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Sequential azomethine imine cycloaddition–palladium catalysed cyclisation processes

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Abstract—In situ generation of azomethine imines from aryl/heteroaryl aldehydes and *N*,*N*′-disubstituted hydrazines followed by cycloaddition to *N*-methylmaleimide generates pyrazolidines, which undergo Pd(0) catalysed cyclisation involving the aldehyde and hydrazine substituents, with formation of 6–8 membered rings in good yield. AMI calculations indicate the preferred configuration of the azomethine imines involved and identify the most likely cycloaddition transition states. © 2003 Elsevier Science Ltd. All rights reserved.

1. Introduction

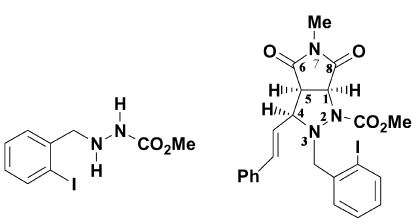
We have developed a number of one-pot sequential or cascade protocols which employ several types of 1,3-dipoles and palladium catalysed cyclisation processes. Such tactical combinations include azomethine ylide cycloaddition cascades with palladium catalysed cyclisation processes[1,2] and/or carbonylation processes,[3] sequential oxypyridinium betaine cycloaddition/palladium catalysed cyclisation–anion capture processes,[4] and cascade palladium catalysed tetramolecular queuing processes involving carbon monoxide and/or allene as relay switches followed by 1,3-dipolar cycloaddition or Diels–Alder reactions.[5,6] The above processes result in molecules possessing a high degree of complexity which would otherwise require tedious and/or technically demanding multistep syntheses. Tactical combinations of this general type can adopt two broad strategies in which the palladium catalysed cascade either precedes or follows the cycloaddition step. This paper is concerned with the latter strategy.

As a part of our ongoing interest in developing tactical combinations of cycloaddition reactions with palladium catalysed cyclisation processes we explored the sequential combination of azomethine imine cycloaddition with palladium catalysed cyclisation processes (Scheme 1) with in situ generation of the azomethine imine.

Condensation of aldehydes with 1,2-disubstituted hydrazines as a route to azomethine imines was described by Huisgen in 1963[7,8] and we later reported a novel 1,2-prototropy route.[9,10] Our strategy in the current studies was to react azomethine imines, generated in situ by the aldehyde condensation route, and containing the requisite functionality for subsequent palladium catalysed Heck or Friedel–Crafts reactions, with *N*-methylmaleimide. Subsequent palladium catalysed cyclisation processes then allow access to novel fused ring heterocycles.

1.1. Formation of 6-membered rings

Cyclic[11] and acyclic[12] *N*,*N*′-disubstituted hydrazines with a variety of substituents have been used as precursors of azomethine imines and a range of inter- and intra-molecular dipolarophiles have been employed. We initially focused on *N*-(2-iodobenzyl)-*N*′-carbomethoxy hydrazine **1**, which was prepared from 2-iodobenzaldehyde and methyl carbazate via condensation followed by the reduction of the hydrazone with $NaCNBH_3$. Initially we studied the cycloaddition of the azomethine imine generated from cinnamaldehyde and **1**. Thus cinnamaldehyde was reacted with **1** and *N*-methylmaleimide (NMM) in xylene 140°C for 10 h to afford a 4:1 mixture of cycloadducts **2** and **3** in 67% yield. The stereochemistry of **2** and **3** were established by n.O.e studies (see Section 2).



1 **2** **3**

1,3-Dipolar cycloadditions often exhibit a preference for an *endo*- over an *exo*-transition state in the absence of

Keywords: azomethine imine; cycloaddition; palladium; cyclisation.

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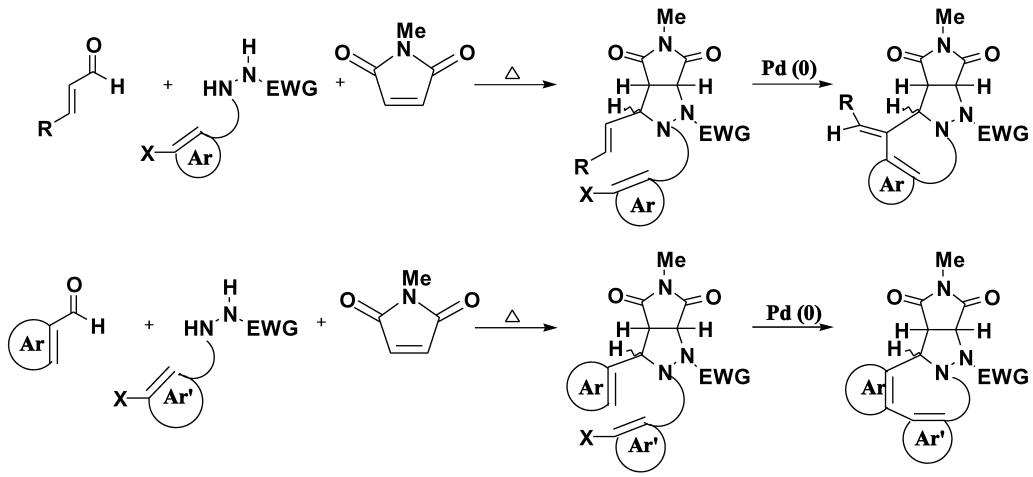
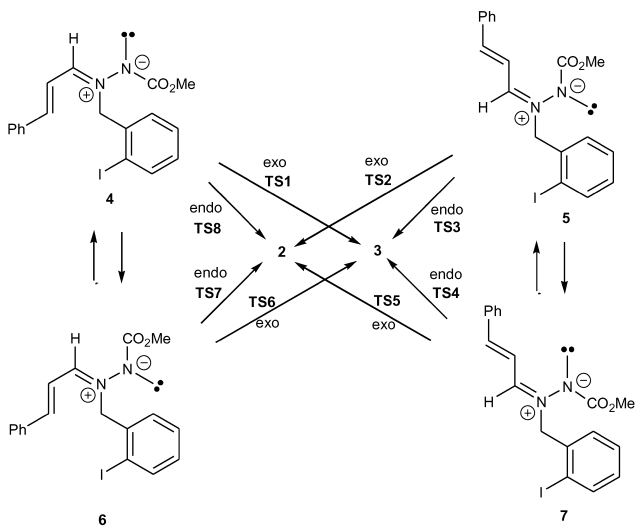


Scheme 1.

overriding steric factors.[13–15] The pyrazolidine products **2** and **3** fail to accurately reflect the azomethine imine stereochemistry or the *exo*/*endo*-nature of the cycloaddition transition states since this stereochemical information is lost due to the presence of a lone pair on each of the two N-atoms in the pyrazolidine products. However, it is instructive to consider the possible dipoles and their transition states. Condensation of cinnamaldehyde with **1** could give rise to four dipoles (Scheme 2).

In principal, each of these can undergo cycloaddition with NMM via either an *exo* or an *endo* transition state to yield either **2** or **3**, respectively. The calculated heats of formation (H_f) of dipoles **4**–**7** together with those for all possible transition states **TS1**–**TS8** are given in Table 1 whilst the corresponding calculated cycloaddition activation energies and the estimated barriers for interconversion of the dipoles are given in Table 2.

These data indicate that all dipoles have similar heats of formation with **6** and **7** being the most thermodynamically stable (Table 1). Additionally, it appears that the barriers to interconversion between dipoles, **4**⇌**6** and **5**⇌**7**, respectively, are small and interconversion can readily occur via



Scheme 2.

Table 1. Calculated heats of formation for 1,3-dipoles and their cycloaddition transition states

Structure	H_f[a]	ν_i[b]
4	73.45	–
5	73.04	–
6	71.48	–
7	70.26	–
TS1	66.38	544.48
TS2	67.06	616.97
TS3	59.59	606.96
TS4	65.51	578.37
TS5	68.62	573.88
TS6	62.91	592.57
TS7	57.82	613.17
TS8	66.57	553.17

[a] Heats of formation in kcal mol^{-1}, obtained using AM1 Hamiltonian after full geometry optimisation.
[b] All transition structures were characterized by observing them to have a single negative vibrational frequency corresponding to the reaction coordinate following a normal mode analysis (expressed in cm^{-1}).

Table 2. Calculated cycloaddition activation energies and dipole interconversion barriers

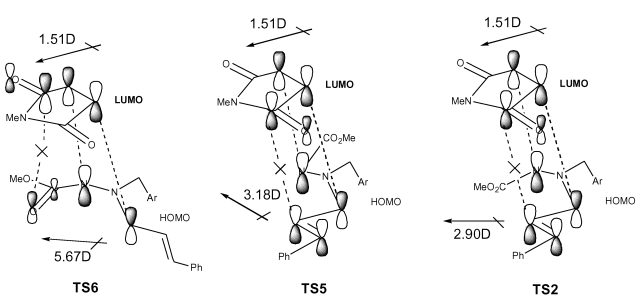
Conversion	ΔH[a]
4→2	22.00
4→3	21.81
4→6	4.68[b]
4→7	24.58[c]
5→2	22.90
5→3	15.43
5→6	28.52[c]
5→7	3.47[b]
6→2	15.22
6→3	20.31
6→4	6.65[b]
6→5	30.08[c]
7→2	27.24
7→3	24.13
7→4	26.98[c]
7→5	5.46[b]

[a] Energies in kcal mol^{-1}. For cycloadditions, the energy is the difference between the sum of the heats of formation of dipole+NMM (H_f=−28.88 kcal mol^{-1}) and the heat of formation of the corresponding transition state.
[b] Barrier to rotation around the dipole N–N bond.
[c] Barrier to rotation around the dipole C–C bond.

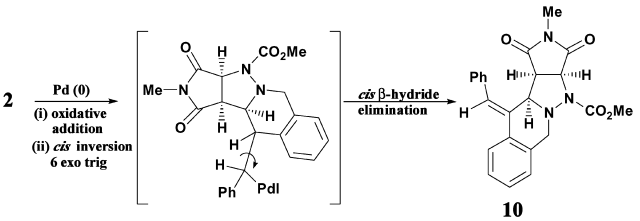
rotation about the N–N dipole bonds. In contrast, dipole interconversions involving rotation about the C–C bonds as in **4**⇌**7** and **5**⇌**6** have relatively high energy barriers and should be much slower (Table 2). Inspection of the data in Table 2 also reveals the stereochemical preferences for the cycloadditions of dipoles **4**–**7** with NMM. The energy differences between the dipoles reflect, in the main, steric effects. Assuming these are the major influences in the dipole forming transition states we would expect **6** and **5** to be the favoured dipoles. The most important reaction pathway thus corresponds to cycloaddition of thermodynamically favoured dipole **6** via *endo* transition state **TS7** to yield adduct **2**. The unfavourable *exo* cycloaddition of this dipole via **TS6** is due to the presence of both an appreciable parallel component in the alignment of the electronic dipole moments of dipole **6** and NMM, and the presence of an antibonding interaction between coefficients on the carbonyl groups within the dipole HOMO and NMM LUMO orbitals, respectively (Scheme 3). Although *endo* addition of dipole **5** to yield **3** is also highly favourable, overall this represents a less prominent pathway due to the lower thermodynamic stability of dipole **5**, in keeping with the experimentally observed stereoisomeric preference.

Cycloadditions of dipoles **4** and **7** require appreciably higher activation energies and represent less prominent reaction pathways. This would appear to be a consequence of the *Z* geometry of the *N*–CO_2Me group within these dipoles and reflects the increase in steric repulsion between the ester and (*o*-iodo)benzyl moieties as the terminal nitrogen of the dipole starts to re-hybridise upon proceeding into the transition state. The particularly unfavourable *exo* cycloadditions of dipoles **7** and **5** may reflect the importance of electronic factors on the stereochemical outcome of these types of 1,3-dipolar cycloaddition reactions. Both *exo* transition states **TS2** and **TS5** possess appreciable antibonding interactions involving HOMO coefficients within the vinyl groups of the dipoles and LUMO coefficients of the NMM carbonyl moiety, respectively (Scheme 3). The *exo* transition state **TS2** of dipole **5** is further disfavoured relative to the alternative *endo* pathway via **TS3** due to an almost parallel alignment of electronic dipoles of the reactants in **TS2** (Scheme 3).

Next we studied the palladium catalysed 6-exo trig cyclisation processes of **2** and **3**. Treatment of **2** with a catalyst system comprising 10 mol% $Pd(OAc)_2$, 20 mol% PPh_3, Et_4NCl (1 mol equiv.) and K_2CO_3 (2 mol equiv.) (catalyst system A) in boiling acetonitrile for 4 h effected clean cyclisation to the Heck product **10** in 81% yield (Scheme 4).



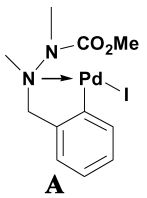
Scheme 3.

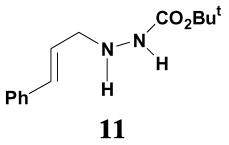


Scheme 4.

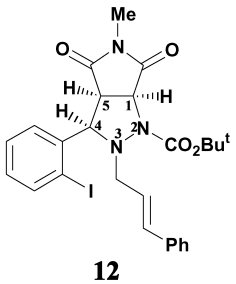
The product **10** was obtained exclusively as the (*Z*)-isomer as expected for *cis*-addition of ArPdI to the styryl moiety followed by *cis*-β-hydride elimination. In contrast isomer **3** failed to cyclise under essentially similar conditions to those used for the cyclisation of **2**. Carrying out the reaction in xylene at 130°C also failed to give any cyclised product. It is not immediately obvious why (**3**) fails to cyclise. A possible explanation is that the conformational differences in the pyrazolidine moiety of the chelated oxidative addition product (**A**) may preferentially destabilize/stabilize this species in the case of (**3**) to the extent that the cyclisation is disfavored.

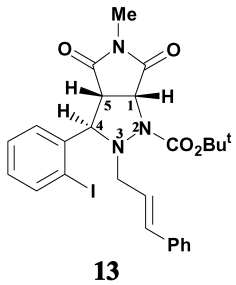
Following the mixed results of the above sequential process, we modified our strategy and transposed the iodide and alkene moieties. Thus 1,2-disubstituted hydrazine **11** was prepared by reductive amination from cinnamaldehyde and *tert*-butyl carbazate.





2-Iodobenzaldehyde was reacted with **11** and NMM (xylene 110°C, 29 h) to give a 1.5:1 mixture of **12** and **13** in 76% yield.

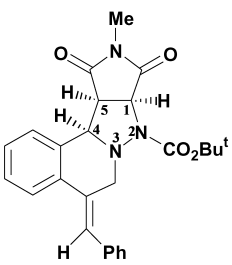




The stereochemistry of **12** and **13** was assigned on the basis of their ^{1}H NMR spectra. In particular **12** exhibited methine proton doublets at δ 5.02 (J=8.1 Hz, 1-H) and δ 4.92 (J=9.2 Hz, 4-H) and a methine proton multiplet at δ 3.88 (J=8.1 and 9.2 Hz, 5-H). Cycloadduct **13** exhibited a broadened methine proton doublet at δ 5.04 (1-H), a methine proton singlet at δ 4.93 (4-H) and a methine proton doublet at δ 3.81 (J=8.2 Hz, 5-H).

When treated with catalyst system A cycloadduct **12** cyclised over 24 h to the Heck reaction product **14** in 53% yield. No 7-*endo trig* cyclisation product was detected.

When the cyclisation was repeated with a catalyst system comprising 10 mol% $Pd(OAc)_2$, 20 mol% PPh_3 and TlOAc (1.2 mol equiv.) (catalyst system B) in xylene (110–120°C) the reaction time was reduced to 2 h and the yield increased to 89%. Similarly cycloadduct **13** cyclised cleanly (catalyst system B) to **15** (xylene 120–130°C, 5 h) in 87% yield. We introduced Tl (I) salts into the Heck reaction to suppress double bond isomerisation of the Heck products.[16] and they have also been shown to accelerate some palladium catalysed processes.[17] The stereochemistry of the styryl moieties in **14** and **15** conforms to that expected for *cis*-addition of ArPdI to the alkene moiety in **12** and **13**, followed by *cis*-β-hydride elimination.



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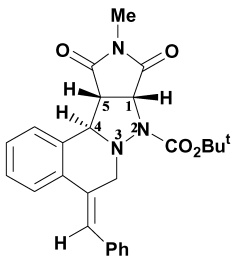
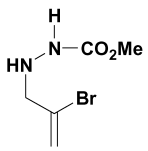


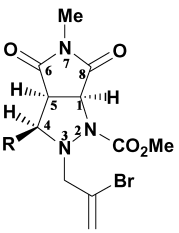
15

Next we incorporated a vinyl bromide into the hydrazine. Thus hydrazine **16** was prepared by alkylation of methyl carbazate with 2,3-dibromo propene.

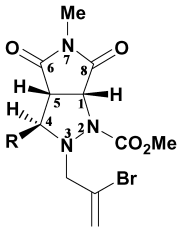


16

Reaction of hydrazine **16** with benzaldehyde and NMM (xylene, 140°C, 14 h) gave a 1.7:1 mixture of **17a** and **18a** in 51% yield. An analogous reaction with thiophene-2-carboxaldehyde (xylene, 140°C, 16 h) gave a 1:1 mixture of **17b** and **18b** in 44% yield.

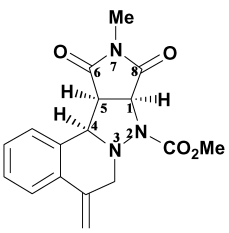


17 a. R = Ph
b. R = 2-thienyl



18 a. R = Ph
b. R = 2-thienyl

Treatment of **17a** with catalyst system B (MeCN, 80°C, 16 h) gave cyclised product **19** in 49% yield. Cyclisation of **18a** under the same conditions over 24 h gave **20** in 47% yield. Similarly **21** was obtained in 54% yield from **17b** upon treatment with catalyst system B (MeCN, 80°C, 16 h) while cyclisation of **18b** gave **22** in 50% yield. No double bond isomeric products were isolated under these conditions.



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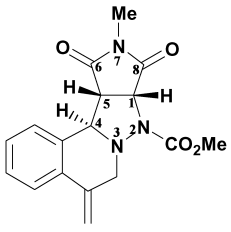

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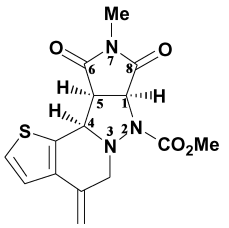

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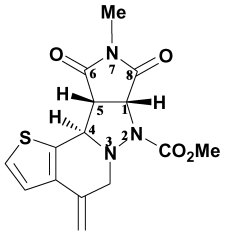
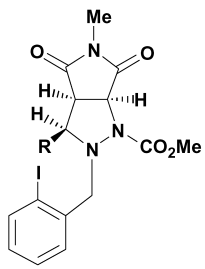


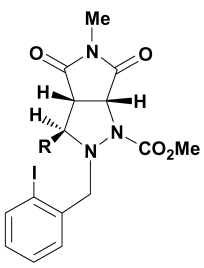
22

1.2. Formation of 7-membered rings

In order to investigate 7-membered ring formation cycloadducts **23a**,**b** and **24a**,**b** were prepared by the reaction of 3-thiophene carboxaldehyde or 3-furan carboxaldehyde, hydrazine **1** and NMM in boiling xylene. Thus the former aldehyde afforded a 2.8:1 mixture of **23a** and **24a** in 67% yield whilst the latter afforded a 2.5:1 mixture of **23b** and **24b** in 46% yield. The stereochemistry of the cycloadducts was established by n.O.e studies (see Section 2).

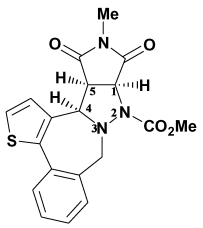


23 a. R =
b. R =



24 a. R =
b. R =

Cyclisation of **23a** with catalyst system B (xylene, 110°C, 19 h) afforded **25** in 80% yield. Similarly **24a** cyclised to **26** in 80% yield while **23b** gave **27** in 73% yield. Cyclisation of **24b** was not attempted.



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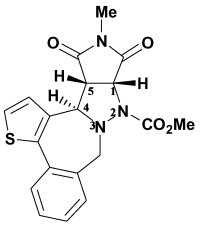

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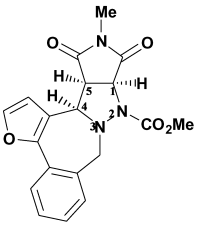
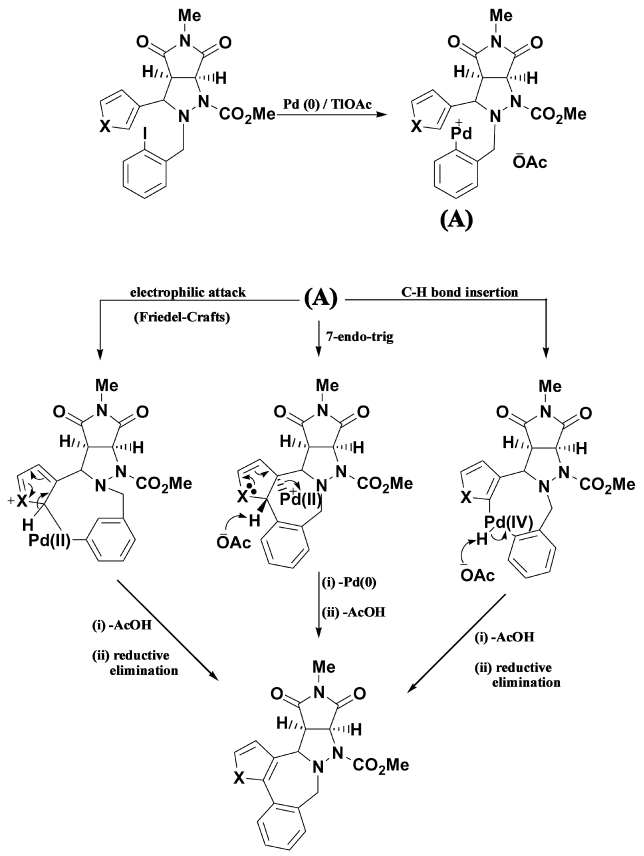


27

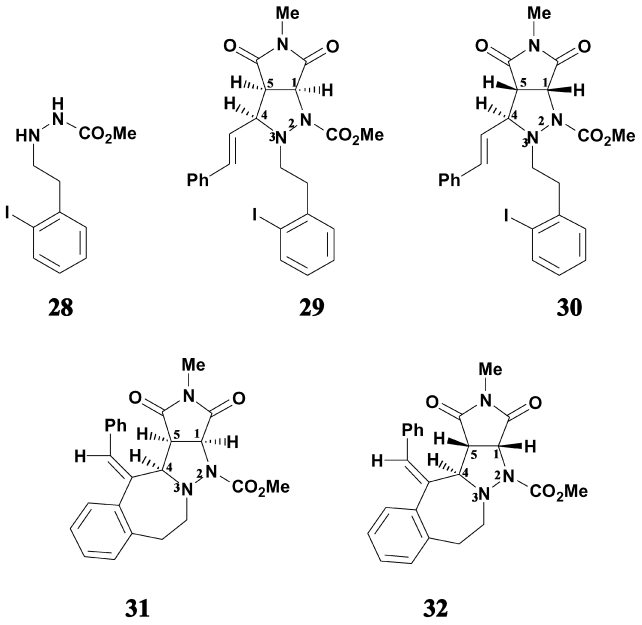
The formal Friedel–Crafts cyclisation of **23a**,**b** and **24a** is regioselective for the C-2 position as opposed to the C-4 position in the furan and thiophene moieties. This suggests an electrophilic component to the cyclisation as summarised in Scheme 5.



Scheme 5.

There is growing support for the palladium catalysed cyclisation of organopalladium (II) species onto a proximate aryl/heteroaryl system proceeding via a Pd(IV) intermediate.[18] We have also carried out the above reaction as a sequential one-pot process. Thus 1,3-DC reaction of thiophene carboxaldehyde with **1** and NMM was allowed to proceed as before (xylene, 140°C, 24 h) then catalyst system B was added, and heating continued at 120°C for 48 h to furnish a 3:1 mixture of **25** and **26** in 52% yield.

1,2-Disubstituted hydrazine **28** was prepared from methyl *N*-carbazate and (2-iodophenyl)-acetaldehyde to explore an alternative strategy for 7-membered ring formation. Reaction of **28**, cinnamaldehyde and NMM in xylene (140°C, 14 h) gave a 3:1 mixture of **29** and **30** in 52% yield. The stereochemistry of the cycloadducts was determined by correlation with ^{1}H NMR chemical shifts and coupling constants with those of **2** and **3**. Both cycloadducts **29** and **30** were cleanly cyclised by catalyst system B (xylene, 110°C, 18 h) to give **31** and **32** in 88 and 89% yield, respectively. Again only the (*Z*)-isomers were observed.



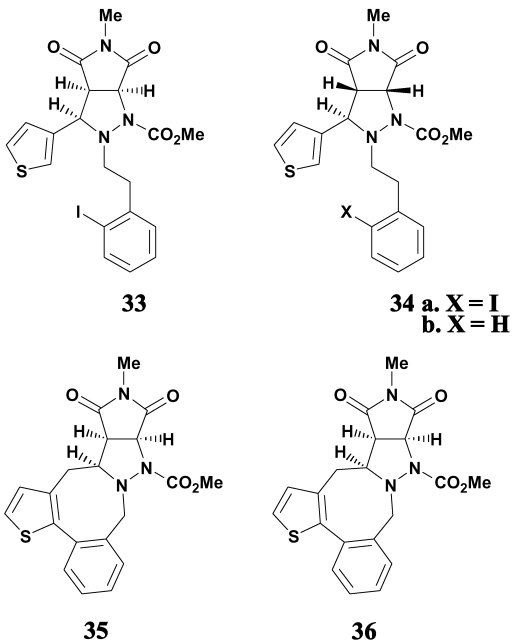
28 **29** **30**

31 **32**

1.3. Formation of 8-membered rings

Reaction of **28**, 3-thiophene carboxaldehyde and NMM in xylene (140°C, 22 h) gave a 1.6:1 mixture of cycloadducts **33** and **34a** in 68% yield. Column chromatography afforded individual isomers.

Palladium catalysed cyclisation of **33** employing catalyst system B (xylene, 130–140°C, 24 h) afforded **35** in 68% yield. Treatment of **34a** with the same catalyst system (xylene, 130–140°C, 24 h) gave a 3:1 mixture of cyclised product **36** and deiodinated product **34b** in 60% combined yield.

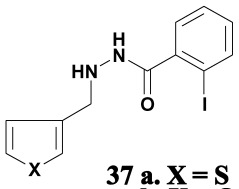


33 **34 a. X = I**
b. X = H

35 **36**

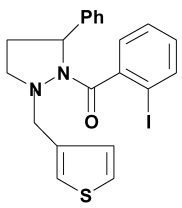
Encouraged by these results, we prepared two further hydrazines **37a**,**b** from 2-iodobenzoic hydrazide and

3-thiophene carboxaldehyde or 3-furaldehyde, respectively, via reductive amination.

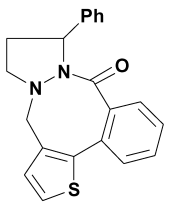


37 a. X = S
b. X = O

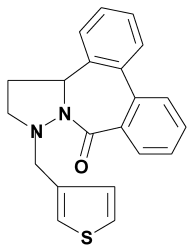
Initially we explored the reaction of *para*-formaldehyde, hydrazine **37a** and styrene in boiling xylene (140°C, 9 h). Cycloadduct **38** was isolated in 94% yield. The attraction of **38** is the presence of two potential cyclisation pathways involving either the thiophene moiety or the 3-phenyl substituent. The former would give rise to an 8-membered product whilst the latter would result in a 7-membered ring. Cyclisation of **38** proceeded smoothly using catalyst system B (toluene, 110°C, 16 h) to give **39** as the sole product in 85% yield. Thus the formation of the 8-membered ring is kinetically favoured and no cyclisation onto the 3-phenyl ring to give the seven membered ring product **40** was observed. The high reactivity of 5- or 6-membered heterocycles in palladium catalysed formal Friedel–Crafts processes has been noted by us previously.[19]



38



39



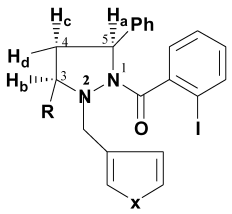
40

The structure of **39** was assigned from 2D-nmr experiments. However, when the cycloaddition reaction was repeated using aryl aldehydes mixtures of cycloadducts **41a**, **41b** and **42a**, **42b** were formed. The results are collected in Table 3.

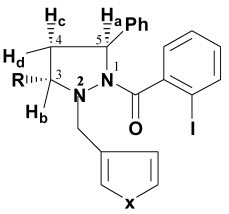
Table 3. Cycloadducts from the reaction of **37a**,**b** with arylaldehydes and styrene

Entry	R	X	Products	Ratio	Yield (%)
1	Phenyl	S	**41a**,**b**	1.3:1	68
2	Phenyl	O	**42a**,**b**	1.2:1	73
3	4-Nitrophenyl	S	**43a**,**b**	3.5:1	57
4	4-Nitrophenyl	O	**44a**,**b**	3.2:1	60
5	2-Fluorophenyl	O	**45a**,**b**	2.8:1	48
6	4-(Dimethylamino)-phenyl	S	**46a**,**b**	1:1.5	62
7	4-(Dimethylamino)-phenyl	O	**47a**,**b**	1:1.8	64
8	3-(Trifluoromethyl)-phenyl	S	**48a**,**b**[a]	2.5:1	77
9	3-(Trifluoromethyl)-phenyl	O	**49a**,**b**[a]	2.5:1	76
10	3-Methoxy phenyl	S	**50a**,**b**[a]	1.5:1	76
11	3-Methoxy phenyl	O	**51a**,**b**[a]	1.3:1	74

All reactions were carried out in toluene (110°C, 16 h) with equimolar amounts of **37a**,**b**, arylaldehyde and styrene.
[a] Diastereoisomers obtained as an inseparable mixture.

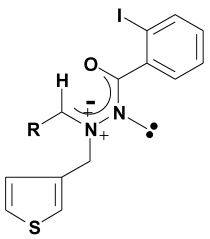


41a - 51a

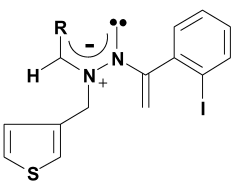


41b - 51b

The stereochemistry of the cycloadducts in Table 3 was established by n.O.e studies (see Section 2). Clearly the presence of an *ortho*-iodo substituent on the phenyl ring has a profound effect on the stereochemical outcome of the cycloaddition reactions. The iodo-substituent affects the relative energies of the dipole **52** and **53**, and also the *endo*- or *exo*-cycloadduct transition state energies.



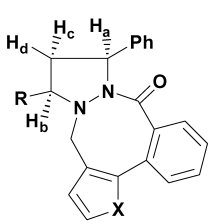
52



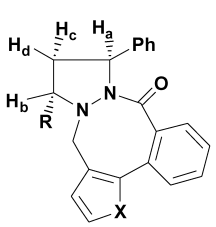
53

There is a general trend discernable in Table 3 in that mesomeric (Table 3, entries 3 and 4) or inductively withdrawing (Table 3, entries 5, 8, 9) substituents favour the 3, 5-*cis* isomer whilst mesomeric donors favour the 3, 5-*trans* isomer (Table 3, entries 6 and 7). The inductive effect of the 3-methoxy group (Table 3, entries 10 and 11) is essentially negligible.

Cyclisation to form 8-membered ring products (**54a**,**b**–**61a**,**b**) was found to be extraordinary facile. These products (Table 4) were obtained in excellent yield upon treatment of the corresponding cycloadducts with catalyst system B (toluene, 110° c, 6 h). The structure of the cyclised products were established by 2D-TOCSY experiments (see Section 2).



54a - 61a



54b - 61b

In conclusion we have successfully demonstrated regio-selective sequential azomethine imine 1,3-DC-palladium catalysed cyclisation processes for the synthesis of fused 6–8-membered heterocycles.

Table 4. Palladium catalysed cyclisation of **41a**,**b**–**51a**,**b**

R	X	Products	Yield(%)
Phenyl	S	**54a**	82
Phenyl	S	**54b**	84
4-Nitrophenyl	O	**55a**	72
4-Nitrophenyl	O	**55b**	69
2-Fluorophenyl	O	**56a**	71
4-(Dimethylamino)-phenyl	S	**57a**	81
4-(Dimethylamino)-phenyl	S	**57b**	77
3-(Trifluoromethyl)-phenyl	S	**58a**+**58b**	79[a]
3-(Trifluoromethyl)-phenyl	O	**59a**+**59b**	73[b]
3-Methoxy phenyl	S	**60a**	85[c]
3-Methoxy phenyl	S	**60b**	83[c]
3-Methoxy phenyl	O	**61a**	70[d]
3-Methoxy phenyl	O	**61b**	70[d]

Catalyst system B, toluene, 110°C, 16 h.
[a] Obtained as a 2.5:1 mixture of **58a** and **58b** from a 2.5:1 mixture of **48a** and **48b**.
[b] Obtained as a 2.5:1 mixture of **59a** and **59b** from a 2.5:1 mixture of **49a** and **49b**.
[c] Obtained from a 1.5:1 mixture of **50a** and **50b**.
[d] Obtained from a 1.3:1 mixture of **51a** and **51b**.

2. Experimental

Melting points were determined using a Reichert apparatus and are uncorrected. Mass spectral data was obtained from a VG Autospec mass spectrometer operating at 70 eV at the National MS Service, Swansea. Nuclear magnetic resonance spectra were recorded on Bruker 250, 300, 400 and 500 MHz machines. Unless otherwise specified deutero-chloroform was used as solvent with tetramethylsilane as internal standard. Microanalyses were obtained using a Carlo Erba MOD 11016 instrument. Thin layer chromatography was carried out on Whatmann PGSIL G/UV polyester Plate coated with a 0.2 mm layer of silica gel 60 (Merck 9385). Column chromatography was performed with silica gel 60 (Merck 9385). Petroleum ether refers to the fraction with bp 40–60° C. Anhydrous toluene and xylene was commercially available (Aldrich). MeCN was distilled from calcium hydride. THF was distilled from sodium.

2.1. Preparation of 1,2-disubstituted hydrazines

These were prepared by one of two general procedures:

(A) *Modified reductive amination*.[20] A mixture of the aldehyde (15 mmol) and monosubstituted hydrazine (15 mmol) in methanol (25 ml) was heated under gentle reflux for 10 min to 2 h. The solution was cooled to 0°C, and dry THF (25 ml), sodium cyanoborohydride (15 mmol) and glacial acetic acid (15 mmol) added with stirring. The solution was then allowed to warm to room temperature and stirred for 10 h. A further portion of sodium cyanoborohydride (15 mmol) was then added at 0°C, followed by glacial acetic acid (15 mmol) and stirring continued at room temperature for 16 h.

The solution was acidified to pH 1 with conc. HCl, and then basified to pH 14 with solid sodium hydroxide. Water (100 ml) was added and the organic solvents removed in vacuo. The basic aqueous layer was extracted with ether (4×50 ml) and the combined ether layers dried ($MgSO_4$). The solvent was evaporated in vacuo and the residue purified by flash chromatography and/or crystallisation.

For *N*-alkyl-*N'*-phenyl hydrazines, the work up procedure was modified due to the instability of these compounds to chromatographic purification. After acidification with conc. HCl as above, the solvent was removed in vacuo, and the residue suspended in water (200 ml). The mixture was washed with CH_2Cl_2 (3×25 ml) and the aqueous layer basified to pH 14 (solid NaOH). The solution was extracted with ether (4×50 ml), and the combined ether extracts dried ($MgSO_4$) and the solvent removed in vacuo to afford product of sufficient purity for subsequent cycloaddition.

(B) *Alkylation*. A mixture of the monosubstituted hydrazine (0.08 mol), a primary alkyl halide (0.04 mol) and potassium carbonate (0.04 mol) in acetonitrile (80 ml) was stirred at room temperature for 24–48 h. The reaction mixture was then poured into water (200 ml) and extracted with dichloromethane (4×50 ml). The combined organic layers were dried ($MgSO_4$) and the solvent removed in vacuo to afford the crude product which was purified by flash chromatography.

2.1.1. *N*-(2-Iodobenzyl)-*N'*-carbomethoxy hydrazine 1. Prepared via method A from 2-iodobenzaldehyde and methyl carbazate. Hydrazone formation was complete after 1 h. Purification by flash chromatography, eluting with 4:1 v/v hexane–ethyl acetate gave the product (97%) which crystallised from ethanol as colourless needles, mp 53–55°C; Found: C, 35.40; H, 3.75; N, 9.15; I, 41.20. $C_9H_{11}IN_2O_2$ requires C, 35.31; H, 3.62; N, 9.15; I, 41.46%; δ_H 7.83 (d, 1H, *J*=7.9 Hz, ArH), 7.37–7.25 (m, 2H, ArH), 6.98 (t, 1H, *J*=7.5 Hz, ArH), 6.52 (s, br, 1H, NH), 4.32 (s, br, 1H, NH), 4.06 (s, 2H, CH_2) and 3.71 (s, 3H, CH_3); *m*/*z* (%): 306 (M^+, 23), 232 (72), 217 (100), 104 (12), 90 (40), 76 (8) and 59 (8).

2.1.2. *N*-(3-Phenyl)-prop-2-enyl-*N'*-^{t}butoxycarbonyl hydrazine 11. Prepared from cinnamaldehyde and ^{t}butyl carbazate according to procedure A. Hydrazone formation was complete after 10 min. Purification by flash chromatography, eluting with 4:1 hexane–ethyl acetate gave the product (62%) as colourless prisms from hexane–ether, mp 52–54°C; Found: C, 67.90; H, 8.25; N, 11.10. $C_{14}H_{20}N_2O_2$ requires C, 67.72; H, 8.16; N, 11.28%; δ_H 7.37–7.21 (m, 5H, ArH), 6.55 (d, 1H, *J*=15.7 Hz, ArCH=), 6.36 (s, br, 1H, NH), 6.23 (dt, 1H, *J*=15.7 and 6.5 Hz, =CH), 4.16 (s, br, 1H, NH), 3.61 (d, 2H, *J*=6.5 Hz, CH_2) and 1.45 (s, 9H, $3CH_3$); *m*/*z* (%): 248 (M^+, 3), 117 (1000, 91 (23), 57 (53) and 41 (17).

2.1.3. *N*-(2-Bromo)-prop-2-en-1-yl-*N'*-acetyl hydrazine 16. Prepared from 2,3-dibromopropene and acetic hydrazide according to procedure B. Purification by flash chromatography, eluting with 7:3 v/v hexane–ethyl acetate gave the product (31%) as colourless needles from methanol, mp 46–48°C; Found: C, 31.30; H, 4.75; N, 14.25. $C_5H_9BrN_2O$ requires C, 31.10; H, 4.70; N, 14.50%; δ_H 8.65 (s, br, 1H, NH), 5.87 and 5.59 (2×s, 2×1H, $=CH_2$), 4.95 (s, br, 1H, NH), 3.67 (s, 2H, CH_2) and 1.99 (s, 3H, CH_3); *m*/*z* (%): 194 (M^+, 7)/192 (M^+, 7), 152 (56), 150 (57), 136 (52), 134 (52), 113 (24), 71 (31), 60 (29), 43 (100) and 39 (73).

2.1.4. *N*-2-(2′-Iodophenyl)-ethyl-*N*′-carbomethoxy hydrazine 28. Prepared from methyl carbazate and (2-iodophenyl)-acetaldehyde. Hydrazone formation was complete after 1 h. Purification by flash chromatography eluting with 7:3 v/v hexane–ethyl acetate gave the product (3.7 g, 77%) as colourless prisms, mp 71–73°C, from hexane–ether; Found: C, 37.65; H, 4.30; N, 8.85; I, 39.50. $C_{10}H_{13}IN_2O_2$ requires C, 37.52; H, 4.09; N, 8.75; I, 39.64%; δ_H 7.78 (d, 1H, *J*=7.9 Hz, ArH), 7.27–7.22 (m, 2H, ArH), 6.91 (s, br, 1H, NH), 6.88 (d, 1H, *J*=8.7 Hz, ArH), 4.17 (s, br, 1H, NH), 3.70 (s, 3H, OCH_3), 3.10 and 2.89 (2×t, 2×2H, *J*=7.4 Hz, 2×CH_2); *m*/*z* (%): 320 (M^+, 1), 103 (100), 90 (13), 71 (58) and 44 (14).

2.1.5. *N*-(3-Thienyl)-ethyl-*N*′-(2-iodobenzoyl) hydrazine 37a. Prepared from thiophene-3-carboxaldehyde and 2-iodobenzoic hydrazide via method A. The product (4.62 g, 86%) crystallized from ethanol as colourless needles, mp 131–133°C; Found: C, 40.35; H, 3.15; N, 8.00; I, 35.30; S, 8.65. $C_{12}H_{11}IN_2OS$ requires C, 40.25; H, 3.10; N, 7.80; I, 35.45; S, 8.95%; δ_H 7.87 (d, 1H, *J*=7.9 Hz, ArH), 7.42–7.28 (m, 4H, ArH), 7.17–7.06 (m, 2H, ArH) and 4.21 (s, 2H, CH_2). The two NH protons were not detected; *m*/*z* (%): 358 (M^+, 1), 248 (43), 231 (97), 203 (40), 112 (56), 97 (100) and 76 (50).

2.1.6. *N*-(3-Furyl)-ethyl-*N*′-(2-iodobenzoyl) hydrazine 37b. Prepared from 3-furaldehyde and 2-iodobenzoic hydrazide via method A. Purification by crystallization from ethanol gave the product (3.64 g, 71%) as colourless needles, mp 120–122°C; Found: C, 42.15; H, 3.05; N, 8.35; I, 37.20. $C_{12}H_{11}IN_2O_2$ requires C, 42.15; H, 3.25; N, 8.20; I, 37.10%; δ_H 7.86 (d, 1H, *J*=8.0 Hz, ArH), 7.46–7.30 (m, 5H, ArH and 1×NH), 7.11 (t, 1H, *J*=7.3 Hz, ArH), 6.47 (s, 1H, ArH), 5.03 (s, br, 1H, NH) and 4.02 (s, 2H, CH_2); *m*/*z* (%): 342 (M^+, 2), 247 (57), 231 (100), 203 (51), 105 (26), 96 (57), 81 (75), 76 (58) and 53 (35).

2.2. General procedure for cycloaddition reactions of aldehydes with *N*,*N*′-disubstituted hydrazines and *N*-methyl maleimide (NMM) and styrene

A solution of the aldehyde (2 mmol), *N*,*N*′-disubstituted hydrazine (2 mmol), and the dipolarophile (2 mol) in anhydrous *m*-xylene or toluene (10 ml) was boiled under an atmosphere of dry nitrogen until TLC or ^{1}H NMR analysis showed the reaction to be complete. The solvent was removed in vacuo and the residue purified by flash chromatography or fractional crystallization to afford the cycloadducts.

2.3. General procedure for palladium catalysed cyclisation reactions using catalysts system A

A mixture of the cycloadduct (0.4 mmol), $Pd(OAc)_2$ (9 mg, 0.04 mmol), PPh_3 (21 mg, 0.08 mmol), NEt_4Cl (0.066 g, 0.4 mmol) and K_2CO_3 (0.111 g, 0.8 mmol) in dry solvent (20 ml) was heated under a dry nitrogen atmosphere until TLC or ^{1}H NMR analysis showed complete reaction. The mixture was cooled, poured into water (100 ml), and extracted with dichloromethane (3×50 ml). The combined organic extracts were dried ($MgSO_4$), the solvent removed in vacuo and the residue purified by flash chromatography.

2.4. General procedure for palladium catalysed cyclisation reactions using catalyst system B

A mixture of the cycloadduct (0.4 mmol), $Pd(OAc)_2$ (9 mg, 0.04 mmol), PPh_3 (21 mg, 0.08 mmol) and TlOAc (0.126 g, 0.48 mmol) in dry solvent (20 ml) was heated under a dry nitrogen atmosphere until tlc or ^{1}H NMR analysis showed complete reaction. The mixture was cooled, filtered through florisil, the solvent removed in vacuo and the crude product purified by flash chromatography.

2.4.1. 2-Carbomethoxy-6,8-dioxo-3-(2′-iodobenzyl)-7-methyl-4-styryl-2,3,7-triazabicyclo [3.3.0] octane 2 and 3. Prepared from cinnamaldehyde (0.264 g, 2 mmol), *N*-(2-iodobenzyl)-*N*′-carbomethoxy hydrazine **1** (0.612 g, 2 mmol) and NMM (0.22 g, 2 mmol). Reaction was complete after 10 h in boiling *m*-xylene. The product comprised a 4:1 mixture of **2** and **3** which was separated by flash chromatography, eluting with 7:3 v/v hexane–ethyl acetate.

2 (0.56 g, 54%) crystallized from hexane–diethyl ether as colourless prisms, mp 158–160°C.

Found: C, 52.15; H, 4.05; N, 7.85; I, 24.00. $C_{23}H_{22}IN_3O_4$ requires C, 52.00; H, 4.15; N, 7.90; I, 23.90%; δ_H(400 MHz) 7.71 (d, 1H, *J*=7.9 Hz, ArH), 7.46 (d, 1H, *J*=7.7 Hz, ArH), 7.32–7.22 (m, 6H, ArH), 6.85 (t, 1H, *J*=7.7 Hz, ArH), 6.79 (d, 1H, *J*=15.6 Hz, =CHPh), 6.27 (dd, 1H, *J*=15.6 and 8.9 Hz, =CH), 5.30 (d, 1H, *J*=8.3 Hz, 1-H), 4.26 (t, 1H, *J*=8.5 Hz, 5-H), 4.22 and 3.61 (2×d, 2×1H, *J*=13.5 Hz, NCH_2), 3.70 (t, 1H, *J*=8.2 Hz, 5H), 3.62 (s, 3H, CO_2CH_3) and 3.11 (s, 3H, NCH_3); *m*/*z* (%) 531 (M^+, 58), 314 (11), 242 (23), 217 (100), 185 (18), 169 913), 141 (48), 128 (110, 115 (40), 90 947), 59 (31) and 32 (22).

n.O.e. data

	Enhancement (%)		
Proton irradiated	1-H	4-H	5-H
1-H	–		9
4-H		–	10
5-H	16	12	

3 (0.14 g, 13%) obtained as a pale yellow foam. HRMS 531.0634. $C_{23}H_{22}IN_3O_4$ requires 531.0655; δ_H(400 MHz) 7.81 (d, 1H, *J*=7.9 Hz, ArH), 7.52 (d, br, 1H, *J*=7.3 Hz, ArH), 7.33–7.25 (m, 6H, ArH), 6.96 (t, 1H, *J*=7.6 Hz, ArH), 6.88 (d, 1H, *J*=15.8 Hz, =CHPh), 5.96 (dd, 1H, *J*=15.7 and 4.3 Hz, =CH), 5.28 (d, 1H, *J*=8.2 Hz, 1-H), 4.37 (d, 1H, *J*=4.2 Hz, 4-H), 3.96 (s, 2H, NCH_2), 3.71 (s, 3H, CO_2CH_3), 3.59 (d, 1H, *J*=8.2 Hz, 5-H) and 3.15 (s, 3H, NCH_3); *m*/*z* (%) 531 (M^+, 45), 242 (220, 217 (1000, 185 922), 141 (470, 115 (47), 90 (61) and 59 (40).

n.O.e. data

	Enhancement (%)		
Proton irradiated	1-H	4-H	5-H
1-H	–		10
4-H		–	6
5-H			

2.4.2. Cyclisation product 10. A mixture of **2** (0.213 g, 0.4 mmol) and catalyst system A in dry acetonitrile (20 ml) was boiled under a dry nitrogen atmosphere for 48 h. Work up by the general procedure followed by flash chromatography of the residue, eluting with 3:2 v/v hexane–ethyl acetate gave the product (0.131 g, 81%), which crystallized from ethanol as colourless needles, mp 201.5–203.5°C.

The reaction was also performed in *m*-xylene (24 h, 110–120°C) according to the general procedure which gave the product in 89% yield.

Found: C, 68.55; H, 5.45; N, 10.35. $C_{23}H_{21}N_3O_4$ requires C, 68.45; H, 5.25; N, 10.40%; δ_H(400 MHz) 7.55 (d, 1H, *J*=7.6 Hz, ArH), 7.41–7.22 (m, 8H, ArH), 7.05 (d, 1H, *J*=7.3 Hz, ArH), 5.14 (d, 1H, *J*=8.6 Hz, 1-H), 4.99 (d, 1H, *J*=9.4 Hz, 4-H), 4.20 and 3.74 (2×d, 2×1H, *J*=15.3 Hz, NCH_2), 3.83 (s, 3H, CO_2CH_3), 3.53 (t, 1H, *J*=9.0 Hz, 5-H) and 2.52 (s, 3H, NCH_3); *m*/*z* (%) 403 (M^+, 50), 344 (8), 292 (15), 218 (1000, 203 (8), 191 (13), 115 (7) and 59 (15).

n.O.e. data

	Enhancement (%)		
Proton irradiated	1-H	4-H	5-H
1-H	–		11
4-H		–	15
5-H	17	17	–

2.4.3. 2-^{t}Butoxycarbonyl-6,8-dioxo-3-(3′-phenyl)-prop-2′-enyl-7-methyl-4-(2′-iodo)-phenyl-2,3,4-triazabicyclo [3.3.0] octane 12 and 13. Prepared from 2-iodobenzaldehyde (0.464 g, 2 mmol), hydrazine **11** (0.546 g, 2 mmol) and NMM (0.222 g, 2 mol). Reaction was complete after 24 h in boiling *m*-xylene and afforded a 1.5:1 mixture of **12** and **13** which was separated by flash chromatography, eluting with 4:1 v/v hexane–ethyl acetate.

12 (0.522 g, 46%) obtained as a pale yellow foam. Found: C, 54.70; H, 4.75; N, 7.35; I, 22.35. $C_{26}H_{28}IN_3O_4$ requires C, 54.45; H, 4.90; N, 7.35; I, 22.15%.

δ_H 7.80 (d, 1H, *J*=7.8 Hz, ArH), 7.33–7.23 (m, 7H, ArH), 6.98 (m, 1H, ArH), 6.51 (d, 1H, *J*=16.2 Hz, =CHPh), 6.22 (dt, 1H, *J*=16.2 and 6.9 Hz, =CH), 5.02 (d, 1H, *J*=8.1 Hz, 1-H), 4.92 (d, 1H, *J*=9.2 Hz, 4-H), 4.12 and 3.63 (2×dd, 2×1H, *J*=13.6 and 6.9 Hz, CH_2), 3.88 (t, 1H, *J*=8.8 Hz, 5-H), 2.63 (s, 3H, NCH_3) and 1.60 (s, 9H, 3×CH_3); *m*/*z* (%) 573 (M^+, 1), 356 (47), 328 (22), 144 (23), 117 (1000, 91 (28) and 57 (28).

13 (0.348 g, 30%) obtained as a yellow foam. Found: C, 54.40; H, 4.65; N, 7.40; I, 21.95; δ_H 7.87 (d, 1H, *J*=7.8 Hz, ArH), 7.41–7.18 (m, 7H, ArH), 6.96 (t, 1H, *J*=7.5 Hz, ArH), 6.42 (d, 1H, *J*=15.9 Hz, =CHPh), 6.24 (dt, 1H, *J*=15.9 and 6.6 Hz, =CH), 5.04 (d, br, 1H, 1-H), 4.93 (s, 1H, 4-H), 3.81 (d, 1H, *J*=8.2 Hz, 5-H), 3.63–3.49 (m, br, 2H, CH_2), 3.01 (s, 3H, NCH_3) and 1.43 (s, 9H, 3×CH_3); *m*/*z* (%) 573 (M^+, 9), 517 (35), 473 (32), 370 (22), 356 (28), 117 91000, 91 928), 57 (69) and 41 (23).

2.4.4. Cyclisation product 14. A mixture of **12** (0.23 g, 0.40 mmol) and catalyst system B was heated in dry *m*-xylene for 2 h at 120–130°C according to the general procedure. Work up followed by flash chromatography of the residue, eluting with 7:3 v/v hexane–ethyl acetate gave the product (0.158 g, 89%) which crystallized from ethanol as colourless prisms, mp &greater;230°C (dec.); Found: C, 70.15; H, 6.15; N, 9.6. $C_{26}H_{27}N_3O_4$ requires C, 70.1; H, 6.1; N, 9.45%; δ_H(400 MHz) 7.62 (d, 1H, *J*=6.6 Hz, ArH), 7.39–7.25 (m, 8H, ArH), 7.15 (s, 1H, =CH), 5.24 (d, 1H, *J*=8.4 Hz, 1-H), 4.84 (d, 1H, *J*=8.4 Hz, 4-H), 4.37 and 3.09 (2×d, 2×1H, *J*=11.7 Hz, CH_2), 3.94 (t, 1H, *J*=8.4 Hz, 5-H), 2.87 (s, 3H, NCH_3) and 1.42 (s, 9H, 3×CH_3).

n.O.e. data

	Enhancement (%)		
Proton irradiated	1-H	4-H	5-H
1-H	–		9
4-H		–	8
5-H	21	18	–

m/*z* (%) 445 (M^+, 1), 345 (95), 234 (62), 218 (92), 205 (43), 115 (23), 91 (29), 57 (100) and 44 (20).

2.4.5. Cyclisation product 15. A mixture of **13** (0.23 g, 0.40 mmol) and catalyst system B was heated in dry *m*-xylene for 5 h at 120–130°C according to the general procedure. After work up, flash chromatography of the residue, eluting with 7:3 v/v hexane–ethyl acetate gave the product (0.155 g, 87%) which crystallized from hexane–ethyl acetate as colourless needles, mp 240–242°C; Found: C, 70.00; H, 6.25; N, 9.59. $C_{26}H_{27}N_3O_4$ requires C, 70.10; H, 6.10; N, 9.45%; δ_H(400 MHz) 7.66–7.28 (m, 9H, ArH), 7.24 (s, 1H, =CH), 5.06 (d, 1H, *J*=8.4 Hz, 1-H), 4.45 and 3.36 (2×d, 2×1H, *J*=10.4 Hz, CH_2), 4.43 (d, 1H, *J*=8.4 Hz, 4-H), 3.73 (t, 1H, *J*=8.4 Hz, 5-H), 3.06 (s, 3H, NCH_3) and 1.12 (s, 9H, 3×CH_3).

n.O.e. data

	Enhancement (%)		
Proton irradiated	1-H	4-H	5-H
1-H	–		1
4-H		–	
5-H	3		–

m/*z* (%) 445 (M^+, 1), 345 (87), 234 (50), 218 (94), 205 (39), 91 (33) and 57 (100).

2.4.6. 3-(2′-Bromoprop-2′-en-1′-yl)-2-carbomethoxy-6,8-dioxo-7-methyl-4-phenyl-2,3,7-triazabicyclo[3.3.0] octane 17a and 18a. Prepared from benzaldehyde (0.21 g, 2.0 mmol), hydrazine **16** (0.43 g, 2.0 mmol) and NMM (0.22 g, 2.0 mmol). Reaction was complete after 14 h in boiling *m*-xylene and afforded a 1.7:1 mixture of **17a** and **18a** which was separated by flash chromatography, eluting with 4:1 v/v hexane–ethyl acetate.

17a (0.277 g, 34%) crystallized from ethanol as colourless needles, mp 161–163°C; Found: C, 50.15; H, 4.35; N, 10.35; Br, 19.75. $C_{17}H_{18}BrN_3O_4$ requires C, 50.00; H, 4.45; N, 10.30; Br, 19.55%; δ_H 7.33–7.24 (m, 5H, ArH), 5.96 and 5.64 (2×s, 2×1H, =CH_2), 5.16 (d, 1H, *J*=8.9 Hz, 1-H), 4.68

(d, 1H, J=8.5 Hz, 4-H), 4.07 and 3.69 (2×d, 2×1H, J=13.9 Hz, NCH_2), 4.01 (t, 1H, J=8.5 Hz, 5-H), 3.93 (s, 3H, OCH_3) and 2.57 (s, 3H, NCH_3); *m/z* (%) 409 (M^+, 12), 407 (M^+, 12), 350 (25), 348 (25), 216 (92), 159 (43), 144 (57), 115 (100), 59 (43) and 39 (40).

18a (0.155 g, 19%) obtained as colourless needles, mp 145–147°C, from ethanol; Found: C, 50.05; H, 4.50; N, 10.45; Br, 19.40; δ_H 7.48–7.25 (m, 5H, ArH), 5.87 and 5.59 (2×s, 2×1H, $=CH_2$), 5.19 (d, 1H, J=8.4 Hz, 1-H), 4.87 (s, 1H, 4-H), 3.86 (d, 1H, J=8.4 Hz, 5-H), 3.80 (s, 3H, OCH_3), 3.77 and 3.45 (2×d, 2×1H, J=13.8 Hz, NCH_2) and 3.11 (s, 3H, NCH_3); *m/z* (%) 409 (M^+, 7), 407 (M^+, 7), 350 (28), 348 (29), 328 (16), 265 (17), 263 (17), 216 (89), 183 (15), 159 (37), 144 (48), 115 (100), 91 (20), 77 (22), 59 (41) and 39 (37).

2.4.7. 3-(2′-Bromoprop-2′-en-1′-yl)-2-carbomethoxy-6,8-dioxo-7-methyl-4-(2′-thienyl)-2,3,7-triazabicyclo[3.3.0] octane 17b and 18b. Prepared from thiophene-2-carboxaldehyde (0.22 g, 2.0 mmol), hydrazine **16** (0.42 g, 2.0 mmol) and NMM (0.22 g, 2.0 mmol). Reaction was complete after 16 h in boiling *m*-xylene and afforded a 1:1 mixture of **17b** and **18b** which was separated by flash chromatography, eluting with 4:1 v/v hexane–ethyl acetate.

17b (0.190 g, 23%) crystallized from ethanol as colourless needles, mp 166–168°C; Found: C, 43.45; H, 3.75; N, 10.05; Br, 19.40; S, 7.50. $C_{15}H_{16}BrN_3O_4S$ requires C, 43.50; H, 3.90; N, 10.15; Br, 19.30; S, 7.75%; δ_H 7.22 (d, 1H, J=4.8 Hz, ArH), 7.00–6.97 (m, 2H, ArH), 5.82 and 5.58 (2×s, 2×1H, $=CH_2$), 5.16 (d, 1H, J=8.8 Hz, 1-H), 4.76 (d, 1H, J=8.0 Hz, 4-H), 4.03 and 3.74 (2×d, 2×1H, J=13.6 Hz, NCH_2), 4.09 (2×t, 1H, J=8.0 and 8.8 Hz, 5-H), 3.88 (s, 3H, OCH_3) and 2.62 (s, 3H, NCH_3).

m/z (%) 415 (M^+, 10), 413 (M^+, 10), 356 (37), 354 (37), 271 (26), 269 (26), 222 (84), 165 (39), 150 (40), 121 (100) and 59 (36).

18b (0.190 g, 23%) crystallized from ethanol as colourless needles, mp 154–156°C; Found: C, 43.65; H, 4.15; N, 10.15; Br, 19.15; S, 7.70%; δ_H 7.24 (d, 1H, J=4.7 Hz, ArH), 7.01–6.97 (m, 2H, ArH), 5.75 and 5.58 (2×s, 2×1H, $=CH_2$), 5.24 (d, 1H, J=8.6 Hz, 1-H), 4.90 (s, 1H, 4-H), 3.89 (d, 1H, J=8.6 Hz, 5-H), 3.72 (s, 3H, OCH_3), 3.84 and 3.50 (2×d, 2×1H, J=13.2 Hz, NCH_2) and 3.16 (s, 3H, NCH_3); *m/z* (%) 415 (M^+, 8), 413 (M^+, 8), 356 (34), 354 (34), 271 (22), 269 (22), 222 (75), 165 (32), 150 (41), 121 (100) and 59 (38).

2.4.8. Cyclisation product 19. A mixture of **17a** (0.16 g, 0.40 mmol) and catalyst system B was boiled under reflux in dry MeCN for 16 h. After work up, flash chromatography of the residue, eluting with 7:3 v/v hexane–ethyl acetate gave the product (64 mg, 49%) which crystallized from ethanol as colourless needles, mp 192.5–194.5°C; Found: C, 62.65; H, 5.15; N, 12.80. $C_{17}H_{17}N_3O_4$ requires C, 62.40; H, 5.25; N, 12.85%; δ_H 7.34–7.20 (m, 4H, ArH), 5.99 and 5.51 (2×s, 2×1H, $=CH_2$), 5.15 (d, 1H, J=8.5 Hz, 1-H), 4.79 (d, 1H, J=8.5 Hz, 4-H), 4.36 and 3.24 (2×d, 2×1H, J=12.1 Hz, NCH_2), 3.91 (s, 3H, OCH_3), 3.82 (t, 1H, J=8.5 Hz, 5-H) and 2.84 (s, 3H, NCH_3); *m/z* (%) 327 (M^+, 54), 268 (10), 216 (17), 142 (100) and 59 (18).

2.4.9. Cyclisation product 20. A mixture of **18a** (0.16 g, 0.40 mmol) and catalyst system B was boiled under reflux in dry MeCN for 24 h. After work up, flash chromatography of the residue, eluting with 7:3 v/v hexane–ethyl acetate gave the product (61 mg, 47%) which crystallized from ethanol as colourless needles, mp 180–182°C; Found: C, 62.45; H, 5.35; N, 12.60. $C_{17}H_{17}N_3O_4$ requires C, 62.40; H, 5.25; N, 12.85%; δ_H 7.37–7.21 (m, 4H, ArH), 5.93 and 5.47 (2×s, 2×1H, $=CH_2$), 5.08 (d, 1H, J=8.4 Hz, 1-H), 4.47 (d, 1H, J=8.4 Hz, 4-H), 4.29 and 3.11 (2×d, 2×1H, J=11.8 Hz, NCH_2), 3.87 (s, 3H, OCH_3), 3.68 (t, 1H, J=8.4 Hz, 5-H) and 3.00 (s, 3H, NCH_3); *m/z* (%) 327 (M^+, 58), 268 (19), 216 (31), 184 (42), 142 (100) and 59 (34).

2.4.10. Cyclisation product 21. A mixture of **17b** (0.16 g, 0.40 mmol) and catalyst system B was boiled under reflux in dry MeCN for 16 h. After work up, flash chromatography of the residue, eluting with 7:3 v/v hexane–ethyl acetate gave the product (72 mg, 54%) which crystallized from ethanol as colourless needles, mp 185–187° C; Found: C, 54.10; H, 4.75; N, 12.35; S, 9.55. $C_{15}H_{15}N_3O_4S$ requires C, 54.05; H, 4.55; N, 12.60; S, 9.60%; δ_H 7.24 (d, 1H, J=5.1 Hz, ArH), 6.99 (d, 1H, J=5.1 Hz, ArH), 5.94 and 5.62 (2×s, 2×1H, $=CH_2$), 5.13 (d, 1H, J=8.4 Hz, 1–H), 4.72 (d, 1H, J=8.4 Hz, 4-H), 3.92 and 3.29 (2×d, 2×1H, J=12.4 Hz, NCH_2), 3.75 (s, 3H, OCH_3), 3.76 (t, 1H, J=8.4 Hz, 5-H) and 2.96 (s, 3H, NCH_3); *m/z* (%) 333 (M^+, 61), 274 (18), 222 (21), 148 (100) and 59 (34).

2.4.11. Cyclisation product 22. A mixture of **18b** (0.16 g, 0.40 mmol) and catalyst system B was boiled under reflux in dry MeCN for 24 h. After work up, flash chromatography of the residue, eluting with 7:3 v/v hexane–ethyl acetate gave the product (67 mg, 50%) which crystallized from ethanol as colourless needles, mp 192–194°C; Found: C, 54.15; H, 4.35; N, 12.70; S, 9.75. $C_{15}H_{15}N_3O_4S$ requires C, 54.05; H, 4.55; N, 12.60; S, 9.60%; δ_H 7.19 (d, 1H, J=5.0 Hz, ArH), 6.98 (d, 1H, J=5.0 Hz, ArH), 6.02 and 5.56 (2×s, 2×1H, $=CH_2$), 5.24 (d, 1H, J=8.2 Hz, 1-H), 4.81 (d, 1H, J=8.2 Hz, 4-H), 4.17 and 3.32 (2×d, 2×1H, J=12.0 Hz, NCH_2), 3.85 (s, 3H, OCH_3), 3.74 (t, 1H, J=8.2 Hz, 5-H) and 2.79 (s, 3H, NCH_3); *m/z* (%) 333 (M^+, 48), 274 (23), 222 (34), 148 (100) and 59 (39).

2.4.12. 2-Carbomethoxy-6,8-dioxo-3-(2′-iodophenyl)-7-methyl-4-(3′-thienyl)-2,3,7-triazabicyclo [3.3.0] octane 23a and 24a. Prepared from thiophene-3-carboxaldehyde (0.22 g, 2.0 mmol), hydrazine **1** (0.61 g, 2 mmol) and NMM (0.22 g, 2.0 mmol). Reaction was complete after 28 h in boiling *m*-xylene and afforded a 2.8:1 mixture of **23a** and **24a** which was separated by flash chromatography, eluting with 7:3 v/v hexane–ethyl acetate.

23a (0.51 g, 50%) crystallized from ethanol as colourless prisms, mp 155–157°C; Found: C, 44.6; H, 3.55; N, 8.15; I, 24.90; S, 6.30. $C_{19}H_{18}IN_3O_4S$ requires C, 44.65; H, 3.55; N, 8.20; I, 24.80; S, 6.25%; δ_H 7.80 (d, 1H, J=7.5 Hz, ArH), 7.56 (d, 1H, J=7.5 Hz, ArH), 7.37–7.18 (m, 3H, ArH), 6.96

(t, 1H, J=7.5 Hz, ArH), 6.90 (d, 1H, J=5.1 Hz, ArH), 5.18 (d, 1H, J=8.3 Hz, 1-H), 4.69 (d, 1H, J=7.6 Hz, 4-H), 4.23 and 3.96 (2×d, 2×1H, J=13.6 Hz, NCH_2), 4.10 (2×t, 1H, J=7.6 and 8.3 Hz, 5-H), 3.86 (s, 3H, OCH_3) and 2.60 (s, 3H, NCH_3).

24a (0.17 g, 17%) obtained as colourless prisms from ethanol, mp 143–145°C; Found: C, 44.85; H, 3.50; N, 8.25; I, 24.85; S, 6.30%; δ_H 7.79 (d, 1H, J=7.7 Hz, ArH), 7.47 (s, br, 1H, ArH), 7.39 (s, br, 1H, ArH), 7.32–7.25 (m, 2H, ArH), 7.02–6.92 (m, 2H, ArH), 5.25 (d, br, 1H, J=8.4 Hz, 1-H), 4.77 (s, 1H, 4-H), 4.02 and 3.95 (2×d, 2×1H, J=13.5 Hz, NCH_2), 3.82 (d, 1H, J=8.4 Hz, 5-H), 3.66 (s, br, 3H, OCH_3) and 3.16 (s, 3H, NCH_3).

m/z (%) 511 (M^+, 39), 294 (19), 222 (61), 217 (100), 165 (34), 121 (37), 90 (59) and 59 (26).

2.4.13. 2-Carbomethoxy-6,8-dioxo-4-(3′-furyl)-3-(2′-iodobenzyl)-7-methyl-2,3,7-triazabicyclo [3.3.0] octane 23b and 24b. Prepared from 3-furaldehyde (0.19 g, 2.0 mmol), hydrazine **1** (0.61 g, 2.0 mmol) and NMM (0.22 g, 2.0 mmol). Reaction was complete after 20 h in boiling *m*-xylene and afforded a 2.5:1 mixture of **23b** and **24b** which was separated by flash chromatography, eluting with 7:3 v/v hexane–ethyl acetate.

23b (0.37 g, 37%) crystallized from ethanol as colourless prisms, mp 155–157°C; Found: C, 46.10; H, 3.60; N, 8.65. $C_{19}H_{18}IN_3O_4$ requires C, 46.10; H, 3.65; N, 8.5%; δ_H 7.76 (d, 1H, J=7.8 Hz, ArH), 7.64 (s, 1H, ArH), 7.52 (d, 1H, J=7.6 Hz, ArH), 7.29 (s, 2H, ArH), 6.93 (t, 1H, J=7.6 Hz, ArH), 6.27 (s, 1H, ArH), 5.24 (d, 1H, J=8.4 Hz, 1-H), 4.55 (d. 1H, J=7.6 Hz, 4-H), 4.12 and 3.77 (2×d, 2×1H, J=13.7 Hz, NCH_2), 4.03 (2×t, 1H, J=8.4 and 7.6 Hz, 5-H), 3.73 (s, 3H, OCH_3) and 2.82 (s, 3H, NCH_3); m/z (%) 495 (M^+, 43), 217 (100), 206 (56), 165 (15), 149 (16), 121 (15), 90 (58), 78 (22) and 59 (35).

24b (0.89 g, 9%) obtained as colourless prisms, mp 138–140°C from ethanol; Found: C, 46.25; H, 3.70; N, 8.60%; δ_H 7.79 (d, 1H, J=7.9 Hz, ArH), 7.48–7.28 (m, 4H, ArH), 6.96 (t, 1H, J=7.6 Hz, ArH), 6.30 (s, 1H, ArH), 5.27 (d, br, 1H, J=8.3 Hz, 1-H), 4.65 (s, 1H, 4-H), 3.98 and 3.59 (2×d, 2×1H, J=13.4 Hz, NCH_2), 3.76 (d, 1H, J=8.3 Hz, 5-H), 3.66 (s, br, 3H, OCH_3) and 3.16 (s, 3H, NCH_3); m/z (%) 495 (M^+, 7), 217 (100), 206 (21), 128 (22), 119 (34), 90 (44) and 59 (19).

2.4.14. Cyclisation product 25. Reaction of **23a** (0.20 g, 0.40 mmol) in the presence of catalyst system B in dry *m*-xylene at 110–120°C for 14 h according to the general procedure followed by flash chromatography, eluting with 1:1 v/v hexane–ethyl acetate gave the product (0.126 g, 82%) which crystallized from ethanol as colourless needles, mp 214–216°C; Found: C, 59.80; H, 4.55; N, 11.20; S, 8.40. $C_{19}H_{17}N_3O_4S$ requires C, 59.50; H, 4.45; N, 10.95; S, 8.35%; δ_H (400 MHz) 7.50 (d, 1H, J=7.7 Hz, ArH), 7.38–7.23 (m, 4H, ArH), 7.12 (d, 1H, J=5.1 Hz, ArH), 5.21 (d, 1H, J=10.2 Hz, 1-H), 5.13 (d, 1H, J=9.3 Hz, 4-H), 4.04 and 3.96 (2×d, 2×1H, J=15.1 Hz, NCH_2), 3.59 (2×t, 1H, J=9.3 and 10.2 Hz, 5-H), 3.91 (s, 3H, OCH_3) and 2.31 (s, br, 3H, NCH_3).

n.O.e. data

	Enhancement (%)		
Proton irradiated	1-H	4-H	5-H
1-H	–		14
4-H		–	10
5-H	17	14	–

m/z (%) 383 (M^+, 77), 324 (55), 308 (49), 272 (37), 239 (42), 198 (100), 184 (51) and 171 (41).

2.4.15. Cyclisation product 26. Reaction of **24a** (0.20 g, 0.40 mmol) in the presence of catalyst system B in dry *m*-xylene at 110–120°C for 14 h according to the general procedure followed by flash chromatography, eluting with 1:1 v/v hexane–ethyl acetate gave the product (0.123 g, 80%) which crystallized from ethanol as colourless needles, mp 199–202°C; Found: C, 59.45; H, 4.70; N, 11.10; S, 8.40. $C_{19}H_{17}N_3O_4S$ requires C, 59.50; H, 4.45; N, 10.95; S, 8.35%; δ_H (400 MHz) 7.55 (d, 1H, J=7.5 Hz, ArH), 7.44–7.32 (m, 4H, ArH), 7.18 (d, 1H, J=5.1 Hz, ArH), 4.64 (d, 1H, J=8.5 Hz, 4-H), 4.55 (d, 1H, J=8.5 Hz, 1-H), 4.09 and 3.80 (2×d, 2×1H, J=14.9 Hz, NCH_2), 3.95 (s, 3H, OCH_3), 3.02 (t, 1H, J=8.5 Hz, 5-H) and 2.92 (s, 3H, NCH_3).

n.O.e. data

	Enhancement (%)		
Proton irradiated	1-H	4-H	5-H
1-H	–		14
4-H		–	4
5-H	19	5	–

m/z (%) 383 (M^+, 45), 324 (35), 308 (100), 239 (54), 198 (87), 184 (44), 171 (42) and 40 (20).

2.4.16. Cyclisation product 27. Reaction of **23b** (0.20 g, 0.40 mmol) in the presence of catalyst system B in dry *m*-xylene at 110–120°C for 14 h according to the general procedure followed by flash chromatography, eluting with 1:1 v/v hexane–ethyl acetate gave the product (0.107 g, 73%) which crystallized from ethanol as colourless needles, mp 212.5–214.5°C; Found: C, 62.10; H, 4.60; N, 11.65. $C_{19}H_{17}N_3O_5$ requires C, 62.10; H, 4.65; N, 11.45%; δ_H 7.47–7.26 (m, 5H, ArH), 6.63 (d, 1H, J=1.8 Hz, ArH), 5.29 (d, 1H, J=10.0 Hz, 1-H), 4.76 (d, 1H, J=9.2 Hz, 4-H), 3.91 (s, 2H, NCH_2), 3.86 (s, 3H, OCH_3), 3.78 (2×t, 1H, J=9.2 and 10.0 Hz, 5-H) and 2.77 (s, br, 3H, NCH_3); m/z (%) 367 (M^+, 68), 308 (45), 292 (50), 256 (34), 223 (40), 182 (100), 168 (48) and 155 (30).

2.4.17. 2-Carbomethoxy-6,8-dioxo-3-[2′-(*o*-iodophenyl)-ethyl]-7-methyl-4-styryl-2,3,7-triazabicyclo [3.3.0]-octane 29 and 30. Prepared from cinnamaldehyde (0.26 g, 2.0 mmol), hydrazine **28** (0.64 g, 2.0 mmol) and NMM (0.22 g, 2.0 mol). Reaction was completed after 10 h in boiling *m*-xylene. The product comprised a 3:1 mixture of **29** and **30** which was separated by flash chromatography, eluting with 4:1 v/v hexane–ethyl acetate.

29 (0.593 g, 52%), crystallised from hexane–ethyl acetate as colourless needles mp 181.5–183.5°C; Found: C, 52.75;

H, 4.60; N, 7.65; I, 23.45. $C_{24}H_{24}IN_3O_4$ requires C, 52.86; H, 4.44; N, 7.70; I, 23.27%; δ_H 7.71 (d, 1H, J=8.0 Hz, ArH), 7.43–7.14 (m, 7H, ArH), 6.82 (d, 1H, J=6.9 Hz, ArH), 6.81 (d, 1H, J=15.6 Hz, =CHPh), 6.32 (dd, 1H, J=15.6 and 9.5 Hz, =CH), 5.37 (d, 1H, J=8.4 Hz, 1-H), 4.23 (t, 1H, J=8.7 Hz, 4-H), 3.80 (s, 3H, OCH_3), 3.63 (2×t, 1H, J=8.7 and 8.4 Hz, 5-H), 2.98 and 2.51 (2×m, 2×2H, 2×CH_2) and 3.00 (s, 3H, NCH_3); *m/z* (%) 545 (M^+, 2), 328 (100), 231 (30), 217 (32), 141 (28), 115 (38), 104 (43), 91 (25), 77 (27), 57 (32) and 43 (38).

30 (0.196 g, 17%), colourless needles, mp 196–198°C, from hexane–ethyl acetate; Found: C, 52.60; H, 4.70; N, 7.45; I, 23.50; δ_H 7.77 (d, 1H, J=7.8 Hz, ArH), 7.38–7.19 (m, 7H, ArH), 6.88 (t, 1H, J=.9 Hz, ArH), 6.77 (d, 1H, J=15.7 Hz, =CHPh), 5.99 (dd, 1H, J=15.7 and 4.4 Hz, =CH), 5.28 (d, 1H, J=8.1 Hz, 1-H), 4.42 (s, 1H, 4-H), 3.83 (s, 3H, OCH_3), 3.56 (d, 1H, J=8.1 Hz, 5-H), 3.02–2.75 (m, 4H, 2×CH_2) and 3.03 (s, 3H, NCH_3); *m/z* (%) 545 (M^+, 2), 328 (100), 231 (17), 141 (24), 128 (11), 115 918), 104 (28), 91 (11) and 77 (11).

2.4.18. Cyclisation product 31. A mixture of **29** (0.22 g, 0.40 mmol) and catalyst system B was heated in dry *m*-xylene for 5 h at 120–130°C according to the general procedure. After work up by the general procedure, flash chromatography of the residue, eluting with 1:1 v/v hexane–ethyl acetate gave the product (0.147 g, 88%), which crystallized from ethanol as colourless needles, mp 233–235°C; Found: C, 69.15; H, 5.50; N, 10.20. $C_{24}H_{23}N_3O_4$ requires C, 69.05; H, 5.55; N, 10.05%; δ_H 7.41–7.17 (m, 8H, ArH), 7.04 (d, 1H, J=7.1 Hz, ArH), 6.98 (s, 1H, =CH), 5.16 (d, 1H., J=8.8 Hz, 1-H), 5.04 (d, 1H, J=9.8 Hz, 4-H), 3.82 (s, 3H, OCH_3), 3.66–2.93 (m, 4H, 2×CH_2), 3.53 (2×t, 1H, J=8.8 and 9.8 Hz, 5-H) and 2.40 (s, 3H, NCH_3); *m/z* (%) 417 (M^+, 82), 358 (1000, 273 (45), 232 (68), 217 (20), 205 (42), 128 (16), 115 (22), 91 (31) and 40 (17).

2.4.19. Cyclisation product 32. A mixture of **30** (0.22 g, 0.40 mmol) and catalyst system B was heated in dry *m*-xylene for 12 h at 120–130°C according to the general procedure. After work up, flash chromatography of the residue, eluting with 3:2 v/v hexane–ethyl acetate gave the product (0.140 g, 84%) as colourless prisms, mp 100–102°C, from hexane–ether; Found: C, 69.30; H, 5.40; N, 9.90. $C_{24}H_{23}N_3O_4$ requires C, 69.05; H, 5.55; N, 10.05%; δ_H 7.57 (d, 1H, J=7.3 Hz, ArH), 7.44–7.25 (m, 7H, ArH), 7.13 (d, 1H, J=7.3 Hz, ArH), 7.01 (s, 1H, =CH), 4.95 (d, 1H, J=8.4 Hz, 1-H), 4.45 (d, 1H, J=10.1 Hz, 4-H), 3.87 (s, 3H, OCH_3), 3.65–2.76 (m, 4H, 2×CH_2), 3.36 (2×t, 1H, J=8.4 and 10.1 Hz, 5-H) and 2.81 (s, 3H, NCH_3); *m/z* (%) 417 (M^+, 59), 358 (100), 273 (43), 232 (49), 217 (14), 203 (21), 128 (12), 115 (17), 91 (28) and 59 (10).

2.4.20. 2-Carbomethoxy-6,8-dioxo-3-[2′-(*o*-iodophenyl)-ethyl]-7-methyl-4-(3′-thienyl)-2,3,7-triazabicyclo[3.3.0]-octane 33 and 34a. Prepared from thiophene-3-carboxaldehyde (0.22 g, 2.0 mmol), hydrazine **28** (0.64 g, 2.0 mmol) and NMM (0.22 g, 2.0 mmol). Reaction was complete after 22 h in boiling *m*-xylene and afforded a 1.6:1 mixture of **33** and **34a** which was separated by flash chromatography, eluting with 3:1 v/v hexane–ethyl acetate.

33 (0.452 g, 43%) obtained as a colourless foam; Found: C, 45.55; H, 3.80; N, 7.95; I, 24.40; S, 6.05. $C_{20}H_{20}IN_3O_4S$ requires C, 45.70; H, 3.85; N, 8.00; I, 24.15; S, 6.10%.

δ_H 7.74 (d, 1H, J=7.9 Hz, ArH), 7.44 (d, 1H, J=1.8 Hz, ArH), 7.24–7.18 (m. 3H, ArH), 6.93–6.86 (m, 2H, ArH), 5.21 (d, 1H, J=8.3 Hz, 1-H), 4.75 (d, 1H, J=7.7 Hz, 4-H), 4.00 (2×t, 1H, J=8.3 and 7.7 Hz, 5-H), 3.87 (s., 3H, OCH_3), 3.11–2.90 (m, 4H, 2×CH_2) and 2.69 (s, 3H, NCH_3); *m/z* (%) 525 (M^+, 1), 308 (100), 231 (18), 197 (17), 104 (31), 84 (40) and 49 (51).

34a (0.263 g, 25%) obtained as a colourless foam; Found: C, 45.75; H, 3.95; N, 7.90; I, 24.30; S, 5.95. $C_{20}H_{20}IN_3O_4$ requires C, 45.70; H, 3.85; N, 8.00; I, 24.5; S, 6.10%; δ_H 7.76 (d, 1H, J=7.9 Hz, ArH), 7.38–7.24 (m, 4H, ArH), 7.01 (d, 1H, J=4.5 Hz, ArH), 6.88 (t, 1H, J=7.7 Hz, ArH), 5.26 (d, br, 1H, J=8.3 Hz, 1-H), 4.85 (s, 1H, 4-H), 3.78 (s, 3H, OCH_3), 3.74 (d, 1H, J=8.3 Hz, 5-H), 3.03 (s, 3H, NCH_3) and 3.01–2.82 (m, 4H, 2×CH_2).

2.4.21. Cyclisation product 35. A mixture of **33** (0.21 g, 0.40 mmol) and catalyst system B was heated in *m*-xylene at 130–140°C for 24 h according to the general procedure. Flash chromatography, eluting with 2:1 v/v hexane–ethyl acetate gave the product (0.108 g, 68%) which crystallized from ethanol as colourless needles, mp 232–234°C; Found: C, 60.65; H, 4.70; N, 10.60; S, 8.00. $C_{20}H_{19}N_3O_4S$ requires C, 60.45; H, 4.80; N, 10.55; S, 8.05%; δ_H 7.37 (d, 1H, J=4.9 Hz, ArH), 7.27–7.16 (m, 4H, ArH), 7.00 (d, 1H, J=4.9 Hz, ArH), 4.81 (d, 1H, J=7.4 Hz, 1-H), 4.67 (d, 1H, J=7.7 Hz, 4-H), 3.77 (s, 3H, OCH_3), 3.48–2.78 (m, 4H, 2×CH_2), 3.42 (2×t, 1H, J=7.4 and 7.7 Hz, 5-H) and 2.62 (s, 3H, NCH_3); *m/z* (%) 397 (M^+, 48), 338 (1000, 253 (69), 197 (21), 184 (43), 91 (30) and 59 (29).

2.4.22. Cyclisation product 36 and 2-carbomethoxy-6,8-dioxo-3-(3′-phenyl)-ethyl-7-methyl-4-(3′-thienyl)-2,3,7-triazabicyclo[3.3.0]octane 34b. A mixture of **34a** (0.21 g, 0.40 mmol) and catalyst system B was heated in *m*-xylene at 130–140°C for 24 h according to the general procedure. Flash chromatography, eluting with 2:1 v/v hexane–ethyl acetate gave **36** (0.76 mg, 46%) which crystallized from ethanol as colourless needles, mp 217–219°C; Found: C, 60.3; H, 4.75; N, 10.55; S, 8.05%; $C_{20}H_{19}N_3O_4S$ requires C, 60.45; H, 4.8; N, 10.55; S, 8.05%; δ_H 7.33–7.21 (m, 5H, ArH), 6.96 (d, 1H, J=4.8 Hz, ArH), 5.22 (, 1H, J=8.7 Hz, 1-H), 4.46 (d, 1H, J=8.7 Hz, 4-H), 3.39 (s, 3H, OCH_3), 3.66 (t, 1H, J=8.7 Hz, 5-H), 3.17–2.63 (m, 4H, 2×CH_2) and 3.04 (s, 3H, NCH_3); *m/z* (%) 397 (M^+,56), 338 (100), 253 (48), 212 (22), 184 (58), 171 (18), 91 (34) and 59 (21).

2.4.23. Deiodination product 34b. (24 mg, 15%) obtained as colourless needles mp 166–168°C from ethanol; Found: C, 60.2; H, 5.05; N, 10.7; S, 8.0%. $C_{20}H_{21}N_3O_4S$ requires C, 60.14; H, 5.3; N, 10.5; S, 8.03%; δ_H 7.31–7.19 (m, 7H, ArH), 7.03 (d, 1H, J=4.8 Hz, ArH), 5.29 (d, 1H, J=8.5 Hz, 1-H), 4.96 (s, 1H, 4-H), 3.79 (s, 3H, OCH_3), 3.69 (t, 1H, J=8.5 Hz, 5-H), 2.99–2.74 (m, 4H, 2×CH_2) and 2.87 (s, 3H, NCH_3); *m/z* (%) 399 (M^+, 2) 308 (100), 105 (37), 97 (15), 91 (23), 77 (18) and 59 (17).

2.4.24. 1-(2′-Iodobenzoyl)-5-phenyl-2-(3′-thienyl)-ethyl-pyrazolidine 38. Reaction of paraformaldehyde (90.0 mg,

3.0 mmol) and hydrazine **37a** (0.72 g, 2.0 mmol) with excess styrene in boiling toluene for 9 h, according to the general procedure afforded, after flash chromatography eluting with 4:1 v/v hexane–ethyl acetate, the product (0.89 g, 94%) as colourless prisms from hexane–ether, mp 117–119°C; Found: C, 53.2; H, 4.1; N, 6.0; I, 26.75; S, 6.8. $C_{21}H_{19}IN_2OS$ requires C, 53.15; H, 4.05; N, 5.9; I, 26.75; S, 6.75%; δ_H 7.88 (d, 1H, *J*=7.5 Hz, ArH), 7.50–7.24 (m, 7H, ArH), 7.13–7.08 (m, 2H, ArH), 6.72 (d, 1H, *J*=1.2 Hz, ArH), 6.21 (d, 1H, *J*=5.0 Hz, ArH), 5..51 (t, 1H, *J*=8.7 Hz, CH), 3.87 and 3.80 (2×d, 2×1H, *J*=12.7 Hz, NCH_2–thienyl), 3.22 and 2.97 (2×m, 2×1H, NCH_2) and 2.74 and 2.41 (2×m, 2×1H, CH_2); *m/z* (%) 474 (M^+, 1), 243 (59), 231 (27), 203 (14), 97 (100) and 76 (19).

2.4.25. Cyclisation product 39. A mixture of **38** (0.19 g, 0.40 mmol) and catalyst system B was heated under reflux in dry toluene for 16 h according to the general procedure. Flash chromatography, eluting with 7:3 v/v hexane–ethyl acetate afforded the product (0.12 g, 85%) as a colourless gum; Found: 72.95; H, 5.2; N, 7.95; S, 9.2. $C_{21}H_{18}N_2OS$ requires C, 72.8; H, 5.25; N, 8.1; S, 9.25%; δ_H 7.63 (d, 1H, *J*=7.4 Hz, ArH), 7.47–7.17 (m, 7H, ArH), 7.04–7.01 (m, 2H, ArH), 6.72 (d, 1H, *J*=5.2 Hz, ArH), 5.56 (t, 1H, *J*=9.0 Hz, CH), 4.21 and 4.00 (2×d, 2×1H, *J*=14.3 Hz, NCH_2–thienyl), 3.13–3.08 (m, 2H, NCH_2) and 2.78 and 2.49 (2×m, 2×1H, CH_2); *m/z* (%) 346 (M^+, 70), 200 (100), 186 (16), 171 (91), 127 (13) 117 (37), 91 (13) 40 (19).

2.4.26. *cis*-3,5-Diphenyl-1-(2′-iodobenzoyl)-2-(3′-thienyl)-ethyl-pyrazolidine 41a and *trans*-41b. Reaction of benzaldehyde (0.21 g, 2.0 mmol) and hydrazine **37a** (0.18 g, 2.0 mmol) with excess styrene in boiling toluene for 12 h, according to the general procedure afforded a 1.3:1 mixture of **42a** and **42b** (0.748 g, 68%) which proved inseparable by flash chromatography, eluting with 4:1 v/v hexane–ethyl acetate. Fractional crystallization from ethanol gave **42a** as colourless prisms, mp 154–156°C; Found: C, 58.95; H, 4.4; N, 5.05; I, 23.0; S, 5.65. $C_{27}H_{23}IN_2OS$ requires C, 58.9; H, 4.2; N, 5.1; I, 23.05; S, 5.8%; δ_H 7.84 (d, 1H, *J*=7.8 Hz, ArH), 7.54–7.04 (m, 13H, ArH), 6.77 (d, 1H, *J*=5.0 Hz, ArH), 6.18 (d, 1H, *J*=1.2 Hz, ArH), 5.88 (d, 1H, *J*=5.0 Hz, ArH), 5.75 (t, 1H, *J*=8.8 Hz, H_a), 5.05 (dd, 1H, *J*=4.9 and 11.7 Hz, H_b), 3.63 and 3.52 (2×d, 2×1H, *J*=13.7 Hz, NCH_2), 3.08 (m, 1H, H_c) and 2.84 (m, 1H, H_d); *m/z* (%) 550 (M^+,1), 319 (88), 231 (41), 203 (14), 97 (100), 91 (12) and 76 (13).

41b obtained as colourless prisms, mp 188–190°C, from ethanol; Found: C, 58.75; H, 4.25; N, 4.95; I, 23.25; S, 5.75; δ_H 7.79 (d, 1H, *J*=7.3 Hz, ArH), 7.66 (d, 2H, *J*=7.5 Hz, ArH), 7.44 (t, 2H, *J*=7.6 Hz, ArH), 7.35–7.02 (m, 10H, ArH), 6.79 (d, 1H, *J*=1.1 Hz, ArH), 6.24 (d, 1H, *J*=5.1 Hz, ArH), 5.87 (t, 1H, *J*=8.6 Hz, H_a), 4.33 and 3.95 (2×d, 2×1H, *J*=12.8 Hz, NCH_2), 4.21 (d, 1H, *J*=7.4 Hz, H_b), 3.22 (dd, 1H, *J*=13.4 and 8.6 Hz, H_c) and 2.79 (m, 1H, H_d); *m/z* (%) 550 (M^+, 1), 319 (79), 231 (36), 203 (11), 97 (100), 91 (16) and 76 (22).

2.4.27. *cis*-2-(3′-Furyl)-ethyl-1-(2′-iodobenzoyl)-3,5-diphenyl-pyrazolidine 42a and *trans*-42b. Reaction of benzaldehyde (0.21 g, 2.0 mmol) and hydrazine **37b** (0.68 g, 2 mmol) with excess styrene in boiling toluene for 12 h, according to the general procedure afforded a 1.2:1 mixture of **42a** and **42b** (0.78 g, 73%) which proved inseparable by flash chromatography, eluting with 4:1 v/v hexane–ethyl acetate. Fractional crystallization from ethanol gave **42a** as colourless prisms, mp 148–150°C; Found: C, 60.8; H, 4.45; N, 5.2; I, 23.55. $C_{27}H_{23}IN_2O_2$ requires C, 60.7; H, 4.35; N, 5.25; I, 23.75%; δ_H 7.79 (d, 1H, *J*=7.8 Hz, ArH), 7.62 (d, 1H, *J*=7.8 Hz, ArH), 7.52–7.05 (m, 12H, ArH), 6.85 (s, 1H, ArH), 6.46 (s, 1H, ArH), 5.76 (t, 1H, *J*=8.8 Hz, H_a), 5.23 (s, 1H, ArH), 5.03 (dd, 1H, *J*=4.9 and 11.7 Hz, H_b), 3.52 and 3.38 (2×d, 2×1H, *J*=13.7 Hz, NCH_2), 3.11 (m, 1H, H_c) and 2.87 (m, 1H, H_d); *m/z* (%) 534 (M^+, 1), 303 (74), 231 (46), 203 (17), 81 (100) and 76 (16).

42b obtained as colourless prisms, mp 181–183°C, from ethanol; Found: C, 60.75; H, 4.5; N, 5.25; I, 23.85; δ_H 7.77 (d, 1H, *J*=7.8 Hz, ArH), 7.61–7.04 (m, 13H, ArH), 6.17 (d, 1H, *J*=7.6 Hz, ArH), 5.84 (t, 1H, *J*=8.6 Hz, H_a), 5.52 (s, 1H, ArH), 4.29 and 3.92 (2×d, 2×1H, *J*=12.6 Hz, NCH_2), 4.18 (d, 1H, *J*=7.4 Hz, H_b), 3.23 (dd, 1H, *J*=13.4 and 8.6 Hz, H_c) and 2.76 (m, 1H, H_d); *m/z* (%) 534 (M^+, 2), 303 (100), 231 (39), 203 (14), 105 (12), 91 (14), 81 (82), and 76 (15).

2.4.28. *cis*-1-(2′-Iodobenzoyl)-3-(4′-nitrophenyl)-5-phenyl-2-(3′-thienyl)-ethyl-pyrazolidine 43a and *trans*-43b. Reaction of 4-nitrobenzaldehyde (0.30 g, 2.0 mmol) and hydrazine **37a** (0.72 g, 2.0 mmol) with excess styrene in boiling toluene for 20 h according to the general procedure afforded a 3.5:1 mixture of **43a** and **43b** which was separated by flash chromatography eluting with 7:3 v/v hexane–ethyl acetate. **43a** (0.52 g, 44%), crystallized from ethanol as colourless prisms, mp 177.5–179.5°C; Found: C, 54.4; H, 3.75; N, 6.85; I, 21.45; S, 5.35. $C_{27}H_{22}IN_3O_3S$ requires C, 54.45; H, 3.7; N, 7.05; I, 21.3; S, 5.4%; δ_H 8.03–7.92 (m, 3H, ArH), 7.51–7.11 (m, 10H, ArH), 6.81 (d, 1H, *J*=4.8 Hz, ArH), 6.24 (s, 1H, ArH), 5.83 (d, 1H, *J*=4.8 Hz, ArH), 5.76 (t, 1H, *J*=8.6 Hz, H_a), 5.08 (dd, 1H, *J*=4.9 and 11.9 Hz, H_b), 3.56 (s, 2H, NCH_2), 3.14 (m, 1H, H_c) and 2.89 (m, 1H, H_d); *m/z* (%) 595 (M^+, 1), 364 (52), 231 (100), 203 (31), 97 (66) and 76 (39).

43b (0.16 g, 13%) obtained as colourless prisms, mp 203–205°C, from ethanol; Found: C, 54.6; H, 3.8; N, 7.0; I, 21.15; S, 5.4%; δ_H 8.12 (d, 2H, *J*=8.4 Hz, ArH), 7.84 (d, 1H, *J*=7.8 Hz, ArH), 7.61–7.04 (m, 11H, ArH), 6.83 (s, 1H, ArH), 6.26 (d, 1H, *J*=5.1 Hz, ArH), 5.80 (t, 1H, *J*=8.4 Hz, H_a), 4.32 (d, 1H, *J*=7.2 Hz, H_b), 4.27 and 3.89 (2×d, 2×1H, *J*=12.8 Hz, NCH_2), 3.17 (dd, 1H, *J*=13.2 and 8.4 Hz, H_c) and 2.85 (m, 1H, H_d); *m/z* (%) 595 (M^+, 1) 364 (53), 231 (42), 203 (17), 97 (100) and 76 (14).

2.4.29. *cis*-2-(3′-Furyl-ethyl-1-(2′-iodobenzoyl)-3-(4′-nitrophenyl)-5-phenyl-pyrazolidine 44a and *trans*-44b. Reaction of 4-nitrobenzaldehyde (0.30 g, 2.0 mmol) and hydrazine **37b** (0.69 g, 2.0 mmol) with excess styrene in boiling toluene for 20 h, according to the general procedure afforded a 3.2:1 mixture of **44a** and **44b** which was separated by flash chromatography eluting with 7:3 v/v hexane–ethyl acetate.

44a (0.53 g, 46%), crystallized from ethanol as colourless prisms, mp 176–178; Found: C, 56.1; H, 3.95; N, 7.25; I, 21.8. $C_{27}H_{22}IN_3O_4$ requires C, 55.95; H, 3.85; N, 7.25; I,

21.9%; δ_H (400 MHz) 8.04 (d, 2H, J=8.3 Hz, ArH), 7.90 (d, 1H, J=8.3 Hz, ArH), 7.47–7.10 (m, 10H, ArH), 6.96 (s, 1H, ArH), 6.37 (s, 1H, ArH), 5.73 (t, 1H, J=8.6 Hz, H_a), 5.18 (s, 1H, ArH), 5.07 (dd, br, 1H, H_b), 3.52 (s, 2H, NCH_2), 3.15 (m, 1H, H_c) and 2.87 (m, 1H, H_d).

n.O.e. data

	Enhancement (%)			
Proton irradiated	H_a	H_b	H_c	H_d
H_a		-	5	–
H_b	–		5	–
H_c	8	7		15
H_d	–	–	12	

m/*z* (%) 579 (M^+, 1), 348 (41), 231 (38), 203 (13), 81 (100) and 76 (22).

44b (0.16 g, 14%), crystallized from hexane–ethyl acetate as colourless prisms, mp 191–193°C; Found: C, 56.0; H, 4.05; N, 7.1; I21.95%; δ_H 8.15 (d, 2H, J=8.5 Hz, ArH), 7.86 (d, 1H, J=7.8 Hz, ArH), 7.63 (d, 2H, J=7.5 Hz, ArH), 7.58–7.08 (m, 9H, ArH), 6.39 (d, 1H, J=7.5 Hz, ArH), 5.82 (t, 1H, J=8.0 Hz, H_a), 5.47 (s, 1H, ArH), 4.31 (d, 1H, J=7.2 Hz, H_b), 4.21 and 3.83 (2×d, 2×1H, J=12.7 Hz, NCH_2), 3.14 (m, 1H, H_c) and 2.88 (m, 1H, H_d).

n.O.e. data

	Enhancement (%)			
Proton irradiated	H_a	H_b	H_c	H_d
H_a		–	6	–
H_b	–		–	8

m/*z* (%) 579 (M^+, 1), 348 (62), 231 (36), 203 (14), 81 (100), 76 (14) and 53 (12).

2.4.30. *cis*-3-(2′-Fluorophenyl)-2-(3′-furyl)-ethyl-1-(2′-iodobenzoyl)-5-phenyl-pyrazolidine 45a and *trans*-45b. Reaction of 2-fluorobenzaldehyde (0.25 g, 2.0 mmol) and hydrazine **37b** (0.68 g, 2.0 mmol) with excess styrene in boiling toluene for 30 h afforded a 2.8:1 mixture of **45a** and **45b** (0.53 g, 48%) which proved inseparable by flash chromatography eluting with 4:1 v/v hexane–ethyl acetate. Fractional crystallization from ethanol gave **45a** as colourless prisms, mp 166–168°C; Found: C, 58.95; H, 3.8; N, 5.15; I, 22.75; F, 3.45%. $C_{27}H_{22}IN_2O_2F$ requires C, 58.7; H, 4.0; N, 5.05; I, 22.95; F, 3.45%; δ_H 7.85 (d, 1H, J=7.9 Hz, ArH), 7.58–7.03 (m, 11H, ArH), 6.89 (s, 1H, ArH), 6.84 (d, 1H, J=7.8 Hz, ArH), 6.32 (s, 1H, ArH), 5.67 (t, 1H, J=8.4 Hz, H_a), 5.14 (s, 1H, ArH), 4.96 (dd, 1H, J=12.0 and 5.3 Hz, H_b), 3.53 (s, 2H, NCH_2) and 3.02–2.89 (m, 2H, H_c, and H_d); *m*/*z* (%) 552 (M^+, 1), 321 (100), 231 (38), 203 (21), 81 (95), 76 (19) and 53 (13).

45b obtained as colourless prisms mp 195–197°C, from ethanol; Found: C, 58.75; H, 4.2; N, 4.95; I, 22.95; F, 3.4%; δ_H 7.81 (d, 1H, J=8.0 Hz, ArH), 7.66 (d, 1H, J=7.8 Hz, ArH), 7.54–7.04 (m, 12H, ArH), 6.06 (d, 1H, 7.8 Hz, ArH), 5.97 (t, 1H, J=8.0 Hz, H_a), 5.47 (s, 1H, ArH), 4.57 (d, 1H, J=7.1 Hz, H_b), 4.14 and 3.72 (2×d, 2×1H, J=12.6 Hz, NCH_2) and 3.04–2.93 (m, 2H, H_c and H_d); *m*/*z* (%) 552 (M^+, 1), 321 (78), 231 (34), 203 (16), 81 (100), 76 (23) and 53 (16).

2.4.31. *cis*-3-[4′-(Dimethylamino)-phenyl]-1-(2′-iodobenzoyl)-5-phenyl-2-(3′-thienyl)-ethyl-pyrazolidine 46a and *trans*-46b. Reaction of 4-(dimethylamino)-benzaldehyde (0.30 g, 2.0 mmol) and hydrazine **37a** (0.72 g, 2.0 mmol) with excess styrene in boiling toluene for 18 h afforded a 1:1.5 mixture of **46a** and **46b** which was separated by flash chromatography eluting with 9:1 v/v hexane–ethyl acetate.

46b (0.297 g, 25%), crystallised from ethanol as colourless prisms, mp 180–182°C; Found: C, 58.85; H, 4.9; N, 7.05; I, 21d.2; S5.35%. $C_{29}H_{28}IN_3OS$ requires C, 58.7; H, 4.75; N, 7.1; I, 21.4; S, 5.4%; δ_H 7.80 (d, 1H, J=7.8 Hz, ArH), 7.61 (d, 1H, J=7.8 Hz, ArH), 7.50–6.97 (m, 10H, ArH), 6.77 (d, 1H, J=4.8 Hz, ArH), 6.63 (s, 2H, J=7.8 Hz, ArH), 6.19 (s, 1H, ArH), 5.83 (d, 1H, J=4.8 Hz, ArH), 5.73 (t, 1H, J=8.6 Hz, H_a), 4.90 (dd, 1H, J=12.1 and 4.8 Hz, H_b), 3.55 and 3.40 (2×d, 2×1H, J=13.2 Hz, NCH_2), 2.98 (s, 6H, 2×CH_3) and 3.05–2.90 (m, 2H, H_c and H_d); *m*/*z* (%) 593 (M^+, 1), 362 (48), 231 (100), 203 (30), 115 (17), 97 (74) and 76 (35).

46b (0.439 g, 37%), obtained as colourless prisms mp 202–204°C, from ethanol; Found: C, 58.65; H, 4.85; N, 7.15; I, 21.6; S, 5.35%; δ_H 7.79 (d, 1H, J=7.8 Hz, ArH), 7.60 (d, 1H, J=7.7 Hz, ArH), 7.48–7.24 (m, 5H, ArH), 7.11–6.96 (m, 5H, ArH), 6.81 (s, 1H, ArH), 6.65 (d, 2H, J=7.8 Hz, ArH), 6.22 (d, 1H, J=4.9 Hz, ArH), 5.84 (t, 1H, J=8.4 Hz, H_a), 4.22 (d, 1H, J=7.3 Hz, H_b), 4.19 and 3.84 (2×d, 2×1H, J=12.8, NCH_2), 3.22 (dd, 1H, J=13.3 and 8.4 Hz, H_c), 3.02 (s, 6H, 2×CH_3) and 2.76 (m, 1H, H_d); *m*/*z* (%) 593 (M^+, 1), 362 (29), 231 (76), 203 (42), 115 (15), 97 (100) and 76 (46).

2.4.32. *cis*-3-[4′-Dimethylamino)-phenyl]-2-(3′-furyl)-ethyl-1-(2′-iodobenzoyl)-5-phenyl-pyrazolidine 47a and *trans*-47b. Reaction of 4-(dimethylamino)-benzaldehyde (0.30 g, 2.0 mmol) and hydrazine **37b** (0.69, 2.0 mmol) with excess styrene in boiling toluene for 18 h afforded a 1:1.8 mixture of **47a** and **47b** which was separated by flash chromatography eluting with 9:1 v/v hexane–ethyl acetate.

47a (0.27 g, 23%), crystallized from ethanol as colourless prisms, mp 171–173°C; Found: C, 60.2; H, 4.85; N, 7.4; I, 22.05. $C_{29}H_{28}IN_3O_2$ requires C, 60.3; H, 4.9; N, 7.3; I, 22.0%; δ_H 7.82 (d, 1H, J=7.8 Hz, ArH), 7.64 (d, 1H, J=7.8 Hz, ArH), 7.52–7.21 (m, 5H, ArH), 7.14–6.90 (m, 5H, ArH), 6.60 (d, 2H, J=7.8 Hz, ArH), 6.52 (s, 1H, ArH), 5.77 (t, 1H, J=8.6 Hz, H_a), 5.26 (s, 1H, ArH), 4.95 (dd, 1H, J=12.1 and 4.8 Hz, H_b), 3.48 and 3.32 (2×d, 2×1H, J=13.1 Hz, NCH_2), 2.95 (s, 6H, 2×CH_3) and 3.03–2.91 (m, 2H, H_c and H_d).

n.O.e. data

	Enhancement (%)			
Proton irradiated	H_a	H_b	H_c	H_d
H_a		–	4	–
H_b	–		5	

m/*z* (%) 577 (M+, 2), 346 (54), 231 (100), 203 (40), 146 (23), 134 (24), 81 (58), 76 (46) and 53 (27).

47b (0.47 g, 41%), obtained as colourless prisms mp 196–198°C, from ethanol; Found: C, 60.25; H, 4.9; N, 7.5; I, 21.9%; δ_H 7.79 (d, 1H, J=7.8 Hz, ArH), 7.62 (d, 1H, J=7.7 Hz, ArH), 7.46–7.25 (m, 5H, ArH), 7.08–6.92 (m, 5H, ArH), 6.69 (d, 2H, J=7.8 Hz, ArH), 5.92 (d, 1H, 7.6 Hz, ArH), 5.86 (t, 1H, J=8.4 Hz, H_a), 5.57 (s, 1H, ArH), 4.20 (d, 1H, J=7.5 Hz, H_b), 4.13 and 3.78 (2×d, 2×1H, J=12.7 Hz, NCH_2), 3.19 (dd, 1H, J=13.3 and 8.4 Hz, H_c), 2.99 (s, 6H, 2×CH_3) and 2.77 (m, 1H, H_d).

n.O.e. data

	Enhancement (%)			
Proton irradiated	H_a	H_b	H_c	H_d
H_a		–	2	–
H_b		–	–	4
H_c	16	6		16
H_d	5	14	11	–

m/z (%) 577 (M^+, 2), 346 (28), 231 (85), 203 (33), 81 (100), 76 (42) and 53 (36).

2.4.33. *cis*-1-(2′-Iodobenzoyl)-5-phenyl-2-(3′-thienyl)-ethyl-3-[3′-(trifluoromethyl)-phenyl]-pyrazolidine 48a and *trans*-48b. Reaction of 3-(trifluoromethyl)-benzaldehyde (0.35 g, 2.0 mmol) and hydrazine **37a** (0.72 g, 2.0 mmol) with excess styrene in boiling toluene for 12 h afforded a 2.5:1 mixture of **48a** and **48b** (0.95 g, 77%) as a colourless foam which proved inseparable by flash chromatography eluting with 4:1 v/v hexane–ethyl acetate.

Found: (mixed isomers) C, 54.65; H, 3.7; F, 9.15; N, 4.4; I, 20.4; S, 5.1. $C_{29}H_{28}F_3IN_3OS$ requires C, 54.4; H, 3.6; F, 9.2; N, 4.55; I, 20.5; S, 5.2%; *m/z* (%) (mixed isomers) 618 (M^+, 1), 387 (62), 231 (37), 203 (12), 105 (10), 97 (100) and 76 (14). The ^{1}H NMR spectra of the individual isomers were assigned from the mixture.

48a δ_H 7.81–7.80 (m, 13H, ArH), 6.74 (d, 1H, J=5.0 Hz, ArH), 6.23 (d, 1H, J=1.2 Hz, ArH), 5.89 (d, 1H, J=5.0 Hz, ArH), 5.75 (t, 1H, J=8.6 Hz, H_a), 5.01 (dd, 1H, J=4.9 and 12.1 Hz, H_b), 3.68 and 3.54 (2×d, 2×1H, J=13.6 Hz, NCH_2), 3.06 (m, 1H, H_c) and 2.87 (m, 1H, H_d).

48b δ_H 7.81–7.08 (m, 14H, ArH), 6.82 (s, 1H, ArH), 6.19 (d, 1H, J=5.0 Hz, ArH), 5.79 (t, 1H, J=8.6 Hz, H_b), 4.29 and 3.91 (2×d, 2×1H, J=12.8 Hz, NCH_2), 4.26 (d, 1H, J=7.4 Hz, H_b), 3.06 (m, 1H, H_c) and 2.87 (m, 1H, H_d).

2.4.34. *cis*-2-(3′-Furyl)-ethyl-1-(2′-iodobenzoyl)-5-phenyl-3-[3′ (trifluoromethyl)-phenyl]-pyrazolidine 49a and *trans*-49b. Reaction of 3-(trifluoromethyl)-benzaldehyde (0.35 g, 2.0 mmol) and hydrazine **37b** (0.68 g, 2.0 mmol) with excess styrene in boiling toluene for 12 h afforded a 2.5:1 mixture of **49a** and **49b** (0.92 g, 76%) obtained as a colourless foam which proved inseparable by flash chromatography eluting with 4:1 v/v hexane–ethyl acetate.

Found: (mixed isomers) C, 55.95; H, 3.8; F, 9.4; N, 4.6; I, 20.85. $C_{28}H_{22}F_3IN_2O_2$ requires C, 55.85; H, 3.7; F, 9.45; N, 4.65; I, 21.05% The ^{1}H NMR spectra of the individual isomers were assigned from the mixture.

49a δ_H 7.80–7.09 (m, 13H, ArH), 6.92 (s, 1H, ArH), 6.31 (s, 1H, ArH), 5.75 (t, 1H, J=8.6 Hz, H_a), 5.14 (s, 1H, ArH), 5.02 (dd, 1H, J=12.0 and 4.9 Hz, H_b), 3.52 (s, 2H, NCH_2), 3.02 (m, 1H, H_c) and 2.85 (m, 1H, H_d).

49b δ_H 7.83–7.09 (m, 14H, ArH), 6.20 (d, 1H, 7.6 Hz, ArH), 5.75 (t, 1H, J=8.6 Hz, H_a), 5.46 (s, 1H, ArH), 4.29 (d, 1H, J=7.2 Hz, H_b), 4.22 and 3.85 (2×d, 2×1H, J=12.6 Hz, NCH_2), 3.02 (m, 1H, H_c) and 2.85 (m, 1H, H_d).

m/z (%) (mixed isomers) 602 (M^+, 1), 371 (53), 231 (30), 203 (9) 81 (100), 76 (11) and 53 (9).

2.4.35. *cis*-1-(2′-Iodobenzoyl)-3-(3′-methoxyphenyl)-5-phenyl-2-(3′-thienyl)-ethyl-pyrazolidine 50a and *trans*-50b. Reaction of *m*-anisaldehyde (0.27 g, 2.0 mmol) hydrazine **37a** (0.72 g, 2.0 mmol) with excess styrene in boiling toluene for 10 h afforded a 1.5:1 mixture of **50a** and **50b** (0.882 g, 76%), obtained as a colourless foam which proved inseparable by flash chromatography eluting with 4:1 v/v hexane–ethyl acetate.

Found: (mixed isomers) C, 57.95; H, 4.5; N, 4.75; I, 22.05; S, 5.35. $C_{28}H_{25}IN_2O_2S$ requires C, 57.95; H, 4.35; N, 4.85; I, 21.85; S, 5.5%. The ^{1}H NMR spectra of the individual isomers were assigned from the mixture.

50a δ_H 7.80 (d, 1H, J=7.8 Hz, ArH), 7.59 (d, 1H, J=7.6 Hz, ArH), 7.47–6.77 (m, 12H, Arh), 6.17 (s, 1H, ArH), 5.78 (d, 1H, J=5.1 Hz, ArH), 5.74 (t, 1H, J=8.6 Hz, H_a), 4.92 (dd, 1H, J=12.0 and 4.7 Hz, H_b), 3.67 (s, 3H, OCH_3), 3.66 and 3.52 (2×d, 2×1H, J=13.2 Hz, NCH_2), 3.12 (m, 1H, H_c), and 2.87 (m, 1H, H_d).

50b δ_H 7.77 (d, 1H, J=7.8 Hz, ArH), 7.64 (d, 1H, J 7.7 Hz, ArH), 7.50–6.78 (m, 13H, ArH), 6.28 (d, 1H, 5.0 Hz, ArH), 5.77 (t, 1H, J=8.6 Hz, H_a), 4.19 (d, 1H, J=7.2 Hz, H_b), 4.14 and 3.80 (2×d, 2×1H, J=12.7 Hz, NCH_2), 3.67 (s, 3H, OCH_3), 3.16 (dd, 1 h, J=13.4 and 8.6 Hz, H_c) and 2.71 (m, 1H, H_d).

m/z (%) (mixed isomers) 580 (M^+, 1), 349 (72), 231 (44), 203 (15), 105 (12), 97 (100) and 76 (16).

2.4.36. *cis*-2-(3′-Furyl)-ethyl-1-(2′-iodobenzoyl)-3-(3′-methoxyphenyl)-5-phenyl-pyrazolidine 51a and *trans*-51b. Reaction of *m*-anisaldehyde (0.27 g, 2.0 mmol) and hydrazine **37b** (0.69 g, 2.0 mmol) with excess styrene in boiling toluene for 10 h afforded a 1.3:1 mixture of **51a** and **51b** (0.84 g, 74%) obtained as a colourless foam which proved inseparable by flash chromatography eluting with 4:1 v/v hexane–ethyl acetate.

Found: (mixed isomers) C, 59.7; H, 4.6; N, 4.85; I, 22.45%. $C_{28}H_{25}IN_2O_3$ requires C, 59.6; H, 4.45; N, 4.95; I, 22.5%. The ^{1}H NMR spectra of the individual isomers were assigned from the mixture.

51a δ_H 7.84 (d, 1H, J=7.8 Hz, ArH), 7.63 (d, 1H, J=7.7 Hz, ArH), 7.52–6.78 (m, 12H, ArH), 6.56 (s, 1H, ArH), 6.51 (s, 1H, ArH), 5.72 (t, 1H, J=8.5 Hz, H_a), 5.24 (s, 1H, ArH), 4.93 (dd, 1H, J=12.2 and 4.7 Hz, H_b), 3.69 (s, 3H, OCH_3), 3.49 and 3.36 (2×d, 2×1H, J=13.4 Hz, NCH_2), 3.04 (m, 1H, H_c) and 2.80 (m, 1H, H_d).

51b δ_H 7.81 (d, 1H, J=7.8 Hz, ArH), 7.63 (d, 1H, J=7.7 Hz, ArH), 7.52–6.78 (m, 12H, ArH), 5.97 (d, 1H, 7.6 Hz, ArH), 5.75 (t, 1H, J=8.6 Hz, H_a), 5.50 (s, 1H, ArH), 4.21 (d, 1H, J=7.2 Hz, H_b), 4.16 and 3.77 (2×d, 2×1H, J=12.8 Hz, NCH_2), 3.69 (s, 3H, OCH_3), 3.18 (dd, 1H, J=13.2 and 8.6 Hz, H_c) and 2.72 (m, 1H, H_d).

m/z (%) (mixed isomers) 564 (M^+, 2), 333 (100), 231 (41), 203 (12), 105 (11), 81 (87) 77 (12).

2.4.37. Cyclisation product 54a. A mixture of **41a** (0.22 g, 0.40 mmol) and catalyst system B was boiled under reflux in dry toluene for 16 h according to the general procedure. Flash chromatography, eluting with 3:2 v/v hexane–ethyl acetate afforded the product (0.14 g, 82%) as a colourless gum; Found: C, 76.65; H, 5.3; N, 6.75; S, 7.45. $C_{27}H_{22}N_2OS$ requires C, 76.75; H, 5.25; N, 6.65; S, 7.6%; δ_H (400 MHz) 7.70 (d, 1H, J=7.4 Hz, ArH), 7.51–7.41 (m, 3H, ArH), 7.32–7.20 (m, 9H, ArH), 7.13–7.11 (m, 2 h, ArH), 6.63 (d, 1H, J=5.2 Hz, ArH), 5.78 (t, 1H, J=8.9 Hz, H_a), 4.51 (dd, 1H, J=12.6 and 5.4 Hz, H_b), 3.82 and 3.59 (2×d, 2×1H, J=14.6 Hz, NCH_2), 3.80 (m, 1H, H_c) and 2.83 (m, 1H, H_d).

n.O.e. data

	Enhancement (%)			
Proton irradiated	H_a	H_b	H_c	H_c
H_a		2	6	
H_b			4	
H_c	2	13		22
H_d	–	–	26	

m/z (%) 422 (M^+, 72), 317 (35), 289 (22), 200 (88), 193 (55), 171 (100), 115 (29), 91 (35), 77 (20).

2.4.38. Cyclisation product 54b. A mixture of **41b** (0.22 g, 0.40 mmol) and catalyst system B was boiled under reflux in dry toluene for 16 h according to the general procedure. Flash chromatography, eluting with 3:2 v/v hexane–ethyl acetate afforded the product (0.14 g, 84%) as a colourless gum; Found: C, 76.8; H, 5.45; N, 6.6; S, 7.6%; δ_H (400 MHz, C_6D_6) 7.70 (d, 1H, J=7.4 Hz, ArH), 6.45 (d, 1H, J=5.2 Hz, ArH), 7.14–6.98 (m, 12H, ArH), 6.92 (d, 1H, J=5.2 Hz, ArH), 6.45 (d, 1H, J=5.2 Hz, ArH), 5.58 (t, 1H, J=8.6 Hz, H_a), 3.90 and 3.62 (2×d, 2×1H, J=14.4 Hz, NCH_2), 3.73 (d, 1H, J=7.2 Hz, H_b), 2.58 (m, 1H, H_c), and 2.43 (m, 1H, H_d).

n.O.e. data

	Enhancement (%)			
Proton irradiated	H_a	H_b	H_c	H_d
H_a		–	7	–1
H_b	–		–	5
H_c	23	4		14

m/z (%) 422 (M^+, 100), 318 (18), 289 (20), 214 (29), 200 (71), 193 (49), 171 (87), 115 (27) and 91 (16).

2.4.39. Cyclisation product 55a. A mixture of **44a** (0.23 g, 0.40 mmol) and catalyst system B was boiled under reflux in dry toluene for 16 h according to the general procedure. Flash chromatography, eluting with 1:1 v/v hexane–ethyl acetate afforded the product (0.13 g, 72%), which crystallized from ethanol as colouless needles, mp 185–187°C.

Found: C, 71.9; H, 4.75; N, 9.15; $C_{27}H_{21}N_3O_4$ requires C, 71.85; H, 4.7; N, 9.3%; δ_H 8.15 (2×d, 2×1H, J=8.6 Hz, ArH), 7.99 (2×d, 2×1H, J=8.5 Hz, ArH), 7.72 (d, 1H, J=7.4 Hz, ArH), 7.59–7.19 (m, 9H, ArH), 6.14 (d, 1H, J=1.6 Hz, ArH), 5.87 (t, 1H, J=9.0 Hz, H_a), 4.59 (dd, 1H, J=12.7, and 5.0 Hz, H_b), 3.40 and 3.65 (2×d, 2×1H, J=14.6 Hz, NCH_2), 3.09 (m, 1H, H_c) and 2.81 (m, 1H, H_d); *m/z* (%) 451 (M^+, 9), 346 (75), 241 (25), 184 (60), 128 (56), 115 (16), 105 (91), 91 (48), 77 (100) and 51 (29).

2.4.40. Cyclisation product 55b. A mixture of **44b** (0.23 g, 0.40 mmol) and catalyst system B was boiled under reflux in dry toluene for 16 h according to the general procedure. Flash chromatography, eluting with 1:1 v/v hexane–ethyl acetate afforded the product (0.12 g, 69%) which crystallized from ethanol as colourless needles, mp 214–216°C.

Found: C, 71.7; H, 4.65; N, 9.3%; $C_{27}H_{21}N_3O_4$ requires C, 71.85; H, 4.7; N, 9.3% δ_H (400 MHz) 8.05 (m, 2H, ArH), 7.62–7.17 (m, 12H, ArH), 6.32 (d, 1H, J=1.8 Hz, ArH), 5.43 (t, J=8.8 Hz, H_a), 4.54 (d, 1H, J=7.2 Hz, H_b), 4.28 and 4.11 (2×d, 2×1H, J=14.5 Hz, NCH_2), 3.14 (dd, 1H, J=13.2 and 8.8 Hz, H_c) and 3.01 (m, 1H, H_d).

n.O.e. data

	Enhancement (%)			
Proton irradiated	H_a	H_b	H_c	H_d
H_a		–	2	–
H_b	–		–	2

m/z (%) 451 (M^+, 17), 346 (38), 241 (26), 184 (100), 128 (57), 105 (44), 91 (28), 77 (40) and 57 (25).

2.4.41. Cyclisation product 56a. A mixture of **45a** (0.22 g, 0.40 mmol) and catalyst system B was boiled under reflux in dry toluene for 16 h according to the general procedure. Flash chromatography, eluting with 3:2 v/v hexane–ethyl acetate afforded the product (0.12 g, 71%) as a colourless gum.

Found: C, 76.55; H, 5.05; F, 4.5; N, 6.6%; δ_H (400 MHz) 7.73 (d, 1H, J=7.8 Hz, ArH), 7.54–7.40 (m, 4H, ArH), 7.32–7.21 (m, 7H, ArH), 7.10 (t, 1H, J=7.3 Hz, ArH), 7.00 (t, 1H, J=9.6 Hz, ArH), 6.18 (d, 1H, J=1.8 Hz, ArH), 5.81 (t, 1H, J=8.9 Hz, H_a), 4.65 (dd, 1H, J=12.7 and 5.7 Hz, H_b), 3.78 and 3.44 (2×d, 2×1H, J=14.6 Hz, NCH_2), 3.03 (m, 1H, H_c) and 2.92 (m, 1H, H_d).

n.O.e. data

	Enhancement (%)			
Proton irradiated	H_a	H_b	H_c	H_d
H_a		3	6	–
H_b	5		4	–

m/z (%) 424 (M^+, 100), 319 (26), 211 (28), 184 (85), 156 (27), 128 (81), 115 (20), 102 (18) and 77 (25).

2.4.42. Cyclisation product 57a. A mixture of **46a** (0.24 g, 0.40 mmol) and catalyst system B was boiled under reflux in dry toluene for 16 h according to the general procedure. Flash chromatography, eluting with 3:2 v/v hexane–ethyl acetate afforded the product (0.15 g, 81%) as a colourless gum; Found: C, 74.85; H, 5.95; N, 8.9; S, 6.95; $C_{29}H_{27}N_3OS$ requires C, 74.8; H, 5.85; N, 9.0; S, 6.9%; δ_H 7.76 (d, 1H, J=7.6 Hz, ArH), 7.48–6.98 (m, 11H, ArH), 6.65–6.59 (m, 3H, ArH), 5.77 (t, 1H, J=8.8 Hz, H_a), 4.38 (dd, 1H, J=12.6 and 5.4 Hz, H_b), 3.70 and 3.58 (2×d, 2×1H, J=14.2 Hz, NCH_2), 3.06 (m, 1H, H_c), 2.88 (m, 1H, H_d), and 2.96 (s, 6H, 2×CH_3); *m/z* (%) 465 (M^+, 20), 360 (32), 332 (24), 200 (100), 171 (86), 115 (21) and 77 (29).

2.4.43. Cyclisation product 57b. A mixture of **46b** (0.24 g, 0.40 mmol) and catalyst system B was boiled under reflux in dry toluene for 16 h according to the general procedure. Flash chromatography, eluting with 3:2 v/v hexane–ethyl acetate afforded the product (0.14 g, 77%) as a colourless gum; Found: C, 74.9; H, 5.8; N, 8.85; S, 6.7; $C_{29}H_{27}N_3OS$ requires C, 74.8; H, 5.85; N, 9.0; S, 6.9%; δ_H 7.64–6.65 (m, 15H, ArH), 5.48 (t, 1H, J=8.8 Hz, H_a), 4.36 (d, 1H, J=7.2 Hz, H_b), 4.31 and 4.07 (2×d, 2×1H, J=14.4 Hz, NCH_2), 3.11 (dd, 1H, J=13.3 and 8.8 Hz, H_c), 2.87 (m, 1H, H_d) and 2.98 (s, 6H, 2×CH_3); *m/z* (%), 465 (M^+, 18), 360 (37), 200 (100), 171 (76), 115 (22), and 77 (34).

2.4.44. Cyclisation products 58a and 57b. Treatment of a 2.5:1 mixture of **48a** and **48b** (0.50 g, 0.80 mmol) with catalyst system B in boiling dry toluene for 16 h according to the general procedure afforded a 2.5:1 mixture of **58a** and **58b** (0.31 g, 79%), obtained as a colourless gum which was found to be inseparable by flash chromatography, eluting with 3:2 v/v hexane–ethyl acetate.

Found: (mixed isomers) C, 68.8; H, 4.5; F, 11.55; N, 5.55; S, 6.35; $C_{28}H_{21}F_3N_2OS$ requires C, 68.55; H, 4.3; F, 11.6; N, 5.7; S, 6.55%. The ^{1}H NMR spectra of the individual isomers were assigned from the mixture.

58a δ_H 7.89–7.12 (m, 14H, ArH), 6.71 (d, 1H, J=5.1 Hz, ArH), 5.84 (t, 1H, J=8.9 Hz, H_a), 4.58 (dd, 1H, J=12.2 and 5.6 Hz, H_b), 3.77 and 3.48 (2×d, 2×1H, J=14.6 Hz, NCH_2), 3.14 (m, 1H, H_c) and 2.88 (m, 1H, H_d).

58b δ_H 7.92–7.12 (m, 14H, ArH), 6.82 (d, 1H, J=5.0 Hz, ArH), 5.51 (t, 1H, J=8.8 Hz, H_a), 4.55 (d, 1H, J=7.2 Hz, H_b), 4.42 and 4.18 (2×d, 2×1H, J=14.6 Hz, NCH_2), 3.14 (m, 1H, H_c) and 2.88 (m, 1H, H_d); *m/z* (%) (mixed isomers) 490 (M^+, 32), 386 (28), 200 (75), 171 (100), 115 (20), 91 (42) and 77 (23).

2.4.45. Cyclisation product 59a and 59b. Treatment of a 2.5:1 mixture of **49a** and **49b** (0.48 g, 0.80 mmol) with catalyst system B in boiling dry toluene for 16 h according to the general procedure afforded a 2.5:1 mixture of **59a** and **59b** (0.28 g, 73%), obtained as a colourless gum which was found to inseparable by flash chromatography, eluting with 3:2 v/v hexane–ethyl acetate.

Found: (mixed isomers) C, 70.95; H, 4.4; F11.8; N, 6.0; $C_{28}H_{21}F_3N_2O_2$ requires C, 70.9; H, 4.45; F, 12.0; N, 5.9%. The ^{1}H NMR spectra of the individual isomers were assigned from the mixture.

59a δ_H 7.93–7.24 (m, 14H, ArH), 6.19 (d, 1H, J=1.8 Hz, ArH), 5.89 (t, 1H, J=8.9 Hz, H_a), 4.60 (dd, 1H, J=12.4 and 5.5 Hz, H_b), 3.68 and 3.41 (2×d, 2×1H, J=14.9 Hz, NCH_2), 3.16 (m, 1H, H_c) and 2.84 (m, 1H, H_d).

59b δ_H 7.96–7.24 (m, 14H, ArH), 6.26 (d, 1H, J=1.8 Hz, ArH), 5.53 (t, 1H, J=8.8 Hz, H_a), 4.53 (d, 1H, J=7.2 Hz, H_b), 4.48 and 4.18 (2×d, 2×1H, J=14.6 Hz, NCH_2), 3.10 (dd, 1H, J=13.6 and 8.8 Hz, H_c) and 2.74 (m, 1H, H_d).

m/z (%) (mixed isomers) 474 (M^+, 18), 369 (94), 264 (35), 184 (100), 128 (76), 115 (20), 105 (63), 91 (54), 77 (77) and 51 (30).

2.4.46. Cyclisation product 60a and 60b. Treatment of a 1.5:1 mixture of **50a** and **50b** (0.46 g, 0.80 mmol) with catalyst system B in boiling dry toluene for 16 h according to the general procedure afforded a 1.5:1 mixture of **60a** and **60b** which was separated by flash chromatography, eluting with 3:2 v/v hexane–ethyl acetate.

60a (0.18 g, 85%), obtained as a colourless gum; Found: C, 74.45; H, 5.3; N, 6.1; S, 7.05; $C_{28}H_{24}N_2O_2S$ requires C, 74.3; H, 5.35; N, 6.2; S, 7.1%; δ_H 7.73 (d, 1H, J=7.5 Hz, ArH), 7.55–7.14 (m, 10H, ArH), 6.85–6.78 (m, 3H, ArH), 6.69 (d, 1H, J=5.0 Hz, ArH), 5.81 (t, 1H, J=8.9 Hz, H_a), 4.51 (dd, 1H, J=12.6 and 5.5 Hz, H_b), 3.72 (s, 3H, OCH_3), 3.72 and 3.55 (2×d, 2×1H, J=14.6 Hz, NCH_2), 3.06 (m, 1H, H_c) and 2.82 (m, 1H, H_d); *m/z* (%) 452 (M^+, 55), 347 (31), 200 (90), 171 (100), 115 (24) and 77 (32).

60b (0.12 g, 83%), obtained as a colourless gum; Found: C, 74.3; H, 5.5; N, 6.25; S, 6.95; $C_{28}H_{24}N_2O_2S$ requires C, 74.3; H, 5.35; N, 6.2; S, 7.1%; δ_H 7.51–6.74 (m, 15H, ArH), 5.48 (t, 1H, J=8.8 Hz, H_a), 4.42 (d, 1H, J=7.2 Hz, H_b), 4.32 and 4.13 (2×d, 2×1H, J=14.6 Hz, NCH_2), 3.59 (s, 3H, OCH_3), 3.12 (dd, 1H, J=13.4 and 8.8 Hz, H_c) and 2.91 (m, 1H, H_d); *m/z* (%) 452 (M^+, 34), 347 (27), 200 (100), 171 (87), 115 (22) and 77 (27).

2.4.47. Cyclisation product 61a and 61b. Treatment of a 1.3:1 mixture of **51a** and **51b** (0.45 g, 0.80 mmol), with catalyst system B in boiling dry toluene for 16 h according to the general procedure afforded a 1.3:1 mixture of **61a** and **61b**, which was separated by flash chromatography, eluting with 3:2 v/v hexane–ethyl acetate.

61a (0.138 g, 70%), obtained as a colourless gum; Found: C, 77.0; H, 5.45; N, 6.55; $C_{28}H_{24}N_2O_3$ requires C, 77.05; H, 5.55; N, 6.4%; δ_H 7.75 (d, 1H, J=7.8 Hz, ArH), 7.54–7.40 (m, 4H, ArH), 7.32–7.24 (m, 6H, ArH), 6.84–6.78 (m, 3H, ArH), 6.13 (d, 1H, J=1.8 Hz, ArH), 5.80 (t, 1H, J=8.9 Hz, H_a), 4.52 (dd, 1H, J=12.6 and 5.6 Hz, H_b), 3.77 (s, 3H, OCH_3), 3.65 and 3.48 (2×d, 2×1H, J=14.6 Hz, NCH_2), 3.05 (m, 1H, H_c) and 2.79 (m, 1H, H_d); *m/z* (%) 436 (M^+, 38), 331 (28), 226 (37), 184 (100), 128 (76), 115 (22), 105 (20), 91 (22) and 77 (31).

61b (0.108 g, 71%), obtained as a colourless gum; Found: C, 77.2; H, 5.5; N, 6.45; $C_{28}H_{24}N_2O_3$ requires C, 77.05; H,

5.55; N, 6.4%; δ_H 7.52–6.75 (m, 14H, ArH), 6.30 (d, 1H, J=1.8 Hz, ArH), 5.51 (t, 1H, J=8.8 Hz, H_a), 4.43 (d, 1H, J=7.2 Hz, H_b), 4.27 and 4.08 (2×d, 2×1H, J=14.5 Hz, NCH_2), 3.62 (s, 3H, OCH_3), 3.14 (dd, 1H, J=13.4 and 8.8 Hz, H_c) and 2.88 (m, 1H, H_d); *m/z* (%) 436 (M^+, 16), 331 (62), 226 (24), 184 (60), 128 (44), 115 (17), 105 (82), 91 (41) and 77 (100).

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