Stereoselective synthesis of 3,4-disubstituted and 3,4,5-trisubstituted piperidines by Lewis acid-catalysed ene cyclisation of 4-aza-1,7-dienes†

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The thermal or Lewis acid-catalysed ene cyclisation of a variety of 4-aza-1,7-dienes afforded 3,4-disubstituted or 3,4,5-trisubstituted piperidines. Activation of the enophile with a single ester facilitated a thermal ene cyclisation, although the reaction was not amenable to Lewis acid catalysis. With other activating groups on the enophile it was found that Lewis acid catalysis was facile, although there was a fine balance between the desired ene cyclisation and the competing hetero-Diels–Alder reaction, with the product distribution being influenced by the activating group on the enophile, the nature of the ene component, and the Lewis acid used. Activation of the enophile with an oxazolidinone function facilitated Lewis acid-catalysed cyclisation to afford mixtures of ene and hetero-Diels–Alder products. Activating the enophile with two ester groups gave a substrate that underwent a very facile ene cyclisation catalysed by $MeAlCl_2$ to give the corresponding *trans* 3,4-disubstituted piperidines with diastereomeric ratios of >200 : 1.

Introduction

Piperidines occupy a central position in the pharmaceutical and agrochemical sectors, a fact that can be attributed to their often potent biological properties.[1] This role is mirrored in Nature, with the piperidine ring system occurring as a key structural element in a vast array of natural products.[2] Numerous stereoselective routes to variously substituted piperidines have been developed,[3] but the demand for piperidines incorporating a range of functionality and substitution patterns continues to drive the development of new routes to these compounds.[4]

Continuing our interest in the synthesis of N-heterocycles by pericyclic processes,[5,6] we wished to explore the possibility of synthesising 3,4-disubstituted piperidines *via* the ene cyclisation of 4-aza-1,7-dienes.[7] The ene reaction is a valuable tool in ring synthesis, generating two contiguous stereocentres with an often high degree of stereocontrol.[8] In particular, Lewis acid catalysis has been shown to lead to very impressive levels of stereoselectivity in the formation of 6-membered rings.[9–11] Despite this, there have been few piperidine syntheses in which the ring is formed by ene chemistry.[12] Oppolzer studied the thermal ene reaction of simple 4-aza-1,7-dienes to afford 3,4-disubstituted piperidines.[13] Cyclisation was achieved on prolonged heating at 290 °C, to afford a 26% yield of the two stereoisomeric products in an undetermined ratio. Takacs and co-workers have reported the transition metal-catalysed cross-coupling of a diene with an allylic ether or another diene to afford piperidines.[14] Formally, these processes can be regarded as [4 + 4]- or [4 + 6]-ene reactions, although mechanistically they are far removed from the classical ene reaction.

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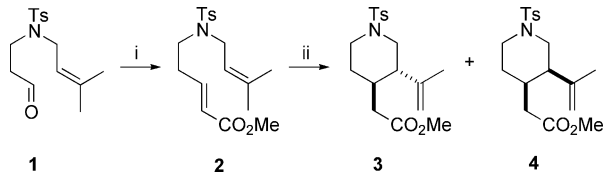
Results and discussion

Since ene reactions proceed most readily when the enophile is electron-deficient, we envisaged that attachment of an electron-withdrawing group such as an ester to the enophile would activate the system towards thermal cyclisation. Moreover, we reasoned that the Lewis basicity of the ester would open up the possibility of Lewis acid catalysis of the reaction.

Thus, our first cyclisation precursor was **2**, in which the enophile is activated with an ester. This was readily prepared by a Wittig reaction between the previously reported[15] aldehyde **1** and methyl (triphenylphosphoranylidene)acetate, affording ester **2**, exclusively as the *E* diastereomer, in 65% yield after chromatography (Scheme 1). Surprisingly, the energy barrier for the uncatalysed ene reaction of **2** was high, with cyclisation occurring on heating in refluxing diphenyl ether (259 °C) for 7 hours. Removal of the solvent by distillation, followed by chromatography, afforded the piperidine products **3** and **4** in a combined yield of 62% as an inseparable mixture, with a *trans* : *cis* ratio determined as 3 : 2 by integration of the ^{1}H NMR spectrum.‡



Scheme 1 *Reagents and conditions*: (i) $Ph_3P{=}CHCO_2Me$, CH_2Cl_2, 65%; (ii) Ph_2O, reflux, 62%.

We were hopeful that Lewis acid catalysis would decrease the activation barrier substantially and hence allow us to effect cyclisation at a lower temperature. With this goal in mind, we

‡ The major product was confirmed as the *trans* diastereomer by comparison of the ^{1}H NMR spectrum with that of **28** (*vide infra*).

screened the Lewis acids $FeCl_3$, $ZnBr_2$, $MeAlCl_2$ and $Sc(OTf)_3$ for their ability to catalyse the cyclisation, at temperatures ranging from −78 °C to 180 °C. The results were disappointing, and in most cases unreacted starting material was recovered. In the reactions employing ferric chloride and scandium triflate at room temperature, cleavage of the ene moiety was observed, yielding **5**. Presumably this results from coordination of the Lewis acid to the sulfonamide, facilitating the dissociation of an allylic cation which then loses a proton to afford **5** and 2-methylbutadiene (Fig. 1).

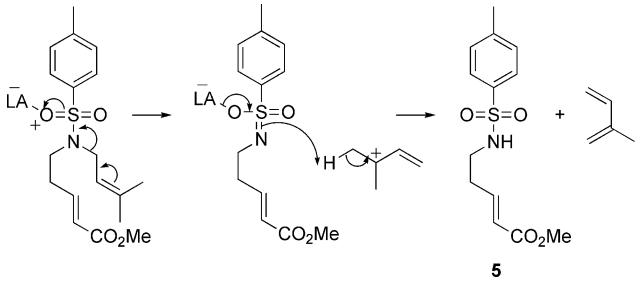
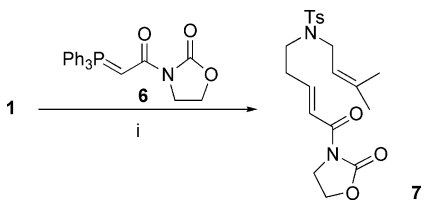


Fig. 1 Cleavage of **2** on treatment with Lewis acids.

This result suggested that we needed to modify our cyclisation precursor to enhance coordination of the Lewis acid to the enophile. Accordingly, we designed the cyclisation precursor **7**, in which the enophile is activated by an oxazolidinone group; it was expected that the two carbonyl groups would be able to chelate a Lewis acid, overcoming the Lewis basicity of the sulfonamide.

Oxazolidinone **7** was prepared in 76% yield as a 25 : 1 *E* : *Z* mixture by a Wittig reaction between **1** and the known[16] ylide **6** (Scheme 2).

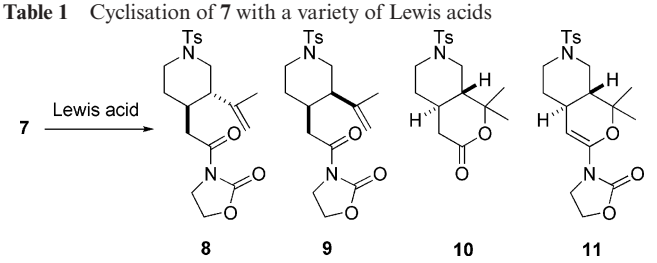


Scheme 2 *Reagents and conditions*: (i) CH_2Cl_2, 76%.

Pleasingly, a range of Lewis acids were found to catalyse the cyclisation of **7** at room temperature, affording the two piperidines **8** and **9** as an inseparable mixture (Table 1), without competitive cleavage of the ene moiety.

Diastereomeric ratios were generally moderate, with titanium tetrachloride affording an 8.2 : 1 *trans* : *cis* ratio of piperidines **8** and **9** in the best case. It proved possible to grow single crystals from chloroform, which allowed us to confirm the identity of the major isomer **8** (Fig. S1†). Preferential formation of the *trans* diastereomer may be explained by the reaction proceeding through

Table 1 Cyclisation of **7** with a variety of Lewis acids



Lewis acid[a]	**8** : **9** : **10**[b]	*Trans* : *cis* ratio of ene product
Me_2AlCl	42 : 36 : 22	1.2 : 1
$MeAlCl_2$	59 : 27 : 14	2.2 : 1
$AlCl_3$	65 : 20 : 15	3.3 : 1
$FeCl_3$	32 : 11 : 57	2.9 : 1
$Sc(OTf)_3$	50 : 11 : 39	4.5 : 1
$ZnBr_2$	28 : 5 : 67	5.6 : 1
$TiCl_4$	49 : 6 : 45	8.2 : 1

[a] All reactions were performed with 1 equivalent of Lewis acid at room temperature in dichloromethane. [b] Ratios determined by integration of ^1H NMR spectra of crude cyclisation products.

a chair-like transition state in which both the ene and enophile adopt pseudo-equatorial positions.

Although crude yields were high, in all cases bicyclic lactone **10** was present as a side product, and with some Lewis acids the lactone was the major product. We propose that this compound arises from hydrolysis of **11**, implying that **7** was undergoing a competing hetero-Diels–Alder reaction.[16] X-Ray crystallography confirmed that lactone **10** was obtained as the *trans* stereoisomer (Fig. S2†), a stereochemical outcome that is in agreement with literature precedent for closely related systems[11] and consistent with the geometrical constraints inherent in such an intramolecular Diels–Alder reaction.

Competition between ene and Diels–Alder pathways has been observed by others, with the balance between the two processes being dependent on the choice of Lewis acid, the reaction temperature and the activating group on the enophile.[10,11,16,17]

It has previously been shown in intermolecular ene reactions[18] and in intramolecular ene reactions leading to 5-membered rings[13] and 6-membered rings[19] that the configuration of the double bond of the ene component influences the stereochemical outcome of the reaction, in agreement with the proposal that these reactions proceed through largely concerted transition states. On this basis, and assuming cyclisation through chair-like transition states, one might expect *E*-crotyl compound **11** to exhibit a preference for the *trans* piperidine **12**, whereas *Z*-crotyl compound **13** would cyclise to the *cis* piperidine **14** *via* a higher activation barrier (Fig. 2). We hoped that this would allow us to tune the product outcome, as well as affording piperidines with a synthetically versatile vinyl substituent at the 4-position.

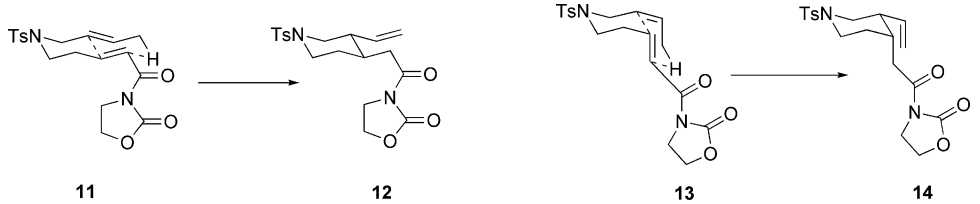
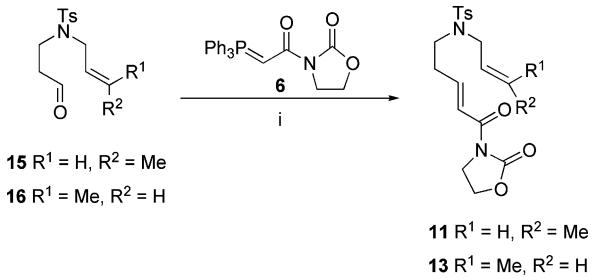


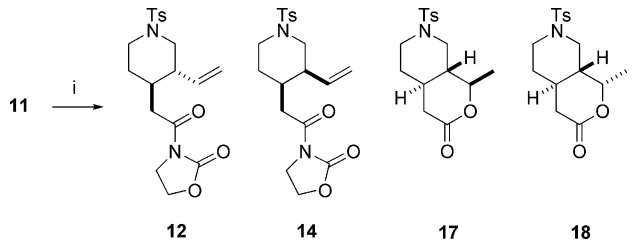
Fig. 2 Expected transition states for cyclisation of **11** and **13**.

To probe this effect we prepared the two cyclisation precursors **11** and **13** by Wittig reaction between the previously reported[15] aldehydes **15** and **16**, as 5 : 1 and 1 : 6 *E* : *Z* mixtures respectively, and ylide **6** (Scheme 3). After chromatographic purification, **11** was obtained in 62% yield as a 3 : 1 *E* : *Z* mixture about the ene double bond, while **13** was produced in 72% yield as a 1 : 7 *E* : *Z* mixture; in both cases the α,β-unsaturated double bond was *E*-configured.



Scheme 3 *Reagents and conditions*: (i) CH_2Cl_2, 62–72%.

Loss of a methyl group from the ene made the system much less reactive, and reaction was only achieved on heating at 60 °C in the presence of 1 equiv. of $MeAlCl_2$. Under these conditions **11** gave a mixture of products from which it was possible to isolate piperidines **12** and **14** as an inseparable 2 : 1 *cis* : *trans* mixture in 15% yield, and the lactones **17** and **18** as a 10 : 1 mixture in 13% yield (Scheme 4).



Scheme 4 *Reagents and conditions*: (i) $MeAlCl_2$, CH_2Cl_2, 60 °C.

The stereochemistry of **12** and **14** were assigned on the basis of spectral similarities with related compounds prepared within our research group, while a crystalline sample of the lactones allowed us to secure the structure of the major epimer **17** by X-ray diffraction (Fig. S3†); spectral similarities indicated that the minor lactone stereoisomer was **18**, differing in the configuration of the carbon bearing the methyl group. Cyclisation of the *Z*-isomer **13** was low-yielding, with only around 10% of the material being recovered after chromatography, although this low yield partly reflected difficulties in removing uncharacterisable decomposition products which necessitated repeated chromatography. The purified product mixture comprised piperidines **12** and **14** in a 4 : 1 *cis* : *trans* ratio, along with a trace of lactones **17** and **18** in an undetermined ratio.

Clearly one must exercise caution in drawing any conclusions from low-yielding reactions. However, assuming that the reactions follow a concerted pathway, the stereochemistry of the major Diels–Alder adduct **17** would suggest that this product is derived from the *E*-crotyl precursor **11**, with a smaller amount going on to afford the *trans* ene product **12**. The same analysis would suggest that the *Z*-crotyl precursor **13** is chiefly transformed into the *cis* ene product **14**, with only a trace reacting through the Diels–Alder pathway.

Transition state diagrams consistent with the observed products are shown in Fig. 3. It would appear that in the case of the *Z*-crotyl precursor **13**, a steric clash between the methyl group and the Lewis acid disfavours the transition state leading to **18**, and hence **13** is preferentially converted into **14**. The steric clash is absent in the transition state leading from *E*-crotyl precursor **11** to the IMDA cycloadduct **17**.

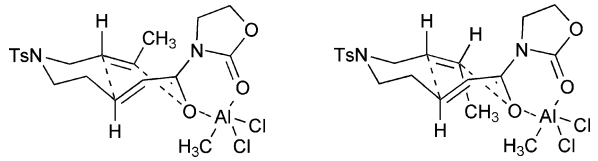
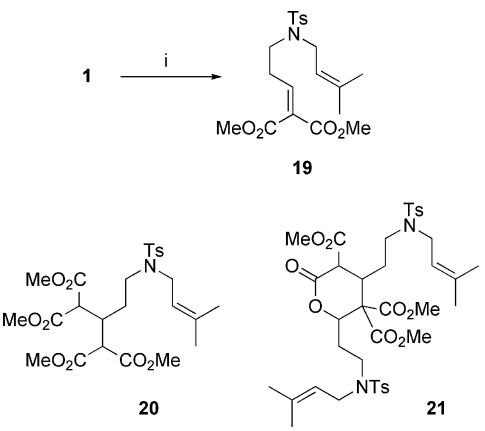


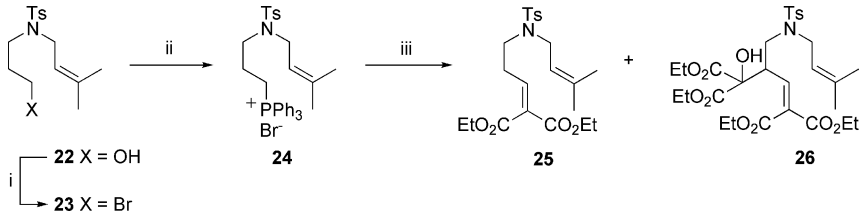
Fig. 3 Left: TS for IMDA of **11** leading to **17**. Right: TS for IMDA of **13** leading to **18**.

In an effort to provide a more highly activated enophile, while retaining the ability to chelate the Lewis acid, we turned our attention to diester **19**. The simplest route to **19** appeared to be *via* a Knoevenagel reaction between aldehyde **1** and a malonate ester (Scheme 5). Surprisingly, all attempts to prepare **19** by these means were unsuccessful. Under the standard conditions employing dimethyl malonate in the presence of piperidine and acetic acid, only trace amounts of the desired diester **19** were produced, inseparable from a complex mixture of compounds. Mass spectrometric evidence suggested side-products had resulted from the addition of a second equivalent of malonate into the α,β-unsaturated diester to give **20**, as well as a molecule consistent with **21** and higher molecular weight species likely to have resulted from base-mediated oligomerisation processes. The reportedly milder conditions employing ammonium acetate and acetic acid were similarly unsuccessful,[20] as was switching to malononitrile as the nucleophile.



Scheme 5 *Reagents and conditions*: (i) dimethyl malonate, piperidine–acetic acid or ammonium acetate–acetic acid, CH_2Cl_2, 0 → 20 °C.

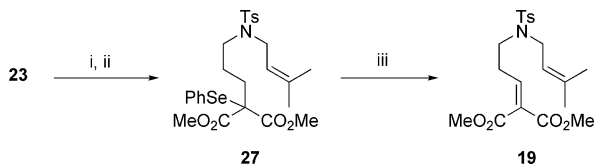
A Wittig approach to **19** leads back to aldehyde **1** and dimethyl (triphenylphosphoranylidene)malonate, or the ylide derived from phosphonium salt **24** and dimethyl ketomalonate. Since dimethyl (triphenylphosphoranylidene)malonate has been reported to be too stable to participate in Wittig reactions,[21] the latter approach was explored.



Scheme 6 *Reagents and conditions*: (i) PPh_3, CBr_4, CH_2Cl_2, 95%; (ii) PPh_3, MeCN, reflux, 87%; (iii) NaHMDS, THF, −78 → 0 °C, 2 h, then $(EtO_2C)_2C{=}O$, −78 → 20 °C.

Treatment of the previously reported[15] alcohol **22** with CBr_4 and PPh_3 to give the bromide **23**, followed by reaction with PPh_3 in refluxing acetonitrile, gave phosphonium salt **24** in excellent yield (Scheme 6). Generation of the ylide by deprotonation of **24** with NaHMDS, followed by reaction with diethyl ketomalonate§ gave the α,β-unsaturated ester **25** and also a side product identified as alcohol **26**. The reaction was capricious; in the best case, **25** was isolated in 39% yield, accompanied by 20% of **26**, resulting from deprotonation of **25** in the γ-position and reaction with another molecule of diethyl ketomalonate. Often the yield of **25** was much lower, with evidence of higher molecular weight products being formed. Variation of the base and reaction conditions, including inverse addition of the ylide to diethyl ketomalonate, did nothing to make the reaction more reliable.

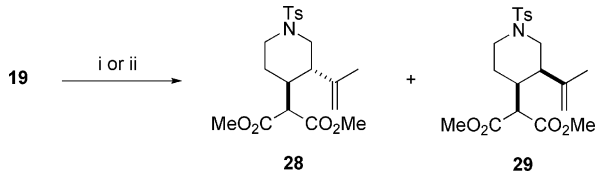
It appeared that many of the problems arose from the highly acidic γ-protons in **25**, and so we adopted an approach in which the α,β-unsaturated system was revealed at a late stage, under essentially neutral conditions (Scheme 7). Alkylation of dimethyl malonate with bromide **23** proceeded in good yield, and deprotonation by LDA with trapping of the resultant anion by phenylselenyl chloride gave phenylselenide **27** in 94% yield after chromatography. Purification of the phenylselenide allowed us to remove traces of the unreacted saturated diester, which proved inseparable from the final α,β-unsaturated product. Oxidation of **27** with hydrogen peroxide resulted in spontaneous elimination to afford diester **19** in 73% yield.



Scheme 7 *Reagents and conditions*: (i) $(MeO_2C)_2CH_2$, NaHMDS, THF, 78%; (ii) LDA, THF, −78 → 20 °C, 30 min, then PhSeCl, THF, −78 → 20 °C, 94%; (iii) H_2O_2, THF, 73%.

Cyclisation of **19** was achieved on heating in refluxing *o*-dichlorobenzene (180 °C) for 7 h to afford an inseparable 5 : 1 mixture of **28** and **29** in 70% yield, with the thermodynamically more favourable *trans* diastereomer predominating as expected (Scheme 8). Moreover, we were delighted to find that, on addition of $MeAlCl_2$, the diester **19** cyclised in CH_2Cl_2 at −78 °C to give essentially a single stereoisomeric piperidine, compound **28**, in 72% yield after chromatography. In a similar fashion, **25** gave the diethyl analogue of **28** in 67% yield. HPLC analysis revealed

§ Diethyl ketomalonate was used because dimethyl ketomalonate is not commercially available.



Scheme 8 *Reagents and conditions*: (i) *o*-dichlorobenzene, reflux, 74%; (ii) $MeAlCl_2$, CH_2Cl_2, −78 °C, 72%.

that the diastereomeric purity of both products was >200 : 1 in favour of the *trans* stereoisomer. The stereochemical assignment was confirmed by X-ray analysis of single crystals of the diethyl ester product grown from petrol and ethyl acetate (Fig. 4).

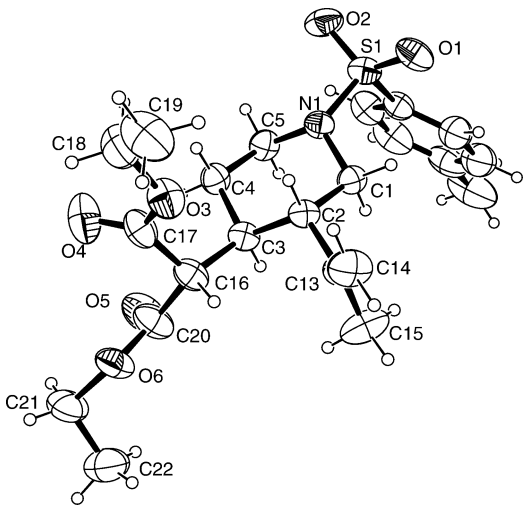
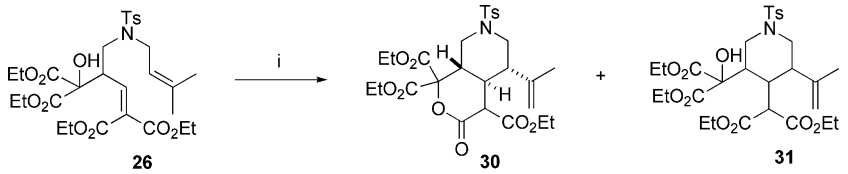


Fig. 4 ORTEP plot of diethyl ester; ellipsoids drawn at 30% probability.

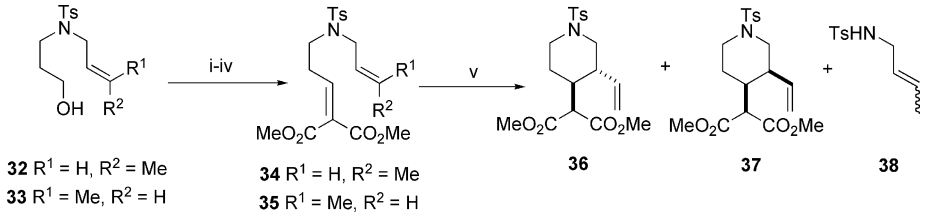
Since we had also isolated, albeit in low yield, the alcohol **26** which contained an α,β-unsaturated diester functionality, we decided to attempt the Lewis acid-catalysed cyclisation of this substrate (Scheme 9).

On treatment with two equivalents of $MeAlCl_2$ at −78 °C, **26** showed no reaction, but at room temperature, consumption of the starting material was observed to be complete after 25 h. Chromatographic purification afforded lactone **30** as the major product in approximately 70% yield, inseparable from a trace side product which mass spectrometry suggested was the alcohol **31**. Single crystals of the major product **30** were grown from petrol and ethyl acetate, and X-ray analysis confirmed the relative stereochemistry of the substituents (Fig. S4†).

Encouraged by these results, we decided to attempt the cyclisation of the *E*- and *Z*-crotyl analogues of **19**, compounds **34** and



Scheme 9 *Reagents and conditions*: (i) $MeAlCl_2$, CH_2Cl_2.



Scheme 10 *Reagents and conditions*: (i) PPh_3, CBr_4, CH_2Cl_2, 97%; (ii) $(MeO_2C)_2CH_2$, NaHMDS, THF, 63–71%; (iii) LDA, THF, −78 → 20 °C, 30 min, then PhSeCl, THF, −78 → 20 °C, 83–90%; (iv) H_2O_2, THF, 77–80%; (v) $MeAlCl_2$, CH_2Cl_2.

35. These were prepared in good yield from alcohols **32** and **33**, using the selenium route (Scheme 10).

Both substrates were sluggish to react on treatment with $MeAlCl_2$, with starting material recovered after 24 h at −78 °C. In both cases complete consumption of the starting material occurred on warming to ambient temperature. Disappointingly, *Z*-substrate **35** (5 : 1 *Z* : *E* mixture) afforded a complex mixture of products from which a small amount of the *trans* piperidine **36** could be isolated by semi-preparative HPLC. Much more pleasingly, the *E*-substrate **34** (5 : 1 *E* : *Z* mixture) gave a 20 : 1 mixture of *trans* and *cis* piperidines **36** and **37** in 60% yield. The amino alkene **38** was isolated in 28% yield, accounting for almost all of the remaining starting material.

In conclusion, we have shown that a number of acyclic precursors will undergo ene cyclisation on heating or under Lewis acid catalysis, to afford 3,4-disubstituted or 3,4,5-trisubstituted piperidines. The balance between the desired ene cyclisation and the competing hetero-Diels–Alder reaction is a delicate one, and the product distribution is influenced by the activating group on the enophile, the nature of the ene component, and the Lewis acid used. Oxazolidinones **7**, **11** and **13** underwent Lewis acid-catalysed cyclisation to afford mixtures of ene and hetero-Diels–Alder products, while diesters **19** and **25** underwent a highly diastereoselective ene cyclisation catalysed by $MeAlCl_2$ at −78 °C to afford almost exclusively the corresponding *trans* piperidines in good yield (diastereomeric ratio >200 : 1). The *E*-crotyl diester **34** with the slightly less nucleophilic ene moiety gave the corresponding *trans* piperidine in 60% yield with a 20 : 1 diastereomeric ratio, along with products derived from Lewis acid-catalysed decomposition. This stereoselective approach to piperidines should find application in the synthesis of more complex targets.

Experimental

General chemical procedures

All chemicals and reagents were obtained from commercial sources and used without further purification unless otherwise stated. THF and diethyl ether were distilled from sodium benzophenone ketyl. Toluene was distilled from sodium. CH_2Cl_2 and acetonitrile were distilled from CaH_2. Anhydrous DMF was purchased from Aldrich. Triethylamine was distilled from KOH and stored over KOH pellets. Diisopropylamine was distilled over NaOH and stored over 4 Å molecular sieves. Solutions of *n*-BuLi were titrated against *N*-pivaloyl-*o*-toluidine following Suffert's method.[22] Flash column chromatography was performed using laboratory-grade solvents on Fluorochem 60A (43–63 μm mesh) silica gel. Thin layer chromatography was carried out using Merck 60 F_{254} 0.25 mm precoated glass-backed silica gel plates and visualised using UV light (254 nm) and basic $KMnO_4$ solution. All R_f values refer to the eluent used in purification unless otherwise stated.

Melting points were measured in open glass capillaries using a Stuart Scientific SMP1 apparatus and are uncorrected.

Elemental analyses were recorded on a Carlo Erba EA1110 simultaneous CHNS analyser.

Infrared spectra were recorded between NaCl plates as neat films, as $CHCl_3$ films or as KBr discs on a Perkin Elmer 1600 series FTIR or a Perkin Elmer FT-IR Paragon 1000 spectrometer.

^1H, ^{13}C, ^{19}F and ^{31}P NMR spectra (300, 75, 282 and 121 MHz respectively) were recorded on Bruker AC-300 and Bruker AV-300 spectrometers. HSQC, HMBC, COSY 90, ^1H and ^{13}C NMR spectra were recorded on a Bruker DRX500 (500 MHz and 125 MHz for ^1H and ^{13}C) or a Bruker AMX400 spectrometer (400 MHz and 100 MHz for ^1H and ^{13}C). ^1H and ^{13}C NMR spectra were recorded using deuterated solvent as the lock and were referenced downfield from tetramethylsilane. ^{13}C spectra NMR were recorded using the PENDANT pulse sequence. *J* values are reported in Hz. The multiplicities of the spectroscopic signals are represented in the following manner; s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, m = multiplet, br s = broad singlet and env = overlapping signals.

Chemical ionisation (CI) and electron impact (EI) mass spectra were recorded on a VG Zabspec mass spectrometer or a VG Prospec mass spectrometer. Chemical ionisation (CI) methods used ammonia as the carrier gas. Liquid secondary ion mass spectra (LSIMS) were recorded using a VG Zabspec instrument. A Micromass LCT mass spectrometer was used for both low-resolution electrospray time of flight (ES-TOF) mass spectrometry

(using a methanol mobile phase) and accurate mass measurement (using a lock mass incorporated into the mobile phase).

HPLC was carried out using Dionex Summit HPLC systems and monitored using Chromeleon 6.11 software. The analytical and semi-preparative systems both incorporated a Summit P580 Quaternary Low Pressure Gradient Pump with built-in vacuum degasser and a Summit UVD 170 s UV/Vis Multi-Channel Detector with analytical flow cell. Analytical HPLC was performed using a Phenomenex Luna 10 μ C18 (250 mm × 4.6 mm) column using either water–acetonitrile or water–methanol methods at a flow rate of 1.0 mL min^{-1}. Semi-preparative HPLC was carried out on a Phenomenex Luna 10 μ C18 (250 mm × 10 mm) column using either water–acetonitrile or water–methanol methods at a flow rate of 5.0 mL min^{-1}.

Single-crystal data were recorded at room temperature on a Bruker Smart 6000 diffractometer equipped with a CCD detector and a copper tube source. Structures were solved and refined using SHELX97.[23] Non-hydrogen atoms were refined anisotropically and a riding model was used for C-H hydrogen atoms.

N-(3-Bromopropyl)-4-methyl-*N*-(3-methylbut-2-enyl)-benzenesulfonamide (23)

Triphenylphosphine (2.29 g, 8.74 mmol) was added to a solution of alcohol **22** (2.0 g, 6.72 mmol) in CH_2Cl_2 (10 cm^3) at ambient temperature. The reaction mixture was stirred for 5 min before carbon tetrabromide (2.90 g, 8.74 mmol) was added and the reaction mixture was stirred for a further 2 h. Removal of the CH_2Cl_2 *in vacuo* followed by flash column chromatography (silica; eluent 8 : 1 hexane–ethyl acetate) gave bromide **23** as a white crystalline solid (2.28 g, 94%); R_f = 0.30; mp = 62–65 °C (from hexane–ethyl acetate); Found: C, 50.23; H, 6.03; N, 3.85. $C_{15}H_{22}BrNO_2S$ requires C, 50.00; H, 6.15; N, 3.89%; ν_{max}(KBr disc)/cm^{-1} 2979 (CH), 2930 (CH), 1676 (C=C), 1673 (C=C), 1596 (ArC=C), 1340 (SO_2), 1161 (SO_2); δ_H (300 MHz) 1.63 (3 H, s, CH_3), 1.67 (3 H, s, CH_3), 2.07–2.16 (2 H, m, CH_2CH$_2$N), 2.43 (3 H, s, CH_3), 3.18 (2 H, t, *J* 7.0, CH$_2$CH_2N), 3.42 (2 H, t, *J* 6.4, CH_2Br), 3.77 (2 H, d, *J* 7.0, CHCH_2N), 4.97–5.03 (1 H, m, CHCH$_2$N), 7.30 (2 H, d, *J* 8.3, Ar CH), 7.69 (2 H, d, *J* 8.3, Ar CH); δ_C (75 MHz) 17.9 (CH$_3$), 21.6 (CH$_3$), 25.9 (CH$_3$), 30.7 (*C*H$_2$CH$_2$Br), 32.3 (*C*H$_2$Br), 46.1 (CH*C*H$_2$N), 46.5 (CH$_2$*C*H$_2$N), 118.8 (*C*HCH$_2$N), 127.3 (CH, Ar), 129.7 (CH, Ar), 136.6 (C^4), 137.4 (C^4), 143.3 (C^4); *m*/*z* (ES$^+$) 384 ([M(^{81}Br) + Na]$^+$, 90%), 382 ([M(^{79}Br) + Na]$^+$, 100); HRMS (ES$^+$) Found: 382.0446, required for $C_{15}H_{22}{}^{79}BrNO_2SNa$: 382.0452.

2-[4-Aza-7-methyl-4-(*p*-toluenesulfonyl)oct-6-enyl]malonic acid dimethyl ester

NaHMDS (5.55 mL, 11.10 mmol, 2 M solution in THF) was added dropwise to a solution of dimethyl malonate (1.27 mL, 1.47 g, 11.11 mmol) in THF (20 mL) at 0 °C. The mixture was stirred for 30 min and allowed to warm to ambient temperature before cooling to 0 °C. A solution of bromide **23** (2.06 g, 5.72 mmol) in THF (20 mL) was added dropwise and the reaction allowed to warm to ambient temperature. After stirring for 18 h the solvent was removed *in vacuo* and the residue dissolved in ethyl acetate (100 mL) and poured into water (100 mL). The aqueous phase was extracted with ethyl acetate (4 × 100 mL) and the combined organic extracts washed with brine (100 mL), dried over $MgSO_4$ and concentrated *in vacuo* before purification by flash column chromatography (silica; eluent 3 : 1 hexane–ethyl acetate) afforded the *title compound* as a colourless oil (1.83 g, 78%); R_f = 0.27; Found: C 58.22, H 7.28, N 3.49; Required for $C_{20}H_{29}NO_6S$: C 58.37, H 7.10, N 3.40; ν_{max} (film)/cm^{-1} 2955 (CH), 1739 (C=O), 1736 (C=O), 1598 (Ar C=C), 1437 (Ar C=C), 1340 (SO_2), 1159 (SO_2); δ_H (300 MHz) 1.45–1.63 (8 H, env, including 1.56 (3 H, s, CH$_3$), 1.60 (3 H, s, CH$_3$) and CH$_2$), 1.79–1.90 (2 H, m, CH$_2$), 2.37 (3 H, s, CH$_3$), 3.04 (3 H, t, *J* 7.4, CH$_2$CH_2N), 3.32 (1 H, t, *J* 7.4, CH(CO$_2$CH$_3$)$_2$), 3.68 (6 H, s, 2 × CO$_2$CH$_3$), 3.72 (2 H, d, *J* 7.0, NCH_2CH), 4.86–4.96 (1 H, t, *J* 7.1, NCH$_2$CH), 7.25 (2 H, d, *J* 8.1, Ar CH), 7.62 (2 H, d, *J* 8.1, Ar CH); δ_C (75 MHz) 18.0 (CH$_3$), 21.7 (CH$_3$), 26.0 (CH$_3$), 26.1 (CH$_2$), 26.4 (CH$_2$), 45.7 (CH$_2$), 46.8 (CH$_2$), 51.3 (*C*H(CO$_2$CH$_3$)$_2$), 52.7 (2 × CO$_2$*C*H$_3$), 119.1 (NCH$_2$*C*H), 127.4 (CH, Ar), 129.8 (CH, Ar), 137.1 (C^4), 137.2 (C^4), 143.3 (C^4), 169.8 (C=O); *m*/*z* (ES$^+$) 434.1 (100% [M + Na]$^+$); HRMS (ES$^+$) Found: 434.1624, required for $C_{20}H_{29}NO_6SNa$: 434.1613.

2-[4-Aza-7-methyl-4-(*p*-toluenesulfonyl)oct-6-enylidine]malonic acid dimethyl ester (19)

n-BuLi (2.1 M solution in hexanes, 1.30 mL, 2.73 mmol) was added to a stirred solution of diisopropylamine (0.50 mL, 0.36 g, 3.55 mmol) in THF (20 mL) at −78 °C. The mixture was stirred at −78 °C for 15 min before warming to ambient temperature and stirring for a further 15 min. The resulting solution of LDA was returned to −78 °C and a solution of 2-[4-aza-7-methyl-4-(*p*-toluenesulfonyl)oct-6-enyl]malonic acid dimethyl ester (1.00 g, 2.43 mmol) in THF (20 mL) was added dropwise. The mixture was allowed to warm to ambient temperature and stirred for 1 h before cooling to −78 °C. A solution of PhSeCl (0.70 g, 3.64 mmol) in THF (20 mL) was added dropwise and the reaction stirred for 18 h. The resulting bright yellow solution was poured into water (100 mL) and the aqueous phase extracted with ethyl acetate (4 × 100 mL). The organic extracts were washed with saturated $NaHCO_3$ solution (100 mL), brine (100 mL), dried over $MgSO_4$ and concentrated *in vacuo* to afford a yellow oil, which was purified by column chromatography (silica; eluent 15 : 1 toluene–diethyl ether) to afford the selenide **27** as a yellow oil (1.29 g, 94%) which was used immediately; R_f = 0.53; ν_{max} (film)/cm^{-1} 2983 (CH), 1739 (C=O), 1598 (Ar C=C), 1439 (Ar C=C), 1374 (SO_2), 1162 (SO_2); δ_H (300 MHz) 1.60–1.74 (9 H env, including 1.60 (3 H, s, CH$_3$), 1.64 (3 H, s, CH$_3$), and CH_2CH$_2$CH$_2$N or CH_2CH$_2$N)), 1.76–1.88 (2 H, m, CH_2CH$_2$CH$_2$N or CH_2CH$_2$N), 2.41 (3 H, s, CH$_3$), 3.02 (2 H, t, *J* 7.2, CH$_2$CH_2N), 3.70 (6 H, s, 2 × CO$_2$CH$_3$), 3.76 (2 H, d, *J* 7.2, NCH_2CH), 4.90–4.99 (1 H, t, *J* 7.2, NCH$_2$CH), 7.23–7.36 (4 H, Ar CH), 7.37–7.45 (1 H, Ar CH), 7.53 (2 H, d, *J* 8.1, Ar CH), 7.66 (2 H, d, *J* 8.1, Ar CH); δ_C (75 MHz) 18.1 (CH$_3$), 21.8 (CH$_3$), 24.9 (CH$_2$), 26.1 (CH$_3$), 31.3 (CH$_2$), 45.8 (CH$_2$), 46.9 (CH$_2$), 53.3 (2 × CO$_2$*C*H$_3$), 59.7 (C^4), 119.3 (NCH$_2$*C*H), 126.6 (C^4), 127.5 (CH, Ar), 129.3 (CH, Ar), 129.9 (CH, Ar), 130.2 (CH, Ar), 137.3 (C^4), 137.4 (C^4), 138.3 (CH, Ar), 143.3 (C^4), 169.6 (C=O); *m*/*z* (ES$^+$) 590 (100% [M + Na]$^+$).

H_2O_2 (0.47 mL, 30% aqueous solution, 4.15 mmol) was added to a solution of selenide **27** (1.17 g, 2.07 mmol) in THF (30 mL) at ambient temperature and stirred for 16 h. The mixture was poured into water (100 mL) and the aqueous phase extracted with ethyl acetate (4 × 100 mL). The organic extracts were washed

with saturated Na_2CO_3 solution (100 mL), dried over $MgSO_4$ and concentrated *in vacuo* to give a pale yellow oil. Purification by flash column chromatography (silica; eluent 15 : 1 toluene–diethyl ether) afforded the α,β-unsaturated diester **19** as a colourless oil (0.62 g, 73%); $R_f = 0.45$; ν_{max} (film)/cm^{-1} 2955 (CH), 2941 (CH), 1752 (C=O), 1731 (C=O), 1649 (C=C), 1598 (Ar C=C), 1494 (Ar C=C), 1438 (Ar C=C), 1339 (SO_2), 1160 (SO_2); δ_H (300 MHz) 1.60 (3 H, s, CH_3), 1.65 (3 H, s, CH_3), 2.41 (3 H, s, CH_3), 2.58 (2 H, apparent q, *J* 7.4, CH_2CH_2N), 3.17 (2 H, t, *J* 7.4, CH_2CH_2N), 3.70–3.81 (8 H, env, including 3.77 (3 H, s, CO_2CH_3), 3.80 (3 H, s, CO_2CH_3) and NCH_2CH)), 4.91–5.02 (1 H, t, *J* 7.1, NCH_2CH), 6.98 (1 H, t, *J* 7.4, C*H*CH_2CH_2N), 7.28 (2 H, d, *J* 8.1, Ar CH), 7.67 (2 H, d, *J* 8.1, Ar CH); δ_C (75 MHz) 18.1 (CH_3), 21.8 (CH_3), 26.1 (CH_3), 30.1 (CH_2), 45.9 (CH_2), 46.4 (CH_2), 52.7 (CO_2CH_3), 52.8 (CO_2CH_3), 119.0 (NCH_2CH) 127.6 (CH, Ar), 129.8 (C^4), 130.0 (CH, Ar), 136.9 (C^4), 137.9 (C^4), 143.6 (C^4), 146.6 (*C*HCH$_2$CH$_2$N), 164.4 (C=O), 165.7 (C=O); *m*/*z* (ES^+) 432.1 (100% $[M + Na]^+$); HRMS (ES^+) Found: 432.1463, required for $C_{20}H_{27}NO_6SNa$: 432.1457.

(3*S,4*S**)-4-[Bis(carbomethoxy)methyl]-3-isopropenyl-1-(*p*-toluenesulfonyl)piperidine (28)**

$MeAlCl_2$ (1 M solution in hexanes, 488 μL, 0.488 mmol) was added dropwise to a solution of diester **19** (200 mg, 0.488 mmol), in CH_2Cl_2 (10 mL) under argon at −78 °C. The reaction was stirred for 5 h before being quenched by addition of water (10 mL). The aqueous phase was extracted with CH_2Cl_2 (4 × 10 mL) and the organic extracts washed with brine (10 mL), dried over $MgSO_4$ and concentrated *in vacuo* to give a colourless oil which was purified by flash column chromatography (silica; eluent 3 : 1 hexane–ethyl acetate) to afford exclusively the *trans* piperidine **28** as a colourless oil (143 mg, 72%); $R_f = 0.36$; mp 97–100 °C (from hexane–ethyl acetate); Found: C 58.67, H 6.89, N 3.31; Required for $C_{20}H_{27}NO_6S$: C 58.66, H 6.65, N 3.42; ν_{max} (film)/cm^{-1} 2953 (CH), 2848 (CH), 1733 (C=O), 1645 (C=C), 1598 (Ar C=C), 1437 (Ar C=C), 1342 (SO_2), 1165 (SO_2); δ_H (300 MHz) 1.58–1.74 (4 H, env, including 1.65 (3 H, s, CH_3) and C*H*HCH$_2$N), 1.84–2.14 (3 H, env, including 2.08 (1 H, t, *J* 11.3, NC*H*HCH), CH*H*CH$_2$N and C*H*CH$_2$CH$_2$N), 2.25 (1 H, dt, *J* 12.0, 2.5, CH$_2$C*H*HN), 2.36 (1 H, dt, *J* 11.3, 3.8, NCH_2CH) 2.43 (3 H, s, CH_3), 3.56 (1 H, d, *J* 3.3, C*H*(CO_2CH_3)$_2$), 3.67 (3 H, s, CO_2CH_3), 3.69–3.87 (5 H, env, including 3.71 (3 H, s, CO_2CH_3), NCH*H*CH and CH_2CHHN), 4.77 (1 H, s, C=C*H*H), 4.93 (1 H, s, C=CH*H*), 7.32 (2 H, d, *J* 8.1, Ar CH), 7.62 (2 H, d, *J* 8.1, Ar CH); δ_C (100 MHz) 20.7 (CH_3), 21.5 (CH_3), 26.8 (*C*H$_2$CH$_2$N), 38.4 (*C*HCH$_2$CH$_2$N), 46.5 (NCH_2CH), 46.6 (CH_2CH_2N), 51.1 (NCH_2CH), 52.1 (*C*H(CO_2CH_3)$_2$), 52.4 (CO_2CH_3), 52.6 (CO_2CH_3), 115.2 (C=*C*H$_2$), 128.3 (CH, Ar), 130.3 (CH, Ar), 133.8 (C^4), 144.0 (C^4), 144.3 (C^4), 169.2 (C=O), 170.2 (C=O); *m*/*z* (ES^+) 432.0 (100% $[M + Na]^+$); HRMS (ES^+) Found: 432.1466, required for $C_{20}H_{27}NO_6SNa$: 432.1457.

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