On the steric acceleration of ene reactions

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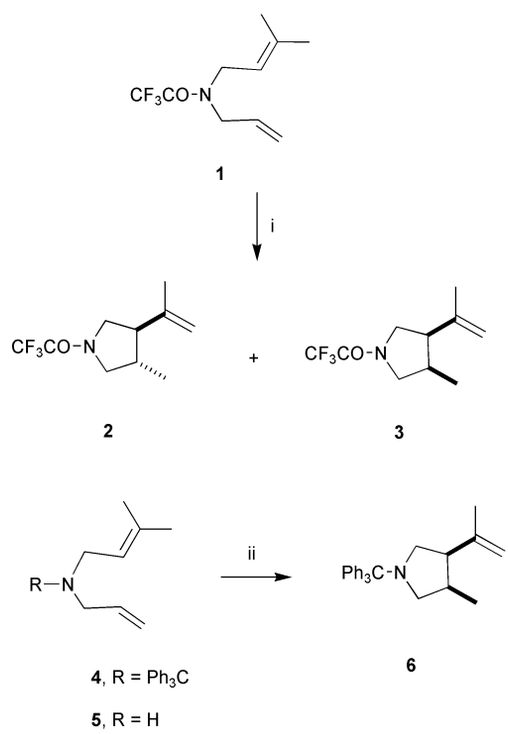
Steric buttressing, using the removable trityl group as a protecting group for substituted allylamines, is used to effect selective cycloadditions and uncatalysed ene reactions under remarkably mild conditions.

The ene reaction is a synthetically useful process that has been exploited in a wide range of chemistry.[1] Normally the ene reaction requires the use of heating at temperatures greater than 140 °C to proceed and, for systems where the enophile is not activated by an electron-withdrawing group, *much* higher temperatures are often required.[2] For systems with electron-deficient enophiles, the process may be catalysed with Lewis acids, whereby the reaction has been observed to proceed at ambient temperatures[3] but such catalysis is not generally effective for non-activated enophiles.

The stereochemistry of the ene process has also been examined and, under vigorous thermal conditions, stereocontrol is often lost. Thus, heating the simple dimethylallylamino compound **1** at 220 °C for 30 min effects an intramolecular ene process and converts it into the mixture of *cis*- and *trans*-pyrrolidines **2** and **3**[4] (Scheme 1). The latter compounds are of

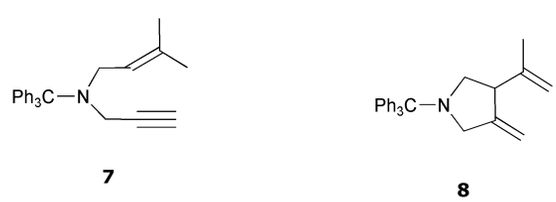


Scheme 1 *Conditions*: i, 220 °C, 30 min; ii, 140 °C, 4 days.

interest as members of the kainic acid family of neuroactive agents,[5] the natural stereoisomer being the *cis*-isomer **3**. Any method for controlling the stereochemistry of the intramolecular ene process in order to maximise the selectivity for producing either the *cis*- or *trans*-stereoisomers would therefore be of great synthetic value.

We have previously used steric buttressing as an aid to assisting cycloaddition reactions;[6] herein we describe examples of use of the trityl steric buttress that assists ene reactions to occur under uncatalysed and relatively low temperature conditions. A preliminary account of this work has been published.[7]

As an initial model system, the trityl-protected *N*-allyl-*N*-dimethylallylamine **4**, prepared by standard methods, was heated in xylene, under argon at 140 °C, for 100 h, by which time all the starting material had disappeared. The reaction produced the ene product **6** in almost quantitative yield. The product was isolated as predominantly one isomer (>95%), assigned, from ^{1}H NOE experiments, as the *cis*-isomer indicated. The *cis*-isomer is known to be the preferred stereoisomer in analogous carbocyclic ene reactions.[2] That a buttressing effect is operating was supported by the observation that no sign of any cyclisation product was obtained upon heating the parent amine **5** under these conditions for extended periods (several weeks). The ease of the buttressed cyclisation, compared with the harsh conditions normally reported for unactivated ene reactions,[2] led us to seek other examples of the sterically assisted ene process. Thus the corresponding propargylamine† derivative **7** was smoothly transformed into the ene-product **8** by heating at 110 °C for 72 h.



In earlier work we had shown that, on heating, the protected *N*-allylfurfurylamine **9** undergoes intramolecular cycloaddition to form the adduct **10**.[8] At room temperature this cycloaddition is slow (months) and the furan ring of the open form could be made to react in a competitive manner by intermolecular cycloaddition to a dienophile. Thus dimethyl butynedioate reacted with compound **9** at room temperature to form the adduct **11**. On heating, this adduct underwent a retro-Diels–Alder reaction to release the acetylenic ester and reform the starting material **9**, which then cyclised intramolecularly to form **10** (Scheme 2).

† The IUPAC name for propargyl is prop-2-ynyl.

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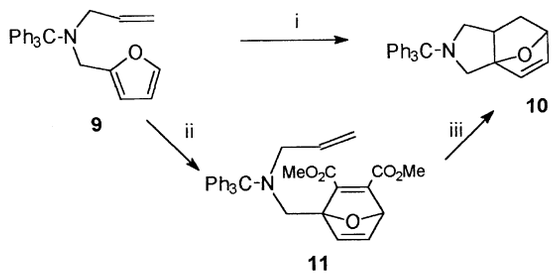
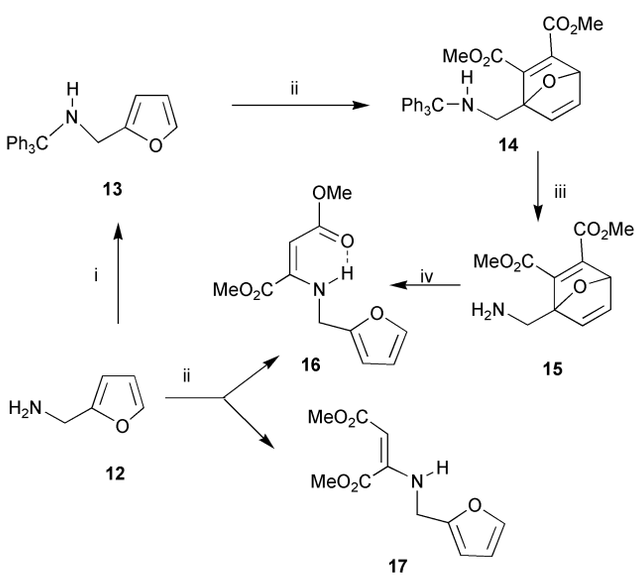


Scheme 2 *Reagents and conditions*: i, 120 °C, 24 h; ii, $MeO_2C–C{\equiv}C–CO_2Me$, rt; iii, 120 °C.

Incidentally, the behaviour of the trityl-protected furfurylamine **13** with dimethyl butynedioate was also studied. This also gave the expected cycloadduct **14** in good yield at room temperature. In its ^{1}H NMR spectrum, it showed loss of the furan ring signals and a characteristic pattern for the ring protons of the oxa-bridged cyclohexadiene system. Deprotection of the cycloadduct **14** with dilute hydrochloric acid in ethanol gave the unstable amine **15** (Scheme 3). On heating this amine

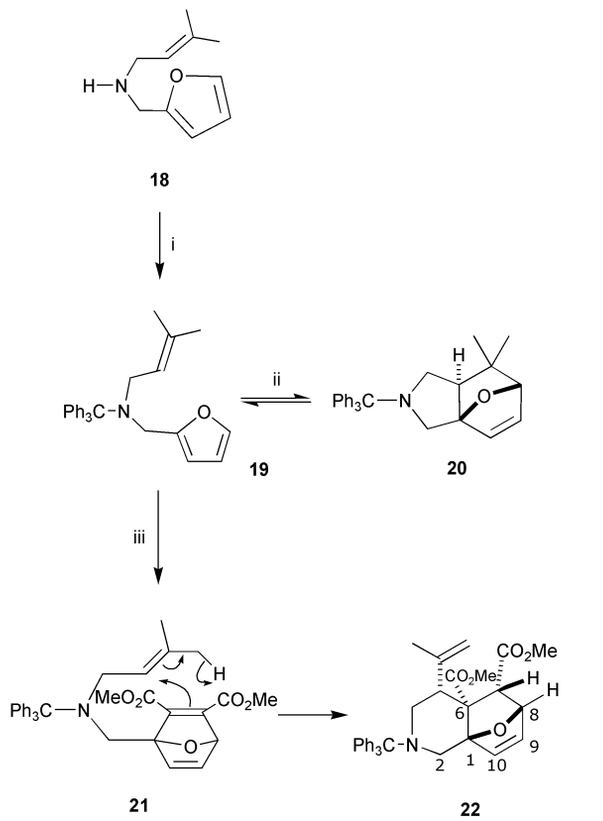


Scheme 3 *Reagents and conditions*: i, Ph_3CCl; ii, $MeO_2C–C{\equiv}C–CO_2Me$, rt; iii, aq. HCl in EtOH; iv, 110 °C.

rearranged to a new isomeric product, shown to be the thermodynamic product **16** obtained from the reaction of furfurylamine **12** with dimethyl butynedioate. The (*Z*)-configuration about the olefinic bond was confirmed by the presence of the intramolecular hydrogen bond between the amino group and the adjacent ester group. This material was identical to one of the two isomers produced by the direct reaction of dimethyl butynedioate with furfurylamine **12**, the other, kinetic, product being the (*E*)-isomer **17**, which, on heating, was converted into the stable isomer **16**. No cycloadducts across the furan ring were obtained in these model studies with the parent furfurylamine **12**. Presumably the thermal rearrangement of the unstable amine **15** into the adduct **16** also involves a retro-Diels–Alder process, the furfurylamine then reacting *via* addition of the amino group to the triple bond of the released butynedioate.

Since the maleic ester group in the intermediate **14** could behave as an enophile, the possibility of using this type of structure in an intramolecular ene reaction was examined. This required preparation of the dimethylallyl analogue **19**, which was obtained by tritylation of the secondary amine **18**, itself prepared *via* alkylation of the trifluoroacetamide of furfurylamine, followed by base-catalysed hydrolysis (see Experimental section).

The intramolecular cycloaddition reaction across the furan group is sensitive to the presence of alkyl substituents on the allylic group and the dimethylallyl derivative **19** undergoes incomplete cyclisation on heating, the corresponding cycloadduct **20** only forming in 80% yield, in equilibrium with uncyclised amine[9] (Scheme 4).



Scheme 4 *Reagents and conditions*: i, Ph_3CCl; ii, 140 °C, 7 days; iii, $MeO_2C–C{\equiv}C–CO_2Me$, rt, 5 days.

When the tritylated amine **19** was allowed to react with dimethyl butynedioate at room temperature over five days, a new product formed in high yield. However, the compound was *not* the expected Diels–Alder product **21** but, instead, the ene product **22**, isolated as a crystalline solid, mp 164–166 °C.

In its ^{1}H NMR spectrum compound **22** showed loss of the isopropylidene group and the furan ring protons and formation of an isopropenyl group. The ring protons showed as a tightly coupled system. An extensive NMR study allowed the assignment of the relative stereochemistry of this product as indicated in structure **22**; assignments and coupling constants are given in Tables 1 and 2. ^{1}H–^{1}H COSY experiments showed the expected cross peaks. The small W-coupling ^4J between H-2$_{eq}$ and H-4$_{eq}$ of 2.1 Hz allows an unambiguous assignment of these protons. The H-5 proton couples by a ^3J to H-4$_{ax}$ in an axial–axial manner, indicating that the isopropenyl substituent must adopt an equatorial position on the azacyclohexane ring. The relative stereochemistry at positions 6 and 7 is derived from two spectroscopic arguments. First, NOE difference spectra show a strong NOE effect between the two methoxy groups, indicating that their *syn* arrangement is retained in the cycloaddition–ene cascade reaction, as expected. Second, a weak NOE is observed between the two methoxy groups and the olefinic protons, H-9 and H-10. These observations indicate that the methoxycarbonyl groups must be in an *endo*-position with respect to the double bond; some of these NOE results are summarised in Fig. 1. Further support for this assignment and the relative stereochemistry of C-7 and C-8 comes from comparison of established values of coupling constants in structurally related camphor systems.[10] According to the Karplus relationship a

Table 1 Assignment of ^{1}H NMR signals to compound **22**, in $CDCl_3$

Assignment[a]	Chemical shift, δ (ppm)	Coupling constants, J/Hz
H-2 (ax)	2.52, d	$^2J = 12.9$
H-2 (eq)	3.59, dd	$^2J = 12.9$, $^4J = 2.1$
H-4 (ax)	2.11, t	$^2J = {}^3J = 11.8$
H-4 (eq)	2.97, dd	$^2J = 11.8$, $^4J = 2.1$
H-5 (ax)	3.04, d	$^3J = 11.8$
H-7	3.35, d	$^3J_{\text{H-7, H-8}} = 4.2$
H-8	5.92, dd	$^3J_{\text{H-7, H-8}} = 4.2$; $^3J_{\text{H-8, H-9}} = 1.6$
H-9	6.74, dd	$^3J_{\text{H-9, H-10}} = 5.7$, $^3{}_{\text{H-8, H-9}} = 1.6$
H-10	5.92, d	$^3J = 5.7$
C=CH [*pro*-(*E*)][b]	4.58, s	
C=CH [*pro*-(*Z*)][b]	4.75, s	
COO*Me* (C-6)	3.63, s	
COO*Me* (C-7)	3.25, s	
=C*Me*	1.76, s	

[a] All assignments from H–H-COSY and H–C-HMBC experiments. [b] Assignments from NOE difference spectra.

Table 2 Assignment of ^{13}C NMR signals to compound **22**, in $CDCl_3$

Assignment	Chemical shift, δ (ppm)[a]	Assignment argument
C-1	90.1 (q)	DEPT-HMBC
C-2	48.0 (−)	HSQC-DEPT
C-4	49.9 (−)	HSQC-DEPT
C-5	56.9 (+)	HSQC-DEPT
C-6	62.3 (q)	DEPT-HMBC
C-7	56.9 (+)	HSQC
C-8	81.0 (+)	HSQC
C-9	139.1 (+)	HSQC
C-10	135.7 (+)	HSQC
C-6 (COOMe)	52.1 (+), 172.3 (q)	HMBC, DEPT, HSQC
C-7 (COOMe)	51.4 (+), 171.1 (q)	HMBC, DEPT, HSQC
Isopropenyl	113.5 (−), 145.2 (q), 23.5 (+)	HMBC, DEPT, HSQC
Trityl	128.0 (+), 127.9 (+), 126.5 (+), 135.1 (q)	

[a] (+) refers to CH_3 or CH, (−) to CH_2 and (q) to quaternary carbons in the DEPT experiment.

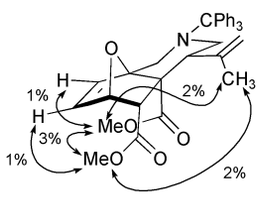
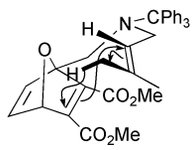


Fig. 1 NOE correlations found for compound **22**.

^3J H-8–H-7$_{exo}$ coupling constant of 4–5 Hz would be expected, as observed, whereas the corresponding H-8–H-7$_{endo}$ coupling constant would be in the range 0–1 Hz.

The preferred transition state leading to the ene product **22** is thus as indicated by structure **21a** and involves reaction from the least hindered *exo*-face of the oxabicycloheptadiene system. It is noteworthy that the ene reaction involves a type 1 process of a 1,7-diene system that would normally proceed in only modest yields at very high temperatures.[2,11]



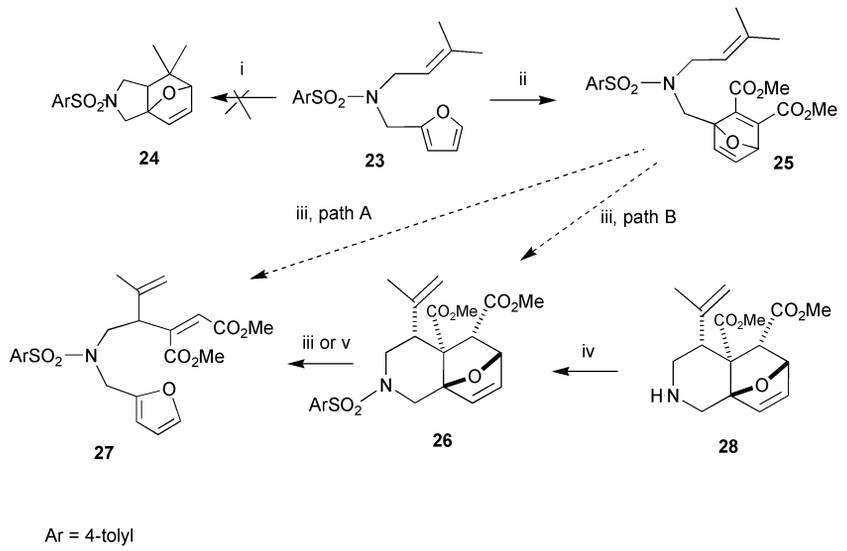
21a

In order to ascertain whether or not the formation of this ene product is principally due to the steric buttressing of the bulky trityl group, a comparison with a model compound incorporating a 'smaller' buttress was made. This was the toluene-4-sulfonamide derivative **23**. The arylsulfonyl group can act as a steric buttress but it is not as effective as the trityl group.[6] Heating compound **23** at 140 °C in xylene for several days gave no indication of the intramolecular cyclisation product **24**.

Reaction of the sulfonamide **23** with dimethyl butynedioate was allowed to proceed for two weeks at room temperature before working up. A new compound slowly formed but this was found to be the intermolecular cycloadduct **25** and *not* the ene product corresponding to compound **22** (see Scheme 4), *viz.* compound **26**. We therefore deduce that the intramolecular ene reaction, **21** to **22**, is effected because of the tight buttressing of the dimethylallyl group and the double bond of the cycloadduct **21**, caused by the presence of the space-demanding trityl group.

Heating the intermolecular cycloadduct **25** in toluene at 110 °C caused an isomerisation and the furan derivative **27** was formed. The formation of the latter could either occur by a *retro*-Diels–Alder process, with extrusion of dimethyl butynedioate, followed by an intermolecular ene reaction (Scheme 5, path A), or, alternatively, involve the transient formation of the ene product **26**, followed by an intramolecular *retro*-Diels–Alder process to give compound **27** (Scheme 5, path B). By conducting the reaction at 70 °C over a period of several days, transient formation of an intermediate corresponding to the ene product **26** could be detected but this was never at a proportion greater than 20% and decayed as the final isomer **27** formed.

In order to prove that the intermediate **26** lay on the pathway between compounds **25** and **27**, an authentic sample was prepared by deprotection of the tritylated ene product **22** at room temperature, to give the amine **28**, followed by tosylation. The pure sample of compound **26** was reasonably stable at room temperature but, on heating to 70 °C, slowly isomerised to the furan derivative **27**, proving it is the intermediate and that the conversion of **25** to **27** follows path B (Scheme 5). Of note is the observation that heating the tritylated cycloadduct **22** at



Scheme 5 *Reagents and conditions*: i, 140 °C, xylene, 7 days; ii, $MeO_2C–C\equiv C–CO_2Me$, rt, 22 days; iii, 100 °C, toluene, 20 h; iv, toluene-4-sulfonyl chloride, pyridine, rt; v, 70 °C, 12 h.

temperatures up to 110 °C does *not* lead to the *retro*-Diels–Alder process and that no tritylated compound corresponding to the furan **27** is observed. Thus the trityl group not only acts as a stimulus for the ene process (*viz.* **21** to **22**) but also holds the cyclic product together, preventing the *retro*-Diels–Alder reaction from occurring.

This assumption is fully compatible with molecular modelling studies; Fig. 2 shows a view of the starting cycloadducts **21** and **25**, adopting the conformation leading to the ene reaction in their energy-minimised conformations.[12] It is clear that the steric crowding is much more evident in the presence of the trityl buttress than when using the much smaller sulfonamide group. Furthermore, in the trityl derivative **21**, the ene reaction centres (depicted in Fig. 2) between the transferred hydrogen and the alkene bond terminus are held much more closely together in space than they are in the corresponding sulfonamide derivative **25**. In the former both the dimethylallyl group and the bicyclic moiety have much less conformational freedom (space in which to move) than in the latter.

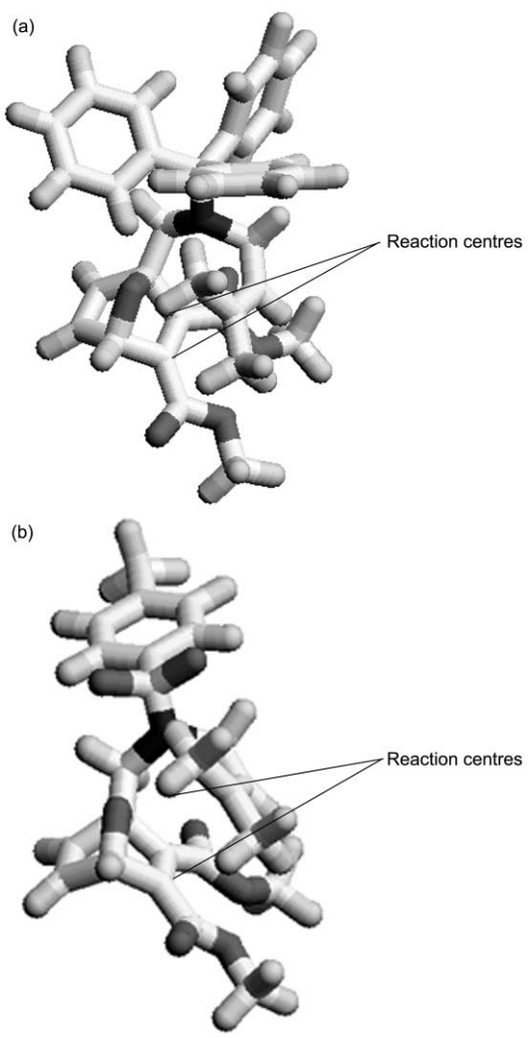


Fig. 2 a) Reactive conformation leading from **21** to **22**; energy minimised using the MM3 geometry optimisation algorithm in Alchemy 2000.[12] b) Reactive conformation leading from **25** to **26**.

Experimental

Melting points were determined on a Kofler hot-stage apparatus and are uncorrected. Mass spectra were obtained from the EPSRC National Mass Spectrometry Service Centre, Swansea; infrared spectra were obtained on a Perkin Elmer System 2000 FTIR spectrometer, as either liquid films or as Nujol mulls. ^{1}H NMR spectra were obtained on a Bruker AC300 at 300 MHz using solutions in $CDCl_3$ with tetramethylsilane as internal reference; chemical shifts are quoted in ppm and coupling constants in Hz. The detailed stereochemical studies on structure **22** were carried out on a Bruker DRX500 Avance instrument using $CDCl_3$ as solvent. Microanalytical determinations were carried out by MEDAC Ltd, Englefield Green, Surrey. Thin layer chromatography was carried out using 0.25 mm GF60A silica plates and column chromatography utilised Sorbisil silica, particle size 50–200 μm (70–290 mesh). Solvent ratios are in volumes prior to mixing. Dichloromethane solvent was dried over calcium hydride and then distilled. THF was obtained dry by distillation in the presence of benzophenone–sodium. Other solvents were purified and dried according to literature methods.[13] Petroleum ether refers to the fraction of boiling range 40–60 °C. Organic extracts were dried using anhydrous sodium sulfate as drying agent. Extraction solvents were mainly removed using a rotary evaporator, followed by evacuation on a high vacuum rotary pump.

Preparation of secondary amines

Method a, direct alkylation. To a stirred solution of the amine, such as furfurylamine (0.25 mol), in dichloromethane containing triethylamine (0.25 mol) cooled in an ice-bath was added, dropwise over 1 h, the allyl halide, such as allyl bromide

(0.25 mol). After addition the solution was stirred for a further 1 h and then washed with water (2 × 150 cm^3), the organic layer dried, the mixture filtered and the organic solvent removed to produce a mobile yellow liquid. This was chromatographed through silica gel, using dichloromethane as eluant, the tertiary amine eluting first, followed by the required secondary amine, obtained in yields in the range 15–45%.

Method b, *via* trifluoroacetamide. Trifluoroacetamide was alkylated with the first component and the product then re-alkylated with the second substituent, using sodium hydride in dimethylformamide as the base, as described in the method reported by Hodge *et al.*[14] The product *N*,*N*-dialkylated trifluoroacetamide could be hydrolysed under mild basic conditions to release the required secondary amine, which was then converted to the tritylated product or toluene-4-sulfonamide, as required, in overall yields of 50–80%.

Using these methods the following compounds were prepared.

N-Allyl-3-methylbut-2-enylamine ***5***. As an oil which showed δ_H 1.64 (3 H, s, Me), 1.72 (3 H, s, Me), 3.19 (2 H, d, *J* 9.5, NCH_2), 3.23 (2 H, d, *J* 6.1, NCH_2), 5.09 (1 H, d, *J* 11.9, C*H*=C), 5.20 (1 H, d, *J* 15.6, C*H*=C), 5.27 (1 H, t, *J* 6.1, C*H*=C), 5.86–5.95 (1 H, m, C*H*=C), NH peak not observed as a sharp signal; ν_{max} (film) 3420, 2975, 644, 995, 942 cm^{-1}; characterised as its trityl derivative, **4**.

N-Prop-2-ynyl-3-methylbut-2-enylamine. ν_{max} (film) 3305, 2971, 2918, 2106, 1093, 650 cm^{-1}; δ_H 1.41 (1 H, br s, N*H*), 1.68 (3 H, s, Me), 1.73 (3 H, s, Me), 2.22 (1 H, t, *J* 2.4, *H*C≡C), 3.31 (2 H, d, *J* 7.0, NCH_2), 3.41 (2 H, d, *J* 2.4, NCH_2), 5.23 (1 H, t, *J* 7, *H*C=C); characterised as its trityl derivative **7**.

N-(Triphenylmethyl)-N-allyl-3-methylbut-2-enylamine ***4***. To a solution of the amine (1.13 g, 8.8 mmol) in dry dichloromethane (25 cm^3) were added dry triethylamine (1.25 g, 12.5 mmol) and then freshly prepared triphenylmethyl chloride (2.93 g, 10.5 mmol). The yellow solution was warmed to reflux under dry nitrogen for 48 h, the mixture cooled and then washed with saturated aqueous sodium hydrogen carbonate solution (3 × 30 cm^3) before drying, filtering and evaporating to dryness. The orange oil obtained was immediately passed through silica gel, eluting with dichloromethane, to give, as a viscous yellow oil, the *title amine* (2.4 g, 75%); δ_H 1.32 (3 H, s, Me), 1.62 (3 H, s, Me), 2.92 (2 H, d, *J* 6.9, NCH_2), 2.95 (2 H, d, *J* 6.5, NCH_2), 4.83 (1 H, dd, *J* 10.4, 1.4, *H*C=C), 4.87 (1 H, dd, *J* 18.0, 1.4, *H*C=C), 5.36 (1 H, t, *J* 6.5, *H*C=C), 5.98 (1 H, m, *H*C=C), 7.10–7.54 (15 H, m, Ar). Found: C, 88.2; H, 8.0; N, 3.7; $C_{27}H_{29}N$ requires C, 88.2; H, 8.0; N. 3.8%.

N-(Triphenylmethyl)-N-prop-2-ynyl-3-methylbut-2-enylamine ***7***. Prepared in a similar manner to the tritylated amine **4**, this compound was obtained in high yield (>80%) as a waxy solid, which was recrystallised from methanol to give the *title amine* as a white solid (33% yield), mp 92–93 °C; δ_H 1.49 (3 H, s, Me), 1.72 (3 H, s, Me), 1.90 (1 H, t, *J* 2.4, *H*C≡C), 3.13 (2 H, d, *J* 6.1, NCH_2), 3.32 (2 H, d, *J* 2.4, NCH_2), 5.51 (1 H, t, *J* 6.1, *H*C=C), 7.12–7.54 (15 H, m, aryl H); ν_{max} (Nujol) 3288, 2360, 1595, 1080, 1032, 746, 708 cm^{-1}. Found: C, 88.4; H, 7.5; N, 3.7; $C_{27}H_{27}N$ requires C, 88.7; H, 7.45; N, 3.8%.

cis-N-(Triphenylmethyl)-3-isopropenyl-4-methylpyrrolidine ***6***. The tritylated amine **4** (0.16 g) in xylene (2 cm^3) was heated under argon for 4 days at 140 °C, before removal of the solvent under reduced pressure to leave an orange oil. The product was dissolved in dichloromethane and chromatographed through silica to give the *title pyrrolidine* as a viscous pale yellow oil (0.14 g, 87%), δ_H 0.57 (3 H, d, *J* 7, Me), 1.61 (3 H, s, Me), 2.05–2.18 (2 H, m, 2 × C*H*), 2.51–2.42 (2 H, m, 2 × NC*H*), 2.70–2.95 (2 H, m, 2 × NC*H*), 4.51 (1 H, br s, *H*C=C), 4.73 (1 H, br s, *H*C=C), 7.1–7.5 (15 H, m, Ar); ν_{max} (film) 3418, 3084, 3058, 3029, 2965, 2927, 2871, 1646, 1597, 1493, 1448, 1032, 898 cm^{-1}. Found: *m*/*z* 367.2287; $C_{27}H_{29}N$ requires 367.2300.

N-(Triphenylmethyl)-3-isopropenyl-4-methylenepyrrolidine ***8***. The tritylated amine **7** (0.51 g, 14 mmol) was dissolved in dry toluene (20 cm^3) and the solution heated to reflux under nitrogen for 72 h. The solvent was then removed and the light brown residue dissolved in the minimum of dichloromethane and then chromatographed through silica gel, eluting with dichloromethane–ether, to afford the *title pyrrolidine* as an off-white powder (0.45 g, 88%), which was recrystallised from methanol to show, mp 143–145 °C; ν_{max} (film) 3475, 3031, 3059, 2977, 1644, 1596, 1490, 1448, 1032, 892 cm^{-1}; δ_H 1.56 (3 H, s, Me), 2.19 (1 H, t, *J* 7, C*H*), 2.81 (2 H, m, NCH_2), 3.28 (2 H, m, NCH_2), 4.75 (1 H, br s, *H*C=C), 4.80 (1 H, br s, *H*C=C), 4.83 (1 H, br s, *H*C=C), 4.91 (1 H, br s, *H*C=C), 7.0–7.6 (15 H, m, Ar); *m*/*z* (CI) 366 (MH^+), 243 (trityl cation). Found: C, 88.5; H, 7.45; N, 3.8; $C_{27}H_{27}N$ requires C, 88.7; H, 7.4; N, 3.8%.

Preparation of compound 11

The tritylated furfurylamine **9**[7] (0.52 g, 1.4 mmol) in dry dichloromethane (10 cm^3) was stirred with dimethyl butynedioate (0.97 g, 6.8 mmol) at room temperature for 5 days. The mixture was evaporated to dryness and the residue chromatographed through silica gel, using dichloromethane as eluant, to afford the *Diels–Alder adduct* **11** (0.15 g, 21%) as a viscous, pale yellow oil; δ_H 3.15 (1 H, dd, *J* 9.9, 16.0, NC*H*), 3.43 (1 H, dd, *J* 6.9, 16.0, NC*H*), 3.14 and 3.55 (2 H, AB q, *J* 14.6, NCH_2), 3.57 (3 H, s, CO_2*Me*), 3.75 (3 H, s, CO_2*Me*), 4.75–4.80 (2 H, m, *H*C=C), 5.10–5.25 (1 H, m, *H*C=C), 5.66 (1 H, d *J* 1.8), 7.03–7.53 (17 H, m, Ar and vinylic H); *m*/*z* 522 (MH^+; $C_{33}H_{31}NO_5 \cdot H^+$ requires 522.

Heating the adduct **11** (0.10 g) in toluene (5 cm^3) at 110 °C under nitrogen for 3 days caused elimination of the acetylenic ester and formation of the known cycloadduct[7] **10** in almost quantitative yield (70 mg), with identical TLC behaviour.

Reaction of *N*-tritylfurfurylamine 13 with dimethyl butynedioate

2-Furfurylamine (0.88 cm^3, 10 mmol) and triethylamine (1.09 cm^3, 15 mmol) were added to a solution of triphenylmethyl chloride (2.8 g, 10 mmol) in dichloromethane (10 cm^3) under nitrogen and the solution stirred for 1 h at room temperature. The solution was then washed with 2 M sodium hydroxide solution (50 cm^3) and water (2 × 50 cm^3), dried, filtered and the solution evaporated to dryness to afford a yellow gum, which crystallised on trituration with hot ethanol and cooling to produce *N*-tritylfurfurylamine **13** as a white solid (2.3 g, 68%), mp 101–102 °C; δ_H 2.00 (1 H, br s, N*H*), 3.30 (2 H, s, NCH_2), 6.22 (1 H, d, *J* 3.2, 3-furyl *H*), 6.32 (1 H, dd, *J* 1.9, 3.2, 4-furyl *H*), 7.17–7.55 (16 H, m, Ar and 5-furyl *H*). Found: C, 85.1; H, 6.2; N, 4.0; $C_{24}H_{21}NO$ requires C, 85.0; H, 6.2; N, 4.1%.

The tritylated amine **13** (2.7 g, 8 mmol) and dimethyl butynedioate (4.55 g, 32 mmol) were stirred in dry dichloromethane (10 cm^3) at room temperature for 20 h. The solvent was then removed under reduced pressure and the product mixture chromatographed through silica gel, using dichloromethane as eluant to afford, as a major fraction, the *cycloadduct* **14** which was recrystallised from ethanol (2.7 g, 72%), mp 118–120 °C, δ_H 2.17 (1 H, dd, *J* 4.3, 10.9, exch. with D_2O, N*H*), 2.76 (1 H, dd, *J* 4.3, 12.6, NC*H*), 3.18 (1 H, dd, *J* 10.9, 12.6, NC*H*), 3.80 (3 H, s, CO_2*Me*), 3.85 (3 H, s, CO_2*Me*), 5.66 (1 H, d, *J* 1.8, *H*CO), 6.93 (1 H, d, *J* 5.3, *H*C=C), 7.15 (1 H, dd, *J* 1.8, 5.3, *H*C=C), 7.18–7.52 (15 H, m, Ar). Found: C, 75.0; H, 5.8; N, 2.8; $C_{30}H_{27}NO_5$ requires C, 74.8; H, 5.65; N, 2.9%.

Preparation of dimethyl 2-[*N*-(2-furfuryl)amino]fumarate 16 and dimethyl 2-[*N*-(2-furfuryl)amino]maleate 17

To a solution of 2-furfurylamine (1.94 g, 20 mmol) in dichloromethane (10 cm^3) at room temperature was added, dropwise, dimethyl butynedioate (2.84 g, 20 mmol) over 15 min and the solution then stirred for a further 4 h. The solvent was removed

under reduced pressure and the residue was chromatographed through silica gel, using dichloromethane as eluant, to afford, initially, the *fumarate ester* **16** (1.90 g, 40%) as a viscous oil, δ_H 3.68 (3 H, s, CO_2Me), 3.83 (3 H, s, CO_2Me), 4.57 (2 H, d, *J* 6.2, NCH_2), 5.24 (1 H, s, *H*C=C), 6.18 (1 H, d, *J* 3.1, 3-furyl *H*), 6.29 (1 H, dd, *J* 1.5, 3.1, 4-furyl *H*), 7.35 (1 H, d, *J* 1.5, 5-furyl *H*), 8.30 (1 H, br s, slowly exch. with D_2O, N*H*). Found: C, 55.0; H, 5.5; N, 5.8; $C_{11}H_{13}NO_5$ requires C, 55.2; H, 5.5; N, 5.9%.

The second fraction was the maleate isomer **17** (1.85 g, 39%) but on standing this isomerised to the more stable fumarate isomer. The ^{1}H NMR spectrum of the impure product isomer showed peaks at δ_H 1.68 (1 H, br s, exch. with D_2O), 3.66 (3 H, s), 3.88 (3 H, s), 4.18 (2 H, d, *J* 5.1), 4.86 (1 H, s), 6.34 (1 H, d, *J* 3.3), 6.47 (1 H, dd, *J* 1.5, 3.3), 7.38 (1 H, d, *J* 1.5).

Deprotection of the cycloadduct 14

The cycloadduct (3.09 g. 6.2 mmol) was dissolved in warm ethanol (15 cm^3) and dilute sulfuric acid (2 M, 5 cm^3) added dropwise. The mixture was stirred for a further 10 min and then filtered to remove the white precipitate that had formed. The filtrate was neutralised with aqueous sodium hydroxide (2 M) and the solution extracted with dichloromethane, washing the organic extract with water (25 cm^3), and then dried, filtered and the solvent removed under reduced pressure to afford the amino cycloadduct **15** as an unstable, hygroscopic solid (1.2 g, 80%). On heating a sample of this material (0.4 g) in toluene (5 cm^3) for several hours, a rearrangement occurred and TLC monitoring indicated the formation of the fumarate **16** as the major product. The solvent was removed under reduced pressure and the residue was purified by filtration through a short column of silica gel, using dichloromethane as eluant, to afford **16** (0.25 g, 62%), which showed an identical ^{1}H NMR spectrum to the fumarate **16**.

N-(Triphenylmethyl)-*N*-(3-methylbut-2-enyl)-2-furfurylamine 19

N-(3-Methylbut-2-enyl)-2-furfurylamine **18** was prepared either by the direct alkylation of furfurylamine with 1-bromo-3-methylbut-2-ene under standard conditions[7] or by use of the trifluoroacetamide route (see above) using *N*-trifluoroacetylfurfurylamine as starting material. The amine, obtained as a pale yellow oil, showed δ_H 1.63 (3 H, s, *Me*), 1.73 (3 H, s, *Me*), 1.92 (1 H, br s, N*H*), 3.27 (2 H, d, *J* 7.0, NCH_2), 3.83 (2 H, s, NCH_2), 5.25 (1 H, t, *J* 7.0, *H*C=C), 6.27 (1 H, d, *J* 3.0, 3-furyl *H*), 6.33 (1 H, dd, *J* 1.9, 3.0, 4-furyl *H*), 7.38 (1 H, d, *J* 1.9, 5-furyl *H*).

The amine **18** (5.05 g, 30 mmol) was tritylated with triphenylmethyl chloride (10.14 g, 36 mmol) in dry dichloromethane (25 cm^3) in the presence of triethylamine (4.29 g, 42 mmol) and the solution heated at reflux under nitrogen for 24 h, after which the solution was cooled to room temperature and stirred for a further 48 h at room temperature. The solution was then washed with saturated aqueous sodium hydrogen carbonate solution (3 × 50 cm^3) and then water (50 cm^3), dried, filtered and the solvent removed under reduced pressure to afford a gummy solid. This was triturated with warm methanol to afford a white solid, which was recrystallised from hot methanol to afford the *title tritylated amine* (6.47 g, 52.5%), mp 134–135 °C; δ_H 1.23 (3 H, s, *Me*), 1.41 (3 H, s, *Me*), 2.92 (2 H, d, *J* 6.0, NCH_2), 3.4 (2 H, s, NCH_2), 4.85 (1 H, t, *J* 6.0, *H*C=C), 6.03 (1 H, d, *J* 3.1, 3-furyl *H*), 6.23 (1 H, dd, *J* 1.6, 3.1, 4-furyl *H*), 7.10–7.69 (16 H, m, Ar and 5-furyl *H*). Found: C, 85.4; H, 7.1; N, 3.3; $C_{29}H_{29}NO$ requires C, 85.5; H, 7.2; N, 3.4%.

Reaction of the tritylated amine 19 with dimethyl butynedioate

The amine (1.02 g, 2.5 mmol) and dimethyl butynedioate (1.77 g, 12.5 mmol) were dissolved in dichloromethane (5 cm^3) containing a few crystals of hydroquinone and the solution was stirred at room temperature under nitrogen for 5 days. After this time monitoring by TLC indicated the formation of one major new compound. The reaction mixture was worked up by chromatography through silica gel, eluting with dichloromethane, in order to remove the excess of the dienophile. One major new fraction was obtained as a crystallising oil (0.48 g). This was recrystallised from methanol to afford *(1SR,5SR,6RS,7RS,8SR)-3-(triphenylmethyl)-5-isopropenyl-6,7-bis-(methoxycarbonyl)-11-oxa-3-azatricyclo[6.2.1.0^{1,6}]undec-9-ene* **22** (0.12 g, 16%), mp 153–155 °C; NMR details as reported in Tables 1 and 2. Found: C: 76.3; H, 6.45; N, 2.5; $C_{35}H_{35}NO_5$ requires C, 76.5; H, 6.4; N, 2.6%.

Preparation of *N*-(3-methylbut-2-enyl)-*N*-(4-tolylsulfonyl)-2-furfurylamine 23

To a solution of furfurylamine (10 g, 103 mmol) in dry pyridine (60 cm^3) at 0 °C was added toluene-4-sulfonyl chloride (23.6 g, 124 mmol) and the solution stirred under nitrogen at 0 °C for 4 h before pouring the mixture into ice–water and collecting the solid formed by filtration, washing well with cold water before recrystallisation from ethanol to afford the *N*-(4-tolylsulfonyl)-2-furfurylamine (21.5 g, 88%), mp 111–112 °C.

The tosylated furfurylamine (10 g, 42 mmol) was added to dry dimethylformamide (50 cm^3) and the solution stirred under nitrogen at room temperature before adding sodium hydride (1.11 g, 46 mmol) and the mixture stirred for 1 h before adding 1-bromo-3-methylbut-2-ene (8.16 g, 55 mmol) and the mixture then stirred at room temperature for a further 20 h. The mixture was poured into ice–water (600 cm^3) and extracted with dichloromethane (3 × 100 cm^3), dried, filtered and the extract evaporated to dryness under reduced pressure. The residual liquid was dissolved in ether (50 cm^3) and washed with water (3 × 50 cm^3) and then dried, filtered and the solvent removed under reduced pressure to afford an orange solid. The product was recrystallised from petroleum ether to give the *title sulfonamide* as a white solid (6.35 g, 50%), mp 48–50 °C; δ_H 1.56 (3 H, s, *Me*), 1.66 (3 H, s, *Me*), 2.39 (3 H, s, Ar*Me*), 3.76 (2 H, d, *J* 7.1, NCH_2), 4.36 (2 H, s, NCH_2), 5.01 (1 H, t, *J* 7.1, *H*C=C), 6.12 (1 H, d, *J* 2.0, 3-furyl *H*), 6.24 (1 H, dd, *J* 2.0, 4.2, 4-furyl *H*), 7.23 (1 H, d, *J* 4.2, 5-furyl *H*), 7.24 (2H, d, *J* 8.3, Ar), 7.65 (2 H, d, *J* 8.3, Ar). Found: C, 63.9; H, 6.7; N 4.3; $C_{17}H_{21}NO_3S$ requires C, 63.9; H, 6.6; N, 4.4%.

Reaction of the tosylated amine 23 with dimethyl butynedioate

The tosylamide (4.85 g, 15 mmol) and dimethyl butynedioate (6.82 g, 48 mmol) in dichloromethane (25 cm^3) containing hydroquinone (5 mg) were stirred at room temperature for 22 days. The solvent was then removed and the residue chromatographed through silica gel, using 1 : 9 methanol–dichloromethane as eluant, to give the *cycloadduct* **25** (3.86 g, 54%), mp (ethanol) 108–109 °C; δ_H 1.54 (6 H, s, 2 × *Me*), 2.43 (3 H, s, Ar*Me*), 3.79 (3 H, s, CO_2Me), 3.87 (3 H, s, CO_2Me), 3.96 (2 H, d, *J* 3.8, NCH_2), 3.83 and 4.23 (2 H, ABq, *J* 15.5, NCH_2), 4.71 (1 H, t, *J* 3.8, *H*C=C), 5.64 (1 H, d, *J* 1.8, *H*CO), 7.18 (1 H, dd, *J* 1.8, 5.2, *H*C=C), 7.22 (1 H, d *J* 5.2, *H*C=C), 7.28 (2 H, d *J* 8.1, Ar), 7.70 (2 H, d, *J* 8.1, Ar); ν_{max} (Nujol) 2927, 1722, 1706, 1277 and 1166 cm^{-1}; *m*/*z* (CI) 479.3 (M + NH_4^+).

Thermal rearrangement of the cycloadduct 25

The cycloadduct **25** (0.38 g, 0.8 mmol) was dissolved in dry toluene (5 cm^3) and the yellow solution heated at 100 °C for 20 h under nitrogen. The solvent was then removed under reduced pressure and the brown residue dissolved in the minimum of dichloromethane before chromatographing through silica gel, eluting with dichloromethane, to afford the *furan derivative* **27**, obtained as a viscous, pale yellow gum (0.32 g, 83%); δ_H 1.67 (3 H, s, *Me*), 2.41 (3 H, s, Ar*Me*), 3.42–3.47 (3 H, m, NCH_2 and C*H*), 3.74 (3 H, s, CO_2Me), 3.77 (3 H, s, CO_2Me), 4.45 and

4.47 (2 H, ABq, *J* 12, NCH_2), 4.80 (1 H, s, *H*C=C), 4.97 (1 H, s, *H*C=C), 5.99 (1 H, s, *H*C=C), 6.08 (1 H, d, *J* 1.9, 3-furyl *H*), 6.21 (1 H, dd, *J* 1.9, 2.4, 4-furyl *H*), 7.17 (1 H, d, *J* 2.4, 5-furyl *H*), 7.22 (2 H, d, *J* 8.1, Ar), 7.60 (2 H, d, *J* 8.1, Ar); *m*/*z* (CI) 479.2 (M + NH_4^+). Found: C: 59.8; H, 6.05; N, 3.0; $C_{23}H_{27}NO_7S$ requires: C, 59.85; H, 5.9; N, 3.0%.

Preparation and reactions of the intermediate 26

To a solution of a sample of the tritylated ene product **22** (0.187 g, 0.34 mmol) in warm ethanol (5 cm^3) was added aqueous hydrochloric acid (0.5 cm^3, 3 M) and the solution stirred for 1 h at room temperature. The solvent was then removed under reduced pressure and the residual crude amine **28** was dissolved in pyridine (5 cm^3) at room temperature before adding toluene-4-sulfonyl chloride (0.10 g, 0.53 mmol) and stirring the solution under nitrogen for 12 h. The reaction mixture was quenched over ice–water (50 cm^3) and then extracted with ether (3 × 30 cm^3) and dichloromethane (2 × 30 cm^3), washing the organic extracts with water (3 × 25 cm^3), before drying, filtering and evaporating to dryness. The product was isolated by preparative TLC (silica gel, using 1 : 1 dichloromethane–ethyl acetate as eluant). The major product was the *tosylated ene product* **26** (84 mg, 54%) isolated as a pale yellow gum; δ_H 1.80 (3 H, s, *Me*), 2.39 (1 H, d, *J* 12.2, C*H*), 2.43 (3 H, s, Ar*Me*), 2.68 (1 H, dd, *J* 3.6, 12.2, NC*H*), 3.05 (1 H, t, *J* 12.2, NC*H*), 3.17 (1 H, d, *J* 4.1, C*H*), 3.48 (3 H, s, CO_2*Me*), 3.63 (3 H, s, CO_2*Me*), 3.65 (1 H, dd, *J* 3.6, 13.3, NC*H*), 4.19 (1 H, d, *J* 13.3, NC*H*), 4.65 (1 H, s, *H*C=C), 4.90 (1 H, s, *H*C=C), 5.03 (1 H, dd, *J* 1.0, 4.1, *H*CO), 6.02 (1 H, d, *J* 5.7, *H*C=C), 6.81 (1 H, dd, *J* 1.0, 5.7, *H*C=C), 7.32 (2 H, d, *J* 7.9, Ar), 7.69 (2 H, d, *J* 7.9, Ar). Found: (FAB MS) 462.1592; $C_{23}H_{27}NO_7S{\cdot}H^+$ requires 462.1598.

A sample of the ene product **26** (25 mg) in deuterated benzene was heated in a sealed NMR tube and the ^{1}H NMR spectrum monitored with time. After 5 h almost complete conversion of the starting material into the retro-Diels–Alder product **27** was observed and, after a further 7 h, none of the starting cycloadduct **26** remained and no sign of the starting material **25** could be detected.

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