Saturated nitrogen heterocycles

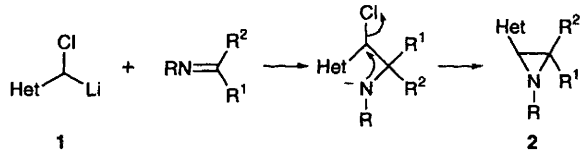
TIMOTHY HARRISON

Merck Sharp and Dohme Research Laboratories, Neuroscience Research Centre, Terlings Park, Eastwick Road, Harlow, Essex CM20 2QR, UK

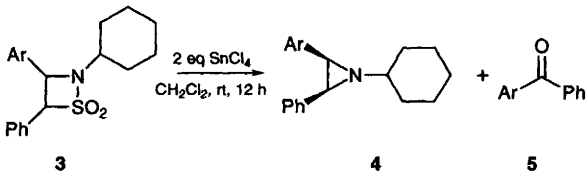
Reviewing the literature published in 1995
Continuing the coverage in *Contemporary Organic Synthesis*, 1995, **2**, 209

1 Three-membered rings

Heteroaryl aziridines **2** (Het = 2-pyridyl, 2-quinolyl and 2-benzathiazoyl) of (*E*)-configuration have been prepared by the diastereoselective Darzens-type reaction of (heteroarylchloromethyl)lithiums **1** with imines. The (heteroarylchloromethyl)lithium species are readily available by lithiation of the corresponding chloromethyl heterocycles (LDA, THF, −78 °C), and the addition works well with both nonenolizable and enolizable imines.[1] Diaryl aziridines **4** can be prepared in moderate to good yields by reaction of *cis*-β-sultams **3** with $SnCl_4$. The desired product is accompanied by smaller amounts of benzophenone derivative **5**. If the *trans*-β-sultams are used, then the benzophenone derivatives predominate.[2]

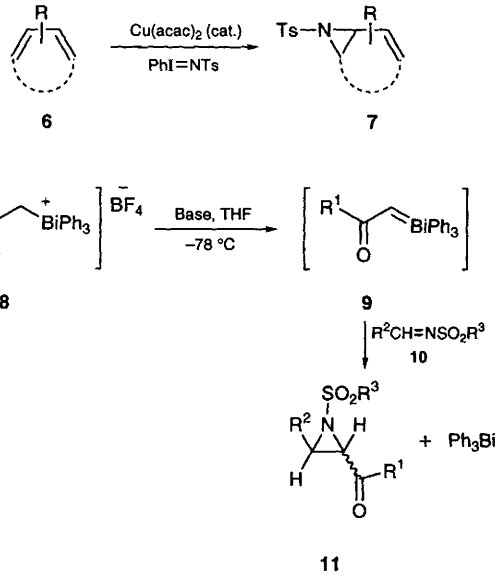


1 **2**



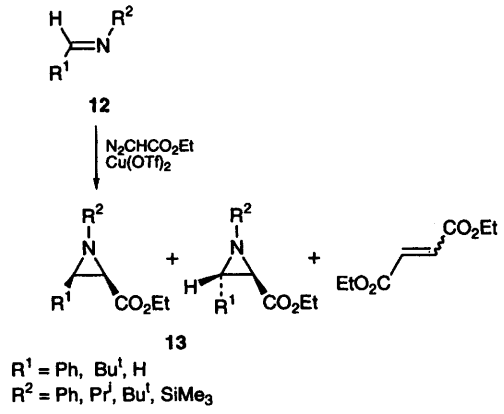
3 **4** **5**

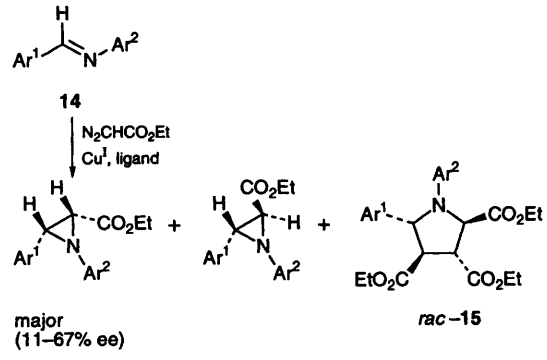
Relatively sensitive *N*-tosyl vinyl aziridines **7** can be prepared in moderate to high yield by the $Cu(acac)_2$-catalysed aziridination of 1,3-dienes using PhI=NTs. Both acyclic and cyclic dienes can be used, and in some cases the reactions appear to be stereospecific with retention of double bond geometry. For unsymmetrical dienes, the more electron rich double bond undergoes aziridination, and when two double bonds are electronically similar, steric factors govern the selectivity.[3] Matano *et al.* have reported a direct route to 2-acylaziridines **11** starting from imines **10** utilising a bismuthonium ylide **9** generated *in situ* from bismuth salt **8**. This mode of reaction stands in marked contrast to that of phosphonium ylides, and the *cis/trans* stereochemistry of the products can be controlled by proper choice of base and additive.[4]



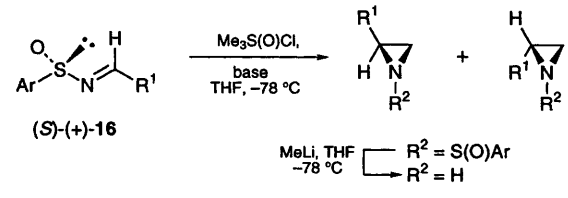
A number of papers detailing asymmetric syntheses of aziridines have appeared. Thus, Jorgensen *et al.* have reported the preparation of aziridines **13** *via* the addition of ethyl diazoacetate to imines **12** catalysed by simple copper complexes. The diastereoselectivity and yield of the reaction is very dependant on the nitrogen substituent R^2, with phenyl giving the highest yields and silicon the highest diastereoselectivity. The incorporation of a chiral auxilliary in the diazoacetate portion produced products with a low de, and the use of

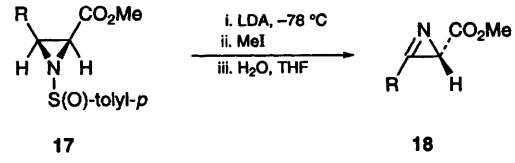
$Cu(OTf)_2$ in the presence of a chiral oxazoline ligand produced aziridines with low ee's.[5] In a related study Jacobsen *et al.* have reported the same reaction using *N*-aryl benzylidine imines **14** as precursors and copper(I) hexafluorophosphate as the catalyst in the presence of homochiral bis-oxazolines. At present enantiomeric excesses are low to moderate, and efforts to extend this aziridination methodology to other classes of imines have not been fruitful. In some instances racemic pyrrolidines **15** are also produced in the reaction.[6]





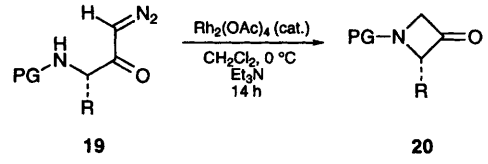
Both Davis[7] and Ruano[8] have reported the asymmetric synthesis of 2-substituted aziridines by addition of dimethyloxosulfonium methylide to enantiomerically pure sulfinimines **16**. In the Davis work the de's proved to be relatively insensitive to the reaction conditions (58–70% de). After separation of the diastereoisomers, the *N*-sulfinyl group can be removed by treatment with 1.5 equiv. of methyllithium at −78 °C followed by quenching with sat. NH_4Cl. Davis *et al.* have also reported an asymmetric synthesis of 2*H*-azirine 2-carboxylic acid derivatives **18** by LDA-induced deprotonation of aziridines **17** in the presence of iodomethane.[9] The 2*H*-azirine structural unit is found in a number of natural antibiotics.





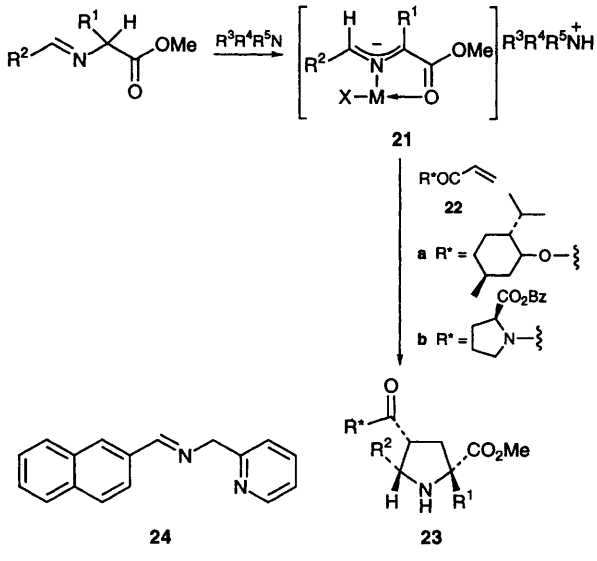
2 Four-membered rings

Seebach *et al.* have described a new synthetic approach to the relatively unexplored azetidine-3-one derivatives **20**. Thus amino acid derived diazo ketone **19** undergoes Rh^{II}-catalysed cyclisation to provide the products in 50–60% yield after chromatography.[10]



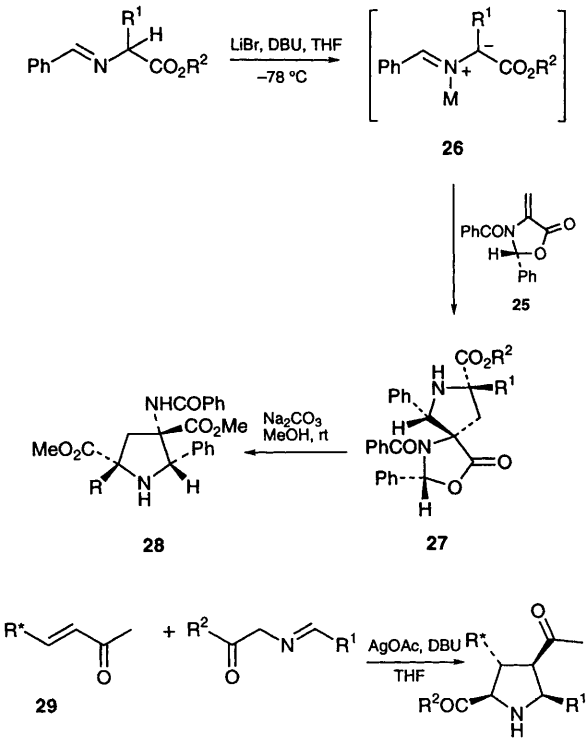
3 Five-membered rings

The asymmetric synthesis of pyrrolidine derivatives by 1,3-dipolar cycloaddition of azomethine ylides with alkenes in the presence of chiral controller groups continues to attract attention. Grigg *et al.* have shown that metallo-azomethine ylides **21**, generated from imines by the action of amine bases, undergo cycloaddition with menthyl acrylate **22a** at room temperature to give homochiral pyrrolidines **23** in excellent yield. The absolute configuration of the newly established pyrrolidine stereocentres is independent of the metal salt and the size of the pyrrolidine C(2)-substituent for a series of aryl aliphatic imines. In addition, other electron-withdrawing groups can replace the ester in the starting imine (*e.g.* **24**).[11] Similar work has also been reported by Waldmann *et al.* in which *N*-metallated azomethine ylides **21** add to *N*-acryloyl-(*S*)-proline



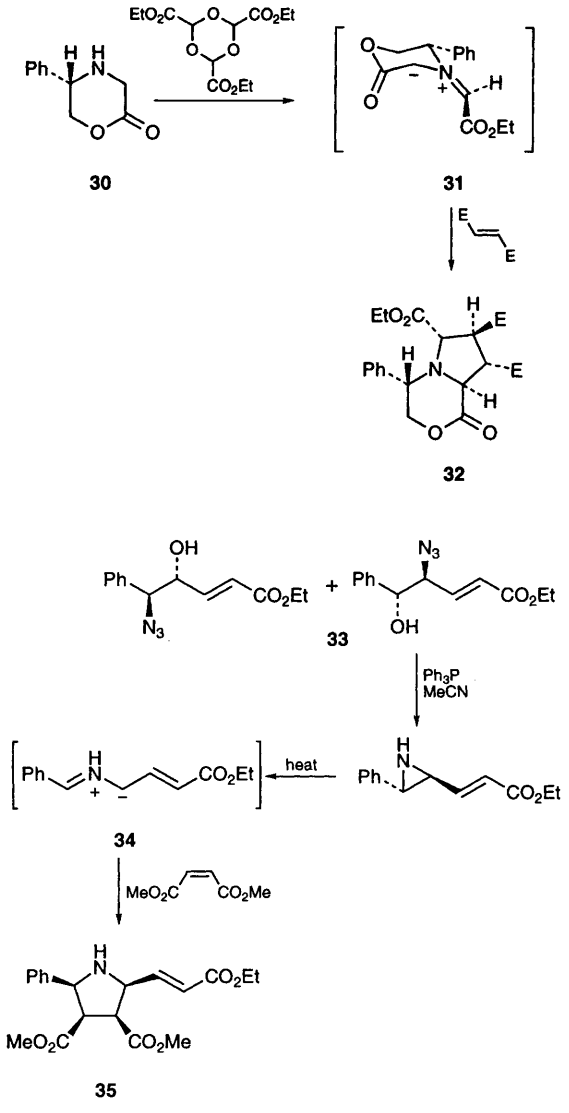
esters **22b** again with high diastereoselectivity furnishing pyrrolidines **23**.[12]

The homochiral oxazolidinone **25**, which is a useful precursor for the synthesis of non-proteinogenic amino acids *via* Diels–Alder reactions, allenyl radical and nitronate anion 1,2-additions, and cyclopropanation, undergoes highly *exo*-diastereoselective 1,3-dipolar cycloadditions with azomethine ylides **26** derived from α-amino acids to provide cycloadducts **27**. These are readily converted to polyfunctional prolines **28** (Na_2CO_3, MeOH) with high enantiomeric purity.[13]



A full account of the diastereoselective synthesis of pyrrolidines by reaction of homochiral α,β-unsaturated ketones **29** bearing alkoxy or amino substituents in the γ-position with azomethine ylides has appeared.[14] Harwood *et al.* have extended the scope of dipolar cycloadditions based on the morpholinone **30** by using ethyl glyoxylate as the condensing agent. The resulting (*E*)-ylide **31** undergoes highly diastereoselective cycloaddition with a range of dipolarophiles, and removal of the template from the cycloadducts **32** furnishes enantiomerically pure pyrrolidine-2,5-dicarboxylate derivatives.[15a] The use of formaldehyde as the condensing agent has also been described.[15b]

Coldham *et al.* have described the synthesis of pyrrolidines by 1,3-dipolar cycloaddition of conjugated azomethine ylides **34**. These are generated *in situ* from a mixture of azido alcohols **33** by treatment with Ph_3P to form the aziridine and then thermal ring opening. The ring opening is conrotatory generating *cis*-2,5-disubstituted pyrrolidines **35**. In all cases the *endo*-cycloaddition products were observed.[16]

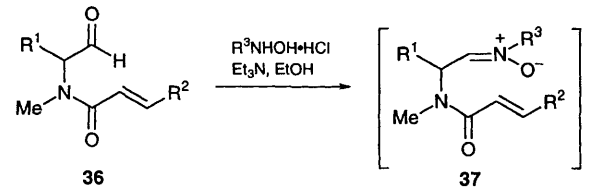


1,3-Dipolar cycloadditions using dipoles other than azomethine ylides can be used to prepare pyrrolidines. Treatment of aldehyde **36** with *N*-alkyl hydroxylamine gives the nitrone **37** which undergoes intramolecular cyclisation yielding the bicycles **38**. The reaction proceeds with high diastereoselectivity. Cleavage of the cycloadducts with zinc in acetic acid–H_2O at 70 °C provides the homochiral pyrrolidin-2-ones **39**, while reduction with $LiAlH_4$ provides pyrrolidines **40**.[17]

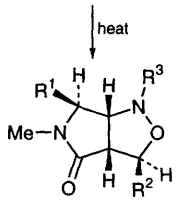
Hassner *et al.* have described the Michael addition of secondary allylamines to nitroalkenes and subsequent trapping as the *O*-silyl α-allylaminoalkylnitronates **41**. These undergo stereoselective intramolecular silylnitronate–olefin 1,3-dipolar cycloaddition to provide highly functionalised pyrrolidines in a one-pot operation.[18]

The dithiolane-isocyanate imminium methylide **43**, generated by desilylation of readily available salt **42**, undergoes efficient cycloaddition to electron deficient dipolarophiles to yield lactams **44** following hydrolysis of the intermediate dithiolanes.[19]

Enantiomerically enriched pyrrolidines **48** can be prepared by the Lewis acid promoted [4+2] cyclo-



36 37



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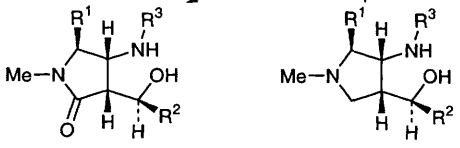
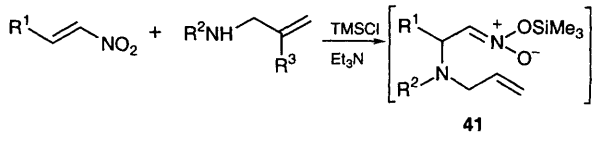


39 40



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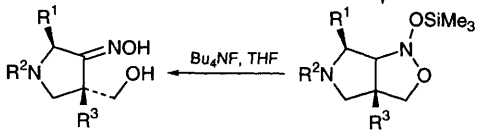
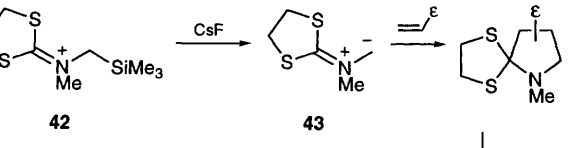
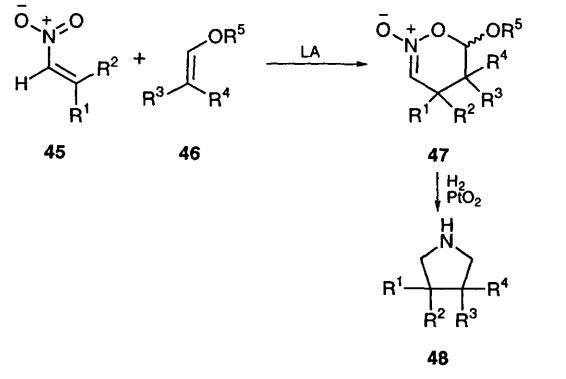




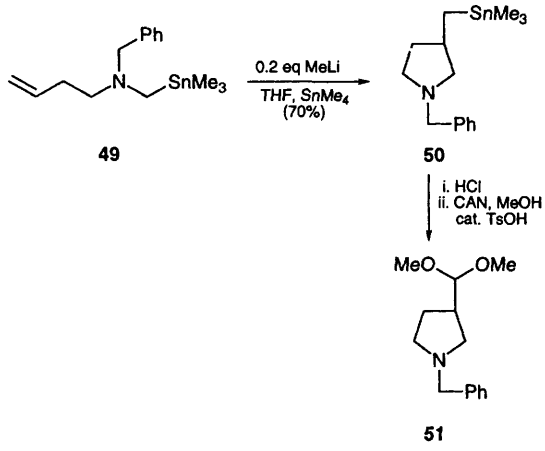
42 43 44



45 46 47 48

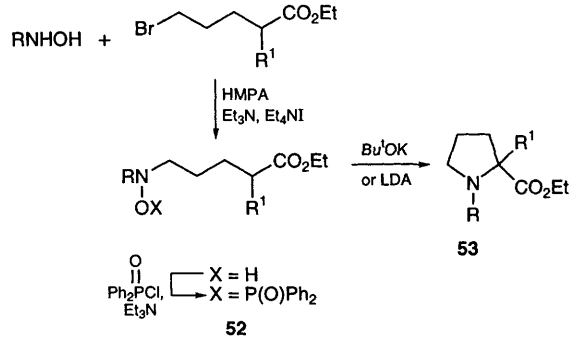
addition with chiral vinyl ethers **46**.[20] The resulting cyclic nitronates **47** are reduced with H_2 (160 psi) in the presence of PtO_2. Yields are generally good.

Coldham *et al.* have reported a new route to pyrrolidines by MeLi-promoted anionic cyclisation of the (aminomethyl)stannane **49** onto the proximal unactivated alkene. The resulting organolithium reincorporates trimethyltin to give the functionalised pyrrolidine **50**. Cleavage of the trimethyltin group with ceric ammonium nitrate in MeOH provides the acetal **51**.[21]



49 50 51

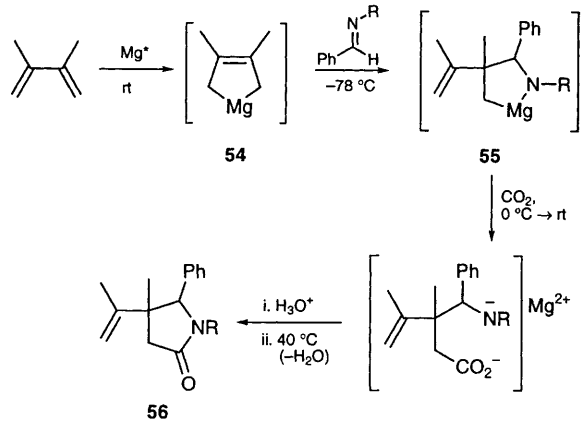
In a reversal of the normal reactivity pattern, pyrrolidines **53** can be prepared by intramolecular nucleophilic substitution on nitrogen by a carbon-based anion, using the diphenylphosphinoxyl group as leaving group. The cyclisation precursors **52** are readily prepared from oximes.[22]



52 53

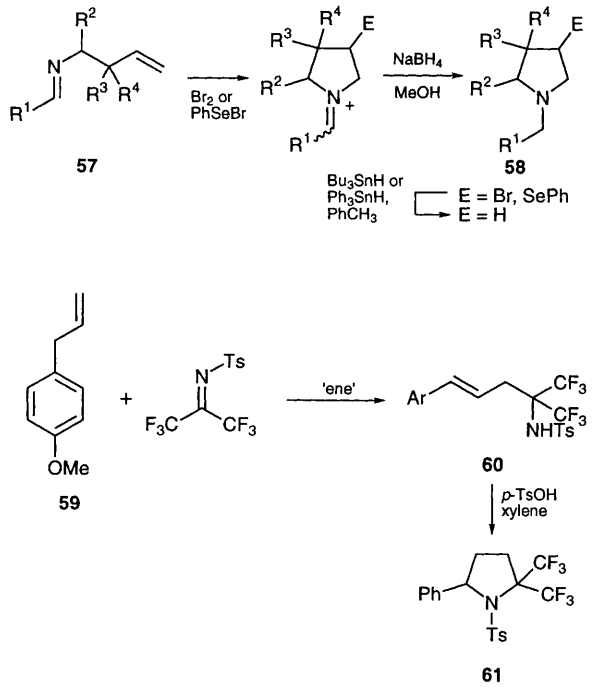
In an extension of their work on the chemistry of diene-magnesium reagents, Rieke *et al.* have described a facile one-pot synthesis of γ-lactams from conjugated dienes and imines (**Scheme 1**). The bis-organomagnesium reagent **54** reacts with complete regioselectivity in the 2-position in the initial step to give intermediate **55**. Carboxylation and acidic hydrolysis provides lactams **56**. The imine derived from cyclohexanone has also been used in this sequence.[23]

The direct electrophile induced cyclisation of alkenylamines to nitrogen heterocycles has been rarely employed in synthesis due to competing side-reactions associated with the process. However,

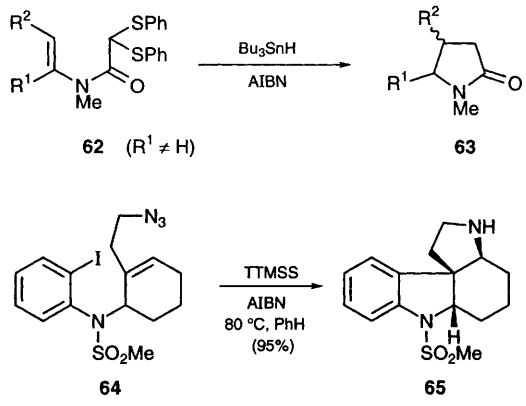


Scheme 1

imines **57**, readily derived from primary homoallylic amines and aldehydes, undergo regioselective cyclisation in the presence of electrophiles (Br_2 or phenylselenyl bromide) to provide pyrrolidines **58** in good yield. The bromine or selenium substituent is readily removed under radical reduction conditions.[24] Electrophilic cyclisation can also be used to prepare bis-trifluoromethyl substituted 2-aryl pyrrolidines **61**. Thus ene reaction of 4-allyl anisole **59** with *N*-tosylhexafluoroacetone imine provides the amine **60**, which cyclises in the presence of toluene-*p*-sulfonic acid to give the pyrrolidine **61**. The reaction appears to be limited to α-aryl substituted amines **61** which are able to form a benzylic cation.[25]

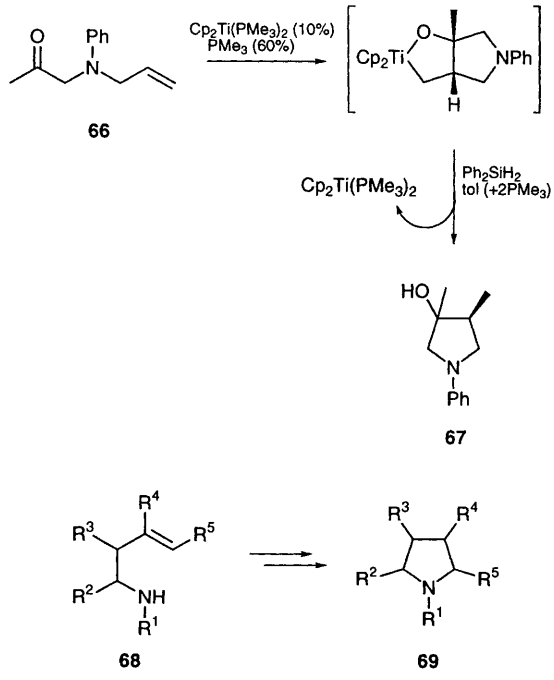


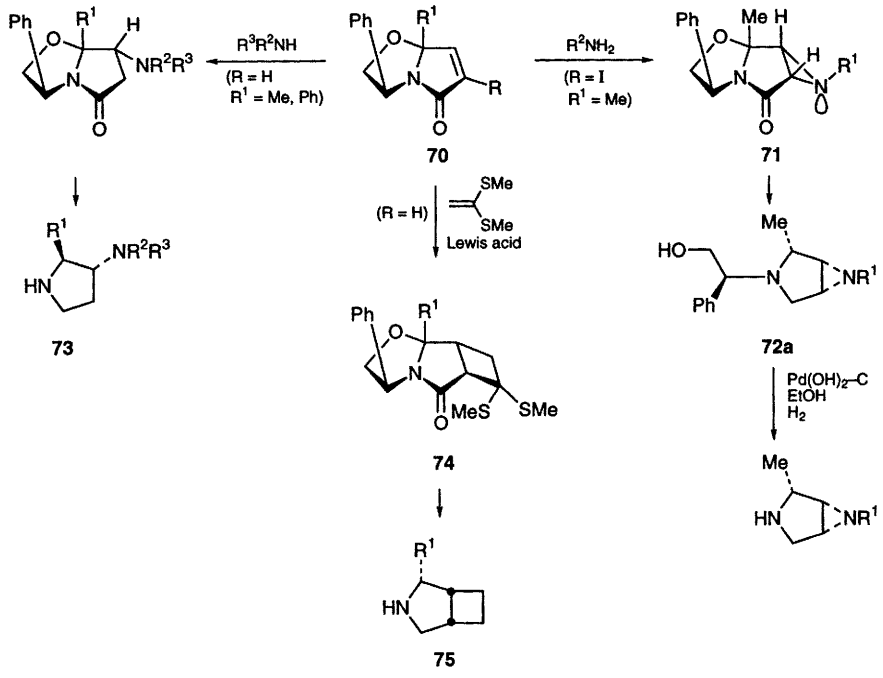
Radical-based methodologies for the synthesis of pyrrolidines continue to prove fruitful. Ikeda *et al.* have reported a 5-*endo-trig* radical cyclisation of acetamide derivatives **62** providing pyrrolidinones **63**. In order for the cyclisation to proceed effectively, it is necessary that the developing α-acylamino radical in the transition state of the cyclisation must be stabilised by an aryl or an alkyl group (*i.e.* R^1 is not H), otherwise simple reduction of the substrate is observed.[26] Murphy *et al.* have described an elegant approach to the ABCE tetracycle of aspidospermidine and related alkaloids **65** by tandem radical cyclisation of the iodo azide precursor **64**, mediated by tris(trimethylsilyl)silane (TTMSS) and AIBN. This work further demonstrates than an aryl C–I bond can be selectively reduced in the presence of an azide using TTMSS.[27]



Buchwald *et al.* have demonstrated that the pyrrolidine ring system **67** can be assembled by reductive cyclisation of the enone **66** by a titanium catalyst.[28] The key to the success of this approach is the use of Ph_2SiH_2 to cleave the Ti–O bond in the metallocycle and regenerate the catalyst. The product is formed as a 1:1 mixture of diastereoisomers.

Homoallylic amines **68** can be converted to pyrrolidines **69** through a five-step sequence which is formally equivalent to a disfavoured direct 5-*endo*-



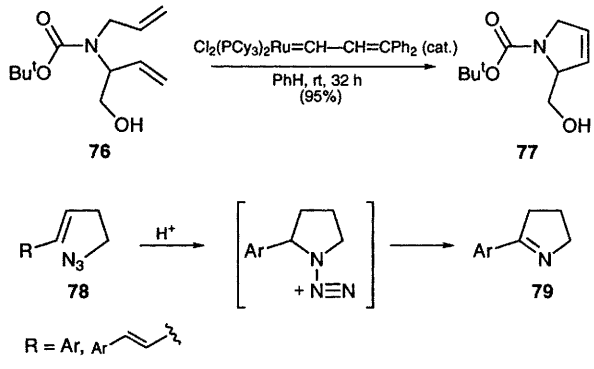


Scheme 2

trig ring closure from **68**.[29] The approach involves epoxidation, intramolecular epoxide opening by a carbamate group and a final zinc mediated reductive cleavage–reductive amination from an intermediate 1,3-oxazine-2-one.

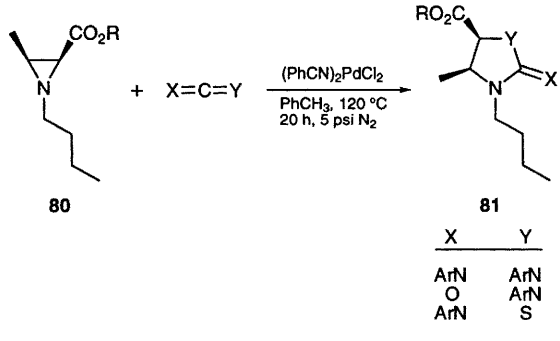
A series of publications by Meyers *et al.* has described the synthesis of pyrrolidine derivatives using the chiral bicyclic lactam **70** as starting material (**Scheme 2**). Thus, reaction of **70** (R = I) with a variety of primary amines afforded *endo*-aziridinolactams **71** (60–92% yield). Treatment of these lactams with AlH_3 provided the *N*-substituted pyrrolidines **72** in which the angular methyl group has undergone facial inversion in the major diastereoisomers (95:5). The *N*-substituent can be removed by hydrogenolysis.[30] Alternatively, bicyclic lactam **70** (R = H) undergoes highly diastereoselective conjugate addition of primary amines to afford homochiral 3-amino pyrrolidines **73** after reductive cleavage. Typical yields ranged from 80–90% with facial diastereoselectivities ranging from 95:5 to >98:2.[31] Finally, addition of methylenedithiolane to **70** (R = H) occurred with very high *endo*-selectivity to give the cyclobutane adduct **74**. Reductive removal of the sulfur (Raney Ni), cleavage of the chiral auxilliary with inversion of the angular methyl group (Et_3SiH, $TiCl_4$) and removal of the phenyl glycinol moiety (Na–NH_3) provided the enantiomerically pure pyrrolidine **75** (R^1 = Me).[32]

The ruthenium catalyst [$Cl_2(PCy_3)_2Ru{=}CH{-}CH{=}CPh_2$], introduced by Grubbs for olefin metathesis, effects clean metathesis of the diene **76** leading to the unsaturated pyrrolidine **77**.[33] 2-Substituted pyrrolines can be prepared using the intramolecular 'carbocation' version of the Schmidt reaction. Thus, 4-substituted but-3-enyl azides **78**,



upon treatment with CF_3SO_2H at 0 °C, provide cyclic imines **79**.[34]

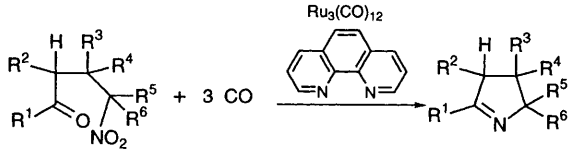
Alper *et al.* have described the Pd^{II}-catalysed cycloaddition of stereochemically defined aziridines (*e.g.* **80**) with heterocumulenes (carbodiimides, isocyanates and isothiocyanates), leading to 5-membered ring heterocycles **81**. The reaction is both regio- and stereo-specific, the cycloaddition occurring with retention of stereochemistry at the



X	Y
ArN	ArN
O	ArN
ArN	S

aziridine carbon centres, providing an enantiospecific general method for the synthesis of imidazolidinones, imidazolidinimines and thiazolidinimines.[35]

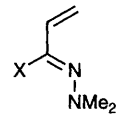
Finally, Watanabe *et al.* have utilised the deoxygenating capability of carbon monoxide to effect a novel synthesis of 1-pyrroline derivative **83** from aliphatic γ-nitrocarbonyl compounds **82**. The reaction is catalysed by a $Ru_3(CO)_{12}$–1,10-phenanthroline system and is thought to proceed *via* a ruthenium nitrene intermediate.[36]



82 **83**

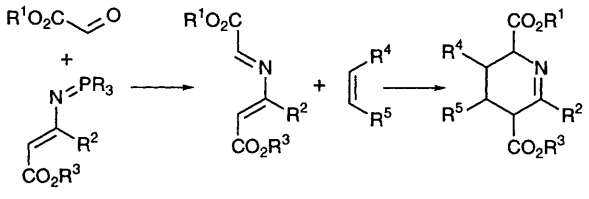
4 Six-membered rings

Ghosez *et al.* have described the Diels–Alder reaction of α,β-unsaturated hydrazones **84** bearing an ester or a nitrile at C-2 with electron-deficient dienophiles. Dramatic rate enhancements are observed if reactions are conducted in concentrated organic solutions of $LiNTf_2$ (a useful replacement for $LiClO_4$).[37] Electron deficient 2-azadienes **86**, which are prepared by aza-Wittig reaction of *N*-vinylic phosphazenes **85** with carbonyl compounds, undergo inverse electron demand Diels–Alder reaction with alkenes leading to the formation of tetrahydropyridines **87**.[38]



84

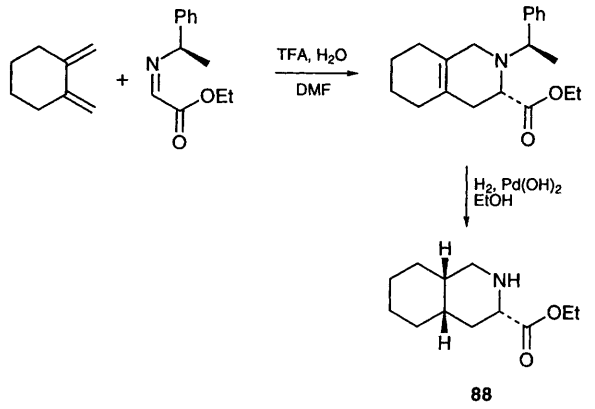
X = CN, CO_2R



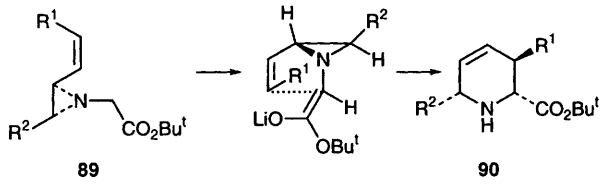
85 **86** **87**

Trova *et al.* have utilised an asymmetric aza-Diels–Alder reaction in the construction of the bicyclic piperidine **88**, a substructure found in a number of HIV-1 protease inhibitors.[39]

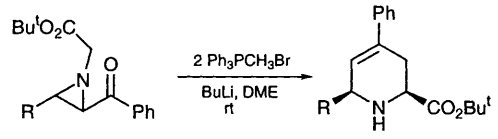
Both Somfai[40,41] and Coldham[42,43] have used the aza-[2,3]-Wittig rearrangement for the construction of tetrahydropyridines. In the Somfai work, treatment of vinyl aziridines **89** with LDA resulted in smooth and rapid (<5 min) conversion to tetrahydropyridines **90** in high yield and as a single diastereoisomer. Coldham *et al.* have utilised 2-keto



88



89 **90**

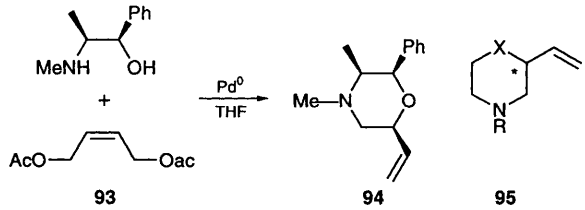


91 **92**

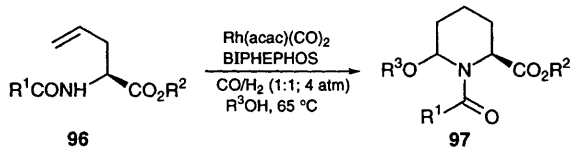
R = Me, Bu, Pr^i

aziridines **91** as starting materials. Treatment with 2 equiv. of a phosphonium ylide again generates vinyl aziridines which rearrange to provide *cis*-2,6-disubstituted tetrahydropyridines **92**.

Muzart *et al.* have described the stereoselective synthesis of vinylmorpholines **94** by the palladium-catalysed tandem allylic substitution of butenediol derivatives **93** with enantiopure amino alcohols.[44] In a similar approach Achiwa *et al.* have demonstrated that both vinyl morpholines and vinyl piperazines **95** can be prepared with low to moderate ee's by reaction of the bis-acetate **93** with achiral amino alcohols and diamines in the presence of a chiral palladium(0)-catalyst.[45] Rhodium catalysts have also been used for construction of the piperidine ring system. Thus, intramolecular cyclohydrocarbonylation of the unsaturated amine **96** in the presence of $Rh(acac)(CO)_2$ (1 mol%) and BIPHEPHOS (2 mol%) provided the pipecolate derivative **97** in quantitative yield. The alkoxy group of **97** undergoes highly diastereoselective substitution with cuprate reagents *via* an iminium ion intermediate to give *trans*-2,6-disubstituted products.[46]

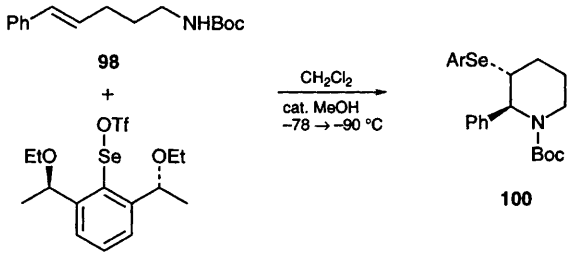


93 **94** **95**

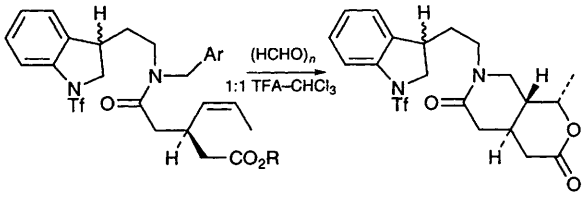


96 97

Deziel *et al.* have described a very facile synthesis of heterocycles *via* asymmetric ring closure mediated by the chiral C_2 symmetrical organoselenium reagent **99**. Thus, treatment of the carbamate **98** with **99** in CH_2Cl_2 in the presence of 2.5% *v/v* methanol provides the piperidine **100** in 89% yield and with 25:1 diastereoselectivity. The selenium moiety is readily removed under radical conditions (Ph_3SnH, AIBN).[47]



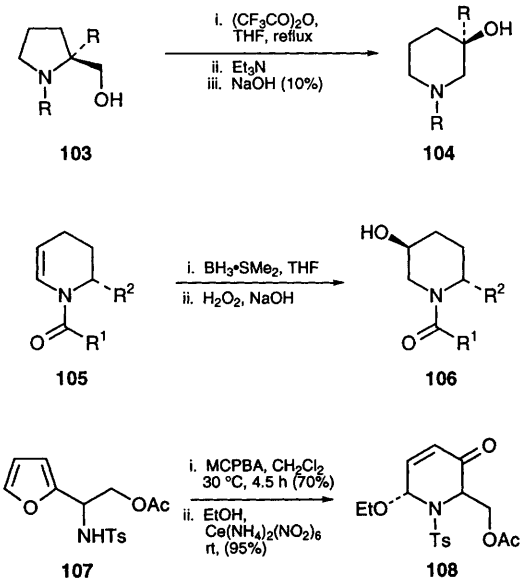
Overman *et al.* have described a carboxylate-terminated *N*-acyl iminium ion bis-cyclisation **101**→**102** for construction of the D and E rings of the heteroyohimbine alkaloid (−)-ajmalicine *en route* to a total synthesis.[48] A related cyclisation provides the central step in an approach to (+)-epiajmalicine.[48]



101 102

3-Hydroxy piperidines **104**, which may contain a quaternary centre at C-3, can be easily prepared with ee's up to 97% by ring expansion of prolinol derivatives **103**. The reaction likely proceeds *via* an aziridinium intermediate.[49] Alternatively, optically pure cyclic enamides **105**, available *via* a three-step sequence starting with Oppolzer sultams, undergo *trans*-selective hydroborations providing 3-hydroxy piperidine derivatives **106** in good yield and with high diastereoselectivity.[50]

Altenbach *et al.* have described a concise route to the highly functionalised dihydropyridine derivative **108**, an intermediate which should prove to be useful in the synthesis of a range of polyhydroxylated piperidines (azasugars). Thus, the readily available protected amino alcohol **107** undergoes stereocontrolled oxidative cyclization in the presence of MCPBA providing **108** after acetal formation.[51]

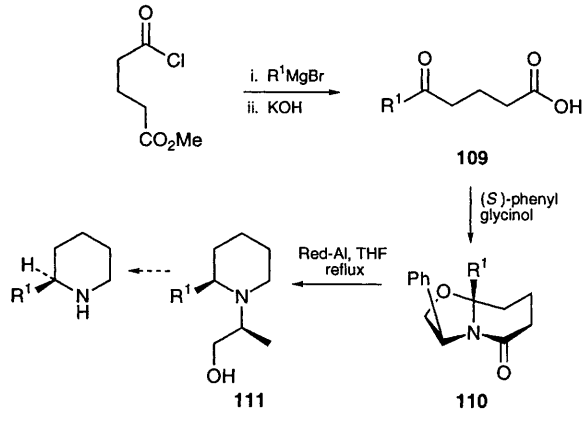


103 104

105 106

107 108

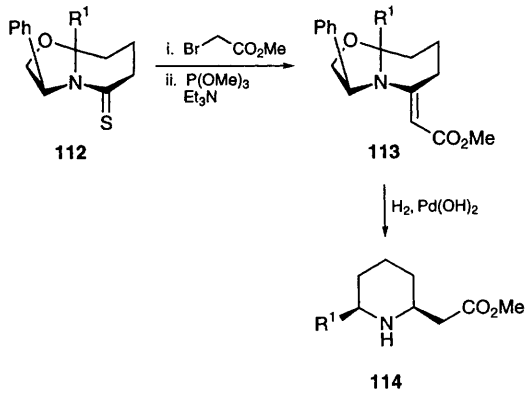
The use of homochiral bicyclic lactams **110** for the synthesis of homochiral 2-substituted piperidines has been described by Meyers *et al.* Reduction of **110** using Red-Al in refluxing THF provides *N*-substituted piperidines **111** in high yield and with excellent diastereoselectivity. The *N*-benzyl substituent can be easily removed by hydrogenation. In order to improve the generality of this method Meyers has demonstrated that a range of 1,5-keto acids **109**, the condensing partners with phenylglycinol in the preparation of bicyclic lactams **110**, are readily prepared by low temperature addition of Grignard reagents to commercially available methyl 4-(chloroformyl)butyrate (**Scheme 3**).[52]



109 110 111

Scheme 3

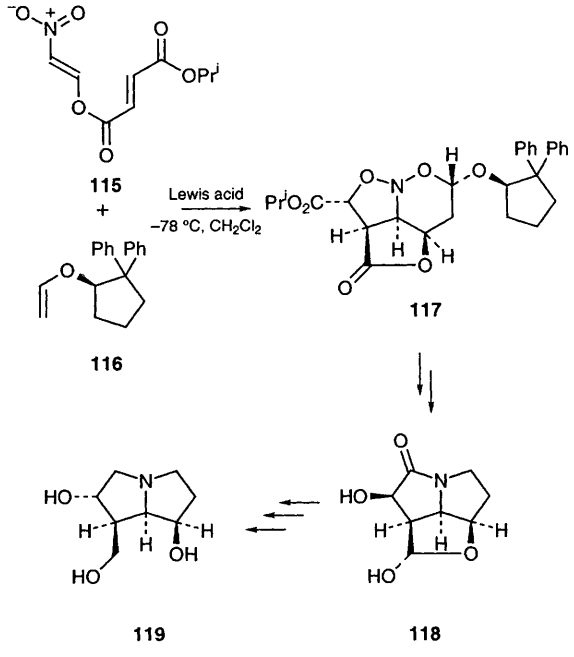
Bicyclic lactam chemistry can be extended to provide a novel asymmetric route to homochiral *cis*-2,6-disubstituted piperidines such as **114**. Thus, the vinylogous urethane **113**, which can be prepared from the bicyclic thiolactam **112** *via* Eschenmoser contraction, undergoes highly diastereoselective hydrogenation in the presence of $Pd(OH)_2$–C to provide **114** in a single step.[53]



Finally, Jacobsen *et al.* have described methodology (diastereoselective triflate alkylation and novel intramolecular Mitsunobu reaction) for the asymmetric synthesis of the complete series of enantiopure 2,6-methylated piperazines.[54]

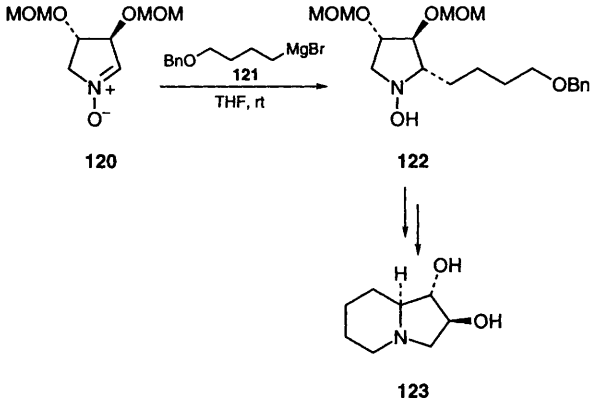
5 Pyrrolizidines, indolizidines and quinolizidines

Denmark *et al.* have described a general strategy for the synthesis of *cis*-substituted pyrrolizidine based alkaloids such as (−)-rosmarinecine **119**. The key feature of this strategy is a tandem [4+2]/[3+2] cycloaddition sequence involving the fumarate-derived nitroalkene **115** and the chiral vinyl ether **116**. The reaction proceeds with very high diastereoselectivity (25:1 *exo*/*endo*) and in high yield (96%). The tricycle **117** is readily converted to the lactam **118** with recovery of the chiral auxiliary, and thence to (−)-rosmarinecine **119** following Mitsunobu inversion of the alcohol at C-6 (**Scheme 4**).[55]

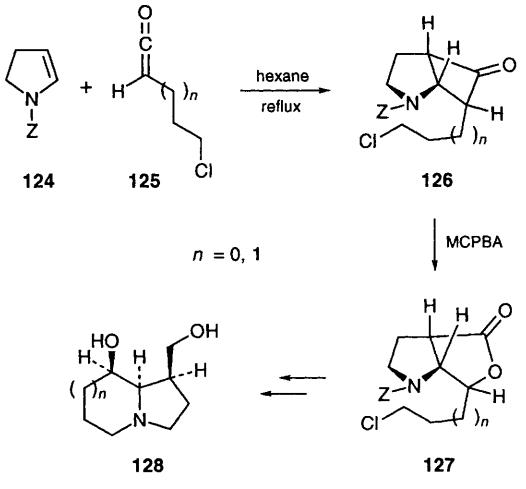


Scheme 4

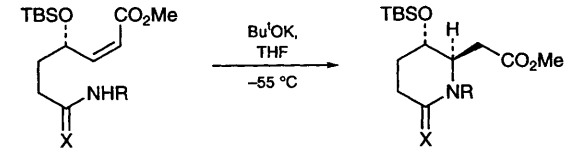
Petrin *et al.* have used the homochiral nitrone **120**, which is readily available in five steps from L-tartaric acid, in a stereoselective total synthesis of (+)-lentiginosine **123**. Addition of the Grignard reagent **121** to this nitrone proceeds with 90% de and in 82% yield to yield the hydroxylamine **122**. Reduction and cyclisation then provides the natural product.[56]



Both the indolizidine and pyrrolizidine frameworks can be accessed *via* [2+2] cycloaddition of endocyclic enecarbamates **124** to alkyl ketenes **125**. The *endo*/*exo* ratio in the cycloadduct **126** is dependent on the reaction conditions and the structure of the ketene. The *exo*-cycloadduct **126** ($n=1$) undergoes highly regioselective Baeyer–Villiger ring expansion with MCPBA and the resultant lactone **127** is converted to the new, nonnatural indolizidine **128** ($n=1$) in two simple steps.[57]

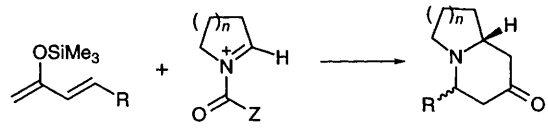


Both the amide **129a** (X=O, R=H) and the carbamate **129b** (X=H_2, R=Boc) undergo highly diastereoselective intramolecular conjugate addition leading to piperidines **130**, which are useful intermediates for the total synthesis of (+)-swainsonine.[58] Pilli *et al.* have described a one-pot preparation of quinolizidine-2-one and indolizidin-7-one ring systems based on the addition of dienes **131** to cyclic *N*-acyliminium ions **132**.[59]



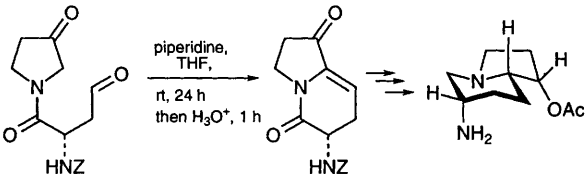
129a X = O, R = H
129b X = H_2, R = Boc

130

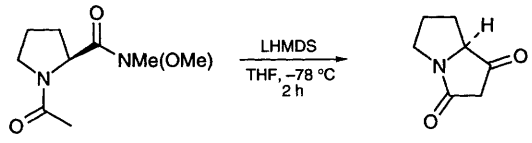


131 132

The indolizidine (−)-slaframine **135** can be accessed *via* the bicyclic lactam **134** which in turn can be prepared by intramolecular aldol reaction of ketoaldehyde **133**.[60] The ketone carbonyl in **134** can be reduced with high diastereoselectivity using the Corey oxazaborolidine. Suitably activated proline derivatives such as **136** undergo 5-*exo-trig* cyclisation to provide the pyrrolizidine ring system **137** with retention of optical integrity. If the corresponding methyl ester is used in the cyclisation then racemisation occurs.[61]

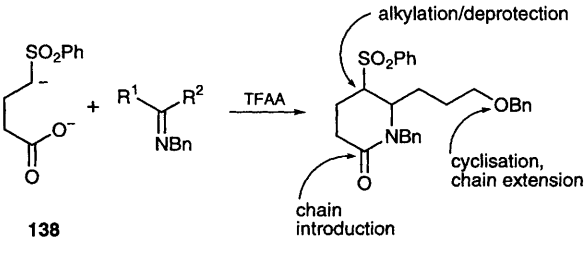


133 134 135



136 137

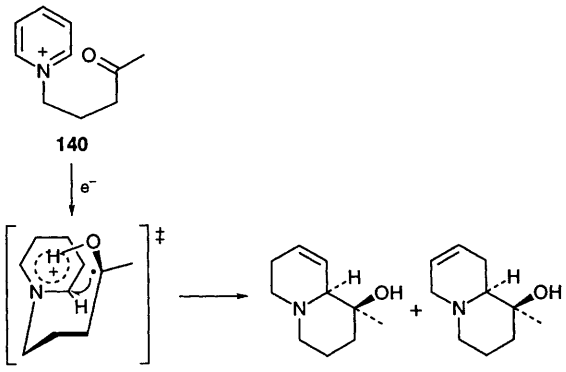
The lactam **139** is a pivotal intermediate which can be used to prepare a range of indolizidines containing alkyl substituents at the 3-, 5- and 8-positions. This intermediate is readily prepared from the dianion of 4-(phenylsulfonyl)butanoic acid **138**.[62]



138

139

The umpolung of reactivity offered by electron transfer has been utilised in an approach to indolizidine and quinolizidine derivatives based on cathodic cyclisation. Thus the pyridinium salt **140** undergoes diastereoselective cathodic cyclisation to give a mixture of regioisomeric hydroxy alkenes **142** with the same relative stereochemistry. The diastereoselectivity of the reaction may occur through the hydrogen-bonded transition structure **141**.[63]

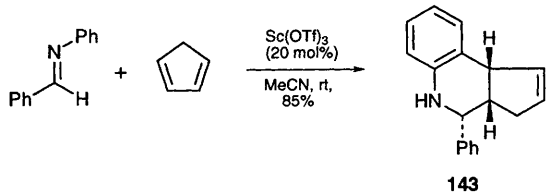


140

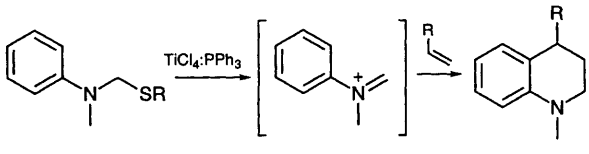
141 142

6 Tetrahydroquinolines and tetrahydroisoquinolines

Kobayashi *et al.* have demonstrated that rare earth metal triflates [$Ln(OTf)_3$ or $Sc(OTf)_3$] are excellent catalysts for the reaction of imines with silyl enolates and for the Diels–Alder reaction of imines with dienes.[64,65] The latter reaction can provide tetrahydroquinolines **143** in good yield. Alternatively, cationic 2-azabutadienes **144**, which are considerably more reactive and selective than their neutral counterparts, undergo highly regio- and diastereo-selective [$4\pi^+ + 2\pi$] cycloaddition with various dienophiles to give tetrahydroquinolines **145** in good yield.[66]

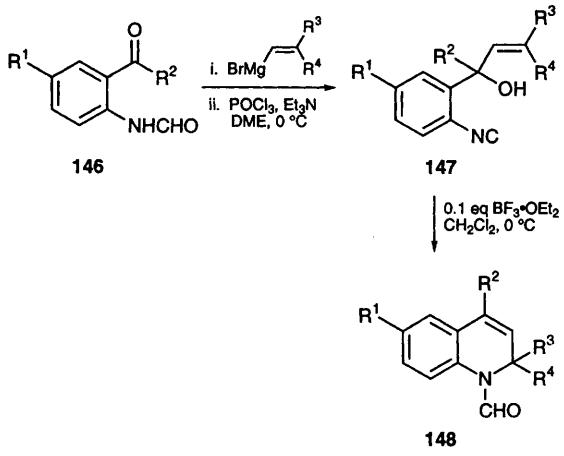


143



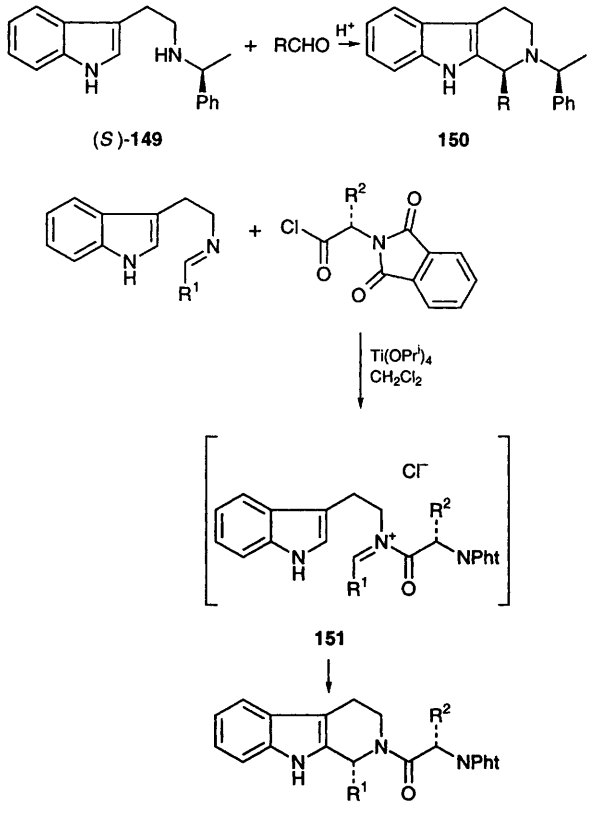
144 145

1-Formyl-1,2-dihydroquinolines **148** are readily accessed in a reasonably efficient manner by the BF_3-catalysed cyclisation of phenyl isocyanides **147**. These intermediates are in turn prepared from (*o*-acylphenyl)formamides **146** following Grignard addition and dehydration.[67]



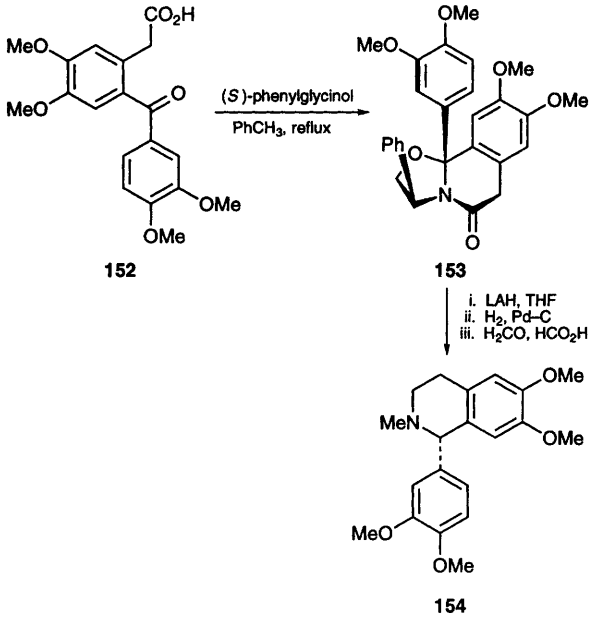
146 147 148

Over the years, the Pictet–Spengler reaction has developed into one of the most important methods for the synthesis of nitrogen heterocycles. Nakagawa *et al.* have reported that the homochiral tryptamine derivative **149** undergoes diastereoselective Pictet–Spengler reaction providing tetrahydro-β-carbolines **150** with de's of up to 72%.[68] Waldmann *et al.* have reported that diastereoisomeric ratios of >99:1 can be achieved in the same reaction by using *N*-acyliminium salts such as **151** which bear an *N,N*-phthaloyl amino acid as chiral auxiliary which can be readily removed by reduction of the amide bond using $LiAlH_4$.[69] Two reports from Katritzky describe novel routes to both 1,3- and 1,4-disubstituted tetrahydroquinolines[70] and 4-(dialkylamino)tetrahydroquinolines[71] starting from benzotriazole-based precursors.



(*S*)-149 150 151

Meyers *et al.* have extended their chiral bicyclic lactam chemistry to provide a general route to 1-alkyl- and 1-aryl-tetrahydroisoquinolines. The application of this chemistry to the synthesis of the isoquinoline alkaloid (+)-cryptostyline **154** is outlined in **Scheme 5**. Condensation of the keto acid **152** with (*S*)-phenylglycinol provides the diastereoisomerically pure bicyclic lactam **153** in 61% yield. Reduction ($LiAlH_4$, 14:1 mixture of diastereoisomers) followed by debenzylation and methylation provides **154** in exellent yield.[72] Finally, Heaney *et al.* have provided a full account of their work on the synthesis of *N*-(arylmethyl)tetrahydroisoquinolines starting from bis-aminol ethers.[73]



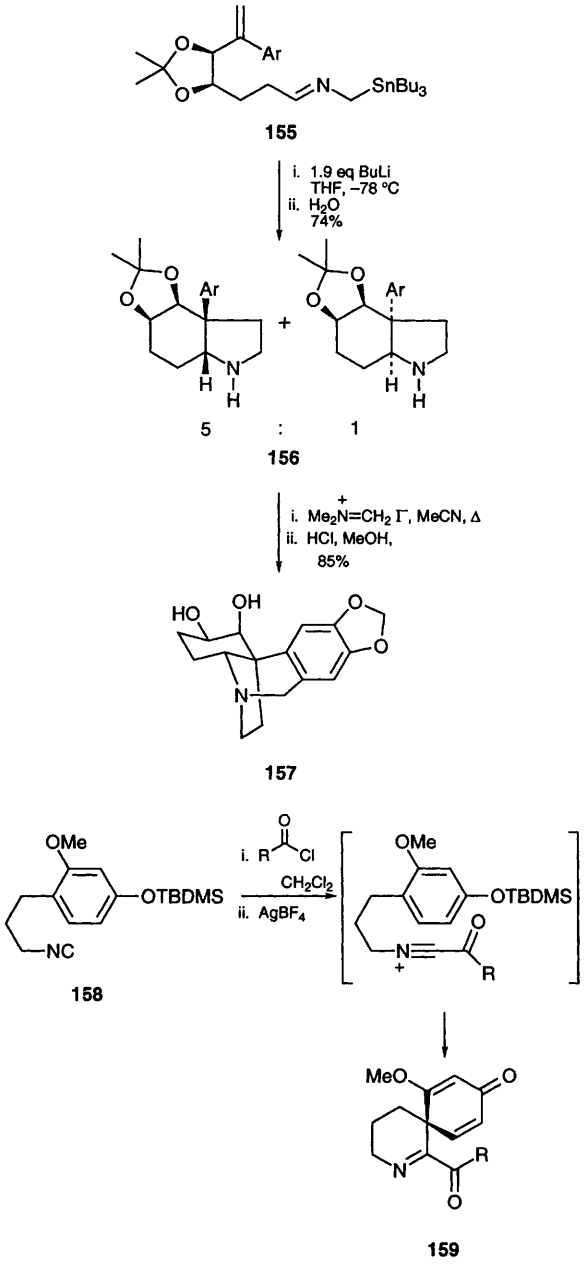
152 153 154

Scheme 5

7 Miscellaneous methods for the synthesis of nitrogen heterocycles of varying ring size

The use of *N*-acylnitroso Diels–Alder methodology for the synthesis of nitrogenous natural products[74] and the use of amino acid esters as chiral auxiliaries for the asymmetric synthesis of nitrogen heterocycles[75] has recently been reviewed. Pearson *et al.* have utilised their 2-azaallyl cycloaddition methodology in an extremely concise synthesis of the amaryllidaceae alkaloids (−)-amabiline and (−)-augustamine. In a key step the 2-(azaallyl)-stannane **155** undergoes intramolecular cycloaddition upon transmetallation at −78°C to provide a 5:1 mixture of the diastereoisomeric hexahydroindoles **156**. The major isomer undergoes further cyclisation in the presence of Eschenmosers's salt to give (−)-amabiline **157** in excellent yield.[76]

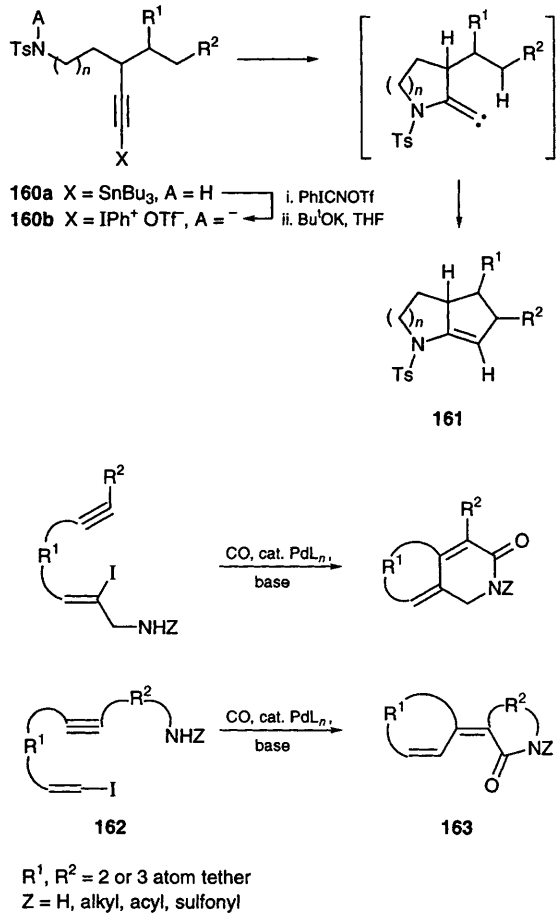
In a series of two publications Livinghouse *et al.* have described the scope of acynitrilium ion initiated cyclisations in heterocycle synthesis.[77,78] The application of this methodology to alkaloid synthesis is demonstrated by the spiroannulation of the isonitrile **158** to provide bicycle **159**, a potentially



useful intermediate for the synthesis of the alkaloid serratine.

An alternative entry into polycyclic alkaloid skeleta has been reported by Feldman in which the unique ability of an iodonium species to form two bonds in tandem by nucleophile capture and subsequent C–H insertion is exploited. The reactive iodonium species **160b** is generated from the stannane **160a** and undergoes cyclisation–insertion to provide bicycles **161**. The reaction is successful for $n = 1$–3 (but not 4) and subsequent alkylidine carbene insertion occurs into a range of C–H bonds (primary, secondary and tertiary) in line with the high reactivity of these species.[79]

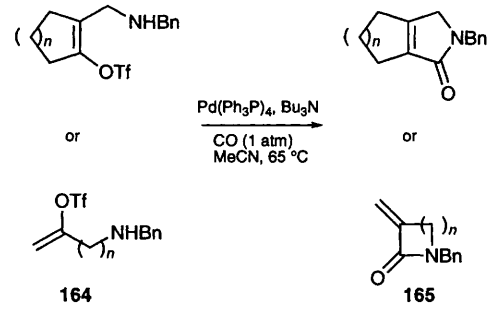
Negishi *et al.* have reported an approach to bicyclic and tricyclic lactams **163** in which acyl palladium intermediates, the products of carbopalladation of alkynes **162**, are trapped intramolecularly using an internal nitrogen nucleophile.



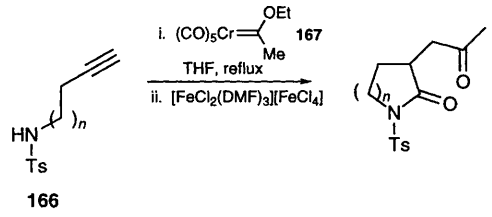
Scheme 6

Both modes of cyclisation have been demonstrated (**Scheme 6**).[80]

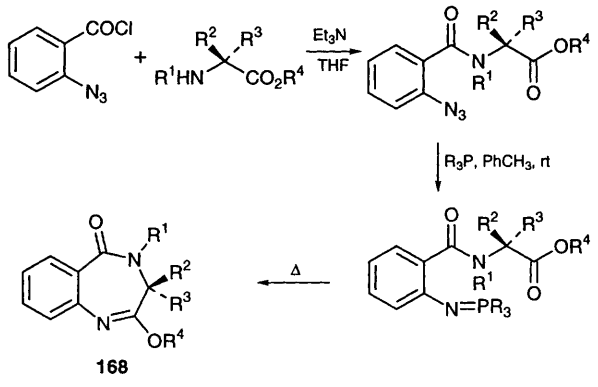
A similar approach to α,β-unsaturated lactams **165** by Pd-catalysed intramolecular carbonylative coupling of amino vinyl triflates **164** has been described by Crisp.[81]



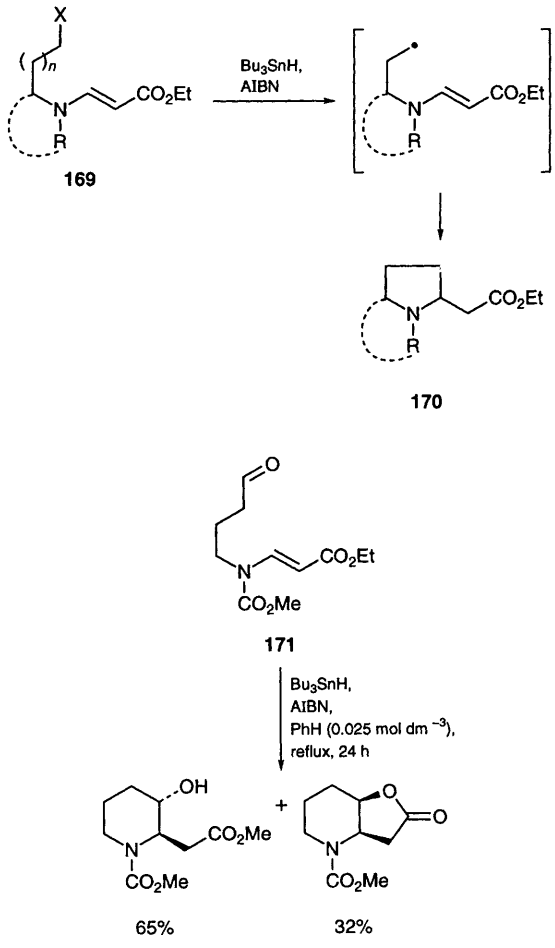
An unusual synthesis of lactams has been described by Mori *et al.* in which alkynyl amino derivatives **166** react with Fischer chromium carbene complex **167** to generate a vinyl ketene complex which is attacked by the tethered sulfonamide. Yields are good for the synthesis of 4–7 membered ring lactams.[82] The use of zirconium η^2-imine complexes for the construction of nitrogen heterocycles has been reported by Whitby.[83]



The intramolecular aza-Wittig reaction is a powerful method for the construction of nitrogen heterocycles and has recently been used to prepare 1,4-benzodiazepin-5-one derivatives **168** in moderate to good yield, (**Scheme 7**).[84] Pearson *et al.* have extended the scope of the intramolecular Schmidt reaction of carbocations with azides to include aliphatic azides. This method can be used to prepare a variety of saturated nitrogen heterocycles of varying ring sizes.[85]



Scheme 7

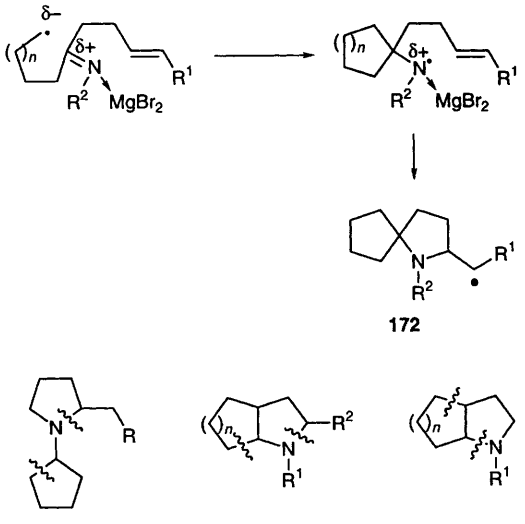


Scheme 8

The synthesis of azacycles using radical based methodology continues to attract interest. Lee *et al.* have reported an efficient synthesis of 5- and 6-membered heterocycles **170** by radical cyclization onto *β*-amino acrylates **169**. In general diastereoselection is not high, and 7- and 8-membered rings are not readily accessible. However, starting with cyclic amino acids as precursor the indolizidine and pyrrolizidine skeleta can be readily accessed, and stannyl ketyl radical precursors **171** can be employed in the radical cyclization although the reaction is slower (**Scheme 8**).[86]

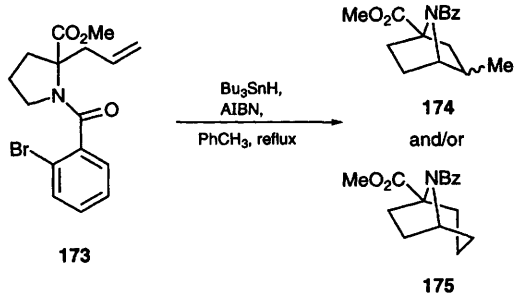
In contrast to aryl radicals, which prefer to cyclise onto imines in a 6-*endo* sense, sp^3 carbon-centred radicals undergo predominantly 5-*exo* or 6-*exo* cyclisation onto either the carbon or nitrogen atom of imines. This finding has been utilised in a synthesis of nitrogen heterocycles **172** using tandem radical cyclisation of imines. Addition of Lewis acid facilitates the tandem reaction, and a number of cyclisation modes have been demonstrated leading to a variety of ring systems (**Scheme 9**).[87]

Ikeda *et al.* have described a synthesis of the bridged azabicyclic compounds **174** and **175** using radical translocation of the proline-derived bromobenzoyl derivatives **173**. The regiochemistry (5-*exo* *vs.* 6-*endo*) of this cyclization can be controlled by



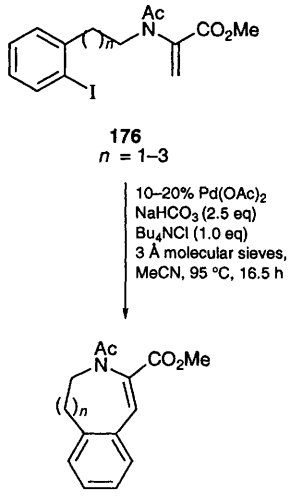
Scheme 9

substitution of the prop-2-enyl group, and substituents at the 2- and/or 4-position(s) of the pyrrolidine ring play an imporant role in this cyclisation.[88]



8 Medium and large ring nitrogen heterocycles

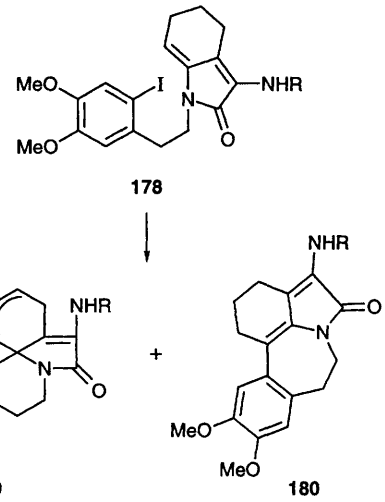
A range of methods have been reported over the last year for the construction of medium and large ring nitrogen heterocycles. Aryl iodides tethered to dehydroalanine units by two to four methylene units **176** undergo *endo*-selective Heck cyclisation under anhydrous Jeffrey conditions to provide 7-, 8- and 9-membered heterocycles **177**.[89]



Rigby *et al.* have reported that the enamide **178** undergoes predominantly the expected *exo*-cyclisation under 'standard' Heck conditions [$Pd(OAc)_2$ (10 mol%), (*o*-Tol)$_3$P (20 mol%), Et_3N (2 equiv.), MeCN–H_2O (10:1), 80 °C] to give the six-membered ring product **179** but remarkably undergoes exclusively *endo*-cyclisation under Jeffrey conditions [$Pd(OAc)_2$ (10 mol%), Bu_4NCl (2 equiv.), KOAc (5.5 equiv.), DMF (0.2 mol dm^{-3}), 100 °C)] to provide the seven-membered ring product **180** (**Scheme 10**). Thus the possibility exists for affecting either *endo*- or *exo*-selective Heck reaction from the same substrate by appropriate choice of reaction conditions.[90]

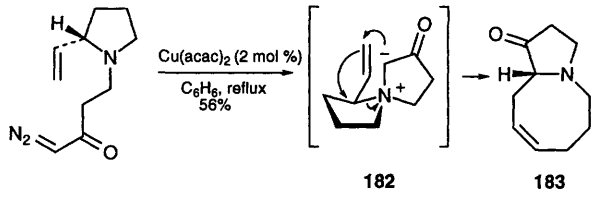
Clark *et al.* have described an enantioselective approach to the CE ring system of the manzamines in which the spiro-fused bicyclic ylide **182**, generated from a copper carbenoid, undergoes [2,3]-sigmatropic rearrangement generating the bicycle **183** with >98% ee.[91]

The synthesis of medium ring lactams (7-, 9-, 11- and 13-membered rings) from protected amino

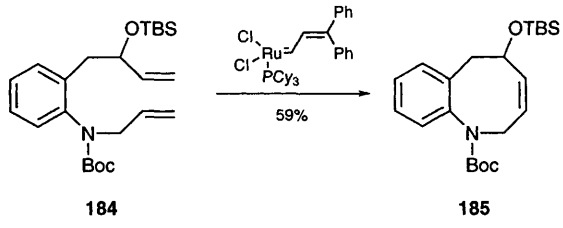


Conditions		
'standard'	46%	26%
'Jeffery'	–	48%

Scheme 10

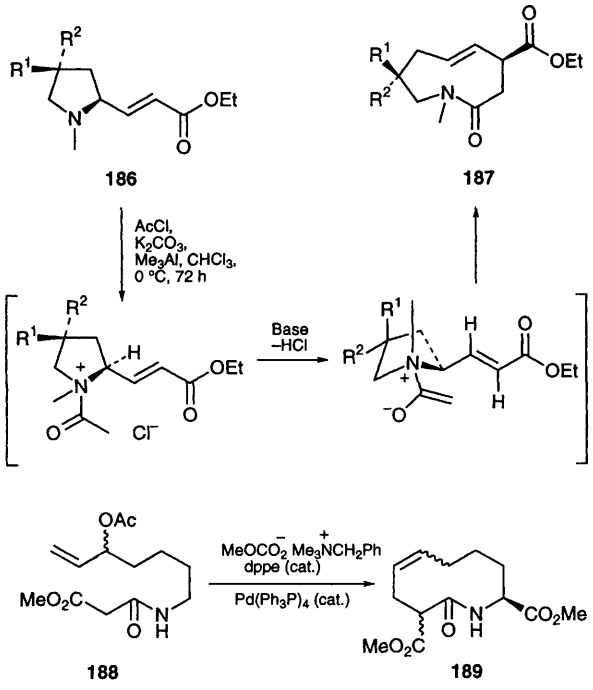


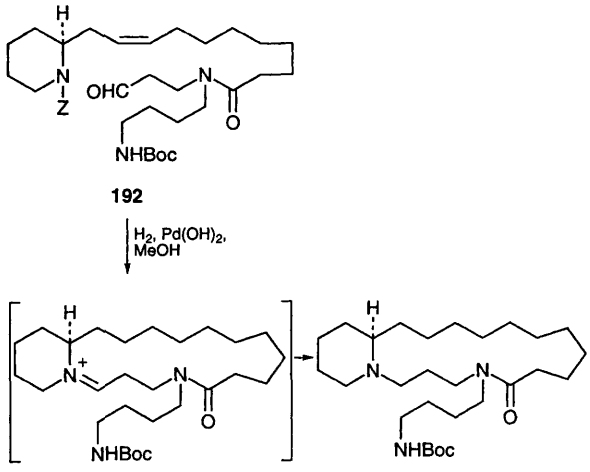
acids *via* cyclization using polymer bound 1-hydroxybenzotriazole (HOBt) has been reported.[92] Grubbs *et al.* have shown that eight-membered rings (*e.g.* **185**) can be formed from acyclic precursors **184** by ring closing metathesis provided the cyclisation precursor contains a suitable conformational constraint to facilitate cyclisation (in this case an aromatic ring). Structures related to **185** can be converted to the anticancer agents mitomycin and FR-900482.[93]

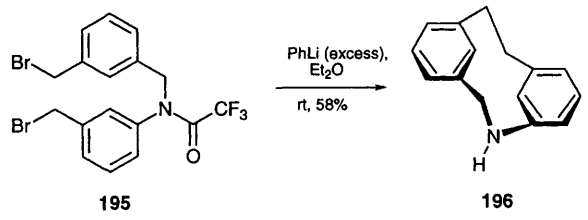


Optically active nine-membered lactams **187** can be prepared in good yield and with complete 1,3-chirality transfer starting from allylic amines **186** by a zwitterionic aza-Claisen reaction.[94] The reaction can be carried out in the presence of acidic protons without epimerisation.

Johnson *et al.* have utilised a Pd-mediated π-allyl alkylation for the synthesis of the ten-membered lactam **189** starting from allylic acetate **188**. The use of benzyltrimethylammonium methyl carbonate

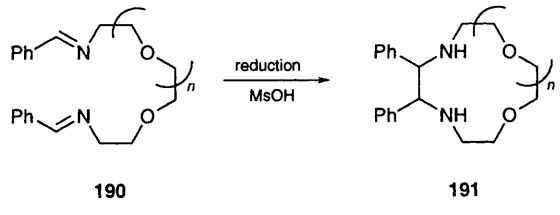






(BTMC) as a source of slowly generated methoxide is crucial to the success of this cyclisation. The allylic acetate moiety of **188** is generated by Ag^+ catalysed addition of NaOAc to the corresponding allene.[95]

A number of reports deal with the synthesis of nitrogen-containing macrocycles. Thus Kise *et al.* have described the synthesis of diazacrown ethers **191** by intramolecular coupling of bis(imino ethers) **190** promoted either by electroreduction or chemical reduction with Zn powder in the presence of methanesulfonic acid. Proton-bridged intermediate diiminium salts have been invoked to explain the relatively high yields in these cyclisations.[96] More highly functionalised systems have been examined and the diastereoselectivity of these cyclisations is discussed.



190 **191**

The 17-membered ring of the macrocyclic spermidine alkaloid (−)-oncinotine has been successfully closed using an iminium cyclization as the key step. Thus, treatment of the aldehyde **192** with H_2 over a $Pd(OH)_2$ catalyst under high dilution (4×10^{-3} mol dm^{-3} in MeOH) leads to *in situ* generation of the transient iminium ion **193** which is further hydrogenated to provide **194** in 66% yield in a single step.[97]

Finally, Vögtle *et al.* have described the synthesis of 1-aza[2.2]metacyclophane **196**, the hitherto most strained cyclophane with a free NH group in the bridge, from dibromide **195**. Crucial to the success of this synthesis is the use of the trifluoroacetate group for *N*-protection, with subsequent C–C bond formation *via* a phenyllithium coupling reaction. Under these conditions the *N*-protecting group is removed following C–C bond formation, and the product is formed in a remarkable 58% yield.[98]

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