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Synthesis of piperidines

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1. Introduction

Functionalised piperidines are among the most common building blocks in natural products, and, more interestingly, in many biologically active compounds such as anopterine, pergoline, scopolamine and morphine (Fig. 1). The syntheses of these types of compounds have been studied extensively as the development of new drugs containing six-membered ring heterocycles becomes more and more common.

Previous syntheses of piperidines have been focused on the diastereoselectivity in the formation of 2,6-piperidines. In order that these compounds could be used as drugs, it was necessary to investigate their stereoselective syntheses. Detailed reviews on the syntheses of 2,6-piperidines can be found in the literature.[1,2]

A new aim in the synthesis of piperidines is to make multisubstituted piperidines. The formation of 3-, 4- and/or 5-substituted piperidines and simple piperidines containing quaternary carbon centres is the next challenge. The first step in this long process is to extend the diastereoselective synthesis to tri- or multisubstituted piperidines, followed by the development of new methodology to synthesise them stereoselectively.

This report will try to give a general overview of the synthetic methodology available for the diastereoselective and stereoselective formation of piperidines. The synthesis of 3-, 4- and/or 5-substituted piperidines, as well as the formation of piperidines containing quaternary carbons, will be mainly examined. Their synthesis via cycloaddition is the most common and more reliable method. This strategy is often used as the final step after the construction of a linear chain containing all the functionality of the final compound. The reduction of pyridines is another method usually used in the synthesis of piperidines. This approach becomes limited, however, when a quaternary carbon is present in the piperidine ring. The syntheses of piperidines using rearrangements and ring expansions has also been studied, but this strategy is a less common method and is more often used in particular cases than as a general method.

2. Heterocycle construction

The construction of heterocycles via cycloaddition is

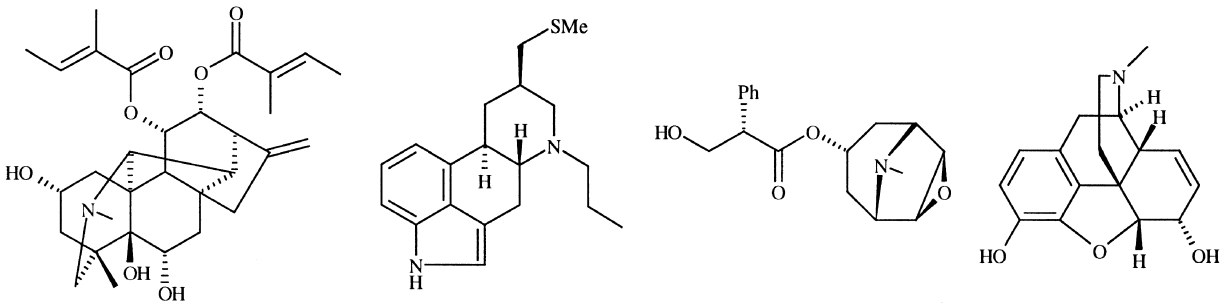
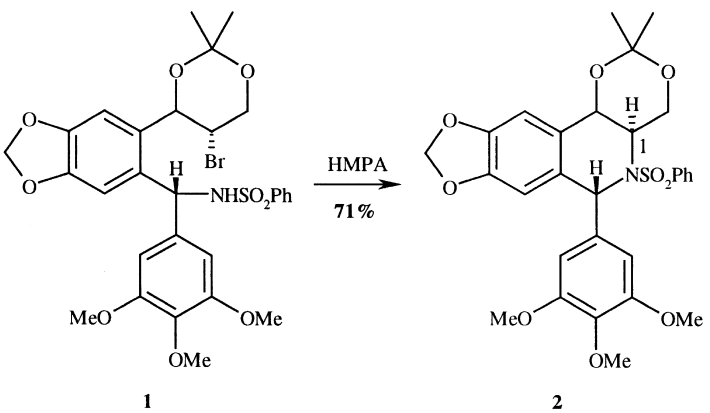
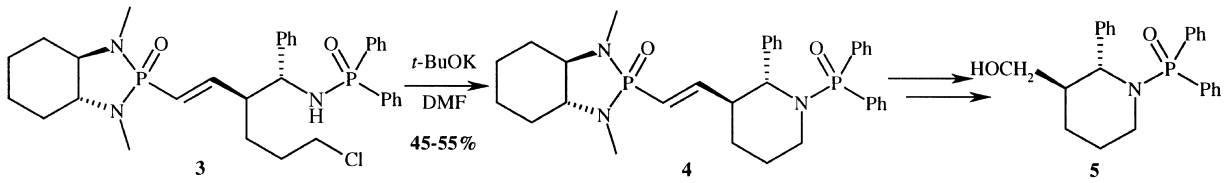


Figure 1.



Scheme 1.



Scheme 2.

probably the most widely used strategy to form piperidines. This approach is diverse and includes simple nucleophilic substitutions, reductive amination, metathesis, aldol reactions, Dieckmann condensations and ene reactions.

2.1. Nucleophilic substitution

2.1.1. Reaction of amines with halides. Nucleophilic substitution is a reliable method of making piperidines and relies on the synthesis of a linear chain which already contains the desired substitution pattern. It is often used as the final step, followed by deprotection of the functional groups, if necessary. Compernolle et al.[3] realised the displacement of a 6-bromide group by a 2-amino group as the main strategy in the formation of polyhydroxylated piperidines using Et_3N as the base. Stronger bases such as sodium hydride can be used for this type of ring closure. Nevertheless, it can be a problem when a tertiary bromide such as **1** is cyclised (Scheme 1). In the synthesis of analogues of podophyllotoxin, Pearce and co-workers[4] observed the formation of two stereoisomers at C-1 when sodium hydride was used as the base. The use of 2 equiv. of HMPA resulted in a longer reaction time, but only the desired stereoisomer **2** was produced in 71% yield.

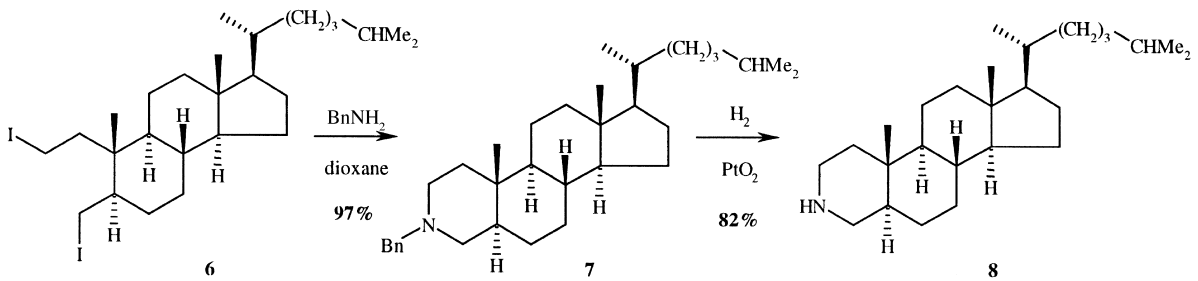
The chloride **3** has been used by Hanessian et al.[5] in the synthesis of enantiomerically pure 2,3-piperidines (Scheme 2). Ring-closure using *tert*-BuOK as the base afforded the piperidine **4** in 45–55% yield. Despite the modest yield, the formation of enantiomerically pure 2,3-piperidines is overall quite effective. Oxidative cleavage, followed by reduction, afforded the target compound **5** in 62% yield.

Cyclisation can also be achieved from a cyano-chloride or -bromide. When Fustero and co-workers[6] added an azaenolate to a cyano-chloride, the resulting iminium anion intermediate cyclised to the corresponding piperidine. Substitution in position 2 and cyclisation occurred in a one-pot procedure.

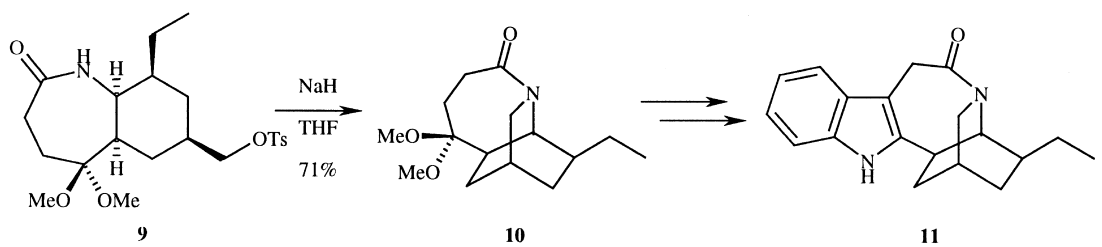
Suginome et al.[7] synthesised 3-aza-5α-cholestane **8** using a bi-molecular reaction rather than an intramolecular cyclisation (Scheme 3). The reaction of benzylamine with the diiodo compound **6** in dioxane afforded the desired piperidine **7** in 97% yield. Deprotection of the amine gave the desired product **8**. The reaction conditions are quite harsh and often require reflux overnight and a large excess of amine. When volatile amines, such as isopropylamine, are used, the reactions are less effective (52% when coupled with **6**) and need to be carried out in a sealed test tube. Mellor and co-workers[8] observed similar yields when starting from a dibromo compound.

The main difficulty of this type of cyclisation compared to the intramolecular nucleophilic substitution is the choice of the correct concentration of reagents. A too dilute reaction mixture gives a slow reaction and, if the reaction mixture is too concentrated or the intramolecular nucleophilic substitution is too slow, polymerisation can occur.

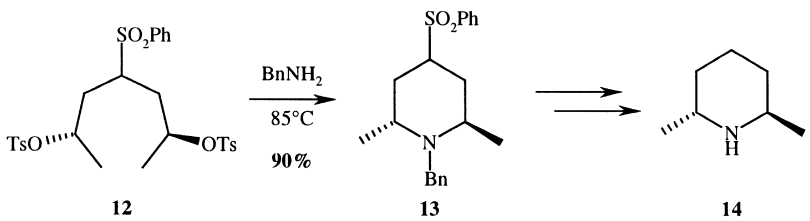
2.1.2. Reaction of amines with acetates and mesylates. Rather than achieving a 6-halogeno displacement by a 2-amino group, it is more common to form a good leaving group such as an acetate[9] or a mesylate from a hydroxy group. Most commonly, mesylates or tosylates are used as



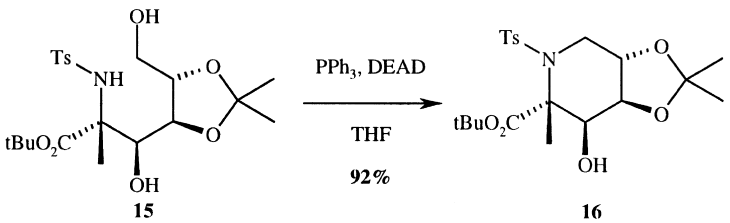
Scheme 3.



Scheme 4.



Scheme 5.



Scheme 6.

the leaving groups to form piperidines via intramolecular cycloaddition. In the synthesis of (−)-ibogamine **11**, White et al.[10] cyclised the amino-tosylate **9** to give the target compound **10** in 71% yield (Scheme 4).

Tertiary mesylates or triflates can also be used and the piperidines are formed with inversion of configuration. Fleet and co-workers[11] demonstrated that polyhydroxy-piperidines can be synthesised from amino-triflates in good yield using sodium acetate in a protic solvent such as ethanol. Holzapfel et al.[12] worked on similar compounds and showed that cyclisation can occur in aprotic solvents without base (e.g., THF, reflux).

Reaction of bis-tosylates with primary amines is also known in the literature and is more common from bis-mesylates/tosylates than halogens. Kurth and co-workers[13] cyclised the bis-tosylate **12** using an excess of benzylamine at 85 °C (Scheme 5). The reaction occurred in 90% yield and gave only the *anti* piperidine **13**.

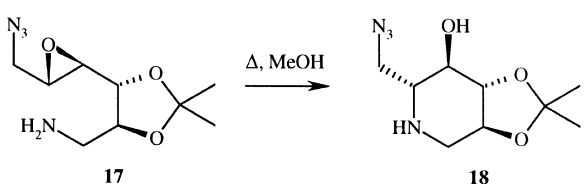
Cyclisation with tosylamine is also known in the literature,[14] but is less common due to its lower reactivity. Finally, coupling with ammonia is possible, but a high pressure is required, as demonstrated by Quallich et al.[15] Reaction with ammonia avoids further steps, such as deprotection, when preparing secondary amines.

2.1.3. Reaction of amines with alcohols. Cyclisation to piperidines can be achieved directly from alcohols. Although, this reaction is less commonly used, it can give very good yields and avoids extra steps such as the formation of halide or mesylate. Kazmaier and co-workers[16] cyclised the *N*-tosylamino alcohol **15** to the desired amine **16** in 92% yield under Mitsunobu conditions (PPh_3, DEAD, THF), (Scheme 6). Cyclisation of the secondary alcohol to give an aziridine did not occur and the desired piperidine **16** was formed as the only reaction product.

When a primary alcohol and an acetate group are present in the same molecule, cyclisation under Mitsunobu conditions only affords the desired piperidine.

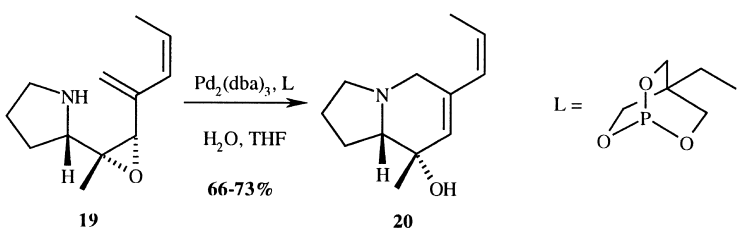
The synthesis of β-lactams using this strategy is more difficult. Ikegami et al.[17] have found that, under Mitsunobu reaction conditions, O-alkylation occurred, rather than N-alkylation.

2.1.4. Reaction of amines with three-membered rings. A very efficient method of forming 3-hydroxypiperidines involves epoxide-opening and subsequent cyclisation. Compernolle and co-workers[18] have used this strategy to prepare the polyhydroxy-piperidine intermediate **18** by refluxing a solution of the primary amino-epoxide **17** in methanol (Scheme 7).

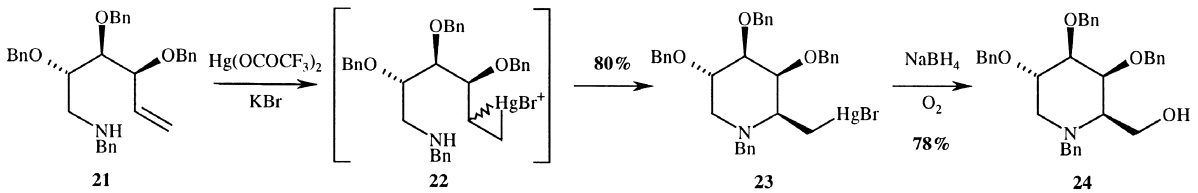


Scheme 7.

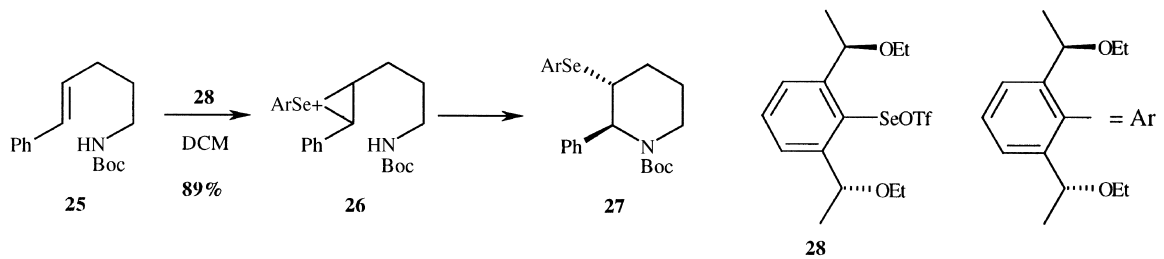
In an approach to catharanthine, Trost et al.[19] used the



Scheme 8.



Scheme 9.



Scheme 10.

formation of a π-allylpalladium intermediate derived from an amino-epoxide. This strategy became more interesting when Trost et al.[20] cyclised the amino-epoxide **19** via a palladium-catalysed reaction equivalent to a '1,4 addition' to the vinyl epoxide **19** (Scheme 8). After optimisation of the palladium catalyst, Trost's group synthesised the indolizidine **20** in 66–73% yield.

D'Angelo and co-workers[21] converted an azido-epoxide to a hydroxypiperidine via a one-step reduction and cyclisation using a Staudinger reduction reaction (PPh_3, THF). Although amines protected with electron-withdrawing groups are less reactive, they can be cyclised under basic conditions.[22] Less commonly, the cyclisation of a bis-aziridine or amino-aziridine can be achieved, this strategy mimicking carbohydrate synthesis.[23]

In a synthesis of aza-analogues of D-galacturonic acid, Ganem et al.[24] used oxymercuration followed by reductive oxygenation of the mercuric salt, to form the 2-hydroxymethylpiperidine **24** (Scheme 9). Treatment of the amino-alkene **21** with mercuric trifluoroacetate and KBr gave the mercuric cation **22**, which immediately cyclised to the piperidine **23** in 80% yield. Reduction of the resulting mercuric intermediate with $NaBH_4$ and O_2 afforded **24** as a single diastereoisomer in 78% yield. Although oxymercuration is a reliable synthetic tool, it is not commonly used, because of its toxicity.

Among the few asymmetric syntheses of piperidines, the method developed by Déziel and co-workers[25] is useful (Scheme 10). The aminoalkene **25** was cyclised in the presence of the chiral arylselenium triflate **28** to give the diastereomerically pure piperidine **27** in 89% yield and 92% ee. The reaction proceeds via an arylselenium cationic intermediate **26**. The resulting selenide can then be reduced, using Ph_3SnH and AIBN, in good yield.

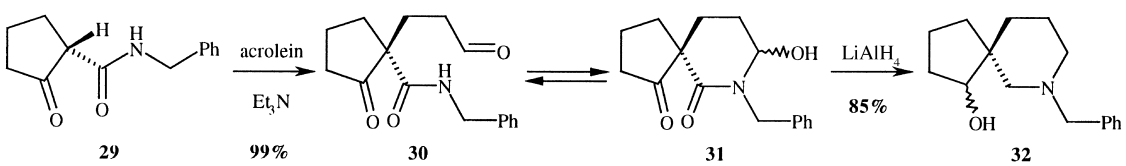
2.2. Reductive amination

One of the most common methods for the synthesis of piperidines, if not the mostly widely used, is reductive amination. Indeed, piperidines can be synthesised from 1,5-amino-aldehydes in a one-pot procedure in the case of secondary amines or a two-pot procedure for primary amines. The two-step process involves the formation of an imine intermediate, followed by its reduction.

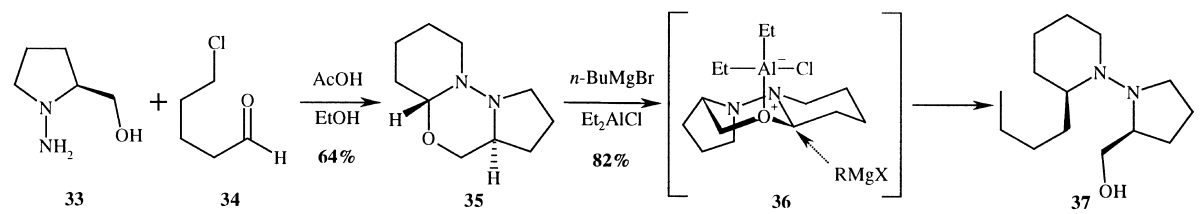
2.2.1. Intramolecular reductive amination. Primary and secondary amino-aldehydes are not highly stable. In most cases, storage leads to mixture of aminals resulting from intramolecular addition of the amine to the formyl function. Reduction of this mixture can afford the secondary amine. Urban et al.[26] achieved the conjugate addition of the β-keto-amide **29** with acrolein to afford the desired aldehyde **30** in 99% yield (Scheme 11). These workers found, however, that complete conversion of **30** to a mixture of aminals **31** occurred on storage over several hours. Reduction of the amino-aldehyde **30** or the aminals **31** with $LiAlH_4$ resulted in a reductive cyclisation, yielding the racemic alcohol **32**.

Other reducing agents such as $NaCNBH_3$ can be used to reduce the aminal or the imine.[27] Moreover, reductive amination can occur during reductive deprotection of tertiary amines.[28]

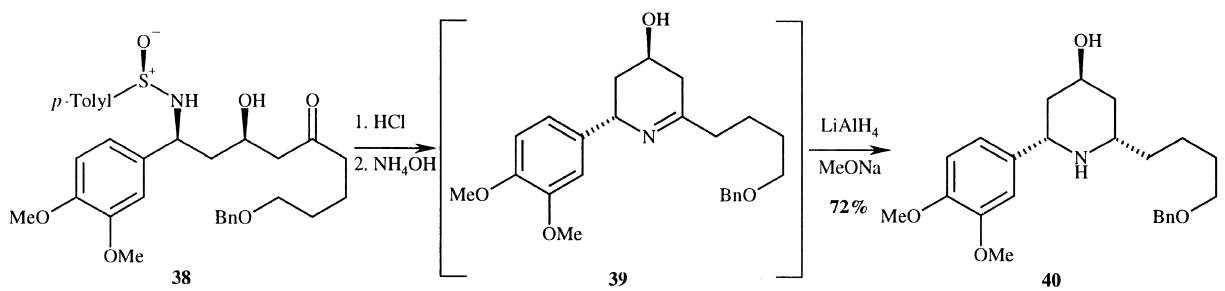
If the imine or an equivalent intermediate can be formed and isolated, addition of organometallics to the 2,3,4,5-tetra-hydropyridine can be completed. Among the enantioselective syntheses of piperidines, the methodology developed by



Scheme 11.



Scheme 12.



Scheme 13.

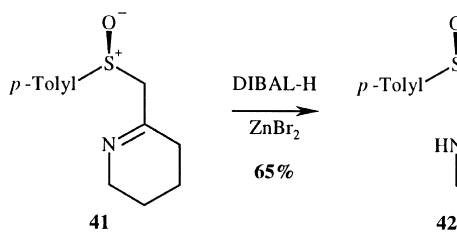
Kibayashi and co-workers[29] is probably the most efficient to synthesise 2-substituted piperidines enantioselectively. When (2*S*)-1-amino-2-pyrrolidinemethanol **33** was refluxed with 5-chloropentanal **34** in acetic acid and ethanol, 1,3,4-oxadiazinane **35** was formed as a single diastereoisomer (Scheme 12). In the presence of a Lewis acid such as Et_2AlCl, **35** exists as the oxonium salt **36**. At low temperature (−80 to −90 °C), the addition of Grignard reagents can occur with good diastereoselectivity (64–98% de). The reaction is believed to occur via an S_N2 process, explaining the good diastereoselectivity and the inversion of configuration at C-2. Using this methodology, **37** was obtained in 82% yield and 98% de. Reductive N–N bond cleavage can easily be achieved using borane in THF, yielding (+)-coniine in 64% yield.

Reductive amination can also be performed with amino-ketones. The usual reduction of the imine intermediate should give a mixture of diastereoisomers. This strategy therefore needs to be complemented with a stereoselective reduction of the imine or needs to be controlled by the formation of the most stable piperidine. This method is very common for preparing *syn* 2,6-piperidines, as the reduction of the 2,6-dialkyl-2,3,4,5-tetrahydropyridine gives the *syn* product. When Davis et al.[30] deprotected the sulphinamide **38**, followed by direct reduction of the imine intermediate **39** with $LiAlH_4$/MeONa, the desired *syn* 2,6-piperidine **40** was obtained in 72% yield (Scheme 13).

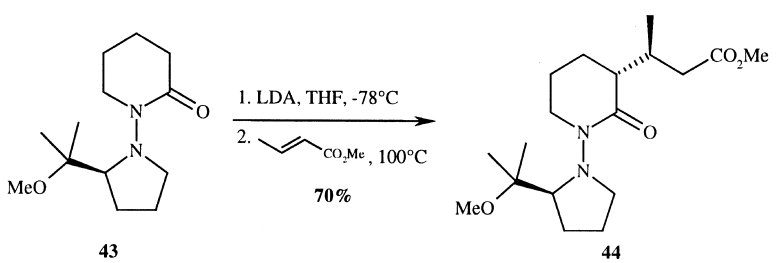
If the diastereoselectivity of the reduction is not satisfactory, a chiral sulphoxide can be used. Ruano et al.[31] developed a stereoselective reduction of α-sulphinyl imines and this methodology can be applied to the synthesis of chiral piperidines. The α-sulphinyl 2,3,4,5-tetrahydropyridine **41** was selectively reduced to the piperidine **42** (65% yield) using DIBAL-H in the presence of $ZnBr_2$ (Scheme 14).

1,5-Amino-esters or acids can be isolated, but undergo rapid cyclisation to lactams under acidic conditions. This can be a good method for forming piperidinones.[32] Moreover, cyclisation can occur when primary or secondary amino-esters are formed. Indeed, reductive hydrogenation of a nitroester by Sas and co-workers[33] afforded the corresponding cyclised piperidinone.

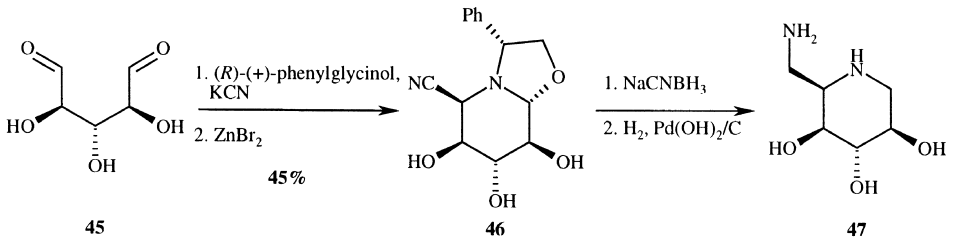
Piperidinones can also be synthesised from an amino-cyanide under acidic conditions. The main problem with this type of cyclisation is the vigorous conditions required that do not tolerate many protecting groups. A saturated solution of HCl in MeOH/H_2O (99:1) was required by



Scheme 14.



Scheme 15.



Scheme 16.

Gmeiner et al.[34] to be able to afford the desired piperidinone in their synthesis of dopamine D_2 receptor agonists.

The advantage of piperidinones is the possibility of functionalisation α to the carbonyl using standard chemistry. Horenstein and co-workers[35] and Yu et al.[36] have used this strategy to synthesise 3,4-di- and 3,4,5-trisubstituted piperidines. Enders and co-workers[37] have been working on the stereoselective synthesis of 3-substituted piperidin-2-ones using a chiral pool strategy. Treatment of the chiral piperidinone **43** with LDA, followed by a Michael electrophile, but-3-enoic acid methyl ester, afforded the piperidinone **44** in 70% yield and 96% ee (Scheme 15).

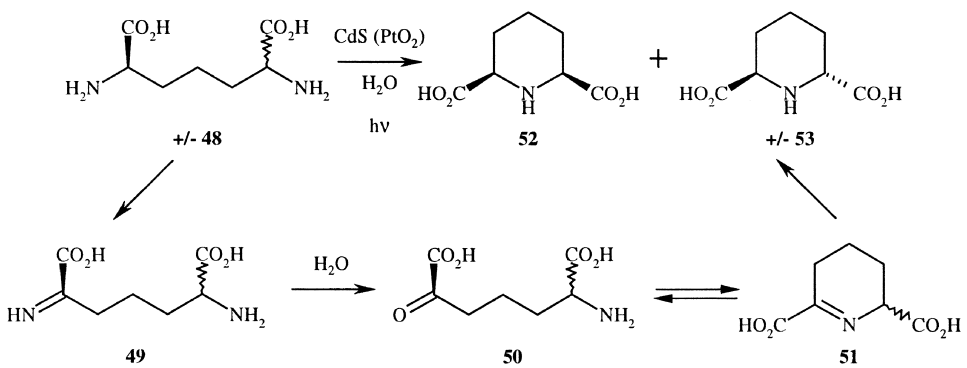
If piperidines are required, piperidinones can be reduced to the desired piperidines with $LiAlH_4$,[38] but problems can be encountered and milder conditions must then be used. In their synthesis of strychnine, Magnus and co-workers[39] reduced a piperidinone in the presence of an ester and an acetal-protected ketone using borane. Nagase et al.[40] reduced a piperidinone to the corresponding enamine using DIBAL-H and treatment with $NaCNBH_3$ afforded the desired piperidine in good yield.

2.2.2. Intermolecular reductive amination. Intermolecular reductive amination can be very useful in the stereoselective synthesis of 3,4,5-trisubstituted piperidines. Husson and co-workers[41] prepared the dialdehyde **45** from the commercially available isopropylidene-α-D-glucofuranose in two steps (Scheme 16). Reaction with (*R*)-(+)-phenylglycinol in the presence of KCN, followed by treatment with $ZnBr_2$, afforded the piperidine **46** in 45% yield. The chirality at the C-2 stereogenic centre is the result of a 1,3-transfer of chirality from the phenyl substituent involving the addition of CN^- from the upper face of the piperidinium chair transition state. Reductive cleavage of the chiral pool component using $NaCNBH_3$ or alane (AlH_3), followed by catalytic hydrogenation with $Pd(OH)_2/C$, afforded the piperidine **47**.[42]

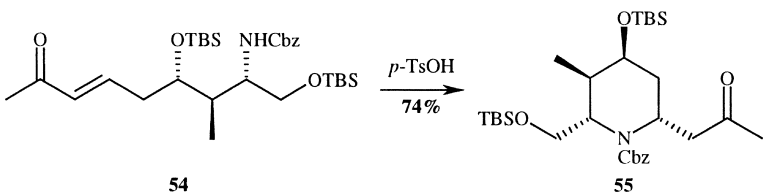
Martin et al.[43] have employed a double reductive amination of a bis-ketone to synthesise piperidines. Reduction of the imine intermediate took place with high diastereoselectivity. The selectivity of the reduction is generally controlled by the formation of the most stable piperidine.

2.2.3. Reaction of bis-amines. Ohtani and co-workers[44] have shown that diamines can undergo photocatalytic deaminocyclisation in a very effective manner. The *syn* or *anti* 2,6-dicarboxylic acid piperidines **52** and **53** can be synthesised from 2,6-diaminopimelic acid (DAP) **48** (1:1:2: (*S*,*R*)/(*R*,*S*)/*meso*). Although photocatalytic deamination with TiO_2 gave the *syn* piperidine **52** as well as a racemic mixture of pipecolinic acid (piperidine-2-carboxylic acid), a negligible amount of the *anti* piperidine **53** was observed (Scheme 17). On the other hand, when CdS (cadmium(II) sulphide) was used in aqueous media, the formation of the *syn* piperidine **52** or the racemic *anti* piperidine **53** could be achieved. When CdS was pre-heated to 300 °C, the racemic *anti* piperidine **53** was mainly formed in 39% yield, along with 48% recovery of the *meso* starting material. When PtO_2-loaded CdS was pre-heated to 300 °C, the *syn* piperidine **52** was mainly formed in 33% yield, with 50% recovery of the *meso* starting material. Although the yields of the *syn* piperidine **52** and the *anti* piperidine **53** were quite low, this was a major improvement, as they are very difficult intermediates to synthesise diastereoselectively. Moreover, they are common intermediates in many syntheses of 2,6-piperidines.

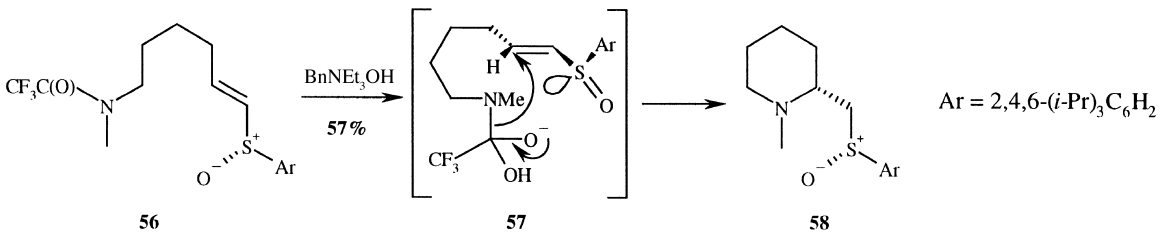
Piperidines can also be synthesised from dicyanide precursors. This method involves reflux under very acidic conditions (H_2SO_4, AcOH) and is therefore only used in the synthesis of very simple piperidines.[45] Moreover, this



Scheme 17.



Scheme 18.



Scheme 19.

method is easy to carry out as the byproduct formed, $(NH_4)_2SO_4$, is simply removed by filtration.

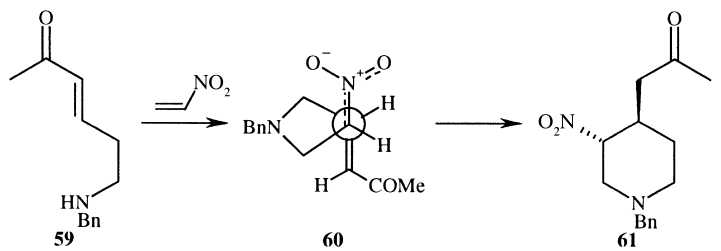
2.3. Reaction of amines with alkenes and alkynes

2.3.1. Intramolecular Michael addition. Michael addition plays an important role in the synthesis of piperidines. Control of the dia- or stereoselectivity is the main difficulty in this type of cyclisation. Armstrong et al.,[46] in their approach towards the synthesis of cylindrospermopsin, synthesised the primary piperidine intermediate **55** via a Michael addition reaction (Scheme 18). Treatment of the compound **54** with a catalytic amount of *p*-TsOH in refluxing benzene gave the most stable N-Cbz-protected piperidine **55**, as a single diastereoisomer in 74% yield.

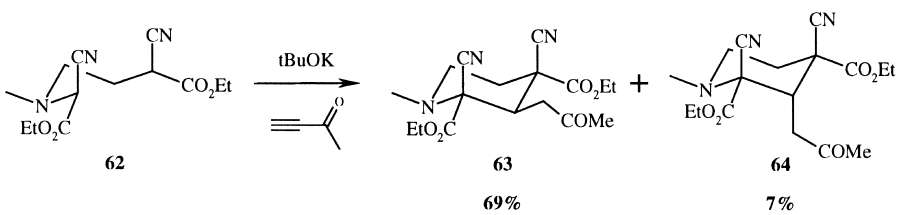
Chiral vinylsulphoxides can also be used in the synthesis of 2-alkylpiperidines. The reaction proceeds via a Michael-type attack of the amine on the vinylsulphoxide. Deprotection of the amino-vinylsulphoxide **56** by Pyne and co-workers[47] under basic conditions using $BnNEt_3OH$ afforded the piperidine **58** in 57% yield (Scheme 19). Only 4% of the undesired diastereoisomer was isolated. The reaction is believed to proceed via the intermediate **57**, where the lone pair of the sulphoxide and the C=C double bond are *syn* coplanar. Attack of the amine occurs on the less hindered face, to afford the desired piperidine **58**.

A one-pot convergent synthesis of 3,4-aminoalkylpiperidines has been developed by Barco et al.[48] The reaction involved an intermolecular addition of a nitrogen nucleophile to an electrophilic olefin, followed by intramolecular trapping of the generated enolate by a built-in α,β-unsaturated acceptor. Indeed, the reaction of the 3-amino-α,β-unsaturated ketone **59** with nitroethylene (generated in situ from 1-benzoyloxynitroethane) afforded the *anti* piperidine **61** in good yield (Scheme 20). The diastereoselectivity of the reaction can be explained via the transition state **60** with an antiperiplanar orientation between the nitro group and the acceptor chain.

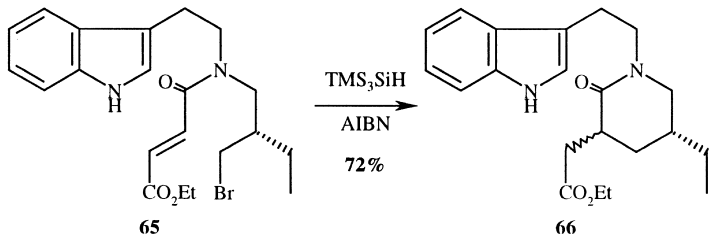
Grossman and co-workers[49] utilised the same type of double Michael addition to synthesise complex functionalised piperidines. Amines of the type **62**, underwent a double Michael addition with 3-butyn-2-one (Scheme 21) in the presence of *tert*-BuOK in DCM, to afford the desired



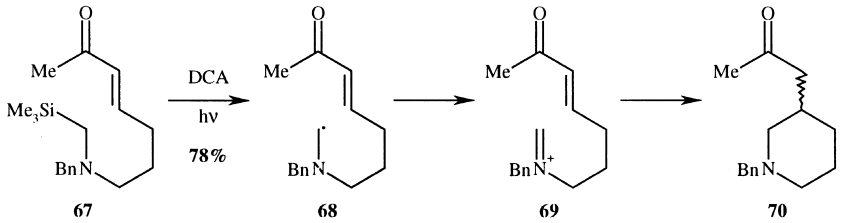
Scheme 20.



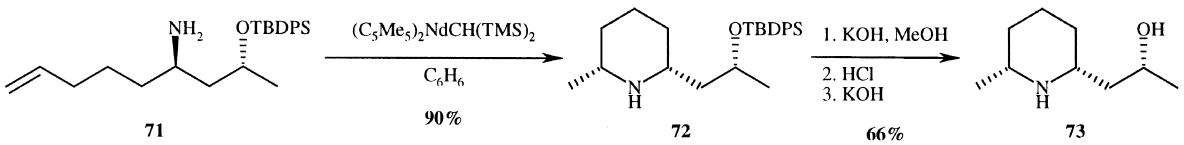
Scheme 21.



Scheme 22.



Scheme 23.



Scheme 24.

piperidine **63** in 69% yield as a single diastereoisomer. Only 7% of the C-3 axial diastereoisomer **64** was obtained. The reaction generally proceeds in relatively good yields and diastereoselectivities, but also gives the 2,3,4-trisubstituted piperidines, which can be easily functionalised to more complex compounds.

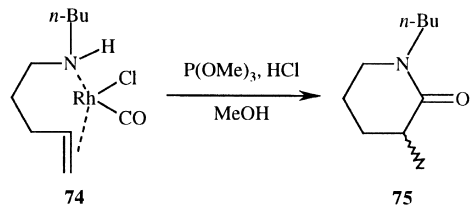
2.3.2. Radical 1,4 reaction of amines with alkenes. 1,4-Radical cyclisation can also be applied to the synthesis of piperidines or piperidinones. In their synthesis of tacamonine, Fukumoto et al.[50] cyclised bromo-vinyl ester **65** to afford the piperidinone **66** in 72% yield as a diastereoisomeric mixture (Scheme 22). With the racemic precursor **65**, the use of TMS_3SiH in the presence of AIBN gave better results than Bu_3SnH. In the same model study, the corresponding iodo-vinyl ester gave a lower yield of the desired piperidine **66**.

The oxidation of silylamino-enones has been studied by Mariano et al.[51] Treatment of the silylamino-enone **67** with 9,10-dicyanoanthracene (DCA) under photosensitisation afforded the piperidine **70** in 78% yield (Scheme 23). The silylamino-enone is believed to first undergo oxidative desilylation, affording the amino radical **68**, followed by oxidative formation of the iminium cation **69**. Cyclisation then occurred, to afford the desired piperidine **70**. This methodology has been extended to the radical cyclisation of bis-silanes. When metal oxidants, such as Ce^{4+} ($nBu_4NCe(NO_3)_6$), were used, better yields were obtained.

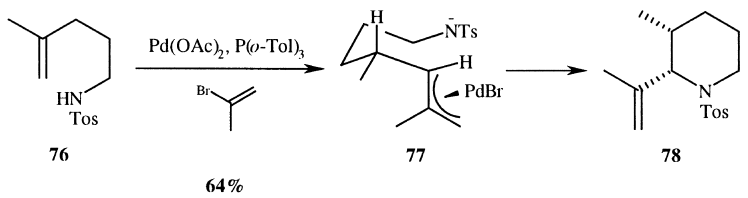
2.3.3. Hydroamination. A diastereoselective lanthanocene-catalysed intramolecular hydroamination has been developed by Molander and co-workers.[52] This methodology is an important procedure for the synthesis of *syn* 2,6-piperidines in high enantiomeric excesses. The aminoalkene **71** was synthesised in a few steps from commercially available reactants (Scheme 24) and was cyclised in 90% yield in the presence of $(C_5Me_5)_2NdCH(TMS)_2$ (9 mol%), to give the piperidine **72**. The presence of bulky ligands and the large size of the metal are believed to be the key factors in determining the diastereoselectivity of the reaction. Deprotection of the alcohol afforded (−)-pinidinol **73** in 66% yield and 99.9% ee.

Yamamoto et al.[53] developed a similar chemistry using $[(\eta^3\text{-}C_3H_5)PdCl]_2$ with 1,1′-bis(diphenylphosphino)ferrocene (dppf), which has been proven to be the best catalyst for the intramolecular hydroamination of allenic alkenes. The desired *syn* 2,6-alkylvinylpiperidine was obtained in modest yield and in up to 90% de.

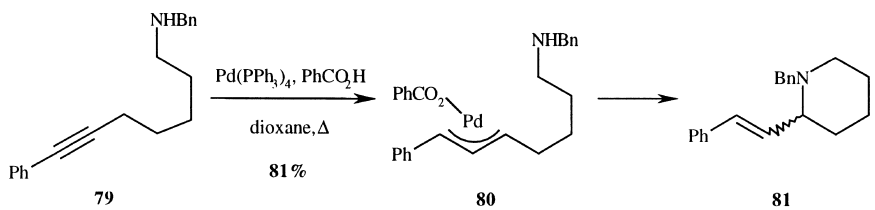
Krafft and co-workers[54] have studied the hydrocarboxylation of aminoalkenes using rhodium. The rhodium complex **74** was synthesised from the corresponding amine and $[(CO)_2RhCl]_2$. Treatment of this complex with an ethereal solution of anhydrous HCl, trimethyl phosphite and MeOH afforded the piperidine **75** in 80% yield (Scheme 25).



Scheme 25.



Scheme 26.



Scheme 27.

Although this methodology is interesting, its applications to the synthesis of complex piperidines are limited, due to the harsh conditions.

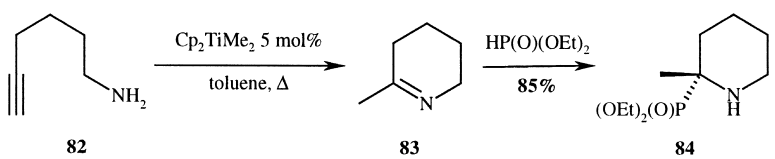
In an investigation by Zang et al.,[55] amino-alkenes in the presence of CO, H_2 and a catalytic amount of $HRh(CO)(PPh_3)_3$, were found to undergo cyclisation to the desired piperidin-2-one, which was reduced in situ to the corresponding piperidine. These conditions are more compatible with the presence of protecting groups, but more studies are required, in order to describe this strategy as a reliable tactic for preparing piperidines.

Larock, Weinreb and co-workers[56] synthesised *syn* 2,3-vinyl-alkylpiperidines via a palladium-catalysed coupling of vinyl bromides and olefinic sulphonamides. Indeed, treatment of the aminoalkene **76** and 2-bromopropene with $Pd(OAc)_2$ (5 mol%) and P(*o*-Tol)$_3$ (10 mol%), afforded the *syn* 2,3-piperidine **78** in 64% yield as a single stereoisomer (Scheme 26). The reaction is believed to occur via the intermediate **77**, in which the π-allylpalladium complex adopts a pseudoaxial position in order to avoid developing a strain in the transition state for ring closure.

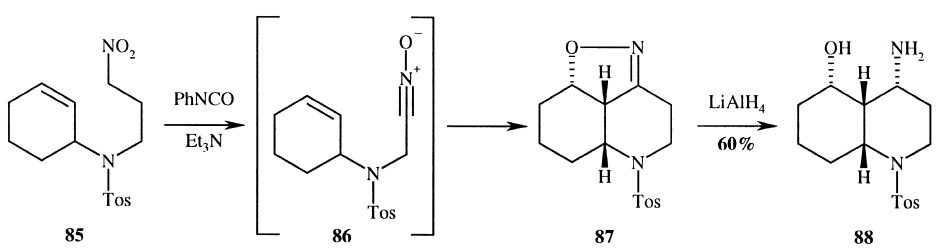
Yamamoto[57] also performed the hydroamination of amino-alkynes with $Pd(PPh_3)_4$ (5 mol%) in the presence of benzoic acid (10 mol%). The first step in the catalytic process is believed to be hydropalladation leading to a vinylpalladium species which undergoes β-elimination, to afford the corresponding allene. Hydropalladation of the intermediate affords the corresponding π-allylpalladium complex of the type **80** (Scheme 27). For the cyclisation of amino-alkynes, such as **79**, to produce analogues of **81**, the nitrogen must be electron rich. Indeed, in the case of a tosyl-protected amine, β-elimination of the π-allylpalladium complex occurred, affording the corresponding aminodiene.

Doye et al.[58] demonstrated that α-phosphate-substituted piperidines could be synthesised using a titanium complex as a catalyst. The aminoalkyne **82** underwent cyclisation in the presence of Cp_2TiMe_2 (5 mol%) in refluxing toluene (Scheme 28). Treatment of the imine intermediate **83** with $HP(O)(OEt)_2$ under acidic conditions (5 mol% Me_2AlCl) afforded the desired piperidine **84** in 85% overall yield.

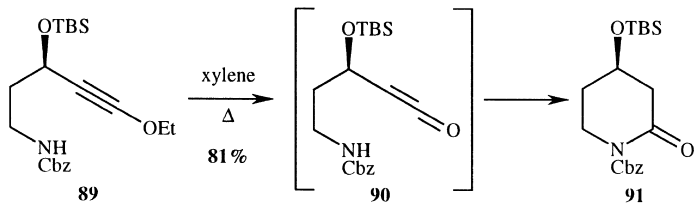
2.3.4. Other reactions of amines with alkenes. Hassner and co-workers[59] studied the reaction of nitro-alkenes such as **85** (Scheme 29) which, in the presence of phenyl isocyanate, afforded the nitrile oxide **86** which spontaneously cyclised to the isoxazoline **87** in good yield. Reductive ring opening with $LiAlH_4$ led to the amino-hydroxypiperidine **88** in 60% overall yield.



Scheme 28.

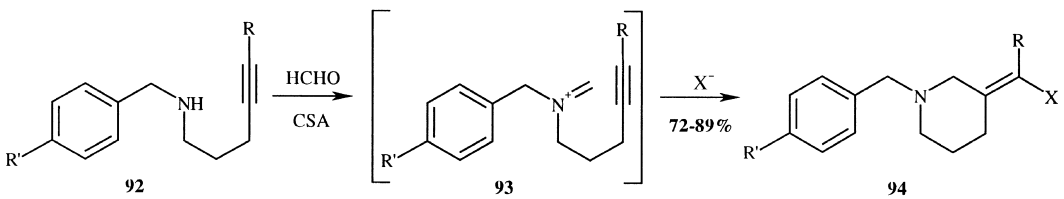


Scheme 29.



89 90 91

Scheme 30.



92 93 94

R = H, Me
R' = H, OMe

R = H, Me
R' = H, OMe
X = I, Br, N_3, SCN

Scheme 31.

2.3.5. Reaction of amines with alkynes. MaGee et al.[60] developed a convenient and general method for the synthesis of cyclic piperidinones via the intramolecular trapping of ketenes. Refluxing the compound **89** in xylene afforded the desired piperidinone **91** in 81% yield (Scheme 30). This reaction is believed to proceed via the ketene **90**, which cyclises spontaneously under the reaction conditions.

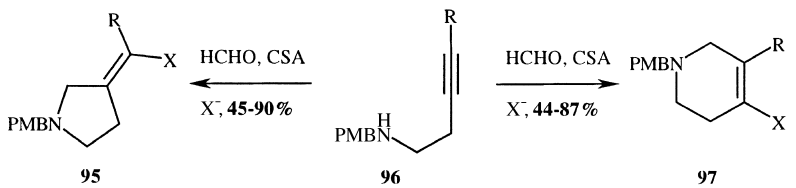
Overman et al.[61] reacted the amino-alkynes **92** with formaldehylde under acidic conditions (CSA), providing the formaldimidium intermediates **93** which, in the presence of a nucleophile (Nu) such as TBAB, NaI, NaN_3 or NaSCN, afforded the corresponding piperidines **94** in good yield (72–89%), (Scheme 31).

Similar studies have been carried out to form pyrrolidines. Treatment of the amino-alkynes **96** (R=Me; X=I, Br, N_3) under the same conditions afforded the pyrrolidines **95** in 45–90% yields (Scheme 32). Treatment of aminoalkynes **96** (R=H, TMS; X=I, Br), under the same conditions, however, afforded piperidines **97** in moderate to good yields (44–87%). Functionalisation of compounds of the type **97** can be very useful in the synthesis of more complex molecules.

2.4. Reaction of dienes, enynes and diynes

2.4.1. Ring-closing metathesis. The synthesis of piperidines via ring-closing metathesis (RCM) has become a widely used approach, providing a reliable synthetic method for the preparation of unsaturated piperidines. Moreover, the double bond formed can easily be further functionalised.

Couty and co-workers[62] published an interesting synthesis of the natural product (−)-β-conhydrine and different analogues using RCM. Metathesis can also be used to



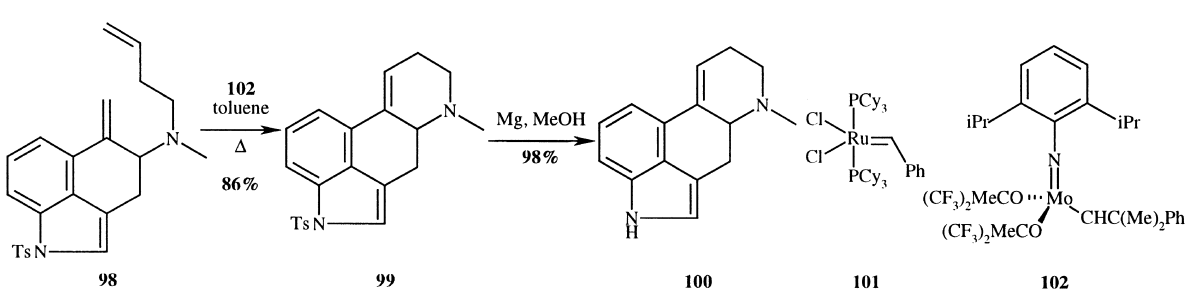
95 96 97

R = Me
X = I, Br, N_3

R = H, Me, TMS

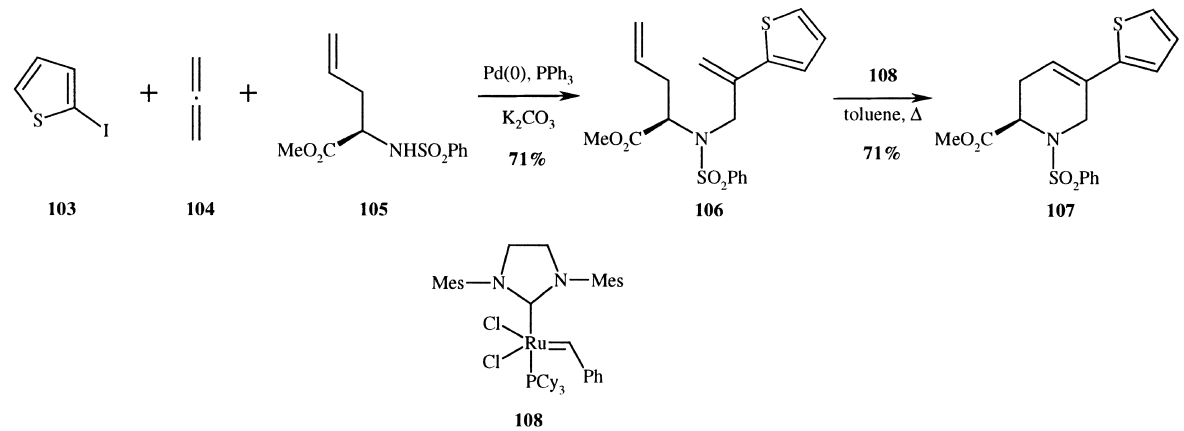
R = H, TMS
X = I, Br

Scheme 32.



98 99 100 101 102

Scheme 33.

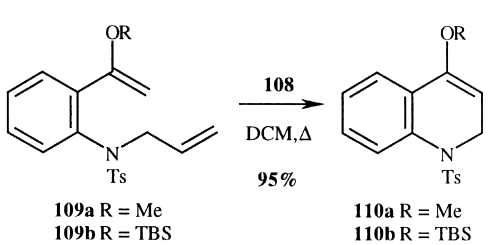


Scheme 34.

synthesise trisubstituted unsaturated six-membered heterocycles. In their synthesis of ergot alkaloids, Martin et al.[63] used RCM as one of the final steps to form the heterocycle **99**. Treatment of the diene **98** with the first generation of Grubbs' catalyst **101** gave only traces of the desired alkaloid **99** (Scheme 33). The more reactive Schrock catalyst **102** was, however, used in this case to afford the tosyl-protected alkaloid **99** in 86% yield. Deprotection of the tosyl protecting group with Mg in methanol afforded ergoline **100** in 98% yield.

Grigg and co-workers[64] have introduced a highly effective synthesis of arylpiperidines via a sequential Pd/Ru-catalysed allene insertion-nucleophile incorporation-olefin metathesis. This strategy involves the reaction of an aryl halide such as **103** with allene **104** and a nucleophile such as the amine **105** in the presence of Pd(0) to afford, in good yields, dienes of type **106** (71% yield for this example), (Scheme 34). RCM using the second generation Grubbs' catalyst **108** (which is more reactive than the Schrock catalyst **102**) was accomplished affording the 1,2,5,6-tetrahydropyridine **107** in good yield (71% in this case). This strategy is a very efficient and short method for the synthesis of 3,4-unsaturated-3-arylpiperidines.

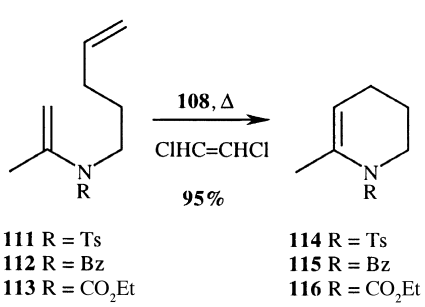
RCM of enol ethers can also be achieved using the highly reactive Grubbs' catalyst **108**. This type of metathesis is still under investigation and examples for the synthesis of piperidines are still limited to simple systems. Although RCM is a very useful synthetic tool for chemists, it does not work for every case. When RCM reactions do not occur, the starting materials are normally recovered. It is still very difficult to understand the reasons for the failure and no general rules have been established. Using RCM of an enol ether as a key step in a total synthesis is therefore still risky,



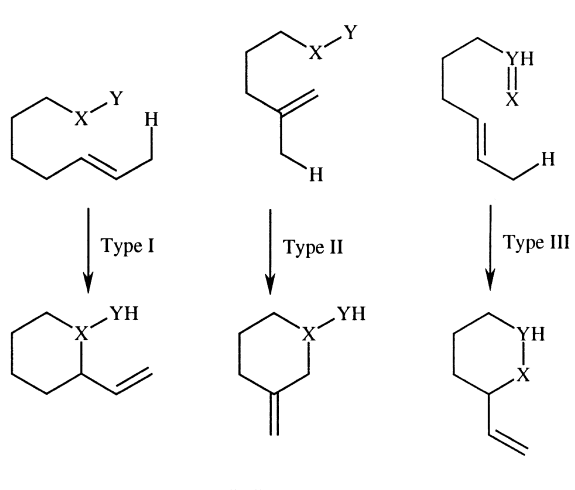
Scheme 35.

as a real understanding of their RCM reactivity is not fully understood. Despite this, Nakagawa et al.[65] realised the synthesis of six-membered heterocycles to afford quinolines via RCM of an enol ether. Both the enol ether **109a** or the silyl enol ether **109b** underwent RCM using the second generation Grubbs' catalyst to provide **110a** and **110b**, each in 95% yield (Scheme 35).

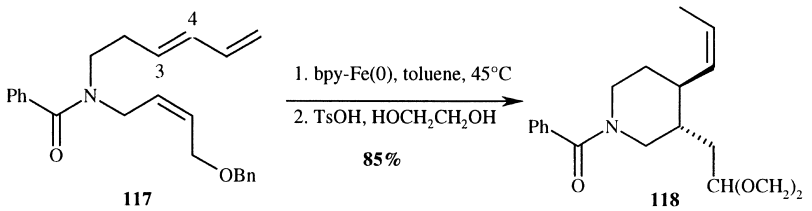
Rutjes and co-workers[66] investigated the RCM of olefinic enamides such as **111** using the Grubbs' catalyst **108** (Scheme 36) to generate 1,2,3,4-tetrahydropyridines. Different electron-withdrawing protecting groups were investigated and the results showed a preference for the



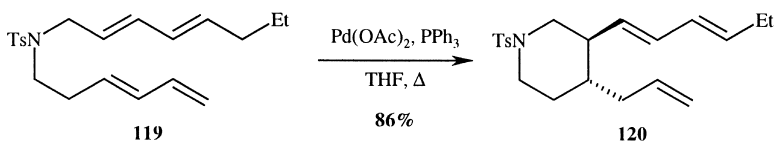
Scheme 36.



Scheme 37.



Scheme 38.



Scheme 39.

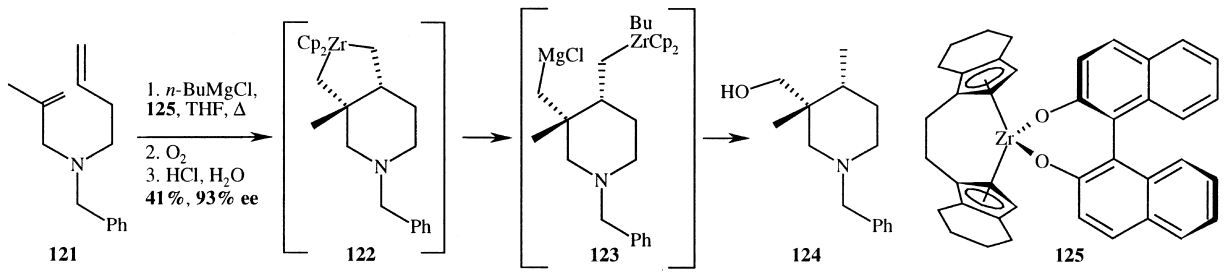
benzoyl protecting group. RCM of the olefinic enamides **111**, **112** and **113** afforded the 1,2,3,4-tetrahydropyridines **114**, **115** and **116** in 75, 93, and 57% yields, respectively.

2.4.2. Intramolecular ene reactions. Intramolecular ene reactions have not been widely applied to the synthesis of piperidines, especially when the desired six-membered-ring heterocycles comprise a relatively complex structure. Nevertheless, a few examples can be found in the literature. Intramolecular ene reactions[67] have been divided by Oppolzer et al. into three different types, I, II and III, depending on the position of attachment of the ene and enophile (Scheme 37).

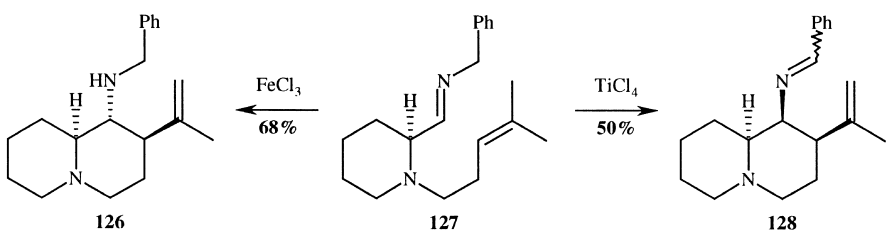
2.4.2.1. Ene reactions (type I). Reactions of the type I are probably the most commonly used intramolecular ene reactions. Takacs and co-workers[68] studied catalytic iron mediated ene reactions and they have applied the ene carbocyclisation to the synthesis of *anti* 3,4-disubstituted piperidines. Indeed, treatment of the triene **117** with 15 mol% of the catalyst bis(2,2′bipyridine)iron(0), (bpy-Fe(0))[69] in toluene, followed by acetylation, afforded the *anti* 3,4-disubstituted piperidiene **118** in 85% overall yield (Scheme 38). According to carbocyclisation studies, the *E*/*Z* geometry of the C3=C4 double bond should control the *syn*–*anti* relation in the resulting piperidine.

The catalytic Pd carbocyclisation of tetraenes has also been investigated by Takacs et al.[70] and, although their study was limited to simple compounds, it is an interesting strategy for the synthesis of *anti* 3,4-disubstituted piperidines. Treatment of the tetraene **119** with $Pd(OAc)_2$ (5 mol%) and PPh_3 afforded the piperidine **120** in 86% yield (Scheme 39). Only the *anti* diastereoisomer was obtained and, interestingly, both newly-formed double bonds had an *E*-geometry.

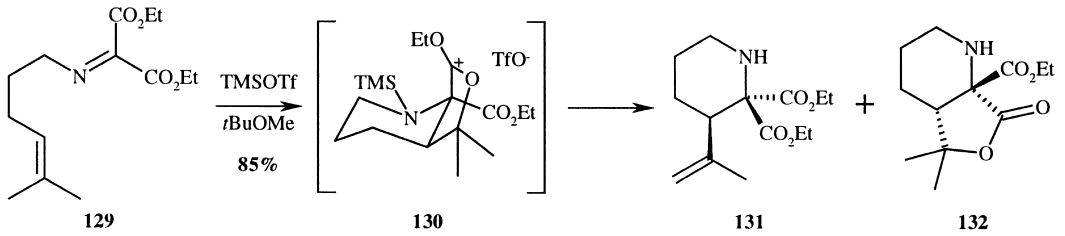
Mori and co-workers[71] worked on an asymmetric version of the zirconocene-mediated synthesis of 3,4-piperidines. Treatment of the diene **121** with *n*-BuMgCl and the zirconocene catalyst **125** (10 mol%), followed by quenching with an electrophile (O_2 in this case), afforded the piperidine **124** in 41% yield and 93% ee (Scheme 40). Although the yield is quite low, this type of reaction is very interesting, as two new chiral centres, one of which is quaternary, have been created. The reaction is believed to proceed via the zirconabicycle **122** and zirconocene **123** intermediates. This chemistry has also been performed with 1,7-enyne and



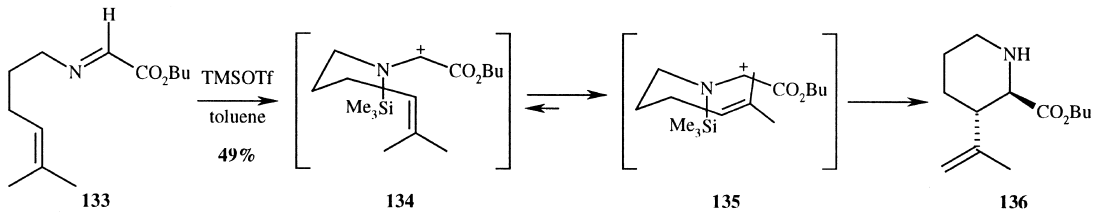
Scheme 40.



Scheme 41.



Scheme 42.



Scheme 43.

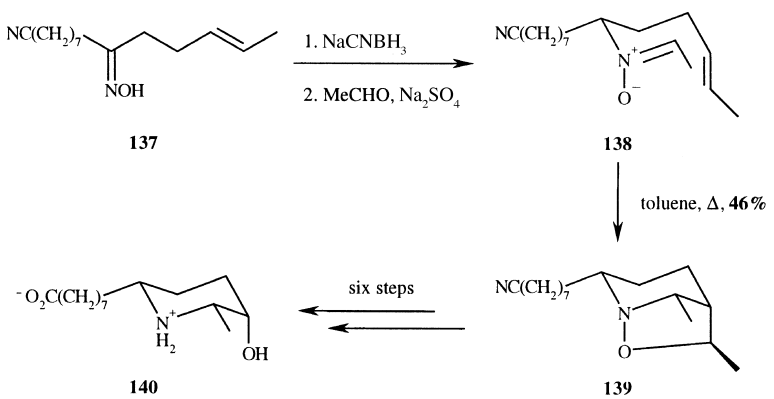
1,7-diyne systems and Whitby et al.[72] generally obtained good yields of the 3,4-disubstituted piperidine products. Trost and co-workers[73] have also reacted 1,7-enynes with CpRu(COD)Cl (10 mol%), to afford similar piperidines in 75% yield.

Imino-ene reactions of type I have been studied for the synthesis of *syn* or *anti* 3,4-diaminopiperidines. Laschat and co-workers[74] investigated the imino-ene reaction of the imino-alkene **127** in the presence of Lewis acids such as $FeCl_3$ or $TiCl_4$ (Scheme 41). The imino-alkene **127** underwent an imino-ene reaction with $FeCl_3$ to give the *anti* piperidine **126** in 68% yield. If, however, $TiCl_4$ was used as the Lewis acid, the *syn* piperidine **128** was formed as the major diastereoisomer in 50% yield.

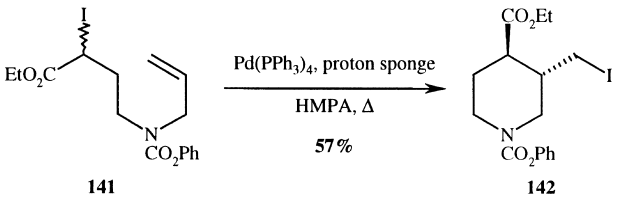
2.4.2.2. Ene reactions (type III). Bratz et al.[75] have used ene reactions of the type III to synthesise 2,3-disubstituted piperidines and they first studied the ene reaction of the dimethylimine **129**, prepared from the corresponding amine (Scheme 42). Treatment of **129** with TMSOTf in *tert*-BuOMe gave a 7.2:1.0 mixture of **131** and **132** in 85% yield. If, however, **129** was treated with TFA in DCM, the ratio of **131** and **132** was reversed, yielding 50% of a 1.0:6.1 mixture of products. The reaction is believed to proceed via the intermediate **130**. The product ratio in the formation of **131** and **132** depends on the nucleophilicity of the counter-ion and the accessibility of the alkyl group in the ester moiety, as well as its ability to form a cation.

Bratz and co-workers[76] then studied the reaction of imino-alkenes of the type **133** (Scheme 43) and the *anti* 2,3-disubstituted piperidines were synthesised in good yield and diastereoselectivity. The best result was obtained when the *n*-butyl ester **133** was treated with TMSOTf in toluene at −78 °C. The 2,3-disubstituted piperidine **136** was obtained in 49% yield and in a 1:33.5 ratio of *syn*/*anti* stereoisomers. The good diastereoselectivity is believed to result from a strong 1,3-diaxial interaction in the intermediate **134**, caused by the bulky trimethylsilyl group, which destabilises **134** severely towards **135**.

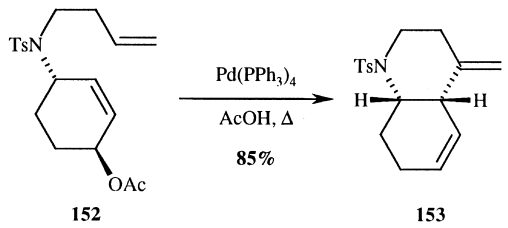
In their synthesis of carpamic acid **140**, Williams and co-workers[77] made use of a type III ene reaction of *N*-oxide alkenes to set up the *syn* 2,3-relationship in the natural product (Scheme 44). Reduction of the oxime **137** afforded the unstable hydroxyamine, which was immediately condensed with acetaldehyde to give the nitrone **138** and the latter compound underwent a type III ene reaction upon reflux in toluene, yielding the desired piperidine **139** in 46% overall yield.



Scheme 44.



Scheme 45.



Scheme 48.

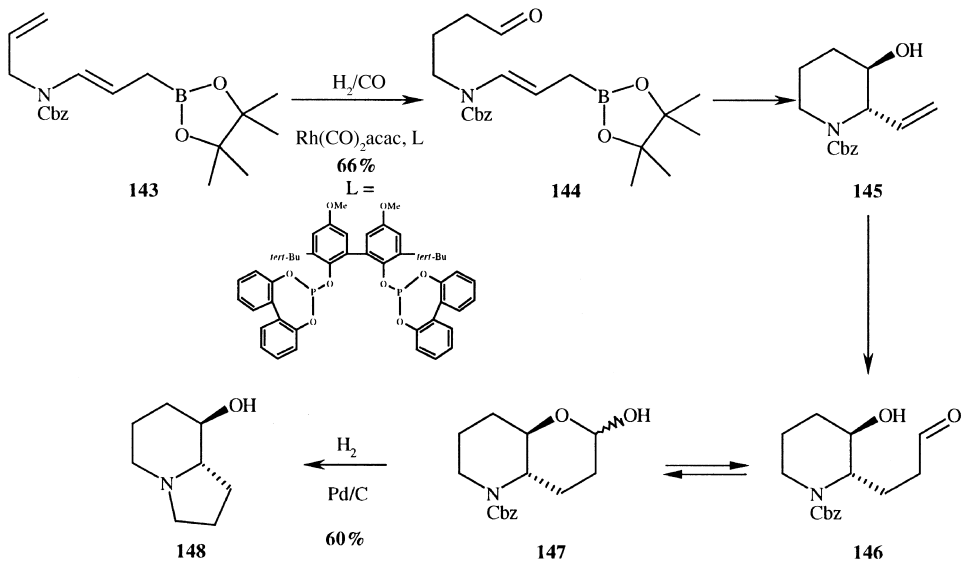
2.4.3. Formal ene reactions

2.4.3.1. Ene halogenocyclisation. Mori et al.[78] studied the palladium-catalysed ene-halogenocyclisations. Treatment of the iodo-alkene **141** with $Pd(PPh_3)_4$ in the presence of a proton sponge afforded the *anti* piperidine **142** (Scheme 45). This strategy is very interesting in the synthesis of 3,4-piperidines which can then be easily functionalised. The reaction, however, shows some disadvantages, as the primary iodide present in the synthesised piperidine can easily be eliminated and a mixture of diastereoisomers can be obtained. A similar cyclisation using $(n\text{-}Bu_3Sn)_2$ has been studied by Curran and co-workers,[79] although a poor yield and a 1:1 mixture of *syn* and *anti* piperidines were obtained.

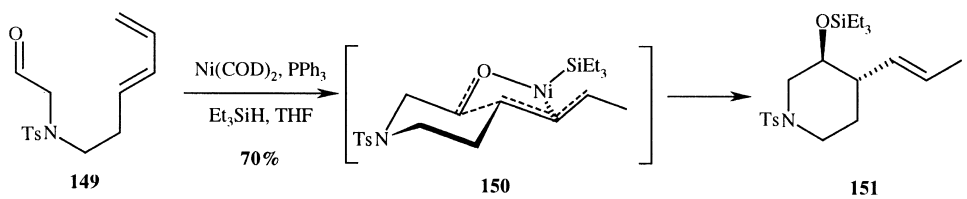
2.4.3.2. π-Allyl complexes. Hoffmann et al.[80] developed an intramolecular allylboration reaction to synthesise *anti* 2-alkylpiperidin-3-ols. The allylamide **143** was hydroformylated to give the aldehyde **144**, which underwent an in situ allylboration to give the vinylpiperidinol **145** (Scheme 46). The reaction does not stop at this stage since **145** has a newly-generated terminal C=C double bond and therefore undergoes a second hydroformylation to expand the carbon skeleton, giving a mixture of **146** and **147** in 66% yield. Hydrogenation of this mixture with Pd/C led to the indolizidine **148** in 60% yield.

In their approach towards the synthesis of (−)-elaeokanine C, Mori et al.[81] investigated the cyclisation of 1,3-dienyl aldehydes via the π-allylnickel complex **150** (Scheme 47). The nickel complex **150** was formed in situ by the treatment of $Ni(COD)_2$ with PPh_3 and Et_3SiH. Treatment of the 1,3-dienyl aldehyde **149** with the desired catalyst and Et_3SiH as the hydride source afforded only the *anti* diastereoisomer **151** in 70% yield.

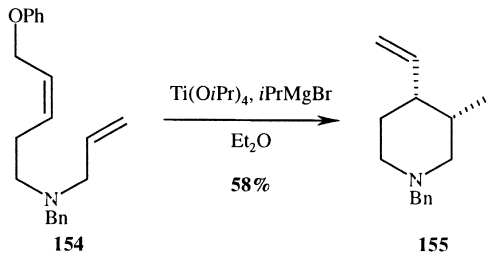
Palladium-catalysed intramolecular olefin allylation is a widely used reaction and it is therefore logical to find it applied to the synthesis of piperidines. Oppolzer and co-workers[82] have studied this process and used $Pd(PPh_3)_4$ in acetic acid to synthesise simple piperidines. In the synthesis of 6,6-bicyclo systems, the *syn*-fused rings were obtained. Indeed, treatment of the compound **152** with $Pd(PPh_3)_4$ (7 mol%) at 80 °C afforded the compound **153** in 85% yield (Scheme 48). Although the choice of solvent limits this strategy to the synthesis of simple piperidines, it



Scheme 46.



Scheme 47.



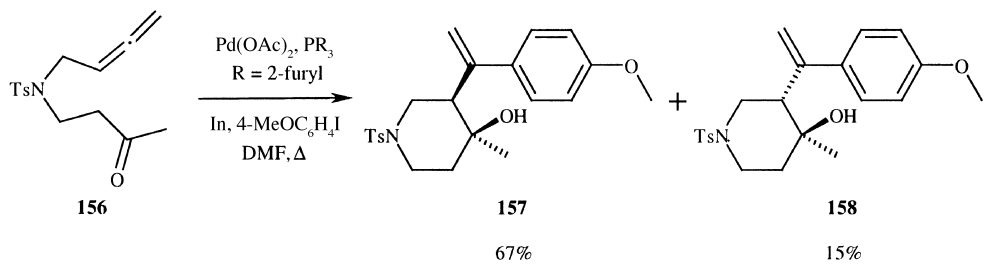
Scheme 49.

can be useful for the synthesis of *syn*-fused rings such as that found in **153**.

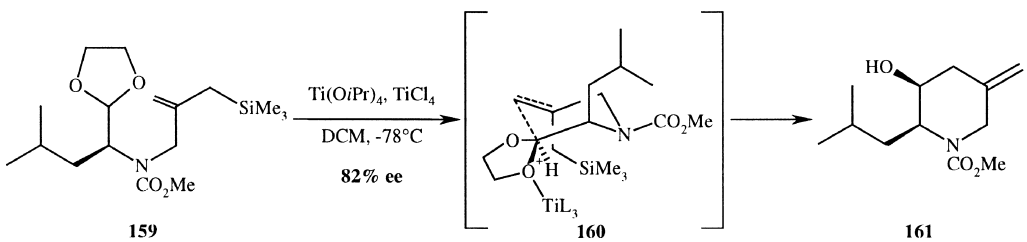
A similar cyclisation of dienes has been investigated by Taylor, who accomplished the cyclisation of the diene **154** to the piperidine **155** in 58% yield (Scheme 49). The diene **154** was treated with $Ti(OiPr)_4$ and *i*PrMgBr, to afford the *syn* piperidine **155**. An asymmetric version of this reaction has been studied using a 1-phenylethyl protecting group instead of the benzyl protecting group, but a 1:1 mixture of *syn* diastereoisomers was obtained. When $ZrCl_2$ was used with *n*-BuLi, an unsatisfactory 1:1.4 mixture of *syn*/*anti* diastereoisomers was obtained.

Barbier allylation has been recently investigated by Kang in the synthesis of piperidines. Interestingly, this strategy is quite general and a wide range of piperidines can be prepared. Both allene aldehydes and ketones can be reacted, to give the 3,4-disubstituted piperidines. 3-Trimethylsilanylvinylpiperidin-4-ol,[83] and 3-arylvinylpiperidin-4-ols[84] have been synthesised using this method. Kang initially treated allene aldehydes and ketones with $(\pi\text{-allyl})_2PdCl_2$ and $Bu_3SnSiMe_3$, to afford the corresponding piperidines in good yields (62–67%). Further studies showed that π-allylpalladium complexes could be formed using $Bu_3SnSnBu_3$ and ArI, leading to the synthesis of 3-arylvinylpiperidin-4-ols. This methodology gave good yields and diastereoselectivity and it could be applied to a wide range of aromatics and aromatic heterocycles. Due to the moderate toxicity of the tributyltin reagents, Kang studied the use of indium in the Barbier allylation. Treatment of a solution of the ketoallene **156** in DMF with $Pd(OAc)_2$, tris(2-furyl)phosphine and indium afforded the desired *syn* piperidine **157** in 67% yield (Scheme 50). Only 15% of the *anti* piperidine **158** was isolated.

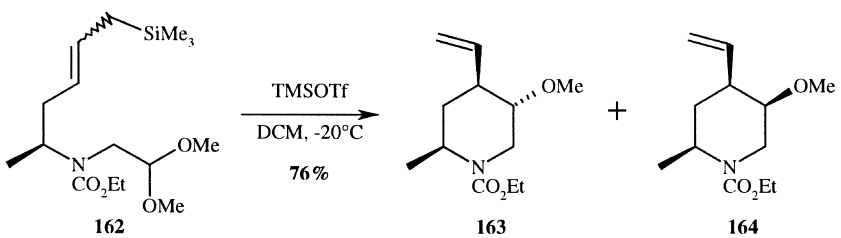
Interesting results were obtained by Kano et al.,[85] who investigated the cyclisation of α-aminoacetal-allylsilanes, resulting in the formation of 2-alkyl-3-hydroxypiperidines. Treatment of the α-aminoacetal-allylsilane **159** with the in situ-generated $Ti(OiPr)Cl_3$ afforded the *syn* piperidinol **161** in 82% ee (Scheme 51). The reaction proceeds via the intermediate **160**, where no interaction between $SiMe_3$ and any of the oxygens is observed. A similar chemistry has been studied by Bonjoch and co-workers,[86] using α,β-unsaturated keto-α-trimethylsilylalkynes. 3-Allene-4-alkyl-disubstituted piperidines were obtained in 57–60% yield using $BF_3{\cdot}Et_2O$ or $TiCl_4$ as Lewis acids. Further



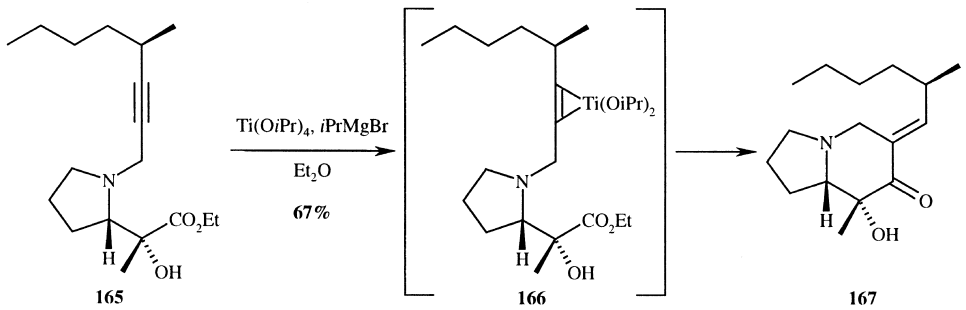
Scheme 50.



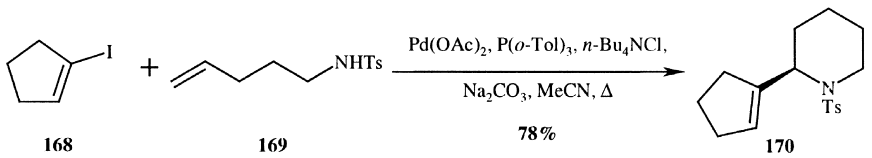
Scheme 51.



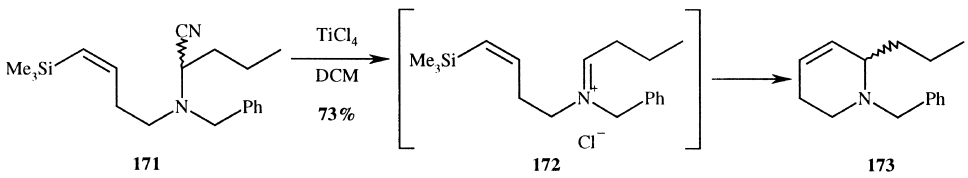
Scheme 52.



Scheme 53.



Scheme 54.



Scheme 55.

functionalisation of the product allenes afforded a range of 3,4-disubstituted piperidines.

Mann et al.[87] have also been working on the synthesis of *anti* 3-hydroxy-4-alkylpiperidines from α-trimethylsilyl-methylalkenes. When the allyltrimethylsilane **162** was treated with a catalytic amount of TMSOTf (10 mol%), only two of the four possible diastereoisomeric piperidines were obtained (Scheme 52) in an 85:15 ratio (**163** and **164**) and in 76% yield. This strategy created two new chiral centres influenced by the stereochemistry present in the starting material.

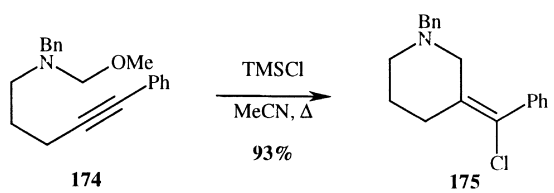
In their synthesis of allopumiliotoxin alkaloid 267A, Sato and co-workers[88] made use of an intramolecular nucleophilic acyl substitution initiated with a low-valent titanium reagent Ti(O*i*Pr)$_2$*i*Pr. Treatment of the ethyl ester **165** with Ti(O*i*Pr)$_4$ and *i*PrMgCl afforded the desired six-membered heterocycle **167** in 67% yield (Scheme 53). The reaction is believed to occur via the intermediate **166**, which undergoes an intramolecular nucleophilic substitution.

2.4.3.3. Palladium cross-coupling. Piperidine synthesis via palladium-catalysed tandem cyclisation cross-coupling can be found in the literature. In their synthesis of ellipticine, Ishikura et al.[89] synthesised the six-membered ring heterocycle via Heck coupling of a vinyl bromide and an alkyne. Crisp and co-workers[90] studied the synthesis of lactams via palladium-catalysed intramolecular carbonyl coupling and reacted an amino enol triflate with carbon monoxide in the presence of Pd(PPh$_3$)$_4$ and (*n*-Bu)$_3$N in acetonitrile. The corresponding lactam was obtained in 72% yield using of *N*-benzyl 3-methylene-piperidin-2-one. Ban et al.[91] worked on a similar synthesis of piperidinones.

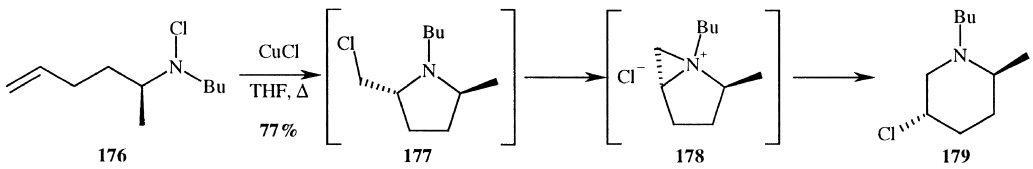
Larock, Weinreb and co-workers[92] studied the palladium cross-coupling of vinyl iodides, vinyl bromides or enol triflates, for example, **168** with *N*-tosyl-pent-4-enylamine **169** (Scheme 54). The 2-substituted-piperidines of type **170** were successfully prepared in modest to good yields.

2.4.3.4. Reactivity of iminium cations. Rotella et al.[93] have investigated the application of TiCl$_4$ in an induced iminium ion cyclisation in order to prepare piperidines. The iminium ion was prepared by the treatment of an α-cyanoamine of type **171** with titanium (IV) chloride (Scheme 55). The corresponding iminium ion **172** underwent cyclisation, to afford the 1,2,5,6-tetrahydropyridine **173** in 73% yield. Reduction of the double bond afforded racemic coniine in 90% yield.

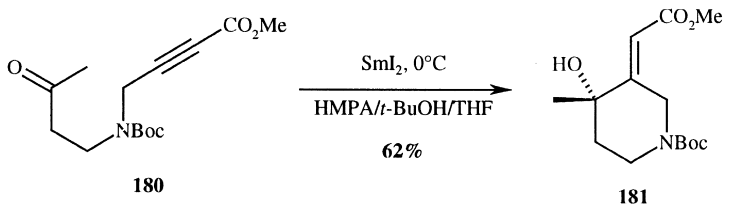
Overman and co-workers[94] worked on a similar methodology and treated *N*-methoxymethyl alkynes such as **174** with TMSCl (Scheme 56). The piperidine **175** was obtained



Scheme 56.



Scheme 57.



Scheme 58.

in 93% yield as a 93:7 mixture of *E*/*Z* isomers. The reaction most probably proceeds via an iminium cation.

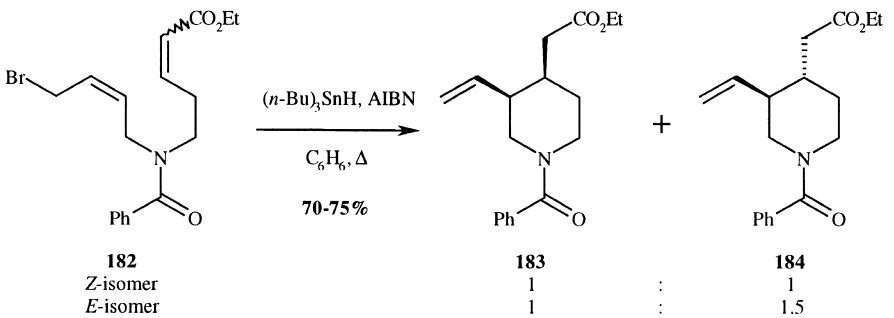
2.5. Radical cyclisations

2.5.1. Radical cyclisation of *N*-chloro amino alkenes. Götflich et al.[95] studied the reactivity of *N*-chloro amino alkenes under radical conditions. The unstable *N*-chloro amine **176** was freshly prepared from the corresponding amine and NCS (Scheme 57). Treatment with a catalytic amount of CuCl (10 mol%) afforded the piperidine **179** in 77% yield as a 7:1 mixture of *syn*/*anti* diastereoisomers. The reaction is believed to proceed via the pyrrolidine **177** and the azonia-bicyclo[3.1.0]hexane **178**. The synthesis of *syn* 3,5-piperidines was also performed in good yield, but the diastereoselectivity was lower (1:4, *anti*/*syn*). Somfai and co-workers[96] studied similar reactions in the presence of a Lewis acid instead of CuCl and obtained good diastereoselectivity (up to 93:7 in favour of the *syn* 3,5-disubstituted piperidine).

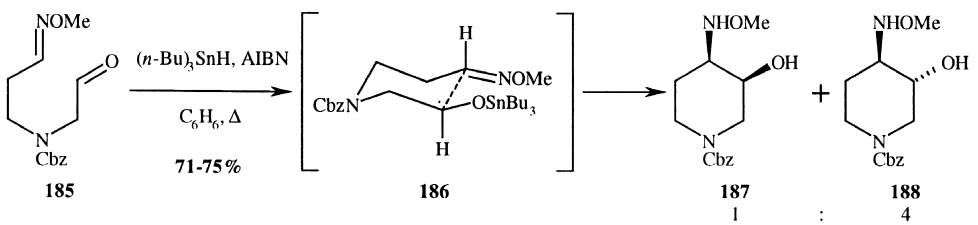
2.5.2. Radical cyclisation using samarium. The use of samarium to synthesise piperidines is rare in the literature. Shim and co-workers[97] have, however, described the synthesis of a 3,4-disubstituted piperidine via an intramolecular reductive cyclisation of aldehydes and ketones with alkynes. Interestingly, the reaction with ketones led to the formation of piperidines containing a quaternary alcohol in position 4. Treatment of the keto-alkyne **180** with SmI_2 in a mixture of HMPA, *tert*-butanol and THF afforded the racemic piperidine **181** in 62% yield (Scheme 58).

2.5.3. Radical cyclisation using tin. Tin allylic radical cyclisation has been investigated in the synthesis of piperidines, although this reaction did not show diastereoselectivity and gave a mixture of diastereoisomers. Indeed, treatment of the allyl bromide **182**[98] with $(n\text{-Bu})_3SnH$ and AIBN afforded a mixture of the diastereoisomers **183** and **184** (Scheme 59).

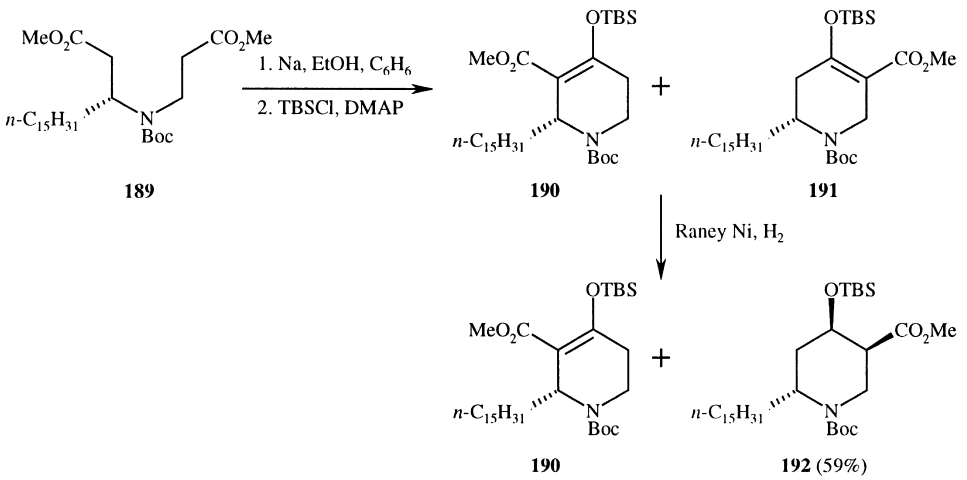
The radical cyclisation of α,β-keto-dienes[99] has also been investigated and, although the yields are relatively high, a low diastereoselectivity was generally obtained. The intramolecular radical cyclisation of oxime ethers with



Scheme 59.



Scheme 60.



Scheme 61.

aldehydes and ketones has been studied by Naito et al.[100] who obtained modest results. Attempts to synthesise 3-amino-4-hydroxypiperidines gave a reasonable yield of 62%, but the diastereoselectivity was poor (1:1.3 in favour of the *anti* diastereoisomer). Treatment of the 'oxime-aldehyde' **185** with $(n\text{-Bu})_3SnH$, and AIBN afforded a 1:4 mixture of the diastereoisomers **187** and **188** (Scheme 60). The most stable intermediate is believed to be the *anti* isomer **186**, where the oxime and tin are *anti* to each other.

2.6. Dieckmann condensation

Dieckmann condensation is an important tool in the synthesis of 3,4-disubstituted piperidines and can provide *syn* piperidines or the more stable *anti* piperidines. This strategy can, however, become problematic with more complex piperidines which contain further substitution in positions 2, 5 or 6. Ma et al.[101] investigated the synthesis of 2,4,6-trisubstituted piperidines and faced problems of diastereoselectivity. Indeed, the bis-methyl ester **189** can undergo two different Dieckmann cyclisations to give after trapping of the intermediate enolate with TBSCl, **190** and **191** in an 1:3.8 diastereomeric mixture (Scheme 61). Fortunately, Ma managed to selectively hydrogenate the less sterically hindered silyl enol ether, to obtain the desired 2,4,6-trisubstituted piperidine **192** in 59% yield from **189**.

In the synthesis of 3,4-disubstituted piperidines, this problem does not occur and the *syn* and *anti* piperidines can be prepared. Pollini and co-workers[102] were able to synthesise *syn* 3,4-disubstituted piperidines and then epimerised them to the more stable *anti* piperidines. This strategy has become very attractive in medicinal chemistry, as both the *syn* and *anti* 3,4-disubstituted piperidines can be easily obtained for testing purposes.

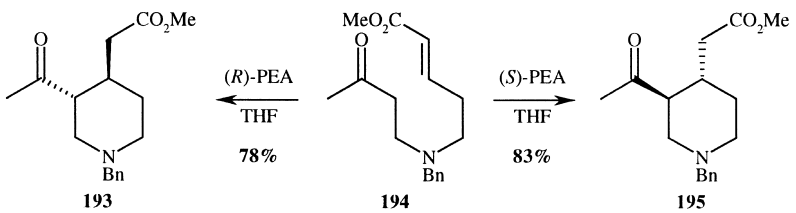
Dieckmann cyclisation can be performed under acidic conditions using Lewis acids such as $TiCl_4$.[103] Chiral bases can be employed to synthesise enantiomerically pure piperidines. Indeed, Hirai et al.[104] realised a 1,4-Michael addition similar to a Dieckmann cyclisation to afford **193** or **195** starting from the ester **194** (Scheme 62). (*R*)- and (*S*)-1-Phenylethylamine (PEA) gave both products in good enantiomeric excess (90% ee). Both enantiomers **193** and **195** were synthesised in 78 and 83% yields, respectively.

3. Cycloadditions

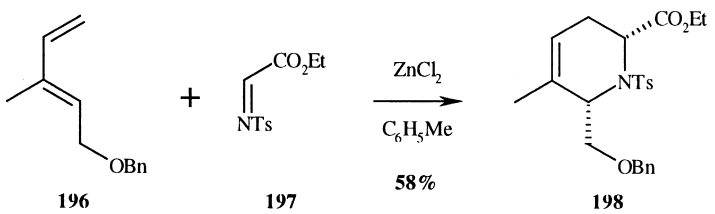
In cycloadditions, the Diels–Alder reaction is one of the most commonly used reactions for preparing six-membered rings. In a similar manner, the aza Diels–Alder reaction is an important tool in the hand of chemists for synthesising piperidines. The method is mostly applied to the reaction of dienes with imines. The reaction of α,β-unsaturated imines (aza dienes) with alkenes is also known in the literature.

3.1. Imino Diels–Alder reactions

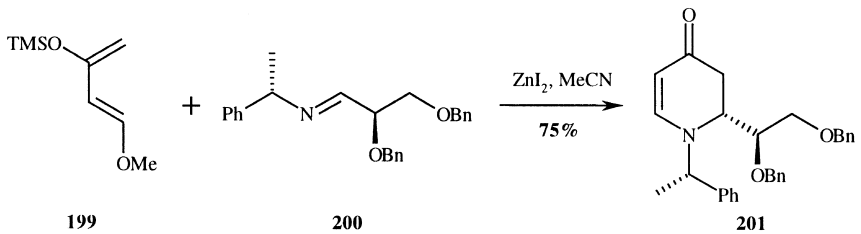
Imino Diels–Alder reactions require an electron-rich diene and an electron-poor imine. In general, the imine is protected as a sulphonamide or as a silylamine, although the reaction of dienes protected as benzylimines is also known. Imino Diels–Alder reactions are generally slow and are typically catalysed by a Lewis acid such as $ZnCl_2$. The



Scheme 62.



Scheme 63.



Scheme 64.

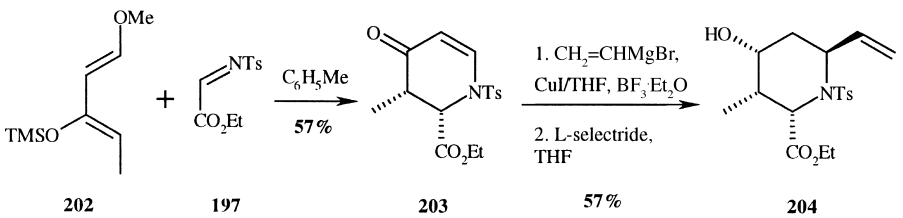
speed of the reaction depends mainly on the reactivity of the starting imine and a wide range of electron-rich dienes can be used.

In their studies towards the synthesis of cylindrospermopsin, Weinreb and co-workers[105] studied the imino Diels–Alder reaction of the diene **196** and the imine **197** (Scheme 63). The piperidine **198** was obtained after 6 days at room temperature in toluene in the presence of $ZnCl_2$ in 58% yield. Although the yield is only modest, a *syn* 2,6-piperidine was synthesised in a one-step process.

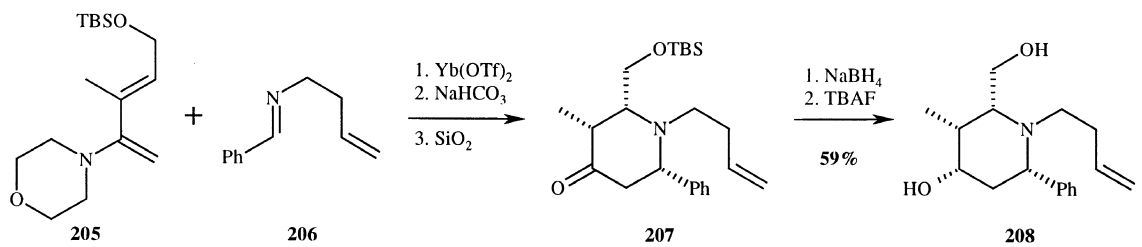
An imino Diels–Alder reaction using Danishefsky's diene has been investigated by Villegas et al.,[106] who studied an enantioselective reaction of the diene **199** with the enantiomerically pure imine **200** (Scheme 64). The reactions in acetonitrile at −40 °C using ZnI_2 were found to be the optimal conditions. The compound **201** was the only diastereoisomer observed and, when the reaction was carried out with the corresponding benzylimine, a 95:5 mixture of diastereoisomers was obtained. Deprotection of the methylbenzyl chiral pool component can accomplished via the usual hydrogenation (H_2, $Pd(OH)_2/C$). Reduction of the α,β-unsaturated piperidinone **201** to the piperidin-4-one can be completed with *L*-selectride.

More interestingly, Weinreb et al.[105] used a 1,4-vinylcopper addition to heterocycle **203** prepared from diene **202**. *L*-selectride reduction of the ketone provided the tetrasubstituted piperidine **204** in 57% yield overall (Scheme 65).

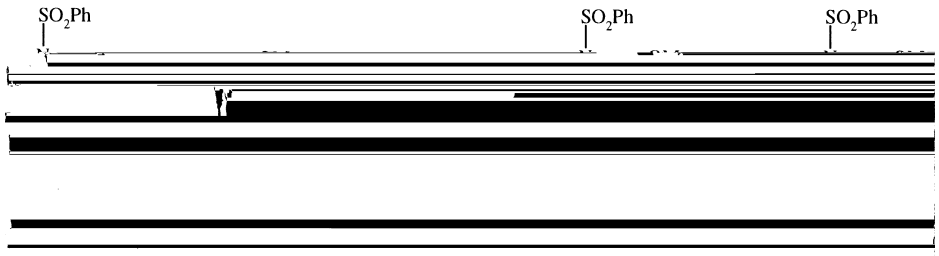
Moreover, aza Diels–Alder reactions can be performed with 2-amino-1,3-butadiene derivatives **205** leading after hydrolysis, to piperidin-4-ones of the type **207** (Scheme 66). The optimal Lewis acid was $Yb(OTf)_3$ and Barluenga and co-workers[107] reported the hydrolysis of the enamine via filtration through a pad of silica. Reduction of the ketone using $NaBH_4$, followed by silyl ether deprotection, led to the tetrasubstituted piperidine **208** in 59% yield overall. In their synthesis towards (−)-nupharamine, Barluenga and co-workers developed an asymmetric version of this type of imino Diels–Alder reaction.[108]



Scheme 65.



Scheme 66.



Scheme 67.

Scheme 68.

3.2. Aza-diene Diels–Alder reactions

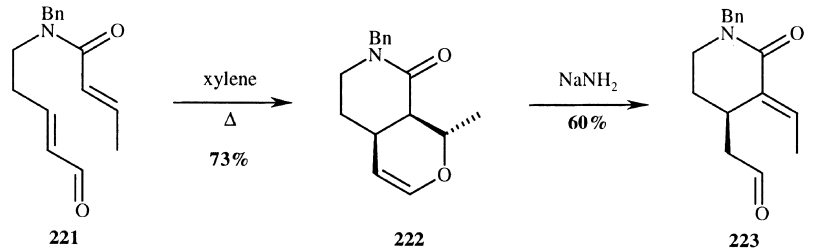
The aza Diels–Alder reaction of a diene with an imine is well known in the synthesis of piperidines, but the aza-diene Diels–Alder reaction is rarely used. Indeed, this type of reaction is difficult to realise as the aza-dienes suffer low conversion and competitive imine addition and/or tautomerisation. Boger and co-workers[109,110] studied the influence of different substituents on the aza-dienes in their reactions with electron-rich alkenes such as enol ethers. Other types of dienophiles are not reactive enough, unless a highly reactive aza-diene is used. According to Boger's studies, an electron-withdrawing group on the nitrogen of the aza-diene facilitates the reaction, substituents in position 2 slow down the reaction and electron-withdrawing groups accelerate it. Groups such as *N*–SO_2Ph and *N*–$P(O)Ph_2$ are good choices, as the starting imine can be easily purified by flash chromatography without decomposition and the steric bulk of the groups prevents the 1,2-imine addition. The *endo* aza Diels–Alder product is favoured (up to 95%) in both the thermal and pressure-promoted (most common) reactions. Both the *anti* and *syn* enol ethers react with conservation of geometry. Alkoxyallenes can also be used, to give the corresponding piperidines with good diastereoselectivity. The solvent does not seem to have any influence on the reactivity or diastereoselectivity of the reaction.

The aza Diels–Alder reaction is very useful for the synthesis of 2,3,4-trisubstituted piperidines. Boger et al.[109] reacted the aza-diene **209** with the dienophile **210**, to afford the desired piperidines **211/212** in 42% yield as a 20:1 ratio of *endo*/*exo* products (Scheme 67).

Fowler and co-workers[111] demonstrated that the aza-diene Diels–Alder reaction is possible with electron-poor dienophiles, although the number of applications is limited. This research group reacted the aza-diene **213** with ethyl acrylate **214** to give the piperidine **215** as a 6:1 *syn*/*anti* mixture of diastereoisomers (Scheme 68). The cyano group in position 2 combined with the presence of the *N*-phenyl group is believed to enhance the 'inverse electron demand' Diels–Alder reaction and therefore the reaction of the aza-diene with electron-poor dienophiles.

Enantioselective aza Diels–Alder reactions have also been studied, although this work is still in its infancy. Tietze et al.[112] studied the reaction of enantiopure α,β-unsaturated sulphinimines with dienophiles. The reactions were performed with electron-rich dienophiles such as enol or thioenol ethers, whereas the reactions with alkenes did not lead to any tetrahydropyridines. The conformation of the sulphinimine **217** is believed to be that shown in Scheme 69, where the sulphur–oxygen bond is coplanar to the aza-diene. The dienophile approaches the aza-diene from the less hindered face. For simple dienophiles, the *endo*/*exo* ratio was good (100:1, **216a** and **b**). When bulky or

Scheme 69.



Scheme 70.

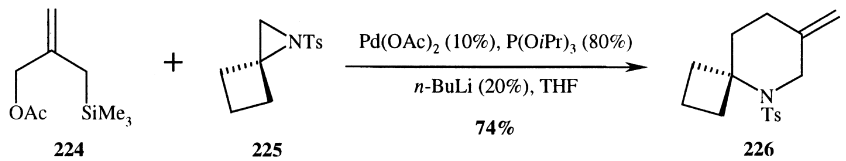
disubstituted enol ethers were reacted, however, the reaction was less diastereoselective (87:13, **216c**; 76:24, **216d**). The facial stereoselectivity was modest and ratios of between 1:1.7 and 1:2.3 were obtained. The piperidine **218a** was therefore formed in 60% yield and only 35% of the other diastereoisomer **219a** was isolated. Intramolecular Diels–Alder reactions seem to proceed more readily, although, in the example studied, the diastereoselectivity was not as good. Removal of the sulphoxide did not occur under conventional conditions ($LiAlH_4$ or Raney Ni), but this group could be removed by nucleophilic substitution with MeLi. After quenching with AcCl, the piperidine **220c** was obtained in 56% yield.

3.3. Other dipolar cycloadditions

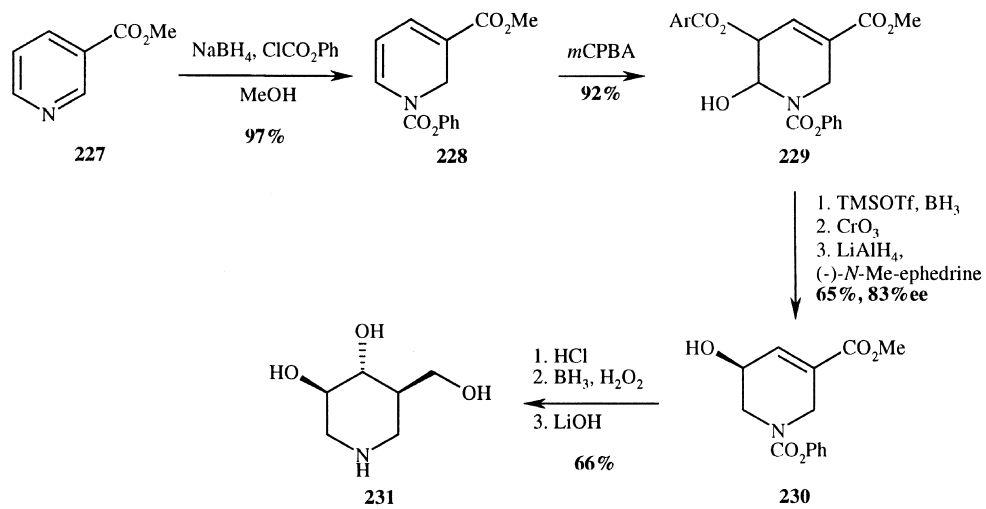
In their approach towards the synthesis of geissoschizine, Martin et al.[113] synthesised the piperidine **223** from **221** via a hetero Diels–Alder reaction (Scheme 70). Cleavage of the dihydropyran **222** gave the 3,4-disubstituted piperidine **223**.

Harrity and co-workers[114] have recently developed a general [3+3] cycloaddition reaction to synthesise 2-substituted piperidines. The reaction proceeds via an intermediate palladium–trimethylenemethane (Pd–TMM) complex **224** (Scheme 71). The study mainly examined the reaction of 1,1-disubstituted aziridines. The reaction seemed to be more efficient when $Pd(OAc)_2$ (10 mol%) was used with $P(OiPr)_3$ (80 mol%) as the ligand in the presence of *n*-BuLi (20 mol%), while THF was found to be the best solvent. A range of alkyl-, aryl- and allyl-aziridines have been investigated, giving modest to good yields of the products (44–82%). Phenylaziridine led to a mixture of diastereoisomers in which the aziridine was preferentially attacked at C-2 rather than C-1 (1.6:1 mixture). Reactions of symmetrical disubstituted aziridines gave similar yields. The reaction with *N*-tosylaziridine **225** afforded the piperidine **226** in 74% yield. When bicyclic aziridines were reacted in order to synthesise fused 5/6-, 6/6- or 7/6-membered rings, disappointing yields were, however, obtained, as the reactions were very slow (0–31%).

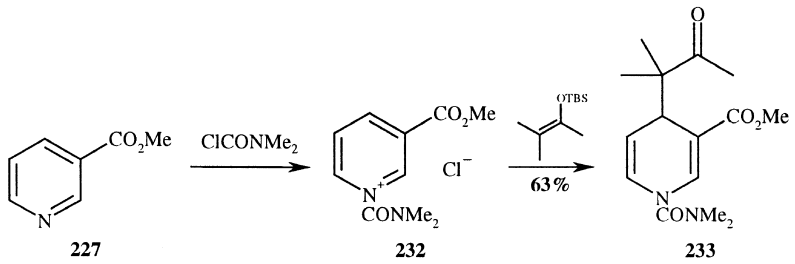
Both nitrones and azides are important building blocks in diastereoselective 1,3-cycloadditions, leading mainly to the 2-substituted piperidines. Further details can be found in previous reviews.[2]



Scheme 71.



Scheme 72.



Scheme 73.

4. Reduction of pyridines

The synthesis of piperidines from pyridines has been widely investigated and shown to be a very important synthetic tool for the preparation of 3,4,5-trisubstituted piperidine derivatives. Access to piperidines containing a quaternary carbon via the reduction of pyridines is, however, not the best strategy. Pyridines can be reduced to dihydropyridines, tetrahydropyridines or piperidines in one- or two-step processes. The most common method of reducing pyridines is by treatment with an electrophile such as phenyl chloroformate and a reducing agent such as $NaBH_4$. The direct hydrogenation of pyridines, however, is also discussed in the literature.

4.1. Reduction to dihydropyridines

Pyridines can be reduced to 1,2-dihydropyridines using $NaBH_4$. This strategy allows the possibility of further functionalisation of the six-membered ring. This type of reduction contains problems of diastereoselectivity and 1,2- or 1,6-reduction can occur. After the investigation, Sundberg et al.[115] have published the possibility of carrying out regioselectively the 1,2-reduction. Indeed, sterically-nondemanding donor substituents lead to 1,2-reduction. Acceptor substituents lead to lower reactivity and a lack of regioselectivity. Formation of the pyridinium salts with alkyl chloroformates, however, led to better results. Moreover, methanol gave a better result, whereas THF led to a mixture of regioisomers and 1,4-reduction.

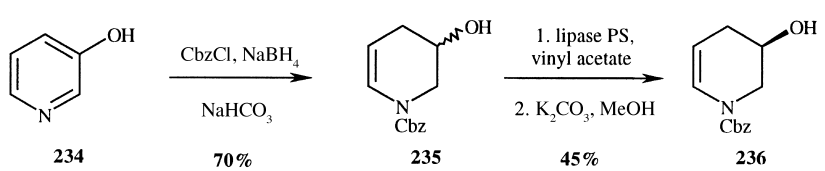
Ganem and co-workers[116] managed to reduce methyl nicotinate **227** to the 1,2-dihydropyridine **228** in 90% yield (Scheme 72). The dihydropyridine **228** was a crucial intermediate in a synthesis of azasugars. Epoxidation using *m*CPBA led to the compound **229** in 92% yield. The alcohol **230** was subsequently obtained in three steps, 65% yield and 83% ee. Saponification, followed by hydroboration and deprotection of the piperidine led to the corresponding azasugar **231** in 66% overall yield.

Formal 1,4-reduction of pyridines can also be performed by the addition of a nucleophile to the pyridinium salts. Akiba and co-workers[117] investigated the synthesis of 1,4-dihydronicotinate by the addition of silyl enol ethers to quaternised pyridines. Indeed, treatment of methyl nicotinate **227** with an electrophile such as dimethylcarbamoyl chloride led to the quaternised nicotinium salt **232** (Scheme 73). Reaction with silyl enol ethers led to 1,4 dihydropyridines such as **233** in 63% yield. 1,2- and 1,6-Dihydropyridines could be observed, depending on the nature of the silyl enol ether. The 1,4 dihydropyridines were, however, always the major isomer. Akiba also demonstrated that copper addition can be performed. The direct 1,4-reduction of pyridinium salts has additionally been achieved by O'Neill et al.[118] using sodium dithionate ($Na_2S_2O_4$) as the reducing agent.

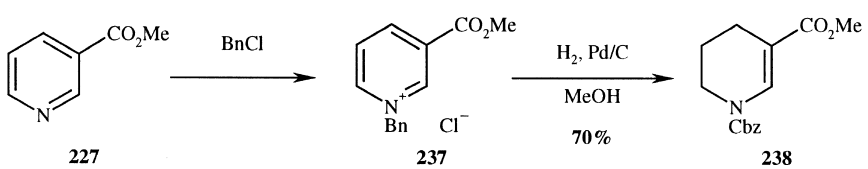
4.2. Reduction to tetrahydropyridine

Reduction to the tetrahydropyridine can also be performed. With substituted pyridines, however, problems of regioselectivity can appear although control can be achieved. Ogasawara and co-workers[119] studied the reduction of 3-hydroxypyridine **234** to the enamide **235** using the usual conditions such as $NaBH_4$ with CbzCl in ethanol (Scheme 74). Resolution of the racemic mixture enzymatically, followed by deprotection, afforded the enantiomerically-pure alcohol **236** in 31% yield over the three steps.

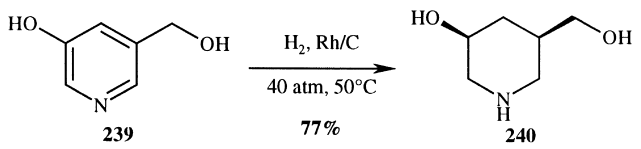
Plaquevent et al.[120] reported the reduction of pyridines having an electron-withdrawing group at C-3. Indeed after



Scheme 74.



Scheme 75.



Scheme 76.

formation of the bromo- or chloropyridinium salt **237**, reduction via hydrogenation afforded the tetrahydropyridine **238** in 70% yield overall (Scheme 75). In the case of the bromide salt, previous treatment with AgCl was necessary as the counteranion could poison the Pd/C catalyst for the hydrogenation.

Liu and co-workers[121] obtained similar 1,4,5,6-tetrahydropyridines from the reduction of 1,4-dihydropyridines using H_2 with 10% Pd/C in a mixture MeOH/THF and 1,2,5,6-tetrahydropyridines[122] can be obtained with sodium borohydride at −15 °C.

4.3. Reduction to piperidines

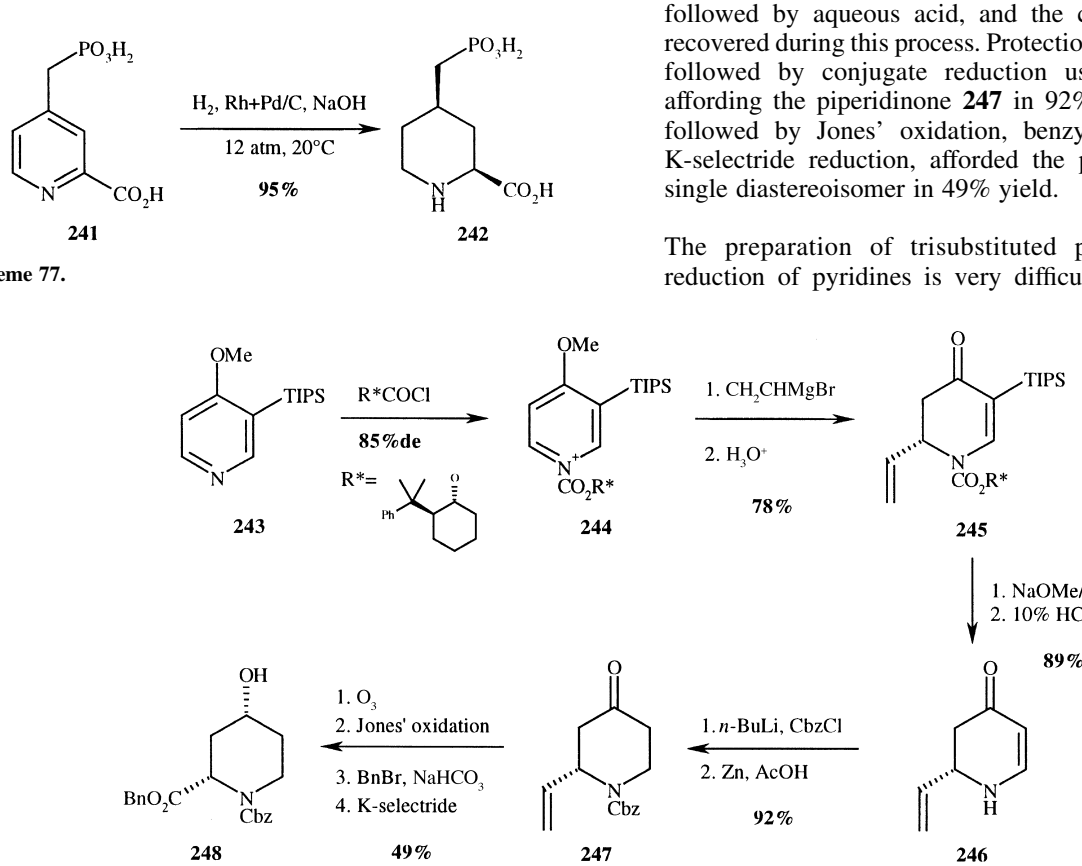
The full reduction of pyridines to piperidines can be achieved using hydrogenation. Different catalysts such as Pd/C, PtO_2 or Rh/C can be used. When substituted pyridines are used, problems with diastereoselectivity can result, with the main product generally being the all-*syn* piperidines, although mixtures of diastereoisomers are observed in most cases. The reduction of the diol **239** by Bols et al.[123] using Rh/C as the catalyst led to *syn* 3,5-hydroxyhydroxymethylpiperidine **240** in 77% yield (Scheme 76). The reduction of 3,5-pyridinedicarboxylic acid diethyl ester using PtO_2 in AcOH afforded a 3:2 mixture of the *anti*/*syn* piperidines.[124]

Steiner et al.[125] studied the reduction of 2,4-pyridines such as **241** using different catalysts, solvents and reaction conditions (Scheme 77). The mixed catalysts gave better results in terms of diastereoselectivity and a 1:9 Rh/Pd ratio was found to be the optimum mixture. Due to solubility reasons, hydrogenation was performed on the corresponding pyridine salt in aqueous solution. The best result in terms of diastereoselectivity was obtained using 1 equiv. of NaOH. An excess of base led to a lower diastereoselectivity. These workers were able to efficiently scale up the reduction of the pyridine **241** to the desired *syn* 2,4-disubstituted piperidine **242**, in 95% yield, which contained 3% of the *anti* diastereoisomer.

The stereoselective reduction of 2-methylnicotinic acid has been investigated by Besson and co-workers,[126] using a chiral auxiliary introduced as an amide. A 4:1 mixture of the *syn*/*anti* diastereoisomers and modest diastereoisomeric excesses of between 17 and 35% were obtained.

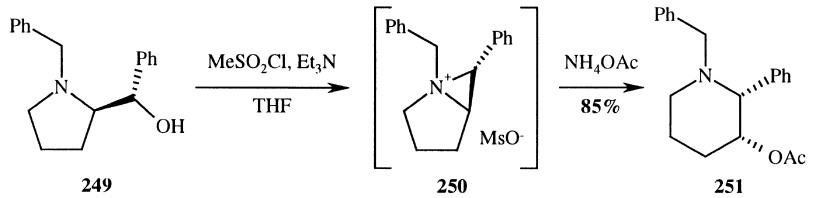
In their approach to the synthesis of palinavir, Comins et al.[127] synthesised 2,4-substituted piperidines enantioselectively from the pyridine **243** (Scheme 78). A chiral pool strategy was used and the enantiomerically-pure (85% de) pyridinium salt **244** was formed. Grignard addition at the C-2 position of the pyridine, followed by methyl ether deprotection, afforded the hydropyridinone **245** as a single diastereoisomer in 78% yield. The hydropyridinone **246** was then formed in 89% yield by treatment with NaOMe, followed by aqueous acid, and the chiral auxiliary was recovered during this process. Protection was then achieved, followed by conjugate reduction using Zn in AcOH, affording the piperidinone **247** in 92% yield. Ozonolysis, followed by Jones' oxidation, benzyl esterification and K-selectride reduction, afforded the piperidine **248** as a single diastereoisomer in 49% yield.

The preparation of trisubstituted piperidines via the reduction of pyridines is very difficult and, as Bols and

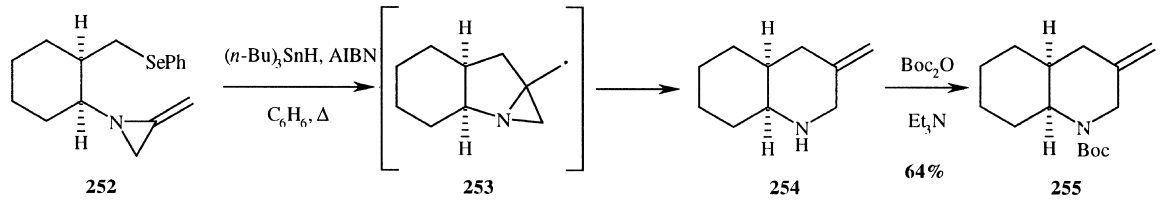


Scheme 77.

Scheme 78.



Scheme 79.



Scheme 80.

co-workers[128] have reported, mixtures of diastereoisomers are formed. Diastereoselective control via this type of reduction is very difficult.

5. Ring expansions and rearrangements

5.1. Ring expansion from pyrrolidines

Lee et al.[129] used an unusual method for making piperidines via a ring expansion of the hydroxymethylpyrrolidine **249** (Scheme 79). This strategy was demonstrated to be a highly stereoselective method for synthesising 2,3-disubstituted piperidines from *N*-benzylpyrrolidines such as **249**. Treatment of the compound **249** with methanesulphonyl chloride and triethylamine is believed to form the azoniabicyclo[3.1.0]hexane intermediate **250**, which, when quenched with ammonium acetate, undergoes a ring expansion to form the acetoxypiperidine **251** in 85% yield and 99% ee.

5.2. Intramolecular radical rearrangement

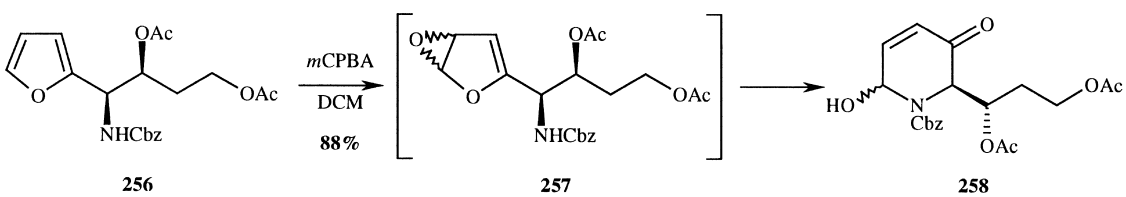
Shipman et al.[130] have been working on the intramolecular 5-*exo* cyclisation of the 3-(2-methyleneaziridin-1-yl)propyl radical generated from the corresponding selenide. Treatment of the 2-methyleneaziridine **252** with $(n\text{-Bu})_3$SnH and AIBN afforded via **253** the corresponding piperidine **254**, which was immediately Boc protected (Scheme 80). The piperidine **255** was obtained in 64% yield over the two steps.

5.3. Oxidation of furans

In their approach towards the synthesis of indolizidines, Padwa et al.[131] oxidised a furan with *m*CPBA to furnish an epoxy intermediate, which rearranged via an aza-Achmatowicz reaction to provide a hemiaminal in 85% yield. Zhou and co-workers[132] used the same strategy in their synthesis of (+)-6-epicastanospermine and demonstrated that rearrangement was favoured over nucleophilic substitution. Indeed, the furan **256** containing both primary and secondary acetates was oxidised with *m*CPBA to afford the hemiaminal **258** via the intermediate **257** in 88% yield (Scheme 81).

6. Conclusions

The synthesis of diversely-functionalised piperidines remains one of the challenges of organic chemistry. Although the synthesis of 2,6-disubstituted piperidines has been widely investigated, the preparations of more complex piperidines such as 3-, 4- and 5-multisubstituted piperidines, as well as piperidines containing quaternary centres, are less prevalent in the literature. The main strategy involved in constructing piperidine rings is via the cyclisation of a linear chain and this method is generally high yielding and reliable, although it demonstrates a lack of convergence. The synthesis of piperidines via the aza Diels–Alder reaction looks promising, but this methodology has not been yet widely applied. The preparation of piperidines through the reduction of pyridines has the advantage that the heterocyclic ring is already present, but the generalisation of this procedure to the synthesis of complex piperidines has been shown to be difficult. Finally, the rearrangement to piperidines is not a commonly-used method, although the technique shows some advantages in the synthesis of 2-mono- or 2,6-disubstituted piperidines. The preparation of piperidines has been widely studied, but their synthesis



Scheme 81.

remains a major challenge as more and more complex piperidine-containing compounds are designed, in order to improve the selectivity and therefore reduce the side effects of potential drugs.

Acknowledgements

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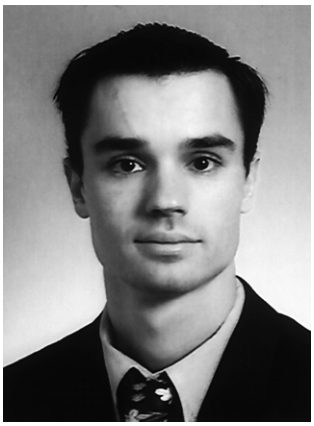
Biographical sketch



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