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[3 + 3] Cycloadditions and related strategies in alkaloid natural product synthesis

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In this article we describe a strategically unusual approach to piperidines *via* formal [3 + 3] cycloaddition reactions. The scope and limitations of these processes are outlined and their employment in the synthesis of alkaloid natural products is delineated.

1 Introduction

The piperidine ring is one of the most common motifs found in natural products and biologically active agents.[1] Throughout history, both the harmful and beneficial biological effects exhibited by these compounds have been widely exploited. For example, coniine from poison hemlock, *Conium maculatum*, was reputedly used to kill Socrates. A large number of therapeutic alkaloids are also based on a piperidine core such as the opium poppy alkaloid morphine and Cincona alkaloid quinine. A cursory inspection of piperidine-based natural products illustrates that the heterocycle ring is present in these compounds within a very broad range of molecular complexities and architectures and, therefore, such compounds represent significant synthetic challenges. For these reasons, the search for general, efficient and stereoselective methods of piperidine synthesis has attracted the attention of the synthetic community for many years.[2]

There are a very large number of strategies available for constructing six membered ring systems and Diels–Alder cycloaddition reactions are amongst the most popular.[3] Not surprisingly therefore, this [4 + 2] cycloaddition approach has been used on many occasions to prepare functionalised dihydropiperidines. In this article however, we will concentrate on an alternative but related approach: the [3 + 3] cycloaddition reaction and its application in the synthesis of naturally occurring alkaloids. These processes are more accurately termed 'formal [3 + 3] cycloadditions' as they are not pericyclic reactions, but rather they are stepwise processes between two fragments with complementary reactivity. Assembly of the piperidine ring by a [3 + 3] cycloaddition may be carried out in one of two distinct ways. We will class 'Type 1' cycloadditions as those in which the heterocycle has been assembled by formation of the C2–C3 and C5–C6 bonds. The alternative 'Type 2' cycloadditions are those in which bond formation takes place between N–C2 and C4–C5 (Fig. 1).

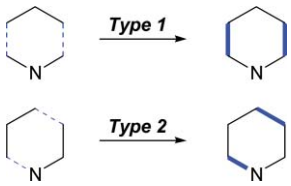
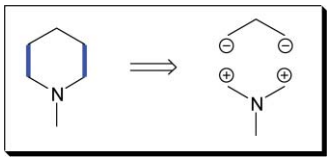


Fig. 1 Type 1 and 2 [3 + 3] cycloaddition reactions.

2 Type 1 cycloadditions

2.1 The double Mannich approach



In 1985, Shono and co-workers reported the direct formation of piperidines by the treatment of α,α′-dimethoxylated amides

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Olivier Provoost received his BSc degree in 2001 from the University of Namur (Facultés Universitaires Notre-Dame de la Paix) where he spent his final year in the C.M.I. (Laboratoire de Chimie des Matériaux Inorganiques) studying the synthesis of mesoporous TiO_4 membranes under the guidance of Professor Bao Lian Su. He spent a year working at Syngenta in the Jealott's Hill International Research Centre before undertaking his PhD studies with Dr Joe Harrity at the University of Sheffield on the investigation of [3 + 3] cycloaddition strategies towards the synthesis of histrionicotoxins and (−)-slaframine.

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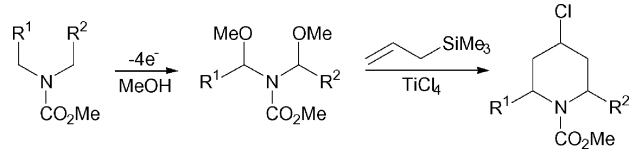
Table 1 Allyltrimethylsilane addition to α,α′-dimethoxylated amides



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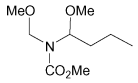
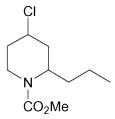
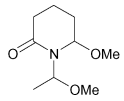
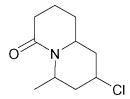
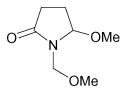
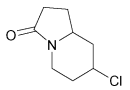
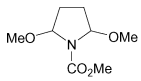
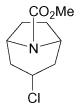
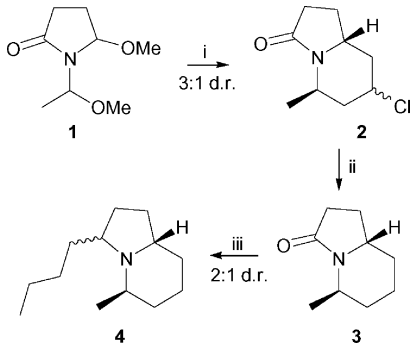
1			75
2			50
3			77
4			41

(prepared by anodic dimethoxylation of *N*,*N*-dialkylamides) with allyltrimethylsilane in the presence of $TiCl_4$.[4] The reaction is proposed to take place *via* a sequence of inter- and intramolecular olefin additions to *in situ* generated acyl iminium ions. This was found to be a general process and furnished a series of mono- and bicyclic heterocycles (Table 1).

The products shown in Entries 1 and 3 of Table 1 were readily elaborated to (±)-coniine and (±)-δ-coniceine, respectively, after simple functional group manipulations. Furthermore, and in an effort to investigate the applicability of this methodology to stereoselective indolizidine formation, the authors carried out the synthesis of the pharaoh ant trail pheromone **4** as outlined in Scheme 1. The piperidine forming [3 + 3] cycloaddition furnished the indolizidinone **2** in good yield and as a 3 : 1 mixture of diastereomers at the stereocentre bearing the chloride. Hydrogenolysis provided **3** as a single stereoisomer that was converted to the target compound by addition of the alkyl unit followed by reduction of the intermediate carbinolamine.



Scheme 1 Reagents and conditions: (i) $CH_2{=}CHCH_2SiMe_3$, $TiCl_4$, 70%; (ii) H_2, Ra, Ni, 74%; (iii) (a) BuLi (b) $NaBH_4$, AcOH, 34%.

More recently, the groups of Brimble and McLeod employed the double Mannich alkylation strategy at an early stage of their studies towards the synthesis of methyl lycaconitine, a potent competitive antagonist of the nicotinic acetylcholine receptor.[5] In this case, the dianion equivalent is a β-ketoester **5** that undergoes sequential addition to two *in situ* generated iminium ions. Preliminary studies were thwarted by the inefficiency of the [3 + 3] reaction, delivering the bicyclic products **6a** and **b** in poor yield (Fig. 2).

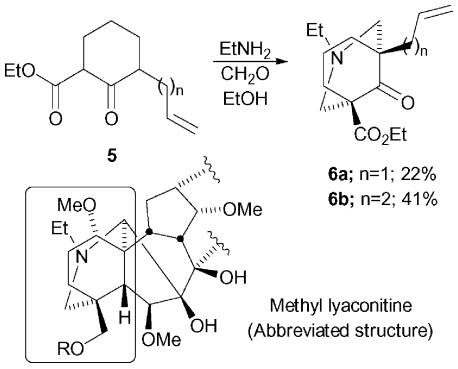


Fig. 2 β-Ketoester alkylation studies.

Inspired by a 1996 report by Heaney and Papageorgiou,[6] the use of acidic promoters was found to have a beneficial effect on this reaction. Specifically, the employment of bis(aminol) ether **7** and $MeSiCl_3$ furnished the AE ring analogue **8** in a much improved 77% yield (Fig. 3).[7]

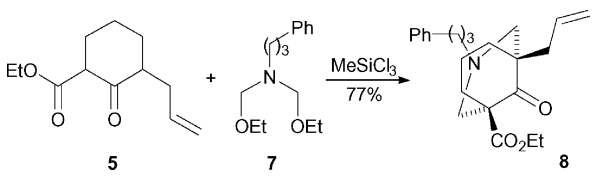
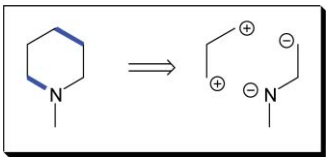


Fig. 3 Acid promoted cycloaddition.

To date, the double Mannich approach represents the only example of Type 1 [3 + 3] cycloaddition reaction to the best of our knowledge. However, processes that involve azomethine ylides or dianionic synthons can be envisaged and would provide access to a wider range of functionalised piperidine targets.

3 Type 2 cycloadditions

3.1 Double alkylation of a *C*,*N*-dianion



Whilst the previous strategy exploited the ability of nitrogen to stabilise cationic charge *via* an iminium species, an alternative approach that employs appropriately activated secondary amides as 1,3-dianion synthons has also been the subject of active research. An elegant application of this concept by Eskici and Gallagher provided an asymmetric approach to piperidines by the addition of *C*,*N*-dianions to 1,3-cyclic sulfates.[8] The basic transformation is outlined in Fig. 4.

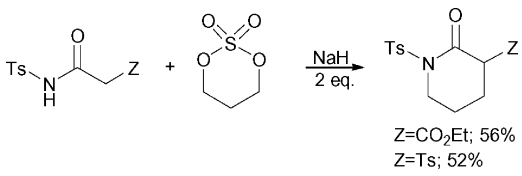
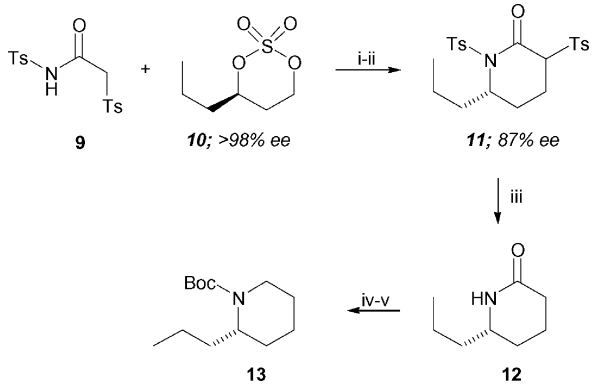


Fig. 4 Alkylation of 1,3-cyclic sulfates.

The employment of chiral non-racemic cyclic sulfates provided the opportunity to prepare enantiomerically enriched

piperidines, and this process was investigated in the context of the synthesis of (*S*)-coniine as outlined in Scheme 2. Cycloaddition of amide **9** with enantiomerically pure sulfate **10** proceeded under forcing conditions to provide the desired piperidine **11** in 34% yield. Unfortunately, some erosion of enantiomeric purity was observed in this step. Notably, a stepwise protocol was also developed that attenuated the drop in ee and proceeded in similar yield to furnish **11** in 96% ee. Finally, Boc-coniine (**13**) was accessed after removal of the Ts groups, reduction of the lactam **12** and Boc-protection.

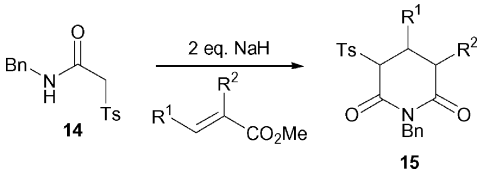


Scheme 2 Reagents and conditions: (i) NaH, DMA, reflux, 34%; (ii) Al–Hg, 87%; (iii) $NaC_{10}H_{10}$, 80%; (iv) $LiAlH_4$; (v) Boc_2O, 84% over two steps.

The ready accessibility of acetamides bearing electron withdrawing groups in the α-position makes them very attractive 1,3-dianion synthons for heterocycle synthesis. However, an alternative class of 1,3-dication synthons to the cyclic sulfates used by Gallagher have been explored. Specifically, Chang and co-workers have investigated the utilisation of α,β-unsaturated esters in this regard as a direct method for the synthesis of substituted glutarimides.[9] Accordingly, treatment of **14** with two equivalents of NaH, followed by addition of the Michael acceptor substrate, furnishes the corresponding heterocycle **15** in good to excellent yields. Additionally, whilst 3,5-disubstituted piperidines are generated as diastereomeric mixtures, the corresponding 3,4-disubstituted isomers are generated with excellent *trans*-selectivity (Table 2).

The authors have also investigated the use of α,β-unsaturated esters bearing electron withdrawing groups in the β-position. In this case, the [3 + 3] cycloaddition reaction is followed by elimination of the Ts group to provide the corresponding 4-substituted piperidine-2,6-diones (Fig. 5).[10]

Table 2 Cycloaddition towards glutarimides



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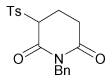
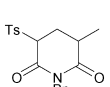
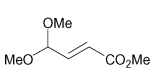
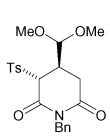
1			90
2			82
3			95

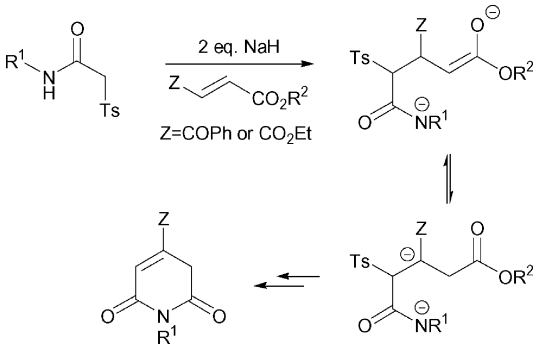
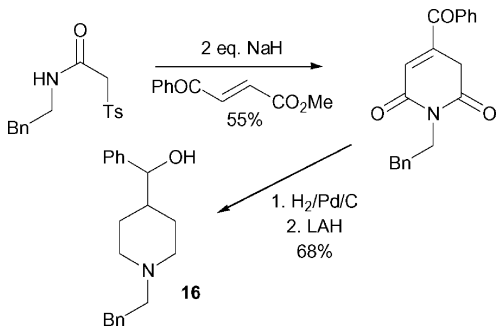


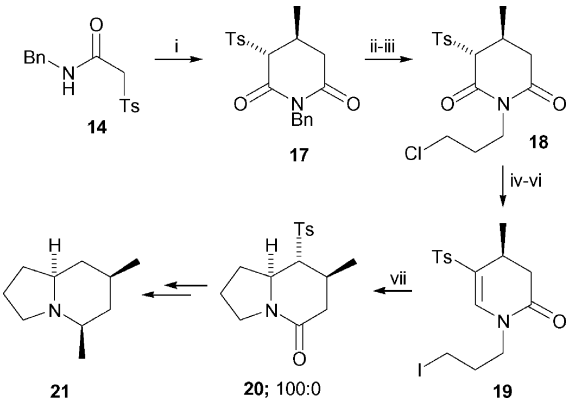
Fig. 5 Cycloaddition towards piperidine-2,6-diones.

This methodology was employed in the synthesis of MDL-11,939 (glemanserin, **16**), a potent class III antiarrhythmic agent (Scheme 3).



Scheme 3 Synthesis of MDL-11,939 (**16**).

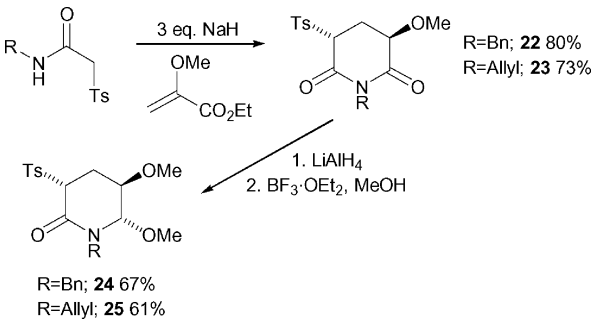
More recently, Chang and co-workers have used this stepwise cycloaddition methodology for the preparation of functionalised piperidines with a view to alkaloid natural product synthesis. As outlined in Scheme 4, *trans*-glutarimide **17** was generated upon addition of **14** to methyl crotonate. The *N*-benzyl group was next exchanged for a chloropropyl group to give **18**. Regioselective reduction of **18** took place with $NaBH_4$ to generate the hemi-aminal that was transformed to the enamide **19** after Lewis acid mediated elimination and a Finkelstein reaction. Finally, a Bu_3SnH mediated radical cyclisation reaction furnished the indolizidinone **20**, an intermediate in the synthesis of 8a-*epi*-dendroprimine (**21**).[11]



Scheme 4 (i) NaH, $CH_3CH{=}CHCO_2Me$, 86%; (ii) $AlCl_3$; (iii) $Cl(CH_2)_3Br$, K_2CO_3, 80% over two steps; (iv) $NaBH_4$; (v) $BF_3{\cdot}OEt_2$; (vi) NaI, 65% over three steps; (vii) Bu_3SnH, AIBN, 81%.

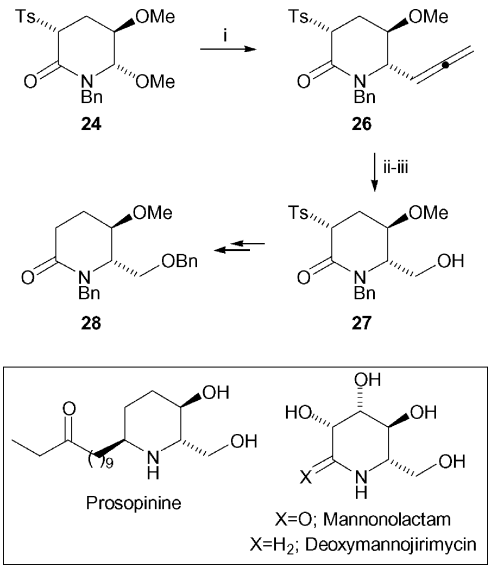
A series of functionalised piperidines that can be used as advanced intermediates in alkaloid synthesis are generated when α-methoxy ethyl acrylate is employed in the [3 + 3] reaction. As

outlined in Scheme 5, cycloadducts **22** and **23** are generated in high yield as single diastereoisomers and undergo stereoselective reduction at C-6 to provide lactams **24** and **25** after Lewis acid mediated methoxylation.[12]



Scheme 5 Diastereoselective lactam synthesis.

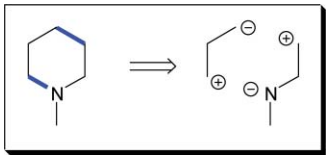
Transformation of **24** to the corresponding acyl iminium ion and addition of propargyl trimethylsilane delivered **26** with excellent levels of diastereocontrol. Ozonolysis of the allene unit followed by reduction provided lactam **27** that was further elaborated to **28**—a key intermediate in the syntheses of prosopinine, mannonolactam and deoxymannojirimycin (Scheme 6).



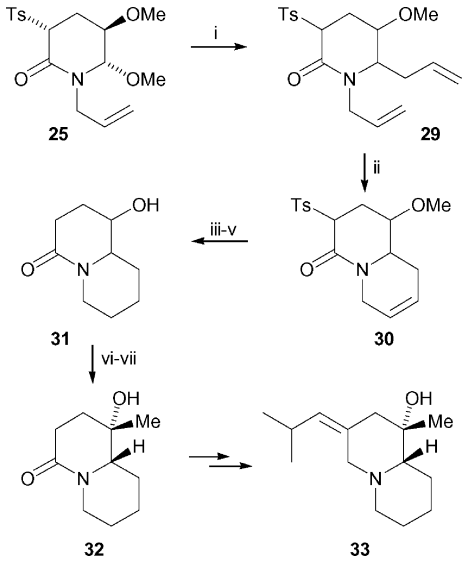
Scheme 6 (i) $HCCCH_2SiMe_3$, $BF_3{\cdot}OEt_2$, 67%; (ii) O_3, DMS; (iii) $NaBH_4$, 76% over two steps.

Surprisingly, allylation of related lactam **25** provided **29** as an equal mixture of three diastereoisomers in high yield. Apparently, epimerisation takes place at C-3 under the reaction conditions. The diastereomeric mixture was not separated at this stage as all three isomers converge to a single product later in the synthetic sequence. A Ru-catalysed RCM reaction provided quinolizidine **30** that was transformed to **31** in three steps. Finally, oxidation of **31** and stereoselective Grignard addition furnished **32**, an advanced intermediate in the synthesis of homopumiliotoxin 223G (**33**) (Scheme 7).

3.2 Cycloaddition of aziridines



Aziridines are reactive and readily available synthetic intermediates that have found widespread use in organic synthesis.[13]

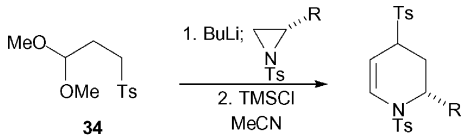


Scheme 7 (i) $CH_2{=}CHCH_2SiMe_3$, $BF_3{\cdot}OEt_2$, 85%; (ii) 4 mol% $PhC(H)RuCl_2(PCy_3)_2$, 71%; (iii) H_2, Pd/C; (iv) TMSCl, NaI; (v) Na–Hg, 57% over three steps; (vi) Jones oxidation; (vii) MeMgBr, 52% over two steps.

They are generally activated by the incorporation of an electron withdrawing group on nitrogen and as such, function as electrophiles at C-2. Accordingly, nucleophilic addition results in ring cleavage and formation of amidic anions. An elegant exploitation of this reactivity in a stepwise [3 + 3] piperidine forming process was described by Craig and coworkers in 1998. Specifically, deprotonation of sulfonylacetal **34** generates a dipole equivalent that adds to aziridines to provide the corresponding dihydropiperidines **35** in high yield after acid-catalysed ring closure.[14] Significantly, this methodology allows access to enantiomerically pure 2-substituted piperidines from the corresponding aziridines, that are in turn readily available from the corresponding α-amino acids. The products were generally isolated from the reaction mixture as a 2 : 1 mixture of diastereoisomers at the sulfone stereocentre, however, these could be readily equilibrated to the *trans*-isomers upon treatment with 10 mol% potassium *tert*-butoxide (Table 3).

The piperidines generated by this technique proved to be highly versatile synthetic intermediates and were readily trans-

Table 3 Craig's enantiospecific approach to dihydropiperidines



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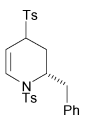
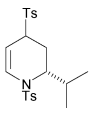
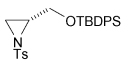
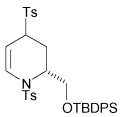
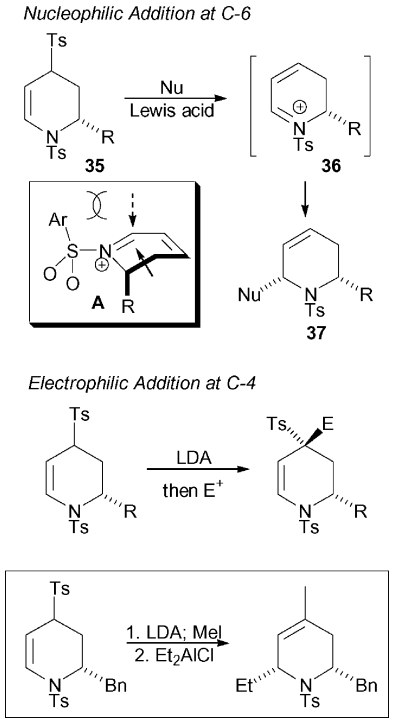
1			84
2			63
3			37

formed to more highly substituted piperidines with excellent levels of stereocontrol. Specifically, functionalisation at C-6 was carried out by Lewis acid promoted nucleophilic addition *via* the conjugated iminium species **36** to give *cis*-2,6-disubstituted piperidines **37**. The authors speculated that the stereoselectivity of the addition process might be due to the favoured approach of the nucleophile along a trajectory away from the bulky sulfonyl group (see **A** in Scheme 8). Alternatively, electrophiles could be introduced at C-4 after removal of the acidic proton with LDA. Moreover, these techniques could be used in combination as depicted in Scheme 8. It is notable that the sulfone moiety plays a central role in the assembly of the heterocycle as well as in the introduction of nucleophilic and electrophilic reagents.



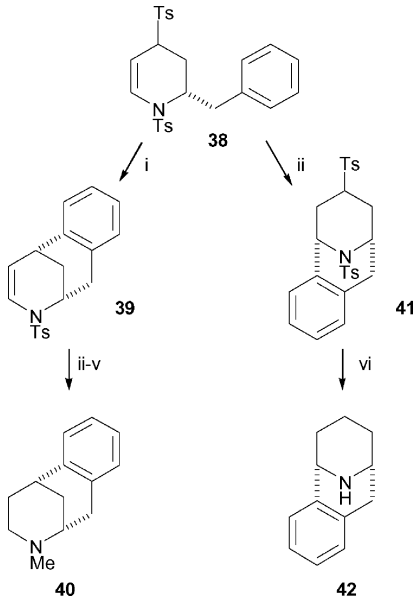
Scheme 8 Stereoselective functionalisation reactions.

These studies were extended to include intramolecular reactions of the piperidine compounds, once again these intermediates were found to display a versatile reactivity profile. Treatment of **38** with $SnCl_4$ generated tricycle **39**, presumably through the intermediacy of a conjugated iminium ion species, but with addition taking place at C-4. This compound was further elaborated to 2-methyl benzomorphan (**40**) in four steps. In contrast, use of a Brønsted acid resulted in capture of the iminium ion at C-2 to provide **41**. Finally, reductive removal of the Ts groups furnished tropane **42** (Scheme 9).[15]

Our group has recently been interested in investigating alternative modes of [3 + 3] cycloaddition processes that also exploit the ready availability of enantiomerically pure aziridines. In particular, we were intrigued by the possibility of using Trost's Pd-TMM methodology as our source of dipolar synthon.[16] This reagent (**44**) is generated from commercial 2-[(trimethylsilyl)methyl]-2-propen-1-yl acetate (**43**) by low valent Pd-complexes, and has been shown to participate in various carbocycle forming cycloaddition processes (Fig. 6).

As outlined in Table 4, the use of Trost's conditions for the *in situ* generation of Pd-TMM was found to be compatible with a range of aziridine substrates, allowing access to 2-alkyl, spirocyclic and bicyclic piperidine products.[17] Notably, this latter class of products was generated in low yield, suggesting that significant substitution around the aziridine was deleterious to the efficiency of the [3 + 3] cycloaddition process.

An important aspect of the TMM-synthon in cycloaddition processes is that it endows the cycloadducts with a readily



Scheme 9 (i) $SnCl_4$, 68%; (ii) catalytic H_2SO_4, 98%; (iii) TFA, Et_3SiH, 97%; (iv) Na–Hg; (v) EtOCOCl, Et_3N, 60% over two steps; (vi) Na–Hg, 67%.

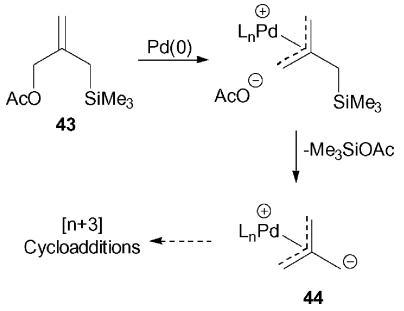
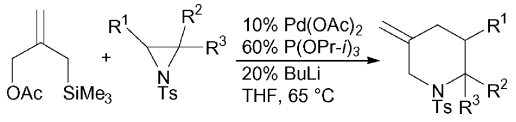
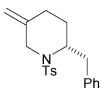
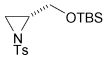
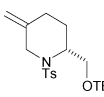
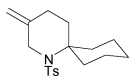
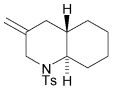


Fig. 6 Generation of Trost's Pd-TMM reagent.

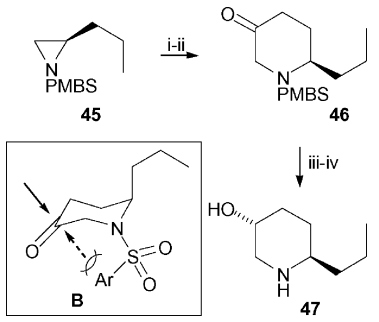
Table 4 Pd-TMM cycloaddition reactions



Entry	Aziridine	Product	Yield (%)
1			79
2			52
3			70
4			31

functionalisable olefin motif. In the context of our piperidine forming reaction, we hoped that the exocyclic alkene unit would allow us to carry out stereoselective functionalisation reactions at C-5 of the heterocycle ring. We decided to test this

hypothesis during the total synthesis of the poison hemlock alkaloid (−)-pseudoconhydrine (**47**) (Scheme 10).[18] The [3 + 3] cycloaddition reaction of *n*-propyl substituted aziridine **45** proceeded in good yield to provide ketone **46** after oxidative cleavage of the alkene. Sulfonamide protected 2-alkyl substituted piperidines are known to adopt a well-defined conformation that places the alkyl group in an axial orientation and the aryl unit over that heterocycle ring. Accordingly, and as illustrated by **B** in Scheme 10, a bulky reducing agent would be expected to deliver a hydride to the carbonyl group to furnish the *trans*-alcohol. In the event, this reaction was highly diastereoselective and allowed (−)-pseudoconhydrine (**47**) to be generated by a short route with complete stereocontrol.



Scheme 10 PMBS: *p*-methoxybenzenesulfonyl; (i) $AcOCH_2C(=CH_2)$-CH_2SiMe_3, 10% $Pd(OAc)_2$, 60% $P(OPr)_3$, 20% BuLi, 63%; (ii) O_3, DMS; (iii) L-selectride, 77% over two steps; (iv) $NaC_{10}H_{10}$, 79%.

More recent studies have been directed towards the synthesis of a family of sesquiterpenoid alkaloids that are isolated from aquatic plants of the genus *Nuphar*. These compounds have a number of common structural features, specifically a trisubstituted piperidine ring with a methyl group at C-3 and 3-furyl substituent at C-6. From a synthetic viewpoint, we anticipated that compounds **48**–**50** could be prepared from a common intermediate **51** after appropriate functionalisation reactions on the olefin moiety (Fig. 7).

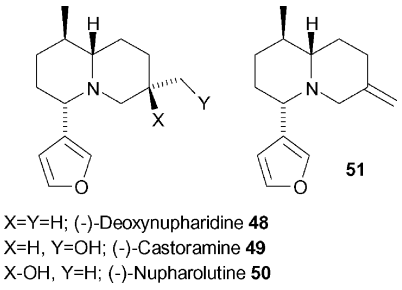


Fig. 7 *Nuphar* alkaloids.

The key cycloaddition reaction required for the synthesis of *Nuphar* alkaloids employed aziridine **52**, in turn readily available in six steps from (*R*)-aspartic acid. Surprisingly however, the reaction of Pd-TMM with **52** was extremely sluggish and provided the corresponding piperidine **53** in only 20% yield (Fig. 8). Attempts to optimise the cycloaddition by exploring alternative ligands resulted in only moderate improvement.[19]

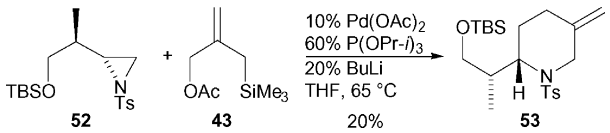
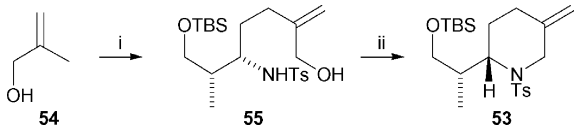


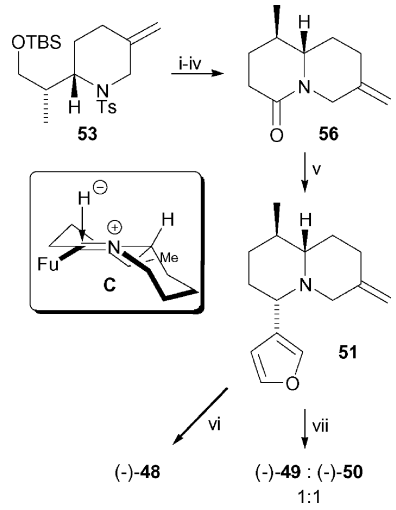
Fig. 8 Pd-TMM cycloaddition towards *Nuphar* alkaloids.

In an effort to improve the efficiency of the transformation of **52** to **53**, a complementary two step protocol was devised. As outlined in Scheme 11, double deprotonation of methallyl alcohol **54**, followed by transmetallation with magnesium bromide to the Grignard reagent, furnished **55** after addition of aziridine **52**. This acyclic intermediate was cyclised in high yield by the employment of a Mitsunobu reaction.[19]



Scheme 11 (i) (a) BuLi (2.6 eq.), TMEDA (3.0 eq.) (b) $MgBr_2$, **52**, 92%; (ii) ADDP, PBu_3, 87%.

The remaining steps of the synthesis are outlined in Scheme 12. Elaboration of the 2-alkyl side chain to the quinolizidone **56** was carried out in four steps that featured an extremely mild Ts deprotection, chemoselective reduction and cyclisation sequence that occurred in one-pot. Addition of the furanyl moiety proceeded smoothly to provide the late stage key intermediate **51** as a single diastereomer. The diastereoselectivity of the iminium reduction step was rationalised by the model illustrated in Scheme 12 as **C**. Hydrogenation of the alkene furnished (−)-deoxynupharidine (**48**) whilst an unusually non-regioselective hydroboration reaction delivered both (−)-castoramine (**49**) and (−)-nupharolutine (**50**), the latter was later accessed selectively by a dihydroxylation-reduction process.[20]



Scheme 12 (i) TBAF, 86%; (ii) Swern; (iii) $Ph_3P{=}CO_2Et$, 78% over two steps; (iv) Mg, MeOH, 72%; (v) (a) 3-LiC_4H_3O (b) Dibal-H, 76%; (vi) H_2, Rh–Al_2O_3, 60%; (vii) BH_3·DMS, H_2O_2, NaOH, 52%.

3.3 Formal aza-[3 + 3] cycloaddition reactions

A piperidine-forming process that uses a Type 2 cycloaddition strategy involves a Knoevenagel condensation reaction followed by a 6π-electron electrocyclic ring closure (Fig. 9).

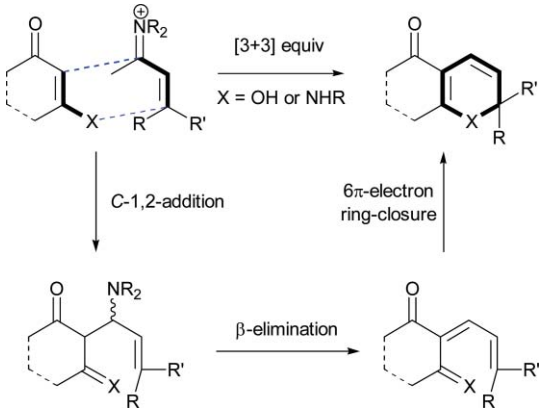
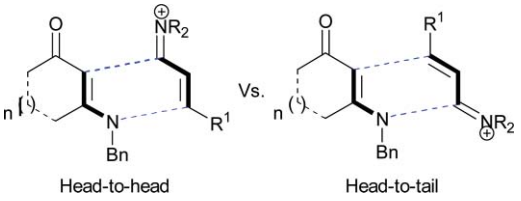
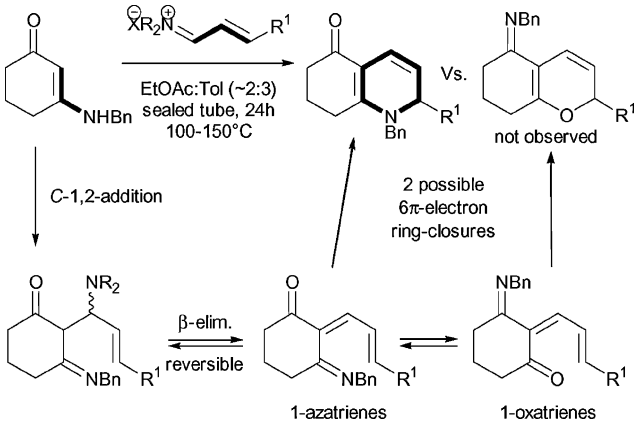


Fig. 9 Formal [3 + 3] *via* Knoevenagel condensation/ring closure.

In principle, the piperidine forming process outlined in Fig. 9 could suffer from a number of competing reactions. In particular, a regiochemistry issue arises from potential head-to-head *vs.* head-to-tail addition (Scheme 13). Hsung and co-workers showed that the addition of vinylogous amides to preformed α,β-unsaturated iminium salts resulted in clean head-to-head addition to furnish the corresponding 1,2-dihydropyridines in high yield.[21] The absence of pyran-derived products suggests that 6π-electron electrocyclic ring closure of 1-azatriene is favored over the corresponding closure of 1-oxatriene under these conditions (Scheme 14).

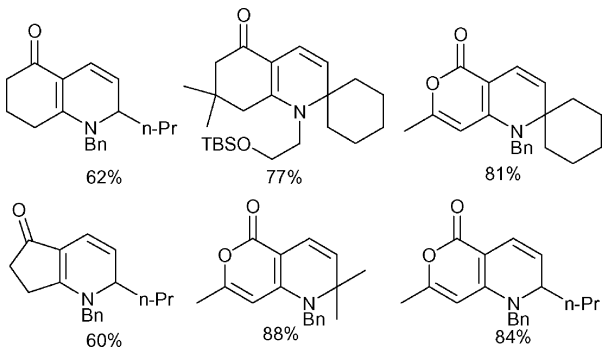


Scheme 13



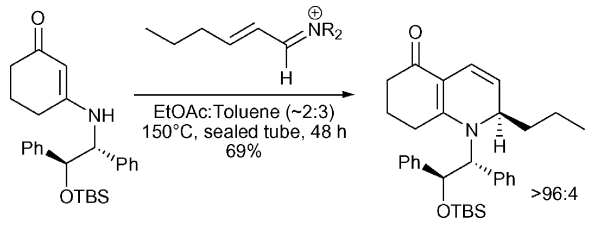
Scheme 14

Notably, whilst the use of iminium salts appeared to preclude formation of the head-to-tail cycloadduct, a recent study demonstrated a dependency of cycloaddition regioselectivity with temperature.[22] Indeed, up to 38% of the cycloadduct derived from head-to-tail addition can be found at temperatures above 130 °C. Nonetheless, with careful temperature control, a broad range of 1,2-dihydropyridines can be formed in high yield; a selection of examples are shown in Scheme 15.[23]



Scheme 15

This cycloaddition process provides the opportunity to generate chiral 2-substituted piperidines. Accordingly, the possibility of controlling the stereochemistry of these products by utilising a chiral auxiliary has been investigated.[24] As outlined in Scheme 16, this approach offers high levels of stereoinduction when a 2-amino 1,2-diphenylethanol derived auxiliary is used.



Scheme 16

The authors proposed a mechanistic model to account for the observed diastereoselection. As shown in Fig. 10, two possible rotations for the alkene strand of imine intermediate **57** can be considered. Ring closure *via* mode **b** suffers from steric congestion between alkyl group R and the proximal phenyl moiety. Therefore, ring closure proceeds *via* mode **a** to provide the observed diastereomer. Additionally, the authors demonstrated that the ring closure can be reversible and it is also likely that the diastereoselectivity is a consequence of the greater thermodynamic stability of the major diastereomer in each case.

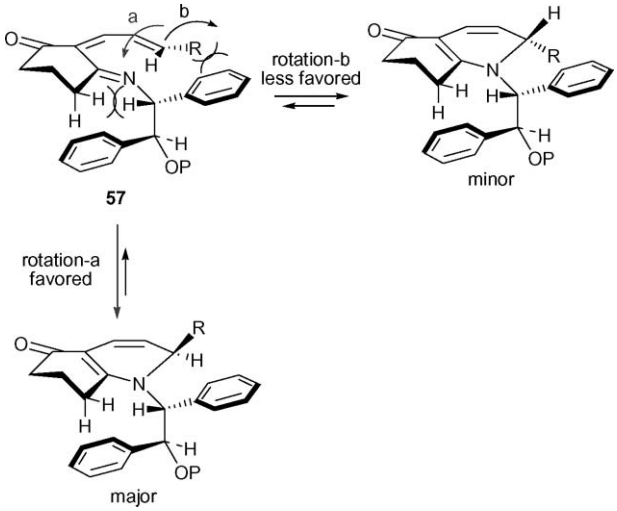
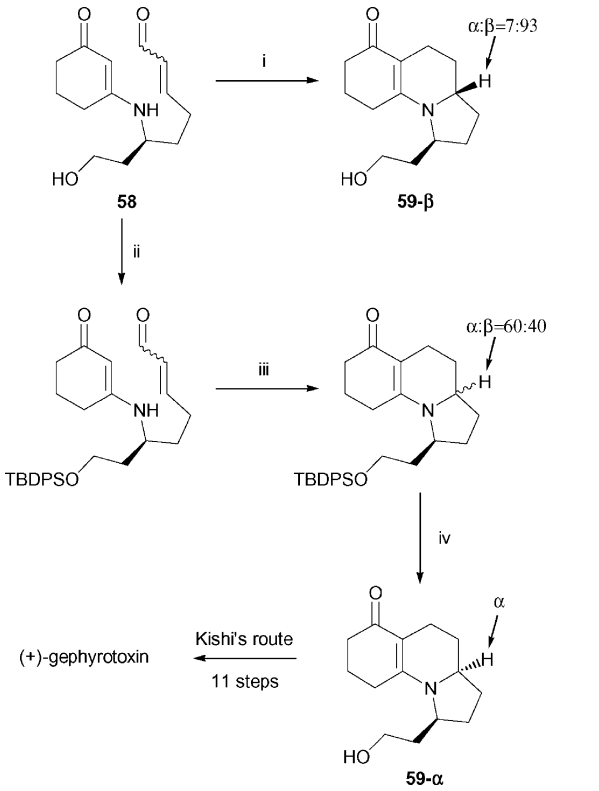


Fig. 10 Proposed mechanistic model.

The scope of this methodology was expanded to include an intramolecular variant and this approach has been utilised towards the synthesis of (+)-gephyrotoxin.[25] Accordingly, and after extensive optimisation, the tricycle **59** was formed after intramolecular cycloaddition and hydrogenation of the unstable dihydropiperidine intermediate. Whilst the diastereoselectivity of this process was high, it favoured the wrong diastereomer for gephyrotoxin synthesis. Interestingly, protection of the pendant alcohol resulted in better α-selectivity in the cycloadduct, with the **59**-α isomer corresponding to the intermediate in Kishi's synthesis of (+)-gephyrotoxin (Scheme 17).[26]

As highlighted in Scheme 15, aza-spirocycles can be accessed by the [3 + 3] methodology. Hsung and co-workers further explored the scope of this chemistry with a view to carrying out the synthesis of perhydrohistrionicotoxin analogues.[27] Due to the possible effect of the C-2 and C-3 substituents on the stereochemical outcome of the formal [3 + 3] cycloaddition, an extensive study of the intramolecular protocol was needed to install the specific stereochemistry necessary for perhydrohistrionicotoxin synthesis. To explore this issue, a series of cycloalkylidene α,β-unsaturated iminium salts containing a substituent at either C-2 or C-3 position were prepared (Table 5).

Submitting these substrates to the cycloaddition conditions revealed that the *N*-protecting group had little effect on the reaction stereoselectivity, whilst substituents at C-2 or C-3 led to the formation of the isomer in which nitrogen and alkyl groups are mutually *trans*. Again the stereoselectivity of this process was



Scheme 17 (i) EtOAc/EtOH, Na_2SO_4, piperidinium acetate (0.5–1 equiv), 100 °C, 1–2 h, then 5% Pd/C, H_2, 50% (<7 : 93); (ii) TBDPSCl, imidazole; (iii) toluene–EtOH, Na_2SO_4, piperidinium acetate (1.0 eq.), 150 °C, 1–2 h, then 5% Pd/C, H_2, 60% from **58** (α : β, 60 : 40); (iv) (a) TBAF, CH_2Cl_2, 0 °C, 80% (b) separation.

rationalised on the basis of a reversible 6π-electron electrocyclic ring closure that leads to the thermodynamically more stable diastereomer (Fig. 11).

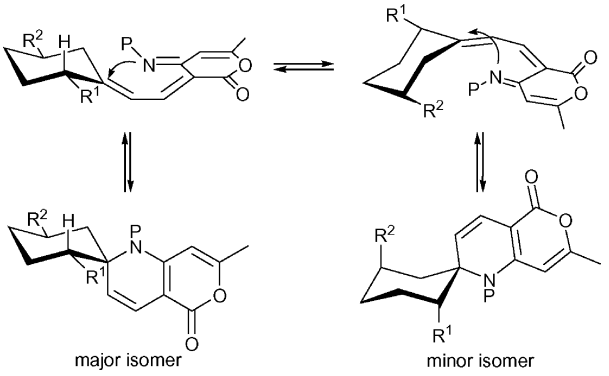
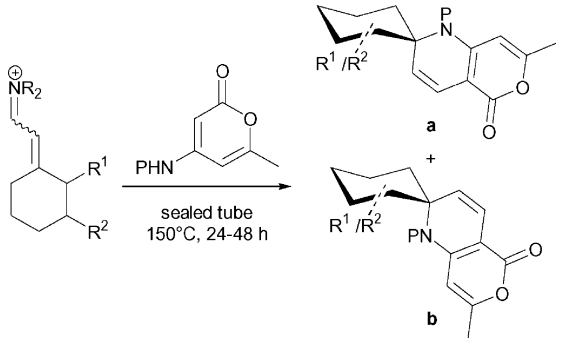


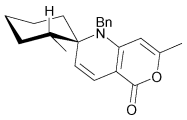
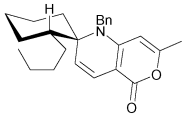
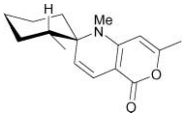
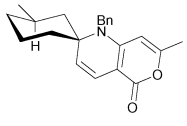
Fig. 11 Equatorial approach of the N-atom during ring closure.

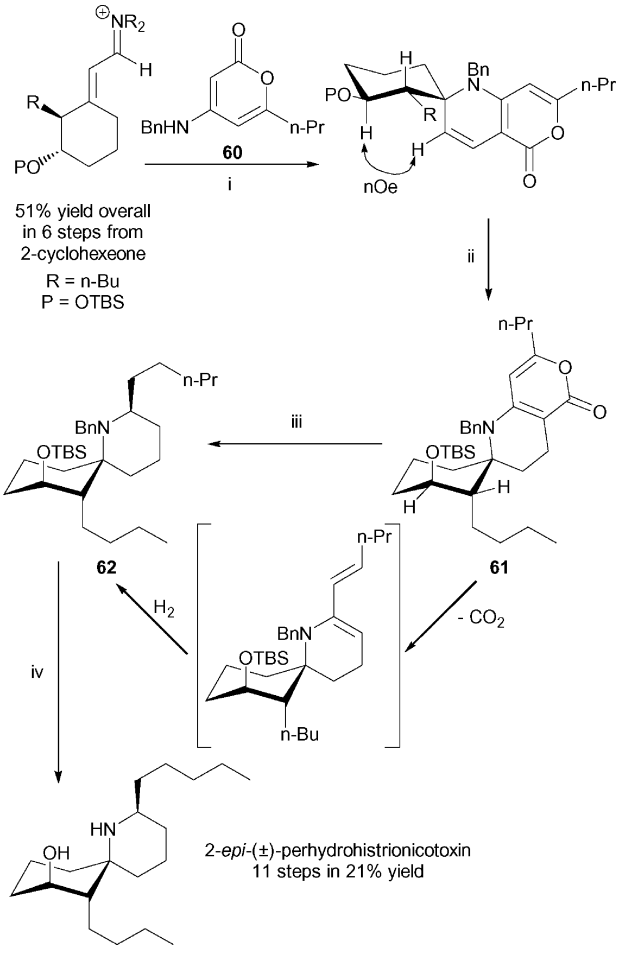
This approach was employed in the synthesis of the core structure of perhydrohistrionicotoxin in a very short sequence. The cycloaddition process proceeded smoothly to furnish spiropiperidine (**61**) after hydrogenation. Reduction of the pyranone with $LiAlH_4$ generated **62** *via* a novel decarboxylation process which was deprotected to produce 2-*epi*-(±)-perhydrohistrionicotoxin in 11 steps and 21% overall yield. The authors speculated that the stereoselectivity of the decarboxylation step originated from the steric hindrance of the TBS group, leading to a hydrogenation occurring from the opposite face (Scheme 18).

More recently, the synthesis of (±)-tangutorine has been reported using the [3 + 3] cycloaddition methodology.[28] As with

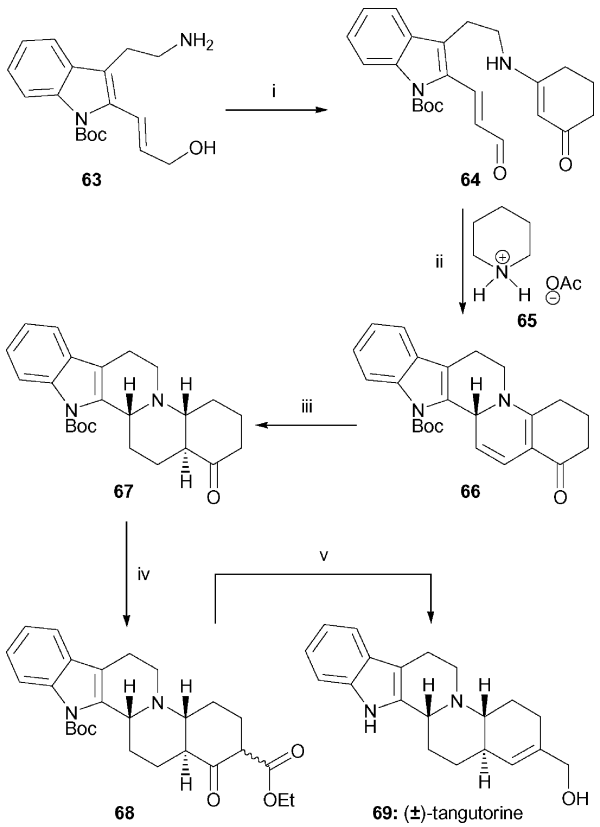
Table 5 Formal aza [3 + 3] towards spirocycloadducts



Entry	Iminium ions	P	Products	Yield (%)	**a** : **b**
1	R^1 = Me R^2 = H	Bn		85%	>95 : 5
2	R^1 = Bu R^2 = H	Bn		63%	>96 : 4
3	R^1 = Me R^2 = H	Me		74%	>95 : 5
4	R^1 = Me R^2 = Me	Bn		69%	>96 : 4



Scheme 18 (i) **60**, toluene, 150 °C, 78%; (ii) Pd–C, H_2, EtOH, rt, 2 h, 98%; (iii) $LiAlH_4$ then 60 psi H_2, Pd–C, EtOH, 60% yield overall; (iv) (a) MeOH, H_2O, HCl, Δ, 20 h (b) H_2, $Pd(OH)_2$, MeOH, rt, 20 h, 90% yield overall.



Scheme 19 (i) (a) 1,3-cyclohexanedione, toluene, reflux, 90% (b) MnO_2, CH_2Cl_2; (ii) 1.1 eq. **65**, EtOAc–toluene [2 : 3], Na_2SO_4, 95 °C; (iii) (a) 20%wt $Pd(OH)_2$, H_2, EtOAc, 99% (b) 6.0 eq. Na, *i*-PrOH, THF, rt, 30 min (c) $Py.SO_3$, DMSO, Et_3N (d) $(Boc)_2O$, DMAP, CH_2Cl_2, 61% over the 3 steps; (iv) NaH, $(EtO)_2CO$, THF, reflux, 75%; (v) (a) $NaBH_4$, MeOH, rt, 10 min, 91% (b) 10 eq. MsCl, Et_3N, CH_2Cl_2, −78 °C, 5 h (c) 3.0 eq. DBU, THF, reflux, 7 h, 75% over 2 steps (d) LAH, THF, 0 °C, 90%.

many of monoterpenoid indole alkaloids, tangutorine contains an indoloquinolizidine substructure. Usually this core structure is synthesised *via* a Pictet–Spengler cyclisation reaction. The use of the formal aza-[3 + 3] provides a complementary approach to these intermediates. As outlined in Scheme 19, the precursor to the cycloaddition step was synthesised by condensation of **63** with cyclohexane-1,3-dione followed by allylic oxidation. Submission of this compound to the cycloaddition reaction conditions proved successful and provided the desired core structure. Hydrogenation of **66** took place not only at the disubstituted alkene, but also at the vinylogous amide and the ketone together with removal of the Boc protecting group. Reoxidation and reprotection was therefore required to give **67**. The β-ketoester **68** was formed by heating **67** in refluxing THF in the presence of NaH and diethyl carbonate. Subsequent transformations were successfully accomplished and provided (±)-tangutorine **69** in 19 steps overall.

4 Conclusion and perspectives

The [3 + 3] cycloaddition concept is a relatively unexplored strategy for the synthesis of carbocyclic and heterocyclic compounds. One can think of this approach as an exercise in synthon design; the cycloaddition relies on intermediates that have the ability to stabilise cationic or anionic charges. Indeed, it is this aspect of the [3 + 3] strategy that makes this method so appealing. Firstly, there are many potential ways of designing processes that involve the conjunction of three-atom fragments bearing complementary charge. In this respect, a number of yet undiscovered reaction pathways can be envisaged and designed. Additionally, the functionality that is essential for stabilising the appropriately charged three-atom fragments endows the cycloadducts with readily manipulated motifs that allow them to be further exploited in target synthesis. Whilst relatively underdeveloped, the [3 + 3] cycloaddition strategy has already been demonstrated to be of significant use in the synthesis of complex organic molecules.

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