Tetrahedron Vol 46 Nos 13/14, pp 4697–4710 1990
Printed in Great Britain

0040-4020/90 $3 00+ 00

ASYMMETRIC SYNTHESIS via ELECTROPHILE-MEDIATED CYCLISATIONS.†

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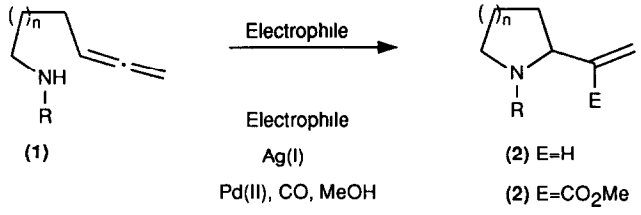
(*Received in UK 2 March* 1990)

*Summary: The electrophile-mediated cyclisation of a series of allenic amines (**8a-e**), carrying a chiral benzylic residue on nitrogen, has been examined using Ag(I) and Pd(II). The cyclised products, (**9/10**)(using Ag(I)) and (**12/13**)(using Pd(II), CO, MeOH), are formed diastereoselectively. With Ag(I) up to 81% d.e. has been observed and the stereochemical course of this reaction has been established. The Pd(II)-mediated cyclisation is less selective (up to 43% d e.) and the factors controlling the selectivities of both of these reactions are discussed*

Introduction.

Electrophile-mediated cyclisations involving nitrogen, oxygen and sulphur nucleophiles to C-C π-bonds has developed as a versatile strategy in heterocyclic synthesis.[1] The π-bond component in these processes is frequently an alkene residue, but other derivatives based on an allene[2] or alkyne[3] are also amenable to electrophile-mediated cyclisation These latter systems have not been as well studied as those involving the alkene moiety but they do offer considerable potential to the synthetic chemist that has yet to be fully exploited. The allene-containing amines (**1**) are of particular interest and undergo cyclisation under very mild conditions using a range of electrophilic triggers to give the corresponding 2-alkenylsubstituted heterocycles (**2**).[2,4]



(**1**)

(**2**) E=H

(**2**) E=CO_2Me

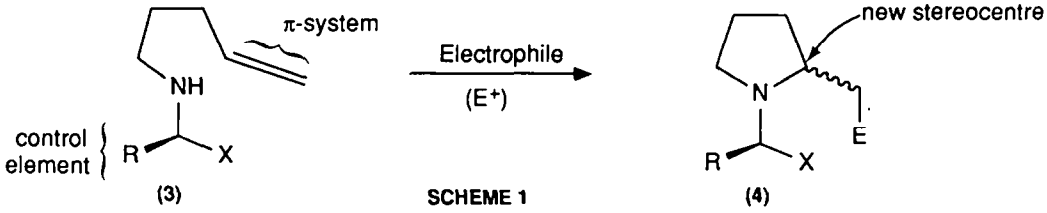
This methodology offers a number of advantages to the more conventional alkene-based cyclisation processes, one of the most obvious of which is the alkenyl substituent in the heterocyclic products (**2**). This provides a high degree of functionality and an opportunity exists to exploit this residue to manipulate the heterocycle at a later stage. The conditions required for the cyclisation of allenic derivatives of this type are very mild and these reactions do not appear to suffer from the problems associated with equilibration by ring-opening/ring-closure tha

† *This paper is dedicated with pleasure to Professor W. D Ollis on the occasion of his 65th birthday.*

have been encountered with some of the alkene-based methods.[5] Some years ago Claesson[2a] showed that simple allenic amines underwent cyclisation to give nitrogen-containing heterocycles in the presence of a *catalytic* quantity of silver(I). Since this report, other groups have successfully applied this methodology though, to date, little is known about the mechanism of this catalytic process. Nevertheless, this is an extremely attractive transformation that takes place at room temperature with a variety of different silver(I) salts ($AgNO_3$, $AgBF_4$, $AgClO_4$, $AgOSO_2CF_3$) and in a range of solvents (CH_2Cl_2, Me_2CO, DMSO, H_2O/MeOH). Under certain circumstances, cyclisation can be effected using a heterogeneous catalyst e.g. $AgNO_3/SiO_2$ which allows direct isolation of the heterocyclic product in pure form.[6] Other electrophiles may also be used to trigger the cyclisation of allenic amines. These include palladium(II), mercury(II), together with nonmetallic electrophiles of general type X^+ (X=O, Br, I, RS and RSe).[7]

There are a number of important stereochemical issues that arise during these electrophile-mediated cyclisation since ring-closure results in the generation of a new stereocentre. The control of relative stereochemistry, that is reactions leading to polysubstituted heterocycles, has been well-studied for cyclisations involving alkenyl substrates and a substantial amount of valuable mechanistic information is now available. Less is known about the corresponding cyclisations involving allenic derivatives but more information will undoubtedly become available in the near future.

There is an alternative method available for controlling the orientation of this new stereocentre that is particularly applicable to cyclisations involving nitrogen nucleophiles which is shown in *Scheme 1*.[8]

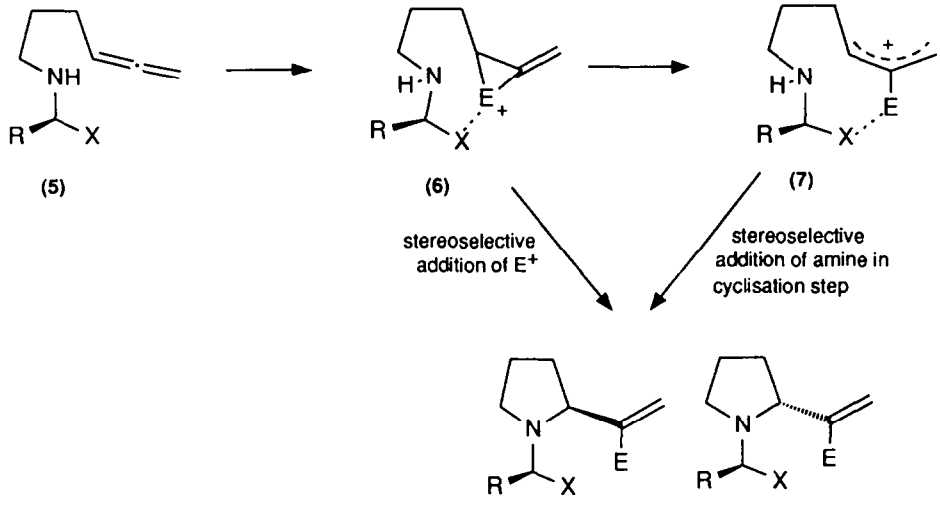


(3) **SCHEME 1** (4)

Here, the stereochemical control element is positioned on the nitrogen nucleophile in (**3**) and although stereochemistry is, once again, established in a diastereoselective fashion, this residue is not incorporated into the newly-formed ring. This process therefore has the advantage that the control element can in principle be removed from (**4**) to give the nitrogen-containing heterocycle enantioselectively. Such a concept has already been examined in a variety of circumstances but, with few exceptions, the level of diastereoselectivity reported have been low.[9] One of the problems of this approach to achieving stereochemical control is that the key stereocentre is on the "wrong" side of the nitrogen nucleophile during the cyclisation step and is, in addition, not under any conformational constraint. We have addressed these issues as part of a general study of the stereochemical aspects of electrophile-mediated cyclisations of allenic amines and in this paper we describe the development of methodology for the synthesis of a variety of 2-alkenylsubstituted pyrrolidines, based on the use of metal ions (Ag(I) and Pd(II)) as electrophilic triggers.

In the case of substrates incorporating the allenic π-system the stereochemistry of the heterocycle resulting from an electrophile-mediated cyclisation may be set in two ways (*Scheme 2*).[7] Firstly, interaction of the π-bond of (**5**) with an electrophile (E^+) leads to a π-complex (or metallocyclopropane) (**6**). The two faces of the allene in (**5**) are

diastereotopic, therefore nucleophilic attack on π-complex (**6**) leads to a heterocycle, the stereochemistry of which was determined by *the face of the allene that reacted with* E^+. Alternatively, under certain circumstances, π-complex (**6**) may rearrange irreversibly to give the σ-complexed allyl cation (**7**). Once again, the two faces of this species are diastereotopic but now the stereochemistry of the heterocycle is determined by addition of the nucleophile i.e. *during the cyclisation step itself.* The problem then becomes one of involving the remote stereogenic centre located on nitrogen in either or both of these processes and, thereby, exerting an influence on the distribution of the diastereomeric heterocyclic products.



SCHEME 2

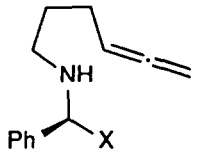
Our approach to this task has been to attempt to influence either of these mechanistic paths by incorporating a ligand (X) into the chiral substituent on nitrogen in (**5**). The role of this ligand could be to interact with the metal-ion electrophile in order that E^+ is delivered to one face of the allene π-system, as in (**6**). Alternatively, stabilisation of (**7**) *via* a macrocyclic complex involving (X) would control the approach of the nitrogen nucleophile to the allyl cation.

A series of derivatives related to (**5**) have been prepared and, starting from a commerically available amino acid, we have been able to vary the nature of the ligand X. Variation of R has also been studied, but in this paper we shall concentrate on the phenylglycine derivatives (**5**, R=Ph). This provides a benzylic residue on nitrogen which would be amenable to cleavage at a later stage.[10]

Results and Discussion

Synthesis of Allenic Amines (8a-e)

A range of N-substituted hexa-4,5-dienylamines (**8a-e**) were prepared in moderate yields *via* a reductive amination sequence involving 4,5-hexadienal, generated *in situ* by reduction of 4,5-hexadienenitrile[11] using diisobutyl aluminium hydride, and the appropriate optically pure primary amine. The hydroxymethyl (**8c**) and amino (**8e**) derivatives were not prepared by direct reductive amination but *via* the corresponding ester (**8b**) by $LiAlH_4$ reduction and aminolysis/reduction respectively.



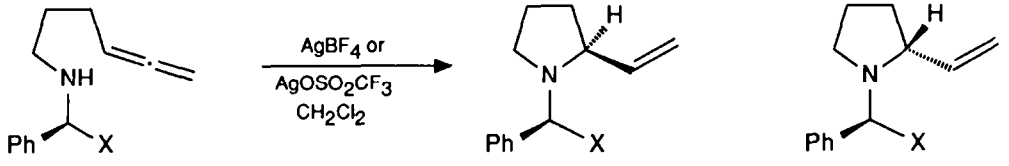
(8a) X=Me
(8b) X=CO_2Me
(8c) X=CH_2OH
(8d) X=CO.NHMe
(8e) X=CH_2NHMe

Electrophile-Mediated Cyclisations.

We have examined the reaction of the optically active allenic amines (**8a-e**) with a wide range of electrophiles but focus of this paper is on the use of Ag(I) and Pd(II)-based processes .

Ag(I)-Mediated Cyclisations

The cyclisation of allenic amines (**8a-e**) was carried out using either $AgOSO_2CF_3$ or $AgBF_4$ in CH_2Cl_2 at room temperature (*Scheme 3*). Reactions were generally complete within 3h and the nature of the silver salt did not appear to have a significant influence on the course of cyclisation. However, the observed diasteroselectivity was markedly influenced by changes in Ag(I) concentration and, to a lesser extent, changes in solvent. On completion of reaction, the diastereoselectivity was determined by high field ^1H n.m.r. analysis of the *crude* reaction mixture after which the pyrrolidine products (**9**) and (**10**) were isolated and characterised.



(8a-e) **(9a-e)** **(10a-e)**

SCHEME 3

The results of this Ag(I)-catalysed cyclisation study in terms of the diastereoselectivity of these two heterocyclic products is shown in Table 1.

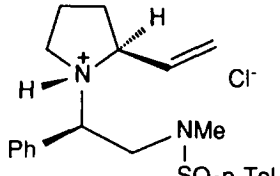
A clear trend emerges from these results; the observed diastereoselectivity increases with the ability of the co-ordinating residue X to complex Ag(I). In the case of amine (**8e**) (entry 12), cyclisation led to a 9:1 mixture of

TABLE 1

Entry	Allenic amine	Mol% Ag(I) *(solvent)*[a]	(9) : (10) (%d.e.)[b]	Yield[c]
1	**(8a)**	46 mol%	**2 : 1** (33%d.e.)	87%
2	**(8b)**	62 mol%	**4 : 1** (60%d.e.)	71%
3	**(8b)**	31 mol% *(acetone)*	**3 : 1** (50% d.e.)	90%
4	**(8b)**	42 mol% *(DMSO)*	**4.7: 1** (65% d.e.)	n.d.
5	**(8b)**	29 mol% *($MeOH/H_2O$)*	**1.1: 1** (5% d.e.)	86%
6	**(8c)**	15 mol%	**4 : 1** (60% d.e.)	90%
7	**(8d)**	23 mol%	**5.5: 1** (69% d.e.)	89%
8	**(8d)**	50 mol%	**9.3: 1** (81% d.e.)	90%
9	**(8d)**	90 mol%	**5 : 1** (67% d.e.)	94%
10	**(8e)**	38 mol%	**6.3 : 1** (73% d.e.)	89%
11	**(8e)**	45 mol%	**8 : 1** (78% d.e.)	63%
12	**(8e)**	57 mol%	**9 : 1** (80% d.e.)	n.d.[d]
13	**(8e)**	54 mol% *(DMSO)*	**4 : 1** (60% d.e.)	90%

[a] CH_2Cl_2 unless otherwise stated; [b] based on ^1H n.m.r. analysis of crude reaction mixture; [c] following purification; [d]yield was not determined.

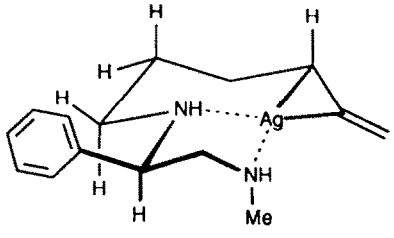
(**9e**) and (**10e**) (80%d.e.) and the stereochemistry of the major diastereoisomer was established by X-ray crystallographic analysis of the N-tosyl derivative (**11**); details of this structural determination have been published.[8] This assignment proved to be very useful since this was correlated using standard transformations



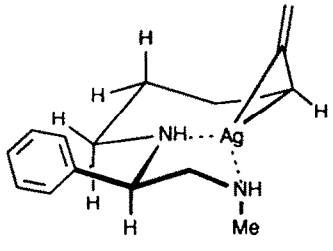
(11)

with the major diastereoisomer resulting from the other phenylglycine derivatives (**8b-d**)). In each of these cases the sense of asymmetric induction was the same i.e. the major isomer corresponded to (**9**) rather than (**10**).

The effect of changing the concentration of Ag(I) (e.g. entries 7-9) is of interest; optimal diastereoselectivity was observed using approximately 50mol% of Ag(I) (see also entries 11/12). This suggests that the key step of the overall cyclisation reaction, at which point the stereochemistry of the product is determined, may not involve a simple bimolecular process but a second molecule of the allenic amine could participate as a chiral ligand on Ag(I). This aspect of the mechanism has yet to be established and clearly a more complete mechanistic appreciation is needed if this chemistry is to reach its full potential. Efforts are being made in this regard, but in light of earlier work[12] and the sense of asymmetric induction observed, we can suggest a working hypothesis based on the face-selective addition of Ag(I) to the π-bond of the allene.[13] Interaction between Ag(I) and the allenic amine is likely to lead to a Ag(I)/π-complex (**6**, E=Ag) that must reasonably involve interaction with the X-residue and the nitrogen atom destined to be incorporated into the heterocyclic ring. Cyclisation must, however, involve *backside* attack by the amine to the π-complex[12] and it may be at this point that involvement of another molecule of allenic amine becomes important. Two chair-like conformations, (**A**)(involving addition of Ag(I) to the *si*-face of the allene) and (**B**)(involving addition of Ag(I) to the *re*-face of the allene), are then suggested but cyclisation *via* the pseudoequatorial conformer (**A**) would lead to the observed stereochemistry i.e. (**9**) rather than (**10**).



(A)



(B)

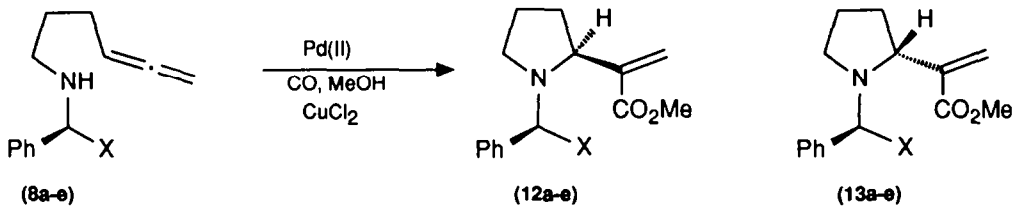
Other mechanistic pathways cannot, of course, be excluded and it would be foolhardy to extrapolate these ideas too readily to other systems. Nevertheless, the cyclisation of amines (**8**) with Ag(I) has shown a promising level of diastereoselectivity and this study will be pursued.

Pd(II)- Mediated Cyclisations.

The cyclisation of allenic amines, as well as alcohols, with Pd(II) in the presence of carbon monoxide and methanol is synthetically a very useful transformation leading to the heterocyclic-substituted acrylates (*Scheme 4*).[4]

The cyclisation of the optically active substrates (**8a-e**) using these conditions was examined in relation to the diastereoselectivity available and the results are displayed in Table 2.

Some selectivity was observed in terms of the distribution of the pyrrolidine products (**12**) and (**13**) but this was uniformly lower than in the corresponding Ag(I)-catalysed cyclisations. This lack of control may be attributed to the mechanism of the reaction of an allene with a Pd(II) species.



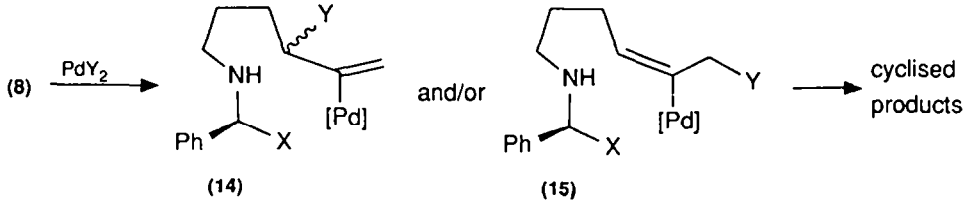
SCHEME 4

TABLE 2

Entry	Allenic amine	$Pd(II)X_2$ (Mol%)	(12) : (13) (%d.e.)[a]	Yield[b]
1	**(8a)**	$PdCl_2$ (4 mol%)	**1.1 : 1** (5%d.e.)	82%
2	**(8a)**	$Pd(PPh_3)_2Cl_2$ (2 mol%)	**1.1 : 1** (5%d.e.)	87%
3	**(8b)**	$Pd(PhCN)_2Cl_2$ (22 mol%)	**1 : 1** (0% d.e.)	44%
4	**(8c)**	$Pd(PhCN)_2Cl_2$ (20 mol%)	**2.5 : 1** (43% d.e.)	71%
5	**(8c)**	$Pd(OAc)_2$ (10 mol%)	**2 : 1** (33% d.e.)	n.d.
6	**(8d)**	$Pd(PhCN)_2Cl_2$ (16 mol%)	**1.7 : 1** (26% d.e.)	74%
7	**(8e)**	$Pd(PhCN)_2Cl_2$ (3 mol%)	n.d.[c]	48%

[a] based on H n.m.r. analysis of crude reaction mixture; [b] following purification; [c] a complex mixture of diastereoisomers was observedresulting from 1,4-addition of the N-methylamino group to the newly formed acrylate function of **(12e)/(13e)**.

This has been shown[14] to involve additon of Pd-Y (Y= e.g. Cl, OAc) across one π-bond of the allenic moiety to generate an allylic halide/acetate such as **(14)** or **(15)**. In the case of **(14)**, the stereochemistry of the heterocyclic product has effectively been set and cyclisation of **(15)** involving an S_N2'-type displacement would not be expected to be subject to control by the stereogenic residue on nitrogen.[15]



A range of other Pd(II) complexes were examined and we also attempted to carry out this reaction using $[Pd(MeCN)_4]^+BF_4^-$, an electrophilic palladium complex without a nucleophilic ligand and although cyclisation

took place, no improvement in diastereoselectivity was detected. Chiral palladium electrophiles have been used to control absolute stereochemistry in alkene-based processes[16] and with this in mind we also carried out the cyclisation of the simple α-methylbenzyl derivative (**8a**)[17] to (**12a**)/(**13a**) using a variety of optically pure ligands; BINAP, CHIRAPHOS and diethyl tartrate. The effect of these external auxiliaries, however, was marginal. Given the relatively low level of asymmetric induction observed during these Pd(II)-mediated cyclisations, no attempt has been made to establish the stereochemistry of any of the adducts. Nevertheless, it should be pointed out that in most cases it was very straightforward to separate the diastereomeric mixture of (**12**) and (**13**) using simple flash chromatography. This, in effect, constitutes a simple resolution of these highly functionalised heterocycles.

In conclusion, we have established that the nature of the stereogenic benzyl residue on nitrogen can markedly influence the outcome of the Ag(I)-mediated cyclisation reaction. The ability of the X-residue to interact with Ag(I) is clearly important in this regard, but the mechanistic details of the reaction remain to be established. The problem with achieving high diastereoselectivity in the Pd(II)-mediated cyclisations is going to be more difficult to overcome given that this process is fundamentally different to the Ag(I)-catalysed pathway. We are currently exploring the use of other electrophiles in this context. In principle, Hg(II) offers a cyclisation pathway that would be anticipated to parallel that based on Ag(I) and the product, an alkenyl mercury, is a synthetically very flexible species that would provide access to a wide range of alkenyl derivatives.[18]

Acknowledgements: We wish to thank SERC for a Quota Studentship and Professor R.D. Gillard for valuable discussions during the course of this work.

Experimental.

Infrared spectra were recorded using a Perkin-Elmer 1310 grating spectrophotometer. Routine mass spectra from electron ionisation (E.I.70eV), chemical ionisation (C.I.,i-butane) and high resolution accurate mass determination were recorded with a VG Analytical 7070E instrument with a VG2000 data system. Where a molecular ion was not observed a high resolution accurate mass determination was carried out on a fragment ion. Proton magnetic resonance (^{1}H n.m.r.) spectra were recorded in $CDCl_3$ at 270MHz on a Jeol GNM GX FT 270 spectrometer. Melting points (m.p.) were determined on commercially available apparatus (Gallenkamp) and are uncorrected. Elemental microanalyses were carried out using a Carlo Erba 1106 Elemental Analyser. Optical rotations were measured using a Perkin-Elmer 141 polarimeter. All reagents and solvents were purified and dried when required using standard methods (D.D. Perrin, W.L.F. Armarego and D.R. Perrin, "Purification of Laboratory Chemicals", 2nd Edn., Pergamon Press, Oxford, 1980).

Synthesis of allenic amines (8).

General procedure for reductive aminations.

To a 0.5M solution of 4,5-hexadienenitrile[10] in dry ether was added 25% solution of DiBAl(diisobutylaluminium hydride) in toluene (1 equiv) at room temperature. The reaction was allowed to proceed for 1hr, then cooled to 0°C and quenched with aqueous hydrochloric acid (2M). The resultant biphasic mixture was stirred for 10 min

then the organic layer was separated and the aqueous phase extracted twice with ether and the combined organic extracts dried ($MgSO_4$). To this suspension was added the appropriate primary amine (1 eq) and the resulting mixture was allowed to stir overnight. Filtration and concentration *in vacuo* afforded the crude imine which was then dissolved in dry ethanol or dry methanol. Sodium borohydride (0.5 eq) was added at room temperature and the reaction mixture was stirred for 30 min. Dilution with water, extraction twice with ether, drying ($MgSO_4$) and concentration *in vacuo* gave the crude amine. Purification by flash chromatography on silica gel gave the appropriate allenic amine (**5**) as a colourless oil.

(R)-N-(α-Methylbenzyl)hexa-4,5-dienylamine (8a). Obtained in 71% yield, b.p.(bulb to bulb) 155°C(1.4mmHg), $[\alpha]_D^{25}$ +52.7°(c 0.15, Et_2O); υ_{max}(film) 3300, 1950, 1600cm^{-1}; δ_H ($CDCl_3$) 7.21-7.31 (5H, m), 5.05 (1H, pentet(p), *J* 7Hz), 4.62 (2H, dt, *J* 7, 3.5Hz), 2.40-2.60 (2H, m), 1.90-2.07 (2H, m), 1.54-1.65 (3H, m), 1.34 (3H, d, *J* 7Hz); *m/e* (E.I.) 201, 186, 105. Exact mass (M^+) 201.1508 (Calcd. for $C_{14}H_{19}N$ 201.1517).

(R)-Methyl 2-(N-hexa-4,5-dienylamino)-2-phenylacetate (8b).
Obtained in 32% yield, $[\alpha]_D^{25}$ -82.4°(c 0.46,Et_2O); υ_{max}(film) 3300, 1960, 1740cm^{-1}; δ_H($CDCl_3$) 7.30-7.38 (5H, m), 5.08 (1H, p, *J* 7Hz), 4.65 (2H, dt, *J* 7, 3.5Hz), 4.37 (1H, s), 3.69 (3H, s), 2.52-2.63 (2H, m), 2.04 (qt, *J* 7, 3.5Hz), 2.00-2.15 (1H, br. s), 1.64 (2H, p, *J* 7Hz); m/e (C.I.) 246, 186; m/e (E.I.) 186. Exact mass (M^+-CO_2Me) 186.1271 (Calcd. for $C_{13}H_{16}N$ 186.1282).

(R)-2-(N-Hexa-4,5-dienylamino)-2-phenylethanol (8c).
To a solution of lithium aluminium hydride (66 mg, 1.74 mmol) in dry ether (5ml) was added a solution of the ester (**8b**) (332 mg, 1.36 mmol) in ether (4ml) at -78°C. The mixture was allowed to warm to room temperature over 1h and then quenched with saturated aqueous sodium sulphate solution. The solution was filtered through celite and the solids washed well with dichloromethane. Concentration *in vacuo* afforded (**8c**) as a light yellow oil (255 mg, 87%), $[\alpha)_D^{25}$ -101°(c 0.47, Et_2O); υ_{max}(film) 3350 (broad), 1950, 1600cm^{-1}; δ_H($CDCl_3$) 7.24-7.39 (5H, m), 5.07 (1H, p, *J* 7Hz), 4.63 (2H, dt, 7, 3.5Hz), 3.68-3.78 (2H, m), 3.53 (1H, dd, *J* 11, 8Hz), 2.46-2.63 (2H, m), 2.20-2.40 (2H, br), 2.03 (2H, qt, *J*, 7, 3.5Hz), 1.55-1.68 (2H, m); m/e (C.I.) 218, 186; (E.I.) 186. Exact mass (M^+-CO_2Me) 186.1292 (Calcd. for $C_{13}H_{16}N$ 186.1282).

(R)-N-Methyl-2(N'-hexa-4,5-dienylamino)-2-phenylacetacemide (8d).
Obtained in 27% yield, $[\alpha]_D^{25}$ -43.7°(c 2.3, Et_2O); υ_{max}(film) 3320, 1955, 1655 cm^{-1}; δ_H (270 MHz, $CDCl_3$) 7.25-7.40 (5H, m), 7.20 (1H, br. s), 5.09 (1H, p, J 7Hz), 4.66 (2H, dt, *J* 7, 3.5Hz), 4.14 (1H, s), 2.83 and 2.81 (3H, 2 x s), 2.61-2.67 (2H, m), 2.06 (2H, qt, *J* 7, 3.5Hz), 1.75 (1H, br. s), 1.63 (2H, p, *J* 7Hz); m/e (C.I.) 245, 186; m/e (E.I.) 186. Exact mass (M^+-CONHMe) 186.1286 (Calcd. for $C_{13}H_{16}N$ 186.1282).

(R)-N-Hexa-4,5-dienyl-N-Methyl-1-phenyldimethylene diamine (8e).
To a solution of the allenic amide (**8d**) (488 mg, 2.0 mmol) in dry ether (10 ml) was added a 25% solution of DiBAl in toluene (5.4 ml, 4 equiv.) and the reaction stirred at room temperature for 14hr. The reaction was quenched with saturated aqueous sodium sulphate solution and extracted with dichloromethane (3 x 10 ml). The extracts were dried (Na_2SO_4) and concentraton *in vacuo* followed by chromatography on silica gel, eluting with

ethyl acetate: methanol (5:1), gave (**8e**) as a light yellow oil (230 mg, 62% based on recovered starting material), $[\alpha]_D^{25}$ -70.0°(c 0.18, Et_2O); υ_{max}(film) 3310, 1955 cm^{-1}; $\delta_H(CDCl_3)$ 7.27-7.35 (5H, m), 5.05 (1H, p, *J* 7Hz), 4.61 (2H, dt, *J* 7, 3.5Hz), 3.81 (1H, dd, *J* 8, 6Hz), 3.00-3.20 (2H, br), 2.82 (1H, d, *J* 6Hz), 2.83 (1H, d, *J* 8Hz), 2.49-2.54 (2H, m), 2.49 (3H, s), 1.88-2.08 (2H, m), 1.60 (2H, p, *J* 7Hz); m/e (C.I.) 231, 186, 134; m/e (E.I.) 186. Exact mass (M^+-CH_2NHMe) 186.1287 (Calcd. for $C_{13}H_{16}N$ 186.1282).

Cyclisation studies.

General procedure for silver(I)-mediated cyclisations.

To a 0.5M solution of the appropriate allenic amine (**8**) in dry dichloromethane was added silver triflate or silver tetrafluoroborate *(see Table 1 for molar proportion)*, the reaction mixture flushed with nitrogen and stirred in the absence of light at room temperature until completion of reaction as indicated by t.l.c., typically 2-3h. Water and dichloromethane were then added and the organic layer separated and the aqueous phase was extracted a further two times. The combined extracts were dried (Na_2SO_4) and after removal of solvent, the reaction mixture was analysed by ^1H n.m.r. Where possible or appropriate, the product was further purified or the diastereoisomers (**9**) and (**10**) were separated by silica gel chromatography.

*N-[(R)-α-Methylbenzyl]-(R)/(S)-2-vinylpyrrolidine (**9a**/**10a**).*
υ_{max}(film) 1640, 1600 1500cm^{-1}; $\delta_H(CDCl_3)$ *major diastereoisomer*: 7.23-7.31 (5H, m), 5.83 (1H, ddd, *J* 17.5, 10, 8.5Hz), 5.13 (1H, dd, *J* 17.5, 2Hz), 5.12 (1H, dd, *J* 10, 2Hz), 3.87 (1H, q, *J* 7Hz), 2.85-2.94 (2H, m), 2.32 (1H, q, *J* 8.5Hz), 1.58-1.82 (4H, m), 1.44 (3H, d, *J* 7Hz); $\delta_H(CDCl_3)$ *minor diastereoisomer*: 7.23-7.31 (5H, m), 5.71 (1H, ddd, *J* 17.5, 10, 8.5Hz), 5.00 (1H, dd, *J* 17.5, 2Hz), 4.93 (1H, dd, *J* 10, 2Hz), 3.80 (1H, q, *J* 7Hz), 3.26 (1H, q, *J* 7Hz), 2.65-2.75 (1H, m), 2.48 (1H, q, *J* 8Hz), 1.58-2.00 (4H, m), 1.34 (3H, d, *J* 7Hz);
m/e (E.I.) 201, 186. Exact mass (M^+) 201.1526 (Calcd. for $C_{14}H_{19}N$ 201.1517).

*(R)-Methyl phenyl[(S)-2-vinylpyrrolidin-1-yl]acetate (**9b**) and (R)-methyl phenyl[(R)-2-vinylpyrrolidin-1-yl]acetate (**10b**)*
Isomer (**9b**) was isolated in pure form and had $[\alpha]^{25}_D$ -85.5°(c 0.22, Et_2O). Minor isomer (**10b**) was not obtained in pure form, but appropriate spectral data for this isomer is indicated below.
Both isomers: $\upsilon_{max}(CHCl_3)$ 1735, 1630cm^{-1}; $\delta_H(CDCl_3)$(*major diastereoisomer with corresponding shift of selected signals of minor isomer indicated*) 7.29-7.40 (5H, m), 5.79 (1H, ddd, *J*18, 10, 9Hz), 5.13 (1H, dd, *J* 18, 2Hz), 5.09 (1H, dd, 10, 2Hz), 4.29 (*4.56 for minor*) (1H, s), 3.62 (*3.70 for minor*)(3H, s), 2.86-3.05 (2H, m), 2.20 (1H, q, *J* 8Hz), 1.58-1.95 (4H, m); m/e (C.I.) 246, 186; m/e(E.I.) 186. Exact mass (M^+-CO_2Me) 186.1284 (Calcd. for $C_{13}H_{16}N$ 186.1282).

*N-[(R)-α-(Hydroxymethyl)benzyl]-(S)-2-vinylpyrrolidine (**9c**) and*
*N-[(R)-α-(hydroxymethyl)benzyl]-(R)-2-vinylpyrrolidine (**10c**).*
Isomer (**9c**) was isolated in pure form and had $[\alpha]^{25}_D$ -149°(c 0.49, $CHCl_3$). Minor isomer (**10c**) was not obtained in pure form, but appropriate spectral data for this isomer is indicated below.

Both isomers: $\upsilon_{max}(CHCl_3)$ 3400 (br), 1630, 1600, 1580cm^{-1}; $\delta_H(CDCl_3)$(*major diastereoisomer with corresponding shift of selected signals of minor isomer indicated*) 7.14-7.40 (5H, m), 5.73 (1H, ddd, *J* 18, 10, 8.5Hz), 5.27 (*5.06 for minor)* (1H, dd, *J* 18, 2Hz), 5.24 (*4.99 for minor*) (1H, dd, *J* 10, 2Hz), 3.92-4.07 (2H, m), 3.62 (1H, dd, *J* 9, 4Hz), 2.50-3.30 (1H, br. s), 2.91-3.04 (2H, m), 2.18 (1H, q, *J* 8Hz), 1.48-1.67 and 1.70-1.87 (4H, 2xm); m/e(C.I.) 218, 186; m/e(E.I.) 186. Exact mass (M^+-CH_2OH) 186.1287 (Calcd. for $C_{13}H_{16}N$ 186.1282).

*(R)-N-Methyl(phenyl)[(S)-2-vinylpyrrolidin-1-yl]acetamide (**9d**) and*
*(R)-N-methyl(phenyl)[(R)-2-vinylpyrrolidin-1-yl]acetamide (**10d**)*
Isomers (**9d**)/(**10d**) were not readily separated and were characterised as the mixture. $\upsilon_{max}(CHCl_3)$ 3360, 1655cm^{-1}; $\delta_H(CDCl_3)$(*major diastereoisomer with corresponding shift of selected signals of minor isomer indicated*) 7.16-7.45 (6H, m), 5.71 (*5.63 for minor*)(1H, ddd, *J* 18, 10, 8.5Hz), 5.23 (1H, dd, *J* 18, 2Hz), 5.19 (1H, dd, *J* 10, 2Hz), 4.39 (*4.15 for minor*)(1H, s), 2.94-3.05, and 2.73-2.83 (2H, 2xm), 2.86 and 2.84 (*2.81 and 2.83 for minor*)(3H, 2xs), 2.00-2.15 (1H, m), 1.52-1.94 (4H, m); m/e (C.I.) 245, 186; m/e (E.I.) 186. Exact mass (M^+-CONHMe) 186.1269 (Calcd. for $C_{13}H_{16}N$ 186.1282).

*N-[(R)-α-N-Methyl(aminomethyl)benzyl]-(S)-2-vinylpyrrolidine (**9e**) and*
*N-[(R)-α-N-methyl(aminomethyl)benzyl]-(R)-2-vinylpyrrolidine (**10e**).*
Isomers (**9e**)/(**10e**) were not readily separated and were characterised as the mixture. $\upsilon_{max}(CHCl_3)$ 3300, 1660, 1580cm^{-1}; $\delta_H(CDCl_3)$ (*major diastereoisomer with corresponding shift of selected signals of minor isomer indicated*) 7.16-7.39 (5H, m), 5.76 (1H, ddd, *J* 18, 10, 8.5Hz), 5.25 (*5.04 for minor*)(1H, dd, *J* 18, 2Hz), 5.23 (*4.96 for minor*)(1H, dd, *J* 10, 2Hz), 4.10 (1H, dd, *J* 10, 5Hz), 3.27-3.42 (3H, m) 2.83-2.97 (2H, m), 2.58 (*2.50 for minor*)(3H, s), 2.19 (1H, q, *J* 8Hz), 1.48-1.87 (4H, m); m/e (C.I.) 231, 186; m/e(E.I.) 186. Exact mass (M^+-CH_2NHMe) 186.1281 (Calcd. for $C_{13}H_{16}N$ 186.1282).

General procedure for palladium(II)-mediated cyclisations under carbomethoxylation conditions.

To a 0.5M solution of the appropriate allenic amine (**8**) in dry methanol was added the palladium(II) catalyst *(see Table 2 in text for catalyst used and molar proportion)* and anhydrous copper(II) chloride (3eq). The dark green reaction mixture was stirred under an atmosphere of carbon monoxide at room temperature until the conversion was complete, as indicated by t.l.c.. Water and ether were then added followed by addition of an excess of ethanolamine. The ether layer was separated and the blue aqueous layer extracted twice more with ether. The combined organic layers were dried (Na_2SO_4) and concentrated *in vacuo*. The mixture was analysed by ^{1}H n.m.r. and, where possible or appropriate, the product was further purified or the diastereoisomers (**12**) and (**13**) were separated by silica gel chromatography.

*Methyl 2-{(R)/(S)-N-[(R)-α-methylbenzyl]pyrrolidin-2-yl}propenoate (**12a**)/(**13a**).*
Both diastereoisomers: υ_{max} (film) 1710, 1630, 1500cm^{-1}; $\delta_H(CDCl_3)$ *major diastereoisomer*: 7.18-7.40 (5H, m), 6.14 (1H, d, *J* 2Hz), 6.02 (1H, dd, *J* 2, 1Hz), 3.70 (3H, s), 3.72-3.82 (2H, m), 2.85-2.92 (1H, m), 2.61 (1H, q, *J* 8Hz), 2.01-2.18 (1H, m), 1.60-1.78 (2H, m), 1.42-1.59 (1H, m). 1.27 (3H, d, *J* 7Hz); *minor diastereoisomer*: 7.18-7.40 (5H, m), 6.30 (1H, d, *J* 2Hz), 6.28 (1H, dd, *J* 2, 1Hz), 3.77 (3H, s), 3.67-3.82 (1H, m), 3.62 (1H, q, *J*

7Hz), 2.85-2.92 and 2.19-2.28 (2H, 2xm), 2.07 (1H, p, *J* 7Hz), 1.46-1.72 (3H, m), 1.35 (3H, d, *J* 7Hz); m/e(E.I.) 259, 244, 154. Exact mass (M^+) 259.1570 (Calcd. for $C_{16}H_{21}NO_2$ 259.1570).

*Methyl 2-{(R)/(S)-N-[(R)-α-(methoxylcarbonyl)benzyl]pyrrolidin-2-yl}propenoate (**12b**)/(**13b**).*
Both diastereoisomers: $\upsilon_{max}(CHCl_3)$ 1730, 1625cm^{-1}; δ_H ($CDCl_3$)(*signals of minor isomer indicated*) 7.29-7.38 (5H, m), 6.21(6.24 *minor*)(1H, d, J 2Hz), 6.05(6.07 *minor*)(1H, dd, J 2, 1Hz), 4.55(4.47 *minor*)(1H, s), 3.80-3.92 (1H, m), 3.74-3.63 (6H, overlapping singlets), 2.34-2.45, 2.78-2.87 and 3.03-3.18 (2H, 3xm), 1.99-2.28 (1H, m), 1.48-1.81 (3H, m); m/e(C.I.) 304, 244; m/e (E.I.) 244 Exact mass (M^+-CO_2Me) 244.1362 (Calcd. for $C_{15}H_{18}NO_2$ 244.1337).

*Methyl 2-{(R)/(S)-N-[(R)-α-(hydroxymethyl)benzyl]pyrrolidin-2-yl}propenoate (**12c**)/(**13c**).*
Isomers (**12c**) and (**13c**) were separated by chromatography. $\upsilon_{max}(CHCl_3)$ 3400(br), 1720, 1650cm^{-1}; $\delta_H(CDCl_3)$ *less polar diastereoisomer:* 7.15-7.39 (5H, m), 6.34 (1H, d, *J* 2Hz), 6.01 (1H, dd, *J* 2, 0.5Hz), 3.57-3.99 (4H, m), 3.79 (3H, s), 2.97-3.05 (1H, m), 2.23-2.32 (1H, m), 1.58-2.02 (5H, m and br. s); *more polar diastereoisomer:* 7.27-7.35 (5H, m), 6.15 (1H, d, *J* 2Hz), 5.89 (1H, dd, *J* 2, 1Hz), 3.74-3.90 (4H, m), 3.70 (3H, s), 3.17-3.23 (1H, m), 2.73-2.83 (1H, m), 1.58-1.88 (5H, m and br.s.); m/e(C.I.) 276, 244; m/e(E.I.) 244. Exact mass (M^+-CH_2OH) 244.1314 (Calcd. for $C_{15}H_{18}NO_2$ 244.1337).

*Methyl 2-{(R)/(S)-N-[(R)-α-(methoxycarbamoyl)benzyl]pyrrolidin-2-yl}propenoate (**12d**)/(**13d**).*
Both diastereoisomers: $\upsilon_{max}(CHCl_3)$ 3400, 1710, 1665, 1620 cm^{-1}; $\delta_H(CDCl_3)$ (*signals of minor isomer indicated*) 7.17-7.38 (5H, m), 6.78 (1H, br. s), 6.06(6.34 *minor*)(1H, d, *J* 2Hz), 5.74(5.91 *minor*) (1H, dd, *J* 2, 1Hz), 4.19(4.33 *minor*) (1H, s), 3.65(3.78 *minor*) (3H, s), 3.43-3.78 (1H, m), 3.13-3.19 and 2.70-2.91 (2H, 2m), 2.86-2.82 (3H, overlapping singlets), 1.94-2.18 (1H, m), 1.52-1.83 (3H, m); m/e (C.I.) 303, 244; m/e(E.I.) 244. Exact mass (M^+-CONHMe) 244.1326 (Calcd. for $C_{15}H_{18}NO_2$ 244.1337).

Stereochemical correlation studies.

*(i) Reduction of ester (**9b**) to alcohol (**9c**):* To a solution of the methyl ester (**9b**)(45.0mg, 0.18mmol) in ether (2ml) was added lithium aluminium hydride (13.0mg, 0.35mmol) at -78°C. The reaction was allowed to warm to room temperature over 1h, quenched with saturated aqueous sodium sulphate solution and filtered through Celite, washing the residue with dichloromethane. Concentration *in vacuo* afforded alcohol (**9c**)(35.6mg, 89%) as a colourless oil.

*(ii) Reduction of amide (**9d**) to amine (**9e**):* To a solution of the amide (**9d**) (19.0mg, 0.08 mmol) in ether (1ml) was added 25% solution of DiBAl in toluene (0.2ml, 4eq) at room temperature. The reaction was continued for 2h, quenched with saturated aqueous sodium sulphate solution, filtered through Celite and the residue washed with dichloromethane. Concentration *in vacuo* afforded amine (**9e**)(14.0mg, 78%) as a colourless oil.

*(iii) Conversion of ester (**9b**) to amide (**9d**):* To a solution of the ester (**9b**) (29.2mg, 0.12 mmol) in methanol (1ml) was added 30% aqueous solution of methylamine (2ml) and the reaction stirred at room temperature

overnight. Addition of water (2ml) and extraction with dichloromethane (2x10ml), drying of combined organic layers (Na_2SO_4) and concentration *in vacuo* afforded amide (**9d**)(13.8mg, 47%) as a colourless oil.

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