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Abstract. New methods for the preparation of 2-azabicyclo[3.1.0]hexane compounds (2,3-methanopyrrolidines) have been developed over the past three decades. Once viewed as rather exotic molecules, they can now be considered as readily accessible, especially by intermolecular Simmons-Smith type reactions or by intramolecular titanium-mediated cyclopropanation (Kulinkovich-de Meijere reaction). Accordingly, a number of applications of these compounds have emerged: in particular, they are being used as mimics of pyrrolidine, piperidine or proline subunits for the development of novel bioactive molecules. The use of 2,3-methanopyrrolidines as precursors of more complex nitrogen-containing heterocyclic systems has also become a relevant idea. This chapter is organised in two sections: a brief review of the main methods of synthesis of 2,3-methanopyrrolidines is first presented. It is followed by a personal account of some of the transformation reactions that have been developed over the last fifteen years.

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1. Introduction

The 2-azabicyclo[3.1.0]hexane heterocyclic system (or 2,3-methanopyrrolidine, Figure 1, top) has attracted the attention of organic chemists, both in the industry and in academic research laboratories, increasingly and for various reasons. It is worthy note that it can be found in the structures of natural products, albeit very rarely. Examples are lundurines A-D^{1,2} and pentacyclic alkaloids recently isolated from holy basil (*Ocimum sanctum*) (Figure 1a).^{3,4} While antimalarial activity is reported for the latter,³ lundurine B exhibits appreciable activity against B16 melanoma cells.²

The potential of 2,3-methanopyrrolidines for applications in life sciences has been explored for more than 25 years. In a pioneering study, the unnatural amino acid 2,3-methanoproline was synthesised and found to be a weak inhibitor of ethylene production in several plants. As an analogue of 1-aminocyclopropanecarboxylic acid (ACC), it is likely that it interacts with the ethylene-forming enzyme (EFE), thus inhibiting the conversion of ACC into ethylene.⁵

2,3-Methanopyrrolidine moieties have also been incorporated in the structures of biologically active compounds to replace other heterocyclic systems, typically pyrrolidine subunits, with the aim of discovering new analogues with superior properties. This strategy is based on the assumption that the cyclopropane ring

induces important conformational constraints that can modify the metabolic stability of the molecule and/or its interaction with the biological target, while being small enough to be tolerated by the latter.⁶

The validity of this approach was demonstrated in the late 1990s by the group of Hanessian, who prepared several analogues of captopril, a drug used for the treatment of hypertension. The new compounds, featuring 4,5-methanoproline (or 5,6-methanopipecolic acid) subunits instead of the proline moiety of the initial molecular structure,⁷ were found to be better selective inhibitors of angiotensin-converting enzyme than captopril.⁶

The most prominent example of application of this principle is probably the development of the synthetic drug saxagliptin (Figure 1b). This molecule is a dipeptidyl peptidase-4 (DPP-4) inhibitor which is being used to treat patients suffering from type 2 diabetes.⁸⁻¹¹ Other studies have been conducted more or less successfully and many 2,3-methanopyrrolidine compounds have been prepared, which often are methanoproline derivatives, to be assessed for activities against various biological targets. Examples include the oestrogen receptor alpha ER α ,¹² the histamine H₃ receptor,^{13,14} the metabotropic glutamate receptor mGluR5,¹⁵ tyrosine kinases,¹⁶ the nonstructural protein 5A encoded by the hepatitis C virus HCV,¹⁷⁻²⁰ the $\alpha_4\beta_2$ nicotinic acetylcholine receptor,²¹ apoptosis proteins,^{22,23} 11 β -hydroxysteroid dehydrogenase type 1,²⁴ the prostaglandin E2 receptor 4,²⁵ and complement factor D.^{26,27}

Applications in catalysis have been investigated as well: *trans*- and *cis*-4,5-methanoproline were thus tested in the Hajos-Parrish-Eder-Sauer-Wiechert reaction. While the *trans* isomer was found to be a less active and less enantioselective catalyst than proline, the *cis* isomer performed nearly as well as the latter.²⁸

Finally, because of the internal strain of their fused bicyclic ring system, 2,3-methanopyrrolidine derivatives can undergo interesting cyclopropane-ring opening reactions, which makes them valuable reactive intermediates for the synthesis of other nitrogen-containing heterocyclic systems (Figure 1c).

The present chapter is intended as a brief account presenting the main methods of preparation of 2,3-methanopyrrolidines, as well as some applications of these compounds as precursors of other heterocyclic systems, with special focus on our own contributions. For the sake of conciseness and to allow for sufficient detail in the discussion, the chemistry of 2,3-methanoindoles and 2,3-methanopyrroles has essentially been excluded from the scope of this report.

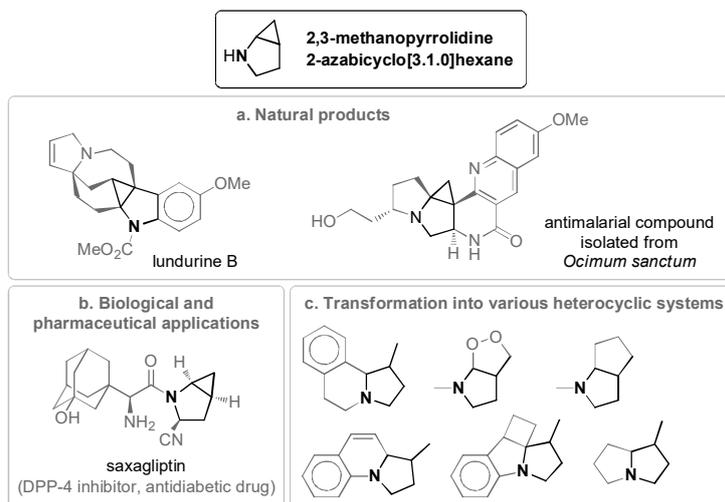
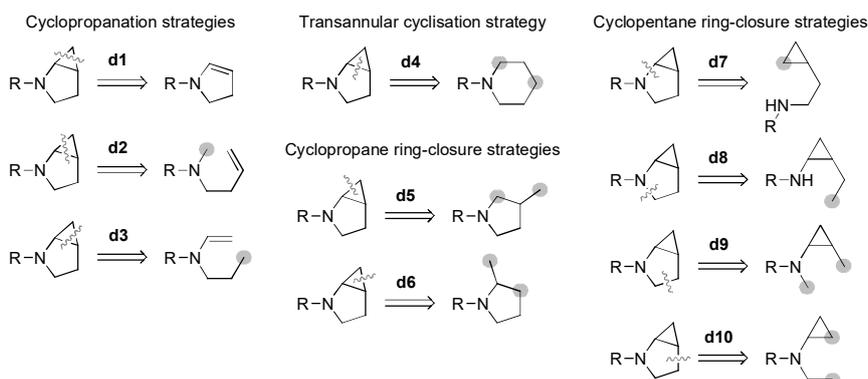


Figure 1. The 2,3-methanopyrrolidine scaffold and its occurrence in the structures of natural products (a) and in the antidiabetic drug saxagliptin (b). A selection of nitrogen-containing polycyclic skeletons that can be accessed from 2,3-methanopyrrolidine precursors is also displayed (c).

2. Methods of preparation

Numerous retrosynthetic disconnections can be envisaged for the formation of 2,3-methanopyrrolidine derivatives (Scheme 1). Among those based on cyclopropanation processes (**d1-d3**), disconnections **d2** and **d3** appear especially powerful, since both the cyclopropane and the pyrrolidine rings are formed in a single operation starting from acyclic precursors. As it will be seen further below, examples corresponding to disconnection **d3** are comparatively scarce. Disconnection **d4**, which relies on the transannular cyclisation of a piperidine compound, is also an interesting strategy, with the formation of only one carbon-carbon bond from simple piperidine precursors. Other single bond disconnections are associated with cyclopropane-ring closure from a pre-existing pyrrolidine unit (**d5** and **d6**), or with the formation of a five-membered ring from an aminocyclopropane substrate (**d7-d10**). It is worth noting that examples of syntheses following **d7** or **d9** are difficult to find. This is perhaps not surprising since **d7** relies on the difficult functionalisation of a cyclopropane ring with a nitrogen-based group, whereas **d9** is not a particularly advantageous strategy, as it involves the reaction of a functionalised precursor that might be more difficult to make than the target 2,3-methanopyrrolidine system.



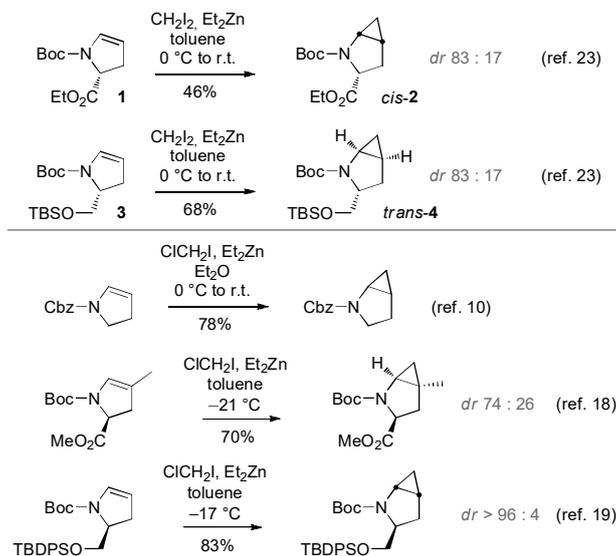
Scheme 1. Selected retrosynthetic disconnections of the 2,3-methanopyrrolidine system. The grey disks represent carbon centres fitted with suitable substituents for the formation of the bond(s) disconnected.

2.1. Cyclopropanation of 2-pyrroline derivatives

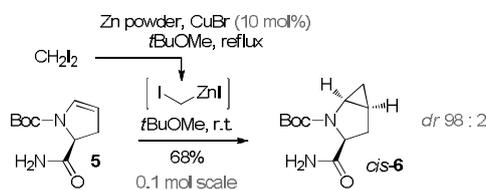
The synthesis of 2,3-methanopyrrolidines by cyclopropanation processes carried out from 2-pyrroline derivatives (Scheme 1, disconnection **d1**) is a particularly successful approach. Since the 2-pyrroline starting materials have to be sufficiently stable to be prepared and handled, these are typically substituted with an electron-withdrawing group at the nitrogen atom. This synthetic route is thus well suited to the preparation of 2,3-methanopyrrolidine building blocks that are protected at the nitrogen atom, usually by a Boc or a Cbz group.

A particularly popular and efficient cyclopropanation method uses the Simmons-Smith reaction under the improved conditions introduced by Furukawa *et al.* ($\text{CH}_2\text{I}_2/\text{Et}_2\text{Zn}$).²⁹ It was first applied in this context by Hanessian *et al.* for the preparation of the important 4,5-methanoproline building block **2**.⁶ Interestingly, while the coordinating effect of the ester group of the dehydroproline derivative **1** directs the approach of the zinc carbenoid reagent to form the *cis* diastereoisomer preferentially,⁶ the reaction of the corresponding *tert*-butyldimethylsilyloxymethyl compound **3** proceeds with reversed diastereoselectivity (Scheme 2, top two examples).²³ This is rationalised by the much reduced coordinating ability of this functional group, which then acts as a bulky substituent blocking one of the faces of the molecule, resulting in the formation of *trans*-**4**. It is worth noting that application of Denmark's procedure, with ICH_2Cl being used instead of CH_2I_2 , usually gives better yields (Scheme 2, bottom three examples).^{9,10,18,19}

An interesting variation has been reported recently, which consists in producing the Simmons-Smith reagent conveniently from CH_2I_2 and Zn powder in the presence of $\text{Cu}^{\text{I}}\text{Br}$. While maintaining good results, it avoids the use of pyrophoric Et_2Zn . Compound *cis*-**6** can thus be synthesised efficiently on multi-gram scale from **5** (Scheme 3).³⁰



Scheme 2. Formation of 2-azabicyclo[3.1.0]hexane systems from dehydropyrroline derivatives using Simmons-Smith-type cyclopropanation reactions.^{10,18,19,23}



Scheme 3. Modified conditions for the convenient scalable Simmons-Smith cyclopropanation of dehydropyrroline derivative **5**.³⁰

The chemistry of carbenes or transition-metal carbenoids generated from diazo compounds has also been used for this kind of transformation. It must be noted that using diazo derivatives that are substituted with an electron-withdrawing group, such as ethyl diazoacetate, the product is a donor-acceptor cyclopropane, that may suffer ring-opening spontaneously if too sensitive.

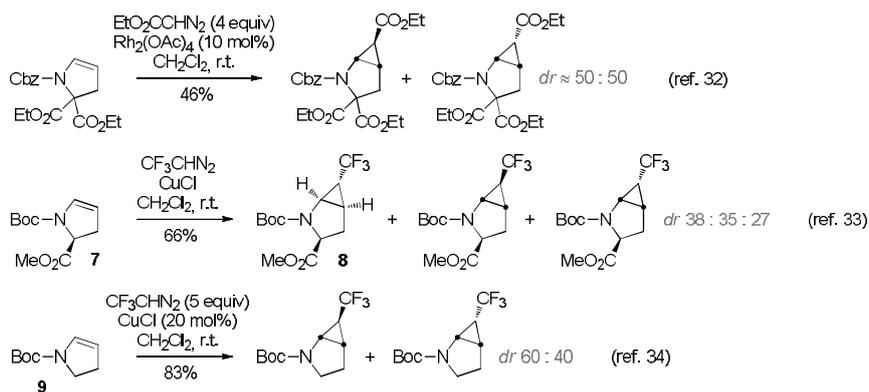
Indeed, initial studies were conducted on indole derivatives and the corresponding cyclopropane products could be isolated only starting from substrates in which the +M donating effect of the nitrogen atom was strongly reduced, *e.g.* *N*-acyl- or *N*-carboalkoxy- indoles.³¹ *N*-Cbz or *N*-Cbz 2-pyrrolines are suitable substrates as well but examples are rather scarce (Scheme 4).^{32–34} It is suggested that after ester hydrolysis and amine deprotection, the CF₃-substituted proline analogue **8** could be a promising label for solid state ¹⁹F NMR spectroscopy of proline-containing peptides.³³

With diazomethane itself, sufficiently electron-poor 2-pyrroline derivatives undergo 1,3-dipolar cycloaddition to afford pyrazoline intermediates. Formation of the corresponding cyclopropane compounds, with loss of dinitrogen, can then be triggered by thermal³⁵ or photochemical activation.⁵ Slow spontaneous cyclopropanation has also been reported.³⁶ Examples are presented in Scheme 5.

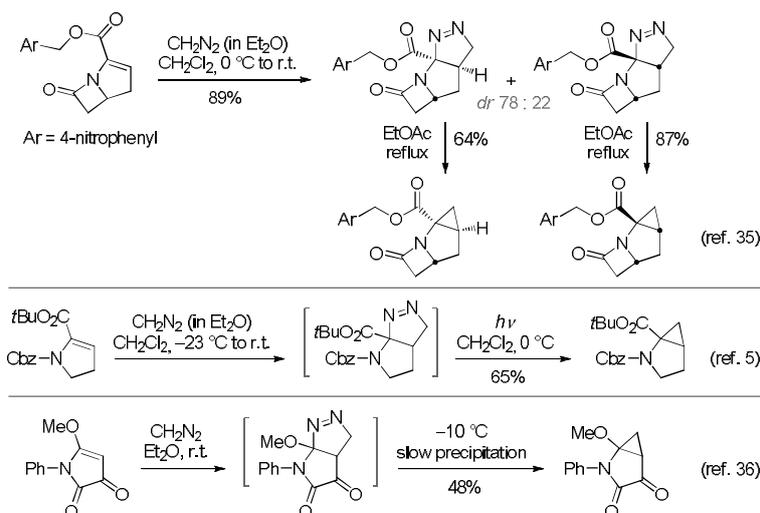
Related 2-pyrroline derivatives in which the C=C double bond is substituted with an ester group at position 2 can also be engaged in cyclopropanation using a sulfoxonium ylid (Corey-Chaykovsky reaction), as illustrated by the two examples displayed in Scheme 6.^{37,38}

Finally, since dichlorocarbene and dibromocarbene can be generated very conveniently and at low cost from chloroform or bromoform under basic conditions, cyclopropanation of 2-pyrroline derivatives by these species is an excellent way to prepare 2,3-methanopyrrolidines that are substituted with halogen atoms

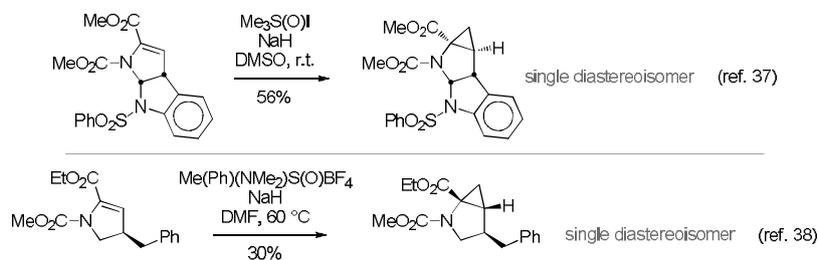
(Scheme 7).^{39,40} These reactions give best results when performed under the conditions developed by Mąkosza *et al.*⁴¹



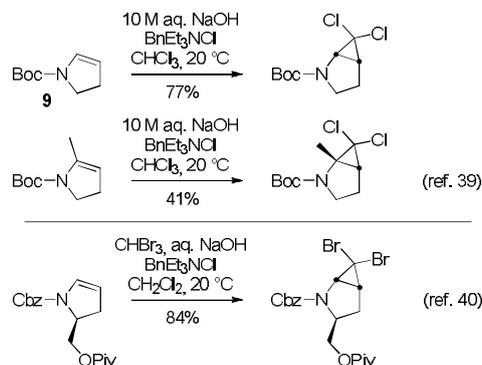
Scheme 4. Rh- or Cu- catalysed cyclopropanation of 2-pyrroline derivatives with diazo compounds.^{32–34}



Scheme 5. Stepwise cyclopropanation of electron-poor 2-pyrroline derivatives with diazomethane.^{5,35,36}

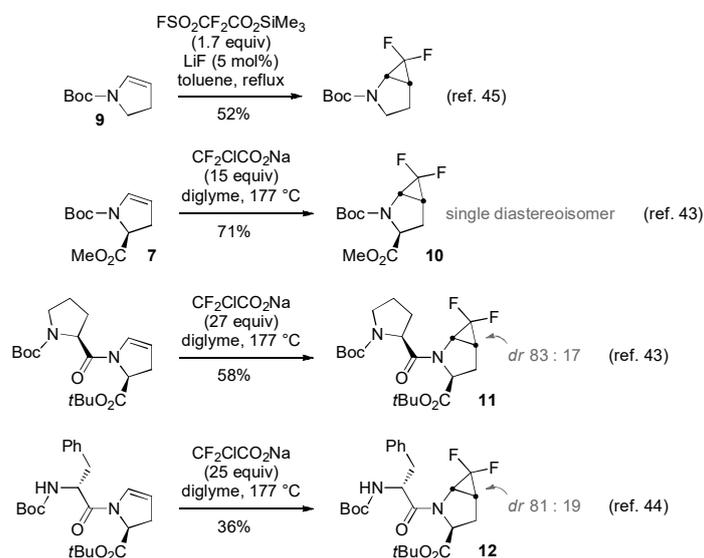


Scheme 6. Synthesis of 2-carboalkoxy-2,3-methanopyrrolidines by the Corey-Chaykovsky reaction.^{37,38}



Scheme 7. Cyclopropanation reactions with dihalocarbenes generated from chloroform or bromoform.^{39,40}

The generation of difluorocarbene, albeit less straightforward, gives good results as well.⁴² The difluorocyclopropane compound **10**, which is a modified proline derivative, can thus be prepared efficiently from **7** (Scheme 8, second example).⁴³ Since this type of molecule is not stable in the free amine form (see paragraph 3.5), a relevant solution for applications in the context of polypeptide synthesis had to be found. This involves the direct use of dipeptide starting materials, which could be transformed into modified difluorocyclopropane-containing dipeptides **11** and **12** that were incorporated in the structures of the “sweet arrow peptide” (SAP) and gramicidin S, respectively (Scheme 8, bottom two examples).^{43,44} It is worthy of note that the Dolbier reagent $\text{FSO}_2\text{CF}_2\text{CO}_2\text{SiMe}_3$ has to be employed for the conversion of the parent *N*-Boc-2-pyrroline **9**, rather than $\text{CF}_2\text{ClCO}_2\text{Na}$ (Scheme 8, top example).⁴⁵



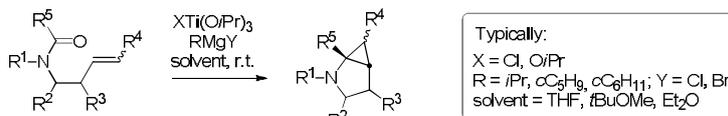
Scheme 8. Cyclopropanation reactions with difluorocarbene.^{43–45}

2.2. Intramolecular cyclopropanation of *N*-homoallylamine derivatives

As already mentioned, strategies based on disconnection **d2** (Scheme 1) are especially powerful because they represent a straightforward access to the 2,3-methanopyrrolidine system from non-cyclic precursors. Nevertheless, it should be noted that in practice, virtually all the current methods developed along this approach lead to tertiary amine products and are therefore not suitable for the direct preparation of

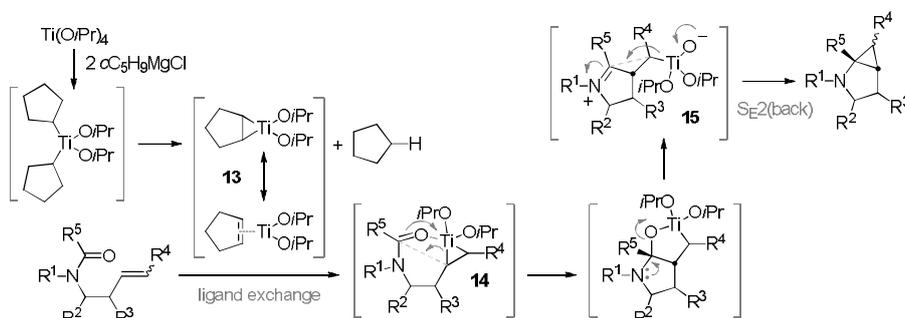
N-protected 2,3-methanopyrrolidines. They can thus be judged as complementary to the reactions described in the previous section.

There is no doubt that today, the most general and well-studied method for the intramolecular cyclopropanation of *N*-homoallylamine derivatives is the reaction of amide substrates with a combination of a Grignard reagent and a titanium(IV) alkoxide complex (Scheme 9).⁴⁶ This process is an application of the de Meijere variation of the reaction first reported by the group of Kulinkovich in 1989.⁴⁷⁻⁴⁹



Scheme 9. Titanium-mediated synthesis of 2,3-methanopyrrolidines from *N*-homoallyl amides.

The generally accepted mechanism of the intramolecular cyclopropanation reaction involves the initial generation of a titanacyclopropane species **13**, resulting from attack of the Ti^{IV} alkoxide by two equivalents of the Grignard reagent (Scheme 10). Ligand exchange with the substrate leads to the formation of the titanacyclopropane complex **14**. The latter is then transformed into the zwitterionic intermediate **15** by intramolecular addition onto the carbonyl group followed by carbon-oxygen bond-cleavage assisted by the lone-pair of the nitrogen atom. Finally, the cyclopropane ring is closed by intramolecular aliphatic electrophilic substitution at the centre bearing the titanium atom. This elementary step has been shown to proceed with inversion of configuration, as shown in the scheme [S_E2(back) mechanism].^{50,51}

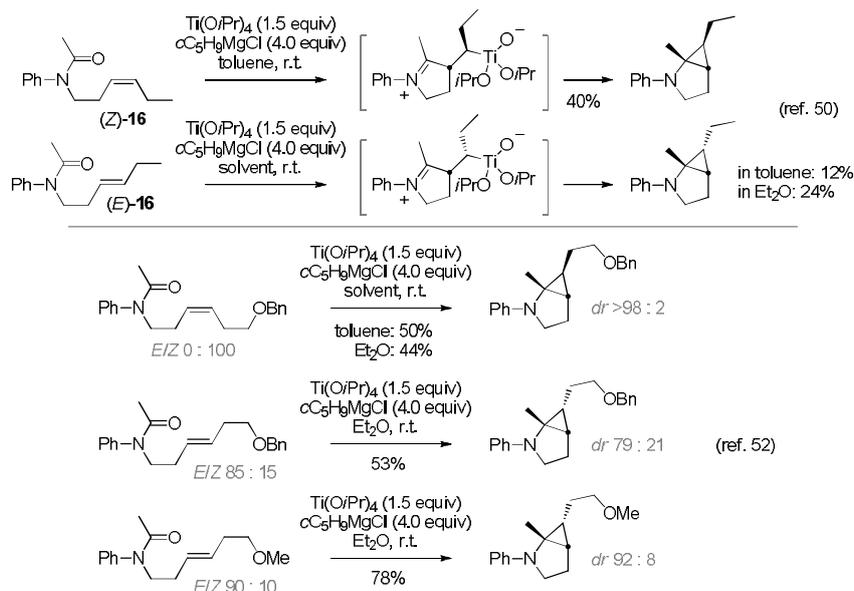


Scheme 10. Mechanism of the Ti-mediated intramolecular cyclopropanation of *N*-homoallyl amides, illustrated with the $Ti(OiPr)_4/cC_5H_9MgCl$ reagent system.^{48a,50,51}

In the case of substrates with $R^4 \neq H$, metal complexation of the substrate leading to the titanacyclopropane complex **14** takes place with retention. As a consequence and taking into account the inversion occurring in the final ring closure, the relative configuration of the R^4 substituent in the product is controlled by the geometrical configuration of the $C=C$ double bond of the starting amide, as illustrated in Scheme 11.^{50,52} It is worthy of note that satisfactory yields are obtained only when a coordinating group (e.g. OMe, OBn) is included in the R^4 substituent, to ensure the ligand exchange step is favourable enough (Scheme 11, compare the reactions of (*E*)- and (*Z*)-**16**, where this effect is absent, with the other examples).

The substitution pattern tolerated by the transformation can be appreciated by looking at the selection of examples presented in Table 1.^{46,53-58} These results show that formamides, acetamides and other amides with a larger acyl group can participate in the reaction, although the poor result obtained in the synthesis of the substituted compound **26** is to be noted.⁵⁸ While unprotected indole systems are acceptable substrates (compounds **20** and **21**),⁵⁴ the pyrrole **23** is not obtained in satisfactory yield under standard reaction conditions. It must either be protected beforehand, as in the preparation of **22**, or special conditions have to be applied, involving temporary protection with a labile trimethylsilyl group.⁵⁵ The structures of the starting *N*-homoallyl amides may include an ester group, as shown by the successful preparations of compounds **24**-

26. However, bulky *tert*-butyl ester groups are preferred and it is advisable to use reduced quantities of the organometallic reagents, in order to minimise the formation of side-products resulting from unwanted intermolecular Kulinkovich reaction.⁵⁸



Scheme 11. Intramolecular cyclopropanation of *N*-homoallyl amides with an internal C=C double bond.^{50,52}

It has recently been pointed out that certain cyclic substrates do not follow the expected reaction course.⁵⁹ Indeed, the formation of the iminium intermediate **15** (Scheme 10) involves a change in carbon hybridisation from sp^3 to sp^2 and this may be forbidden for geometrical reasons (Bredt's rule). A relevant example is presented in Scheme 12 (top).⁵⁹ Conversely, starting from the larger lactam **27**, the corresponding bridged bicyclic iminium intermediate suffers from less internal strain and becomes accessible, as evidenced by the formation of the aminocyclopropane **28** (Scheme 12, bottom).⁵⁹

With respect to the diastereoselectivity of the cyclopropanation process, results indicate that chiral substituents attached to the nitrogen atom of *N*-homoallylacetamides generally exercise a very moderate influence (Scheme 13).^{60–63} Indeed, in the examples presented, a 2:1 selectivity is obtained at best, starting from the very bulky substrate **30** derived from 1-(2,4,6-triisopropylphenyl)ethylamine.^{62,64}

Moreover, the use of benzyl-type substituents as chiral auxiliaries is also largely thwarted by the difficulty of cleaving such groups from the aminocyclopropane products. There are some reports of successful hydrogenolysis reactions catalysed by Pd/C;^{13,23,65} however, cyclopropane-ring opening is often observed under such conditions.^{61,66,67} Alternative methods have thus been applied, for instance *N*-dealkylation with chloroethyl chloroformate (see Scheme 17 for an example).^{9,10,66,68}

Another possibility is to use the Polonovski reaction,⁶⁹ which leads to the *N*-Boc protected compound **32** directly by reaction of the *N*-oxide **31** with Boc₂O (Scheme 14, top).⁶¹ Nevertheless, although this method works well for the cleavage of the benzyl group, it gave poor results in our hands when more substituted benzyl-type substituents had to be removed. A solution for the cleavage of the 1-phenyl-2-methoxyethyl group is to perform the E2 elimination of methanol using potassium *tert*-butoxide in DMSO. This generates an enamine intermediate **33** that is readily hydrolysed to the free amine **34**, as illustrated in Scheme 14 (bottom).⁶¹

Another interesting situation is associated with the use of substrates for which a substituent is attached to the *N*-homoallyl chain. Two diastereoisomers can be produced, with typically better control, since the substituent is connected to the cycle being formed.

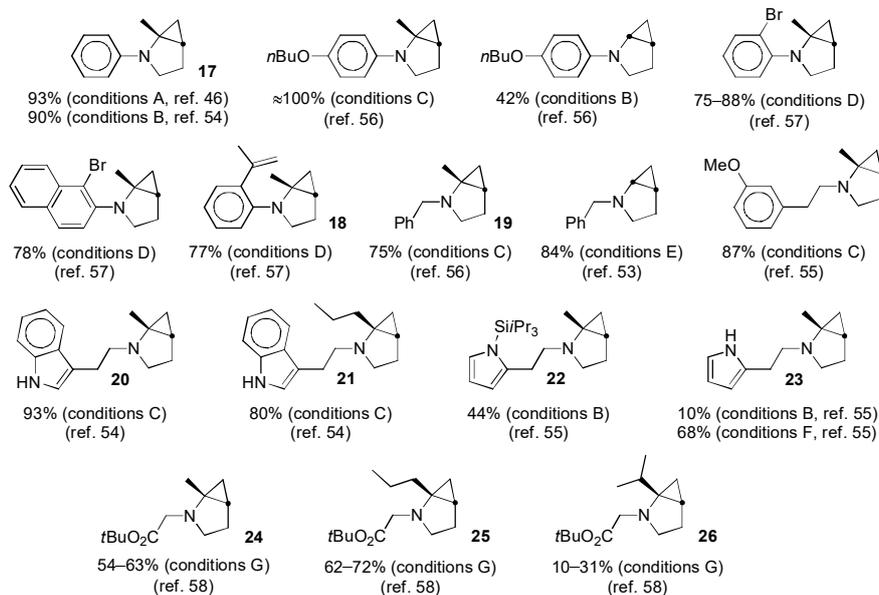
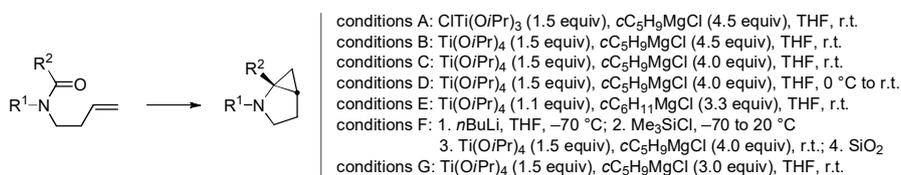
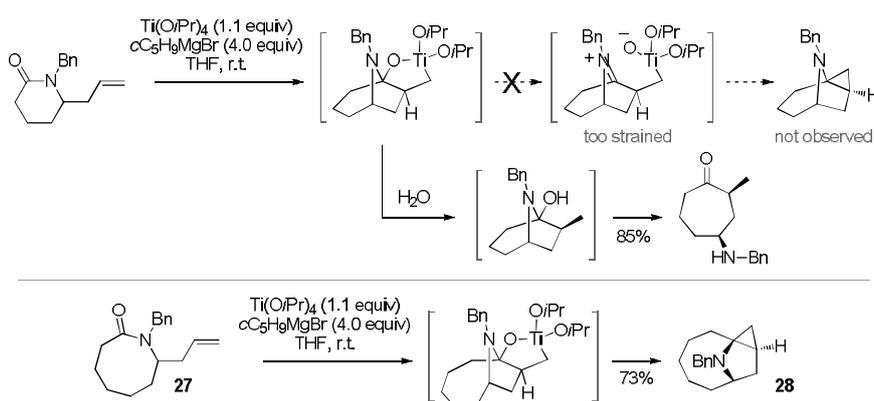
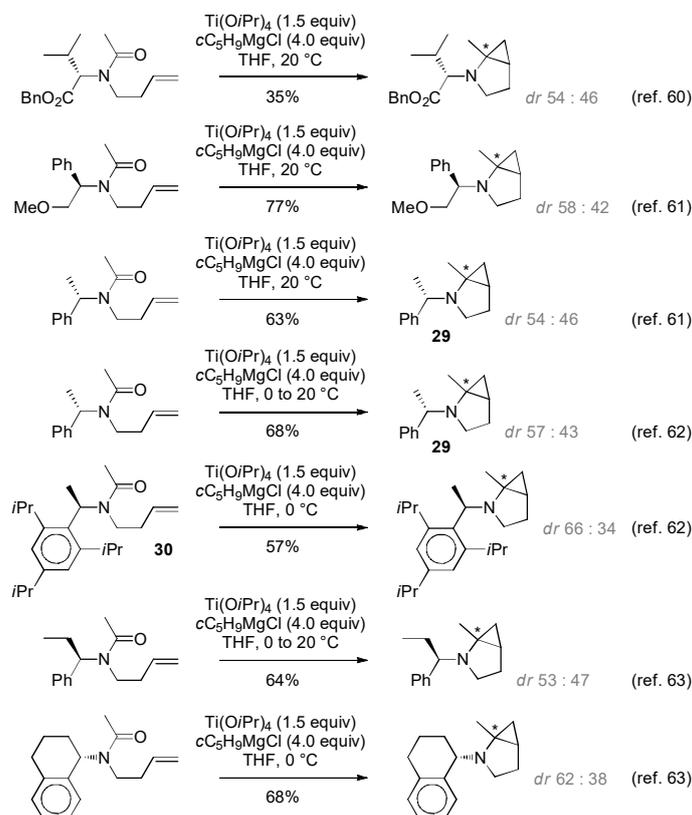


Table 1. Various 2,3-methanopyrrolidine compounds prepared by intramolecular Kulinkovich-de Meijere reactions.^{46,53-58}

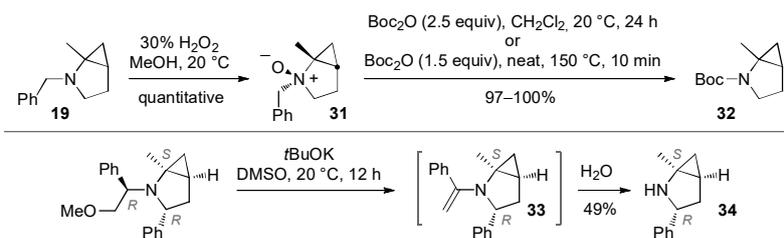


Scheme 12. Examples of titanium-mediated reactions of lactam derivatives.⁵⁹

Indeed, an interesting limited study carried out on *N*-benzyl acetamide derivatives demonstrates that satisfactory diastereoselectivities are achieved when the chiral centre of the substrate is located next to the $\text{C}=\text{C}$ double bond, the best results being observed with the largest R groups (Table 2).⁵³



Scheme 13. Intramolecular Kulinkovich-de Meijere reactions of *N*-homoallylacetamides bearing a chiral group attached to the nitrogen atom.⁶⁰⁻⁶³



Scheme 14. Cleavage of benzyl-type substituents from the nitrogen atom of 2,3-methanopyrrolidines, with preservation of the cyclopropane ring.⁶¹

When the substituent of the *N*-homoallyl chain is fitted at the position adjacent to the nitrogen atom, diastereoselectivity tends to be lower (Table 3).^{70,71} It increases with the size of all three groups R^1 , R^2 and R^3 and acetamides having an aromatic group attached to the nitrogen atom ($R^1=Me$, $R^2=Ar$) lead to selectivities ranging from 89:11 to 98:02 in the examples presented. It is noteworthy that experiments carried out in Et_2O or in *t*BuOMe constantly give better results than in the more coordinating solvent THF. Starting from substrates with a disubstituted olefinic part, the same kind of control is still observed but the degree of diastereoselectivity is somewhat modified by the geometry of the $C=C$ double bond. Indeed, the *Z* compounds lead to increased diastereoselectivity, while the *E* substrates are converted with lower

diastereoselectivity (Scheme 15).⁷² As for the relative configuration of the additional substituent originally attached to the olefin, it is still fully dictated by the *E* or *Z* geometry of the C=C double bond, as in the simpler situation where the substrate is not a chiral molecule (see Scheme 11).

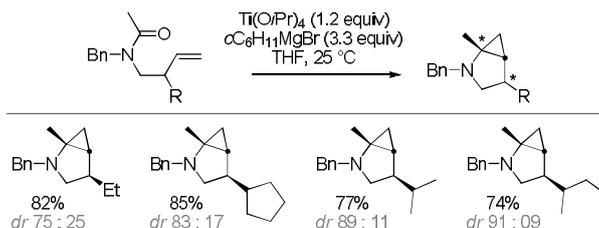


Table 2. Intramolecular Kulinkovich-de Meijere reactions of substrates with a *N*-homoallyl chain substituted at the position adjacent to the olefin function.⁵³

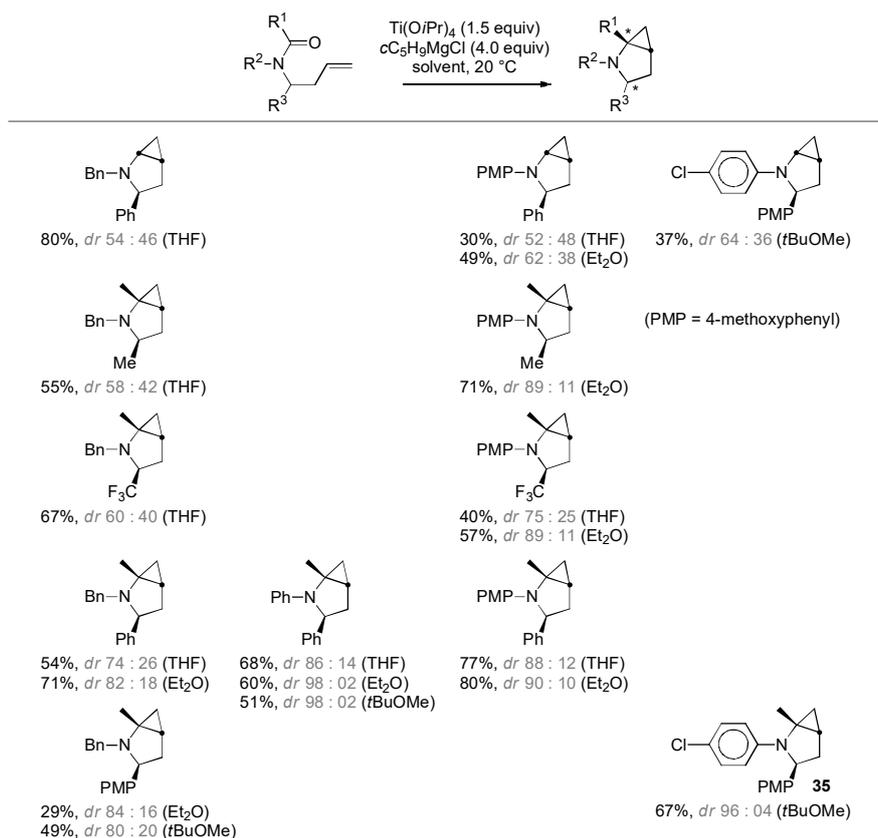
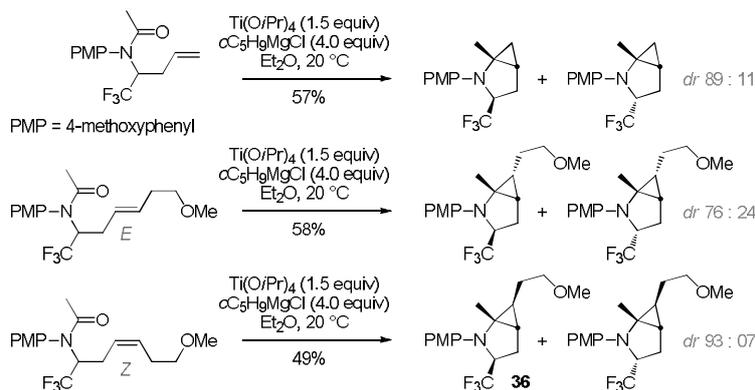


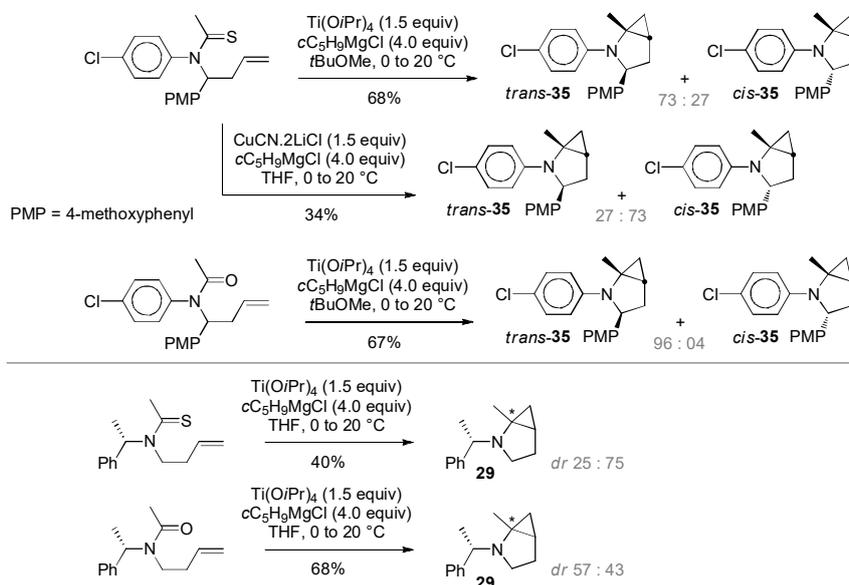
Table 3. Intramolecular Kulinkovich-de Meijere reactions of substrates with a substituent at the position adjacent to the nitrogen atom, on the *N*-homoallyl chain.^{70,71}

Starting from thioamide compounds instead of carboxylic amides in reactions of this type has been investigated recently. Although the results have established that thioamides generally undergo a reductive alkylation process when treated with a Grignard reagent in the presence of Ti(OiPr)_4 ,^{73,74} *N*-homoallyl thioamides display non-typical behaviour and are transformed into the same 2,3-methanopyrrolidines that

would be produced from the corresponding amides (Scheme 16).⁷¹ However, yields tend to be significantly lower and strikingly different diastereoselectivities may sometimes be observed. Interestingly, preliminary investigations have shown that the use of Grignard reagents in the presence of ZnBr_2 or $\text{CuCN}\cdot 2\text{LiCl}$ instead of $\text{Ti}(\text{O}i\text{Pr})_4$ may lead to the formation of the same products. The mechanism operating in such cases has not been elucidated; it may involve radical species.



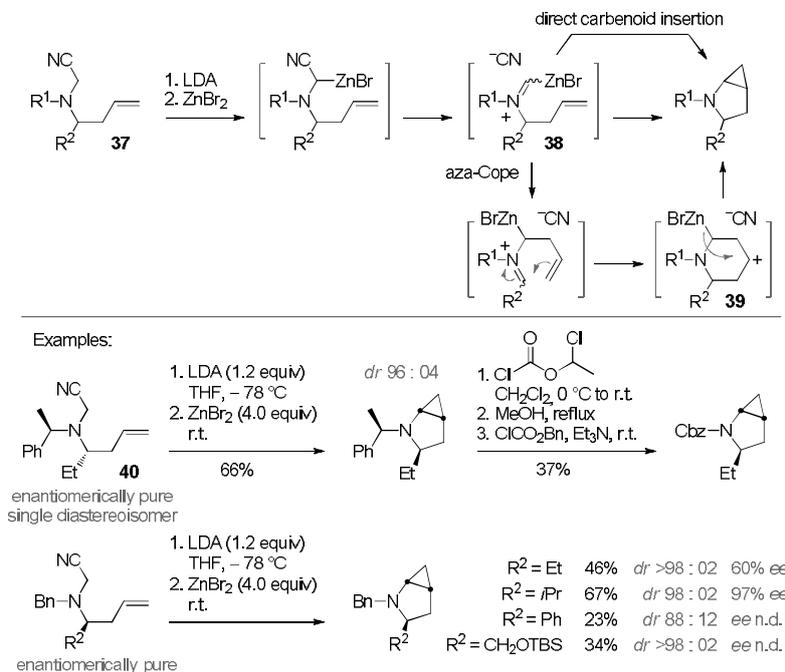
Scheme 15. Intramolecular Kulinkovich-de Meijere reactions of substrates bearing a disubstituted olefin part and a substituent next to the nitrogen atom, on the *N*-homoallyl chain.⁷²



Scheme 16. Metal-mediated transformation of an *N*-homoallyl thioamides into 2,3-methanopyrrolidines, compared with the intramolecular Kulinkovich-de Meijere reactions of the corresponding amides.⁷¹

An interesting alternative method for the production of 2,3-methanopyrrolidine compounds was reported fairly recently, from *N*-cyanomethyl-*N*-homoallyl tertiary amines **37** (Scheme 17).^{66,68} It relies on the generation of a zinc-substituted iminium ion **38**, after lithiation with LDA followed by transmetallation with ZnBr_2 . Experimental evidence is in agreement with two different possible mechanistic pathways that may operate depending on the substitution pattern. Starting from substrates having a bulky substituent

attached to the nitrogen atom (1-phenylethyl, diphenylmethyl), **38** is proposed to undergo an aza-Cope rearrangement. This process would be followed by cyclisation to the cation **39**. Eventual ring-closure by intramolecular electrophilic substitution accounts for the formation of the 2,3-methanopyrrolidine products. After conformational analysis of the transition states possibly involved, this provides a satisfactory explanation for the spectacular net inversion of the absolute configuration of the ethyl group in the reaction of compound **40** (Scheme 17). In contrast, starting from substrates having a simple benzyl group attached to the nitrogen atom, there appears to be a mechanism shift: the metallated iminium ion **38** behaves predominantly as a zinc carbenoid that inserts directly into the C=C double bond, although some erosion of the enantiomeric excess observed in the case where $R^1 = \text{Bn}$, $R^2 = \text{Et}$ remains to be explained.



Scheme 17. Zinc-mediated cyclopropanation of *N*-cyanomethyl-*N*-homoallyl tertiary amines.^{66,68}

Another original reaction provides a unique access, at least among the methods associated with disconnection **d2**, to functional *N*-tosyl 2,3-methanopyrrolidines **42** (Table 4).⁷⁵ This transformation involves the gold(I)-catalysed cycloisomerisation of *N*-homoallyl ynamide substrates **41**, proceeding with good to excellent diastereoselectivity.

One cannot close this subsection without mentioning isolated examples of other methods for the synthesis of 2,3-methanopyrrolidines, which involve the intramolecular cyclisation of carbene, metal-carbene complexes or metal carbenoid species.^{65,76-78} Two of them are presented in Scheme 18.

2.3. Intramolecular cyclopropanation of enamine derivatives

Although conceptually very powerful as well, the intramolecular cyclopropanation of enamine derivatives, corresponding to disconnection **d3** (Scheme 1), is less general. Indeed, only a limited range of enamine starting compounds are stable enough to be prepared and isolated. Therefore, examples are comparatively few. In the work reported by the group of Gharpure,^{79,80} the substrates are vinylogous carbamates **43** that are fitted with a chain containing an α -diazoketone function located at the suitable distance. Intramolecular copper-catalysed cyclopropanation provides access to the 2,3-methanopyrrolidine substructure. This is illustrated by the highly diastereoselective synthesis of the tricyclic compound **44**,

which was used as an intermediate in the context of the synthesis of the natural lanosterol synthase inhibitor ephelmin A (Table 5).⁸⁰

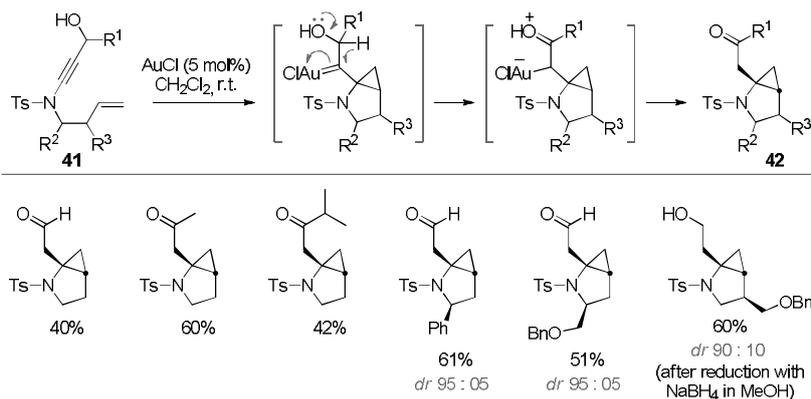
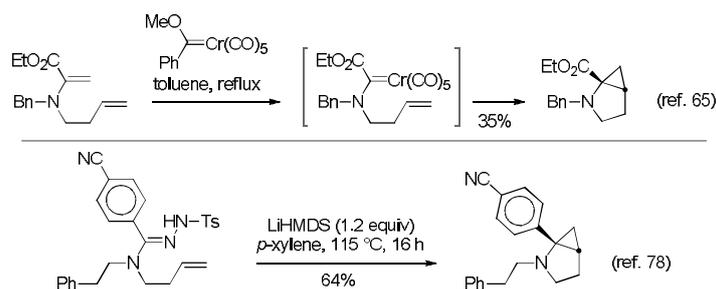


Table 4. Gold(I)-catalysed cycloisomerisation of well-chosen *N*-homoallyl ynamides.⁷⁵



Scheme 18. Intramolecular cyclopropanation reactions of α -amino -carbenes or -carbene complexes.^{65,78}

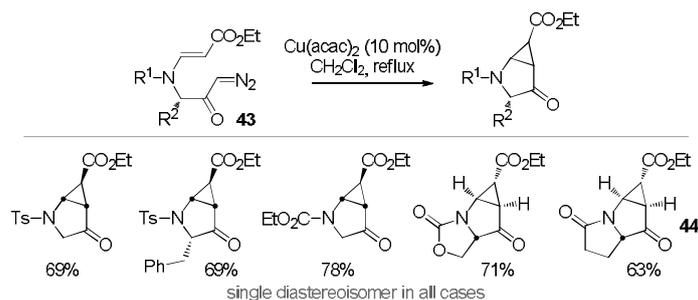


Table 5. Intramolecular cyclopropanation of α -diazo ketones with a vinylogous carbamate moiety.^{79,80}

Another interesting method has recently been reported, featuring 1-naphthylamine derivatives that are *N*-substituted with a chain fitted with a tosylhydrazone, the latter acting as a masked diazo function. In the presence of potassium carbonate, a cobalt(II) porphyrin-type complex-catalysed cyclopropanation process takes place leading, with partial dearomatisation of the naphthyl moiety, to the production of original tetracyclic methanopyrrolidines **45** (Table 6).⁸¹ It must be noted, however, that this method is neither applicable to 2-naphthylamine substrates nor to simple aniline derivatives. In these cases, the cyclopropane products are not stable and suffer spontaneous ring-opening to yield Büchner reaction products.

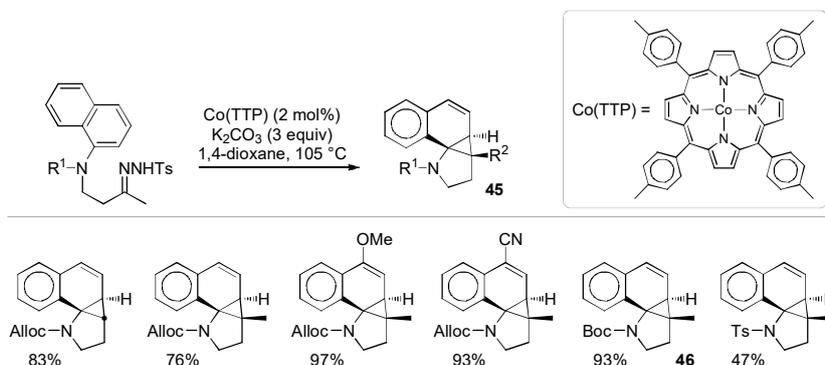


Table 6. Intramolecular Co-catalysed dearomative cyclopropanation of 1-naphthylamine derivatives.⁸¹

2.4. Transannular cyclisation

An elegant and fairly general method for the synthesis of *N*-protected 2,3-methanopyrrolidine derivatives has been developed by the group of Beak.⁸² It involves deprotonation of *N*-Boc 4-chloropiperidine **47** by *s*BuLi/TMEDA at the α -position relative to the nitrogen atom. Transannular cyclisation takes place (Scheme 1, disconnection **d4**). A distinct advantage is the possibility to introduce functionality in the same synthetic step. Indeed, using excess amounts of *s*BuLi/TMEDA, the product initially formed is deprotonated again and the resulting organolithium derivative **48** can be trapped with a variety of electrophilic reagents (Table 7).

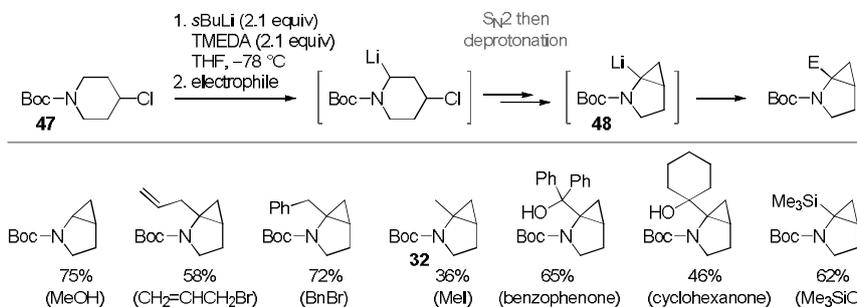
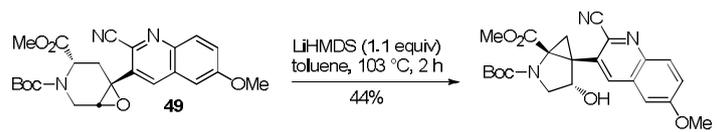


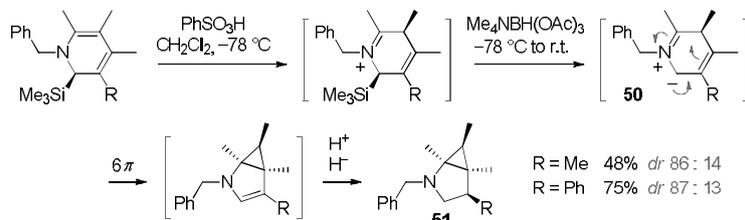
Table 7. Transannular cyclisation of *N*-Boc 4-chloropiperidine with 2 equiv of *s*BuLi/TMEDA and subsequent trapping with electrophilic reagents (indicated in parentheses).⁸²

This strategy has found interesting applications.^{14,83,84} Especially noteworthy is the transformation of the epoxide **49**, carried out in the context of a total synthesis work targeting antimalarial alkaloids (Scheme 19).⁸⁵



Scheme 19. Synthesis of a 2,3-methanopyrrolidine by transannular cyclisation.⁸⁵

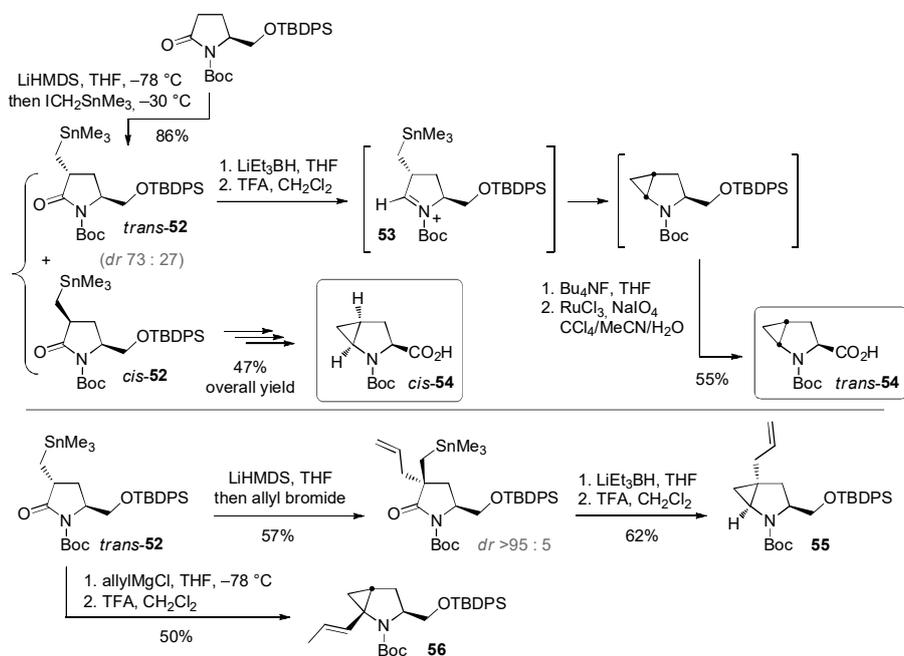
Another kind of reaction also furnishes 2,3-methanopyrrolidines via transannular cyclisation. A completely different mechanism operates, involving the cyclic azomethine ylid intermediate **50**. The latter is proposed to undergo a six electron electrocycloisomerisation. The resulting 2,3-methanopyrrolidine is reduced in situ to the product **51** (Scheme 20).⁸⁶



Scheme 20. Synthesis of 2,3-methanoproline by the electrocycisation of cyclic azomethine ylids.⁸⁶

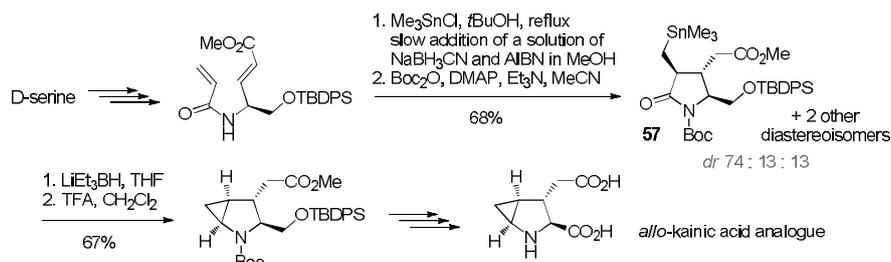
2.5. Formation of the cyclopropane ring from a pyrrolidine precursor

Alkylation of the lithium enolates of pyrrolidin-2-one derivatives with $\text{ICH}_2\text{SnMe}_3$ produces functionalised organostannanes such as **52** (Scheme 21).⁸⁷ The latter polar organometallic species are direct precursors of 2,3-methanopyrrolidines (Scheme 1, disconnection **d5**). Indeed, reduction of the carbonyl group with superhydride followed by treatment with a Brønsted acid generates the iminium species **53**, which is analogous to the final intermediate **15** appearing in the mechanism of the intramolecular Kulinkovich-de Meijere reaction previously mentioned (Scheme 10) and reacts in a similar fashion, delivering the target cyclopropane-containing heterocyclic system. Although it is still being used,²⁵ this method, developed by the group of Hanessian in the mid-1990s,^{87,88} may be regarded as rather obsolete today because of the well-known toxicity issues associated with organostannane compounds and the later emergence of alternative tools. The fact that it has allowed the achievement of the first synthesis of both diastereoisomers of 4,5-methanoproline, an important molecule, deserves to be highlighted (Scheme 21, top).⁸⁷ Very interestingly, more substituted products **55** and **56** can also be prepared from the same precursors (Scheme 21, bottom).⁸⁷



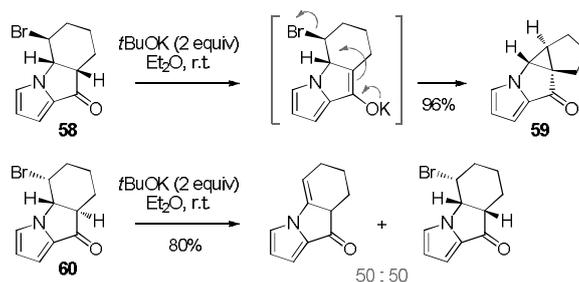
Scheme 21. Synthesis of both diastereoisomers of *N*-Boc 4,5-methanoproline **54** (top), as well as of more substituted derivatives (bottom).⁸⁷

The preparation of the key organostannane intermediate **57** by a radical chain-reaction represents an interesting and elegant variation of this approach (Scheme 22).⁸⁸



Scheme 22. Synthesis of an *allo*-kainic acid analogue via organostannane intermediates.^{88b}

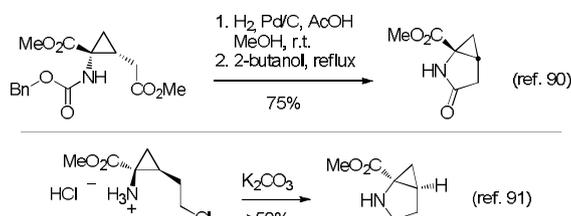
To end up section 2.5, one can mention the synthesis of compound **59** from **58** (Scheme 23) as an example illustrating disconnection **d6** (Scheme 1).⁸⁹ It is noteworthy that the starting diastereoisomer molecule **60** does not undergo the same transformation. Indeed, the corresponding $\text{S}_{\text{N}}2$ reaction would afford an unacceptably strained product.



Scheme 23. Cyclopropane-ring formation by the transannular $\text{S}_{\text{N}}2$ reaction of the potassium enolate of **58**.⁸⁹

2.6. Pyrrolidine ring-closure from an aminocyclopropane precursor

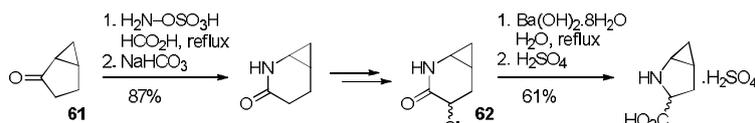
The preparation of 2-azabicyclo[3.1.0]hexane derivatives by the intramolecular creation of a nitrogen-carbon bond, starting from a substituted aminocyclopropane derivative (Scheme 1, disconnection **d8**), is illustrated by the examples shown in Scheme 24, where free primary amines are generated and then acylated by condensation with an ester group⁹⁰ or alkylated by an $\text{S}_{\text{N}}2$ reaction.⁹¹ The synthetic challenge is here associated with the previous steps leading to the substituted aminocyclopropane starting materials.



Scheme 24. Formation of 2,3-methanoproline derivatives by intramolecular *N*-acylation or -alkylation of substituted cyclopropylamines.^{90,91}

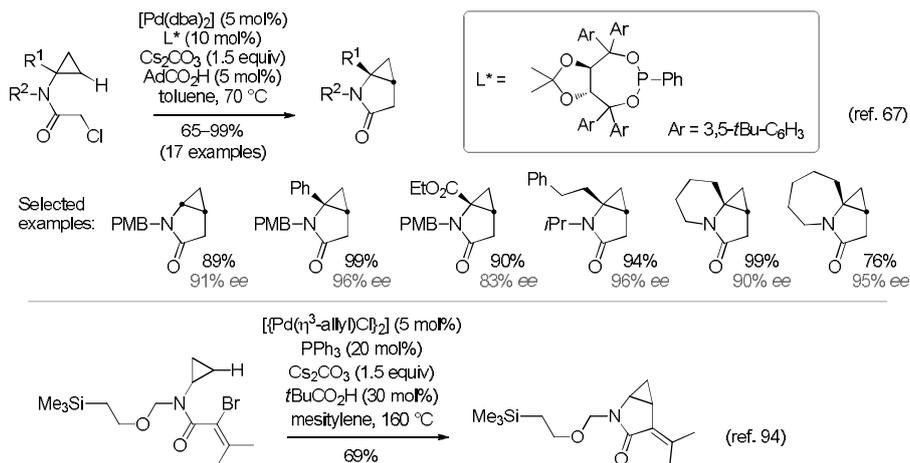
Another approach, reported in the early 1980s, is displayed in Scheme 25, where the 4,5-methanoproline skeleton is formed by a ring contraction reaction, proceeding by a Favorskii-like

rearrangement of the chlorinated molecule **62**, itself prepared using a Beckmann rearrangement performed on ketone **61**.^{92,93}



Scheme 25. Formation of 4,5-methanoproline by a Favorskii-type rearrangement.⁹²

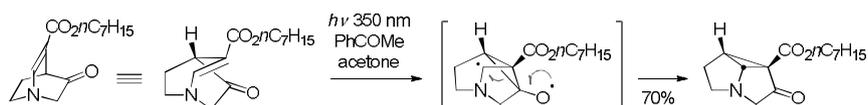
Finally, cyclisation by intramolecular functionalisation of the cyclopropane ring of an aminocyclopropane subunit, along disconnection **d10** (Scheme 1), is not a straightforward transformation but successful results have been reported recently. These interesting reactions involve palladium-catalysed remote CH functionalisation starting from well-chosen *N*-acyl cyclopropylamine derivatives (Scheme 26).^{67,94} It is worthy of note that good enantiomeric excesses are achieved using a chiral TADDOL-based phosphonite ligand (Scheme 26, top).⁶⁷



Scheme 26. Access to 2,3-methanopyrrolidine products by intramolecular Pd-catalysed CH functionalisation.^{67,94}

2.7. Miscellaneous methods

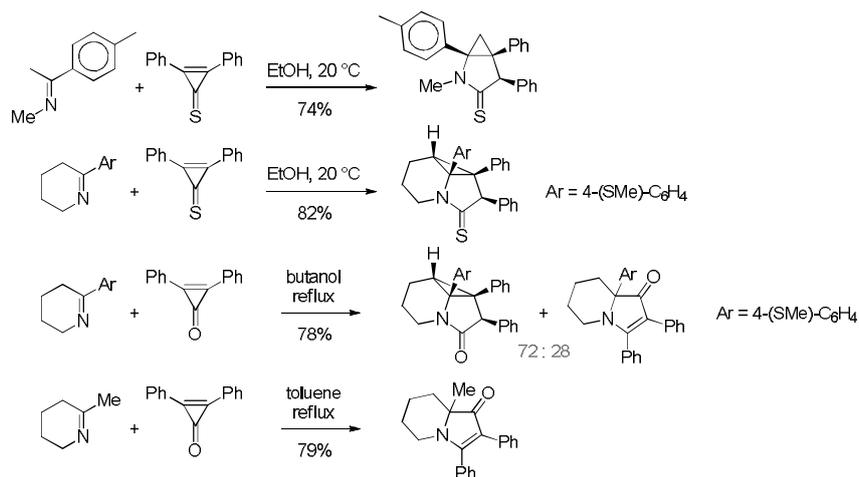
Only a few of the hitherto not mentioned methods will be cited in this section. For instance, various photochemical di- π -methane or oxa-di- π -methane rearrangements of bridged nitrogen heterocycles have been reported to give 2,3-methanopyrrolidines embedded in polycyclic systems.^{95,96} A selected example is displayed in Scheme 27.⁹⁶



Scheme 27. Synthesis of a 2,3-methanopyrrolidine derivative by the oxa-di- π -methane rearrangement of a bridged nitrogen bicycle.⁹⁶

Another original transformation involves cycloaddition reactions between imines and certain cyclopropene compounds derived from diphenylcyclopropenone (Scheme 28).⁹⁷⁻⁹⁹ The reaction course

strongly depends on the substitution pattern of the reactants and protic solvents tend to favour the formation of the cyclopropane products.⁹⁸



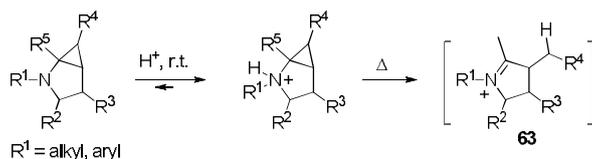
Scheme 28. Cycloaddition reactions of imines with diphenylcyclopropenethione and diphenylcyclopropenone.^{97,98}

3. Transformation into other nitrogen-containing heterocyclic systems

As has been seen in the preceding part, several preparation methods have been developed over the last decades and a whole range of variously substituted 2,3-methanopyrrolidine compounds have become accessible. Some of them involve the transformation of readily available simple starting materials, in a reduced number of steps and with cheap reagents. Moreover, the 2,3-methanopyrrolidine scaffold is a fairly strained bicyclic system; thermodynamically favourable ring-opening reactions can thus be devised with a view to generating interesting reactive intermediates. A number of new applications of 2,3-methanopyrrolidine compounds as precursors of various nitrogen-containing heterocycles have been developed in this context. A selection of these methods is presented in this part, with some focus on the work carried out by our group. The special case of donor-acceptor cyclopropane derivatives, which exhibit enhanced reactivity in ionic transformations, has been the topic of dedicated reviews¹⁰⁰ and therefore, is not covered in this section.

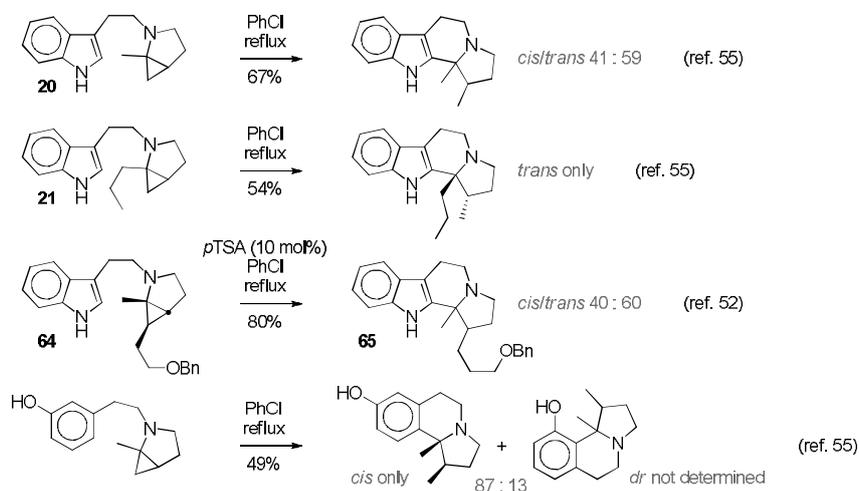
3.1. Cyclisation of an iminium intermediate generated by protonation

As amines, *N*-Aryl- or *N*-alkyl- 2,3-methanopyrrolidines simply undergo protonation at the nitrogen atom in the presence of Brønsted acids. However, if enough energy is provided to the system by thermal activation, protonation of the cyclopropane ring can actually take place. This process occurs with high regioselectivity to generate the iminium species **63** (Scheme 29), due to proper geometrical alignment of the C–C bond being broken with the orbital occupied by the lone pair of the nitrogen atom.



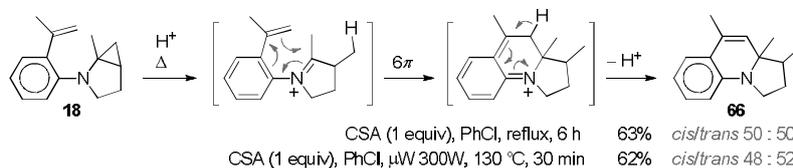
Scheme 29. Generation of endocyclic iminium species by protonation of 2,3-methanopyrrolidines.

Endocyclic cation **63** can then participate in a variety of reactions. In particular, it can be trapped in an intramolecular fashion by a neighbouring nucleophilic aromatic ring, thus giving access to more complex nitrogen-containing polycyclic frameworks, as illustrated in Scheme 30.⁵⁵ It is interesting to note that the mechanism of these Friedel-Crafts type reactions involves the eventual loss of a proton from the corresponding Wheland intermediates. The proton used to generate the iminium **63** is thus regenerated. Only a trace of acid is thus necessary, which explains why the first two examples displayed are successful, even though no acidic reagent is introduced.⁵⁵ The conversion of the more substituted substrate **64** was found to be much slower; nonetheless, the addition of 0.1 equiv of *p*TSA enabled its transformation into the tetracyclic product **65** in 80% yield.⁵² In the case of the last example, the role of the Brønsted acid is played by the phenol moiety.⁵⁵



Scheme 30. Intramolecular aromatic electrophilic substitution reactions.^{52,55}

Another possible pathway, starting from suitably chosen *ortho*-vinyl aniline derivatives, involves a 6π electrocyclic process undergone by the iminium intermediate. Once again, a proton is eventually lost. The dihydroquinoline compound **66** can thus be synthesised, either under classic thermal conditions or with microwave irradiation, with no qualitative difference apart from the time required for full conversion (Scheme 31).⁵⁷



Scheme 31. Preparation of the tricyclic dihydroquinoline **66** from the 2-aminostyrene derivative **18**.⁵⁷

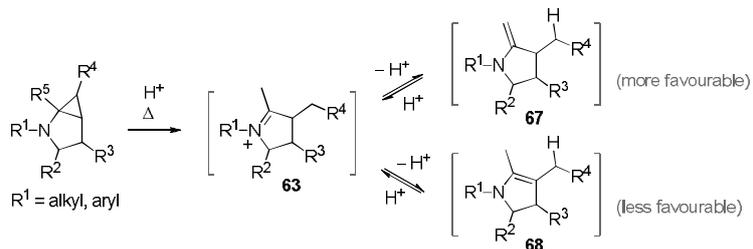
3.2. Isomerisation into an enamine intermediate and subsequent transformations

After protonation of 2,3-methanopyrrolidines, the resulting iminium species **63** may have time to lose a proton to generate enamine intermediates **67** or **68**, especially if they cannot follow any productive pathway or if such pathways are comparatively slow (Scheme 32).

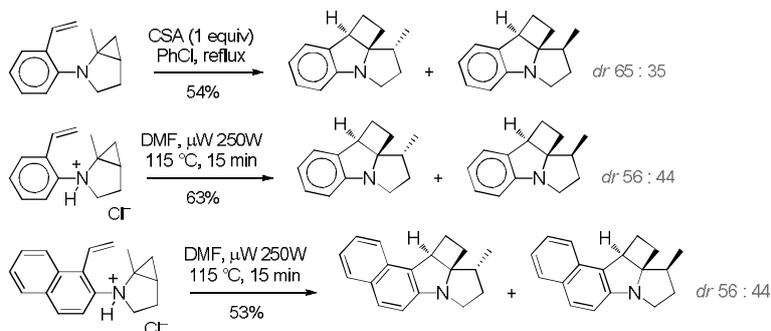
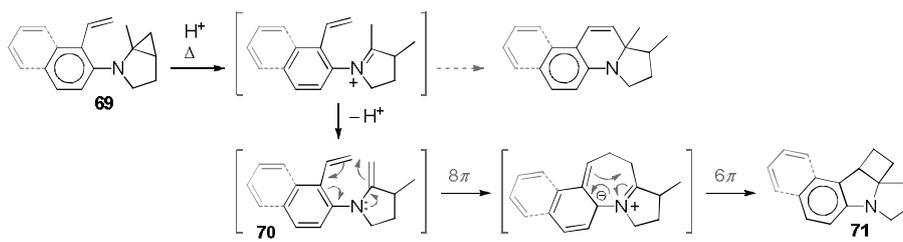
For instance, starting from similar *ortho*-vinyl aniline derivatives to compound **18** that are deprived of the methyl substituent at the vinyl moiety (*e.g.* **69**), the 6π electrocyclic process is slowed down to such an extent that a different reaction course is observed, leading to original polycyclic aminocyclobutane

products **71** (Scheme 33).⁵⁷ This transformation is likely to proceed via an exocyclic enamine **70**, which undergoes two electrocyclicisation reactions successively: 8π then 6π .

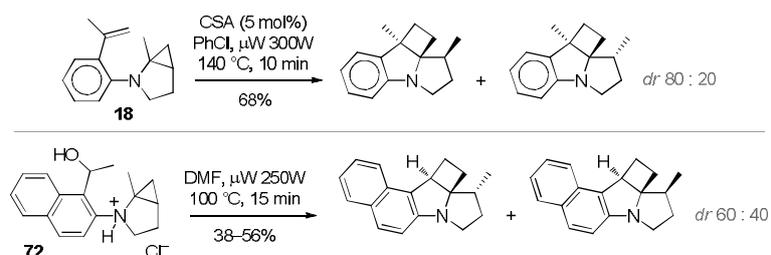
Quite remarkably, the methyl derivative **18** can also follow this pathway, provided only a catalytic amount of Brønsted acid is employed (Scheme 34, top). Finally, it is interesting to note that the vinyl part of the substrate can be generated *in situ*, by elimination of the hydroxyl group of **72**, under the same conditions as the subsequent transformation (Scheme 34, bottom).⁵⁷



Scheme 32. Isomerisation of 2,3-methanopyrrolidine compounds into cyclic enamines.

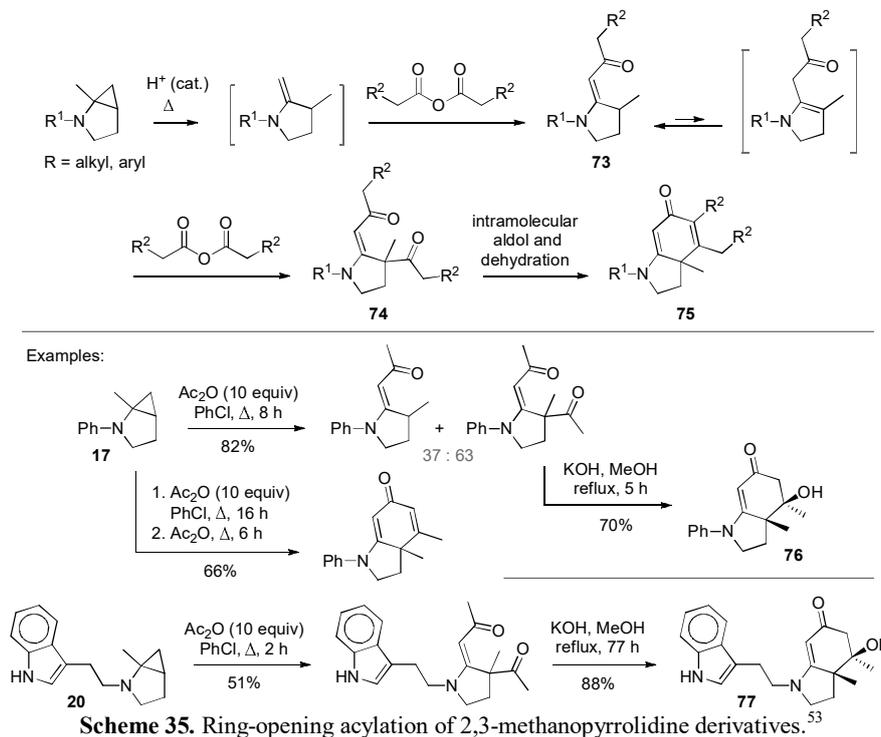


Scheme 33. Transformation of well-chosen 2,3-methanopyrrolidine derivatives **69** into polycyclic aminocyclobutane compounds.⁵⁷

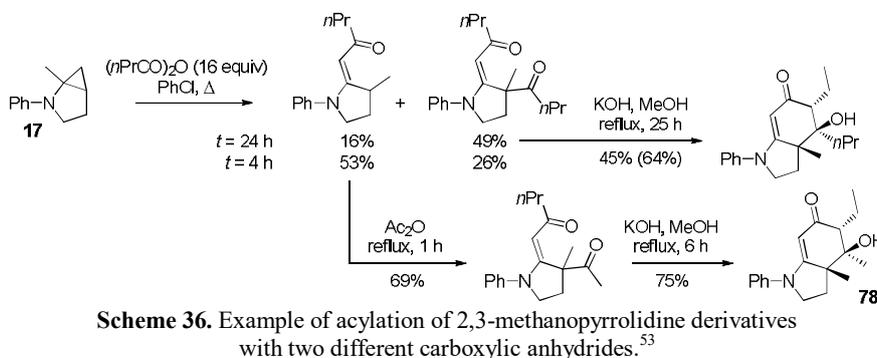


Scheme 34. Transformation into polycyclic aminocyclobutane compounds; additional examples.⁵⁷

An entirely different application is based on the reaction of the enamine intermediates with carboxylic anhydrides (Scheme 35).⁵³ Depending on the concentration of the latter reactants and the reaction time, it is possible to produce vinylogous amides **73**, diketones **74** or cyclised compounds **75**. The dehydration process occurring after the intramolecular aldol reaction of diketones **74** can be avoided by reacting the latter with KOH in refluxing methanol, as illustrated by the syntheses of the aldols **76** and **77** (Scheme 35, bottom).

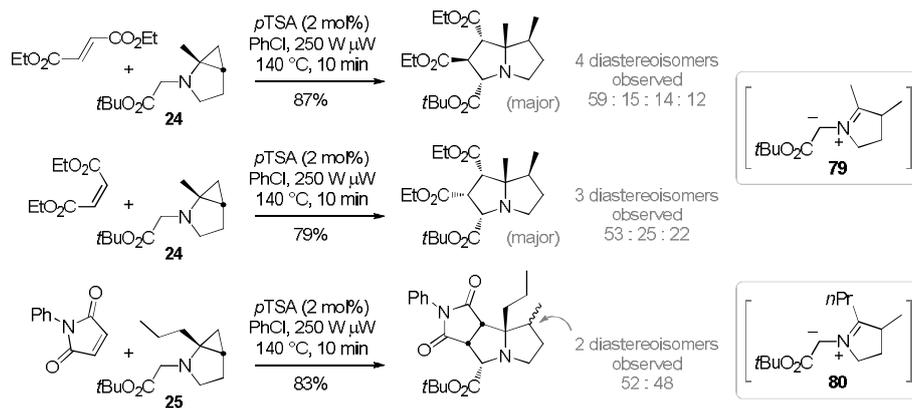


Interestingly, conditions can be generally found for the selective formation of the monoacylated product **73** in satisfactory yield (Scheme 36). This allows the further reaction with a different carboxylic anhydride, thereby extending the range of the functional compounds that are accessible, as demonstrated by the synthesis of compound **78**, which is obtained as a single diastereoisomer (Scheme 36).⁵³



3.3. 1,3-Dipolar cycloaddition taking place after isomerisation into an azomethine ylid

2,3-Methanopyrrolidines that are *N*-substituted with a carboxymethyl group have been demonstrated to undergo [3+2] cycloaddition reactions with electron-poor alkenes in chlorobenzene at reflux, with opening of the three-membered ring.⁵⁸ This can be readily explained by acid-catalysed thermal isomerisation of the aminocyclopropane substrates into azomethine ylid species. It must be pointed out that these reactions generally suffer from rather poor diastereoselectivity, which results in the production of complex mixtures of diastereoisomers that are typically extremely difficult to separate. However, these problems can be somewhat minimised by (i) applying microwave heating conditions, which dramatically reduces the reaction time; (ii) using ethyl fumarate or ethyl maleate as the dipolarophile reactant, rather than phenyl vinyl sulfone or *N*-phenyl-maleimide; (iii) or, in the case of the latter dipolarophile, start from the propyl-substituted substrate **25** rather than the methyl derivative **24**. Examples obtained under these conditions are presented in Scheme 37. The major diastereoisomers produced correspond, when relevant, to *endo* transition states that are attained from the azomethine ylid intermediates **79** or **80** reacting in the conformations shown. The fact that ethyl fumarate and ethyl maleate lead to the production of different diastereoisomers is in agreement with a concerted cycloaddition process.



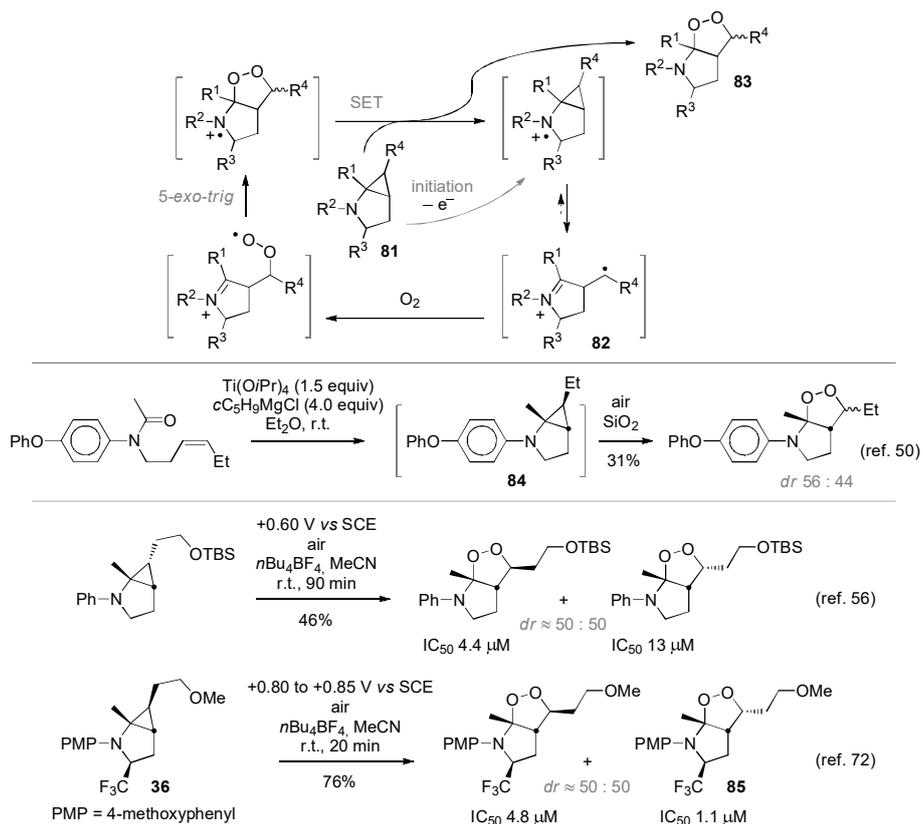
Scheme 37. 1,3-Dipolar cycloaddition reactions of suitable 2,3-methanopyrrolidines with activated alkenes.⁵⁸

3.4. Single-electron oxidation followed by formal [3+2] cycloaddition

From sufficiently electron-rich 2,3-aminopyrrolidines **81**, radical intermediates can be generated very simply by single-electron oxidation, as it is the case with other aminocyclopropanes that have been used as mechanistic probes for the study of oxidative enzymes.¹⁰¹ The single-electron oxidation process triggers the cleavage of the cyclopropane ring. A distonic radical **82** is thus generated and can participate in formal [3+2] cycloadditions. For instance, in the presence of dioxygen, species **82** can be transformed into endoperoxides **83** by a radical-chain mechanism (Scheme 38, top).¹⁰² Starting from the particularly electron-rich substrate **84**, the transformation occurs spontaneously upon purification by flash chromatography on silica gel, in the presence of air (Scheme 38, middle).⁵⁰ More generally, electrochemistry techniques can be used, both for the accurate determination of the ionisation potentials of the starting 2,3-aminopyrrolidines and for the reliable preparative electrosyntheses of the endoperoxide products (Scheme 38, bottom).^{56,72} The presence of a substituent $R^4 \neq H$ was found to be essential for these molecules to be reasonably stable. Interestingly, all of the endoperoxides isolated were found to exhibit moderate activity against chloroquine-resistant FcB1 strains of *Plasmodium falciparum*. The most active compound identified so far is the CF_3 -substituted molecule **85**.

This transformation was later transposed to formal [3+2] cycloaddition reactions with activated alkenes, using a ruthenium complex in the presence of visible light as the redox system.^{103,104} Selected examples are presented in Table 8. These developments are also related to previously reported formal [3+2]

cycloaddition reactions performed in an intramolecular fashion from suitably substituted aminocyclopropanes.¹⁰⁵



Scheme 38. Aerobic oxidation of *N*-aryl 2,3-methanopyrrolidine derivatives into endoperoxide compounds and IC_{50} of the latter against *Plasmodium falciparum* (see text).^{50,56,72}

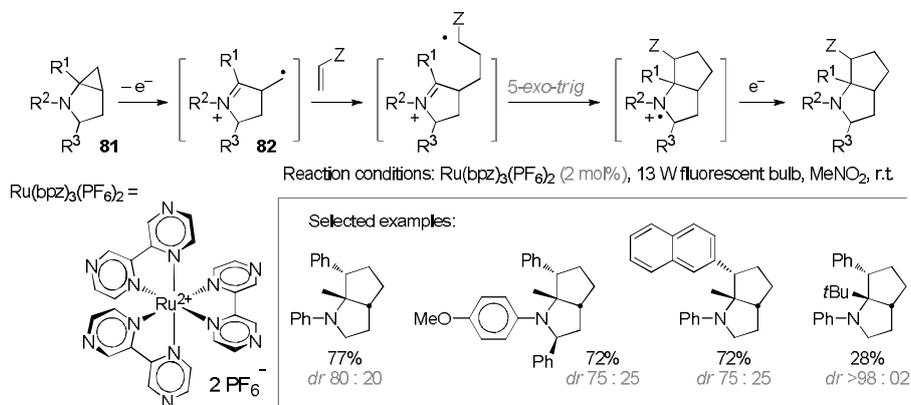
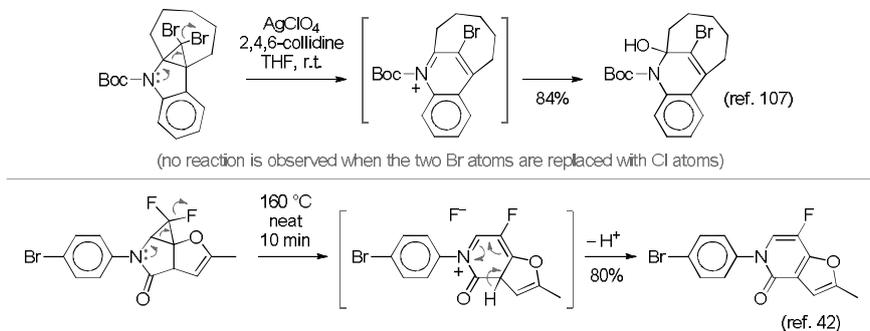


Table 8. Formal [3+2] cycloaddition of *N*-aryl 2,3-methanopyrrolidines with activated alkenes.^{103,104}

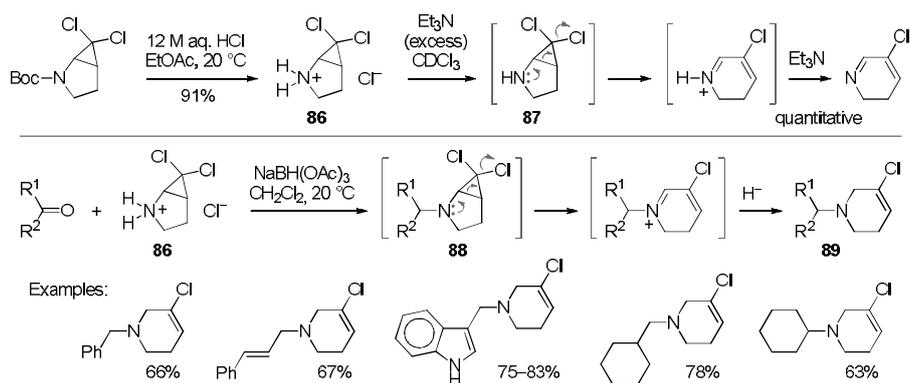
3.5. Ring expansion of 2-halo aminocyclopropane derivatives

The transformation of halocyclopropanes into allylcation species, with departure of a halide ion, is a well-known process.¹⁰⁶ Examples involving 2,3-methanopyrrolidines are scarce but interesting since they result in ring-expansion, thereby providing access to substituted piperidine systems. Typically, thermal activation⁴² or the use of silver(I) salts¹⁰⁷ are necessary for the reaction to take place (Scheme 39). However, the ring opening can become a facile process at room temperature when the lone pair of the nitrogen atom is not delocalised into a neighbouring carbonyl group, i.e. when the substrate is an amine.^{45,108} This observation can be explained by the more efficient stabilisation of the developing positive charge along the reaction coordinates, as the halide ion leaves the molecule.



Scheme 39. Ring-expansion reactions starting from dihalomethanopyrrolidine derivatives, promoted by silver perchlorate or performed under thermal conditions.^{42,107}

Accordingly, the ring-opening process can be triggered by simple deprotonation of the stable hydrochloride salt **86**, readily accessible from the corresponding *N*-Boc methanopyrrolidine (Scheme 40, top). More interestingly, under typical reductive amination conditions, the ring-opening of the free amine **87** is sufficiently slow to allow its conversion into the corresponding *N*-alkylated derivative **88**. The latter can be observed by NMR but opens up slowly at room temperature. Trapping of the resulting iminium ion by the hydride reagent, used in excess, produces 1,2,3,6-tetrahydropyridine compounds **89** (Scheme 39, bottom).³⁹

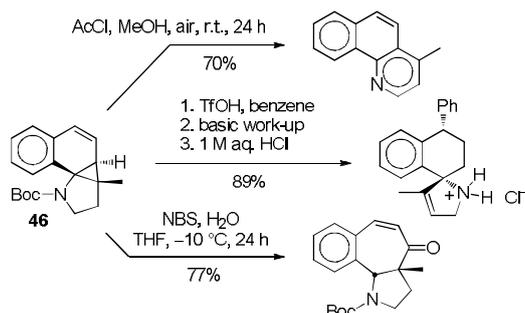


Scheme 40. Room-temperature ring-expansion reactions of hydrochloride salt **86**, without or with concomitant *N*-alkylation.³⁹

3.6. Miscellaneous transformations

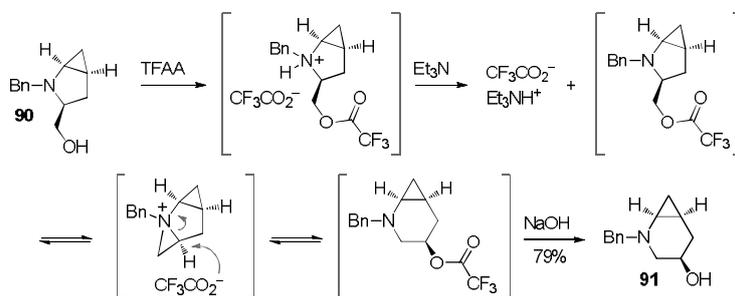
The particular ring-fused 2,3-methanopyrrolidine compound **46** (see Table 6) exhibits interesting reactivity, providing efficient access to different polycyclic systems depending on the reaction conditions

applied (Scheme 41).⁸¹ Remarkably, all three possibilities for cyclopropane-bond cleavage are illustrated from this single substrate.



Scheme 41. Transformations of polycyclic compound **46**.⁸¹

Another recently reported interesting reaction is the rearrangement of the suitably substituted 2,3-methanopyrrolidine derivative **90** into the 2,3-methanopiperidine compound **91** (Scheme 42),¹⁰⁹ an application of a well-studied ring-expansion of prolinol compounds.¹¹⁰ With the transformation of the lactam **62** already presented in sub-section 2.6 (Scheme 25), it nicely illustrates the possible interconversion of 2-azabicyclo[3.1.0]hexane and 2-azabicyclo[4.1.0]heptane systems.



Scheme 42. Ring expansion of a 2-azabicyclo[3.1.0]hexane derivative into a 2-azabicyclo[4.1.0]heptane compound.¹⁰⁹

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