# The *endo*-aza-Michael addition in the synthesis of piperidines and pyrrolidines

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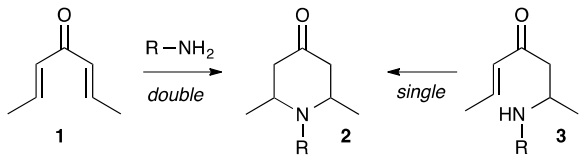
*Abstract*: Intramolecular *endo*-aza-Michael additions are categorised in various ways. Firstly whether they are single or double reactions, secondly whether they are *endo*- or *exo*-activated (or both), thirdly whether the Michael acceptor is an alkene or an alkyne, and finally whether the product is a six or a five membered ring. Reactions in the various categories are illustrated by syntheses of piperidines and pyrrolidines, including a range of natural products. The question of the stereochemical outcome and whether it is understood is discussed.

## 1. Introduction

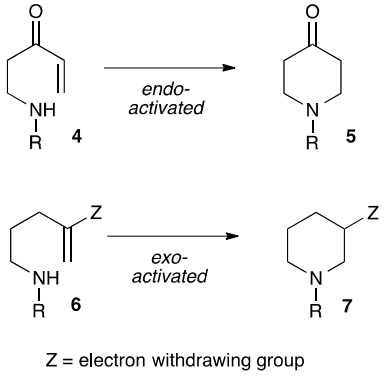
Michael addition, the nucleophilic addition of a stabilised carbanion to an electron poor alkene or alkyne, is widely used to form carbon-carbon bonds. A variation is to replace the carbon nucleophile with a heteroatom nucleophile, such as oxygen (oxa-Michael) or nitrogen (aza-Michael). One aspect of such hetero-Michael additions is in the formation of heterocyclic rings. A very widely applied reaction is the formation of tetrahydropyrans in a 6-*exo*-trig manner.[1] This reaction has been extensively used in the synthesis of tetrahydropyran natural products. The analogous reaction with a nitrogen nucleophile is also known,[2] as is the corresponding 6-*endo*-trig cyclisation to give a tetrahydropyran. The 6-*endo*-trig cyclisation with a nitrogen nucleophile, giving rise to piperidines, is less common, but has found application in a number of elegant syntheses. A few examples of the analogous 6-*endo*-dig reaction have been reported. The 5-*endo* reaction is even less frequently encountered. Indeed, 5-*endo*-trig is listed as "unfavourable" by Baldwin,[3] although 5-*endo*-dig is favourable. The objective of this review is to summarise work on these aspects of the *endo*-aza-Michael reaction. This review is limited to the formation of saturated systems and excludes reactions leading to benzofused heterocycles.

Intramolecular *endo*-aza-Michael additions leading to piperidines **2** can firstly be divided into two categories: single and double (Scheme 1). In the case of the double-aza-Michael, the starting material is a dienone **1** and the first step of the mechanism is an intermolecular aza-Michael addition (which would give a structure such as **3** as an intermediate), followed in rapid sucession by a single intramolecular *endo*-aza-Michael addition. In the case of the single addition, the starting material **3** already has the nitrogen nucleophile in place. For both reactions, questions arise about the experimental conditions: acidic or basic, about the stereochemical outcome if the alkenes are substituted, and about the effect of the substituent on nitrogen, R, if any.



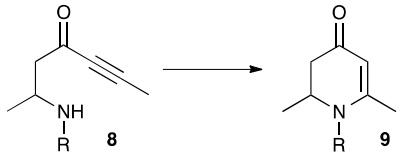

Scheme 1. Single and double intramolecular *endo*-aza-Michael additions

In the case of the single aza-Michael, two further possibilities exist, depending on whether the electron withdrawing group is within the ring that is formed, or outside of the ring. While both reactions are *endo* in the Baldwin sense, they might be further termed *endo*-activated and *exo*-activated respectively (Scheme 2). The former is much more widely used than the latter. A third possibility is that two electron withdrawing groups are present, providing both *endo*- and *exo*-activation.[4]




Scheme 2. *Endo*- and *exo*-activated additions

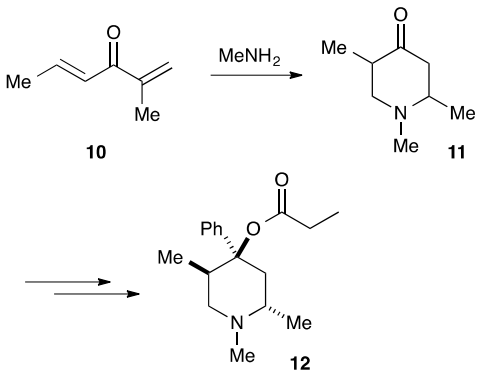
A final variant is that the Michael acceptor may be an alkyne, leading to a vinylogous amide **9** (Scheme 3). This reaction may also be applied to the formation of five membered rings.




Scheme 3. Addition to an alkyne

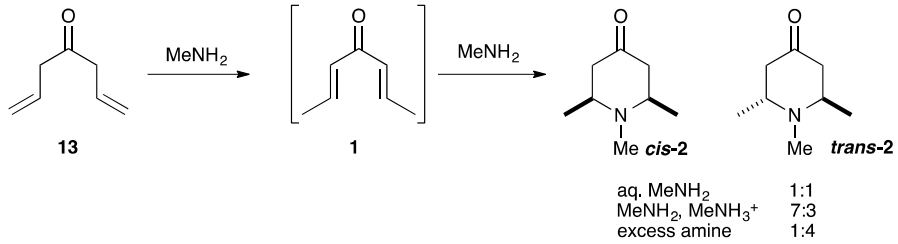
## 2. The double Michael approach

Given the nature of the starting materials, it is no surprise that many of the earlier papers on this topic come from the laboratory of Nazarov. This work is entirely in the old Soviet literature and just a few examples will suffice.[5] Treatment of dienone **10** bearing two methyl groups with methylamine yielded the trimethylpiperidine **11** as a mixture of isomers (Scheme 4). The *trans* isomer could be isolated by low temperature crystallisation and converted to the opioid analgesic promedol (trimeperidine) **12**.



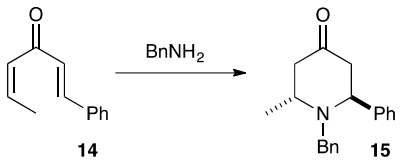

Scheme 4. Synthesis of (±)-promedol

A later study from the same laboratory focused on the stereochemical outcome in the case of 2,6-disubstituted piperidine formation (Scheme 5).[6] Thus diallylketone **13** was treated with various primary amines to give, firstly isomerisation to the sensitive ketone **1**, followed by the double aza-Michael addition. While the equilibrium ratio of the two products, ***cis*-2** and ***trans*-2**, was claimed to be about 1:1, a more acidic medium, achieved by addition of ammonium salts, favoured formation of the *cis* isomer, while a more basic medium biased the ratio in favour of the *trans* isomer.



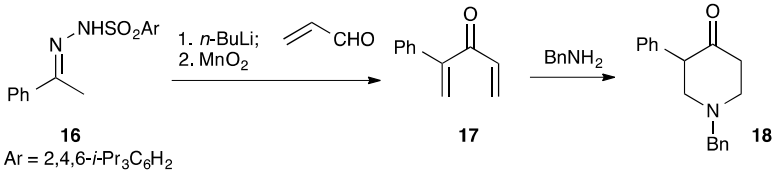

Scheme 5. Stereoselectivity in the double addition according to Korshevets and Mistryukov

These results are, however, in some contrast to a report of a double aza-Michael addition to ketone **14** proceeding with very high *trans* selectivity (Scheme 6).[7] The authors published this reaction twice. In one of the two papers, they noted the sensitivity of the stereochemical outcome to conditions.[6a]



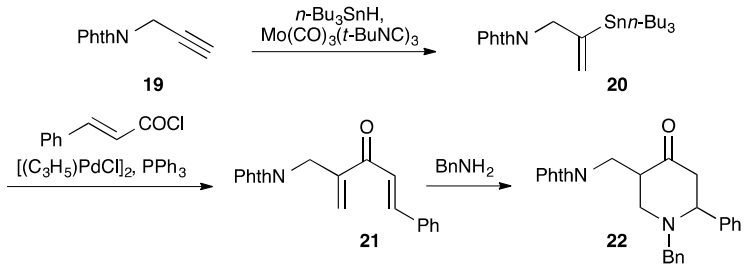

Scheme 6. Stereoselectivity in the double addition according to Nakamura *et al.*

A number of applications of this reaction have been reported.[8] Curiously, some of them fail to comment on the stereochemistry despite using the compounds as enzyme inhibitors[9] or other biomedical purposes![10] The reaction has also been applied to dienones with other substitution patterns. 3-Substituted piperidinones, such as **18**, have been prepared in this way (Scheme 7), with the precursor dienone **17** being derived in these examples by the use of a Shapiro reaction.[11]



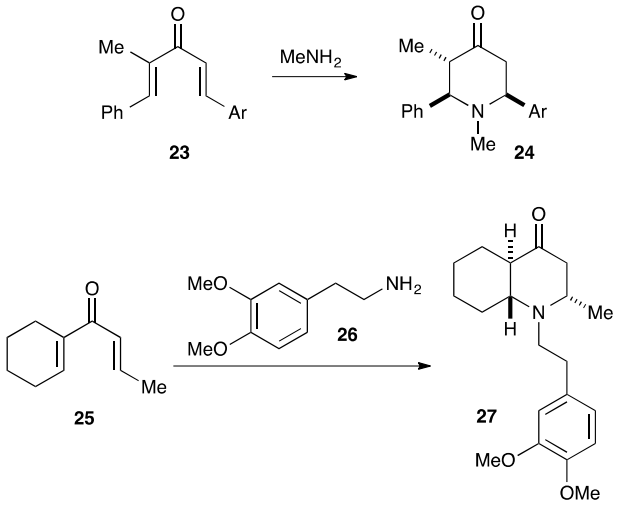

Scheme 7. Synthesis of a 3-substituted piperidinone

In addition to the Nazarov example cited earlier, the double aza-Michael addition has been employed for additional examples of 2,5-disubstituted piperidinones (Scheme 8).[12] In this case, the starting dienone **21** was readily available by a combination of regioselective alkyne hydrostannylation and Stille coupling. It was found during this study that the aza-Michael process may be accelerated by the addition of lithium chloride, presumably acting as a Lewis acid; in addition, the Stille and Michael chemistry could be combined in a one-pot process. The product **22** was isolated as an unspecified mixture of diastereoisomers.



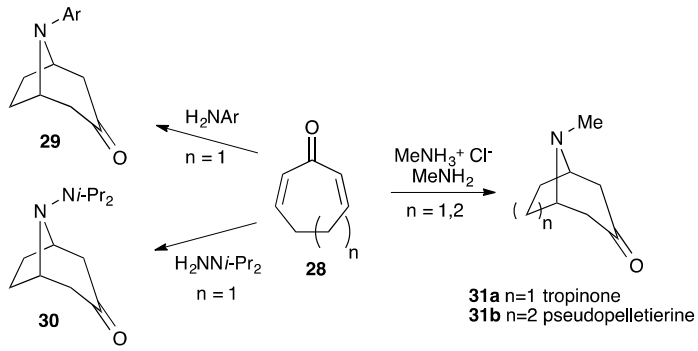

Scheme 8. Synthesis of a 2,5-disubstituted piperidinone

Trisubstituted piperidinones have also been prepared (Scheme 9). In the first case a single isomer of the product **24** was obtained, with the stereochemistry determined by means of $^1$H NMR.[13] In the second case, "primarily one isomer" of the product was obtained, the structure of which is likely to be quinolizidinone **27**.[14] In both of these cases, the suggested product is the "all equatorial isomer" which may reflect thermodynamic control.




Scheme 9. Synthesis of trisubstituted piperidinones

A special case involves cyclic dienones **28** which give rise to bicyclic addition products (Scheme 10). A series of such compounds have been synthesised for physical organic chemistry studies using various nitrogen nucleophiles yielding bicylic anilines **29**,[15] hydrazines **30**,[16] and amines **31**,[17] although attempts to use hydroxylamines ran into difficulties and an indirect route to the products had to be devised.

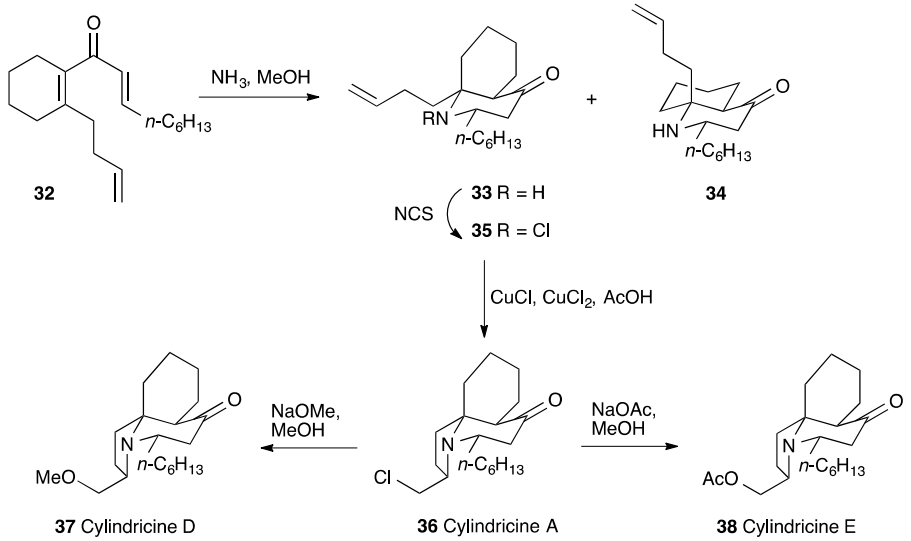



Scheme 10. Synthesis of bicyclic compounds

It may be noted that **31a** is tropinone. The reaction also works for the higher homolog (n = 2), yielding pseudopelletierine **31b**,[18] and this constitutes syntheses of these two natural product derivatives.

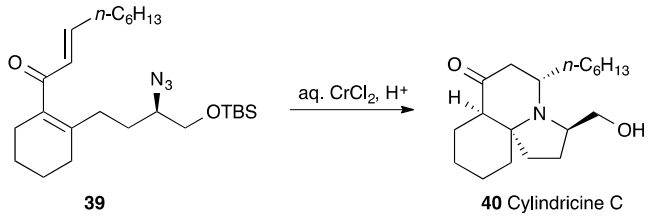
### 3. Applications of the double addition in the synthesis of natural products

Snider and Liu used the double addition of ammonia in a synthesis of (±)-cylindricine (Scheme 11).[19] Exposure of dienone **32** to ammonia yielded the piperidinones **33** and **34**. As expected from the earlier Soviet work, the ratio of diastereoisomers was influenced by the acidity of the medium, with addition of ammonium chloride giving more of the undesired isomer **34**. The desired isomer **33** could be converted into cylindricine A **36** with very modest stereoselectivity by a Hoffman-Loffler-Freytag type cyclisation. Cylindricine A **36** could then be converted to cylindricine D **37** and to cylindricine E **38**.



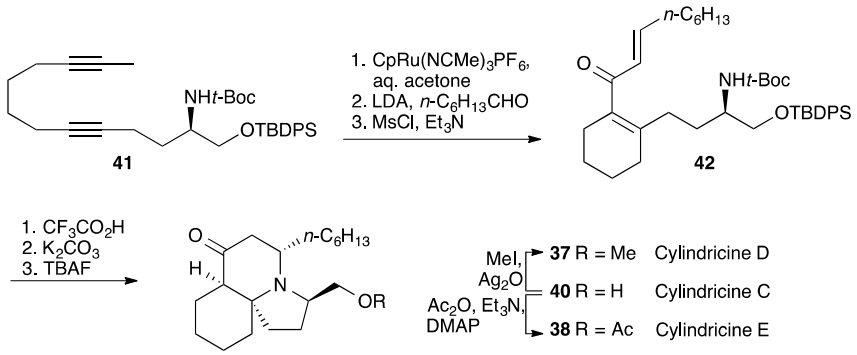
Scheme 11. Synthesis of cylindricines by Snider and Liu

Both Molander and Trost also employed double aza-Michael additions in syntheses of cylindricines, but made the reaction intramolecular through the third valency of nitrogen. Thus, in both cases, formation of the piperidinone involves an *exo*-aza-Michael addition, followed by an *endo* addition. Molander and Röhm were able to prepare the double Michael acceptor by carbonylative Stille coupling, then instal the azide group to form dienone **39** (Scheme 12).[20] Aqueous chromium(II) chloride proved to be the reducing reagent with the best chemoselectivity giving cylindricine C **40** directly. The high diastereoselectivity was ascribed to a steric clash in the transition state leading to the alternative product of the second aza-Michael addition.



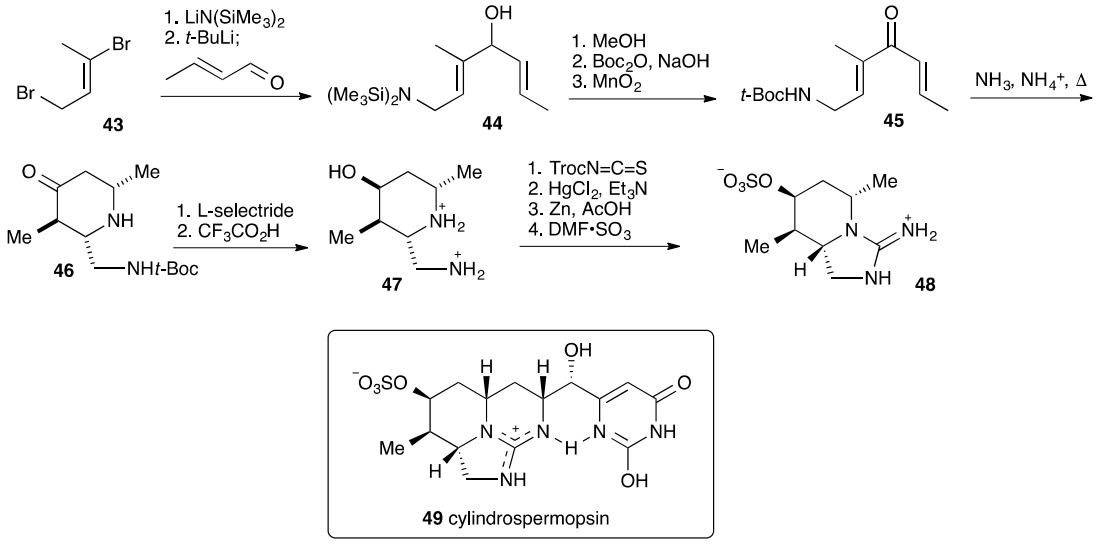

Scheme 12. Synthesis of cylindricine C by Molander and Röhm

Trost and Rudd were able to prepare an analogous dienone **42** from diyne **41** using a ruthenium catalysed hydrative cyclisation (Scheme 13).[21] As they employed a Boc protected amine, an acidification-neutralisation sequence delivered cylindricine C **40**. In turn, cylindricine C **40** could be converted into its methyl ether, cylindricine D **37**, and its acetate, cylindricine E **38**.



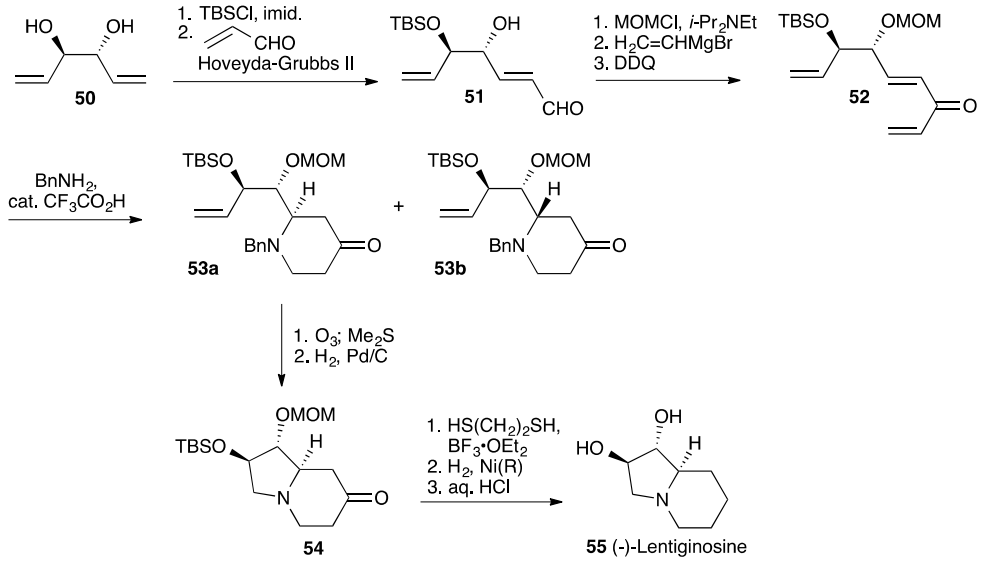

Scheme 13. Synthesis of cylindricines by Trost and Rudd

A double addition was employed in the synthesis of **48**, a model for cylindrospermopsin **49** (Scheme 14).[22] The dienone **45** was built up using organolithium chemistry, then exposed to ammonia and ammonium chloride. This gave the piperidine **46** as the major product, while additional material could be obtained by equilibration of the other isomers formed. It may be noted that **46** is the isomer with all substituents in equatorial positions. Interestingly, attempts to form a guanidine resulted in epimerisation at the α-position. Consequently, the ketone was reduced prior to guanidine and then sulfate formation.



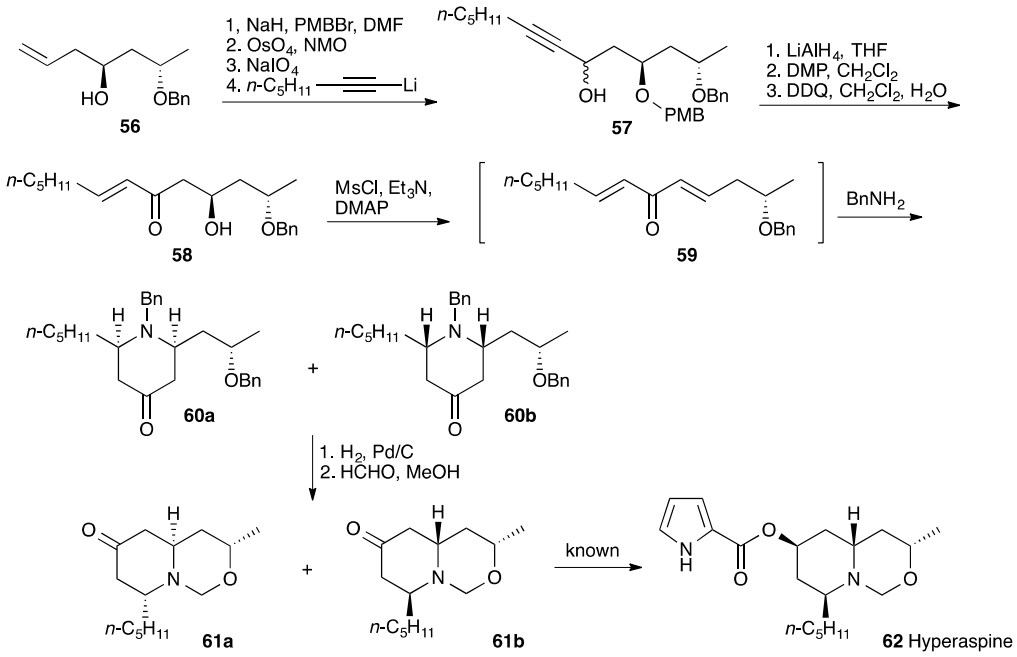

Scheme 14. Synthesis of a cylindrospermopsin model

A modestly diastereoselective double addition was employed to construct the piperidine moiety of (-)-lentiginosine **55** (Scheme 15).[23] The dienone **52** was assembled using a combination of metathesis chemistry and Grignard chemistry. Exposure to benzylamine provided the piperidinones **53a** and **53b** as a 5.2:1 mixture of diastereoisomers at best. Interestingly, while addition of a little trifluoroacetic acid as a catalyst resulted in a faster reaction, it also resulted in lower diastereoselectivity. Upon exposure of the mixture to a benzylamine-trifluoroacetic acid mixture, equilibration occurred to lower the ratio to 2.4:1. Thus, the desired isomer **53a** is favoured both kinetically and thermodynamically, though the margin of ΔG is slight. The second ring could be formed by a combination of ozonolysis of the alkene of the major isomer **53a** and reductive amination to give indolizidine **54**. Removal of the ketone group by the Mozingo method and deprotection yielded the natural product **55**.




Scheme 15. Synthesis of (-)-lentiginosine

The alkaloid (+)-hyperaspine **62** has also been prepared using an intramolecular *endo*-aza-Michael addition (Scheme 16).[24] A conventional sequence converted the known alcohol **56** to the hydroxyenone **58**. Exposure of this material to mesyl chloride and a base resulted in dehydration, thereby eliminating one of the stereogenic centres, and forming the dienone **59** *in situ*. This material was not isolated, but trapped by addition of benzylamine. This yielded a 3:1 mixture of two piperidines **60a** and **60b**. These turned out to be both 2,6-*cis* piperidines, but diastereoisomeric with respect to the pre-existing stereogenic centre bearing the benzyloxygroup. Fortuitously, the major isomer **60a** had the correct stereochemistry and could be converted to the natural product **62**. While the authors advanced some rather dubious explanations involving conformations of cyclisation to rationalise the stereochemical outcome, it firstly has to be borne in mind that the stereochemistry of the piperidinone is established during the first addition, and that may occur at either of the two alkenes; secondly, such speculation is premature until it can be established whether the reported ratio is the result of thermodynamic or kinetic effects.

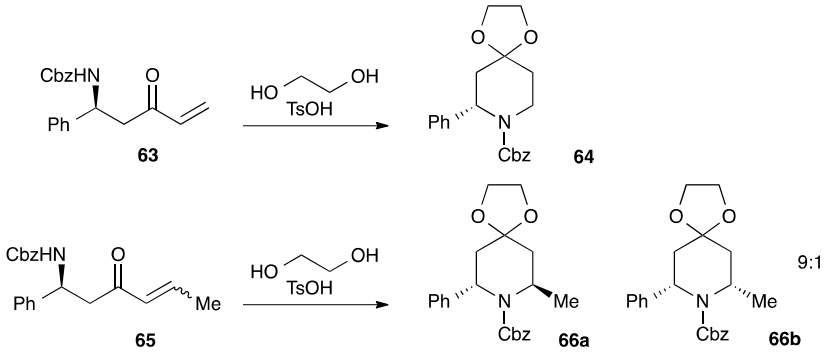



Scheme 16. Synthesis of (+)-hyperaspine

## 4. Single Addition to alkene acceptors

In this approach, the starting material already possess the nitrogen nucleophile and, thus, one stereogenic centre can be defined prior to the Michael addition (though equilibration during cyclisation may remain a possibility). One example was found to proceed most efficiently under the conditions that would be employed for ketal formation (Scheme 17).[25] Thus, when enones such as **63** were exposed to ethylene glycol and tosic acid, a tandem cyclisation-protection occurred giving the product **64** in much better yield than when a straight forward Lewis acid mediated reaction was attempted. Interestingly, when the analogous starting material **65** with a methyl group on the alkene was subjected to the reaction conditions, a 9:1 mixture in favour of the higher energy *trans*

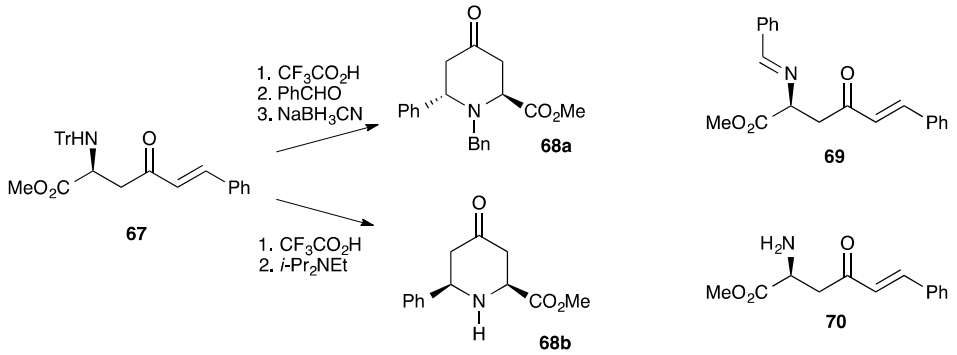
product **66a** over the *cis* product **66b**, was obtained, regardless of the stereochemistry (E or Z) of the starting material. This may indicate facile isomerisation of the alkenes under these conditions.




Scheme 17. aza-Michael addition with ketal formation

More detailed studies showed that a number of factors could have an effect on the diastereoselectivity.[26] For instance, changing from ethylene glycol to propane-1,3-diol resulted in an increase. Methanol could also be used in place of a diol. The amount of acid is also a significant variable. With amounts of acid that are well below stoichiometric, the *trans* isomer was favoured, but, with much larger amounts of acid or with a much longer reaction time, the *cis* product could become the major product. This is likely to be due to the promotion of equilibration.

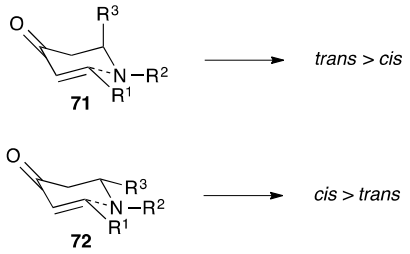
Illustrating how the stereoselectivity depends on the substituent on nitrogen, treatment of a trityl protected amine **67** with acid, followed by a reductive amination procedure yielded the *trans*-disubstituted piperidine **68a** with high selectivity (Scheme 18).[27] On the other hand, treatment of the trityl protected amine **67** with acid, followed by base yielded the *cis* isomer **68b** as the major product with a ratio of isomers of 75:25.[28] In the former case, it is likely that the nucleophilic species is the imine **69**, with an *N*-substituent that is sterically demanding due to $sp^2$-hybridisation. In the latter case it is likely that the nucleophilic species is the sterically undemanding primary amine **70**.




Scheme 18. aza-Michael addition with reductive amination

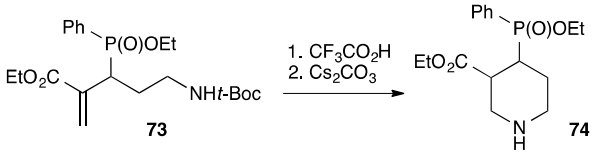
Thus there are numerous examples in which 2,6-disubstituted piperidines can be formed with varying degrees of stereoselectivity, but few attempts to rationalise the results (Scheme 19).[29] When the substituent on the nitrogen atom, $R^2$, is

sterically demanding, the *trans* isomer is typically preferred. Such groups may compel the α–substituent, $R^3$, to be pseudo-axial in the transition state **71**. Examples are shown in schemes 17 and 18 with CBZ and imine groups on the nitrogen. When the group, $R^2$, on nitrogen is absent or sterically undemanding, then the *cis* isomer tends to be favoured via transition state **72** in which both substituents $R^1$ and $R^3$ are equatorial. Examples can be found in schemes 9, 14, 16 and 18 above, as well as scheme 32. The reaction shown in scheme 6 seemingly bucks this trend but, it may be noted that one alkene of the starting material has Z geometry. The reaction shown in scheme 27 also fails to fit into this classification due to very low stereoselectivity. While this is a necessarily simplistic analysis as it disregards equilibration, it may prove to be helpful.



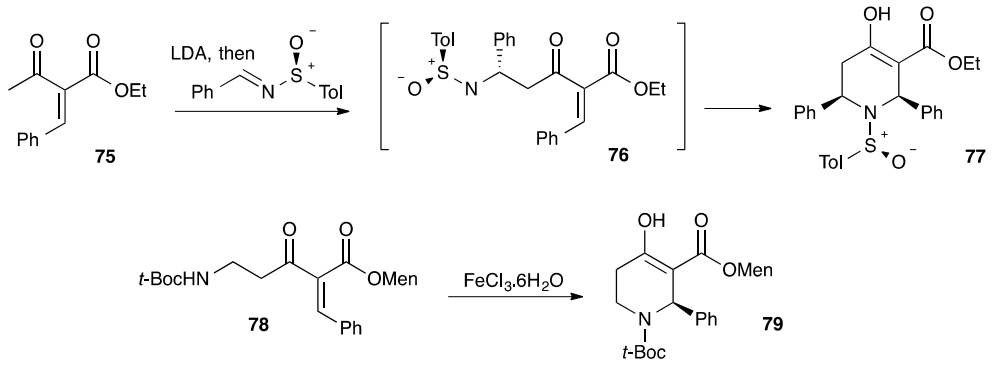

Scheme 19. Rationalisation of the stereochemical outcome

In addition, there is one report outside of the natural product synthesis literature of an *exo*-activated *endo*-aza-Michael addition giving the phosphorus substituted heterocycle **74** (Scheme 20).[30] In this report, while there was no mention of the stereochemical outcome, it was noted that the use of a cesium base was important to avoid the alternative pathway of attack by nitrogen on the ester group.




Scheme 20. An *exo*-activated addition

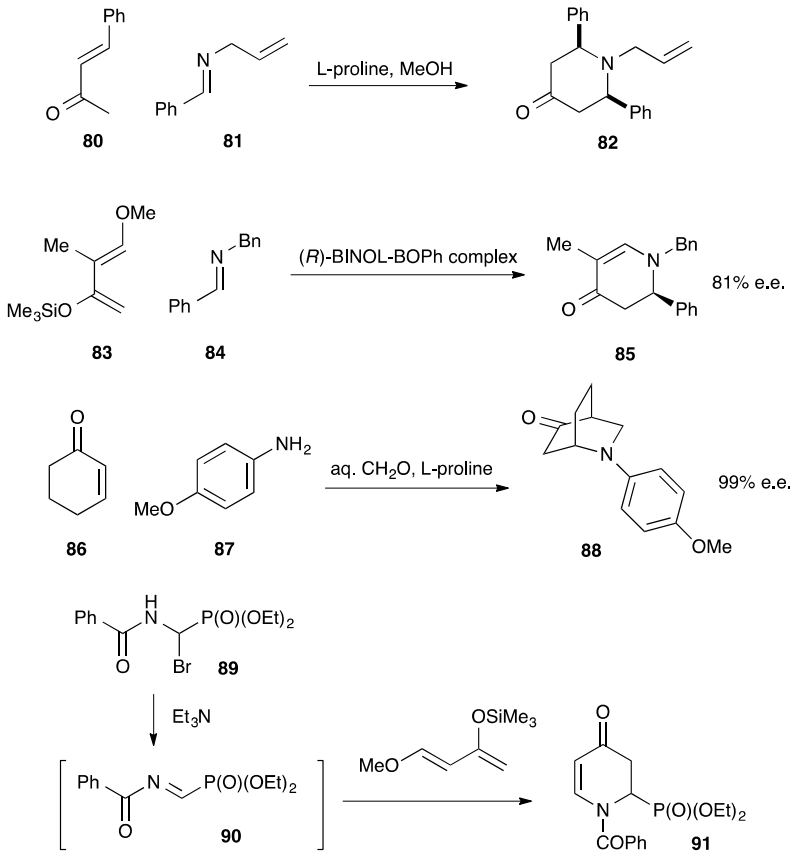
There are two examples of alkenes which, as a Knoevenagel products, are both *exo*- and *endo*-activated (Scheme 21). In one report, the aza-Michael precursor **76** is generated *in situ* by an imino-aldol reaction.[31] It is notable that there is very high diastereoselectivity for the 2,6-*cis* isomer **77** which exists as the 2,6-diaxial conformer. While this was attributed to π-stacking,[32] it may simply be due to the steric demand of the *N*-substituent disfavouring the 2,6-diequatorial conformer.[33] High diastereoselectivity arose from the use of a chiral auxiliary on the nitrogen nucleophile. In another report, an L-menthyl group was incorporated into Michael precursor **78** as a chiral auxiliary, but proved to be less effective in terms of stereocontrol.[34]



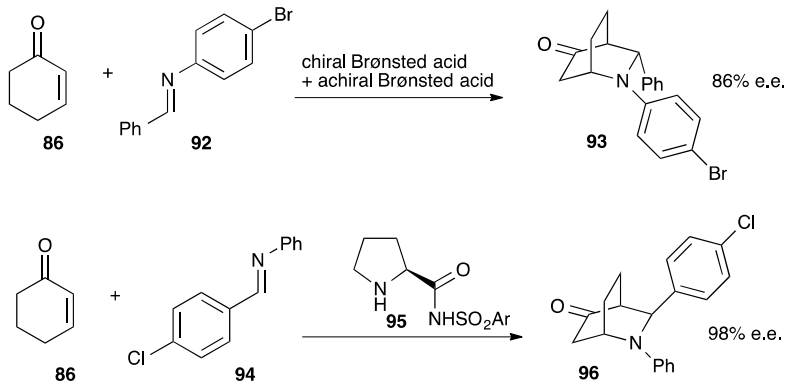

Scheme 21. Doubly activated aza-Michael additions

## 5. The hidden *endo*-aza-Michael

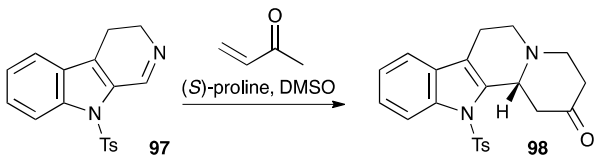
*endo*-aza-Michael reactions may be hidden inside tandem sequences. Specifically, the reaction between an imine (or an iminium ion) and the enol (or enolate) of an α,β-unsaturated ketone can be formulated as a combination of a Mannich reaction and an *endo*-aza-Michael addition. It can also be formulated as a Diels-Alder reaction in which the Michael acceptor participates through an enol or enamine derivative.[35] Some reports clearly claim a Diels-Alder reaction (Scheme 22),[36,37,38,39] some indicate the tandem Mannich-Michael process (Scheme 23),[40,41] while others make no comment on the mechanism (Scheme 24).[42] One report acknowledges the dichotomy[43] and one further report says "Diels-Alder", but draws "Mannich-Michael"![44] Syntheses of three piperidine alkaloids appears to involve what is clearly a Diels-Alder reaction and, hence, are not discussed here.[45] In many of these reactions, whatever the mechanism, the use of an organocatalyst results in an efficient asymmetric process. The method has been found useful, for instance in the synthesis of antihypertensive compounds,[46,47] adrenoceptor antagonists,[48] and novel β-lactam antibiotics.[49] Some applications to natural product synthesis are discussed in the following section.




Scheme 22. Piperidinone syntheses reported as hetero-Diels-Alder reactions



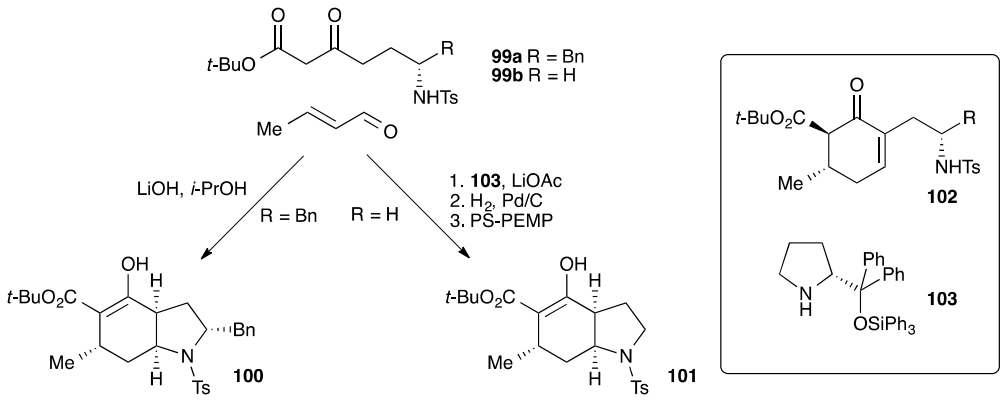

Scheme 23. Piperidinone syntheses reported as Mannich-Michael sequences




Scheme 24. A piperidinone synthesis that may involve a Mannich-Michael sequence

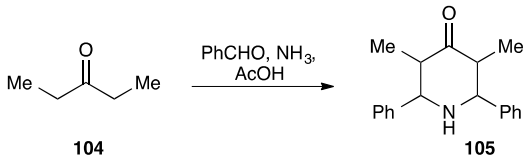
An *exo*-activated *endo*-aza-Michael is a component of a rather complex tandem process leading to octahydroindoles **100** and **101** (Scheme 25).[50] The sequence

involves a Michael addition of a β-ketoester, **99**, to an unsaturated aldehdye, followed by an intramolecular Aldol process. This generates an intermediate **102** which then undergoes an *exo*-activated *endo*-aza-Michael addition. With a starting material, **99a**, containing a stereogenic centre, a highly diastereoselective reaction could be achieved with just lithium hydroxide as the base. Alternatively, a stepwise organocatalytic version gave good enantioselectivity using the Hayashi catalyst **103**.




Scheme 25. Formation of octahydroindoles

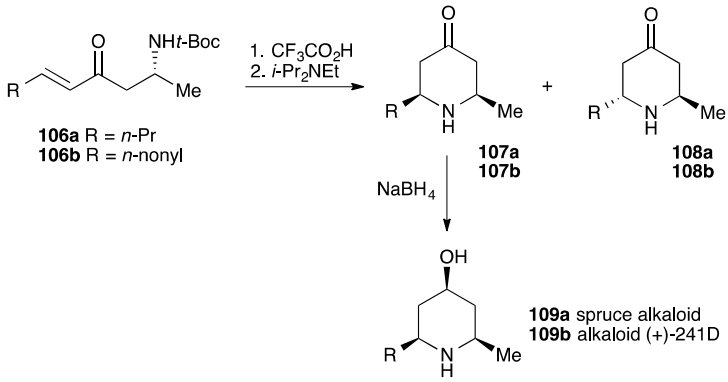
The condensation of a ketone **104**, an aldehyde (twice over) and an amine to give a highly substituted piperidinone **105** may also be formulated as a tandem process incorporating an intramolecular aza-Michael addition (Scheme 26). On the other hand, a combination of two Mannich processes is likely.[51,52]




Scheme 26. A tandem process for piperidinone formation

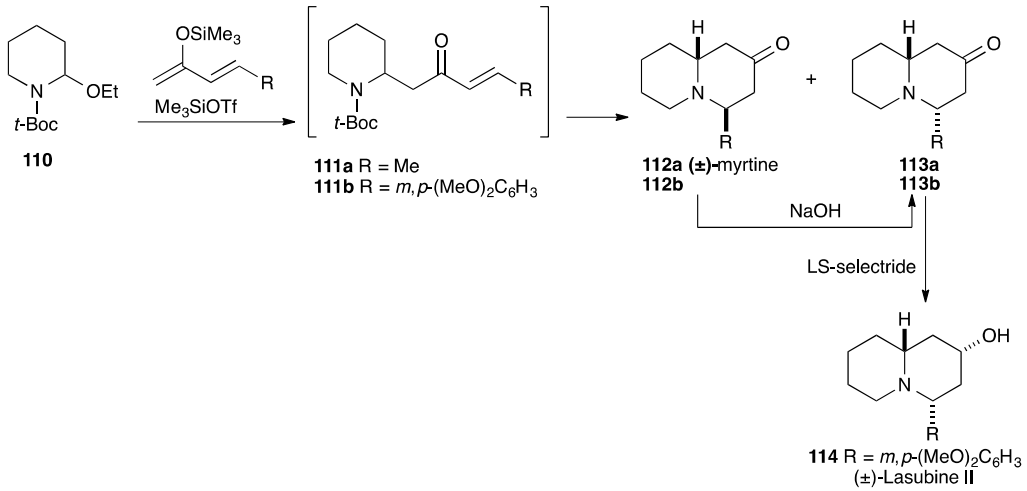
## 6. Applications of the *endo*-activated single addition in the synthesis of natural products

A simple application of this reaction to piperidine alkaloids is in the syntheses of spruce alkaloid **109a** and (+)-241D **109b** (Scheme 27).[53] Exposure of the enone **106a** to the sequence of trifluoroacetic acid and an amine base, as discussed earlier, gave a mixture of piperidinone **107a** and **108a**. Although the yields were good, the reaction almost completely lacked diastereoselectivity. This was attributed to the small size of the methyl group. The desired *cis* isomer **107a** could be reduced with good selectivity to give the spruce alkaloid **109a**. Likewise, enone **106b** could be converted to alkaloid (+)-241D **109b**. A related synthesis of this alkaloid is shown in Scheme 36.



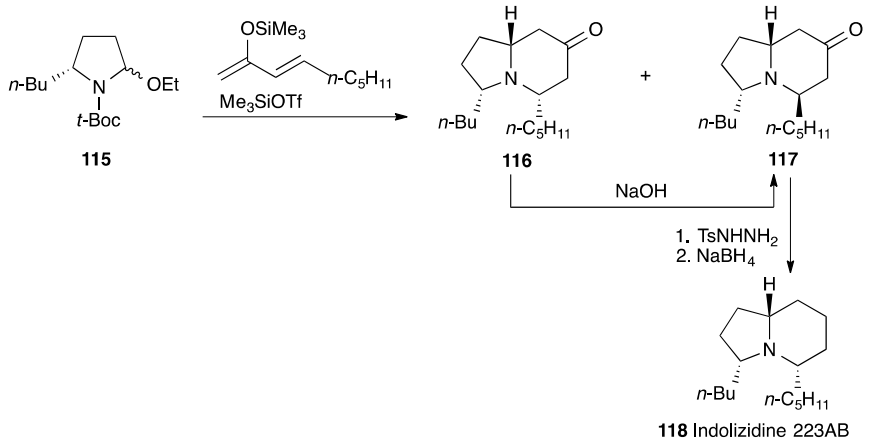

Scheme 27. Synthesis of spruce alkaloid and alkaloid (+)-241D

The single *endo*-aza-Michael addition has been used in several syntheses of lasubine **114** (Scheme 28). Probably the first example is in a synthesis reported by Pilli *et al.*[54] In this case, the Michael substrate **111** was generated by addition of an enol ether to an iminium ion generated *in situ* from *N*,*O*-acetal **110**. Given the acid lability of the Boc protecting group, a one pot protocol was developed to deliver the quinolizidines **112** and **113** via an *in situ endo*-aza-Michael addition. The quinolizidines were obtained as mixtures of diastereoisomers. In the case where R = Me, the major product **112a** had this substituent in an axial position and, thus, this is the alkaloid (±)-myrtine. When R was 3,4-dimethoxyphenyl, the diastereoselectivity was a little lower, but the mixture could be converted to **113b** by equilibration with base. Diastereoselective ketone reduction then yielded (±)-lasubine II **114**.



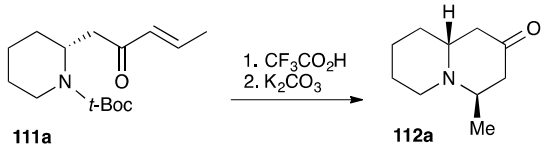

Scheme 28. Synthesis of (±)-myrtine and (±)-lasubine II by Pilli *et al.*

The same chemistry could also be applied to indolizidine synthesis, in this case (-)-indolizidine 223AB **118**, a dendrobatid frog alkaloid (Scheme 29). The starting material, *N*,*O*-acetal **115**, was obtained from pyroglutamic acid.



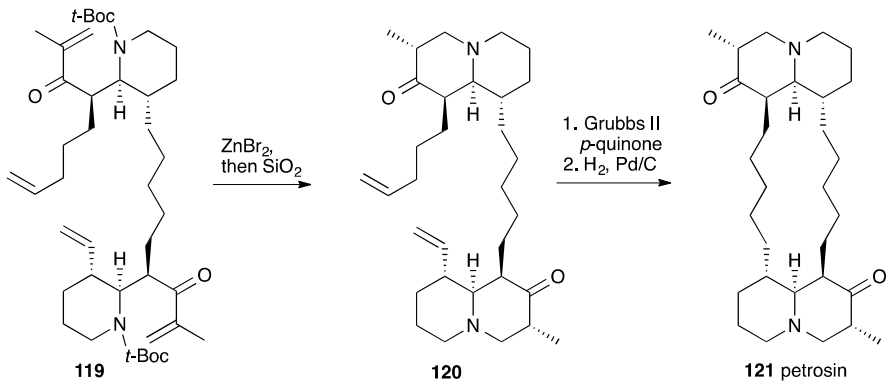

Scheme 29. Synthesis of (-)-Indolizidine 223AB

Another synthesis of myrtine **112a** also employed an intramolecular aza-Michael addition (Scheme 30).[55] The addition was reported to proceed with complete selectivity. The Michael precursor **111a**, the same one as in Scheme 27, was obtained in optically active form by an organo-catalysed asymmetric *exo*-aza-Michael addition, so that the synthesis delivers (+)-myrtine **112a**.




Scheme 30. Synthesis of (+)-myrtine.

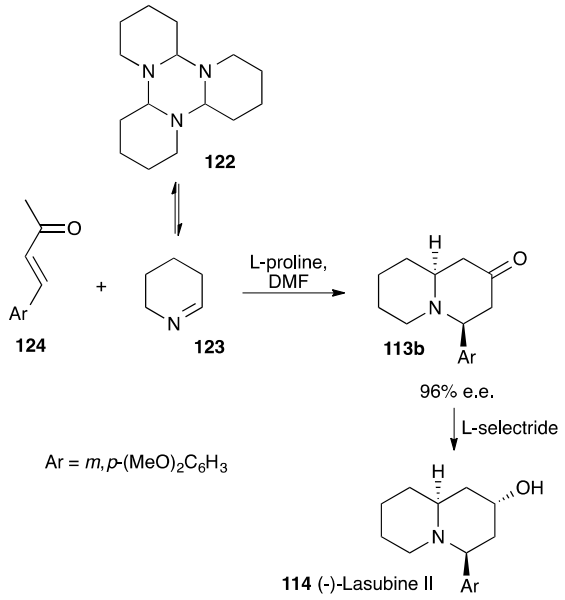
A more ambitious double *endo*-aza-Michael was part of a synthesis of both enantiomers of the macrocyclic alkaloid petrosin **121** (Scheme 31).[56] The two quinolizidine moieties were established together by a deprotection-aza-Michael sequence of the dimeric material **120** using the an unusual sequence of reagents. Model studies had shown that wet silica gel was the optimum reagent to give the quinolizidine as "effectively a single isomer". The synthesis was completed by ring closing metathesis and hydrogenation.




Scheme 31. Synthesis of petrosin

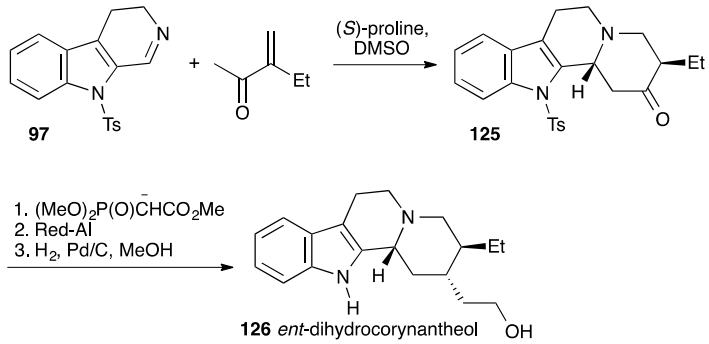
An asymmetric synthesis of (-)-lasubine II **114** that is very closely related in concept to the chemistry of Scheme 28, but quite distinct in execution, has been

reported (Scheme 32).[57] This method was inspired by the biosynthesis which involves the cyclic imine $\Delta^1$-piperideine **123**. The key to the success of the synthesis was organocatalysis. Thus, the reaction between the cyclic trimer **122**, which acts as a source of piperideine **123**, and enone **124** in the presence of (*S*)-proline as the organocatalyst in DMF gave the quinolizidinone **113b** in 96% e.e. and with very high diastereoselectivity in a single step. Diastereoselective reduction then gave (-)-Lasubine II **114**. (+)-Subcosine II, the dimethylcaffeoyl ester, could then be prepared. Corresponding indolizidines could be prepared similarly and the formal syntheses of a number of other quinolizidines could be claimed.



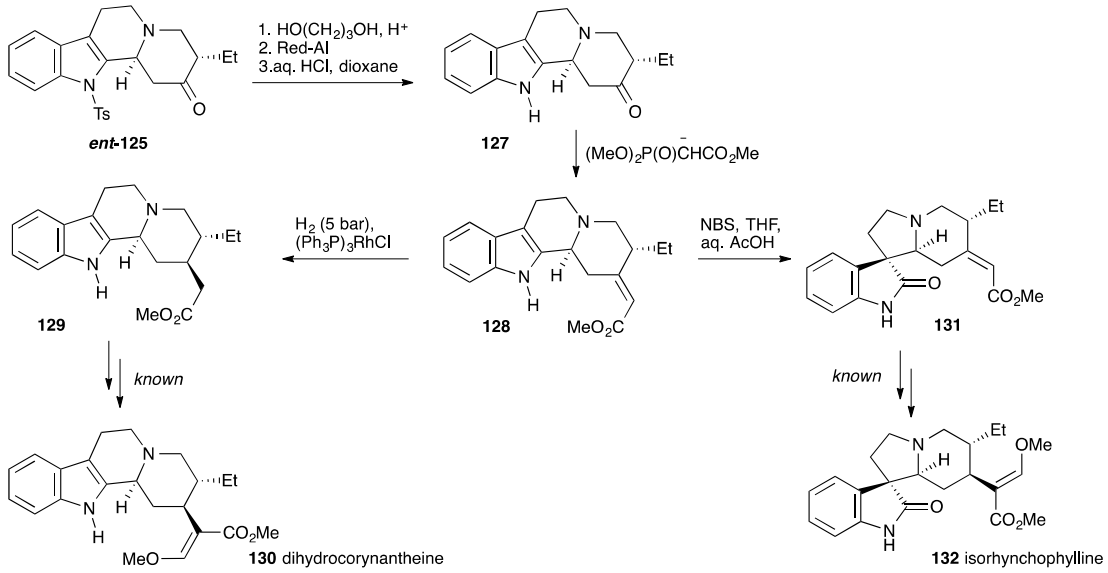

Scheme 32. Biomimetic synthesis of (-)-lasubine II

In addition, to the Lasubine example given above, the "hidden" aza-Michael reaction has been used in a short synthesis of *ent*-dihydrocorynantheol **126** (Scheme 33).[58] The Mannich-aza-Michael (or Diels-Alder) product **125**, produced by an asymmetric organocatalytic reaction as in scheme 24 (with a seven day reaction time) could be converted to the *ent*-natural product **126** in just three steps.



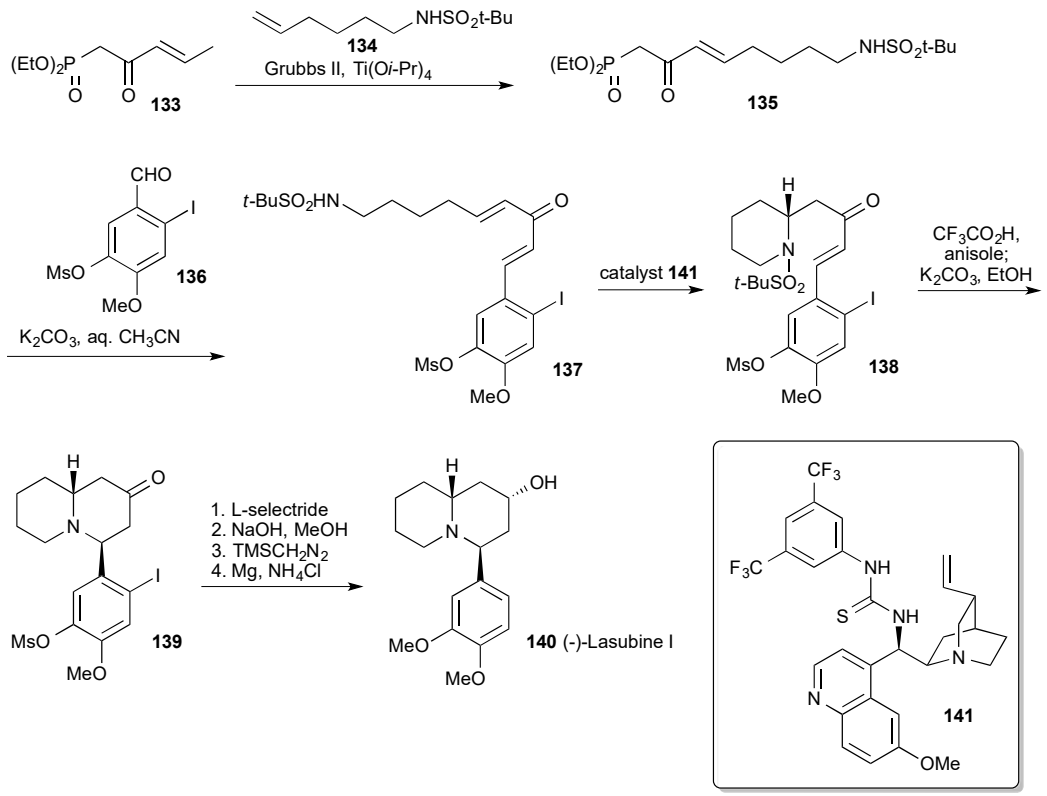

Scheme 33. Synthesis of *ent*-dihydrocorynantheol

Use of (*R*)-proline, naturally, gave access to the enantiomer of **125**.[59] This could be converted to ester **128**, a known precursor of dihydrocorynantheine **130**, and, by an elegant ring contraction, to ester **131**, a known precursor of isorhynchophylline **132** (Scheme 34).



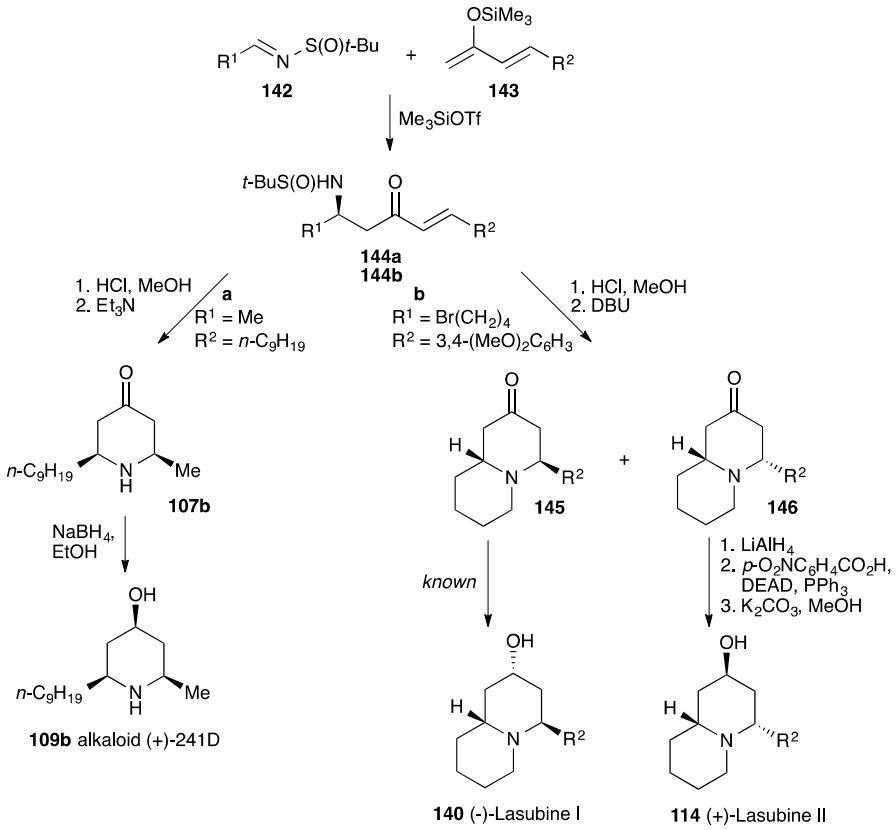

Scheme 34. Synthesis of dihydrocorynantheine and isorhynchophylline

In a synthesis of (-)-lasubine I **140**, the *endo*-aza-Michael addition was combined with an organo-catalysed asymmetric *exo*-aza-Michael, although in separate steps (Scheme 35).[60] The dienone substrate **137** was prepared by a sequence of cross-metathesis and a mild Horner-Wadsworth-Emmons reaction. The *exo*-aza-Michael addition could then be effected using the organocatalyst **141**, giving the piperidine **138** in 95% e.e. The corresponding tosyl and nosyl protected compounds behaved similarly, but the Boc analog failed to react. Removal of the sulfonyl group then triggered the *endo*-aza-Michael addition giving the quinolizidine **139**. Interestingly, while this reaction proceeded with high diastereoselectivity (though seemingly under quite carefully defined conditions), some loss of enantiopurity was observed, implying that the retro-Michael-Michael reaction competes with the second Michael addition. The product was converted into (-)-lasubine I **140** in four steps. Quinolizidine **139** is also a promising intermediate for the synthesis of other alkaloids, such as vertine.



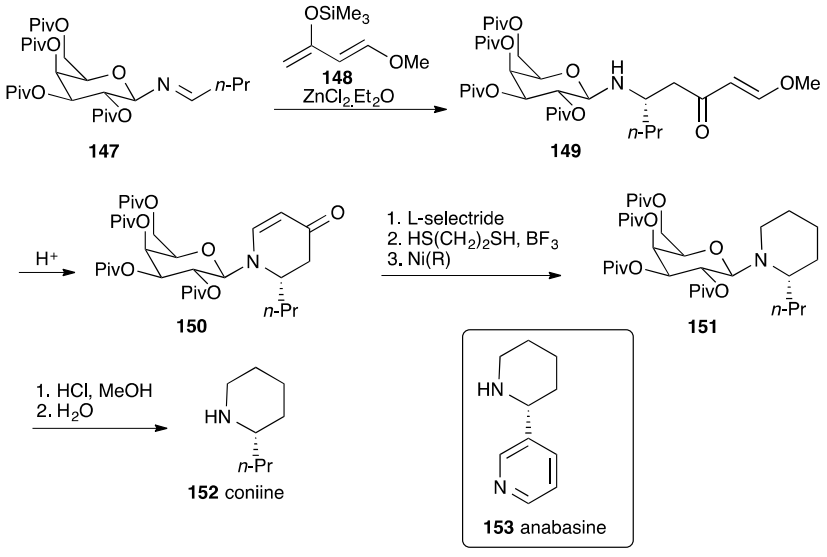

Scheme 35. Two aza-Michael additions in a synthesis of (-)-lasubine I

A synthesis of two of the lasubines, plus another alkaloid, employs the addition of a silyl enol ether **143** to Ellman-type imines **142** to generate the aza-Michael substrates **144** (Scheme 36).[61] An acid-base sequence removes the auxiliary, resulting in the *endo*-aza-Michael addition. In the case of the substrate with a nonyl side chain **144a**, simple reduction of the resulting piperidinone **107b** delivered alkaloid (+)-241D **109b**. A related synthesis of this alkaloid is shown in Scheme 27. Alternatively, with the more functionalised enone **144b**, removal of the chiral auxiliary resulted the *endo*-aza-Michael addition and a second cyclisation in tandem fashion to give a mixture of the diastereoisomeric quinolizidinones **145** and **146**. The conversion of quinolizidine **145** to (-)-lasubine I **140** is well known; quinolizidine **146** could be converted to (+)-lasubine II **114.** Additional syntheses of lasubine may be found in Schemes 28, 32 and 46.




Scheme 36. Synthesis of three piperidine alkaloid natural products

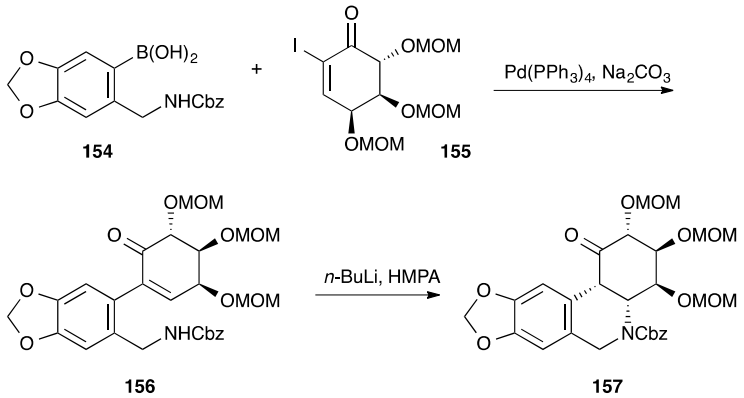
Addition of a silyl enol ether also features in the synthesis of some other piperidine alkaloids (Scheme 37).[62] In this case the use of a chiral auxiliary derived from galactose resulted in high diastereoselectivity when imine **147** reacted with enol ether **148** in the presence of a Lewis acid. Acidic treatment of the Mannich adduct **149** results in tandem aza-Michael addition-elimination to give the unsaturated piperidinone **150**. After stripping out of most of the functionality of the heterocycle, removal of the chiral auxiliary delivered the alkaloid coniine **152**. Anabasine **153** could be prepared in a likewise fashion.



Scheme 37. Synthesis of coniine

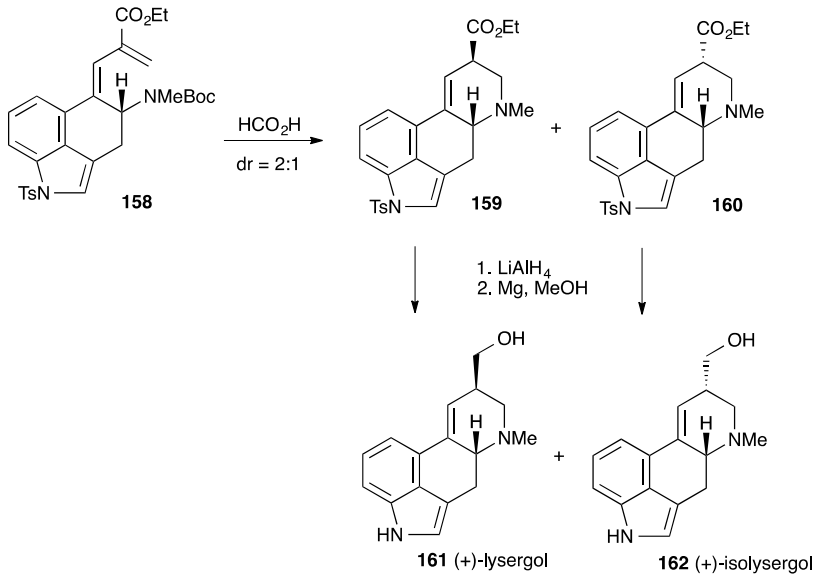
## 7. Applications of the *exo*-activated addition in the synthesis of natural products

As pointed out in the introduction, the *exo*-activated variant of the *endo*-aza-Michael addition is less frequently encountered in the literature. One application is in a synthesis of *epi*-deoxypancratistain (Scheme 38).[63] The aza-Michael precursor **156** could be prepared by a straightforward Suzuki coupling and the *endo*-aza-Michael effected by treatment with a strong base. To the disappointment of the authors, the product **157** was the *cis*-fused isomer, presumably due to protonation of the intermediate on the less hindered face. In this case, attempted equilibration resulted in a host of side reactions. Michael product **157** could be converted to a stereoisomer of deoxypancratistin.



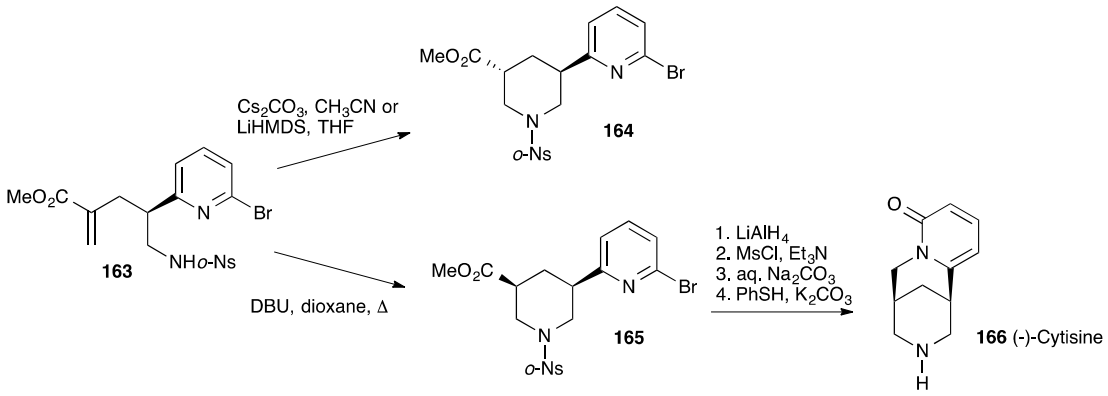

Scheme 38. Synthesis of *epi*-deoxypancratistain

An *endo*-aza-Michael was used in a synthesis of (+)-lysergol **161** (scheme 39).[64] The starting material **158**, arising from a organocatalysed Michael addition, cyclised in 6-*endo* fashion (rather than 6-*exo* attack on the ester group) to give a mixture of diastereoisomers, **159** and **160**, with reasonable selectivity. The isomers could be taken through to (+)-lysergol **161** and its epimer, (+)-isolysergol **162**.




Scheme 39. Synthesis of (+)-lysergol

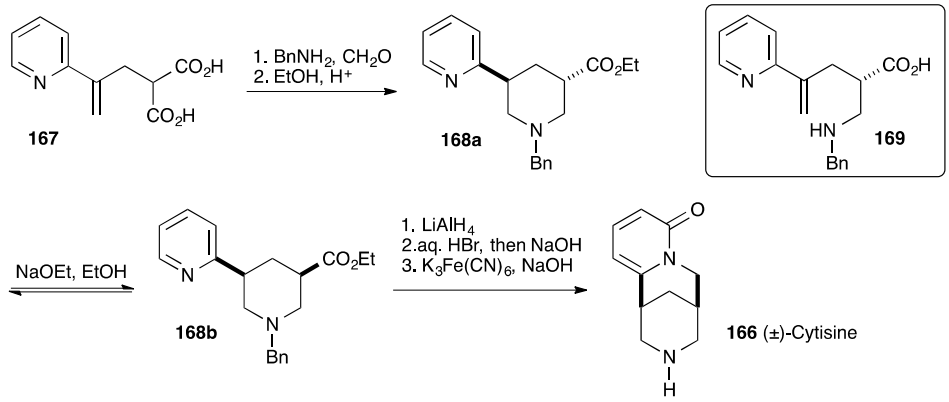
In a synthesis of (-)-cytisine **166**, it was shown that either diastereoisomer of the product of an *endo*-aza-Michael addition could be formed according to the reaction conditions (Scheme 40) in a stereodivergent fashion.[65] Treatment of the ester **163** with either fresh cesium carbonate or with LiHMDS gave the kinetic *trans* product **164**, arising from face selective protonation of the intermediate enolate. On the other hand, heating with DBU delivered the thermodynamically favoured *cis* product **165** as the major isomer. This could be converted to cytisine in four steps.




Scheme 40. Synthesis of (-)-cytisine

An *endo*-aza-Michael addition is also a part of the first synthesis of cytisine **166**, reported by van Tamelen in 1950s (Scheme 41).[66] This involved a tandem Mannich-aza-Michael process with decarboxylation to convert the malonic acid **167** to the *trans*-piperidine **168a**. After base catalysed equilibration, the *cis*-ester **168b** could be converted to (±)-cytisine **166**. The intermediate species that undergoes the *exo*-activated-*endo*-aza-Michael addition is presumably amine

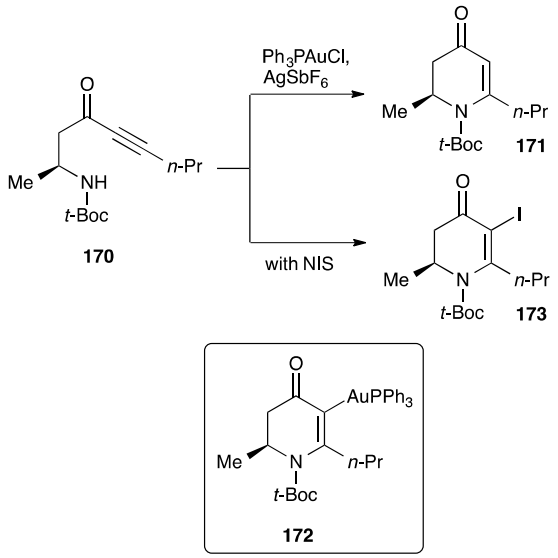
**169**. This is an unusual example, perhaps unique, of a pyridine being the activating group for an *endo*-aza-Michael addition.




Scheme 4**1**. van Tamelen's synthesis of (±)-cytisine

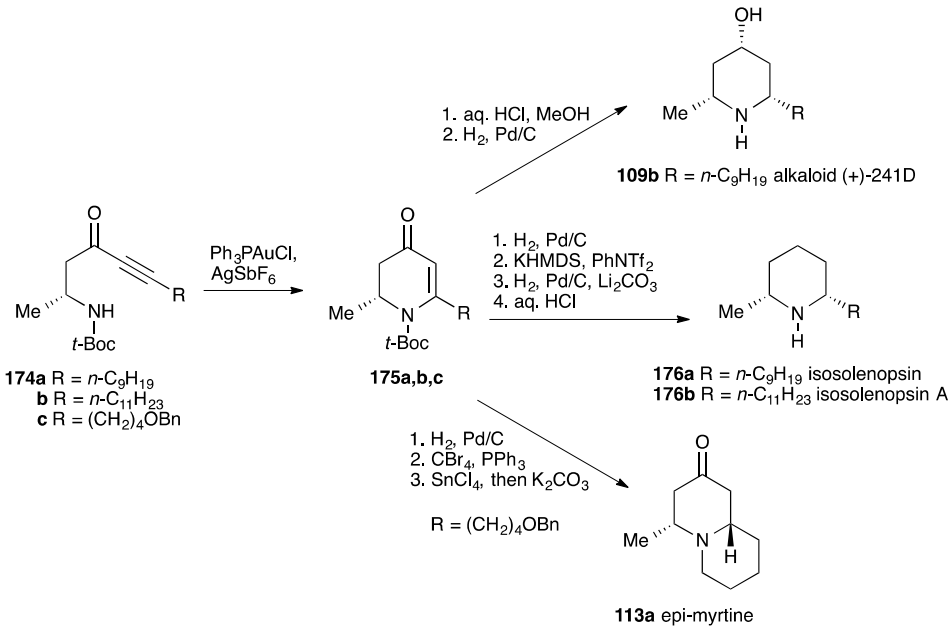
## 8. Addition to alkyne acceptors

Alkynones can also be very effective Michael acceptors. Both the 5-*endo* and 6-*endo* intramolecular aza-Michael reactions are known. The majority of reports, however, employ gold catalysis and thus are not, in terms of mechanism, purely Michael additions. For instance Gouault *et al.* showed that ynones such as **170** underwent cyclisation in good yield on exposure to a gold(I) hexafluorophosphate catalyst[67] or a gold(I) bistriflamide catalyst[68] to give unsaturated piperidinones, such as **171**, presumably via an α-aurated species **172** (Scheme 4**2**). Indeed, when the cyclisation was carried out in the presence of an electrophilic halogen source, such as NIS, then the α-halo derivative **172** was obtained.[69] The products can be subjected to a wide range of transformations which tend to take place on the face opposite to the existing substituent. Good stereocontrol arises because this substituent is axial.




Scheme 4**2**. Gold catalysed cyclisation

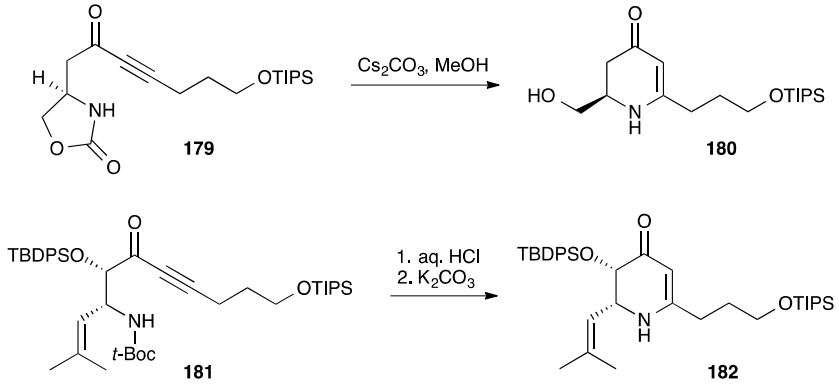
An example of the power of this stereocontrol is in the same laboratory's synthesis of a series of piperidine alkaloids: (+)-241D **109b**, isosolenopsin **176a**, isosolenopsin A **176b**[70] and epi-myrtine **113a** (Scheme 43).[71] epi-Myrtine is also shown in Scheme 28; other syntheses of alkaloid 241D are shown in Schemes 27 and 36. The reaction has also been used in the synthesis of enzyme inhibitors.[72]




Scheme 43. Alkaloid synthesis using gold catalysis

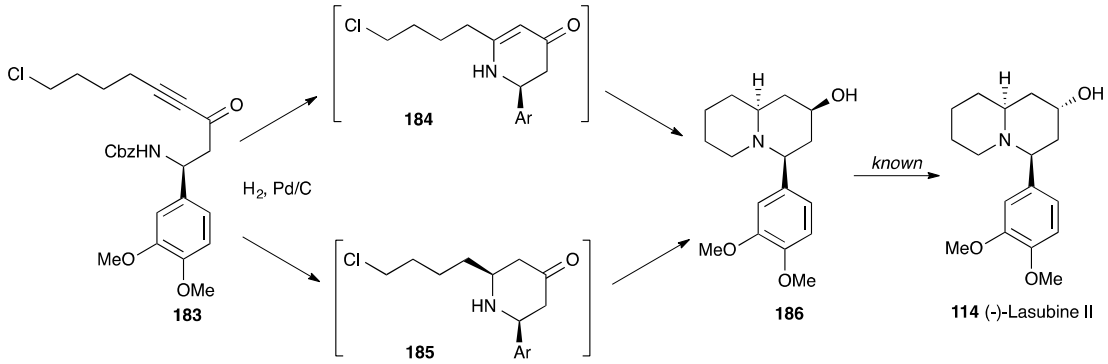
Silver has also been used to catalyse the cyclisation, although only one example of an *endo*-aza-Michael reaction, the conversion of ynone **177** to heterocycle **178**, was given in a paper otherwise devoted to the *endo*-oxa-Michael addition (Scheme 44).[73] It may be noted, however, that a metal catalyst is not necessarily needed. There are a number of examples in which the simple nucleophilicity of an amine is sufficient (Scheme 45).[68,72,74,75]


Scheme 44. Silver catalysed cyclisation



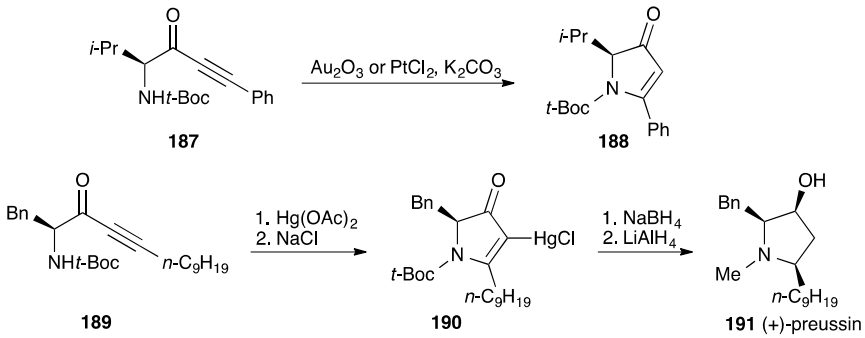
Scheme 45. 6-*endo*-dig aza-Michael additions

A 6-*endo* addition onto an alkyne may be involved in a formal synthesis of (-)-lasubine II **114** in which both rings of the indolizidine are established in a single laboratory step (Scheme 46).[76] Exposure of the ynone **183** to hydrogen gas in the presence of a palladium catalyst directly delivers the indolizidine **186** in a tandem process that involves deprotection, Michael addition, carbon-carbon π-bond reduction and nucleophilic substitution, as well as carbonyl reduction. The precise mechanism depends on the order of events: is the CBZ group cleaved before or after the alkyne is reduced? Thus either **184** or **185** may be intermediates (or both). The indolizidine product **186** may be converted to (-)-Lasubine II **114** by a known Mitsunobu process.




Scheme 46. Formal synthesis of (-)-lasubine II via an alkynone

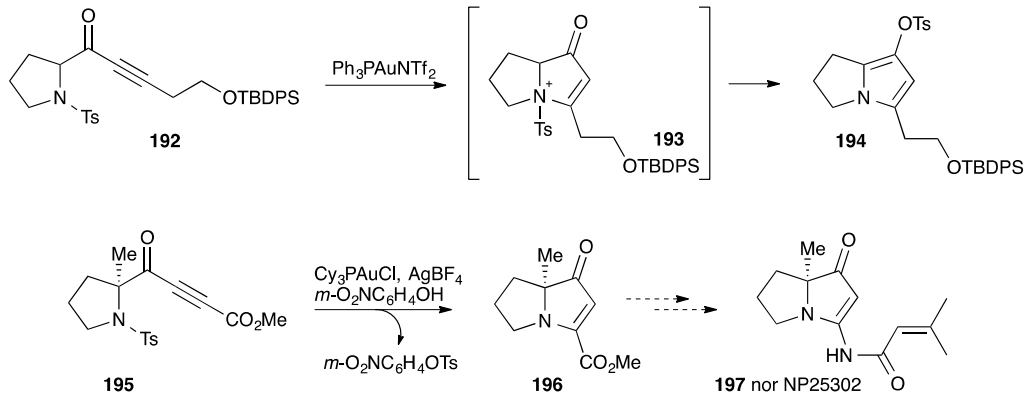
An advantage of the alkyne as the acceptor is that the corresponding 5-*endo*-aza-Michael addition is possible.[77] Examples include reactions with gold catalysis[78] and with platinum catalysis (Scheme 47).[79] In the case of gold catalysis, use of the oxide resulted in the least epimerisation of the product **188** during cyclisation. Mercury has also been used, although, given the kinetic stability of the carbon-mercury bond, this is in a stoichiometric fashion with additional steps required to yield a metal-free product and thence obtain the alkaloid (+)-preussin **191**.[80]




Scheme 47. 5-*endo*-dig addition reactions

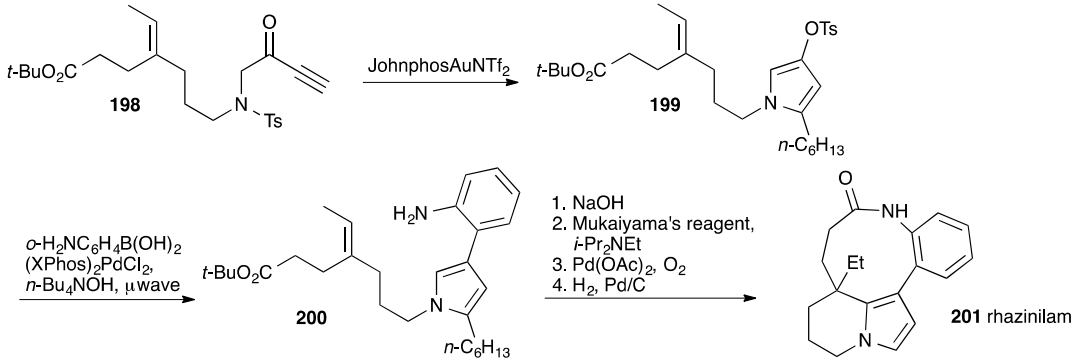
Quite surprisingly, sulfonamides can participate in such gold catalysed reactions, despite the strongly electron withdrawing nature of the sulfonyl group (Scheme 48).[81] Treatment of alkynones such as **192** with a gold catalyst yields the β-tosyloxypyrroles **194**. The reaction appears to proceed by gold catalysed

addition of the sulfonamide nitrogen to the alkynone, initially yielding a cationic sulfonamide **193**. An intramolecular translocation of the sulfonyl group from N to O then yields the functionalised pyrrole **194**. On the other hand, if pyrrole formation is blocked by the presence of a quaternary centre, as in pyrrolidine **195**, an external nucleophile, such as *m*-nitrophenol, can remove the sulfonyl group to yield a bicyclic enone **196**. This aspect of the chemistry was applied to a formal synthesis of (+)-nor NP25302 **197**, an anti-leukemia agent.



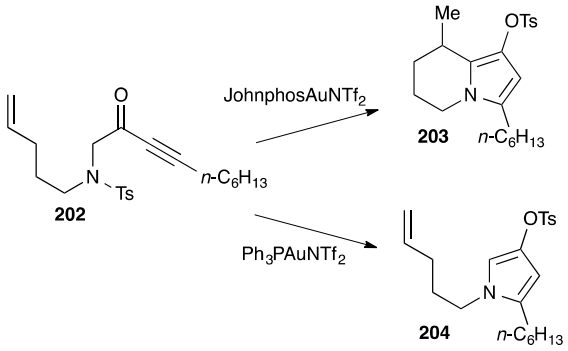

Scheme 48. Gold catalysed sulfonamide cyclisation reactions

As the tosyloxy moiety on the pyrrole can participate in Suzuki coupling reactions, this chemistry was applied to a synthesis of rhazinilam **201** (Scheme 49).[82] This synthesis employed the gold catalysed cyclisation of ynone **198** to form the pyrrole ring and a CH-activation reaction to form the six-membered ring in transannular fashion. A Suzuki coupling between tosyloxypyrrole **199** and an *o*-borylated aniline derivative was a key step.




Scheme 49. Synthesis of rhazinilam.

An extension of this chemistry is to employ a substrate, such as **202**, with an additional alkene or alkyne (Scheme 50).[83] As the pyrrole rings produced are electron rich, a second cyclisation catalysed by gold can ensue to give bicyclic product **204**, although the balance between the singly cyclised products and doubly cyclised products was quite dependent on the ring size, degree of substitution, and choice of catalyst.




Scheme 50. Single and double gold catalysed annulations

## 9. Conclusion

The importance of the intramolecular aza-Michael reaction for organic synthesis has been amply demonstrated for *endo*-activated processes. The application of asymmetric catalysis, especially through organocatalysis, has resulted in some processes of remarkable efficiency. Despite the multiple applications of the reaction, there appears to be little understanding of the stereochemical outcome of these reactions. Studies of this issue are overdue. Few examples, however, have been reported for *exo*-activated processes and, while the stereoselectivity of this reaction appears to be now better understood, there is considerable scope for its wider application.

## Conflicts of interest

There are no conflicts of interest to declare.

## Acknowledgement

We thank the Singapore Ministry of Education Academic Research Fund Tier 1 (grant RG62/10) for financial support of our own work in this area. RWB thanks IISER Tirupati for hospitality during much of the reading and writing for this review.

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[1] For an analysis of this reaction, see D. Csókás, A. X. Y. Ho, R. O. Ramabhadran and R. W. Bates, *Org. Biomol. Chem.*, 2019, **17**, 6293.

[2] A number of examples can be found in some recent reviews: (a) M. G. Vinogradov, O. V. Turova and S. G. Zlotin, *Org. Biomol. Chem.*, **2019**, *17*, 3670; (b) M. Sánchez-Roselló, J. L. Aceña, A. Simón-Fuentes, C. del Pozo, *Chem. Soc. Rev.*, 2014, **43**, 7430; (c) Z. Amara, J. Caron, D. Joseph, *Nat. Prod. Rep.*, 2013, **30**, 1211.

[3] J. E. Baldwin, *J. Chem. Soc., Chem. Commun.*, 1976, 734.

[4] For an unusual example of a double *exo*-activated *endo*-aza-Michael addition leading to 7-membered sulfur heterocycles, see (a) Q. Zang, S. Javed, F. Ullah, A. Zhou, C. A. Knudtson, D. Bi, F. Z. Basha, M. G. Organ, P. R. Hanson, *Synthesis* **2011**, 2743; (b) Q. Zang, S. Javed, D. Hill, F. Ullah, D. Bi, P. Porubsky, B. Neuenswander, G. H. Lushington, C. Santini, M. G. Organ, P. R. Hanson, *ACS Comb. Sci.*, 2010, **14**, 456.

[5] I. N. Nazarov and N. I. Shvetsov, *Russ. Chem. Bull.*, 1959, **8**, 2059 and references therein.

[6] I. K. Korshevets and É. A. Mistryukov, *Bull. Acad. Sci. USSR*, 1987, 1420.
[7] (a) E. Nakamura, K. Kubota and M. Isaka, *J. Org. Chem.*, 1992, **57**, 5809 (b) K. Kubota, M. Isaka and E. Nakamura, *Heterocycles* 1996, **42**, 565.
[8] S. Selvaraj, S. Maragathasundaram, S. Perumal and N. Arumugam, *Ind. J. Chem. B*, 1987, **26**, 1104.
[9] (a) W. M. Weber, L. A. Hunsaker, C. N. Roybal, E. V. Bobrovnikova-Marjon, S. F. Abcouwer, R. E.; Royer, L. M. Deck and D. L. Van der Jagt, *Bioorg. Med. Chem.*, 2006, **14**, 2450; (b) W. M. Weber, L. A. Hunsaker, A. M. Gonzales, J. J.; Heynekamp, R. A. Orlando, L. M. Deck and D. L. Van der Jagt, *Biochem. Pharm.*, 2006, **72**, 928.
[10] G.-P. Zeng, Y.-G. Hu and M.-W. Ding, *J. Heterocyclic Chem.*, 2008, **45**, 1809.
[11] (a) H. Teramoto, T. Yamauchi, S. Sasaki and K. Higashiyama, *Chem. Pharm. Bull.*, 2016, **64**, 420; (b) A. Rosiak, C. Hoenke and J. Christoffers, *Eur. J. Org. Chem.*, 2007, 4376.
[12] S. Dörrenbächer, U. Kazmaier and S. Ruf, *Synlett*, 2006, 547.
[13] V. Padmavathi, T. V. R. Reddy, K. A. Reddy and D. B. Reddy, *J. Heterocyclic Chem.*, 2003, **40**, 149.
[14] K. D. Praliev, E. V. Fishchuk, V. B. Rozhnov, N. M. Kurbat, V. P. Vdovichenko and P. B. Stankevich, *Pharma. Chem. J.*, 1989, **23**, 648.
[15] S. F. Nelsen, G. Li and A. Konradsson, *Org. Lett.*, 2001, **3**, 1583.
[16] (a) S. F. Nelsen, L.-J. Chen, D. R. Powell and F. A. Neugebauer, *J. Am. Chem. Soc.*, 1995, **117**, 11434; (b) S. F. Nelsen, C. R. Kessel, L. A. Grezzo and D. J. Steffek, *J. Am. Chem. Soc.*, 1980, **102**, 5482 – 5485.
[17] S. F. Nelsen, C. R. Kessel and D. J. Brien, *J. Am. Chem. Soc.*, 1980, **102**, 702.
[18] (a) A. T. Bottini and J. Gal, *J. Org. Chem.*, 1971, **36**, 1718; (b) K. C. Nicolaou, T. Montagnon, P. S. Baran and Y.-L. Zhong, *J. Am. Chem. Soc.*, 2002, **124**, 2245.
[19] B. B. Snider and T. Liu, *J. Org. Chem.*, 1997, **62**, 5630.
[20] G. A. Molander and M. Röhm, *J. Org. Chem.*, 1999, **64**, 5183.
[21] B. M. Trost and M. T. Rudd, *Org. Lett.*, 2003, **5**, 4599.
[22] B. B. Snider and T. C. Harvey, *Tetrahedron Lett.*, 1995, **36**, 4587.
[23] S.-W. Liu, H.-C. Hsu, C.-H. Chang, H.-H. G. Tsai and D.-R. Hou, *Eur. J. Org. Chem.*, 2010, 4771.
[24] R. P. Krishna and A. Sreeshailam, *Tetrahedron Lett.*, 2007, **48**, 6924.
[25] I. Abrunhosa-Thomas, O. Roy, M. Barra, T. Besst, P. Chalard and Y. Troin, *Synlett*, 2007, 1613.
[26] I. Abrunhosa-Thomas, A. Plas, A. Vogrig, N. Kandpedu, P. Chalard and Y. Troin, *J. Org. Chem.*, 2013, **78**, 2511-2526.
[27] L. S. Fowler, L. H. Thomas, D. Ellis and A. Sutherland, *Chem. Commun.*, 2011, **47**, 6569.
[28] M. Daly, A. A. Cant, L. S. Fowler, G. L. Simpson, H. M. Senn and A. Sutherland, *J. Org. Chem.*, 2012, **77**, 10001.
[29] For an exception, and similar proposed transition states,s ee reference 27.
[30] M. Kalyva, A. L. Zografos, E. Kapourani, E. Giambazolias, L. Devel, A. Papakyriakou, V. Dive, Y. G. Lazarou and D. Georgiadis, *Chem. Eur. J.*, 2015, 3278.
[31] M. K. Ghorai, S. Halder and R. K. Das, *J. Org. Chem.*, 2010, **75**, 7061.
[32] Is π-stacking overrated: C. R. Martinez and B. L. Iverson *Chem. Sci.*, 2012, **3**, 2191?
[33] (a) F. Johnson, *Chem. Rev.*, 1968, **68**, 375; (b) R. W. Bates and Y. Lu, *Org. Lett.*, 2010, **12**, 3938 and references therein.

[34] L. V. R. Babu Syamala and R. G.Bhat, *Tetrahedron Lett.*, 2017, **58**, 4836.
[35] For a disucssion of this issue, see P. R. Girling, T. Kiyoi and A. Whiting, *Org. Biomol. Chem.*, **2011**, *9*, 3105.
[36] F. Aznar, A.-B. Garcia and M.-P. Cabal, *Adv. Syn. Cat.*, 2006, **348**, 2443; N. Quiñones, F. Aznar and M.-P. Cabal, *Heterocycles* 2009, **78**, 2963.
[37] K. Hattori and H. Yamamoto, *Tetrahedron,* 1993, **49**, 1749.
[38] H. Sundén, I. Ibrahem, L. Eriksson and A. Córdova, *Angew. Chem. Int. Ed.*, 2005, **44**, 4877.
[39] T. Schrader and W. Steglich, *Synthesis*, 1990, 1153.
[40] M. Rueping C. and Azap, *Angew. Chem. Int. Ed.*, 2006, **45**, 7832.
[41] H. Yang and R. G. Carter, *J. Org. Chem.*, 2009, **74**, 5151.
[42] T. Itoh, M. Yokoya, K. Myauchi, K. Nagata and A. Ohsawa, *Org. Lett.*, 2003, **5**, 4301.
[43] M. P. Lalonde, M. A. McGowan, N. S. Rajapaksa and E. N. Jacobsen, *J. Am. Chem. Soc.*, 2013, **135**, 1891.
[44] H. Liu, L.-F. Cun, A.-Q. Mi, Y.-Z. Jiang, and L.-Z. Gong, *Org. Lett.*, 2006, **8**, 6023.
[45] A. B. Holmes, J. Thompson, A. J. G. Baxter and J. Dixon, *J. Chem. Soc., Chem. Commun.*, 1985, **37**; T. N. Birkinshaw and A. B. Holmes, *Tetrahedron Lett.*, 1987, **28**, 813.
[46] J. M. Caroon, R. D. Clark, A. F. Kluge, C.-H. Lee and A. M. Strosberg, *J. Med. Chem.*, 1983, **26**, 1426.
[47] B. Oussaid, M. J. Aurell, B. Garrigues and M. Soufiaoui, *Phosphorus Sulfur Relat. Elem.*, 1993, **85**, 17.
[48] J. R. Huff, J. J.; Baldwin, S. J. deSolms, J. P. Guare Jr. C. A. Hunt, W. C. Randall, W. S. Sanders, S. J. Smith, J. P. Vacca and M.M. Zrada, *J. Med. Chem.*, 1988, **31**, 641.
[49] B. Alcaide, P. Almendros, J. M. Alonso and M. C. Redondo, *J. Org. Chem.*, 2003, **68**, 1426.
[50] C. Parra, C. Bosch, E. Gómez-Bengoa, J. Bonjoch, B. Bradshaw, *J. Org. Chem.*, 2016, **81**, 10172.
[51] P. Petrenko-Kritschenko and M. Lewin *Chem. Ber.*, 1907, **40**, 2882; C. R. Noller, V. Baliah, *J. Am. Chem. Soc.* **1948**, *70*, 3853; V. Baliah, and T. S.Govindarajan, *Curr. Sci.*, 1954, **23**, 91.
[52] The early work on this reaction has been surveyed: V. Baliah, R. Jeyaraman, and L. Chandrasekaran, *Chem. Rev.*, 1983, **83**, 379.
[53] A. H. Harkiss and A. Sutherland, *J. Org. Chem.*, 2018, **83**, 535.
[54] R. A. Pilli, L. C. Dias and A. O. Maldaner, *J. Org. Chem.*, 1995, **60**, 717.
[55] S. Fustero, J. Moscardó, M. Sánchez-Roselló, S. Flores, M. Guerola, C. del Pozo, *Tetrahedron,* 2011, **67**, 7412.
[56] H. Toya, K. Okano, K. Takasu, M. Ihara, A. Takahshi, H. Tanaka, H. Tokuyama *Org. Lett.*, 2010, **12**, 5196.
[57] S. Virk and S. V. Pansare, *Org. Lett.*, 2019, **21**, 5524.
[58] T. Itoh, M. Yokoya, K. Miyauchi, K. Nagata and A. Ohsawa, *Org. Lett.*, 2006, **8**, 1533.
[59] K.; Nagata, H. Ishikawa, A. Tanaka, M. Miyazaki, T. Kanemitsu,and T. Itoh, *Heterocycles*, 2010, **81**, 1791.
[60] T. Jirama, T. Uemura, N. Kogure, M. Kitajima and H. Takayama, *Tetrahedron Lett.*, 2017, **58**, 223.
[61] A. A. Reddy, P. O. Reddy and K. R. Prasad, *J. Org. Chem.*, 2016, **81**, 11363.

[62] H. Kunz and W. Pfrengle, *Angew. Chem. Int. Ed.*, 1989, **28**, 1067.
[63] G. Pandey, M. Balakrishnan and P. S. Swaroop, *Eur. J. Org. Chem.*, 2008, 5839.
[64] S. Bhunia, S. Chaudhuri and A. Bisai, *Chem. Eur. J.*, 2017, **23**, 11234.
[65] V. Barát, D. Csókás and R. W. Bates, *J. Org. Chem.*, 2018, **83**, 9088.
[66] (a) E. E. van Tamelen and J. S. Baran, *J. Am. Chem. Soc.*, 1955**, 77**, 4944; (b) E. E. van Tamelen and J. S. Baran, *J. Am. Chem. Soc.*, 1958**, 80**, 4659.
[67] N. Gouault, M. Le Roch, A. Cheignon, P. Uriac and M. David, *Org. Lett.*, 2011, **13**, 4371. For an additional example, see B. M. Trost and C.-I. Hung, *J. Am. Chem. Soc.*, 2015, **137**, 15940.
[68] H.-D. Vu, J. Renault, L. Toupet, P. Uriac, and N. Gouault, *Eur. J. Org. Chem.*, 2013, 6677.
[69] K. H. Nguyen, S. Tomasi, M. Le Roch, L. Toupet, J. Renault, P. Uriac, and N. Gouault, *J. Org. Chem.*, 2013, **78**, 7809.
[70] N. Gouault, M. Le Roch, G. de Campos Pinto and M. David, *Org. Biomol. Chem.*, **2012**, *10*, 5541.
[71] T. T. H. Trinh, K. H. Nguyen, P. de Aguiar Amaral and N. Gouault, *Beilstein J. Org. Chem.*, 2013, **9**, 2042.
[72] C. G. Eiden and C. C. Aldrich, *J. Org. Chem.*, 2017, **82**, 7806.
[73] H. Fuwa, K. Mizunuma, S. Matsukida and M. Sasaki, *Tetrahedron,* 2011, **67**, 4995.
[74] H. P. Acharya and D. L. J. Clive, *J. Org. Chem.*, 2010, **75**, 5223.
[75] A. Pepe, M. Pamment, G. I. Georg and S. V. Malhotra, *J. Org. Chem.*, 2011, **76**, 3527.
[76] J. Lim, and G. Kim, *Tetrahedron Lett.*, 2008, **49**, 88.
[77] Is a 5-*endo*-trig reaction possible? A quick structure search seems to reveal one example (M. Gerspacher and H.Rapoport, *J. Org. Chem.*, 1991, **56**, 3700), but closer inspection reveals that the cyclisation in this example is really 5-*exo*-tet.
[78] N. Gouault, M. Le Roch, C. Cornée, M. David and P. Uriac, *J. Org. Chem.*, 2009, **74**, 5614.
[79] R. Spina, E. Colacino, B. Gabriele, G. Salerno, J. Martinez and F. Lamaty, *J. Org. Chem.*, 2013, **78**, 2698.
[80] M. Overhand and S. M. Hecht, *J. Org. Chem.*, 1994, **59**, 4722.
[81] (a) S. Miaskiewicz, B. Gaillard, N. Kern, J.-M., Weibel, P. Pale, A. Blanc, *Angew. Chem. Int. Ed.* 2016, **55**, 9088; (b) S. Miaskiewicz, J.-M., Weibel, P. Pale, A. Blanc, *Org. Lett.* 2016, **18**, 844.
[82] F. Sirindel, J.-M., Weibel, P. Pale, A. Blanc, *Org. Lett.* 2019, **21**, 5542.
[83] F. Sirindel, S. Golling, R. Lamare, J.-M., Weibel, P. Pale, A. Blanc, *Org. Lett.* 2019, **21**, 8997.