STUDIES ON FACE SELECTIVITY IN 1,7-ELECTROCYCLISATION REACTIONS OF NITRILE YLIDES

by

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FOR AILEEN

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Finally, I must apologise to my wife, Aileen, for all of the lost evenings and weekends. I am indebted to her for all of her help, especially the unswerving moral support.

Declaration

I declare that this thesis is my own composition, that the work of which it is a record was carried out by myself, and that it has not been submitted in any previous application for a Higher Degree.

P. G. Taylor

Post-Graduate Courses

The following is a statement of the post-graduate courses attended during the period of this work:

Post-graduate Research Seminars (3 years)	1990-93
Topics in Medicinal Chemistry (Ray Baker & Victor Mattassa; Merck, Sharp & Dohme)	1991
Topics in Organic Chemistry (R. Ramage, R. Baxter, S. Chapman, I. Gosney & H. McNab; University of Edinburgh)	1991
Introductory German Reading Course (University of Edinburgh)	1991
Topics in Medicinal Chemistry (Ray Baker & Paul Leeson; Merck, Sharp & Dohme)	1992
Discovery, Development and Pharmacology of Zovadex for Treatment of Cancer (ICI Pharmaceuticals)	1992
Recent Advances in the Synthesis and Activity of Agrochemicals (Schering Agrochemicals)	1992
Aspects and Applications of NMR Spectroscopy (I. Sadler, D. Reed; University of Edinburgh)	1992
Concepts in Medicinal Chemistry (Ray Baker & Paul Leeson; Merck, Sharp & Dohme)	1993
Research and Development in the Pharmaceutical Industry (A. McKillop)	1993

ABSTRACT

This work is concerned with the cyclisation reactions of α,β and γ,δ-unsaturated nitrile ylides which have a chiral substituent on the terminal carbon atom of the diene system. The objective was to develop a method for the synthesis of chiral benzazepines using known chiral auxiliaries.

The first and major part was targeted on the development of a synthetic route to *N*-(*o*-alkenylbenzyl)-benzamides functionalised at the alkene terminus with amide groups linked to Oppolzer's sultam or Evans's oxazolidinone as chiral substituents. Several synthetic routes were explored but, although model compounds could be prepared, the target compounds remained elusive.

The second part was concerned with similar compounds that had chiral ester rather than amide substituents. These proved easier to prepare and some preliminary work on the cyclisation of an achiral model system gave rise to some new chemistry involving the expected 1,7-electrocyclisation. This was followed by an unprecedented base catalysed migration to give a 5*H*-2-benzazepine. The occurrence of this migration led to a modification of the structure of the chiral target compounds and was followed by the preparation and cyclisation of two chiral esters that gave novel chiral cyclopropa[*c*]isoquinolines. In both cases the face selectivity shown was greater than observed in analogous intermolecular Diels-Alder reactions. The first X-ray crystal structures of cyclopropa[*c*]isoquinolines derived from 1,7-electrocyclisations were also obtained.

CONTENTS

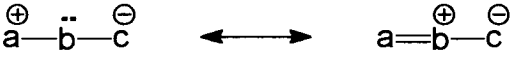
INTRODUCTION

1. NITRILE YLIDES

1.1. 1,3-Dipoles

1.1.1. Structure

A 1,3-dipole has been defined by Huisgen[1] as "a system **a-b-c** in which atom **a** possesses an electron sextet, *ie* an incomplete valence shell combined with a positive formal charge, and atom **c**, the negatively charged centre, has an unshared electron pair." The electron deficiency at atom **a** can be relieved if atom **b** is capable of donating an electron pair to form an additional bond. This gives a more stable 'all-octet' structure as shown in **Scheme 1**. Only such 'octet stabilised' 1,3-dipoles will be considered here.



Sextet formula Octet formula

Scheme 1

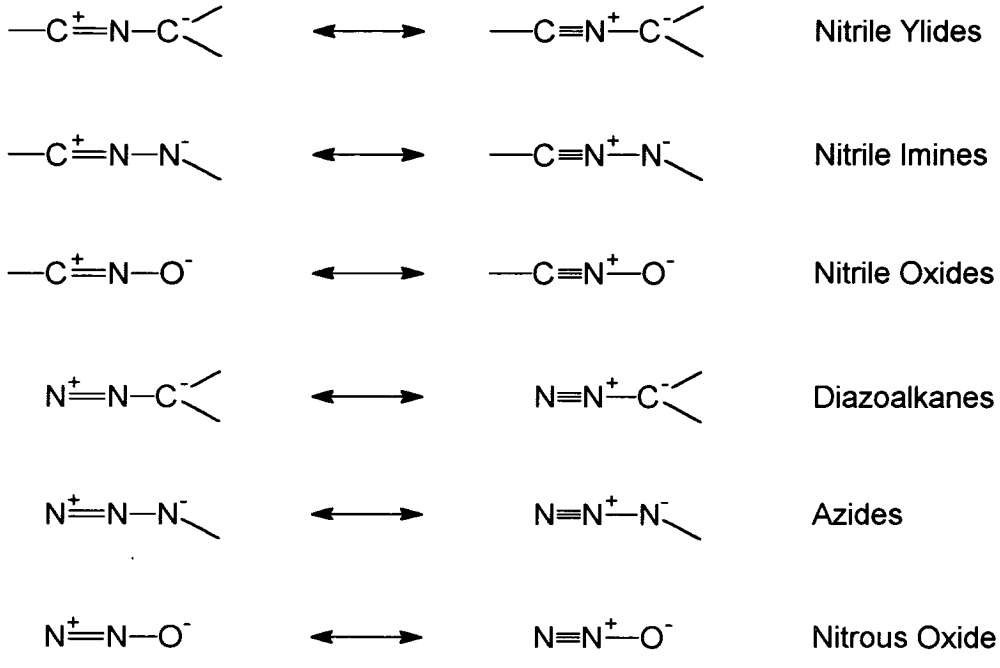
Octet stabilised 1,3-dipoles can be divided into two classes:

(a) The allenyl-propargyl type (**Table 1**), with a double bond orthogonal to an allyl anion type π-system. These have nitrogen as the central atom, **b**, since this is the only element capable of contributing an unshared electron pair whilst in a neutral, trivalent state.

(b) The allyl type (**Table 2**), with an allyl anion type π-system but no orthogonal double bond. Here atom **b** can be oxygen or nitrogen.

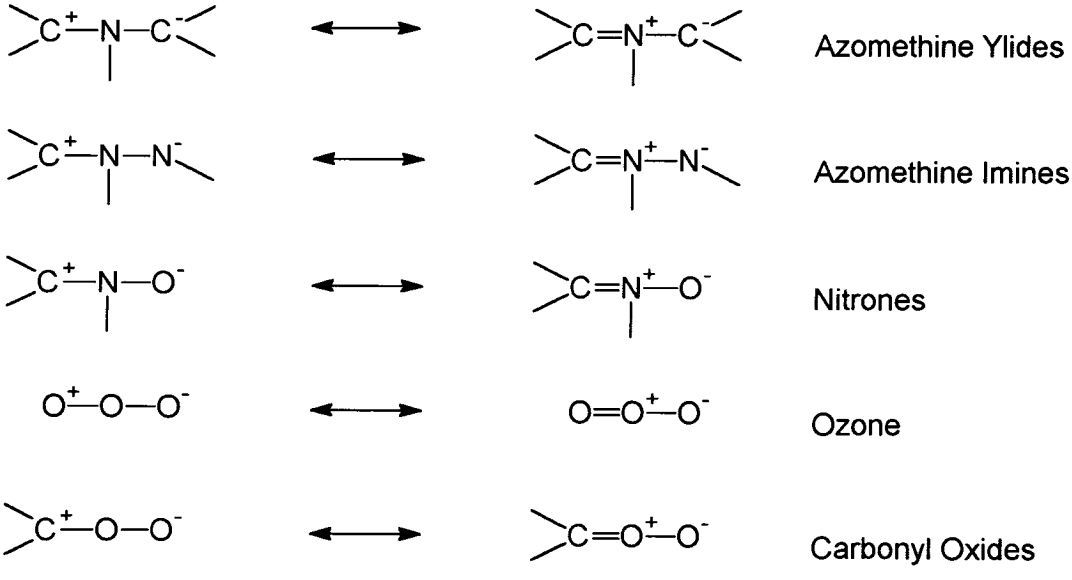
Both classes of 1,3-dipole are best represented by a series of resonance forms, rather than any single structure (as will be exemplified later with nitrile ylides).

Table 1. 1,3-Dipoles of the Allenyl-propargyl Type*



*Only two canonical forms are shown for each dipole

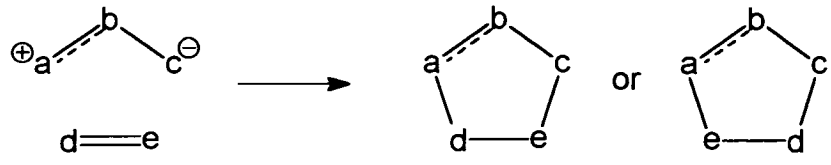
Table 2. Some 1,3-Dipoles of the Allyl Type*



*Only two canonical forms are shown for each dipole

1.1.2. Overview of reactions

1,3-Dipoles react readily with most multiple bond systems[2] to give five-membered rings as shown in **Scheme 2**.

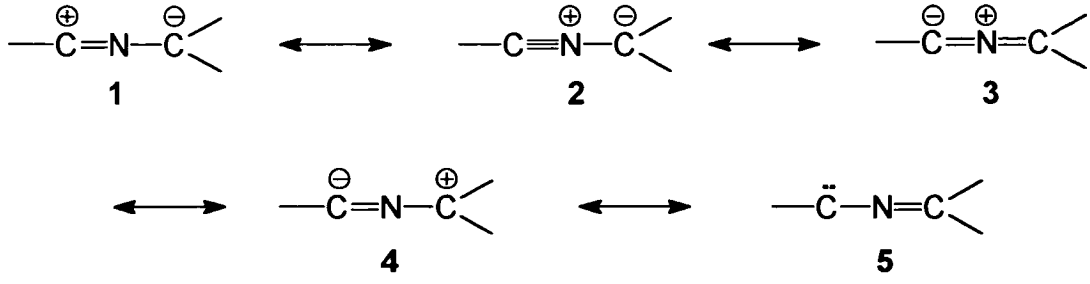


Scheme 2

The addition, which is stereoselective, regioselective and *syn*, has been shown to have a concerted mechanism.[3] Regio-selectivities have been rationalised by consideration of molecular orbital interactions.[4] Intramolecular 1,3-dipolar cycloadditions are well known[5] and there are many examples of 1,3-dipolar electrocyclic reactions such as 4π-retro-electrocyclisations and 6π-[6] and 8π-[7] electrocyclisations. These reactions will be discussed later in detail for nitrile ylides.

1.2. Structure of Nitrile Ylides

Nitrile ylides belong to the nitrilium betaine class of 1,3-dipoles. Nitrilium betaines have a central nitrogen atom and an orthogonal double bond to carbon. Nitrile ylides are the least stable member of this class and are only isolable in a low temperature matrix.[8] As with all 1,3-dipoles, the structure of nitrile ylides is best represented through a series of resonance structures, *ie* the canonical forms **1**-**5**.



The all-octet configurations **2** and **3** contribute most to the stability of the nitrile ylide although, in the strictest sense, the term 1,3-dipole applies only to the structures **1** and **4**. It is, however, conventional that the term is applicable to the molecule as a whole as it best describes the observed reactivity.

For allenyl-propargyl 1,3-dipoles the presence of the π-bond in the plane perpendicular to the allyl π-system generally leads to a linear conformation. In 1963, Huisgen[1] suggested that maximum allyl resonance and overlap of the orthogonal double bond was consistent with a linear and planar conformation. The results of Molecular Orbital calculations based on this premise are summarised in **Figure 1**.[9(a)]

These calculations explained observed regioselectivity and periselectivity for many 1,3-dipoles but the predicted regiochemistry for nitrile ylides was opposite to that observed.[9(b)] Houk concluded that these calculations were incorrect for nitrile ylides, and the larger MO coefficient of the HOMO must be on the C-1 (nitrile) carbon, not on the C-3 (methylene) carbon as predicted. Further calculations[10] indicated that a bent structure for the nitrile ylide, **6**, is 46.4 $kJmol^{-1}$ more stable than the planar, linear structure **7**, and thus the molecule resembles a bent allenyl anion rather than a planar propargyl anion.

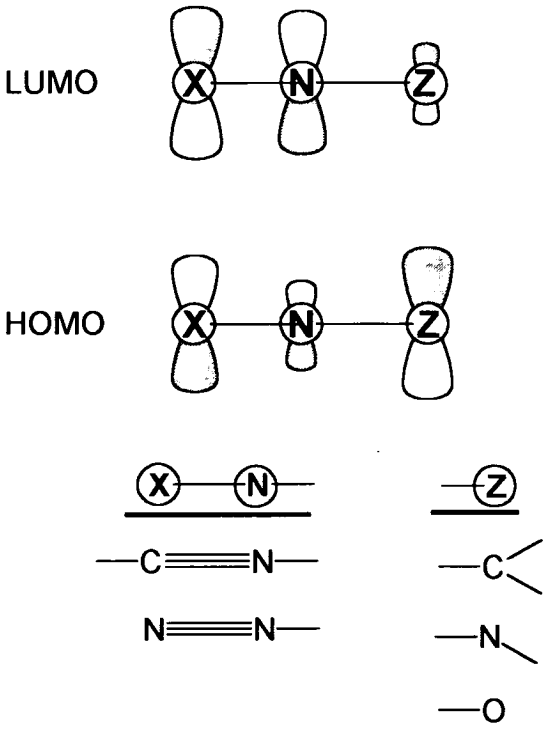
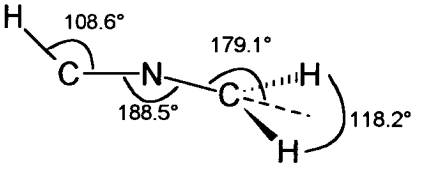


Figure 1

The frontier molecular orbitals for this optimised structure are shown in **Figure 2**. The HOMO is now heavily localised at the C-1 (nitrile) terminus, but still resembles the normal three-orbital, 4π-electron system of 1,3-dipoles.



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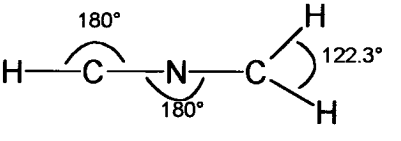

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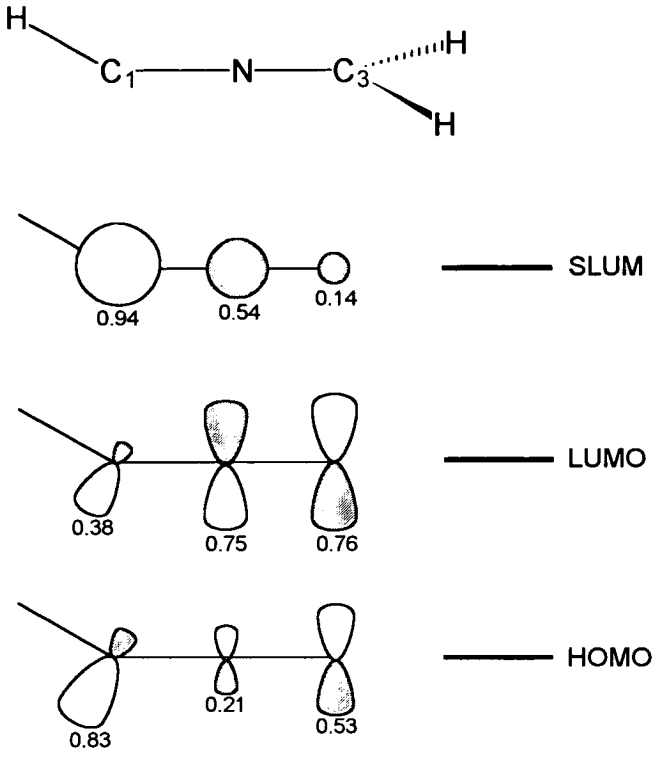


Figure 2. Numbers are absolute values of coefficients.

The calculations also showed that electron-withdrawing groups on C-3 (methylene) would favour planarity by stabilising the increased negative charge at this carbon in the planar structure. Electron-donating, alkyl or aryl substitution at C-3 was calculated to favour the bent form, as was 1-aryl substitution.

It should be noted that the HOMO and SLUMO of a bent nitrile ylide are very similar at C-1 to the HOMO and LUMO of a singlet carbene, **Figure 3** (*cf* canonical form **5**). This accounts for some otherwise unexpected reactions of nitrile ylides (which will be discussed in Section 1.5.).

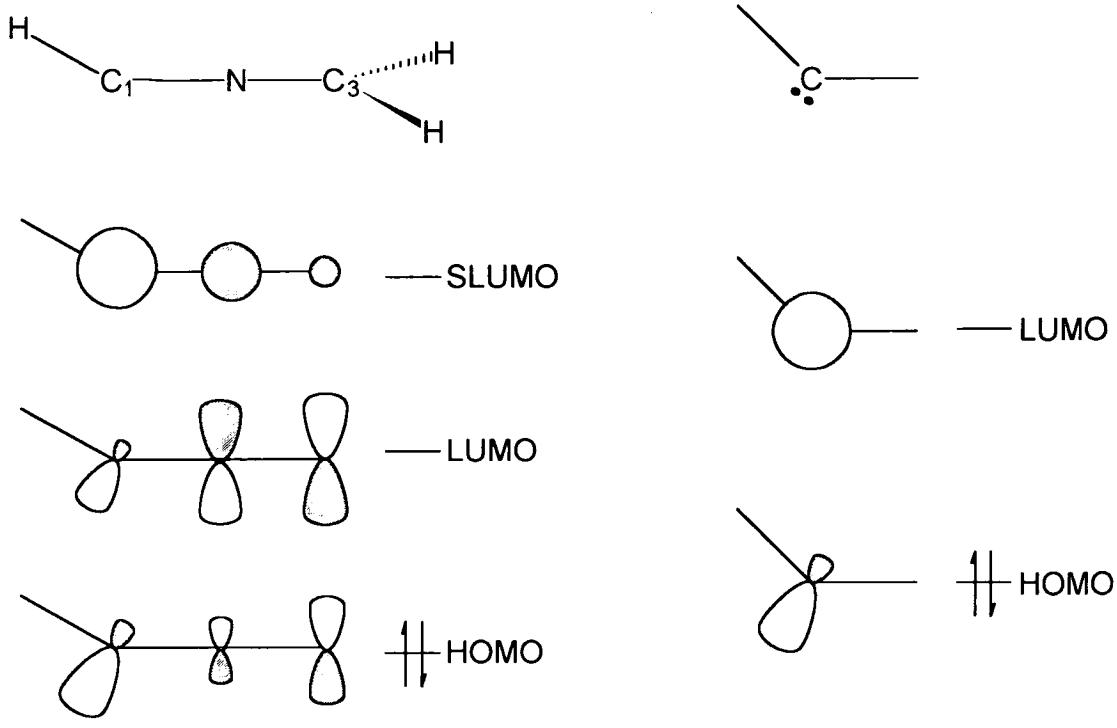
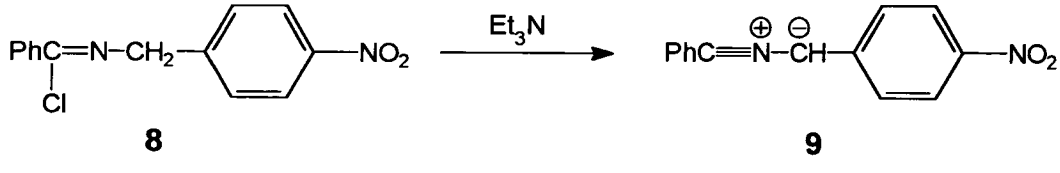


Figure 3

1.3. Generation of Nitrile Ylides

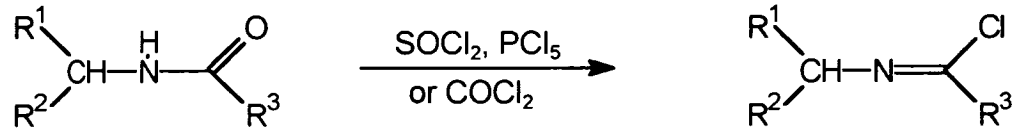
The original method of Huisgen[11] involved the base-induced 1,3-dehydrochlorination of an imidoyl chloride bearing an α-hydrogen. Thus, *N*-(*p*-nitrobenzyl)-benzimidoyl chloride **8** was treated with triethylamine to give benzonitrile *p*-nitrophenylmethanide **9**, **Scheme 3**. The 1,3-dipolar nature of the intermediate was demonstrated by trapping it with a dipolarophile.



8 **9**

Scheme 3

This method provides a general route to many nitrile ylides as imidoyl chlorides are readily prepared from the corresponding amides **11** by treatment with thionyl chloride, phosphorus pentachloride or phosgene,[12] **Scheme 4**.



11 **12**

Scheme 4

The dehydrochlorination of imidoyl chloride **12** is only successful with triethylamine if R^1 or R^2 is *p*-nitrophenyl. Otherwise a stronger base, such as potassium *tert*-butoxide, must be used.[13]

One of the most widely used methods of generating nitrile ylides is the photolytic ring opening of 2*H*-azirines **13**, **Scheme 5**, developed by Padwa. This has been comprehensively reviewed[14] and will not therefore be discussed further here.

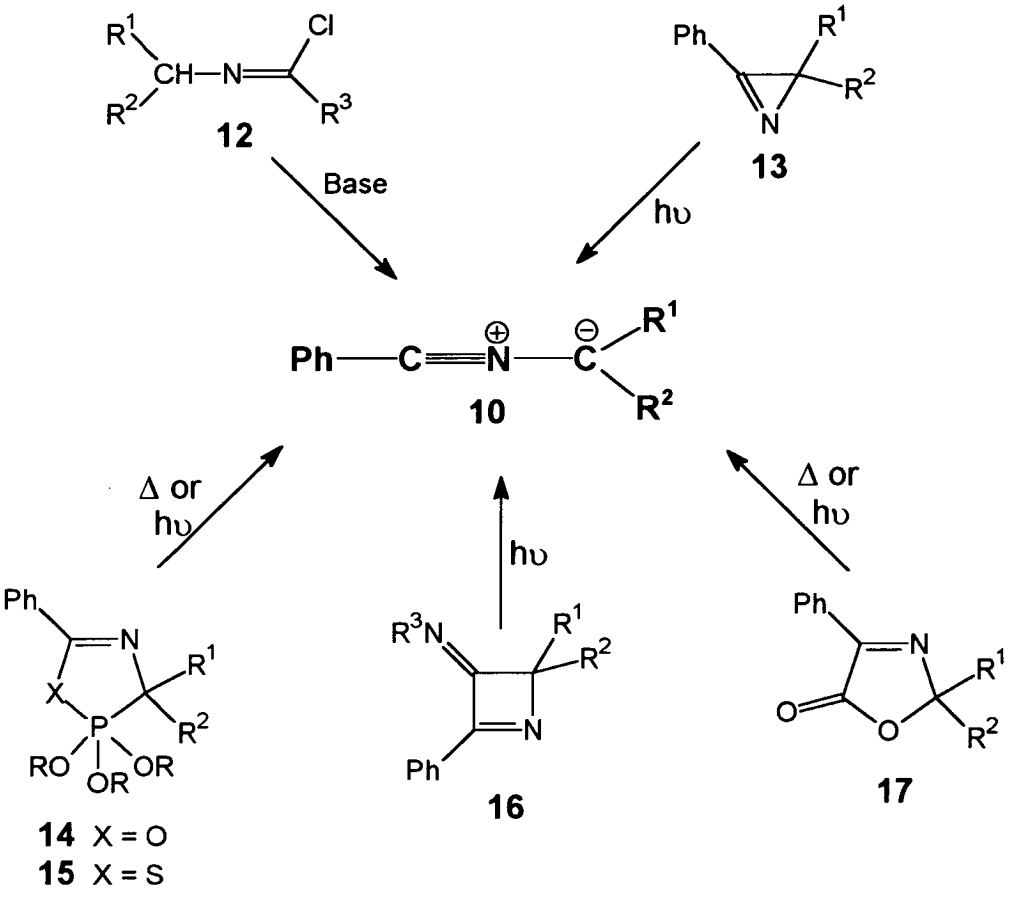
Other methods include:

(i) elimination of phosphoric acid esters from 2,3-dihydro-1,4,2λ^5-oxaphosphates **14**[15] ;

(ii) elimination of alkylthiophosphates from 2,3-dihydro-1,4,2λ^5-thiazophospholes **15**[16] ;

(iii) elimination of isocyanides from 3-imino-1-azetidines **16**[17] and

(iv) thermal extrusion of carbon dioxide from 3-oxazolin-5-ones **17**,[18] **Scheme 5**.

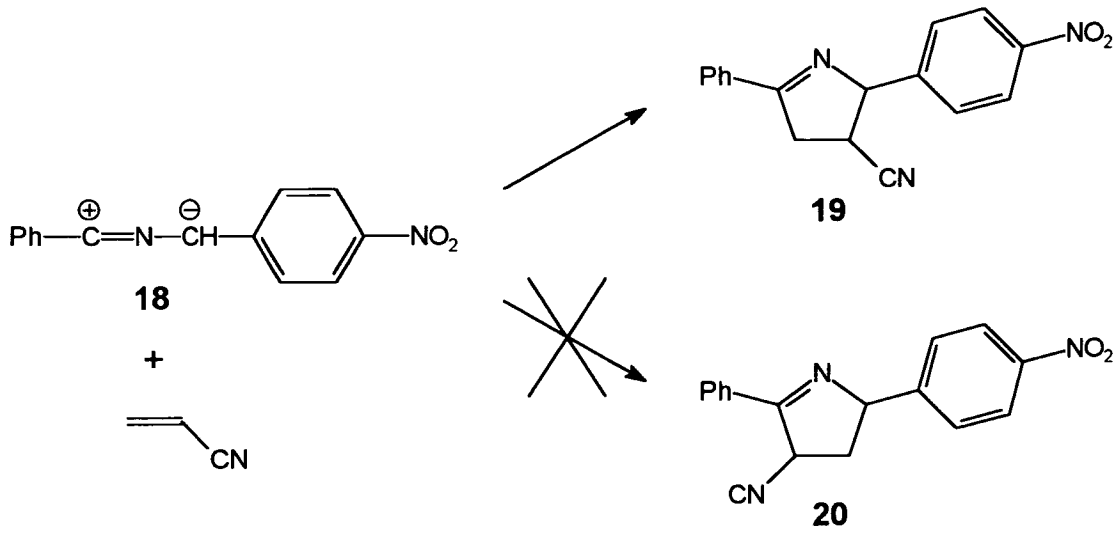


Scheme 5

1.4. Intermolecular Reactions of Nitrile Ylides

Nitrile ylides undergo normal 1,3-dipolar reactions such as dimerisation[8,14] and regioselective [2+3]cycloadditions to multiple bonds to form five-membered heterocycles.[2] For example, reaction of the nitrile ylide **18** with acrylonitrile (**Scheme 6**) gave only the 4-substituted pyrroline **19**. The 3-substituted isomer **20** was not observed.[1]

The regioselectivity observed in each of these reactions has been explained by frontier molecular orbital theory. According to Sustmann's classification,[4(a)] the 1,3-dipolar cycloadditions of nitrile ylides are HOMO controlled (except



Scheme 6

with very electron-rich dipolarophiles). The dominant interaction is between the dipole HOMO and the dipolarophile LUMO (**Figure 4**)

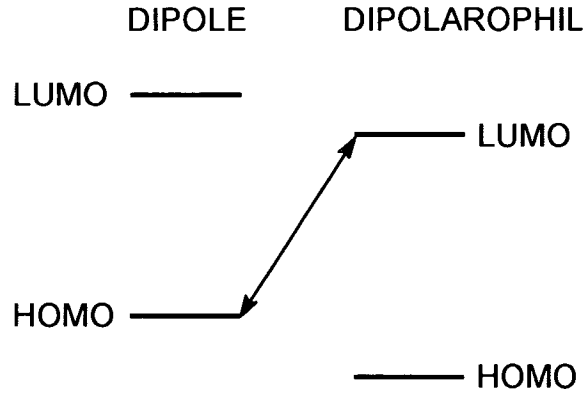
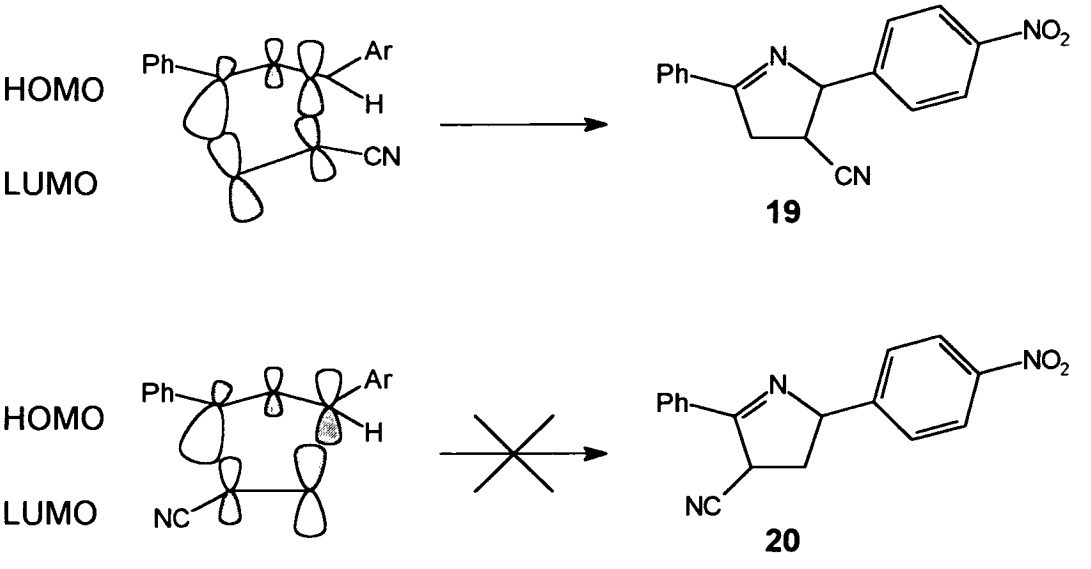


Figure 4

This explains the observed regioselectivity seen with, for example, the reaction of the nitrile ylide **18** with acrylonitrile.[1] The preferred mode of reaction involves bond formation between the termini of the dipole and dipolarophile with the largest frontier molecular orbital coefficients, **Scheme 7**. This gives the 4-substituted pyrroline **19**.



Scheme 7

Nitrile ylides also undergo 1,3-dipolar cycloadditions with C=O, C=N, C=S and cumulated double bonds[19] as well as with alkynes[20] (to give pyrroles).

The mechanism of nitrile ylide 1,3-dipolar cycloaddition has been demonstrated to proceed *via* a 'parallel planes' transition state.[1,21] This means that the 1,3-dipole and the dipolarophile approach each other to form a two-plane orientation complex, **Figure 5**.

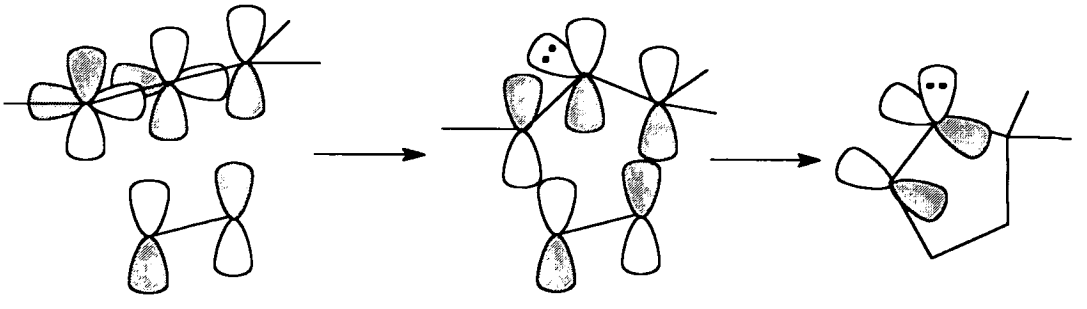


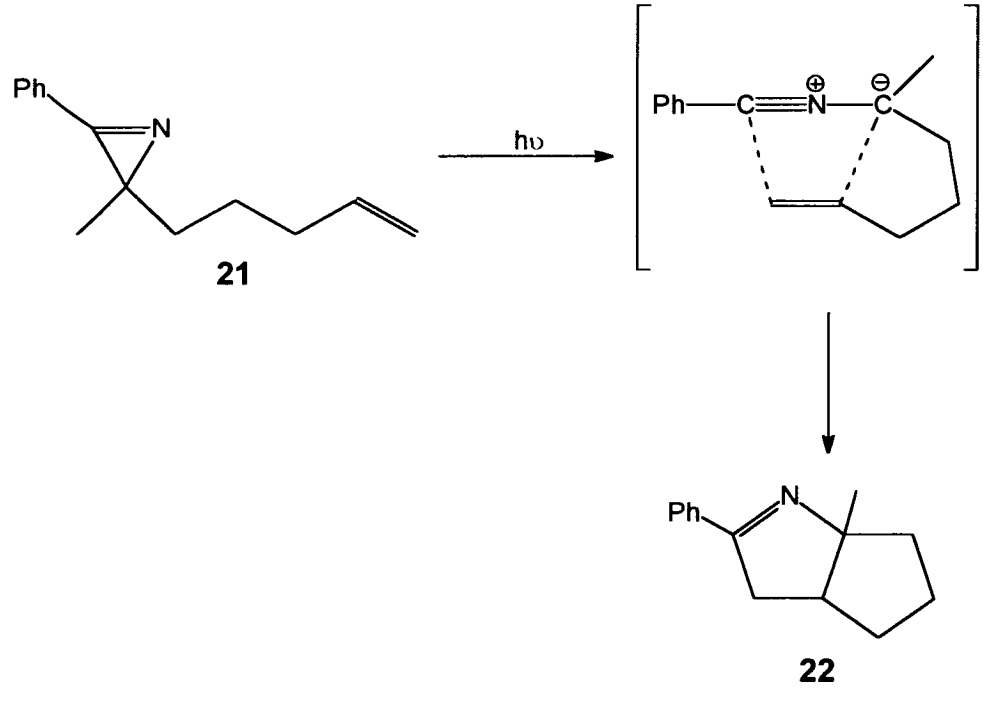
Figure 5

During the reaction, the nitrile ylide must bend further. This disrupts the orthogonal double bond but leaves intact the allylic π-system. This loss of π-bond energy is partially compensated for by stabilisation resulting from rehydridisation and accomodation of a lone pair in an orbital of high s-character.

1.5. Intramolecular Reactions of Nitrile Ylides

1.5.1. Intramolecular 1,1- and 1,3-Dipolar Cycloaddition

In molecules which contain both a nitrile ylide and a dipolarophile moiety, an internal 1,3-dipolar cycloaddition may take place, provided the two groups can attain the 'parallel planes' transition state geometry. For example, photolysis of the azirine **21** gave the expected cycloadduct **22** in quantitative yield,[22] **Scheme 8**.

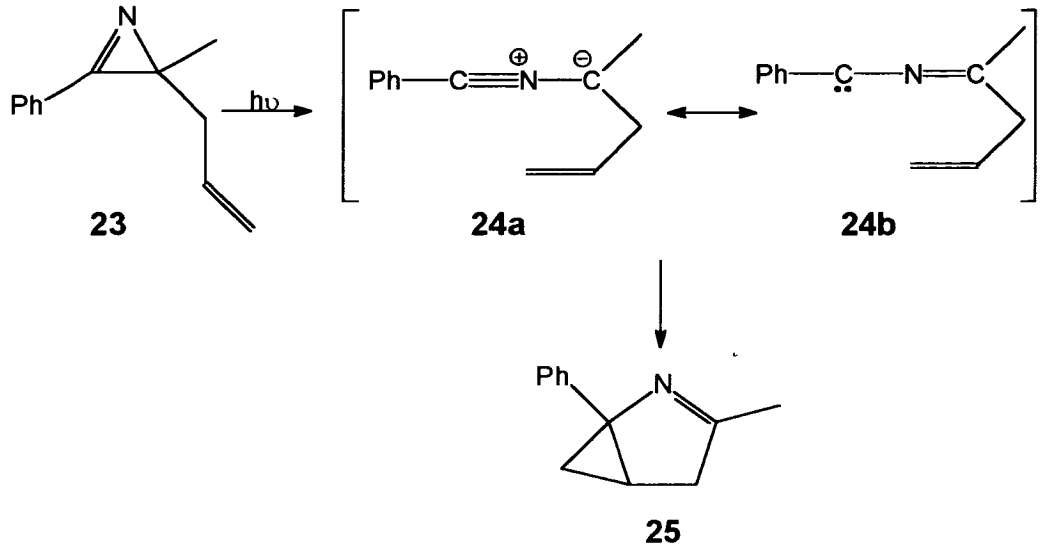


21 **22**

Scheme 8

If this approach geometry cannot be attained, a different mode of reaction becomes dominant. This type of reaction was first observed by Padwa[23] when irradiation of the 2-allyl-2*H*-azirine **23** gave the 1,1-cyclo-adduct **25**, **Scheme 9**. The intermediacy of the nitrile ylide **24** was demonstrated by trapping with a reactive dipolarophile. The observed 1,1-cycloaddition can be empirically

understood by invoking the carbene-like resonance form of the nitrile ylide **24b** as the reacting species.

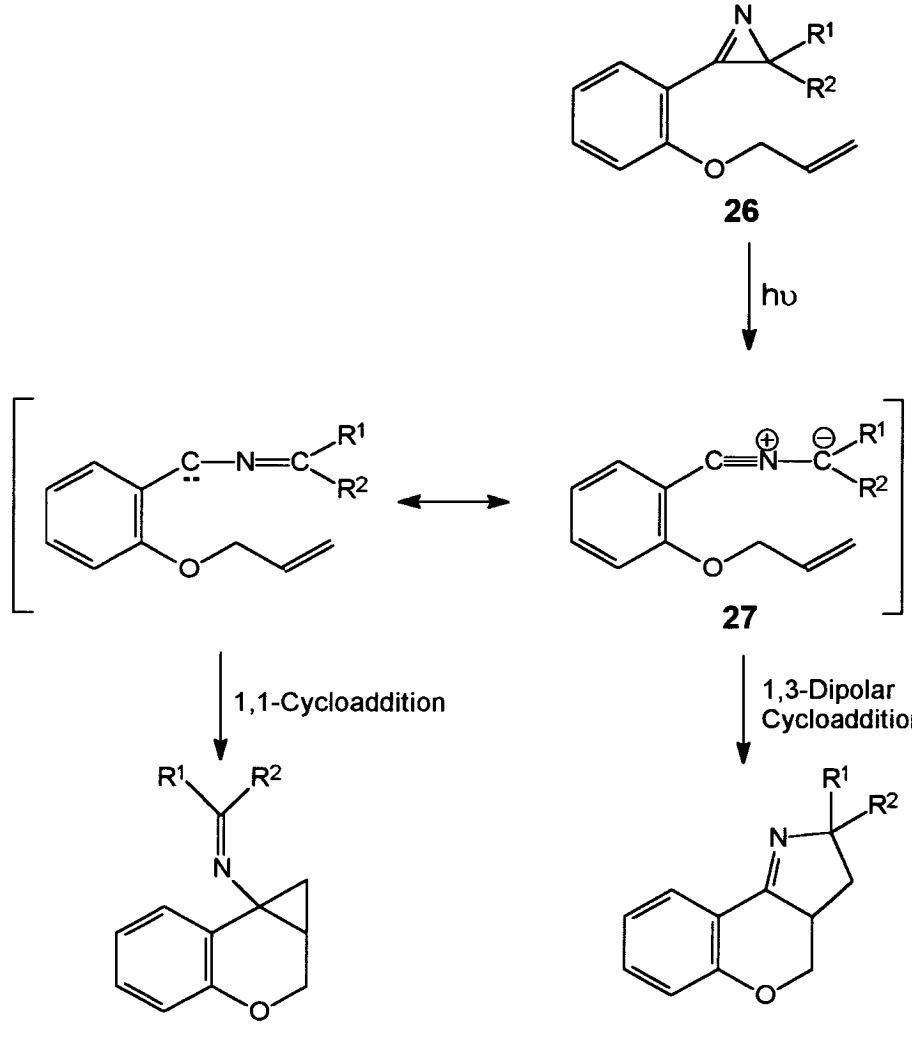


Scheme 9

Houk's revised calculations have shown that the HOMO and SLUMO of a bent nitrile ylide bear a strong resemblance to the HOMO and LUMO of a singlet carbene, **Figure 3**. Since singlet carbenes readily react with double bonds, the analogous 1,1-cycloaddition of nitrile ylides can be rationalised.

Many other examples of the 1,1-cycloaddition of nitrile ylides have been reported[24] and the mechanism has been shown to be stereospecific and probably therefore concerted.[25] In certain cases the preference between 1,3-dipolar and 1,1-cycloaddition is slight. For example, photolysis of the 3-(*o*-allyloxyphenyl) substituted 2*H*-azirines **26** gave both modes of reaction,[26] **Scheme 10**. The dimethyl nitrile ylide **27** (R^1=R^2=Me) reacted exclusively by 1,1-cycloaddition to give the cyclopropabenzopyran **28** (R^1=R^2=Me) in very high yield. On the other hand, the dihydro analogue **27** (R^1=R^2=H) underwent 1,3-dipolar cycloaddition to give cycloadduct **29** (R^1=R^2=H) as the sole product.

The monomethyl analogue (R^1=Me, R^2=H) gave a 1:1 mixture of the 1,1- and 1,3-cycloadducts. In all cases the intermediacy of the nitrile ylide was demonstrated by trapping with methyl acrylate.



	28	**29**
$R^1 = R^2$ = Me	100	nil
R^1 = H, R^2=Me	50	50
$R^1 = R^2$ = H	nil	100

Scheme 10

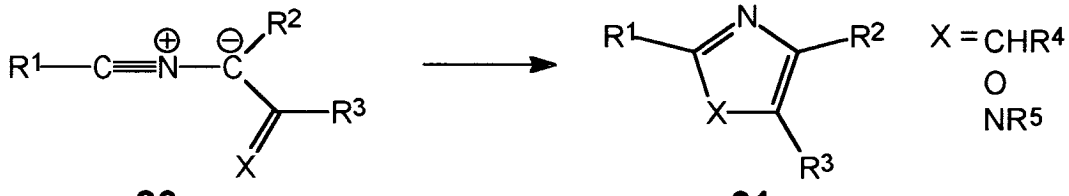
These results were rationalised in terms of electron donation by the methyl groups resulting in further bending of the nitrile ylide. This, according to MO

calculations, increases the carbene-like nature of C-1 and so promotes 1,1-cycloaddition.

The mode of intramolecular cycloaddition also depends upon dipolarophile substitution.[14,24(b)] If the energy of the dipolarophile LUMO is lowered sufficiently, 1,3-dipolar cycloaddition is favoured over carbene insertion.

1.5.2. 1,5-Electrocyclisation

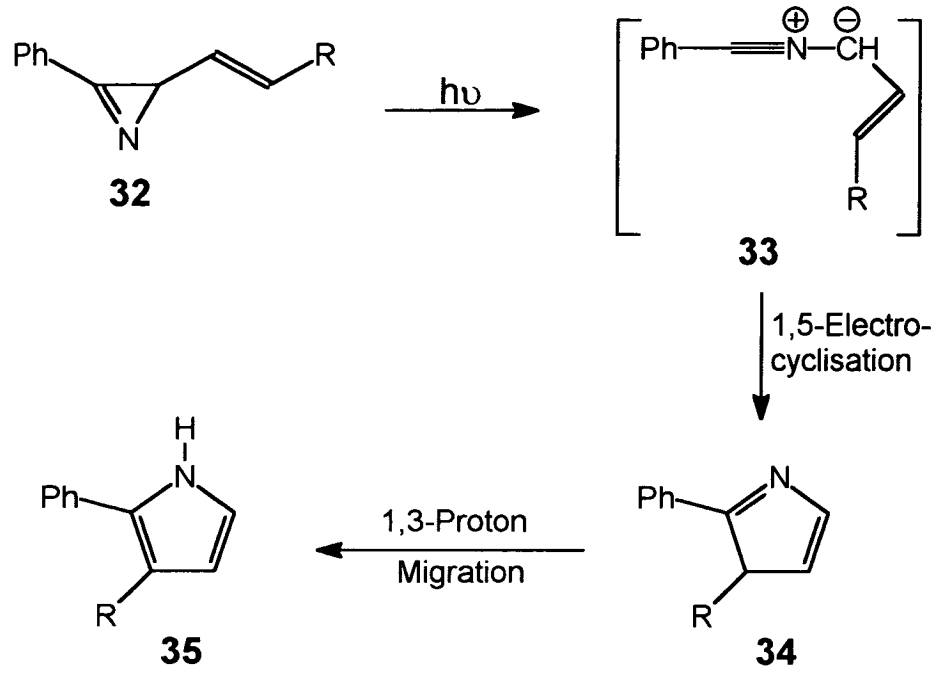
Another common intramolecular reaction of nitrile ylides is 1,5-electrocyclisation. Here an α,β-unsatured nitrile ylide **30** cyclises to give a five-membered heterocycle **31**, **Scheme 11**. This is analogous to the disrotatory electrocyclisation of the isoelectronic pentadienyl anion.



Scheme 11

As an example, photolysis of the 2-vinyl-2*H*-azirines **32** gave the vinyl substituted nitrile ylides **33** which underwent 1,5-electrocyclisation[27] to give the 3*H*-pyrroles **34**, **Scheme 12**. These initial products rearranged *via* a 1,3-proton migration to the more stable pyrroles **35**.

The 1,5-electrocyclisation reactions of nitrile ylides have been extensively reviewed[6] and will not be discussed further here.



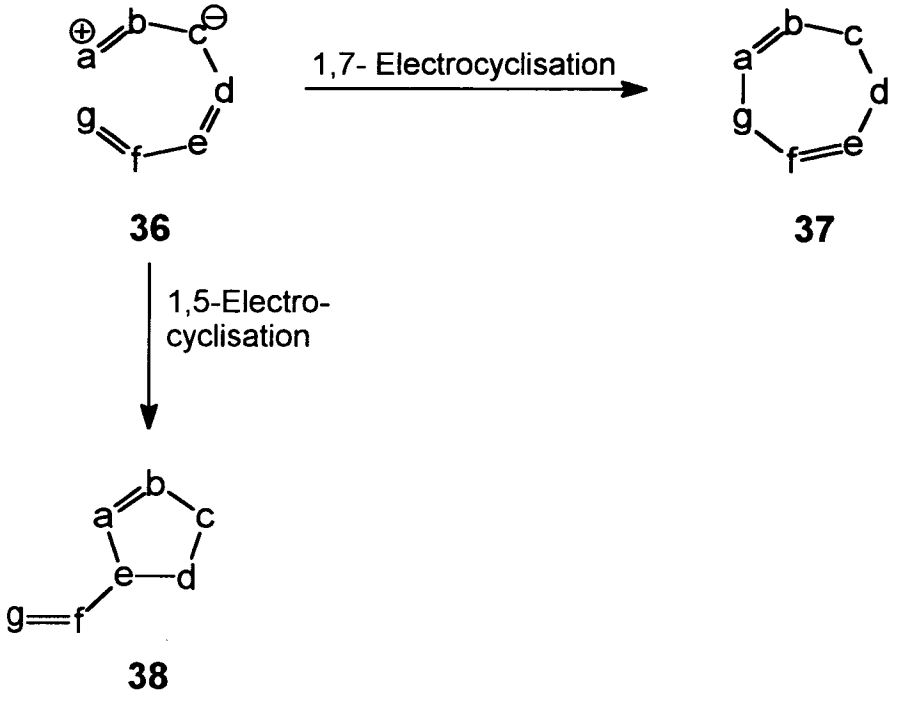
Scheme 12

1.5.3. 1,7-Electrocyclisations of Nitrile Ylides

When a 1,3-dipole is both α,β- *and* γ,δ-unsaturated (*eg* **36)** it may undergo a 1,7-electrocyclic ring closure of the 8π-electron system to give a seven-membered heterocycle **37**, **Scheme 13**. This reaction is analogous to the thermal conrotatory electrocyclisation of the isoelectronic heptatrienyl anion. 1,5-Electrocyclisation to give the pentatomic heterocycle **38** is also possible, giving rise to the question of periselectivity. 1,7-Electrocyclisation is favoured by a mutual Z-relationship between the 1,3-dipole and the γ,δ-double bond and for nitrile ylides there is a preference for 1,7- over 1,5-electrocyclisation.

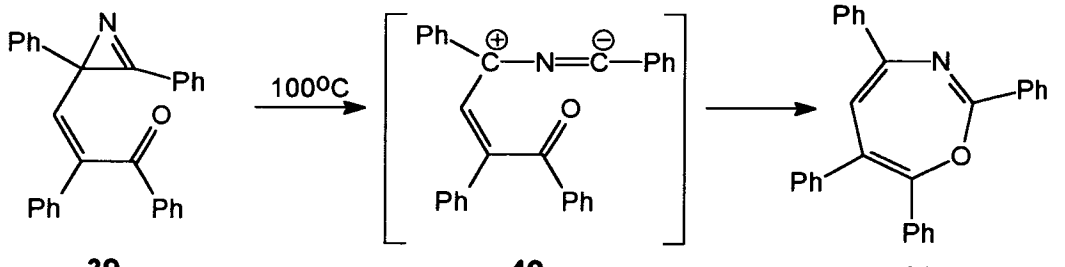
1,7-Electrocyclisations have been the subject of a recent review[7] and only selected nitrile ylide reactions will be discussed here. For example, the

thermolysis of the 2*H*-azirine **39** gave the 1,3-oxazepine **41** *via* the nitrile ylide **40**, **Scheme 14**.[28]



36 **37** **38**

Scheme 13

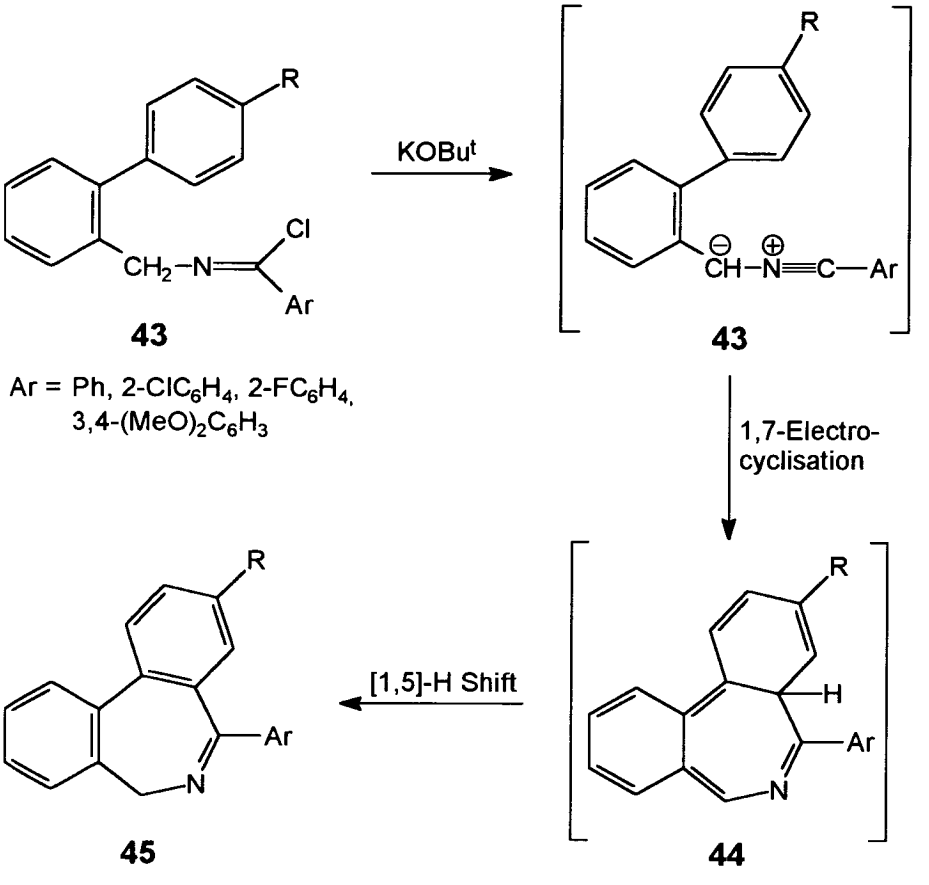


39 **40** **41**

Scheme 14

If the α,β- and/or γ,δ-double bonds are part of an aromatic or heteroaromatic ring, the initial 1,7-electrocyclisation disrupts the aromaticity of this ring. If a δ-hydrogen is present, aromaticity is restored by a sigmatropic [1,5]-hydrogen shift. Thus, the biphenyl substituted nitrile ylide **43**, generated from the imidoyl

chloride **42**, underwent 1,7-electrocyclisation to give the unstable intermediate **44**. Aromaticity in both rings was restored by a sigmatropic [1,5]-hydrogen shift to give the dibenzazepine **45**, **Scheme 15**.[29]



Scheme 15

The 1,7-electrocyclisation of nitrile ylides has been shown to be irreversible,[30] in contrast to the reversible reaction of diazoalkanes.

The [1,5]-sigmatropic hydrogen shift has been shown to be wholly intramolecular.[31] The migration is suprafacial, *ie* the σ-bond is made and broken on the same side of the conjugated system, **Figure 6**.

The related system **46** followed a more complex reaction path.[13] When the reaction was carried out at RT or below the only product was the cyclopropa[*c*]isoquinolines **48**, **Scheme 16**. However on heating at 50°C or

above these products were cleanly converted into the 2-benzazepines **49**. It is not clear whether these products **48** derive from 1,7-electrocyclisation reactions followed by ring contraction of the intermediate **47**, or from the stereospecific

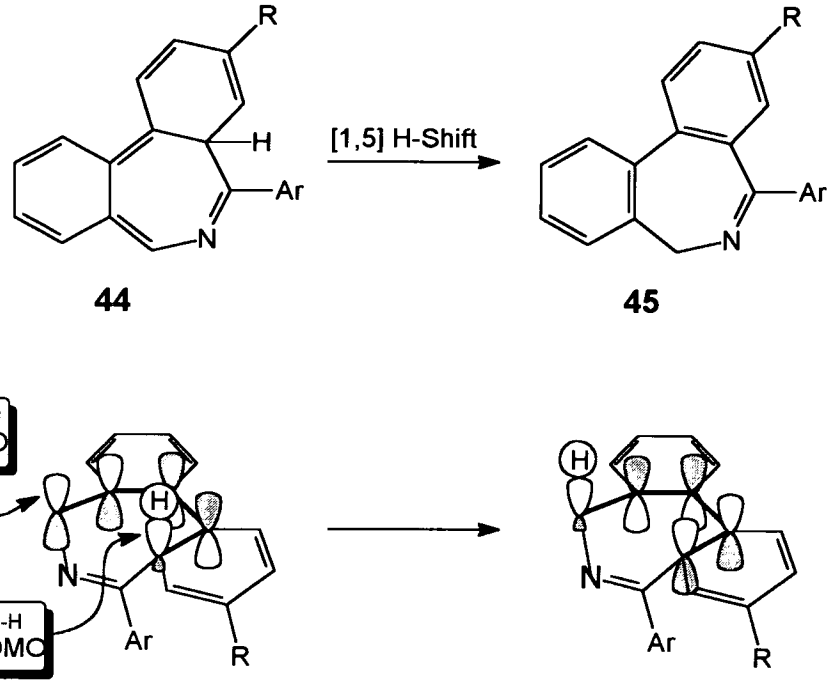
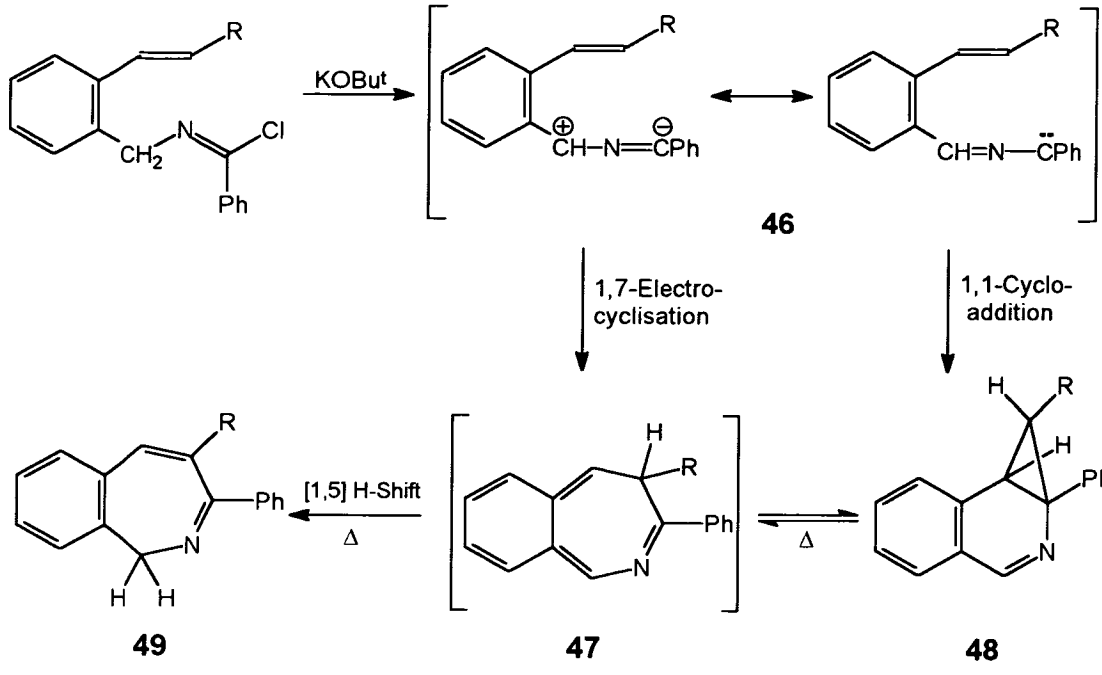


Figure 6

1,1-cycloaddition of the nitrile ylide across the γ,δ-double bond. The former may occur if ring contraction is faster than the [1,5]-H shift. The hydrogen shift does occur if the isoquinolines **48** are heated, giving the 2-benzazepines **49**.


R
KOBut
N
Cl
CH2
Ph
CH–N=CPh
CH=N—CPh
46
1,7-Electro-
cyclisation
1,1-Cyclo-
addition
H
R
Ph
N
[1,5] H-Shift
Δ
H H
49
47
48

Scheme 16

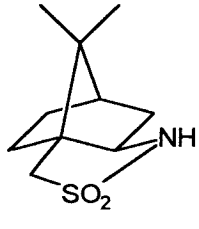
2. SOME ASPECTS OF FACE SELECTIVITY IN PERICYCLIC REACTIONS

2.1. Introduction

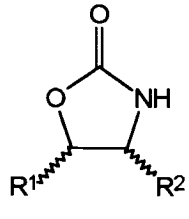
A pericyclic reaction[125] occurs *via* a concerted cyclic shift of electrons. This classification includes cycloadditions (*eg* Diels-Alder, 1,3-dipolar), electrocyclisations, sigmatropic rearrangements and fragmentations (such as ester pyrolysis and the M^{c}Lafferty rearrangement). The induction of face selectivity in pericyclic reactions has been extensively investigated and space here only allows for the discussion of a few relevant examples.

2.2. Diels-Alder Cycloadditions

The most widely studied asymmetric pericyclic reaction is the face selective Diels-Alder reaction.[32] Face selectivity of greater than 99% has been observed,[33] although without Lewis acid catalysis the figure is much lower. The most commonly used method of inducing face selectivity in Diels-Alder reactions is the use of chiral auxiliaries[34] such as Oppolzer's sultam **50**[32(a)] and Evans' auxiliaries **51**.[35] Both antipodal sultams are readily available, as are a variety of substitution patterns and stereochemistries for the oxazolidinones **51**. Thus, any observed face selectivity can be reversed by changing the chiral auxiliary. Both auxiliaries are easily removed under mild conditions to yield useful functional groups.

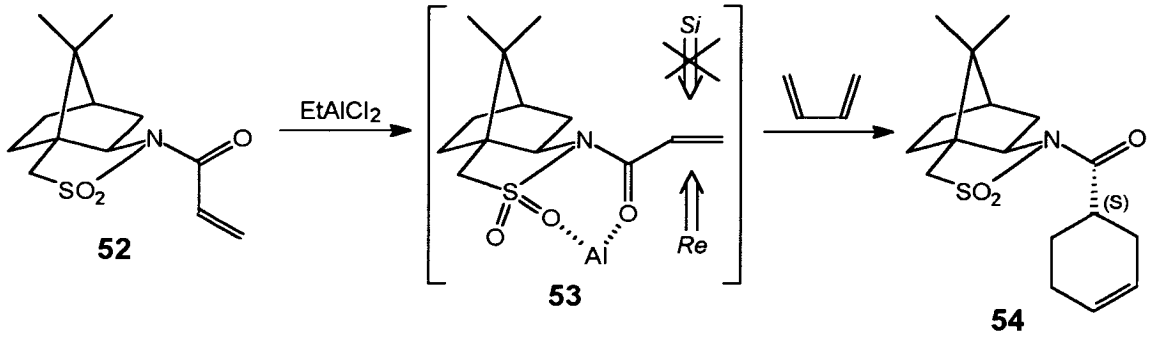


50



51

The acryloyl sultam **52** reacted with butadiene in the presence of ethylaluminium dichloride to give the adduct **54** with a diastereomeric excess (d.e.) of 97%, **Scheme 17**.[36]



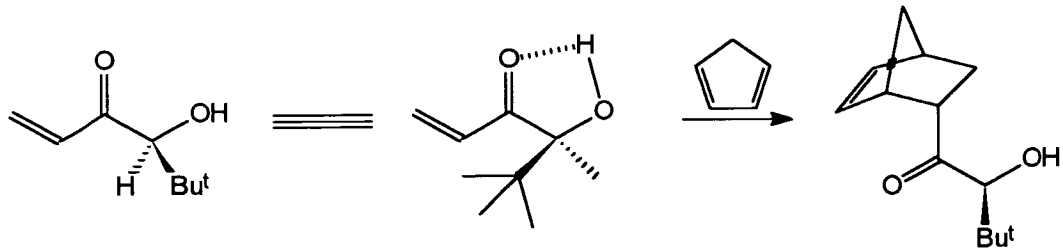
52 53 54

Scheme 17

The very high face selectivity is due to complexation of the SO_2 and CO by the metal to give the complex **53**. The bulky alkyl group blocks the C_α-*Si* face and reaction occurs at the less hindered C_α-*Re* face of the alkene.

Although in the presence of Lewis acids the acryloyl sultam **52** shows a preference for the SO_2 and CO to be *anti* to one another,[37] the absence of a conformational lock prevents high face selectivities being observed in thermal Diels-Alder cycloadditions.

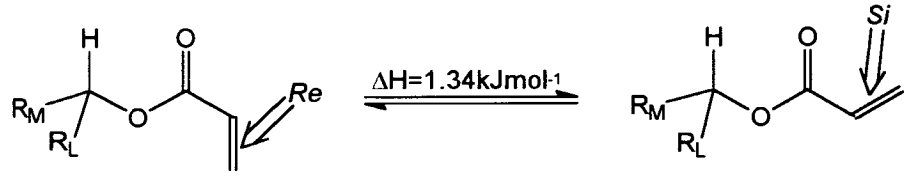
Of the few examples reported of high face selectivity in thermal Diels-Alder cycloaddition, most relied upon internal complexation. For example, the enone **55** was reacted with cyclopentadiene to give the adduct **57** with greater than 100:1 face selectivity, **Scheme 18**.[38] Strong H-bonding between the hydroxyl and the ketone effectively locked the conformation and the bulky *tert*-butyl group blocked off one face of the now diastereotopic enone **56**.



55 **56** **57**

Scheme 18

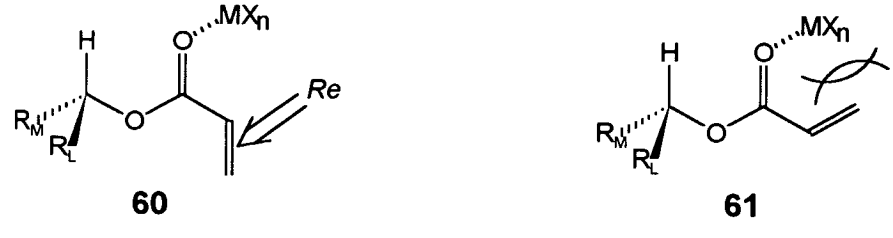
Chiral acrylates have also been studied in face selective Diels-Alder cycloadditions.[32(a)] In the absence of Lewis acid catalysts face selectivity is low, as there is an easy equilibrium between the conformers **58** and **59**, **Scheme 19**. If the diene adds exclusively to the π-face opposite the larger substituent (R_L), conformers **58** and **59** induce reversed face selectivity.



58 **59**

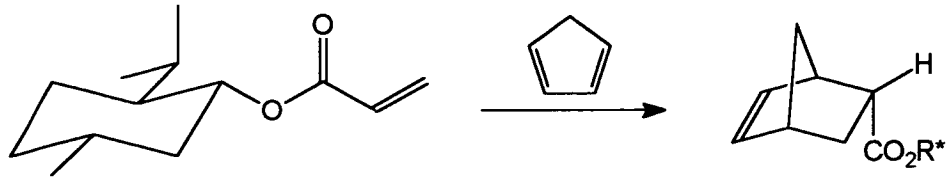
Scheme 19

In the presence of Lewis acids, complexation of the metal *anti* to the alkyl oxygen disfavours the conformation **61** and attack occurs predominantly at the *Re* face of the conformer **60**.



60 **61**

For example, reaction of menthyl acrylate **62** with cyclobutadiene in the presence of a Lewis acid gave the adduct **63** with 85% diastereoselectivity, **Scheme 20**. In the thermal reaction, face selectivity was less than 10%.[39]

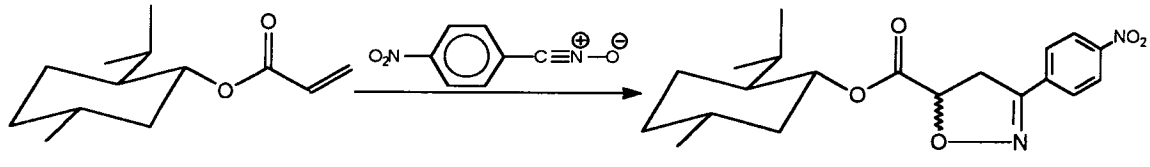


62 **63**

Scheme 20

2.3. 1,3-Dipolar Cycloadditions

Another extensively studied asymmetric pericyclic reaction is 1,3-dipolar cycloaddition.[40] Face selectivity is usually lower than in the Diels-Alder reaction as the presence of Lewis acid lowers yields. As an example, reaction of menthyl acrylate **62** with *p*-nitrobenzonitrile oxide gave the adduct **64** with less than 4% diastereoselectivity, **Scheme 21**.[41] This compares with 10% diastereoselectivity for the corresponding thermal Diels-Alder reaction with cyclopentadiene and 85% for the Lewis acid catalysed Diels-Alder.



62 **64**

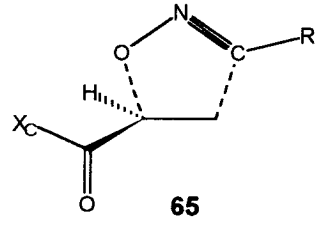
Scheme 21

Although most reports relate to asymmetric 1,3-dipolar cycloadditions of nitrile oxides, there are several reports of the face selective reaction of

diazoalkanes[42] and nitrones.[43] Azides have also been reported to react asymmetrically.[44]

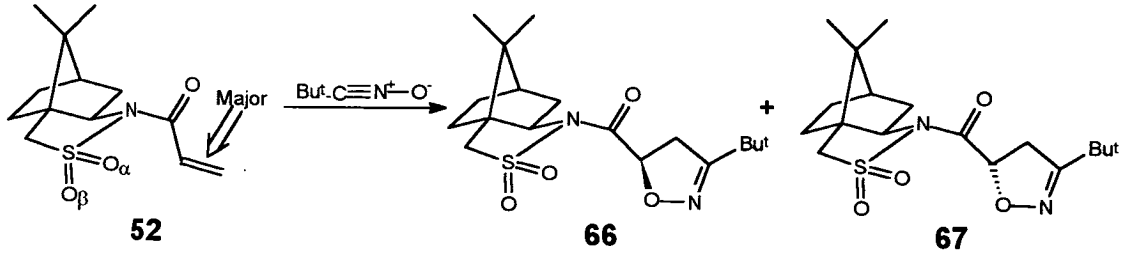
Houk and co-workers have studied the nitrile oxide cycloadditions of alkenes bearing a chiral α-carbon. Observed face selectivity was rationalised in terms of an 'outside crowded' transition state model[45] which is also applicable to Diels-Alder cycloadditions.[46]

Face selectivity in nitrile oxide cycloaddition is particularly difficult to induce by the use of chiral auxiliaries. In the transition state[45] **65** the forming ring is loosely planar and the two atoms closest to the auxiliary (O and N) bear no substituents. The carbon atom of the nitrile oxide bears only a single substituent but this projects away from the auxiliary. Hence, face selectivity is usually independent of nitrile oxide substitution.[41,47]



65

Use of Oppolzer's sultam **50** as a chiral auxiliary has, however, consistently given high face selectivity in nitrile oxide cycloadditions. For example reaction of the acryloyl sultam **52** with 2,2-dimethylpropane nitrile oxide gave a 95:5 mixture of the diastereomers **66** and **67**, **Scheme 22**.[47]

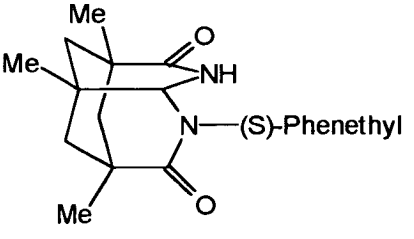


52 **66** **67**

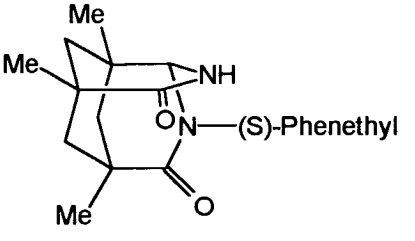
Scheme 22

Of the four planar conformations of the acryloyl sultam **52** three are disfavoured by either dipole-dipole interactions or steric destabilisation.[47] In contrast to the Diels-Alder reaction, attack by the nitrile oxide occurred at the 'top' side of the alkene. It was proposed[47] that this was due to a combination of steric or electronic hindrance by O_α together with a favourable stereoelectronic directing effect of the nitrogen lone pair.[37]

The highest consistent degree of face selectivity in nitrile oxide cycloaddition was obtained by use of the diasteromeric bis(lactams) **68** and **69**.[48]

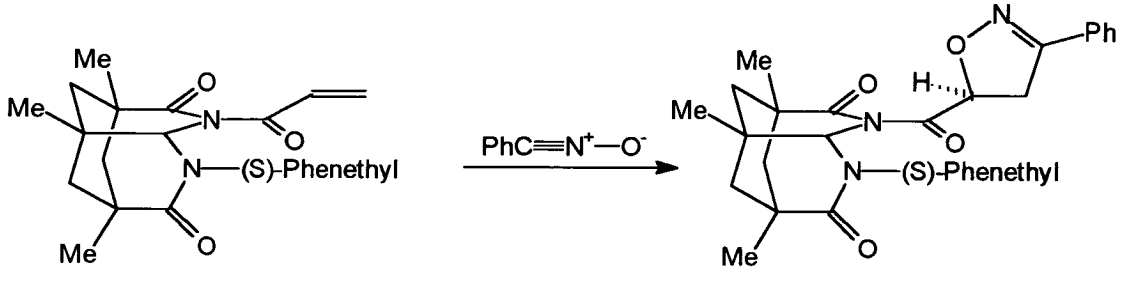


68



69

Reaction of the acrylimide derivative **70** with benzonitrile oxide gave the adduct **71** with 99% diastereoselectivity, **Scheme 23**. The sense of face selectivity was reversed by use of the antipodal auxiliary **69** and again gave 99% diastereoselectivity.



70 **71**

Scheme 23

The high face selectivity arises from a strong *anti* preference of the lactam and amide carbonyls. Steric hindrance ensures the s-*cis* disposition of the alkene

and acryloyl carbonyl groups. The bulky (*S*)-phenylethyl group then efficiently shields the 'lower' face of the alkene and attack by the nitrile oxide occurs almost exclusively from 'above'.

2.4. 1,7-Electrocyclisation

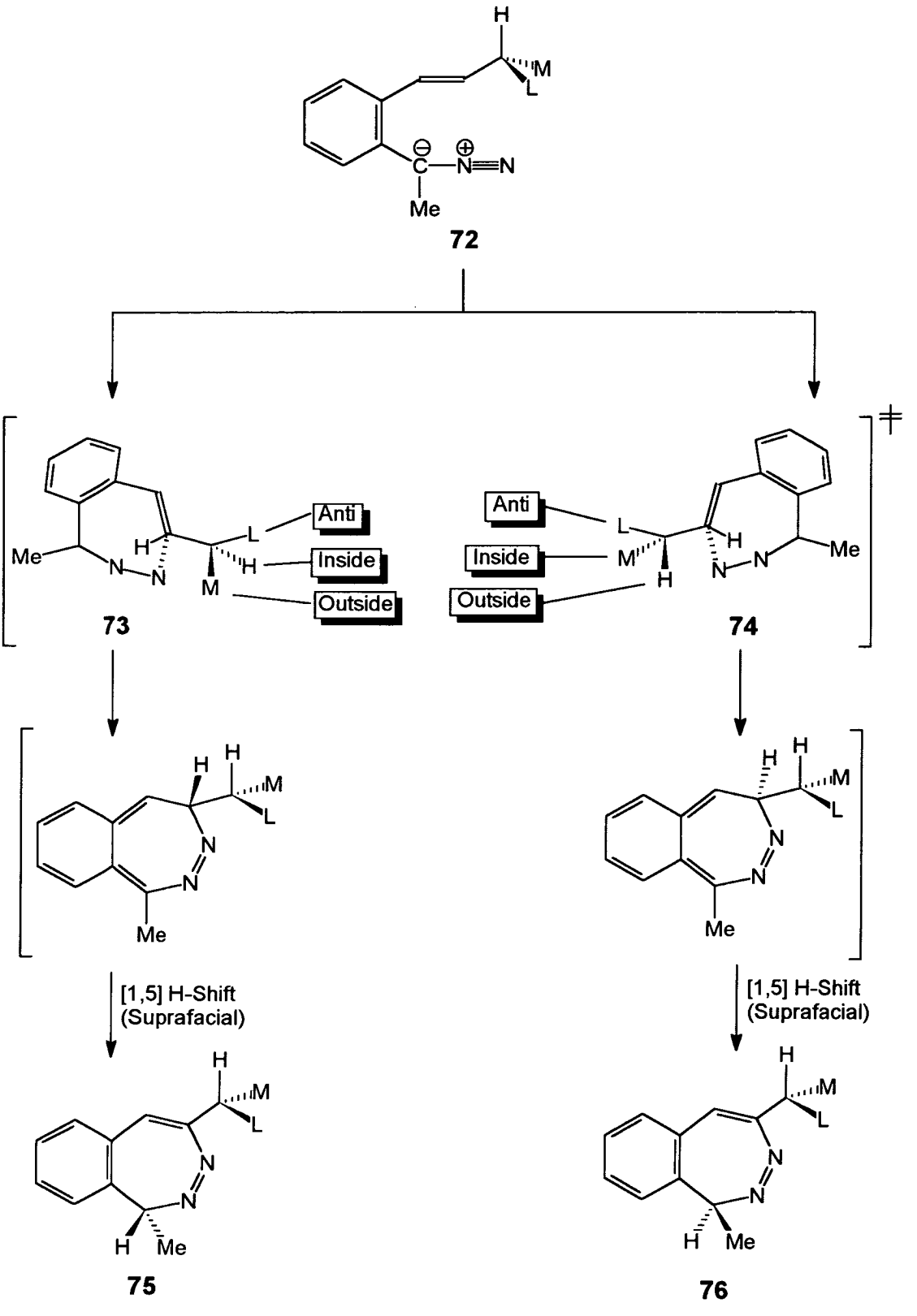
There is only one report of face selectivity in 1,7-electrocyclisation.[49] This was carried out using the α,β- and γ,δ-unsaturated diazoalkanes **72**, which had a chiral centre attached to the δ-carbon, **Scheme 24**. Intramolecular attack at this δ-carbon could occur from either face and any chirality induced at C-4 would be transferred to C-1 by a suprafacial [1,5]-hydrogen shift.

The results obtained are shown in **Table 3**.

	M	L	75:76
(a)	Me	Ph	55:45
(b)	Me	Bu^t	58:42
(c)	Et	Bu^t	63:37
(d)	OMe	Ph	44:56
(e)	OMe	Bu^t	8:92
(f)	OTBDMS	Bu^t	9:91
(g)	O$^-$	Bu^t	85:15

Table 3. Diastereomer Ratios for the products from Scheme 24

To account for the observed diastereomer ratios it was assumed that in the transition state, **73** and **74**, the largest group L was *anti* to the attacking N. This leaves the disposition of group M to determine face selectivity.


H
M
L
Me
72
Anti
Inside
Outside
73
74
[1,5] H-Shift
(Suprafacial)
75
76

Scheme 24

In cases where M was an alkoxy group (**Table 3**, entries **(d)** and **(e)**) there was a marked inside preference giving a diastereomer ratio of up to 92:8. This is in agreement with Houk's work on face selective cycloadditions.[45] In contrast, when $M{=}O^-$ (**Table 3**, entry **(g)**) there was a strong outside preference giving 85% face selectivity. Alkyl groups (**Table 3**, entries **(a)-(c)**) also showed an outside preference but to a much lesser degree. This is the opposite result to that observed by Houk for cycloadditions.

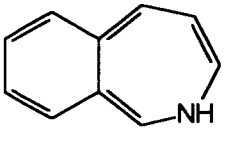
Thus it was shown that face selectivity was dependent upon both the steric and stereoelectronic effects of M. The inside alkoxy effect was rationalised as a consequence of polar repulsion between the incoming N and the O of the alkoxy group. The outside alkoxide effect was attributed to a combination of the bulk of the solvated O^-M^+ preferring the outside position, together with chelation *via* Li^+ to the incoming nitrogen. This 'bulky group' outside preference was also used to rationalise the moderate outside alkyl effect observed.

The synthetic utility of this approach was limited by the difficulty of removing the chiral directing groups after cyclisation.

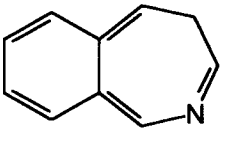
3. 2-BENZAZEPINES

3.1. Structure of 2-Benzazepines

For fully unsaturated 2-benzazepines there are five possible isomers depending upon the position of saturation. 2*H*-2-Benzazepine **77** has been the subject of theoretical studies[50] which predicted it would be very unstable. Indeed, no such systems have been reported. The instability arises from a negative resonance energy due to loss of benzenoid character of the carbocyclic ring. Although a 10π-electron species, the planarity required for aromaticity brings the nitrogen lone pair into conjugation with the π-system. The resultant 12π-electron system would be antiaromatic and thus it is not surprising that no 2*H*-2-benzazepines have been prepared. The same situation applies to the unknown 4*H*-isomer **78**.

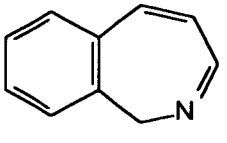


77

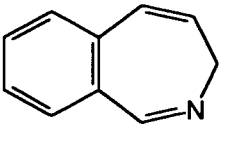


78

1*H*-, 3*H*- and 5*H*-2-benzazepines (**79**, **80** and **81**) are all known, with the azepine ring being non-planar. This non-planarity avoids the destabilising overlap of the nitrogen lone pair with the π-electrons which would give an antiaromatic π-system.



79



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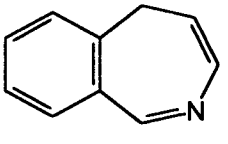
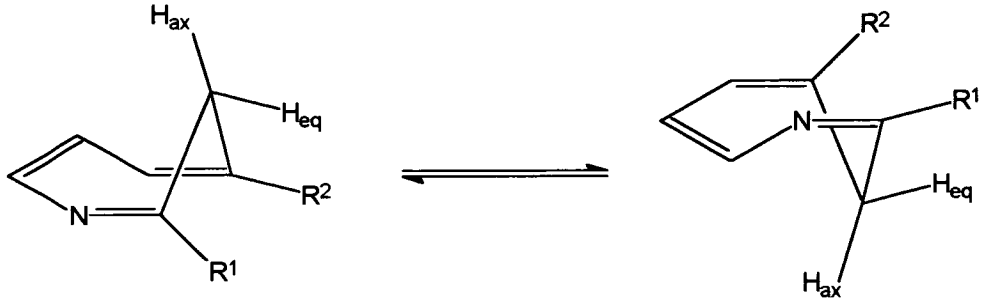


81

X-Ray diffraction studies[51] have shown that azepines adopt a boat configuration. Proton n.m.r. studies[52] further showed that the azepine ring inverts *via* a planar intermediate (**82** → **83**), **Figure 7**.



82 **83**

Figure 7

At low temperatures, when ring flipping is slow, H_{ax} and H_{eq} can be distinguished by ^1H n.m.r., appearing as two doublets (R^1, $R^2 \neq H$). If the temperature is raised, the two signals broaden and coalesce as ring inversion speeds up. At high temperatures ring flipping is faster than the n.m.r. timescale and a single average absorbtion for the methylene group is observed. The temperature at which the signals merge is called the coalescence temperature (T_c). Using this, it is possible to calculate the free enthalpy of the barrier to ring inversion from the equation:[52]

$$\Delta G_c^{\#} = RT_c\left(\ln\frac{\sqrt{2}kb}{h\pi} + \ln\frac{T_c}{\sqrt{\Delta\nu^2 + 6J_{AB}^2}}\right)$$

$$i.e.\quad \Delta G_c^{\#} = 8.31T_c\left(22.96 + \ln\frac{T_c}{\sqrt{\Delta\nu^2 + 6J_{AB}^2}}\right)$$

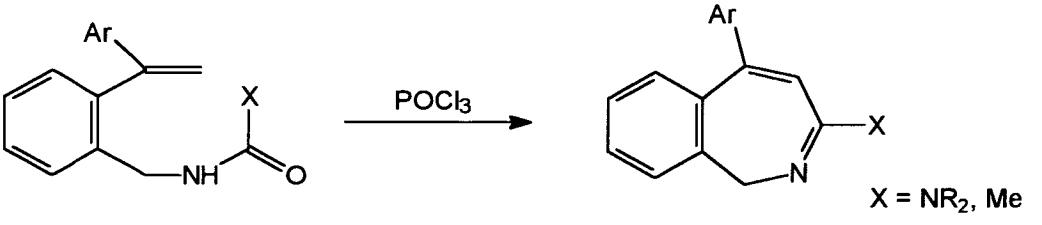
Where $\Delta G_c^{\#}$ is the free enthalpy of activation for ring inversion in $Jmol^{-1}$ at the coalescence temperature (T_c/K), $\Delta\nu$ is the difference in ^1H n.m.r. frequency of H_A and H_B in Hz and J_{AB} is the coupling constant between H_A and H_B in Hz.

For 2-benzazepines the coalescence temperature is typically in the range 270-360K with a $\Delta G_c^{\#}$ of 50-70 $kJmol^{-1}$. The absolute value is dependent upon substitution.

3.2. Synthesis of 2-Benzazepines

The synthesis and reactions of 2-benzazepines have been extensively reviewed[53] and only routes to the fully saturated systems will be discussed here.

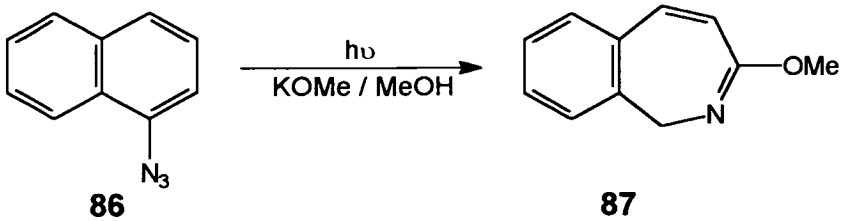
Gast and co-workers[54] prepared the 1*H*-2 benzazepines **85** in good yield by a Bischler-Napieralski type cyclisation of the unsaturated amides **84**, **Scheme 25**.



84 **85**

Scheme 25

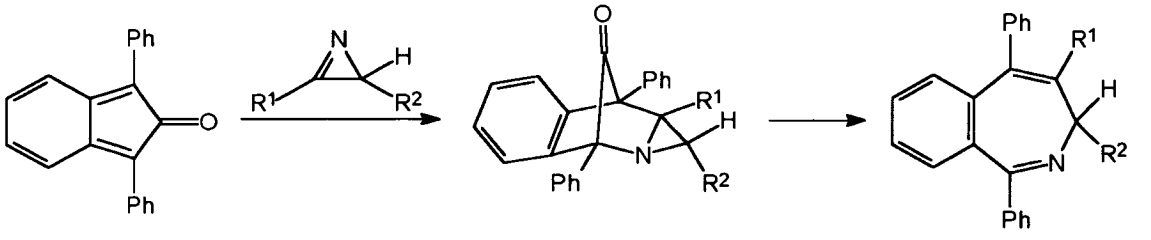
The photolysis of 2-azidonaphthalene **86** in the presence of potassium methoxide in methanol gave 3-methoxy-1*H*-2-benzazepine **87** in high yield,[55] **Scheme 26**.



86 **87**

Scheme 26

An extensively studied[56] azepine synthesis involves the Diels-Alder cycloaddition of 2*H*-azirines to cyclopentadienones. Thus, reaction of 1,3-diphenylinden-2-one **88** with 2*H*-azirines gave the intermediates **89**. These lost carbon monoxide with a disrotatory ring opening of the aziridine ring to give the 3*H*-2-benzazepines **90** in high yields,[56] **Scheme 27**.

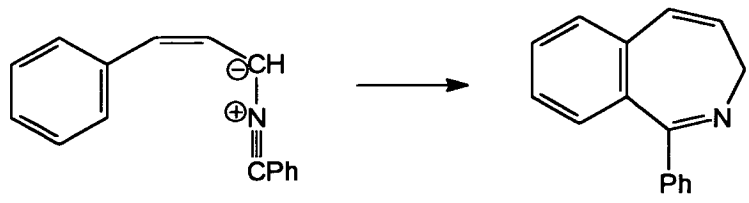


88 **89** **90**

R1 = Ph, Me, Et
R2 = H, Ph, Me, Et

Scheme 27

As mentioned previously, diene conjugated nitrile ylides provide a useful route to 1*H*- and 3*H*-2-benzazepines. For example, the nitrile ylide **91**, generated by azirine photolysis, gave the 3*H*-2-benzazepine **92** after a [1,5]-hydrogen shift, **Scheme 28**.[27]

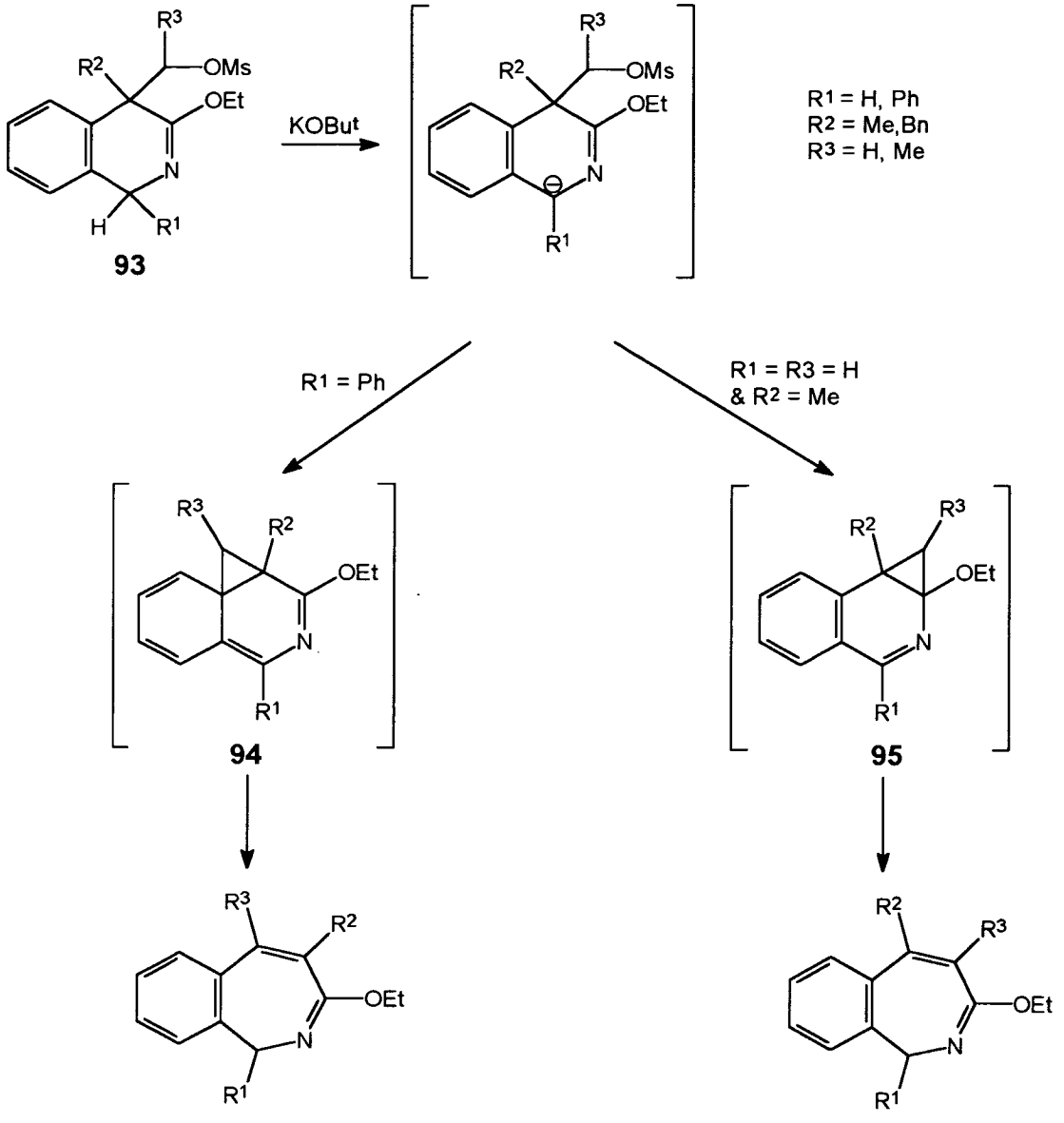


91 **92**

Scheme 28

In cases where the initial product is formally derived from a 1,1-cycloaddition of the nitrile ylide to the γ,δ-double bond, the cyclopropa[*c*]isoquinolines produced have been thermally ring opened to 1*H*-2-benzazepines.[13]

This thermal ring expansion was also observed where the cyclopropa-isoquinolines, **94** and **95**, were generated by treatment of the mesylates **93** with potassium *tert*-butoxide in DMSO **Scheme 29**[129]. The cyclopropaisoquinoline formed depends upon the substitution pattern.

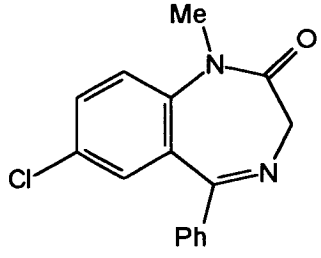


Scheme 29

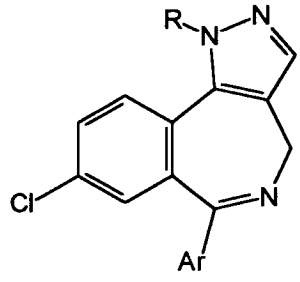
3.3 Biological Activity of 2-Benzazepines

2-Benzazepines have great medicinal potential as they are carbon isosteres of the extensively investigated 1,4-benzodiazepines.[57] Gschwend showed that replacement of the amide functionality in diazepam (Valium), **96,** with two sp^2-hybridised carbon atoms did not affect the desired pharmacological profile.[58]

For example, the pyrazolobenzazepines **97** were found to have a potency and selectivity at the benzodiazepine receptor similar to diazepam **96**.[59]



96



97

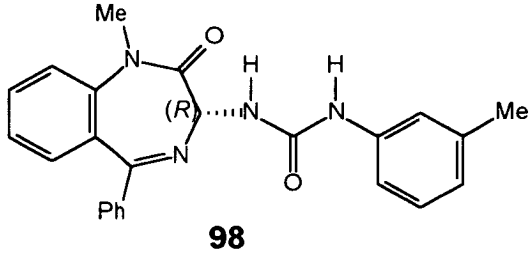
One area of great potential for the little-investigated 2-benzazepines is as cholecystokinin (CCK) receptor antagonists.[60] Cholecystokinin is a major intestinal hormone and is also one of the most widely distributed neuropeptides. There are at least two types of receptor, designated CCK-A and CCK-B. The CCK-A receptors are found along the gastrointestinal tract, whereas CCK-B receptors are found mainly in the brain.

CCK antagonists have many potential therapeutic applications,[60(a)] a few of which are discussed below.

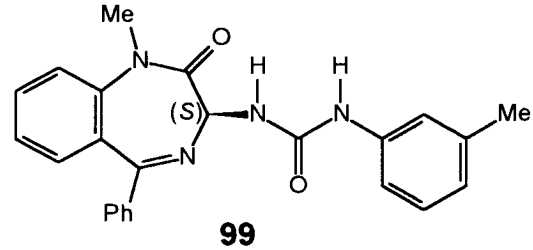
CCK-A receptor antagonists inhibit pancreatic amylase secretion and thus may be useful in the treatment of pancreatitis.[61] Inhibition of the CCK-stimulated pancreatic growth may be of value in the control of pancreatic cancer.[62] CCK-A antagonists also reduce gallbladder contraction and have been successfully used to alleviate biliary colic.[63]

CCK-B receptor antagonists are known to potentiate morphine analgesia and reduce opiate tolerance.[64] They also have potential in the treatment of Parkinson's disease[65] since CCK inhibits dopamine function.

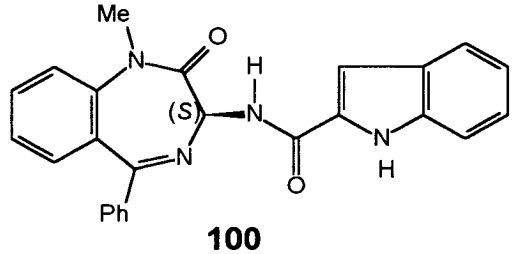
The action of cholecystokinin at the CCK-B receptors is known to cause anxiety and panic attacks.[66] Thus CCK-B antagonists have been developed as non-addictive anxiolytics.[67] One such compound is the chiral 1,4-benzodiazepine L 365 260, **98**.[67] The chirality is essential as when the 3-position has *S*-stereochemistry, **99**, potency at the CCK-B receptor is lost. The S-isomer is instead a good CCK-A receptor antagonist,[67(a)] although not as active as the more potent Devazepide **100**.[68]



98



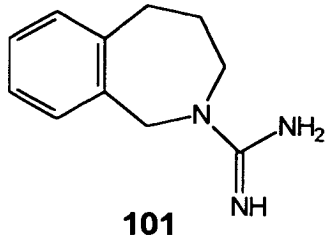
99



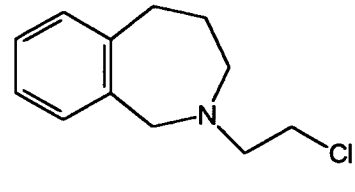
100

Since the diazepine amide can be replace with 2 sp^2-hybridised carbons without affecting the pharmacological profile,[58] 2-benzazepines offer a new series of potential CCK receptor antagonists.

2-Benzazepines also have potential in other therapeutic fields. The guanidine derivative **101** is a potent hypotensive agent [69] whereas the β-chloroethyl-2-benzazepine **102** is a potent adrenergic blocking agent.[70]

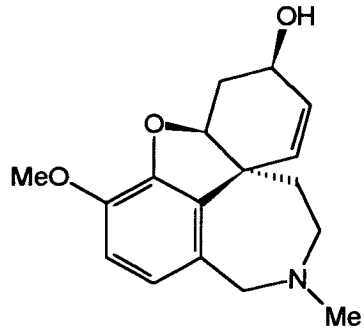


101



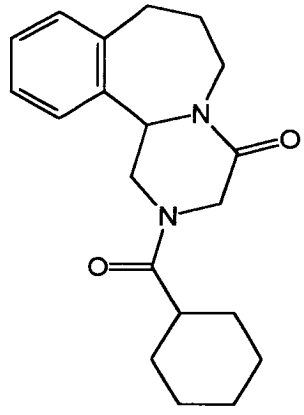
102

The natural product Galanthamine **103**, isolated from Caucasian snowdrops, has been marketed as a cholinesterase inhibitor.[71]

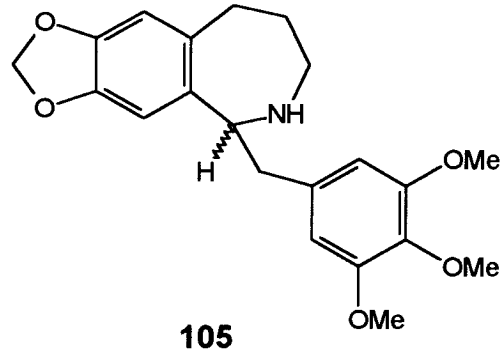


103

Other examples include Epsiprantel **104** which exhibits high cestocidal activity[72] and the tetrahydro-2-benzazepine **105** which is a selective platelet antiaggregatory agent.[73]



104

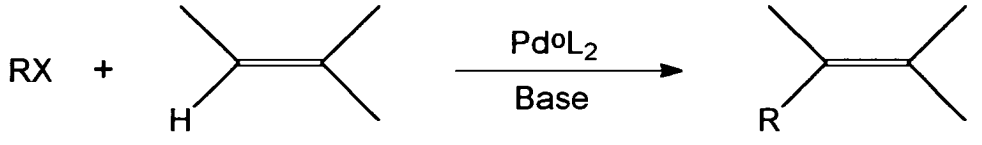


105

4. HECK REACTION

4.1. Introduction

The palladium catalysed vinylation of organic halides is known as the Heck reaction, **Scheme 30**. This reaction has been extensively reviewed[74] and only a brief summary is presented here.



R = Aryl, heterocyclic, vinylic or benzyl.
X = Br, I, (Cl) or pseudohalogen
L = A ligand, usually a triarylphosphine or solvent

Scheme 30

The main limitation of this reaction is that the organic halide must not have an easily eliminated β-hydrogen. Thus, alkyl halides are unsuitable substrates. Palladium acetate is usually the catalyst of choice and is used in conjunction with tri-*o*-tolylphosphine (PAr_3)[75] as ligand for the reaction of organic bromides.

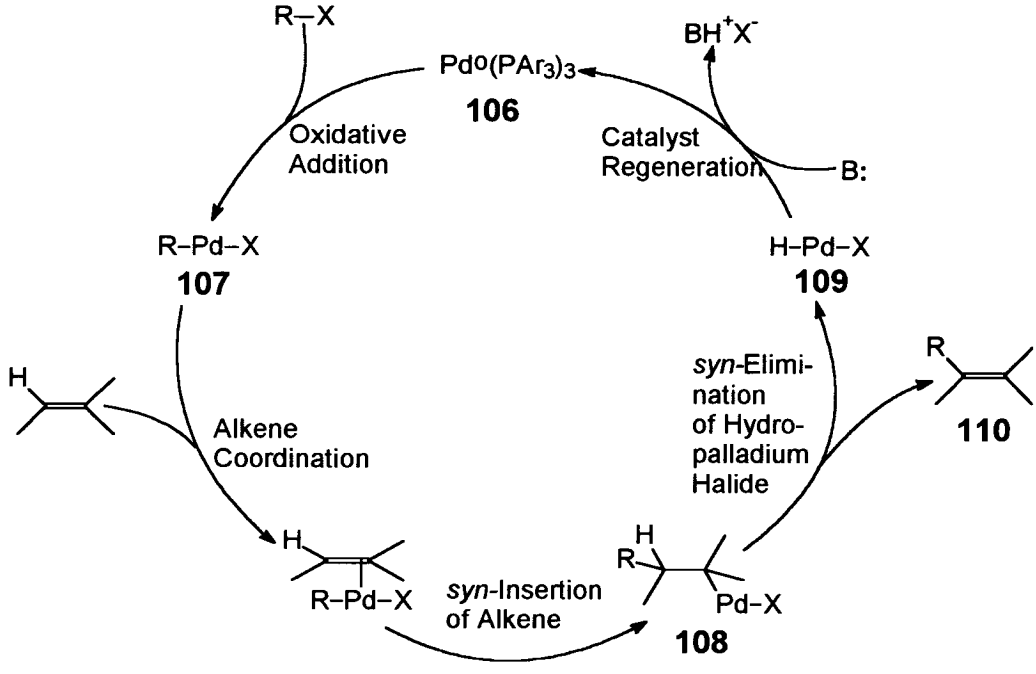
4.2. Mechanism

The mechanism is not yet fully understood. For example, the coordination state of the palladium during the catalytic cycle is unknown and therefore only 'active' ligands are shown here.

The first step involves reduction of palladium(II)acetate to $Pd^0(PAr_3)_2$ by a Wacker-type alkene oxidation, **Scheme 31**.[76]

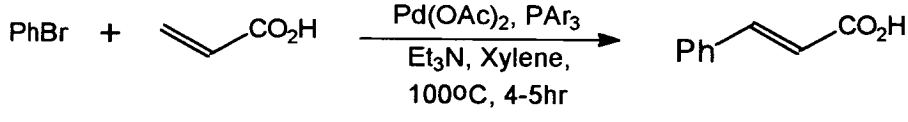
Scheme 31

The active catalyst **106** then undergoes oxidative addition with the organic halide to give the organopalladium(II)complex **107**. The alkene coordinates and *syn*-insertion gives the adduct **108**. *syn*-Elimination of a hydridopalladium halide **109** gives the most stable alkene **110**. The active catalyst **106** is then regenerated by removal of HX by the base, **Scheme 32**.



Scheme 32

The R group adds extensively (or at worst, predominantly) to the least substituted olefin terminus. For example, bromobenzene reacts with acrylic acid in the presence of 1mol% palladium acetate and tri-*o*-tolylphosphine to give only *trans*-cinnamic acid in 98% yield, **Scheme 33**.[77]



Scheme 33

4.3. Scope and Limitations

4.3.1. The Organic Halide

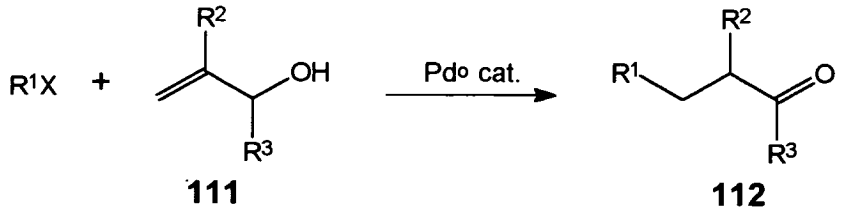
As mentioned earlier, the organic halide must not have an easily eliminated β-hydrogen as only elimination products are obtained. Aryl, heterocyclic, benzylic and vinylic halides all react well and a wide range of functional groups may be present. *o*-Halobenzoic acids do not react as a very stable chelate is formed with the palladium.[74(a)] The methyl esters react normally, however.

Iodides react faster than bromides and chlorides react poorly.[78] Pseudohalogens such as diazonium salts[79] and acid chlorides[88] react well. They form the organopalladium (II) complex **107** with loss of nitrogen and carbon monoxide respectively.

4.3.2. The Alkene

Reactivity decreases with increasing substitution of the alkene. Mono-substituted alkenes react well whereas tri-substituted alkenes give low yields. Steric effects dominate over electronic effects with reaction occurring exclusively (or predominantly) at the least substituted alkene terminus. The reaction is stereospecific with 1,2-disubstituted alkenes. If the alkene bears a good leaving group (*eg* halide or acetate), this group is eliminated in preference to a hydrogen.

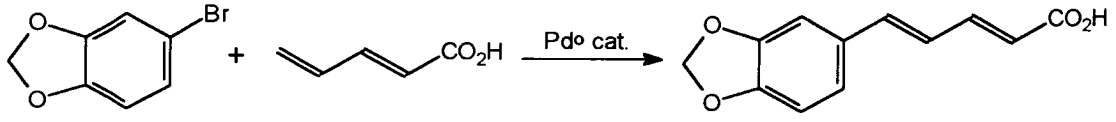
Allylic alcohols **111** undergo reductive elimination toward the alcohol carbon, producing the carbonyl compound **112**, **Scheme 34**.[81]



111 **112**

Scheme 34

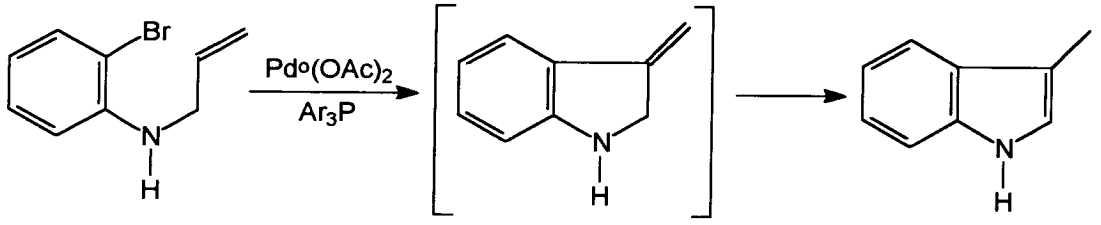
Conjugated dienes bearing conjugating substitutents react normally (**Scheme 35**),[82] although without such substitutents reaction is slow.



Scheme 35

4.3.3. Extensions of the Heck Reaction

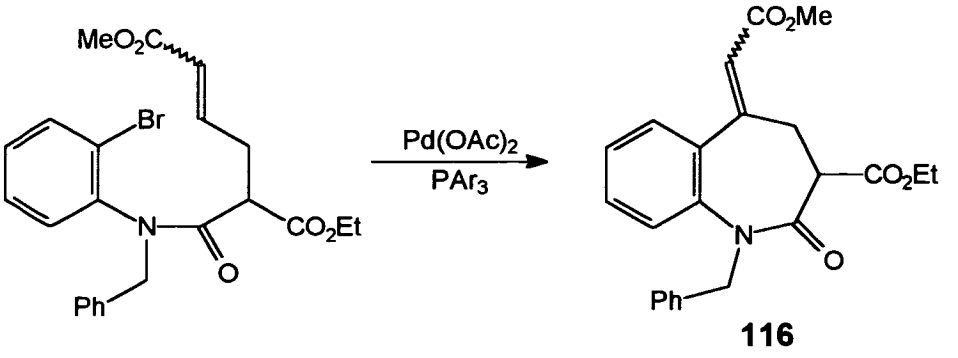
Intramolecular Heck reactions have been utilised in the synthesis of carbocyclic and heterocyclic ring systems. Here the regiochemistry is not always predictable. For example, the bromide **113** reacted at the *more* substituted carbon of the alkene to give the exocyclic alkene product **114**. This isomerised to the thermodynamically more stable 3-methylindole **115**, **Scheme 36**.[83]



113 **114** **115**

Scheme 36

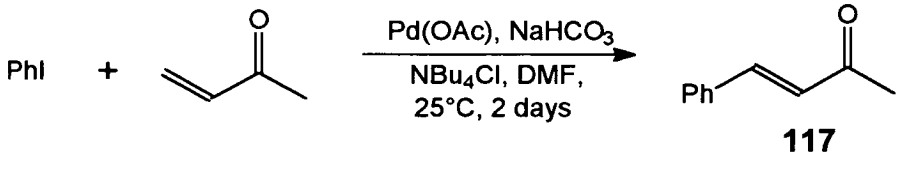
The Heck reaction has even been utilised in the synthesis of the 1-benzaz-epine **116**, **Scheme 37**.[84]



116

Scheme 37

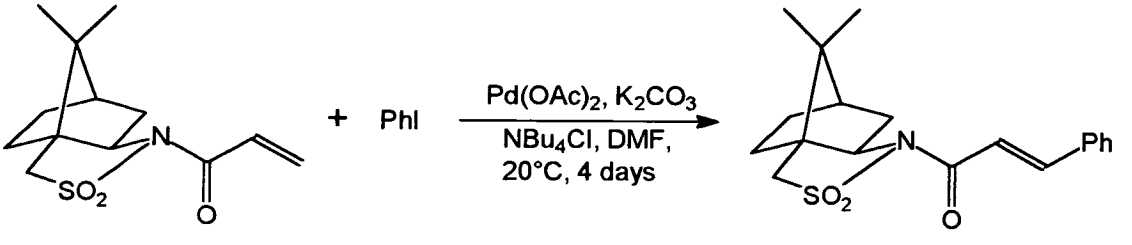
Recent advances include phase-transfer Heck reactions[85] which, for aryl iodides, allow the reaction to be carried out at room temperature. This has the advantage that alkenes which polymerise under the normal Heck reaction temperatures (>100°C) can now be utilised. For example, methyl vinyl ketone was coupled with iodobenzene at room temperature to give only the *trans*-alkene **117** in 98% yield, **Scheme 38**.[85]



117

Scheme 38

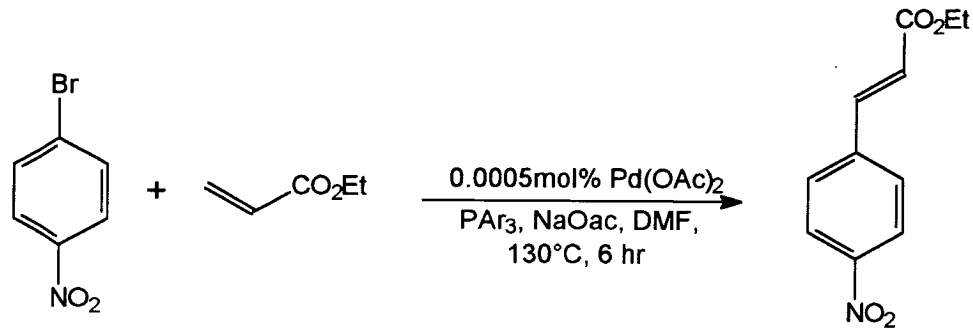
The N-propenyl sultam **52** was coupled with iodobenzene at room temperature, again yielding only the *trans*-alkene **118**, **Scheme 39**.[86]



52 **118**

Scheme 39

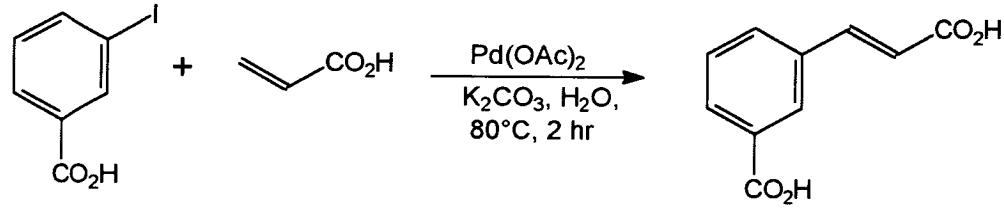
Variation of solvent, base and mode of addition by Spencer[128] has increased catalyst turnover considerably. In effect, one gramme of palladium acetate would be sufficient to catalyse the synthesis of at least 130kg of *trans*-ethyl-*p*-nitrocinnamate **119**, **Scheme 40**.[80]



119

Scheme 40

The Heck reaction has even been extended to aqueous media[127] for acidic aryl iodides which form water soluble salts. For example, *m*-iodobenzoic acid was coupled with acrylic acid to give only the *trans*-alkene **120** in 97% yield, **Scheme 41**.[127]

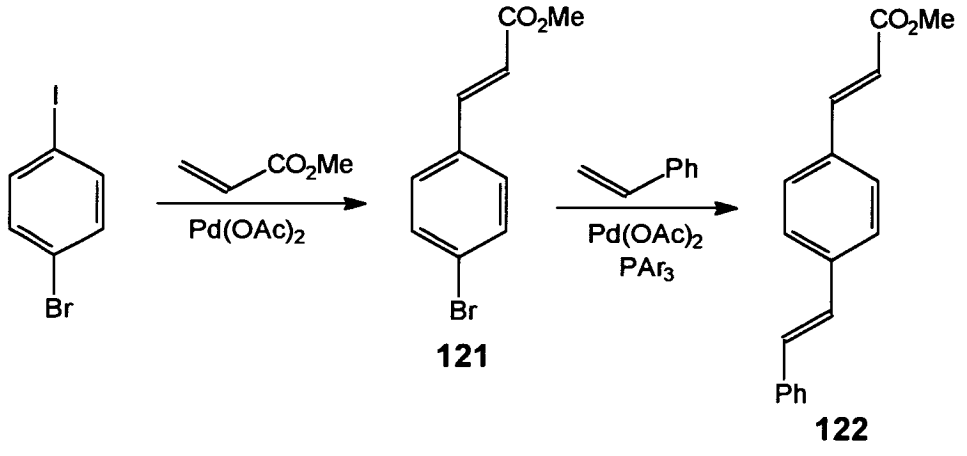


120

Scheme 41

Aryl bromides are less reactive than aryl iodides and require the presence of a triarylphosphine for reaction to occur. Thus, an iodo group may be reacted preferentially when an arene contains both iodo and bromo substituents. For example, *p*-bromoiodobenzene was reacted with methyl acrylate to give trans-

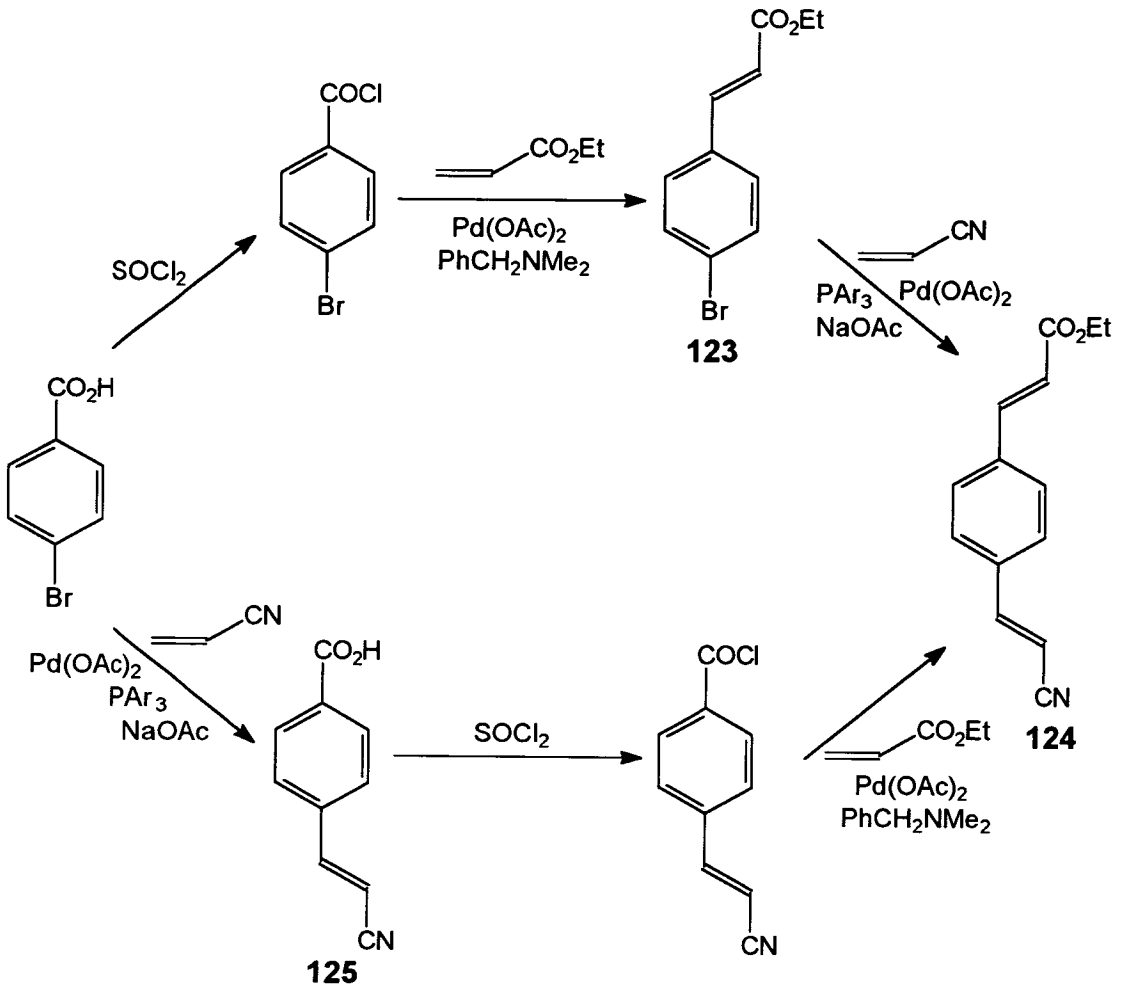
methyl 4-bromocinnamate **121**. This was then reacted with styrene to give (*E*,*E*)-methyl 4-styrylcinnamate **122**, **Scheme 42**.[87]



Scheme 42

Further selectivity was obtained by Spencer[88] with bromobenzoic acids. In the presence of palladium acetate and triarylphosphine the free acids reacted as aryl bromides. In the absence of triarylphosphines only the corresponding aroyl chlorides reacted. Thus it was possible to select which substituent was to react first.

For example, *p*-bromobenzoic acid was reacted as an aroyl chloride to give the *p*-bromocinnamate **123** which was then coupled with acrylonitrile to give the divinylbenzene **124**. Alternatively, *p*-bromobenzoic acid was reacted with acrylonitrile in the presence of a triarylphosphine to give the *p*-vinylbenzoic acid **125**. This was then converted to the aroyl chloride and coupled with ethyl acrylate to give the same divinylbenzene **124**, **Scheme 43**.[88]

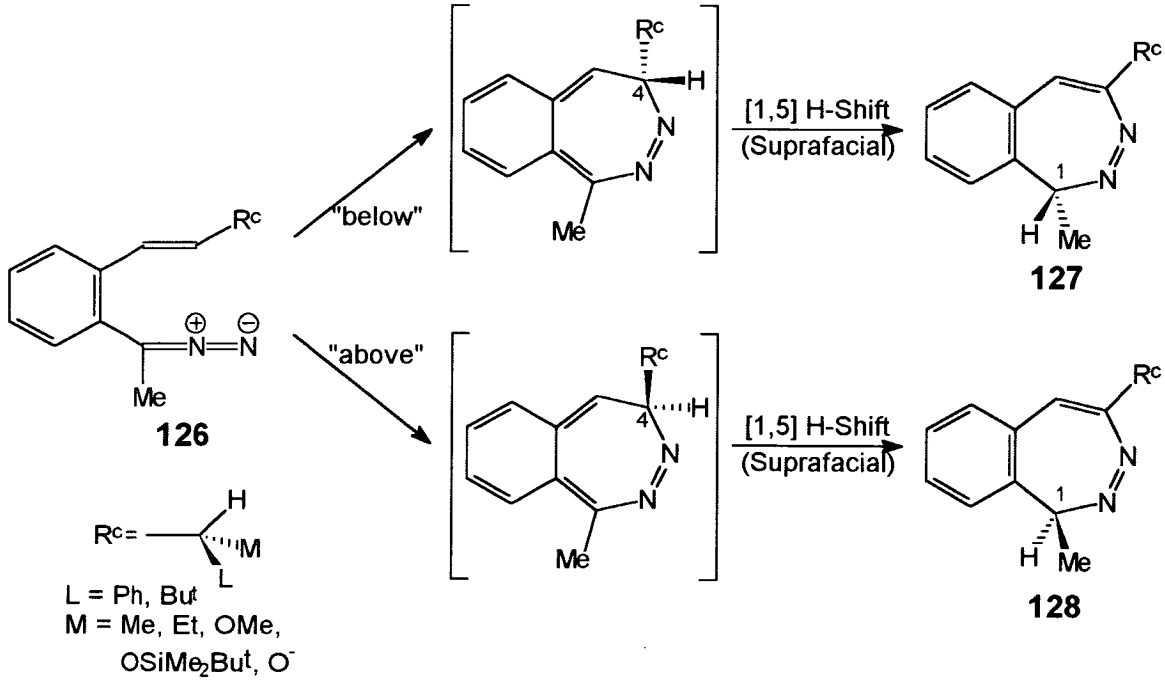

CO2Et
COCl
CO2Et
SOCl2
Pd(OAc)2
PhCH2NMe2
Br
Br
123
CN
PAr3
Pd(OAc)2
NaOAc
CO2H
CO2Et
Br
CN
Pd(OAc)2
PAr3
NaOAc
CO2H
COCl
SOCl2
CO2Et
Pd(OAc)2
PhCH2NMe2
CN
CN
125
CN
124

Scheme 43

DISCUSSION

1. PROGRAMME OF RESEARCH

It has recently been shown that the diazoalkanes **126** undergo asymmetric 1,7-electrocyclisation,[49] **Scheme 44**. Good face selectivity (up to 93:7) was obtained in the cyclisation step by use of suitable chiral groups, R^c. The suprafacial nature of the [1,5]-sigmatropic hydrogen shift ensured that any induced chirality at C-4 was transferred to C-1 to give the diastereomeric 2,3-benzodiazepines **127** and **128**.

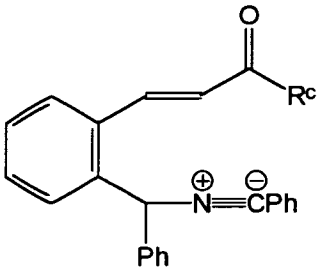


SCHEME 44

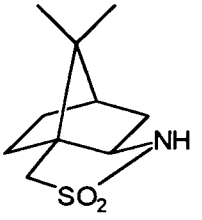
The synthetic utility of this approach was severely restricted by the difficulty of removing the chiral directing groups, R^c.

The work described in this thesis was carried out in order to investigate the asymmetric 1,7-electrocyclisation of the analogous nitrile ylides **129**. It was hoped that the greater steric bulk at the attacking carbon of the nitrile ylide would result in even higher levels of face selectivity than in the diazo case. A

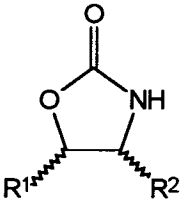
variety of chiral directing groups were to be investigated, particularly the easily cleaved Oppolzer's sultam **50**, Evans's auxiliaries **51** and chiral esters.



129



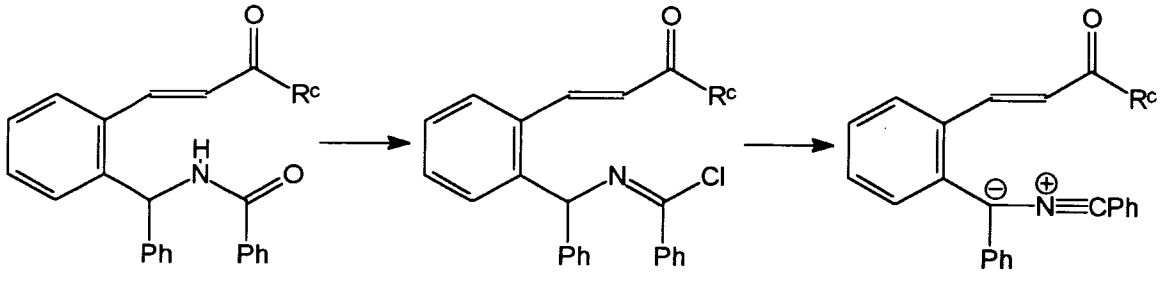
50



51

The 1,7-electrocyclisation of nitrile ylides of the type **129** was of interest for two reasons, the first being to establish the synthetic viability of the reaction as a stereoselective route to chiral 2-benzazepines which have great pharmaceutical potential. Secondly, it was hoped that the results would be of use in elucidating the factors controlling electrocyclisation reactions.

Given the complications that can arise with photochemical generation,[27] it was decided to generate the nitrile ylides by a non-photochemical route. The method of choice was 1,3-dehydrochlorination of imidoyl chlorides **131** which can be prepared by the chlorination of amides[12] **130**, **Scheme 45**.



130 **131** **129**

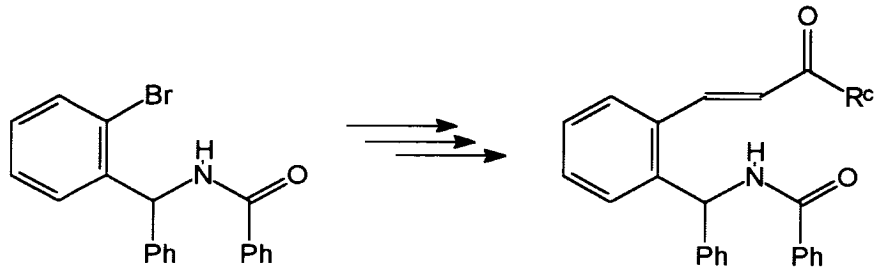
SCHEME 45

Thus, the first objective was the synthesis of a series of compounds of the type **130** - *N*-benzoyl benzhydrylamines substituted in the 2-position with chiral

acrylamides and acrylates. The synthetic strategies adopted are discussed in the following sections.

2. SYNTHESIS OF A KEY INTERMEDIATE

The amides **132** and **133** were identified as key intermediates in many of the possible synthetic strategies towards the target compounds **130**.



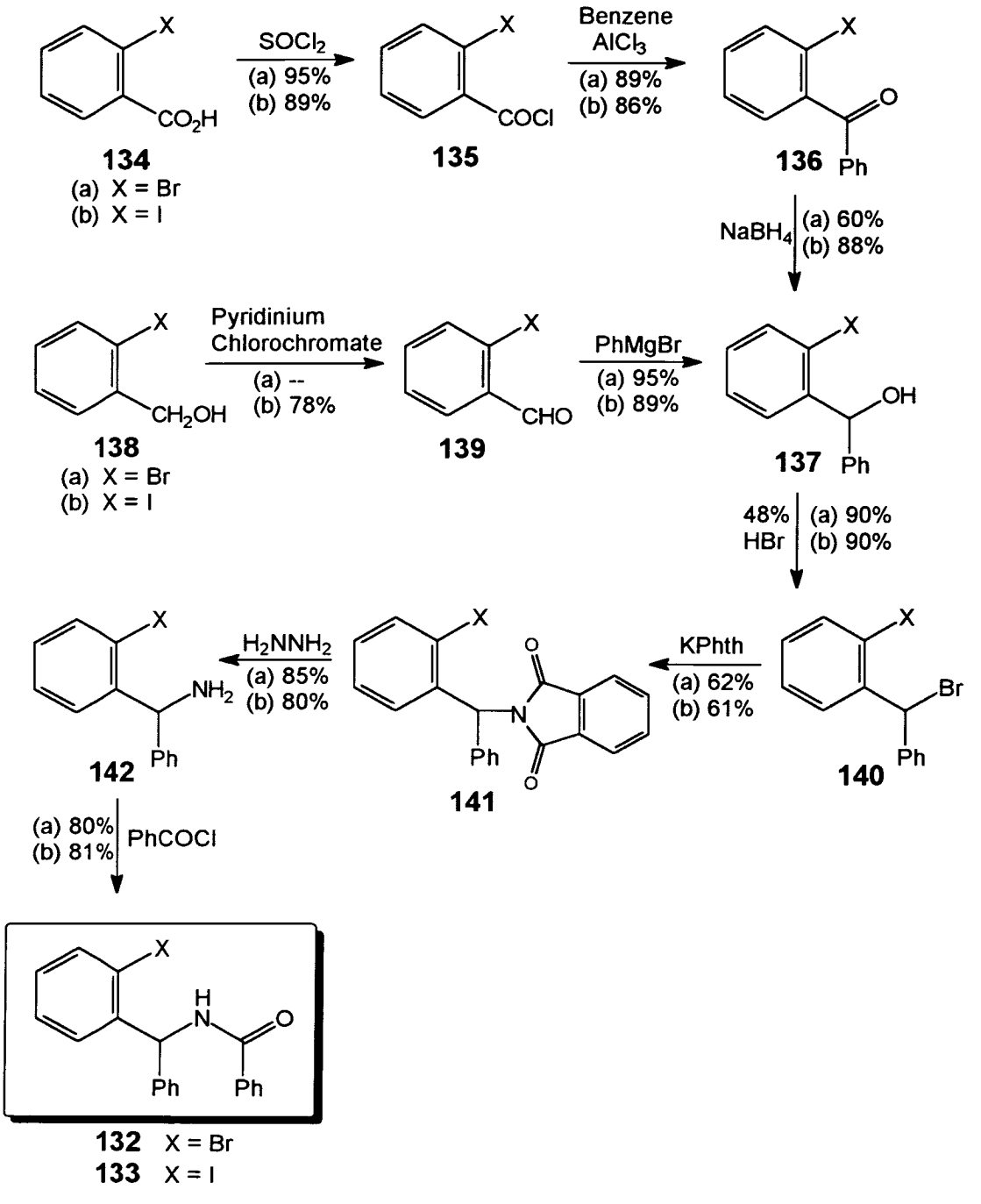
132 X = Br
133 X = I

130

Consequently, much work was undertaken to provide a quick, convenient synthesis of these amides. The routes adopted are summarised in **Scheme 46**.

The 2-halobenzoic acids **134** were readily converted to the acid chlorides **135**. Friedel-Crafts acylation of benzene gave the benzophenones **136** in good yield. Biaryl ketones are known to be unreactive to reductive amination[89] so an attempt was made to prepare the iodo-substituted amine **142b** directly from the benzophenone **136b** by means of the Leuckart reaction.[90] Prolonged heating of the ketone **136b** with formamide and various catalysts failed to give any products other than recovered starting material and a dark green intractable tar. Presumably thermal decomposition of the formamide and the ketone **136b** occurred faster than the desired condensation.

It was then decided to reduce the benzophenones **136** to the benzhydrols **137** to allow introduction of nitrogen *via* the Gabriel synthesis.[91] This reduction was accomplished with sodium borohydride in methanol.



SCHEME 46

In the Friedel-Crafts acylation, benzene was used as both reactant and solvent. In order to avoid the hazards associated with large volumes of benzene, an alternative synthesis of the benzhydrols **137** was devised. Grignard reaction of

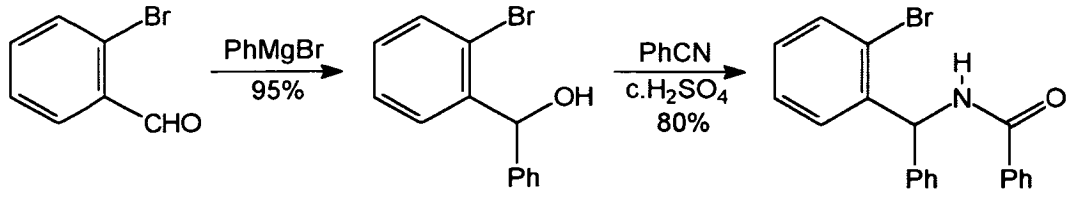
phenylmagnesium bromide with the 2-halobenzaldehydes **139** gave the alcohols **137** in good yield. 2-Bromobenzaldehyde **139a** was commercially available and 2-iodobenzaldehyde **139b** was prepared by oxidation of 2-iodo-benzylalcohol **138b** with pyridinium chlorochromate.

Of the two routes above, the latter was preferable in terms of both safety and convenience. Thus, this became the preferred route to the benzhydrols **137**.

The next step involved bromination in order to allow introduction of a nitrogen functionality *via* the Gabriel synthesis.[91] Two methods of conversion of the benzhydrols **137** to the benzhydryl bromides **140** were investigated. Prolonged heating of the alcohol under reflux in 48% hydrobromic acid gave the required bromo-compounds **140** in high yield. Bromination at lower temperatures was achieved with carbon tetrabromide/triphenylphosphine. These conditions gave the bromide **140a** more quickly but in lower yield than with hydrobromic acid. This reduced yield, together with practical difficulties in separating the product from the triphenylphosphine oxide by-product, made bromination with hydrobromic acid preferable.

Gabriel synthesis gave the phthalimido derivatives **141** in reasonable yield and the Ing-Manske procedure[92] gave the free amines **142**. Benzoylation then yielded the required amides **132** and **133**.

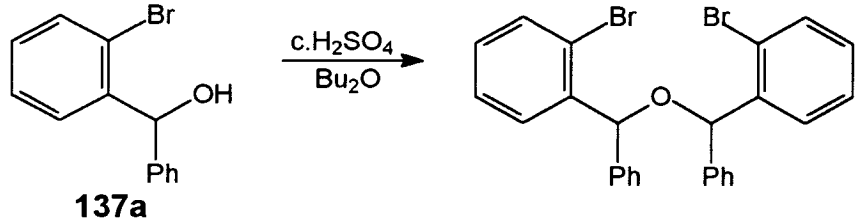
Although satisfactory, the above route was rather long and later a more concise route to the amide **132** was found. This involved a Ritter reaction[93] of the benz-hydrol **137a** and benzonitrile to give the amide **132** in 80% yield in one step. Thus was found a convenient two-step synthesis of the amide **132** from 2-bromobenzaldehyde *via* the benzhydrol **137a**, **Scheme 47**.



137a **132**

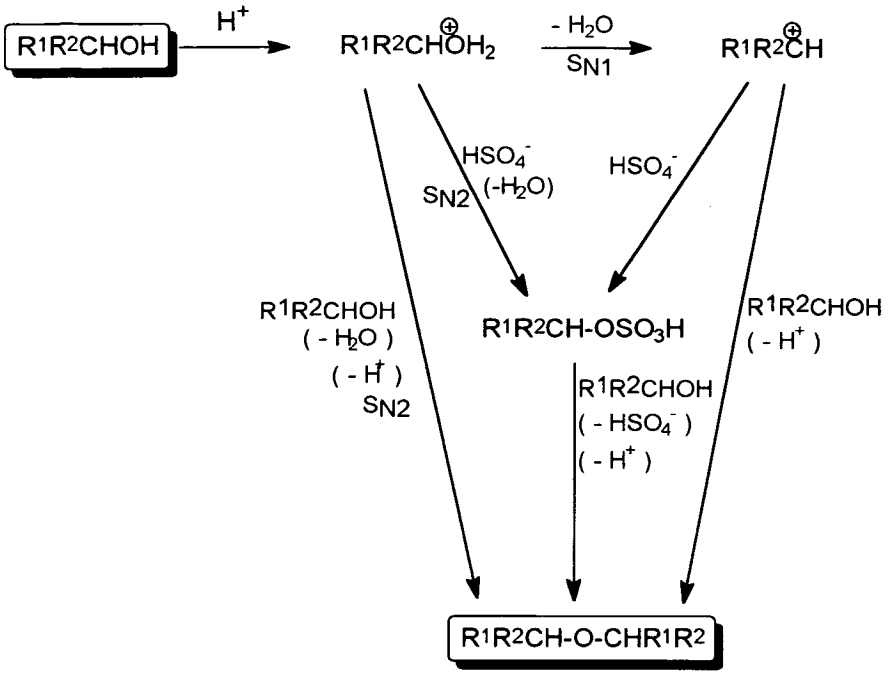
SCHEME 47

This reaction is usually carried out with di-*n*-butyl ether as solvent. It was found that when di-*n*-butyl ether was used as a solvent in the above Ritter reaction, only the ether was isolated in good yield. This reaction also occurred in the absence of benzonitrile, **Scheme 48**. Ether formation was attributed to dehydration of the alcohol **137a** with conc. sulphuric acid. This reaction is well documented[94] and the various mechanisms are shown in **Scheme 49**. When only excess benzonitrile was used as solvent, only the desired amide **132** was produced.



137a

Scheme 48


R1R2CHOH
H+
R1R2CHOH2
- H2O
SN1
R1R2CH
HSO4-
SN2
(-H2O)
HSO4-
R1R2CHOH
(- H2O)
(- H+)
SN2
R1R2CH-OSO3H
R1R2CHOH
(- HSO4-)
(- H+)
R1R2CHOH
(- H+)
R1R2CH-O-CHR1R2

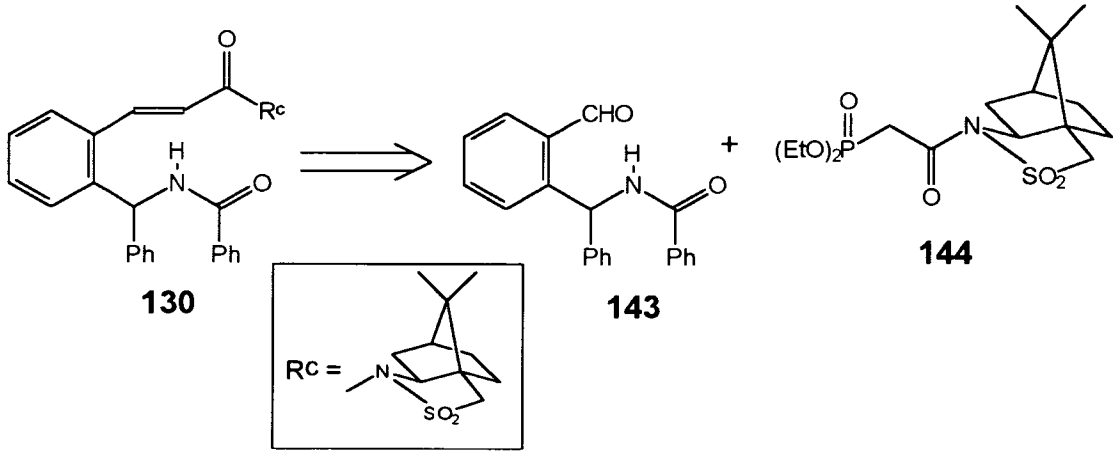
Scheme 49

3. INVESTIGATION OF THE USE OF OPPOLZER'S SULTAM

3.1. Wadsworth-Emmons Route

3.1.1. Introduction

The first retrosynthetic strategy applied to the synthesis of the required amide **130** was disconnection of the alkene bond. This required the aldehyde **143** and a phosphonate such as the known chiral phosphonate **144**.[95]

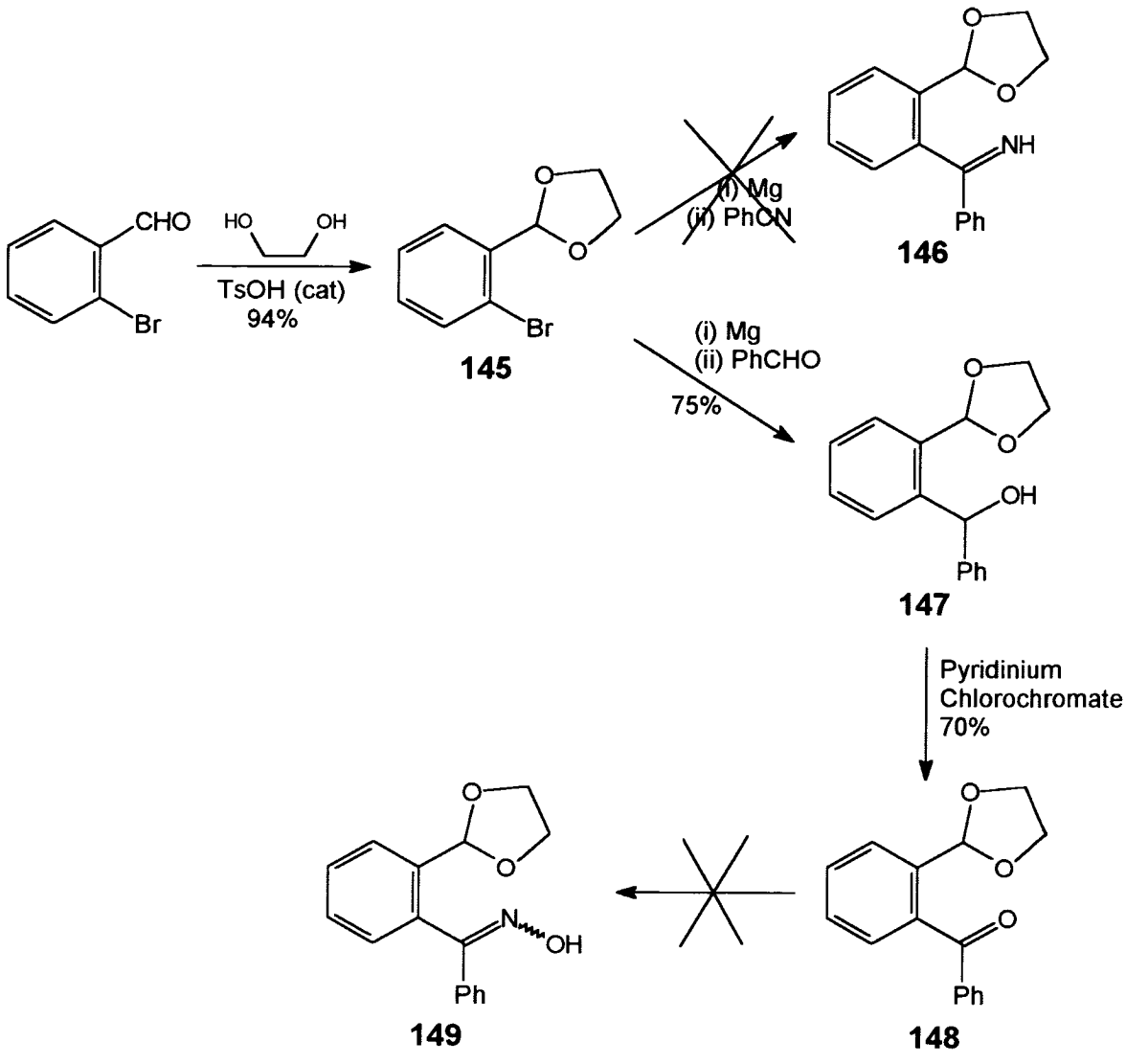


130 **143** **144**

This section describes the various routes followed in the attempted synthesis of the aldehyde **143**.

3.1.2. From 2-Bromobenzaldehyde

This route, **Scheme 50**, relied upon protection of the aldehyde moiety of 2-bromobenzaldehyde as the ethylene acetal **145**. The corresponding Grignard reagent was prepared and reacted with benzonitrile in an attempt to form the imine **146**, which could then be reduced to the amine. It was found that this imine was too unstable to be isolated or reduced and thus the Grignard reagent was reacted with benzaldehyde to give the benzhydrol **147**.



SCHEME 50

Attempted tosylation of this alcohol **147** was unsuccessful, probably due to deactivation of the central carbon to nucleophilic attack by the two phenyl groups. These should deactivate by both steric and electronic effects. The use of more forcing conditions in the tosylation merely resulted in loss of the acetal protecting group.

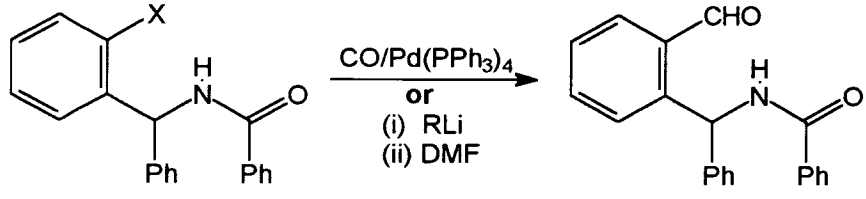
It was then decided to oxidise the benzhydrol **147** to the benzophenone **148** in order to facilitate introduction of a nitrogen functionality. Oxidation with chromium trioxide/pyridine gave only a 26% yield of ketone, whereas

pyridinium chlorochromate[96] (buffered with sodium acetate) gave the benzophenone **148** in 70% yield.

As mentioned earlier, biaryl ketones are known to be unreactive to reductive amination[89] and thus introduction of a nitrogen moiety was attempted *via* the oxime **149**. No oxime formation was observed and use of more forcing conditions resulted only in deprotection of the aldehyde. At this point it was decided to investigate other routes to the aldehyde **143**.

3.1.3. By Carbonylation of Aryl Halides

It was expected that the halides **132** and **133** could be carbonylated to yield the aldehyde **143**, **Scheme 51**.



132 X = Br
133 X = I

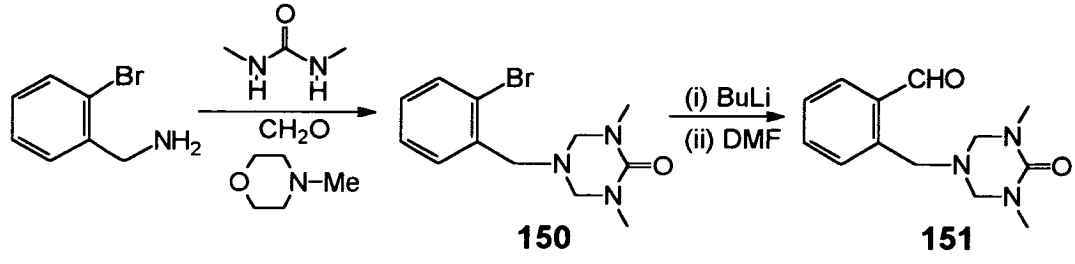
143

SCHEME 51

Carbonylation of the iodide **133** with carbon monoxide, tributyltin hydride and a palladium catalyst was unsuccessful, probably due to catalyst decomposition *via* a stable chelate, as will be discussed later. Di-lithiation of the bromide **132** with alkyllithiums and reaction with dimethylformamide gave only a small amount of an unstable carbonyl compound.

As the desired aldehyde **143** appeared to be unstable, it was decided to synthesise the aldehyde **151** as a model to test the viability of the this approach. It was hoped that this aldehyde would undergo a Wadsworth-Emmons reaction,

after which the amine could be deprotected and benzoylated. 2-Bromo-benzyl-amine was protected as the triazinone **150**, **Scheme 52**. Lithiation and reaction of the anion with dimethylformamide gave the aldehyde **151** in poor yield, the product again being too unstable for further development.



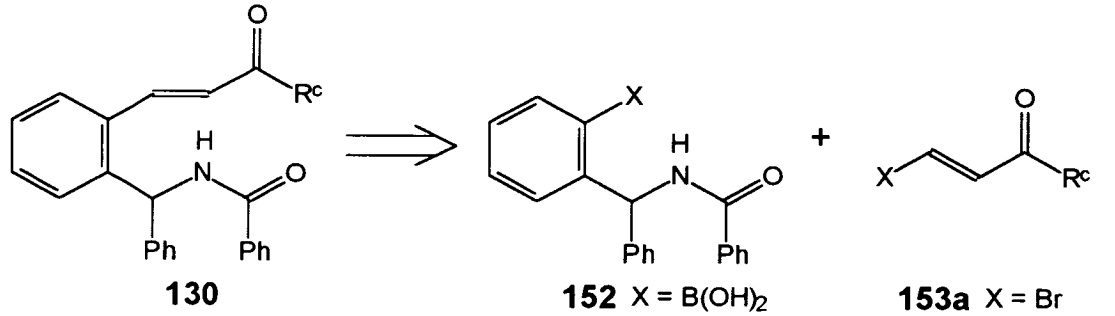
SCHEME 52

Due to the instability of the aldehydes **143** and **151**, other routes to the target compounds **130** were investigated.

3.2. Boronic Acid Coupling Reactions

3.2.1. Introduction

Disconnection of the alkenyl-aryl bond in the target **130** introduced the strategy of carbon-carbon bond formation by boronic acid coupling. This required either the arene **152** or alkene **153** to bear a boronic acid, the other portion bearing a bromine, **Scheme 53**.



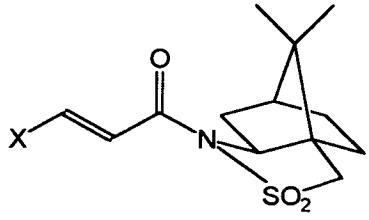
130

152 X = $B(OH)_2$
132 X = Br

153a X = Br
153b X = $B(OH)_2$

SCHEME 53

In an initial study of this route, Oppolzer's sultam was used as the chiral auxiliary, thus requiring synthesis of the bromoacryloyl sultam **154**.



154a X = Br
154b X = $B(OH)_2$

3.2.2. Preparation of the Bromoacryloyl Sultam **154a**

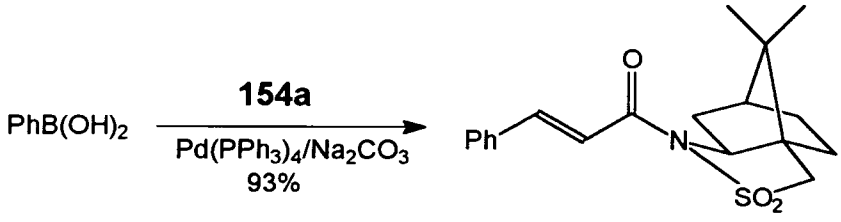
The bromoacryloyl sultam **154a** was prepared in good yield from (E)-3-bromo-acryloyl chloride and the sodium salt of Oppolzer's sultam. Attempts to prepare the boronic acid **154b** with alkyl lithiums followed by tri-isopropyl borate failed with both *n*-butyl and *tert*-butyl lithium. Even at -100°C, nucleophilic attack by the base appeared to predominate.

The lack of success in the preparation of the boronic acid **154b** was not totally unexpected as no alkenyl boronic acids bearing such a strong electron withdrawing group have been reported in the literature. It was necessary, therefore, to rely upon coupling of the bromoacryloyl sultam **154a** with a boronic acid.

3.2.3. Model Couplings

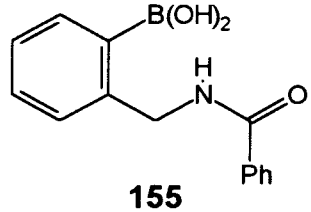
The boronic acid coupling of the bromoacryloyl sultam **154a** was investigated with various model systems as a prelude to the synthesis of the target

compound **130**. Coupling with phenylboronic acid proceeded in very high yield, **Scheme 54**, boding well for future couplings.



SCHEME 54

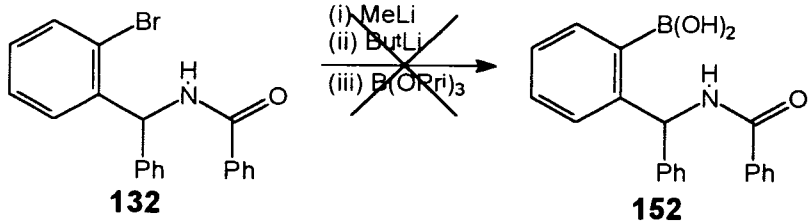
The next model coupling investigated was with the boronic acid **155**, developed by Reece.[97]



155

Although this boronic acid has been successfully coupled with various aryl and heterocyclic bromides, coupling with the bromoacryloyl sultam **154a** gave only very small amounts of the desired product. Close monitoring of the reaction by h.p.l.c. showed that several products were being produced simultaneously.

At this time, attempts to synthesise the boronic acid **152** from the bromide **132** by di-lithiation and reaction with tri-isopropyl borate, **Scheme 55**, had proven unfruitful. This, together with the disappointing results of the coupling with the boronic acid **155**, led to the investigation of other routes to the target **130**.



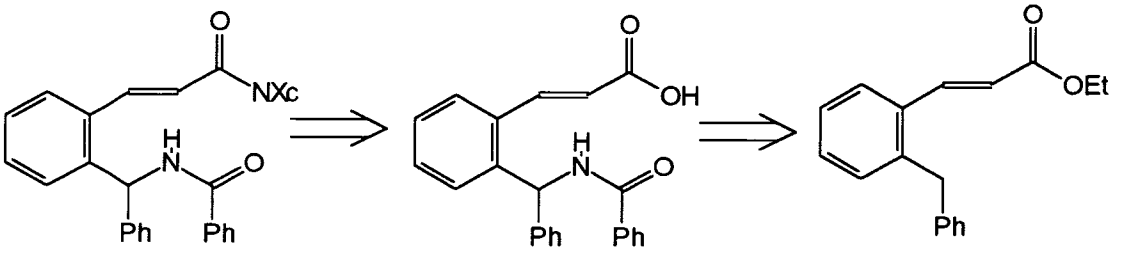
132 **152**

SCHEME 55

3.3. via the *o*-Benzylcinnamate 157

3.3.1. Introduction

This approach involved disconnection of the bond to the chiral auxiliary, **Scheme 56**. The advantage of this route was that the expensive chiral auxiliaries could be attached in the final step of the synthesis of the target **130**. The acid **156** was to be prepared from the o-benzylcinnamate **157**, with the acid functionality protected as the ethyl ester.

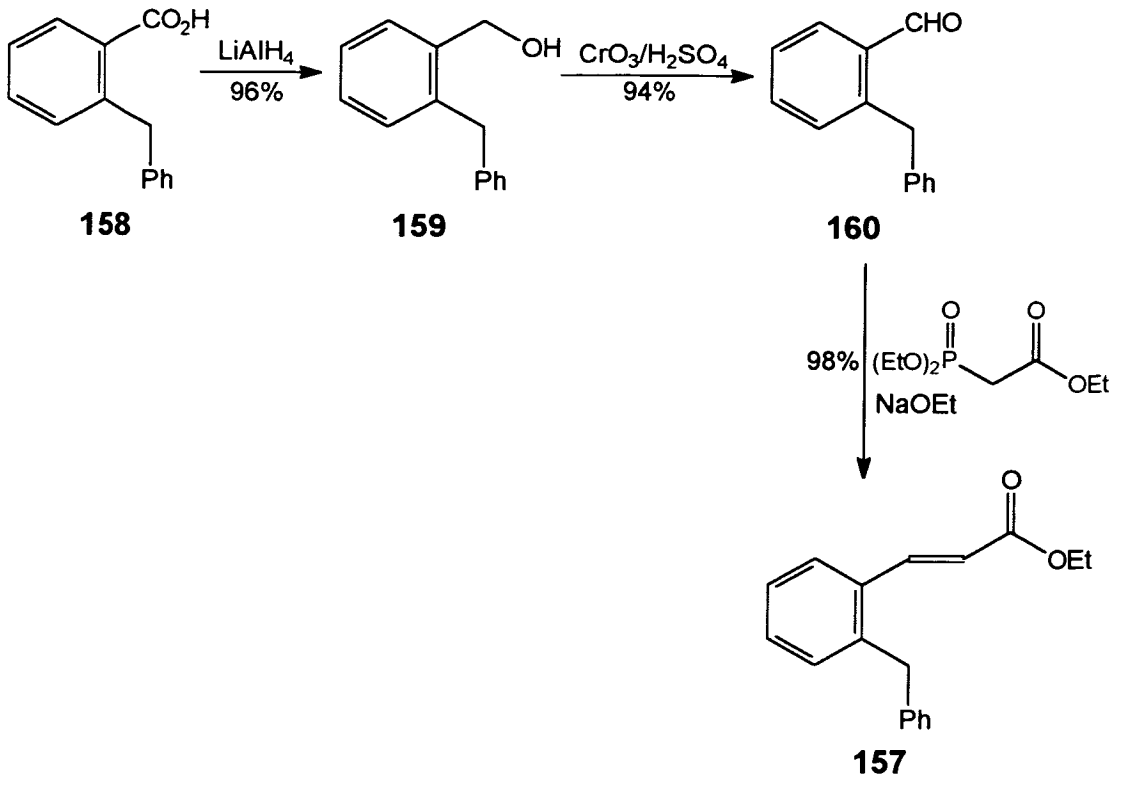


130 **156** **157**

SCHEME 56

3.3.2. Preparation of the *o*-Benzylcinnamate **157**

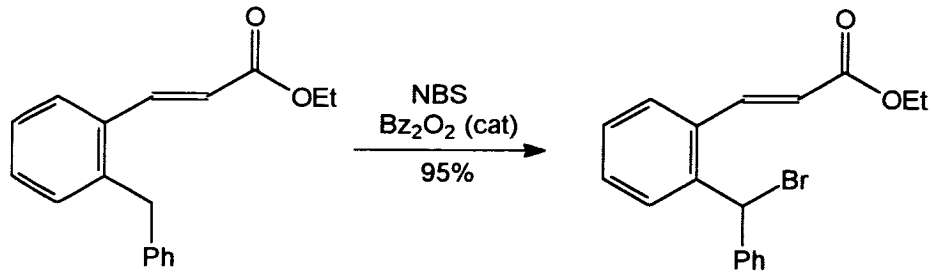
The *o*-benzylcinnamate **157** was synthesised by the route shown in **Scheme 57**. Reduction of 2-benzylbenzoic acid **158** with lithium aluminium hydride gave 2-benzylbenzylalohol **159** in very high yield. Jones oxidation of this alcohol gave 2-benzylbenzaldehyde **160**, again in very high yield. Wadsworth-Emmons reaction with triethyl phosphonoacetate and ethoxide afforded the required *o*-benzylcinnamate **157** in almost quantitative yield.



SCHEME 57

3.3.3. Attempted Introduction of the Amide Moiety

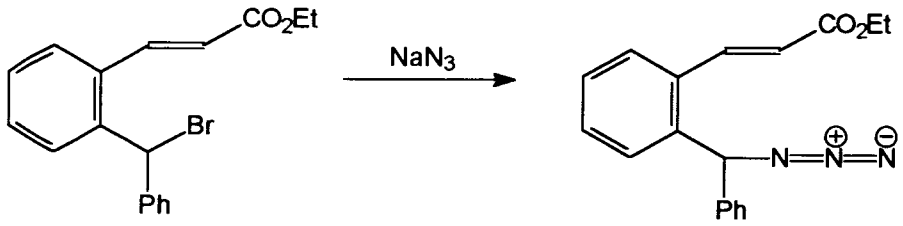
Once a viable synthetic route to the *o*-benzylcinnamate **157** had been established it was necessary to introduce the amide moiety, after which hydrolysis of the ester would give the required acid **156**. In order to accomplish this, the *o*-benzylcinnamate **157** was brominated with *N*-bromosuccinimide to give the bromo-compound **161** in high yield, **Scheme 58**.



157 **161**

SCHEME 58

From this bromide it was hoped that a nitrogen functionality could be introduced by, for example, the Gabriel[91] or Delepine[98] amine syntheses. In practice, the bromo-compound **161** gave only complex mixtures of products with either potassium pthalimide or hexamine. This was probably due to the poor thermal stability of the bromo-compound **161**. The bromo-compound **161** failed to react successfully with liquid ammonia, guanidine[99] or the sodium salt of diformylamide,[100] all of which are alternatives to the Gabriel amine synthesis. The only nucleophiles which were found to react with the bromo-compound **161** were hydroxide ion (giving the benzhydrol) and azide. Reaction with sodium azide gave an intensely coloured dark green syrup which was not the required azide **162**, **Scheme 59**. The azide **162** may have undergone an intramolecular 1,3-dipolar cycloaddition with the reactive acrylate moiety to give an uncharacterised product.



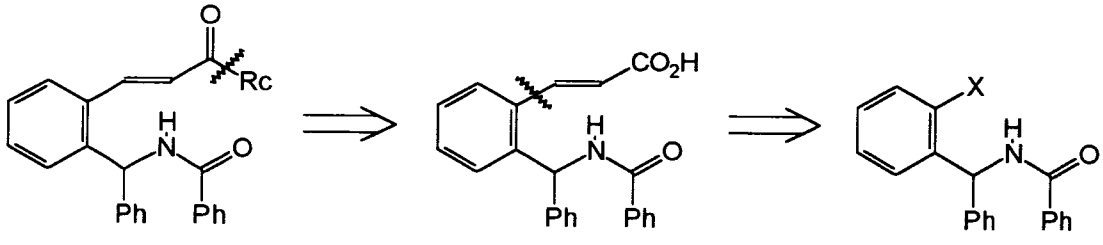
161 **162**

SCHEME 59

3.4. *via* Heck Reaction I

3.4.1. Introduction

This approach again involved the synthetically appealing disconnection of the bond to the chiral auxiliary, **Scheme 60**. It was expected that the acid **156** could be prepared from the aryl halides **132** or **133** *via* a Heck reaction[74] with acrylic acid, **Scheme 60**.



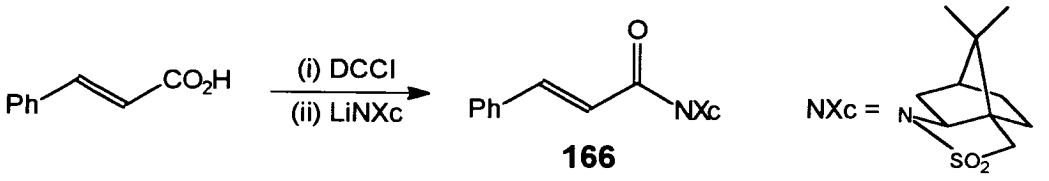
130 **156** **132** X = Br
133 X = I

SCHEME 60

3.4.2. Model Coupling

In order to investigate the viability of the final step of this synthesis an attempt was made to couple cinnamic acid with Oppolzer's sultam **50**. Activation of the acid with dicyclohexylcarbodiimide (DCCI) and reaction with the lithium salt of

Oppolzer's sultam **50** gave the coupled product **166** in acceptable yield, **Scheme 61**.

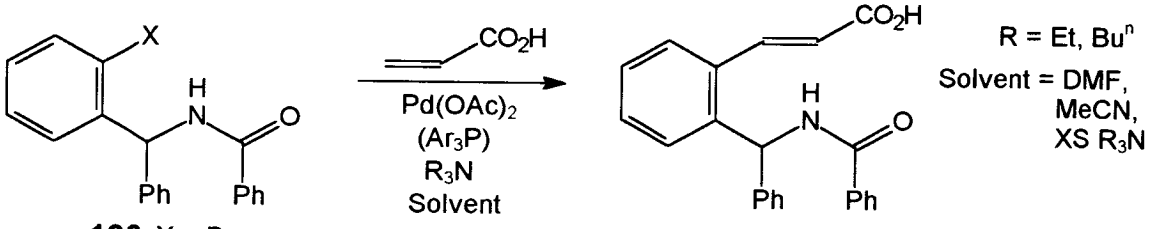


SCHEME 61

The success of this coupling provided encouragement for further investigation of this route.

3.4.3. Heck Reaction

The coupling of the aryl halides **132** and **133** with acrylic acid, **Scheme 62**, proceeded in moderate yield (20-45%). As would be expected, only the *trans* isomer was produced. The variation in yield depended upon the choice of amine and solvent.



SCHEME 62

Highest yields (40-45%) were obtained with the iodide **133** (in neat tri-*n*-butylamine) and also with the bromide **132** (in neat triethylamine and in the presence of tri-*o*-tolylphosphine). The bromide **132** gave the product **156** in a form that was much more easily isolated; in the iodo case, tri-*n*-butylamine was

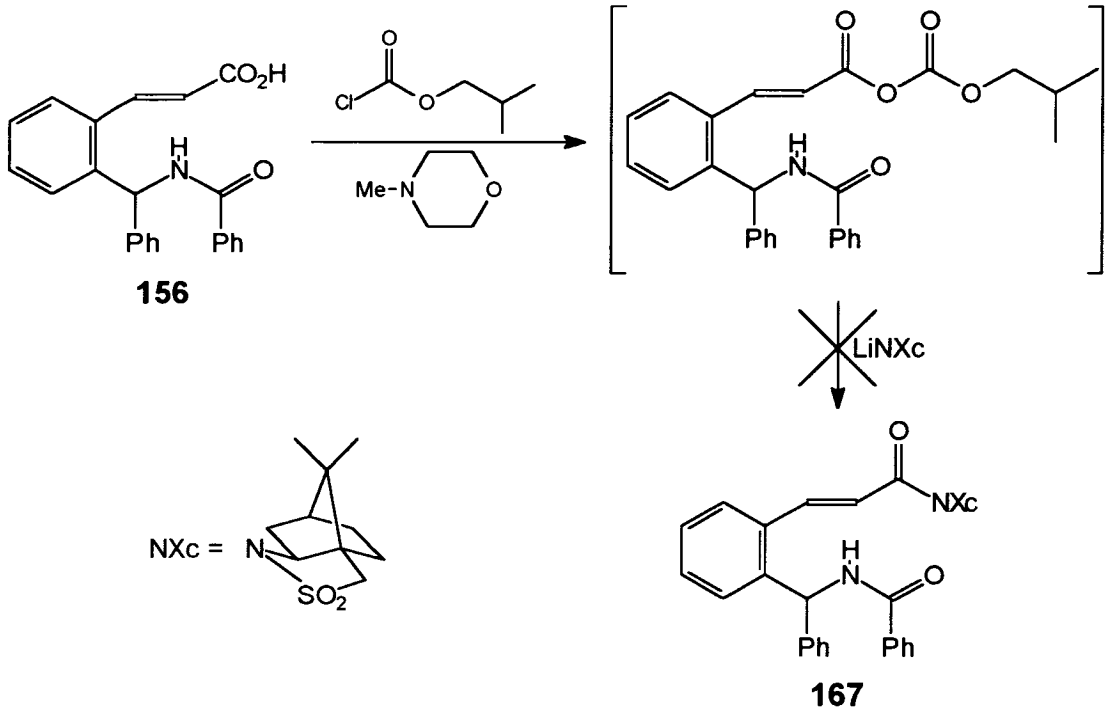
difficult to separate from the product. The simpler work-up and the greater ease of preparation of the starting material **132** made these conditions preferable.

The low yields obtained were attributed to destruction of the palladium catalyst. In reaction of the iodide **133**, an almost stoichiometric amount of catalyst had to be added to drive the reaction to completion. For the bromide **132** a lower ratio of catalyst was required (*ca.* 0.3 meq). This was another factor which favoured use of the bromide **132** over the iodide **133**.

3.4.4. Attempted Coupling to Oppolzer's Sultam

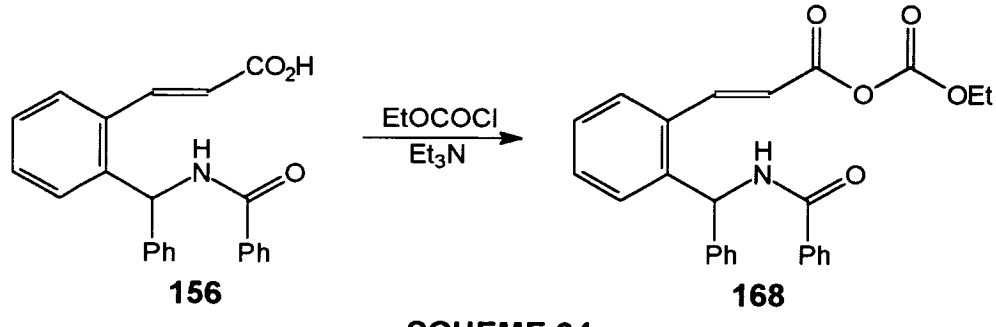
Several methods of coupling the acid **156** with Oppolzer's sultam **50** were investigated. As the sultam **50** would have to be deprotonated it was decided that the carbodiimide methodology would be unsuitable. The use of mixed anhydrides[102] was investigated as a first approach.

Reaction of the acid **156** with isobutyl chloroformate in the presence of *N*-methylmorpholine followed by addition of the lithium salt of the sultam **50**, **Scheme 63**, mainly gave recovered starting materials.



SCHEME 63

Use of ethyl chloroformate with triethylamine, *N*-methylmorpholine or *N,N*-dimethylaniline followed by the lithium salt of the sultam **50** failed to give any of the coupled product **167**. It was then decided to investigate further the formation of the mixed anhydride **168**, **Scheme 64**, to determine whether anhydride formation or reaction with the sultam was causing problems.

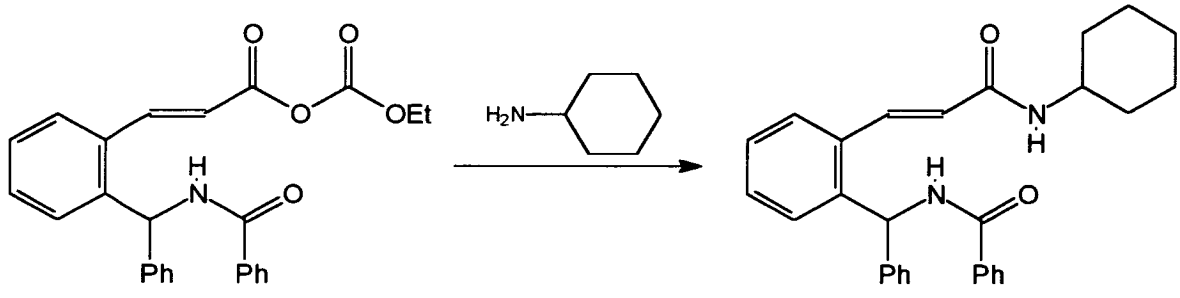


SCHEME 64

The formation of the mixed anhydride **168** was monitored by n.m.r. in d_8-THF. Conversion of the acid **156** to the mixed anhydride **168** was found to be complete in less than one hour at 0°C and the product was stable for several

days. Thus it was concluded that reaction with the lithium salt of the sultam **50** was the problem step.

This conclusion was further confirmed when the mixed anhydride **168** was reacted with cyclohexylamine to give the amide **169** in good yield, **Scheme 65**.

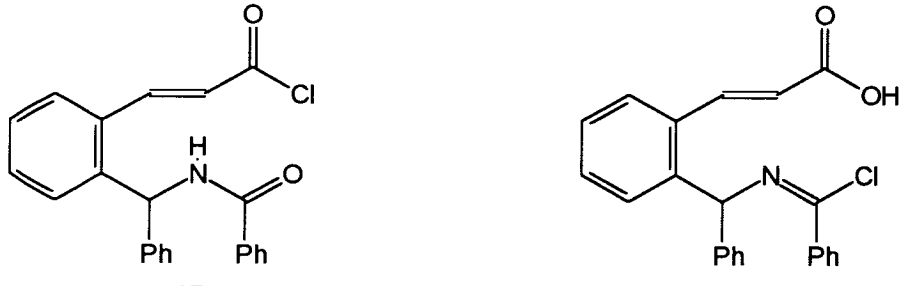


168 **169**

SCHEME 65

Presumably the lithiated sultam is reacting with the amide functionality, either by deprotonation to give the free sultam, or by reacting at the amide oxygen to give a product which hydrolyses upon work-up.

Other routes to activating the acid **156** were investigated. Attempted formation of the acid chloride **170** using oxalyl chloride was not successful, due to preferential formation of the imidoyl chloride **171**.

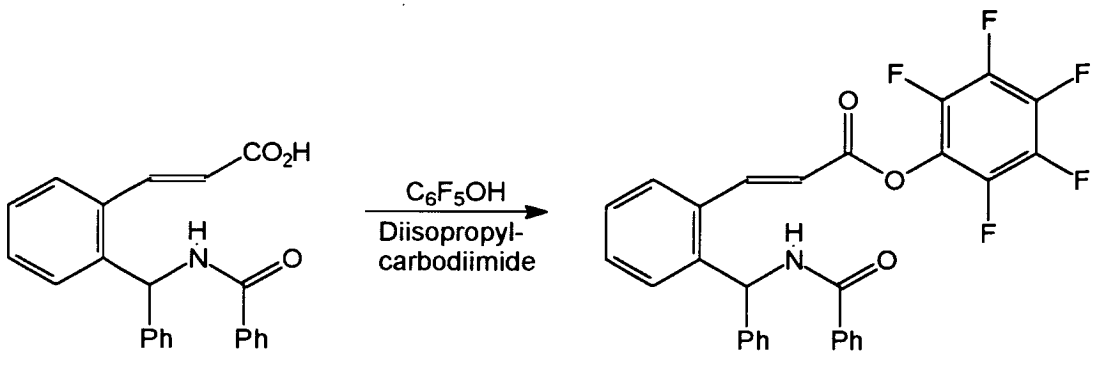


170 **171**

Next, activation with *N,N'*-carbonyl-diimidazole[103] was explored. Reaction of the acid **156** with *N,N'*-carbonyl-diimidazole followed by addition of the lithium salt

of Oppolzer's sultam failed to give any of the desired product **167**. Only starting materials were recovered.

Activation as the pentafluorophenyl ester[104] was then examined. Reaction of the acid **156** with pentafluorophenol in the presence of diisopropylcarbodiimide gave the pentafluorophenyl ester **172** in reasonable yield, **Scheme 66**.



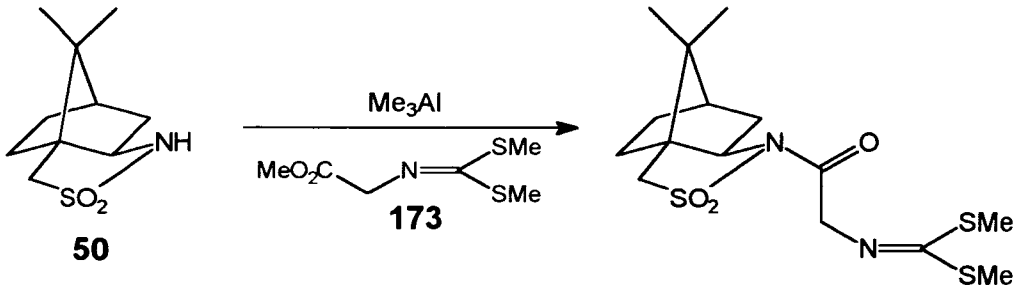
156 **172**

SCHEME 66

Addition of the lithium salt of Oppolzer's sultam to the ester **172** again gave only recovered starting materials.

In order to eliminate any problem caused by the use of butyllithium as base, 1,8-diazobicyclco[5.4.0]undec-7-ene (DBU) was used. Addition of Oppolzer's sultam **50** and DBU to a solution of the mixed anhydride **168** gave a complex mixture from which the desired product **167** could not be isolated.

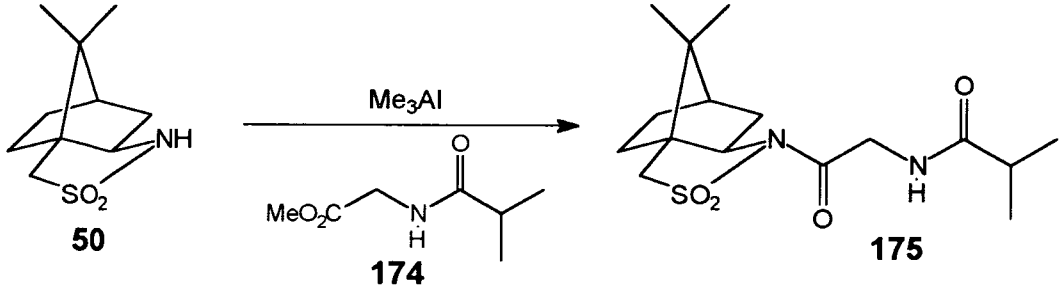
A related approach was then investigated. Oppolzer[105] found that the sultam **50** underwent trimethylaluminium mediated acylation with the *N*-protected methyl glycinate **173** in good yield, **Scheme 67**.



50 **173**

SCHEME 67

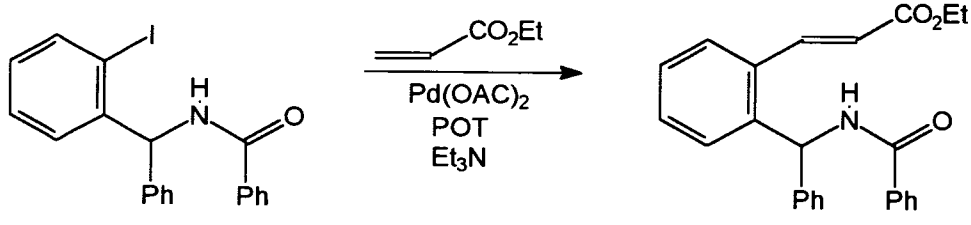
In order to investigate the viability of this reaction when the ester moiety was part of a compound which also contained an amide functionality, the model compound **174** was used. Reaction of Oppolzer's sultam **50** with trimethyl-aluminium followed by the ester **174** gave the acylated sultam **175** in quantitative yield, **Scheme 68**.



50 **174** **175**

SCHEME 68

In order to utilise this reaction in the synthesis of the target compound **167** it was necessary to prepare the ester **176**. Heck reaction of the iodide **133** with ethyl acrylate gave the ester **176** in reasonable yield, **Scheme 69**.



133 **176**

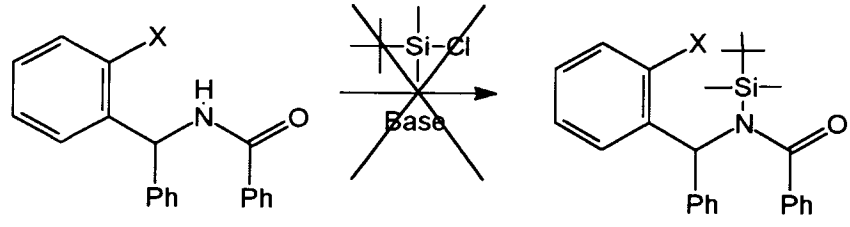
SCHEME 69

Reaction of this ester with the trimethylaluminium-sultam adduct gave a complex mixture from which only the sultam **50** could be recovered. No trace of the desired product **167** could be identified. Again, it can be presumed that the metallated sultam reacted with the amide functionality to give a system which, in this case, reacted further to give a variety of products.

3.4.5. Attempted Amide Protection

3.4.5.1. By Silylation

It was suspected that the amide proton in the activated derivatives of the acid **156** interfered in the reaction of the metallated sultam **50**. Thus, attempts were made to protect the amide as the *tert*-butyldimethylsilyl derivative. No attempt was made to silylate the amide in the acid **156** as the acid functionality would be silylated preferentially. Instead the halo-amides **132** and **133** were chosen to be protected as the *tert*-butyldimethylsilyl derivative **177**, **Scheme 70**. It was hoped that the protected products could easily be converted into the acid.



132 X = Br
133 X = I

177 a X = Br
b X = I

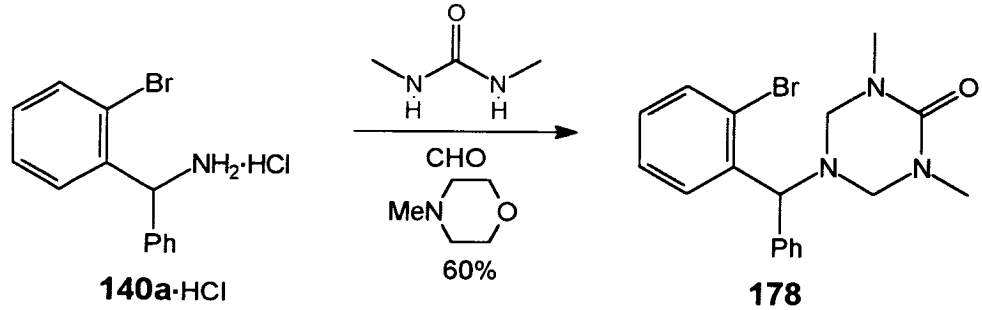
SCHEME 70

Reaction of the amides **132** and **133** with triethylamine, 1,8-diazabi-cyclo-[5.4.0]undec-7-ene, sodium hydride or lithium diisopropylamine followed by addition of *tert*-butyldimethylsilyl chloride gave only recovered starting

materials. Two explanations were probable. Firstly, the amide anion may be stabilised by the three adjacent phenyl groups to such an extent that it is no longer nucleophilic enough to attack the silyl chloride. Alternatively, silylation may occur at the amide oxygen to give an O-silylated system which hydrolyses back to the amide upon work-up. Attempts to monitor the reaction by n.m.r. spectroscopy failed to give any further information due to inadequate resolution of the reaction mixture.

3.4.5.2. Protection as a Triazone

As no convenient method could be found to protect the amide, protection of the free amine precursor **140a** was investigated. This would allow Heck reaction and coupling with Oppolzer's sultam followed by amine deprotection and benzoylation to give the target **130**. Reaction of the hydrochloride salt of the amine **140a** with *N,N*-dimethylurea and formaldehyde in the presence of *N*-methylmorpholine gave the triazone **178** in reasonable yield, **Scheme 71**.

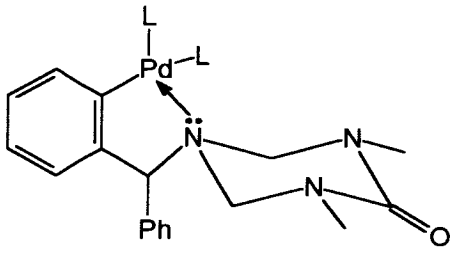


140a·HCl **178**

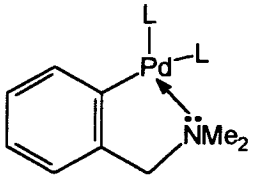
SCHEME 71

The bromotriazone **178** failed to give any vinylated product in attempted Heck reactions with various alkenes. Presumably once the palladium catalyst was co-ordinated a stable chelate **179** was formed which did not participate further

in the catalytic cycle. Literature precedent exists for this hypothesis in that 2-palladated *N,N*-dimethylbenzylamine **180** is a stable, isolable compound which was not vinylated under Heck reaction conditions.[106]



179



180

L = Ligands

Formation of a stable chelate may also explain the high catalyst requirement and low yields found with the Heck reactions of the bromide **132** and the iodide **133**.

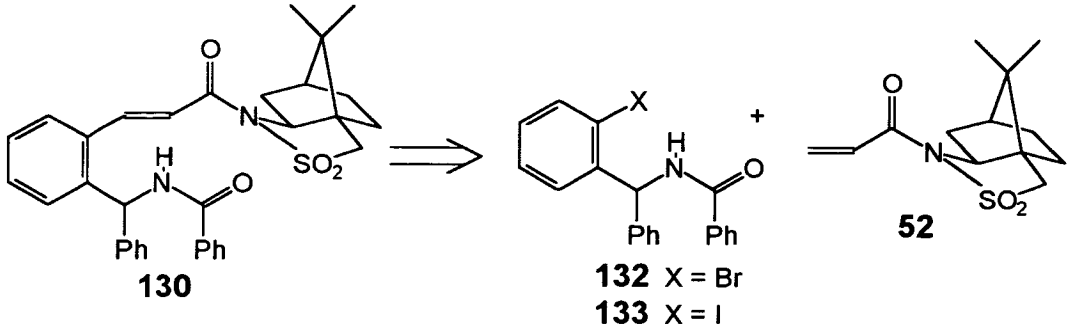
Given the lack of success in the attempted coupling of Oppolzer's sultam **50** to the acid **156** and the disappointing protecting group results, it was decided to investigate another route to the target **167** *via* the Heck reaction.

3.5. *via* Heck Reaction II

3.5.1. Introduction

As the sultam **50** could not be coupled to the acid, **156**, it was decided to investigate the feasibility of attaching an acryloyl sultam **52** by means of a Heck reaction. Retrosynthetically, this involved disconnection of the aryl-alkenyl bond, **Scheme 72**.

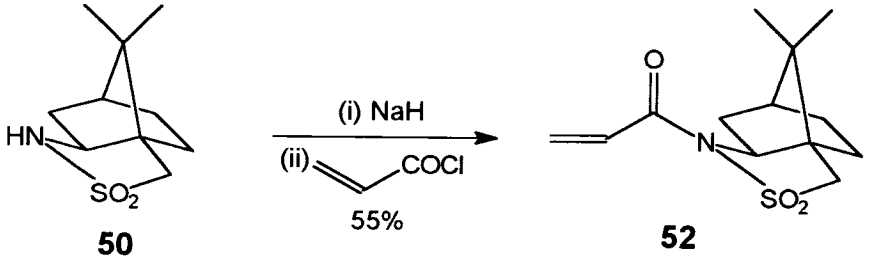
The synthesis of the halides **132** and **133** has been discussed previously.



SCHEME 72

3.5.2. Preparation of the Acryloyl Sultam **52**

Reaction of acryloyl chloride with the lithium salt of Oppolzer's sultam **50** gave a polymeric product, probably due to lithium cation initiated polymerisation. Reaction with the sodium salt of the sultam **50** gave the acryloyl sultam **52** in moderate yield, **Scheme 73**. The low yield was due to a combination of ketene formation[107] and the thermal instability of the product **52**, which polymerised readily.



SCHEME 73

3.5.3. Attempted Heck Reaction

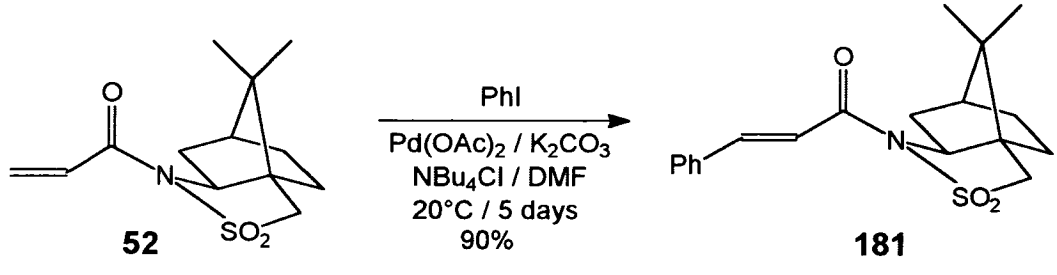
Reaction of the acryloylsultam **52** with the bromide **132** failed to give any of the desired product **130**, despite the use of various reaction conditions. This result can be explained in terms of a combination of the poor performance of the

bromide **132** in the Heck reaction and the poor thermal stability of the acryloyl-sultam **52**, which polymerised under the reaction conditions.

3.5.4. Phase-Transfer Heck Reaction

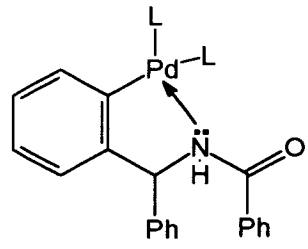
Recent developments[108] have extended the scope of the Heck reaction to phase-transfer conditions. As this allows these reactions to be carried out at room temperature, these conditions are particularly suitable for thermally unstable alkenes. Thus, phase-transfer conditions were thought to be appropriate in this case.

As a model, iodobenzene was reacted with the acryloyl sultam **52** at 20°C in the presence of tetra-*n*-butylammonium bromide to give the cinnamoyl sultam[86] **181** in high yield, **Scheme 74**.

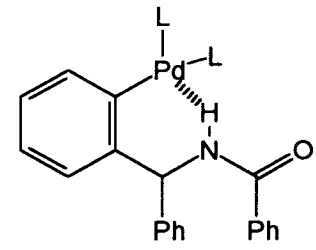


SCHEME 74

Reaction of the iodide **133** under the same conditions failed to give any of the desired product **167**. Variation of reaction temperature, base and phase-transfer reagent did not lead to any formation of the desired product. Either intractable tars were produced or starting materials were recovered. Presumably the palladated intermediate forms either a stable chelate[106] **182**, as discussed earlier, or decomposes by hydride transfer *via* an agostic hydrogen **183**.



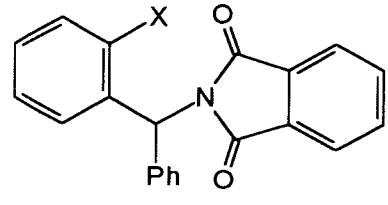
182



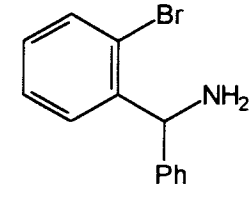
183

3.5.5. Alternative Heck Reactions

As the amide functionality appeared to interfere in the Heck reactions and could not be successfully protected, an investigation was made into alternative substrates which could then be converted to the amide after the Heck reaction. The halo-phthalimides **141a** and **141b** and the amine **142a** all failed to react with the acryloylsultam **52** under a variety of Heck conditions. Again, the substrates, when palladated, probably formed stable chelates which would then not react further.



141 a X = Br
b X = I



142a

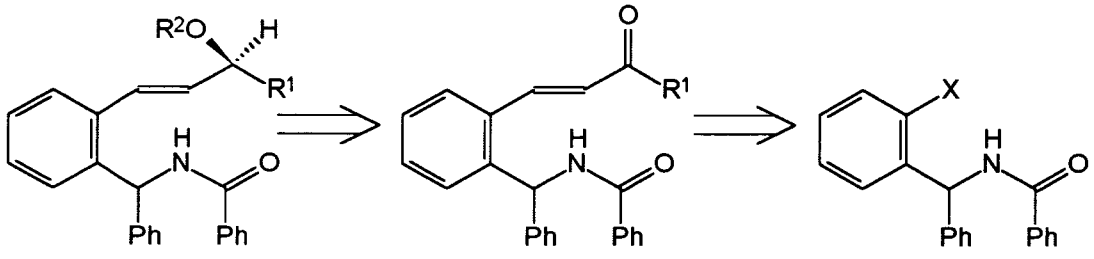
3.6. Conclusion

Given that all the routes investigated to the target molecules **130** had proven unproductive, it was decided to investigate functionalities other than Oppolzer's sultam. This approach is discussed in the following section.

4. INVESTIGATION OF OTHER POTENTIAL CHIRAL DIRECTING GROUPS

4.1. A Chiral Group δ to the Nitrile Ylide

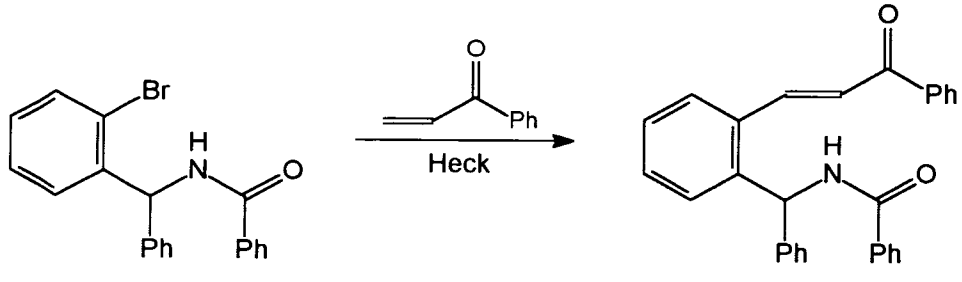
In order to investigate the 1,7-electrocyclisation of nitrile ylides analogous to the chiral diazo compounds **126**, **Scheme 44**, an attempt was made to synthesise the chiral ether **184**. Retrosynthesis required the halo-amides **132** or **133** which could undergo a Heck reaction with an α,β-enone to give the ketone **185**. This could then be reduced and etherified to give the chiral ethers **184**, **Scheme 75**.



184 **185** **132** X = Br **133** X = I

SCHEME 75

The required Heck reaction was investigated with the bromo-amide **132** and phenyl vinyl ketone, **Scheme 76**.



132 **186**

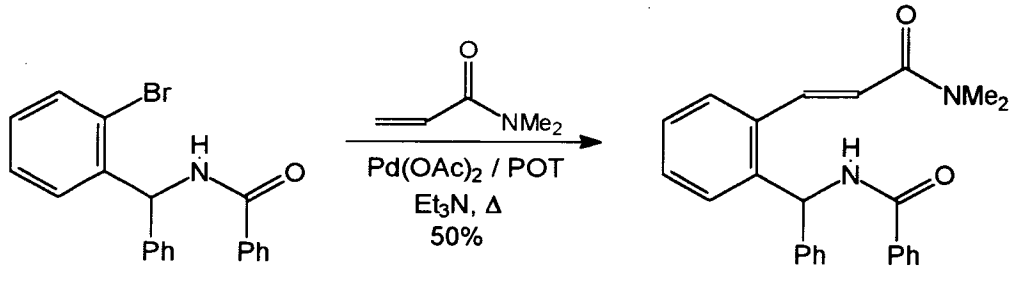
SCHEME 76

Under standard Heck reaction conditions (100°C) the high thermal instability of the phenyl vinyl ketone led to polymerisation in preference to arylation. The use of phase transfer conditions, particularly suitable for thermally unstable alkenes, failed to give any of the desired product **186**. The amides **132** and **133** have already been shown to be very poor substrates in phase transfer Heck reactions.

Given the lack of success of this approach, other potential chiral directing groups were investigated.

4.2. Amides as Potential Chiral Directing Groups

In order to investigate the viability of an amide functionality connecting a chiral directing group to the δ-position of a diene-conjugated nitrile ylide, the model dimethyl amide **187** was prepared. Heck reaction of the bromo-amide **132** with *N,N*-dimethylacrylamide gave the acrylamide **187** in acceptable yield, **Scheme 77**.

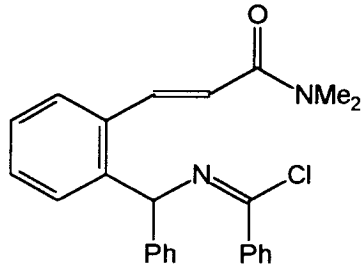


132 **187**

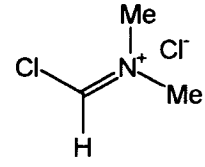
SCHEME 77

In order to generate the nitrile ylide derived from the amide **187** it was necessary to prepare the imidoyl chloride **188**. Reaction of the amide **187** with thionyl or oxalyl chloride gave no evidence of imidoyl chloride formation. Use of

formamidinium chloride[97] **189** (a Vilsmeier-type reagent), again gave no evidence of imidoyl chloride formation, despite the use of a more reactive chlorinating agent under milder conditions. Under all of the above conditions it is conceivable that the dimethyl amide of the bis-amide **187** preferentially forms an iminium salt which then reacts further.



188



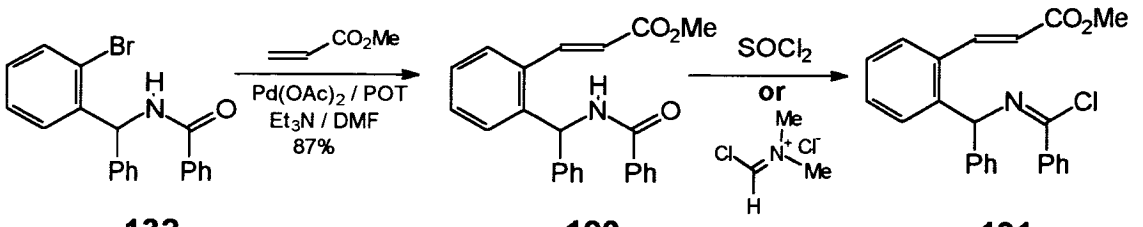
189

Given that no suitable route could be found to the imidoyl chloride **188**, amides were disqualified as suitable δ-substituents.

4.3. Esters as Potential Chiral Auxiliaries

The next functionality to be investigated as a potential chiral auxiliary was the ester moiety. An achiral model, the methyl ester **190**, was prepared in good yield by the Heck reaction of the bromo-amide **132** with methyl acrylate, **Scheme 78**. The imidoyl chloride **191** was then generated in quantitative yield with both thionyl chloride and dimethylformamidinium chloride **189**. Of these two methods, thionyl chloride was the reagent of choice as it resulted in gaseous by-products and excess chlorinating agent could be readily removed under vacuum. In contrast, the Vilsmeier-type reagent **189**, although used under milder conditions, produced the less volatile dimethylformamide as a

by-product. Also, in this case, any excess chlorinating agent could not be readily separated from the imidoyl chloride **191**.



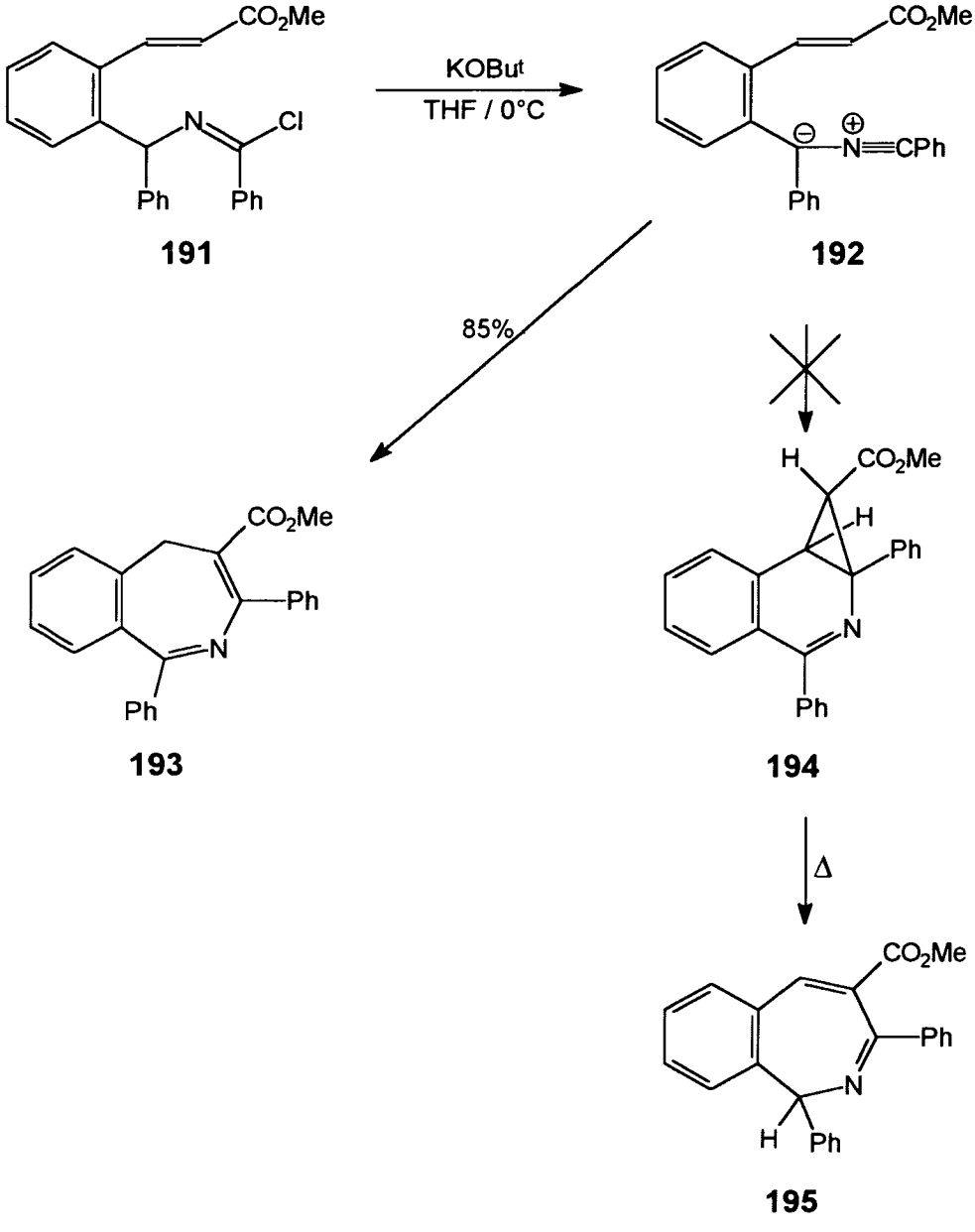
132 **190** **191**

SCHEME 78

1,3-Dehydrochlorination of the imidoyl chloride **191** with an excess of potassium *tert*-butoxide gave the 5*H*-2-benzazepine **193** in good yield, rather than the expected cyclopropa[*c*]isoquinoline **194**, **Scheme 79**. Compounds of the type **194** are normally obtained as primary products when these cyclisation reactions are carried out at room temperature or below. They are usually stable to chromatography and crystallisation but on prolonged heating at 80°C they rearrange smoothly to give 1*H*-2-benzazepines such as **195** in high yield.[13]

The structure of the 5*H*-2-benzazepine **193** was confirmed by X-ray crystallography, **Figure 8**. This unexpected result was rationalised as shown in **Scheme 80**. It seems likely that the cyclopropa[*c*]isoquinoline **194** was formed in the usual manner. However, we believe that the presence of the ethoxycarbonyl group in this species renders the α-hydrogen acidic enough to be deprotonated under the reaction conditions. Deprotonation and spontaneous ring expansion gives the anion **196**. This anion is highly resonance stabilised; the negative charge can be delocalised over the whole molecule (a total of eighteen resonance structures can be drawn). That protonation of the anion **196** gives the 5*H*-2-benzazepine **193** rather than the

1*H*-2-benzazepine **195** indicates that the former is more thermodynamically stable, **Figure 9**.



SCHEME 79

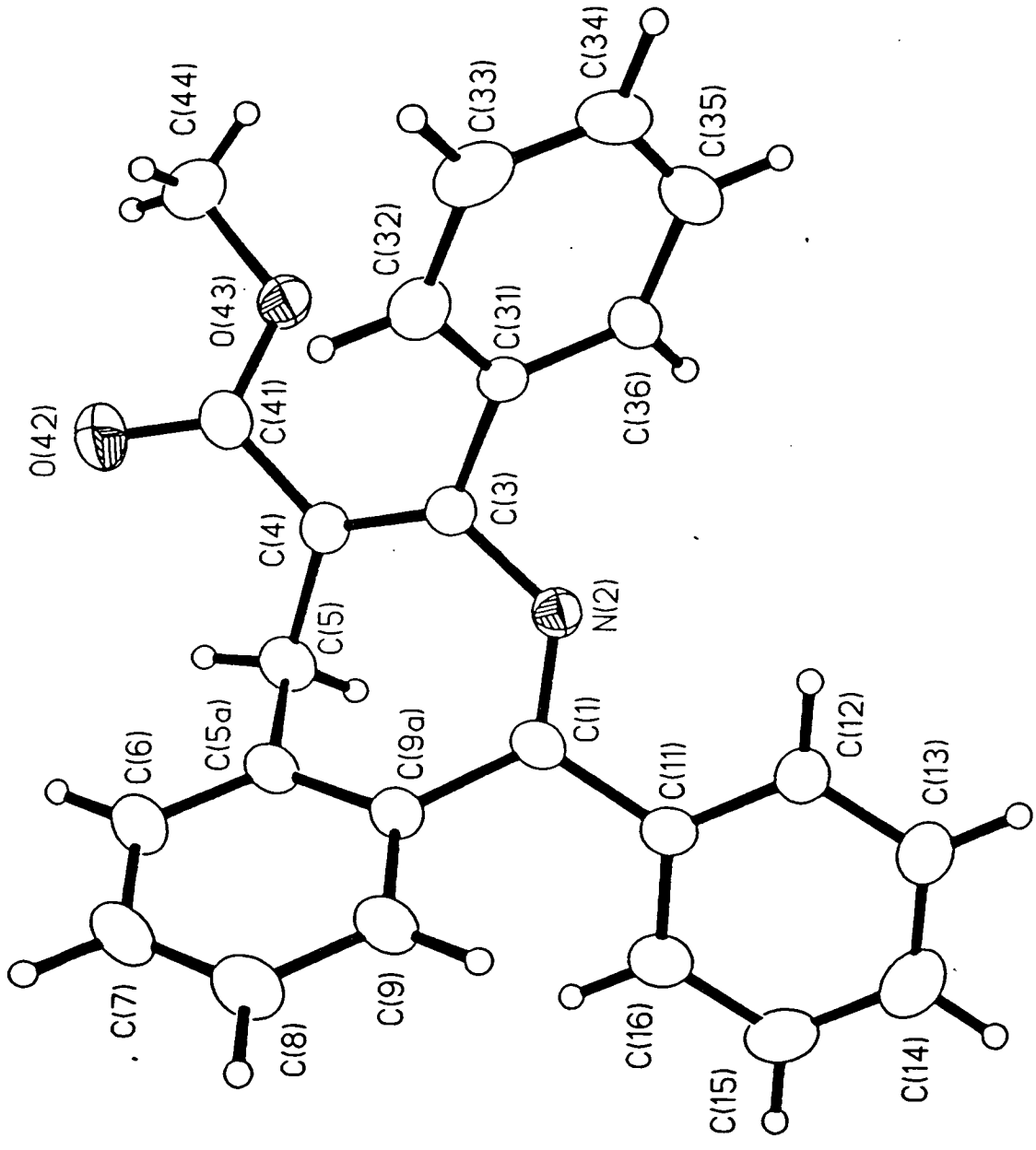
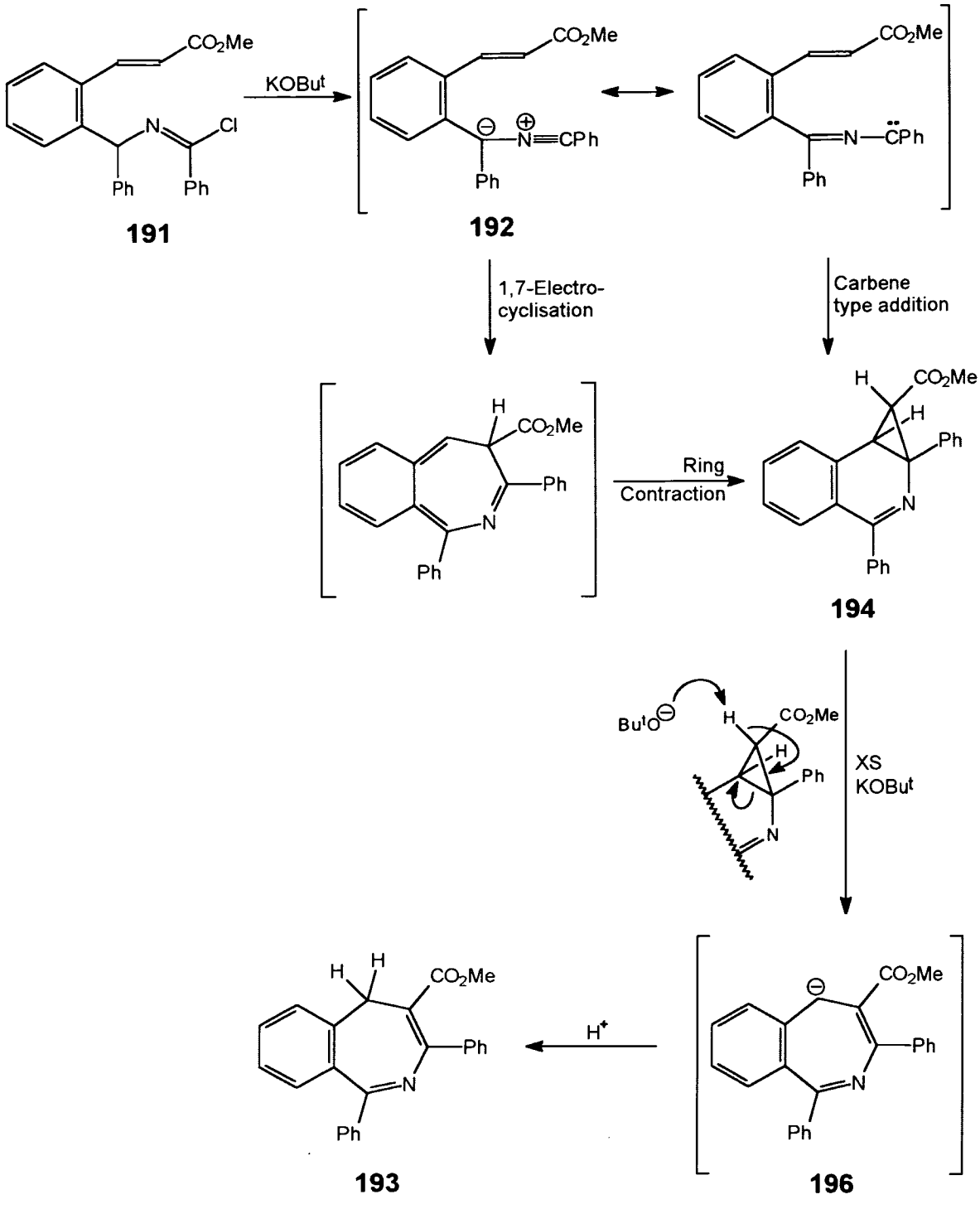
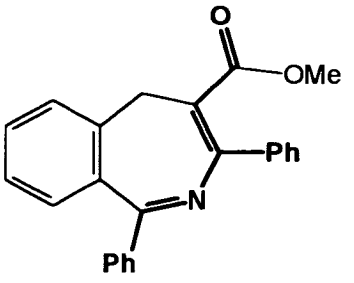


Figure 8. X-Ray Structure of 1,3-Diphenyl-5*H*-benz[*c*]azepine carboxylic acid methyl ester **193**

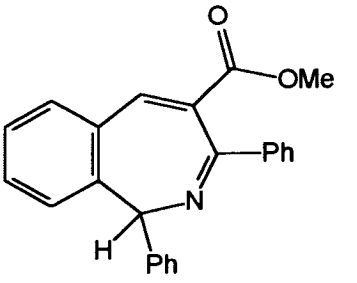

CO2Me
KOBut
N
Cl
Ph
Ph
191
CO2Me
N≡CPh
Ph
192
CO2Me
N—CPh
Ph
1,7-Electro-
cyclisation
Carbene
type addition
H
CO2Me
Ph
N
Ph
Ring
Contraction
H
CO2Me
H
Ph
N
Ph
194
But O
H
CO2Me
H
Ph
N
XS
KOBut
H
H
CO2Me
Ph
N
Ph
193
H+
CO2Me
Ph
N
Ph
196

SCHEME 80



193

(i) Through conjugated
(ii) Both phenyls in conjugation



195

(i) Cross conjugated
(ii) One phenyl not in conjugation

FIGURE 9

In order to confirm the above proposed mechanism, attempts were made to isolate the intermediate cyclopropa[*c*]isoquinoline **194** from the reaction. Reduction of the amount of potassium *tert*-butoxide used at 0°C (in THF or DMF) to less than one equivalent gave primarily the amide **190** (from hydrolysis of the imidoyl chloride **191** during workup) and a lower yield of the 5*H*-2-benzazepine **193**. Other bases, such as triethylamine, Hünig's base and DBU, failed to 1,3-dehydrochlorinate the imidoyl chloride **191**. Use of a deficiency of potassium *tert*-butoxide at -78°C gave recovered amide **190**, the 5*H*-2-benzazepine **193** and a low yield of the cyclopropa[*c*]isoquinoline **194**. The structure of the cyclopropa[*c*]isoquinoline was confirmed by X-ray chrystallography **Figure 10**.. This result implies that the cyclopropa[*c*]isoquinoline **194** is indeed an intermediate in the formation of the 5*H*-2-benzazepine **193**.

Gentle thermal rearrangement of the cyclopropa[*c*]isoquinoline **194** at 80°C gave the 1*H*-2-benzazepine **195** in quantitative yield within a few hours, **Scheme 81**. Extended heating of the 1*H*-2-benzazepine **195** at 80°C gave no formation of the 5*H*-2-benzazepine **193**, even after several days.

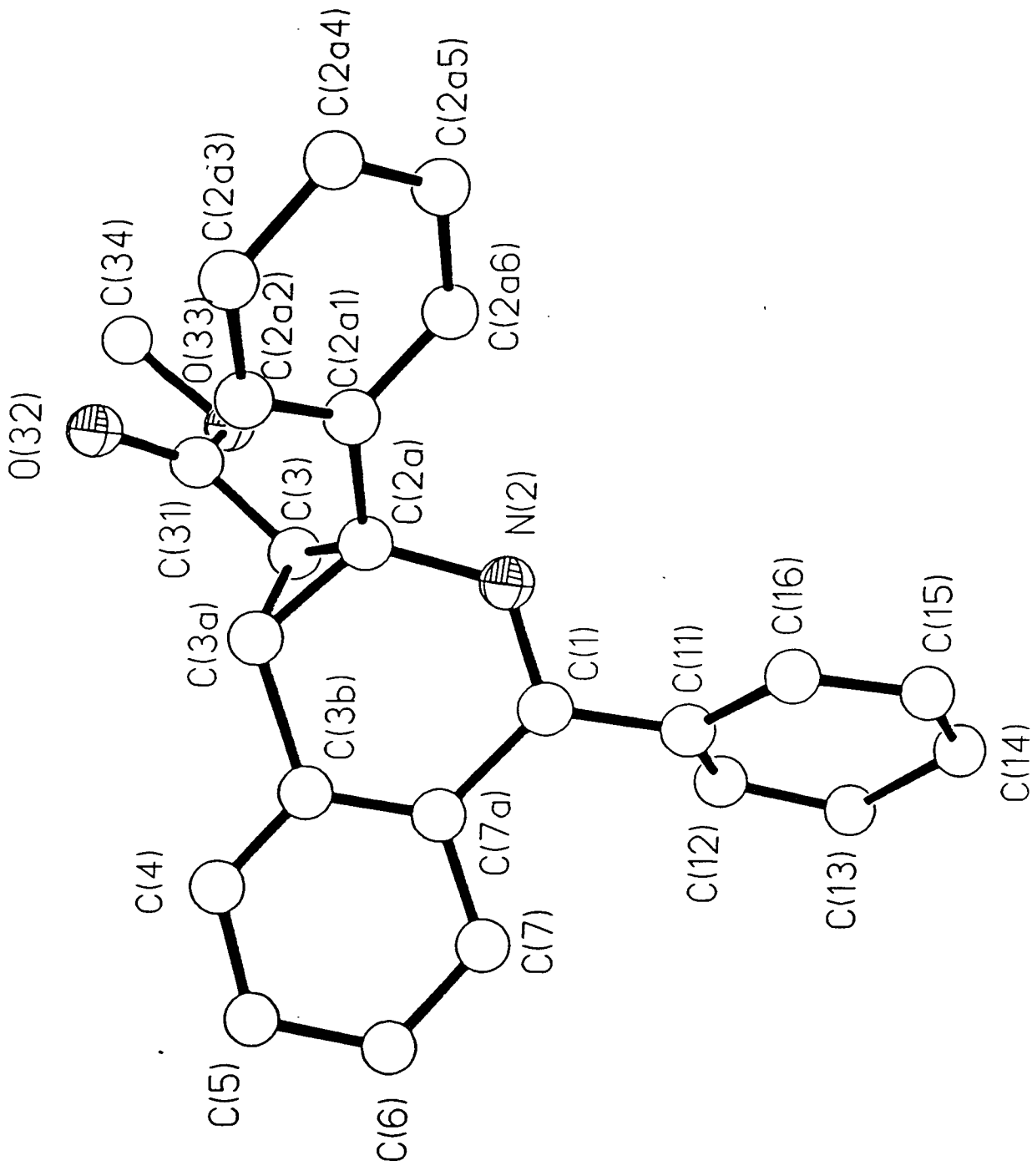
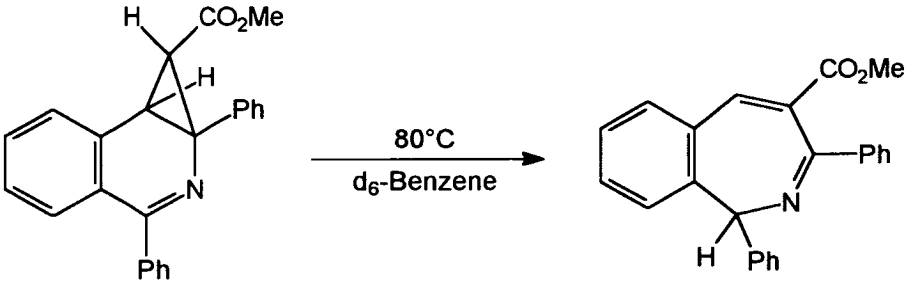


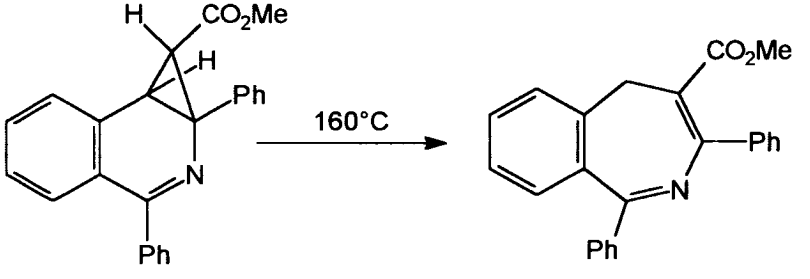
Figure 10. X-Ray Structure of 3-Methyl-1,2a-diphenyl-2a,3,3a-trihydrocyclopropa[*c*]isoquinoline-3-carboxylic acid methyl ester **194**



194 **195**

SCHEME 81

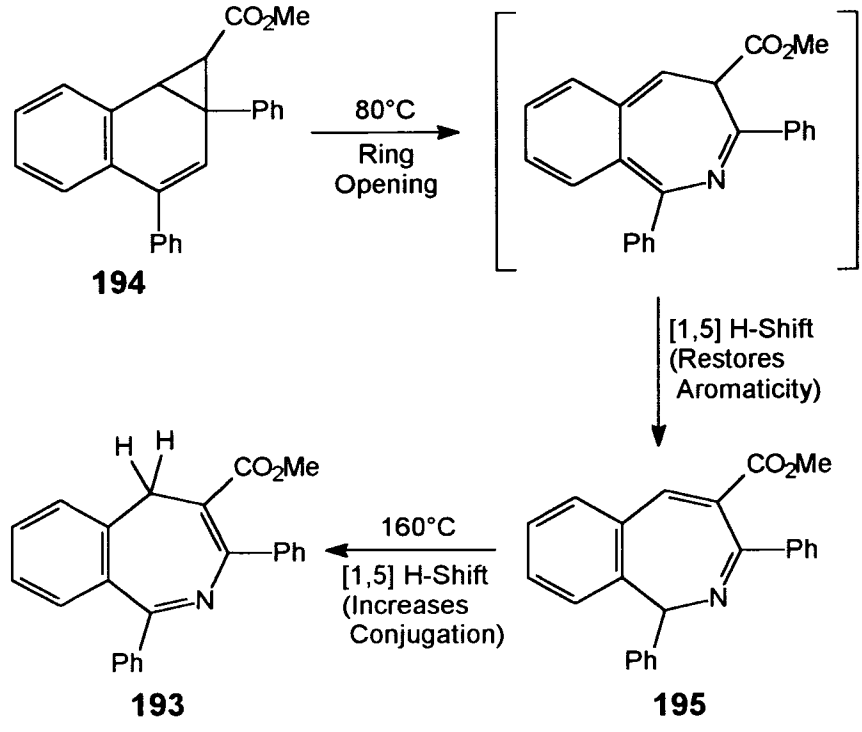
The cyclopropa[*c*]isoquinoline **194** was also thermally converted to the 5*H*-2-benzazepine **193** at higher temperatures, **Scheme 82**. Kugelrohr distillation of the isoquinoline **194** at 160°C gave partial conversion to the 5*H*-2-benzazepine **193**.



194 **193**

SCHEME 82

This rearrangement could occur by ring opening followed by a [1,5] hydrogen shift to give the 1*H*-isomer **195**. Another [1,5] hydrogen shift then gives the more thermodynamically stable 5*H*-isomer **193**, **Scheme 83**.



SCHEME 83

This work shows that the 'normal' reaction sequence (*ie* cyclisation to give the cyclopropa[*c*]isoquinoline, followed by rearrangement to the 1*H*-2-benzazepine) is rendered much more difficult by the presence of the ethoxycarbonyl group. While it is still possible, it requires a low reaction temperature and a deficiency of the base to avoid the dominance of the base-induced ring expansion of the cyclopropa[*c*]isoquinoline **194**. Hence this is hardly viable as a practical synthetic sequence.

The base-induced rearrangement of the isoquinoline **194** is an interesting new reaction of cyclopropa[*c*]isoquinolines and provides a route to the novel 5*H*-2-benzazepine **193**. However, as far as this research was concerned, this rearrangement constituted a major setback. As the first formed cyclopropa[*c*]isoquinoline **194** was deprotonated to give the anion **196**, any chirality induced by the use of chiral ester analogues would be lost. Thus, this reaction

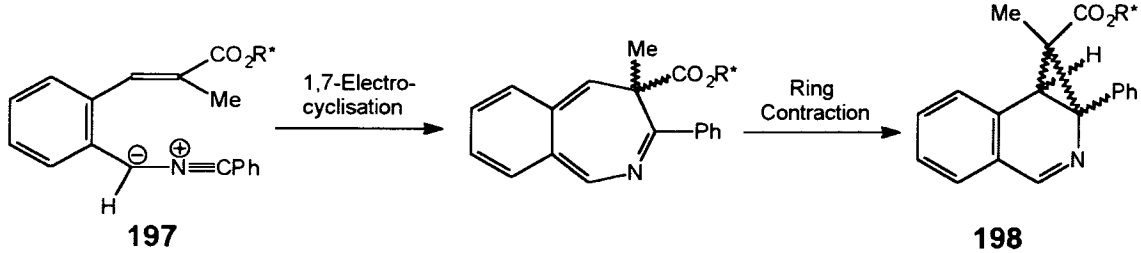
is not viable as a diastereoselective approach to chiral 1*H*-2-benzazepines such as **195**.

Despite this outcome, this work showed that it is possible to prepare and cyclise the nitrile ylide **192**. In order to capitalise on this chemistry it was decided to investigate the cyclisations of chiral analogues of the ester **192** in which the acidic proton was replaced by a methyl group. It was hoped that this substitution would prevent the base-catalysed ring opening of the cyclopropa[*c*]isoquinolines without inhibiting 1,7-electrocyclisation of the nitrile ylides. This approach is discussed in the next section.

5. FACE SELECTIVE 1,7-ELECROCYCLISATIONS

5.1. Introduction

As discussed in the last section, 1,7-electrocyclisation of nitrile ylides of the type **192** does not allow study of face selectivity - any induced chirality is lost due to deprotonation of the intermediate cyclopropa[*c*]isoquinoline. However, the results showed that δ-alkoxycarbonyl substituted nitrile ylides readily undergo 1,7-electocyclisation. In order to allow investigation of face selectivity it was decided to replace the proton α to the alkoxycarbonyl group. Substitution with a methyl group (and removal of the now redundant phenyl group) gives nitrile ylides of the type **197**. It was expected that their cyclisation would follow the path shown in **Scheme 84** to give the cyclopropa[*c*]isoquinolines **198** which would be stable to the basic reaction conditions. The overall objective here was to determine how face-selectivity would be affected by the nature of the chiral substituent R*.

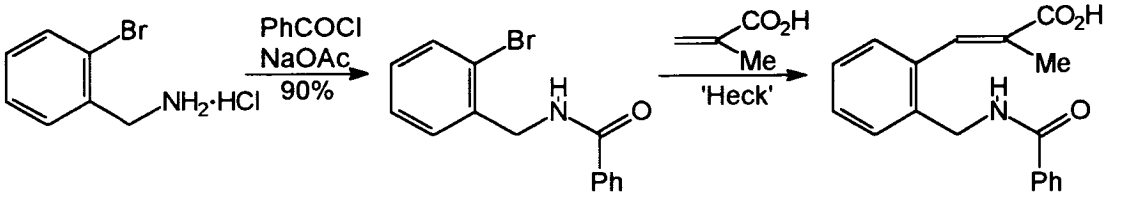


197 **198**

SCHEME 84

5.2. Preparation of the Nitrile Ylide Precursors

2-Bromobenzylamine hydrochloride was benzoylated in good yield to give the amide **199**, **Scheme 85**. Heck coupling with methyl acrylic acid, using the conditions of Spencer,[80] gave only the *E*-acid **200** in reasonable yield. The esterification of this acid was then investigated.

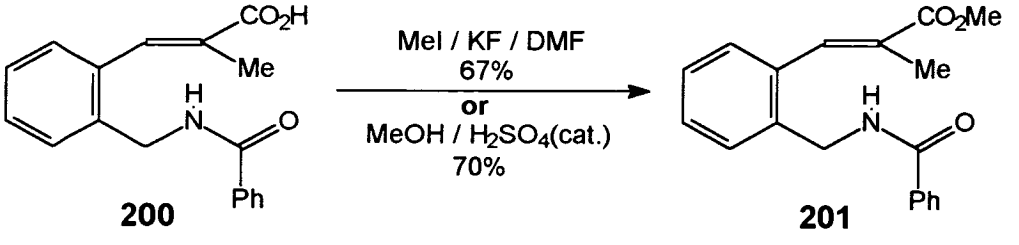


199 **200**

SCHEME 85

5.2.1. Preparation of the Methyl Ester **201**

The methyl ester **201** was prepared under two sets of conditions. Reaction of the acid **200** with methyl iodide and potassium fluoride in DMF gave the ester **201** in 67% yield, **Scheme 86**. Heating the acid **200** with methanol (c.H_2SO_4 catalyst) gave the ester **201** in 70% yield. Given the higher yield and easier work-up, the methanol/sulphuric acid esterification conditions were preferable.

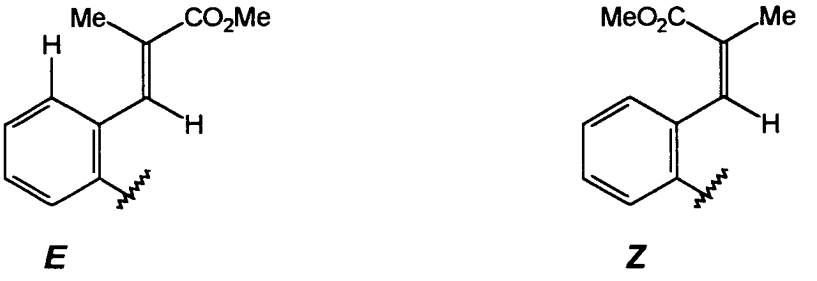


200 **201**

SCHEME 86

The *E*-configuration of the ester **201** was confirmed by NOE experiments. Irradiation of the methyl signal at δ1.7 changed the signal intensity of *only* one

aromatic proton. Thus, this methyl must lie in close proximity to an aromatic proton, **Figure 11**, and the alkene therefore has *E*-configuration. Irradiation of the methyl group in the *Z*-isomer would be expected to produce a change in the intensity of the vinyl proton only. No such effect was observed.

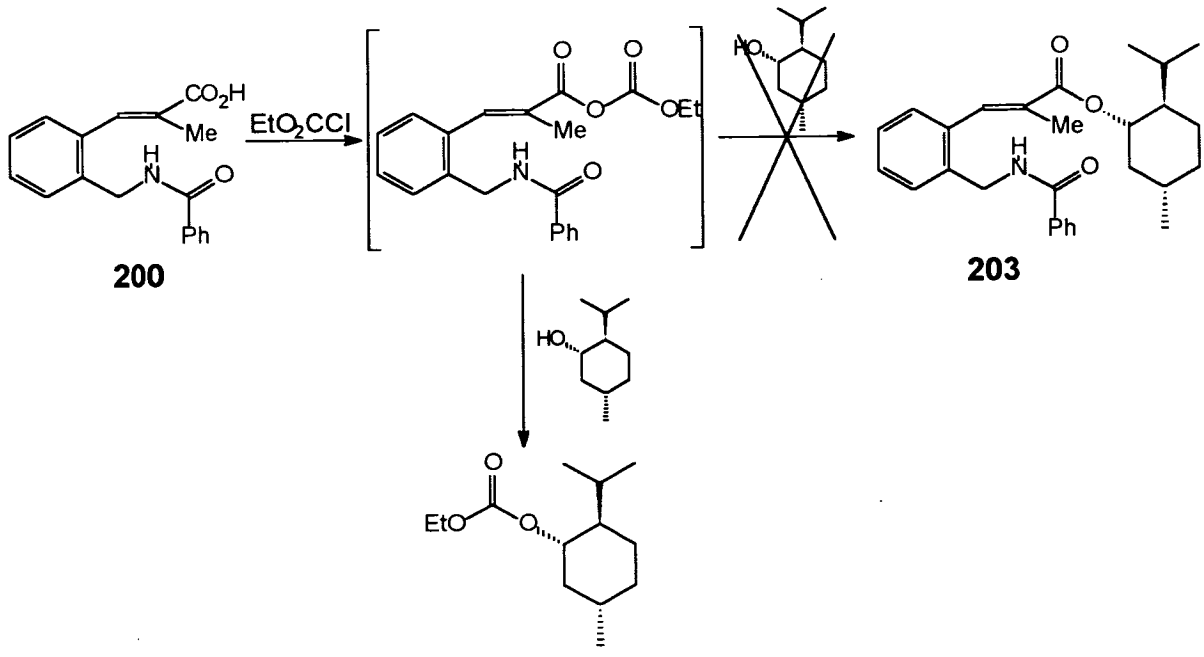


E ***Z***

FIGURE 11

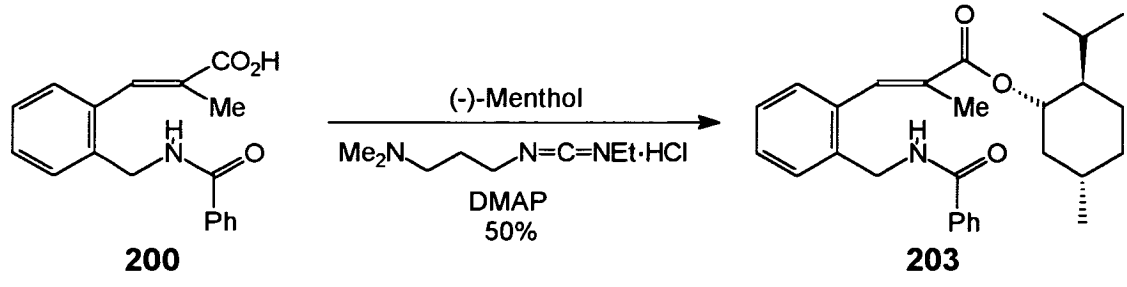
5.2.2. Preparation of the Menthyl Ester **203**

The two routes used to prepare the methyl ester **201** were unsuitable for preparation of the menthyl ester due to the low volatility of menthyl alcohol and iodide. Thus, other conditions were investigated. Reaction of the acid **200** with ethyl chloroformate and triethylamine followed by (-)-menthol gave ethyl menthylcarbonate **202** due to attack at the ethoxycarbonyl centre, **Scheme 87**. Although this carbonyl would be expected to be the less reactive of the two, presumably the combined steric bulk of the menthyl and methylcinnamate moieties blocks reaction at the desired site.



SCHEME 87

Reaction of the acid **200** with 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide in the presence of (-)-menthol gave only recovered starting materials. Activation of the acid by addition of the "hypernucleophilic" catalyst 4-dimethylaminopyridine (DMAP) gave a reasonable yield of the menthyl ester **203**, **Scheme 88**.



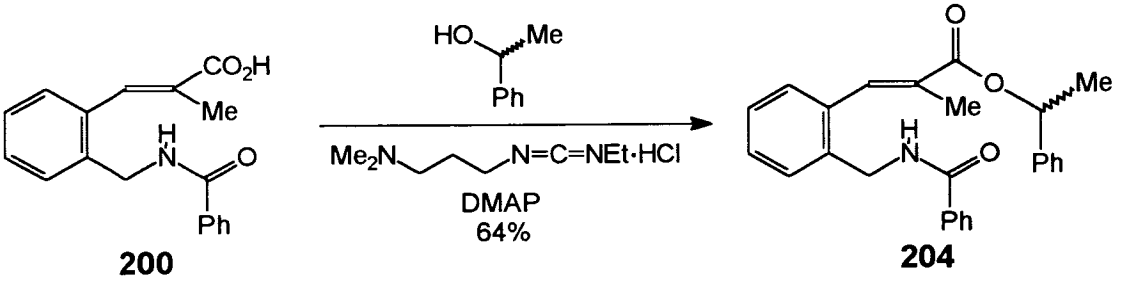
SCHEME 88

The ester **203** was also prepared by reaction of the acid **200** with (-)-menthol in the presence of catalytic *p*-toluenesulphonic acid. Heating in toluene (with

azeotropic removal of water) gave a low yield of the ester **203**. This reaction was complicated by slow thermal decomposition of either the starting material or product under the prolonged heating required for esterification. As thermal decomposition occurred at a similar rate to ester formation these conditions were less attractive than the carbodiimide route.

5.2.3. Preparation of the α-Methylbenzyl Ester **204**

Using the best conditions found for preparation of the menthyl ester **203**, the α-methylbenzyl analogue **204** was prepared, **Scheme 89**.

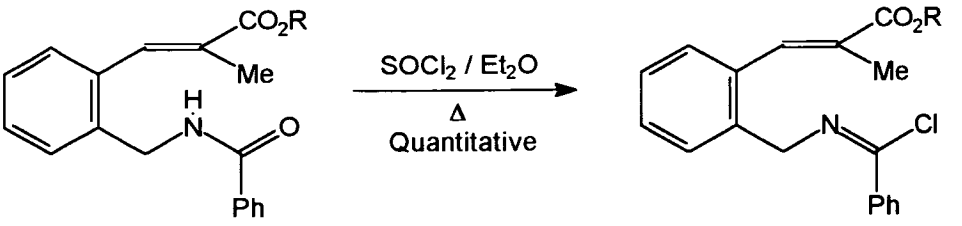


200 **204**

SCHEME 89

5.2.4. Preparation of the Imidoyl Chlorides **205**, **206** and **207**

The imidoyl chlorides of the esters **201**, **203** and **204** were prepared quantitatively by heating the appropriate ester with thionyl chloride in diethyl ether, **Scheme 90**.

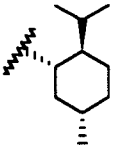


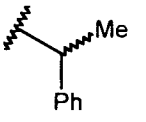
201 R = Me

203 R = (-)-Menthyl

204 R = (±)-α-Methylbenzyl

205 R = Me

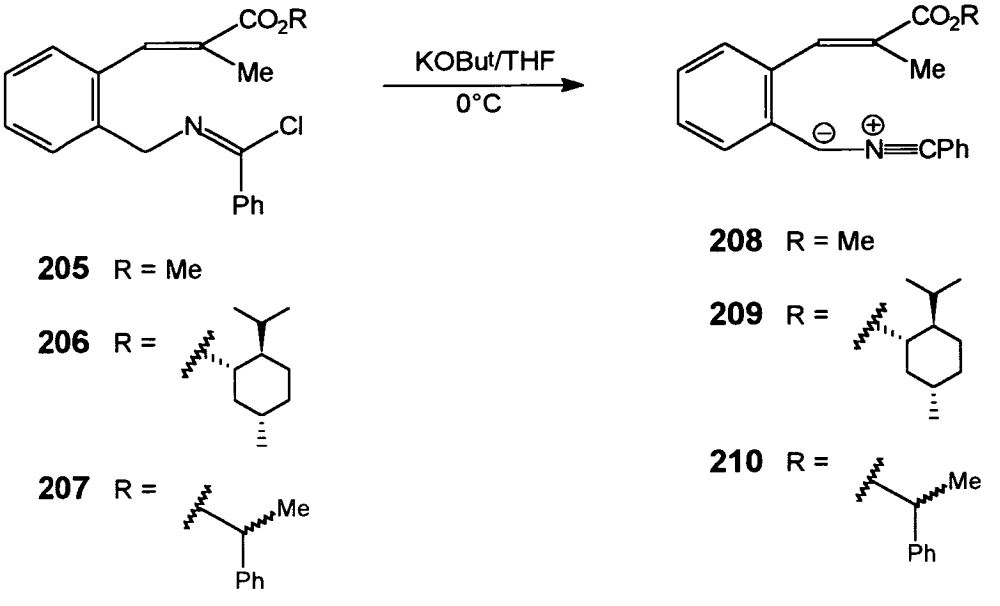
206 R = 

207 R = 

SCHEME 90

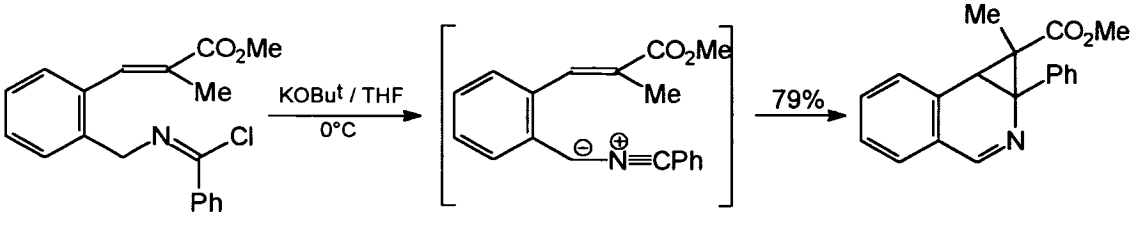
5.3. Generation and 1,7-Electrocyclisation of the Nitrile Ylides 208, 209 and 210

The nitrile ylides **208**, **209** and **210** were generated by 1,3-dehydrochlorination of the corresponding imidoyl chlorides **205**, **206** and **207** using potassium *tert*-butoxide at 0°C, **Scheme 91**.



SCHEME 91

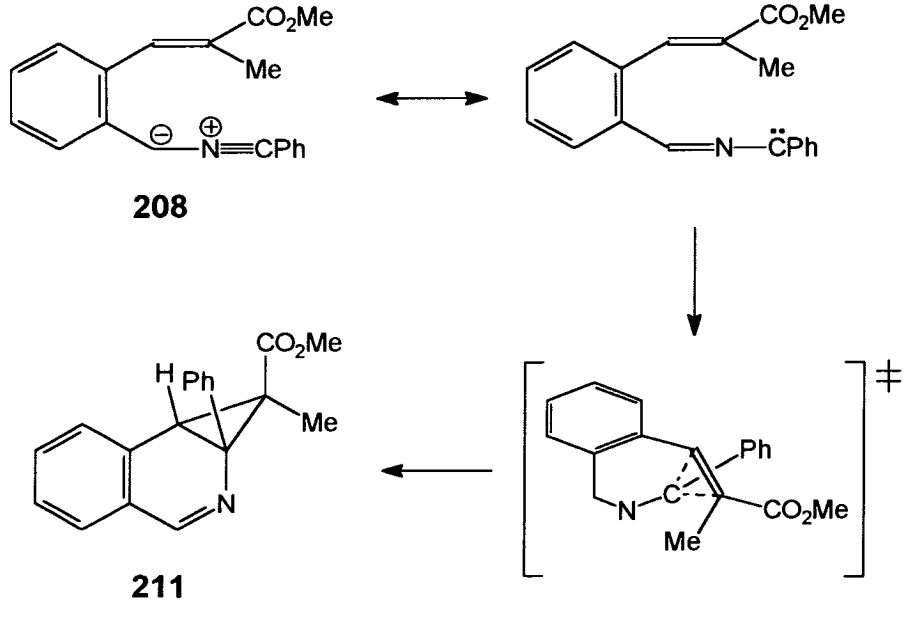
The δ-carboxymethyl substituted nitrile ylide **208** underwent smooth 1,7-electrocyclisation to give the cyclopropa[*c*]isoquinoline **211** in good yield, **Scheme 92**. As expected, no face selectivity was observed and no diastereotopic characteristics were seen in the ^{1}H n.m.r. spectrum.



205 **208** **211**

SCHEME 92

A crystal structure of the cyclopropa[*c*]isoquinoline **211** was obtained, **Figure 12**. This clearly shows that the phenyl and carboxymethyl groups are on the same face of the cyclopropyl ring, indicating a concerted mechanism. This is consistent with both the carbene type addition, **Scheme 93**, and 1,7-electrocyclisation followed by fast ring contraction, **Scheme 94** (*i.e.* the ring contraction step is much faster than ring inversion). To date no method has been found to distinguish between the two possible mechanisms. However, work by Groundwater[109] has shown that without an α,β-double bond no cyclisation products are obtained. This suggests that α,β-conjugation is required for intramolecular cyclisation of the nitrile ylide, providing evidence favouring the 1,7-electrocyclisation mechanism.



SCHEME 93

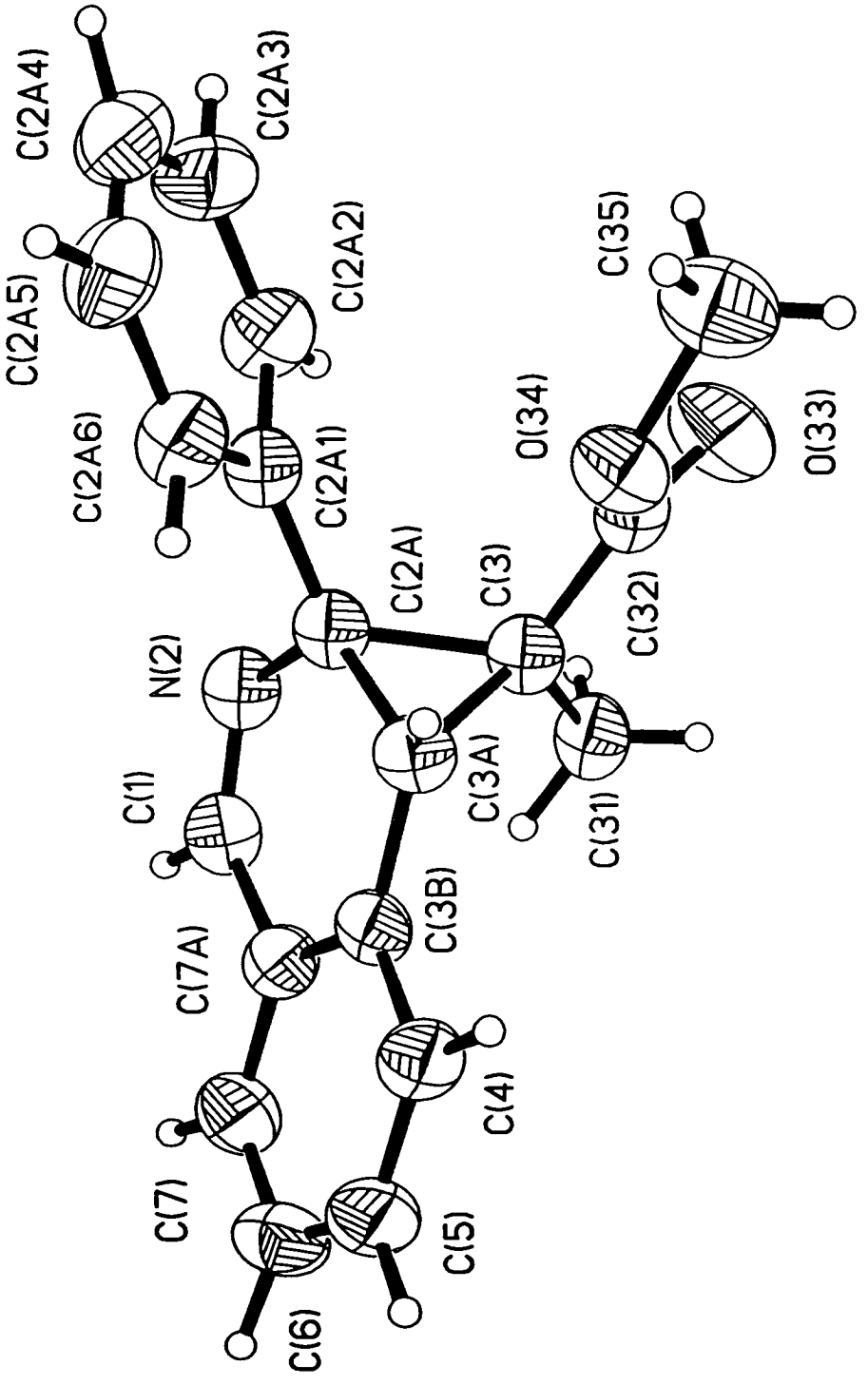
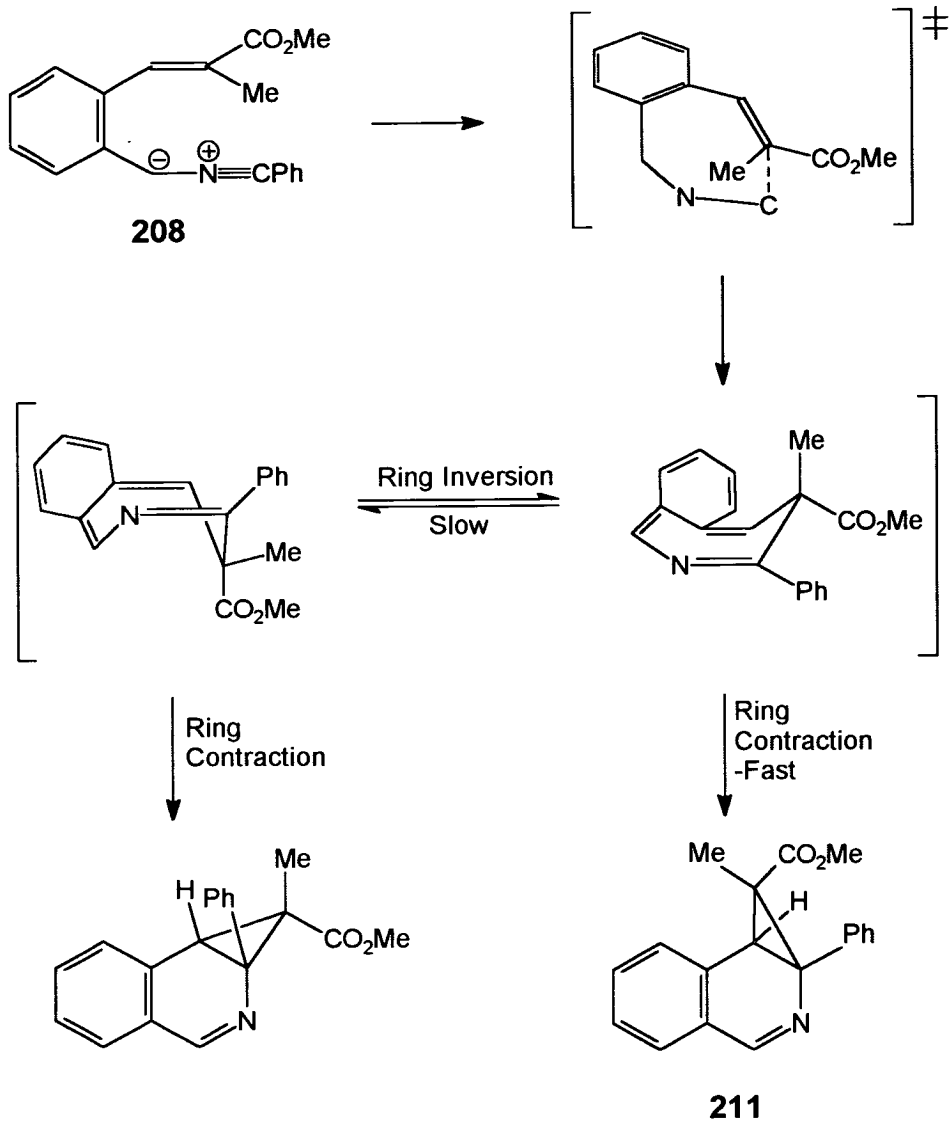


Figure 12. X-ray Structure of 3-Methyl-2a-phenyl-2a,3,3a-trihydrocyclopropa-[*c*]isoquinoline-3-carboxylic acid methyl ester **211**



SCHEME 94.

In the cyclopropa[*c*]isoquinoline **211**, the phenyl and carboxymethyl groups are on the same face of the cyclopropyl ring and the ring junction has *cis* geometry. Thus, although three new chiral centres are generated, only two of the theoretically possible eight diastereomers can be formed, **Figure 13**. Therefore, for chiral esters, any induced face selectivity will fix the chirality of three new chiral centres.

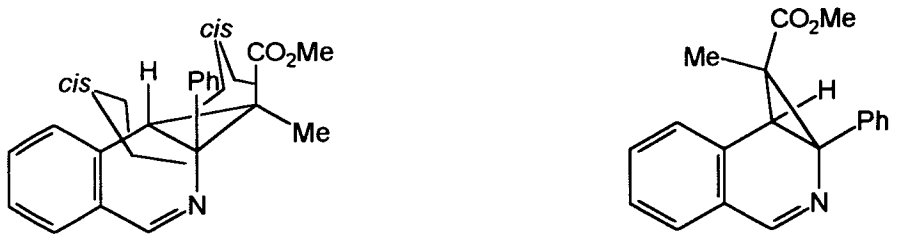
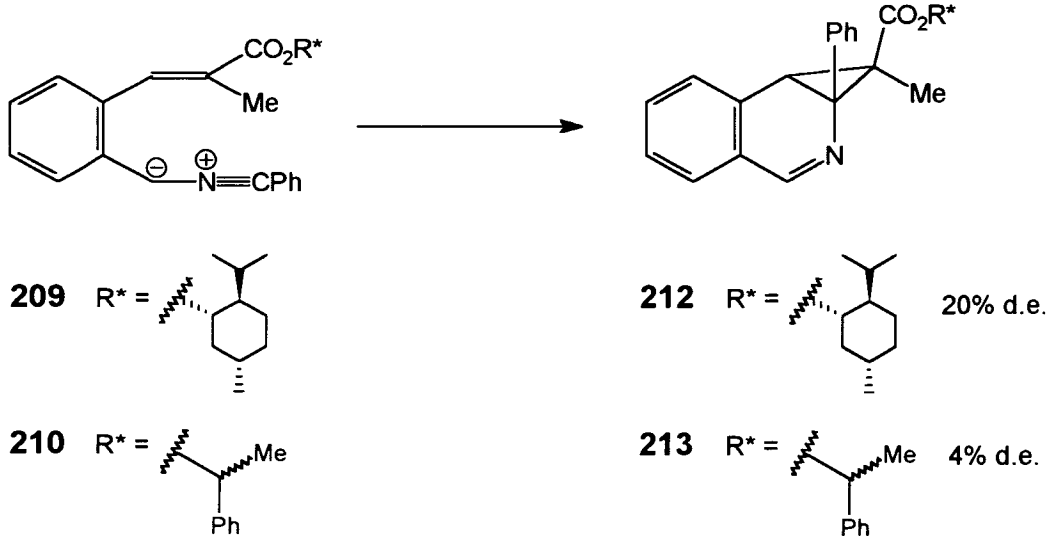


FIGURE 13. The two possible diastereomers of **211**

Given the success of the 1,7-electrocyclisation of the nitrile ylide **208**, the cyclisation of the chiral nitrile ylides **209** and **210** was investigated, **Scheme 95**. The menthyl nitrile ylide **209** gave the chiral cyclopropa[*c*]isoquinoline **212** in 67% yield with 20% d.e. The α-methylbenzyl nitrile ylide **210** gave the cyclopropa[*c*]isoquinoline **213** in 70% yield and 4% d.e. The diastereomer ratios in both cases were determined from the ^{1}H n.m.r. integrals of the imine protons (which had different chemical shifts in each diastereomer).

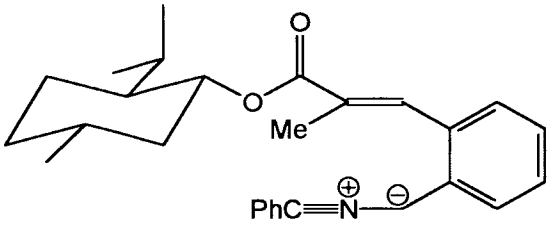


SCHEME 95

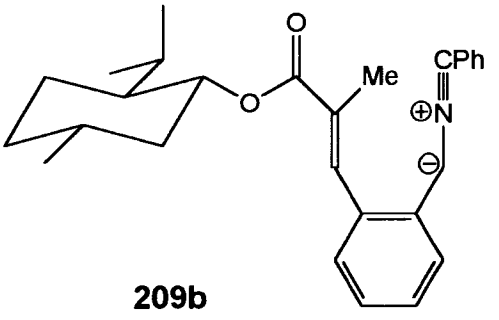
As described earlier, in the absence of Lewis acids, chiral acrylates are poor chiral auxiliaries in electrocyclic reactions. This is due to the low rotational barrier between the conformers **58** and **59**. The results above show that both

the menthyl and α-methylbenzyl esters gave high degrees of face selectivity in comparison to results obtained previously with these auxiliaries in uncatalysed Diels Alder and 1,3-dipolar cycloadditions.

One basic problem with systems of this type is that there is an easy equilibrium between the conformers **209a** and **209b**. Even if the nitrile ylide attacks the π-bond exclusively from one face relative to the menthyl group, conformers **209a** and **209b** will lead to reversed topicity.



209a



209b

The fact that the face selectivity was surprisingly high can be rationalised by looking at the helical transition states for the electrocyclisation process, **Figure 14**. In these it can be seen that although the menthyl group is a long way away from the reaction site it does come into effective steric interaction with the phenyl group at the terminus of the nitrile ylide. This interaction must be largely responsible for the greater selectivity seen here compared with other uncatalysed electrocyclic reactions involving this auxiliary.

The relatively high level of selectivity obtained also lends some support to the contention that the reaction *does* proceed *via* electrocyclisation rather than in a one-step carbene type addition. The latter mechanism would require transition states like those shown in **Figure 15** in which the chiral auxiliary and the phenyl group are further apart.

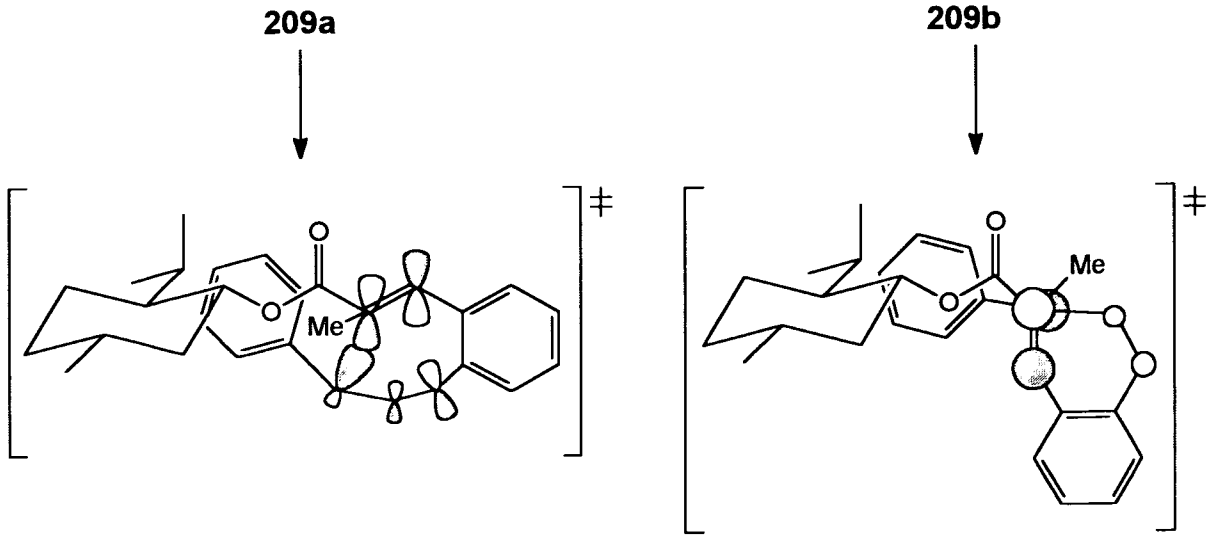


FIGURE 14. Two possible helical transition states
(each shown for attack at one face of the alkene only).

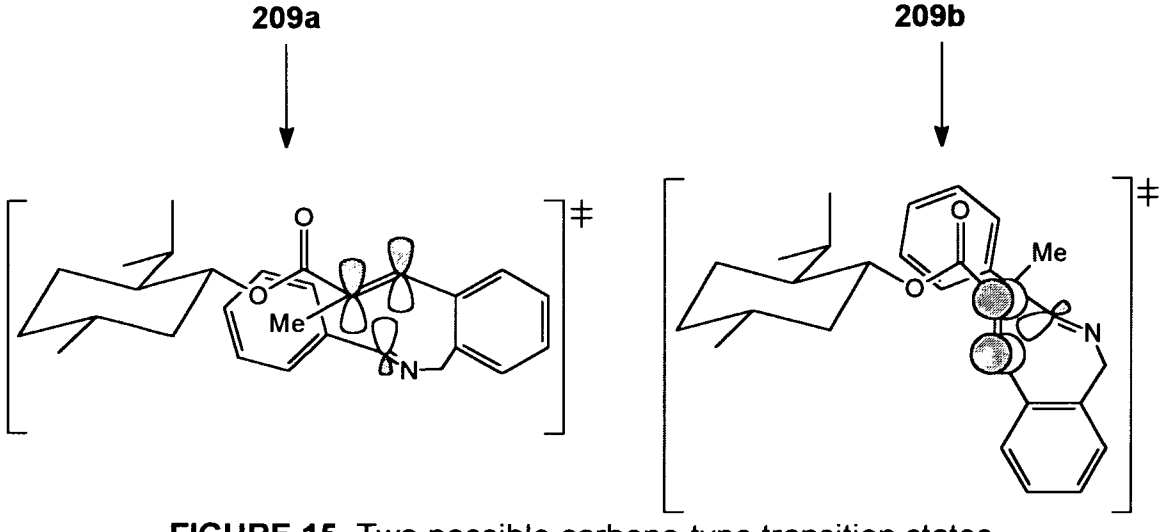
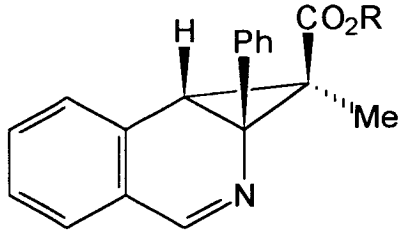


FIGURE 15. Two possible carbene-type transition states
(each shown for attack at one face of the alkene only)

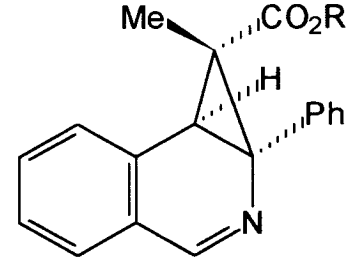
The above arguments should also apply to the α-methylbenzyl ester. The lowered face selectivity being due to the reduced steric bulk of the chiral ester.

6. CONCLUSION

This work has shown that asymmetric 1,7-electrocyclisation occurs with surprisingly high face selectivity. Despite the use of "inefficient" chiral directing groups, asymmetric 1,7-electrocyclisation followed by ring contraction has provided a route to chiral cyclopropa[*c*]isoquinolines. These two steps generate three new chiral centres with an unexpectedly high degree of stereocontrol. In summary, a route to the chiral cyclopropa[*c*]isoquinolines **214** and **215** has been identified.



214



215

This work has also provided the first X-ray crystal structure of cyclopropa[*c*]isoquinolines derived from 1,7-electrocyclisation reactions of nitrile ylides. Thus, the structure of these products has been confirmed conclusively.

EXPERIMENTAL

1. SYNTHESIS OF THE KEY INTERMEDIATES 132 & 133

2-Bromobenzophenone **136a**

This was prepared by the method of Lees and Burawoy[110] using 2-bromobenzoyl chloride (209.5g, 0.95mol) and anhydrous aluminium chloride (253.4g, 1.9mol) in anhydrous benzene (1.4l). Distillation of the crude product gave 2-bromobenzophenone **136a** (221.75g, 89%) as a yellow oil, b.p. 133-5°C/0.02mmHg (lit.[111] 345°C) (Found M^+ 259.9838. $C_{13}H_9{}^{79}BrO$ requires M, 259.9842); ν_{max}(film)/cm^{-1} 3059, 1670 (C=O), 1589, 928; δ_H(200.13MHz; $CDCl_3$) 7.31-7.52 (5H, m), 7.56-7.68 (2H, m), 7.79-7.85 (2H, m); δ_H(90.556MHz; $CDCl_3$) 119.3 (quat, C-Br), 127.0 (CH), 128.4 (CH, 2xCH), 128.7 (CH), 130.0 (CH), 131.0 (CH), 133.0 (CH), 133.5 (CH), 135.9 (quat), 140.4 (quat), 195.6 (quat, C=O); m/z 262 (M^+, 92%), 260 (M^+, 97) 185 (81, M-C_6H_5), 183 (84, M-C_6H_5), 181 (27, M-Br), 105 (100, $PhCO^+$), 77 (100, $C_6H_5{}^+$).

2-Iodobenzophenone **136b**

This was prepared by the method of Lees and Burawoy[110] using 2-iodobenzoyl chloride (2.0g, 7.5mmol) and anhydrous aluminium chloride (2.0g, 15mmol) in anhydrous benzene (20ml). Kugelrohr distillation of the crude product gave 2-iodobenzophenone **136b** (1.98g, 86%) as a pale yellow oil, b.p. 200°C (oven)/0.1mmHg (lit.[110] 210-211°C/13mmHg) which solidified on standing. ν_{max}(film)/cm^{-1} 3068, 1662 (C=O), 1601, 1426, 1314, 1250, 1154, 927, 764, 703; δ_H(80.13MHz; $CDCl_3$) 7.03-7.59 (6H, m), 7.65-7.95 (3H, m); δ_C(50.32MHz; $CDCl_3$) 92.0 (quat, C-I), 127.6 (CH), 128.4 (CH, 2 x CH), 130.2 (CH, 2 x CH),

130.9 (CH), 133.5 (CH), 135.2 (quat), 139.4 (CH), 140.4 (quat), 196.9 (quat, C=O).

(2-Bromophenyl)-phenylmethanol **137a**

(a) Grignard Method

2-Bromobenzaldehyde (50.0g, 0.27mol) in anhydrous diethyl ether (400ml) was added to a solution of phenylmagnesium bromide [prepared from magnesium turnings (7.55g, 0.31mol) and bromobenzene (46.67g, 0.30mol) in anhydrous diethyl ether (450ml)]. The reaction was refluxed for 0.5h, cooled and hydrolysed with dilute hydrochloric acid. The organic layer was separated and the aqueous layer was extracted with diethyl ether (2x150ml). The organic layers were combined, washed with saturated sodium hydrogen carbonate solution and brine. After drying ($MgSO_4$), the solvent was removed *in vacuo* leaving a cloudy yellow oil. Kugelrohr distillation gave (2-bromophenyl)-phenylmethanol **137a** (67.65g, 95%) as a white solid, b.p. 150°C(oven)/0.05mmHg. The product could be crystallised from petroleum ether (b.p. 40-60°C) to give white cubes, m.p. 57-57.5°C (lit.[112] 56°C) (Found C, 59.07; H, 4.25; M^+, 263.9973 and 261.9987. $C_{13}H_{11}BrO$ requires C, 59.34; H, 4.21; M^+, 263.9967 and 261.9961); ν_{max}(film)/cm^{-1} 3180 (br, OH), 3060, 3028, 1566, 1436, 1181, 1011, 849; δ_H(360.136MHz; $CDCl_3$) 2.60 (1H, br s, OH), 6.17 (1H, s, CH-O), 7.15 (1H, ddd, J 7.6, 1.8 and 1.8, ArH), 7.25-7.41 (6H, m, ArH), 7.53-7.59 (2H, m, ArH); m/z 264 (M^+, 79%), 262 (M^+, 81), 185 (60), 183 (60), 165 (26, M-Br-H_2O), 105 (68), 77 (52), 28(100).

(b) Reduction Method

Sodium borohydride (40.0g, 1.06mol) was added portionwise to a stirred solution of 2-bromobenzophenone **136a** (221.75g, 0.85mol) in methanol (1.5l). The solvent was removed *in vacuo* and water (800ml) and diethyl ether (1l) were added. The organic layer was separated and the aqueous layer was extracted with diethyl ether (100ml). The combined organic layers were dried ($MgSO_4$) and the solvent was removed *in vacuo* to leave a pale yellow solid. This was recrystallised from petroleum ether (b.p. 40-60°C) to give white cubes of (2-bromophenyl)-phenylmethanol **137a** (131.88g, 60%) which had melting point and spectral characteristics identical to an authentic sample.

(2-Iodophenyl)-phenylmethanol **137b**

(a) Grignard Method

2-Iodobenzaldehyde **139b** (207.58g, 0.89mol) in anhydrous diethyl ether (1.0l) was added to a solution of phenylmagnesium bromide [prepared from magnesium turnings (22.84g, 0.94mol) and bromobenzene (154.53g, 0.98mol) in anhydrous diethyl ether (2.0l)]. The reaction was refluxed for 0.25h, cooled and hydrolysed with dilute hydrochloric acid. The organic layer was separated and the aqueous layer was extracted with diethyl ether (2 x 250ml). The organic layers were combined, washed with saturated sodium hydrogen carbonate solution and brine. After drying ($MgSO_4$), the solvent was removed *in vacuo* leaving a cloudy yellow oil (279.69g, 99%). which was used without further purification. The product decomposed under vacuum distillation but Kugelrohr distillation of a small sample gave (2-iodophenyl)-phenylmethanol **137b** as a

clear colourless oil, b.p. 200°C(oven)/0.01mmHg (Found C, 50.04; H, 3.80; M^+, 310.99349. $C_{13}H_{11}IO$ requires C, 50.35; H, 3.58; M^+, 310.99347); ν_{max}(film)/cm^{-1} 3279 (br, OH), 3060, 3028, 1562, 1434, 1181, 1006; δ_H(250MHz; $CDCl_3$) 2.37 (1H, br s, OH), 6.05 (1H, s, CH-O), 6.86-7.07 (1H, m, ArH), 7.23-7.59 (6H, m, ArH), 7.75-7.89 (2H, m, ArH); δ_C(50.32MHz; $CDCl_3$) 78.8 (CH, CH-O), 98.5 (quat, C-I), 127.1 (CH, 2 x CH), 127.6 (CH), 128.2 (CH, 2 x CH), 128.3 (CH), 128.4 (CH), 129.3 (CH), 139.4 (CH), 142.0 (quat), 145.2 (quat); m/z(FAB) 311 (M+1), 293 (M+1-H_2O), 166, 105, 77.

(b) Reduction Method

Sodium borohydride (2.85g, 75.3mmol) was added portionwise to a stirred solution of 2-iodobenzophenone **136b** (11.13g, 36.1mmol) in methanol (100ml). The solvent was removed *in vacuo* and water (100ml) and diethyl ether (100ml) were added. The organic layer was separated and the aqueous layer was extracted with diethyl ether (2x50ml). The combined organic layers were dried ($MgSO_4$) and the solvent was removed *in vacuo* to leave (2-iodophenyl)-phenyl-methanol **137b** as a pale yellow oil (11.06g, 99%) which had boiling point and spectral characteristics identical to an authentic sample.

2-Iodobenzaldehyde **139b**

This was prepared by the method of Acheson and Lee[113] using 2-iodobenzyl alcohol (268.55g, 1.15mol) and pyridinium dichromate (669.11g, 1.78mol) in DCM (3.5l). The crude product was distilled *in vacuo* affording 2-iodobenzaldehyde **139b** (207.58g, 78%) as a yellow oil, b.p. 69-72°C/0.5mmHg (lit.[113] 98-100°C/2.0mm/Hg); δ_H(250MHz; $CDCl_3$) 7.18-7.46 (2H, m, ArH), 7.81-7.94 (2H,

m, ArH), 10.00 (1H, s, CHO). Kugelrohr distillation of the product gave the aldehyde as a white solid, m.p. 37°C (lit.[113] 37°C).

Bromo(2-bromophenyl)phenylmethane **140a**

(a) With Hydrobromic Acid

(2-Bromophenyl)-phenylmethanol **137a** (124.8g, 0.47mol) and a 48% solution of hydrobromic acid (1.0l) were refluxed with mechanical stirring for 1h. Once cool, the organic layer was separated and the aqueous layer was extracted with DCM (2 x 200ml). The combined organic layers were dried ($MgSO_4$) and the solvent removed *in vacuo* to leave a brown oil which was distilled to give bromo (2-bromophenyl) phenylmethane **140a** (142.2g,92%) as a clear colourless oil, b.p. 92-3°C/0.1mmHg (lit.[114] 144-6°C/2mmHg) [Found (FAB) $(M+1)^+$, 326.92092. $C_{13}H_{11}Br_2$ requires (M+1) 326.92088]; ν_{max}(film)/cm^{-1} 3059, 3027, 1438, 1195, 1160, 1026, 750; δ_H(200.13MHz; $CDCl_3$) 6.70 (1H, s, CHBr), 7.10-7.18 (2H, m, ArH), 7.23-7.39 (3H, m, ArH), 7.43-7.57 (3H, m ArH), 7.63-7.71 (1H, m, ArH); m/z (FAB) 329 (M+1), 327 (M+1), 247 (M+1-Br), 245 (M+1-Br), 166, 165 (100%, M+1-2HBr), 77.

(b) With Carbon Tetrabromide and Triphenylphosphine

Carbon tetrabromide (1.26g, 3.8mmol) was added to a mixture of (2-bromophenyl)-phenylmethanol **137a** (2.0g, 7.6mmol) and triphenylphosphine (2.99g, 11.4mmol) in chloroform at 45°C. After 5 minutes the solvent was removed *in vacuo* affording a purple oil. Wet flash chromatography on silica gel with diethyl ether as eluant and distillation yielded bromo(2-bromophenyl) -

phenylmethane **140a** (1.39g, 56%) as a clear colourless oil with b.p., i.r. and n.m.r. identical to an authentic sample.

Bromo(2-iodophenyl)phenylmethane **140b**

(2-Iodophenyl)-phenylmethanol**137b** (155.1g, 0.50mol) and a 48% solution of hydrobromic acid (1.0l) were refluxed with mechanical stirring for 2h. Once cool, the organic layer was separated and the aqueous layer was extracted with DCM (2 x 200ml). The combined organic layers were dried ($MgSO_4$) and the solvent removed *in vacuo* to leave bromo (2-iodophenyl) phenylmethane **140b** (181.5g, 97%) as a brown oil which was used without further purification. Kugelrohr distillation of a small portion gave pure bromo-(2-iodo-phenyl)-phenyl-methane **140b** as a clear colourless oil, b.p. 190°C(oven)/0.1mmHg [Found (FAB) $(M+1)^+$, 372.90915. $C_{13}H_{11}BrI$ requires (M+1) 372.90912]; ν_{max}(film)/cm^{-1} 3059, 3027, 1562, 1451, 1161, 1013; δ_H (200.13MHz; $CDCl_3$) 6.56 (1H, s, CHBr), 6.92-7.00 (1H, m, ArH), 7.24-7.51 (5H, m, ArH), 7.53-7.69 (1H, m ArH), 7.70-7.95 (2H, m, ArH); δ_C(50.32MHz; $CDCl_3$) 58.7 (CH, CHBr), 99.1 (quat, C-I), 128.0 (CH), 128.5 (CH, 2 x CH), 128.7 (CH, 2 x CH), 129.6 (CH), 130.4 (quat), 131.0 (CH), 139.6 (CH), 139.7 (CH), 143.1 (quat): m/z (FAB) 375 (M+1), 373 (M+1), 293 (M-Br), 165 (100%, M+1-HBr-HI), 77.

N-[(2-Bromo-phenyl)-phenylmethyl]-phthalimide **141a**

Bromo-(2-bromo-phenyl)-phenyl-methane**140a** (24.12g, 74.00mmol) and potassium phthalimide (16.44g, 88.80mmol) were heated to 100°C in dry DMF (200ml) for 1hr. After removal of the solvent under high vacuum, sodium

hydroxide (2M, 150ml) and ethyl acetate (300ml) were added. The organic layer was washed with water and dried (Na_2SO_4). Removal of the solvent *in vacuo* and crystallisation from toluene gave white needles of *N*-[(2-bromo-phenyl)-phenylmethyl]-phthalimide **141a** (17.86g, 62%) m.p. 152-3°C (Found: C, 64.11; H, 3.66; N, 3.42. $C_{21}H_{14}BrNO_2$ requires C, 64.31; H, 3.60; N, 3.57); ν_{max} (nujol) 1716 (C=O), 1384, 1102, 1028, 895, 752, 719, 648; δ_H(200.13MHz; d_6DMSO) 6.75 (1H, s, CH-N), 7.18-7.45 (8H, m, ArH), 7.65 (1H, dd, J 7.6 & 1.4, ArH), 7.83-7.92 (4H, m, ArH); δ_C(50.32MHz; d_6DMSO) 57.2 (CH-N), 123.5, 127.6, 128.0, 128.7, 130.0, 131.6, 132.9, 135.0, 137.2, 167.4 (2 x C=O); m/z (FAB; Thioglycerol) 394 (M+1), 392 (M+1), 312 (M - Br), 247 (Base peak, M - Phth), 245 (Base peak, M - Phth), 167, 166 (M - Br - Phth), 77 (Ph).

N-[(2-Iodo-phenyl)-phenylmethyl]-phthalimide **141b**

Bromo-(2-iodo-phenyl)-phenyl-methane **140b** (12.65g, 33.9mmol) and potassium phthalimide (8.79g, 47.5mmol) were heated to 100°C in dry DMF (100ml) for 1hr. After removal of the solvent under high vacuum, sodium hydroxide (2M, 50ml) and DCM (100ml) were added. The organic layer was washed with water and dried (Na_2SO_4). Removal of the solvent *in vacuo* and crystallisation from toluene gave white needles of *N*-[(2-iodo-phenyl)-phenylmethyl]-phthalimide **141b** (9.13g, 61%) m.p. 192-3.5°C (Found: C, 57.35; H, 3.44; N, 3.22. $C_{21}H_{14}INO_2$ requires C, 57.42; H,3.21; N, 3.19); ν_{max} (nujol) 1714 (C=O), 1384, 1334, 1115, 1014, 897, 722, 697; δ_H(200.13MHz; d_6DMSO) 6.60 (1H, s, CH-N), 7.04-7.26 (4H, m, ArH), 7.28-7.42(4H, m, ArH), 7.89-7.94 (5H, m, ArH); δ_C(50.32MHz; d_6DMSO) 61.6 (CH-N), 100.3 ,(C-I),

123.5, 127.8, 128.0, 128.2, 128.7, 129.9, 131.0, 135.0, 137.5, 139.6, 140.3, 167.5 (2 x C=O); m/z (FAB; Thioglycerol) 440 (M+1), 325, 293 (M - Phth), 274, 257, 234, 180, 77 (Base peak, Ph).

(2-Bromophenyl)-phenyl-methylamine **142a**

and (2-Bromophenyl)-phenyl-methylamine hydrochloride

This was prepared using the Ing-Manske procedure[92] as part of the Gabriel synthesis[91] *N*-[(2-bromo-phenyl)-phenylmethyl]-phthalimide **141a** (16.0g, 40.8mmol) and hydrazine hydrate solution (64% hydrazine, 6.05g, 120.9mmol) were refluxed in methanol (250ml) for 1.0h. The solvent was removed *in vaccuo* and diethyl ether (200ml) was added. The solid hydrazine phthalhydrazide was filtered off and dilute hydrochloride acid (100ml) was added to the filtrate. The aqueous layer was separated, washed with diethyl ether (25ml) and then made basic with 2M sodium hydroxide solution. The mixture was extracted with diethyl ether (2x100ml). The combined organic layers were dried ($MgSO_4$) and the solvent removed *in vaccuo* to afford (2-bromophenyl)-phenyl-methylamine **142a** (8.65g, 85%) as a pale yellow syrup which was used without further purification, [Found: (FAB) $(M+1)^+$ 262.02320. $C_{13}H_{12}{}^{79}BrN$ requires (M+1) 262.02318]; ν_{max}(film)/cm^{-1} 3372 and 3303 (NH_2), 3071, 3025, 1601, 1565, 1185; δ_H(200.13MHz; $CDCl_3$) 1.86 (2H, br s, NH_2), 5.64 (1H, s, CH-N), 7.10 (1H, td, *J* 7.6 and 1.8, ArH), 7.21-7.58 (8H, m, ArH); δ_C(50.32MHz; $CDCl_3$) 57.9 (CH, CH-N), 123.5 (quat, C-Br), 126.9 (CH), 127.1 (CH, 2 x CH), 127.5 (CH), 128.2 (CH, 2 x CH), 128.3 (CH), 128.5 (CH), 132.7 (CH), 143.6 (quat), 144.3 (quat); m/z (FAB) 264 (M+1), 262 (M+1), 247 (M+1-NH_3), 245 (M+1-NH_3), 180,

165 (M-NH_3-Br), 106 (M-C_6H_4Br), 77; m/z (EI) 263 (M, 37%), 261 (M, 38), 186, (45, M-Ph), 185 (35), 184 (47, M-Ph), 183 (34), 106 (100, M-C_6H_4Br), 104 (35, M-Ph-NH_3), 77 (30).

As the amine was too thermally unstable for distillation, a sample was characterised as the hydrochloride salt. Dry hydrogen chloride was bubbled through a solution of (2-bromophenyl)-phenyl-methylamine **142a** (8.12g, 31mmol) in anhydrous diethyl ether (200ml) for 15 minutes. The solid precipitated was filtered off, washed with a little diethyl ether and dried yielding (2-bromophenyl)-phenyl-methylamine hydrochloride 8.37g, 90%) as a finely divided white solid. Recrystallisation of a portion from ethyl acetate-ethanol gave white needles of (2-bromophenyl)-phenyl-methylamine hydrochloride, m.p. 251-253°C(dec) [Found: (FAB) $(M+1)^+$ 264.02121 and 262.02320. $C_{13}H_{13}BrN$ requires 264.02122 and 262.02319]; ν_{max}(nujol)/cm^{-1} 3187, 3055, 2586, 1592, 1189, 1026, 747, 695; δ_H(360.13MHz; d_6-DMSO) 5.77 (1H, s, CH-N), 7.30-7.40 (4H, m, ArH), 7.47 (2H, d, *J* 7.2, ArH), 7.53 (1H, t, *J* 7.6Hz, ArH), 7.66 (1H, dd, *J* 8.0 and 1.4, ArH), 7.95 (1H, d, *J* 7.8, ArH), 9.60 (3H, br s, NH_3); m/z (FAB) 264 (M), 262 (M), 245 (M-NH_3), 243 (M-NH_3), 166 (M-NH_3-Br), 165 (Base peak, M-NH_3-HBr), 76.

(2-Iodophenyl)-phenyl-methylamine **142b**

This was prepared using the Ing-Manske procedure[92] as part of the Gabriel synthesis.[91] *N*-[(2-Iodo-phenyl)-phenylmethyl]-phthalimide **141b** (70.60g, 0.161mol) and hydrazine hydrate solution (64% hydrazine, 20.60g, 0.643mol) were refluxed in methanol (1600ml) for 1.0h. The solvent was removed *in vacuo*

and diethyl ether (2.0l) was added. The solid hydrazine phthalhydrazide was filtered off and the filtrate was washed with saturated sodium carbonate solution and then water. The organic layer was dried ($MgSO_4$) and the solvent removed *in vaccuo* to afford (2-iodophenyl)-phenyl-methylamine **142b** (53.34g, 100%) as a pale yellow syrup which was used without further purification, [Found: (FAB) $(M+1)^+$ 310.00943. $C_{13}H_{12}IN$ requires (M+1) 310.00945]; ν_{max}(film)/cm^{-1} 3370 and 3300 (NH_2), 3071, 3025, 1599, 1375, 1185; δ_H(200.13MHz; $CDCl_3$) 2.08 (2H, br s, NH_2), 5.50 (1H, s, CH-N), 6.94 (1H, td, *J* 7.5 and 1.9, ArH), 7.21-7.47 (7H, m, ArH), 7.85 (1H, dd, *J* 7.9 and 1.2, ArH); ν_C(50.32MHz; $CDCl_3$) 62.6 (CH, CH-N), 99.9 (quat, C-I), 126.9 (CH), 127.2 (CH, 2 x CH), 128.2 (CH, 2 x CH), 128.3 (CH), 128.4 (CH), 128.7 (CH), 139.5 (CH) 143.5 (quat), 147.1 (quat); m/z (FAB) 310 (M+1), 293 ($M+1-NH_3$), 209, 197, 166 ($M-NH_3$-I), 135, 77, 73; m/z (EI) 309 (M, 22%), 183, (22), 180 (21), 106 (100, $M-C_6H_4I$), 105 (37),104 (41), 77 (22).

N-[(2-Bromophenyl)-phenyl-methyl]-benzamide **132**

(a) Ritter Reaction

(2-Bromophenyl)-phenylmethanol **137a** (55.66g, 0.212mol) in benzonitrile (100ml) was added dropwise over four hours to a stirred solution of cH_2SO_4 (25.40g, 0.254mol) in benzonitrile (150ml). Evaporation of most of the benzonitrile under high vacuum gave a viscous brown oil. Addition of water (500ml) and neutralisation with solid sodium carbonate gave precipitation of a pale yellow solid. The solid was filtered off, washed with water (3 x 100ml), and left in a dessicator for 24hrs under high vacuum. Continuous extaction of the

solid with ethanol-toluene (1:4) gave white needles of *N*-[(2-bromophenyl)-phenyl-methyl]-benzamide **132** (62.25g, 80%) m.p. 181-182°C (Found: C, 65.44; H, 4.57; N, 3.86. $C_{20}H_{16}BrNO$ requires C, 65.58; H, 4.40; N, 3.82); ν_{max} (nujol)/cm^{-1} 3316 (NH), 1624 (C=O), 1522, 1350, 1291, 752, 720, 696; δ_H(360MHz; d_6DMSO) 6.69 (1H, d, J 8.3, CH-N), 7.23-7.31 (4H, m, ArH), 7.33-7.38 (2H, m, ArH), 7.40-7.49 (3H, m, ArH), 7.52-7.58 (1H, m, ArH), 7.65 (2H, dd, J 8.0 & 1.2, ArH), 7.92-7.95 (2H, m, ArH), 9.33 (1H, d, J 8.3, NH); δ_C(50.32MHz; d_6DMSO) 56.1 (CH, CH-N), 123.7 (quat, CBr), 127.4 (CH), 127.8 (CH), 128.0 (CH), 128.3 (CH), 128.5 (CH), 129.4 (CH), 129.6 (CH), 131.5 (CH), 132.8 (CH), 134.2 (quat), 140.6 (quat), 141.2 (quat), 166.0 (quat, C=O); m/z (FAB; Thioglycerol) 368 (M+1), 366 (M+1), 287 (M - Br), 245 (M - PhCONH), 165 (M - Br - PhCONH), 77 (Ph).

(b) Benzoylation

Benzoyl chloride (4.70ml, 5.69g, 40.50mmol) was added to a mixture of (2-bromophenyl)-phenyl-methylamine **142a** (8.37g, 33.73mmol) and anhydrous sodium carbonate (3.93g, 37.1mmol) in dry DCM (250ml). After stirring overnight, the solvent was removed *in vacuo* and water (100ml) was added. Extraction with ethyl acetate (2 x 100ml), drying of the organic layer and evaporatiion to dryness gave a white solid. Crysallisation from ethanol-toluene gave white needles of *N*-[(2-bromophenyl)-phenyl-methyl]-benzamide **132** (9.88g, 80%), the physical and spectral characteristics of which were identical to an authentic sample.

N-[(2-Iodophenyl)-phenyl-methyl]-benzamide **133**

Benzoyl chloride (17.26ml, 20.88g, 0.149mol) was added to a mixture of (2-iodophenyl)-phenyl-methylamine **142b** (38.27g, 0.124mol) and anhydrous sodium carbonate (14.43g, 0.136mol) in dry DCM (750ml). After stirring overnight, the solvent was removed *in vacuo* and water (500ml) and hexane (250ml) were added. Filtration gave a pink solid which was crysallised from ethanol-toluene to give white needles of *N*-[(2-iodophenyl)-phenyl-methyl]-benzamide **133** (41.51g, 81%) m.p.183-4°C (Found: C, 58.07; H, 3.96; N, 3.35. $C_{20}H_{16}INO$ requires C, 58.13; H, 3.90; N, 3.39%); ν_{max} (nujol)/cm^{-1} 3225 (NH), 1631 (C=O), 1518, 1308, 1203, 873, 746, 698, 672; δ_H(200.13MHz; d_6DMSO) 6.55 (1H, d, J 8.2, CH-N), 7.07 (1H, td, J 7.4 & 2.0, ArH), 7.21-7.58 (10H, m, ArH), 7.89-7.98 (3H, m, ArH), 9.34 (1H, d, J 8.2, NH); δ_C(50.32MHz; d_6DMSO) 60.5 (CH, CH-N), 100.9 (quat, C-I), 127.3 (CH), 127.7 (CH), 128.1 (CH), 128.3 (CH), 128.5 (CH), 129.1 (CH), 129.4 (CH), 131.4 (CH), 134.2 (quat), 139.4 (CH), 140.8 (quat), 144.2 (quat), 165.9 (quat, C=O); m/z (FAB; Thioglycerol) 414 (M+1), 325, 293, 257, 199, 165 (M - I - PhCO NH_2), 105 (COPh), 77 (Ph).

Di-(2-bromo-phenyl)-phenyl-methyl ether

(2-Bromophenyl)-phenylmethanol **137a** (1.00g, 3.8mmol) and c.H_2SO_4 (0.93g, 9.6mmol) in di-*n*-butyl ether were heated to 50°C for 24hr. The reaction mixture was poured into saturated sodium carbonate solution (50ml), extracted with diethyl ether (2 x 25ml) and the combined organic layers were washed with saturated brine (15ml). Drying ($MgSO_4$) and removal of the solvent *in vacuo* gave a yellow semi-crystalline oil. Recrystallisation from ethyl acetate gave

white crystals of di-(2-bromo-phenyl)-phenyl-methyl ether (0.84g, 87%) m.p. 127-128.5°C (Found: C, 61.35; H, 4.08. $C_{26}H_{20}Br_2O$ requires C, 61.44; H, 3.97); ν_{max} (smear/cm^{-1}) 3061, 3029, 2918, 1600, 1566, 1493, 1438, 1254, 1183, 1024, 908, 749, 698; δ_H (200.13MHz; $CDCl_3$) 5.86 (2H, s, 2 x CH-O), 7.10-7.41 (14H, m, ArH), 7.51-7.72 (4H, m, ArH); δ_C (50.32MHz; $CDCl_3$) 78.6 (CH, CH-O), 123.7 (quat, C-Br) 127.4 (CH), 127.7 (CH), 128.1 (CH), 128.6 (quat), 128.9 (CH), 129.0 (CH), 132.6 (CH), 140.7 (quat); m/z 508 (M, 0.3%), 352 (35), 350 (35), 263 (70), 261 (73), 247 (65), 246 (58), 245 (66), 183 (68), 167 (68), 166 (75), 165 (100), 164 (96), 103 (69).

2. INVESTIGATION OF THE USE OF OPPOLZER'S SULTAM

2.1. Wadsworth-Emmons Route

2-(2-Bromo-pheny;)-[1,3]-dioxolane **145**

2-Bromobenzaldehyde (86.0g, 0.465mol), *p*-toluenesulphonic acid (1.00g, 5.30mmol) and ethylene glycol (80.0g, 1.29mol) were refluxed in benzene (200ml) for 24h, water being removed by means of a Dean-Stark trap. The solvent was removed *in vacuo* and the resulting yellow oil was distilled to give 2-(2-bromo-pheny;)-[1,3]-dioxolane **145** (99.7g, 94%) as a clear colourless oil, b.p. 102-3°C/0.75mmHg (lit.[115] 102°C/0.5mmHg), (Found: M^+, 227.9784. $C_9H_9{}^{79}BrO_2$ requires M 227.9784); ν_{max}(film)/cm^{-1} 3070, 2955, 2885, 1590, 1540, 1385, 1210, 1090; δ_H(80.13MHz; $CDCl_3$) 4.07 (4H, m, 2 x OCH_2), 6.08 (1H, s, O-CH-O), 7.06-7.65 (4H, m, ArH); δ_C(50.32MHz; $CDCl_3$) 65.2 (CH_2, 2xOCH_2), 102.3 (CH, O-CH-O) 122.7 (quat, C-Br), 127.2 (CH), 127.6 (CH), 130.4 (CH), 132.7 (CH), 136.3 (quat); m/z 229 (M^+, 54%), 227 (M^+, 61), 185 (24), 183 (21), 149 (30), 73 (100).

(2-[1,3]-Dioxolan-2-yl-phenyl)-phenylmethanol **147**

Benzaldehyde (10.0g, 94.2mmol) in anhydrous THF (20ml) was added dropwise to an ice-cooled solution of the Grignard reagent of **145** [prepared from magnesium turnings (2.23g, 91.7mmol) and 2-(2-bromo-pheny;)-[1,3]-dioxolane **145** (20.0g, 87.3mmol) in anhydrous THF (50ml)]. The reaction was stirred at room temperature for 0.5h and hydrolysed with saturated ammonium chloride solution until just clear. The organic layer was separated, dried ($MgSO_4$) and evaporated to dryness. Recrystallisation of the crude pale green

solid from ethyl acetate-cyclohexane gave white crystals of (2-[1,3]-dioxolan-2-yl-phenyl)-phenylmethanol **147** 16.95g, 76%), m.p. 109-109.5°C (Found: C, 74.20; H, 6.10. $C_{16}H_{16}O_3$ requires C, 74.50; H, 5.90%); ν_{max} (nujol)/cm^{-1} 3420 (br, OH), 1605, 1215, 1065, 1035, 945, 770; δ_H(80.13MHz; $CDCl_3$) 3.50 (1H, d, J 4.4, OH), 3.94-4.14 (4H, m, O-CH_2CH_2-O), 5.94 (1H, s, O-CH-O), 7.22-7.43 (8H, m, ArH), 7.50-7.66 (1H, m, ArH); m/z (FAB) 257 (M+1), 255 (M-1), 239, 311, 196, 195 (Base peak), 194, 178 (M-1-Ph), 165, 105, 77.

(2-[1,3]-Dioxolan-2-yl-phenyl)-phenylmethanone **148**

A solution of (2-[1,3]-dioxolan-2-yl-phenyl)-phenylmethanol **147** (5.00g, 19.5mmol) in anhydrous DCM (10ml) was added to a stirred suspension of pyridinium chlorochromate (6.31g, 29.3mmol) and anhydrous sodium acetate (0.48g, 5.85mmol) in anhydrous DCM (40ml) at room temperature. After 1.5hr, dry diethyl ether (50ml) was added and the supernatant liquid was filtered through a pad of silica. The filtrate was evaporated to dryness *in vacuo* to give a yellow oil which was recrystallised from ethyl acetate-cyclohexane to yield white needles of (2-[1,3]-dioxolan-2-yl-phenyl)-phenylmethanone **148** (3.45g, 70%), m.p. 49-50°C (Found M^+ 254.0937. $C_{16}H_{14}O_3$ requires 254.0193); ν_{max}(film)/cm^{-1} 3070, 2960, 2890, 1730 (C=O), 1600, 1455, 1270, 1075, 930, 705; δ_H(80.13MHz; $CDCl_3$) 3.85 (4H, s, O-CH_2CH_2-O), 6.00 (1H, s, O-CH-O), 7.28-7.84 (9H, m, ArH); δ_C(50.32MHz; $CDCl_3$) 65.0 (CH_2, O-CH_2CH_2-O), 101.3 (CH, O-CH-O), 126.9 (CH), 127.9 (CH), 128.2 (CH, *o*- & *m*-Ph), 129.9 (CH, 2 x CH), 132.9 (CH), 136.7 (quat.), 137.4 (quat.), 138.3 (quat.), 197.4 (quat., C=O);

m/z 254 (M^+, 21%), 209 (74), 182 (37), 181 (12), 165(19), 149 (43, M-PhCO), 105 (100, PhCO), 77 (29).

5-(2-Bromobenzyl)-1,3-dimethyl- 1,3,5-triazin-2-one **151**

To 2-bromobenzylamine hydrochloride (5.0g, 22.5mmol), dimethylurea (1.98g, 22.5mmol) and 37% formaldehyde solution (22.5ml, 300mmol) stirred at 40°C was added a solution of *N*-methylmorpholine (4.94ml, 44.9mmol) in 1,4-dioxane (5ml) and toluene (200ml). The mixture was refluxed (85°C) and the distillate was collected in a Dean-Stark trap. After 2.5h, during which 100ml of toluene was added to the reaction mixture, the temperature had risen to 110°C and 174ml of distillate had been collected. The solvent was removed *in vacuo* to leave a cloudy brown oil (6.08g). Chromatography on alumina with ethyl acetate as the eluant and crystallisation from toluene yielded 5-(2-bromobenzyl)-1,3-dimethyl- 1,3,5-triazin-2-one **151** (4.84g, 72%) as white needles, m.p. 95.5-96°C (Found: C, 48.41; H, 5.63; N, 14.02. $C_{12}H_{16}BrN_3O$ requires C, 48.33; H, 5.41; N, 14.09%); δ_H(200.13MHz; $CDCl_3$) 2.78 (6H, s, 2 x CH_3), 3.94 (4H, s, 2 x N-CH_2-N), 7.02-7.33 (3H, m, ArH), 7.45-7.49 (1H, m, ArH); δ_C(50.32MHz; $CDCl_3$) 32.1 (CH_3, 2 x NMe), 54.8 (CH_2), 67.5 (CH_2, 2 x N-CH_2-N), 124.4 (quat, CBr), 127.1 (CH, ArH), 128.8 (CH, ArH), 130.5 (CH, ArH), 132.7 (CH, ArH), 136.4 (quat), 155.5 (quat, urea C=O).

2.2.Boronic Acid Coupling Reactions

Ammonium *E*-3-Bromopropenoate

This was prepared by the method of Stack and Coates[116] by bubbling gaseous ammonia through a solution of *E*-3-bromopropenoic acid (7.0g, 50mmol) in anhydrous ether (200ml), giving ammonium E-3-bromopropenoate as a finely divided white solid (7.72g, 99%); ν_{max} (Nujol)/cm^{-1} 1610 (CO_2), 1380 (CO_2); δ_H(60MHz; d_6DMSO) 5.16 (4H, br. s, NH_4), 6.34 (1H, d, *J* 13.6, =CH), 7.08 (1H, d, *J* 13.6, =CH).

E-3-Bromopropenoyl Chloride

This was prepared according to the method of Stack and Coates[116] from ammonium *E*-3-bromopropenoate (8.75g, 56mmol) and oxalyl chloride (10.13ml, 118mmol) in anhydrous hexane (30ml). The crude product was distilled *in vacuo* to give E-3-bromopropenoyl chloride as a pale yellow oil (9.34g, 96%), b.p. 43-5°C/60mmHg (lit.[117] 74-6°C/80mmHg), ν_{max}(film)/cm^{-1} 3095, 1770 (C=O),1600, 1580, 1330, 1105, 990, 825, 755.

E-3-Bromopropenoic Acid

This was prepared by the method of Gryszkiewicz-Trochimowski *et al*[117] from propiolic acid (5.00g, 86.1mmol) and a 30% solution of hydrobromic acid (60ml). The crude product was crystallised from cyclohexane-ethyl acetate to give *E*-3-bromopropenoic acid (9.17g, 71%) as colourless needles, m.p. 114-5°C (lit.[117] 115-7°C) (Found M^+ 149.9317, $C_3H_3BrO_2$ requires 149.9317);

ν_{max}(smear)/cm^{-1} 1690 (C=O), 1605, 1295 (C-O); δ_H(80MHz; $CDCl_3$) 6.52 (1H, d, *J* 13.9, =CH), 7.74 (1H, d, *J* 13.9Hz, =CH), 10.99 (1H, br. s, CO_2H); δ_C(50.32MHz; $CDCl_3$) 128.0 (CH), 130.0 (CH), 169.6 (CO_2H); m/z (FAB) 149 (M^+), 133, 110, 90, 72, 62.

E-3-Bromo-1-(10,10-dimethyl-3,3-dioxo-3-thia-4-aza-tricyclo[5.2.1.$0^{1,5}$]dec-4-yl-prop-2-en-1-one **154a**

A solution of (+)-2,10-camphorsultam (2.0g, 9.28mmol) in anhydrous toluene (50 ml) was added dropwise at r.t. to a stirred suspension of sodium hydride (80% dispersion in mineral oil, 0.31g, 10.2mmol of hydride) in anhydrous toluene (25ml). After 1.5h a solution of *E*-3-bromoacryloyl chloride (3.22g, 10.2mmol) in anhydrous toluene (20ml) was added dropwise and the mixture stirred for 3h. Water (20ml) was added, after which the organic layer was separated and was washed with water and brine. After drying ($MgSO_4$), the solvent was removed *in vaccuo* and the crude product was recrystallised from ethyl acetate-hexane affording white crystals of *E*-3-bromo-1-(10,10-dimethyl-3,3-dioxo-3-thia-4-aza-tricyclo[5.2.1.$0^{1,5}$]dec-4-yl-prop-2-en-1-one **154a** (2.46g, 76%), m.p. 212-213°C (dec. 220°C) (Found; M^+, 349.0172 and 347.0198. $C_{13}H_{18}BrNO_3S$ requires M, 349.0173 and 347.0219); ν_{max}(nujol)/cm^{-1} 3075, 1675 (C=O), 1590, 1320 & 1130 (SO_2), 945, 765, 695; δ_H(80.13MHz, $CDCl_3$) 0.95 (3H, s, Me), 1.14 (3H, s, Me), 1.23-1.43 (2H, m), 1.84-1.94 (3H, m), 2.03-2.12 (2H, m), 3.46 (1H, s, SO_2 CH_2), 3.89 (1H, dd, *J* 6.5 and 6.5, N-CH), 7.21 (1H, d, *J* 13.2, =CHBr), 7.69 (1H, d, *J* 13.2, =CH-CON); δ_C(50.32MHz,$CDCl_3$) 19.7

(CH_3), 20.6 (CH_3), 26.3 (CH_3), 32.6 (CH_2), 38.1 (CH_2), 44.4 (CH), 47.7 (quat.), 48.5 (quat.), 52.9 (CH_2, CH_2SO_2), 64.9 (CH, CH-N), 127.9 (CH, 2 x =CH), 161.5 (quat., C=O); m/z 349 (M, 3%), 347 (M, 3), 204 (36, M-SO_2), 135 (100), 134 (44), 133 (98), 108 (28), 93(18).

2-(N-Benzoylaminomethyl)phenylboronic acid **155**

This was prepared according to the method of Reece[97] from *N*-(2-bromobenzyl)-benzamide **199** (5.00g, 17.23mmol), methyllithium (1.5meq), tert-butyllitium (3.0meq) and triisopropyl borate (5.7meq). Recrystallisation from DMSO-water gave pale cream needles of 2-(N-benzoyaminomethyl) phenyl-boronic acid **155** (3.40g, 77%). The spectroscopic details of this were identical to an authentic sample provided by Dr. Reece.

2.3. *via* the o-Benzylcinnamate 157

(2-Benzyl)-benzyl alcohol **159**

This was prepared according to the method of Nystrom and Brown[118] by the reduction of 2-benzylbenzoic acid (Aldrich) with lithium aluminium hydride. Kugelrohr distillation (180°C/0.02mmHg) gave (2-benzyl)-benzyl alcohol **159** (96%) as a low melting white solid, the spectral characteristics of which were identical to an authentic sample (Aldrich).

2-Benzylbenzaldehyde **160**

This was prepared by the method of Durst *et al*[119] using 2-benzylbenzyl alcohol (1.0g, 5.0mmol) and aqueous chromic acid (5.0mmol). The crude product, a pale yellow oil, was found to be greater than 99% pure by glc. The crude 2-benzylbenzaldehyde **160** was used without further purification and had spectral characteristics identical to the reported data.[119] ν_{max}(film)/cm^{-1} 3065, 3030, 2860, 2750, 1695 (C=O), 1600, 1455, 1210, 735; δ_H(80.13MHz; $CDCl_3$) 4.45 (2H, s, CH_2), 7.12-7.55 (8H, m, ArH), 7.81-7.92 (1H, m, ArH), 10.26 (1H, s, CHO).

Ethyl 3-(2-benzyl-phenyl)-acrylate **157**

Sodium (1.30g, 56.4mmol) was added portionwise to superdry ethanol (100ml) to give an ethanolic solution of sodium ethoxide. Triethyl phosphonoacetate (11.21g, 50.0mmol, Aldrich) was added dropwise, followed by 2-benzylbenzaldehyde **160** (8.55g, 43.0mmol) in superdry ethanol (35ml). The reaction was stirred at room temperature for 0.5hr and then diluted to 450ml

with water. The mixture was extracted with DCM, the organic layer dried (Na_2SO_4) and the solvent was removed in vaccuo. Wet flash chromatography on silica gel with DCM as the eluant yielded ethyl 3-(2-benzyl-phenyl)-acrylate **157** (11.36g, 98%) b.p. 150°C/0.02mmHg (Kugelrohr) (Found: C, 81.30; H, 6.92. $C_{18}H_{18}O_2$ requires C, 81.17; H, 6.81%); ν_{max} (film)/cm^{-1} 3065, 3030, 2985, 1715 (C=O), 1635, 1605, 1455, 1315, 1175, 1035, 980, 770, 700; δ_H(200.13MHz;$CDCl_3$) 1.35 (3H, t, J 7.1, CH_3), 4.16 (2H, s, $ArCH_2Ph$), 4.27 (2H, q, J 7.1, Ethyl-CH_2), 6.36 (1H, d, J 15.8, =$CHCO_2$), 7.14-7.39 (8H, m, ArH), 8.07 (1H, d, J 15.8, =CHAr); δ_C(50.32MHz; $CDCl_3$) 14.1 (Me), 38.8 (CH_2, $ArCH_2Ph$), 60.2 (CH_2, OCH_2), 119.6 (CH, =CH-Ester), 126.0 (CH), 126.5 (CH), 126.7 (CH), 128.3 (CH, o- or m-Ph), 128.5 (CH, o- or m-Ph), 129.9 (CH), 130.6 (CH), 133.3 (quat), 139.9 (quat), 141.9 (CH, =CHAr), 166.6 (quat, C=O); m/z 266 (M^+, 10.9%), 221 (7.8, M-OEt), 193 (14, M-CO_2Et), 192 (39, M-HCO_2Et), 178 (100), 175 (15), 115 (22), 91 (24).

Ethyl 3-[2-(bromo-phenyl-methyl)-phenyl]-acrylate **161**

ethyl 3-(2-benzyl-phenyl)-acrylate **157** (4.00g, 15.0mmol) and benzoyl peroxide (0.055g, 0.23mmol) were dissolved in dry carbon tetrachloride (30ml) and heated to reflux. N-Bromosuccinimide (3.29g, 18.5mmol) and benzoyl peroxide (0.065g, 0.27mmol) were added in three portions over three hours. The mixture was refluxed overnight, cooled and the succinimide was filtered off. The filtrate was washed with water (20ml), dried ($MgSO_4$) and evaporated to dryness to give ethyl 3-[2-(bromo-phenyl-methyl)-phenyl]-acrylate **161** as a clear yellow oil (5.18g, 100%). The product was too thermally unstable to be distilled and

decomposed on both silica and alumina. Thus, the product was used without further purification. ν_{max}(film)/cm^{-1} 3065, 2985, 2940, 1715 (C=O), 1625, 1455, 1315, 1175, 1030, 980, 765, 700; δ_H(200MHz; $CDCl_3$) 1.34 (3H, t, J 7.1, CH_3), 4.27 (2H, J 7.1, CH_2), 6.35 (1H, d, J 15.7, =$CHCO_2R$), 6.63 (1H, s, CHBr), 7.12-7.62 (9H, m, ArH), 8.11 (1H, d, J 15.7, =CHAr); δ_C(50.32MHz; $CDCl_3$) 14.2 (CH_3), 51.5 (CH, CHBr), 60.6 (CH_2), 121.3 (CH, =$CHCO_2$), 127.1 (CH), 128.0 (CH), 128.5 (CH), 130.0 (CH), 132.6 (quat.), 139.5 (quat.), 140.9 (CH, =CHAr), 142.1 (quat.), 166.4 (quat., C=O); m/z(FAB) 346 (M+1), 344 (M+1), 265 (M-Br), 202. 191. 165. 147. 136. 115. 106. 76 (Base peak).

2.4. *via* Heck Reaction I

E-3-[2-Benzoylamino-phenyl-methyl)-phenyl]-acrylic acid **156**

N-[(2-Bromophenyl)-phenyl-methyl]-benzamide **132** (0.50g,1.37mmol), acrylic acid (0.15g,2.05mmol), palladium(II) acetate (0.02g, 0.9mmol) and tri-*o*-tolylphosphine (0.16g, 0.53mmol) in dry ethylamine (10ml) were heated under reflux for 5hrs. The reaction was poured into hydrochloric acid (2M, 25ml) and extracted with ethyl acetate (2 x 20ml). The organic layer was washed with water, dried ($MgSO_4$) and the solvent was removed *in vacuo*. Wet flash chromatography on silica gel with ethyl acetate-hexane-acetic acid (40:60:1) as the eluent yielded *E*-3-[2-benzoylamino-phenyl-methyl)-phenyl]-acrylic acid **156** (0.21g,43%) m.p. 209°C (Found: $(M+1)^+$, 358.14430. $C_{23}H_{19}NO_3$ requires M+1, 358.14431); ν_{max} (nujol) 3319 (NH), 3028, 2688, 1686 (Acid C=O), 1635 (Amide C=O), 1520, 1420, 1314, 1220, 1001, 763, 701; δ_H(80MHz; d_6DMSO) 6.40 (1H, d, J 15.7, $=CHCO_2$), 6.74 (1H, d, J 8.2, CH-N), 7.19-7.55 (11H, m, ArH), 7.67-7.98 (3H, m, ArH), 7.96 (1H, d, J 15.7, =CHAr), 9.34 (1H, d, J 8.2, NH); δ_C(50.32MHz; d_6DMSO) 52.9 (CH, CH-N), 122.0 (CH, =CH-Acid), 127.0 (CH), 127.3 (CH), 127.7 (CH), 127.9 (CH), 128.3 (CH), 128.6 (CH), 130.0 (CH), 131.4 (CH), 133.2 (quat), 134.3 (quat), 140.6 (CH, =CH-Ar), 141.0 (quat), 141.1 (quat), 165.9 (quat, C=O), 167.5 (quat, C=O); m/z (FAB; Thioglycerol) 358 (M+1), 345, 274, 257, 232, 165 (M - $C{=}CCO_2H$ - $PhCONH_2$), 105 (PhCO), 77 (Ph).

1-(10,10-Dimethyl-3,3-dioxo-3-thia-4-aza-tricyclo[5.2.1.$0^{1,5}$]dec-4-yl)-3-phenyl-prop-2-en-1-one **166**

(a) With Cinnamic Anhydride

Butyl lithium (0.33ml of a 2.5M solution in hexanes, 0.84mmol) was added to a solution of (+)-2,10-camphorsultam (0.15g, 0.70mmol) in dry THF (10ml) at -10°C. After 10mins this solution was added via a syringe to a solution of cinnamic anhydride (0.23g, 0.84mmol) in dry THF (10ml) at -10°C. The reaction was stirred at -10°C for 30mins after which satd. ammonium chloride solution (10ml) and DCM (20ml) were. The organic layer was separated and washed with sodium bicarbonate solution and brine. Drying ($MgSO_4$) and rotary evaporation gave a yellow solid. Dry flash chromatography on silica gel with diethyl ether-petroleum ether (0-20%) as the eluant gave white crystals of 1-(10,10-dimethyl-3,3-dioxo-3-thia-4-aza-tricyclo[5.2.1.$0^{1,5}$]dec-4-yl)-3-phenyl-prop-2-en-1-one **166** (0.18g, 62%), m.p. 170-170.5°C (Found: C, 65.91; H, 7.01; N, 4.05. $C_{19}H_{23}NO_3S$ requires C, 66.06; H, 4.71; N, 4.05%); ν_{max} (nujol)/cm^{-1} 1677 (C=O), 1629 (C=C str), 1330 (SO_2), 1215, 1115, 990; δ_H(200.13MHz; $CDCl_3$) 0.96 (3H, s, Me), 1.18 (3H, s, Me), 1.27-1.48 (2H, m), 1.87-2.02 (3H, m), 3.50 (2H, d, J 4.5, SO_2CH_2), 3.98 (1H, dd, J 7.1 & 5.5, CH-N), 7.16 (1H, d, J 15.5, =CH-CON), 7.33-7.40 (3H, m, ArH), 7.52-7.59 (2H, m, ArH), 7.77 (1H, d, J 15.5, =CHAr); δ_C(50.32MHz; $CDCl_3$) 19.8 (CH_3), 20.7 (CH_3), 26.4 (CH_2), 32.7 (CH_2), 38.4 (CH_2), 44.5 (CH), 47.7 (quat), 48.4 (quat), 53.0 (CH_2, SO_2CH_2), 65.1 (CH, NCH), 117.3 (CH, =CH-Amide), 128.5 (CH, m-Ph), 128.7 (CH, *o*-Ph), 130.5 (CH, *p*-Ph), 134.1 (quat, *ipso* -Ph), 145.5 (CH,

=CHPh), 164.1 (quat, C=O); m/z (FAB; Thioglycerol) 346 (M+1), 270, 216, 135, 131 (M-HNXc), 107, 77.

(b) *via* Heck Reaction

This was prepared by the method of Vallgarda[86] to give 1-(10,10-dimethyl-3,3-dioxo-3-thia-4-aza-tricyclo[5.2.1.$0^{1,5}$]dec-4-yl)-3-phenyl-prop-2-en-1-one **166** in 90% yield. The physical and spectral properties of this were identical to an authentic sample.

Carbonic acid {3-[2-(benzoylamino-phenyl-methyl)-phenyl]-acryloyl} ester ethyl ester **168**

Ethyl chloroformate (6.07mg, 0.056mmol) was added to *E*-3-[2-benzoylamino-phenyl-methyl)-phenyl]-acrylic acid **156** (20mg, 0.056mmol) and triethylamine (5.66mg, 0.056mmol) in d_8-THF at 0°C. ^{1}H n.m.r.indicated complete conversion to carbonic acid {3-[2-(benzoylamino-phenyl-methyl)-phenyl]-acryloyl} ester ethyl ester **168** within 2 hours. δ_H (250.13MHz; d_8-THF) 1.20 (3H, t, *J* 7.2, CH_3), 4.17 2H, q, *J* 7.2, O=CH_2), 6.35 (1H, d, *J* 15.5, =$CHCO_2$), 6.78 (1H, d, *J* 7.0, CH-N), 7.13-7.36 (11H, m, ArH), 7.66-7.69 (1H, m, ArH), 7.76-7.80 (2H, m, ArH), 8.18 (1H, d, *J* 15.5, =CHAr), 8.37 (1H, d, *J* 8.0, NH).

3-[2-(Benzoylamino-methyl)-phenyl]- acrylic acid 2,3,4,5,6-pentafluoro-phenyl ester **172**

Diisopropylcarbodiimide (0.053g, 0.42mmol) was added to 3-[2-(Benzoylamino-methyl)-phenyl]- acrylic acid (0.10g, 0.28mmol) and pentafluorophenol (0.155g, 0.84mmol) in dry THF (10ml) at 0°C. The reaction was stirred at 0°C for 2hr

and the at 20°C overnight, after which the solvent was removed *in vacuo*. DCM (25ml) was added and this was washed with saturated sodium carbonate solution (2 x 10ml) and then brine (10ml). The organic layer was dried and the solvent was removed *in vacuo*. Chromatography on silica gel with ethyl acetate-hexane (1:1) as the eluent yielded 3-[2-(benzoylamino-methyl)-phenyl]- acrylic acid 2,3,4,5,6-pentafluoro-phenyl ester **172** (0.081g, 60%) as a white solid which was too reactive for elemental analysis and failed to give a parent ion in the mass spectrum; ν_{max} (nujol)/cm^{-1} 3315 (NH), 1759 (Ester C=O), 1636 (Amide C=O), 1521, 1261, 1115, 1001, 802, 698; δ_H(250.134MHz; d_6-DMSO) 6.76 (1H, d, *J* 8.0, CH-N), 6.86 (1H, d, *J* 15.5, =CH-Ester), 6.96-7.48 (11H, m, ArH), 7.82-7.86 (2H, m, ArH), 8.31 (1H, d, *J* 15.5, =CH-Ar), 9.41 (1H, d, *J* 8.0, NH).

N-[2-(10,10-Dimethyl-3,3-dioxo-3-thia-4-aza-tricyclo[5.2.1.0^{1,5}]dec-4-yl)-2-oxo-ethyl]-isobutyramide **175**

To a solution of (+)-2,10-camphorsultam (0.50g, 2.32mmol) in dry toluene (15ml) was added trimethylaluminium (2.0M in hexane, 1.4ml, 2.78mmol) and the reaction was stirred at room temperature for 15min. isobutyrylamino-acetic acid methyl ester (0.52g, 3.25mmol) in dry toluene was added dropwise and the solution was heated to 50°C for 4hr. Methanol (1ml) was added, followed by dilute hydrochloric acid (10ml). The organic phase was separated, washed with satd. sodium bicarbonate solution (10ml) and water (10ml) and dried (Na_2SO_4). Evaporation of the solvent and recrystallisation from ethanol-hexane gave large white cubes of *N*-[2-(10,10-dimethyl-3,3-dioxo-3-thia-4-aza-tricyclo[5.2.1.0^{1,5}]-

dec-4-yl)-2-oxo-ethyl]-isobutyramide **175** (0.75g, 95%), m.p. 138-9°C (Found: C, 56.08; H, 7.74; N, 8.02. $C_{16}H_{25}N_2O_4S$ requires C, 56.28; H, 7.38; N, 8.20%); ν_{max} ($CHBr_3$)/cm^{-1} 3434 (NH), 2964, 1680 (C=O), 1669 (C=O), 1510, 1336 (SO_2), 1272, 1061, 779; δ_H(250MHz; $CDCl_3$) 0.91 (3H, s, sultam-Me), 1.07 (3H, s, sultam-Me), 1.10 (6H, d, J 6.9, isopropyl Me), 1.23-1.39 (2H, m), 1.81-1.87 (3H, m), 1.94-2.16 (2H, m), 2.38 (1H, hep, J 6.9, isopropyl CH), 3.38 (1H, d, J 13.9, SO_2CH_α), 3.44 (1H, d, J 13.9, SO_2CH_β), 3.80 (1H, dd, J 7.7 and 5.0, CHN), 4.34 (2H, dd, J 5.8 and 3.0, CH_2N), 6.12 (1H, br t, J 5.0, NH).

3-[2-(Benzoylamino-phenyl-methyl)-phenyl]-acrylic acid ethyl ester **176**

N-[(2-Iodophenyl)-phenyl-methyl]-benzamide **133**, (0.50g, 1.21mmol), ethyl acrylate (0.242g, 2.42mmol), palladium acetate (0.10g, 0.48mmol) and tri-*o*-tolyl phosphine (0.015g, 0.024mmol) in triethylamine (15ml) were heated under reflux for 6hr. Once cool the reaction mixture was poured into 2M HCl (50ml) and extracted with ethyl acetate (3 x 50ml). The combined organic layers were filtered (Celite), washed with water and dried ($MgSO_4$). Removal of the solvent *in vacuo* and column chromatography on silica (30% ethyl acetate-hexane as eluant) followed by recrystallisation from toluene gave white needles of 3-[2-(benzoylamino-phenyl-methyl)-phenyl]-acrylic acid ethyl ester **176** (0.23g, 50%) (Found: C, 77.64; H, 6.32; N, 3.42. $C_{25}H_{23}NO_3$ requires C, 77.90; H, 6.01; N, 3.63%);ν_{max} (nujol/cm^{-1}) 3344 (NH), 1693 (Ester C=O), 1658 (Amide C=O), 1372, 1322, 1203; δ_h(250.134MHz;d_6-DMSO) 1.20 (3H, t, *J* 7.0, Me), 4.12 (2H, q, *J* 7.0, O-CH_2), 6.50 (1H, d, *J* 15.5, =CHEster), 6.71 (1H, d, *J* 8.0, CH-N),

7.26-7.54 (12H, m, ArH), 7.69-7.94 (2H, m, ArH), 7.98 (1H, d, *J* 15.5, =CHAr), 9.41 (1H, d, *J* 8.0, NH).

5-[(2-Bromo-phenyl)-phenyl-methyl]-1,3-dimethyl-[1,3,5]triazinan-2-one **178**

To a mixture of 2-bromodiphenylmethylamine hydrochloride (1.00g, 3.35mmol), 1,3-dimethylurea (0.30g, 3.35mmol, Aldrich) and 37% aqueous formaldehyde (5.0ml, 67mmol) at 40°C was added a solution of N-methylmorpholine (0.74ml, 0.68g, 6.7mmol) in 1,4-dioxane (1ml) and toluene (4ml). Azeotropic removal of water at reflux for 2.5hr, followed by removal of the solvent in vaccuo gave a pale brown oil. Wet flash chromatography on silica gel with acetone-chloroform as the eluant gave a clear, colourless oil which crystallised when scratched. Recrystallisation from toluene-hexane gave white needles of 5-[(2-bromo-phenyl)-phenyl-methyl]-1,3-dimethyl-[1,3,5]triazinan-2-one **178** (0.61g, 49%) m.p. 128-128.5°C (Found: C, 57.83; H, 5.62; N, 11.16. $C_{18}H_{20}N_3O$ requires C, 57.76; H, 5.39; N, 11.23); ν_{max} (nujol)/cm^{-1} 1656 (C=O),1512, 1294, 1023, 848, 748, 724, 702; δ_H(200.13MHz; $CDCl_3$) 2.66 (6H, s, 2 x Me), 4.01 (4H, s, 2 x CH_2), 5.63 (1H, s, CH-N), 7.00-7.08 (1H, m, ArH), 7.19-7.34 (4H, m, ArH), 7.41-7.47 (3H, m, ArH), 7.84 (1H, dd, J 7.8 & 1.7, ArH); δ_C(50.32MHz; $CDCl_3$) 32.1 (CH_3, 2 x NMe), 64.1 (CH, CH-N), 65.9 ((CH_2, 2 x N-CH_2-N), 124.2 (quat, C-Br), 127.6 (CH,2 x CH) 128.4 (CH, 2 x CH), 128.5 (CH, 2 x CH), 133.0 (CH), 139.0 (quat), 140.2 (quat), 155.7 (quat, C=O); m/z (Thioglycerol) 376 (M+1), 374 (M+1), 294 (M-Br), 245, 167, 166, 165, 91, 76, 72, 43 (Base peak).

2.5. *via* Heck Reaction II

1-(10,10-Dimethyl-3,3-dioxo-3-thia-4-aza-tricyclo[5.2.1.$0^{1,5}$]dec-4-yl-prop-2-en-1-one **52**

A solution of (+)-2,10-camphorsultam (2.0g, 9.28mmol) in anhydrous toluene (50 ml) was added dropwise at r.t. to a stirred suspension of sodium hydride (80% dispersion in mineral oil, 0.36g, 12.08mmol of hydride) in anhydrous toluene (30ml). After 0.5h, a solution of acryloyl chloride (1.26g, 13.93mmol) in anhydrous toluene (50ml) was added dropwise and the mixture stirred for 2h. After water (50ml) was added, the organic layer was separated and was washed with water and brine. After drying ($MgSO_4$), the solvent was removed *in vaccuo*. Chromatography of the crude product on silica gel with ethyl acetate-hexane as the eluant yielded 1-(10,10-dimethyl-3,3-dioxo-3-thia-4-aza-tricyclo-[5.2.1.$0^{1,5}$]dec-4-yl-prop-2-en1-one **52** (1.37g, 55%)as a white solid which was used without further purification. A sample was recrystallised from ethanol-hexane affording white needles, m.p. 190°C (Found; C, 57.85; H, 7.19; N, 5.20. $C_{13}H_{19}NO_3S$ requires C, 57.97; H, 7.11; N, 5.20); ν_{max}(nujol)/cm^{-1} 1674 (C=O),1618, 1329 & 1164 (SO_2), 1132, 1060, 801, 770; δ_H(80.13MHz, $CDCl_3$) 0.96 (3H, s, Me), 1.15 (3H, s, Me), 1.26-1.53 (2H, m), 1.79-1.94 (3H, m), 2.07-2.18 (2H, m), 3.45 (1H, s, SO_2 CH_2), 3.92 (1H, dd, *J* 6.3 and 6.3, N-CH), 5.82 (1H, dd, *J* 9.8 and 2.3, $=CH_{trans}$), 6.45 (1H, dd, *J* 16.6 and 2.3, $=CH_{cis}$), 6.87 (1H, dd, *J* 16.6 and 6.3, $=CH_{gem}$); δ_C(50.32MHz,$CDCl_3$) 19.6 (CH_3), 20.7 (CH_3), 26.3 (CH_2), 32.7 (CH_2), 38.3 (CH_2), 44.5 (CH), 47.6 (quat.), 48.4 (quat.), 53.0 (CH_2, CH_2SO_2), 65.0 (CH, CH-N), 127.6 (CH, =CHR), 131.3 (CH_2, $=CH_2$), 163.9 (quat., C=O); m/z (FAB) 270 (M+1), 228 (Base peak), 135, 107, 91, 79.

3. INVESTIGATION OF OTHER POTENTIAL CHIRAL DIRECTING GROUPS

3.1. A Chiral Group δ to the Nitrile Ylide

1-Phenyl-3-propenone

This was prepared by steam distillation of 3-dimethylaminopropriophenone hydrochloride (50.0g, 0.234mol).Solid sodium chloride was added to the distillate which was then extracted with diethyl ether. The organic layer was separated, dried ($MgSO_4$) and the solvent removed *in vacuo* to give a yellow oil which was Kugelrohr distilled *in vacuo* yielding 1-phenyl-3-propenone (10.92g, 35%) as a pale yellow oil, b.p. 50°C (oven temp.)/0.1mm/Hg (lit.[120] */*mmHg); ν_{max}(film)/cm^{-1} 3080, 1672 (C=O), 1608, 1233; δ_H(360.136MHz; $CDCl_3$) 5.92 (1H, dd, J 10.6 and 1.7, H_{trans}), 6.43 (1H, dd, J 17.1 and 1.7, H_{cis}), 7.15 (1H, dd J 17.1 and 10.6, H_{gem}), 7.44-7.49 (2H, m, *m*-ArH), 7.54-7.59 (1H, m, *p*-ArH), 7.92-7.95 (2H, m, *m*-ArH); δ_C(50.32MHz; $CDCl_3$) 128.4 (CH, *o* & *m*), 130.0 (CH_2), 132.1 (CH), 132.8 (CH), 137.0 (quat, *ipso*), 190.8 (quat, C=O).

3.2. Amides as Potential Chiral Directing Groups

N-({2-[2-(Dimethyl-carbamoyl)-vinyl]-phenyl}-phenyl-methyl)-benzamide **187**

This was prepared by the method of Spencer[80] from *N*-[(2-iodophenyl)-phenyl-methyl]-benzamide **133** (2.00g, 5.4mmol), *N,*N-dimethyl-acrylamide (1.35g, 13.6mmol), triethylamine (20ml), palldium acetate (0.07g, 0.3mmol), tri-*o*-tolyl phosphine (0.55g, 1.8mmol) and DMF (10ml). Continuous extraction of the crude product with chloroform gave white needles of *N*-({2-[2-(dimethyl-carbamoyl)-vinyl]-phenyl}-phenyl-methyl)-benzamide **187** (1.03g, 49%) m.p. 218-9°C (Found: C, 77.83; H, 6.57; N, 7.22. $C_{25}H_{24}N_2O_2$ requires C, 78.10; H, 6.29; N, 7.29); ν_{max})nujol/cm^{-1}) 3251 (NH), 1650 (2 x C=O), 1598, 1536, 703; δ_H (360.136MHz; d_6-DMSO) 2.89 (3H, s, Me), 3.07 (3H, s, Me), 6.72 (1H, d, *J* 8.3, CH-N), 7.04 (1H, d, *J* 15.4, =CHAmide), 7.21-7.53 (11H, m, ArH), 7.76-7.93 (3H, m, ArH), 7.80 (1H, d, *J* 15.4, =CHAr), 9.35 (1H, d, *J* 8.3, NH); δ_c (50.32MHz; d_6-DMSO) 35.4 (CH_3, NMe), 36.9 (CH_3, NMe), 52.9 (CH, CH-N), 121.2 (CH, =CHC[O]N), 127.1 (CH), 127.3 (CH), 127.8 (CH), 127.9 (CH), 128.3 (CH), 128.6 (CH), 129.4 (CH), 131.5 (CH), 134.0 (quat), 134.2 (quat), 137.7 (CH, =CHAr), 140.6 (quat), 141.5 (quat), 165.3 (quat, C=O), 165.9 (quat, C=O); m/z (FAB; Thioglycerol) 385 (M+1), 338, 322, 267, 192, 179, 165, 105, 103, 76, 71.

3.3. Esters as Potential Chiral Directing Groups

3-[2-(Benzoylamino-phenyl-methyl)-phenyl]-acrylic acid methyl ester **190**

This was prepared by the method of Spencer[80] from *N*-[(2-iodophenyl)-phenyl-methyl]-benzamide **133** (4.00g, 9.68mmol), methyl acrylate (2.50g, 29.0mmol), triethylamine (35ml), palldium acetate (0.11g, 0.48mmol), tri-*o*-tolyl phosphine (0.88g, 2.9mmol) and DMF (15ml). Recrystallisation of the crude product from toluene gave white needles of 3-[2-(benzoylamino-phenyl-methyl)-phenyl]-acrylic acid methyl ester **190** (3.14g, 83%) m.p. 151-2°C (Found: C, 77.32; H, 5.86; N, 3.85. $C_{24}H_{21}NO_3$ requires C, 77.61; H, 5.70; N, 3.77); ν_{max} (nujol/cm^{-1}) 3313 (NH), 1702 (Ester C=O), 1634 (Amide C=O), 1521, 1584; δ_H(80.13MHz; $CDCl_3$) 3.68 (3H, s, OMe), 6.49 (1H, d, *J* 15.8, =CHEster), 6.74 (1H, d, *J* 8.3, CH-N), 7.20-7.56 (11H, m, ArH), 7.71-7.98 (3H, m, ArH), 8.02 (1H, d, *J* 15.8, =CHAr), 9.36 (1H, d, *J* 8.3, NH); δ_c(90.556MHz; $CDCl_3$) 51.5, (CH, CH-N), 54.6 (CH_3, OMe), 120.4 (CH, =CHEster, 126.9 (CH), 127.2 (CH), 127.3 (CH), 127.5 (CH), 127.6 (CH), 127.8 (CH), 128.4 (CH), 128.7 (CH), 129.2 (CH), 131.5 (CH), 133.3 (quat), 140.0 (quat), 140.4 (quat), 141.6 (CH, =CHAr), 166.1 (quat, C=O), 166.6 (quat, C=O); m/z (FAB; thioglycerol) 372 (M+1), 321, 266 (M - PhCO), 167, 115, 105 (Base peak, PhCO), 76.

3-{2-[(Chloro-phenyl-methyleneamino)-phenyl-methyl]-phenyl}-acrylic acid methyl ester **191**

3-[2-(benzoylamino-phenyl-methyl)-phenyl]-acrylic acid methyl ester **190** (0.27g, 0.73mmol) and thionyl chloride (1ml) in anhydrous diethyl ether were heated under reflux for 8hr. The solvent was removed *in vacuo* to give 3-{2-

[(chloro-phenyl-methyleneamino)-phenyl-methyl]-phenyl}-acrylic acid methyl ester **191** as a yellow oil which was used without further purification. δ_H(80.13MHz; $CDCl_3$) 3.77 (3H, s, Ome), 6.23 (1H, d, *J* 15.8, =CH-Ester), 6.51 (1H, s, CH-N), 7.16-7.74 (11H, m, ArH), 8.01-8.19 (3H, m, ArH), 8.31 (1H, d, *J* 15.8, =CHAr).

1,3-Diphenyl-5*H*-benz[*c*]azepine-4-carboxylic acid methyl ester **193**

3-{2-[(Chloro-phenyl-methyleneamino)-phenyl-methyl]-phenyl}-acrylic acid methyl ester **191** (0.51g, 1.35mmol) was dissolved in anhydrous THF (50ml) and cooled to -78°C. Frshly distilled potassium *tert*-butoxide (0.55g, 4.46mmol) in anhydrous THF (3ml) was added in three portions over 1hr. The reaction was maintained at -78°C for one hour and then allowed to warm to r.t. Saturated ammonium chloride solution (20ml) was added and stirred vigorously. Ethyl acetate (50ml) was added, the organic layer was separated and dried with magnesium sulphate. The solvent was removed *in vacuo* and the resultant yellow oil was subjected to column chromatography on silica (ethyl acetate-hexane 3:10 as eluant) to give a yellow solid. Kugelrohr distillation (oven temp 230°C/0.05mmHg) gave a yellow solid identified as 1,3-diphenyl-5*H*-benz[*c*]azepine-4-carboxylic acid methyl ester **193** (0.38g, 83%), m.p. 169-170°C (from toluene) (Found M^+, 354.14940. $C_{19}H_{17}NO_2$ requires M, 354.14939); X-ray data below; ν_{max} (smear/cm^{-1}) 3058, 2943, 2850, 1694 (C=O), 1600, 1554, 1345, 1282, 788; δ_H(360.136MHz; $CDCl_3$) 3.09 (1H, d, *J* 13.8, ArCH), 3.52 (3H, s, Me), 3.82 (1H, d, *J* 13.8, ArCH), 7.23-7.56 (12H, m, ArH), 7.74-7.56 (2H, m, ArH); δ_c(50.32MHz; $CDCl_3$) 33.4 (CH_2), 51.3 (CH,

Ome), 116.4 (quat), 125.9 (CH), 126.6 (CH), 127.6 (CH), 128.0 (CH), 128.1 (CH), 128.9 (CH), 129.9 (CH), 130.6 (CH), 131.4 (quat), 131.5 (CH), 138.3 (quat), 139.2 (quat), 144.5 (quat), 153.5 (quat), 165.2 (quat, C=O or C=N), 168.5 (quat, C=O or C=N); m/z (FAB; thioglycerol) 354 (M+1), 294 (M - OMe), 250, 191, 165, 90, 77.

Bond	Bond Length/Å	Bond	Bond Length/Å
C(1)-N(2)	1.297	C(1)-C(9A)	1.481
C(1)-C(11)	1.488	N(2)-C(3)	1.403
C(3)-C(4)	1.345	C(3)-C(31)	1.472
C(4)-C(5)	1.516	C(4)-C(41)	1.463
C(5)-C(5A)	1.501	C(5A)-C(6)	1.387
C(5A)-C(9A)	1.403	C(6)-C(7)	1.379
C(7)-C(8)	1.370	C(8)-C(9)	1.375
C(9)-C(9A)	1.394	C(41)-C(42)	1.203
C(41)-O(43)	1.336	O(43)-C(44)	1.445

Bond Lengths in 1,3-diphenyl-5*H*-benz[*c*]azepine-4-carboxylic acid methyl ester.

Atoms	Bond Angle/°	Atoms	Bond Angle/°
N(2)-C(1)-C(9A)	124.7	N(2)-C(1)-C(11)	115.8
C(9A)-C(1)-C(11)	119.4	C(1)-N(2)-C(3)	126.7
N(2)-C(3)-C(4)	123.1	N(2)-C(3)-C(31)	111.4
C(4)-C(3)-C(31)	125.4	C(3)-C(4)-C(5)	119.3
C(3)-C(4)-C(41)	123.8	C(5)-C(4)-C(41)	116.9
C(4)-C(5)-C(5A)	108.8	C(5)-C(5A)-C(6)	121.9
C(5)-C(5A)-C(9A)	118.8	C(6)-C(5A)-C(9A)	119.3
C(5A)-C(6)-C(7)	120.6	C(6)-C(7)-C(8)	120.1
C(7)-C(8)-C(9)	120.6	C(8)-C(9)-C(9A)	120.3
C(1)-C(9A)-C(5A)	120.3	C(1)-C(9A)-C(9)	120.7
C(5A)-C(9A)-C(9)	119.1	C(1)-C(11)-C(12)	119.2
C(1)-C(11)-C(16)	120.7	C(3)-C(31)-C(32)	120.7
C(3)-C(31)-C(36)	119.2	C(4)-C(41)-O(42)	123.8
C(4)-C(41)-O(43)	113.7	O(42)-C(41)-O(43)	122.4
C(41)-O(43)-C(44)	116.7		

Bond Angles in 1,3-diphenyl-5*H*-benz[*c*]azepine-4-carboxylic acid methyl ester.

Atoms				Torsion Angle/°	Atoms				Torsion Angle/°
C9A	C1	N2	C3	-2.6	C9A	C1	C11	C12	-143.7
C11	C1	N2	C3	-179.1	C9A	C1	C11	C16	39.7
C1	N2	C3	C4	-45.7	C1	C11	C12	C13	-176.6
C1	N2	C3	C31	137.1	C16	C11	C12	C13	0.0
N2	C3	C4	C5	8.2	C11	C12	C13	C14	0.0
N2	C3	C4	C5	-172.6	C12	C13	C14	C15	0.0
C31	C3	C4	C5	-174.9	C13	C14	C15	C16	0.0
C31	C3	C4	C41	4.2	C1	C11	C16	C15	176.6
C3	C4	C5	C5A	62.9	C12	C11	C16	C15	0.0
C41	C4	C5	C5A	-116.3	C14	C15	C16	C11	0.0
C4	C5	C5A	C6	108.9	N2	C3	C31	C32	-127.8
C4	C5	C5A	C9A	-69.7	N2	C3	C31	C36	51.0
C5	C5A	C6	C7	178.1	C4	C3	C31	C32	55.0
C9A	C5A	C6	C7	-3.3	C4	C3	C31	C36	-126.2
C5A	C6	C7	C8	0.9	C3	C31	C32	C33	178.8
C6	C7	C8	C9	1.0	C36	C31	C32	C33	0.0
C7	C8	C9	C9A	-0.4	C31	C32	C33	C34	0.0
N2	C1	C9A	C5A	41.5	C32	C33	C34	C35	0.0
N2	C1	C9A	C9	-136.6	C33	C34	C35	C36	0.0
C11	C1	C9A	C5A	-142.0	C3	C31	C36	C35	-178.8
C11	C1	C9A	C9	39.8	C32	C31	C36	C35	0.0
C5	C5A	C9A	C1	4.3	C34	C35	C36	C31	0.0
C5	C5A	C9A	C9	-177.5	C3	C4	C41	O42	-146.0
C6	C5A	C9A	C1	-174.4	C3	C4	C41	O43	38.1
C6	C5A	C9A	C9	3.8	C5	C4	C41	O42	33.2
C8	C9	C9A	C1	176.2	C5	C4	C41	O43	-142.7
C8	C9	C9A	C5A	-2.0	C4	C41	O43	C44	-174.4
N2	C1	C11	C12	33.1	O42	C41	O43	C44	9.6
N2	C1	C11	C16	-143.5					

Torsion Angles in 1,3-diphenyl-5*H*-benz[*c*]azepine-4-carboxylic acid methyl ester.

3-Methyl-1,2a-diphenyl-2a,3,3a-trihydrocyclopropa[*c*]isoquinoline-3-carboxylic acid methyl ester **194**

To 3-{2-[(chloro-phenyl-methyleneamino)-phenyl-methyl]-phenyl}-acrylic acid methyl ester **191** (1.35mmol) in anhydrous THF (50ml) at -78°C was added a solution of potassium *tert* -butoxide (3.70M in DMF) until a purple colour was observeded (0.63ml, 2.33mmol of KOBut). The reaction was quickly warmed to

room temperature and poured into 50% ammonium chloride solution (50ml). Immediate extraction with ethyl acetate (50ml), drying of the organic layer and evaporation to dryness gave a brown oil which, by nmr, was a mixture of 3-[2-(benzoylamino-phenyl-methyl)-phenyl]-acrylic acid methyl ester **190**, 1,3-diphenyl-5H-2-benzazepine-4-carboxylic acid methyl ester **193** and 3-methyl-1,2a-diphenyl-2a,3,3a-trihydrocyclopropa[*c*]isoquinoline-3-carboxylic acid methyl ester **194**. Wet flash chromatography on silica with ethyl acetate-hexane as the eluant, followed by crystallisation from toluene gave 3-methyl-1,2a-diphenyl-2a,3,3a-trihydrocyclopropa[*c*]isoquinoline-3-carboxylic acid methyl ester **194** (0.05g, 10%); x-ray data below. The product failed to give a parent ion in the mass spectrum and, after crystallisation for X-ray analysis, too little material remained for satisfactory elemental analysis to be obtained. ν_{max} (film)/cm^{-1} 3058, 2947, 2849, 1726 (C=O), 1619 (C=N), 1606, 1557, 1436, 1344, 1171, 1037, 788; δ_H(80.13MHz; $CDCl_3$) 1.49 (1H, d, J 5.4, $CHCO_2$), 3.54 (3H, s, CO_2Me), 3.88 (1H, d, J 5.4, 7b-H), 7.25-7.67 (14H, m, ArH); δ_H(80.13MHz; benzene-d_6) 1.54 (1H, d, J 5.5, $CHCO_2$), 3.18 (3H, s, CO_2Me), 4.04 (1H, d, J 5.5, 7b-H), 6.87-7.49 (12H, m, ArH), 7.69-7.85 (2H, m, ArH);

Bond	Bond Length/Å	Bond	Bond Length/ Å
C(1)-N(2)	1.292	C(1)-C(7A)	1.481
C(1)-C(11)	1.493	N(2)-C(2A)	1.439
C(2A)-C(3)	1.555	C(2A)-C(3A)	1.520
C(2A)-C(2A1)	1.497	C(3)-C(3A)	1.521
C(3)-C(31)	1.475	C(3A)-C(3B)	1.468
C(3B)-C(4)	1.396	C(3B)-C(7A)	1.398
C(4)-C(5)	1.367	C(5)-C(6)	1.376
C(6)-C(7)	1.384	C(7)-C(7A)	1.398
C(31)-O(32)	1.197	C(31)-O(33)	1.348
O(33)-C(34)	1.451		

Bond Lengths for 3-methyl-1,2a-diphenyl-2a,3,3a-trihydrocyclopropa[*c*]isoquinoline-3-carboxylic acid methyl ester **194**

Atoms	Bond Angle/°	Atoms	Bond Angle/°
N(2)-C(1)-C(7A)	124.6	N(2)-C(1)-C(11)	114.9
C(7A)-C(1)-C(11)	120.5	C(1)-N(2)-C(2A)	120.9
N(2)-C(2A)-C(3)	113.0	N(2)-C(2A)-C(3A)	117.9
C(3)-C(2A)-C(3A)	59.3	N(2)-C(2A)-C(2A1)	112.2
C(3)-C(2A)-C(2A1)	120.8	C(3A)-C(2A)-C(2A1)	123.5
C(2A)-C(3)-C(3A)	59.2	C(2A)-C(3)-C(31)	120.6
C(3A)-C(3)-C(31)	116.8	C(2A)-C(3A)-C(3)	61.5
C(2A)-C(3A)-C(3B)	117.9	C(3)-C(3A)-C(3B)	119.7
C(3A)-C(3B)-C(4)	121.6	C(3A)-C(3B)-C(7A)	119.3
C(4)-C(3B)-C(7A)	119.1	C(3B)-C(4)-C(5)	121.1
C(4)-C(5)-C(6)	120.2	C(5)-C(6)-C(7)	120.0
C(6)-C(7)-C(7A)	120.5	C(1)-C(7A)-C(3B)	118.5
C(1)-C(7A)-C(7)	122.1	C(3B)-C(7A)-C(7)	119.1
C(1)-C(11)-C(12)	120.0	C(1)-C(11)-C(16)	119.9
C(2A)-C(2A1)-C(2A2)	121.5	C(2A)-C(2A1)-C(2A6)	118.4
C(3)-C(31)-O(32)	126.4	C(3)-C(31)-O(33)	109.6
O(32)-C(31)-C(33)	123.9	C(31)-O(33)-C(34)	115.4

Bond Angles for 3-methyl-1,2a-diphenyl-2a,3,3a-trihydrocyclopropa[*c*]isoquinoline-3-carboxylic acid methyl ester **194**

Atoms				Torsion Angle/°	Atoms				Torsion Angle/°
C7A	C1	N2	C2A	-5.1	C4	C3B	C7A	C1	-174.4
C11	C1	N2	C2A	176.7	C4	C3B	C7A	C7	-0.1
C1	N2	C2A	C3	-67.9	C6	C7	C7A	C1	175.9
C1	N2	C2A	C3A	-1.7	C6	C7	C7A	C3B	1.8
C1	N2	C2A	C2A1	151.4	N2	C1	C11	C12	-127.5
N2	C2A	C3	C3A	109.8	N2	C1	C11	C16	48.0
N2	C2A	C3	C31	-145.3	C7A	C1	C11	C12	54.2
C3A	C2A	C3	C3A	0.0	C7A	C1	C11	C16	-130.3
C3A	C2A	C3	C31	104.9	C1	C11	C12	C13	175.5
C2A1	C2A	C3	C3A	-113.2	C16	C11	C12	C13	0.0
C2A1	C2A	C3	C31	-8.3	C11	C12	C13	C14	0.0
N2	C2A	C3A	C3	-101.5	C12	C13	C14	C15	0.0
N2	C2A	C3A	C3B	9.0	C13	C14	C15	C16	0.0
C3	C2A	C3A	C3	0.0	C1	C11	C16	C15	-175.5
C3	C2A	C3A	C3B	110.5	C12	C11	C16	C15	0.0
C2A1	C2A	C3A	C3	108.7	C14	C15	C16	C11	0.0
C2A1	C2A	C3A	C3B	-140.8	N2	C2A	C2A1	C2A2	-134.7
C2A	C3	C3A	C2A	0.0	N2	C2A	C2A1	C2A6	41.8
C2A	C3	C3A	C3B	-107.7	C3	C2A	C2A1	C2A2	88.0
C31	C3	C3A	C2A	-111.3	C3	C2A	C2A1	C2A6	-95.5
C31	C3	C3A	C3B	141.0	C3A	C2A	C2A1	C2A2	16.6
C2A	C3A	C3B	C4	168.1	C3A	C2A	C2A1	C2A6	-166.9
C2A	C3A	C3B	C7A	-9.8	C2A	C2A1	C2A2	C2A3	176.5
C3	C3A	C3B	C4	-120.5	C2A6	C2A1	C2A2	C2A3	0.0
C3	C3A	C3B	C7A	61.6	C2A1	C2A2	C2A3	C2A4	0.0
C3A	C3B	C4	C5	-179.9	C2A2	C2A3	C2A4	C2A5	0.0
C7A	C3B	C4	C5	-1.9	C2A3	C2A4	C2A5	C2A6	0.0
C3B	C4	C5	C6	2.2	C2A	C2A1	C2A6	C2A5	-176.6
C4	C5	C6	C7	-0.4	C2A2	C2A1	C2A6	C2A5	0.0
C5	C6	C7	C7A	-1.6	C2A4	C2A5	C2A6	C2A1	0.0
N2	C1	C7A	C3B	4.3	C2A	C3	C31	O32	-53.4
N2	C1	C7A	C7	-169.8	C2A	C3	C31	O33	128.5
C11	C1	CA7	C3B	-177.6	C3A	C3	C31	O32	15.0
C11	C1	C7A	C7	8.3	C3A	C3	C31	O33	-163.1
C3A	C3B	C7A	C1	3.6	C3	C31	O33	C34	174.6
C3A	C3B	C7A	C7	177.6	O32	C31	O33	C34	-3.6

Torsion Angles for 3-methyl-1,2a-diphenyl-2a,3,3a-trihydrocyclopropa[*c*]isoquinoline-3-carboxylic acid methyl ester **194**

1,3-Diphenyl-1*H*-benz[*c*]azepine-4-carboxylic acid methyl ester **195**

3-Methyl-1,2a-diphenyl-2a,3,3a-trihydrocyclopropa[*c*]isoquinoline-3-carboxylic acid methyl ester **194** (6.0mg) in d_6-benzene (0.5ml) was heated to 75°C for five hours. ^{1}H n.m.r. spectroscopy showed quantitative conversion to 1,3-diphenyl-1*H*-benz[*c*]azepine-4-carboxylic acid methyl ester **195**, δ_H(80.13MHz; d_6-benzene) 3.27 (3H, s, Me), 5.07 (1H, s, ArPhC**H**-N), 6.87-6.92 (2H, m, ArH), 7.03-7.25 (9H, m, ArH), 7.29-7.49 (2H, m, ArH), 7.68-7.92 (3H, m, ArH), 8.59 (1H, s, =CHAr).

4. FACE SELECTIVE 1,7-ELECTROCYCLISATIONS

4.1. Preparation of the Nitrile Ylide Precursors

N-(2-Bromobenzyl)-benzamide **199**

To 2-bromobenzylamine hydrochloride (10.26g, 45.49mmol) and anhydrous sodium carbonate (12.06g, 113.7mmol) in anhydrous DCM (300ml) was added benzoyl chloride (6.34ml, 7.67g, 54.6mmol). The mixture was heated under reflux for 0.5h and then stirred at r.t. overnight. Water (100ml) was added and the organic layer was separated. The aqueous layer was extracted with DCM (50ml). Ethanol (5ml) was added to the combined organic layers and the solution was dried ($MgSO_4$). Removal of the solvent *in vacuo* and recrystallisation from ethanol gave white needles of *N*-(2-bromobenzyl)-benzamide **199** (11.83g, 90%), m.p. 135°C (lit.,[97] 133-4°C) ν_{max}(nujol)/cm^{-1} 3289 (NH), 1630 (C=O), 1601, 1539, 1305, 1026, 748; δ_H(360.13MHz; d_6-DMSO) 4.69 (2H, d, *J* 6.0, CH_2), 6.73 (1H, br t, *J* 6.0, NH), 7.14 (1H, td, *J* 7.7 and 1.8, ArH), 7.27 (1H, td, *J* 7.5 and 1.3, ArH), 7.38-7.51 (4H, m, ArH), 7.55 (1H, dd, *J* 8.0 and 1.3, ArH), 7.76-7.79 (2H, m, ArH); δ_C(50.32MHz; d_6-DMSO) 43.3 (CH_2), 122.4 (quat, CBr), 127.5 (CH, 2 x CH), 127.8 (CH), 128.5 (CH, 2 x CH), 128.6 (CH), 128.9 (CH), 131.6 (CH), 132.5 (CH), 134.2 (quat), 138.0 (quat), 166.6 (quat, C=O); m/z 289 (M^+, 2%), 210, (M-Br, 100), 107 (22), 105 (66), 104 (11), 77 (59).

3-[2-(Benzylamino-methyl)-phenyl]-2-methyl-acrylic acid **200**

To *N*-(2-bromobenzyl)-benzamide **199** (2.50g, 8.62mmol), anhydrous sodium acetate (1.91g, 23.3mmol) and methacrylic acid (1.11g, 12.9mmol) in anhydrous DMF (20ml) was added a catalyst solution [prepared from palladium

acetate (0.097g, 0.43mmol) and tri-*o*-tolylphosphine (0.52g, 1.72mmol) in anhydrous DMF (5ml), stirred under nitrogen until homogeneous]. The reaction was heated to 145°C for 2 hrs, cooled and poured into water (100ml). Ethyl acetate (50ml) was added and the organic layer was separated, filtered through Celite and extracted with 2M NaOH (10 x 20ml). The combined basic layers were acidified with 2M HCl and extracted with ethyl acetate (3 x 40ml). The combined organic layers were dried ($MgSO_4$) and evaporated to dryness. Recrystallisation from glacial acetic acid-water gave white needles of 3-[2-(benzylamino-methyl)-phenyl]-2-methyl-acrylic acid **200** (1.35g, 52%), m.p. 150°C (dec.) (Found: M^+, 295.1204. $C_{18}H_{17}NO_3$ requires M, 295.1191); ν_{max}(nujol)/cm^{-1} 3355 (NH), 1687 (Acid C=O), 1635 (Amide C=O), 1528, 1295, 987, 762, 690; δ_H(200MHz; d_6-DMSO) 1.88 (3H, d, J 1.3, Me), 4.47 (2H, d, J 5.7, CH_2-N), 7.20-7.57 (7H, m, ArH), 7.86-7.96 (3H, m, ArH & =CH), 9.03 (1H, t, J 5.7, NH), 10.4 (1H, br. s, CO_2H); m/z 295 (M^+, 6%), 249 (6, M-HCO_2H), 144(11), 130 (18), 129 (30), 128 (19), 122 (21), 115 (12), 105 (100, PhCO), 77 (53, Ph).

3-[2-(Benzoylamino-methyl)-phenyl]-2-methyl-acrylic acid methyl ester **201**

(a) With Methanol and Sulphuric Acid

3-[2-(Benzylamino-methyl)-phenyl]-2-methyl-acrylic acid **200** (0.10g, 0.339mmol) in methanol (20ml) with one drop of conc. sulphuric acid were heated under reflux overnight. The solvent was removed *in vacuo* and water (10ml) was added. This was extracted with DCM (2 x 15ml) and the organic layer was washed with satured sodium bicarbonate, water and brine. After

drying ($MgSO_4$) the solvent was removed *in vacuo* to give a white solid. Recrystallisation from toluene-hexane gave white crystals of 3-[2-(benzoyl-amino-methyl)-phenyl]-2-methyl-acrylic acid methyl ester **201** (0.105g, 70%) m.p. 150°C(dec.) (Too hygroscopic for elemental analysis. Found: M^+, 309.1377. C19H19NO3 requires M, 309.1417); ν_{max} (nujol) 3265 (NH), 1715 (Ester C=O), 1633 (Amide C=O), 1545, 1267, 1121, 986, 757, 699; δ_H(200.13MHz; $CDCl_3$) 1.93 (3H, d, J 1.5, Me), 3.78 (3H, s, CO_2Me), 4.60 (2H, d, J 5.6, CH_2-N), 6.48 (1H, br t, J 5.6, NH), 7.19-7.52 (7H, m, ArH), 7.72-7.81 (3H, m, ArH and =CH); m/z 309 (8%,M^+), 294 (1, M - Me), 278 (2, M - OMe), 250 (2, M - CO_2Me), 204 (13), 188 (13), 172 (11), 144 (11), 1289 (32), 128 (21), 105 (100, PhCO), 77 (48, Ph).

(b) <u>With Methyl Iodide and Potassium Fluoride</u>

3-[2-(Benzylamino-methyl)-phenyl]-2-methyl-acrylic acid **200** (2.00g, 6.77mmol), potassium fluoride (5.0g) and methyl iodide (10ml) were stirred in DMF (20ml) at room temperature overnight. The solvent was removed under high vacuum and ethyl acetate (50ml) was added. After filtration the filtrate was washed with water, sodium hydroxide (2M) and brine. Drying ($MgSO_4$) and removal of the solvent *in vacuo* gave a cloudy yellow oil. Wet flash column chromatography on alumina with ethyl acetate-hexane (2:3) as eluant gave white cystals of 3-[2-(benzoylamino-methyl)-phenyl]-2-methyl-acrylic acid methyl ester **201**, identical to an authentic sample.

3-[2-(Benzoylamino-methyl)-phenyl]-2-methyl-acrylic acid 2-isopropyl-5-methyl-cyclohexyl ester **203**

1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.53g, 2.75mmol) was added to a solution of 3-[2-(benzylamino-methyl)-phenyl]-2-methyl-acrylic acid **200** (0.74g, 2.50mmol), (-)-menthol (0.35g, 2.25mmol) and 4-dimethylaminopyridine (0.16g, 1.29mmol) in DMF (15ml) at 0°C. After 5 mins the reaction was warmed to 20°C and stirred overnight. The solvent was removed *in vacuo* and the residue was dissolved in ethyl acetate (20ml). This was washed with 2M HCl, 2M NaOH and then brine solution. The organic layer was dried ($MgSO_4$) and the solvent was removed *in vacuo*. Chromatography on silica gel with ethyl acetate-hexane as eluent and Kugelrohr distillation gave a clear colourless glass which was identified as 3-[2-(benzoylamino-methyl)-phenyl]-2-methyl-acrylic acid 2-isopropyl-5-methyl-cyclohexyl ester **203** (0.48g, 49%), b.p. 200°C (oven)/0.1mmHg, (Found: C, 77.39; H, 8.32; N, 3.20. $C_{28}H_{35}NO_3$ requires C, 77.56; H, 8.14; N, 3.23); ν_{max} (film)/cm^{-1} 3327 (NH), 3062, 2963, 2925, 1704 (Ester C=O), 1643 (Amide C=O), 1538, 1453, 1364, 1253, 1120, 959, 759; δ_H(200.13MHz; $CDCl_3$) 0.60-1.11 (12H, m, Menthyl-H), 1.38-1.51 (2H, m, Menthyl-H), 1.65-1.72 (3H, m, Menthyl-H), 1.82-1.98 (1H, m, Menthyl-H), 1.95 (3H, s, =CMe), 4.62 (2H, d, *J* 5.6, CH_2-N), 4.78 (1H, td, *J* 10.8 & 4.3, Menthyl CH-O), 6.36 (1H, t, *J* 5.6, NH), 7.10-7.52 (7H, m, ArH), 7.63-7.86 (2H, m, ArH); m/z 433 (M^+, 22%), 295(43), 249 (24, M - Menthyl), 222 (29), 138 (70), 123 (70), 123 (57), 105 (72), 95 (100), 82 (91), 72 (84).

3-[2-(Benzoylamino-methyl)-phenyl]-2-methyl-acrylic acid 1-phenyl-ethyl ester **204**

1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (1.36g, 7.11mmol) was added to a solution of 3-[2-(benzylamino-methyl)-phenyl]-2-methyl-acrylic acid **200** (1.91g, 6.47mmol), (±)-*sec*-phenethyl alcohol (0.71g, 5.82mmol) and 4-dimethylaminopyridine (0.16g, 1.29mmol) in DMF (15ml) at 0°C. After 5 mins the reaction was warmed to 20°C and stirred overnight. The solvent was removed *in vacuo* and the residue was dissolved in ethyl acetate (20ml). This was washed with 2M HCl, 2M NaOH and then brine solution. The organic layer was dried ($MgSO_4$) and the solvent was removed *in vacuo*. Chromatography on silica gel with ethyl acetate-hexane as eluent gave a clear colourless glass which was identified as 3-[2-(benzoylamino-methyl)-phenyl]-2-methyl-acrylic acid 1-phenyl-ethyl ester **204** (1.49g, 64%), (Found: C, 78.20; H, 6.51; N, 3.52. $C_{26}H_{25}NO_3$ requires C, 78.17; H, 6.31; N, 3.51); ν_{max} (film)/cm^{-1} 3324 (NH), 3062, 3030, 2978, 2928, 1707 (Ester C=O), 1642 (Amide C=O), 1537, 1488, 1356, 1252, 1120, 1063, 992, 760, 698; δ_H(200.13MHz; $CDCl_3$) 1.57 (3H, d, *J* 6.6, CH-**Me**), 1.96 (3H, d, *J* 1.3, =CMe), 4.61 (2H, d, *J* 5.7, CH_2N), 5.97 (1H, q, *J* 6.6, C**H**-Me), 6.43 (1H, t, *J* 5.7, N-H), 7.20-7.52 (11H, m, ArH), 7.70-7.86 (3H, m, ArH); m/z 399 (M^+, 0.7%), 295 (31, M - PhCO), 172 (12), 105 (100, PhCO), 77 (20, Ph).

3-[2-(Chlorophenyl-methyleneamino-methyl)-phenyl]-2-methyl-acrylic acid methyl ester **205**

3-[2-(Benzoylamino-methyl)-phenyl]-2-methyl-acrylic acid methyl ester **201** (0.31g, 1.00mmol) and thionyl chloride (3ml) in dry diethyl ether (10ml) were heated under reflux overnight. The solvent was removed in vacuo and the residue was dried under high vacuum for three hours to give 3-[2-(chloro-phenyl-methyleneamino-methyl)-phenyl]-2-methyl-acrylic acid methyl ester **205** as a clear yellow oil (quantitative by nmr) ν_{max} ($CDCl_3$)/cm^{-1} 3067, 2952, 1709 (C=O), 1663 (C=N), 1438, 1262, 1122, 922, 766, 690; δ_H(200.13MHz; $CDCl_3$) 1.98 (3H, s, Me), 3.81 (3H, s, CO_2Me), 4.89 (2H, s, CH_2-N), 7.25-7.51 (7H, m, ArH), 7.89 (1H, s, =CH), 8.04-8.07 (2H, m, ArH); δ_C(50.32MHz; $CDCl_3$) 13.9 (CH_3, Me), 51.9 (CH_3, Ester Me), 55.4 (CH_2), 126.9 (CH), 128.2 (CH), 128.9 (CH), 129.0 (CH), 129.8 (quat), 131.7 (CH), 134.6 (quat), 134.9 (quat), 136.1 (quat), 137.4 (CH), 145.2 (quat), 168.4 (quat, C=O).

3-[2-(Chloro-phenylnethyleneamino-methyl)-phenyl]-2-methyl-acrylic acid 2-isopropyl-5-methyl-cyclohexyl ester **206**

3-[2-(Benzoylamino-methyl)-phenyl]-2-methyl-acrylic acid 2-isopropyl-5-methyl-cyclohexyl ester **203** (0.25g, 0.577mmol) and thionyl chloride (3ml) in dry diethyl ether were heated under reflux overnight. Removal of the solvent and excess thionyl chloride *in vacuo* gave 3-[2-(chloro-phenylnethyleneamino-methyl)-phenyl]-2-methyl-acrylic acid 2-isopropyl-5-methyl-cyclohexyl ester **206** in quantitative yield as a clear pale yellow oil. ν_{max} ($CDCl_3$)/cm^{-1} 2958, 2927, 2870, 1697 (C=O), 1662 (C=N), 1518, 1485, 1450, 1342, 1258, 1124, 923, 765,

690, 650; δ_H(200.13MHz; $CDCl_3$) 0.75-1.20 (12H, m, Menthyl-H), 1.29-1.49 (2H, m, Menthyl-H), 1.58-1.70 (3H, m, Menthyl-H), 1.79-2.08 (1H, m, Menthyl-H), 1.96 (3H, s, =CMe), 4.63-4.90 (3H, m, CH_2-N & Menthyl-CH-O), 7.25-7.43 (7H, m, ArH), 7.79-7.92 (2H, m, ArH), 8.08 (1H, s, =CH).

3-[2-(Chloro-phenyl-methyleneamino-methyl)-phenyl]-2-methyl-acrylic acid 1-phenyl-ethyl ester **207**

3-[2-(benzoylamino-methyl)-phenyl]-2-methyl-acrylic acid 1-phenyl-ethyl ester **204** (0.25g, 0.626mmol) and thionyl chloride (3ml) in dry diethyl ether were heated under reflux overnight. Removal of the solvent and excess thionyl chloride *in vacuo* gave 3-[2-(chloro-phenyl-methyleneamino-methyl)-phenyl]-2-methyl-acrylic acid 1-phenyl-ethyl ester **207** in quantitative yield as a clear pale yellow oil. ν_{max} ($CDCl_3$)/cm^{-1} 3080, 2983, 2929, 1704 (C=O), 1662 (C=N), 1517, 1485, 1257, 1124, 1063, 764, 699; δ_H(200.13MHz; $CDCl_3$) 1.57 (3H, d, *J* 6.2, CH-**Me**), 1.98 (3H, s, =CMe), 4.92 (2H, s, CH_2-N), 5.99 (1H, q, J 6.2, C**H**-Me), 7.25-7.54 (11H, m, ArH), 7.73-8.06 (3H, m, ArH).

4.2. Generation and 1,7-Electrocyclisation of the Nitrile Ylides 208, 209 and 210.

3-Methyl-2a-phenyl-2a,3,3a-trihydrocyclopropa[*c*]isoquinoline-3-carboxylic acid methyl ester **211**

Freshly sublimed potassium *tert*-butoxide (0.224g, 2.00mmol) was added in one portion to a rapidly stirred solution of 3-[2-(chlorophenyl-methyleneamino-methyl)-phenyl]-2-methyl-acrylic acid methyl ester **205** (1.00mmol) in dry THF (20ml) at 0°C. The reaction was stirred at 0°C for 10 mins and then at r.t. for 30mins. Ammonium chloride solution (25% w/v, 10ml) and DCM (20ml) were added, the organic layer was separated and the aqueous layer was extracted with DCM (2 x 10ml). The combined organic layers were washed with brine, dried ($MgSO_4$) and then evaporated to dryness. Wet flash chromatography on silica gel with 20-30% ethyl acetate-haxane as eluant gave white crystals of 3-methyl-2a-phenyl-2a,3,3a-trihydrocyclopropa[*c*]isoquinoline-3-carboxylic acid methyl ester **211** (0.23g, 79%), m.p. 130-131°C (Found M^+, 291.1251. $C_{19}H_{17}NO_2$ requires M, 291.1279); X-ray data below; ν_{max} (nujol)/cm^{-1} 1713 (C=O), 1642 (C=N), 1620, 1561, 1319, 1146, 759, 690; δ_H(200.13MHz; $CDCl_3$) 1.48 (3H, s, Me), 3.37 (3H, s, CO_2Me), 3.91 (1H, s, H_{3a}), 7.25-7.45 (8H, m, ArH), 7.52-7.78 (1H, m, ArH), 8.43 (1H, s, H1); m/z 291 (M^+, 100%), 276 (24, M - Me), 260 (12, M-OMe), 232 (92, M-CO^2Me), 129 (50), 77 (13, Ph).

Bond	Bond Length/Å	Bond	Bond Length/Å
C(1)-N(2)	1.311	C(5)-C(6)	1.411
C(1)-C(7A)	1.364	C(6)-C(7)	1.264
N(2)-C(2A)	1.477	C(7)-C(7A)	1.446
C(2A)-C(3)	1.561	C(2A1)-C(2A2)	1.273
C(2A)-C(3A)	1.423	C(2A1)-C(2A6)	1.306
C(2A)-C(2A1)	1.533	C(2A2)-C(2A3)	1.407
C(3)-C(3A)	1.411	C(2A3)-C(2A4)	1.292
C(3)-C(31)	1.495	C(2A4)-C(2A5)	1.253
C(3)-C(32)	1.566	C(2A5)-C(2A6)	1.420
C(3A)-C(3B)	1.522	C(32)-O(33)	1.116
C(3B)-C(5)	1.277	C(32)-O(34)	1.282
C(3B)-C(7A)	1.420	O(32)-C(35)	1.517
C(4)-C(5)	1.431		

Bond Lengths for 3-methyl-2a-phenyl-2a,3,3a-trihydrocyclopropa[*c*]isoquinoline-3-carboxylic acid methyl ester **211**.

Atoms	Bond Angle/°	Atoms	Bond Angle/°
N(2)-C(2)-C(7A)	124.2	C(3B)-C(4)-C(5)	118.5
C(1)-N(2)-C(2A)	126.0	C(4)-C(5)-C(6)	127.5
N(2)-C(2A)-C(3)	117.4	C(5)-C(6)-C(7)	115.1
N(2)-C(2A)-C(3A)	115.3	C(6)-C(7)-C(7A)	117.4
N(2)-C(2A)-C(2A1)	115.9	C(1)-C(7A)-C(3B)	114.0
C(3)-C(2A)-C(3A)	56.2	C(1)-C(7A)-C(7)	118.1
C(3)-C(2A)-C(2A1)	116.8	C(3B)-C(7A)-C(7)	127.8
C(3A)-C(2A)-C(2A1)	122.0	C(2A)-C(2A1)-C(2A2)	122.8
C(2A)-C(3)-C(3A)	57.0	C(2A)-C(2A1)-C(2A6)	127.3
C(2A)-C(3)-C(31)	118.0	C(2A2)-C(2A1)-C(2A6)	109.9
C(2A)-C(3)-C(32)	114.8	C(2A1)-C(2A2)-C(2A3)	123.8
C(3A)-C(3)-C(31)	114.8	C(2A2)-C(2A3)-C(2A4)	126.3
C(3A)-C(3)-C(32)	119.7	C(2A3)-C(2A4)-C(2A5)	110.5
C(31)-C(3)-C(32)	118.2	C(2A4)-C(2A5)-C(2A6)	124.0
C(2A)-C(3A)-C(3)	66.8	C(2A1)-C(2A6)-C(2A5)	125.5
C(2A)-C(3A)-C(3B)	114.3	C(3)-C(32)-O(33)	125.2
C(3)-C(3A)-C(3B)	120.1	C(3)-C(32)-O(34)	120.6
C(3A)-C(3B)-C(4)	120.4	O(33)-C(32)-O(34)	114.2
C(2A)-C(3B)-C(7A)	125.9	C(32)-O(34)-C(34)	123.5
C(4)-C(3B)-C(7A)	113.7		

Bond Angles for 3-methyl-2a-phenyl-2a,3,3a-trihydrocyclopropa[*c*]isoquinoline-3-carboxylic acid methyl ester **211**.

Atoms				Torsion Angle/°	Angle				Torsion Angle/°
C7A	C1	N2	C2A	1.1	C2A	C3	C32	O34	61.4
N2	C1	C7A	C3B	-1.7	C3A	C3	C32	O33	177.8
N2	C1	C7A	C7	174.4	C3A	C3	C32	O34	-3.3
C1	N2	C2A	C3	67.1	C31	C3	C32	O33	29.1
C1	N2	C2A	C3A	3.7	C31	C3	C32	O34	-152.0
C1	N2	C2A	C2A1	-148.2	C2A	C3A	C3B	C4	-169.9
N2	C2A	C3	C3A	-103.5	C2A	C3A	C3B	C7A	6.7
N2	C2A	C3	C31	-0.7	C3	C3A	C3B	C4	113.8
N2	C2A	C3	C32	146.0	C3	C3A	C3B	C7A	-69.6
C3A	C2A	C3	C31	102.8	C3A	C3B	C4	C5	177.4
C3A	C2A	C3	C32	-110.5	C7A	C3B	C4	C5	0.4
C2A1	C2A	C3	C3A	112.2	C3A	C3B	C7A	C1	-2.3
C2A1	C2A	C3	C31	-145.0	C3A	C3B	C7A	C7	-178.0
C2A1	C2A	C3	C32	1.7	C4	C3B	C7A	C1	174.5
N2	C2A	C3A	C3	107.2	C4	C3B	C7A	C7	-1.2
N2	C2A	C3A	C3B	-6.7	C3B	C4	C5	C6	0.1
C3	C2A	C3A	C3B	-113.9	C4	C5	C6	C7	0.0
C2A1	C2A	C3A	C3	-102.7	C5	C6	C7	C7A	-0.6
C2A1	C2A	C3A	C3B	143.4	C6	C7	C7A	C1	-174.2
N2	C2A	C2A1	C2A2	-65.4	C6	C7	C7A	C3B	1.3
N2	C2A	C2A1	C2A6	112.6	C2A	C2A1	C2A2	C2A3	179.8
C3	C2A	C2A1	C2A2	79.5	C2A6	C2A1	C2A2	C2A3	1.5
C3	C2A	C2A1	C2A6	-102.5	C2A	C2A1	C2A6	C2A5	-179.5
C3A	C2A	C2A1	C2A2	144.7	C2A2	C2A1	C2A6	C2A5	-1.3
C3A	C2A	C2A1	C2A6	-37.3	C2A1	C2A2	C2A3	C2A4	-1.5
C2A	C3	C3A	C3B	105.6	C2A2	C2A3	C2A4	C2A5	1.0
C31	C3	C3A	C2A	-108.4	C2A3	C2A4	C2A5	C2A6	-0.7
C31	C3	C3A	C3B	-2.8	C2A4	C2A5	C2A6	C2A1	1.0
C32	C3	C3A	C2A	101.8	C3	C32	O34	C35	-174.8
C32	C3	C3A	C3B	-152.6	O33	C32	O34	C35	4.2
C2A	C3	C32	O33	-117.5					

Torsion Angles for 3-methyl-2a-phenyl-2a,3,3a-trihydrocyclopropa[*c*]isoquinoline-3-carboxylic acid methyl ester **211**.

3-Methyl-2a-phenyl-2a,3-dihydro-cyclopropa[*c*]isoquinoline-3-carboxylic acid 2-isopropyl-5-methyl-cyclohexyl ester **212**

Freshly sublimed potassium tert-butoxide (0.16g, 1.44mmol) was added to 3-[2-(chloro-phenylnethyleneamino-methyl)-phenyl]-2-methyl-acrylic acid 2-isopropyl-5-methyl-cyclohexyl ester **206** (0.25g, 0.58mmol) in dry THF (20ml) at

0°C. The reaction was stirred at 0°C for 10mins and then at 20°C for 30mins. Ammonium chloride solution (25% w/v, 10ml) and ethyl acetate (20ml) were added, the organic layer was separated and the aqueous layer was extracted with ethyl acetate (10ml). The combined organic layers were dried ($MgSO_4$) and the solvent was removed *in vacuo*. Chromatography on silica gel with 40% ethyl acetate in hexane as the eluent gave a colourless syrup of 3-methyl-2a-phenyl-2a,3-dihydro-cyclopropa[*c*]isoquinoline-3-carboxylic acid 2-isopropyl-5-methyl-cyclohexyl ester **212** (0.16g, 67%), d.e. 20% by ^1H n.m.r. integrals (Found: C, 77.39; H, 8.32; N, 3.20. $C_{28}H_{33}NO_2$ requires C, 77.56; H, 8.14; N, 3.20); ν_{max} (film)/cm^{-1} 3059, 2955, 2869, 1713 (C=O), 1622 (C=N), 1567, 1453, 1386, 1275, 1147, 1088, 823, 753, 697; δ_H(300.136MHz; $CDCl_3$) 0.61-1.12 (12H, m, Menthyl-H), 1.23-1.45 (2H, m, Menthyl-H), 1.53-1.80 (6H, m, Menthyl-H & Cyclopropyl-Me), 1.91-1.97 (1H, m, Menthyl-H), 3.90 & 3.93 (1H, 2 x s, Cyclopropyl-H, ratio 3:2), 4.31-4.46 (1H, m, Menthyl-CH-O), 7.19-7.60 (9H, m, ArH), 8.44 & 8.45 (1H, 2 x s, -N=CH, ratio 3:2); m/z (FAB; Thioglycerol) 416 (M+1), 278, 277 (M + 1- Menthyl), 276, 260 (M + 1- Menthol); 232, 217, 206 (Base peak), 129.

3-Methyl-2a-phenyl-2a,3-dihydro-cyclopropa[*c*]isoquinoline-3-carboxylic acid 1-phenyl-ethyl ester **213**

Freshly sublimed potassium tert-butoxide (0.18g, 1.61mmol) was added to 3-[2-(chloro-phenyl-methyleneamino-methyl)-phenyl]-2-methyl-acrylic acid 1-phenyl-ethyl ester **207** (0.26g, 0.63mmol) in anhydrous THF (20ml) at 0°C. The reaction was stirred at 0°C for 10mins and then at 20°C for 30mins. Ammonium

chloride solution (25% w/v, 10ml) and ethyl acetate (20ml) were added, the organic layer was separated and the aqueous layer was extracted with ethyl acetate (10ml). The combined organic layers were dried ($MgSO_4$) and the solvent was removed *in vacuo*. Chromatography on silica gel with 40% ethyl acetate in hexane as the eluent gave a yellow syrup of 3-methyl-2a-phenyl-2a,3-dihydro-cyclopropa[*c*]isoquinoline-3-carboxylic acid 1-phenyl-ethyl ester **213** (0.18g, 75%), 4% d.e. by ^1H n.m.r.integrals, (Found: M^+ 382.18070. $C_{26}H_{24}NO_2$ requires 382.18069); ν_{max} (film)/cm^{-1} 3053, 2996, 2977, 2932, 2878, 1713 (C=O), 1621 (C=N), 1566, 1450, 1275, 1155, 1061, 941, 761, 689; δ_H (200.13MHz; $CDCl_3$) One diastereomer, 1.07 (3H, d, *J* 6.5, CH-**Me**), 1.50 (3H, s, cyclopropyl-Me), 3.91 (1H, s, cyclopropyl-H), 5.60 (1H, q, *J* 6.5, -OCH-), 7.17-7.77 (14H, m, ArH), 8.42 (1H, s, -N=CH-), Other diastereomer, 1.27 (3H, d, *J* 6.5, CH-**Me**), 1.47 (3H, s, cyclopropyl-Me), 3.91 (1H, s, cyclopropyl-H), 5.59 (1H, q, *J* 6.5, -OCH-), 7.18-7.66 (14H, m, ArH), 8.43 (1H, s, -N=CH-); m/z (FAB/Thioglycerol) 382 (M+1), 278 (M+1-PhCHMe), 206, 185 (Base peak), 105.

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