as treatments for allergic inflammatory diseases.[99–104] Zhao and Lee (Scheme 58)[99] have described the reaction of the oxime **173** to form tricycle **174** in a single transformation. This reaction proceeds initially by intramolecular formation of a nitrone from the oxime and the conjugated double bond, followed by a 1,3-dipolar cycloaddition with the remaining double bond to give **174** as a single isomer. Reductive cleavage gave **175**, which could be epimerized (*via* a retro-Michael reaction) at 180 °C to give **176**, having the desired stereochemistry at all the newly formed stereocenters for a synthesis of halichlorine. Analogously, the C-14 epimer was prepared as an intermediate *en route* to pinnaic acid.

Forsyth and Koviach[100] have described a different but still efficient route to an intermediate similar to **176** (Scheme 59). Treatment of aldehyde **177** with TFA, followed by the addition of allyltrimethylsilane, led to formation of **179** as a single diastereomer *via* the intermediate iminium ion **178**.

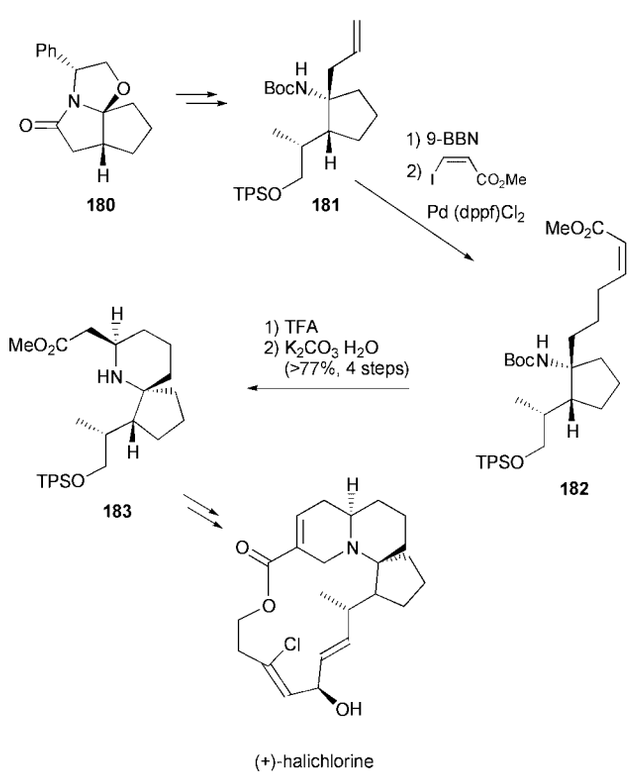
Danishefsky and co-workers have described the first total synthesis of (+)-halichlorine (Scheme 60).[101,102] The spiropiper-



Scheme 58



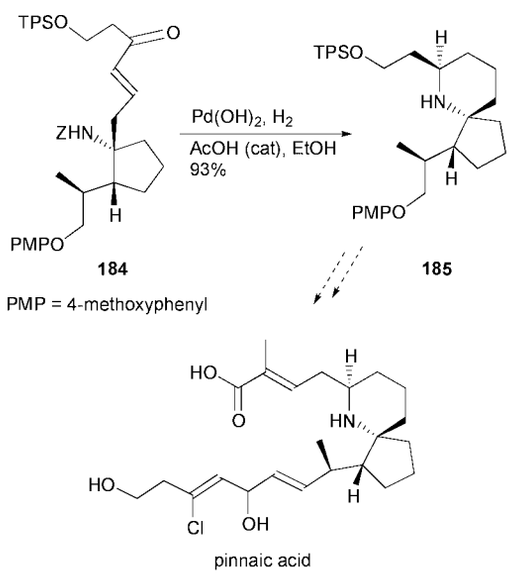
Scheme 59



Scheme 60

idine unit (**183**) was assembled from Meyers' lactam **180** by a sequence of reactions involving, amongst others, an unusual sp^3–sp^2 Suzuki coupling reaction (**181**→**182**). The α,β-unsaturated ester thus obtained was readily cyclized by a highly stereoselective intramolecular Michael reaction to yield **183**. The spiroquinolizidine portion was then formed by means of a two-carbon extension of the pendant methyl ester group and a Mannich reaction, and the total synthesis was completed by an elegant series of organometallic manipulations that assembled the 1,4-diene moiety.

Arimoto and co-workers have described a related approach to the synthesis of the pinnaic acid core structure (**184**→**185**, Scheme 61).[103] In this reaction sequence, the piperidine ring is formed in 93% yield and with very high diastereoselectivity by *in situ* reduction of an intermediate imine (formed by intramolecular condensation of the amine functionality with the ketone).

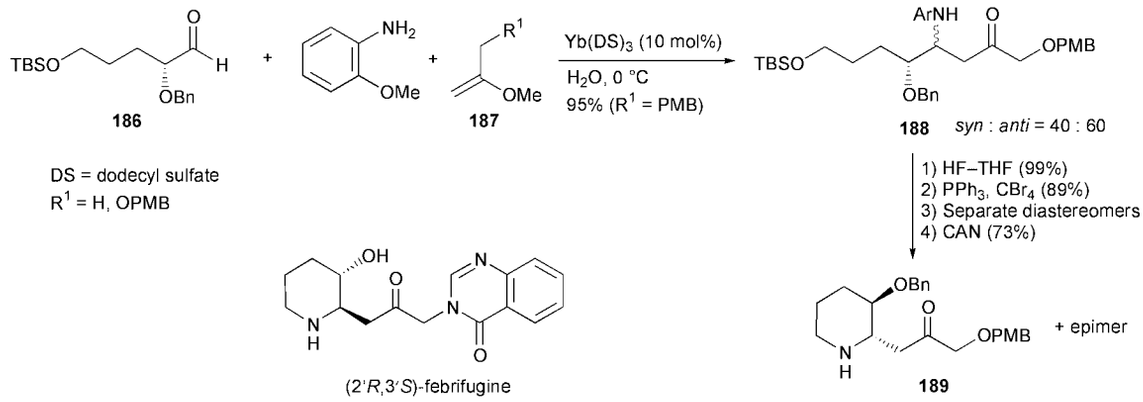


Scheme 61

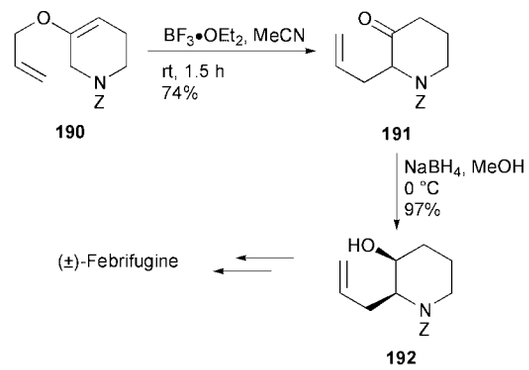
Kobayashi and co-workers[105,106] have finally obtained the correct stereostructure of the antimalarial agent febrifugine, some 50 years after its first isolation from natural sources (Scheme 62). The key step in the reaction sequence is the three-component Mannich reaction of enantiomerically pure aldehyde **186** with 2-methoxyaniline and a vinyl ether **187**. For the simple case (R^1 = H), ytterbium(III) triflate (10 mol%) in THF–water (9 : 1) was a suitable catalyst, but for a more complicated example (R^1 = OPMB), the yield under these conditions was much lower. However, ytterbium(III) dodecylsulfate ($Yb(DS)_3$) in water was tried, and found to give higher yields of **188** and tolerate more diverse functionality in the starting material. Aldehydes other than **186** also underwent this reaction successfully. With **188** in hand, simple functional group manipulation, cyclization and deprotection gave **189**, which was readily converted to the enantiomer of the natural product.

Takeuchi and co-workers[107] have used an abnormal Claisen rearrangement as a key step in a synthesis of febrifugine (Scheme 63). Treatment of **190** (obtained from 3-hydroxypyridine) with boron trifluoride–diethyl ether afforded the 2-substituted piperidone **191** in excellent yield, a reaction that presumably involves isomerization of the double bond to the $\Delta^{2,3}$ position prior to Claisen rearrangement. Under purely thermal conditions, the expected 4-substituted piperidone was obtained. Compound **191** was selectively reduced to **192** and readily converted to the natural product by a conventional sequence of reactions. The same research group have also prepared (±)-deoxyfebrifugine, a less active analogue of febrifugine.[108]

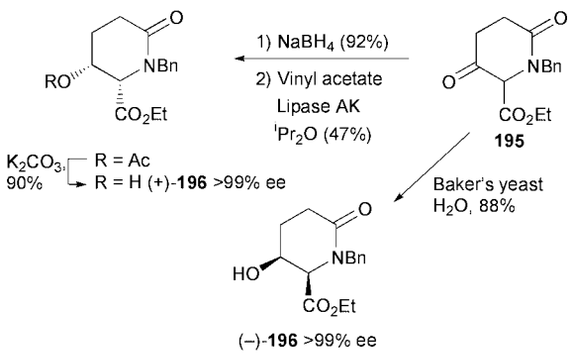
The aza Achmatovicz rearrangement has been used by Haroutounian[109] and Zhou[110] in syntheses of (+)-desoxoprosophylline and other closely related alkaloids. A number of routes to the key β-hydroxyfurfurylamine moiety (*e.g.* **193**) have been reported, starting from 2-vinylfuran,[111,112] and



Scheme 62

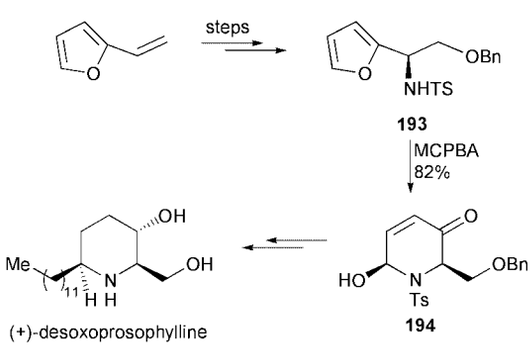


Scheme 63



Scheme 65

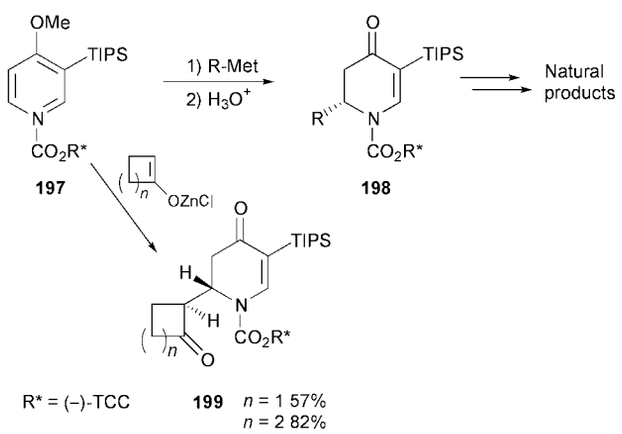
D-glucal.[109,113] In Zhou's synthesis (Scheme 64), the oxidative cleavage of **193** occurred in 82% yield, giving **194**, a key building block for many alkaloids.



Scheme 64

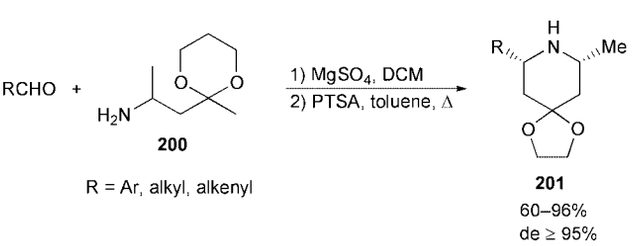
The related building blocks, (+)- and (−)-**196** have been synthesized by Toyooka and co-workers (Scheme 65).[114] Straightforward reduction of **195** with Baker's yeast gives (−)-**196**, whereas sodium borohydride reduction followed by lipase-mediated kinetic resolution gives (+)-**196** (after hydrolysis of the acetate group). 2-Piperidone **196** was readily functionalized at the 2-position by an Eschenmoser sulfide contraction reaction or *via* the enol triflate, and at the 6-position by reduction to make a number of natural products including the *prosopis* alkaloids and the marine alkaloid lepadin B.[115]

The addition of Grignard reagents and other organometallics to an enantiomerically pure 1-acylpyridinium salt generates pyridones (**197**→**198**, Scheme 66) with high diastereoselectivity. This reaction has been used to make a number of piperidine and indolizidine alkaloids.[116–120] Comins and co-workers have now extended this reaction to include the reaction of **197** with zinc enolates of ketones and lactones to give **199**.[121] This reaction proceeds with excellent *anti*-selectivity and provides an opportunity for the synthesis of more complex natural products.



Scheme 66

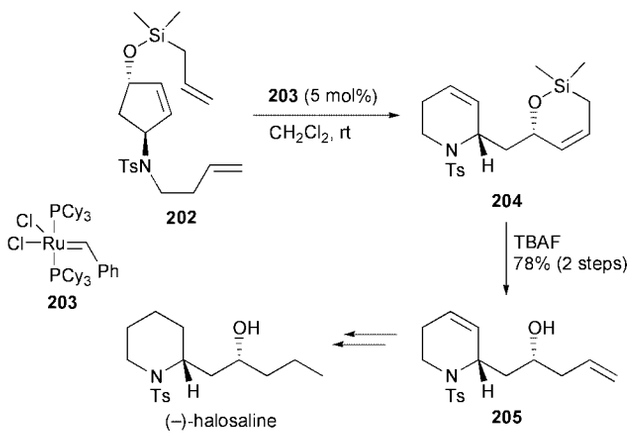
Troin and co-workers have described a simple preparation of *cis*-2,6-disubstituted piperidines (Scheme 67).[122] This intramolecular Mannich cyclization of an aldehyde with amine **200** (either as a single enantiomer or a racemate) gave piperidines **201** in good yield with extremely high diastereoselectivity. A variant on this theme was used in the first enantioselective synthesis of (+)- and (−)-dienomycin C.[123]



Scheme 67

Ring-closing metathesis (RCM) continues to be applied to the synthesis of piperidines, including (+)-coniine[124] and

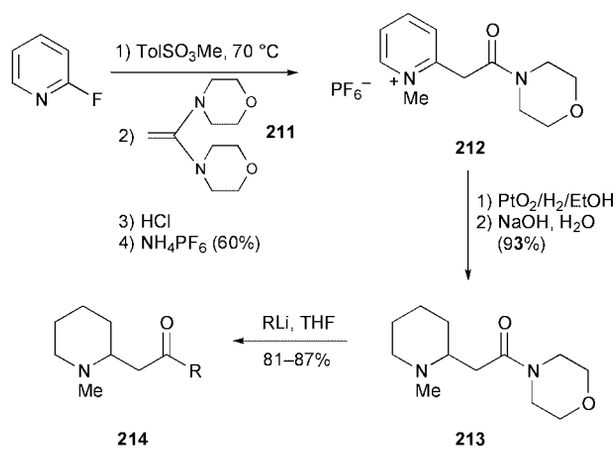
(±)-perhydrohistrionicotoxin.[125] A particularly interesting example is in the synthesis of (−)-halosaline by Blechert and Stragies (Scheme 68).[126] Thus treatment of the cyclopentene **202** with the Grubbs' catalyst **203** (5 mol%) resulted in a "domino metathesis" and the formation of piperidine **204** in excellent yield. Desilylation with TBAF then gave **205** in an overall yield of 78%. Full details of an alternative synthesis of (−)-halosaline and a plethora of related natural products have been described by Takahata and co-workers.[127]



Scheme 68

Holmes and co-workers have described an efficient new synthesis of the neurotoxin (−)-histrionicotoxin (Scheme 69).[128] Thermal cyclization of hydroxylamine **206** gave nitrone **207**, which was trapped immediately with styrene to give **208** as a single regio- and stereoisomer. A few functional group interconversions gave **209**, which on heating in toluene at 190 °C gave **210**, formally the product of a cycloreversion (to eliminate styrene and regenerate the nitrone) followed by intramolecular cycloaddition with the acrylonitrile moiety. From **210**, simple functional group interconversions and cross-coupling reactions gave the natural product.

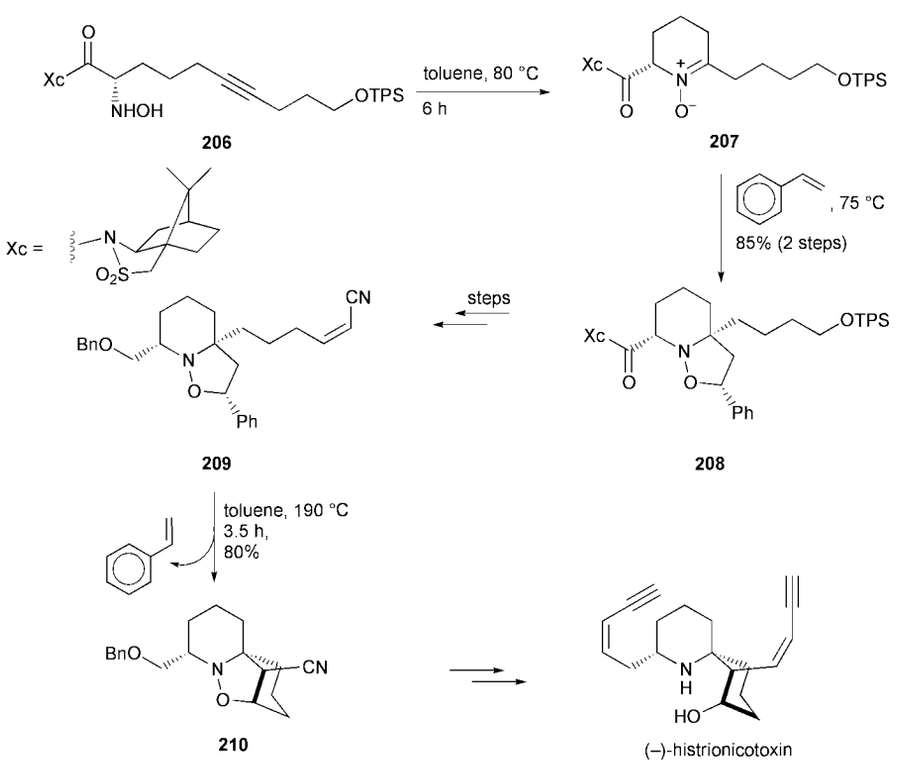
Meth-Cohn has described some interesting transformations of 2-halopyridinium salts, leading to *sedum* and *lobelia* natural products (Scheme 70).[129,130] For example, quaternization of 2-fluoropyridine with methyl tosylate, followed by displacement with the enamine **211** and work-up gave the amide **212**. Hydrogenation gave **213** (93%) which could be reacted with a range of organolithiums to give (for example when R = Ph) (±)-sedaminone (**214**). A range of other natural products was made from the same intermediate. Furthermore with a slight change in reaction conditions, 2,6-difluoropyridine could be induced to undergo analogous transformations to give the "two-armed" piperidines, also natural products. Marazano and co-workers have described an alternative route to *lobelia* alkaloids, also starting from a quaternized pyridine.[131]



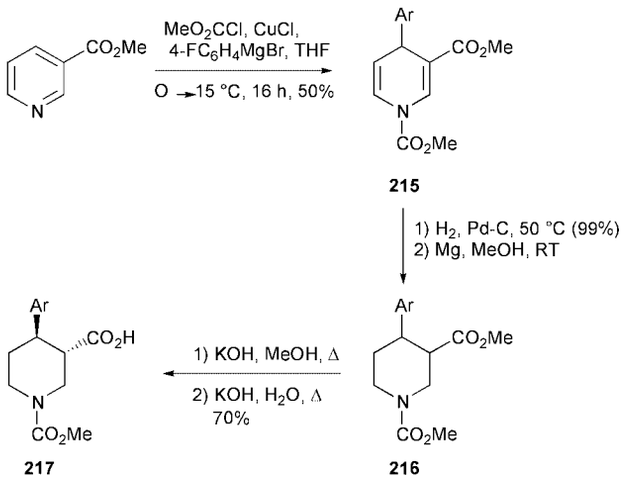
Scheme 70

A synthesis of 3,4-disubstituted piperidines has been described by Liu and co-workers (Scheme 71).[132] Quaternization of methyl nicotinate with methyl chloroformate, followed by addition of an aryl Grignard reagent gave the dihydropyridine **215**. Stepwise reduction, first with H_2 and Pd/C, then magnesium powder, and hydrolysis gave **216** as a mixture of diastereomers. Refluxing with potassium hydroxide gave the pure *trans* diastereomer **217**.

A multi-component synthesis of a range of pipecolic acids

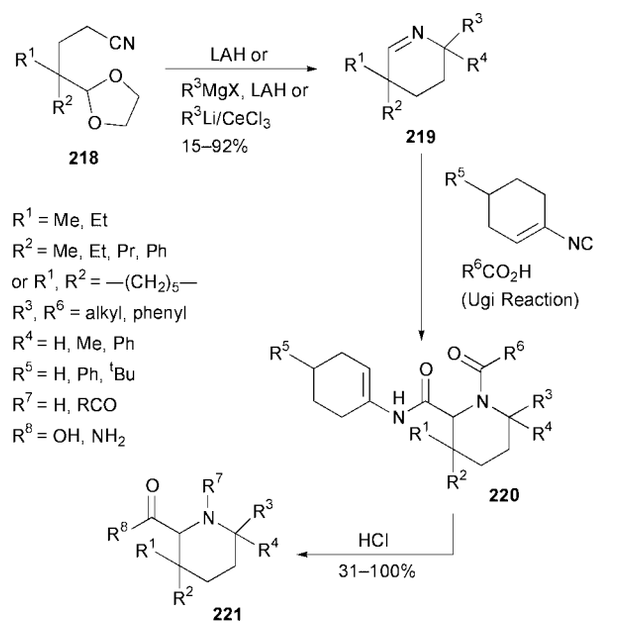


Scheme 69



Scheme 71

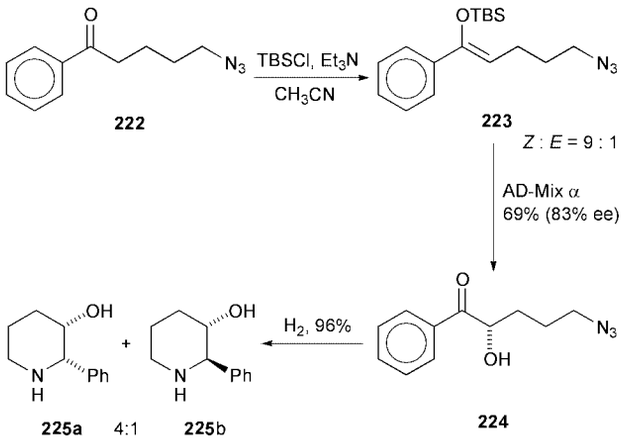
has been described by Martens and co-workers (Scheme 72).[133] Transformation of nitrile **218** into imine **219** was achieved by use of organometallic reagents. Treatment of imine **219** with an isonitrile and a carboxylic acid resulted in a three-component Ugi reaction to give the protected pipecolic acid **220**. Hydrolysis effected deprotection to give **221**, but in some cases unexpected products from rearrangements were observed. Homopipecolic acids have been synthesized by the same researchers from imine **219**.[134] Varela and DiNardo[135] and Lubell and co-workers[136] have described chiral-pool syntheses of substituted pipecolic acids.



Scheme 72

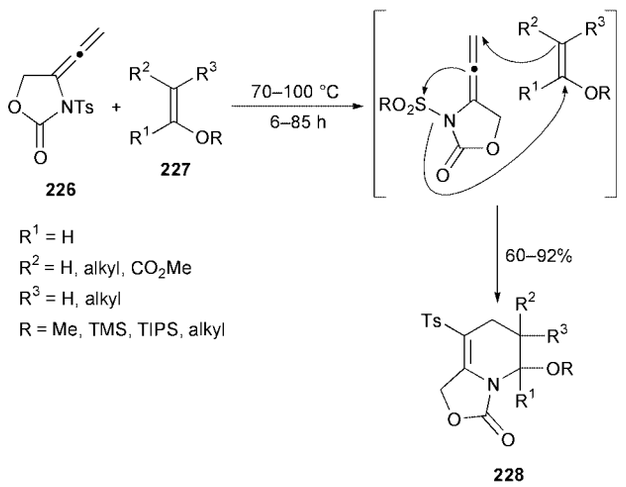
A simple synthesis of 2-phenyl-3-hydroxypiperidine, a common building block in the NK_1 antagonist field, has been described by Stadler and Bös (Scheme 73).[137] Thus treatment of ketone **222** with *tert*-butyldimethylsilyl chloride and triethylamine gave the silyl ether **223** as a 9:1 mixture of *Z*:*E* isomers. Dihydroxylation with AD-Mix α gave the α-hydroxyketone (83% ee), which on hydrogenolysis gave a 4:1 mixture of *cis*- and *trans*-piperidines **225**. Repeating the sequence of reactions with pure (*Z*)-enol ether **223** and with AD-Mix β gave the enantiomer of piperidine **225a** in 95% ee. An alternate route to **225a** has been described by Langlois and Calvez[138] and to the 3-aza-analogues by Chandrasekhar and Mohanty.[139]

Tetrahydropyridines of structure **228** have been synthesized by Tamaru and co-workers from allenesulfonamide **226** and enol ether **227** (Scheme 74).[140] In this thermal reaction, a novel



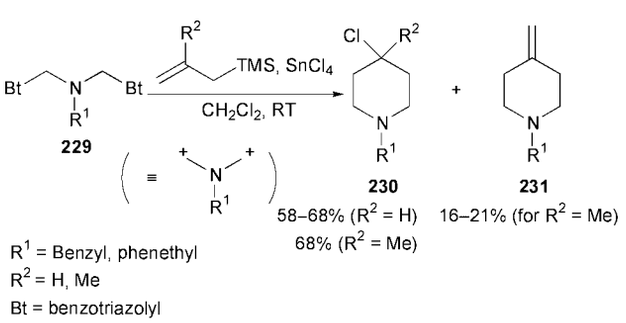
Scheme 73

1,3-sulfonyl shift occurs, transferring the tosyl group from the nitrogen substituent to the piperidine ring. A wide range of substituents on the (silyl)enol ether is tolerated.



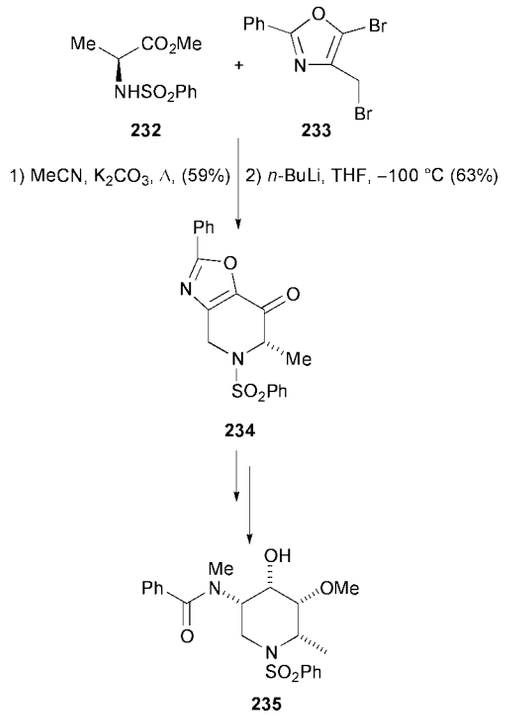
Scheme 74

Katritzky and co-workers have described the reaction of *N*,*N*-bis[(benzotriazolyl)methyl]amines **229** with allyltrimethylsilanes to give substituted piperidines, in which **229** functions essentially as a nitrogen-centered 1,3-dication equivalent (Scheme 75).[141] For example, treatment of **229** with tin tetrachloride and allyltrimethylsilane gave **230** in 58–68% yield. With R^2 = Me, some competitive elimination occurred to give the 4-methylenepiperidine **231**.

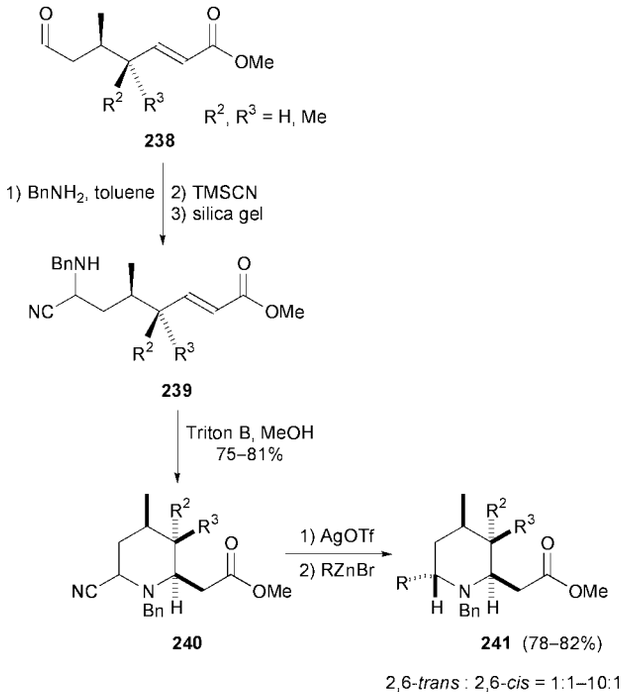


Scheme 75

The deoxyamino sugar **235** has been synthesized by an interesting route (Scheme 76).[142] Alkylation of the alanine derivative **232** with bromoxazole **233**, followed by BuLi-mediated cyclization gave the 3-piperidone **234** in quite good yield. Quaternization of the oxazole nitrogen atom followed by cleavage and other functional group manipulations finally gave **235**. The



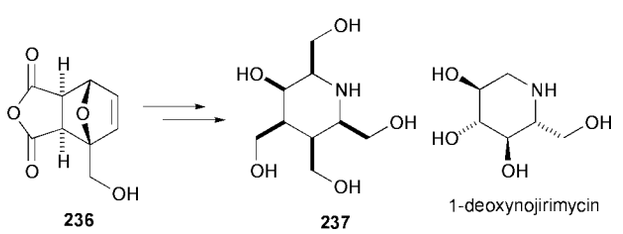
Scheme 76



Scheme 78

syntheses of other deoxyamino sugars have also been published.[143–146]

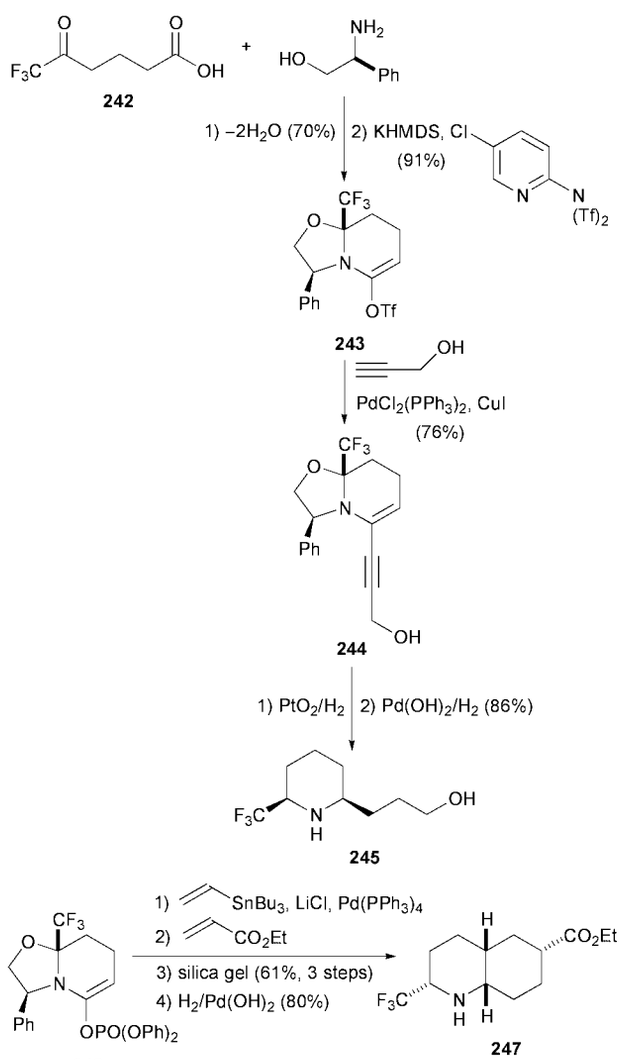
The interesting homologated polyhydroxylated piperidine **237** has been synthesized by Vogel and Jotterand[147] (Scheme 77) from **236**, the Diels–Alder adduct of maleic anhydride and furfuryl alcohol. In contrast to normal polyhydroxylated piperidines and pyrrolidines (*e.g.* 1-deoxynojirimycin), **237** is a very weak inhibitor of the enzyme β-galactosidase.



Scheme 77

Schneider has described the elaboration of **238** (obtained from a chiral auxiliary-controlled Cope rearrangement) to highly substituted piperidines (Scheme 78).[148] Thus imination of **238** with benzylamine followed by treatment with trimethylsilyl cyanide and silica gel gave the amino nitrile **239**. This was cyclized by the action of Triton B in methanol to give **240**. Formation of the iminium ion by treatment with silver triflate, followed by reaction with an alkylzinc reagent, gave the heavily substituted piperidines **241** in excellent yield and good selectivity.

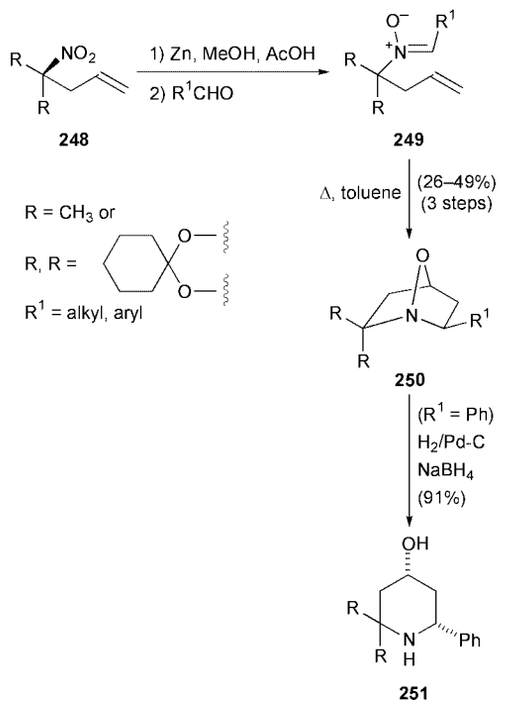
The asymmetric synthesis of non-racemic trifluoromethyl-substituted piperidines has been reported by Jiang and co-workers (Scheme 79).[149] Condensation of **242** and (+)-phenylglycinol, followed by enolization and triflation with Comins' reagent gave the lactam triflate **243**. This underwent a variety of palladium-catalyzed cross-coupling reactions with acetylenes, carbon monoxide, organocuprates and organozinc reagents. For example, treatment of **243** with propargyl alcohol, followed by a two-step hydrogenation gave the 2,6-disubstituted piperidine **245**. The analogous phosphate **246** was also prepared and shown to undergo Stille couplings. The so-formed 1,3-diene was trapped by an *in situ* Diels–Alder reaction with ethyl acrylate, leading to the decahydroquinoline **247** (after



Scheme 79

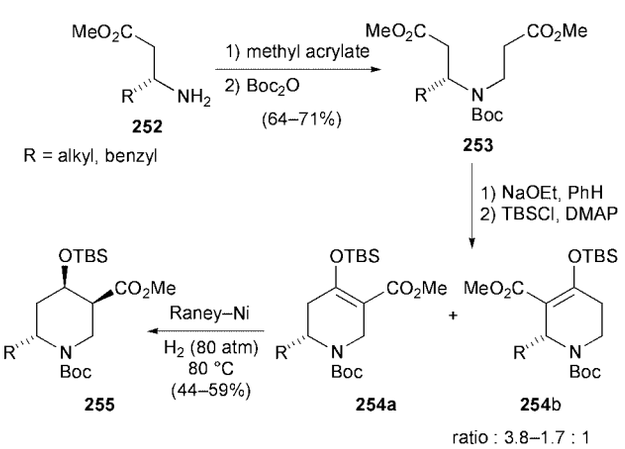
double-bond isomerization and hydrogenation). A similar transformation has been used in studies towards a synthesis of clavepictines A and B by Cha and co-workers.[150]

The 4-nitrobut-1-ene derivatives **248** have been reduced to hydroxylamines and condensed with aldehydes to give nitrones **249** by Sas and co-workers (Scheme 80).[151] Thermally promoted intramolecular 1,3-dipolar cycloaddition gave the bicycles **250**, which on hydrogenation gave the tetrasubstituted piperidines **251**.



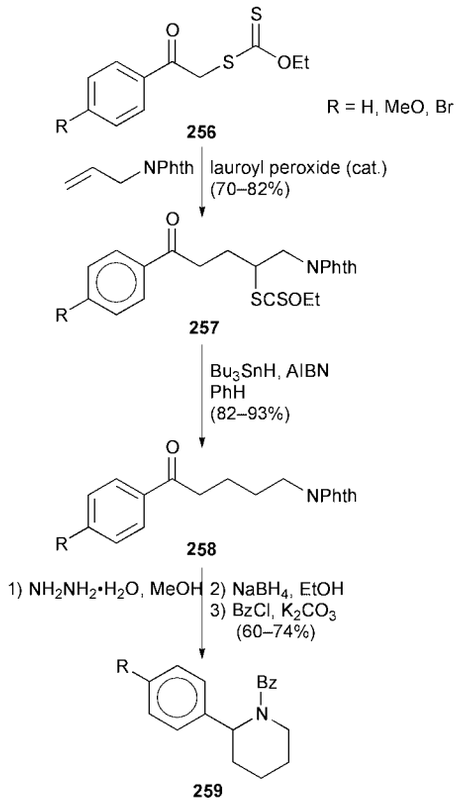
Scheme 80

Ma and Sun have described the synthesis of 2,4,5-trisubstituted piperidines (Scheme 81).[152] Starting with a β-amino ester **252**, addition of methyl acrylate gave diester **253**, following Boc-protection. Dieckman cyclization and protection of the hydroxy functionality as a silyl ether gave **254a**,**b** as an inseparable mixture. Fortunately, hydrogenation with Raney nickel selectively reduced **254a**, leaving **254b** unchanged, thus affording enantiomerically and diastereomerically pure **255** in reasonable yield.



Scheme 81

Zard and co-workers have described the synthesis of δ-aminoarylketones (*e.g.* **258**) by an intermolecular radical reaction (Scheme 82).[153] Treatment of **256** with lauroyl peroxide and a suitably protected allylic amine gave **257** in excellent yield. Removal of the xanthate grouping followed by cyclization in a conventional manner gave **259**. This reaction can also be extended to include the preparation of azepines.

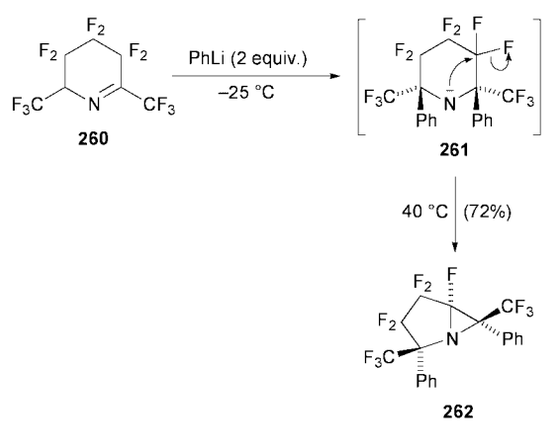


Scheme 82

6 Pyrrolizidines, indolizidines and quinolizidines

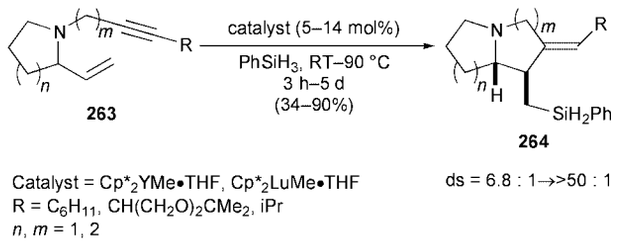
The large number of syntheses of pyrrolizidines and indolizidines that involve a 1,3-dipolar cycloaddition have been reviewed by Zecchi and Broggini.[154]

The curious polyfluorinated 1-azabicyclo[3.1.0]hexane **262** has been prepared, serendipitously, by Banks, Lawrence and co-workers (Scheme 83).[155] Starting from imine **260**, addition of two equivalents of phenyllithium, followed by warming to 40 °C, gave **262** in 72% yield. The driving force for the ring contraction was attributed to the release of strain caused by 1,3-diaxial interactions of the trifluoromethyl groups in **261**.



Scheme 83

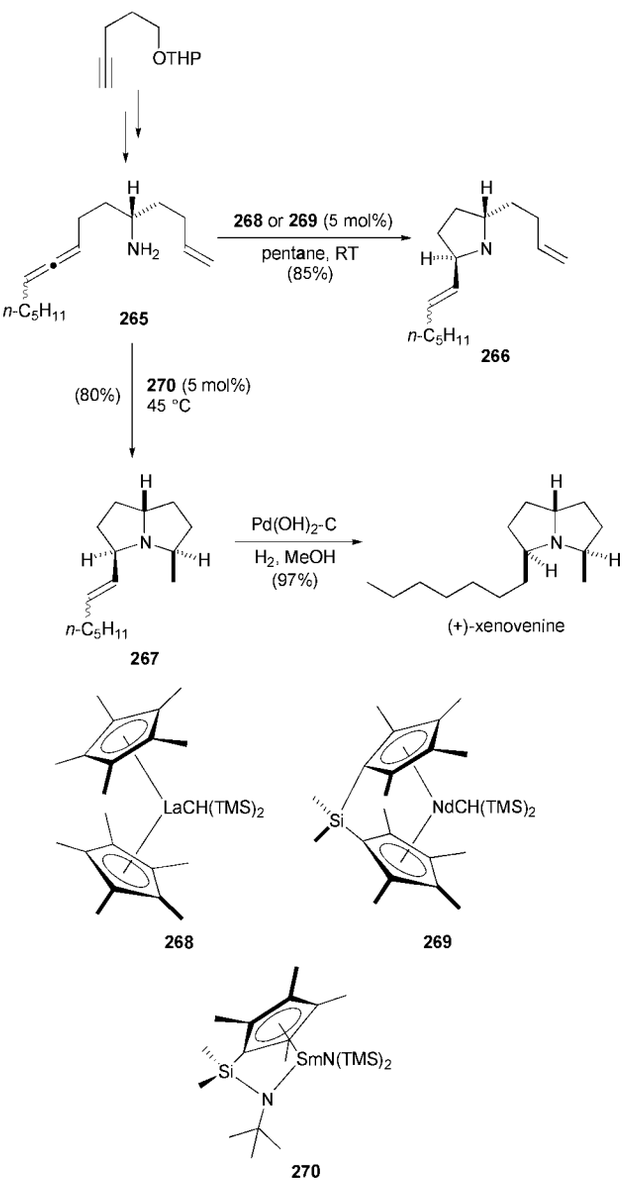
Molander and Corrette have described the organolanthanide-catalyzed cyclization–silylation of enynes to give nitrogen heterocycles (**263**→**264**, Scheme 84).[156] The Lu-containing catalyst, $Cp^*_2LuMe{\cdot}THF$, was found to be more active than the analogous yttrium catalyst, enabling the reaction to be performed at lower temperature. Unfortunately, it



Scheme 84

was not possible to convert the silane to the corresponding alcohol in reasonable yield, limiting the synthetic potential of this method at the moment.

Marks and co-workers have described the use of hydroamination pre-catalysts **268**–**270** in the synthesis of the natural product (+)-xenovenine (Scheme 85).[157] Pre-catalysts **268** and

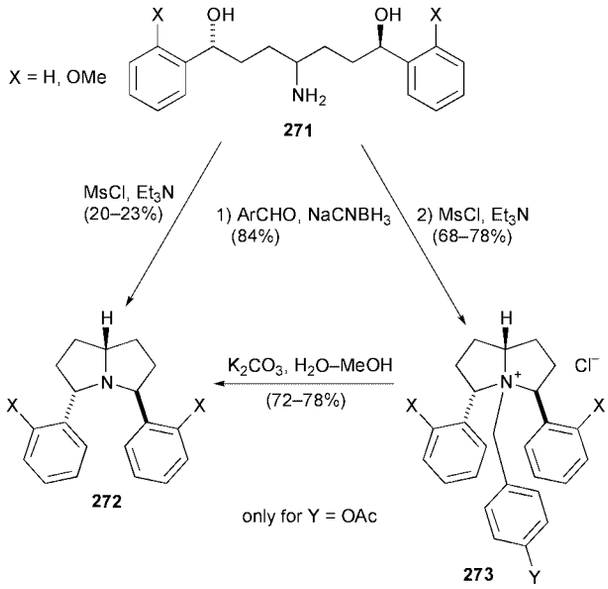


Scheme 85

269 gave only the monocyclic pyrrolidine **266** from **265**, whereas the organolanthanide **270** gave the bicyclic pyrrolizidine **267** directly in 80% yield.†

3,5-Diarylpyrrolizidines have been synthesized in more conventional fashion by Guarna and co-workers (Scheme 86).[158]

† Pyrrolizidine = hexahydropyrrolizine.



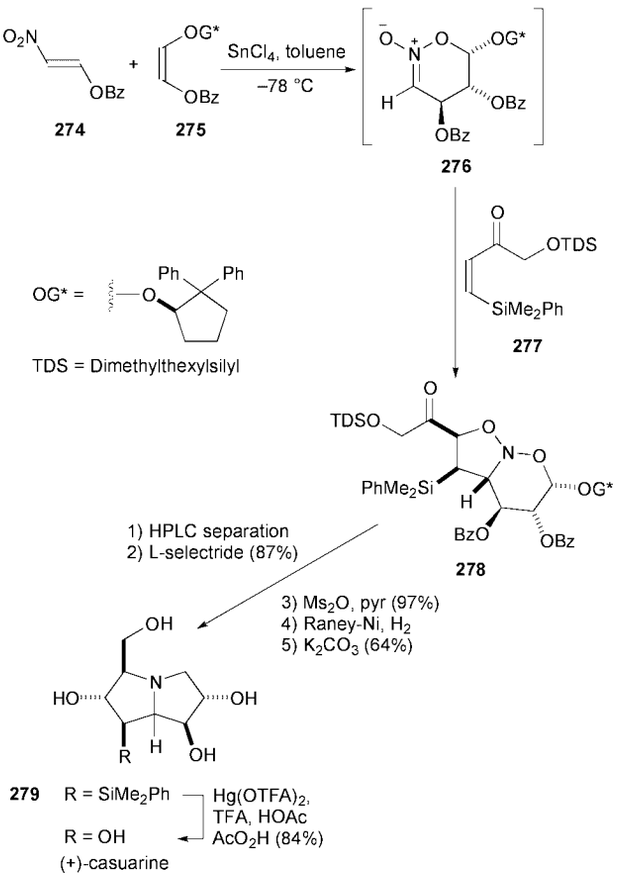
Scheme 86

Starting with enantiomerically pure aminodiol **271**, methanesulfonyl chloride-mediated ring closure gave the desired pyrrolizidine **272** with no loss of stereochemical purity, but only in modest yield. However, by benzylating the primary amino group prior to ring formation, the overall yield for forming the pyrrolizidinium salt **273** was greater. Deprotection proved very difficult, except for the 4-acetoxybenzyl derivative, which could be deprotected in excellent yield with aqueous base.

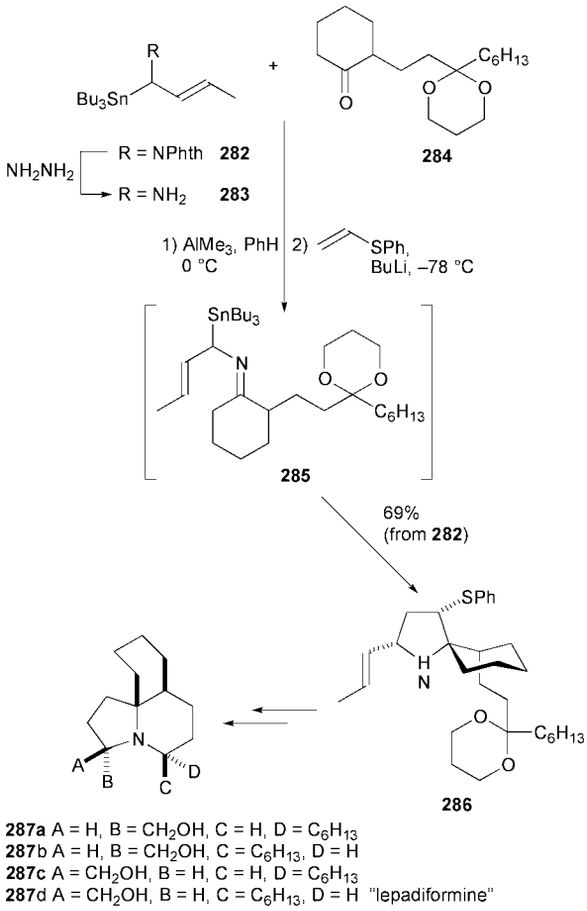
Denmark and Hurd have described the application of the [4 + 2]/[3 + 2] nitroalkene cycloaddition reaction to the total synthesis of the polyhydroxylated pyrrolizidine, (+)-casuarine (Scheme 87).[159] Starting with nitroalkene **274** and vinyl ether **275**, [4 + 2] cycloaddition afforded nitronate **276**, which was immediately reacted with **277** to give nitrosoacetal **278** as a complex mixture of diastereomers. The main diastereomer was isolated by HPLC; reduction, cyclization and deprotection then gave **279** in excellent yield. Finally, Fleming–Tamao oxidation furnished the natural product. Full details of a similar synthesis of a range of other polyhydroxylated pyrrolizidines and indolizidines, including (+)-australine and (+)-castanospermine have been disclosed.[160] Carretero and co-workers have described syntheses of related trihydroxylated pyrrolizidines.[161]

Montgomery and Tang have described the preparation of a range of pyrrolizidine, indolizidine and quinolizidine skeletons based on the nickel-catalyzed, triethylsilane-mediated reductive cyclization of pyrrolidines such as **280** (Scheme 88).[162] The diastereoselectivity was high, generally favoring **281a** (for $x = 2$, $y = 1$) and **281b** (for $x = 1$, $y = 0$). By constructing the appropriate cyclization precursor, (+)-allopumiliotoxin 267A was synthesized using this methodology. Two other pumiliotoxins, A and 225F, have been synthesized by Kibayashi and co-workers.[163] In addition, Holmes and co-workers have described a synthesis of the indolizidine core of the allopumiliotoxins that features an intramolecular nitrone dipolar cycloaddition as the key step.[164]

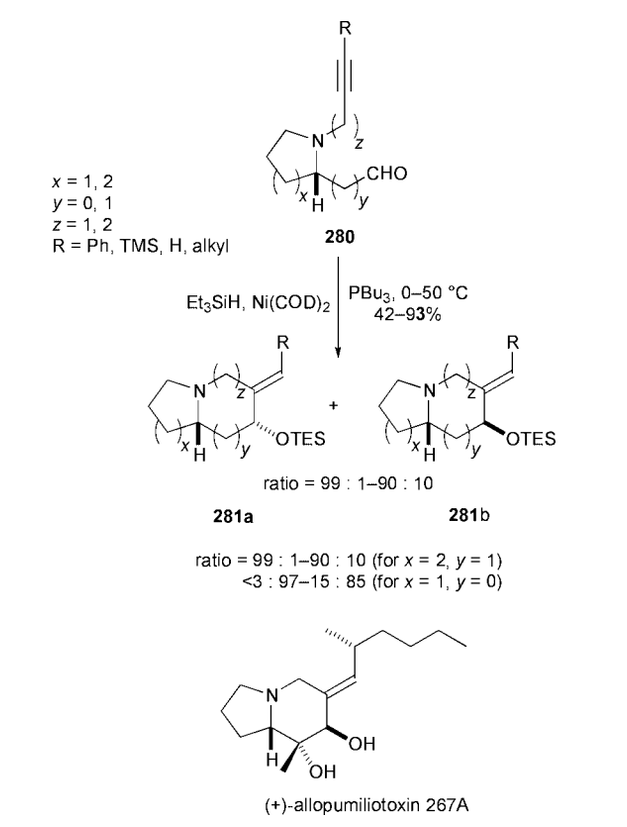
Two epimers of the putative structure of the marine alkaloid lepadiformine **287b**,**c** have been synthesized by Pearson and Ren (Scheme 89),[165] neither of which were found to be identical to naturally occurring lepadiformine. Isomer **287a** had been synthesized earlier and also found to be different to the natural product. The synthesis makes use of a 2-azaallyl anion cycloaddition between the anion obtained from Sn–Li exchange on **285** (itself derived from **283** and **284**) and vinyl phenyl sulfide to give **286** in 69% yield from **282**. This one-pot procedure results in higher yields than earlier attempts that involved isolation of the imine intermediate. Furthermore, Weinreb and co-workers



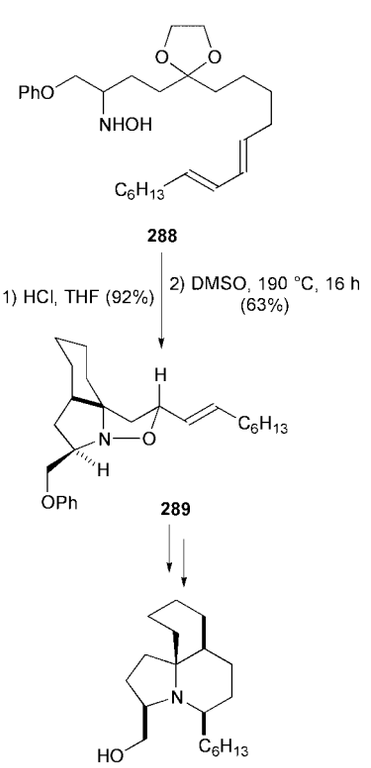
Scheme 87



Scheme 89



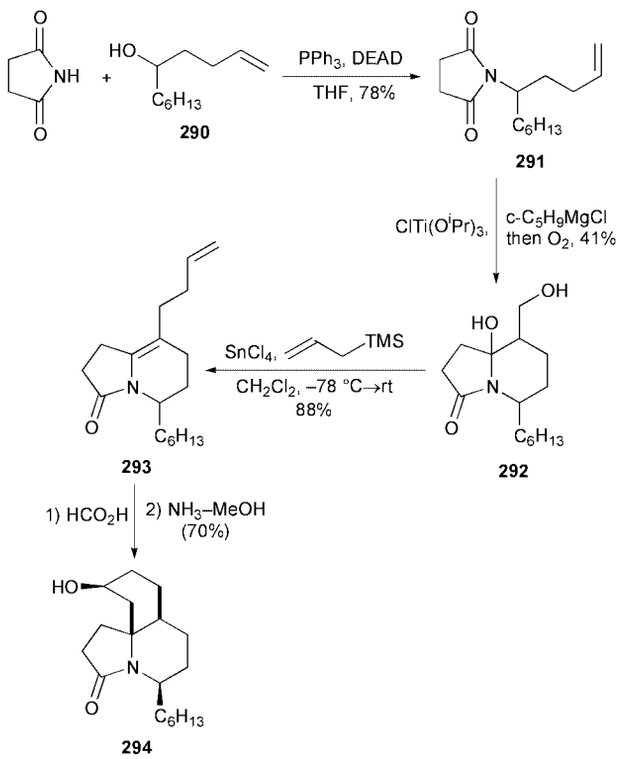
Scheme 88



Scheme 90

have described the synthesis of the remaining diastereoisomer, **287d** (Scheme 90),[166,167] which was also not identical to the natural product. The key step in Weinreb's synthesis was the intramolecular cycloaddition of the nitrone formed by hydrolysis of the acetal group in **288**. The product of this reaction (isoxazolidine **289**, obtained as a single regioisomer) was converted to the putative structure of lepadiformine **287d**. The structure of naturally occurring lepadiformine remains unclear.

Hiemstra, Rutjes and co-workers[168] have applied some chemistry reported in full by Cha and co-workers[169] to the very efficient synthesis of the lepadiformine skeleton (Scheme 91). Thus, alkylation of succinimide with **290** gave **291**. Treatment of this with the Kulinkovich reagent effected cyclization to give **292**. Formation of an extended iminium ion by treatment of **292** with tin tetrachloride, followed by quenching with allyltrimethylsilane gave **293**. Treatment of **293** with formic acid, followed by quenching with ammonia–methanol gave **294** (again *via* an iminium ion) in 70% yield.



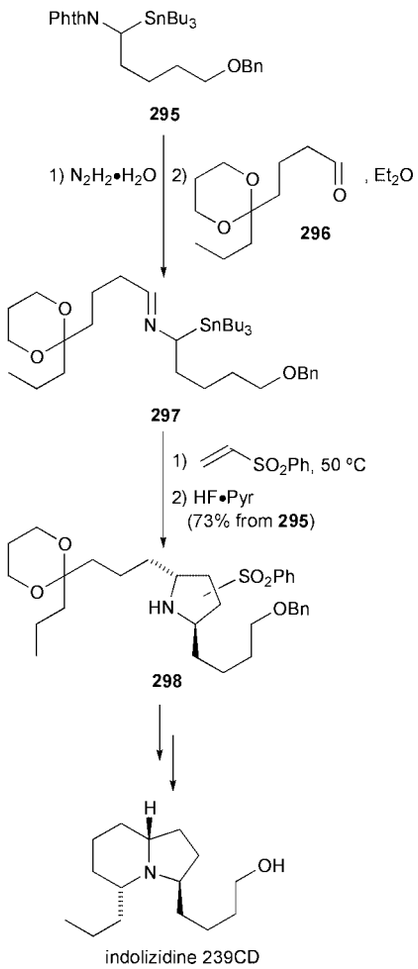
Scheme 91

The synthesis of indolizidine 239CD has been reported by Pearson and Clark (Scheme 92).[170] Condensation of the amine derived from **295** and aldehyde **296** gave imine **297**, which was treated directly with phenyl vinyl sulfone and HF·pyridine to give **298**, *via* a *non-stabilized* azomethine ylide. Two further steps, followed by reductive desulfonylation gave the natural product. Grigg and co-workers[171] have described a similar approach to pyrrolizidines and indolizidines, making use of an azomethine ylide cycloaddition reaction, followed by an intramolecular reductive amination.

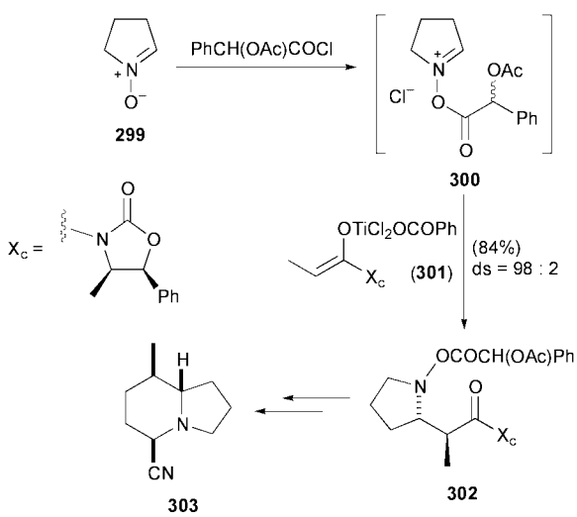
Indolizidine 167B has been synthesized by Back and Nakajima,[172] Chênevert and co-workers[173] and Remuson and co-workers.[174] Chênevert and co-workers have also described the synthesis of indolizidine 209D;[175] indolizidine 237A has been synthesized by Lhommet and co-workers;[176] monomorine I by Bäckvall and co-workers,[177] and slaframine by a number of research groups.[120,178,179] Many syntheses of polyhydroxylated indolizidines have been reported, reflecting their potential as antiviral glycosidase inhibitors.[180–185]

Murahashi and co-workers have described the synthesis of β-amino acid derivatives **302**, by the diastereoselective addition of a chiral titanium enolate **301** to the acyloxyiminium ion **300** (Scheme 93).[186] The product obtained from this reaction can be readily converted into nitrile **303**, a key intermediate for the synthesis of many indolizidine alkaloids.

The interesting transannular cyclization of *meso*-epoxide **304** to give the indolizidine skeleton has been reported (Scheme 94).[187] Under optimal conditions, deprotonation of **304** at the position α to the epoxide with *i*PrLi gave **307** in 57% yield



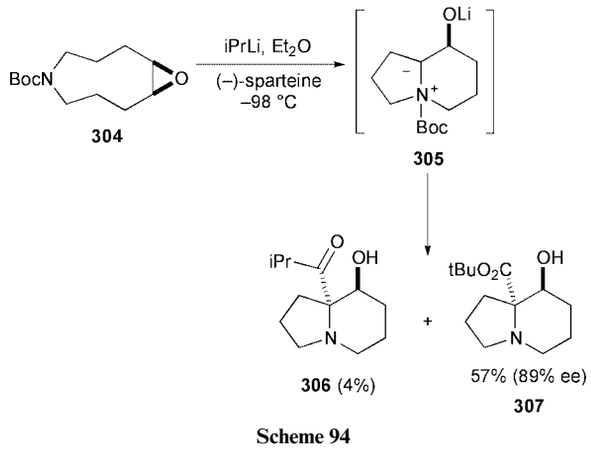
Scheme 92



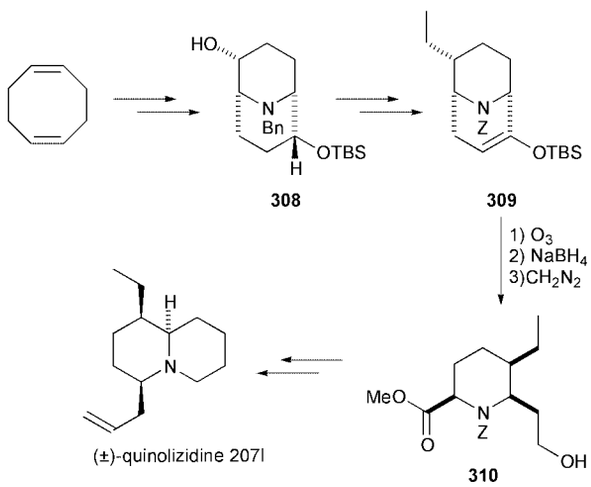
Scheme 93

(89% ee). The reaction was postulated to proceed *via* ammonium ylide **305** and subsequent [1,2]-migration of the Boc group. The side product **306** was also formed in variable amounts.

The quinolizidine natural products clavepictine A and B have been synthesized by Cha and Ha[150] and Toyooka and co-workers.[188] A synthesis of (±)-quinolizidine 207I, an alkaloid obtained from a Madagascan mantelline frog, from cycloocta-1,5-diene has been reported (Scheme 95).[189] The key step in this synthesis involves ozonolysis of the bicyclic structure **309**, to give **310** after reductive work-up. Homologation and functional



Scheme 94

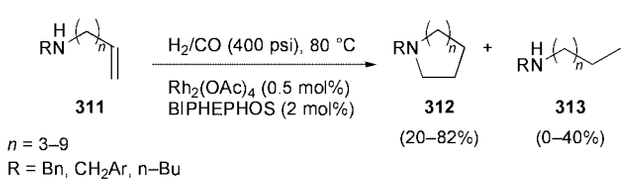


Scheme 95

group interconversion then gave the natural product in 17 steps and 6.8% overall yield from **308**.

7 Medium and large rings

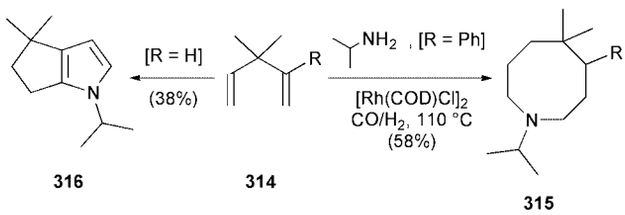
The rhodium-catalyzed hydroformylation of a range of aminoalkenes to give medium- and large-ring cyclic amines has been reported (Scheme 96).[190] Treatment of **311** with H_2–CO (ratio between 9 : 1 and 1 : 5) gave the cyclic amine **312** in good to excellent yield (particularly for smaller ring sizes) but also significant quantities of the aminoalkane **313**.



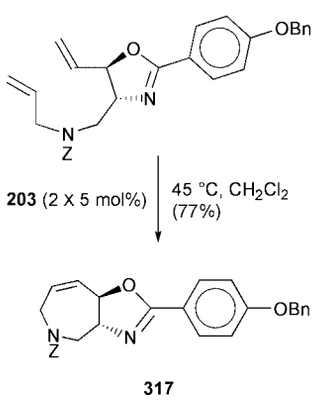
Scheme 96

Eilbracht and co-workers have reported a single example of a hydroformylation of 1,4-diene **314** in the presence of a primary amine (Scheme 97)[191] yielding 8-membered heterocycle **315** in 58% yield. If the double bond is not substituted (R = H), the pyrrole **316** is formed instead.

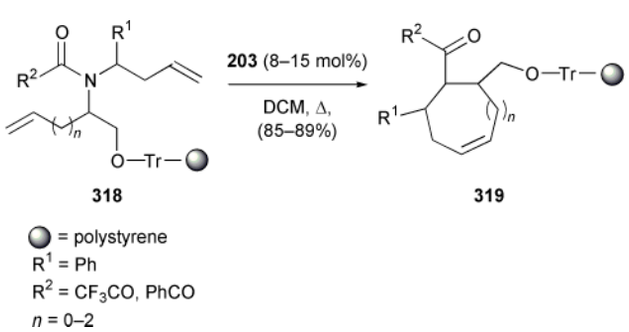
Ring-closing metathesis continues to feature heavily in the synthesis of medium and large rings. Examples include Cook's synthesis of balanol (**317**, Scheme 98),[192] Blechert's solid-phase synthesis of a series of 6-, 7- and 8-membered azacycles (**318**→**319**, Scheme 99),[193] Holmes' synthesis of bicyclic lactams



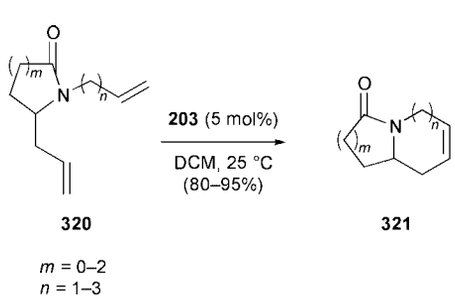
Scheme 97



Scheme 98



Scheme 99

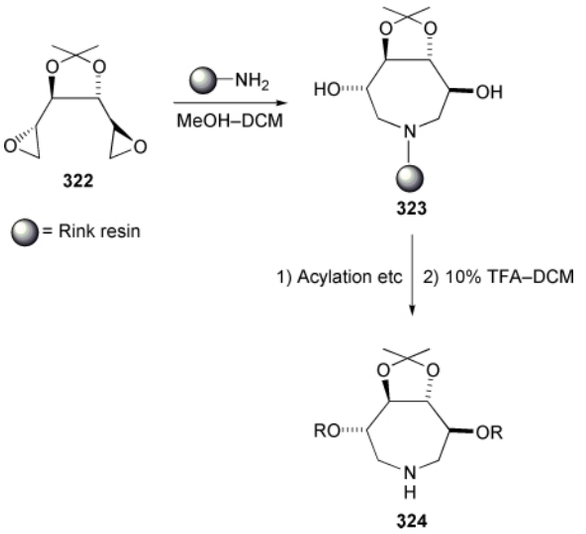


Scheme 100

(**320**→**321**, Scheme 100)[194] and Goldring's synthesis of motuporamines A–C.[195]

The synthesis of azepines on a solid support has been described.[196] Reaction of L-iditol-bis(epoxide) **322** in dichloromethane–methanol solution with Rink resin (Scheme 101) gave azepine **323** at a loading of 0.23 mmol g^{-1}. Higher loadings could be achieved by heating the reactants in DMF at 80 °C, but this caused some degradation of the resin. The secondary hydroxy groups could be readily acylated or alkylated and the products released from the resin by treatment with TFA in dichloromethane (**323**→**324**).

Polyhydroxylated azepines have also been synthesized from a variety of glycosylenamines as shown in Scheme 102.[197] Treatment of these with one equivalent of sodium methoxide in HMPT, followed by cleavage of the enamido protecting group gave azaanhydrosugar **326**. This was converted into the hemi-



Scheme 101

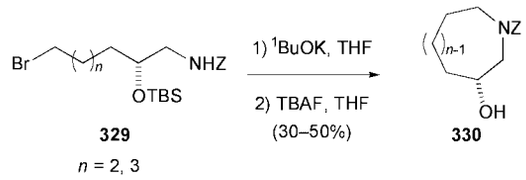
aminal **327** by treatment with acid, or the azepine **328** by reduction.

The seven- and eight-membered nitrogen heterocycles **330** have been formed in moderate yield by cyclization of ω-bromoaminoalcohols **329** (obtained by reduction of the corresponding enantiomerically pure cyanohydrin) by treatment with potassium *tert*-butoxide (Scheme 103).[198] Larger ring sizes ($n = 4$, 5) did not undergo cyclization and other bases were unsuccessful at promoting the reaction.

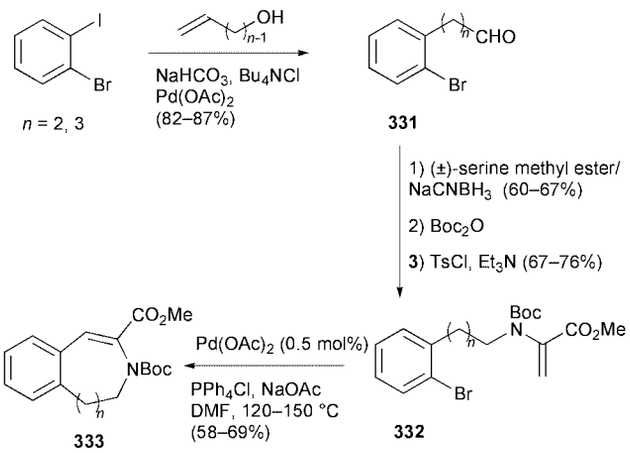
Constrained phenylalanine mimics **333** ($n = 2$, 3) have been synthesized in only five steps from 1-bromo-2-iodobenzene as shown in Scheme 104.[199] The key step involved the intramolecular Heck reaction of bromide **332**, a reaction that only works well in the presence of PPh_4Cl.

8 Tetrahydroisoquinolines and tetrahydroquinolines

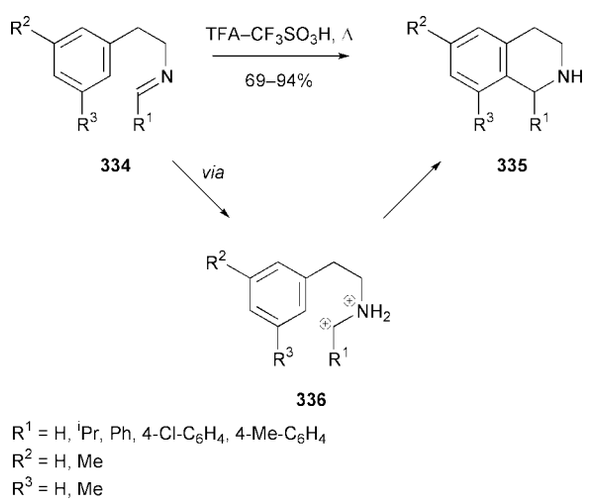
New studies on the Pictet–Spengler reaction, in which the imine of a (2-arylethyl)amine **334** gives a 1,2,3,4-tetrahydroisoquinoline **335**, have shown that superacids can act as catalysts for the cyclization (Scheme 105).[200] Kinetic studies revealed that ammonium carbenium dications **336** act as superelectrophiles in these reactions. The implication of this is that Pictet–Spengler reactions need not necessarily be restricted to activated substrates with strongly electron-donating groups on the cyclizing benzene ring. Variations of the Pictet–Spengler reaction in which chiral auxiliaries[201] or aryl groups in the imine[202] have been used to control stereochemistry in the product have also been described. Asymmetric reductions of 3,4-dihydroisoquinolines to yield their 1-substituted tetrahydro analogues have been reported, using Noyori transfer hydrogenation[203,204] or chiral auxiliary control.[205]



Scheme 103

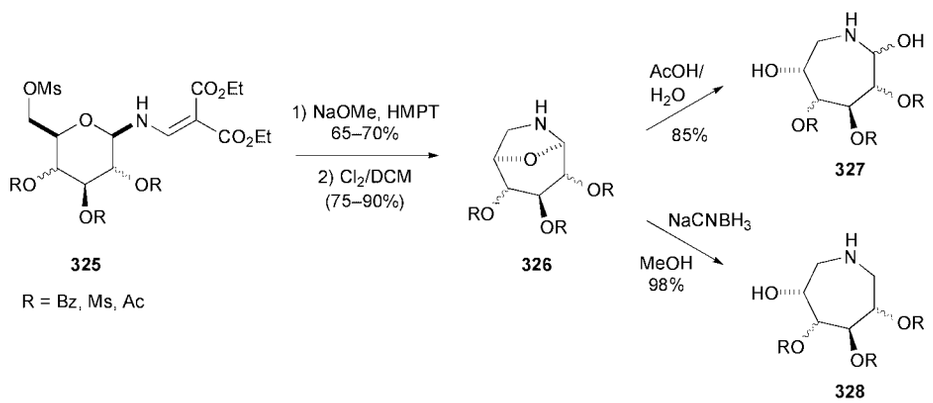


Scheme 104

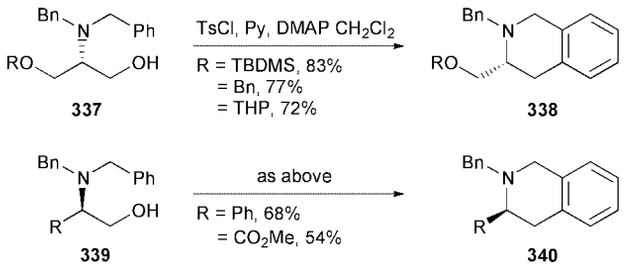


Scheme 105

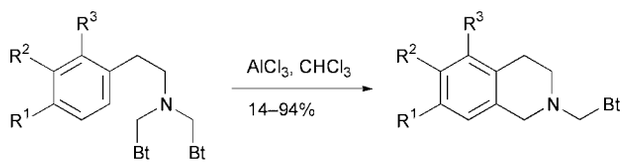
A serendipitous discovery of a new tetrahydroisoquinoline synthesis was made during the tosylation of *N*,*N*-dibenzylaminols **337** and **339** (Scheme 106).[206] The products **338** and **340** were thought to arise from tosylation of the alcohol followed by Friedel–Crafts cyclization. Friedel–Crafts cyclizations medi-



Scheme 102



Scheme 106

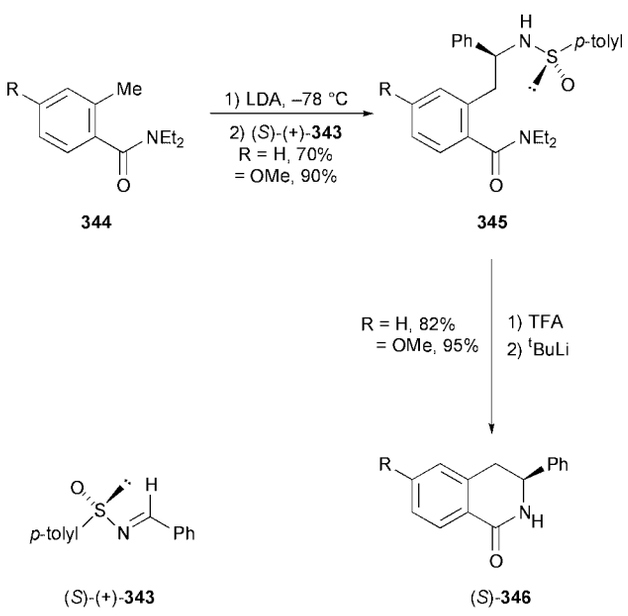


R^1 = H, Cl, OMe
R^2 = H, OMe
R^3 = H, Cl
(R^1 = R^3 = Cl, R^2 = H, no reaction)

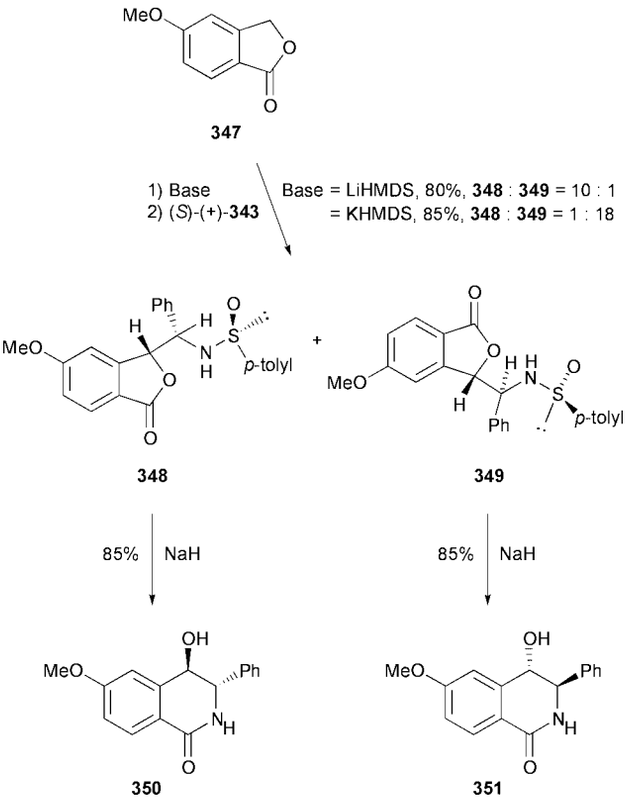
Scheme 107

ated by the benzotriazole auxiliary have also been reported (Scheme 107).[207] The readily prepared phenylethylamines **341** were ring-closed under the action of aluminium trichloride, yielding tetrahydroisoquinolines **342**. Ring-closure did not occur if the phenyl ring was too deactivated by electron-withdrawing groups.

Enantiopure sulfinimine **343** has been used in the asymmetric synthesis of tetrahydroisoquinolines (Scheme 108).[208] Two approaches were used; in the first, lithiated toluene-2-carboxamide **344** was treated with **343** to yield intermediate **345**. Removal of the sulfur moiety with trifluoroacetic acid was followed by ring-closure to yield the product **346**, as the (*S*)-isomer. Alternatively, the phthalide **347** was reacted with **343** in the presence of base, yielding predominantly **348** or **349**, depending on the counterion used (Scheme 109). Treatment with sodium hydride then yielded the appropriate tetrahydroisoquinolone **350** or **351**. After further derivatization, the products could be reduced to tetrahydroisoquinolines with borane–dimethyl sulfide complex.

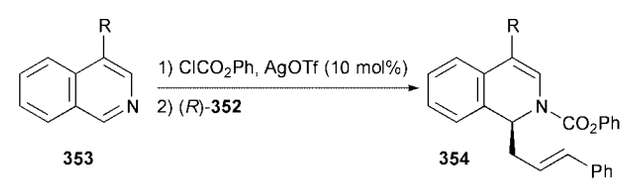


Scheme 108

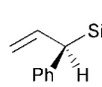


Scheme 109

Chiral allylsilane **352** has been added stereoselectively to isoquinolines **353** upon activation with silver triflate and phenyl chloroformate (Scheme 110).[209] The chirality transfer was excellent (93–95%) but the silane **352** was only available in 81–83% enantiomeric excess, thus limiting the enantiopurity of the products **354**.



(*R*)-**352** =



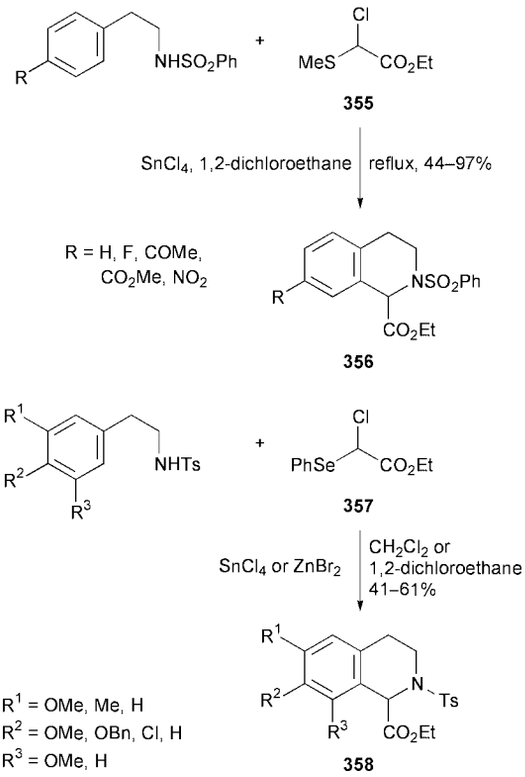
ee = 81–83%

R	Yield (%)	Ee (%)	Enantioselectivity (%)
H	54	77	95
Br	86	78	94
CO_2Me	78	77	93

Scheme 110

Two very similar procedures have been published for the preparation of tetrahydroisoquinolines from *N*-sulfonyl-β-phenethylamines and either α-chloro-α-thio-[210] or α-chloro-α-selenoesters (Scheme 111).[211] In the reactions with thioester **355**, products **356** were obtained in good yield, but problems were encountered in removing the benzenesulfonyl group. The yields of **358** obtained from reactions with the selenoester **357** were not as high, but modest diastereoselectivity was observed when a chiral sulfonamide and/or optically active ester were used.

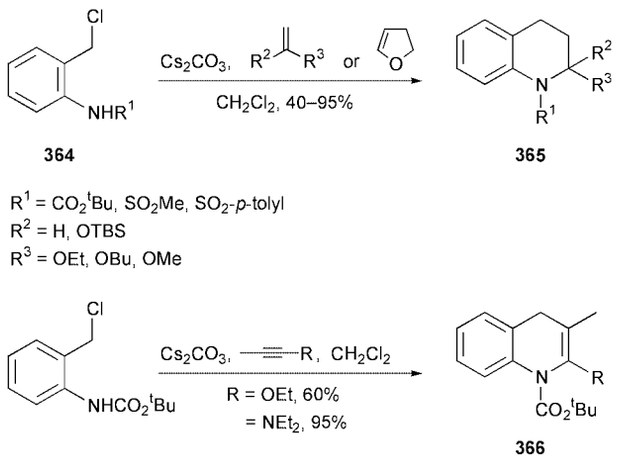
Trimethylsilyl tetrahydroquinolines **361** have been prepared by the addition of allylsilanes **360** to *N*-aryl-1*H*-benzotriazol-1-ylmethanamines **359** (Scheme 112).[212] The reaction proceeds *via* the ion pair **362**, which yields cationic intermediate **363** upon reaction with allylsilane. Intramolecular electrophilic aromatic attack finally yields the products **361** in good yields.



Scheme 111

The procedure allows the formation of a quaternary carbon at the 4-position of the product, which is difficult to achieve by other methods.

Base-induced elimination of hydrogen chloride from amide or sulfonamide derivatives of 2-chloromethylaniline **364** has been reported, generating 2-azaxylylenes, which could then be trapped with electron-rich alkenes to afford tetrahydroquinolines **365** (Scheme 113).[213] Electron-rich alkynes yielded dihydroquinolines **366**.



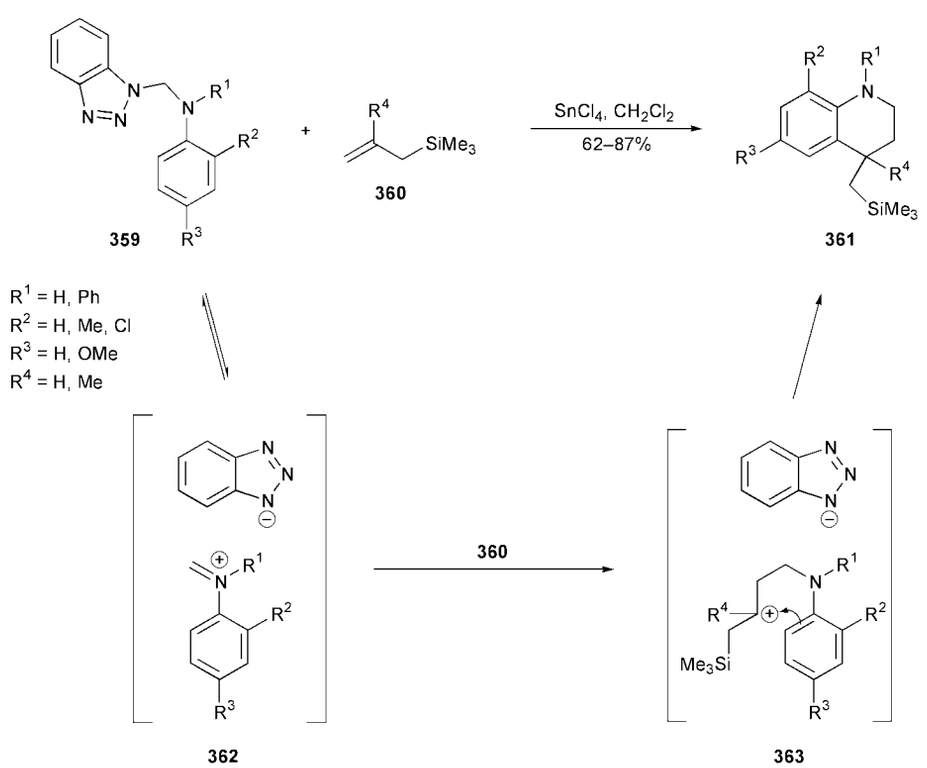
Scheme 113

Isoindolines **369** have been prepared in two steps from furans **367** (Scheme 114).[214] Intramolecular Diels–Alder reactions of **367** yielded the oxatricycloadducts **368**, which aromatized in a mixture of hydrobromic acid and acetic acid, affording products **369**. Other acids were ineffective at aromatization, or furnished intractable resins.

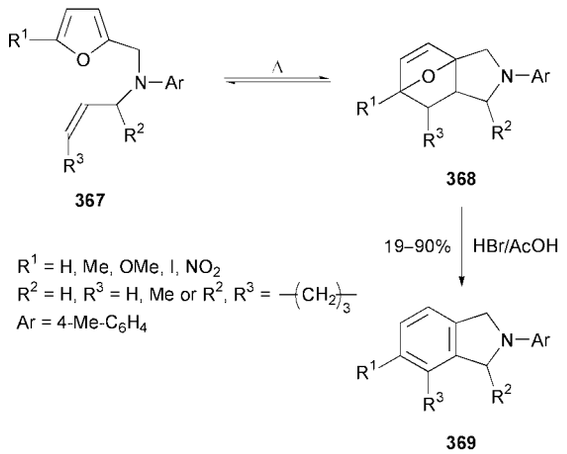
9 Methods for the synthesis of two or more ring sizes

3-Oxoazetidines, -pyrrolidines and -piperidines **371** have been prepared by copper(II)-catalyzed intramolecular N–H insertion of α-diazocarbonyls **370** (Scheme 115).[215] Competitive C–H carbenoid insertion was not found to be a problem, as is often the case for the rhodium(II)-catalyzed reaction. Azepines could not be prepared in this way, and *N*-Boc protected substrates yielded complex mixtures. Simple substituents such as methyl, benzyl and $MeSCH_2CH_2$ could be accommodated by these conditions.

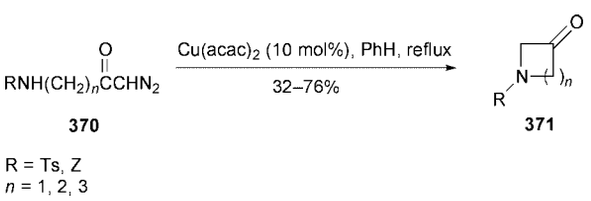
Palladium(0)-catalyzed cyclizations of β-aminoallenes **372** have been reported, yielding azetidines **373** or piperidines **374** depending on the reaction conditions (Scheme 116).[216] Reactions of **372** with aryl iodides afforded predominantly



Scheme 112



Scheme 114



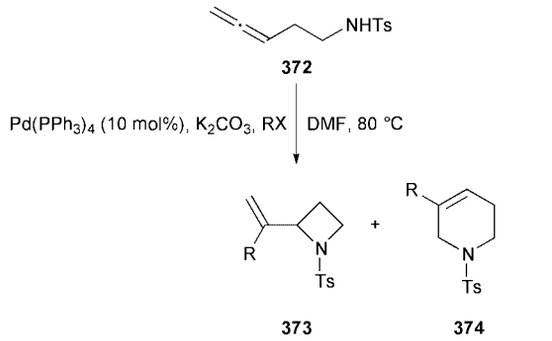
Scheme 115

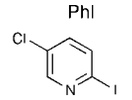
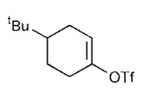
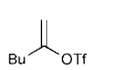
piperidines, although with shorter reaction times the kinetically preferred azetidines could be isolated as major products. Vinyl triflates favored azetidine formation.

Palladium(0)-catalyzed cyclizations of allenes **375** in the presence of hypervalent iodonium salts have also been reported, yielding pyrrolidines and piperidines **376** (Scheme 117).[217] Treatment of allenes **375** with the aryl salt 4-MeO-$C_6H_4I^+PhBF_4^-$ resulted in a mixture of products, in which either of the two aryl groups had been incorporated into the final heterocycle.

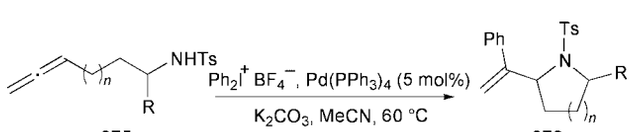
Moderately enantioenriched 2-substituted pyrrolidines **378** and piperidines **380** have been prepared from *N*-(haloalkyl)-allylamines **377** and **379** (Scheme 118).[218] Asymmetric deprotonation occurred in the presence of (−)-sparteine, but the enantio-determining step was found to be asymmetric cyclization influenced by the chiral ligand. Intramolecular ring opening of an epoxide ring was also demonstrated under these conditions.

Katritzky's benzotriazole methodology has been applied to



RX	Reaction time	Ratio **373** : **374**	Yield (%)
PhI	0.5 h	67 : 33	67
PhI	40 h	10 : 90	34
	4 h	25 : 75	55
	10 min	100 : 0	34
	15 min	95 : 5	41

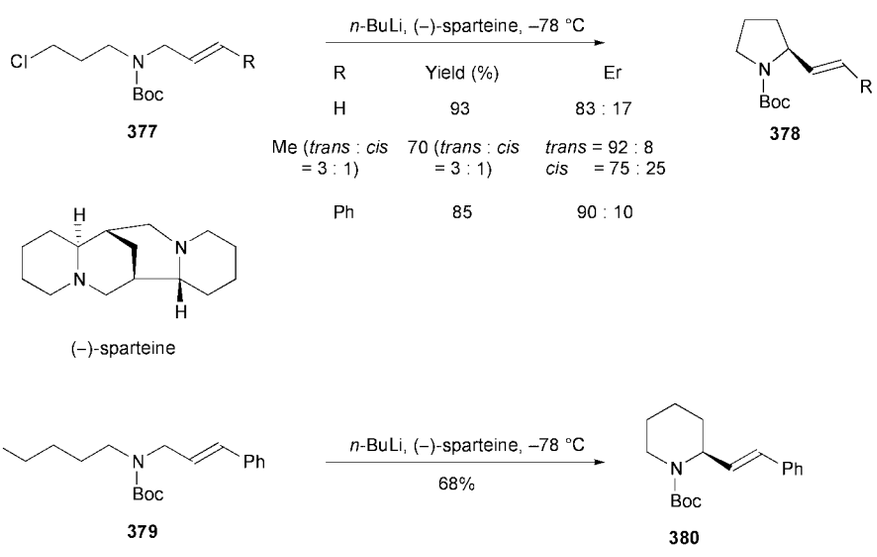
Scheme 116



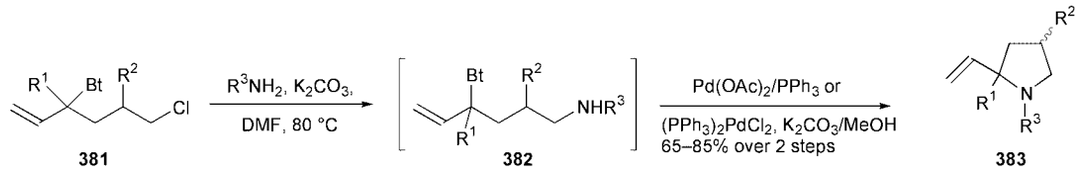
n	R	Yield (%)	
1	H	95	
1	Me	78	(*cis* : *trans* = 2 : 3.2)
2	H	82	

Scheme 117

palladium(II)-catalyzed intramolecular allylamination reactions, allowing the preparation of 2-vinylpyrrolidines **383** and piperidines **385** (Scheme 119).[219] A one-pot procedure was developed, so that chlorides **381** and **384** could be converted to the products **383** and **385** respectively without purification of the intermediates (*e.g.* **382** in the pyrrolidine preparations).

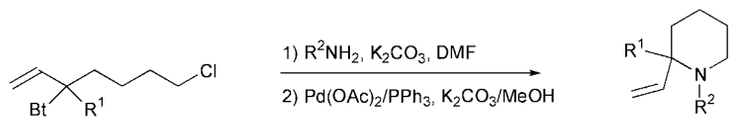


Scheme 118



381 **382** **383**

R^1 = H, Me, Bn
R^2 = H, Me
R^3 = alkyl, Bn, $EtOCH_2CH_2$, $Et_2NCH_2CH_2$

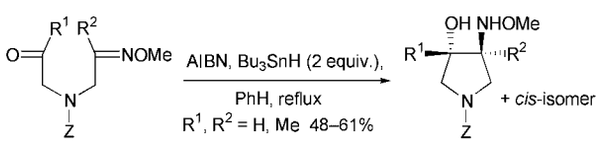


384 **385**

R^1	R^2	Yield (%)
H	Bn	85
H	*n*-C_6H_{13}	80
Bu	Bn	80

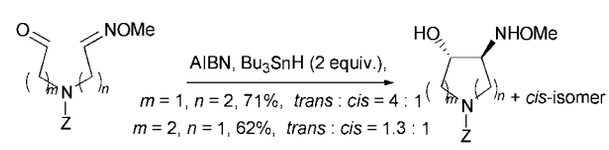
Scheme 119

Radical addition–cyclization of oxime ethers connected to aldehydes or ketones (**386**–**388**) has furnished predominantly *trans*- five- to seven-membered cyclic aminoalcohols (**389** to **391**, Scheme 120).[220] Portionwise addition of stoichiometric AIBN improved the cyclization yields, and no reduction products of the carbonyls or oxime ethers were seen. The attempted formation of an eight-membered ring was unsuccessful.

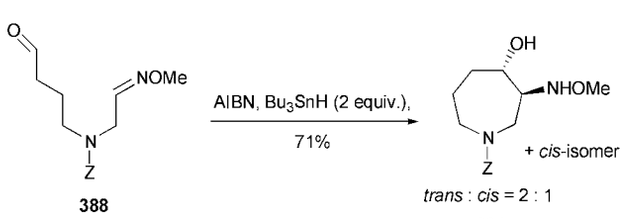


386 **389**

trans : *cis* = 14 : 1 to 2.3 : 1



387 **390**



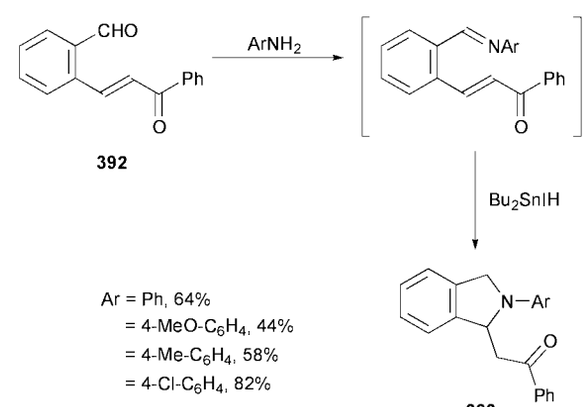
388

trans : *cis* = 2 : 1

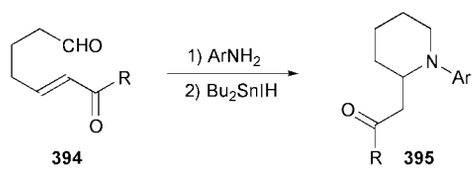
391

Scheme 120

Di-*n*-butyliodotin hydride has been shown to selectively reduce imines in the presence of enones, allowing a new preparation of isoindolines **393** and piperidines **395** (Scheme 121).[221] The imines were prepared *in situ* by condensation of aldehydes **392** or **394** with anilines. It was suggested that the tin iodide promoted the formation of iminium ion **396**, which would be more rapidly reduced than the enone (Scheme 122). The resulting iodo-substituted tin amide **397** is still sufficiently nucleophilic to effect intramolecular Michael addition.



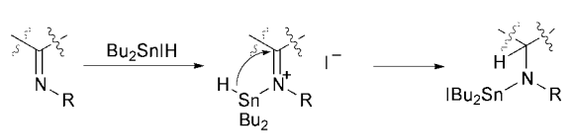
392 **393**



394 **395**

R	Ar	Yield (%)
Ph	Ph	56
Ph	4-Me-C_6H_4	67
Ph	4-Cl-C_6H_4	80
Me	4-Cl-C_6H_4	64

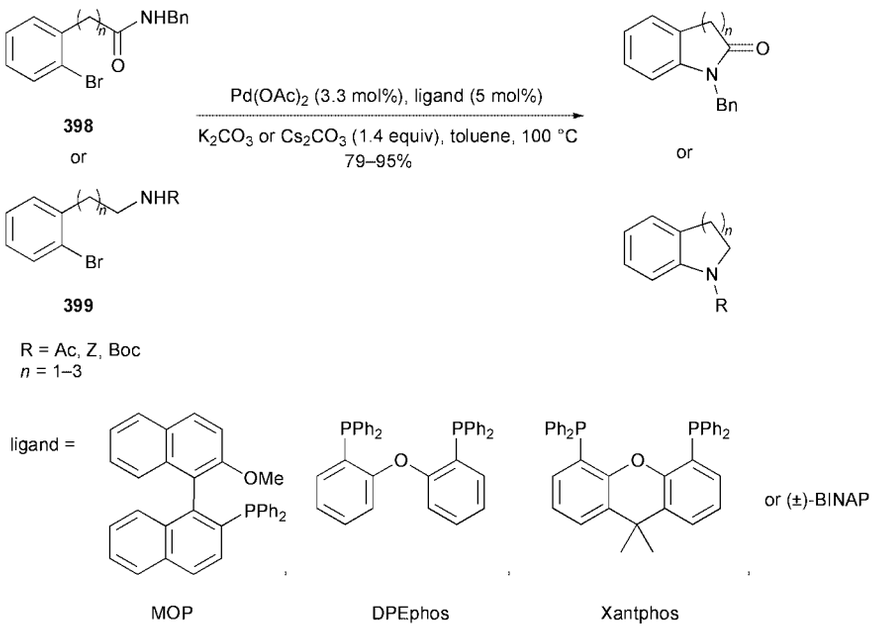
Scheme 121



396 **397**

Scheme 122

Buchwald and Yang have revisited the palladium(II)-catalyzed cyclization of aryl bromides with pendant secondary amides **398** or carbamates **399** (Scheme 123).[222] The use of ligands capable of chelation, such as (±)-MOP, DPEphos and Xantphos, has enabled the reactions to proceed in higher yields, but with less catalyst than in previously reported procedures. Seven-membered ring formations have also been performed in good yields for the first time.



Scheme 123

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