Saturated nitrogen heterocycles

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Covering: 1998
Previous review: *J. Chem. Soc., Perkin Trans. 1*, 1998, 3493

1 Introduction

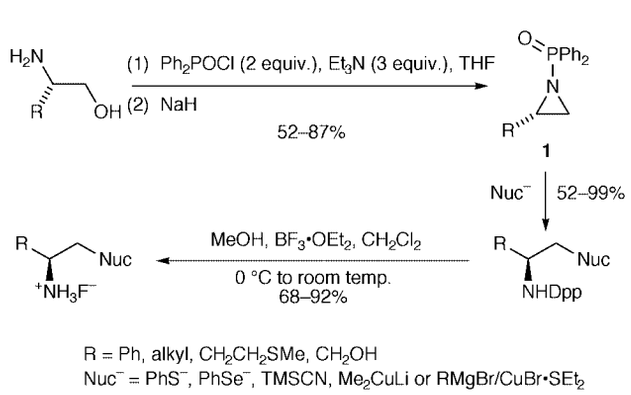
This review covers the literature relating to saturated nitrogen heterocycles published in 1998. The classification of the chemistry described is similar to that described in the previous survey in *J. Chem. Soc., Perkin Trans. 1*.[1]

2 Three-membered rings

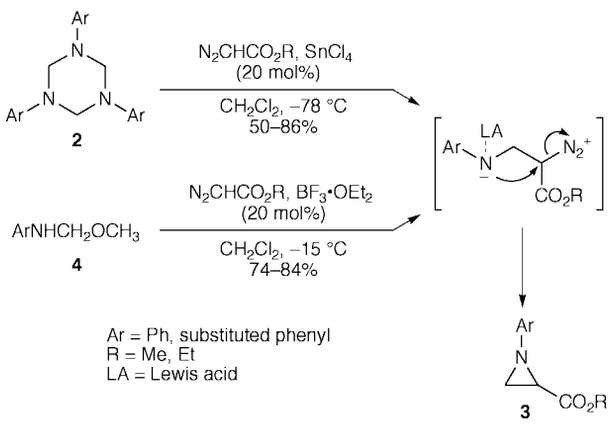
Aggarwal has recently written an account of his development of catalytic asymmetric epoxidations and aziridinations using sulfur ylides.[2]

Sweeney and co-workers have described a one-pot procedure for the preparation of *N*-diphenylphosphinyl (Dpp) aziridines **1** from amino alcohols.[3] These compounds were ring-opened by the attack of various nucleophiles, and the Dpp group was then removed by treatment with excess boron trifluoride–diethyl ether and methanol at room temperature (Scheme 1). Interestingly, the copper(I)-mediated reaction of *N*-Dpp aziridines with Grignard reagents only occurred at temperatures greater than 40 °C; many organocopper species are reported to decompose at this temperature. As the conditions for dephosphinylation are mild, Dpp-activation of aziridines may offer a practical alternative to the more traditional sulfonamides.

Ha and co-workers have described the use of hexahydro-1,3,5-triazines **2**, in the presence of catalytic tin(IV) chloride, as *N*-methyleneamine equivalents for the synthesis of aziridine-2-carboxylates **3** (Scheme 2).[4] The use of other Lewis acids led to substantial ring opening of the desired products. An alternative procedure employing anilines **4** was also reported; these reactions were best performed using boron trifluoride–diethyl ether as the Lewis acid at a higher temperature, and gave comparable yields. Both reactions presumably go through the same intermediate.



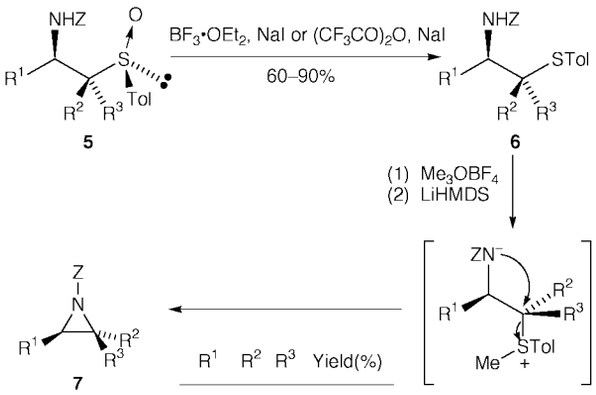
Scheme 1



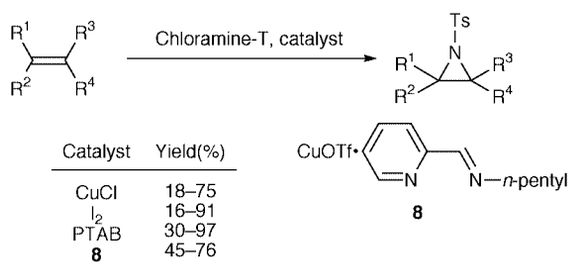
Scheme 2

The first report of 2-sulfinyl amines as precursors to optically pure aziridines was published by Ruano.[5] The sulfinyl amines **5**, which were prepared in high enantiomeric purity from 2-sulfinylketimines, were reduced to their analogous sulfides **6** with boron trifluoride–diethyl ether and sodium iodide, or with trifluoroacetic anhydride and sodium iodide, in high yield. Cyclization was effected in one pot by methylation of the sulfur and treatment with base. Enantiomerically pure products **7** were obtained from an internal S_N2 process in moderate to good yields (Scheme 3).

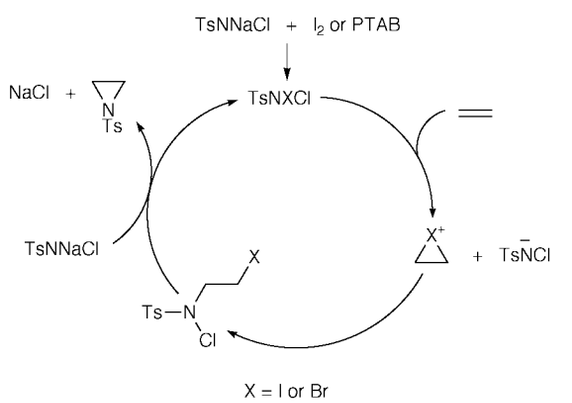
A number of papers have been published concerning the use of commercially available Chloramine-T (TsNClNa) for the aziridination of alkenes (Scheme 4). Komatsu and co-workers disclosed that anhydrous Chloramine-T would transfer nitrogen to a variety of alkenes in the presence of catalytic copper(I) chloride.[6] The same group also reported an iodine-catalyzed version of the reaction, using Chloramine-T trihydrate, which generally gave improved yields.[7] Sharpless entered the field, with arguably the widest range of examples, by describing how phenyltrimethylammonium tribromide ($PhNMe_3^+Br_3^-$, PTAB) could catalyze this nitrogen transfer.[8] The best results were obtained with anhydrous Chloramine-T, but the trihydrate could be successfully used with only a small decrease in yield, for some alkenes. Komatsu and Sharpless suggested essentially the same catalytic cycle for their halogen-promoted reactions (Scheme 5). Finally, Taylor showed that the copper catalyst **8** could be used for the aziridination of aryl alkenes with Chloramine-T trihydrate, giving moderate yields, although the demonstrated scope of this reaction was much smaller than that described in the other papers.[9]



Scheme 3



Scheme 4



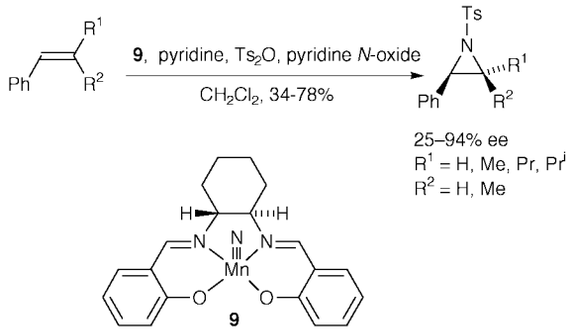
Scheme 5

Komatsu has also reported the use of the chiral nitridomanganese complex **9** for the asymmetric aziridination of styrene derivatives (Scheme 6).[10] Toluene-*p*-sulfonic anhydride was used to activate the complex, and pyridine *N*-oxide was required to obtain the best enantiomeric excesses.

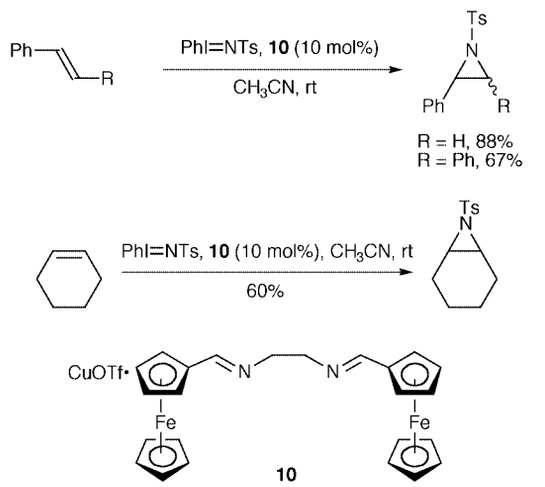
Kim and co-workers described a new catalyst for the aziridination of alkenes with [(4-tosylsulfonyl)imino]phenyliodinane (PhI=NTs).[11] The copper(I) complex **10**, whilst originally intended for cyclopropanations, was also found to produce high yields in aziridinations (Scheme 7).

The aziridination of α,β-unsaturated ketones **11** has been described, using ethyl *N*-(4-tolylsulfonyloxy)carbamate ($TsONHCO_2Et$) and caesium carbonate (Scheme 8).[12] In the reaction with (*R*)-dihydrocarvone, the desired α,β-aziridino ketone **12** was produced in 51% diastereomeric excess.

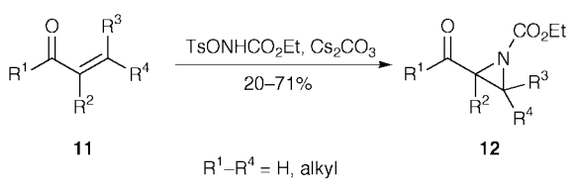
Kobayashi has found that catalytic ytterbium triflate will activate imines to aziridination with ethyl diazo esters.[13] The diazo compounds were reacted with alkyl and aryl imines, prepared *in situ* from the corresponding aldehydes and amines, including examples of unstable imines containing α-hydrogen



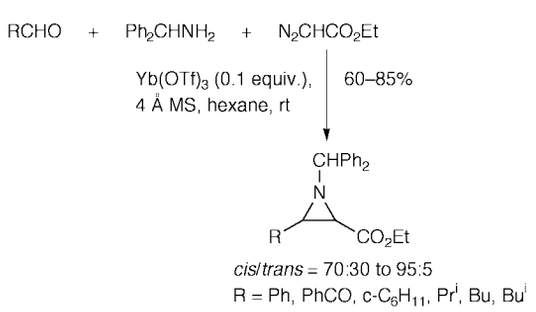
Scheme 6



Scheme 7



Scheme 8

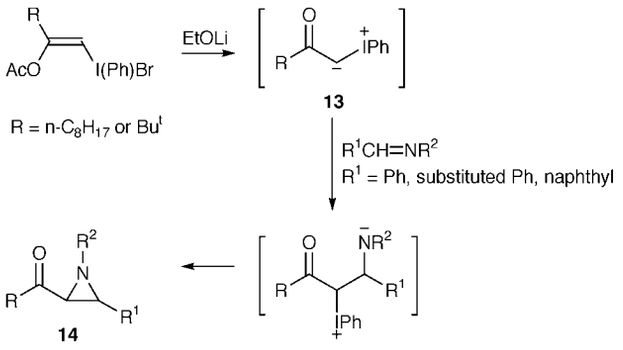


Scheme 9

atoms (Scheme 9). The yields and diastereoselectivities of these reactions were good to excellent.

α,β-Aziridino ketones **14** have been prepared by the reaction of monocarbonyl iodonium ylides **13** with activated imines (Scheme 10).[14] The use of *N*-sulfonyl aldimines generated predominantly *cis*-aziridines, with the best *cis*:*trans* ratios being observed for *N*-(2,4,6-trimethylphenylsulfonyl)imines. Conversely, *N*-benzoylimines yielded predominantly *trans*-α,β-aziridino ketones, with some 2-oxazoline side-product formation also being observed. The ylide did not react with unactivated imines.

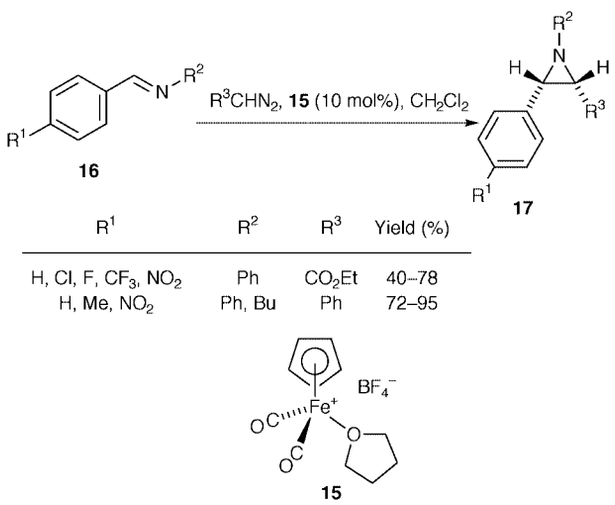
The iron Lewis acid **15** has been reported as an effective catalyst for the aziridination of substituted aryl imines **16** with



R^2	Yield (%)	*cis*:*trans*
$SO_2(2,4,6\text{-}Me_3)C_6H_2$	73–89	82:18 to 95:5
COPh	66–72	8:92 to 2:98

Scheme 10

diazo compounds (Scheme 11).[15] The products **17** were generally *cis*-isomers. In reactions with ethyl diazoacetate, electron-donating groups at the 4-position on the benzylidene part of the imine completely prevented aziridine formation, whilst electron-withdrawing groups improved the reaction yields. However, the reactions of phenyldiazomethane tolerated both kinds of substituents. Evidence was presented for the mechanism shown in Scheme 12, proceeding through an electrophilic iminium ion, rather than by the reaction of an iron carbene with an imine.

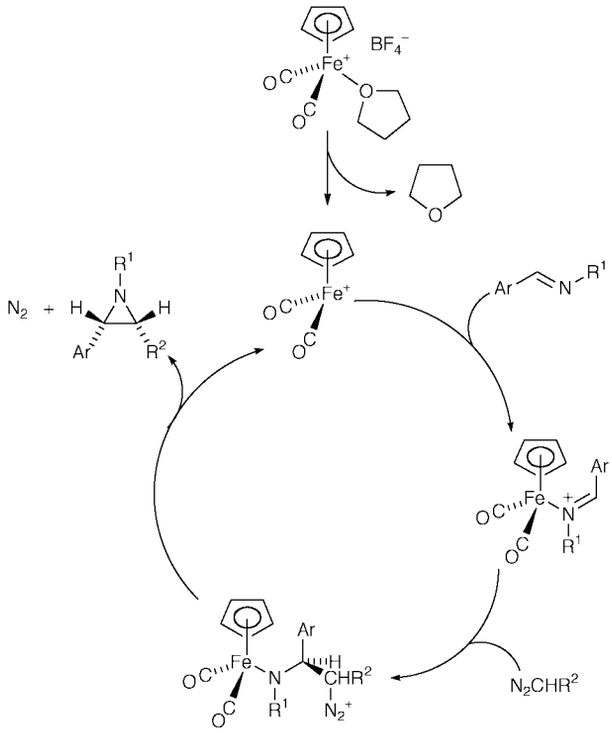


R^1	R^2	R^3	Yield (%)
H, Cl, F, CF_3, NO_2	Ph	CO_2Et	40–78
H, Me, NO_2	Ph, Bu	Ph	72–95

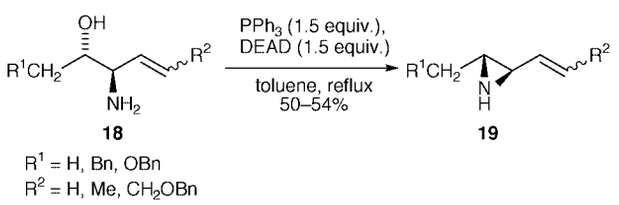
Scheme 11

A number of papers were published concerning the synthesis of aziridines substituted with vinyl or ethynyl groups. The enantioselective synthesis of *N*-unsubstituted vinyl aziridines **19** from vicinal amino alcohols **18** has been reported (Scheme 13).[16] The amino alcohols were prepared from epoxy alcohols using conventional methods, and dehydration to yield aziridines was achieved under Mitsunobu conditions. Ring-closure failed to occur if the alcohol was sterically hindered.

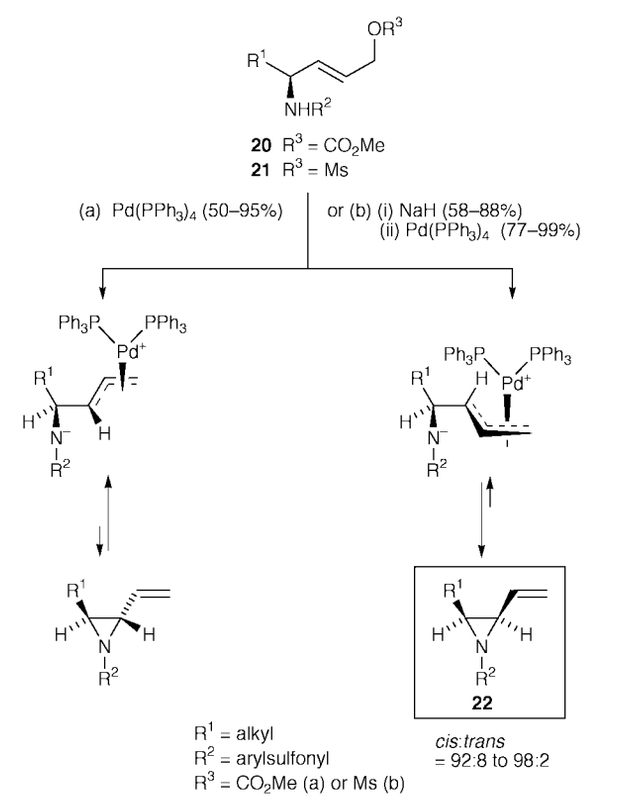
A palladium(0)-catalyzed reaction of methyl allylic carbonates **20** has been described for the synthesis of *cis*-vinylaziridines **22** (Scheme 14).[17] The heterocycles were prepared in good to excellent yields *via* a decarboxylative ring-closure; the small amount of *trans*-isomer produced could be recycled for palladium(0)-catalyzed isomerization to the *cis*-isomer. In cases where the carbonates failed to react, the analogous mesylates **21** were prepared, treated with base to yield a mixture of *cis*- and *trans*-aziridines, and then isomerized to the *cis*-isomer **22** as before.



Scheme 12



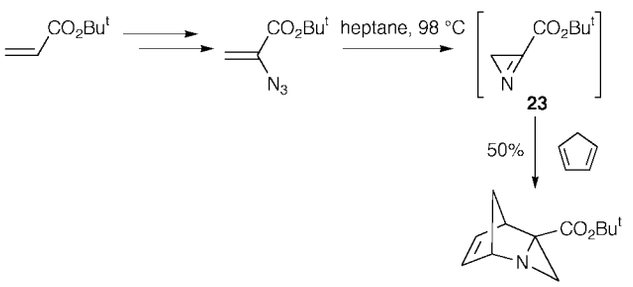
Scheme 13



Scheme 14

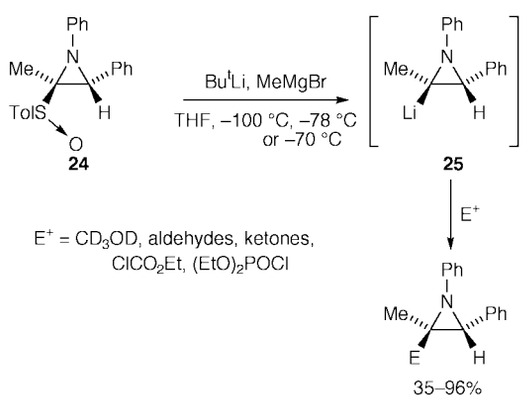
Ibuka's group have published the synthesis of activated chiral ethynylaziridines starting from commercially available (*S*)-amino acids.[18] 3-Alkyl-2-(1-bromovinyl)aziridines were prepared from the corresponding allylic mesylates, and subsequent base-induced dehydrobromination yielded a mixture of *cis*- and *trans*- ethynylaziridines, which could then be separated.

The first preparation of an azirine unsubstituted at C-2 with an activating group at C-3 (**23**) has been reported.[19] *tert*-Butyl 2-azidoacrylate was prepared from *tert*-butyl acrylate by standard methods, and decomposed upon heating in heptane to yield the desired azirine (Scheme 15). The product was very unstable, but could be trapped with a variety of conjugated dienes, such as cyclopentadiene. A high degree of *endo*-selectivity was observed in all the cycloadditions.



Scheme 15

Aziridinyllithiums **25** have been generated by the ligand exchange reaction of sulfoxides **24** with *tert*-butyllithium, and were then reacted with a range of electrophiles.[20] The best results were obtained when a Grignard reagent was used to scavenge any adventitious moisture in the solvent (Scheme 16).

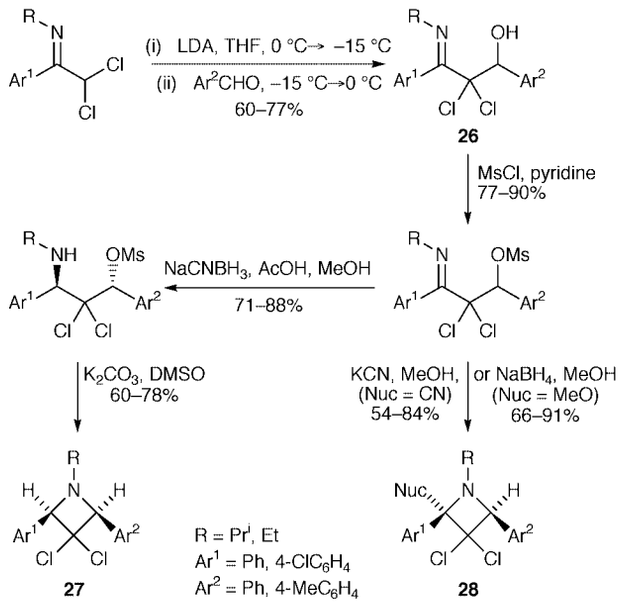


Scheme 16

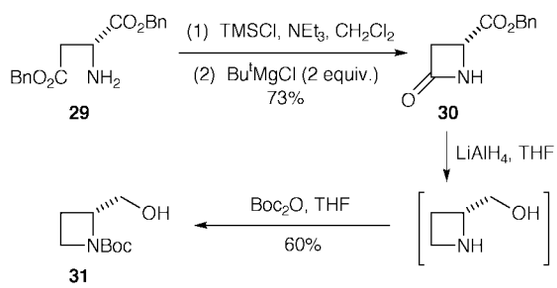
3 Four-membered rings

De Kimpe has described a synthesis of 3,3-dichloroazetidines **27** and **28**, which are poorly represented in the literature.[21] His approach was based on a new directed aldol condensation of 3,3-dichloro-1-azaallylic anions with aryl aldehydes, yielding α,α-dichloro-β-hydroxyketimines **26** (Scheme 17). Mesylation of these products was followed by ring closure to form azetidines, either by reduction of the imine and treatment with base, or through reaction with a nucleophile. The latter approach allowed the synthesis of 2-cyano- or 2-alkoxyazetidines **28**, which are also scarcely reported in the literature. De Kimpe also reported very similar methodology as a route to 3,3-dimethylazetidine-2-carboxylic acid derivatives.[22]

A concise and practical synthesis of (2*R*)-*N*-*tert*-butoxycarbonylhydroxymethylazetidine **31** has been reported,[23] proceeding in just three steps and 44% overall yield, and thus considerably improving upon previously reported routes (Scheme 18). The commercially available dibenzyl ester of D-aspartic acid **29** was converted to a β-lactam **30** by reaction



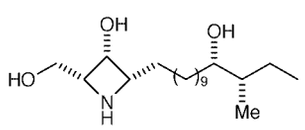
Scheme 17



Scheme 18

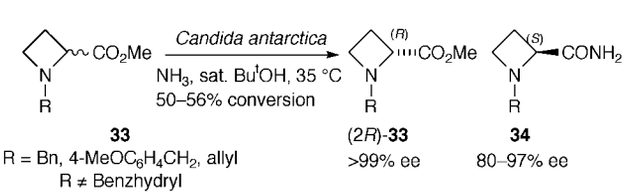
with trimethylsilyl chloride and subsequent addition of *tert*-butylmagnesium chloride in one pot. Lithium aluminium hydride reduction and protection of the resultant amine furnished the desired product **31** in >99% enantiomeric excess.

Lin and Liu have synthesized the natural product 2-*epi*-penaresidin A (**32**),[24] isolated from Okinawan marine sponges, in which the azetidine ring was constructed by an intramolecular Mitsunobu reaction. Perhaps surprisingly, such an approach is rarely reported in the literature.



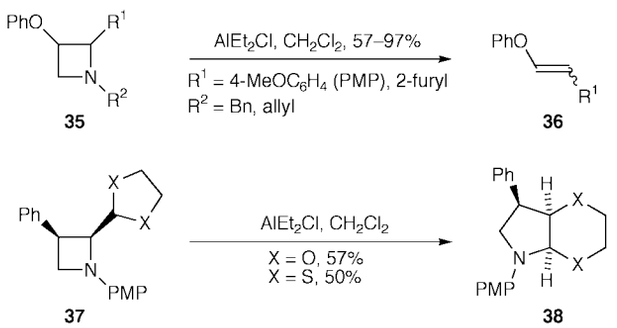
32

Enzymatic resolution of methyl *N*-alkylazetidine-2-carboxylates **33** has been achieved in ammonolysis reactions using the lipase of *Candida antarctica* (Scheme 19).[25] In *tert*-butyl alcohol saturated with ammonia, the (2*S*)-esters were converted to their primary amides **34** with good to excellent enantiomeric excesses, leaving the (2*R*)-esters [(2*R*)-**33**] intact. The *N*-benzhydrylazetidine was not accepted by the lipase, probably for steric reasons.



Scheme 19

Alcaide has described new fragmentations and rearrangements of azetidines **35**, promoted by diethylaluminium chloride.[26] In most cases, alkenes **36** were produced in a reaction analogous to the thermal fragmentation of azetidines, but occurring at room temperature (Scheme 20). However, when the 2-position was substituted with an acetal or thioacetal (**37**), bicyclic fused pyrrolidines **38** were formed instead. A mechanism was postulated involving a zwitterionic intermediate (Scheme 21), although this fails to explain the high stereoselectivity often observed in these reactions.



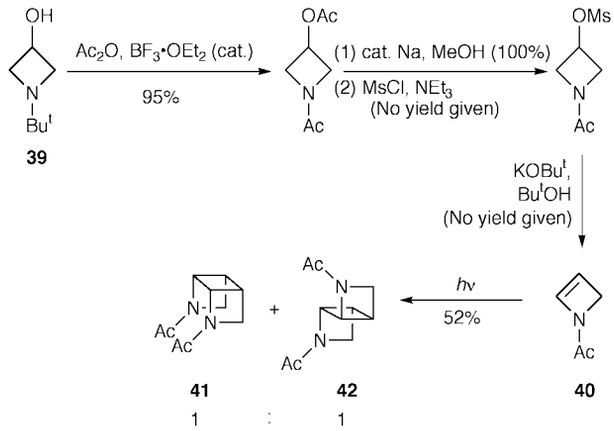
Scheme 20

A simple preparation of *N*-acetyl-2-azetine **40** *via* acylative dealkylation of *N*-*tert*-butyl-3-hydroxyazetidine **39** has been described.[27] The product was studied in its [2 + 2] photodimerization, in which only "head-to-head" dimers **41** and **42** were formed (Scheme 22).

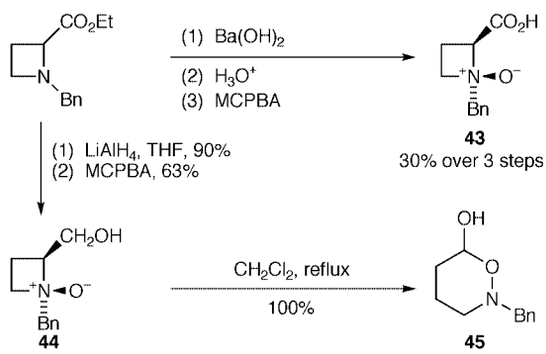
The first simple azetidine *N*-oxides have been prepared as reported by O'Neil and Potter (Scheme 23).[28] Usually azetidine *N*-oxides are unstable at room temperature, but these compounds were stabilized by intramolecular hydrogen-bonding to either an adjacent carboxylic acid (**43**) or alcohol (**44**). The alcohol was found to rearrange to a tetrahydro-1,2-oxazine **45** upon refluxing in dichloromethane.

4 Five-membered rings

Katritzky and co-workers have reported a practical short synthesis of 2,5-disubstituted pyrrolidines starting from **46**, which is easily prepared from benzotriazole, (*S*)-phenylglycinol and succinaldehyde (Scheme 24).[29] Treatment of **46** with Grignard reagents yielded diastereomeric pairs of pyrrolidines **47** and **48**, which were easily separated by flash chromatography. Hydrogenation of the products gave enantiomerically pure *trans*- or *cis*-2,5-disubstituted pyrrolidines (**49** and **50** respectively) in good yields.



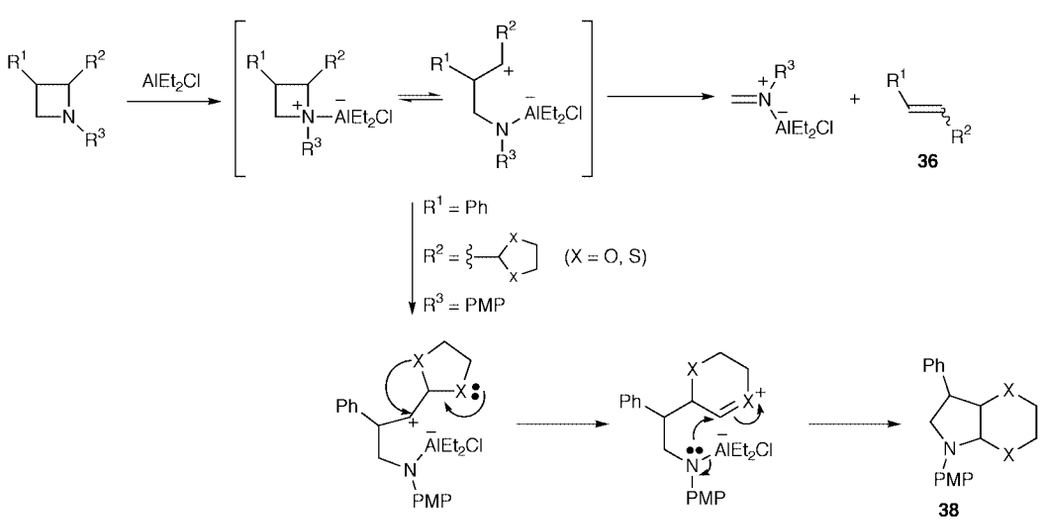
Scheme 22



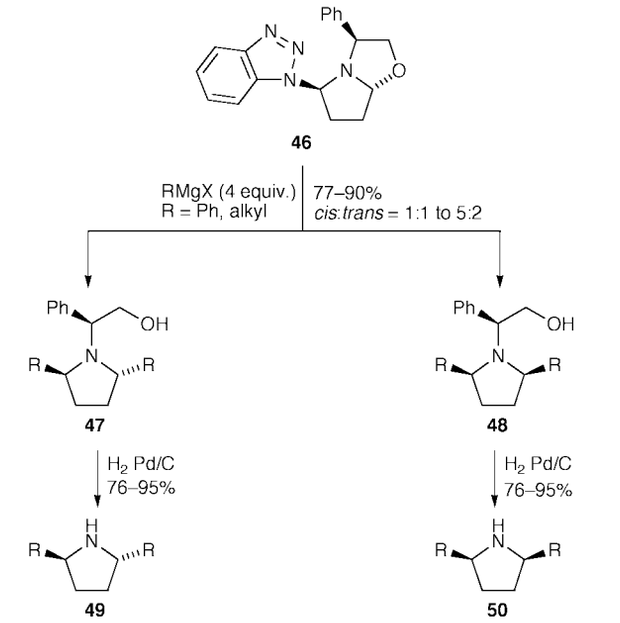
Scheme 23

A diastereoselective mercury(II)-promoted cyclization was used as the key step in a new synthesis of (+)-pseudohygroline (Scheme 25).[30] Treatment of the aminoalkene **51** with mercury(II) acetate yielded the desired pyrrolidine **52** as a single diastereomer after recrystallization. Demercuration proceeded in high yield, and the product **53** was then converted by standard techniques to the target compound. By analogy with previous work on ring closures of oxygen heterocycles, the use of a (*Z*)-alkene and a bulky silyloxy group at the remote allylic carbon was thought to be critical for the observed diastereoselectivity.

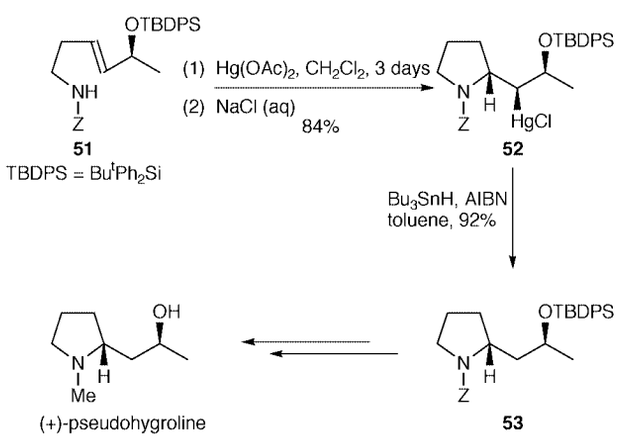
Wang has used the Wolff rearrangement of diazo ketones **54** derived from *N*-tosylated β-amino acids to prepare 5-substituted pyrrolidinones **55** in good yields (Scheme 26).[31] It was necessary to use a non-nucleophilic solvent, such as THF, to



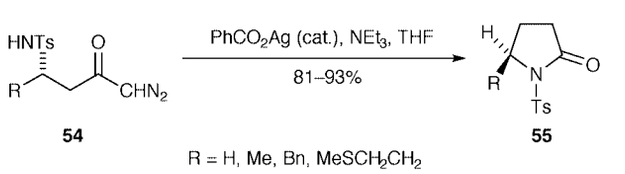
Scheme 21



Scheme 24



Scheme 25



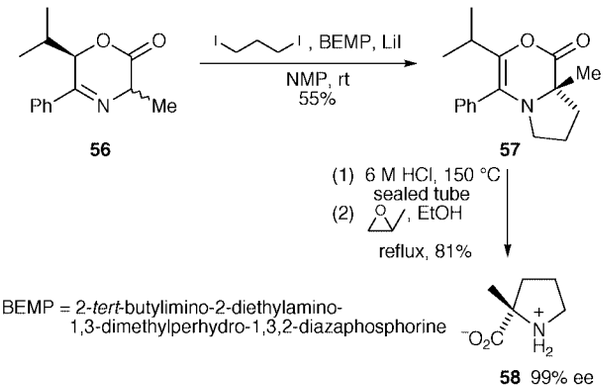
Scheme 26

prevent the formation of unwanted side-products from the ketene intermediate.

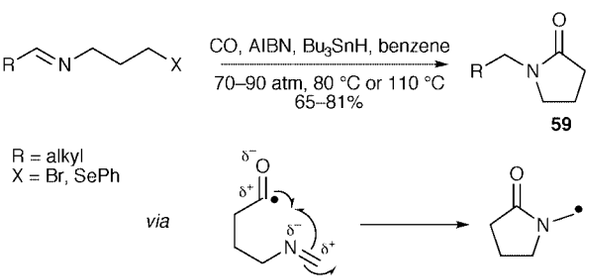
Nájera and co-workers have extended their work with chiral oxazinones **56**, describing asymmetric alkylations with unactivated alkyl halides (Scheme 27).[32] When diiodopropane was used, a bicyclic oxazinone **57** was produced, which could be hydrolyzed and treated with propylene oxide to yield (*S*)-α-methylproline **58** in 99% enantiomeric excess.

The first intramolecular addition of acyl radicals onto N–C double bonds with complete selectivity for *N*-philic cyclization has been described (Scheme 28).[33] A variety of 2-pyrrolidones **59** were prepared from a [4 + 1] type carbonylation–annulation reaction, in good to high yields. The *N*-philic selectivity was thought to arise from the polar components of the intermediate radical, matching the $\delta+/\delta-$ acyl radical with the $\delta-/\delta+$ character of the N–C acceptor double bond.

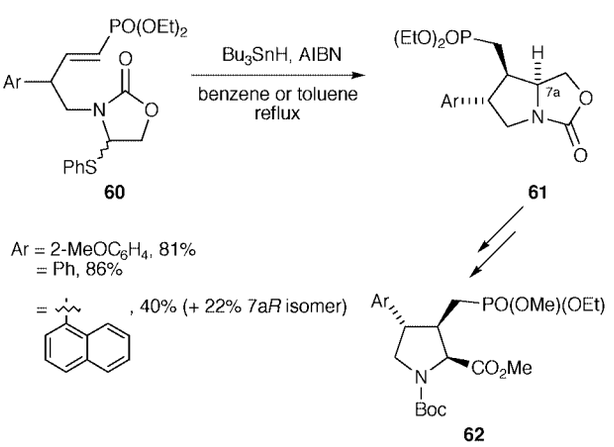
A diastereoselective synthesis of ω-phosphinic acid analogs of 4-arylkainoids **62** has been reported (Scheme 29).[34]



Scheme 27



Scheme 28

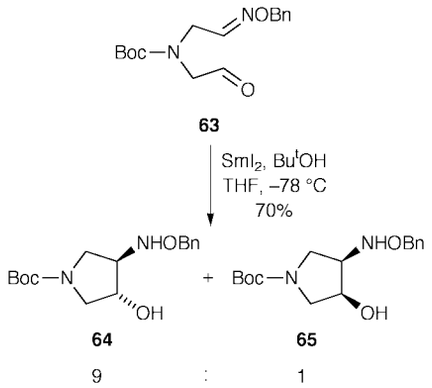


Scheme 29

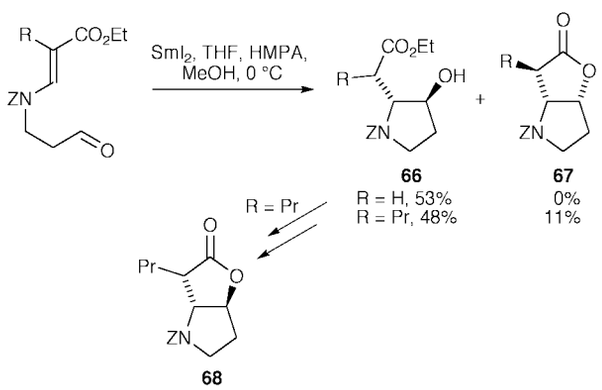
Unsaturated phosphonates attached to oxazolidinones (**60**) were used as radical acceptors for the key cyclization step, which gave a single diastereomer **61** as the product, except when the substituent β to the nitrogen was a naphthyl group. In the latter case, hindered rotation due to the steric bulk of the naphthyl group allowed some cyclization *via* a less preferred transition state. The cyclization products could then be converted to 4-arylkainoids **62** using standard methodology.

Naito has described an extension of his work on the intramolecular radical cyclization of oxime ethers with aldehydes or ketones. To improve stereoselectivity, samarium iodide was used to induce the ring-closure (Scheme 30; *cf.* Scheme 109).[35] Thus for the oxime ether connected to a formyl group (**63**), an optimal ratio of 9 : 1 *trans* (**64**) to *cis* (**65**) products was observed in the cyclization at −78 °C, with *tert*-butyl alcohol added as a proton source.

The first examples of reductive cyclization of aldehydes onto urethane acrylates were described by Macdonald and co-workers (Scheme 31).[36] The ring closure only occurred when mediated by samarium iodide, and yielded racemic *trans*-hydroxy ester **66** exclusively for the unsubstituted acrylate. For the propyl-substituted acrylate, some *cis*-lactone **67** was also



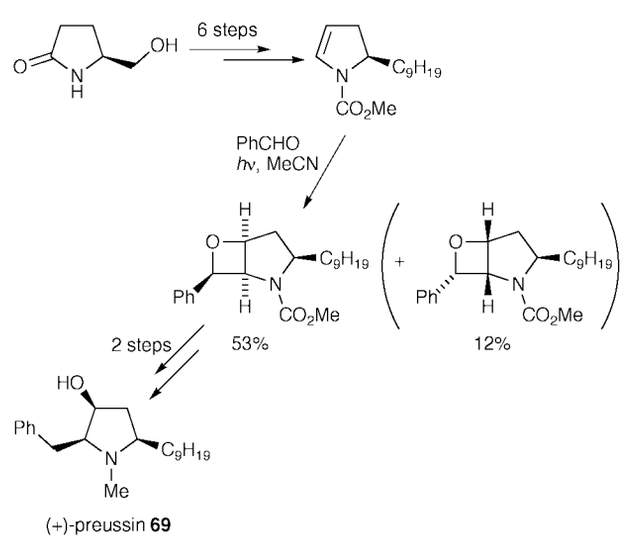
Scheme 30



Scheme 31

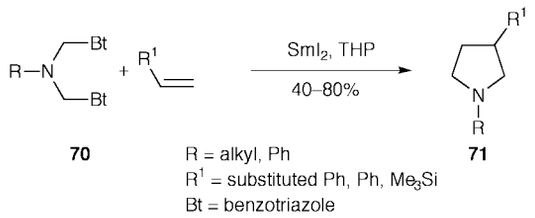
produced. The propyl-substituted *trans*-hydroxy ester was converted into a *trans*-2-oxohexahydro-2*H*-furo[3,2-*b*]pyrrole **68**, a previously unknown class of compounds.

A new synthesis of (+)-preussin **69** has been reported, in which a Paternò–Büchi reaction was used as the key step (Scheme 32).[37] The facial diastereoselectivity was remarkable, in that the attack of benzaldehyde occurred predominantly *syn* to the bulky substituent on the dihydropyrrole ring, whereas all previously reported examples proceed by *anti* attack.



Scheme 32

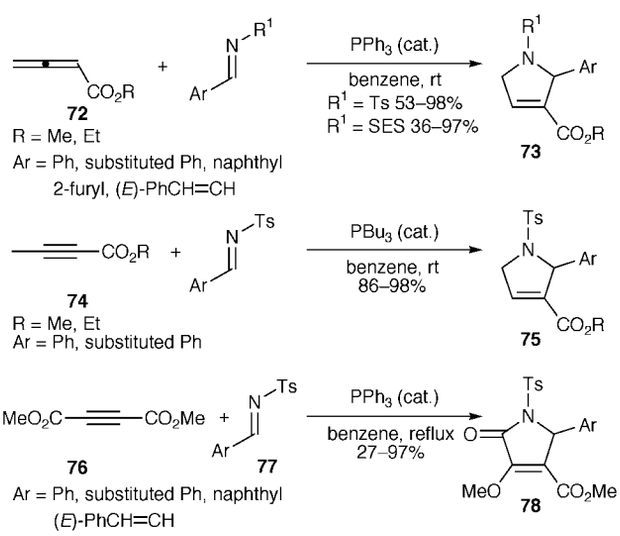
A one-pot procedure for the synthesis of 1-substituted-3-arylpyrrolidines **71** has been reported, employing the cycloaddition of *N*,*N*-bis(benzotriazolylmethyl)amines **70** with styrenes (Scheme 33).[38] The ring closure was again mediated by samarium iodide, affording the products in moderate to good



Scheme 33

isolated yields. Vinyltrimethylsilane could also be used as the anionophile, but not unactivated alkenes.

Xu and Lu have published the first full paper on the [3 + 2] cycloaddition of buta-2,3-dienoates **72** or but-2-ynoates **74** with aryl imines.[39] Of the imine-activating groups tested, tosyl and β-trimethylsilylethylsulfonyl (SES) were found to be the most effective, giving the cycloaddition products **73** and **75** in good to excellent yields (Scheme 34). The reaction of but-2-ynoates also proceeded with alkyl imines, albeit in low to moderate yields (14–57%). The reaction of tosylated imines **77** with dimethyl acetylenedicarboxylate **76** was found to yield pyrrolin-2-ones **78**.

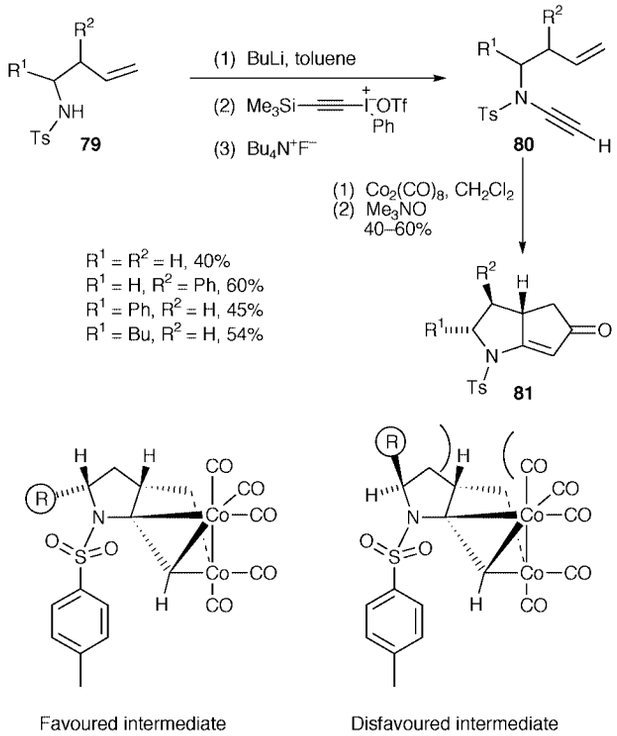


Scheme 34

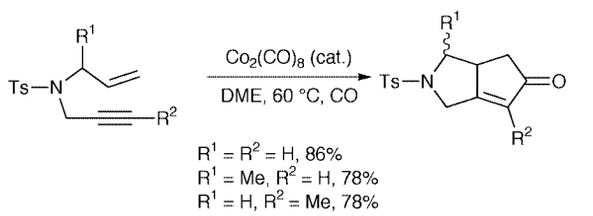
Witulski and Stengel have reported a new synthesis of 1-alkynylamides **80** and their use in [2 + 2 + 1] cycloadditions to produce α,β-unsaturated α-amidocyclopentenones **81**.[40] Ethynylation of sulfonamides **79** with trimethylsilylethynyliodonium triflate (28–89% yields) followed by desilylation with tetrabutylammonium fluoride (78–93% yields) afforded suitable precursors **80** for the intramolecular Pauson–Khand reaction. The stereoselectivity in these cyclizations was remarkable—in all cases only one diastereomer was seen (Scheme 35). This was attributed to minimization of the pseudo-axial interactions between the α-substituent and the cobalt carbonyl fragment in the reaction intermediate.

A thermally promoted version of the Pauson–Khand reaction was the subject of a paper by Livinghouse and coworkers.[41] A very narrow thermal window was observed for efficient cobalt-catalyzed enyne cyclization, with 60 °C being the optimal temperature. High purity $Co_2(CO)_8$ was also found to be necessary (Scheme 36).

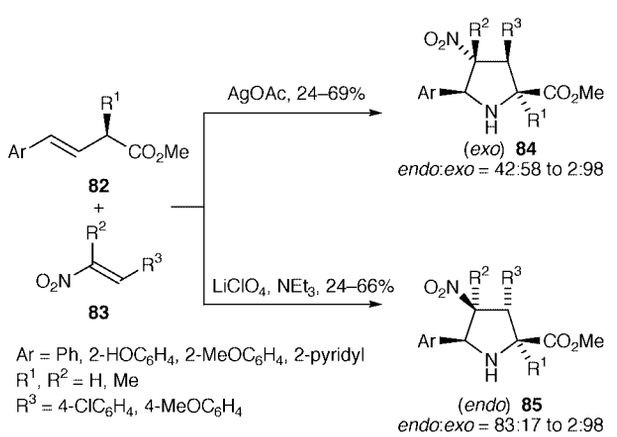
Cossío has discussed the effect of the metal counterion of azomethine ylides upon the diastereoselectivity of their [3 + 2] cycloaddition reactions with nitroalkenes **83**.[42] In general, silver azomethine ylides led to preferential formation of the *exo*-cycloadduct **84**, whereas lithium azomethine ylides yielded the *endo*-stereoisomer **85** (see Scheme 37). However, if a Lewis acid base center was present at the 2-position of the aromatic group



Scheme 35



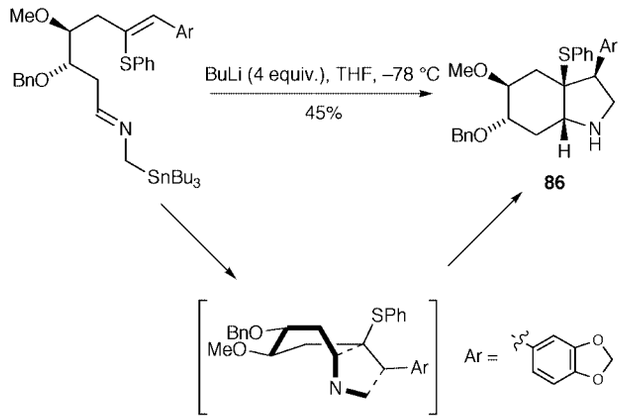
Scheme 36



Scheme 37

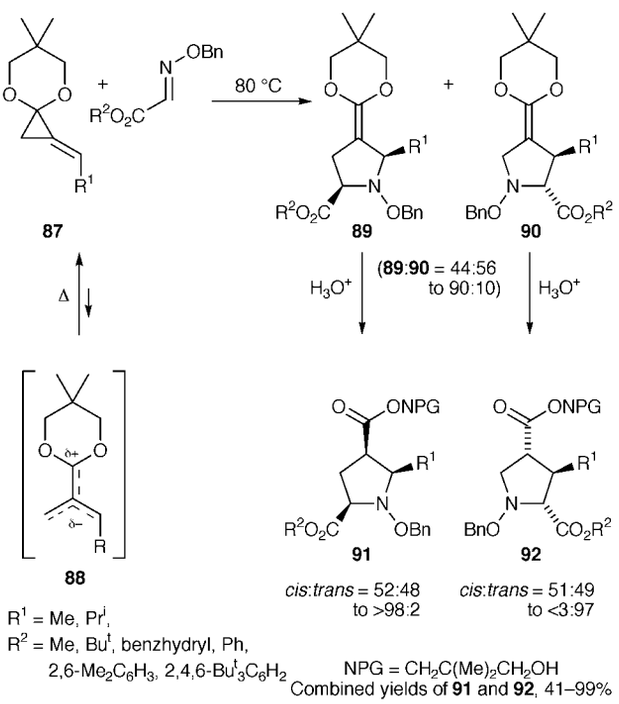
in the imine (**82**), *exo*-formation could still predominate with lithium ylides, as a result of intramolecular coordination to the metallic center. The addition of compounds with highly coordinating groups, such as nitro or phenoxy, could also reverse the stereochemical outcome of lithium ylide reactions. Diastereoselectivity was still observed when a chiral nitroalkene was used.

Pearson and Lian have used a 2-azaallyl anion cycloaddition in their construction of (+)-coccinine (Scheme 38).[43] The diastereomer produced (**86**) was unexpected, and arose from a twist-boat conformation in the transition state, rather than from a more conventional chair-like conformation.



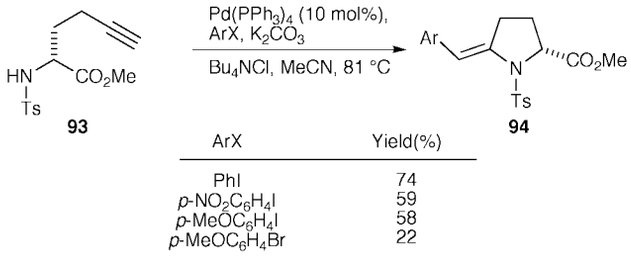
Scheme 38

A thermal [3 + 2] cycloaddition of dipolar trimethylenemethanes **88** to *O*-alkyloximes has been discovered (Scheme 39).[44] Thus, readily available alkylidenecyclopropanone acetals **87** yielded dipolar species upon heating, which then took part in an apparently concerted cycloaddition with a range of *O*-alkyloximes. No solvent was required, although aprotic solvents were tolerated. Slow reactions were forced to proceed under high pressure, and cycloadditions with *anti*-*O*-alkyloximes were found to be much faster than with their *syn*-counterparts. Alkylidenecyclopropane acetals substituted on the double bond with methyl or isopropyl would only react with *O*-alkyloximes derived from glyoxalic esters. The best regioselectivity and *cis*/*trans* selectivity was observed in reactions of isopropyl alkylidenes with *O*-alkyloximes containing bulky esters.



Scheme 39

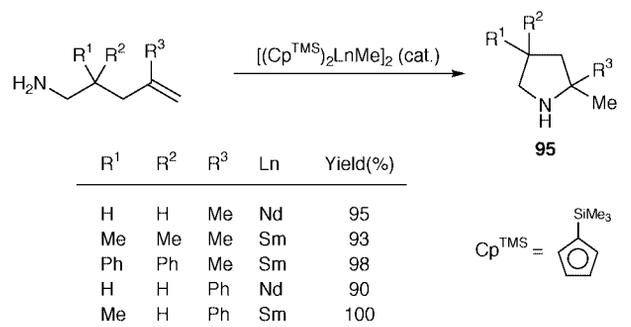
Palladium-catalyzed ring closures of ethynyl-containing amino acids have been used to form enantiomerically pure pyrrolidines.[45] Enantiopure amino acid was obtained from *Pseudomonas putida*-mediated hydrolysis of the corresponding racemic amide. Ring closure with palladium(0) catalyst of the *N*-tosyl amide **93** in the presence of aryl halides led to enantiopure products **94**, with the aryl substituent incorporated (*E*) to the heteroatom on the resultant double bond (Scheme 40). An enol triflate was also successfully used in place of an aryl halide.



ArX	Yield(%)
PhI	74
p-$NO_2C_6H_4I$	59
p-$MeOC_6H_4I$	58
p-$MeOC_6H_4Br$	22

Scheme 40

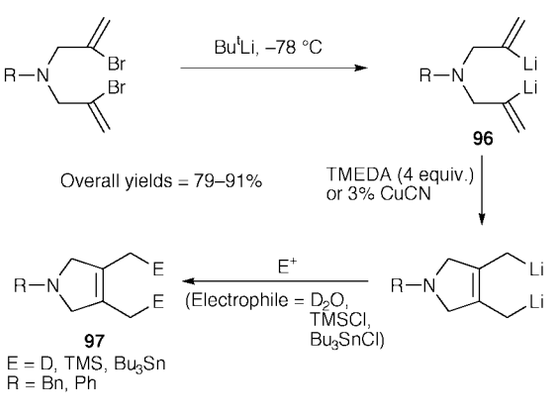
Organolanthanide-catalyzed hydroaminations have been extended to more hindered substrates than previously explored.[46] The use of easily prepared samarium or neodymium catalysts allowed the preparation of pyrrolidines **95** bearing quaternary centers α to the nitrogen (Scheme 41), and the Thorpe–Ingold effect was found to accelerate reaction rates for substrates substituted along the linking chain. Bicyclic heterocycles were also prepared.



R^1	R^2	R^3	Ln	Yield(%)
H	H	Me	Nd	95
Me	Me	Me	Sm	93
Ph	Ph	Me	Sm	98
H	H	Ph	Nd	90
Me	H	Ph	Sm	100

Scheme 41

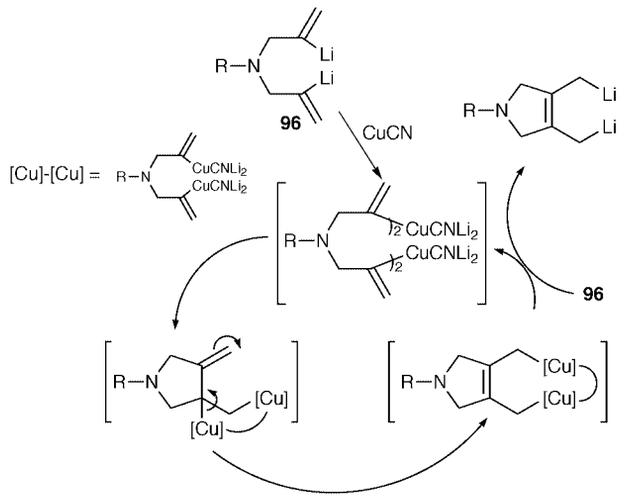
The first intramolecular carbometalation of lithiated double bonds was described by Barluenga and co-workers.[47] *N*,*N*-Bis-vinyllithium compounds **96** afforded dihydropyrroles **97** upon treatment with four equivalents of TMEDA or catalytic copper(I) cyanide, and then quenching with electrophiles (Scheme 42). A mechanism for the catalytic process was suggested involving the formation of a high order cuprate, intramolecular carbocupration, and allylic rearrangement (Scheme 43).



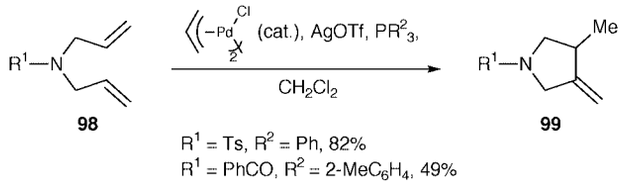
Scheme 42

Palladium-catalyzed cyclization of α,ω-dienes **98** has been used for the preparation of pyrrolidines **99** (Scheme 44).[48] The reaction was sensitive to the amine protecting group used; protection of the nitrogen with tosyl or acyl groups was acceptable, but benzyldiallylamine and other tertiary amines failed to react under these conditions.

Delgado and co-workers have explored further their nickel-promoted tandem cyclization–quenching of amino-tethered

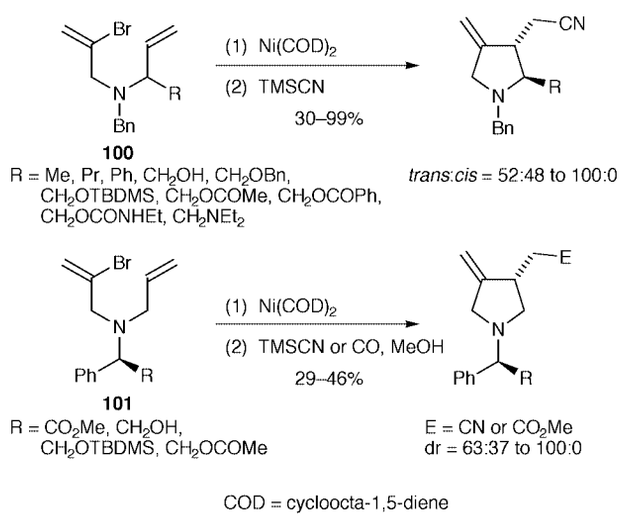


Scheme 43



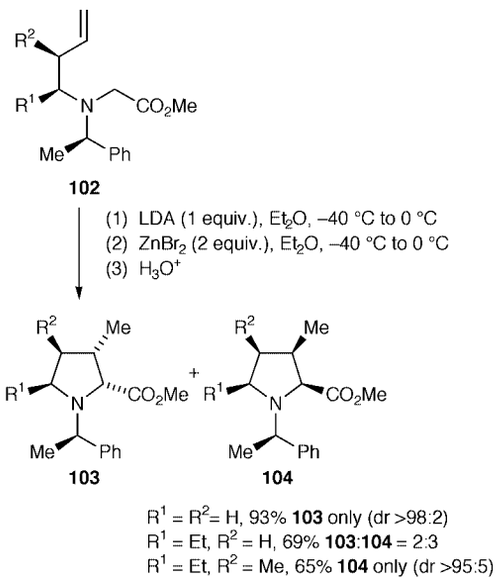
Scheme 44

vinyl bromides, to improve diastereoselectivity in the process (Scheme 45).[49] Two series of substrates were studied. Substitution α to the nitrogen on the allyl group (**100**) gave excellent diastereoselectivity for bulky substituents; substitution at the benzylic position (**101**) was also effective.



Scheme 45

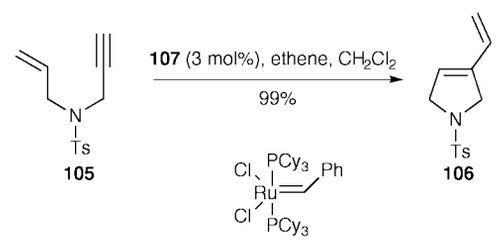
Intramolecular amino–zinc–enolate carbometalations have been performed, yielding polysubstituted pyrrolidines with moderate to excellent diastereoselectivities (Scheme 46).[50] Treatment of the precursors **102** with base, then with two equivalents of zinc bromide, generated pyrrolidines **103** and/or **104** in good yields. In general, the diastereoselectivity was postulated to arise from a chair-like amino–zinc–enolate transition state, in which π-chelation between the aromatic ring of the chiral benzyl group and the enolate could occur. The excess of zinc was thought to stabilize this chelation. However, the preferred transition state could be strongly influenced by substituents on the chain, thus changing the diastereoselectivity.



102 **103** **104**

Scheme 46

Mori has reported that terminal alkynes **105** may be used in intramolecular enyne metathesis reactions when they are performed under an atmosphere of ethene gas.[51] Thus the pyrrolidine **106** shown in Scheme 47 was prepared in 99% yield under an ethene atmosphere, but in only 15% yield under an argon atmosphere. The procedure was used successfully to synthesize other carbo- and heterocycles.

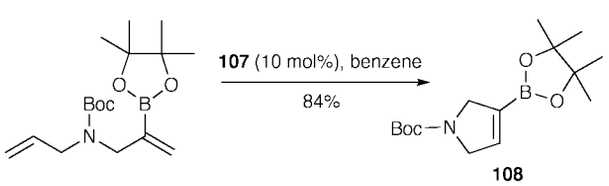


105 **106**

107

Scheme 47

Ring-closing metathesis (RCM) has also been used to prepare a series of cyclic alkenylboronates, including a dihydropyrrole **108** (Scheme 48).[52]

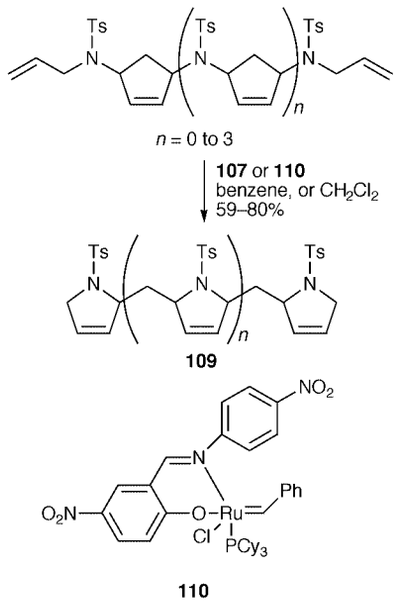


108

Scheme 48

Grubbs and co-workers have shown that polycyclic molecules may be produced from metathesis cascade reactions.[53] Polycyclic amines **109** were prepared in moderate to good yields with ruthenium catalysts. The yields tended to drop off as the number of cyclopentene relays increased, but this could be remedied by using a lower reaction temperature and concentration. For the most demanding substrates, catalyst **110** could be used to improve yields (Scheme 49).

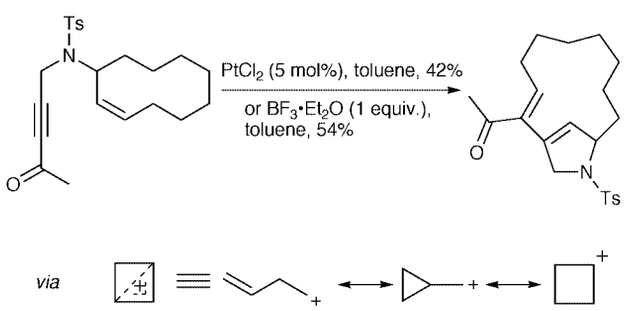
Platinum- and acid-mediated enyne metathesis has been studied as part of the syntheses of streptorubin B and metacycloprodigiosin (Scheme 50).[54] The reaction proceeded with catalytic platinum or with one equivalent of boron trifluoride–diethyl ether, although in model studies catalytic quantities of Lewis acid were sufficient. The reactive intermediate was



109

110

Scheme 49

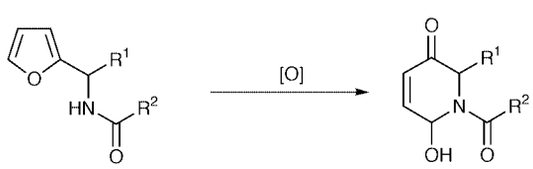


Scheme 50

thought to be a non-classical homoallyl–cyclopropylmethyl–cyclobutyl cation, formation of which was triggered either by π-complexation of the alkyne onto the platinum salt, or by coordination of the Lewis acid onto the adjacent carbonyl group.

5 Six-membered rings

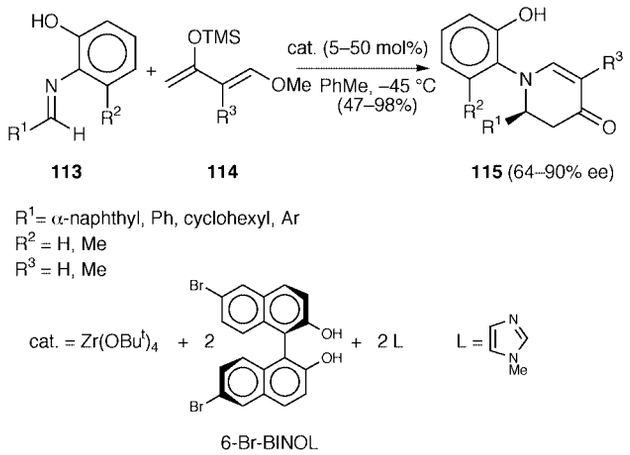
Bailey and co-workers have reviewed the main asymmetric routes to substituted piperidines, focussing on the use of chiral-pool starting materials, reactions involving chiral catalysts, and reactions involving a chiral auxiliary.[55] Synthetic routes to the 1-azasugars, potential glycosidase inhibitors, have been reviewed by Bols.[56] The utility of the aza-Achmatowicz reaction (**111**→**112**, Scheme 51) for the synthesis of nitrogen heterocycles has been reviewed by Ciufolini and co-workers.[57]



111 **112**

Scheme 51

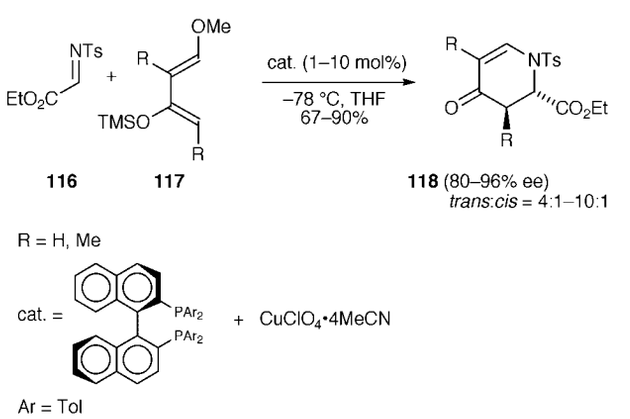
Progress continues to be made on the development of the imine-variant of the Diels–Alder reaction for the synthesis of piperidones. Kobayashi and co-workers[58] have described the first catalytic, enantioselective Diels–Alder reaction of aldimines **113** (derived from the corresponding aldehyde and 2-aminophenol) with the Danishefsky-type diene (**114**) (Scheme 52). The optimal catalyst system involved the combination of



Scheme 52

[6-Br-BINOL] and $Zr(OBu^t)_4$ with a ligand (often 1-methylimidazole) in toluene at −45 °C. Yields ranged from good to excellent, and with optimal substrates (R^1 = α-naphthyl, $R^2 = R^3 = H$ and 50 mol% of catalyst) the enantiomeric excess of the resultant piperidone **115** reached 90%.

Jørgensen and co-workers have described similar results with ethyl glyoxylate-derived imines **116** with the Danishefsky-type diene **117** (Scheme 53).[59] In this instance, the optimal catalyst system was found to be $CuClO_4$·4MeCN in combination with tol-BINAP in THF. Impressively, **118** [R = Me, *trans*:*cis* ratio = 4:1; 93% ee (*trans* isomer)] was obtained on a gram scale with a catalyst loading of only 1 mol%.



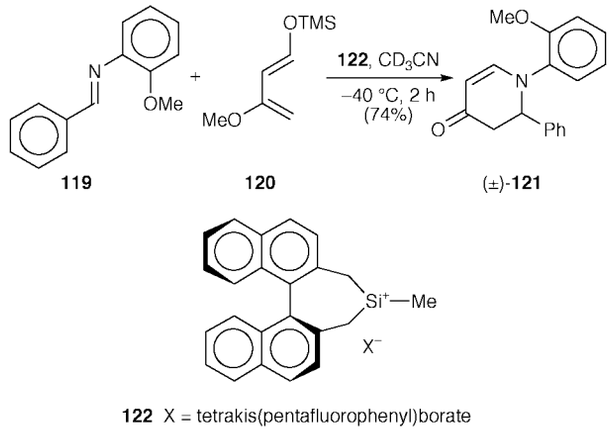
Scheme 53

Jørgensen and Helmchen[60] have described the Diels–Alder reaction of imine **119** with diene **120**, catalyzed by the novel Lewis acidic silyl cationic catalyst **122** (Scheme 54). In this case however, the product (**121**) was found to be racemic.

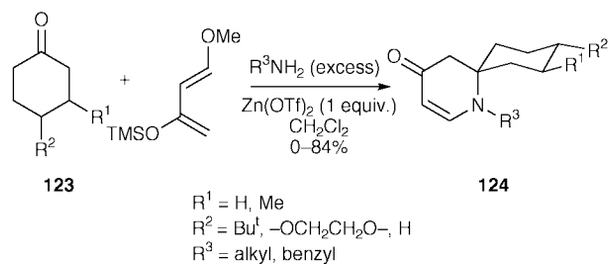
Some rare examples of an imine Diels–Alder reaction with a ketone-derived imine (to give aza-spiranes) have been described by Oh and co-workers (**123**→**124**, Scheme 55).[61] Yields of the aza-spirane products (**124**) ranged from 0–84% (typically 50–70%). 2-Substituted cyclohexanones did not give Diels–Alder products probably because of steric crowding. For **123** (R^1 = H, $R^2 = Bu^t$ and R^1 = Me, R^2 = H), the reaction was highly diastereoselective giving only the product in which the diene approached the imine from the equatorial direction.

Barluenga and co-workers have described further applications of the imine Diels–Alder reaction between the chiral diene **125** and TMS-imine **126** (Scheme 56).[62] The resulting products **127** were transformed into a number of pipecolic acid derivatives, notably the dipeptide isosteres **128** and **129**.

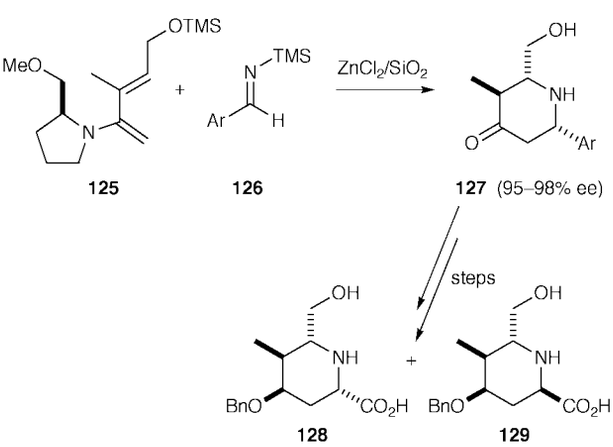
Creswell and co-workers have described the application of the increasingly popular scavenger-resin technology to the synthesis of a library of dihydropyridones by the imine Diels–



Scheme 54



Scheme 55



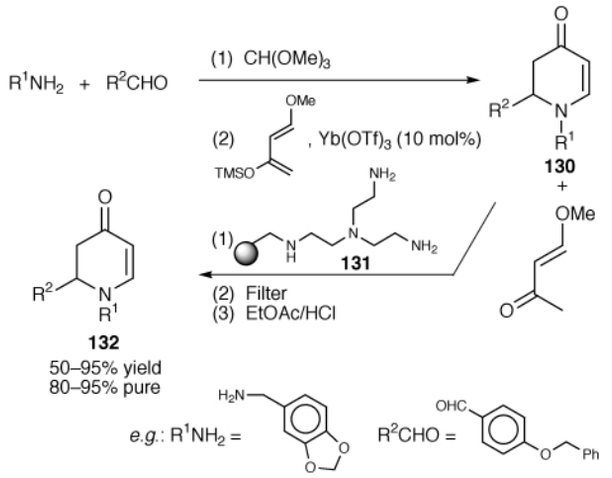
Scheme 56

Alder reaction.[63] Thus, treating an equimolar mixture of an amine and an aldehyde (Scheme 57) with trimethyl orthoformate (to generate the imine) followed by addition of a slight excess of Danishefsky's diene afforded the dihydropyridone **130**, together with the 4-methoxybut-3-en-2-one side-product and occasionally small amounts of unreacted imine. These were both readily removed with the amine resin **131**, affording **132** in good yield, but most importantly in excellent purity. Daughter libraries were also prepared from the original library.

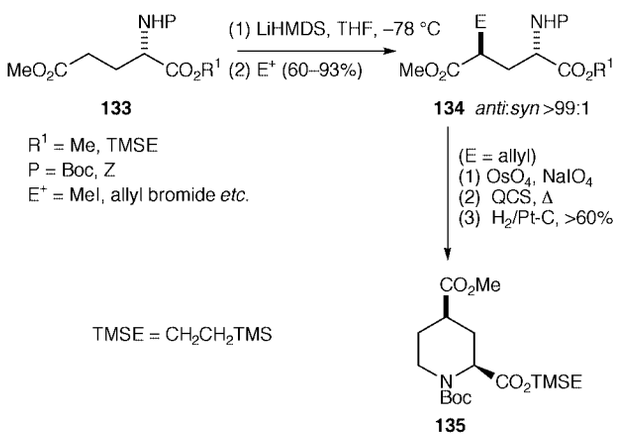
Further theoretical insight into the imine Diels–Alder reaction has been provided by Whiting and Windsor,[64] and into the Diels–Alder reaction of acrylates with 2-azadienes by Gonsalves and co-workers.[65]

As in previous years, many new syntheses of substituted pipecolic acids have been published, some of which are essentially demonstrations of new methods of generating and controlling remote stereocenters.

For example, Hanessian and Margarita have described the highly diastereoselective *anti*-alkylation of glutamate esters with a range of reactive electrophiles (**133**→**134**, Scheme 58).[66]



Scheme 57



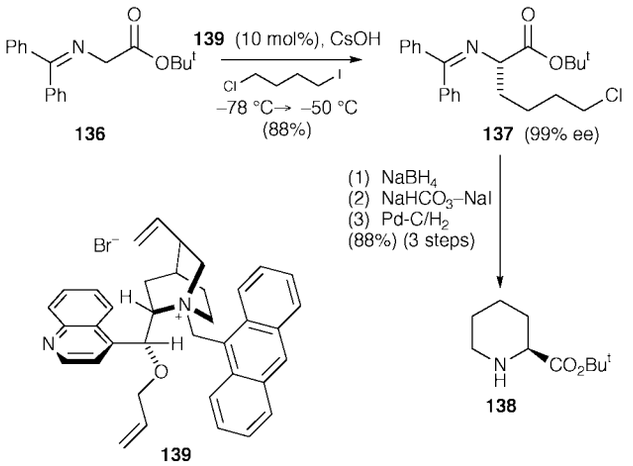
Scheme 58

The reaction gives >99 : 1 stereoselectivity in many instances with either methyl or 2-(trimethylsilyl)ethyl (TMSE) ester derivatives and Boc or Z carbamates. For **134** (E = allyl; R^1 = TMSE; P = Boc), a simple series of functional group transformations gave the 2,4-dicarboxylated pipecolic acid **135**, with each carboxy group usefully differentiated.

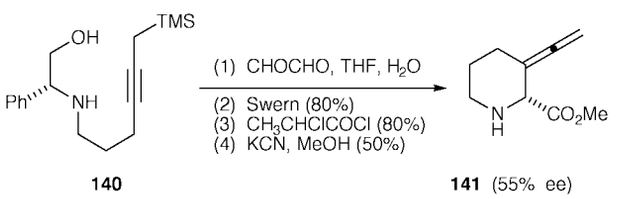
Corey and co-workers have described the catalytic, asymmetric alkylation of the O'Donnell glycine-derived imine **136**, mediated by the chiral cinchona alkaloid-derived phase transfer catalyst **139**.[67] With 1-chloro-4-iodobutane as the (bis)electrophile, **137** was obtained in 99% ee (88% yield) (Scheme 59). Reduction of the imine, alkylative ring closure and deprotection gave the protected pipecolic acid **138** in 88% overall yield from **137**.

The unusual 3-allenyl pipecolic acid **141** has been synthesized by Kadouri-Puchot and co-workers (Scheme 60).[68] Treatment of the phenylglycinol derivative **140** with aqueous glyoxal gave initially a lactol, formed by cyclization of the propargylsilane onto an intermediate iminium ion. Oxidation and deprotection (using carefully controlled conditions to preserve the allene moiety) then gave **141** in 55% ee, partial racemization having occurred at some stage. The same methodology (except with a tethered allylsilane) was used to synthesize *cis*- and *trans*-3-vinylpipecolic acids.[69]

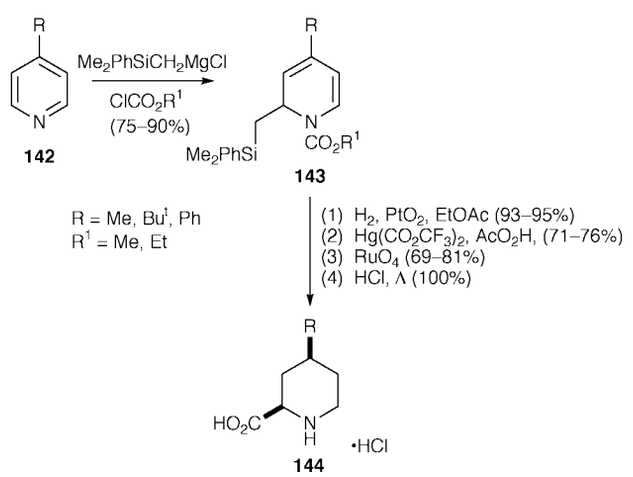
Mann, Nazih and co-workers have described the synthesis of 4-substituted pipecolic acids from 4-alkylpyridines (**142**→**144**, Scheme 61).[70] Addition of [(phenyldimethylsilyl)methyl]-magnesium chloride to **142** in the presence of an alkyl chloroformate gave dihydropyridine **143** in good yield. Reduction, followed by oxidative desilylation and functional group manipulation then gave racemic **144** in good overall yield. For R = Ph or Bu^t the products were obtained as single (*cis*)



Scheme 59



Scheme 60



Scheme 61

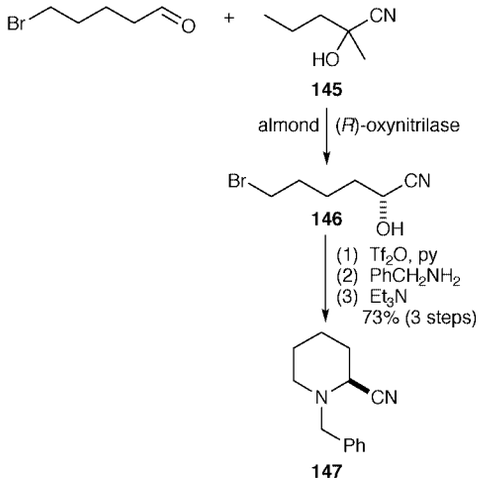
isomers; for R = Me the reduction was less selective, affording instead a 7 : 3 *cis* : *trans* mixture.

A biotransformational route to pipecolic acids has been described by Gotor and co-workers (Scheme 62).[71] Treatment of 5-bromopentanal with (*R*)-oxynitrilase and cyanohydrin **145** results in the formation of the enantiomerically enriched cyanohydrin **146** (91% ee). Triflation, amination and cyclization then gave the nitrile **147**, which under suitable conditions was transformed into (−)-pipecolic acid without detectable racemization.

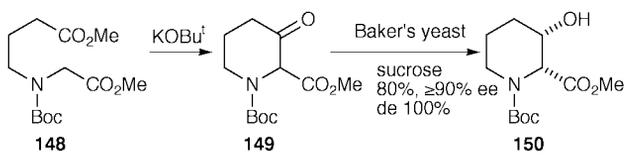
Knight and co-workers[72] have reported full details of the bakers' yeast-mediated reduction of β-ketopiperidinecarboxylates (obtained by Dieckman cyclization) to *cis*-β-hydroxypiperidinecarboxylates (*e.g.* **148**→**149**→**150**, Scheme 63).

The fungus *Beauveria bassiana* has been shown to hydroxylate the ring of Z-protected piperidines (**151**→**152**, Scheme 64).[73] The precise site of hydroxylation, stereoselectivity and yield were found to depend on the nature of the substituents at R^2–R^6, but generally hydroxylation at the 4-position was preferred.

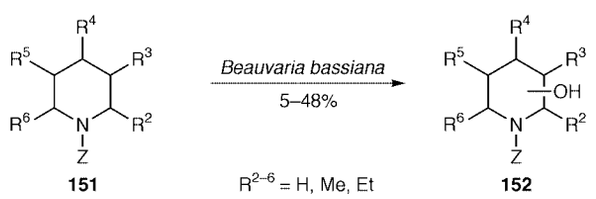
The asymmetric desymmetrization of **153a** and the corresponding diacetate **153b** has been described by Lesma and



Scheme 62

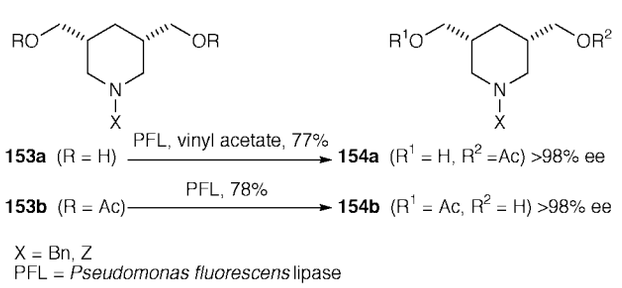


Scheme 63



Scheme 64

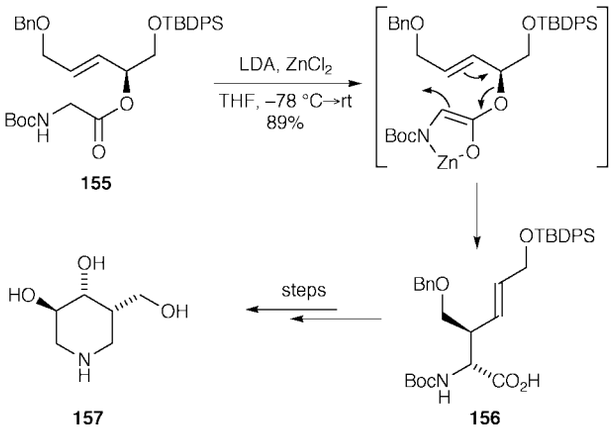
co-workers (Scheme 65).[74] The best enzyme for this conversion appears to be the commercially available *Pseudomonas fluorescens* lipase (PFL) with vinyl acetate (for the esterification) or without vinyl acetate (for the alcoholysis), reactions which give enantiocomplementary products. Under suitably optimized conditions, **154a** could be obtained in >98% ee (77% yield); **154b** was also obtained in >98% ee (78% yield).



Scheme 65

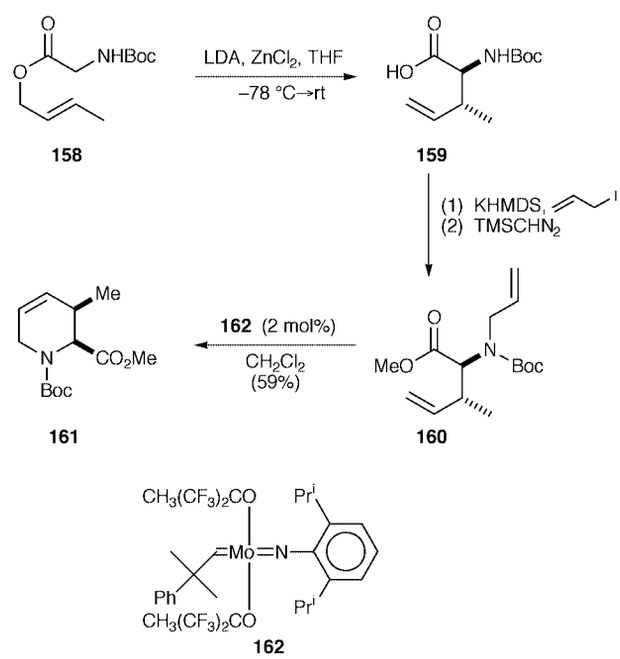
The Kazmaier variant of the Claisen rearrangement has proved to be useful in the synthesis of functionalized piperidines, principally owing to the ease with which it sets up functionalized 1-aminopentanes from glycine and homoallylic alcohols. For example, the key step (**155**→**156**) in a synthesis of 5-*epi*-isofagomine (**157**, Scheme 66)[75,76] proceeded in 89% yield with complete stereocontrol. Compound **156** was readily functionalized to give the natural product. Alternatively an aldol reaction can be used to create the related 1-aminopentane ring-closure precursor.[77]

Piscopio and co-workers have described the synthesis of racemic 3-substituted *cis*-pipecolinic acids **161** by the RCM



Scheme 66

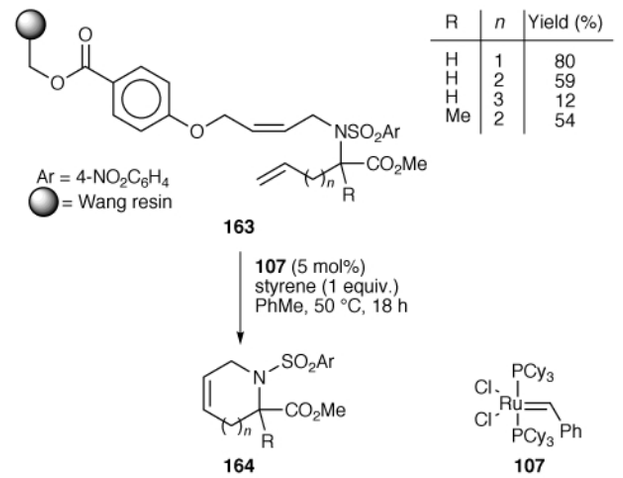
of **160** using Schrock's molybdenum catalyst (**162**, 2 mol%) (Scheme 67).[78] The diene **160** was obtained by allylation of **159**, the product of Kazmaier–Claisen rearrangement of glycine ester **158**. The alternative *trans*-disubstituted pipecolinic acids may be obtained by using the (*Z*)-alkene starting material (47% overall yield).



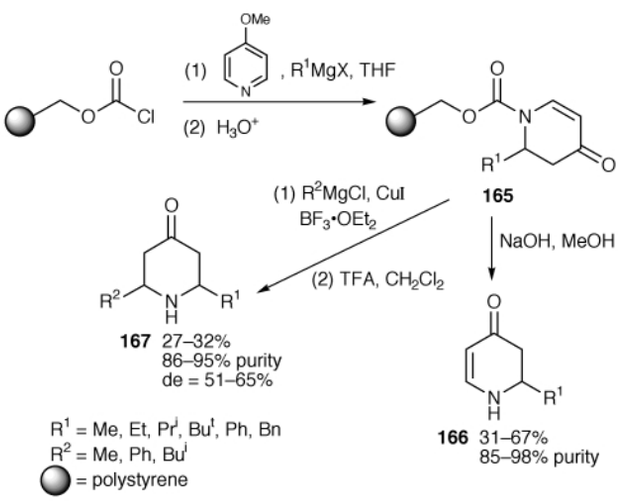
Scheme 67

The useful RCM cyclization–cleavage strategy to make substituted nitrogen heterocycles has been examined in greater detail by Rutjes and co-workers (**163**→**164**, Scheme 68).[79] By fine-tuning the reaction conditions (principally by using styrene instead of an unconjugated alkene as the sacrificial additive) the rate of metathesis–cleavage and the yield were both dramatically improved. For example, even an eight-membered ring could be formed in modest yield, a reaction that failed completely in the solution variant.

Munoz and co-workers have described the application of Comins' acylpyridinium chemistry to a solid support (Scheme 69) to generate a combinatorial library of dihydropyridones.[80] The initially-formed dihydropyridone **165** can either be cleaved directly from the resin to afford **166** in good yield and in acceptable purity, or further functionalized by a 1,4-organocuprate addition reaction to afford **167**. This approach is referred to as REACAP technology (REsin Activation/Capture APproach) by the authors, the idea being that the initially formed reactive pyridinium ion intermediate either reacts as intended or is



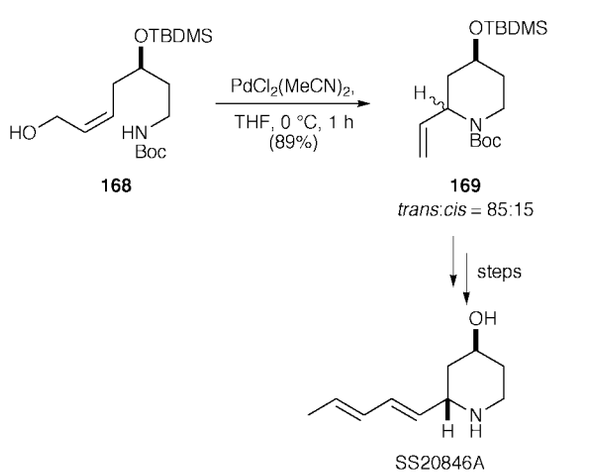
Scheme 68



Scheme 69

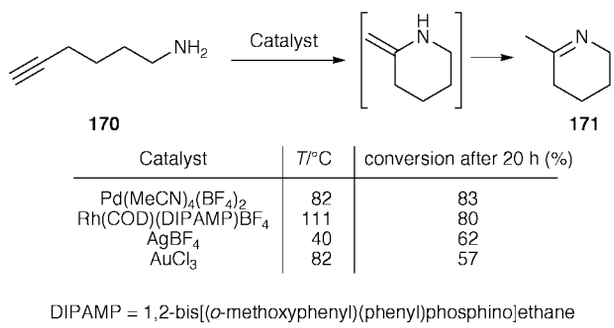
readily quenched and removed from the resin on workup, thus leading to products of greater purity.

Hirai and co-workers[81] have described the application of a Pd(II)-catalyzed intramolecular alkene hydroamination reaction to the synthesis of SS20846A, isolated from a strain of *Streptomyces*. The key cyclization (**168**→**169**, Scheme 70) proceeded in excellent yield with $PdCl_2(MeCN)_2$ (10 mol%) and good selectivity (*trans*:*cis* = 85:15). Several conventional steps then furnished the natural product. Full details of Troin's synthesis of the same natural product have now been reported.[82]

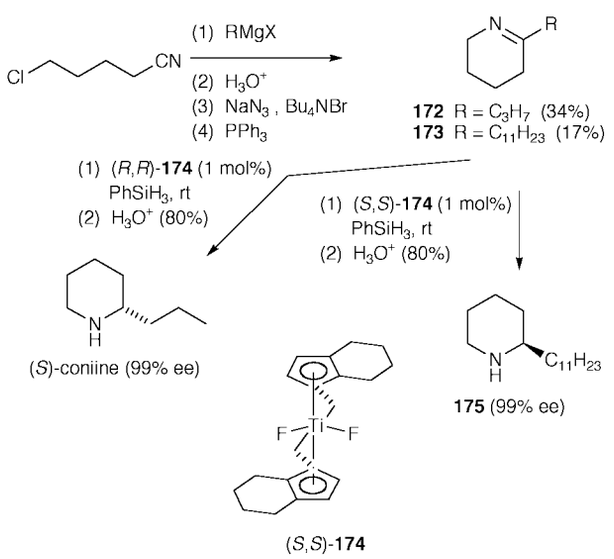


Scheme 70

Müller has described the related catalytic hydroamination of ω-aminoalkynes to 1,2-dehydropiperidines (**170**→**171**, Scheme 71).[83] An initial screen of Group 9, 10 and 11 transition metal catalysts revealed that $Pd(MeCN)_4(BF_4)_2$ and Rh(COD)-(DIPAMP)BF_4 were the most active catalysts, although less exotic ones such as $AuCl_3$ and $AgBF_4$ retained some activity. These endocyclic imines are similar to the substrates used by Buchwald in his asymmetric synthesis of coniine and solenopsin A (Scheme 72).[84] In this instance, the endocyclic imines were obtained in a multi-step procedure from 5-chlorovaleronitrile, *via* (1) Grignard addition; (2) ω-azido ketone formation and (3) aza-Wittig cyclization. Enantioselective reduction of **172** and **173** with the appropriate enantiomer of the titanium(II) catalyst **174** and phenylsilane as the stoichiometric reductant led to (*S*)-coniine and **175** respectively in good yield and 99% ee. Compound **175** was subsequently transformed into solenopsin A using Beak's directed lithiation methodology.

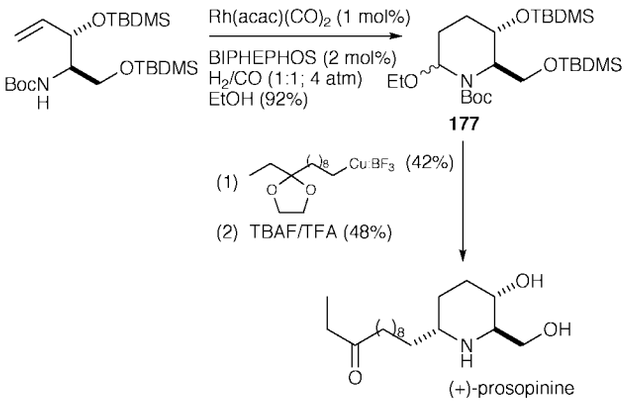


Scheme 71



Scheme 72

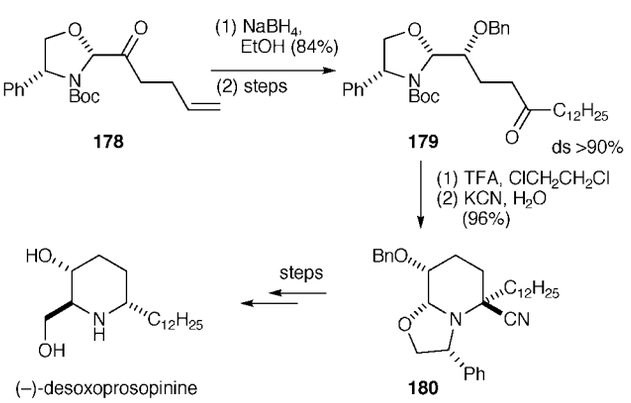
In syntheses of (+)-prosopinine and (−)-deoxoprosophylline, Ojima and Vidal have described the Rh-catalyzed cyclohydrocarbonylation of homoallylic amines to give piperidines (Scheme 73).[85] Starting with **176** (derived ultimately from serine), treatment with $Rh(acac)(CO)_2$ (1 mol%) and BIPHEPHOS under a slight pressure of H_2/CO gas gave the ethoxypiperidine **177** in 92% yield. If the reaction was conducted in THF instead of ethanol the corresponding dihydropyridine was formed instead in 96% yield [which was converted to (+)-prosopinine by an alternative route]. Formation of the iminium ion from **177** and addition of the appropriate organocuprate gave, after deprotection, (+)-prosopinine in reasonable yield. (−)-Deoxoprosophylline, which features a 2,6-*cis* ring substitution pattern, was also synthesized using a similar route.



Scheme 73

The synthesis of precursors for the preparation of indolizidine and quinolizidine alkaloids by the analogous mono-cyclohydrocarbonylation reaction and subsequent functionalization of amido-ω,ω′-dienes has also been described.[86] (+)-Desoxoprosophylline has been made by Zhou and co-workers through application of the aza-Achmatowicz reaction.[87]

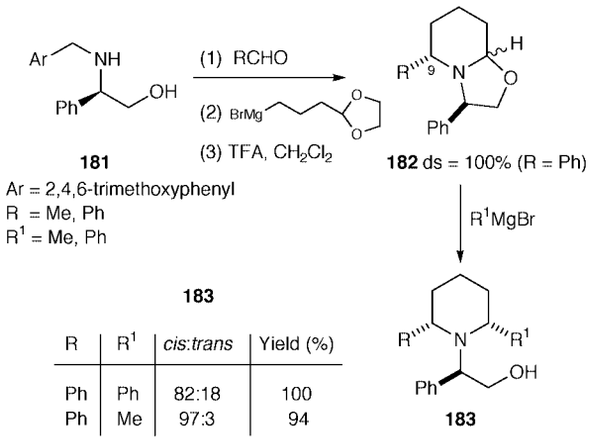
Couty and co-workers have described syntheses of (−)-desoxoprosopinine and related alkaloids (Scheme 74).[88,89] The key intermediate is the 2-acyloxazolidine **178**, which can be diastereoselectively reduced to yield either diastereomeric alcohol. For the synthesis of (−)-desoxoprosopinine, sodium borohydride gave the desired stereoselectivity. A series of conventional steps then gave the ketone **179**, which on sequential treatment with TFA and aqueous potassium cyanide gave **180** (*via* the intermediate iminium ion). This was then transformed to the natural product in a multi-step fashion.



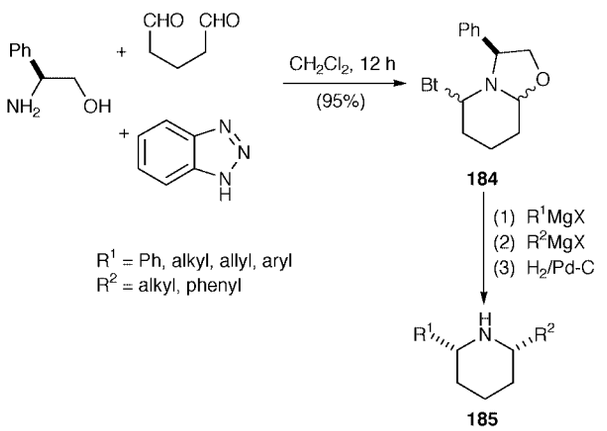
Scheme 74

Higashiyama and co-workers have synthesized a late-stage intermediate similar to **180** in their syntheses of *cis*-2,6-dialkylpiperidines, including the natural products pinidine, solenopsin and isosolenopsin (Scheme 75).[90,91] Treatment of **181** with benzaldehyde or acetaldehyde, followed by treatment with the four-carbon Grignard reagent, deprotection and concomitant cyclization gave **182**. The C9 diastereomer could be readily made by installing the R-group and the four-carbon fragment (as the dialdehyde) in the opposite order. Treatment of **182** with another Grignard reagent then gave the 2,6-*cis*-disubstituted piperidine **183** in excellent yield and selectivity.

Katritzky and co-workers have described a very concise and general route to 2- and 2,6-disubstituted piperidines (Scheme 76).[92] Treatment of aqueous glutaraldehyde and phenylglycinol with benzotriazole gave oxazole **184** as a diastereomeric mixture of benzotriazole regioisomers in 95% yield. Addition of a Grignard reagent (R^1MgX) resulted in displacement of the benzotriazole moiety (*via* the iminium ion) to give (after hydrogenolysis) the 2-substituted piperidine as a single isomer.



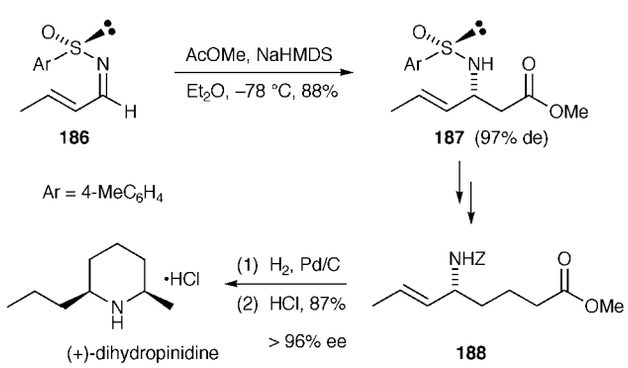
Scheme 75



Scheme 76

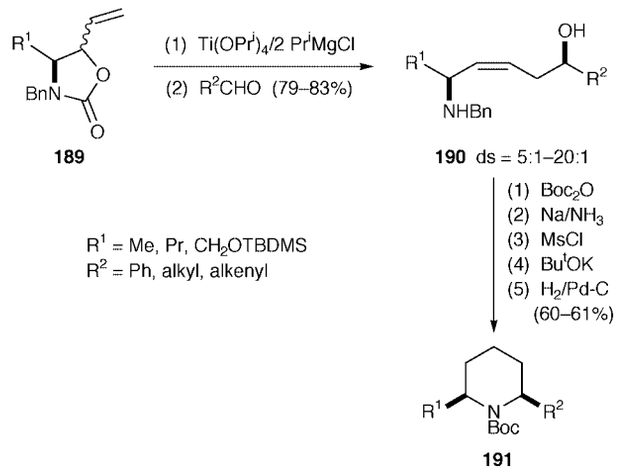
Alternatively, addition of a further Grignard reagent in a separate step gave after hydrogenolysis the *cis*-2,6-disubstituted piperidine **185** also as a single isomer. Overall, (+)-coniine (R^1 = Pr; R^2 = H) was obtained in three steps from glutaraldehyde in 45% yield, making this the most efficient route yet to this natural product.

Davis has described a synthesis of the related natural product (+)-dihydropinidine.[93] The key step in this synthesis is the diastereoselective addition of an enolate to the enantiomerically pure sulfinimine (**186**) (Scheme 77). The resulting β-amido ester **187** was transformed to **188**, which then underwent intramolecular reductive amination to give (+)-dihydropinidine in 87% yield.



Scheme 77

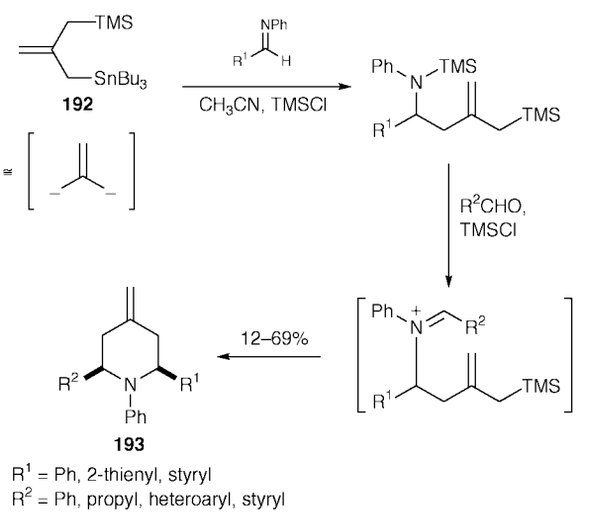
Sato and co-workers have described a new route to 2,6-*cis*-disubstituted piperidines (**189→191**, Scheme 78).[94] Starting with cyclic carbamate **189** (obtained from an amino acid), treatment with $Ti(OPr^i)_4/2Pr^iMgCl$ followed by an aldehyde



Scheme 78

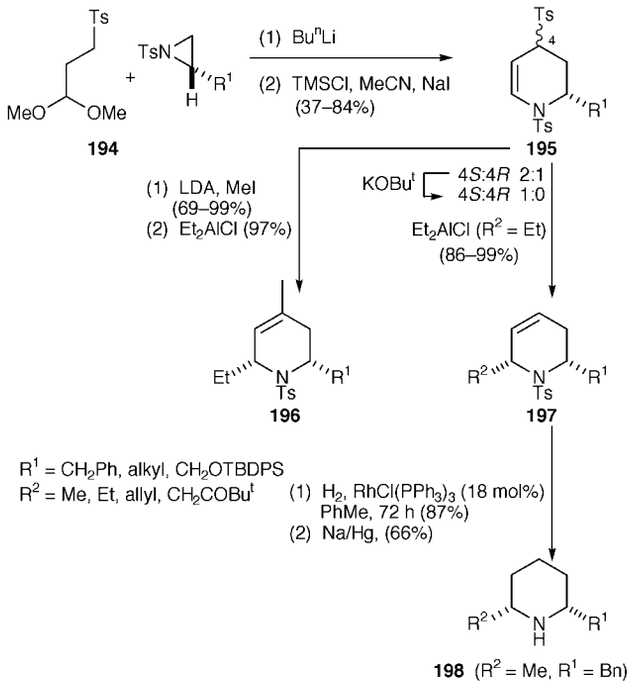
gave the 1,5-amino alcohol **190** (*via* the allyltitanium species) in good yield and selectivity depending on the precise nature of R^1 and R^2. An efficient multi-step sequence mainly involving protecting group manipulation was then employed to form the piperidine ring.

Kang and co-workers have described the stepwise reaction of **192** (an isobutene dianion synthon) with TMS-complexed imines to give 2,6-*cis*-disubstituted 4-methylenepiperidines (**192**→**193**, Scheme 79).[95] Only a single isomer is obtained in the reaction. Intriguingly, the analogous reaction to make *N*-benzylpiperidines (but with $BF_3{\cdot}OEt_2$ in place of TMSCl as the activator) gives predominantly the 2,6-*trans*-isomer.



Scheme 79

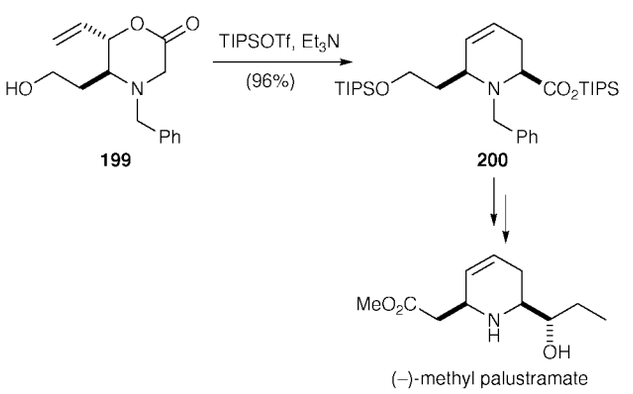
Craig and co-workers have described a powerful new approach to the synthesis of 2,6-*cis*-disubstituted piperidines (Scheme 80).[96] Alkylation of the anion of **194** with an aziridine, followed by TMSI-mediated ring closure gave the tetrahydropyridine **195** in good overall yield initially as a mixture of diastereoisomers, which could be converted to a single isomer on treatment with base. Treatment of **195** with a Lewis acid and a nucleophile [*e.g.* Et_2AlCl, $SnCl_4$/allylTMS or $SnCl_4$/TBDMSOC(CH$_2$)OBu^t] then led to the 1,2,5,6-tetrahydropyridine **197** as single *cis* isomers (*via* S_N1' reaction) in excellent overall yield. In addition, the 4-position can be alkylated to give exclusively the 2,4-*anti*-substituted tetrahydropyridine. This compound also undergoes the S_N1' reaction (with Et_2AlCl) to give the trialkyltetrahydropyridine **196** in virtually quantitative yield. Hydrogenation of **197** to give the piperidine **198** was unexpectedly difficult, probably due to steric hindrance,



Scheme 80

although Wilkinson's catalyst eventually proved effective. The *N*-deprotection proved uneventful with sodium amalgam. An extension of this promising new methodology to the synthesis of more complex ring systems was presented in a later paper.[97]

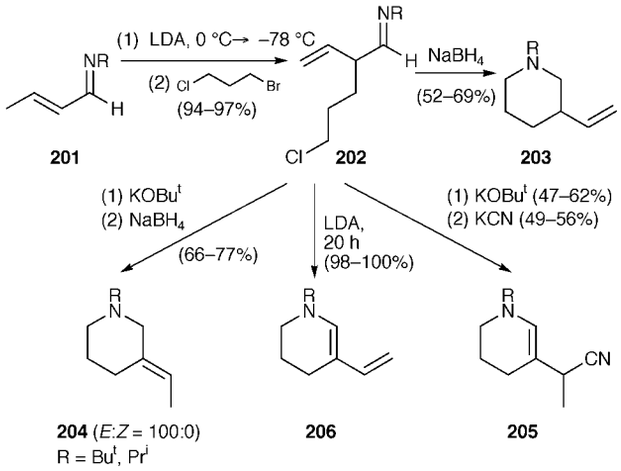
Angle and Henry have described an extension of their work directed toward the synthesis of indolizidine 167B to the synthesis of (−)-methyl palustramate (Scheme 81).[98] Thus, Claisen rearrangement of the silyl ketene acetal derived from **199** gave the silyl pipecolate **200** in excellent yield. This was then functionalized in a multi-step fashion to give the natural product.



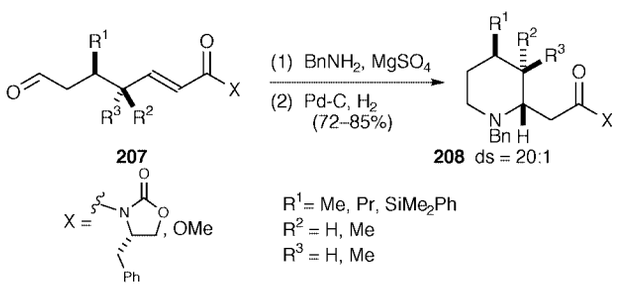
Scheme 81

DeKimpe and Aelterman have described a number of useful transformations of the (relatively unstable) β,γ-unsaturated imines **202**, obtained from alkylation of the α,β-unsaturated imine **201** with 1-bromo-3-chloropropane (Scheme 82).[99] Treatment of **202** with sodium borohydride leads simply to reduction and the piperidine **203**, whereas isomerization leads to the 3-ethylidenepiperidine **204** (after reduction) or the cyanoethyl derivative **205** (by treatment with potassium cyanide). Alternatively treatment of **202** with LDA for 20 h led to the 1,3-diene **206**, which although unstable proved to be a useful substrate for a Diels–Alder reaction.

Schneider has described the synthesis of heavily substituted piperidines by the double nucleophilic addition of benzylamine to 7-oxo-2-enimides **207** (Scheme 83).[100] After hydrogenation of the initially formed (and sensitive) tetrahydropyridines, the



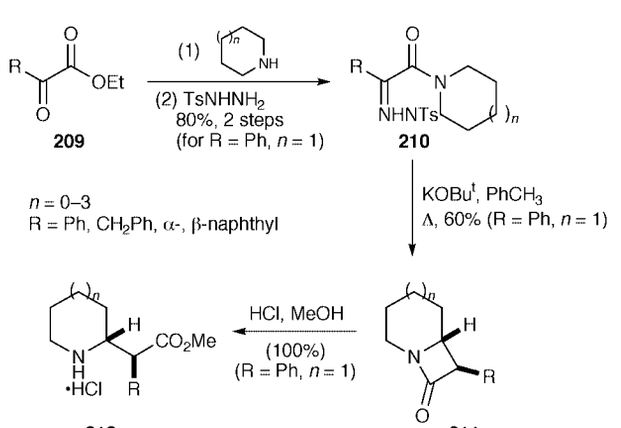
Scheme 82



Scheme 83

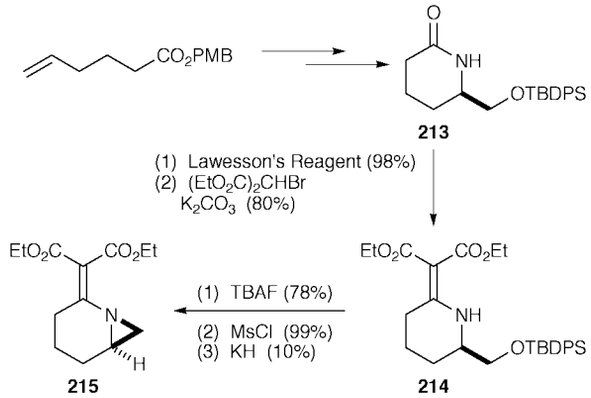
desired piperidines **208** were obtained in excellent yield and high diastereoselectivity (*ca.* 20:1). Remarkably, with 7-oxo-2-enoates (X = OMe) (obtained by methanolysis) only trivial imine formation was observed, with no subsequent cyclization occurring.

Winkler and co-workers have described an interesting procedure for functionalizing the 2-position of saturated nitrogen heterocycles (**209**→**212**, Scheme 84).[101] Thus, treatment of the glyoxylate **209** with a cyclic amine followed by tosylhydrazone gave hydrazone **210**. Treatment with potassium *tert*-butoxide in refluxing toluene gave β-lactam **211** in 60% yield (for R = Ph) by a carbene C–H insertion reaction. The strategy takes some precedent from work by Corey in the 1960s but clarifies the stereochemical outcome and demonstrates the reaction on a wider range of substrates. The resulting compounds proved useful in defining the pharmacophoric model of the dopamine transporter receptor.



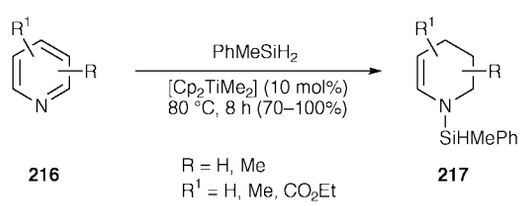
Scheme 84

Shipman and co-workers have described the synthesis of **215**, an analog of the azinomycin family of antitumor agents (Scheme 85).[102,103] A sequence of conventional steps was used to make lactam **213** (involving a Sharpless asymmetric dihydroxylation as the key step) which was then thionated with Lawesson's reagent. Treatment of this with diethyl bromomalonate gave **214** which was readily converted into the 1-azabicyclo[4.1.0]heptane **215** in three simple steps.



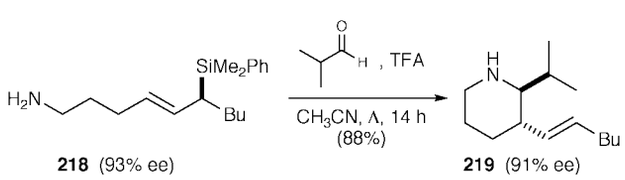
Scheme 85

The first homogeneously catalyzed hydrosilation of pyridines has been reported by Harrod and Samuel and co-workers (Scheme 86).[104] Treatment of a range of mono- and disubstituted pyridines **216** with methylphenylsilane and a titanocene complex gave the tetrahydropyridine **217** in excellent yield, except for when R = 3-ethoxycarbonyl, when the dihydropyridine is formed.



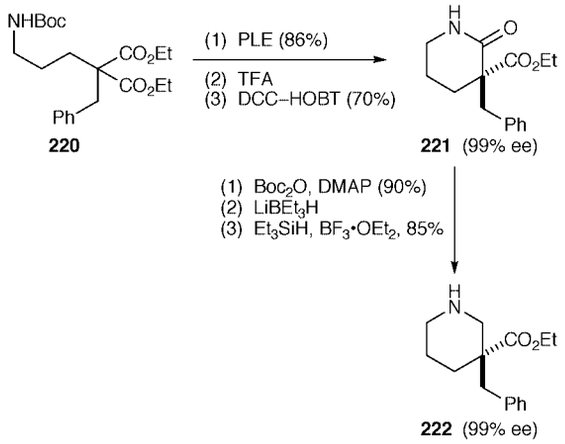
Scheme 86

Ito and co-workers have described the formation of 2,3-disubstituted piperidines from allylic dimethylphenylsilanes and aldehydes (Scheme 87).[105] Treatment of **218** (obtained from readily available homochiral allylic alcohols) with TFA and isobutyraldehyde in refluxing acetonitrile gave the piperidine **219** as a single isomer and with essentially no loss of optical purity. A similar reaction was also highly effective for the formation of tetrahydropyrans.



Scheme 87

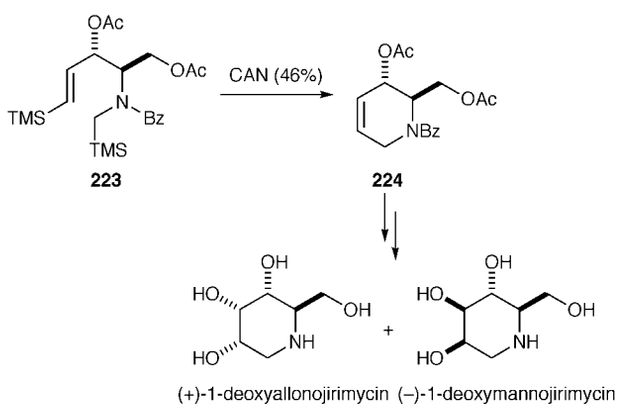
Maligres and co-workers have described a large-scale synthesis of **222** (Scheme 88), an intermediate for the synthesis of a human growth hormone secretagogue clinical candidate.[106] Starting from racemic **220** (obtained from acrylonitrile and diethyl benzylmalonate), enzymatic resolution with pig liver esterase (PLE), deprotection and cyclization gave the lactam **221**. The addition of oxalic acid to remove traces of excess DCC from the reaction mixture was found to be an efficient solution to the well-known problem of purification of reactions involving DCC and its urea by-product. The lactam was then chemoselectively reduced, first by imide formation and partial reduction (to the aminal) with lithium triethylborohydride, then further reduction with triethylsilane–BF_3·OEt_2 to piperidine



Scheme 88

222. This proved superior to the more common Lawesson thionation–Raney Nickel reduction strategy.

Finally, Mariano and co-workers have described in detail the factors affecting cleavage of α-silylamino vinylsilanes under oxidative Mannich conditions (*e.g.* **223**→**224**, Scheme 89).[107] In the instance illustrated, the product of the oxidative Mannich cyclization was efficiently transformed into the natural products (+)-1-deoxyallonojirimycin and (−)-1-deoxymannojirimycin.



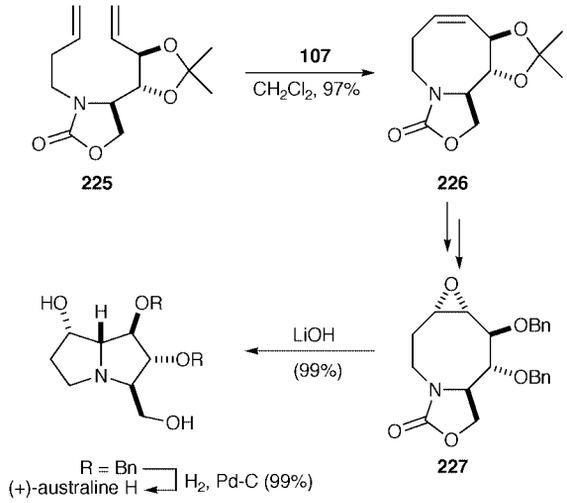
Scheme 89

6 Pyrrolizidines, indolizidines and quinolizidines

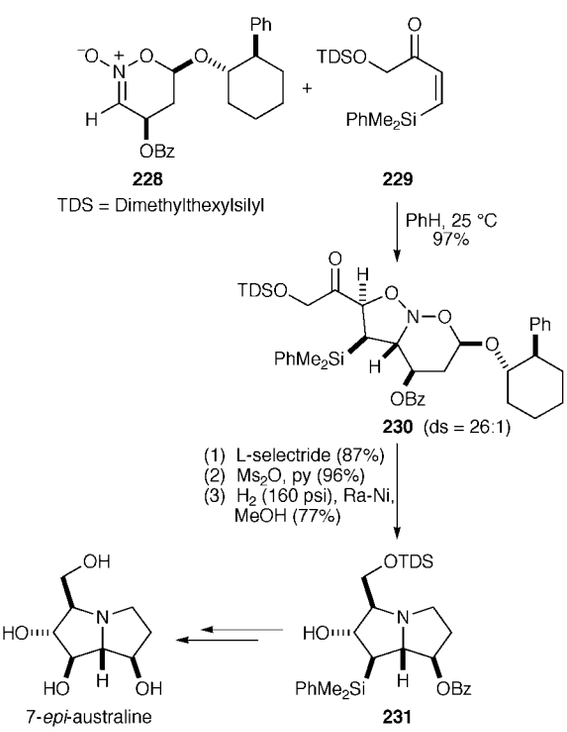
The pyrrolizidine alkaloid literature from July 96 to June 97 has been reviewed by Liddell.[108] The indolizidine and quinolizidine literature covering the same period has been reviewed by Michael.[109]

White and co-workers have described a synthesis of the alkaloid (+)-australine (Scheme 90).[110] The key step in the synthesis is the RCM of **225** to give the unsaturated eight-membered ring **226**, a reaction which proceeds in a remarkable 97% yield. A few simple transformations then gave **227**, which on treatment with lithium hydroxide furnished the dibenzyl ester of (+)-australine by transannular cyclization in 99% yield.

Denmark and Herbert have described an asymmetric synthesis of 7-*epi*-australine, featuring the intermolecular nitronate–alkene cycloaddition as a key step (Scheme 91).[111] Nitronate **228** [prepared from (1*S*,2*R*)-2-phenylcyclohexanol] reacted with vinylsilane **229** to give nitroso acetal **230** in 97% yield, virtually as a single diastereoisomer. Reduction of the ketone with L-Selectride, followed by mesylation and hydrogenation resulted in N–O bond cleavage, cyclization and reduction to give the pyrrolizidine **231** in 64% yield. The dimethylphenylsilyl group was then unmasked to introduce the C-1 hydroxy of 7-*epi*-australine. A crystal structure of the final product was obtained, which provided clarification of some



Scheme 90



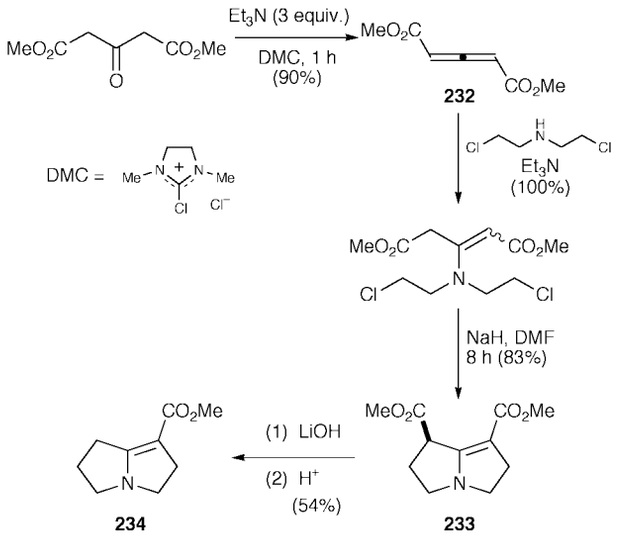
Scheme 91

earlier confusion in the literature about the exact stereochemistry of australine and 7-*epi*-australine.

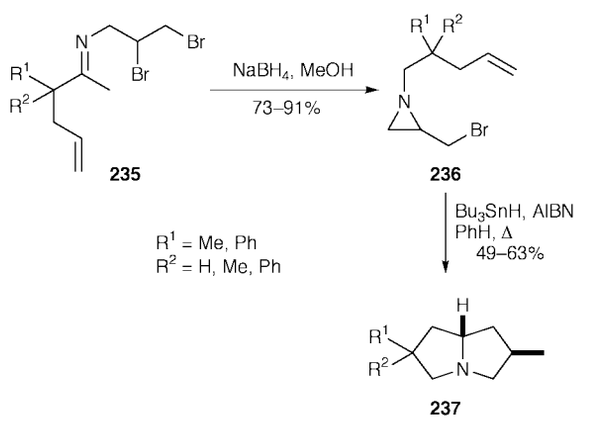
Node and co-workers[112] have described an interesting synthesis of the intermediate **234**, which has been used in syntheses of a number of pyrrolizidine alkaloids (Scheme 92). Treatment of dimethyl 3-oxopentane-1,5-dioate with 2-chloro-1,3-dimethylimidazolinium chloride (DMC) and triethylamine resulted in dehydration to the allene-1,3-dicarboxylate **232**. Michael addition of bis(2-chloroethyl)amine followed by cyclization gave **233**, which gave **234** on hydrolysis and decarboxylation.

A radical cyclization approach to the synthesis of pyrrolizidines has been described by De Kimpe and co-workers (Scheme 93).[113] Treatment of imine **235** with sodium borohydride resulted in cyclization to the 2-(bromomethyl)aziridine **236**. Addition of Bu_3SnH–AIBN *via* syringe pump to **236** gave **237** in good yield, presumably by formation of an *N*-centered radical through intramolecular opening of the aziridine, and then two 5-*exo*-*trig* radical cyclizations. Attempts to form the indolizidine skeleton using this strategy failed.

Denmark and Middleton have described a synthesis of

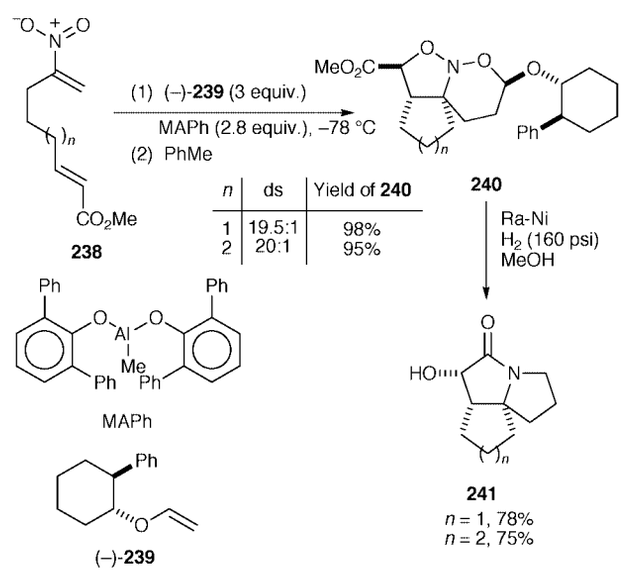


Scheme 92



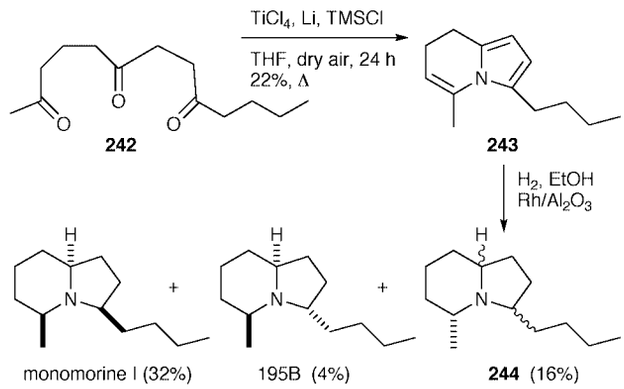
Scheme 93

interesting azapropellanes through application of an inter [4 + 2]–intra [3 + 2] nitroalkene cycloaddition cascade (Scheme 94).[114] Treatment of **238** (n = 1 or 2) with an excess of the homochiral vinyl ether **239** and the Lewis acid MAPh at −78 °C, followed by workup and heating in toluene gave nitroso acetal **240** as nearly a single isomer in excellent yield by first intermolecular formation of a nitronate (*cf.* Scheme 91) then intramolecular [3 + 2] cyclization to give **240**. Reduction of **240** with Raney nickel/H_2 then gave the azapropellanes **241**.



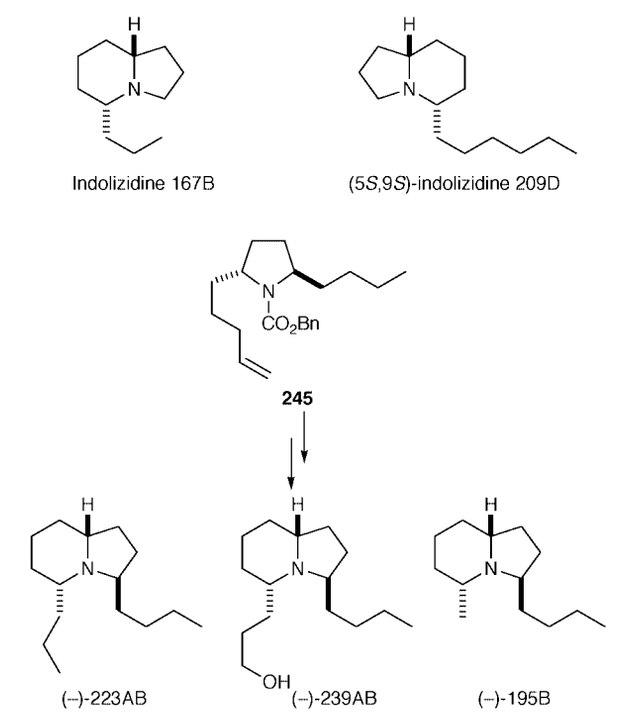
Scheme 94

Mori and co-workers have used their remarkable discovery that a mixture of $TiCl_4$, TMSCl and lithium can "fix" atmospheric nitrogen [as a $N(TMS)_3$–$TiN(TMS)_n$ complex] in a synthesis of the alkaloids monomorine I and indolizidine 195B (Scheme 95).[115,116] Thus treatment of triketone **242** with "titanium nitrogen complex" (2 equiv.) prepared from $TiCl_4$–TMSCl–Li and dry air gave the indolizidine derivative **243** in 22% yield. With pure nitrogen, the yield increased to 30%. Reduction of **243** then gave monomorine I (32%), an epimer identified as indolizidine 195B (4%) and a mixture of other diastereomers **244** (16%).



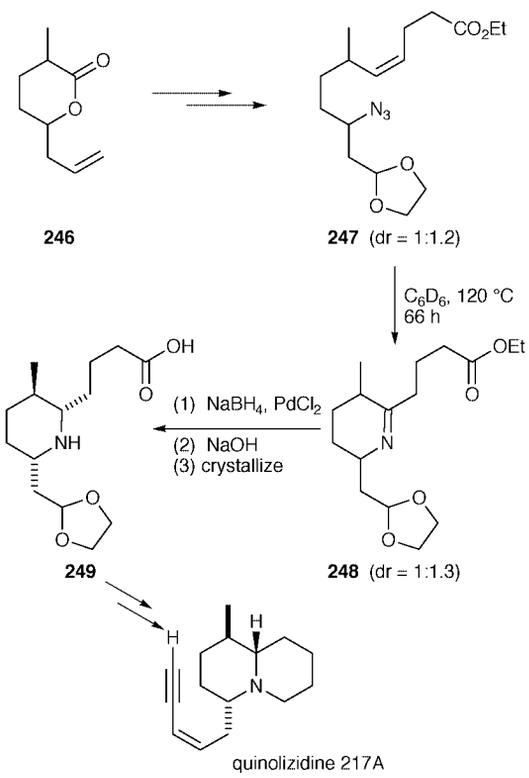
Scheme 95

A number of syntheses of indolizidine alkaloids obtained from the Dendrobatid "poison dart" frogs have been reported. Michael and Gravestock have synthesized indolizidine 167B using their earlier reported route based on an Eschenmoser sulfide contraction.[117] All four stereoisomers of indolizidine 209D have been synthesized by Takahata and co-workers, using two successive Sharpless asymmetric dihydroxylation (AD) reactions to separately introduce each chiral center.[118] By using the Sharpless AD reaction twice, enhanced levels of asymmetric induction were obtained (up to 98% ee). Lhommet has described the synthesis of indolizidine (−)-223AB, (−)-239AB and (−)-195B from pyrrolidine **245** by a series of straightforward functional group manipulations (Scheme 96).[119]



Scheme 96

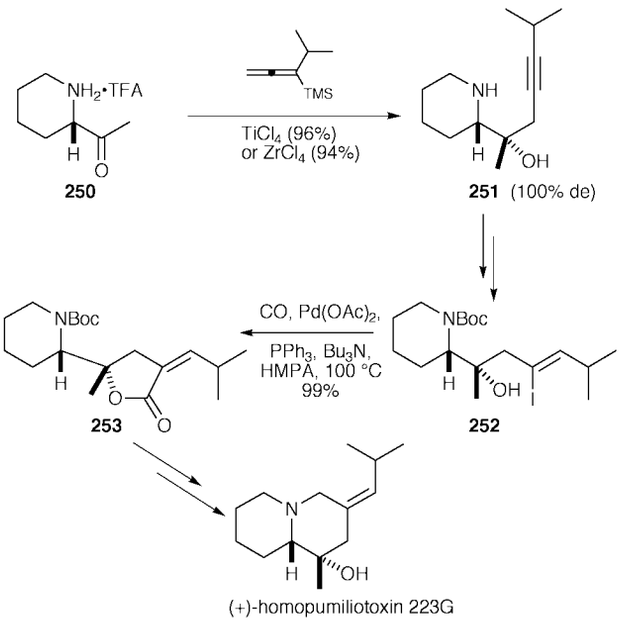
Quinolizidine 217A, one of very few quinolizidine alkaloids isolated from the skins of poisonous frogs and toads, has been synthesized by Pearson and Suga (Scheme 97).[120] Starting with azide **247** (obtained in a few straightforward steps from lactone **246**) prolonged heating gave the imine **248**, *via* [3 + 2]-cycloaddition followed by loss of nitrogen. Stereoselective reduction of **248** under conditions described by Lhommet for pyrrolidines ($PdCl_2$–$NaBH_4$) gave selectively the *cis*-2,6-disubstituted piperidine, still as a 1 : 1.3 mixture of α/β-Me epimers. Fortunately these could be separated by hydrolysis of the ethyl ester moiety to the corresponding acid, followed by crystallization. Diastereomerically pure **249** was then transformed into quinolizidine 217A, which was identical to a sample derived from natural sources.



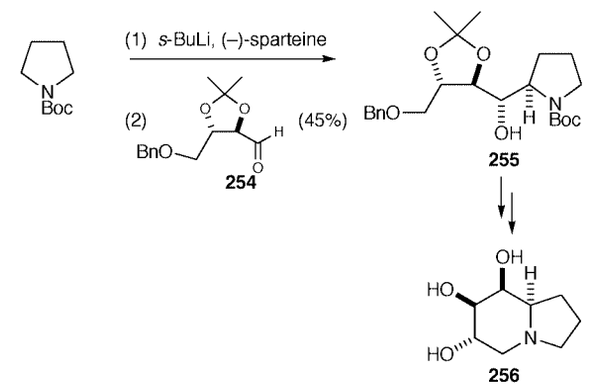
Scheme 97

The first Dendrobatid alkaloid discovered to have a quinolizidine skeleton was homopumiliotoxin 223G, synthesized recently from ketone **250** by Kibayashi and co-workers (Scheme 98).[121] The key step is the completely diastereoselective Lewis acid-catalyzed propargylation of the ketone with 1-isopropyl-1-(trimethylsilyl)allene, a reaction that proceeds in excellent yield (94% with $ZrCl_4$; 96% with $TiCl_4$). Acetylene **251** was then regioselectively stannylated and iodinated to give **252** and the remaining carbon atom introduced by Pd-catalyzed carbonylation to give lactone **253**. Deprotection, DIBAL-H mediated reduction and ring closure then furnished homopumiliotoxin 223G.

A number of syntheses of polyhydroxylated indolizidines have been reported. That by Majewski and co-workers (Scheme 99)[122] efficiently combines the traditional chiral-pool approach with more modern asymmetric synthesis. Thus, lithiation of the Boc-protected pyrrolidine under conditions originally developed by Beak and co-workers, and addition to the L-tartrate-derived aldehyde **254** gave **255** as the main component of the reaction in 45% yield. Only one other diastereomer was observed in the reaction and this was in low yield. A few trivial steps were then used to furnish the indolizidine **256**. A similar sequence of reactions with the D-tartrate-derived aldehyde *ent*-**254** gave slightly lower diastereoselectivity (ratio *ca.* 4 : 1).

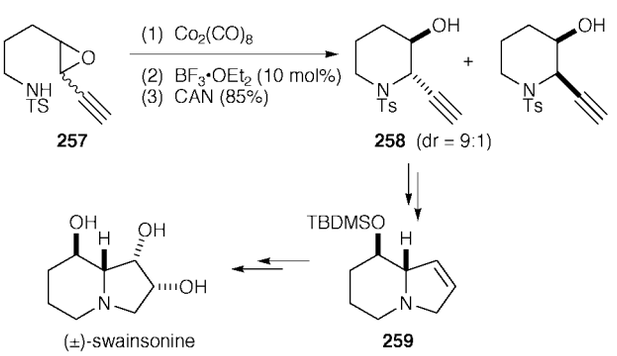


Scheme 98



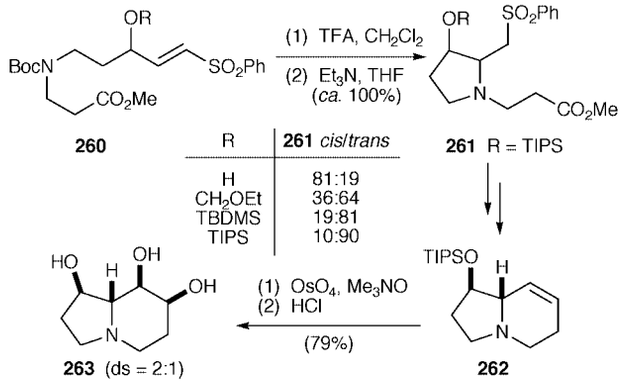
Scheme 99

In a synthesis of (±)-swainsonine, Mukai and Hanaoka and co-workers have described the exclusively 6-*endo*-selective ring closure of Co-complexed alkynes to give piperidines (**257**→**258**, Scheme 100).[123] This reaction is also highly diastereoselective, affording **258** in 85% yield (ratio = 9 : 1). Compound **258** was then transformed into **259**; dihydroxylation installed the final two stereocenters (ds = 88 : 12).



Scheme 100

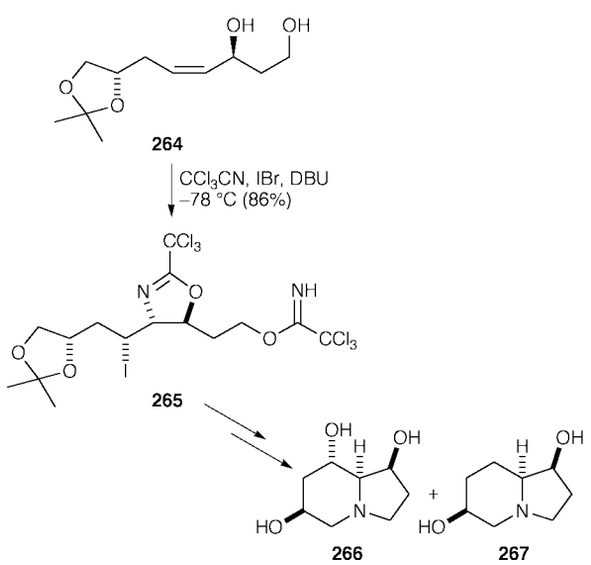
Carretero and Arrayás have described the stereoselective cyclization of γ-hydroxy-α,β-unsaturated sulfones to give pyrrolidines (**260**→**261**, Scheme 101).[124] An interesting dependence of the diastereoselectivity on the size of the protecting group was observed, with larger groups leading to an



Scheme 101

increase in the proportion of the *trans* isomer. Conventional chemical transformations then furnished the indolizidine skeleton **262** from **261**, which was further dihydroxylated to give **263**.

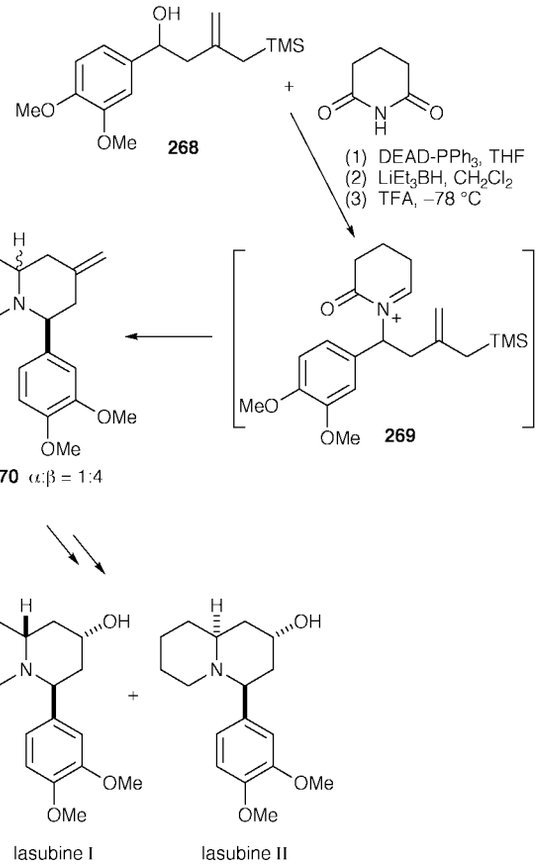
Alkene **264**, obtained from a Wittig reaction between two chiral pool-derived starting materials, was used by Kang and co-workers in a synthesis of some analogs of castanospermine (Scheme 102).[125] The key step in the synthesis was the completely stereoselective iodocyclization of an intermediate bis(trichloroacetimidate) to yield **265**. This was readily transformed into a number of polyhydroxylated indolizidines, including **266** and **267**.



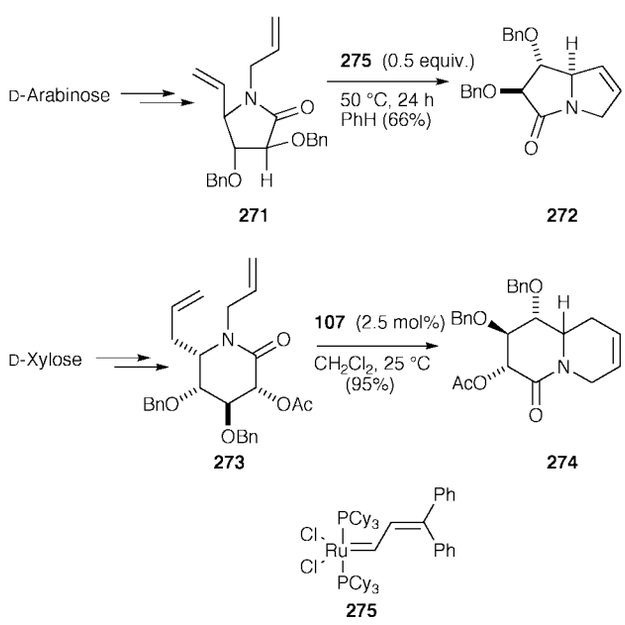
Scheme 102

The quinolizidine alkaloids lasubine I and II have been synthesized by Remuson and co-workers in both racemic and optically-active form (Scheme 103).[126,127] In the racemic series, homoallylic alcohol **268** (obtained by an indium-mediated allylsilylation reaction) was treated with glutarimide under Mitsunobu-type conditions. Reduction, and treatment with TFA led transiently to the *N*-acyliminium ion **269**, which spontaneously cyclized to give **270** as a mixture of diastereoisomers (ratio 4 : 1). These were separated and converted into the natural products.

A combination of traditional carbohydrate chemistry and the fashionable RCM reaction has been used to synthesize polyhydroxylated indolizidinones and quinolizidinones (Scheme 104).[128] Dienes **271** and **273** were obtained in multi-step sequences from D-arabinose and D-xylose respectively. RCM with either **275** or **107** gave the alkaloid frameworks **272** and **274** respectively, usefully functionalized for further manipulation, in good yield. In the case of the pyrrolizidinone **272**, up



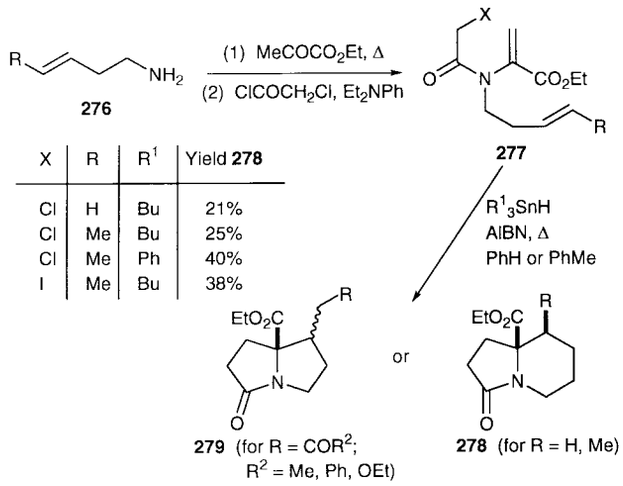
Scheme 103



Scheme 104

to 50 mol% of the catalyst was required to make the reaction go to completion, presumably a result of ring strain in the 5,5-bicyclic system.

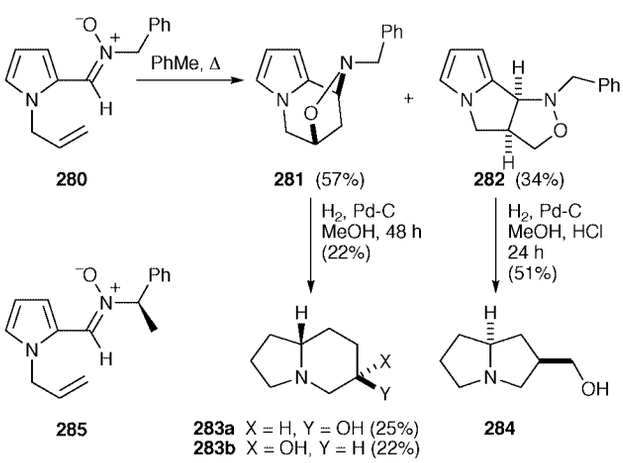
A radical cascade sequence for the synthesis of pyrrolizidinones and indolizidinones has been reported (Scheme 105).[129] Starting with homoallylic amine **276**, a two-step, one-pot double alkylation gave **277**. Treatment of **277** with AIBN–R_3SnH resulted in 5-*endo*–6-*endo* cyclization to give the indolizidinone **278** in modest yield as a single (*cis*) diastereomer. As expected, with R = COR^2 (R^2 = Me, Ph, OEt), the 5-*endo*–5-*exo* mode was observed instead giving the pyrrolizidinone skeleton



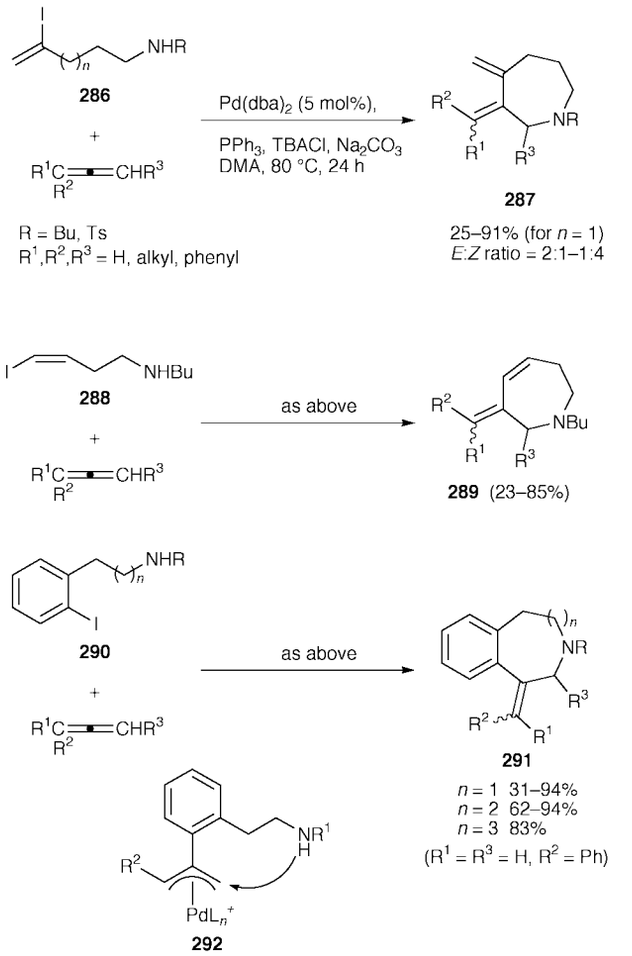
Scheme 105

279 in similar yield but as a mixture of diastereomers (*ca.* 2.5:1).

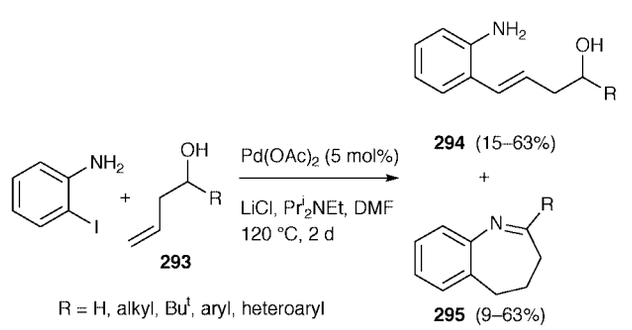
The intramolecular nitrone [3 + 2] cycloaddition reaction of **280** gives a mixture of regioisomeric products **281** and **282** (Scheme 106).[130] Exhaustive hydrogenation of these then gave the indolizidine or pyrrolizidine frameworks **283a/b** and **284** respectively, together with other pyrrole-containing intermediates. By using the nitrone **285** (derived ultimately from optically-active α-methylbenzylamine) enantiomerically-pure **283a/b** and **284** were obtained.



Scheme 106



Scheme 107



Scheme 108

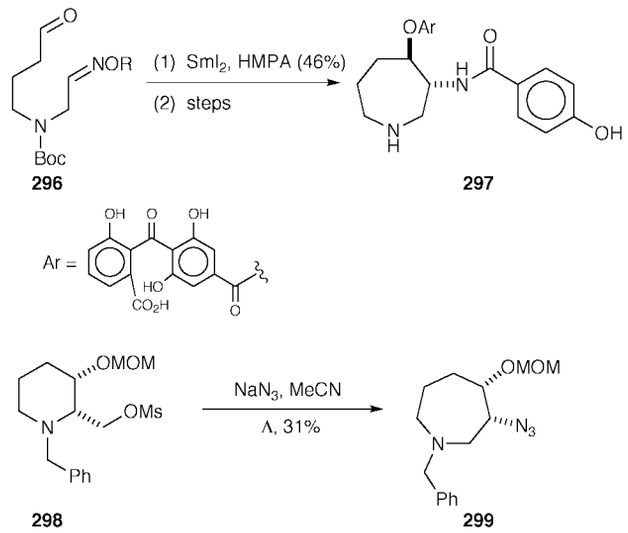
7 Medium and large rings

Larock and co-workers have described the formation of seven-, eight- and nine-membered nitrogen heterocycles by the Pd-catalyzed heteroannulation of allenes with aryl or vinylic halides bearing a remote amine functionality (**286**→**287** and **288**→**289**, Scheme 107).[131] The reaction was sensitive to all the reaction variables, but after some optimization, the best conditions were found to be $Pd(dba)_2/PPh_3/TBACl/Na_2CO_3$ in DMA for 1–3 days at 80–100 °C. The reaction is quite efficient for the formation of seven-membered rings and tolerates a range of R–R^3 substituents. For the larger ring sizes, the reaction failed with alkenyl iodides, but was successful with aryl iodides (**290**→**291**), although for the nine-membered ring, the reaction only worked with phenylallene. The reaction is thought to proceed by regioselective (but not very stereoselective) ring closure of a π-allylpalladium species, such as **292**.

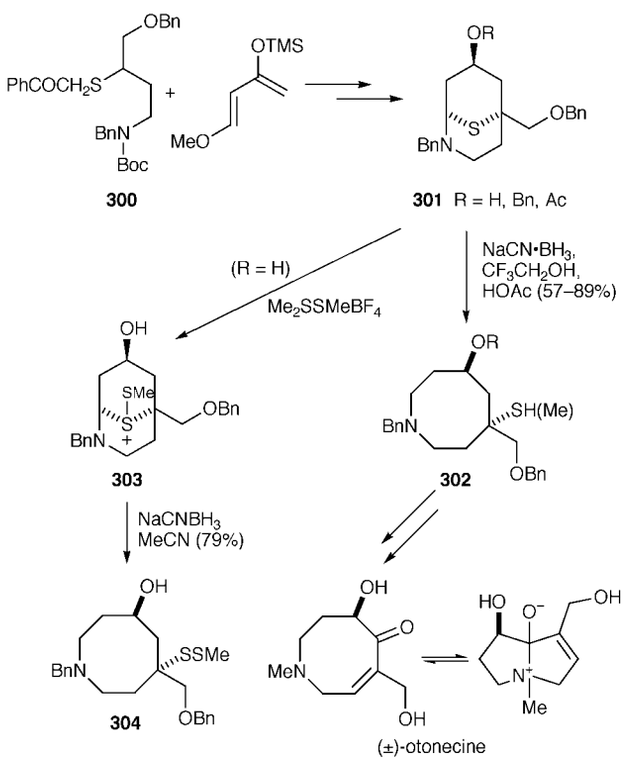
A related heteroannulation has been reported by Dyker and Markwitz (Scheme 108).[132] Treatment of 2-iodoaniline with a homoallylic alcohol **293** and a catalytic amount of palladium acetate gave a mixture of styrene **294** and 1-benzazepine **295**. The reaction was presumed to proceed through a Heck reaction, followed by dehydrative cyclization.

Naito and co-workers have reported full details of a synthesis of balanol which features a radical cyclization reaction to close the hexahydroazepine ring (**296**→**297**, Scheme 109).[133] Morie and Kato have described an approach to the same molecule using a ring expansion method (**298**→**299**).[134]

Vedejs and co-workers[135] have described a total synthesis of (±)-otonecine, a natural product that exists in two isomeric forms: an eight-membered ring form and a pyrrolizidine form (Scheme 110). The key step for the construction of the eight-membered ring was the reductive cleavage of the thioaminal **301** (derived ultimately from **300** and Danishefsky's diene) with sodium cyanoborohydride in acetic acid and trifluoroethanol. The reductive cleavage could be rendered more efficient by prior treatment of **301** with a dimethyldisulfide sulfonium salt (to generate **303**) but later removal of the sulfur moiety was less efficient from **304** than from **302**. A number of functional group



Scheme 109

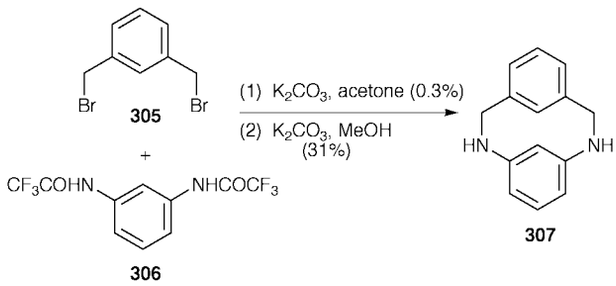


Scheme 110

interconversions were used to finally transform **302** into the natural product.

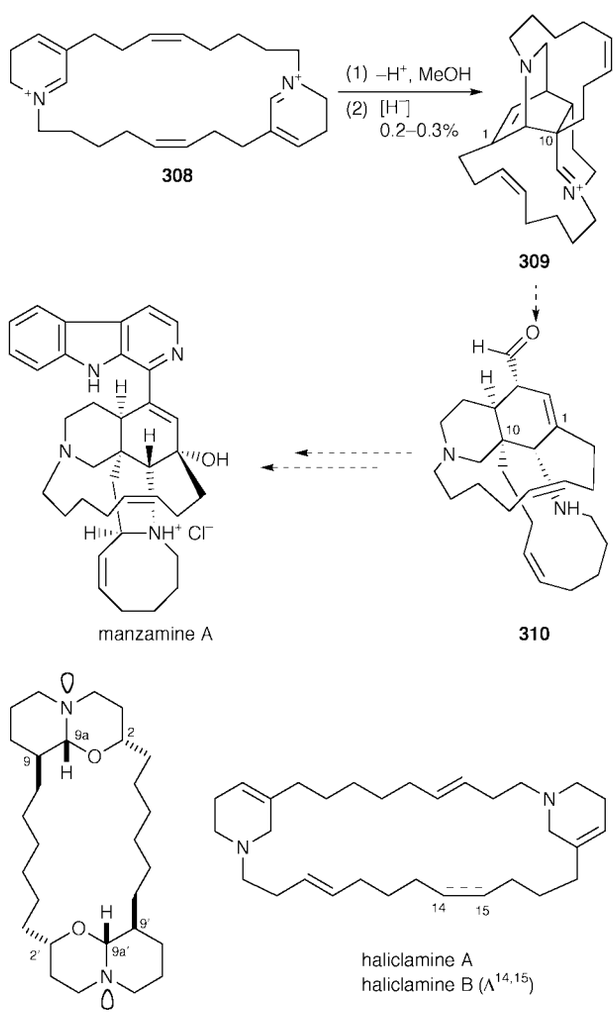
The curious ten-membered cyclophane **307** has been synthesized (admittedly in *ca*. 0.1% yield) from dibromide **305** and the *m*-phenylenediamine **306** by Vögtle and co-workers, after nearly 30 years of effort (Scheme 111).[136] Molecular mechanics calculations indicated that the strain energy present in **307** is approximately 50 kJ mol^{-1}, making it one of the most strained hetera[2.2]metacyclophanes yet made.

A timely review on the isolation and synthetic approaches to the manzamines has been published by Langlois and Magnier.[137] The first total synthesis of manzamine A, coming some twelve years after its first isolation from natural sources, has been reported by Winkler and Axten[138] in only 31 steps from commercially available starting materials. The xestospongines and haliclamines, putative biosynthetic intermediates *en route* to the manzamines, have been synthesized by Baldwin[139] and Morimoto[140] respectively. In particular, Baldwin has provided



Scheme 111

the first direct *in vitro* evidence (Scheme 112)[141] for this biosynthetic hypothesis, by observing a small (0.2–0.3%), but definite, conversion of the haliclamine analog **308** into **309**, which when mentally oxidized, hydrolyzed and redrawn gives **310**, recognizably a potential biosynthetic precursor to the manzamines. In addition, further syntheses of the ABC,[142,143] ABE[144] and ABCE[145,146] rings have been reported.

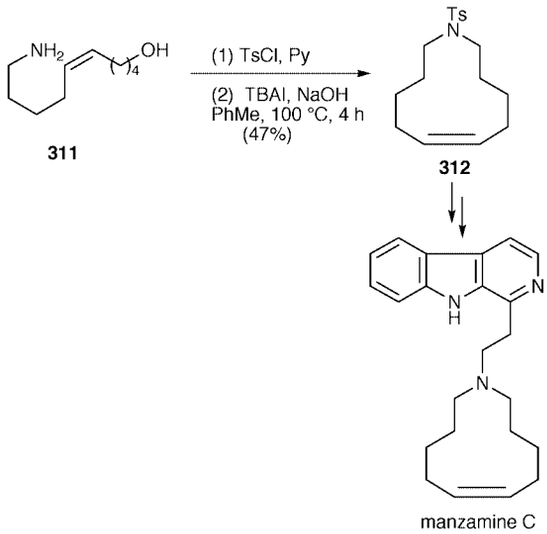


Scheme 112

The direct ring-closure to form the eleven-membered ring of manzamine C has been reported by Langlois and coworkers (Scheme 113).[147] Simply forming the ditosylate of **311**, followed by treatment with TBAI–NaOH formed the sulfonamide **312** in 47% yield, together with 3% of the 22-membered dimer and 5% of unchanged starting material. Sulfonamide **312** has previously been transformed into manzamine C.

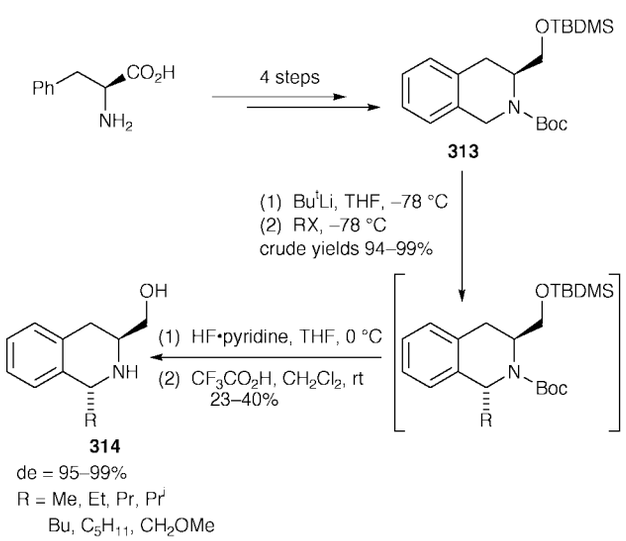
8 Tetrahydroquinolines and tetrahydroisoquinolines

New reagents for the reduction of quinolines and isoquinolines



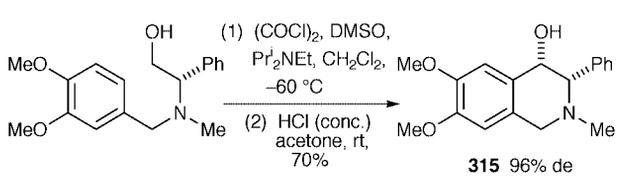
Scheme 113

to their tetrahydro analogs include indium[148] and zinc borohydride.[149] Highly diastereoselective alkylations of 3-substituted tetrahydroisoquinolines **313** have been reported (Scheme 114).[150] Crude yields in these reactions were almost quantitative, but isolation problems after deprotection were found to greatly reduce the overall yields of amino alcohols **314**.



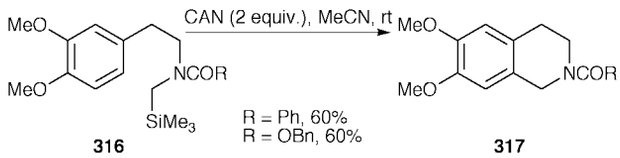
Scheme 114

High diastereoselectivity was also observed in a classical acid-catalyzed aromatic substitution to form tetrahydroisoquinoline **315** (Scheme 115).[151] In a later communication, studies on a series of analogs revealed that for diastereoselectivity, a substituent adjacent to the new stereogenic center was required.[152] Conversely, bulky substituents at C-1 of the product were detrimental to diastereoselectivity.



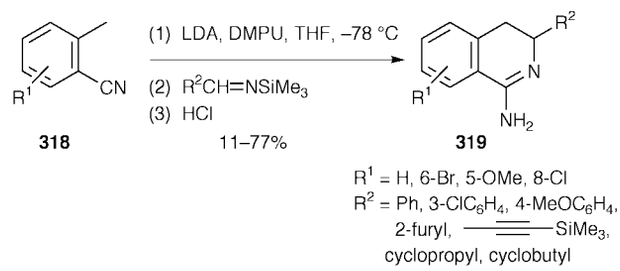
Scheme 115

An oxidative version of the Pictet–Spengler cyclization has been described.[153] CAN was used to promote the cyclization of arylethyl α-silylamides and carbamates **316**, yielding tetrahydroisoquinolines **317** (Scheme 116). The method was also applicable to the formation of 3-oxohydroisoquinolines, isoindoles and benzo- and indolohydroazepines. Lower yields were obtained for cyclization with electron-deficient aryl-substituted systems.



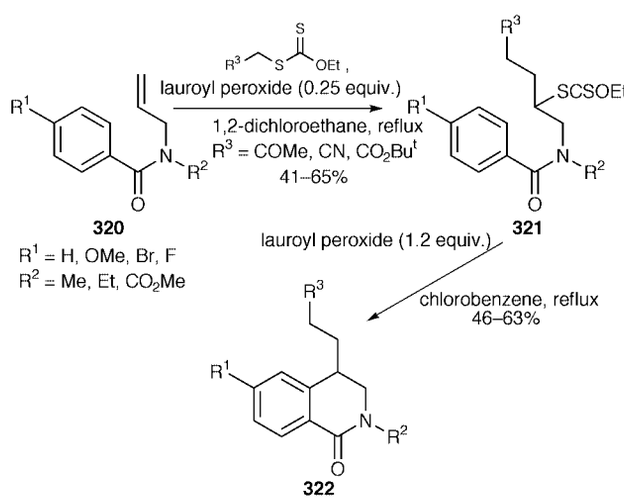
Scheme 116

A one-pot imine addition–cyclization reaction was reported for the preparation of 1-aminodihydroisoquinolines.[154] Addition of *N*-trimethylsilylimines, prepared *in situ* from aldehydes and LiHMDS, to deprotonated 2-methylbenzonitriles **318** afforded the products **319** in moderate to good yields (Scheme 117). DMPU was essential for the reaction to proceed. Yields were generally lower with the imines of electron-rich aldehydes. Enolizable aldehydes apparently failed to give imines at all.



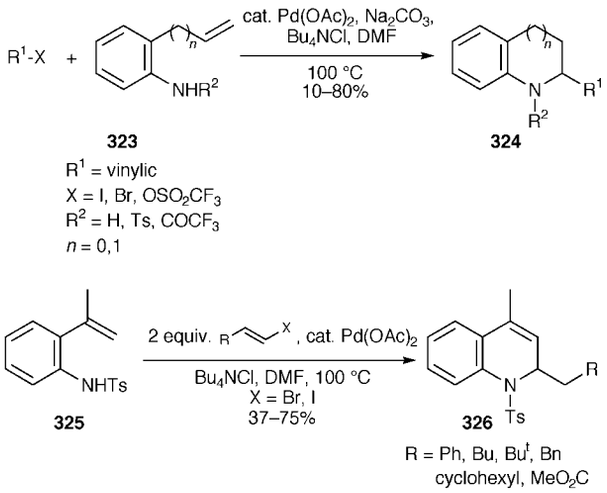
Scheme 117

Tetrahydroisoquinolin-1-ones **322** have been prepared using a radical ring closure.[155] Xanthates were added to *N*-allylbenzamides **320** in a radical chain reaction initiated with lauroyl peroxide (Scheme 118). The cyclization step then required stoichiometric amounts of the peroxide to generate the radical from the intermediates **321**, and to aromatize the intermediate cyclohexadienyl radical adduct.



Scheme 118

Larock has published papers describing the synthesis of dihydroindoles and tetrahydroquinolines **324** by palladium-catalyzed cross-coupling of alkenyl anilides **323** with vinylic halides and triflates (Scheme 119).[156,157] Although the reactions could be performed with unprotected anilines, anilides gave better yields. Tosylated anilines gave the best results with vinyl triflates, whilst *N*-trifluoroacetanilides reacted more efficiently



Scheme 119

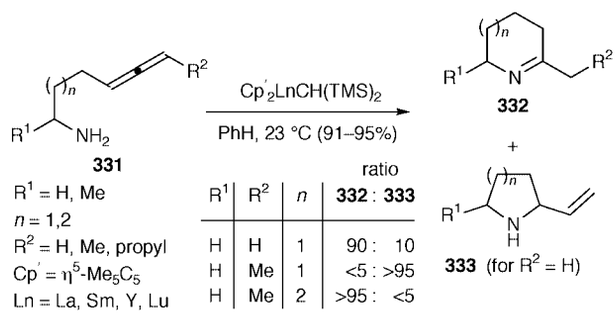
with vinyl halides. The reactions of 2-isopropenyl-*N*-tosylaniline **325** surprisingly gave some dihydroquinolines **326**, and conditions could be optimized to make this the major product.

Kiselyov developed the scope of a solid-supported three-component condensation of aldehydes, alkenes and amines for the preparation of tetrahydroisoquinolines, by immobilizing the aldehydes or the alkenes (Scheme 120).[158] 4-Methoxybenzaldehyde was tethered to Acid sensitive MEthoxy Benz-Aldehyde (AMEBA) resin (**327**), giving good yields and purities of heterocycles **328** after condensation and cleavage from the support. Alternatively alkenes **329** (prepared from 4-hydroxybenzaldehyde bound to Wang resin) could be used as the solid-supported component, giving yields and purities of products **330** comparable to the first method.

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

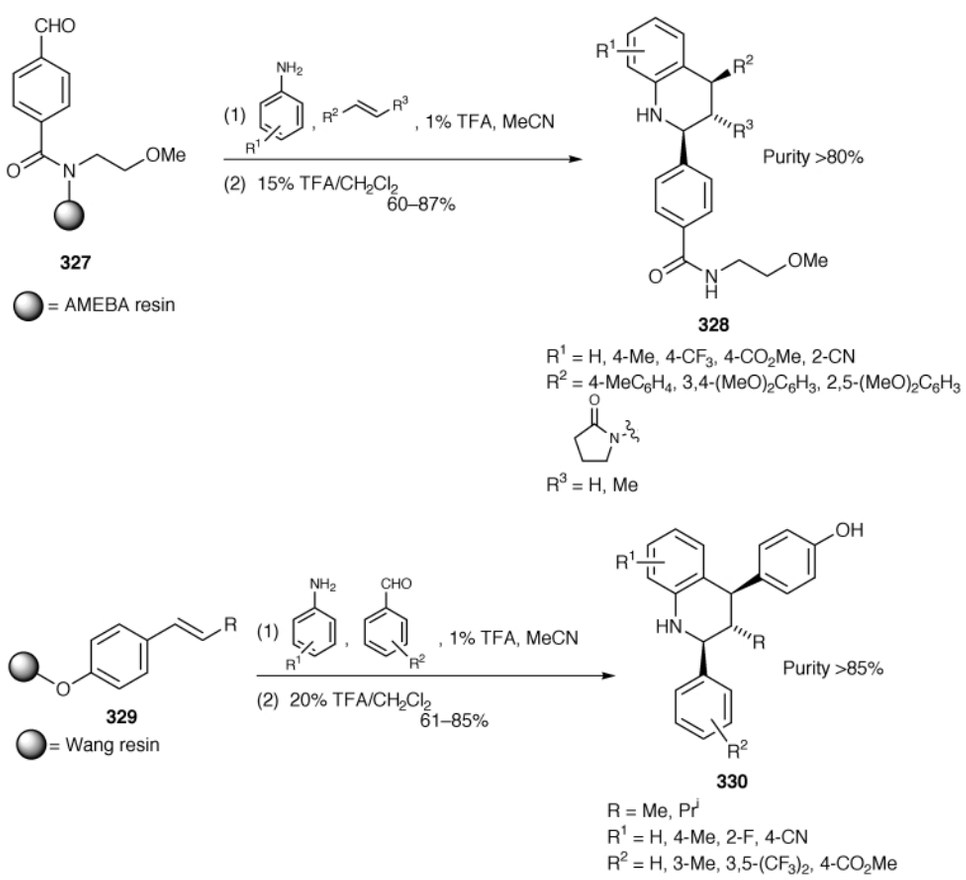
Padwa has reviewed the use of the domino cycloaddition–*N*-acyliminium ion cyclization cascade for the synthesis of nitrogen heterocycles.[159] Müller and Beller have reviewed the metal-mediated hydroamination route to synthesize cyclic amines.[160]

Marks and co-workers have described the organolanthanide-mediated intramolecular hydroamination reaction of amino-allenes for the synthesis of pyrrolidines and piperidines (**331**→**332** + **333**, Scheme 121).[161] With 1,3-disubstituted aminoallenes **331** ($R^2 \neq H$) the cyclization proceeds in a highly regioselective 5- or 6-*endo*-*trig* fashion to give pyrrolidines ($n = 1$) or piperidines ($n = 2$) respectively. With monosubstituted allenes, the ring closure was slightly less regioselective. Full details of the use of these organolanthanide catalysts in the formation of pyrrolizidine and indolizidine skeletons have also been reported, together with mechanistic investigations.[162]

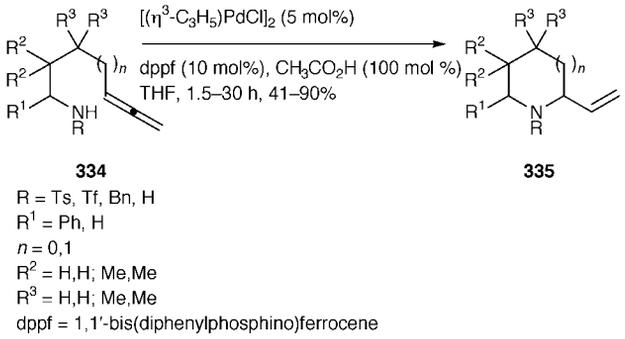


Scheme 121

A similar intramolecular hydroamination of aminoallenes has been reported by Yamamoto and Meguro (**334**→**335**, Scheme 122).[163] In this case, the catalyst is $[\eta_3\text{-}(C_3H_5)PdCl]_2$–



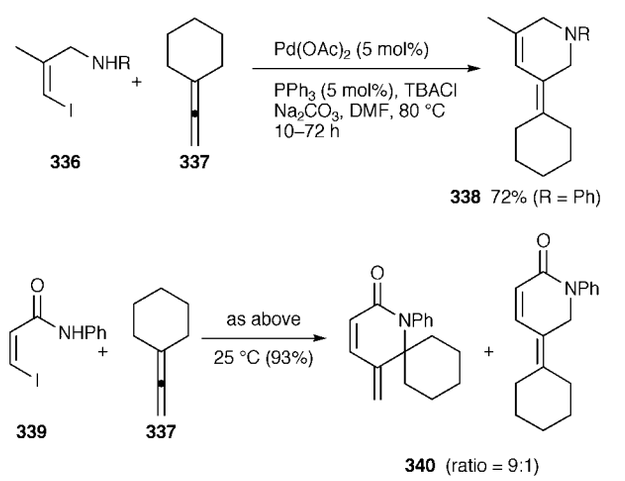
Scheme 120



Scheme 122

dppf. In the presence of acetic acid, the reaction was much quicker and a greater yield was obtained.

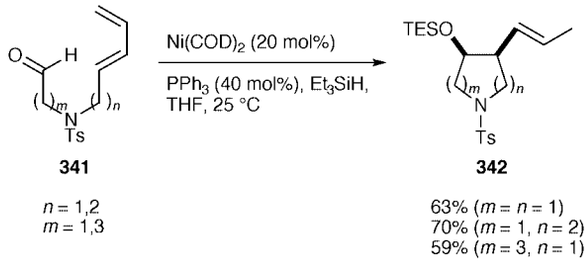
Larock and co-workers have described a palladium(0)-catalyzed heteroannulation reaction between vinyl iodides and allenes to form nitrogen heterocycles (**336/339→338/340**, Scheme 123).[164] For example, treatment of **336** with $Pd(OAc)_2$/PPh_3/TBACl/Na_2CO_3 and an excess of the allene **337** led to **338** in 72% yield (R = Ph) as a single regioisomer. The reaction was demonstrated with a range of allenes of different substitution patterns. In contrast, the amide **339**, under the same conditions gave predominantly the opposite regiochemistry. Pyrrolidines can also be obtained by using the appropriate vinyl iodide, although the yields are lower.



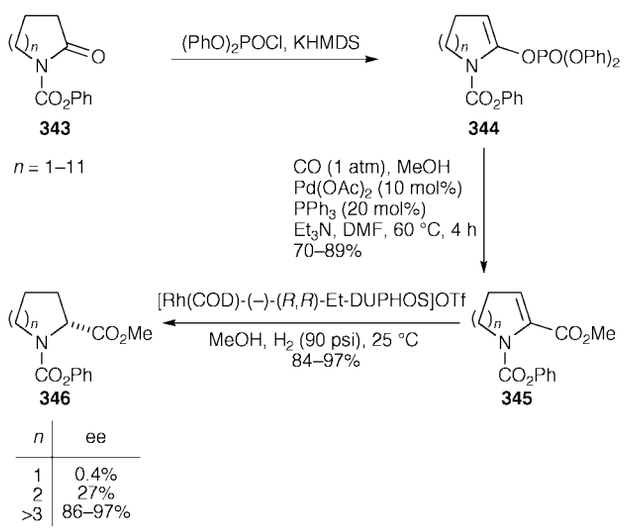
Scheme 123

The nickel-catalyzed cyclization of amines bearing a 1,3-diene and an aldehyde to give five-, six- and seven-membered cyclic amines has been reported (**341→342**, Scheme 124).[165] The key step in the reaction involves the use of $Ni(COD)_2$, PPh_3 and triethylsilane to generate a catalytically active NiH complex, an improvement over an earlier procedure that used stoichiometric quantities of $Ni(acac)_2$ and DIBAL-H. The ring closure was diastereoselective for the formation of the five- and six-membered rings, but gave an approximate 2:1 mixture for the seven-membered ring. This reaction was also successful for the synthesis of the pyrrolizidine and indolizidine ring systems.

Nicolaou and co-workers have described a high-yielding, asymmetric route to cyclic amino acids (Scheme 125).[166] Starting with the protected lactam **343**, enolization and trapping with diphenyl chlorophosphate generated the enol phosphate **344**. Enol phosphates exhibit similar reactivity to enol triflates, undergoing a range of Pd(0)- and Ni(0)-catalyzed reactions, but have the advantage of being rather more stable. Carbonylation and asymmetric hydrogenation (**345→346**) then generated the protected cyclic amino acids in excellent yield and generally good enantiomeric excess, except for the five- and six-



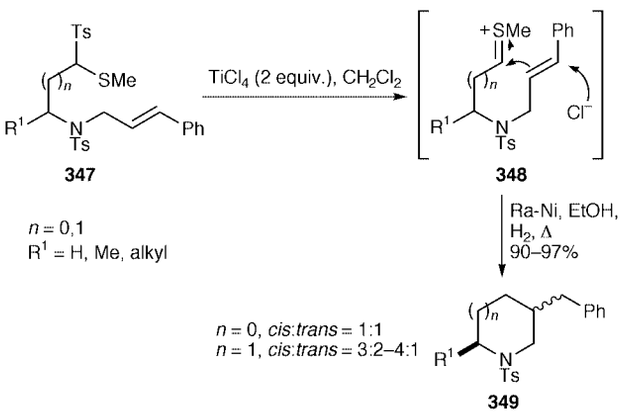
Scheme 124



Scheme 125

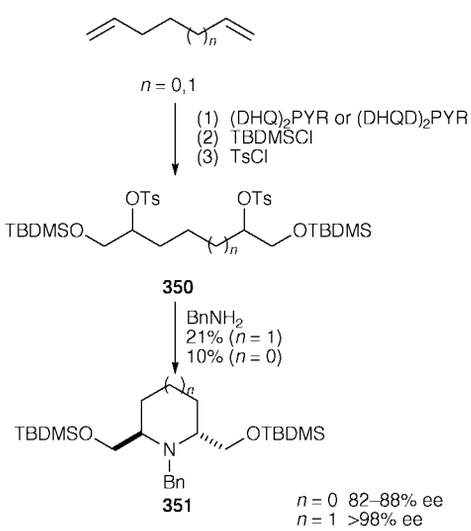
membered rings, where it was much lower (0.4% and 27% respectively).

The thionium ion-mediated cyclization of appropriately substituted dithioacetal *S*,*S*-dioxides (*e.g.* **347**, Scheme 126) to form piperidines and pyrrolidines has been described by Craig and co-workers.[167] Treatment of **347** with titanium tetrachloride at room temperature led to thionium ion **348** (by loss of toluene-*p*-sulfinate) which then cyclized in a non-selective fashion to give a complex mixture of isomeric piperidines. Reduction with Raney nickel simplified the mixture somewhat giving the pyrrolidine **349** ($n = 0$) or the piperidine ($n = 1$), as mixtures of isomers.



Scheme 126

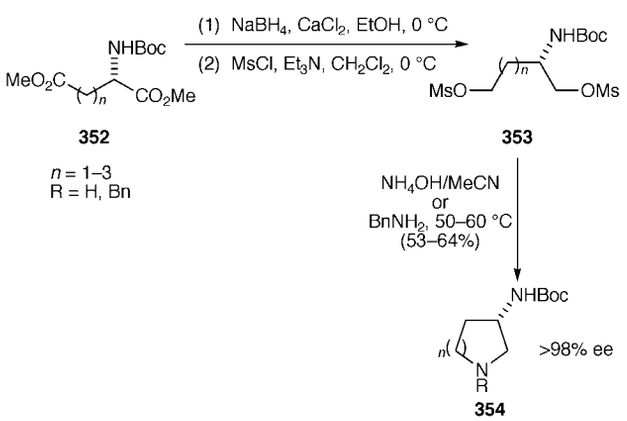
Momose and co-workers have described a synthesis of C_2-symmetric *trans*-α,α′-bis(hydroxymethyl)-pyrrolidine and -piperidines by application of the Sharpless AD reaction (Scheme 127).[168] Starting with either hexa-1,5-diene or hepta-1,6-diene, AD (with the PYR family of ligands), followed by selective silylation and tosylation gave the functionalized tetraol



Scheme 127

350. Finally, cyclization was effected with benzylamine to give **351** ($n = 0$, 1) in modest overall yield and enantiomeric excess.

The practical and large-scale synthesis of 3-amino five-, six- and seven-membered cyclic amines has been reported by Moon and Lee (Scheme 128).[169] Starting with a commercially available protected amino acid **352**, reduction and mesylation afforded **353**, which cyclized in the presence of ammonia or benzylamine to give **354** (R = H, Bn respectively) in excellent overall yield and without any detectable racemization.



Scheme 128

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