Organic & Biomolecular Chemistry

Cite this: *Org. Biomol. Chem.*, 2011, **9**, 3105

www.rsc.org/obc

PERSPECTIVE

Mannich–Michael *versus* formal aza-Diels–Alder approaches to piperidine derivatives

P. Ricardo Girling,[a] Takao Kiyoi[b] and Andrew Whiting*[a]

Received 8th November 2010
DOI: 10.1039/c0ob00996b

A review into the aza-Diels–Alder reaction, mainly concentrating on literature examples that form piperidin-4-ones from the reaction of imines and electron rich dienes or enones, either through a Lewis acidic/Brønsted acid approach or through the use of an organocatalyst. This review questions whether the mechanism of the aza-Diels–Alder reaction is step wise as opposed to concerted when using oxygenated dienes.

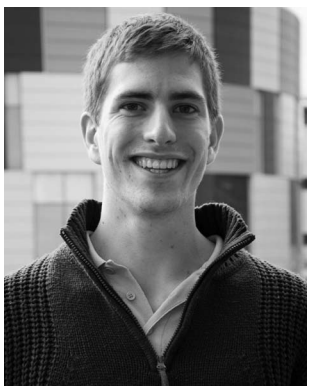
1 Introduction

The piperidine ring system[1] is widely found within nature[2] with the natural products possessing these ring systems showing a large range of biological activities.[3] Consequently, there is considerable interest in these types of compounds[4] due to their medicinal properties[5] and as a result, many analogues have been developed as therapeutic agents.[6] One way of making these six-membered rings is *via* an aza-Diels–Alder reaction involving an imino dienophile and a conjugated diene. The cycloaddition can be a relatively concerted process with less polarised dienes.[7–10] However, when using more electron rich dienes (*i.e.* oxygenated dienes or enone equivalents) only a formal Diels–Alder process occurs, generally assisted by an activating agent such as a Lewis acid[11] or an organocatalyst.[12] In this review, we consider the development of the formal cycloaddition of imino dienophiles with highly electron rich dienes and enones to derive tetrahydropiperidine frameworks and compare the different reaction conditions, reagents and applications, and the mechanisms which are operating.

[a]*Centre for Sustainable Chemical Processes, Durham University, Department of Chemistry, South Road, Durham, UK DH1 3LE. E-mail: andy.whiting@durham.ac.uk*
[b]*Department of Chemistry, Merck Research Laboratories, MSD, Newhouse, Lanarkshire, UK ML1 5SH*

1.1 Aza–Diels–Alder reaction

The Diels–Alder reaction is a concerted pericyclic cycloaddition between a conjugated diene and dienophile and in the aza-Diels–Alder reaction a carbon is replaced by a nitrogen atom, typically in the dienophile (*i.e.* an imine). The result is the formation of a six-membered nitrogen-containing tetrahydropyridine (or equivalent) ring which may also occur in a concerted manner. However, in many cases, the reaction may be better thought of as a



Ricardo Girling

Ricardo carried out his undergraduate MSci degree at University College London. During his time there, he spent a summer working with Novartis in Horsham on Ionic Tags, and carried out his Master's project on PFP propiolate under the supervision of Professor S. Caddick. He is currently studying for his PhD at Durham University with Professor A. Whiting and Dr T. Kiyoi in the area of applications of bifunctional asymmetric catalysis, particularly involving aminoboronic acid-based systems, for the synthesis of piperidine derivatives.

Takao Kiyoi

Takao is a Senior Scientist in the Department of Chemistry at the Merck Research Laboratories, MSD at Newhouse. He obtained his Bachelor's and Master's degrees in synthetic chemistry from Kyoto University in Japan. During a period in industry with Kanebo Ltd., he carried out PhD studies on carbohydrate chemistry with Professor A. Hasegawa and M. Kiso at Gifu University. After working for Nippon Organon in Japan, he moved to the UK and joined Organon Laboratories (now Merck Research Laboratories) in 2002. He has contributed to various research projects in disease areas such as CNS and immunology.

step-wise Mannich–Michael reaction. Both concerted and Mannich–Michael processes might be assisted by the use of catalysts, either Lewis acids and organocatalysts, and this is the subject of this review.

The Lewis acid-catalysed approach to achieving overall aza-Diels–Alder addition relies upon activating the imine, which in turn activates the initial Mannich reaction to proceed. In contrast, the organocatalytic approach is generally based upon activating the diene (in the form of an α,β-unsaturated ketone) through the formation of an enamine. As such, the organocatalytic process tends to involve chiral pyrrolidine-derived systems which permit asymmetric induction to be developed, with the simplest and most commonly available catalyst being L-proline.[13] Earlier research has tended to concentrate on Lewis acid-catalysis,[14] however, in recent years there has been a shift towards organocatalysis because it is possible to achieve highly enantioselective transformations.[15] This shift in concentration has been brought about by the increasing importance of organocatalysis in the last decade[16] and our understanding of the underlying concepts that has enabled application on different systems,[17] including the aza-Diels–Alder reaction.

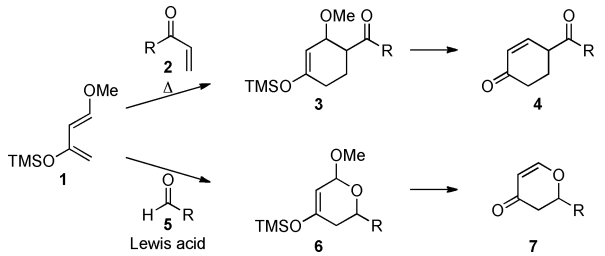
1.2 Asymmetric construction using Lewis acids

In 1974, Danishefsky *et al.* reported an electron rich diene, silyl enol ether **1**, suggesting that it could be used as an activated diene in the Diels–Alder reaction to mask carbonyl groups. This compound has ever since been known as Danishefsky's diene **1**.[18] Over the years, Danishefsky *et al.* have successfully investigated the use of this diene in the concerted Diels–Alder reaction, including the use of enones **2** as dienophiles[19] carried out under thermal (uncatalysed) conditions. They went on to find that aldehydes **5** could undergo "cyclocondensation" with Danishefsky's diene **1** in the presence of Lewis acids (Scheme 1).[20]

In the early 80s, Danishefsky *et al.* reported the first general cycloadditions involving simple, unactivated imines **8** catalysed by Lewis acids to form piperidine rings **9**. This formal aza-Diels–Alder reaction was shown to work between the Danishefsky diene **1** and α,β-unsaturated imines **8** in the presence of zinc(II) chloride

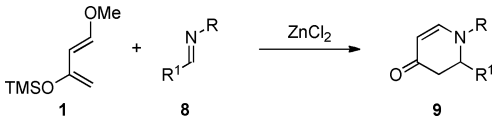
Andy Whiting

Andy carried out PhD studies with Professor R. J. Stoodley at the Newcastle University, working on β-lactam chemistry, before moving on to postdoctoral research at Boston College, with Professor T. Ross Kelly working on natural product synthesis and the development of chiral Diels–Alder Lewis-acid catalysts. After a short period in industry Ciba-Geigy Central Research, he moved to his first academic position as Lecturer in Chemistry at UMIST, and in 2001, moved to a Readership at Durham University, becoming Professor in 2009.



Scheme 1 The Diels–Alder reaction between Danishefsky's diene **1** and an enone **2** or an aldehyde **5**.

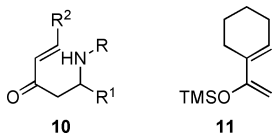
($ZnCl_2$)[21,22] (eqn (1)). The reactions were relatively slow (1–2 days), with stoichiometric amounts of Lewis acid and a large excess (4 equivalents) of the diene being required.



(1)

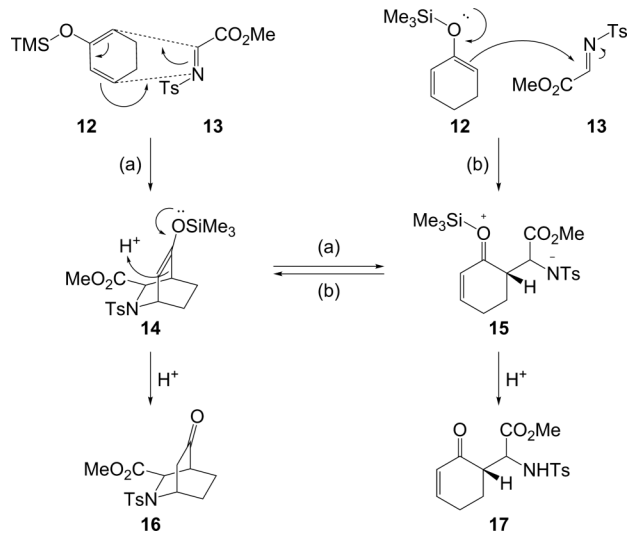
This methodology was later used in the synthesis of different alkaloids.[23] Analogously to the use of aldehydes **5** in place of imines **8**, it was mentioned that the mechanism went through either a concerted or Mannich–Michael process.[24] However, with the lack of evidence to disprove the concerted theory, Danishefsky *et al.* went on to describe the Lewis acid catalysed aza-Diels–Alder reactions as "cyclocondensation reactions."[25]

This aza-Diels–Alder procedure was subsequently tried and tested by different research groups. Some groups followed the procedure without focusing on the mechanism,[26] whilst others questioned the presence of a Mannich product **10**, acknowledging the possibility of two conceivable mechanisms for this reaction.[27] The observation of Mannich products led some to believe that this Diels–Alder process was probably a "non-synchronous concerted one."[28] It was also found that instead of Danishefsky's diene, the silyl enol ether of acetyl cyclohexene **11** could also be used.[29]



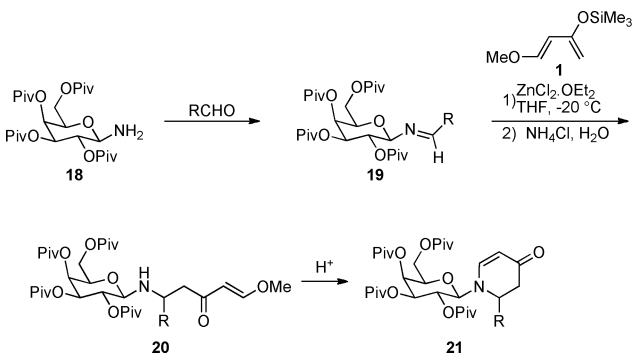
Meanwhile, Raithby *et al.* formed bicyclic rings **16** from an electron deficient imine **13** and an electron rich diene **12** in the presence of a Lewis acid, during which they observed minor Mannich products **17**. They proposed that the mechanism could either be: a) concerted; b) stepwise; or c) even occur simultaneously in competition with each other (Scheme 2).[30] They also suggested that different reaction conditions (such as solvent and temperature) make the reaction proceed through a different process.[31]

In their aza-Diels–Alder reactions, Kunz *et al.* used the more active $ZnCl_2$ as the Lewis acid and have argued that this process initially proceeds *via* a Mannich reaction followed by a cyclisation *via* nucleophilic intramolecular attack of the intermediate amine **20**. In their examples, imines attached to a sugar acting as a chiral auxiliary **19** were reacted highly selectively with Danishefsky's diene **1** in the presence of stoichiometric amounts of $ZnCl_2$ to give high yields of the piperidine ring **21**. They showed that if the reaction was stopped after 2–12 h with aqueous ammonium chloride solution, the Mannich compounds **19** could be isolated. After direct acid hydrolysis with either the reaction



Scheme 2 Proposed competing mechanisms for the formation of products **16** and **17**.

mixture or isolated Mannich products **19**, the subsequent Michael addition occurs immediately. This is followed by elimination of methanol to give the desired unsaturated piperidine ring **21**; thus proving the reaction proceeds *via* a Mannich–Michael mechanism (Scheme 3).[32] It was also shown that the Mannich product **20** governs the diastereoselectivity of the Michael product **21**.

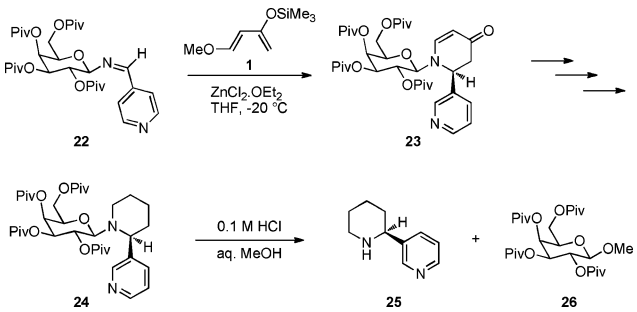


Scheme 3 Kunz's procedure for piperidine ring formation using sugars as chiral auxiliaries.

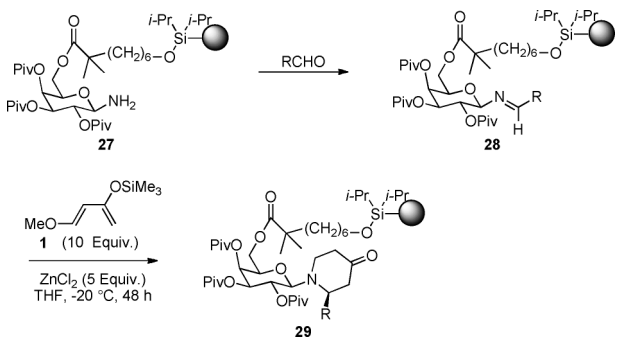
Changing the R-substituent of the imine did not make a difference to the reaction unless R was a large group; in such cases the yields started to diminish.[33] The sugar **26** was subsequently recovered almost quantitatively after acidic cleavage of the *N*-glycosidic bond. Through this method the tobacco alkaloid (*S*)-anabasin **25** was successfully synthesised in a few steps (Scheme 4).[34]

With the rise of resin-bound solid phase chemistry in the last decade, resin-bound aryl dialkylsilyl ethers have been used in numerous syntheses of oligosaccharides,[35] glycopeptides,[36] polyketides[37] and prostaglandins[38] to name but a few. Accordingly, Kunz *et al.* bound their chiral auxiliaries to dialkylsilyl resins **27** in order to facilitate the isolation of their subsequent piperidine ring products **29** (Scheme 5). In this case, 5 equivalents of $ZnCl_2$ were used in THF at rt, the reaction taking 2 days.[39]

Through the use of amino acids as chiral auxiliaries on the imine **30**, Waldmann *et al.* have shown that in the presence



Scheme 4 The route taken for the formation of (*S*)-anabasin **25**.

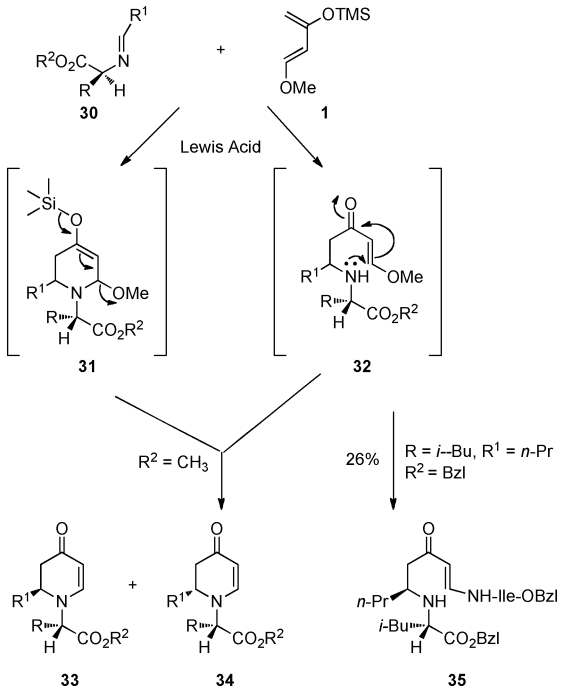


Scheme 5 Kunz *et al.*'s procedure using sugars bound to a resin.

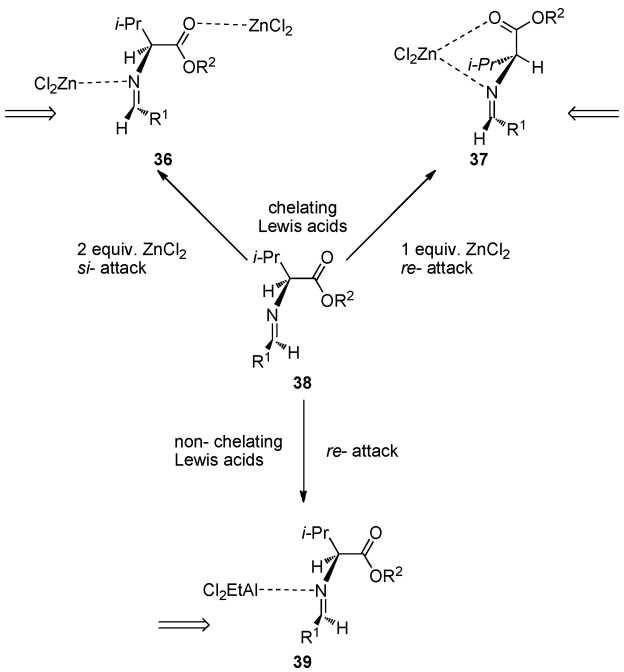
of stoichiometric amounts of $ZnCl_2$, electron rich Danishefsky's diene **1** was sufficiently reactive to react with unactivated imines **30** to form unsaturated piperidine ring structures **33** and **34**. The chiral auxiliary was subsequently removed in a few steps.[40] Depending on the imine used, poor to moderate yields were obtained with good enantioselectivity. When performing this reaction with different imines, it was noticed that the electronics of the imine substituent (R^1) did not make a difference to the reaction outcome. Additionally, if the reaction were concerted, it would have proceeded *via* intermediate **31**. However, by-product **35** from one of the reaction mixtures was isolated, most probably formed by nucleophilic attack of a free amino acid ester. This means the reaction must have gone through intermediate **32**, thus suggesting the reaction proceeds *via* a Mannich–Michael process (Scheme 6).

It was also found that chelating Lewis acids (such as $ZnCl_2$ and $TiCl_4$) afforded the same stereoisomers as non-chelating Lewis acids (such as boron and aluminium). The non-chelating Lewis acids would coordinate with the nitrogen of the imine **38** to form the conformation **39** as explained in the Felkin–Anh model[41] for nucleophilic addition to carbonyl groups. Hence, according to this model, attack of the diene happens on the *Re*-face. The opposite would then be expected with chelating Lewis acids as they can also chelate to the oxygen of the carbonyl group. However, under the reaction conditions ($ZnCl_2$: 0 °C to –20 °C; $TiCl_4$: warming from –78 °C to rt) the imine double bond is isomerised as previously reported by Ojima *et al.*,[42] and hence, the diene also attacks from the *Re*-face to give the same diastereoisomer **37**. Conversely, having two equivalents of $ZnCl_2$ affords the opposite diastereoisomer **36** (Scheme 7).

Weinreb *et al.* have shown the imine **41** can also cyclise with silyl enol ethers **40** to give unsaturated piperidine rings **42** and **43** in moderate yields.[43] When using catalytic amounts of $ZnCl_2$, the



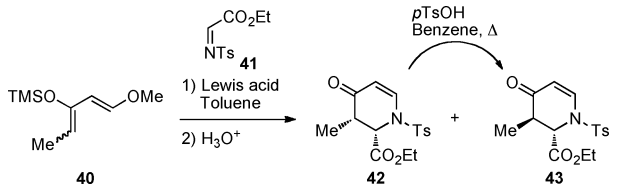
Scheme 6 Aza-Diels–Alder reaction using amino acids as chiral auxiliaries.



Scheme 7 The different sides of attack to **38**.

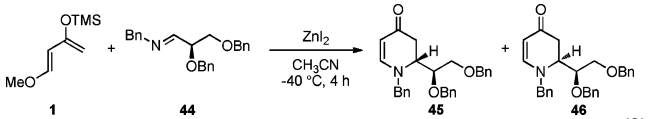
syn-piperidine ring **42** was obtained in a ratio of 22 : 1 to *trans*-**43**, which was a higher dr than when using $AlCl_3$ as a Lewis acid. If needed, the *syn*-product **42** can be isomerised to the *anti*-product **43** by refluxing the product with *p*-TsOH in benzene (Scheme 8).

By screening different Lewis acids, Gálvez *et al.* further demonstrated that the Lewis acid catalysed aza-Diels–Alder reaction showed good stereoselectivity towards the diastereoisomer of *R*,*R*-configuration **45**, regardless of the complexing properties (eqn (2)). The best selectivity was observed with stoichiometric amounts



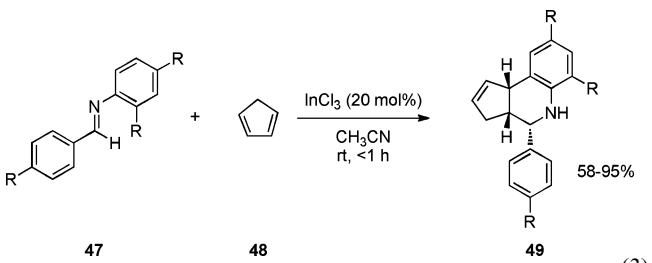
Scheme 8 Formation of **43** from **40**, showing improved yield from conversion of **42**.

of ZnI_2, followed by Et_2AlCl and $BF_3{\cdot}Et_2O$, whilst the Lewis acids $MgBr_2$, $Eu(fod)_3$, $SnCl_4$ and $TiCl_4$ seemed to be inactive.[44] Different solvents were also screened with the best results being obtained with acetonitrile followed by dichloromethane, tetrahydrofuran, diethyl ether, and, lastly, toluene. This suggested that polar solvents may be important in stabilising the chelated intermediate. However, the diastereoisomers proved challenging to separate, whilst higher temperatures were needed when using less reactive imines in order to obtain acceptable yields. Mannich intermediates were also observed, suggesting the aza-Diels–Alder reaction proceeds *via* a Mannich–Michael process.



(2)

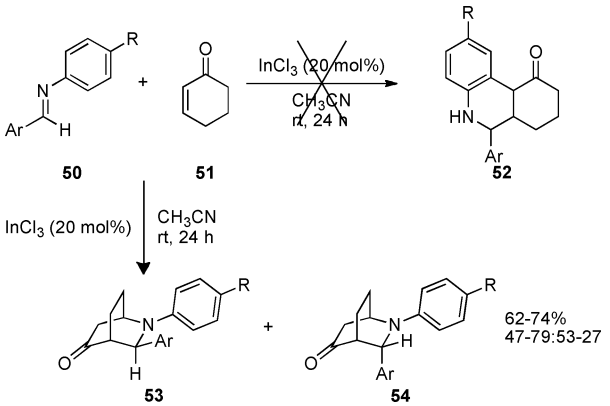
Imines with the nitrogen attached to an aromatic ring **47** can undergo a Lewis acid catalysed imino-Diels–Alder reaction with alkene **48** to form a new piperidine ring fused to the aromatic **49** (eqn (3)). Hence, the imine **47** acts as a heterodiene, which is activated by the Lewis acid.[45]



(3)

This high yielding reaction is completed in under an hour with the Lewis acid $InCl_3$ present in 20 mol%. However, when changing the alkene **48** to a cyclohexenone **51**, Perumal *et al.* observed that bicyclic rings **53** and **54** were formed with poor selectivity instead of **52**. This shows that when enones **51** are present, these are activated over the imines **50** by the Lewis acid (Scheme 9). Despite the poor selectivity, it was thus serendipitously shown that the aza-Diels–Alder reaction could be performed in the presence of catalytic amounts of Lewis acid using unactivated diene equivalents, such as enone **51**.

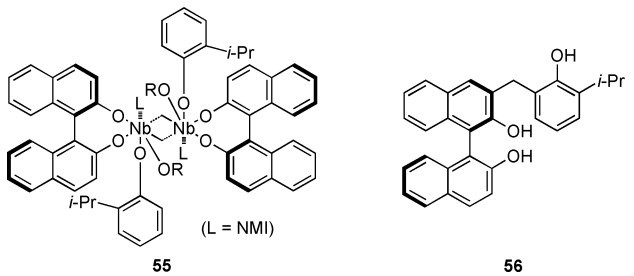
Enantioselective reactions of carbonyl compounds catalysed by chiral Lewis acids have been known for some time[46] although the analogous asymmetric reactions with imines took longer to be established.[47] This is partly due to the flexible (*E*,*Z*)-conformational structure of the imine double bond, the tendency to form enamines if an α-acidic proton is present, as well as the fact that some imines are highly unstable and cannot be isolated. However, the main reason is that the imine nitrogen is more Lewis



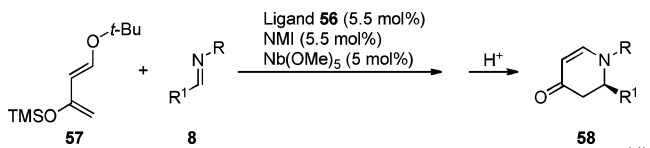
Scheme 9 Imine **52** acting as a dienophile, as opposed to a diene.

basic than the oxygen of the carbonyl group, thus Lewis acids tend to strongly coordinate to the nucleophilic nitrogen atom of the reactants or product, which can result in inhibition or decomposition of the chiral Lewis acid complex and low catalyst turnover. Hence, for a long time, stoichiometric amounts of Lewis acids have always been needed.[48]

In 1998 Kobayashi *et al.* reported the first chiral Lewis acid that was needed in catalytic amounts for the enantioselective aza-Diels–Alder reaction between an imine **8** and the Danishefsky diene **1**. They used a chiral zirconium catalyst based on complexes with substituted 2,2′-binaphthol (BINOL) in 20 mol%, obtaining *ee* as high as 93%.[49] From Zr(IV)[50] they subsequently went on to investigate chiral niobium Lewis acids.[51] Their preferred catalyst **55** is formed *in situ* from ligand **56** and $Nb(OMe)_5$ in the presence of *N*-methylimidazole (NMI).

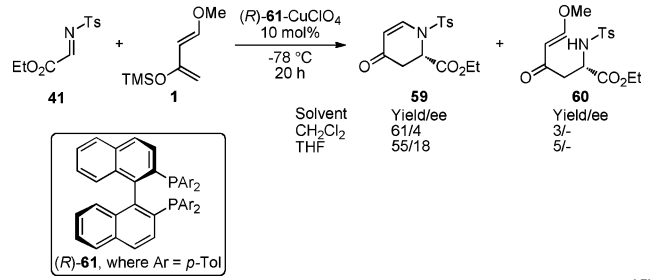


The catalyst **55** has been shown to give highly enantioselective unsaturated piperidine rings **58** from a silyloxy diene **57** and an aromatic or aliphatic imine **8** (eqn (4)).



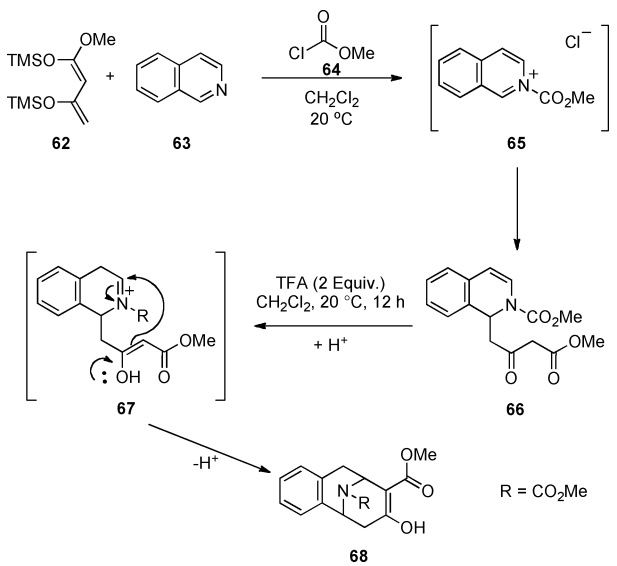
(4)

Meanwhile, Jørgensen *et al.* have formed piperidine rings **59** from imines **41** and the Danishefsky diene **1** with the aid of catalytic amounts (10 mol%) of Lewis acid.[52] The catalyst was made up of a metal Lewis acidic salt and a chiral ligand to induce asymmetry. Different metal salts that were screened include $CuClO_4 \cdot 4$ MeCN, $2CuOTf \cdot C_6H_6$, $CuPF_6 \cdot 4$ MeCN, $Cu(OTf)_2$, AgOTf, $AgSbF_6$, $AgClO_4$, $Pd(SbF_6)_2$, $Pd(ClO_4)_2$, $Pd(OTf)_2$, $RuSbF_6$ and $Zn(OTf)_2$. The chiral ligands were either BINAP or phosphino-oxazoline systems **61**, which were individually synthesised.[53] The best combination was found to be a phosphino-oxazoline-copper(I) catalyst, which afforded 96% yields and up to 87% ee. X-ray analysis suggests that the reaction proceeds *via* a Mannich–Michael process, evidence that was further supported by the detection of Mannich product intermediates **60** in some reactions (eqn (5)).



(5)

Isoquinolines **63** have been shown by Langer *et al.* to act as a *N*-dienophile when reacted with electron rich dienes **62** and stoichiometric amounts of Lewis acids in the aza-Diels–Alder reaction. The reaction proceeds in a stepwise fashion, with the Lewis acid activating the imine **65**. Hence, nucleophilic attack by the Brassard's type diene[54] **62** affords intermediate **66**. Treatment of **66** with 2 equivalents of trifluoroacetic acid (TFA) aids in the tautomerisation of the carbonyl to the enol, as well as activation of the imine **67** for a subsequent intramolecular Michael addition. The end result was a new piperidine ring **68** exhibiting an enol over a ketone (Scheme 10). The enol form is more stable by 3.3 kcal mol^{-1}, which is partly due to the electron withdrawing ester group situated beside it.[55] This methodology has been used to form simple structural analogues of morphine.

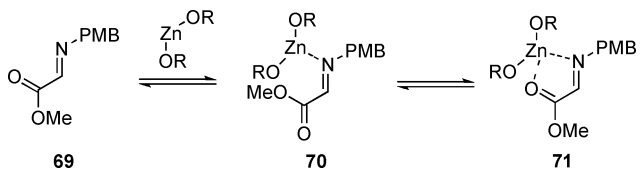


Scheme 10 The use of Brassard's diene **62** for the formation of new piperidine rings.

The use of ytterbium(III) triflate[56] was shown by Whiting *et al.* to catalyse the aza-Diels–Alder reaction asymmetrically.[57] However, as with many aza-Diels–Alder examples, these reactions proved difficult to reproduce and scale up,[58] which prompted the development of robust catalytic asymmetric methods. Prior to this, it was necessary to clearly understand the reaction mechanism as it was generally accepted that the aza-Diels–Alder reaction

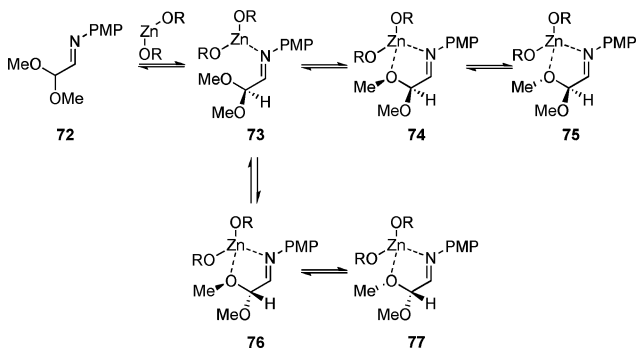
could either proceed through a concerted (either standard or inverse electron-demand Diels–Alder cycloadditions) or a stepwise process. Indeed, after screening different dienes against electron-deficient imines in the presence of Lewis acid under different conditions, the isolated piperidine ring products gave evidence towards all three reaction pathways. However, the intermediates that were subsequently isolated showed that a stepwise addition-cyclisation process derived by imine activation of the Lewis acid could explain all the reactions.[59] Further investigations into this reaction to gather evidence for and against the different plausible mechanisms resulted in findings that disproved a concerted mechanism, thus suggesting that a step-wise Lewis-acid catalysed process was occurring.[60]

Zinc(II)-binol has been shown to be an efficient asymmetric catalyst in the Diels–Alder reaction[61] as well as the hetero-Diel–Alder reaction between dienes and aldehydes.[62] Subsequently, Whiting *et al.* showed that zinc(II)-binol could also be used in the asymmetric aza-Diels–Alder reactions between electron-deficient imines **69** and the electron rich Danishefsky's diene **1**.[63] Following on from this finding, they observed that these reactions, along with efficient asymmetric induction, were dependent upon the formation of bidentate zinc-imine complexes **71** (Scheme 11).[64]



Scheme 11 Binding of zinc(II)-binol to imine **69**.

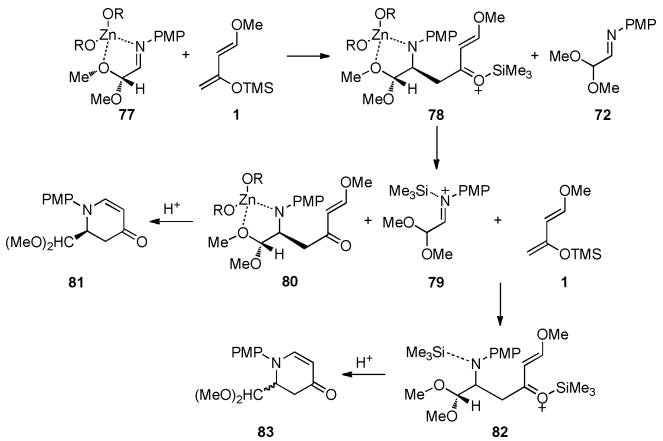
As expected, the cycloaddition happens *via* a two-step process. The imine must be suitably activated for the initial Mannich-like step, which means that, when possible, the zinc(II)-binol forms a bidentate ligand with the imine (Scheme 11 and Scheme 12) (aromatic imines would form monodentate ligands).



Scheme 12 Binding of Zn(II)-binol to imine **72**.

After formation of the bidentate ligand **77**, addition of the diene **1** to the imine **77** can take place. Ring closure of **80** is a slow process that can be accelerated with an acidic work up. Since *S*-binol is used in this case, the *S*-enantiomer product **81** is obtained. However, this process can also activate another imine **79** to form a silyl imminium ion, which after reacting with a diene **1** ends up forming a racemic cycloadduct **83** (Scheme 13).

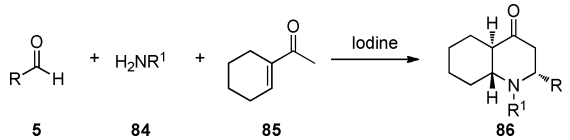
For these reactions, there seem to be two competing effects. Firstly, the presence of a catalytic equilibrium between monomer



Scheme 13 Piperidine ring formation between Danishefsky's diene **1** and the imine-Lewis acid complex **77**.

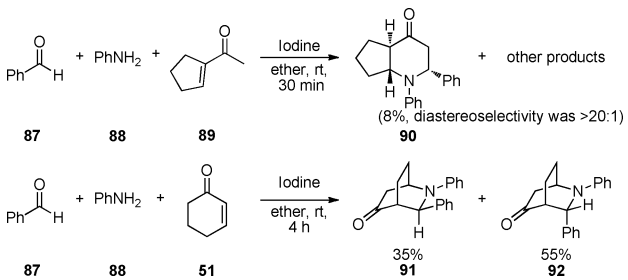
and dimer complexes in solution is important, and secondly, low catalyst loadings seems to be less effective due to the likelihood of competing silicon transfer effects.

The use of iodine has been shown by Yao *et al.* to be effective as a Lewis acidic catalyst in the aza-Diels–Alder reaction.[65] These iodine-catalysed reactions can either be performed neat or at high concentrations. Additionally, as iodine is a strong Lewis acid, the reaction can be performed without the need of an electron rich diene such as Danishefsky's diene **4**. The best results were also obtained with the use of 0.5 equivalents of iodine. Hence, it was shown that aldehydes **83**, amines **84** and cyclic enones **85** react together in the presence of iodine to form fused piperidine rings **86** in 55–95% yield; slightly better yields being obtained when R^1 was electron withdrawing (eqn (6)).



(6)

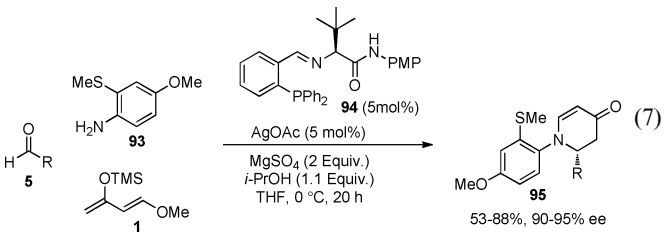
Similar results were obtained when using cyclohexenone **51** as the diene to form bicyclic compounds **91** and **92**. However, when using the 5-membered ring acetylcyclopentene **89** as opposed to the six-membered cyclohexenone **51**, the yields obtained for **90** were drastically diminished to less than 10% (Scheme 14). This may suggest that the spatial alignment of the enone is important in order for the aza-Diels–Alder reaction to proceed effectively.



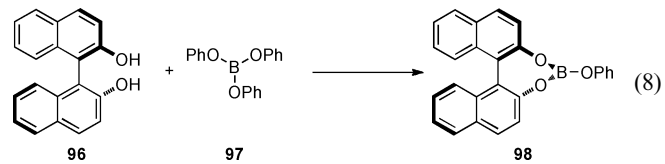
Scheme 14 Comparing acetylcyclopentene **89** and cyclohexenone **51** as the enone within the aza-Diels–Alder reaction.

Understanding that the aza-Diels–Alder proceeds *via* a Mannich–Michael process, Hoveyda *et al.* optimised their silver

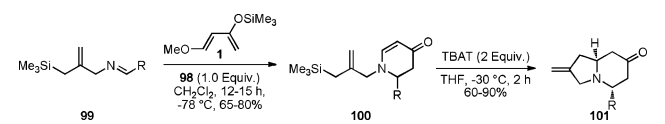
catalysed Mannich reactions prior to performing the aza-Diels–Alder reaction between imines **8** and the Danishefsky diene **1**.[66] These silver catalysed reactions required an additive (*i*-PrOH) and performed well in an atmosphere of air using THF as solvent. This was subsequently optimised into a three-component, one-pot synthesis using 5 mol% of the silver Lewis acid and 5 mol% of the chiral ligand **94** to give the desired piperidine ring **95** in good yield and high diastereo- and *enantio*-selectivity (eqn (7)).



The Lewis acid catalysed aza-Diels–Alder reaction has also been shown to be useful in the formation of indolizidines **101**, an important biologically active class of alkaloid found in numerous natural products.[67] An imine such as **99** derived from allylsilane amine[68] has been shown by Furman *et al.* to be necessary to react smoothly with Danishefsky's diene **1** in the presence of 10 mol% $Yb(OTf)_3$ to form piperidine ring **100** in good yields.[69] Nonetheless, it was subsequently found that the best chiral Lewis acid at their disposal was the chiral boron complex **98**, which was used in stoichiometric amounts. This boron complex was formed *in situ* from **96** and **97** (eqn (8)).[70]



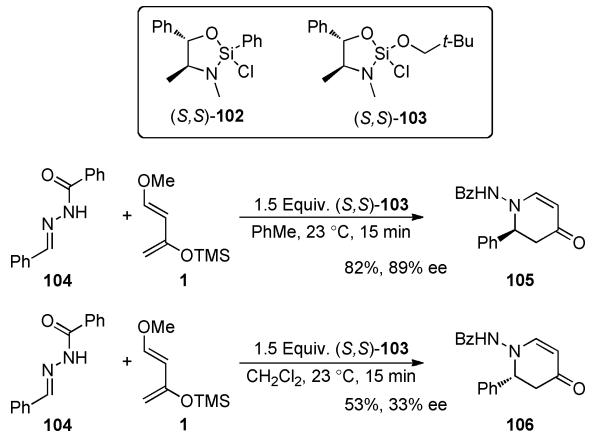
The key final step to form the indolizidine **101** involves a cyclocondensation reaction in the presence of tetrabutylammonium triphenyldifluorosilicate (TBAT).[71] This reaction is stereospecific, the stereochemistry subsequently proved through circular dichroism spectroscopy (Scheme 15);[70] a technique first used on such systems by Whiting *et al.*[60]



Scheme 15 A route to indolizidines *via* the aza-Diels–Alder reaction.

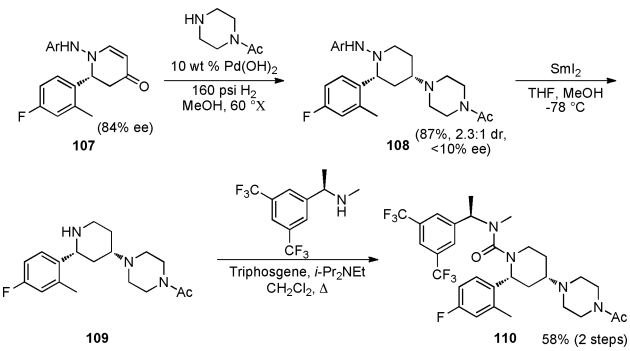
The use of silicon Lewis acids within the aza-Diels–Alder reaction between hydrazones **104** and Danishefsky's diene **1** has been investigated by Leighton *et al.* Good yields and high enantioselectivities (up to 85% and 92% respectively) were generally observed with these reactions.[72] There seems to be a strong solvent effect when using silicon Lewis acids, shown by the observation that using dichloromethane instead of toluene gives the opposite enantiomer of the aza-Diels–Alder product (Scheme 16).

It is also mechanistically interesting to note that two silicon catalysts were synthesised and tested; **102** and **103**. Catalyst **102** had previously been proven to be effective for a variety of transformations of acylhydrazones.[73] However, it proved to be ineffective in the Mannich reaction.[74] Consequently, when catalyst



Scheme 16 Silicon Lewis acids and their use within the aza-Diels–Alder reaction.

102 was used as the Lewis acid in the aza-Diels–Alder reaction, the reaction didn't proceed. Instead, catalyst **103** had been proven to perform well in enantioselective Mannich reactions[74] and when subsequently used within the aza-Diels–Alder reaction, the reaction proceeded efficiently. These findings show that the aza-Diels–Alder must be proceeding through a Mannich reaction, thus adding evidence that the aza-Diels–Alder reaction goes through a two-step process *via* a Mannich–Michael pathway as opposed to being concerted. Armed with these findings, Leighton *et al.* went on to synthesise casopitant **110**, a neurokin 1 receptor antagonist,[75] after forming the core piperidine ring **107** *via* an aza-Diels–Alder reaction using their silicon Lewis acid **103** (Scheme 17).

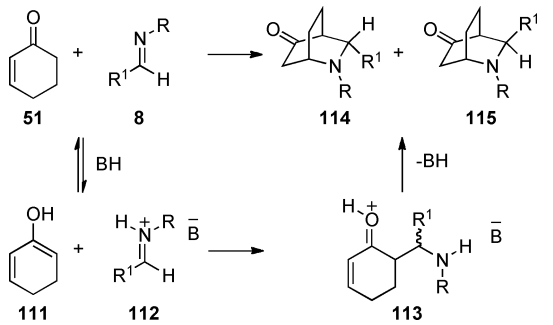


Scheme 17 Synthesis of casopitant **110** from the aza-Diels–Alder reaction product **107**.

1.3 Asymmetric construction using Brønsted acids

The use of Brønsted acids in the aza-Diels–Alder process can be simply explained in the context of the reaction between a cyclic enone **51** and an imine **8**, whereby the Brønsted acid activates both these reagents. As seen in Scheme 18, under acidic conditions, the ketone tautomerises to enol **111**. This then undergoes a Mannich reaction with the protonated imine **112**, followed by an intramolecular aza–Michael addition to give the *endo*-**114** and *exo*-**115** bicyclic products and regenerating the acid catalyst at the same time.

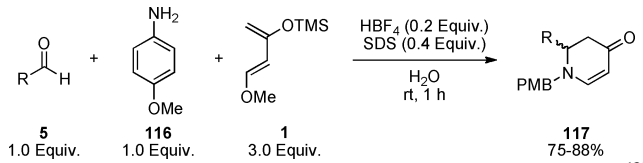
The success of this reaction depends on the proton-donating capacity of the catalyst (acidity) and on the experimental conditions, particularly the solvent. Piermatti *et al.* have been able



Scheme 18 General procedure for the Brønsted acid catalysed aza-Diels–Alder reaction.

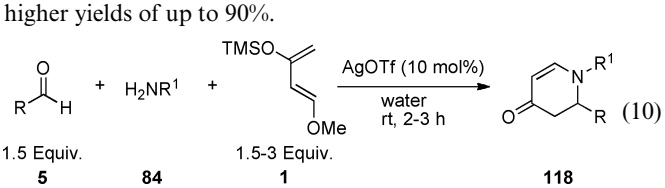
to perform such reactions in water using α-zirconium hydrogen phosphate (α-$Zr(HPO_4)_2 \cdot H_2O$) as the Brønsted acid to give yields of 70–90%, although with hardly any enantioselectivity between the *endo*-**114** and *exo*-**115** products (50 : 50–55 : 45).[76]

Prior to this finding, Akiyama *et al.* made significant progress in this field of green chemistry by demonstrating that the three-component, one-pot aza-Diels–Alder reaction between an aldehyde **5**, amine **116** and Danishefsky's diene **1** can be performed solely in water, using sodium dodecyl sulfate (DSD) as a surfactant.[77] This reaction proceeds giving the racemic product **117** in good yield, using fluoroboric acid (10 mol%) as a catalyst (eqn (9)).



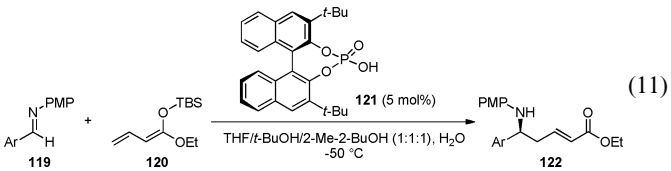
(9)

Following on from this work, Kobayashi *et al.* carried on experimenting with the aza-Diels–Alder reaction in water. In one set of reactions, amines **84**, aldehydes **5** and the Danishefsky diene **1** were reacted together in the presence of catalytic AgOTf at rt for 2–3 h (eqn (10)).[78] The use of Danishefsky's diene **1** in this reaction using water as a solvent was believed to be beneficial because it was thought that Danishefsky's diene **1** probably hydrolyses slower under these heterogeneous reaction conditions, thus preventing formation of side products. However, only the racemic product was obtained. It was subsequently found that the slow addition of the diene **1** over a period of an hour dramatically helped to improve yields. Yields were subsequently increased by up to 20% through the use of non-ionic surfactants such as "Triton X-100". It was thought that the role of this surfactant was to help the formation of the imine, as no improvements were observed in the two-component reaction. Higher equivalents of diene **1** also gave higher yields of up to 90%.



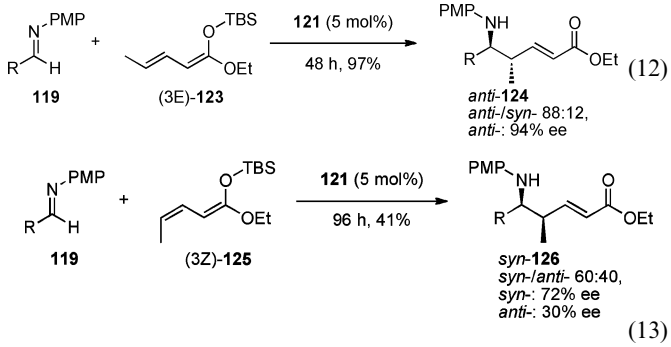
(10)

Through the use of α,β-unsaturated esters over ketones, the Mannich reaction can be investigated and optimised independently, in order to give a greater understanding of the Mannich–Michael ring forming process. Hence, Mannich reactions between imines **119** and acyclic silyl dienolates **120** using catalytic amounts of Brønsted acids have been optimised by Schneider *et al.*[79] This they did with 5 mol% of their BINOL-based phosphoric acid catalyst **121** with a solvent mixture at –50 °C. The low temperature was necessary in order to improve enantioselectivity without the solvent freezing over (eqn (11)).



(11)

After optimisation of their chiral Brønsted acid, Schneider *et al.* found that higher enantioselectivities were observed when the R group on the ester is small. When using aromatic protecting groups on the imine, having electron-donating groups on the *para*-position afforded high enantioselectivities, whereas the reaction became non-selective when this group was on the *ortho*-position. The main effect that the R-substituent of the imine had on this reaction was to slow the reaction down. Hence, the reaction times ranged from half a day to a week, with most reactions going to completion within two days; increasing the low catalytic concentration would undoubtedly speed up the reaction. When using γ-substituted silyl dienolates, it was found that an *E*-geometry **123** would afford the *anti*-product **124** (eqn (12)), whilst the *Z*-geometry **125** would afford the *syn*-product **126**, although with lower yield and poor enantioselectivity (eqn (13)).

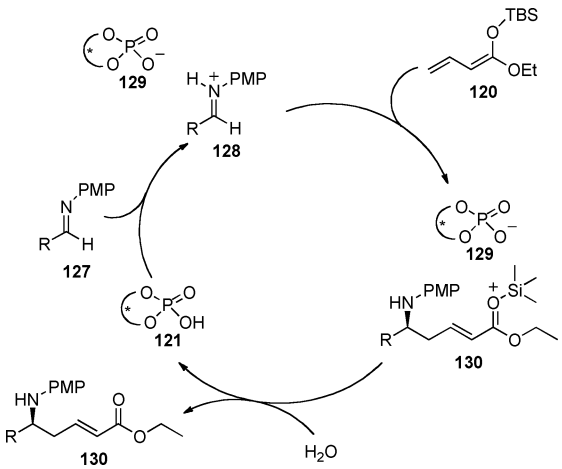


(12)

(13)

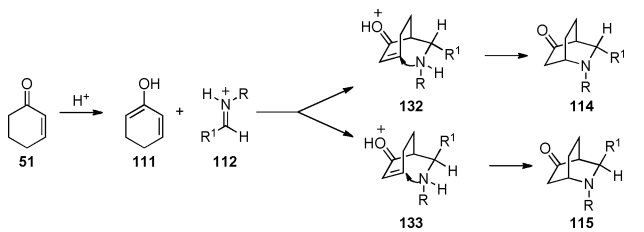
Mechanistic investigations were carried out to explain the role of the solvent system (equal amounts of *t*-BuOH, 2-methyl-2-butanol and THF with 1 equivalent of water) as well as the reaction mechanism. Hence, the alcohol component was shown to be important for the rate of the reaction, with the water content further accelerating the reaction. 2-Methyl-2-butanol was needed in order to decrease the allowed reaction temperature, whilst THF had a beneficial effect on the selectivity of the reaction. This solvent system is thought to trap the cationic silicon species as silanol and regenerate the chiral Brønsted acid catalyst through protonation. Thus, in the proposed catalytic cycle, the Brønsted acid **121** protonates the imine **127** whilst shielding the *Re*-face, making the imine **128** sufficiently activated to undergo the Mannich reaction with the silyl dienolates **120** from the opposite side. The intermediate **130** was subsequently hydrolysed to give the Mannich product **131** (Scheme 19). This reaction was also shown to proceed well in a one-pot, three-component manner by forming the imine *in situ*.

The first Brønsted acid catalysed aza-Diels–Alder reaction using unactivated cyclohexenones **51** as opposed to the activated



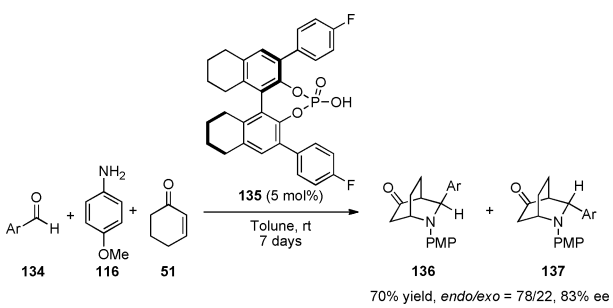
Scheme 19 Proposed catalytic cycle for the formation of **131** from **127** and **120**.

Danishefsky diene **1** was reported by Gong *et al.* through their use of chiral phosphoric acids.[80] The reaction relies on the acid enolising the carbonyl group of **51** in order to make an electron-rich diene **111** *in situ* and, thus, attack the protonated imine **112** in order to undergo a Mannich reaction, followed by an intramolecular Michael addition (Scheme 20).



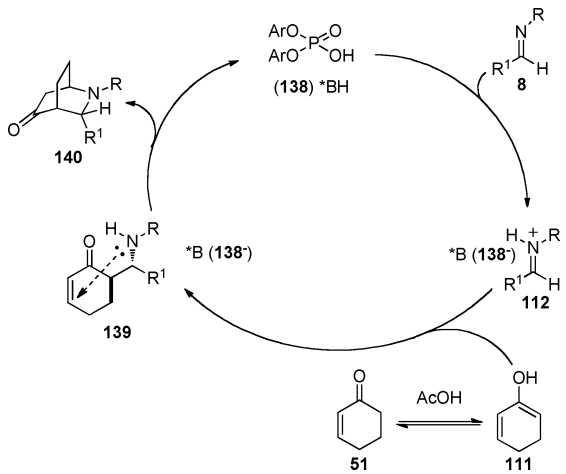
Scheme 20 The route to bicyclic piperidine rings **114** and **115** from a cyclic enone **51**.

The reaction, shown in Scheme 20, took 6 days with two equivalents of enone **51** and 5 mol% of optimised chiral phosphoric acids **135** at rt. It was found that lower temperatures gave higher enantioselectivities; nevertheless the overall yields were notably decreased. The use of different solvents only affected the yields, with non-polar solvents such as toluene affording the highest yields. Dichloromethane follows this, with polar solvents such as THF exhibiting the lowest yields. Similar results in terms of yields and stereoselectivities were observed when the aromatic electronics of the nitrogen-protecting group were changed. Finally, the optimised reaction was effectively performed in a three-component one-pot fashion (eqn (14)).



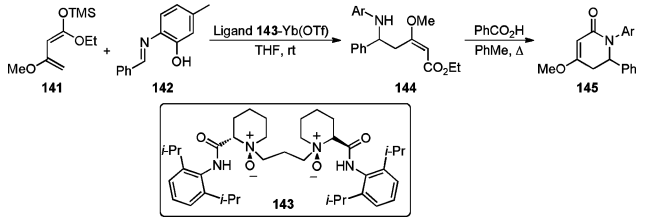
(14)

A double Brønsted acid catalysed reaction using the chiral BINOL-phosphoric acid **138** (10 mol%) and acetic acid as an achiral acid (20 mol%) was successfully performed to form bicyclic piperidine rings **140** from imines **8** and cyclohexenones **51**. Rueping *et al.*[81] have shown that both catalytic acids need to be of different strengths, with the achiral catalyst having a much higher pK_a so that it would not be able to compete with the chiral acid **138** in activating the imine **8**, which would have resulted in reduced enantioselectivity. Hence the chiral acid **138** activates the imine **8**, making it more electrophilic **112**, whilst the achiral acid tautomerises the ketone **51** into a nucleophilic enol **111**. Consequently, the imine and enone are able to cyclise *via* a Mannich–Michael process (Scheme 21) to give **140** in moderate yields and high enantioselectivity.



Scheme 21 Proposed catalytic cycle for piperidine ring formation using two acid catalysts.

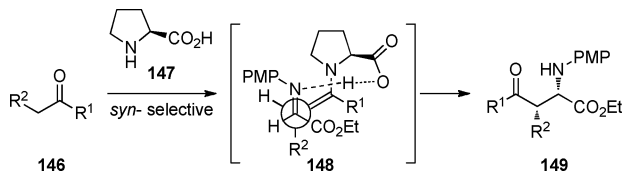
Work done by Feng *et al.* have also shown that Yb is the Lewis acid of choice when performing the aza-Diels–Alder reaction; Sc, Sm, Y and La all gave lower yields than Yb.[82] Furthermore, Brassard's type diene **141** was used instead of Danishefsky's diene **1**; the use of Brassard's diene[54] using chiral Brønsted acid catalysts had only been mentioned once before within the literature.[83] The double substitution at the terminus of Brassard's type diene **141** makes this diene less enantioselective, which can explain the previous low usage of this diene.[84] It was observed that after reacting Brassard's type diene **141** with an imine **142** in the presence of the Brønsted acid, the Mannich product **144** was obtained. **144** was subsequently cyclised by heating it with benzoic acid to form the piperidine ring **145**, thus suggesting that the overall mechanism of the cycloaddition is stepwise as opposed to being concerted (Scheme 22). The use of ligand complexes was shown to greatly increase the enantioselectivities (up to 81% ee), with yields of up to 58% being obtained. Feng *et al.* have also shown that with their aza-Diels–Alder reactions, higher yields are also obtained when the reaction is performed in solvent-free conditions and that this also applies to the 3-component, 1-pot reactions.[85] Hence, these findings suggest that it may be best to use the minimum amount of solvent within the aza-Diels–Alder reactions.



Scheme 22 The use of chiral Yb complexes within the aza-Diels–Alder reaction.

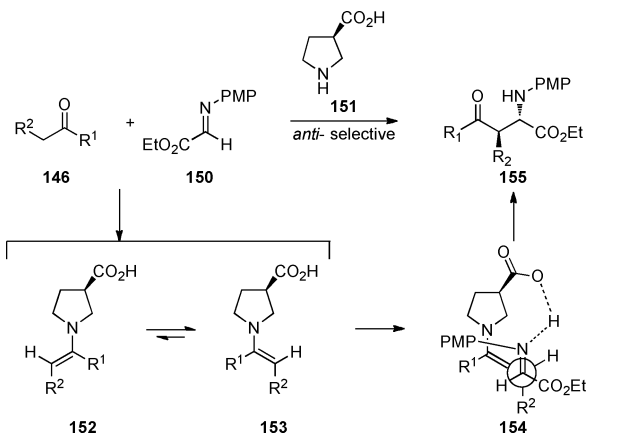
1.4 Asymmetric construction using organocatalysis

As it is generally accepted that the aza-Diels–Alder reaction proceeds *via* a Mannich–Michael process, understanding each of these processes is highly important. Asymmetric Mannich reactions can afford high diastereo- and *enantio*-selectivities with the use of pyrrolidine derived catalysts.[86] It has been widely shown that having an *R*-carboxylic acid group on the 2-position of pyrrolidine **147** (*i.e.* L-proline) makes the Mannich reaction *syn*-selective **149** (Scheme 23).[87]



Scheme 23 *syn*-Selectivity of the L-proline **147** catalysed Mannich reaction between an imine and a ketone or an aldehyde compound.

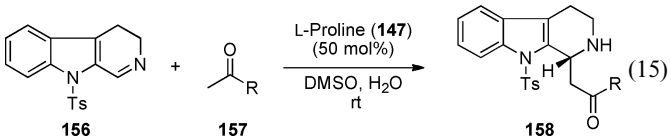
Conversely, Tanaka *et al.* have shown that having the *R*-carboxylic acid group on the 3-position of pyrrolidine **151** makes this an *anti*-Mannich catalyst, thus giving the *anti*-product **155** (Scheme 24).



Scheme 24 *anti*-Selectivity of the catalyst **151** between imines and ketones.

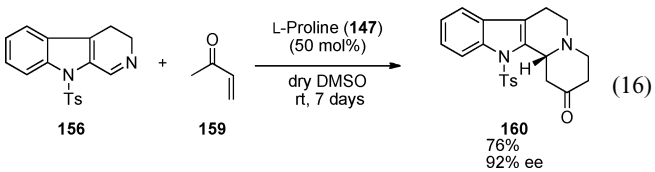
Condensation of the catalyst with the ketone would afford an imine interconverting between conformations **152** and **153**. However, only conformation **153** will react further with the imine **150** because in doing so the reaction proceeds *via* a preferred transition state **154** whereby the acid and the nitrogen of the imine are H-bonding with each other. Hence, stereoselective Mannich product **155** is formed.

When exploring the L-proline **147** catalysed Mannich reaction between methyl-ketones **157** and imines **156**, Ohsawa *et al.* found that at rt with 5 mol% of catalyst, high yields of Mannich product **158** were obtained after three days when 50 equivalents of water were present in the reaction mixture; under dry conditions almost no stereoselectivity was observed whilst too much water drastically decreased the reaction rate (eqn (15)).[88]



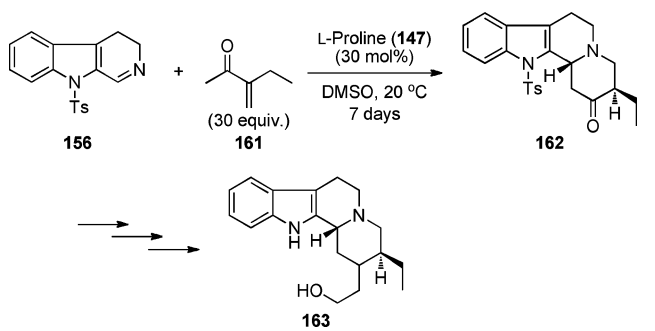
(15)

Lower temperatures also greatly decreased the rate of reaction, however, in return, the stereoselectivity was improved. When the same reaction was performed using methyl vinyl ketone **159**, dry conditions were necessary in order to sufficiently increase the rate of reaction, with 50 mol% of catalyst **147** being used. Even then, the reaction took a week to proceed (eqn (16)). This work was published in 2003, and was one of the first to show that L-proline **147** can be used in the aza-Diels–Alder reaction.



(16)

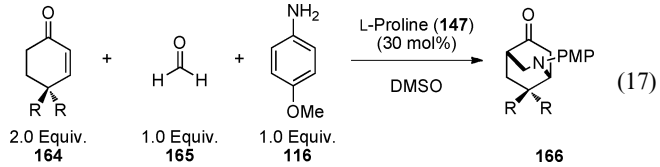
The unprotected **160** is a precursor for the synthesis of some indole alkaloids such as deserpidine[89] and yohimbine.[90] To access one of these alkaloids, three years later in 2006[91] Ohsawa *et al.* reported their findings using different enones catalysed with 30 mol% of L-proline **147**. Despite the reaction taking a week to go through to completion, using 30 equivalents of enone **166**, high yields and *enantio*- and diastereo-selectivities were obtained. With three further steps, the alkaloid *ent*-dihydrocorynantheol **163** was asymmetrically synthesised (Scheme 25). Seeing as this reaction was proceeding in the same manner as when simple methyl ketones **157** were used as a reagent over enones, it was thought the reaction was proceeding *via* a Mannich–Michael process. Hence, the high equivalents of enone **161** that were needed would suggest that the initial Mannich reaction was the rate-determining step.



Scheme 25 The aza-Diels–Alder reaction for the formation of the alkaloid *ent*-dihydrocorynantheol **156**.

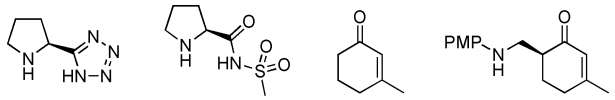
The use of cyclohexenones **164** in the aza-Diels–Alder reaction with pyrrolidine derived organocatalysts were first mentioned in 2005 by Córdova *et al.* in order to produce enantioselective bicyclic piperidine rings **166** in moderate yields. This reaction was

performed in a three-component one-pot manner using enones **164**, formaldehyde **165** and *p*-anisidine **116** (eqn (17)).[12]



(17)

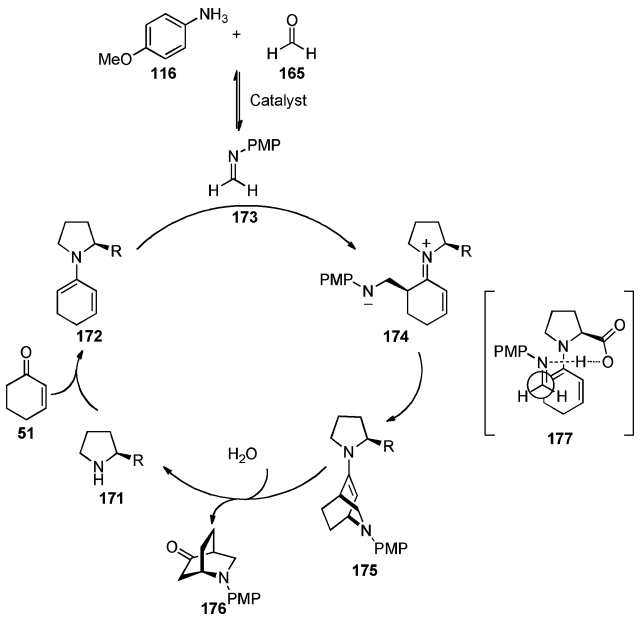
Different solvents were used, and it was found that after 24 h at 50 °C, DMSO gave better yields (52%), followed by DMF (35%), NMP (10%) and toluene (<5%). High ee of 99% were obtained from L-proline **147** and the catalyst **167**, with slightly lower ee (94%) obtained with the amide catalyst **168**. When performing the reaction at rt, a lower yield of 30% was obtained when using catalyst **147**. However, at rt catalyst **167** obtained a slightly higher yield of 61%. After deciding to use the cheaper L-proline **147** catalyst, the reaction was performed using different enones to give different bicyclic piperidine rings in similar ee and yield. For one example when using enone **169**, only the α,β-unsaturated Mannich product **170** was obtained.



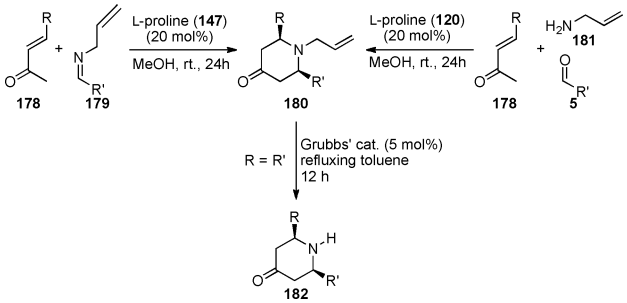
Formation of **170** was used as evidence to propose that the aza-Diels–Alder reaction was proceeding *via* a Mannich–Michael, as opposed to a concerted process; presumably the methyl group on the enone was blocking the amine's access to the Michael receptor. Different aromatic amines were also screened and it was found that neutral aromatic rings gave lower yields than the electron donating PMP ring, with *p*-halogenated aromatics giving the lowest yields. Furthermore, trace amounts of Mannich adduct were also observed when using the *p*-halogenated aromatic amines, which is further proof that this reaction proceeds *via* a Mannich–Michael process. Hence, a chiral enamine **172** is first formed; with the *in situ* generated imine **173** attacking it from the *Si*-face *via* transition state **177** (Scheme 26). The trace amounts of *p*-halogenated aromatic amines observed could be attributed to the lower nucleophilicity of the secondary amine intermediate in the Michael step.

When using L-proline **147** as the organocatalyst, the *syn*-selectivity of the Mannich reaction can be used to form *cis*-2,6-diarylpiperidin-4-ones **180** from their corresponding enones **178** and imines **179**.[92] However, the advantages of using L-proline are limited by the fact that 4 equivalents of the enone were needed to produce a moderate yield, as well as the limited number of solvents this reaction was effective in. Despite this, high diastereoselectivity was observed with these reactions, although with no enantioselectivity when the R-substituents on the ring were different (Scheme 27).

It is also interesting to note that the reaction only seems to proceed efficiently with an aliphatic protecting group on the nitrogen **179**. Low conversions were obtained when this protecting group was aromatic, meaning more traditional nitrogen protecting groups such as *p*-methoxyphenyl cannot be used. Aznar *et al.* have shown that a convenient aliphatic protecting group in such cases would be an allyl group as this group could easily be removed after the cycloaddition using Grubbs' catalyst, the methodology

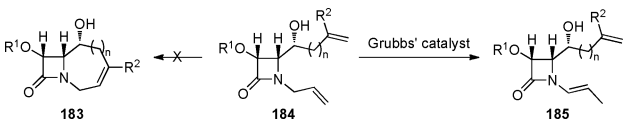


Scheme 26 Proposed catalytic cycle for the formation of bicyclic piperidine rings *via* the aza-Diels–Alder reaction.



Scheme 27 Different routes for the formation of the deprotected piperidine ring **182**.

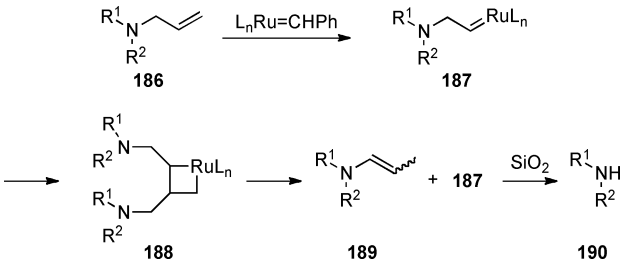
of which was serendipitously found by Alcaide *et al.*[93] In their quest for synthesising bioactive β-lactams **183**, they found that in some cases isomerisation of the internal double bond in a *N*-allyl amide **184** is favoured over ring-closing metathesis (Scheme 28).



Scheme 28 An observed ring-closing anomaly with Grubbs' catalyst.

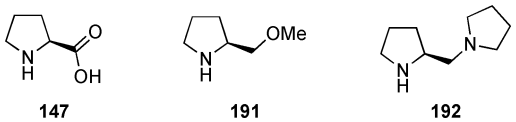
Consequently Alcaide *et al.* looked into this phenomena using different *N*-allyl amines and found that Grubbs' catalyst efficiently catalysed the deprotection of tertiary amines **186**. Mechanistic studies showed that the reaction proceeds *via* a ruthenium-catalysed isomerisation to a more stable olefin **189**, followed by hydrolysis to afford the amine **190** (Scheme 29).

Regarding the organocatalyst, Aznar *et al.* also screened the aza-Diels–Alder reaction against the pyrrolidine derived catalysts **191** and **192**.[94] Both of these catalysts were ineffective by themselves in the reaction between enone **178** and imine **179**. However, in the presence of 20 mol% of *p*-toluenesulfonic acid, piperidine ring

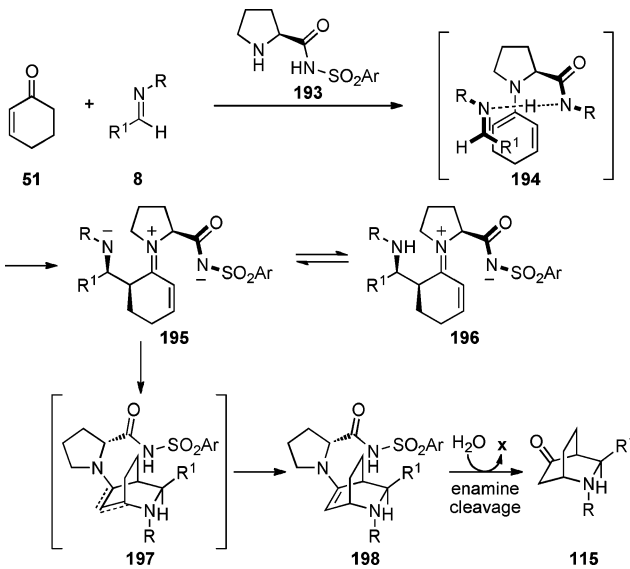


Scheme 29 Deprotection of allylic tertiary amines using Grubbs' catalyst.

180 was formed in 58% and 61% yields respectively. These results suggest that some acidic source is required to promote formation and equilibration of the initial imminium ion to the reactive enamine. In the case of L-proline **147**, the acid is incorporated into the organocatalyst. Hence, no extra acidic source is needed to promote the aza-Diels–Alder reaction, unlike with the pyrrolidines **191** and **192**.

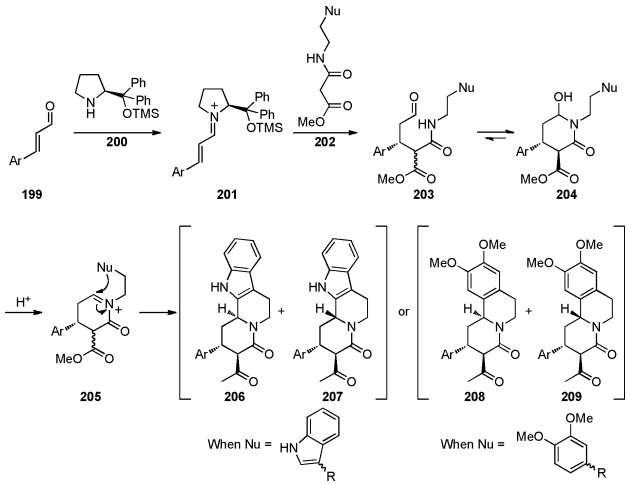


When looking into organocatalysed methods for accessing nitrogen-containing bicyclic rings **115** in a highly enantioselective and diastereoselective manner, Carter *et al.*[95] suggested that the initial Mannich reaction proceeds *via* the transition state put forward by Houk (Scheme 30).[96] In this system, the *syn*-zwitterionic product **195** governs the subsequent aza-Michael cycloaddition in order to form the enamine **198**. This mechanism would explain the strong *exo*-preference observed in these reactions. However, higher catalyst loadings of **193** (30 mol%) compared to standard aldol[97] and Mannich reactions[98] were necessary because cleavage of the enamine **198** in this example was slow due to increased steric congestion.



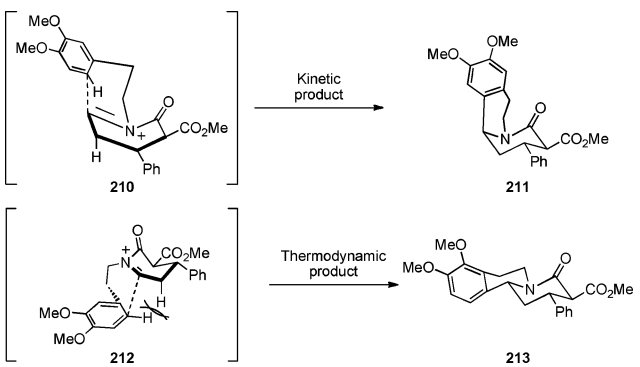
Scheme 30 The aza-Diels–Alder reaction using the organocatalyst **193**.

Franzén *et al.* have found proline-derived organocatalyst **200** to be useful in the direct synthesis of quinolizidine skeletons **206–209**, with the formation of three new stereocentres (Scheme 31).[99]



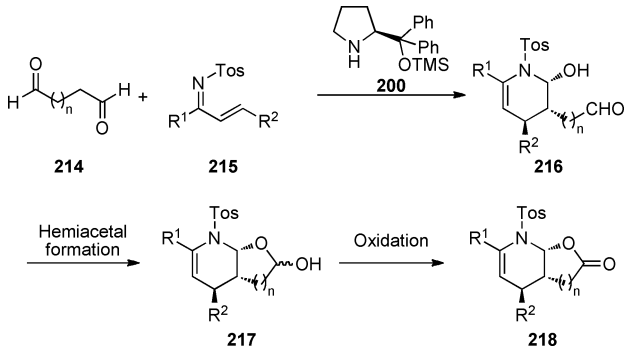
Scheme 31 The use of the aza-Diels–Alder reaction for the formation of fused-piperidine ring compounds.

Thus, catalyst **200** attacks the enone **199** to form the chiral iminium intermediate **201**. This shields the *Re*-face; hence conjugate addition of the amide would happen on the *Si*-face. After the addition, compound **203** cyclised spontaneously to form the hemiacetal **204**. This compound was observed to be in the thermodynamically stable 2*R*,3*S*-*trans*-configuration due to epimerisation of the stereochemically labile stereocentre at C3. In the presence of catalytic amounts of acid, the hemiacetal **204** then converted into the acyliminium ion **205**, which could then undergo aromatic substitution to give the quinolizidine products **206–209**. This reaction is noted to be under kinetic control, with high to excellent enantioselectivity and moderate diastereoselectivity. This was thought to be due to less steric hindrance from the equatorial α-proton in the transition state **210** (Scheme 32).



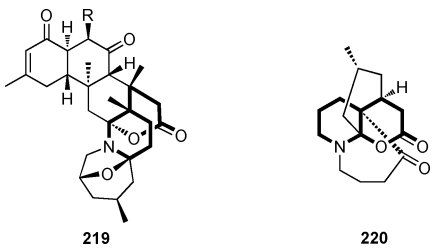
Scheme 32 The transition states for the kinetic **211** and thermodynamic **213** products.

A further example of the use of organocatalyst **200** has been shown by Chen *et al.* in the presence of benzoic acid within the aza-Diels–Alder reaction of aldehydes **214** and aza-dienes **215**.[100] The piperidine ring product **216** subsequently undergoes an intramolecular hemiacetal formation to **217**, which can then be oxidised to give the lactone **218** (Scheme 33). High yields of 90% were obtained using MeCN as the solvent, whilst THF gave low yields of 30%. MeOH, toluene and DCM gave similar high yields of 81–83%, with good efficiency and excellent stereocontrol.

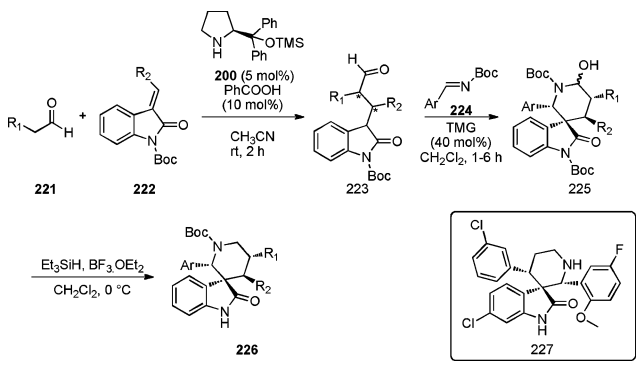


Scheme 33 Formation of lactones *via* the aza-Diels–Alder reaction.

These types of lactone-piperidine containing compounds are frequently observed within natural products. Examples include the biologically active marine natural product zoanthamines **219**,[101] and the alkaloid lycojapodine A **220**, which acts as an inhibitor towards acetylcholinesterase and HIV-1.[102]

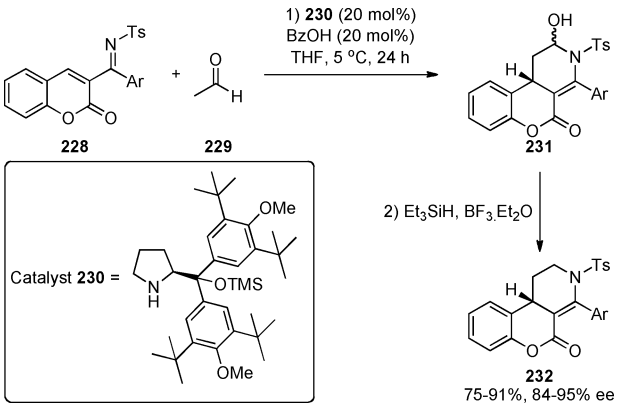


Recently, a one-pot three-component tandem reaction has been shown by Chen *et al.* to form piperidine containing spirocyclic oxindoles **226**.[103] They had previously found that with the aid of a chiral organocatalyst **200**, achiral bifunctional compound **223** could be formed from the asymmetric Michael addition of aliphatic aldehydes **221** to electron-deficient olefinic oxindoles **222**. They subsequently found that *N*-Boc-imines **224** could be used as electrophiles in the reaction with intermediate **223**, with tetramethylguanidine (TMG) catalysing this highly diastereoselective Mannich reaction to afford the hemiaminal **225** in the same pot. This hemiaminal **225** was directly dehydroxylated to afford the piperidine derivatives **226** in moderate yields with high enantioselectivities (Scheme 34). Thus, by altering the aromatic groups, spirocyclic oxindoles such as **227** can be synthesised. **227** is a potent non-peptide MDM2 inhibitor, which may be useful as an anticancer agent.[104]



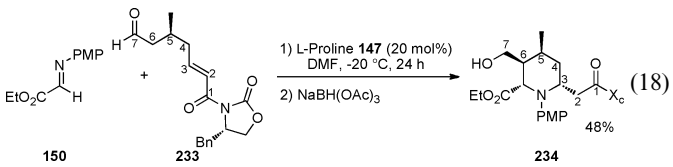
Scheme 34 The use of the aza-Diels–Alder reaction to form spirocyclic piperidine ring compounds.

The use of acetaldehyde **229** in direct cycloadditions is not normally an effective strategy *via* enamine activation.[105] Reasons are given that this may be due to self-condensation, oligomerisation, as well as poor stereocontrol.[106] Despite this, Chen *et al.* have also demonstrated that acetaldehyde **229** can be used in the inverse-electron-demand aza-Diels–Alder reaction with azadiene coumarin derivative **228** to form piperidine rings **231**.[107] This reaction was catalysed by proline-type organocatalyst **230** (20 mol%) and benzoic acid (20 mol%) and gave good yield and high ee after 24 h. The newly formed piperidine ring **231** was subsequently dehydroxylated **232** to aid with the analysis (Scheme 35). Hence this reaction used the coumarin skeleton **228**, a natural product first isolated in 1830 from tonka beans.[108] Its derivatives exhibit broad biological activities, ranging from anti-inflammatory agents[109] and coronary vasodilators,[110] to tautomerase inhibitors[111] and selective FXIIa inhibitors.[112]



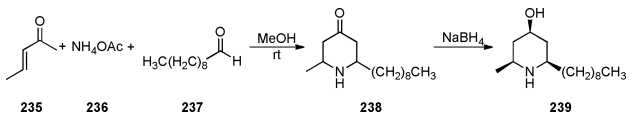
Scheme 35 The use of coumarin derivatives within the aza-Diels–Alder reaction.

Interestingly, Schneider *et al.* have recently shown that Mannich–Michael reactions can be performed from imines **150** and an aldehyde tethered to an enone **223** in the presence of catalytic amounts of L-proline **147** (20 mol%); the tether forming part of the synthesised piperidine ring **234**.[113] The enone group in **233** has a chiral auxiliary attached to it; hence it contains no acidic α-protons. Thus, the organocatalyst **147** solely formed an enamine with the aldehyde group in **233**, through which a Mannich reaction occurred with the imine **150**. The Mannich adduct subsequently underwent an intramolecular aza-Michael reaction to the enone, thus forming the highly substituted piperidine ring **234** in moderate yields and good stereocontrol after subsequent aldehyde reduction (eqn (18)). Small amounts (<5%) of the uncyclised Mannich product were also observed. Reaction time was 24 h at –20 °C and it was found that if the imine was not reactive enough, no reaction was observed as the initial Mannich reaction did not precede. The reaction was also performed using D-proline as the catalyst, which afforded the piperidine ring with opposite configuration at the 2- and 3-positions. This demonstrated that the initial Mannich step was catalyst-controlled, whereas the subsequent Michael addition was substrate controlled, hence the need for a chiral auxiliary in this case.



1.5 Other piperidine ring formations

To overcome the need to protect the amine in the aza-Diels–Alder reaction, Edwards *et al.* have shown that piperidine rings can be formed in a one-pot, three-component fashion when using ammonia as the nitrogen source. However, low yields of 20–35% were generally observed.[114] This methodology was subsequently used in the synthesis of frog alkaloids such as the biologically active piperidine 241D (**239**).[115] Hence, reaction of an enone **235** and aldehyde **237** with NH_4OAc (**236**) in methanol predominantly afforded the *cis*-isomer of the piperidine ring **238** (80 : 1 *cis* to *trans*) in 25% yield. Subsequent reduction of the carbonyl group using sodium borohydride gave *cis*,*cis*-4-hydroxy-2-menthyl-6-nonylpiperidine (**239**) as the major product (Scheme 36). Edwards *et al.* noted that the one-step ring-closing reaction most probably goes *via* Mannich and Michael processes.

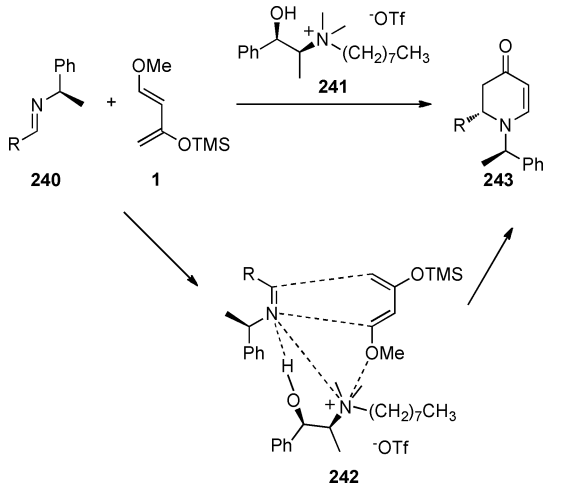


Scheme 36 Synthesis of the frog alkaloid **239** *via* an aza-Diels–Alder reaction.

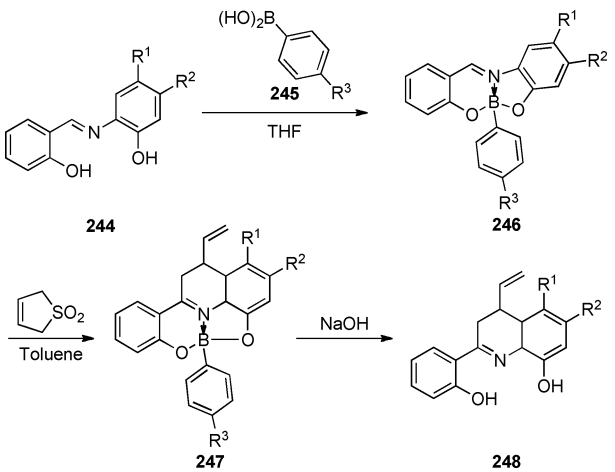
The use of chiral ionic liquids within the aza-Diels–Alder reaction has also been explored by Vo-Thanh *et al.*[116] Interestingly, in this case the ionic liquid **241** is also being used as the solvent, which removes the need of acids or any other catalyst within the reaction mixture.[117] It is noted that these chiral ionic liquids are recycled, with their efficiency being preserved, thus making this a green alternative to the traditional Lewis acid mediated aza-Diels–Alder reaction between Danishefsky's diene **1** and imines **240**. It is thought that the reaction proceeds though intermediate **242**, with yields of up to 66% and de of 60% of **243** being obtained at room temperature. Higher yields were obtained at lower temperatures due to a reduction in decomposition of Danishefsky's diene **1**. However, in such cases only the racemic product was obtained. Thus in order to reduce decomposition of Danishefsky's diene **1** at room temperature, the diene **1** was added in three phases at equal intervals, thus improving the yield by 20% compared to when the diene **1** was added all at once (Scheme 37).

Boronates **246** derived from imines **244** have also been shown to be effective in the formation of piperidine rings in order to access funtionalised dihydroquinolines **248**.[118] In these cases, the imine nitrogen **246** coordinates to and polarises the C═N bond. This, in turn, increases the reactivity of the arylamine towards the imino-Diels–Alder reaction (however, this route is limited to specific imines that are capable of forming the boronate) (Scheme 38).

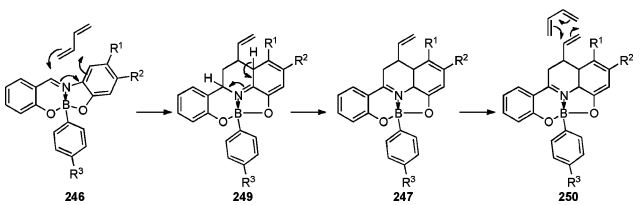
Once the boronate complex **246** was formed, a diene could cyclise with the activated imine bond, thus forming the unsaturated piperidine ring **249** (Scheme 39). This reaction proceeded by inverse electron demand, because the 2-azabutadiene system present in the boronates was electron deficient and it reacted with the



Scheme 37 The use of ionic liquid **241** within the aza-Diels–Alder reaction, showing its possible interaction with the substrates **240** and **1**.



Scheme 38 Piperidine ring formation using boronic acids.

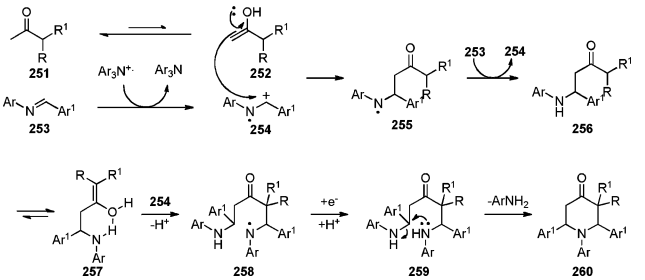


Scheme 39 Mechanism for the formation of piperidine rings *via* a boronate complex.

butadiene, an electron-activated dienophile. Subsequent hydrolysis under basic conditions afforded the desired dihydroquinolines **248**.

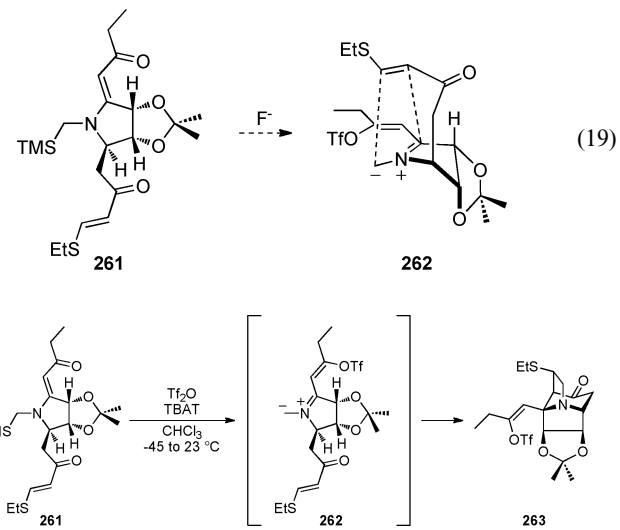
Whilst looking into the formation of β-amino ketones from ketones and aromatic imines *via* a Mannich reaction induced by radicals, Wang *et al.* found that piperidine rings **260** could also be formed in this method.[119] To form their β-amino ketones **256**, the imine **253** was activated by a radical cation salt ($TBPA^+$), whilst the tautomerisation of the ketone **251** to the enol **252** was aided with a Lewis acid. Hence, the activated starting materials reacted with each other to give the desired β-amino ketone **256**. Depending on the aromatic substituent of the imine, **256** could react further to form a piperidine ring **260**. Formation of this ring structure was

dependent on having a *p*-NO_2 group on Ar^1. This was thought to be due to the increased electrophilicity of the radical cation intermediate **254** that the electron-withdrawing group brings, thus making the second addition to the enol tautomer of **256** more favourable. Electron transfer followed by intramolecular substitution then afforded the piperidine ring **260** in mild yields (Scheme 40).



Scheme 40 A radical initiated aza-Diels–Alder reaction.

Through the use of azomethine ylides **262**, aza-Diels–Alder cyclisation reactions are also possible in a complete intramolecular fashion, where the imine and enone are tethered together as one starting material **261**. Thus the stereochemistry of the product **263** was locked in place from the start. Gin *et al.* have used this idea in their quest for the first non-racemic synthesis of stemofoline,[120] a biologically active alkaloid first isolated in 1970 by Irie and co-workers.[121] Thus, in the presence of trifluoromethanesulfonic anhydride (Tf_2O) and tetrabutylammonium triphenyldifluorosilicate (TBAT), the carbonyl oxygen conjugated with the amine in **261** was activated, followed by desilylation with the anhydrous fluoride source to form the azomethine ylide **262**. It was thought that this was followed by an intramolecular [3+2]-cyclisation in order to stereoselectively afford the desired polycyclic alkaloid **263** in good yield (71%) (Scheme 41). Eqn (19) shows the proposed interaction prior to cyclisation.



(19)

Scheme 41 The aza-Diels–Alder reaction *via* an azomethine ylide intermediate.

Additionally, piperidine rings can also be formed *via* routes that did not involve the Mannich reaction. These include: 1) ring formation *via* alkylation of a nitrogen centre with an acyclic precursor containing pre-established stereogenic centres; 2) asymmetric generation of stereocentres and substitution patterns on an existing six-membered heterocycle; 3) ring expansion of pyrrolidine or furan derivatives; and 4) ring closing-metathesis on dialkyl substituted nitrogen derivatives where each alkyl group contains an appropriately positioned alkene functional group.[122]

1.6 Summary

In summary, the present evidence suggests that the aza-Diels–Alder reaction proceeds *via* the Mannich–Michael process as opposed to a concerted mechanism when using electron rich dienes. This is largely supported by the presence of Mannich-intermediates, which have been observed within reaction mixtures. Generally, Lewis acids or organocatalysts catalyse this reaction.

With the use of Lewis acids, activated enones in the form of the Danishefsky's diene have traditionally been necessary, along with stoichiometric amounts of the Lewis acid. However, with more recent optimised examples, the Lewis acids have been shown to be effective in catalytic amounts using enones as the diene, although a secondary acid is sometimes needed to activate the enone to the enol. With regards to the reaction conditions, a lower temperature in general gives higher stereoselectivity. Conversely, a lower temperature also lowers the yield obtained, hence a compromise is usually reached between 0 °C to rt. Depending on the Lewis acid used, different polarities of solvent are effective. For example, Zn(II) catalysts tend to operate more effectively in polar solvents, whereas phosphoric acid catalysts prefer non-polar solvents. Additionally, the diene used seems to be limited to the electron rich Danishefsky's diene or cyclic enones.

The use of organocatalysts in the aza-Diels–Alder reaction has only been investigated in the last decade. Higher catalyst loadings are needed compared to their individual Mannich and Michael reaction counterparts and this is due to the increased steric congestion. Proline-derived organocatalysts seem to work well here, although if the catalyst has no acidic character, then an additional catalytic amount of acid tends to be needed in the reaction. The main disadvantages of using organocatalysts are the necessity of including a large excess of enone (typically 4 equivalents, although sometimes as much as 30), as well as their low reactivity; many days are required for the reactants to cyclise. As a result, the reactions are normally carried out at rt. Additionally, it seems to be of preference to abstain from having aromatic groups on the nitrogen of the imine.

Nonetheless, the field of the aza-Diels–Alder reaction is still in its infancy, and no doubt the same advances will be seen with the use of organocatalysts as have been seen with Lewis acids.

Notes and references

1 P. D. Bailey, P. A. Millwood and P. D. Smith, *Chem. Commun.*, 1998, 633–640.
2 M. Amat, N. Llor, J. Hidalgo, C. Escolano and J. Bosch, *J. Org. Chem.*, 2003, **68**, 1919–1928.
3 N. Asano, R. J. Nash, R. J. Molyneux and G. W. J. Fleet, *Tetrahedron: Asymmetry*, 2000, **11**, 1645–1680.
4 P. S. Watson, B. Jiang and B. Scott, *Org. Lett.*, 2000, **2**, 3679–3681.
5 X. G. Huang, A. Q. Zhang, D. L. Chen, Z. H. Jia and X. S. Li, *Bioorg. Med. Chem. Lett.*, 2010, **20**, 2859–2863.
6 V. H. Lillelund, H. H. Jensen, X. F. Liang and M. Bols, *Chem. Rev.*, 2002, **102**, 515–553.

7 S. D. Larsen and P. A. Grieco, *J. Am. Chem. Soc.*, 1985, **107**, 1768–1769.
8 S. K. Bertilsson, J. K. Ekegren, S. A. Modin and P. G. Andersson, *Tetrahedron*, 2001, **57**, 6399–6406.
9 P. D. Bailey, D. J. Londesbrough, T. C. Hancox, J. D. Heffernan and A. B. Holmes, *J. Chem. Soc., Chem. Commun.*, 1994, 2543–2544.
10 D. Ager, N. Cooper, G. G. Cox, F. Garro-Hélion and L. M. Harwood, *Tetrahedron: Asymmetry*, 1996, **7**, 2563–2566.
11 K. Hattori and H. Yamamoto, *J. Org. Chem.*, 1992, **57**, 3264–3265.
12 H. Sundén, I. Ibrahem, L. Eriksson and A. Córdova, *Angew. Chem., Int. Ed.*, 2005, **44**, 4877–4880.
13 B. List, *Tetrahedron*, 2002, **58**, 5573–5590.
14 P. Buonora, J. C. Olsen and T. Oh, *Tetrahedron*, 2001, **57**, 6099–6138.
15 P. I. Dalko and L. Moisan, *Angew. Chem., Int. Ed.*, 2001, **40**, 3726–3748.
16 P. I. Dalko and L. Moisan, *Angew. Chem., Int. Ed.*, 2004, **43**, 5138–5175.
17 A. Dondoni and A. Massi, *Angew. Chem., Int. Ed.*, 2008, **47**, 4638–4660.
18 S. Danishefsky and T. Kitahara, *J. Am. Chem. Soc.*, 1974, **96**, 7807–7808.
19 S. Danishefsky, C. F. Yan, R. K. Singh, R. B. Gammill, P. M. McCurry, N. Fritsch and J. Clardy, *J. Am. Chem. Soc.*, 1979, **101**, 7001–7008.
20 S. Danishefsky, J. F. Kerwin and S. Kobayashi, *J. Am. Chem. Soc.*, 1982, **104**, 358–360.
21 S. Danishefsky and J. F. Kerwin, *J. Org. Chem.*, 1982, **47**, 3183–3184.
22 J. F. Kerwin and S. Danishefsky, *Tetrahedron Lett.*, 1982, **23**, 3739–3742.
23 S. Danishefsky, M. E. Langer and C. Vogel, *Tetrahedron Lett.*, 1985, **26**, 5983–5986.
24 E. R. Larson and S. Danishefsky, *Tetrahedron Lett.*, 1982, **23**, 1975–1978.
25 S. J. Danishefsky and C. Vogel, *J. Org. Chem.*, 1986, **51**, 3915–3916.
26 M. M. Midland and J. I. McLoughlin, *Tetrahedron Lett.*, 1988, **29**, 4653–4656.
27 S. M. Brandstadter and I. Ojima, *Tetrahedron Lett.*, 1987, **28**, 613–616.
28 L. Lecoz, L. Wartski, J. Seydenpenne, P. Charpin and M. Nierlich, *Tetrahedron Lett.*, 1989, **30**, 2795–2796.
29 C. Veyrat, L. Wartski and J. Seydenpenne, *Tetrahedron Lett.*, 1986, **27**, 2981–2984.
30 T. N. Birkinshaw, A. B. Tabor, A. B. Holmes, P. Kaye, P. M. Mayne and P. R. Raithby, *J. Chem. Soc., Chem. Commun.*, 1988, 1599–1601.
31 T. N. Birkinshaw, A. B. Tabor, A. B. Holmes and P. R. Raithby, *J. Chem. Soc., Chem. Commun.*, 1988, 1601–1602.
32 H. Kunz and W. Pfrengle, *Angew. Chem., Int. Ed. Engl.*, 1989, **28**, 1067–1068.
33 M. Weymann, W. Pfrengle, D. Schollmeyer and H. Kunz, *Synthesis*, 1997, 1151–1160.
34 W. Pfrengle and H. Kunz, *J. Org. Chem.*, 1989, **54**, 4261–4263.
35 J. T. Randolph, K. F. McClure and S. J. Danishefsky, *J. Am. Chem. Soc.*, 1995, **117**, 5712–5719.
36 J. Y. Roberge, X. Beebe and S. J. Danishefsky, *Science*, 1995, **269**, 202–204.
37 I. Paterson, M. Donghi and K. Gerlach, *Angew. Chem.-Int. Ed.*, 2000, **39**, 3315–3319.
38 D. R. Dragoli, L. A. Thompson, J. O'Brien and J. A. Ellman, *J. Comb. Chem.*, 1999, **1**, 534–539.
39 G. Zech and H. Kunz, *Chem.–Eur. J.*, 2004, **10**, 4136–4149.
40 H. Waldmann and M. Braun, *J. Org. Chem.*, 1992, **57**, 4444–4451.
41 N. T. Anh, *Top. Curr. Chem.*, 1980, **88**, 145–162.
42 I. Ojima and S. I. Inaba, *Tetrahedron Lett.*, 1980, **21**, 2081–2084.
43 G. R. Heintzelman, S. M. Weinreb and M. Parvez, *J. Org. Chem.*, 1996, **61**, 4594–4599.
44 R. Badorrey, C. Cativiela, M. D. Diaz-de-Villegas and J. A. Gálvez, *Tetrahedron*, 1999, **55**, 7601–7612.
45 G. Babu and P. T. Perumal, *Tetrahedron*, 1998, **54**, 1627–1638.
46 K. A. Jørgensen, M. Johannsen, S. L. Yao, H. Audrain and J. Thorhauge, *Acc. Chem. Res.*, 1999, **32**, 605–613.
47 K. Ishihara, M. Miyata, K. Hattori, T. Tada and H. Yamamoto, *J. Am. Chem. Soc.*, 1994, **116**, 10520–10524.
48 K. Hattori and H. Yamamoto, *Tetrahedron*, 1993, **49**, 1749–1760.
49 S. Kobayashi, S. Komiyama and H. Ishitani, *Angew. Chem., Int. Ed.*, 1998, **37**, 979–981.
50 S. Kobayashi, K. Kusakabe, S. Komiyama and H. Ishitani, *J. Org. Chem.*, 1999, **64**, 4220–4221.
51 V. Jurčík, K. Arai, M. M. Salter, Y. Yamashita and S. Kobayashi, *Adv. Synth. Catal.*, 2008, **350**, 647–651.
52 S. L. Yao, S. Saaby, R. G. Hazell and K. A. Jørgensen, *Chem.–Eur. J.*, 2000, **6**, 2435–2448.
53 F. W. Grevels, W. E. Klotzbucher, G. Russell and K. Schaffner, *Recl. Trav. Chim. Pays-Bas*, 1995, **114**, 571–576.
54 J. Savard and P. Brassard, *Tetrahedron Lett.*, 1979, 4911–4914.
55 M. A. Yawer, I. Hussain, J. P. Gütlein, A. Schmidt, H. J. Jiao, H. Reinke, A. Spannenberg, C. Fischer and P. Langer, *Eur. J. Org. Chem.*, 2008, 4193–4199.
56 S. Kobayashi, H. Ishitani and S. Nagayama, *Synthesis*, 1995, 1195–1202.
57 S. Bromidge, P. C. Wilson and A. Whiting, *Tetrahedron Lett.*, 1998, **39**, 8905–8908.
58 A. Bundu, S. Guillarme, J. Hannan, H. L. Wan and A. Whiting, *Tetrahedron Lett.*, 2003, **44**, 7849–7850.
59 S. Hermitage, D. A. Jay and A. Whiting, *Tetrahedron Lett.*, 2002, **43**, 9633–9636.
60 S. Hermitage, J. A. K. Howard, D. Jay, R. G. Pritchard, M. R. Probert and A. Whiting, *Org. Biomol. Chem.*, 2004, **2**, 2451–2460.
61 T. Akiyama, Y. Tamura, J. Itoh, H. Morita and K. Fuchibe, *Synlett*, 2006, 141–143.
62 H. F. Du, J. Long, J. Y. Hu, X. Li and K. L. Ding, *Org. Lett.*, 2002, **4**, 4349–4352.
63 S. Guillarme and A. Whiting, *Synlett*, 2004, 711–713.
64 L. Di Bari, S. Guillarme, J. Hanan, A. P. Henderson, J. A. K. Howard, G. Pescitelli, M. R. Probert, P. Salvadori and A. Whiting, *Eur. J. Org. Chem.*, 2007, 5771–5779.
65 C. C. Lin, H. L. Fang, Z. J. Tu, J. T. Liu and C. F. Yao, *J. Org. Chem.*, 2006, **71**, 6588–6591.
66 H. Mandai, K. Mandai, M. L. Snapper and A. H. Hoveyda, *J. Am. Chem. Soc.*, 2008, **130**, 17961–17969.
67 J. W. Daly, T. F. Spande, N. Whittaker, R. J. Highet, D. Feigl, N. Nishimori, T. Tokuyama and C. W. Myers, *J. Nat. Prod.*, 1986, **49**, 265–280.
68 X. D. Lin, R. W. Kavash and P. S. Mariano, *J. Org. Chem.*, 1996, **61**, 7335–7347.
69 B. Furman and M. Dziedzic, *Tetrahedron Lett.*, 2003, **44**, 6629–6632.
70 B. Furman, J. Frelek, M. Dziedzic and A. Kamińska, *Pol. J. Chem.*, 2005, **79**, 1919–1928.
71 A. S. Pilcher, H. L. Ammon and P. Deshong, *J. Am. Chem. Soc.*, 1995, **117**, 5166–5167.
72 S. K. Lee, U. K. Tambar, N. R. Perl and J. L. Leighton, *Tetrahedron*, 2010, **66**, 4769–4774.
73 R. Berger, P. M. A. Rabbat and J. L. Leighton, *J. Am. Chem. Soc.*, 2003, **125**, 9596–9597.
74 G. T. Notte and J. L. Leighton, *J. Am. Chem. Soc.*, 2008, **130**, 6676–6677.
75 M. Macapinlac, D. D. Biggs, M. Guarino, B. M. Johnson, P. F. Lebowitz and S. F. Su, *Breast Cancer Res. Treat.*, 2006, **100**, S285–S285.
76 U. Costantino, F. Fringuelli, M. Orrú, M. Nocchetti, O. Piermatti and F. Pizzo, *Eur. J. Org. Chem.*, 2009, 1214–1220.
77 T. Akiyama, J. Takaya and H. Kagoshima, *Tetrahedron Lett.*, 1999, **40**, 7831–7834.
78 C. Loncaric, K. Manabe and S. Kobayashi, *Adv. Synth. Catal.*, 2003, **345**, 475–477.
79 M. Sickert, F. Abels, M. Lang, J. Sieler, C. Birkemeyer and C. Schneider, *Chem.–Eur. J.*, 2010, **16**, 2806–2818.
80 H. Liu, L. F. Cun, A. Q. Mi, Y. Z. Jiang and L. Z. Gong, *Org. Lett.*, 2006, **8**, 6023–6026.
81 M. Rueping and C. Azap, *Angew. Chem., Int. Ed.*, 2006, **45**, 7832–7835.
82 Z. L. Chen, L. L. Lin, D. H. Chen, J. T. Li, X. H. Liu and X. M. Feng, *Tetrahedron Lett.*, 2010, **51**, 3088–3091.
83 J. Itoh, K. Fuchibe and T. Akiyama, *Angew. Chem., Int. Ed.*, 2006, **45**, 4796–4798.
84 K. A. Jørgensen, *Angew. Chem., Int. Ed.*, 2000, **39**, 3558–3588.
85 K. Cheng, L. L. Lin, S. K. Chen and X. M. Feng, *Tetrahedron*, 2005, **61**, 9594–9599.
86 H. L. Zhang, M. Mifsud, F. Tanaka and C. F. Barbas, *J. Am. Chem. Soc.*, 2006, **128**, 9630–9631.
87 W. Notz, F. Tanaka, S. Watanabe, N. S. Chowdari, J. M. Turner, R. Thayumanavan and C. F. Barbas, *J. Org. Chem.*, 2003, **68**, 9624–9634.

88 T. Itoh, M. Yokoya, K. Miyauchi, K. Nagata and A. Ohsawa, *Org. Lett.*, 2003, **5**, 4301–4304.
89 C. Szántay, G. Blasko, K. Honty, L. Szabó and L. Toke, *Heterocycles*, 1977, **7**, 155–160.
90 T. Kametani, Y. Hirai, M. Kajiwara, T. Takahashi and K. Fukumoto, *Chem. Pharm. Bull.*, 1975, **23**, 2634–2642.
91 T. Itoh, M. Yokoya, K. Miyauchi, K. Nagata and A. Ohsawa, *Org. Lett.*, 2006, **8**, 1533–1535.
92 F. Aznar, A. B. García, N. Quinones and M. P. Cabal, *Synthesis*, 2008, 479–484.
93 B. Alcaide, P. Almendros, J. M. Alonso and M. F. Aly, *Org. Lett.*, 2001, **3**, 3781–3784.
94 F. Aznar, A. B. García and M. P. Cabal, *Adv. Synth. Catal.*, 2006, **348**, 2443–2448.
95 H. Yang and R. G. Carter, *J. Org. Chem.*, 2009, **74**, 5151–5156.
96 S. Bahmanyar and K. N. Houk, *Org. Lett.*, 2003, **5**, 1249–1251.
97 H. Yang and R. G. Carter, *Org. Lett.*, 2008, **10**, 4649–4652.
98 H. Yang and R. G. Carter, *J. Org. Chem.*, 2009, **74**, 2246–2249.
99 J. Franzén and A. Fisher, *Angew. Chem., Int. Ed.*, 2009, **48**, 787–791.
100 Z.-Q. He, B. Han, R. Li, L. Wu and Y.-C. Chen, *Org. Biomol. Chem.*, 2010, **8**, 755–757.
101 G. Hirai, H. Oguri, M. Hayashi, K. Koyama, Y. Koizumi, S. M. Moharram and M. Hirama, *Bioorg. Med. Chem. Lett.*, 2004, **14**, 2647–2651.
102 J. He, X. Q. Chen, M. M. Li, Y. Zhao, G. Xu, X. Cheng, L. Y. Peng, M. J. Xie, Y. T. Zheng, Y. P. Wang and Q. S. Zhao, *Org. Lett.*, 2009, **11**, 1397–1400.
103 K. Jiang, Z. J. Jia, S. Chen, L. Wu and Y. C. Chen, *Chem.-Eur. J.*, 2010, **16**, 2852–2856.
104 Q. Ding, J-J. Liu and Z. Zhang, *WO 2007/104714*, 2007.
105 J. L. Li, B. Han, K. Jiang, W. Du and Y. C. Chen, *Bioorg. Med. Chem. Lett.*, 2009, **19**, 3952–3954.
106 A. Córdova, W. Notz and C. F. Barbas, *J. Org. Chem.*, 2002, **67**, 301–303.
107 J. L. Li, S. L. Zhou, B. Han, L. Wu and Y. C. Chen, *Chem. Commun.*, 2010, **46**, 2665–2667.
108 S. M. Sethna and N. M. Shah, *Chem. Rev.*, 1945, **36**, 1–62.
109 C. A. Kontogiorgis and D. J. Hadjipavlou-Litina, *J. Med. Chem.*, 2005, **48**, 6400–6408.
110 D. S. Bariana, *J. Med. Chem.*, 1970, **13**, 544–546.
111 M. Orita, S. Yamamoto, N. Katayama, M. Aoki, K. Takayama, Y. Yamagiwa, N. Seki, H. Suzuki, H. Kurihara, H. Sakashita, M. Takeuchi, S. Fujita, T. Yamada and A. Tanaka, *J. Med. Chem.*, 2001, **44**, 540–547.
112 S. Robert, C. Bertolla, B. Masereel, J. M. Dogné and L. Pochet, *J. Med. Chem.*, 2008, **51**, 3077–3080.
113 S. Khaliel, M. V. Nandakumar, H. Krautscheid and C. Schneider, *Synlett*, 2008, 2705–2707.
114 M. W. Edwards, H. M. Garraffo and J. W. Daly, *Synthesis*, 1994, 1167–1170.
115 R. S. Aronstam, M. W. Edwards, J. W. Daly and E. X. Albuquerque, *Neurochem. Res.*, 1988, **13**, 171–176.
116 O. N. Van Buu, A. Aupoix, N. D. T. Hong and G. Vo-Thanh, *New J. Chem.*, 2009, **33**, 2060–2072.
117 B. Pegot, O. N. Van Buu, D. Gori and G. Vo-Thanh, *Beilstein J. Org. Chem.*, 2006, **2**, 18.
118 M. Rodríguez, M. E. Ochoa, R. Santillan, N. Farfán and V. Barba, *J. Organomet. Chem.*, 2005, **690**, 2975–2988.
119 X. D. Jia, X. E. Wang, C. X. Yang, C. D. Huo, W. J. Wang, Y. Ren and X. C. Wang, *Org. Lett.*, **12**, 732–735.
120 R. J. Carra, M. T. Epperson and D. Y. Gin, *Tetrahedron*, 2008, **64**, 3629–3641.
121 H. Irie, N. Masaki, K. Ohno, K. Osaki, T. Taga and S. Uyeo, *Chemical Communications (Journal of the Chemical Society Section D)*, 1970, **17**, 1066.
122 R. K. Dieter and F. H. Guo, *J. Org. Chem.*, 2009, **74**, 3843–3848.