Saturated nitrogen heterocycles

Alan Nadin

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

Covering: 1997
Previous review: *Contemp. Org. Synth.*, 1997, 4, 387

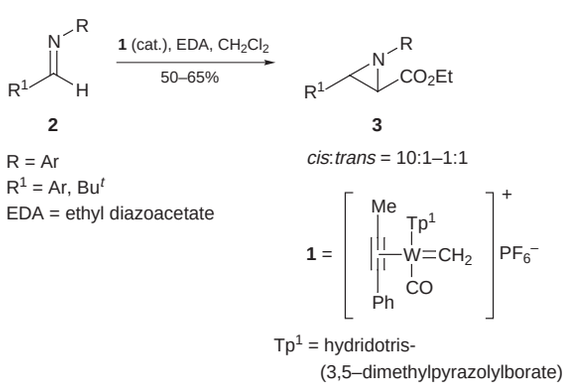
1 Introduction

This review covers the literature relating to saturated nitrogen heterocycles published in 1997. The classification of the chemistry described is similar to that described in the previous survey in *Contemporary Organic Synthesis*.[1]

2 Three-membered rings

Osborn and Sweeney have recently reviewed asymmetric methods for the synthesis of aziridines.[2]

Templeton and co-workers have described a novel electrophilic tungsten(II) methylene carbene complex (**1**) that transfers the methylene moiety to alkenes to produce cyclopropanes, but not to imines to form aziridines.[3] However, in the presence of ethyl diazoacetate (EDA), imines **2** are readily converted to aziridines **3** (**Scheme 1**) in moderately good yield, although here the role of **1** is postulated to be no more than as a humble Lewis acid catalyst to promote addition of the EDA-derived carbene to the imine.



2

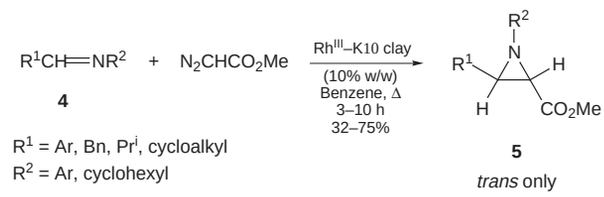
R = Ar
R^1 = Ar, Bu^t
EDA = ethyl diazoacetate

3

Tp^1 = hydridotris-(3,5–dimethylpyrazolylborate)

Scheme 1

Sudalai and co-workers have described the preparation of *trans*-disubstituted aziridines by addition of methyl diazoacetate to imines catalysed by Rh^{III}- and Mn^{III}-exchanged montmorillonite K10 clay (**4**→**5**, **Scheme 2**).[4] It is notable



4

R^1 = Ar, Bn, Pr^i, cycloalkyl
R^2 = Ar, cyclohexyl

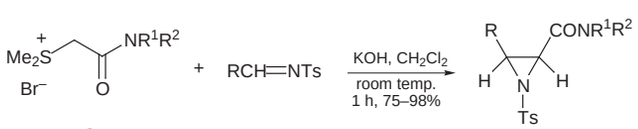
5

trans only

Scheme 2

that only a single aziridine isomer was obtained, that non-aromatic imines successfully undergo the reaction, and that the catalyst can be readily removed by filtration and re-used. Rh^{III}-exchanged K10 clay was more active than Mn^{III}-exchanged clay. Rh/SiO_2 gel and Rh/Al_2O_3 were also effective, although slightly less efficient catalysts for the process.

Hou and co-workers have described the aziridination of *N*-tosylimines by the addition of carboxamide ylides such as those derived from **6** (**Scheme 3**).[5] Surprisingly, the reaction failed with the corresponding carboxylate-stabilized ylides. Treatment of the tosylimine with the sulfonium salt and potassium hydroxide in dichloromethane gave the aziridine carboxamide **7** in excellent yield (75–98%), as a mixture of *cis*:*trans* isomers (ratio = 1:3–2:1). With the camphor-derived sulfonium salt **8** attached as a chiral auxiliary, modest asymmetric induction could be obtained (R = 4-ClC_6H_4, $R^1 = R^2$ = Et, 88% yield, 70% ee for the *trans* isomer).



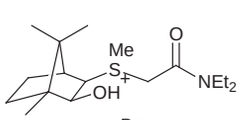
6

R^1, R^2 = alkyl, cycloalkyl
R = aryl, alkyl

7

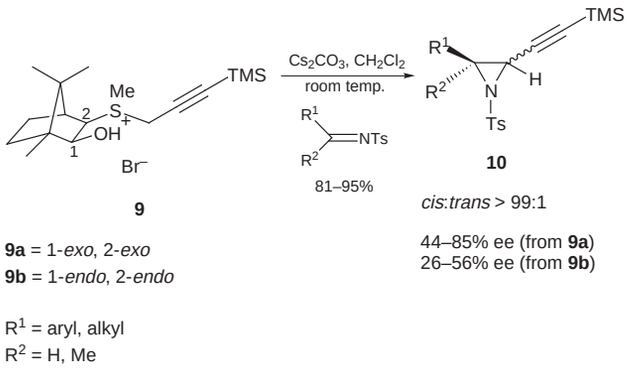
cis:*trans* = 1:3–2:1

Scheme 3



8

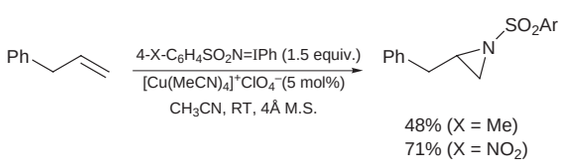
Acetylenyl-*N*-sulfonylaziridines have been prepared by the addition of similar camphor-derived sulfonium ylides (stabilized by an alkyne) to *N*-tosylimines (**9**→**10**, **Scheme 4**).[6] The reaction was uniformly highly stereoselective (*cis*:*trans* ratio >99:1) for the formation of *cis*-substituted aziridines and ees up to 85% were obtained (R^1 = cyclohexyl, R^2 = H). Notably the reaction worked well with aliphatic aldimines and ketimines, compounds that are normally poor substrates for more conventional carbene-based methods. By changing the chiral auxiliary from **9a** to **9b**, asymmetric induction in the



Scheme 4

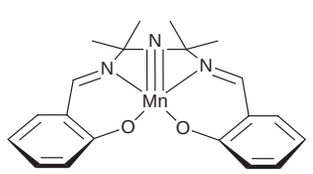
opposite sense was achieved, although the magnitude was lower with **9b**.

Andersson and co-workers have shown that 4-$NO_2C_6H_4$-SO_2N=IPh and 4-$MeOC_6H_4SO_2N$=IPh are superior reagents for the Cu-catalyzed aziridination of alkenes than the more commonly used TsN=IPh (**Scheme 5**).[7] The new reagents can be conveniently prepared from the corresponding sulfonamide and $PhI(OAc)_2$. The new reagents appear to have a number of important advantages: (1) the yields of aziridine are consistently higher; (2) only one equivalent of alkene is necessary; and (3) the 4-nitrobenzenesulfonamide moiety is more readily cleavable than the methanesulfonamide protecting group. The reaction was demonstrated on a range of mono- and di-substituted alkenes.

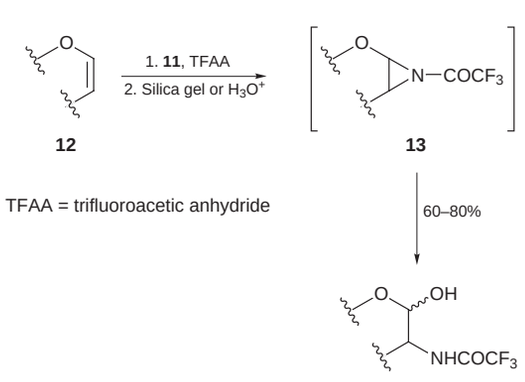


Scheme 5

Carreira and co-workers have described (saltmen)Mn(N) **11** as a reactive nitrogen transfer reagent that reacts with glycals to provide 2-amino saccharides, *via* an isolable trifluoroacetamido-protected aziridine (**12**→**13**→**14**, **Scheme 6**).[8] The stereoselectivity at C-2 is controlled by the substituent at C-3, and was generally high (6–15 : 1).

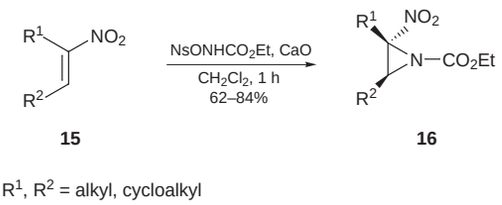


11 (saltmen) Mn^{IV}(N)



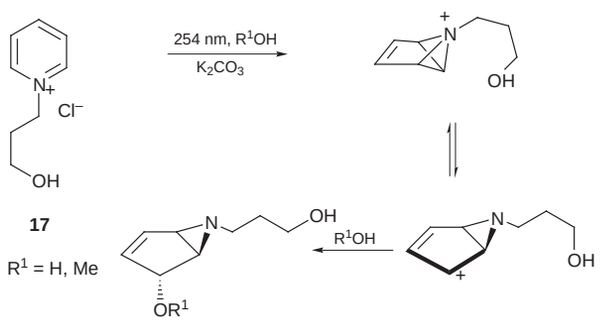
Scheme 6

The direct aziridination of nitroalkenes has been reported for the first time (**15**→**16**, **Scheme 7**).[9] Treatment of the nitroalkene with an excess of CaO and $NsONHCO_2Et$ gave the α-nitroaziridine in good yield. Other more soluble bases gave lower yields.



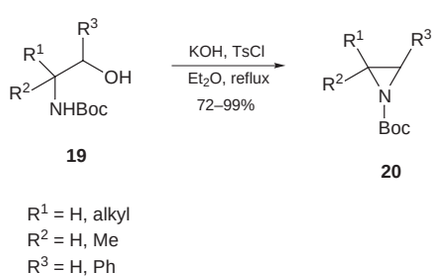
Scheme 7

Irradiation of the pyridinium salt **17** in aqueous or methanolic K_2CO_3 has been reported to yield the bicyclic vinylaziridine **18** in good yield (**Scheme 8**).[10]



Scheme 8

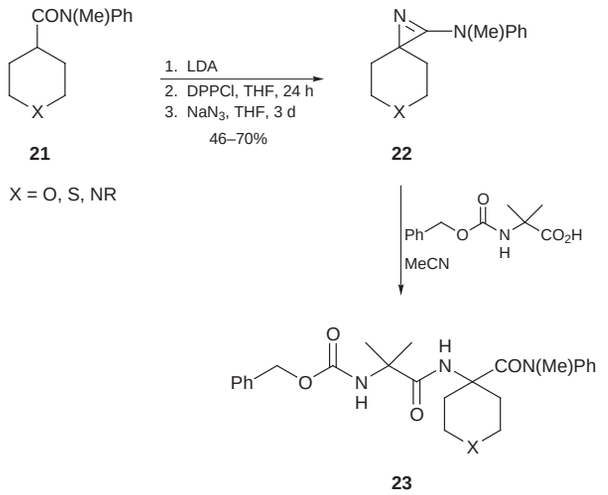
A rather practical method for the synthesis of *N*-Boc aziridines has been reported by Wessig and Schwartz.[11] Treatment of a 1,2-amino alcohol with powdered KOH and TsCl in refluxing ether leads directly to the *N*-Boc aziridine in excellent yield (72–99%) (*e.g.* **19**→**20**, **Scheme 9**).



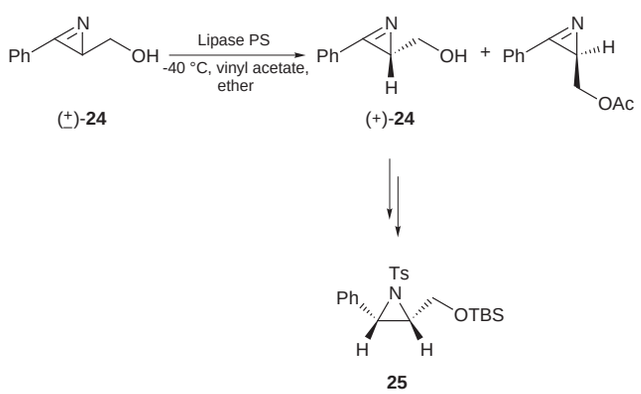
Scheme 9

Heimgartner and co-workers have described further work on the use of 2*H*-azirines as intermediates for the synthesis of unusual α-amino acid derivatives.[12] Starting with the appropriate amide, sequential treatment with LDA, diphenylphosphoryl chloride and sodium azide gave the spirocyclic 2*H*-azirine-3-amine in 46–70% yield (**21**→**22**, **Scheme 10**). Treatment of **22** with a carboxylic acid effected opening of the azirine ring and formation of the constrained dipeptide **23**.

The remarkable *Pseudomonas cepacia* PS enzyme has been shown to acetylate racemic 3-phenyl-2*H*-azirine-2-methanol **24** in diethyl ether–vinyl acetate solution at temperatures as low as −40 °C, far colder than that tolerated by most enzymes (**Scheme 11**).[13] The ee of the product was dependent on the temperature at which the resolution was carried out—at room temperature it was only 72% ee compared with 97% ee at −40 °C. The resolved (*S*)-(+)-**24** was converted to the known aziridine **25** for chemical correlation.

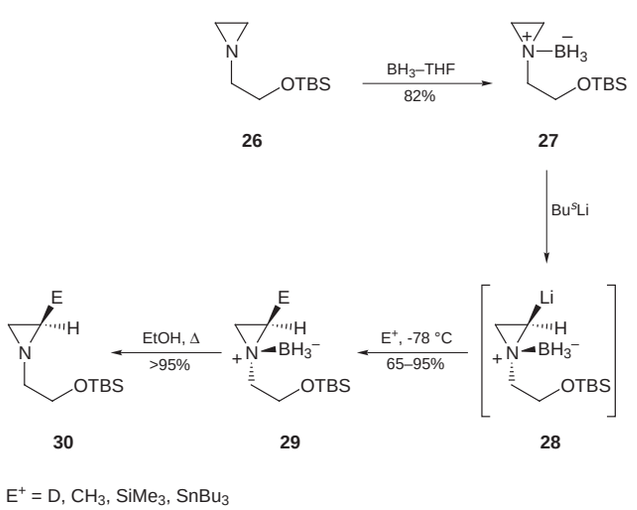


Scheme 10



Scheme 11

Vedejs and Kendall have described a very useful direct lithiation of aziridines.[14] Starting with **26**, reaction with borane–THF produced the amine–borane complex **27** (**Scheme 12**). Treatment with Bu^{s}Li and quenching the resulting anion at low temperature with a range of electrophiles gave the substituted aziridine **29**, predominantly as the *syn* diastereoisomer. Further experiments demonstrated that this selectivity was due to a kinetic preference for lithiation *syn* to the BH_3 group, rather than reflecting a thermodynamically controlled process. This kinetic preference is thought to be due in part to an attractive electrostatic interaction between the lithium atom in Bu^{s}Li and a H–B bond of **27**. The borane grouping in **29** can be readily removed by refluxing in ethanol to yield **30**.



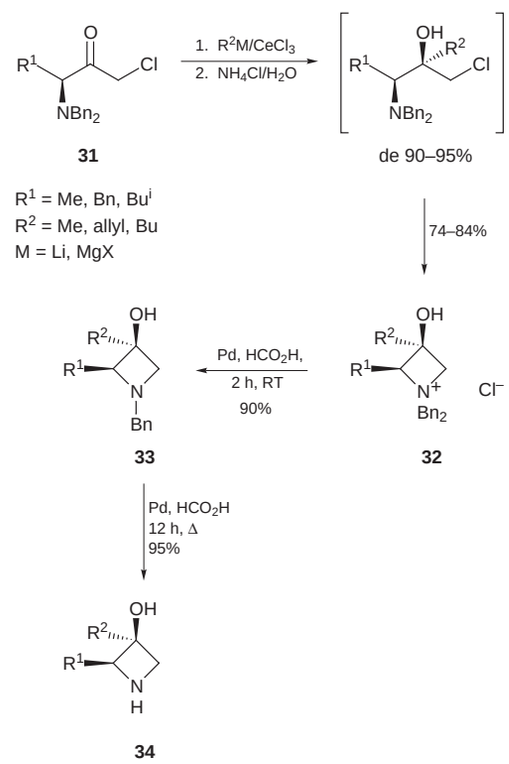
Scheme 12

Ibuka *et al.*[15] reveal, through a series of experimental results and *ab initio* calculations, the superficially surprising result that 2,3-*cis*-*N*-(sulfonyl)-3-alkyl-2-vinylaziridines are rather more stable than their 2,3-*trans* counterparts by around 1.5 kcal mol^{-1}. If the aziridine nitrogen is instead substituted with a hydrogen atom, the 2,3-*trans* isomer is more stable than the 2,3-*cis* isomer.

3 Four-membered rings

Bartnik and Marchand have published a comprehensive review on the synthesis and chemistry of substituted 1-azabicyclo-[1.1.0]butanes.[16] The main reaction of 1-azabicyclo[1.1.0]-butanes involves cleavage of the C3–N bond to give 3-substituted azetidines.

The preparation of enantiomerically pure 3-azetidinols from 1-aminoalkyl chloromethyl ketones has been described by Barluenga (**Scheme 13**).[17] Starting with the readily available chloromethyl ketone **31**, addition of an organocerium reagent gave the azetidinium salt **32** in 74–84% overall yield. Hydrogenation removes either one or both benzyl protecting groups to give **33** or **34**, depending on the reaction conditions.

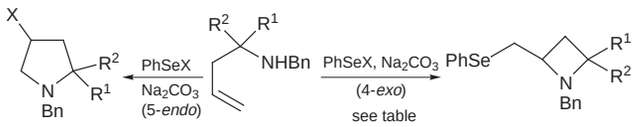


Scheme 13

Paulmier and co-workers have described a selenium-induced *exo*-selective cyclization of homoallylic benzylamines (**35**→**37**, **Scheme 14**).[18] The competing 5-*endo* product pyrrolidine **36** was usually also formed in significant amounts (6–38%), but by careful control of solvent (acetonitrile), selenylating agent (PhSeBr) and substrate, it could be suppressed entirely. In general the 4-*exo*:5-*endo* ratio was greatest with PhSeCl as selenylating agent and with increased steric bulk around the α-carbon of the substrate.

The application of the three-component Passerini-type reaction to the synthesis of β-lactams has been reported by Marcaccini and co-workers (**Scheme 15**).[19] Treatment of (*E*)-cinnamaldehyde (**38**) with chloroacetic acid, cyclohexyl isocyanide and an amine gave the α-chloroacetamides **39** in good yield and with sufficient purity to be cyclized without purification to the β-lactams **40**.

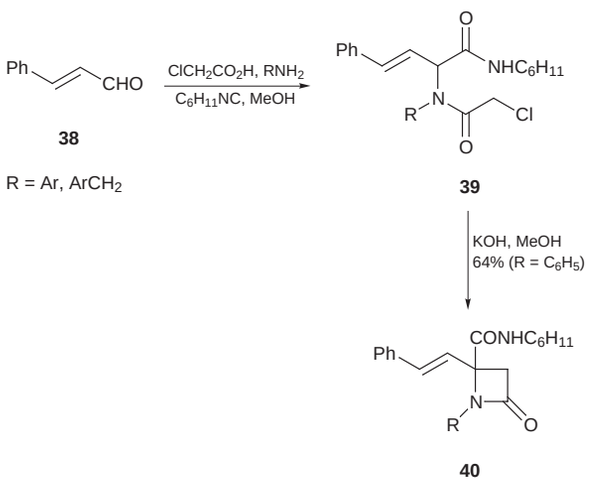
Palomo *et al.* have synthesized *N*-methylidene[bis(trimethyl-



36 **35** **37**

R^1	R^2	X	Solvent	**36**(%)	**37**(%)
Ph	H	Br	MeCN	16	62
Et	Me	Br	MeCN	0	55
Pr^i	H	Cl	CH_2Cl_2	10	23
Pr^i	H	Br	CH_2Cl_2	31	19

Scheme 14



38

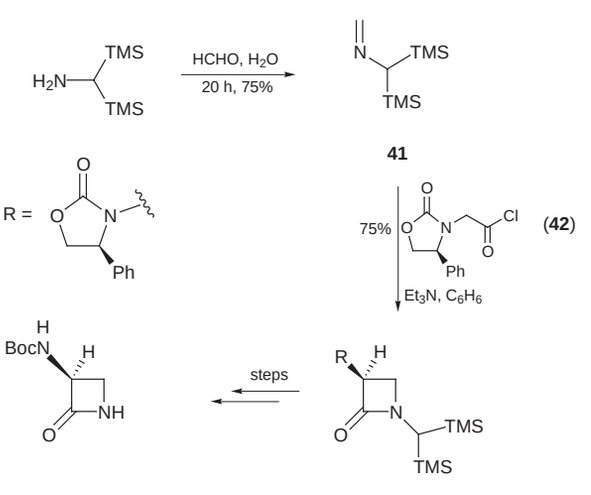
R = Ar, $ArCH_2$

39

40

Scheme 15

silyl)methyl]amine **41**, which acts as a methanimine equivalent (CH_2=NH) in cycloaddition reactions.[20] This was exemplified by reaction with **42**, a precursor to the corresponding ketene, to give **43**, which could be readily deprotected to yield **44** in excellent yield (**Scheme 16**).



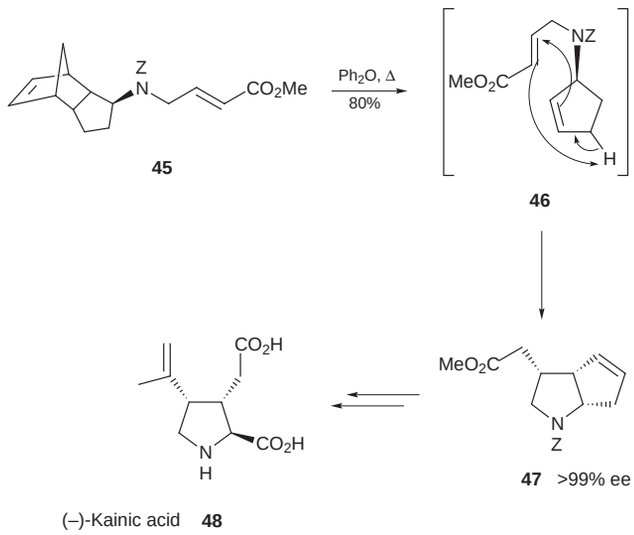
41

44 **43**

Scheme 16

4 Five-membered rings

Ogasawara and co-workers have described a novel synthesis of an intermediate *en route* to kainic acid, *via* a retro-Diels–Alder/ene reaction.[21] Starting with **45**, heating in diphenyl ether effected a retro-Diels–Alder reaction to give allylic amine **46**, which underwent an intramolecular ene reaction to give the bicyclic pyrrolidine **47** in 80% overall yield (99% ee) (**Scheme 17**). A number of straightforward steps were used to convert this into kainic acid (**48**).



45

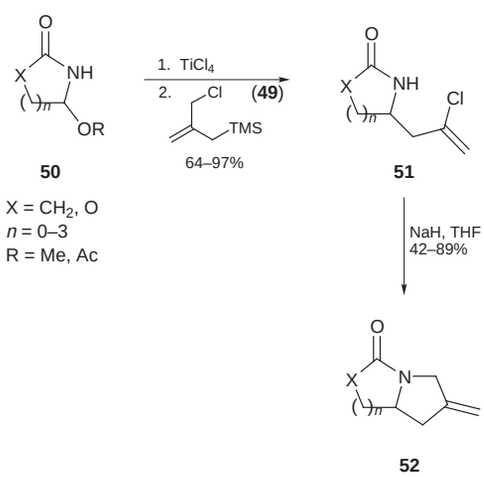
46

47 >99% ee

(–)-Kainic acid **48**

Scheme 17

The addition reaction between 2-chloromethyl-3-(trimethylsilyl)prop-1-ene **49** and a cyclic *N*-acyliminium ion has been used by Steckhan and co-workers in the synthesis of bicyclic 3-methylenepyrrolidines.[22] The *N*-acyliminium ions were generated from the corresponding α-methoxy- or α-acetoxy-amides (*e.g.* **50**) by treatment with $TiCl_4$ at −78 °C (**Scheme 18**). After isolation of the intermediate allylic chloride **51**, treatment with NaH gave the 3-methylenepyrrolidine **52** in generally good yield.



50

X = CH_2, O
n = 0–3
R = Me, Ac

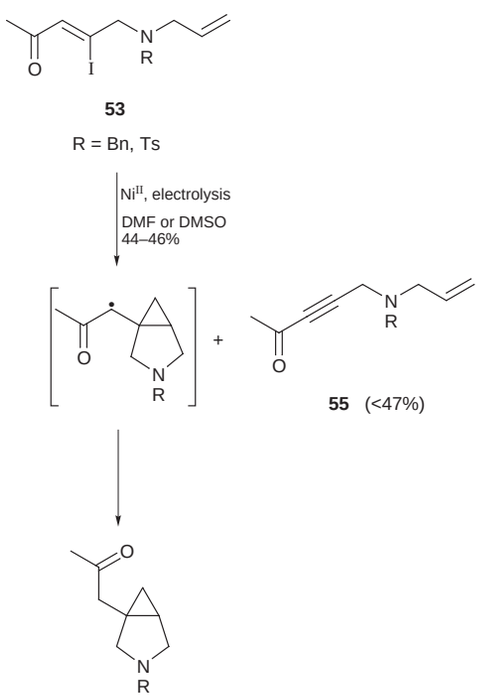
51

52

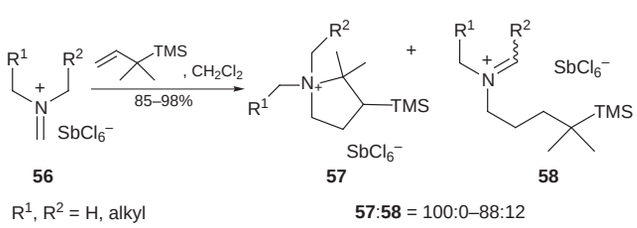
Scheme 18

Ozaki *et al.* have used a tandem [2+1]-radical cycloaddition/Ni complex-catalyzed electroreduction sequence to obtain cyclopropyl-fused pyrrolidines.[23] Thus, electrolysis of **53** in the presence of $Ni^{II}(teta)(ClO_4)_2$ or $Ni^{II}(tmc)(ClO_4)_2$ afforded the desired product **54** in 44–46% yield, together with the enyne **55** as a major by-product (teta = 5,5,7,12,12,14-hexamethyl-1,4,8,11-tetraazacyclotetradecane and tmc = 1,4,8,11-tetramethyltetraazacyclotetradecane) (**Scheme 19**).

The synthesis of pyrrolidinium salts by the reaction of an allylsilane and an unactivated *N*,*N*-dialkyliminium ion (*e.g.* **56**) has been reported by Mayr and Ofial (**Scheme 20**).[24] The reaction is proposed to proceed *via* initial attack of the allylsilane at the imine methylene carbon to give the β-silyl-stabilized carbocation. This then cyclizes to give the desired product **57** or suffers hydride transfer to give the iminium ion **58**, formally a product of an ene reaction.

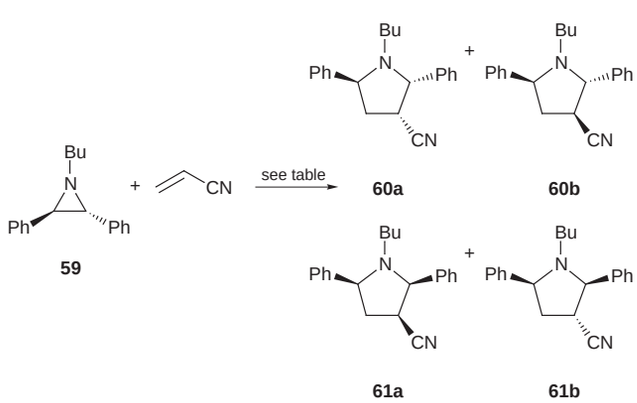


Scheme 19



Scheme 20

The interesting [3+2]-cycloaddition of the dipole obtained on photochemical ring opening of (*E*)-1-butyl-2,3-diphenylaziridine **59** with acrylonitrile has been reported (**Scheme 21**).[25] Direct irradiation of the reaction mixture produced **60a** and **60b** in modest yield, but under photoinduced electron transfer (PET) conditions (in the presence of 9,10-dicyanoanthracene) all possible stereoisomers (**60a,b** and **61a,b**) were obtained. A detailed mechanism explaining this observation was proposed.

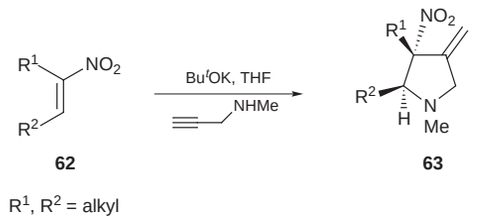


Conditions	**60a** (%)	**60b** (%)	**61a** (%)	**61b** (%)
hν, quartz, MeCN	40	18	0	0
DCA, MeCN	29	17	4	4

DCA = 9,10-dicyanoanthracene

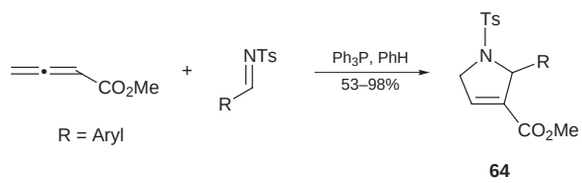
Scheme 21

3-Methylenepyrrolidines have been synthesized by Dumez *et al.* through application of the aza Michael reaction between substituted nitroalkenes and *N*-methylpropargylamine (**62→63**, **Scheme 22**).[26] The reaction was claimed to be both regio- and diastereo-selective.



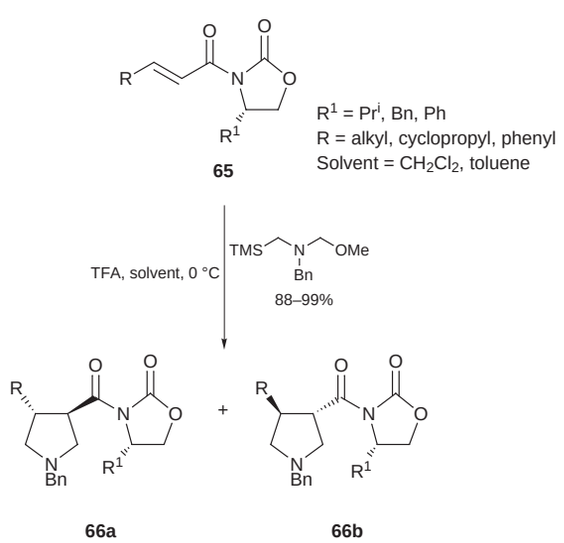
Scheme 22

Lu and Xu have described the triphenylphosphine-catalyzed [3+2]-cycloaddition reaction of methyl buta-2,3-dienoate with aromatic and heteroaromatic *N*-tosylimines to give disubstituted dihydropyrroles **64** in excellent yield (**Scheme 23**).[27]



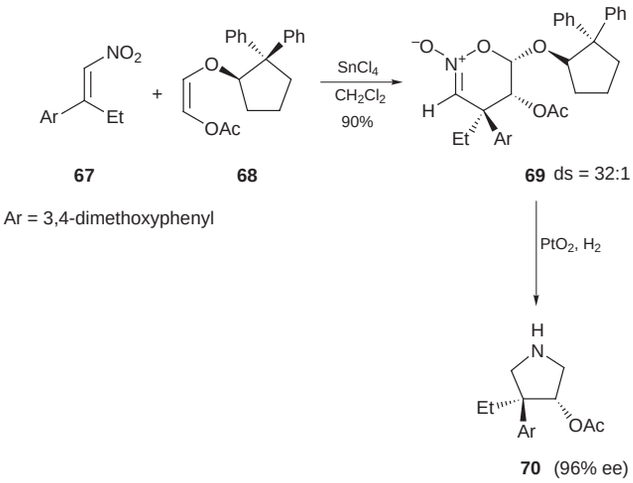
Scheme 23

Ma *et al.* have described the synthesis of a range of *trans*-3,4-disubstituted pyrrolidines through application of an azomethine ylide cycloaddition to chiral α,β-unsaturated *N*-acyloxazolidinones (**65→66a,b**, **Scheme 24**).[28] Although diastereoselectivities were generally modest (*ca.* 4–1 : 1, depending on substrate and conditions) the yields were excellent (88–99%) and the reaction practical enough to run on a large scale.



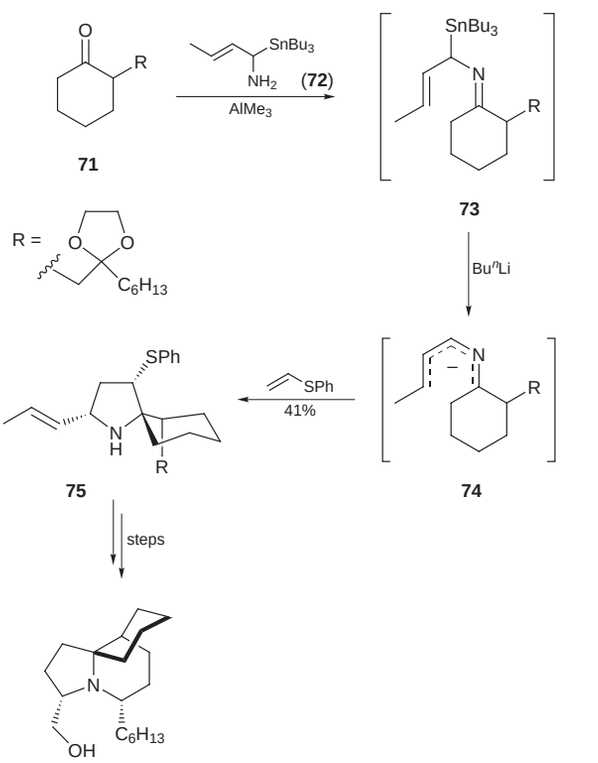
Scheme 24

During a synthesis of (−)-mesembrine, Denmark and Marcin demonstrated the highly enantioselective [4+2]-cycloaddition of a 2,2-disubstituted 1-nitroalkene **67** and a chiral, non-racemic 2-(acyloxy)vinyl ether **68**.[29] This reaction yields initially the nitronate **69** in 90% yield; reductive removal of the chiral auxiliary then yields the pyrrolidine **70** (**Scheme 25**). A similar strategy was used to prepare the natural products (−)-detoxinine and (+)-crotanecine.[30,31]



Scheme 25

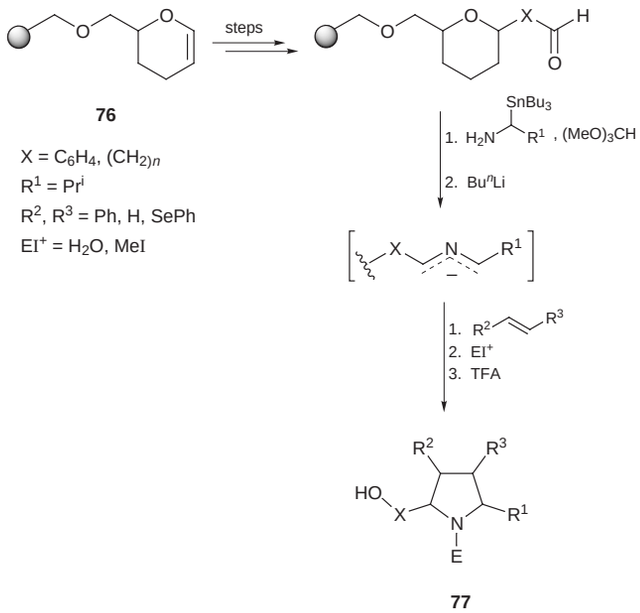
Pearson *et al.* have described a useful example of a [4+2]-cycloaddition of a 2-azapentadienyl anion **74** with phenyl vinyl sulfide during the synthesis of 2,13-diepilepadiformine (**Scheme 26**).[32] Treatment of ketone **71** with α-stannylamine **72** gave the imine **73**, which was immediately treated with BuLi and phenyl vinyl sulfide to give **75** (*via* **74**) as a single stereo- and regio-isomer.



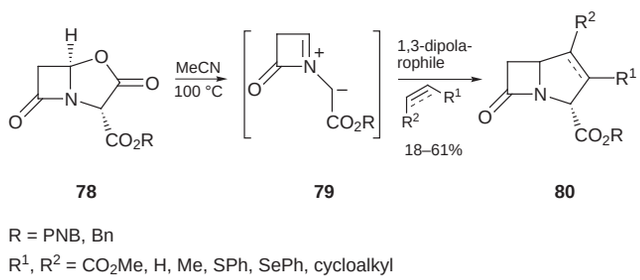
Scheme 26

A similar reaction, this time of a 2-azaallyl anion, has been utilized to generate a solid-phase library of pyrrolidines (**76**→**77**, **Scheme 27**).[33] It is notable that this approach allows all of the substituents on a pyrrolidine to be changed. Maclean *et al.* at Affymax have described a complementary approach (using an azomethine ylide/electron deficient olefin cycloaddition) in the synthesis of a tagged library of pyrrolidines.[34]

The five-membered ring of the carbapenem antibiotics has been synthesized for the first time through an azomethine ylide strategy (**Scheme 28**).[35] Thermolysis of **78** in the presence of a dipolarophile is thought to generate *in situ* the stabilized



Scheme 27



Scheme 28

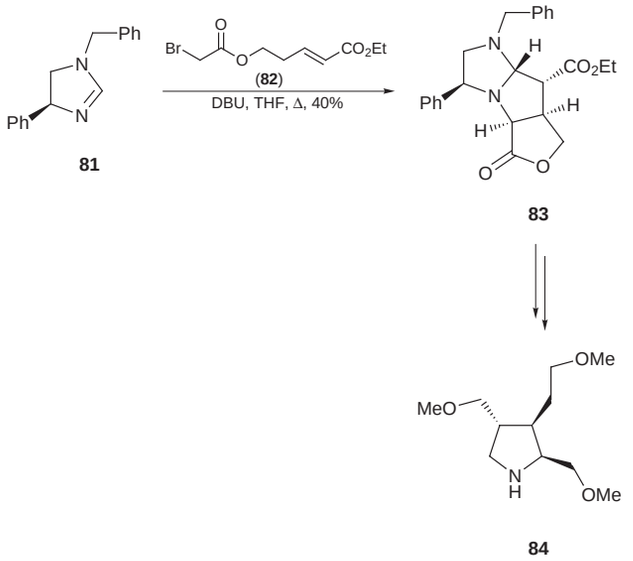
azomethine ylide **79** which subsequently undergoes cycloaddition with an alkene or alkyne to give the desired product **80**. The *endo* product predominated, and the reactions were highly regioselective.

The intramolecular cycloaddition of enantiomerically pure dihydroimidazolium ylides has been used to generate 2,3,4-trisubstituted pyrrolidines.[36] Treatment of **81** with **82**, containing both an alkylating agent and dipolarophile, at reflux gave the cycloadduct **83** as a single diastereoisomer (**Scheme 29**). A number of functional group transformations then revealed useful functionality in an ordered fashion at the 2-, 3- and 4- positions to give **84**.

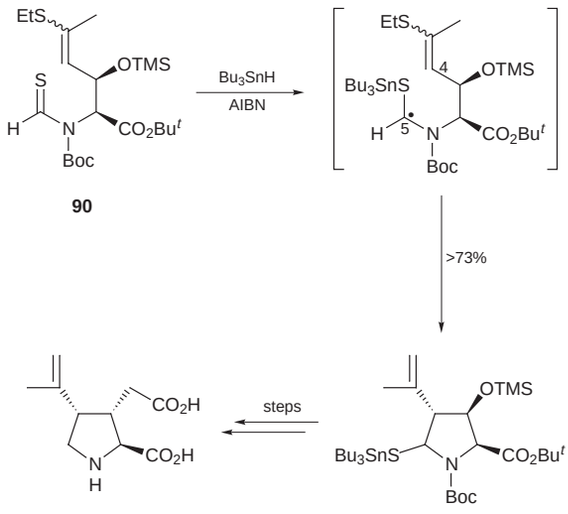
Kercher and Livinghouse have described the application of an intramolecular isopropylidene-1,3-bis(silane)–acylnitrilium ion cyclization to the synthesis of diversely substituted pyrrolidines (**Scheme 30**).[37] Treatment of isonitrile **85** with an acid chloride generates chemospecifically the α-ketoimido chloride **86** in quantitative yield. Cyclization was achieved by exposure of **86** to AgOTf, followed by stereoselective reduction and tosylation to give **87** in good overall yield.

Naito and co-workers have described further studies on a radical route to (−)-α-kainic acid.[38] The kainic acid framework is efficiently generated from **88** by treatment with thiophenol and AIBN (**Scheme 31**). The diastereoselectivity is poor, however, being slightly in favour of the undesired stereoisomer (**89a**:**89b** = 1:1.5). An alternative radical route has been reported by Bachi and Melman (**Scheme 32**).[39] In this instance, the C4–C5 bond is formed by a radical cyclization of **90** to give **91**.

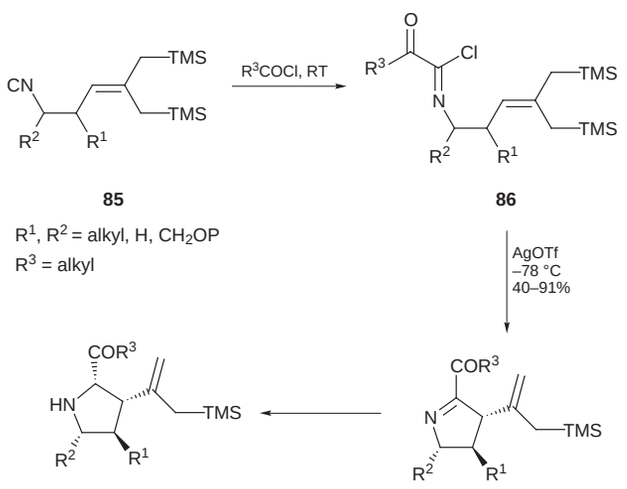
Bowman *et al.* have demonstrated the 5-*exo*-trig radical cyclization of *N*-pent-4-enyl amino acids to pyrrolidines



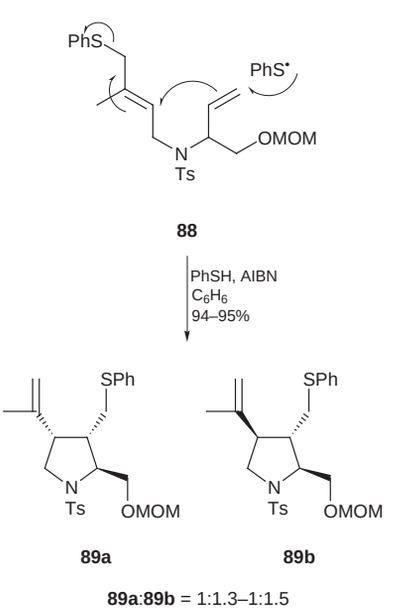
Scheme 29



Scheme 32

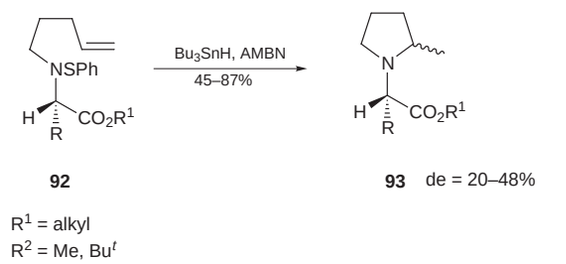


Scheme 30



Scheme 31

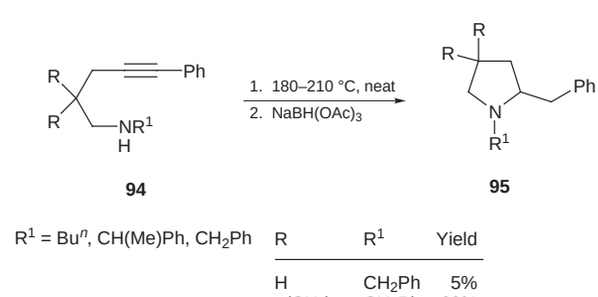
(**92**→**93**, **Scheme 33**).[40] The yields obtained are much higher than for the cyclization of ordinary *N*-alkylpent-4-enamines, which was postulated to be because of the increased



Scheme 33

electrophilicity of the aminyl radical bearing an α-carboxy group.

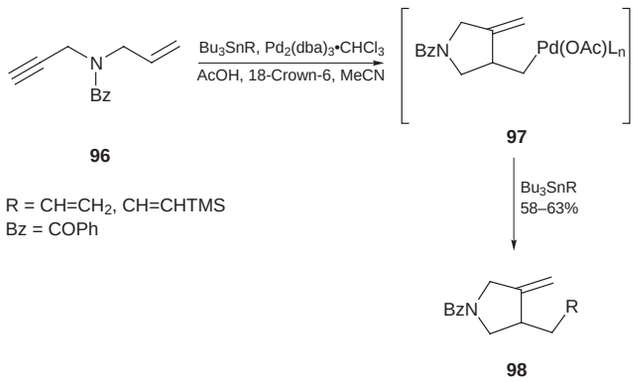
The hydroaminative cyclization of δ,ε-acetylenic amines to pyrrolidines *via* enamines has been reported by Cossy *et al.* (**94**→**95**, **Scheme 34**).[41] The intermediate enamine is readily reduced to the pyrrolidine with $NaBH(OAc)_3$. Unfortunately, the reaction conditions for cyclization are quite harsh, and only robust starting materials containing *gem*-dialkyl groups at C-3 gave satisfactory yields.



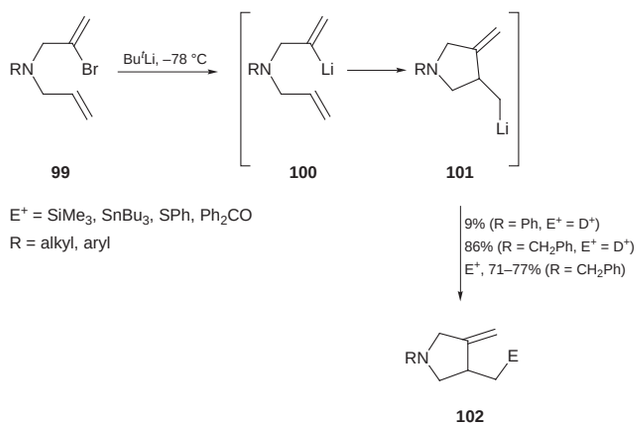
Scheme 34

A tandem carbopalladation/vinylation sequence has been used for the synthesis of 3,4-disubstituted pyrrolidines (**96**→**97**→**98**, **Scheme 35**).[42] It is noteworthy that phosphine-free conditions were optimal for the carbopalladation (**96**→**97**), as this suppressed unwanted β-elimination of the organopalladium intermediate **97**.

Similarly substituted pyrrolidines have been made by a 5-*exo* cyclization of *N*-allyl-*N*-(2-lithioallyl)amines **100**, derived from the corresponding bromide **99** (**Scheme 36**).[43] The ratio of 5-*exo* to 6-*endo* ring closure was found to depend heavily on the nitrogen protecting group; the 5-*exo* mode being more favoured only



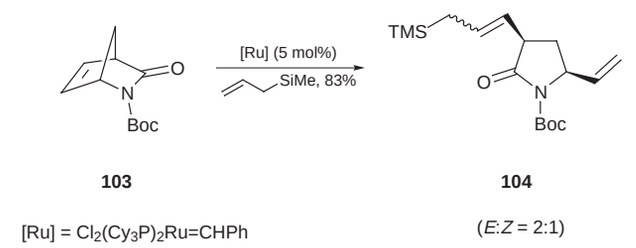
Scheme 35



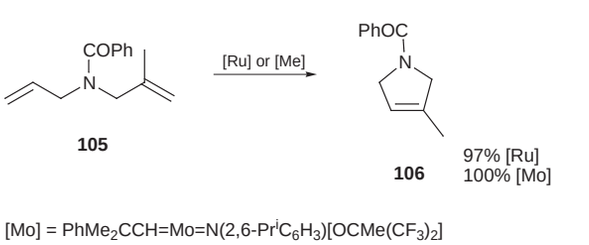
Scheme 36

with more basic nitrogen atoms (R = CH_2Ph, $CH_2C_6H_{11}$). The intermediate lithiopyrrolidines **101** could be captured by a range of electrophiles to give 3,5-disubstituted pyrrolidines **102** in good overall yields. Similar ionic cyclizations have been reported by Coldham and co-workers.[44,45]

The ring-opening metathesis of bicyclic imide **103** by allyltrimethylsilane and Grubbs' ruthenium catalyst, gave the 3,5-*cis*-disubstituted γ-lactam **104** in 83% yield (**Scheme 37**).[46] The same catalyst has also been applied to the ring-closing metathesis (RCM) of **105** (**Scheme 38**).[47] A very slightly higher yield of **106** was obtained with Schrock's molybdenum-based catalyst, illustrating a general trend that this catalyst is often superior for the RCM of heavily substituted dienes.

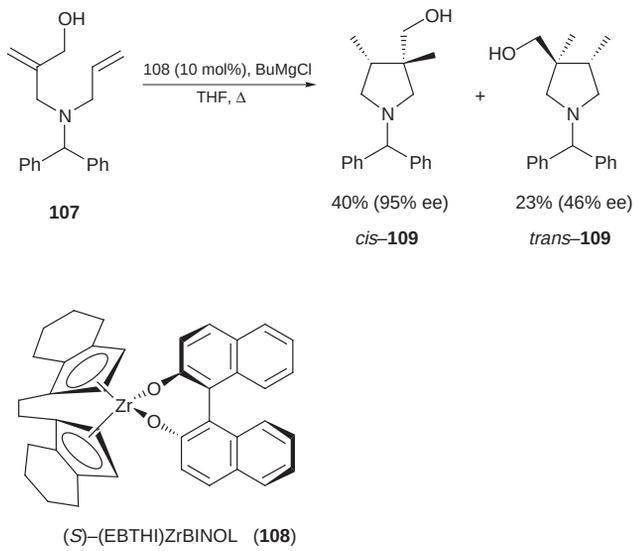


Scheme 37



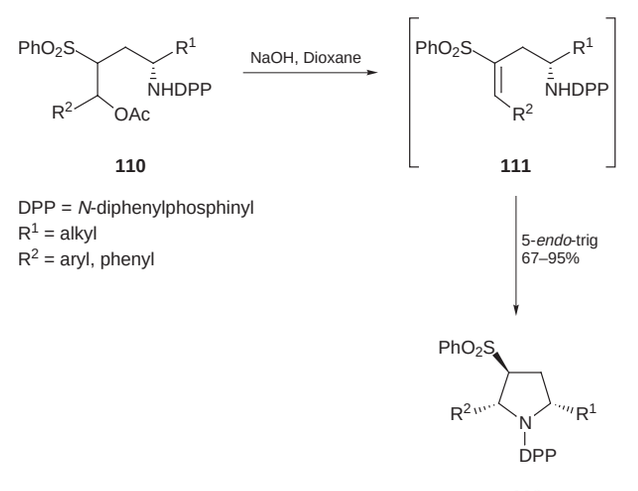
Scheme 38

Conceptually similar to the RCM, Mori and co-workers have described an asymmetric zirconium-catalysed diene cyclization.[48] For example, treatment of **107** with (*S*)-(EBTHI)-Zr(BINOL) **108** and BuMgCl affords a mixture of two pyrrolidines *cis*-**109** and *trans*-**109** in 40 and 23% yields respectively. Notably, the *trans* product was formed in 95% ee (**Scheme 39**).



Scheme 39

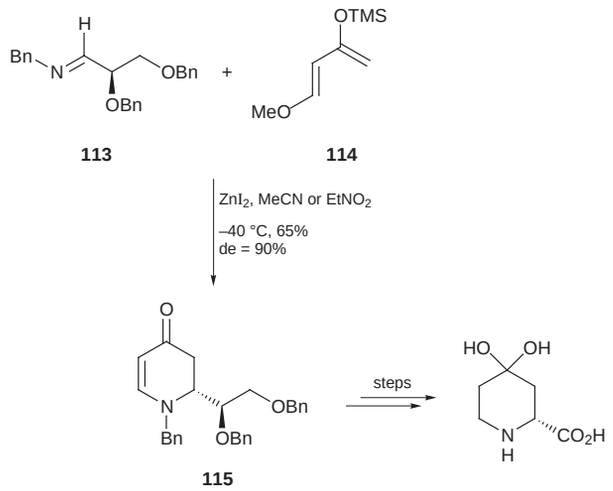
Craig and co-workers have described the synthesis of 2,5-disubstituted 3-(phenylsulfonyl)pyrrolidines **112** *via* an unusual 5-*endo*-trig cyclization (**111**→**112**, **Scheme 40**).[49] Treatment of **110** with freshly powdered NaOH in dioxane gave the pyrrolidine **112**, predominantly as the 2,5-*syn* diastereoisomer, in excellent yield. This strategy has also been applied to a synthesis of (+)-monomorine I.[50]



Scheme 40

5 Six-membered rings

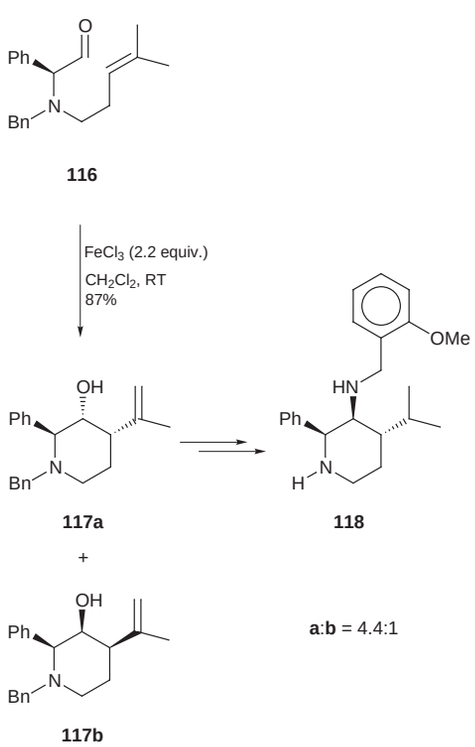
The imino Diels–Alder reaction between **113**, derived from D-glyceraldehyde, and Danishefsky's diene **114** has been used to make **115**, an intermediate *en route* to (2*R*)-4-oxopipecolic acid hydrate (**Scheme 41**).[51] The optimal conditions for the Diels–Alder reaction involved ZnI_2 catalysis in acetonitrile or nitroethane at −40 °C, resulting in a diastereomeric excess of 80%; other solvents and catalysts gave inferior results. A practical (kg scale) route to homochiral 4-oxopipecolic acid has been



Scheme 41

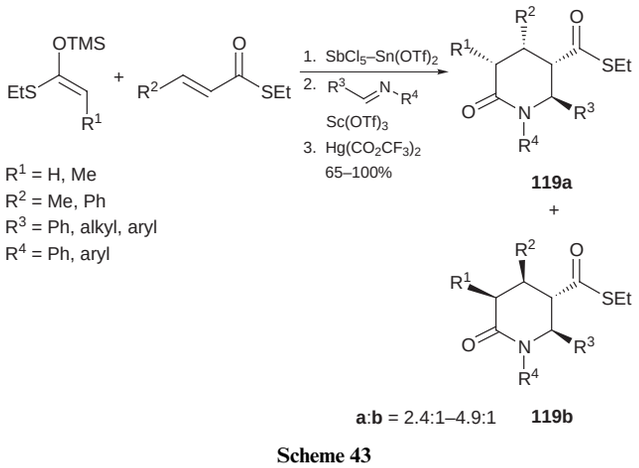
reported by Bousquet *et al*.[52] Danishefsky's diene has also been used in an imino-Diels–Alder reaction with imines derived from indole-3-carboxaldehyde,[53] the best Lewis acid in this case being $Zn(OTf)_2$; and with a series of enantiomerically pure aldimines derived from galactosylamine.[54] Akiba and co-workers have also investigated the role of the Lewis acid in the stereoselectivity of the imino-Diels–Alder reaction of 2-siloxybuta-1,3-diene and simple imines.[55]

Laschat and Fox have utilized a hetero-ene reaction, promoted by $FeCl_3$, to synthesize potential Substance P antagonists such as **118** from the acyclic phenylglycine-derived **116**.[56] The key reaction gave **117a,b** in a combined yield of 87% (ratio 81.4 : 18.6) (**Scheme 42**).



Scheme 42

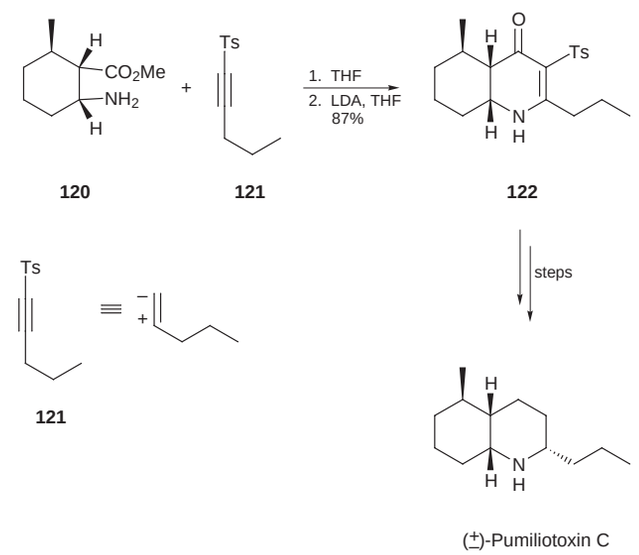
Kobayashi *et al*. have described a powerful multi-component coupling reaction approach to δ-lactams (**Scheme 43**).[57] Treatment of an *O*-silyl thioenol ether and an α,β-unsaturated thioester with $SbCl_5$–$Sc(OTf)_2$ catalyst (5 mol%), followed by treatment of the resulting Michael adduct with an imine (either



Scheme 43

preformed or from an aldehyde and an amine) and another Lewis acid catalyst gave, after Hg-mediated cyclization, a mixture of δ-lactams **119a** and **119b**. The optimal Lewis acid for the second step was determined to be $Sc(OTf)_3$ (2.5 mol%), resulting in remarkable overall yields and acceptable diastereomeric ratios.

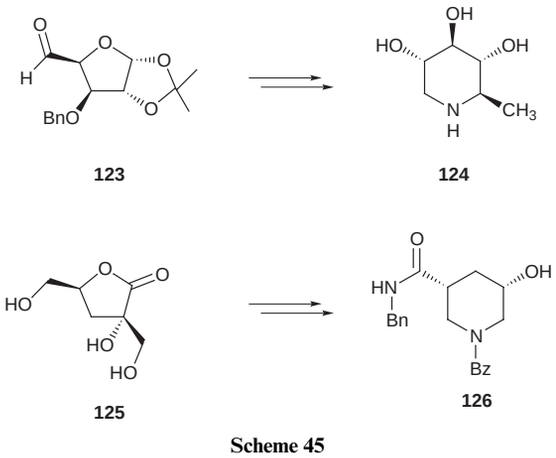
The use of an acetylenic sulfone, *e.g.* **121**, as a 1,2-dipole equivalent has been illustrated by Back and Nakajima in a synthesis of (±)-pumiliotoxin C (**Scheme 44**).[58] Starting with β-amino ester **120** (obtained from a Diels–Alder reaction), addition of **121**, followed by addition of LDA gave in 87% overall yield the enaminone **122**, which was ultimately converted to the natural product.



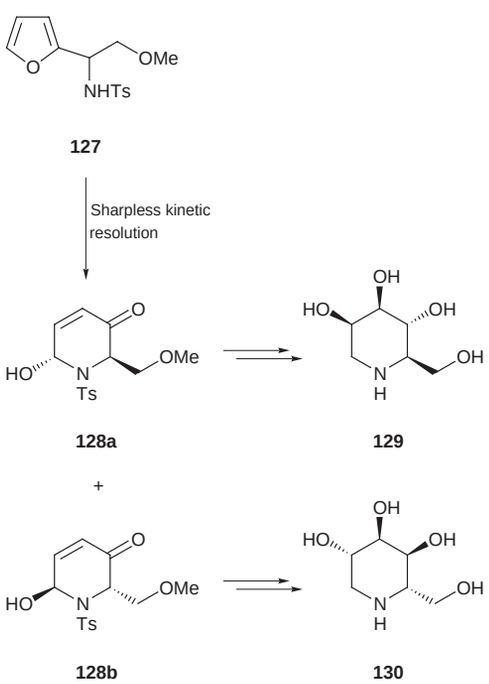
Scheme 44

The hydroxylated and polyhydroxylated piperidine alkaloids have again received much attention. 1,6-Dideoxynojirimycin **124** has been synthesized from the protected xylose **123** by Dhavale *et al*.;[59] while Gelas and co-workers described the synthesis of usefully hydroxylated intermediates from the sugar-derived lactone **125** (**Scheme 45**).[60] A non-chiral pool-derived approach has been described by Xu and Zhou (**Scheme 46**).[61] Kinetic resolution of racemic **127** by Sharpless epoxidation afforded **128a** and its enantiomer **128b**. Compound **128a** was converted to (−)-deoxymannojirimycin **129**, whereas **128b** was a substrate for the synthesis of (+)-1-deoxyaltrojirimycin **130**.

A short synthesis of (−)-coniine and (+)-pseudoconhydrine has been reported by Moody *et al*.[62] The key step involved the



Scheme 45

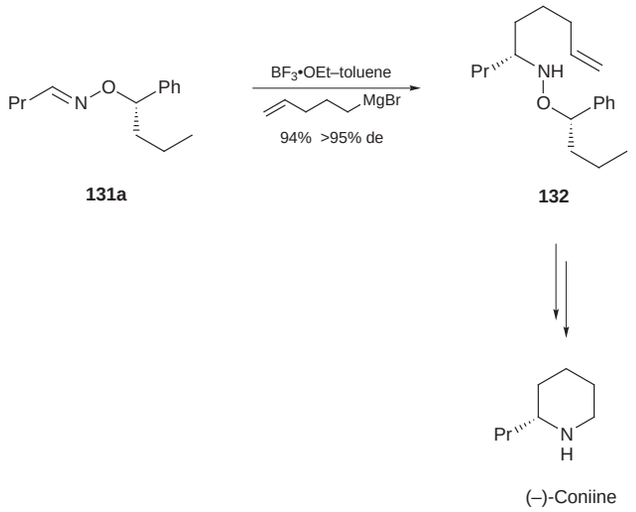


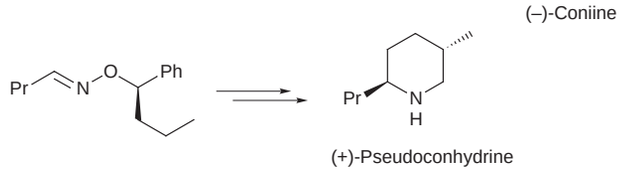
Scheme 46

diastereoselective addition of pent-4-enylmagnesium bromide to the enantiomerically pure oxime ether (**131a**→**132**, **Scheme 47**, 94% yield, >95% de). Following reductive cleavage of the N–O bond, cyclization and reduction, (−)-coniine was obtained in excellent overall yield. Similarly (+)-pseudoconhydrine was obtained from **131b**. (−)-Pseudoconhydrine has also been synthesized by ring expansion of an L-proline derivative.[63]

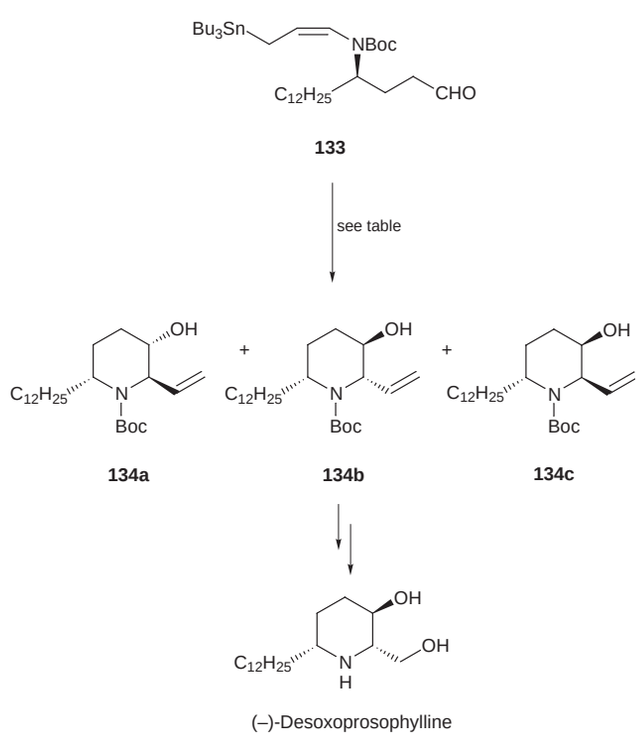
Yamamoto and co-workers have applied the Lewis acid-mediated cyclization of γ-aminoallylstannanes to the synthesis of the alkaloids (+)-desoxoprosopinine and (−)-desoxoprosophylline (**133**→**134a**–**c**, **Scheme 48**).[64] A range of Lewis and protic acids were screened in order to optimize diastereoselectivity and yields, but mixtures were always obtained, except in the absence of any catalyst, when none of the desired diastereoisomers were obtained. Desoxoprosophylline has also been made by Speckamp and co-workers, through functionalization of the lactam triflate **135** (**Scheme 49**).[65,66]

The transition metal-mediated cyclization of **136** (X = Cl or MOM) was the key step in Hirai *et al.*'s synthesis of (+)-prosopinine and an intermediate *en route* to (+)-palustrine (**136**→**137**, **Scheme 50**).[67] The key cyclization was achieved with $PdCl_2$(MeCN) (X = MOMO) or Ag(OCOCF$_3$) (X = Cl); in each case the product was a single (but different) diastereoisomer obtained in 72% yield.





Scheme 47



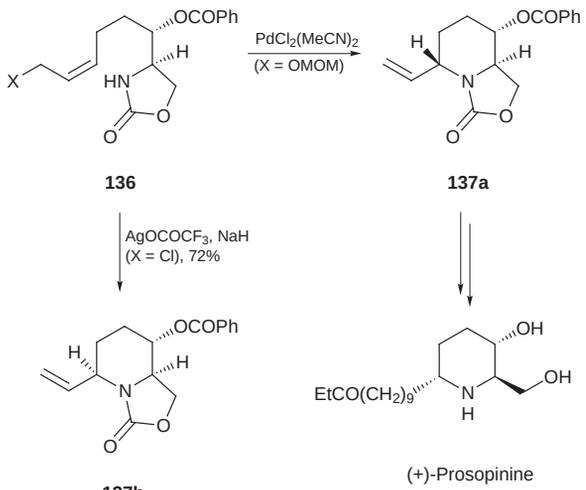
Lewis acid	Ratio 134a	134b	134c	Total yield (%)
$TiCl_4$	68	32	0	93
$SnCl_4$	47	53	0	42
TFA	22	0	78	72
Δ	0	0	100	72

Scheme 48

trans-2,6-Disubstituted piperidines (where one substituent is an allyl group) can be isomerized to an equilibrium mixture containing a majority of the more stable *cis* isomer, by heating with triallylborane (**138a**→**138b**, **Scheme 51**).[68] Since the *trans* isomers are often readily available from pyridine, this represents

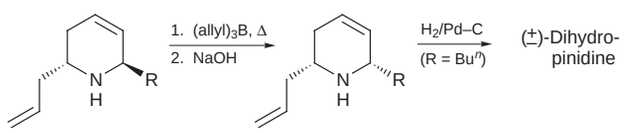
135

Scheme 49



136 **137a** **137b**

Scheme 50



138a **138b**

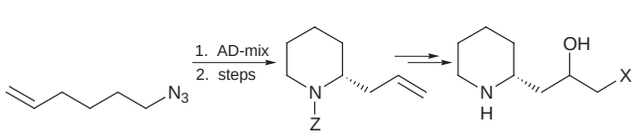
R = Me, Bu^n, Ph

R	**138a**:**138b** at equilibrium
Me	1:99
Bu^n	3:97
Ph	20:80

Scheme 51

a useful conversion. The product **138b** was converted to the natural product (±)-dihydropinidine by hydrogenation.

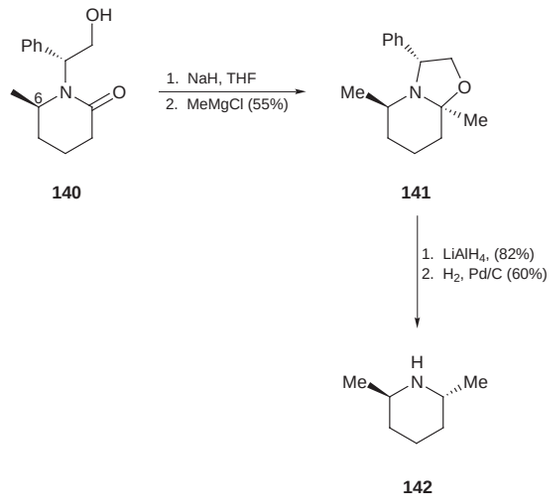
An asymmetric dihydroxylation (AD) approach to 2-(2-hydroxyalkyl)piperidines has been described by Takahata *et al.* (**Scheme 52**).[69] Starting with hex-5-enyl azide, AD gave a diol which could be readily converted to piperidine **139**. Another AD, or epoxidation followed by further functionalization gave separately a large range of enantiomerically pure natural products (Scheme 52).



139 X = H, Me, Et, *etc.*

Scheme 52

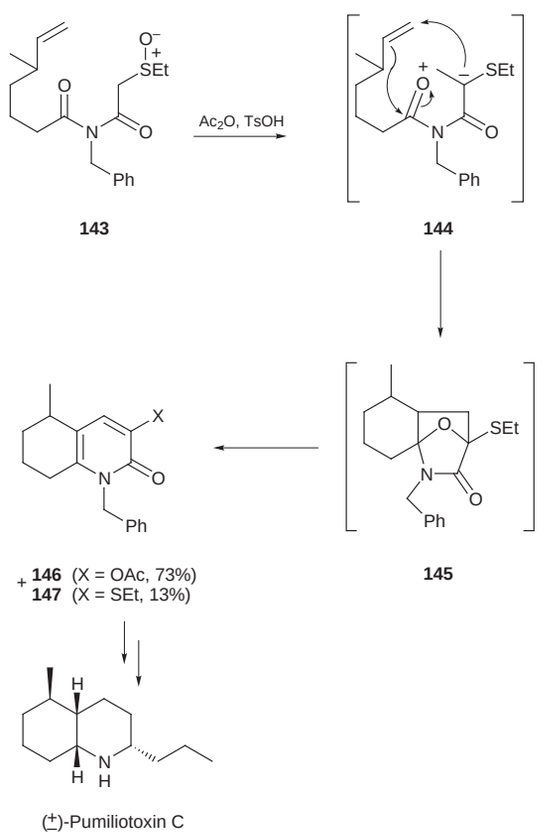
The preparation of (+)- and (−)-*trans*-2,6-dimethylpiperidines has been reported by Lhommet and co-workers (**Scheme 53**).[70] Treatment of **140** [derived from (*R*)-phenylglycinol] with NaH and MeMgCl afforded the oxazolopiperidine **141** (>98% de), which was diastereoselectively reduced with $LiAlH_4$ or $NaBH_4$ and deprotected to give (−)-**142**. The enantiomer (+)-**142** and a diastereomer were obtained from the 6α epimer of **140**.



140 **141** **142**

Scheme 53

A number of applications of the novel tandem Pummerer-induced cyclization–isomünchnone dipolar cycloaddition sequence have been reported by Kuethe and Padwa.[71,72] Illustrative of this is the synthesis of (±)-pumiliotoxin C in **Scheme 54**. Starting with the imidosulfoxide **143**, Pummerer rearrangement gave pyridones **146** and **147** in 86% overall yield, *via* the isomünchnone **144** and intermediate cycloadduct **145**. A series of reactions and other functional group transformations on **146** then gave the natural product.



143 **144** **145**

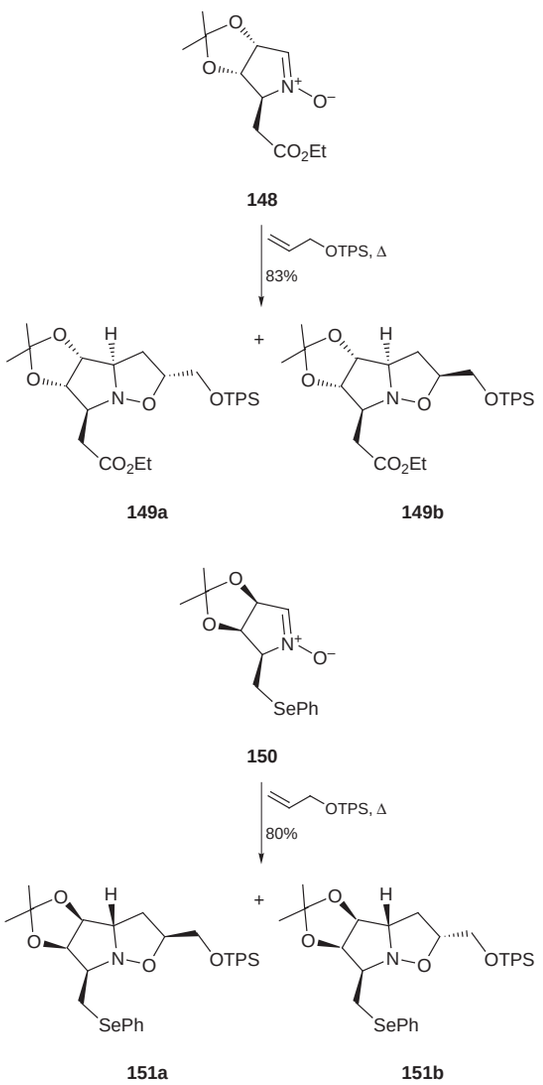
Scheme 54

6 Pyrrolizidines, indolizidines and quinolizidines

Two extensive reviews on indolizidine and quinolizidine alkaloids have been published this year,[73,74] together with reviews on pyrrolizidine alkaloids[75] and quinolone, quinazoline and acridone alkaloids.[76]

Wightman and co-workers are the latest to apply the inter-

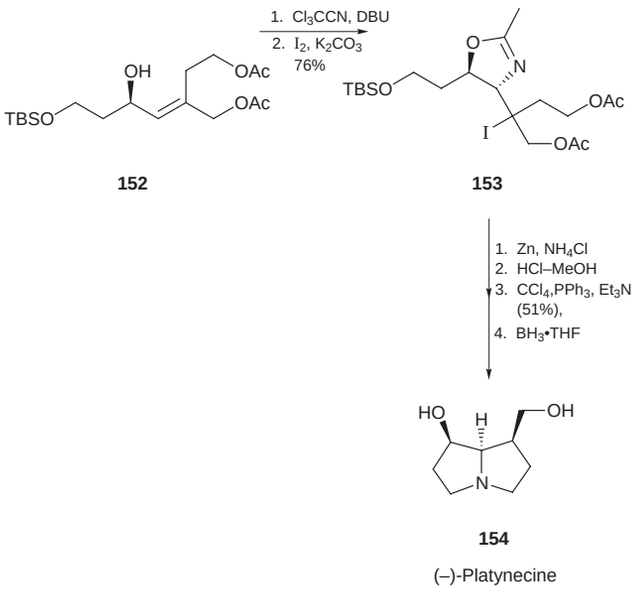
molecular cycloadditions of nitrones to the synthesis of polyhydroxylated pyrrolizidines.[77] The sugar-derived nitrone **148** was treated with allyl triisopropylsilyl ether to give the isoxazolidines **149a** and **149b** (ratio *ca*. 3 : 1) (**Scheme 55**). Both are the expected *exo*-adducts, with **149a** arising from the reaction at the less hindered face of the nitrone. The major cycloadduct was then converted into an isomeric form of the natural product australine in five simple steps. Interestingly, the analogous cycloaddition of all-*cis* nitrone **150** gave predominantly **151a**, with only small amounts of the *endo* adduct **151b** (8%).



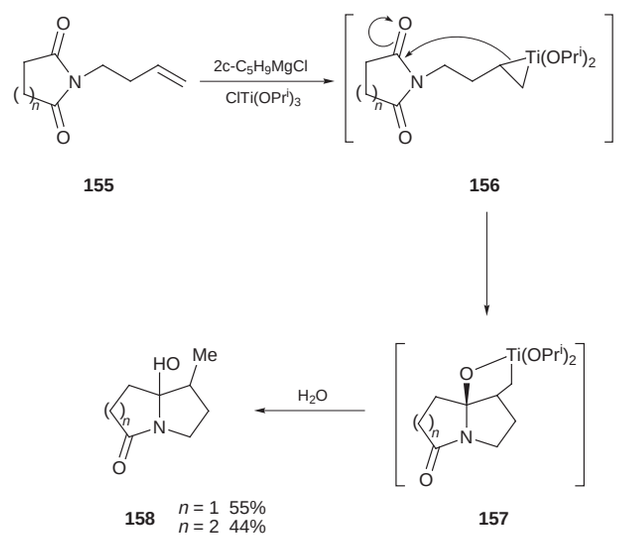
Scheme 55

(−)-Platynecine has been made by a multi-step sequence beginning with D-malic acid (**Scheme 56**).[78] The key steps involve (a) the iodine-promoted oxazoline formation (**152**→**153**) and (b) the two step bicyclization (**153**→**154**).

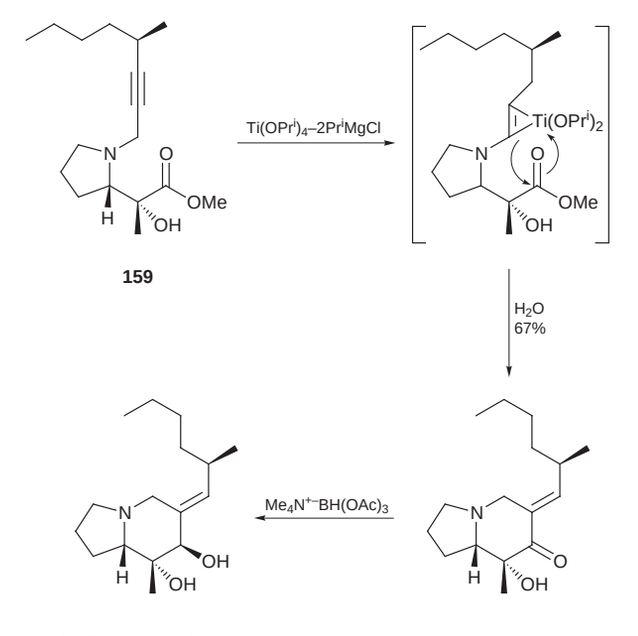
Cha and co-workers have described the titanium-mediated cyclization of ω-vinylimides to the pyrrolizidine and indolizidine frameworks (**155**→**158**, **Scheme 57**).[79] Treatment of **155** with Kulinkovich's reagent [2*c*-C_5H_9MgCl–$ClTi(OPr^i)_3$] afforded after aqueous work-up the bicycle **158**, probably *via* intermediates **156** and **157**. Sato and co-workers have independently described the synthesis of a number of *N*-heterocyclic compounds using a similar strategy, but most notably in a synthesis of (+)-allopumiliotoxin 267A (**Scheme 58**).[80] Thus, in the key step, treatment of **159**, derived from L-proline, with $Ti(OPr^i)_4$/2Pr^iMgCl gave **160** after work-up in 67% yield. Sato and co-workers have applied this to the stereoselective



Scheme 56



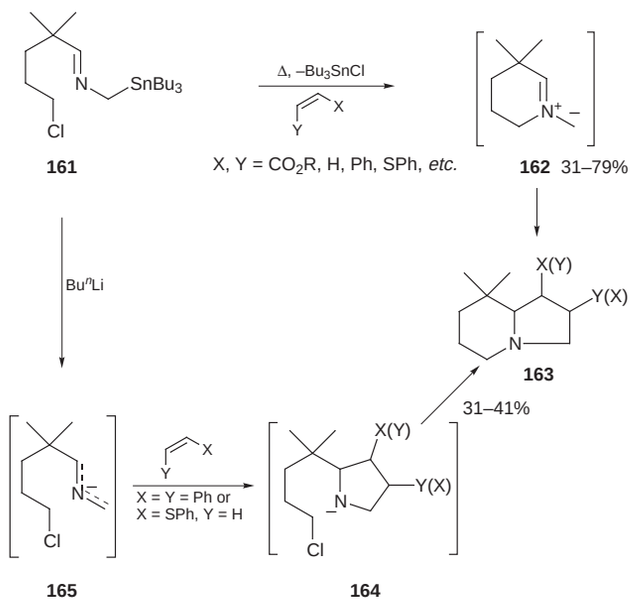
Scheme 57



Scheme 58

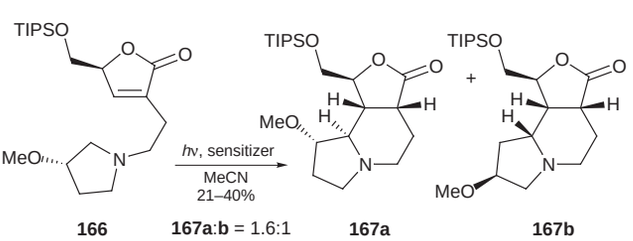
synthesis of a number of other functionalized nitrogen heterocycles.[81]

In an extension to an earlier paper, Pearson and Mi have reported the synthesis of indolizidines from a common precursor *via* either an azomethine ylide route or an azaallyl anion route (**Scheme 59**).[82] Since azomethine ylides add best to electron deficient dipolarophiles and azaallyl anions generally react with electron-rich alkenes, then the two methods are complementary. The common precursor, stannyl- or trimethylsilylimine **161**, is heated in toluene at reflux in the presence of a dipolarophile to generate the indolizidine **163**, presumably *via* the azomethine ylide **162**. Alternatively, transmetallation of **161** with Bu^{n}Li in the presence of an alkene gave the indolizidine **163** in more modest yield, *via* **164** and the azaallyl anion **165**.



Scheme 59

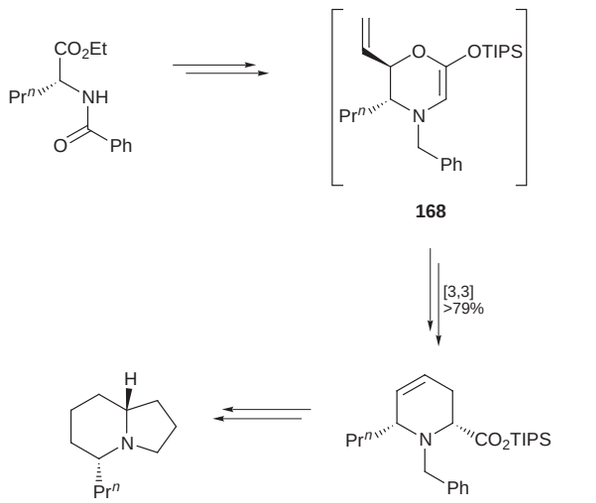
The irradiation of butenolide **166** in acetonitrile in the presence of a sensitizer (benzophenone or 1,4-dicyanonaphthalene) gives indolizidines **167a** and **167b** in the ratio 1.6:1 (**Scheme 60**).[83]



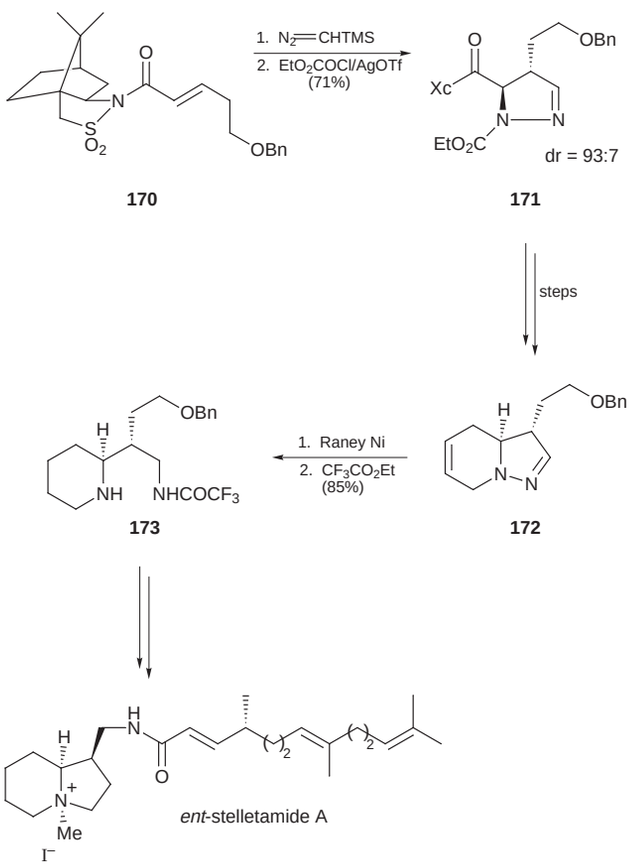
Scheme 60

Angle and Henry have described the synthesis of (−)-indolizidine 167B by application of a Claisen rearrangement (**168**→**169**, **Scheme 61**).[84]

Carreira and co-workers have described a further application of the [3+2]-cycloaddition between a dipolarophile and $TMSCHN_2$.[85,86] In this instance, treatment of the sultam **170** with $TMSCHN_2$ gave **171** as the major diastereomer (ratio = 93:7) in 71% yield after treatment with ethyl chloroformate and silver triflate (**Scheme 62**). The carboxamide functionality was readily functionalized to create the six-membered ring, and following reductive cleavage of the N–N bond and cyclization (**172**→**173**) the indolizidine framework was completed. Acylation and *N*-alkylation then gave the enantiomer of the natural product stelletamide A.



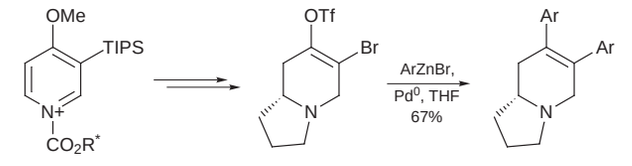
Scheme 61



Scheme 62

A number of indolizidines have been prepared by Comins *et al.* using *N*-acyldihydropyridones as intermediates. Particularly notable is the synthesis of (−)-septicine **175** and (−)-tylophorine *via* Pd-catalysed Negishi coupling of the versatile intermediate **174** (**Scheme 63**),[87] and the synthesis of alkaloids 205A, 207A and 235B from a common intermediate.[88]

The assembly of the indolizidine and quinolizidine frameworks by an intramolecular hetero-Diels–Alder reaction has been reported.[89] Unsubstituted 1-azabuta-1,3-dienes apparently do not undergo this reaction, requiring the addition of an activating cyano group. With this in place, the diene **176** is sufficiently reactive for the reaction to be complete after 24 h,

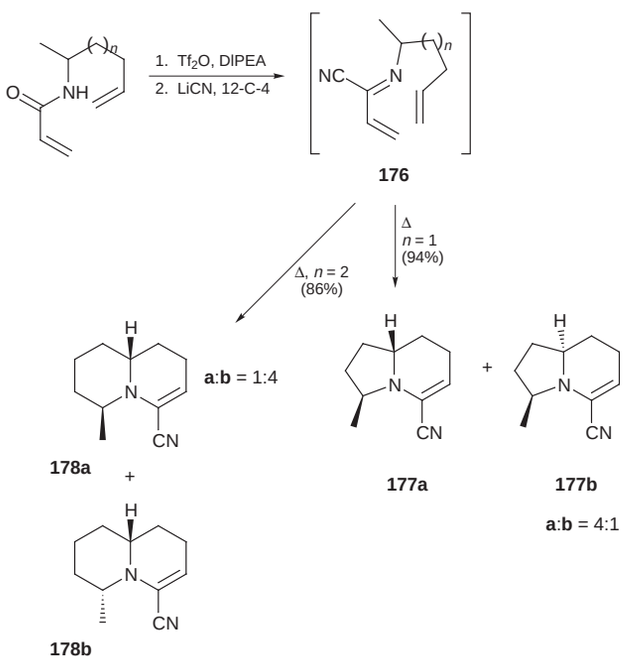


174 **175**

R* = (–)-*trans*-2-(α-cumyl)cyclohexyl
Ar = 3,4-(MeO)$_2$C$_6$H$_3$

(–)-Septicine

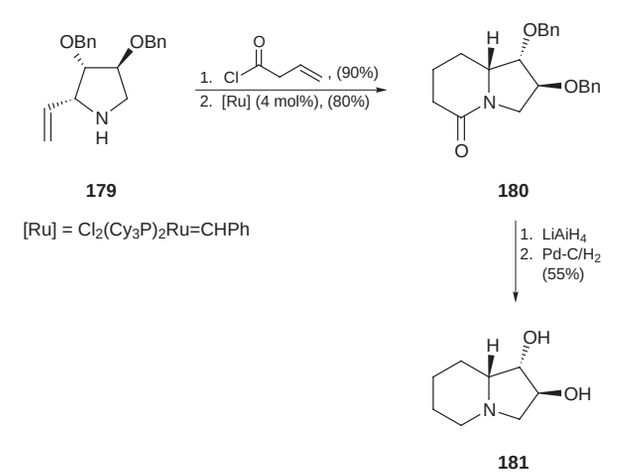
Scheme 63



Scheme 64

giving a 94% yield of a 4 : 1 mixture of **177a** and **177b** (**Scheme 64**). With the homologue ($n = 2$), the stereoselectivity was reversed, although the yield of **178a,b** was virtually unchanged.

The ring closing metathesis (RCM) reaction mediated by Grubbs' ever-popular Ru catalyst has been used by Paolucci *et al*. to assemble the indolizidine framework (**Scheme 65**).[90] Acylation of **179**, ultimately derived from mannitol, with but-3-enoyl chloride followed by exposure to the RCM catalyst gave **180**. Reduction then gave (−)-**181**, the 8α epimer of the natural product lentiginosine.

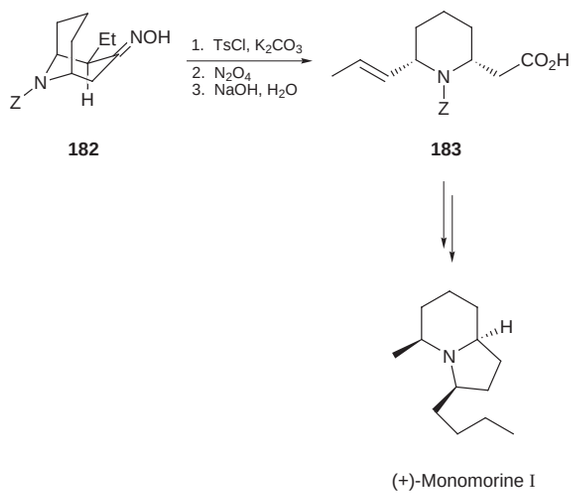


179 **180** **181**

[Ru] = $Cl_2(Cy_3P)_2Ru{=}CHPh$

Scheme 65

The little-used Huisgen–White rearrangement was used in the synthesis of piperidine **183**, an intermediate for the synthesis of many alkaloids, including (+)-monomorine I.[91] Thus, Beckmann rearrangement of **182** gave the corresponding lactam, which on treatment with dinitrogen tetroxide (N_2O_4) underwent Huisgen–White rearrangement to give **183** (**Scheme 66**).

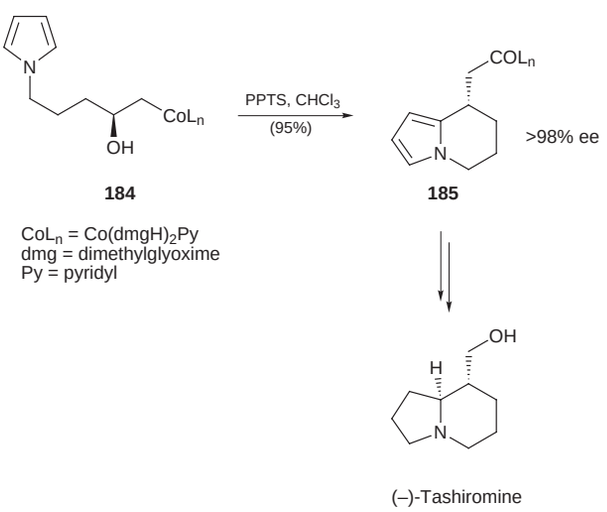


182 **183**

(+)-Monomorine I

Scheme 66

Treatment of **184** with mild acid generates a reactive cobaloxime π-cation, which can be trapped by a nucleophile. In a synthesis of (−)-tashiromine, Gage and Branchaud have shown that if this nucleophile is a suitably located pyrrole, a useful C–C bond forming reaction occurs (**184**→**185**, **Scheme 67**).[92] Even more remarkably, the enantiomeric excess of the reaction was extremely high, suggesting that the reaction is either highly enantioselective or enantiospecific.



184 **185**

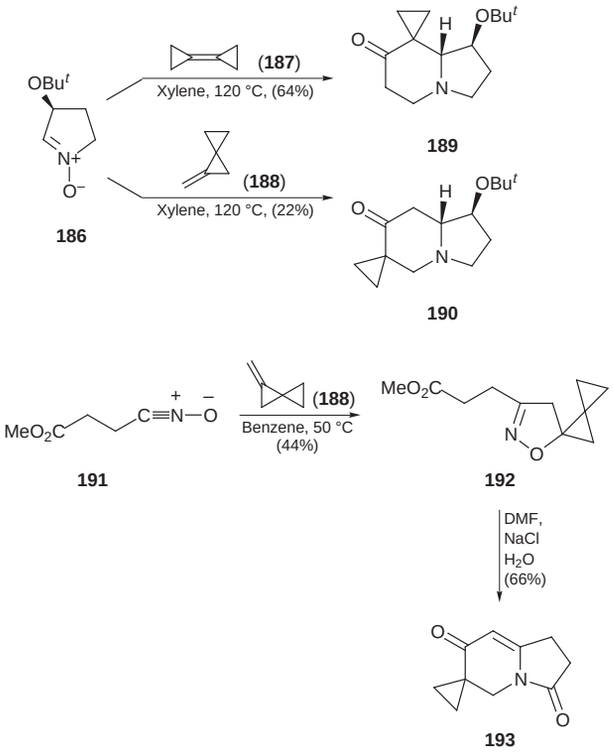
CoL_n = $Co(dmgH)_2Py$
dmg = dimethylglyoxime
Py = pyridyl

(–)-Tashiromine

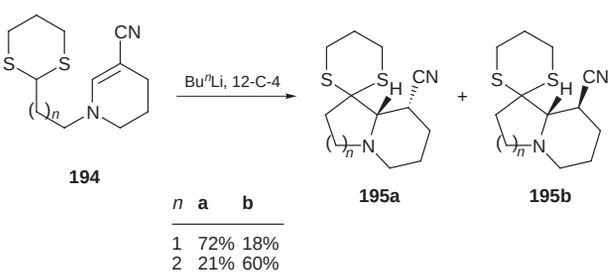
Scheme 67

The reaction of nitrones with alkenes to make indolizidines is not new, but Brandi and co-workers have shown that with unusual alkenes (*e.g.* **187** and **188**, **Scheme 68**) further reactions can occur in tandem to give indolizidines in one pot.[93] For example, treatment of **186** with **187** gives **189**, whereas treatment with **188** gives the regioisomer **190**. With an acyclic dipole, such as nitrile oxide **191**, cycloaddition with **188** gives the spiropentane **192**, which under Krapcho conditions rearranges to give **193**.

Formation and reaction of the dithiane anion from **194** (**Scheme 69**) was only successful in the presence of 12-crown-4.[94] Once formed, however, it underwent an efficient and stereo-



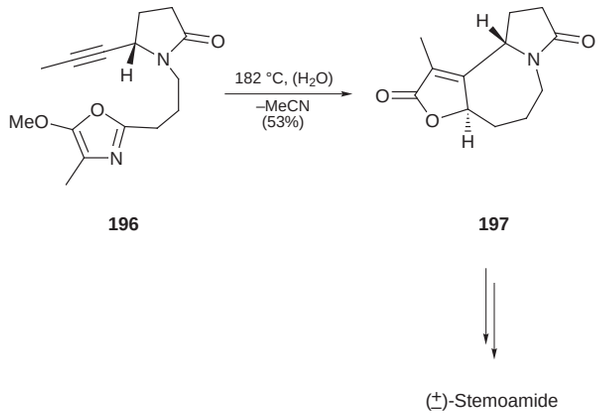
Scheme 68



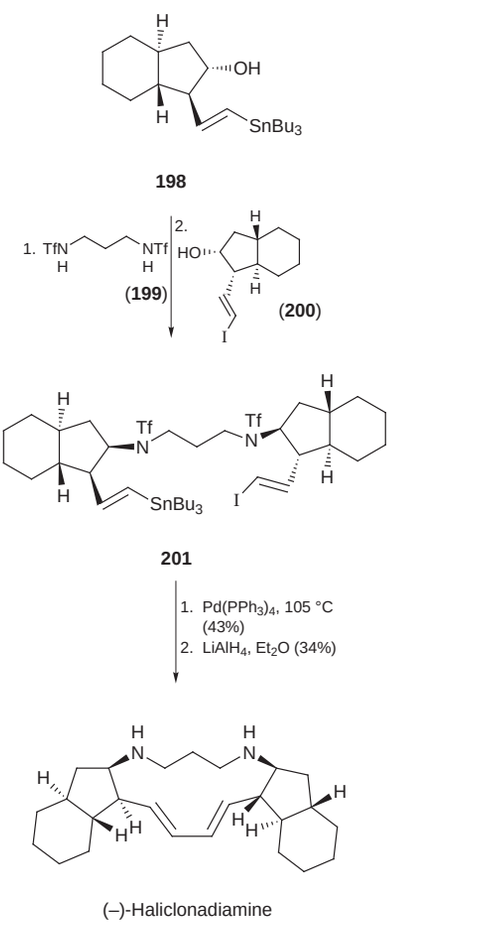
Scheme 69

selective conjugate addition to the adjacent α,β-unsaturated nitrile to give **195a,b** ($n = 1$, ratio = 4 : 1, 90% yield). Surprisingly, the axial isomer predominated. Similar results were obtained in the quinolizidine series ($n = 2$).

(±)-Stemoamide, containing a perhydroazulene skeleton, was synthesized efficiently by Jacobi and Lee (**Scheme 70**).[95] Heating **196** at 182 °C (refluxing diethylbenzene) induced a Diels–Alder-retro-Diels–Alder reaction sequence eliminating acetonitrile and generating butenolide **197**. It was suspected that the hoped-for Diels–Alder-retro-Diels–Alder sequence might in fact not be concerted, but may proceed in a stepwise electron transfer fashion.



Scheme 70



Scheme 71

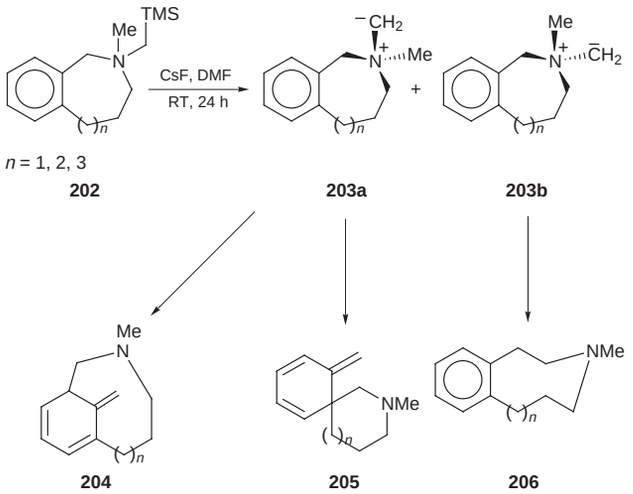
7 Medium and large rings

The 13-membered ring natural product (−)-haliclonadiamine has been synthesized by Taber and Wang (**Scheme 71**).[96] Two Mitsunobu reactions were used to join the bis(triflamide) moiety **199** to the vinylstannane **198** and the vinyl iodide **200**. Ring closure was effected by slow addition of the iodostannane **201** to a solution of $Pd(PPh_3)_4$ in refluxing toluene. Removal of the protecting groups with $LiAlH_4$ in diethyl ether gave the natural product in an overall yield of 14% (two steps from **201**).

Sato and co-workers have analysed the products of the reaction of 2-benzocycloammonium *N*-methylides **202** (**Scheme 72**).[97] In the first step, a mixture of ylides **203a** and **203b** is formed from **202**. Ylide **203a** has two reaction pathways available to it, leading to the unstable isotoluene **204** or the spirocycle **205**. **203b** gives the Stevens rearrangement product **206** *via* a radical cleavage and recombination pathway. The exact product distribution depended to a large extent on the length of the tether (n) and the reaction conditions.

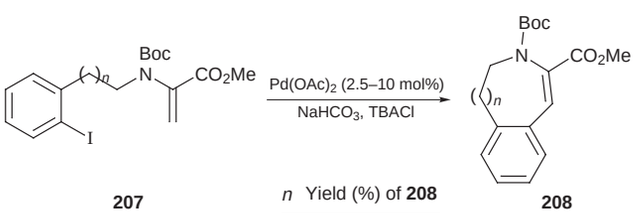
Three constrained phenylalanine analogues **208** ($n = 1$–3) have been made by the 7-, 8- or 9-*endo* Heck cyclizations of aryl iodides **207** ($n = 1$–3) (**Scheme 73**).[98] It was found necessary to carefully optimize the conditions for each of the ring closure reactions. Under optimal conditions, yields were 55, 73 and 86% respectively. The significantly lower yield for the formation of the seven-membered ring was tentatively attributed to a competing 6-*exo* ring closure pathway.

The smallest heterametacyclophane **209**, has been synthesized by Bickelhaupt and co-workers.[99] The crystal structure



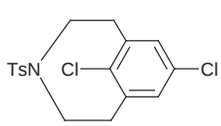
n	Ratio 204	205	206	Total yield (%)
1	27	0	73	82
2	38	14	48	46
3	0	84	9	23

Scheme 72



n	Yield (%) of 208
1	55
2	73
3	86

Scheme 73



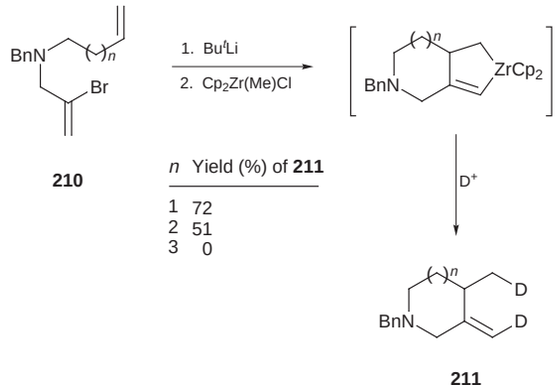
209

of 8,11-dichloro-*N*-tosyl-3-aza[5]metacyclophane **209** shows the aromatic ring to have equivalent and expected C–C bond lengths, but to be quite distorted from planarity.

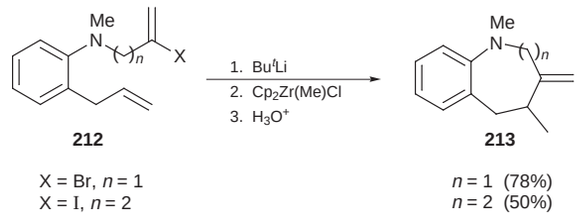
Barluenga *et al*. have examined the zirconium-mediated intramolecular cyclization of dienes to form seven- and eight-membered heterocycles.[100] Thus treatment of **210** (**Scheme 74**) with Bu^{t}Li followed by $Cp_2Zr(Me)Cl$ and hydrolysis gave the corresponding heterocycles **211** in good to moderate yield, except for the 8-membered ring, which was not formed at all. However, with the additional constraint of a benzene ring fused to the system, the eight-membered ring could be formed in respectable yield (**212**→**213**).

The aza[3,3]Claisen rearrangement has been used to prepare substituted seven-membered lactams, important motifs in many peptide turn mimetics.[101] Treatment of **214** (readily prepared from the corresponding epoxide in three steps) with LiHMDS gave on warming the lactam **216** in excellent yield and with very high stereoselectivity, probably *via* the boat-like transition state **215** (**Scheme 75**).

The hexahydroazepine ring of the natural product (−)-balanol has been synthesized by Naito and co-workers.[102] Treatment of **217** (**Scheme 76**) with samarium iodide in Bu^{t}OH–



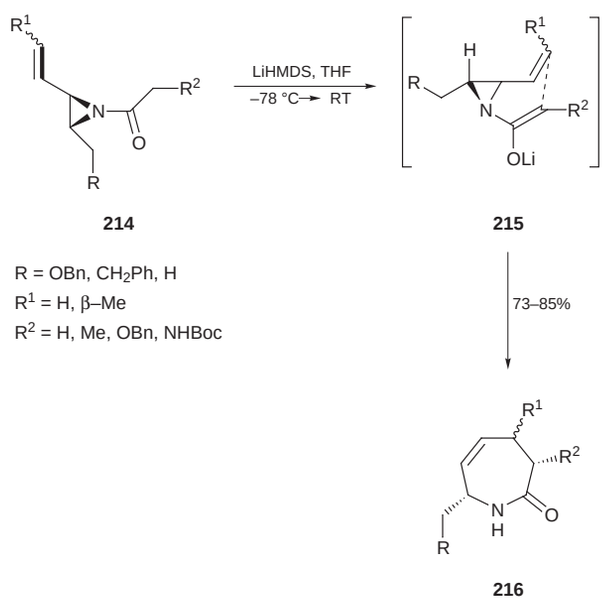
n	Yield (%) of 211
1	72
2	51
3	0



X = Br, *n* = 1
X = I, *n* = 2

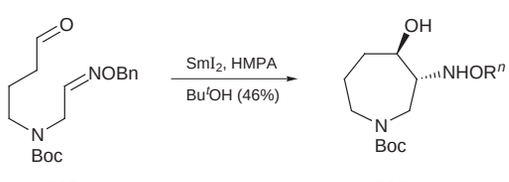
n = 1 (78%)
n = 2 (50%)

Scheme 74



R = OBn, CH_2Ph, H
R^1 = H, β–Me
R^2 = H, Me, OBn, NHBoc

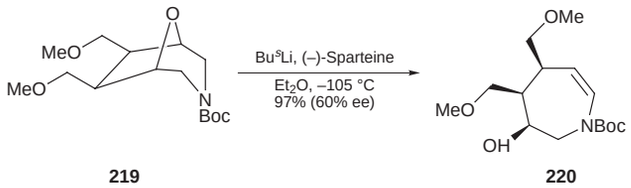
Scheme 75



Scheme 76

HMPA resulted in the formation of the *trans*-1,2-amino alcohol **218** in 46% yield, together with 7% of the *cis*-product. Enzymatic resolution and addition of the two side-chains then successfully completed the synthesis of the natural product.

A useful desymmetrization of **219** (**Scheme 77**) with a chiral lithium amide base promotes an efficient access to optically enriched azepines such as **220**.[103] Treatment of **219** with Bu^{s}Li–(−)-sparteine gave **220** in virtually quantitative yield, the best ee being obtained at very low temperature.



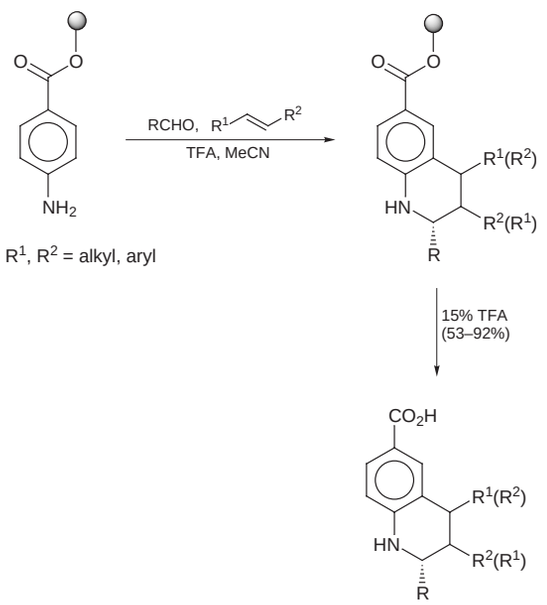
219 220

Scheme 77

8 Tetrahydroquinolines and tetrahydroisoquinolines

A review on β-phenethylamine and isoquinoline alkaloids has been published.[104]

A new solid phase synthesis of tetrahydroquinolines *via* a three-component, one-pot coupling has been reported.[105] The aromatic ring portion was conveniently tethered to the solid support (Wang resin) by an ester linkage (**Scheme 78**). Addition of five different alkenes and eight different aldehydes in the presence of TFA in acetonitrile led to formation of the tetrahydroquinolines **221** in good yield (53–92%), following cleavage from the resin.



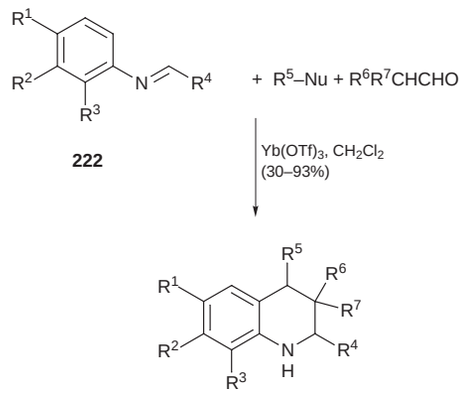
221

Scheme 78

An alternative multicomponent synthesis of tetrahydroquinolines **223** has been reported by Annunziata and coworkers (**Scheme 79**).[106] The reaction involves treatment of an imine **222** (either pre-formed or formed *in situ*) with an aldehyde and a nucleophile under Yb(OTf)$_3$ catalysis. Suitable nucleophiles were found to be anilines, thiols, alcohols and water, whereas the aldehyde component was restricted to those that were enolizable and α-branched. The aromatic portion tolerates much more substitution, whether electron-donating or electron-withdrawing in character.

Tetrahydroisoquinolines can be synthesized by the intramolecular addition of a nitrile-stabilized carbanion to an (η_6-arene)Cr(CO)$_3$ complex (**224**→**225**, **Scheme 80**).[107] Some substitution around the aromatic ring is tolerated, and the desired tetrahydroisoquinolines can be obtained in moderate-to-good yield after decomplexation with iodine.

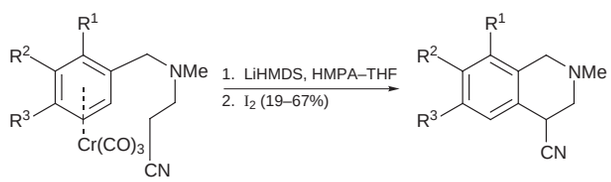
The synthesis of 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid derivatives from α,α′-dibromo-*o*-xylenes has been reported.[108] Treatment of the glycine derivative **226** with NaHMDS and **227** gave initially **228**, which on reduction with NaCNBH$_3$ and acetic acid gave the cyclized material **229** (**Scheme 81**). Importantly, the ring-closing reaction works well



222 **223**

R^1, R^2, R^3 = H, Cl, F, Me, MeO
R^4 = alkyl, aryl
R^{5}Nu = thiol, amine, alcohol, H$_2$O
R^6, R^7 = alkyl, *O*-alkyl

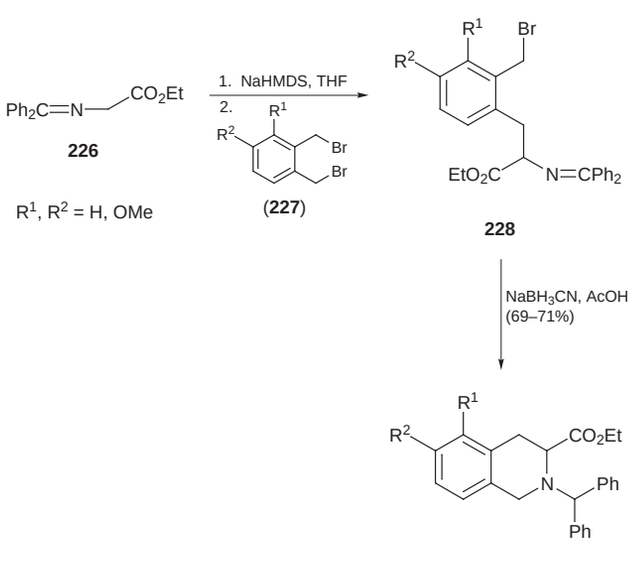
Scheme 79



224 **225**

R^1, R^2, R^3 = H, Me, OMe

Scheme 80



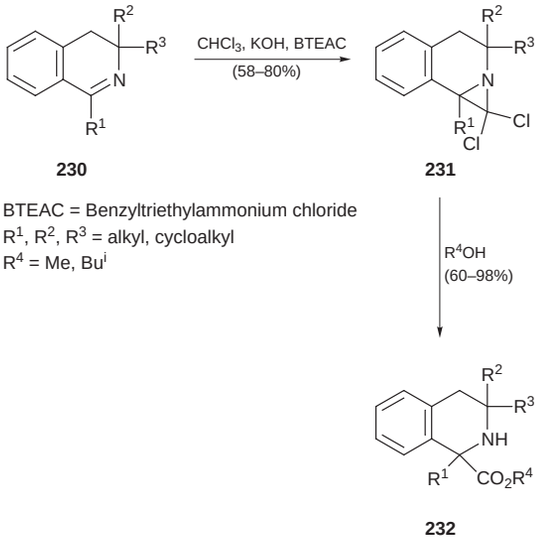
226 (**227**) **228** **229**

R^1, R^2 = H, OMe

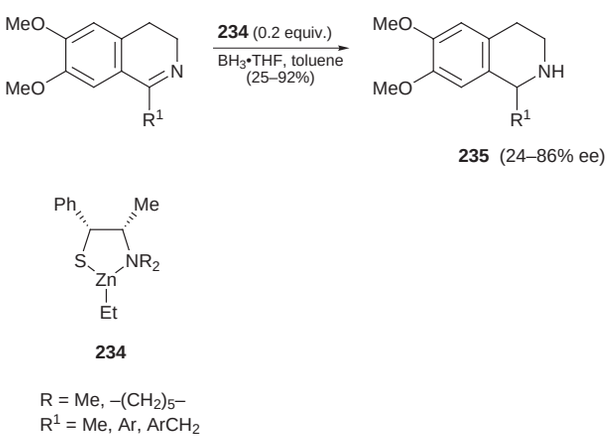
Scheme 81

with electron-donating groups on the aromatic ring giving access to tetrahydroisoquinolines normally difficult to make by other means. Where possible, a mixture of regioisomers was obtained.

1,2,3,4-Tetrahydroisoquinoline-1-carboxylate esters have been prepared from the corresponding 3,4-dihydroisoquinolines (**Scheme 82**).[109] Addition of dichlorocarbene to **230** under phase-transfer conditions produced aziridines **231** in 58–80% yield. Heating these in an alcoholic solvent formed the ring-opened ester **232** in excellent yield.



Scheme 82



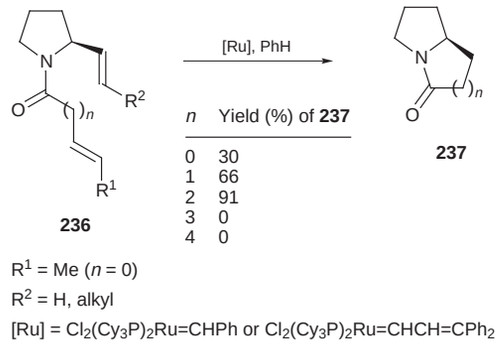
Scheme 83

A new catalyst for the catalytic, enantioselective reduction of 3,4-dihydroisoquinolines has been reported (**Scheme 83**).[110] The optimal conditions were found to involve treatment of **233** with thiazazincolidine **234** (20 mol%) with BH_3·THF in toluene at −5–0 °C. This gave respectable yields of a variety of optically enriched tetrahydroisoquinolines **235**.

9 Methods for the general synthesis of two or more ring sizes

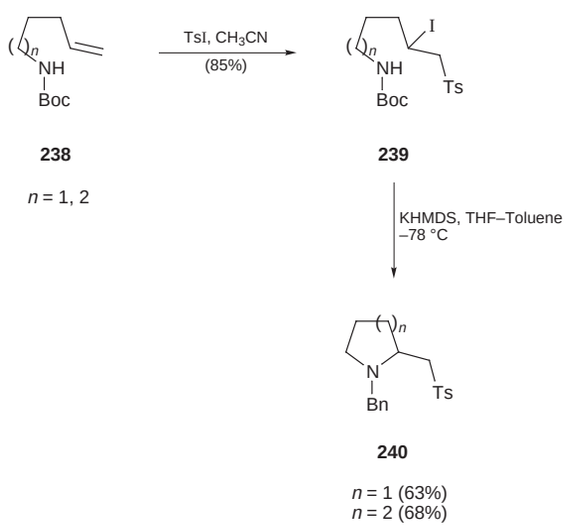
Meyers and Brengel have reviewed the use of chiral bicyclic lactams for the asymmetric synthesis of a number of heterocycles, including pyrrolidines, piperidines and tetrahydroisoquinolines.[111] Laschat has reviewed the use of pseudo-hetero-Diels–Alder and hetero-ene reactions in the synthesis of saturated nitrogen heterocycles,[112] and O'Hagan has reviewed the pyrrolidine, piperidine and azepine alkaloids.[113]

A number of reports detailing the application of RCM to a variety of sized nitrogen heterocycles have been published.[114–117] Treatment of a range of 2-alkenyl-*N*-acyl pyrrolidines **236** (**Scheme 84**) with Grubbs' ruthenium catalyst gave the corresponding bicycles **237** in variable yield.[114] Low yields were obtained for the formation of the five-membered ring (attributed to the reactivity of the product under the reaction conditions), while the six- and seven-membered rings formed more efficiently. Attempted formation of eight- and nine-membered rings was unsuccessful. Similar findings are reported by Rutjes and Schoemaker[115] and Piscopio *et al.*[116] and by Barrett *et al.* for the formation of bicyclic β-lactams.[117]



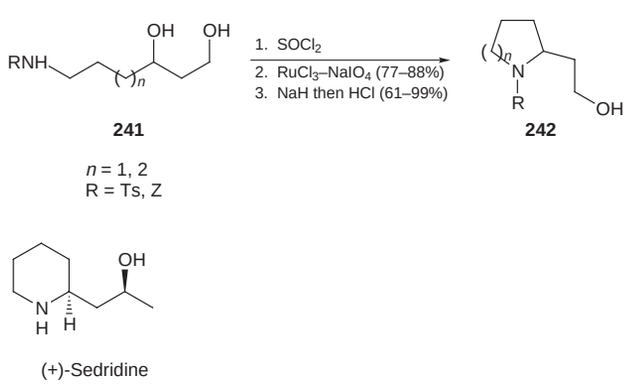
Scheme 84

The radical addition of tosyl iodide to ω-unsaturated amines (*e.g.* **238**) generates the corresponding β-iodosulfone **239** in excellent yield (**Scheme 85**).[118] Subsequent treatment with a base results in cyclization to the heterocycle **240** in acceptable yield. By protecting the nitrogen atom with an α-methylbenzyl group, the ring closure reaction became moderately diastereoselective.



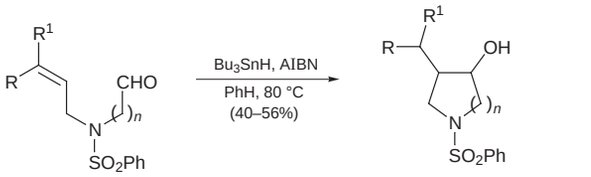
Scheme 85

Although 1,2-cyclic sulfates have been shown to be equivalent to epoxides in many instances, 1,3-cyclic sulfates have been rather less well investigated. However, Gallagher and coworkers have shown that the cyclic sulfates of amino diols such as **241** readily open intramolecularly to give 2-(2-hydroxyethyl)-pyrrolidines and -piperidines **242** but not -azetidines (**Scheme 86**).[119] This methodology was demonstrated by the synthesis of (+)-sedridine.



Scheme 86

The radical 5- or 6-*exo* cyclization of amino aldehydes by Bu_3SnH has been described.[120] Addition of **243** to Bu_3SnH generates the *O*-stannylketyl radical which then adds intramolecularly to the double bond to give after hydride capture and stannyl ether hydrolysis, piperidines or pyrrolidines **244** (**Scheme 87**) as an approximately equimolar mixture of diastereoisomers.

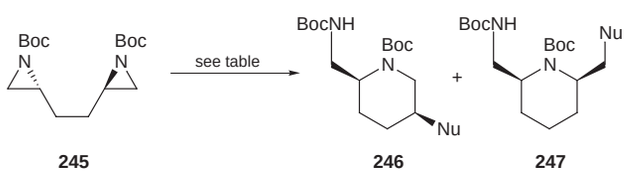


243 **244** dr = 1–1.6:1

R, R^1 = H, Me, Ph
n = 1, 2

Scheme 87

Duréault and co-workers have studied the ring-opening of the bis(aziridine) **245** (**Scheme 88**).[121] In acetic acid, **245** yields predominantly piperidine **246** *via* a presumed S_N1 pathway. A similar outcome is obtained if the reaction conditions utilize $Yb(OTf)_3$ and aqueous THF. However, in aprotic media, reaction of **245** with nucleophiles such as NaCN and PhSNa give predominantly the pyrrolidines **247**.

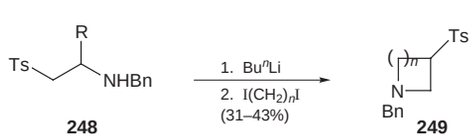


245 **246** **247**

Conditions	**246** (%)	**247** (%)
AcOH	70	15
H_2O–THF, $Yb(OTf)_3$	55	25
NaCN, DMF	0	65
NaSPh, DMF	0	32

Scheme 88

Treatment of β-aminoalkyl sulfone **248** with BuLi generates the α-lithiosulfone (**Scheme 89**).[122] Addition of a dielectrophile then generates a nitrogen heterocycle **249** in relatively good yield. Suitable dielectrophiles were shown to be 1,3- and 1,4-dihalides, α-bromoacetates and α-chloroketones.

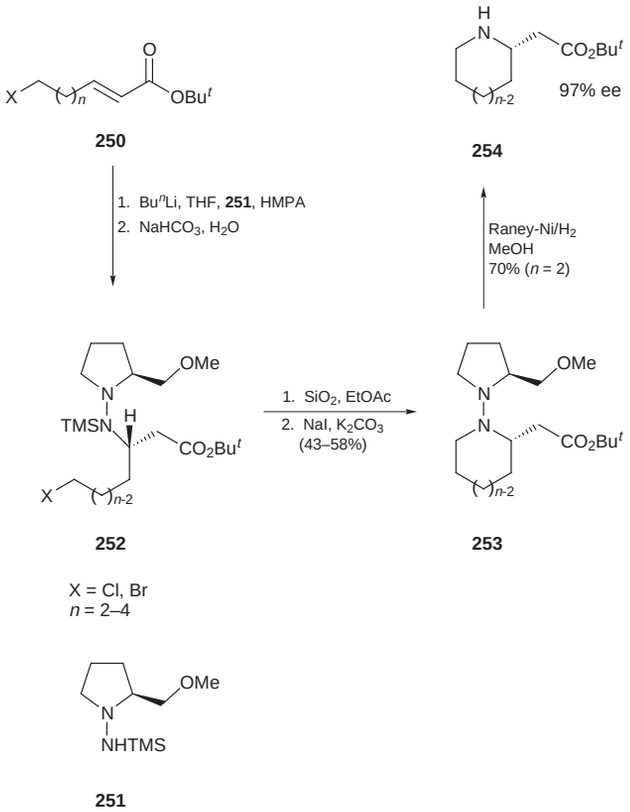


248 **249**

R = H, Ph
n = 3, 4

Scheme 89

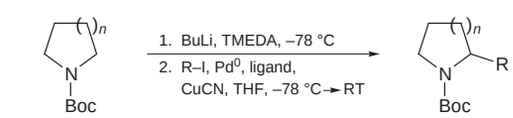
An efficient synthesis of heterocyclic β-amino acids from ω-halo-α,β-unsaturated esters has been reported (**Scheme 90**).[123] Treatment of the ester **250** with Enders' hydrazone **251** results in a highly diastereoselective conjugate addition reaction to give **252**. Desilylation, ring closure and cleavage of the chiral auxiliary (**252**→**254**) gives the five- to seven-membered β-amino esters in excellent overall yields.



250 **254** **252** **253** **251**

X = Cl, Br
n = 2–4

Scheme 90



R = aryl, heteroaryl, alkenyl, alkynyl
n = 1, 2
ligand = dppf, $AsPh_3$, $SbPh_3$, PPh_3

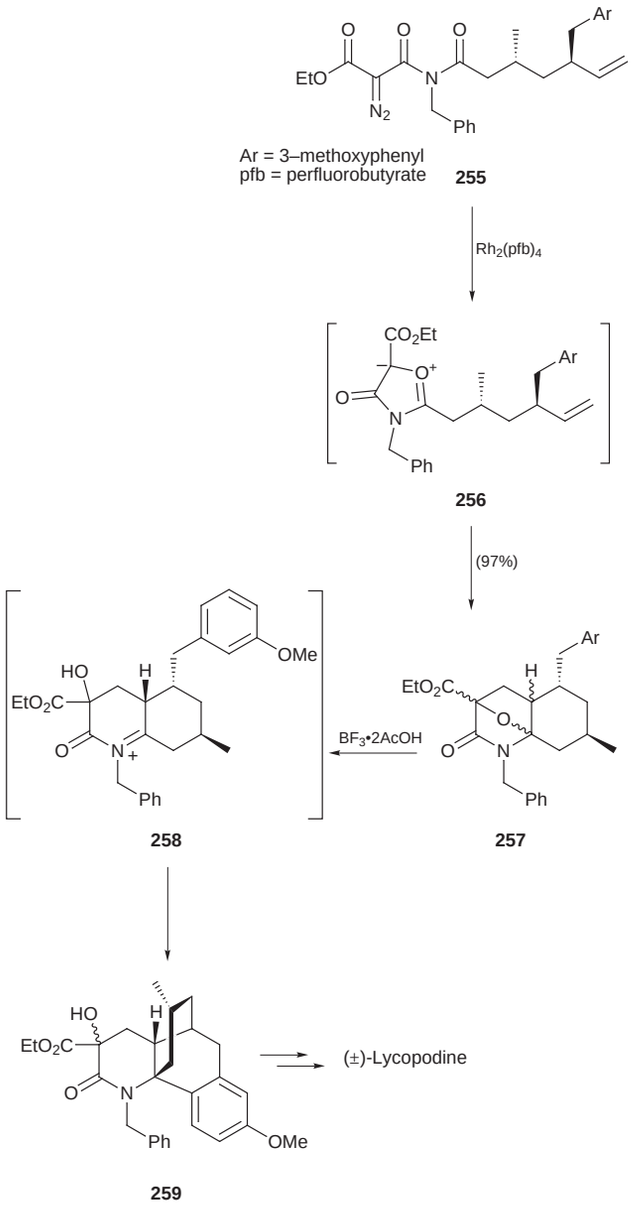
(10–79%)

Scheme 91

Functionalization of the 2-position of *N*-Boc-pyrrolidine and *N*-Boc-piperidine has been reported by Dieter and Li (**Scheme 91**).[124] Lithiation of the substrate under standard conditions, followed by the addition of an aryl (or vinyl or alkynyl) iodide, CuCN, palladium catalyst and a ligand [bis(diphenylphosphino)ferrocene, triphenylantimony or triphenylarsine] resulted in a quite efficient coupling reaction. The reaction only works with electron-rich aryl iodides, not electron-poor aryl iodides, and only in poor yield with alkenyl and alkynyl iodides.

10 Miscellaneous

Finally, we conclude with the remarkable formal total synthesis of (±)-lycopodine reported by Padwa and co-workers (**Scheme 92**).[125,126] Treatment of **255** with a catalytic amount of $Rh_2(pfb)_4$ results in carbenoid formation and concomitant reaction with the distal imide carbonyl group, generating isomünchnone **256**, which then undergoes an intramolecular 1,3-dipolar cycloaddition to give the oxabicyclic structure **257** as a 3:2 diastereomeric mixture in 97% yield. Treatment of this mixture with BF_3·2AcOH results in cleavage of the oxacycle, *N*-acyliminium ion formation and Pictet–Spengler-type cyclization (**258**→**259**) with the electron rich aromatic ring to give **259** as a 4:1 mixture of diastereoisomers in 71% yield. This was readily converted to an intermediate used in Stork's synthesis of lycopodine.



Scheme 92

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