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**DOCTOR OF PHILOSOPHY**

**Synthesis and applications of guanidine heterocycles**

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# Synthesis and Applications of Guanidine Heterocycles

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A thesis presented for the

Degree of PhD

In the

Department of Chemistry

By

Deiniol Hedd Davies

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PRIFYSGOL  
**BANGOR**  
UNIVERSITY



Prifysgol Bangor University

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# Abbreviations

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App.	Apparent
Bn	Benzyl
Br.	Broad
Boc	<i>tert</i> -Butoxycarbonyl
CbZOSu	Benzyloxycarbonyl
DCM	Dichloromethane
DEPT	Distortionless enhancement by polarisation transfer
DMDO	2, 2-Dimethyldioxirane
DME	1, 2-Dimethoxyethane
DMF	N, N-Dimethylformamide
FTIR	Fourier transform infra-red
h	Hour(s)
HRMS	High resolution mass spectrometry
HPLC	High Performance Liquid Chromatography
IMS	Industrial Methylated Spirits
NMR	Nuclear magnetic resonance
Ph	Phenyl
PTC	Phase Transfer Catalysis
PG	Protecting group
r.t	Room temperature
TAA	Tetra- <i>N</i> -alkylammonium
TBDMS	<i>Tert</i> -butyldimethylsilyl
TBDPS	<i>Tert</i> -butyldiphenylsilyl
THF	Tetrahydrofuran
TEBA-Cl	Tetraethyl ammonium chloride
TFA	Trifluoroacetic acid
Tos/Ts	Tosyl
TPP	Tetraphenylporphyrin
Z	Benzyloxycarbonyl



# Contents

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Acknowledgements.....	i
Declaration.....	ii
Abbreviations.....	iii
 <b>Abstract .....</b>	 <b>01</b>
 <b>Electrocyclisation reactions involving guanidines</b>	
<b>Introduction .....</b>	<b>03</b>
<b>Aims .....</b>	<b>12</b>
<b>Results and Discussion .....</b>	<b>13</b>
<b>Conclusion .....</b>	<b>34</b>
 <b>Applications of cyclic guanidines to phase transfer catalysis</b>	
<b>Introduction .....</b>	<b>37</b>
<b>Aims .....</b>	<b>66</b>
<b>Results and Discussion .....</b>	<b>70</b>
<b>Conclusion .....</b>	<b>85</b>
 <b>Experimental .....</b>	 <b>93</b>
<b>References.....</b>	<b>155</b>
<b>Appendices.....</b>	<b>159</b>

# Abstract

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The thesis describes a method for the synthesis of 5- and 6-membered guanidine heterocycles *via* iodocyclisation of *N*-Boc-allylguanidine, *N*-Z-allylguanidine and *N*-Z-*N'*-(dimethylallyl)guanidine. The unstable intermediate products from these reactions were rearranged in the presence of trifluoroacetic acid to form the heterocycles 2-imino-4-iodomethyl-imidazolidine-1-carboxylic acid *tert*-butyl ester, 2-imino-4-iodomethyl-imidazolidine-1-carboxylic acid benzyl ester, (5-iodo-4,4-dimethyl-tetrahydro-pyrimidin-2-ylidene)-carbamic acid benzyl ester and (5-iodomethyl-4,4-dimethyl-imidazolidin-2-ylidene)-carbamic acid benzyl ester.

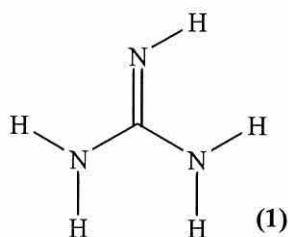
Synthetic routes to the previously synthesised catalyst (6*R*, 6''*R*, 2*R*, 2''*R*)-6,6'-dimethyldispiro[tetrahydropyran-2,2'-(2,3,4,6,7,8-hexahydro-1*H*-pyrimido[1,2-*a*]pyrimidine)-8',2''-tetrahydropyran]-9'-ium tetrafluoroborate and the novel chiral non-racemic bicyclic guanidine (4*R*,8*R*)-3,8-dibenzyloxy-2,4,5,6,7,8,9,10-octahydro-3*H*-5*a*,10-diaza-1-azonia-heptalene tetrafluoroborate are also detailed. The application of these compounds as phase transfer catalysts in the asymmetric epoxidation of chalcones was investigated leading to enantiomeric excesses of 85-94% (4 examples).

# **Electrocyclisation reactions involving guanidines**

# Introduction

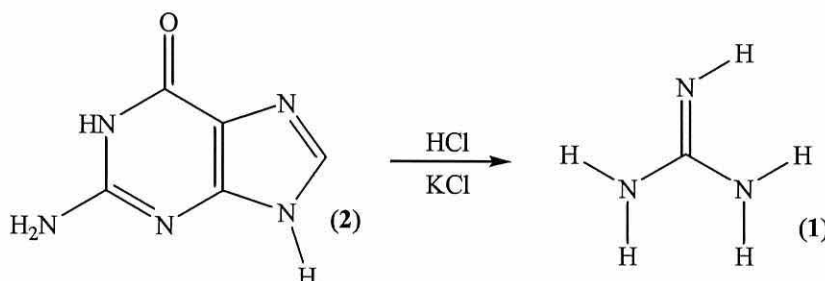
## Guanidines and their chemistry

Guanidine **1** is a naturally occurring colourless crystalline solid, which is readily soluble in water and alcohol. (Fig. 1)



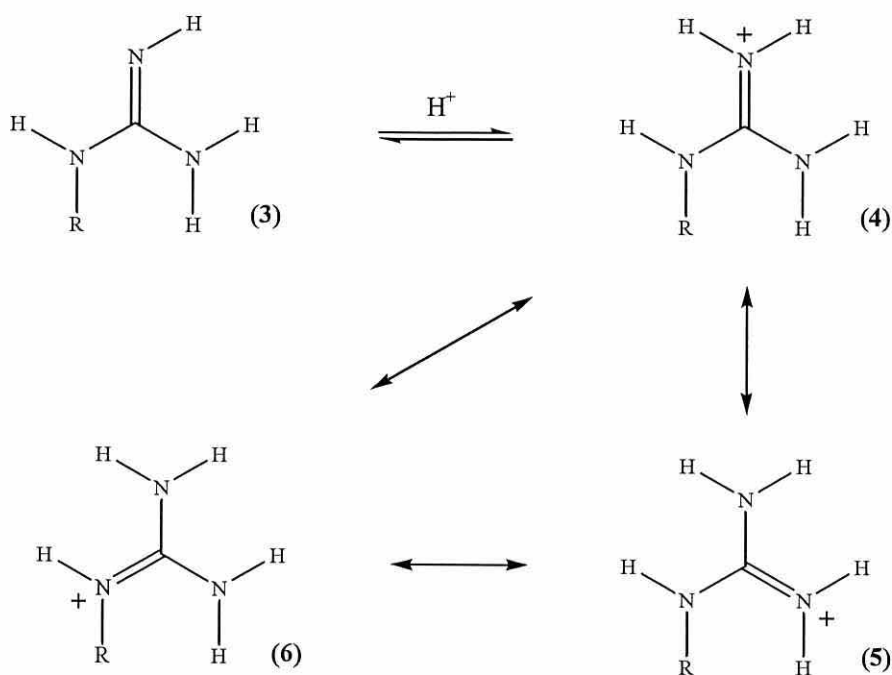
**Figure 1:** General form of Guanidine

Guanidine was first prepared in 1861 by Strecker,<sup>1</sup> who hydrolysed guanine **2** using hydrochloric acid and potassium chloride. (Scheme 1)



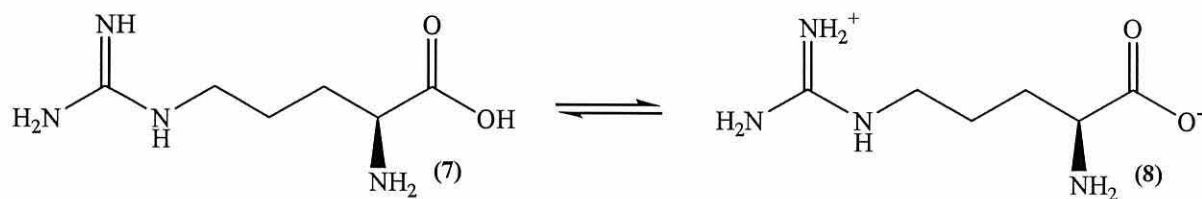
**Scheme 1:** formation of guanidine **1** from guanine **2**.

The chemistry of the functional group guanidine, and related compounds, is of particular interest to the synthetic organic chemist due to its presence in many biologically active compounds. One of the most interesting properties of guanidine is the fact that it is one of the strongest organic bases currently known.<sup>2</sup> This is due to the observation that when a guanidine **3** is protonated it can be represented in the resonances form **4** - **6** in which the positive charge is delocalised over the three nitrogen atoms within the structural motif. (Fig. 2)



**Figure 2:** Equilibria of free and resonance forms of guanidine.

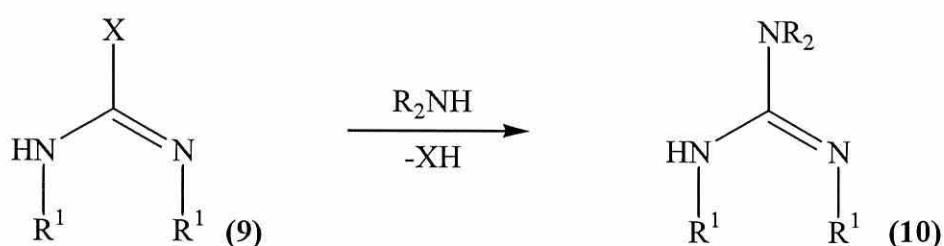
This observation has consequences for simple guanidines found in nature as they are protonated at physiological pH, existing as the guanidinium ion.<sup>3</sup> This can be seen in one of the common 20 amino acids arginine which is represented as the guanidine **7** but is present as the zwitterionic guanidinium form **8**. Arginine is very common in proteins as the planar geometry of the protonated form allows for easy complexation of negatively charged groups particularly at enzyme active sites.<sup>4</sup> (Fig. 3)



**Figure 3:** Arginine in both guanidine **7** and guanidinium **8** form.

## Synthetic Routes to Guanidines

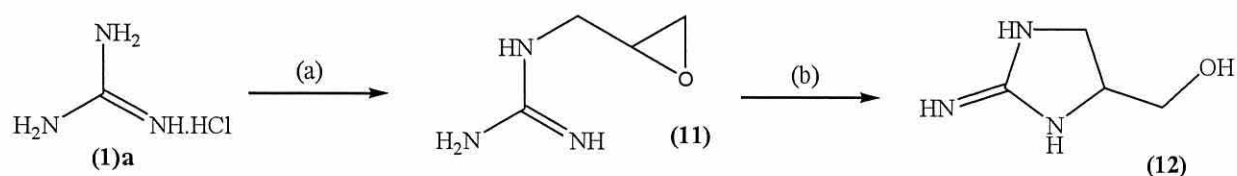
The most effective general methodology for the synthesis of guanidines is the nucleophilic attack of an amine on a suitably substituted amidine such as **9**, which leads to the substituted guanidines *via* displacement of the substituent X **10**. (Scheme 2)<sup>5</sup>



**Scheme 2:** X = Hal, SR, OR, NHet.

## Synthesis of Guanidine Heterocycles *via* electrocyclisation

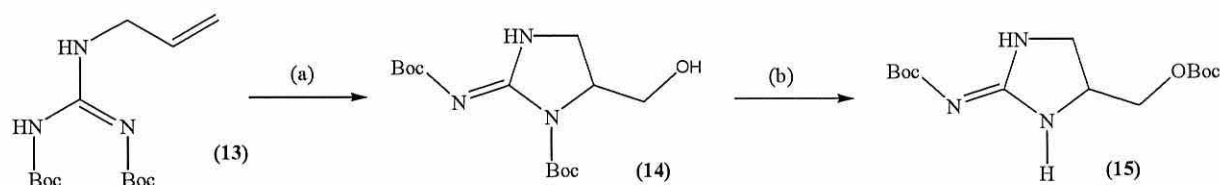
In contrast to traditional methods for guanidine synthesis our research group has focused on electrophilic cyclisation methods for the synthesis of guanidines. For example work directed towards the total synthesis of the marine natural products involved the study of cyclisation reactions of guanidines with epoxides.<sup>6</sup> Initially reactions in which guanidine.HCl **1a** was treated with epibromohydrin to give the intermediate epoxide **11** which on warming and subsequent treatment with trifluoroacetic acid cyclised to give the 5-membered heterocycle **12** in 33% yield.<sup>6</sup> (Scheme 3)



**Scheme 3:** (a) i) Epibromohydrin, *t*BuOH. ii) KO*t*Bu. (b) i) 60 °C, 96 h. ii) TFA, MeOH; 33%.

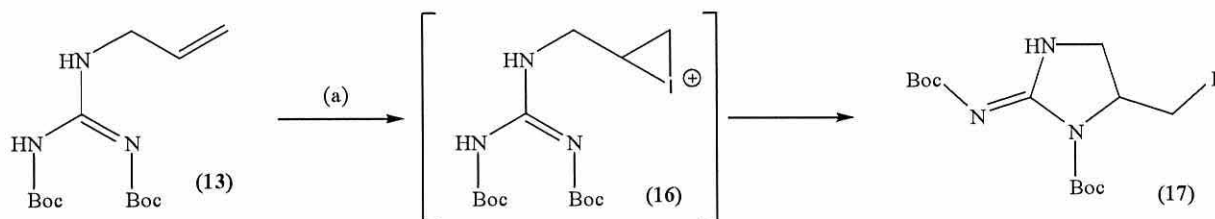
The product **12** represents the 5-*exo*-tet cyclisation product which was formed almost exclusively, however, the synthetic method suffered from the formation of dimeric and polymeric by-products and the formation of small quantities of the 6-membered product which led to purification problems.

With this in mind the reaction of the protected allyl guanidine **13** using the neutral epoxidising reagent DMDO was investigated. It was found that the intermediate alcohol **14** was initially formed which could be isolated by rapid chromatographic separation from by-products, its structure being determined by X-ray crystallography. However, it was observed that on standing on silica gel **14** undergoes rearrangement to the *O*-protected isomer **15** in 63% yield. This product was stable and easily purified by column chromatography and recrystallisation; again the structure was determined by X-ray crystallography.<sup>7</sup> (Scheme 4)



**Scheme 4:** (a) DMDO, stir 10 days (b) silica gel; 63%

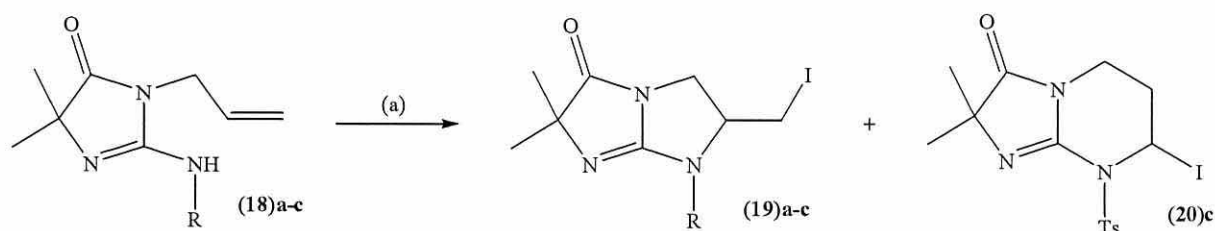
Substrate **13** was also employed in an iodocyclisation reaction and it was found that treatment with iodine in the presence of excess potassium carbonate led to the formation of heterocycle **17** in 85% yield. The reaction is presumably proceeding *via* the iodonium intermediate **16**. (Scheme 5)



**Scheme 5:** (a) 4 eq. I<sub>2</sub>, 4 eq. K<sub>2</sub>CO<sub>3</sub>, MeCN, 48 h; 85%.

Several relevant examples of the formation of nitrogen containing heterocycles by iodocyclisation are known in the literature. Watanbe<sup>8</sup> examined the iodocyclisation of 3-(alk-2-enyl)-2-(substituted amino)-1-imidazolin-4-ones **18a-c** (Scheme 6) and reported that the

regio- and stereo-selectivity of cyclisations was predominantly 5-*exo*-tet which led to the 5-membered product **19a-c** in the majority of cases. (Table 1)



**Scheme 6:** (a) I<sub>2</sub>, base, solvent. See table 1, R = Ph, 1-naphthyl, Ts.

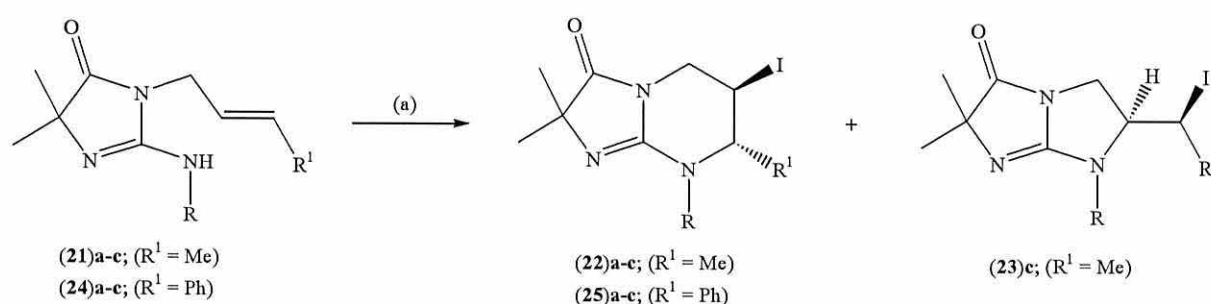
**Table 1:** Iodocyclisations of 3-allyl-5,5-dimethyl-2-(substituted amino)-1-imidazolin-4-ones (**18**).

Entry	Substrate	R	Solvent	K <sub>2</sub> CO <sub>3</sub>	Time	Products	Yield	Ratio
1	<b>18a</b>	Ph	DME	None	1d	<b>19a</b>	65%	N/A
2	<b>18a</b>	Ph	DME	2 eq	3h	<b>19a</b>	98%	N/A
3	<b>18b</b>	1-Naphthyl	DME	None	1d	<b>19b</b>	80%	N/A
4	<b>18b</b>	1-Naphthyl	DME	2 eq	1d	<b>19b</b>	83%	N/A
5	<b>18c</b>	Ts	DME	None	3d	<b>19c</b> <b>20c</b>	79% 9%	8.7:1
6	<b>18c</b>	Ts	DME	2 eq	3d	<b>18c</b> <b>19c</b> <b>20c</b>	70% 21% 4%	5.25:1
7	<b>18c</b>	Ts	MeCN	None	3d	<b>19c</b> <b>20c</b>	74% 8%	9.25:1

The reaction of imidazolinone **18a-c** with I<sub>2</sub> in DME (entries 1, 3 and 5) were generally high yielding leading to the products **19a-c** in 65-80% yield. The addition of two equivalents of potassium carbonate (K<sub>2</sub>CO<sub>3</sub>) led to higher yields for **19a** and **19b** (entries 2 and 4, 98 and 83%), however in the case of **18c** the reaction did not go to completion and the yield was low (entry 6). In the case of substrate **18c** where a tosyl group was present the 6-membered 6-*endo*-trig cyclisation product **20c** was formed in 4-9% yield (entry 5, 6) an attempt to suppress its formation using acetonitrile as solvent (entry 7) had little effect on regiochemistry or yield for the process.



Watanbe<sup>8</sup> also investigated the cyclisation of the 3-(*trans*-but-2-enyl) **21** and 3-(*trans*-cinnamyl)- **24** substrates. (Scheme 7 and table 2). Both imidazolines **21a-c** and **24a-c** yielded the 6-membered products **22a-c**, **25a-c** as single diastereomers in good yields (35-90%), with the reaction proceeding *via* the 6-*endo*-trig pathway. The addition of K<sub>2</sub>CO<sub>3</sub> led to very high yields (94% and 96%, entries 2 and 6) in the two examples given and only in one example, where again a tosyl group was present, (entry 7) was the 5-*exo*-trig product **23c** found in low yield.



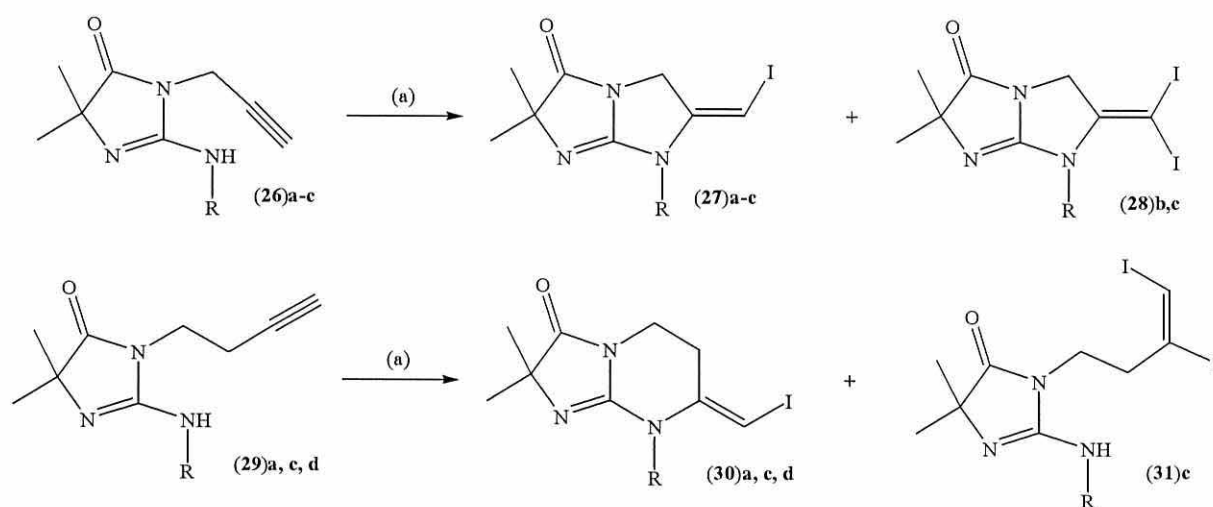
**Scheme 7:** (a) I<sub>2</sub>, base, solvent. See table 2, R = Ph, 1-naphthyl, Ts.

**Table 2:** Iodocyclisation of 3-(*trans*-cinnamyl)- (**21**) and 3-(*trans*-but-2-enyl)-5,5-dimethyl-2-(substituted amino)-1-imidazolin-4-ones (**24**).

Entry	Substrate	R	R <sup>1</sup>	K <sub>2</sub> CO <sub>3</sub>	Time (h)	Yield (%)
1	<b>21a</b>	Ph	Ph	None	24	<b>22a</b> 80%
2	<b>21a</b>	Ph	Ph	2 eq	3	<b>22a</b> 94%
3	<b>21b</b>	1-Naphthyl	Ph	None	24	<b>22b</b> 90%
4	<b>21c</b>	Ts	Ph	None	24	<b>22c</b> 77%
5	<b>24a</b>	Ph	Me	None	24	<b>25a</b> 35%
6	<b>24a</b>	Ph	Me	2 eq	3	<b>25a</b> 96%
7	<b>24c</b>	Ts	Me	None	24	<b>25c</b> 89% <b>23c</b> 3%

It was suggested that the stereoselectivity of the reaction was due to the formation of an iodonium ion which proceeds with retention of configuration of the alkenyl moiety and this ion is ring opened by the amino nitrogen in an S<sub>N</sub>2 fashion resulting in the inversion of configuration at this site.

Noguchi *et al.*<sup>9</sup> undertook further work examining the iodocyclisations of 3-alkynyl-2-(substituted amino)-1-imidazolin-4-ones. The propargyl containing substrates **26a-c** underwent smooth cyclisation to give the 5-*exo* products **27a-c** in 54-87% yield and in the case of the substrates **26b** and **26c** the diiodinated products **28b** and **28c** were also obtained in lower yields. The homologated substrates **29a,c,d** also cyclised smoothly to give the 6-*exo* products **30a,c,d** in 52-89% yield with only the diiodide addition product **31c** being obtained as a minor by-product in one example (entry 8). (Scheme 8 and Table 3)



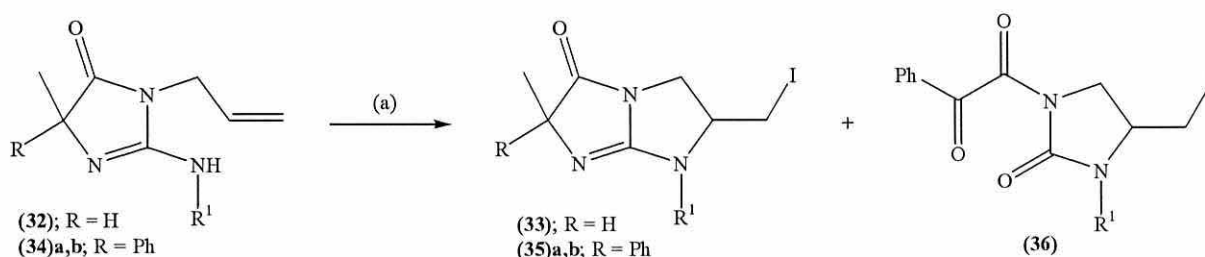
**Scheme 8:** (a) See table 3, R = Ph, *m*-Tol, 1-naphthyl, Ts.

**Table 3:** Iodocyclisation of Reactions of 3-alkynyl-5,5-dimethyl-2-(substituted amino)-1-imidazolin-4-ones (**26**) and (**29**).

Entry	Substrate	R	K <sub>2</sub> CO <sub>3</sub>	Time (h)	Yield (%)
1	<b>26a</b>	Ph	None	24	<b>27a</b> (77%)
2	<b>26a</b>	Ph	1 eq	6	<b>27a</b> (81%)
3	<b>26a</b>	Ph	2 eq	3	<b>27a</b> (74%)
4	<b>26b</b>	1-Naphthyl	None	24	<b>27b</b> (87%) <b>28b</b> (3%)
5	<b>26c</b>	Ts	None	24	<b>27c</b> (54%) <b>28c</b> (26%)
6	<b>29a</b>	Ph	None	24	<b>30a</b> (52%)
7	<b>29a</b>	Ph	1 eq	8	<b>30a</b> (89%)

8	<b>29c</b>	Ts	None	24	<b>30c</b> (67%) <b>31c</b> (8%)
9	<b>29d</b>	<i>m</i> -Tol	None	24	<b>30d</b> (80%)
10	<b>29d</b>	<i>m</i> -Tol	1 eq	24	<b>30d</b> (81%)

Further work by Noguchi *et al.*<sup>10</sup> used similar structures to those of Watanbe<sup>8</sup> and involved the iodocyclisation of the imidazolin-4-ones **32** and **34** which are either unsubstituted (R = H) or phenyl substituted (R = Ph) on the 5-position. (Scheme 9 and table 4).



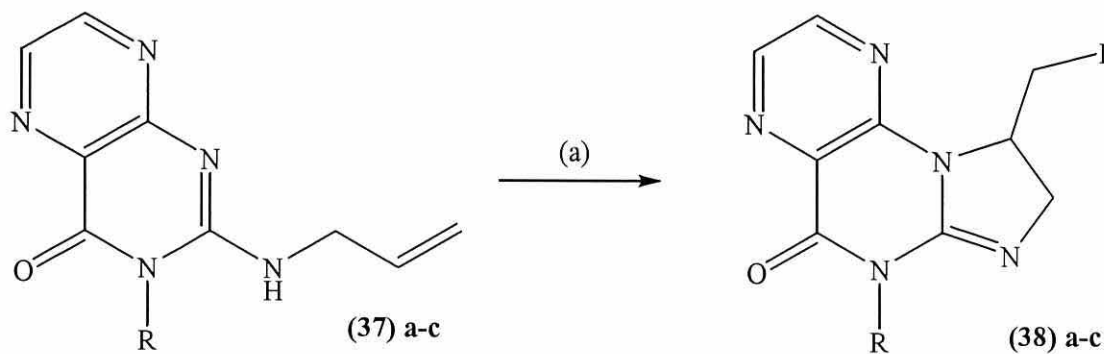
**Scheme 9:** (a) See table 4, R = Ph, *m*-Tol, 1-naphthyl, Ts.

**Table 4:** Iodocyclisation of imidazolin-4-ones **32** and **34a-b**.

Entry	Substrate	R	R <sup>1</sup>	K <sub>2</sub> CO <sub>3</sub>	Time (h)	Yield	Ratio Of Diastereoisomers
1	<b>32</b>	H	Ph	None	48	<b>33</b> (47%)	---
2	<b>32</b>	H	Ph	2 eq	2	<b>33</b> (75%)	---
3	<b>34a</b>	Ph	Ph	None	24	<b>35a</b> (88%)	(1:2)
4	<b>34b</b>	Ph	Ts	None	18	<b>36</b> (24%)	---

The 5-unsubstituted substrate **32** underwent iodocyclisation to give the 5-*exo* product **33** in good yield using iodine (entry 1), however a much improved yield of 75% was obtained using iodine in the presence of potassium carbonate (entry 2). The 5-phenyl substrate **34a** again underwent cyclisation to give a similar result in that **35a** was obtained in 88% yield as a 1:2 mixture of both diastereoisomers (entry 3), however in the case of **34b** where R<sup>1</sup> was a tosyl group the imidazolidin-2-one **36** was isolated in 24% yield together with an unidentifiable mixture of by-products.

Eguchi *et al.*<sup>11</sup> reported the iodocyclisation reactions of 2-allylaminopteridin-4-(3*H*)-one derivative **37a-c** with iodine/NaHCO<sub>3</sub> to give the imidazole-[1,2-*a*]-pteridines **38a-c** in excellent yields. (Scheme 10 and Table 5)



**Scheme 10:** (a) See table 5, R = Ph, 4-ClC<sub>6</sub>H<sub>4</sub>, 4-MeOC<sub>6</sub>H<sub>4</sub>.

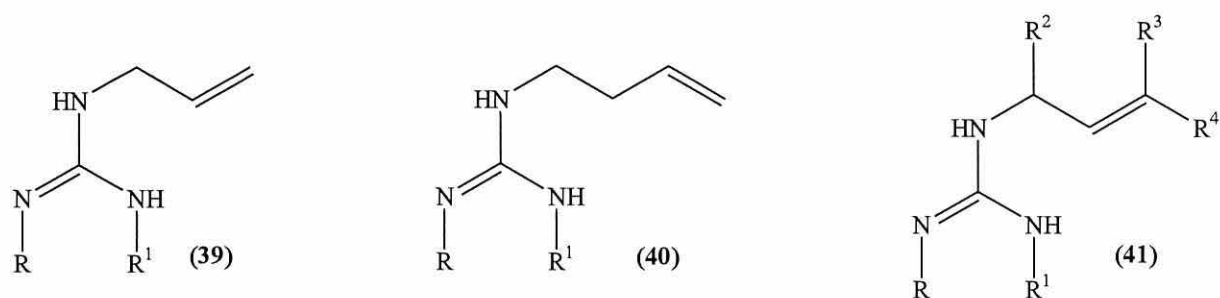
**Table 5:** Reactions of 2-allylaminopteridin-4-(3*H*)-one compounds with iodine.

Entry	Solvent	I <sub>2</sub>	Base	R	Product	Yield (%)
<b>37a</b>	dry THF	2.1 eq	NaHCO <sub>3</sub>	Ph	<b>38a</b>	99
<b>37b</b>	dry THF	2.1 eq	NaHCO <sub>3</sub>	4-ClC <sub>6</sub> H <sub>4</sub>	<b>38b</b>	100
<b>37c</b>	dry THF	2.1 eq	NaHCO <sub>3</sub>	4-CH <sub>3</sub> OC <sub>6</sub> H <sub>4</sub>	<b>38c</b>	87

## Aims of the Project

Previous work within the group<sup>6,7</sup> has focused on the ring opening of epoxides using guanidine itself together with *bis*-Boc protected guanidines leading to a range of heterocycles, as well as related iodocyclisation reactions. The reactions involving guanidine, whilst successful, presented problems associated with purification, as the unprotected guanidines are highly polar materials and difficult to separate from by-products of the process. Thus the aim of this study was to investigate the cyclisation reactions of protected *N*-allylated guanidines, with variations of the protecting group and nature of the allylic side chain.

The study of a range of simple substrates such as **39-40** in which a variation of protecting group, structure **39**, chain length, structure **40**, and level of substitution, structure **41** is envisaged. (Scheme 11)

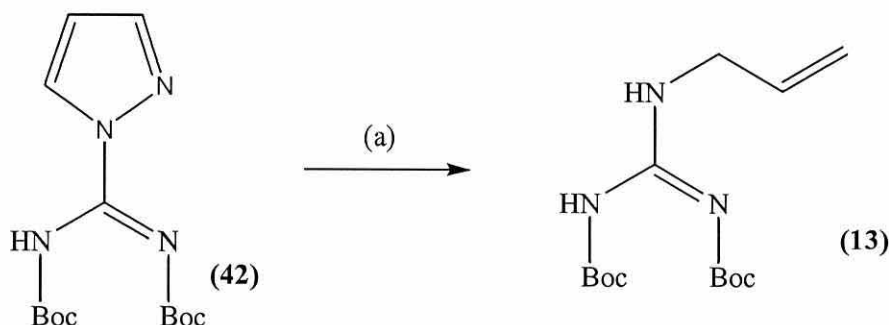


**Scheme 11:** R, R<sup>1</sup> = H, Boc, Z; R<sup>2</sup> - R<sup>4</sup> = H, alkyl, Aryl.

## Results and Discussion

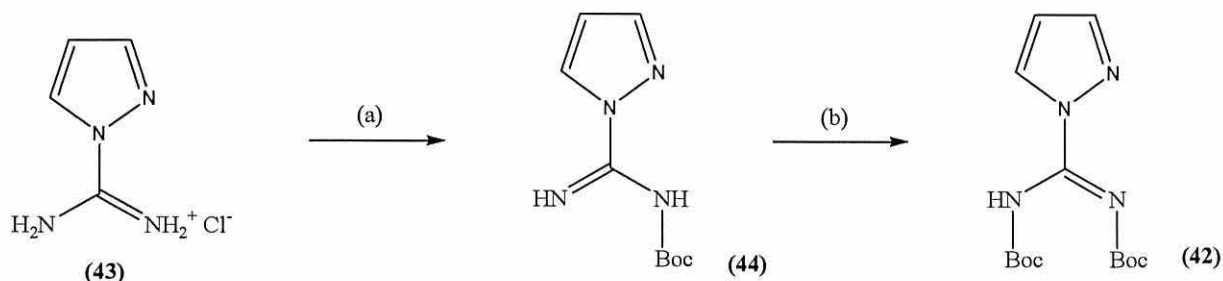
### Preparation of guanylyating agents

In order to access the substrates a convenient preparation of a range of protected allyl substituted guanidines was required. The previously prepared *bis*-Boc protected allyl guanidine **13** was prepared in 79% yield from the reaction of the commercially available (Aldrich<sup>®</sup> chemical company) *bis*-Boc-pyrazole-1-carboxamidine with allyl amine as reported by Drake *et al.*<sup>12</sup> (Scheme 12)



**Scheme 12:** (a) Allyl amine, CH<sub>3</sub>CN, rt., 16 h; 79%.

This reaction relies upon the leaving group ability of the pyrazole heterocycle and should offer a reasonable route to the required substrates. The reagent **42** is prepared in turn from 1*H*-pyrazole-1-carboxamidine **43** in a two stage process involving the *mono*-Boc protection with di-*tert*-butyl dicarbonate and diisopropylethyl amine to give **44** and the second protection using NaH as base also with di-*tert*-butyl dicarbonate. (Scheme 13)

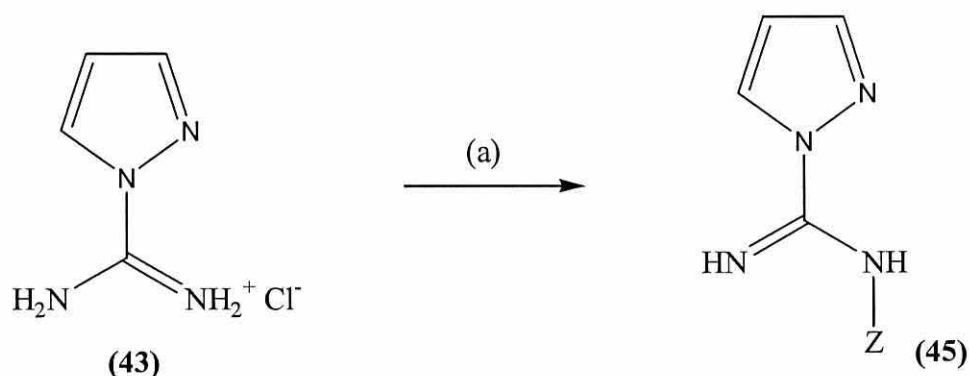


**Scheme 13:** (a) (*t*BuOCO)<sub>2</sub>O, THF, Et<sub>2</sub>iPrN, rt 16 h; 79%

(b) (i) (*t*BuOCO)<sub>2</sub>O, THF, NaH, 0 °C, 5mins, (ii) 67 °C, 4h.

We wished to prepare the *mono*-protected precursor **44** and thus treated 1*H*-pyrazole-1-carboxamidine **43** with di-*tert*-butyl dicarbonate and *N*-diisopropylamine in THF to give the required **44** as a crystalline product in 79% yield. The  $^1\text{H}$  NMR spectrum of **44** gave several diagnostic signals the first of which at  $\delta$  1.53 (9H) ppm is due to *t*-butyl of the Boc-protecting group. The signals of the pyrazole were seen at 6.38 (1H, d,  $J$  = 1.5 Hz), 7.66 (1H, m, obscured) and 8.44 (1H, d,  $J$  = 2.2 Hz) ppm whilst two broad NH signals were observed at 7.66 and 9.07 ppm. The  $^{13}\text{C}$  NMR spectrum gave seven diagnostic signals, with the protecting group signals at 28.1 (Me), 80.1 (C) and 163.2 (C=O) ppm and the pyrazole methynes at 108.9, 128.8 and 143.3 ppm. The guanidine gave a very characteristic signal at 155.0 ppm which is typical of other guanidines prepared within the research group. The IR spectrum had a carbonyl stretch at  $1667\text{ cm}^{-1}$ . The data was in accordance with the literature.<sup>13</sup>

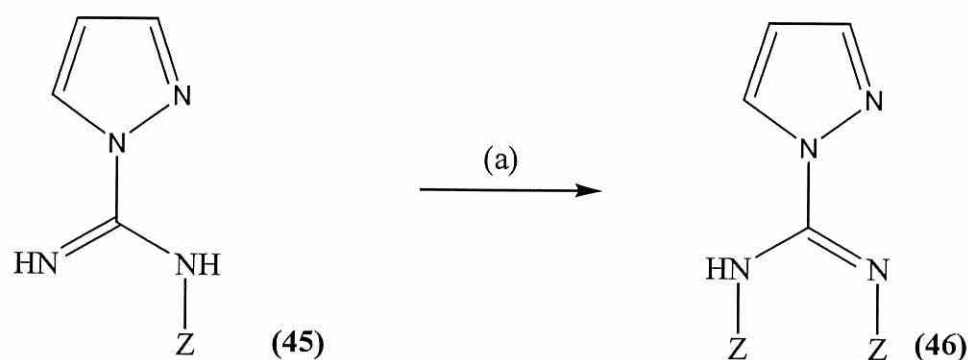
The preparation of the *mono*- and *bis*-Z protected guanidines **45** and **46** has also been reported and these were also prepared. Thus 1*H*-pyrazole carboxamidine hydrochloride **43** was treated with benzyl chloroformate and *N*-diisopropylethylamine in THF to yield **45** as a white solid in 88% yield. (Scheme 14)



**Scheme 14:** (a) Benzyl chloroformate, *N*-diisopropylethylamine, THF, 12 h; 88%.

The  $^1\text{H}$  NMR spectrum of **45** gave signals at  $\delta$  5.23 (s, 2H) and 7.40 (m, 5H) ppm for the benzyl group as well as signals at 6.44 (br s, 1H), 7.71 (br s, 1H) and 8.47 (br s, 1H) ppm for the pyrazole. The NH protons were observed at 7.70 (br s, 1H) and 9.06 (br s, 1H) ppm. As well as the required 10 signals in the  $^{13}\text{C}$  NMR, the IR spectrum gave stretches at  $3457$  and  $3275$  (N-H),  $1669$  (C=O) and  $1628$  (C=C)  $\text{cm}^{-1}$ . The data was in accordance with the literature.<sup>13</sup>

The second Z- protecting group was introduced by treatment of **45** with sodium hydride and CbzOSu in THF over 16 h to give the *bis*-Z-protected guanidine **46** in 46% yield after column chromatography. (Scheme 15)



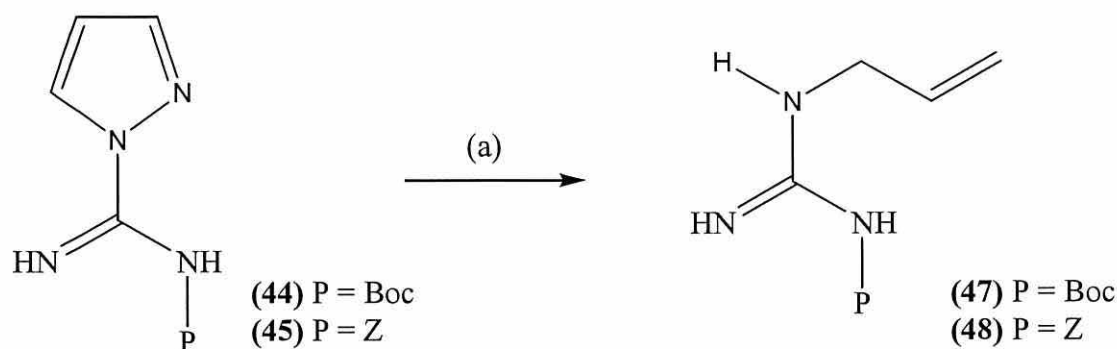
**Scheme 15:** (a) NaH, THF, 0 °C, CbzOSu, 16h; 46%.

The  $^1\text{H}$  NMR spectrum of **46** has a signal at  $\delta$  5.25 (s, 4H) and 7.39 (m, 10H) ppm due to the Z-protecting groups and three signals at 6.46 (dd,  $J = 2.7, 1.5$  Hz, 1H), 7.64 (br. s, 1H) and 8.30 (d,  $J = 2.7$  Hz, 1H) ppm for the pyrazole protons and a signal at 9.35 (br. s, 1H) ppm for the NH proton. The data was in accordance with the literature.<sup>13</sup>

## Preparation of the guanidine substrates

Having successfully prepared the desired guanylation agents we initially required a method for preparing the simple allyl substituted substrates **47** and **48**. Initial attempts followed the procedures reported by Drake *et al.*<sup>12</sup> in which the guanylation agent was added to a solution of the amine in acetonitrile and stirred overnight. This however was unsuccessful as the reactivity of the substrates **44** and **45** is lower than the corresponding *bis*-protected analogues. We next attempted the reaction of these substrates with neat allyl amine and found that after refluxing for 2.5 hours the substrates **47** and **48** were formed in 80% and 61% respectively. (Scheme 16)



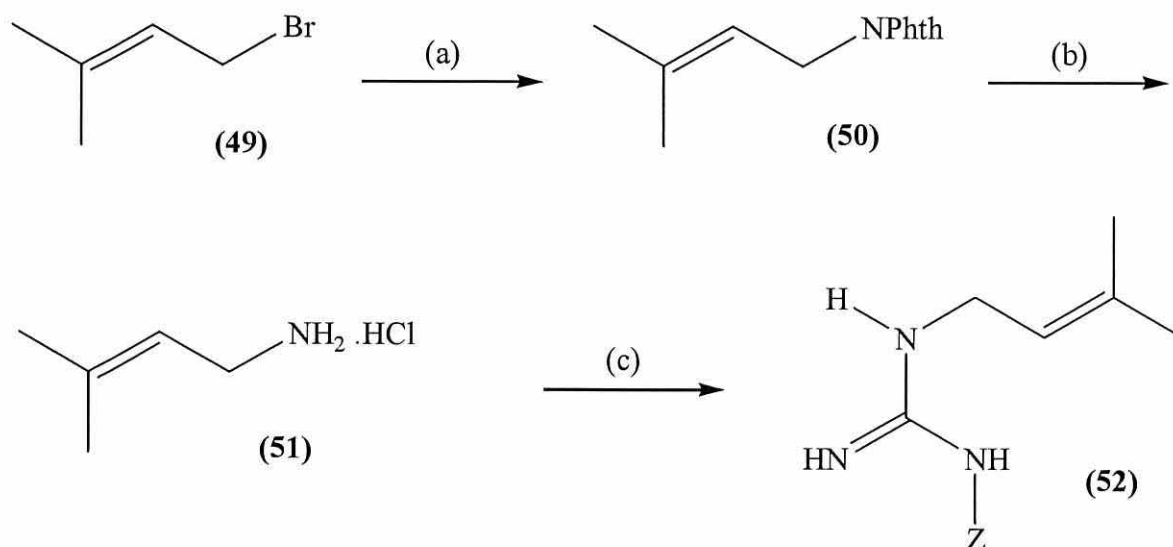


**Scheme 16:** (a) allyl amine reflux 2.5 h; 80% (**47**), 61% (**48**).

The  $^1\text{H}$  NMR spectrum of **47** has diagnostic signals at  $\delta$  1.46 (9H, s) ppm for the Boc-protecting group and the methylene of the allyl group at 3.83 (2H) ppm appearing as a doublet ( $J = 4.9$  Hz). Three signals at 5.24 (1H, d,  $J = 10.4$  Hz), 5.33 (1H, d,  $J = 17.1$  Hz) and 5.83 (1H, ddt,  $J = 17.1$  Hz, 10.4 Hz, 4.9 Hz) confirm the presence of the alkene protons and NH signals were also observed at 6.34 (1H) and 7.60 (2H) ppm. The  $^{13}\text{C}$  NMR spectrum of **47** gave diagnostic signals at 28.4 and 78.1 ppm for the methyls and quaternary carbon of the Boc-protecting group together with an alkene signal at 133.5 and two methylene signals at 43.9 and 117.3 ppm for the allyl group. Quaternary signals at 162.1 and 163.6 ppm were from the guanidine and Boc carbonyl groups. High resolution mass spectrometry gave an observed mass of 200.1391 which correlates well with the expected mass of 200.1394.

The  $^1\text{H}$  NMR spectrum of **48** had many similarities to the previously prepared Boc-protected **47**, with a methylene at  $\delta$  3.73 (2H, d,  $J = 4.9$  Hz) and signals at 5.23 (1H, d,  $J = 11.3$  Hz), 5.25 (1H, d,  $J = 16.8$  Hz) and 5.73 (1H, ddt,  $J = 16.8, 11.3, 4.9$  Hz) for the allyl group. The Z-protecting group gave a singlet at 5.07 (2H) ppm for the methylene and a multiplet at 7.35 (5H) ppm for the phenyl group. The  $^{13}\text{C}$  NMR spectrum of **48** gave signals at 133.6 (CH) ppm and two methylene signals at 41.9 and 116.4 ppm for the allyl function as well as diagnostic quaternary signals at 162.5 and 163.6 ppm for the guanidine and Z carbonyl groups. High resolution mass spectrometry gave an observed mass of 234.1245 which correspond well with the predicted mass of 234.1243.

We next required a synthesis of the dimethylallyl substituted guanidine **52** which we accessed from the commercially available dimethylallyl bromide **49** as shown below. (Scheme 17)

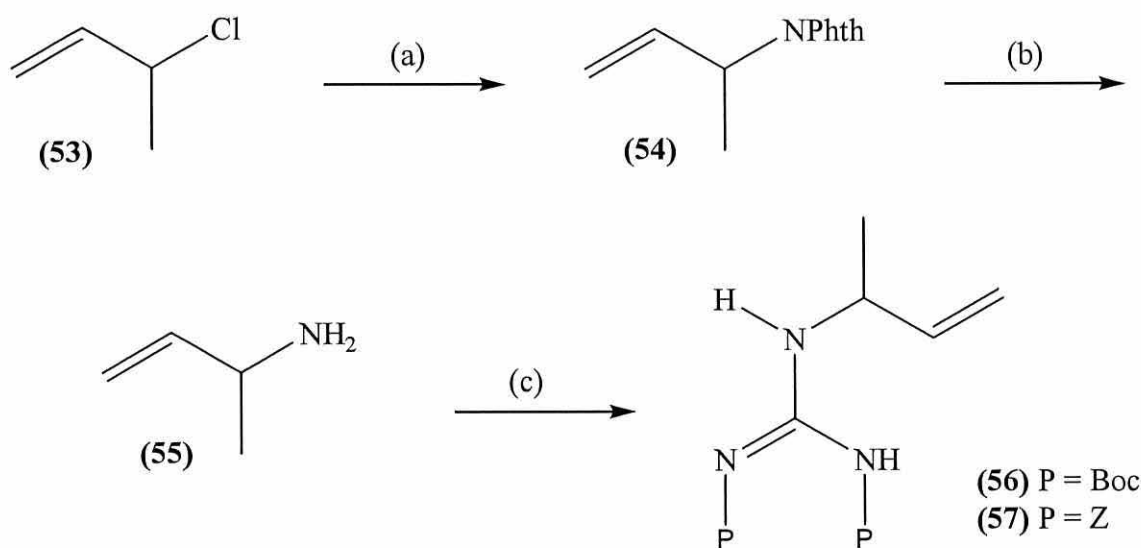


**Scheme 17:** (a) Potassium Phthalimide, DMF, stir 1 h, reflux 18 h; 65%. (b) i) IMS,  $\text{NH}_2\text{NH}_2 \cdot \text{H}_2\text{O}$ , Reflux 1.5 h; ii)  $0^\circ\text{C}$ , HCl (10N), iii) KOH (c) *N*-Z-1*H*-Pyrazole-1-Carboxamide **48**,  $\text{NEt}_3$ ,  $\text{CH}_3\text{CN}$ , 16 h; 39%.

Thus potassium phthalimide was reacted with 3,3-dimethylallyl bromide **49** in DMF at rt for 16 hours then at reflux for 8 hours following a literature procedure<sup>12, 14</sup> to give the N-allyl phthalamide **50** as an off-white solid in 65%. The  $^1\text{H}$  NMR spectrum of **50** has signals at  $\delta$  1.71 (3H) and 1.84 (3H) for the methyl groups and a doublet at 4.28 (2H,  $J = 7.3$  Hz) for the methylene group. A triplet was observed at 5.28 (1H,  $J = 7.3$  Hz) for the vinyl proton and the aromatic protons were a multiplet at 7.71-7.83 (4H). In addition the I.R of **50** had a band at  $1722\text{ cm}^{-1}$  for the C=O group. The data was in accordance with the literature.<sup>14</sup>

Treatment of **50** with hydrazine monohydrate in methylated spirits at reflux removes the phthalimido- protecting group and after the addition of HCl and drying yields a solution of dimethylallylamine hydrochloride. This was then treated with *N*-Z-1*H*-Pyrazole-carboxamide **48** and triethylamine. After stirring overnight and purification *via* column chromatography gave the required guanidine **52** was obtained in 39% together with unreacted **48** in 60% yield. The  $^1\text{H}$  NMR of **52** gave signals at  $\delta$  1.58 (3H, s) and 1.69 ppm for the two methyl groups as well as a doublet at 3.63 ppm (2H,  $J = 7.3$  Hz) for the methylene and a broad multiplet at 5.10 ppm for the vinyl proton. The Z protecting group was apparent at 5.05 (2H, s) and 7.31 (5H, m) ppm and a broad signal was present at 9.0 ppm (3H) for the amine protons. The  $^{13}\text{C}$  NMR spectrum gave 12 signals as expected and a carbonyl stretch was present at  $1627\text{ cm}^{-1}$  for the Z-protecting group within the I.R spectrum. High resolution mass spectrometry gave a mass of 262.1551 which in agreement for the required mass of 262.1550.

We next investigated the preparation of the  $\alpha$ -methyl substituted guanidines **56** and **57** and envisaged that they would be easily accessed from the known  $\alpha$ -methyl allylamine **55**. We thus took 3-chlorobut-1-ene **53** and treated it with potassium phthalimide in DMF to give the known<sup>11</sup> compound **54** as an off-white solid in 71% yield which had a melting point of 83-85 °C which was identical to the reported value. Treatment of **54** with hydrazine monohydrate in refluxing ethanol was followed by removal of the by-product by filtration and evaporation of the ethanol. After acidification the product was extracted with ether and fractionally distilled to give the required amine **55** which was unfortunately contaminated with ethanol from the deprotection step. Analysis of the NMR of **55** showed an approximate ratio of 1:1 for the amine: ethanol composition. This was felt not to be a problem as guanylation reactions of this nature had been reported using ethanol as the solvent.<sup>12</sup> The NMR of **55** gave a doublet at  $\delta$  1.15 (3H,  $J$  = 6.7 Hz) ppm for the methyl group as well as distinctive doublets at 4.95 ( $J$  = 10.4 Hz) and 5.08 ( $J$  = 17.1 Hz) ppm for the terminal vinylic protons. The other vinylic signal was a ddd at 5.85 ( $J$  = 17.1, 10.4, 6.1 Hz) ppm with the amine protons at 1.42 (2H) ppm and the methyne proton appearing as a multiplet at 3.47 (1H, m) ppm. The data was in accordance with the literature.<sup>8</sup> (Scheme 18)



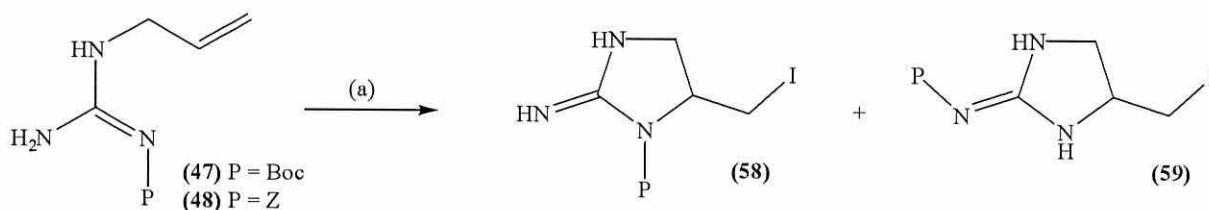
**Scheme 18:** (a) Potassium, Phthalimide, DMF, stir 16 h, reflux 8 h; 71%. (b) i)  $\text{NH}_2\text{NH}_2 \cdot \text{H}_2\text{O}$ , EtOH, reflux 3 h; ii) 0 °C, 10N HCl; iii) KOH. (c) *N,N'*-bis-Z-1*H*-Pyrazole-Carboxamidine **46**/ *N,N'*-bis-Boc-1*H*-Pyrazole-Carboxamidine **42**, EtOH,  $\text{CH}_3\text{CN}$ , 10 days; 70% (**57**).

We next investigated the reaction of **55** with the guanylation agent **42** and found that the reaction failed to give the desired guanidine **56** under standard conditions (excess amine in acetonitrile at RT). The reason for this failure may have been that the secondary amine is

more bulky than the normal primary amines we utilise and as the Boc protecting groups are also bulky the combined effect might have been preventing a rapid reaction. We thus envisaged that the reaction of the Z-protected guanylated agent **46** might offer a better alternative and attempted this reaction. We were pleased to find that the reaction, whilst sluggish (10 days), did proceed and if we used a sealed Carius tube this prevented evaporation of the amine which was a problem even with well sealed ground glass joints. After purification we obtained the protected guanidine **57** in 70% yield as a white crystalline solid. The  $^1\text{H}$  NMR spectrum of **57** has diagnostic signals  $\delta$  1.30 (3H, d,  $J = 7.0$  Hz) ppm for the methyl group and a ddd at 5.89 (1H,  $J = 17.5, 10.3, 4.6$  Hz) ppm for the vinylic proton. Other distinct signals were observed at 8.38 (1H, br. d,  $J = 6.7$  Hz) and 11.80 (1H, br. s) ppm for the guanidine NH protons. The  $^{13}\text{C}$  NMR was in agreement with the proposed structure with the vinylic carbons being present at 114.6 ( $\text{CH}_2$ ) and 138.3 (CH) ppm as well as high resolution mass spectrometry which gave an observed mass of 382.1789 which is in good agreement with the calculated mass of 382.1767. The data was in accordance with the literature.<sup>13</sup>

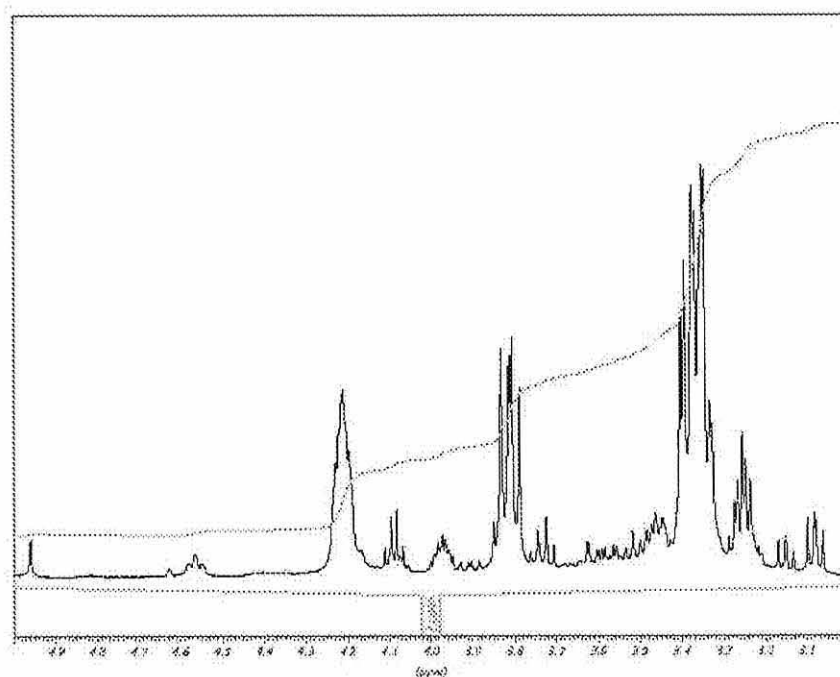
## Guanidine Iodocyclisations

With the precursor guanidines **47**, **48**, **52**, and **57** in hand, we next investigated the cyclisation reactions and initially studied the allyl substituted guanidines **47** and **48**. It was envisaged that the cyclisation of these substrates would lead to the 5-*exo*-products **58** and/or **59** which was in line with the studies on the *bis*-protected analogues **17**. (Scheme 19)



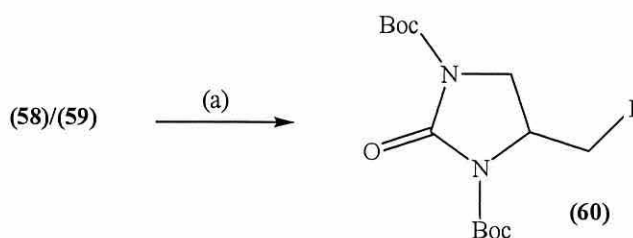
**Scheme 19:** (a) CH<sub>3</sub>CN, 4 eq. K<sub>2</sub>CO<sub>3</sub>, 4 eq I<sub>2</sub>.

Thus the guanidine **47** was treated with excess I<sub>2</sub> in acetonitrile containing a suspension of K<sub>2</sub>CO<sub>3</sub> at -15 °C to room temperature and stirred overnight. Analysis of the crude <sup>1</sup>H NMR (Fig. 4) indicated that predominantly one compound had been formed which had signals at δ 1.51 (9H, s) ppm for the tertiary butyl group and at 3.35 (3H, m), 3.81 (1H, dd, J = 9.3, 12.8 Hz) and 4.21 (1H, m) ppm for the 5 CH groups and at 6.58 (2H, br s) ppm for the guanidine NH protons. The crude <sup>13</sup>C NMR gave clear signals at 9.3 (CH<sub>2</sub>), 28.1 (3 x CH<sub>3</sub>), 53.8 (CH<sub>2</sub>), 57.7 (CH) for the ring CH and CH<sub>2</sub> carbons which would be expected for the structures **58/59**.



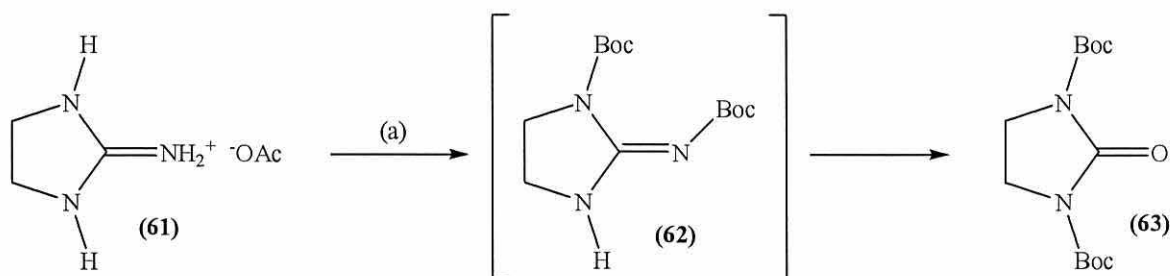
**Figure 4:** 500 MHz  $^1\text{H}$  NMR spectrum of crude compound **58/59**.

We attempted to purify this product by column chromatography and were surprised to find that we obtained a mixture of several compounds none of which appeared to be the originally isolated **58/59** as evidenced by  $^{13}\text{C}$  NMR. Previous workers in the group<sup>7</sup> had observed a migration of the Boc and Z-functional groups from the protected ring nitrogen (as in structure **58** for example) and had used a pre-stir with silica gel to effect a complete migration before purification. We thus took our crude product and stirred it with an excess of silica gel in dichloromethane for 5 days to effect complete rearrangement. This mixture was filtered through a sinter and washed first with dichloromethane and then with methanol and the two fractions were examined by NMR. The dichloromethane fraction which comprised 20% of the original reaction mass contained at least three different compounds with signals at  $\delta$  4.08, 4.18, 4.35 and 4.55 for the ring CH proton. Attempts to purify this by chromatography gave a single compound in 1.5% yield, which on analysis by MS gave a molecular weight of 427.0726 corresponding to the formula  $\text{C}_{14}\text{H}_{23}\text{N}_2\text{O}_5\text{I}$ . This appears to be the structure **60** in which the guanidine nitrogen has been substituted with an oxygen atom and an extra Boc protecting group has been acquired. (Scheme 20)



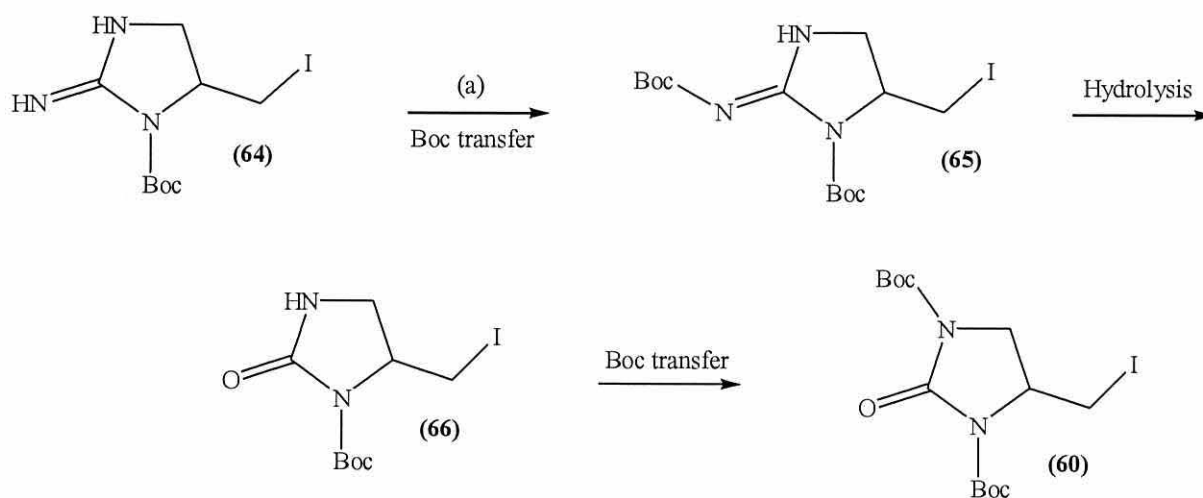
**Scheme 20:** (a) SiO<sub>2</sub>, DCM, stir, 5 days.

This strange result was supported by <sup>1</sup>H NMR evidence in which two <sup>t</sup>Bu groups of the Boc protecting groups were present at  $\delta$  1.49, 1.50 (18H, s, 2 x <sup>t</sup>Bu) ppm together with the 5 CH signals for the ring CH/CH<sub>2</sub> and the side chain CH<sub>2</sub>. The <sup>13</sup>C NMR spectrum had corresponding signals at  $\delta$  7.7 (CH<sub>2</sub>) ppm for the CH<sub>2</sub>I, at  $\delta$  28.0 (<sup>t</sup>Bu), 29.7 (<sup>t</sup>Bu), 83.7 (C) and 84.1 (C) ppm for the Boc protecting groups and at  $\delta$  45.9 (CH<sub>2</sub>) and 51.2 (CH) ppm for the ring carbons and at  $\delta$  148.1 (C), 150.0 (C) 150.1 (C) ppm for the guanidine and carbonyl quaternaries. As to how this compound has arisen, it was observed in the group<sup>15</sup> that protection of the simple guanidine **61** using excess NaH and (Boc)<sub>2</sub>O led to the urea **63** as the main product. It was put forward that this was occurring due to the hydrolysis of the intermediate **62** by NaOH which was present in the reaction mixture (from moisture and NaH) and protection of the second urea NH by excess reagent. (Scheme 21)



**Scheme 21:** (a) NaH, (Boc)<sub>2</sub>O, THF, 0 °C, 16 h.

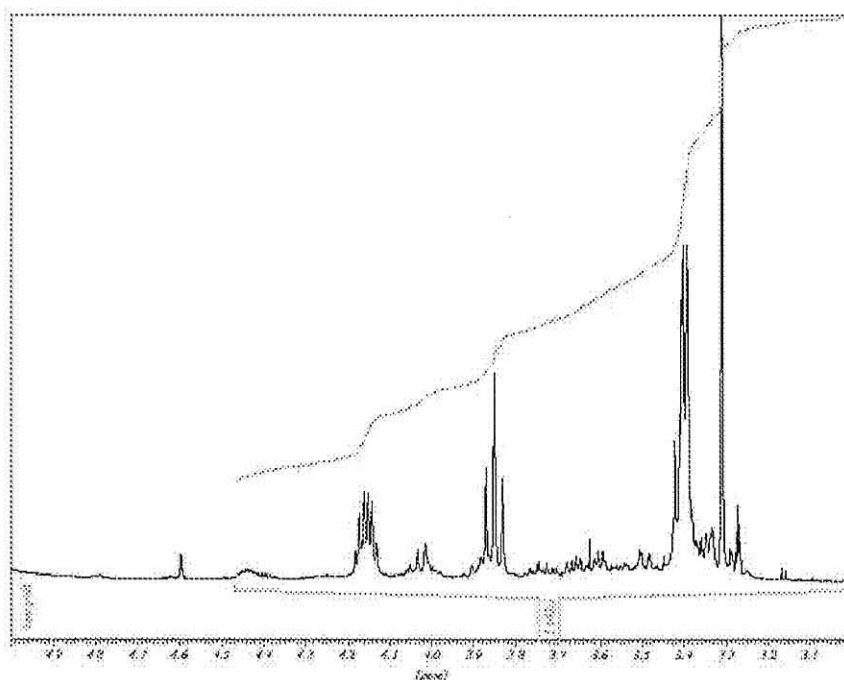
In the case of our work it is probable that the compound formed in the initial reaction is **64** and it is this which is acting as a Boc transfer agent leading to reactions with itself and giving several by-products, one of which might be **65**. This in turn is being hydrolysed to give the *mono*-protected urea **66**, which is then protected to give **60**. (Scheme 22)



**Scheme 22:** (a) SiO<sub>2</sub>, DCM, stir, 5 days.

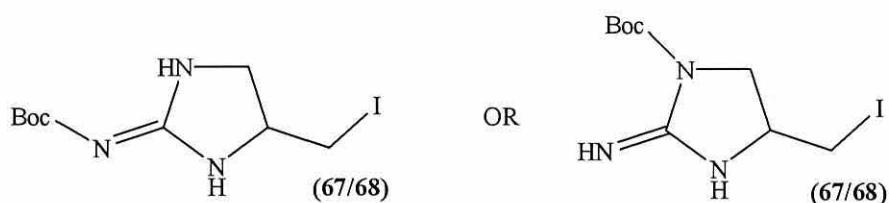
A consequence of this mechanism is that a completely unprotected iodo-guanidine should be formed in addition and it is likely that this will be found in the more polar methanolic fractions which comprised 57% by mass of the original crude product. Analysis of the <sup>1</sup>H NMR spectrum again suggested mainly one compound (Fig. 5) with signals at δ 3.40 (3H, m), 3.85 (1H, t, J = 10.0 Hz) and 4.15 (1H, m) ppm for the 5 CH groups. Analysis of the <sup>13</sup>C NMR spectrum again gave three major signals at signals at δ 11.9 (CH<sub>2</sub>) ppm for the CH<sub>2</sub>I, at 50.6 (CH<sub>2</sub>) and 57.1 (CH) ppm for the ring carbons again suggesting one compound however minor signals at δ 12.1/14.7 (CH<sub>2</sub>), 50.9/52.2 (CH) and 58.5/58.8 (CH<sub>2</sub>) suggested two other compounds as did the presence of multiple Boc signals at δ 27.9-29.4.





**Figure 5:** 500 MHz  $^1\text{H}$  NMR spectrum of crude MeOH extract.

Purification of the methanol fraction by chromatography gave two higher running compounds and a lower running compound. The higher running compounds were isolated in 6% yield and were partially separable giving similar spectral data which was indicative of the *mono*-protected compounds **67/68**. (Scheme 23)

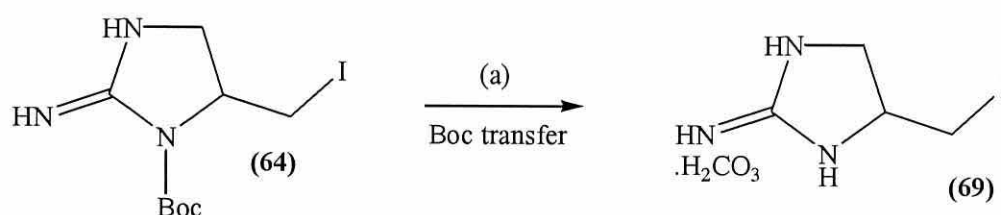


**Scheme 23:** *Mono*-Boc-protected guanidine.

Both compounds gave signals in the  $^{13}\text{C}$  NMR spectrum for the  $\text{CH}_2\text{I}$  carbon at 11.4/10.6 ppm and  $^t\text{Bu}$  carbons at 28.8/28.9, 83.6/88.6 and 165.4/169.0 ppm and other signals were seen for the ring  $\text{CH}_2$  at 57.8/49.1 and the CH at 55.5/59.0 ppm. In addition, analysis by high resolution MS confirmed the gross structures of the compound as **67** and **68**.

The final, more polar compound from the initial methanol fraction was isolated in 18% yield which from high resolution MS was found to be the deprotected guanidine **69**, with a measured mass of 225.9832 corresponding closely to the expected mass of 225.9836 for

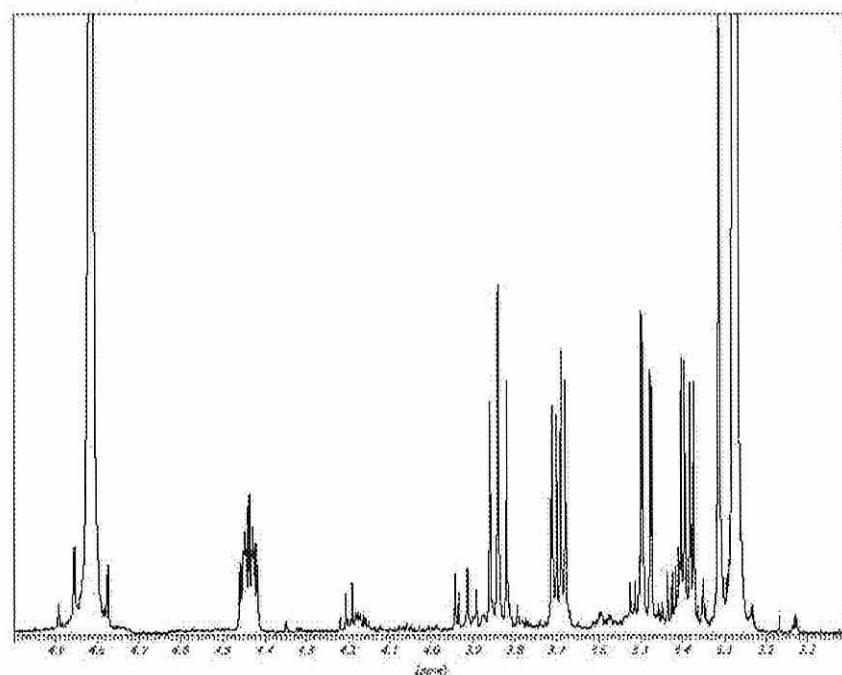
$C_4H_8N_3I$  ( $M+H$ )<sup>+</sup>. This was further confirmed by the  $^1H$  NMR which had a simple spectrum composed of a multiplet at  $\delta$  3.40 (3H, m) a triplet at 3.85 (1H, t,  $J = 10.0$  Hz) and a multiplet at 4.15 (1H, m) ppm. Analysis of the  $^{13}C$  NMR spectrum again gave four signals at  $\delta$  11.5 ( $CH_2$ ), 51.0 ( $CH_2$ ), 57.2 (CH) and 151.5 (C) ppm, together with a signal at 161.4 ppm which appears to be a carbonate carbon. The formation of a carbonate is to be expected as free guanidines are very hydroscopic and form hydrates readily<sup>16</sup> which then slowly convert to carbonates on exposure to air.



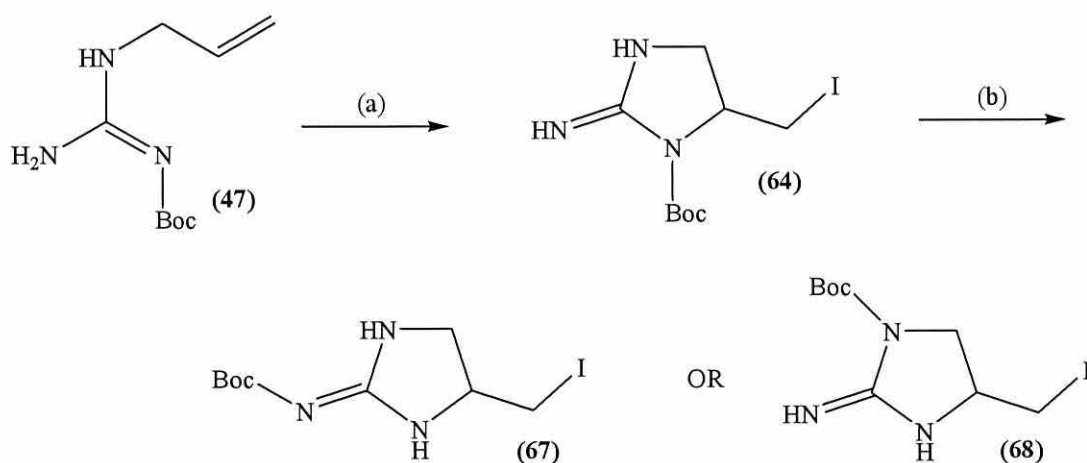
**Scheme 24:** (a)  $SiO_2$ , DCM, stir, 5 days.

The overall outcome of this reaction was quite disappointing, however on analysis of the original material from the cyclisation reaction we observed that a chloroform solution of the crude product **64** on standing in the freezer at  $-20$  °C underwent considerable decomposition/rearrangement and analysis of the NMR indicated the presence of at least four compounds. It was thus proposed that an acid catalysed rearrangement is occurring in solution and that this might be easier to control than the silica mediated rearrangement.

Based on this observation the reaction was repeated to give as before mostly one compound by NMR which was assumed to be **64**. The crude reaction mixture was then dissolved in methanol and a 5 fold excess of trifluoroacetic acid was added and the reaction stirred for 16 h. On NMR analysis it was apparent that the initial compound **64** had been converted to a single major compound which had a spectrum (Fig. 6) identical to the lower running *mono*-Boc protected isomer from the initial silica rearrangement experiments. (Scheme 25)



**Figure 6:** Product from rearrangement of crude 64.



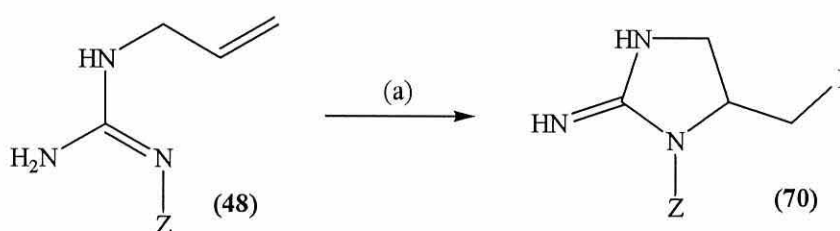
**Scheme 25:** (a)  $\text{CH}_3\text{CN}$ , 4 eq.  $\text{K}_2\text{CO}_3$ , 4 eq  $\text{I}_2$ ., (b) TFA, MeOH, 16 h; 70%.

The product was analysed by TLC and was again found to be unstable to chromatography as a 2 dimensional TLC analysis indicated considerable decomposition of the major spot. We were however able to purify the compound by recrystallisation from chloroform/petrol leading to a 70% yield of the single *mono*-Boc-protected compound **67/68** as a trifluoroacetic acid salt. The major question remaining to be answered was the exact structure of this compound and by using HMBC correlation studies it was found that the ring  $\text{CH}_2\text{N}$  signal had a strong correlation with the Boc carbonyl which indicates that the structure

of the compound formed is **68**. Analysis of the HMBC data is discussed later in this thesis (page 31).

The overall conclusion from this initial study is that the cyclisation appears to be fairly selective with a major product **64** being formed but that this compound is unstable to chromatography and undergoes rearrangement on treatment with acid to give **68** as the sole product.

We next investigated the cyclisation of the Z-protected guanidine **48** as it was thought that the Z-group might be less likely to undergo rearrangement. In line with the previous reaction, compound **48** was treated with  $\text{K}_2\text{CO}_3$  and  $\text{I}_2$  in acetonitrile at  $-15\text{ }^\circ\text{C}$  then warmed to room temperature slowly over 16 h. After aqueous work up, analysis of the chloroform  $^1\text{H}$  NMR spectrum indicated the presence of a major product **70** with signals at  $\delta$  3.28 (dd,  $J = 6.5, 9.8\text{ Hz}$ ), 3.38 (dd,  $J = 4.7, 9.8\text{ Hz}$ ), 3.70 (dd,  $J = 5.7, 10.7\text{ Hz}$ ), 4.05 (dd,  $J = 9.1, 10.5\text{ Hz}$ ) and 4.16 (dddd,  $J = 6.5, 4.7, 5.7, 9.1\text{ Hz}$ ) for the five expected CH protons. Similarly in the  $^{13}\text{C}$  NMR, the signal at 9.5 ppm corresponded to the  $\text{CH}_2\text{I}$  group which together with other resonances at 51.7 ( $\text{CH}_2$ ), 57.3 (CH) and 68.0 ( $\text{CH}_2$ ) ppm confirmed that cyclisation had occurred and that the product appeared to have a similar structure to the Boc-protected compound **64**. (Scheme 26)

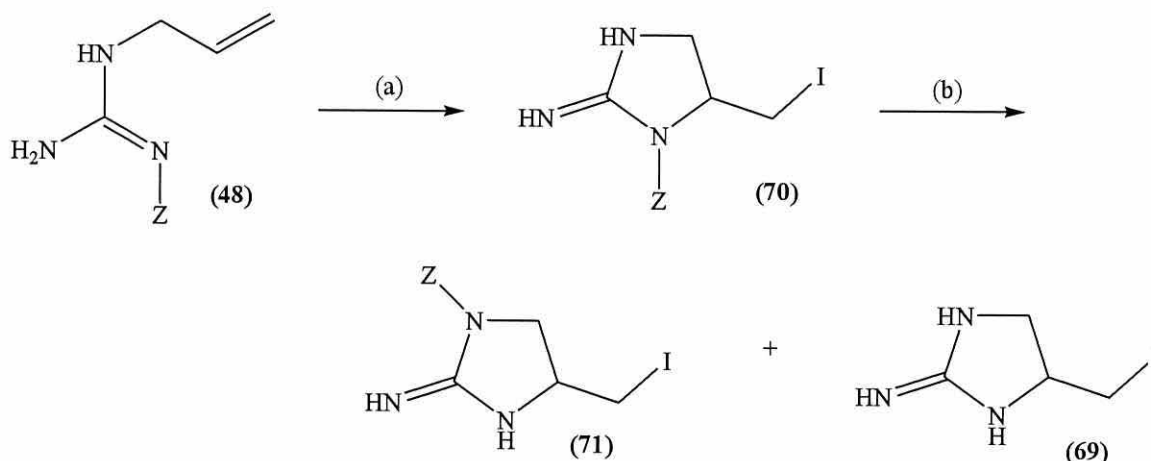


**Scheme 26:** (a)  $\text{CH}_3\text{CN}$ ,  $-15\text{ }^\circ\text{C}$ , 4.5 eq.  $\text{K}_2\text{CO}_3$ , 4.5 eq.  $\text{I}_2$ , stir.

Unfortunately on chromatography a similar process to that observed in the Boc series occurred and a mixture of compounds were formed in an irreproducible manner. Analysis of these compounds using high resolution MS indicated that they were isomeric with **70** but had dissimilar  $^1\text{H}$  and  $^{13}\text{C}$  data.

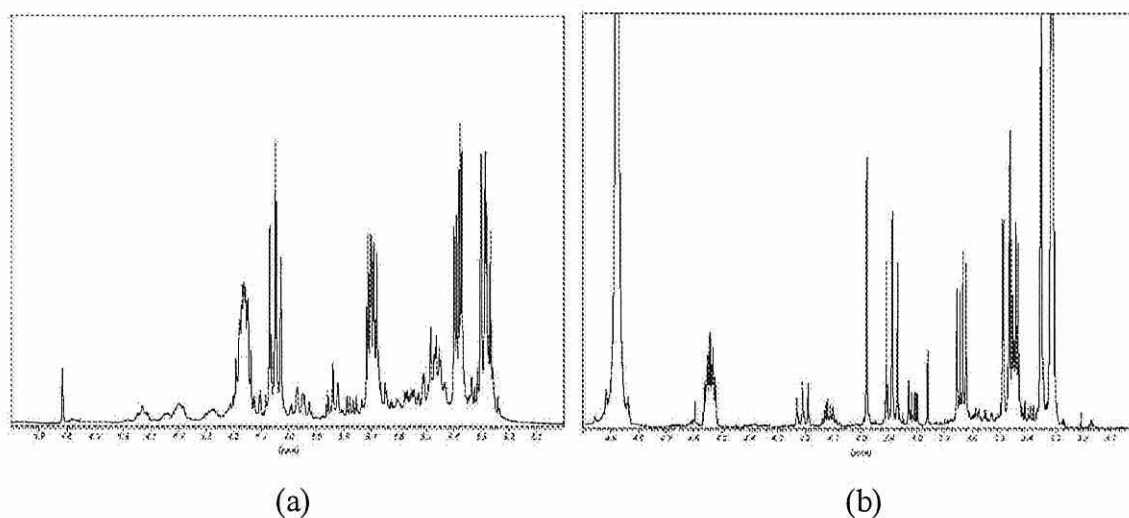
We again treated the crude mixture **70** with silica gel in dichloromethane and again found that two separate fractions were obtained, a dichloromethane soluble fraction and a methanol soluble fraction. The dichloromethane fraction appeared to contain one major compound and was subject to chromatography to give the isomeric *mono*-protected guanidine

**71** in 10% yield as determined by spectral data. In addition the methanolic extract on chromatography gave the previously isolated deprotected guanidine **69** in 22% yield. (Scheme 27)



**Scheme 27:** (a) CH<sub>3</sub>CN, 4 eq. K<sub>2</sub>CO<sub>3</sub>, 4 eq. I<sub>2</sub>, (b) TFA, MeOH, 16 h.

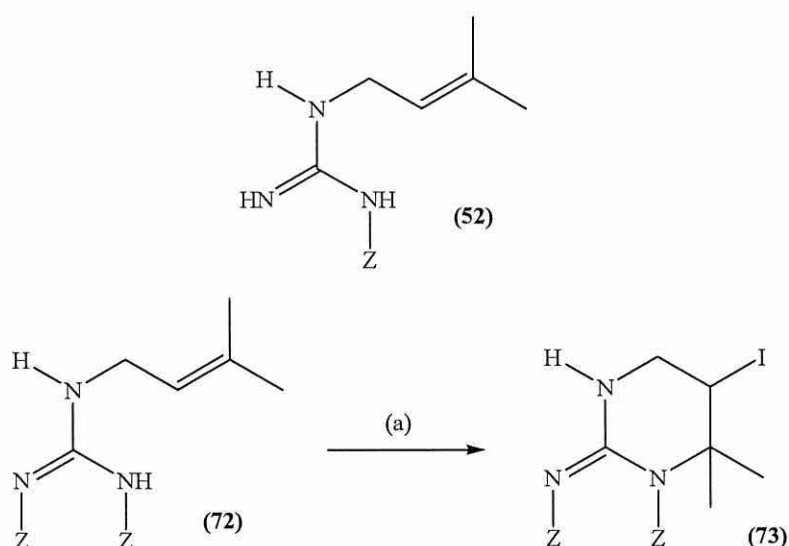
In order to ascertain if the Z-protecting group was migrating in a similar manner to that observed in the Boc-protected series, the reaction was repeated and the resulting crude compound **70** was treated with excess TFA in methanol overnight. This resulted in the formation of a major compound **71** (*ca* 92% from NMR) which was identical to the product isolated in the silica gel mediated migration and a previously unidentified minor product (*ca* 8% from NMR). A comparison of the crude unrearranged product **70** and the product from TFA treatment are shown in Fig. 7 and the new spectrum has CH signals at  $\delta$  3.45 (1H, dd,  $J = 10.7, 4.1$  Hz), 3.47 (1H, dd,  $J = 10.7, 1.9$  Hz), 3.64 (1H, dd,  $J = 10.7, 5.5$  Hz), 3.88 (1H, dd,  $J = 10.7, 9.8$  Hz), 4.54 (1H, dddd,  $J = 4.1, 1.9, 5.5, 9.8$  Hz) ppm which correlate very closely to the corresponding rearranged Boc protected guanidine **68**. The spectrum also shows partial data at  $\delta$  3.84 (1H, dd, 4.7, 10.7 Hz, CH), 4.14 (1H, app. pentet, 4.7, 9.4 Hz, CH), 4.23 (1H, dd, 9.4, 10.7 Hz, CH) ppm relating to the minor product, which upon attempts at isolation decomposed.



**Figure 7:** 500  $^1\text{H}$  MHz spectrum of crude **70** before (a) and after (b) treatment with trifluoroacetic acid.

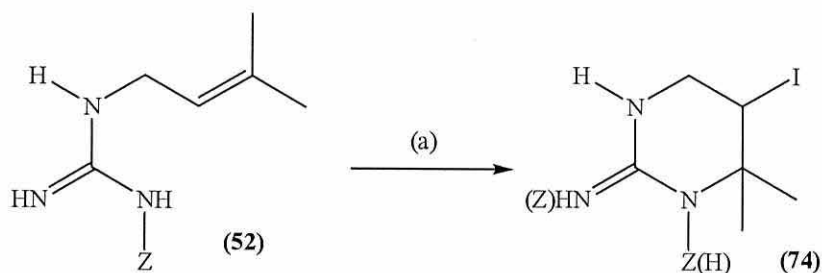
Analysis of **71** by 2D-TLC indicated that decomposition on silica was occurring, however, a high purity product could be obtained in 21% yield by two recrystallisations from dichloromethane/ether/hexane.

We next investigated the cyclisation of the *Z*-dimethylallyl guanidine **52**. In related work<sup>7</sup> it had been reported that the *bis-Z*-dimethylallyl guanidine **72** underwent cyclisation to give the 6-membered product **73** in 64% yield and we wished to see if a similar reaction was possible with **52**.

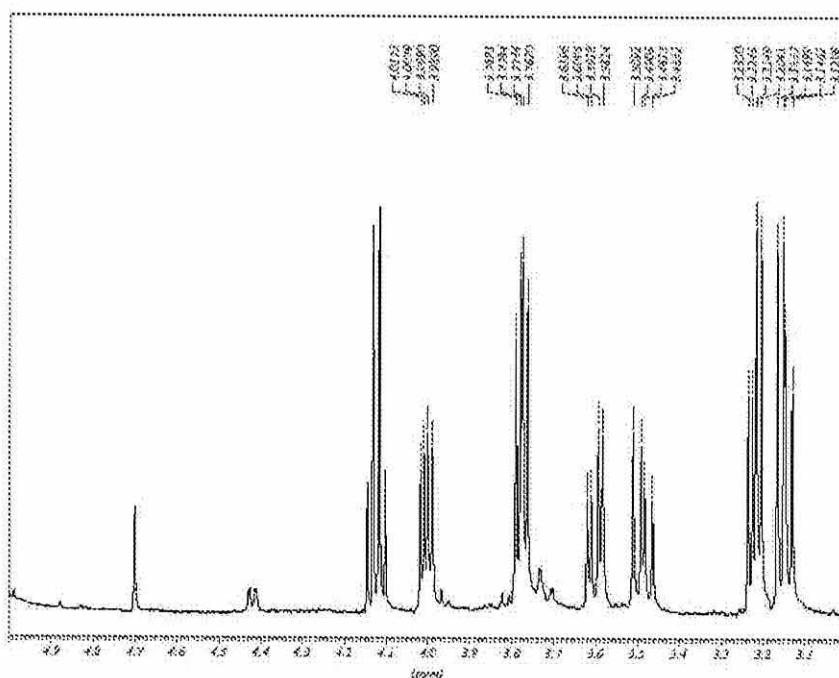


**Scheme 28:** (a)  $\text{CH}_3\text{CN}$ , 4 eq.  $\text{K}_2\text{CO}_3$ , 4 eq.  $\text{I}_2$ , 16 h, 64%.

We thus cyclised **52** under the previously utilised conditions and on work up obtained a product which appeared to be composed of two compounds in a 63:37 ratio by  $^1\text{H}$  NMR. Further analysis of the proton NMR indicated that the minor compound had an ABX coupling pattern at  $\delta$  3.49 (dd,  $J = 9.5, 13.6$  Hz), 3.60 (dd,  $J = 4.9, 13.6$  Hz) and 4.00 (dd,  $J = 4.9, 9.5$  Hz) ppm whilst the major product had a similar pattern at  $\delta$  3.14 (dd,  $J = 8.0, 10.0$  Hz), 3.22 (dd,  $J = 5.3, 10.0$  Hz) and 3.77 (dd,  $J = 5.3, 8.0$  Hz) ppm. (Fig. 8) Analysis of the  $^{13}\text{C}$  NMR was however quite perplexing in that the expected  $\text{CH}_2\text{N}$  signals were at 46.4 and 5.8 ppm. The first of these is as expected for  $\text{CH}_2\text{N}$  however the signal at 5.8 ppm suggests that a structure containing  $\text{CH}_2\text{I}$  has been formed. The corresponding CHI signal expected for **74** (Scheme 29) was observed at 29.3 ppm whilst a signal at 72.2 ppm was indicative of a CHN subunit.



**Scheme 29:** (a)  $\text{CH}_3\text{CN}$ , 4.5 eq.  $\text{K}_2\text{CO}_3$ , 4.5 eq.  $\text{I}_2$ , 16 h; 15%.



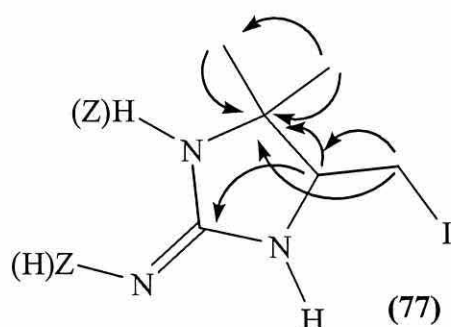
**Figure 8:** 500 MHz  $^1\text{H}$  spectrum of the crude product from the cyclisation of Z-dimethylallyl guanidine **52**.

As the spectroscopic data was somewhat confusing, attempts were made to separate the fractions by column chromatography, however as before considerable decomposition was observed. To circumvent this decomposition the mixture was treated as before with methanolic TFA to give on analysis a crude rearranged mixture containing two products. NMR analysis of the crude mixture indicated that the signals for the major product remained unchanged whilst the minor compound now had an ABX coupling pattern at  $\delta$  3.71 (br. dd,  $J = 7.3, 14.0$  Hz), 3.92 (br dd,  $J = 4.5, 14.0$  Hz) and 4.11 (dd,  $J = 4.5, 7.3$  Hz) ppm.

We next attempted to separate this mixture and found that on dissolving this crude product in dichloromethane, followed by dilution with diethyl ether and cooling ( $-20$  °C) overnight caused the precipitation of a pale yellow solid in 17% yield which proved to be the rearranged minor product. Chromatography of the residue on base washed silica enabled the separation of a low yield of the 6-membered product **74** in 15% yield.

The structure of the major product **74** was established by HMBC which indicated that no cross peak between the  $\text{CH}_2\text{N}$  and the carbonyl of the Z-group was observed, but a long range correlation between the  $\text{CH}_2$  in the Z group and the guanidine carbon was present. This suggests that the structure of **74** is as shown in Scheme 30 in which the cyclisation has occurred using the unsubstituted guanidine nitrogen leading to a stable structure which does not undergo rearrangement on treatment with acid.

The nature of the cyclic portion of the rearranged product was also established by a series of HMBC correlations and was found to be the 5-membered ring system **77** (Fig. 9). It is likely that a similar process is occurring to that observed in earlier examples in which the Z-group is migrating from one NH to a less hindered position. The position of the Z-group in **77** was not clear and could not be established by HMBC.

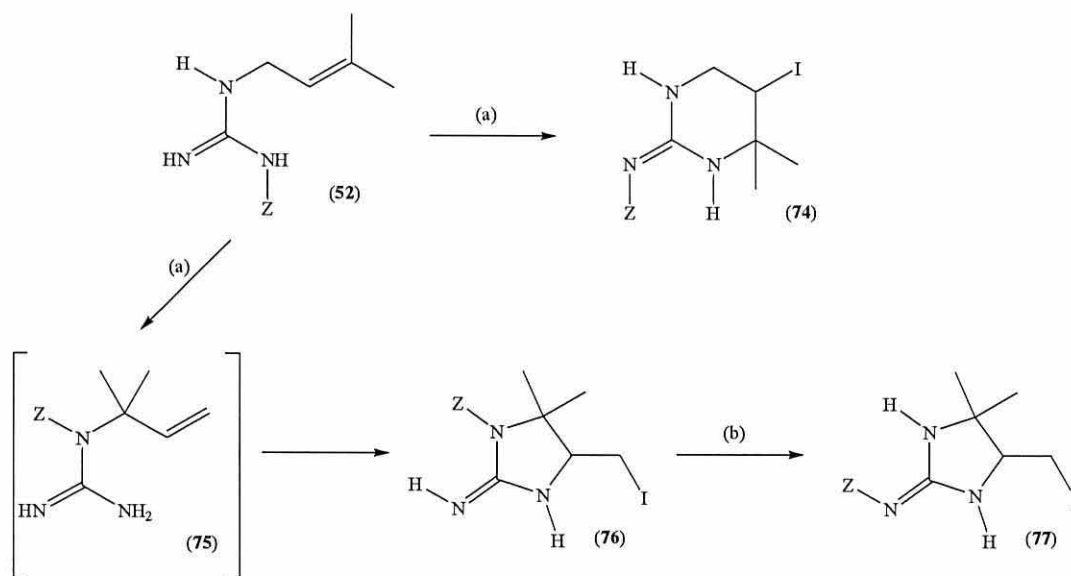


**Figure 9:** HMBC correlations in **77**.



We sought to investigate this reaction further and repeated it with a larger excess of potassium carbonate (6 equivalents) and were able to reduce the ratio of the two compounds to 80:20 in favour of **74**. We also performed a reaction where the amount of the base was reduced to 3 equivalents and this led to the formation of more of the rearranged intermediate product **76** to such an extent that it was now the major product in 35:65 ratio.

It was also found that dissolution of the crude mixture in methanol followed by cooling led to the complete precipitation of **74** leaving almost pure **76** in the mother liquor. HMBC analysis of **76** demonstrated that no correlation was present between the ring CH signals to the carbonyl of the Z-group which indicates that the cyclisation has led to the structure **76** (Scheme 30) and that the precursor to this must be the rearranged *N*-allyl guanidine **75**. In turn this establishes the structure of **77** as one in which the Z-group is on the exocyclic guanidine nitrogen, as again no correlation to the ring CH was observed by HMBC. (Scheme 30)



**Scheme 30:** (a) CH<sub>3</sub>CN, 4.5 eq. K<sub>2</sub>CO<sub>3</sub>, 4.5 eq. I<sub>2</sub>, 16 h; 15% (**74**). (b) TFA, MeOH, 16 h; 17% (**77**).

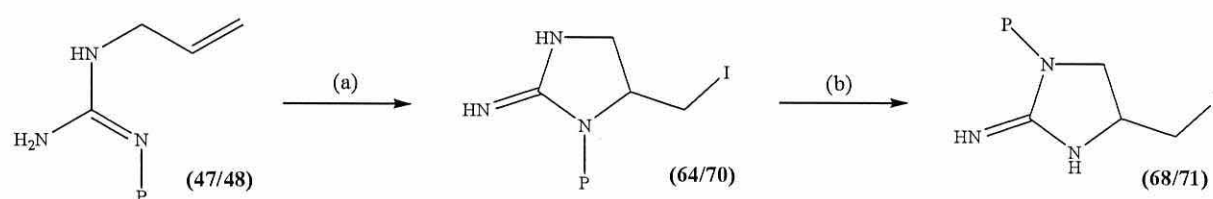
The nature of the rearrangement is interesting in that a formal [3,3]-shift of the dimethylallyl group in **52** is required in order that **76** might be formed. It is possible that rearrangement of the dimethylallyl group is occurring under acid catalysed conditions, however it is interesting that only a single rearranged product is observed and no isomer of the intermediate **75** are observed as might be expected if the rearrangement was *via* a prenyl

carbocation. This might suggest a different mechanistic pathway and investigation of this will require the synthesis of a range of isomers of **52** with differing substitution patterns.

Due to the complexity of the results for the iodocyclisation reactions, no detailed work was undertaken on the *N,N'*-Bis-*Z*-*N''*-(1-methyl-allyl)-guanidine **57** as it was envisaged that this would be extremely complex due to the introduction of diastereomeric isomerism as an additional factor on top of the protecting group migrations.

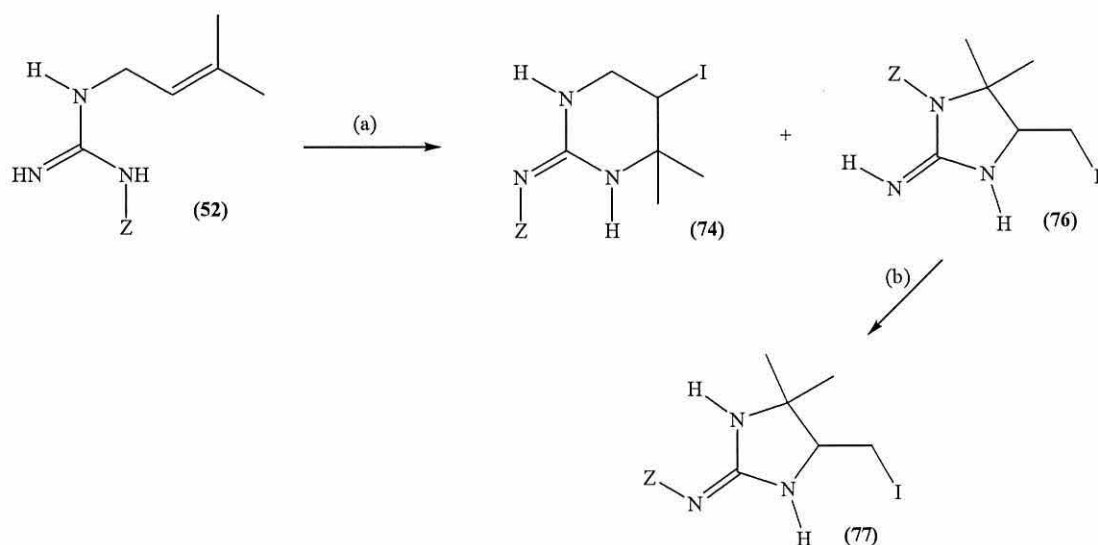
## Conclusion

The major conclusion from this work is that the cyclisation of the *mono*-protected guanidines is a considerably more complex process than for the *bis*-protected analogues. The initial cyclisation pathway in the 5-membered series involves the formation of a 5-membered product in which the N-protected position in the guanidine is intercepting the intermediate iodonium ion to generate the cyclic products **64** and **70**. These proved to be very sensitive to silica gel chromatography and are easily rearranged on treatment with dilute TFA to give the compounds **68** and **71**. These are probably formed in preference to the alternate exocyclic substitution products because of the increased nucleophilicity of the secondary amine position. (Scheme 31)



**Scheme 31:** (a) CH<sub>3</sub>CN, K<sub>2</sub>CO<sub>3</sub>, I<sub>2</sub>, 16 h. (b) TFA, MeOH, 16 h.

The dimethylallyl *mono*-Z-protected guanidine **52** however behaved in a totally different manner to the previously studied *bis*-Z-protected compound **72**. This underwent cyclisation to give the 6-membered product **74** which was stable to rearrangement with mild acid but not to silica gel and in contrast to **47** and **48** has cyclised on the unsubstituted guanidine nitrogen. In addition to this a rearranged compound **76** was formed which has arisen from a formal prenyl migration and this was unstable to acid and rearranged to give **77**.



**Scheme 32:** (a)  $\text{CH}_3\text{CN}$ ,  $\text{K}_2\text{CO}_3$ ,  $\text{I}_2$ , 16 h. (b) TFA, MeOH, 16 h.

The results of this study whilst somewhat complex could be of synthetic use and a more thorough investigation of the prenyl rearrangement will be of interest. Due to the nature of the PhD programme undertaken the direction of the work was changed after year 1 and was now directed towards the preparation of homochiral guanidines for use in asymmetric phase transfer catalysis.

**Applications of cyclic guanidines to  
phase transfer catalysis**

# Introduction

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## Phase Transfer Catalysis

A necessary condition for a reaction to proceed is to effect the collision of two reactant molecules. It is obvious that the reaction rate of two immiscible reactants is low is due to their low solubilities. A general method for overcoming this difficulty was to employ a protic or an aprotic solvent in order to improve their mutual solubilities (although this improvement was not very significant). A major step forward in solving the problems of two phase reactions was found by Jarousse in 1951<sup>17</sup> in which he reported that phenylacetonitrile can be alkylated with ethyl chloride and ~20% molar benzyltriethylammonium chloride in 50% aqueous NaOH solution. It was also noted that the reaction works less efficiently with ethyl bromide and does not proceed when ethyl iodide was used. At the time this contradicted the general knowledge within the organic chemistry community. Between 1965 and 1969 Makosza developed a general method for catalytic generation and reactions of carbanions<sup>18-23</sup> and dichlorobarbene<sup>24</sup> using aqueous NaOH and tetra-alkyl-ammonium (TAA) salts in a two phase system.

The term “phase transfer catalysis” was coined by Starks,<sup>25</sup> who in 1971 studied the reactions of inorganic anions catalysed by lipophilic tetra-*N*-alkyl-ammonium salts in two phase systems.

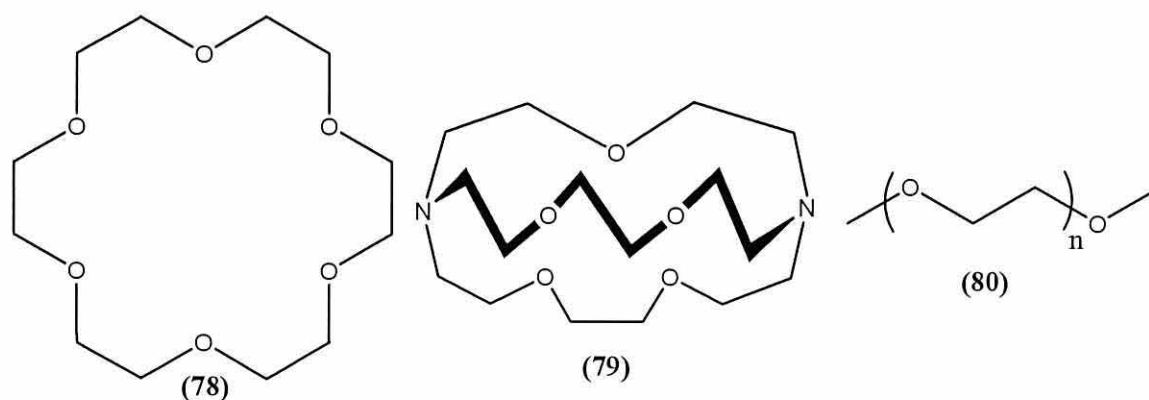
## Basic Principles

PTC differs from the general organic synthesis because the reactions are carried out in a heterogeneous two phase system in which the two phases observe negligible mutual solubility. In these systems the catalyst (a source of cations), located in the organic phase continuously introduces the reactive anionic species in the form of lipophilic ion pairs into the organic phase. There are two major groups which PTC methodology can be applied too: -

- 1) The reacting anions are available in the form of Na or K salts (e.g. NaCN,  $\text{KN}_3$ ,  $\text{KMnO}_4$ , etc.). In this system the cations of the catalyst simply transfer the anions into either the organic phase or the interface in the form of lipophilic ion pairs which are produced *via* ion exchange.
- 2) The reacting anions are generated in situ from the corresponding precursors (e.g. CH, OH, NH, etc.) due to the presence of base in the inorganic phase. In this system the catalyst is involved in both the formation and transfer of the reacting anions into the organic phase.

Organic syntheses carried out in heterogeneous system generally proceed *via* adsorption of reacting molecules on the solid surface, chemical transformations in the adsorbed state, and the release of the products from the surface to the bulk of the gas or liquid phase. PTC's operate in a different way; the organic reactants (neat or in an organic solvent) are located in the liquid organic phase, whereas inorganic salts or bases as aqueous solutions or in a solid state form the inorganic phase. The catalyst is dissolved in the organic phase and continually introduces the reacting species into the organic phase. This means that although PT-catalysed reactions occur in heterogeneous systems they can also proceed to a substantial extent in homogeneous solutions.

As well as the previously mentioned TAA salts, stable organic cations such as trialkylsulfonium, tetraalkylphosphonium, arsonium, *etc.* can also function as PT catalysts. Another category of PT catalyst also exists, neutral organic molecules which are able to form stable complexes or solvates with  $\text{Na}^+$  or  $\text{K}^+$  cations. These complexes are lipophilic cationic species, which enable the introduction of anions into the nonpolar organic phase. Crown ethers and cryptands (**78**, **79**) are the most common species used for this purpose.<sup>26</sup> However, ethers, polyethylene glycols (**80**) and solvents such as HMPT, DMSO and DMF can behave similarly.



**Figure 11:** Representative structures for compounds able to complex alkali metal cations.

A fundamental rule of PT-catalyzed reactions is that the concentration of the anions in the organic phase cannot exceed the concentration of the catalyst (usually 1% molar). This means that most PT-catalyzed reactions can be carried out without organic solvents (provided that the starting materials are liquid and hence can act as the solvents for the reacting species). Because the anions in the organic phase are salts in which partial covalent bonding and coordination between anions and cations are negligible the anions are in a very reactive form; hence, the rate constant of the reactions are usually high. Therefore in spite of the low concentration of the reacting species the overall rate for the process is satisfactory, mainly because the low concentration of the anion is compensated by the high concentration of the second reactant (more so when used neat).

As previously stated PT-catalyzed reactions are carried out in systems comprising of two mutually immiscible phases, two types of which are: liquid-liquid and liquid-solid

## Liquid-Liquid PTC

Quaternary salts, crown ethers, cryptands and polyethylene glycol (PEG) are the most common agents used for liquid-liquid phase transfer catalysis (LLPTC). There are two reaction mechanisms which have been used to describe the phenomena of two-phase PTC – Stark's extraction mechanism<sup>25, 27-31</sup> and Makosza<sup>32, 33</sup> interfacial mechanism.

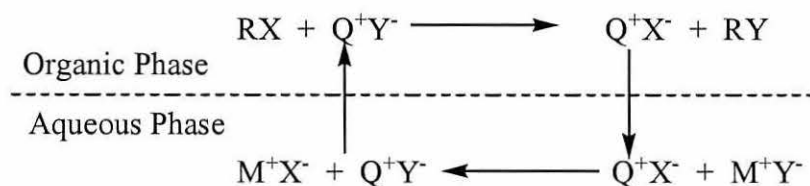
### 1) Stark's extraction mechanism

This reaction mechanism is widely accepted for a catalyst transferring between the two phases. These reactions involve the reactant reacting with the catalyst in the normal phase forming an intermediate catalytic species. Transfer of the intermediate catalytic species from



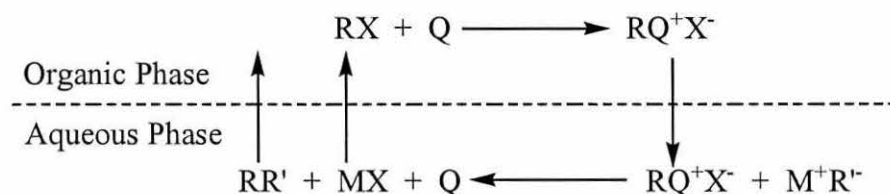
the normal phase to the reaction phase then occurs and the reformed catalyst is then transferred from the reaction phase to the normal phase and the process repeated. The reaction mechanism can be separated based upon the reaction path:

a) Normal Liquid-Liquid Phase Transfer Catalysis (N-LLPTC)



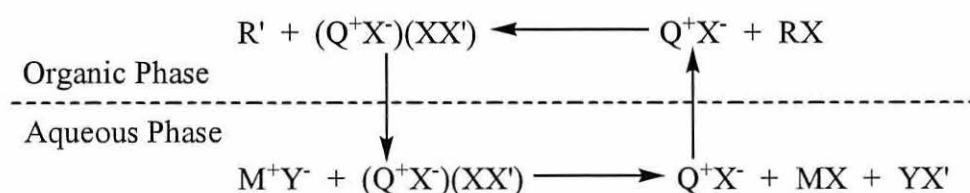
Normal Liquid-Liquid Phase Transfer Catalysis is traditionally the most widely reported LLPTC. The reaction mechanism above was first presented by Starks for the reaction of 1-chloro-octane and aqueous sodium cyanide in 1971.<sup>25</sup> This reaction method is mostly applied to alkylation, esterification, etherification and simple displacement reactions in which the nucleophilic agent transferred to the organic phase through the soluble catalyst.

b) Inverse Liquid-Liquid Phase Transfer Catalysis (I-LLPTC)



In this method the organic reactant is converted into a reactive ionic intermediate (by means of a reagent, e.g. pyridine-1-oxide). The intermediate can then be transferred into the aqueous phase where reaction takes place to produce the desired product. This process has been termed inverse phase transfer catalysis.<sup>34-36</sup> There are several examples where I-LLPTC has been used to synthesise acid anhydrides *via* substitution reactions and ketones *via* oxidation reactions.<sup>37-40</sup>

c) Reverse Liquid-Liquid Phase Transfer Catalysis (R-LLPTC)

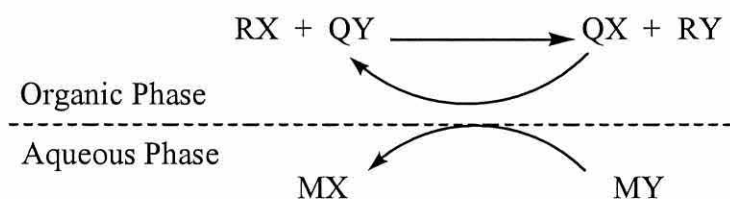


The dehydrohalogenation reactions of alkyl halides take place in the presence of hydroxide ion and quaternary salts to form the alkenes and alkynes.<sup>41-43</sup> The

dehydrohalogenation in this system is promoted by the hydroxide ion. In general, two reaction types conducted in this system were with highly lipophilic ammonium cation and 50% aqueous sodium hydroxide.

## 2) Makosza's interfacial mechanism

The mechanism described by Makosza and Bialecka<sup>32,33</sup> is also accepted as a method for anion transport between two phases. Reactions occurring in these systems involve the transfer of ionic reactant from its normal phase as well as the catalyst from the reaction phase to the interfacial region. The ionic reactant reacts with the catalyst in the interfacial region, forming an intermediate catalytic reactant, which is transferred into the reaction phase. The intermediate catalytic reactant then reacts with untransformed reactant to form the product and the recovery of the catalyst. The reaction mechanism can be expressed as follows:



The mechanism above can be applied to carbanion reactions, carbene reactions, condensation polymerization and C-alkylation of active methylene compounds. In the majority of cases the reaction involves the  $Q^+OH^-$  complex as the  $QOH$  is highly hydrophilic and has extremely low solubility in the organic phase. The mechanism is also applied when the quaternary salt is too lipophilic to dissolve in the aqueous phase, thus residing in the organic phase. This type of reaction proceeds *via* anion exchange occurring at or near the interface. This mechanism is called the Brändström-Montanari mechanism. The ion exchange reaction at the interface was verified by both Brändström<sup>44</sup> and Landini *et al.*<sup>45</sup>

## Liquid-Solid-Liquid PTC

LSLPTC is used as a method for solving the problem of the mutual insolubility of nonpolar and ionic compounds.<sup>27-30, 46</sup> Two compounds in immiscible phases can react because of the PT catalyst. However, in processes involving two phase PT-catalysed reactions separating the product from the catalyst can be problematic. Regen<sup>47</sup> first used a solid phase catalyst in which a tertiary amine was immobilised on a polymer support in the reaction between organic and aqueous reactants. From an industrial application point of view the

catalyst can be separated easily *via* filtration or centrifugation. Most methods used for triphase catalysis were studied by Regen and Beese<sup>47-51</sup> and Tomoi and co-workers.<sup>52-56</sup>

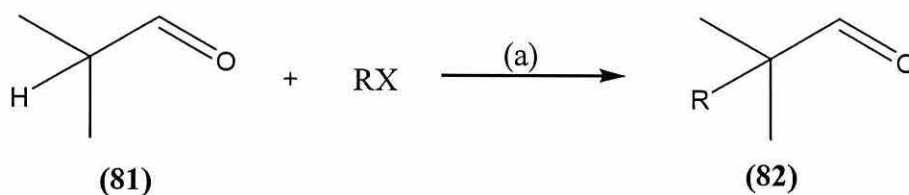
Generally the reaction mechanism involves (i) transfer of reactants from the bulk solution to the surface of the catalyst pellet, (ii) diffusion of the reactant to the interior of the catalyst pellet through pores and (iii) reaction of reactant with the active sites. Triphase catalysis is more complicated than traditional heterogeneous catalysts as both the organic species and aqueous species exist within the pores of the polymer pellet. Various mechanisms have been proposed for triphase catalysis by research groups such as Tundo and Venturello,<sup>57, 58</sup> Telford *et al.*<sup>59</sup> Schulnt and Chau<sup>60</sup> and Tomoi and Ford<sup>52</sup> *e.t.c.* However, each mechanism can only explain a single reaction system.

## Practical Applications of PTC

### Alkylation

#### 1) Alkylation of Carbanions

Dietl and Brannock<sup>61</sup> found that the alkylation of aldehydes containing only one  $\alpha$ -hydrogen atom, **81** proceeded when the aldehyde was treated with certain organic halides in the presence of 50% aqueous NaOH and catalytic amounts of tetra-butyl ammonium ions. They carried out a series of experiments using isobutyraldehyde (Scheme 33). Yields of 15-75% were observed with  $R = C_6H_5CH_2$ ,  $X = Cl$  and  $Y = I$  being the most successful.

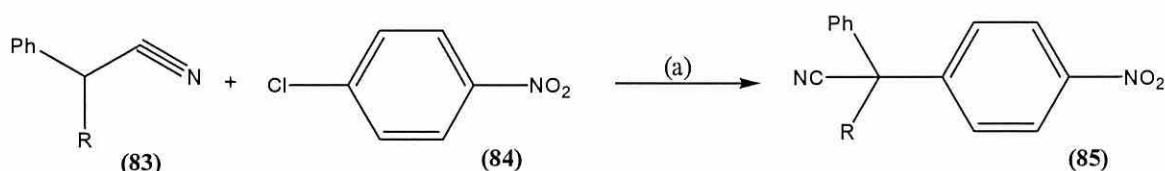


**Scheme 33:** (a) NaOH, Bu<sub>4</sub>N<sup>+</sup>Y<sup>-</sup>; 15-75%.

One of the problems associated with the alkylation of isobutyraldehyde is its tendency towards base-catalysed self-condensation. To help avoid this side reaction an inert solvent

(benzene) and an elevated temperature (50-80 °C) was used in order to minimize the formation of an *O*-alkylated trimer of isobutraldehyde. It was found that whilst reactive halides and benzylic halides could alkylate isobutraldehyde relatively successfully the less reactive halides could not compete with the base-catalysed self-condensation.

Makosza<sup>62</sup> showed that no reaction occurred between 2-phenylpropionitrile, **83**, *p*-chloronitrobenzene, **84**, in 50% NaOH solution. However, the addition of catalytic amounts of tetraethyl ammonium chloride resulted in an exothermic reaction forming 2-(*p*-nitophenyl)-2-phenylpropionitrile, **85** in a yield of 82%.

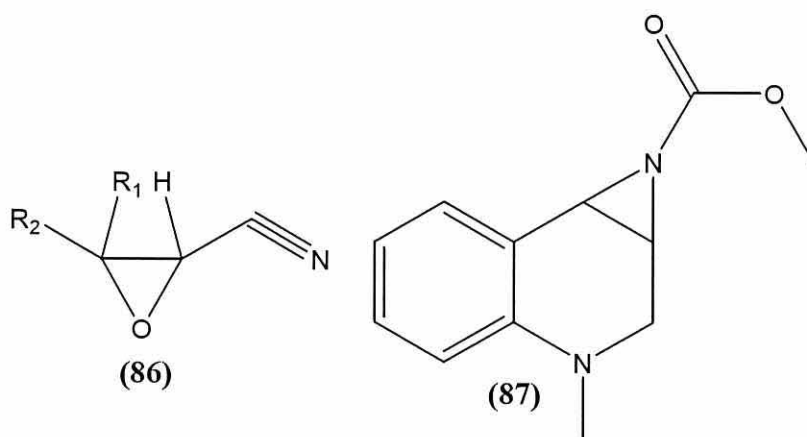


**Scheme 34:** (a) NaOH, TEBA-Cl; 82%.

Similar results were obtained for other nitriles of this type; however, benzene was needed in the case of solid nitriles. Makosza extended his studies, adding a third substituent in the benzene ring. In all the cases studied the chlorine atom in the *para* position (relative to the nitro group) was replaced and the nitroarylated nitrile products were obtained in good yields (52-92%).

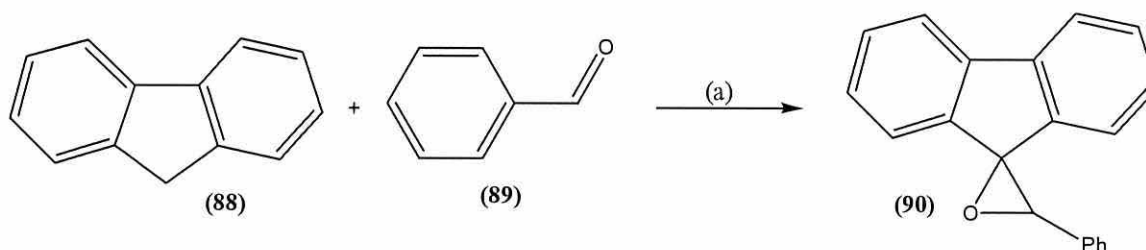
## 2) Darzens Reaction

Whilst the Darzens condensation was previously thought to need strictly anhydrous conditions and strongly basic agents Makosza<sup>63</sup> found that with PT-catalysis the reaction could be carried out in aqueous NaOH with quaternary ammonium catalyst. The resulting oxirane **86** could be achieved with yields as high as 45% (Fig. 12). Greibrokk<sup>64</sup> used similar PT conditions to synthesise the aziridine **87** in a yield of 73% although the product was not formed *via* a Darzens condensation. (Fig. 12)



**Figure 12:** Oxirane **86**, and Aziridine **87**.

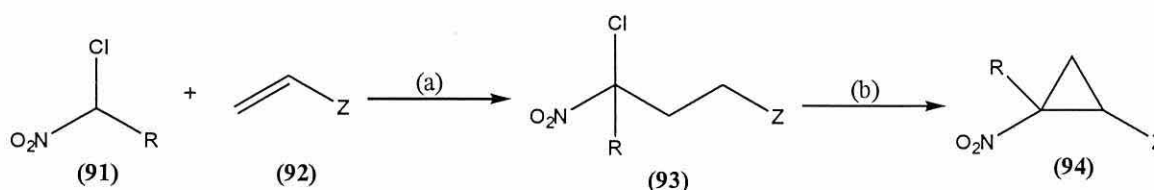
Makosza<sup>65</sup> found that using phase transfer catalysis the oxirane below **90** could be synthesised from 9*H*-Fluorene, **88**, benzaldehyde, **89** and CCl<sub>4</sub>, utilizing benzytriethylammonium chloride as the catalyst (Scheme 35). Upon recrystallisation from methanol the oxirane underwent a ring opening reaction.



**Scheme 35:** (a) NaOH, BnEt<sub>3</sub>NCl, CCl<sub>4</sub>.

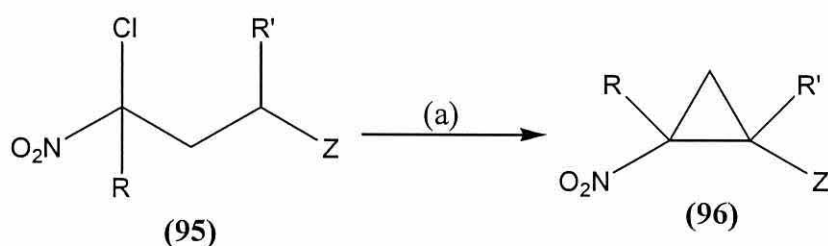
### 3) Michael Addition

Russell<sup>66</sup> synthesised a series of cyclopropanes *via* the Michael addition reactions of 4-chloro-4-nitro esters, nitriles, ketones and aldehydes. This was done *via* a two step synthesis initially forming the intermediate **93**. This intermediate was then cyclised by treatment with sodium hydride in DMF (Scheme 36). Whilst the synthesis of the intermediate was successful with yields of 52-79% the yields of the nitrocyclopropane product **94** were low (20%).



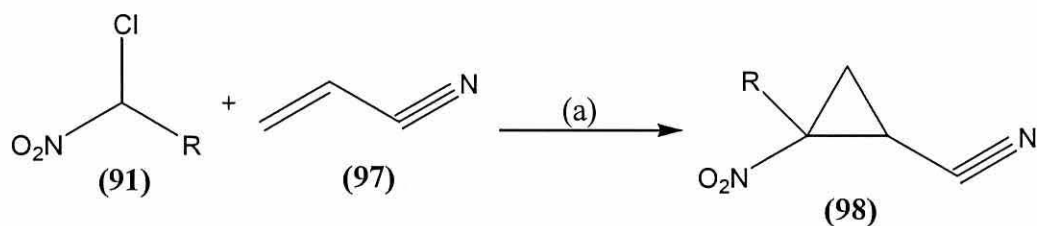
**Scheme 36:** (a) NaOH, BnEt<sub>3</sub>NCl; 52-79% (b) NaH, DMF; 20%.

The second step of the synthesis was then carried out in a two phase system with benzytriethylammonium chloride as the catalyst in the presence of 40% NaOH and acetonitrile. Yields ranging from 48% ( $R = \text{CH}_3$ ,  $R' = \text{CH}_3$ ,  $Z = \text{CO}_2\text{Me}$ ) to 74% ( $R = \text{C}_2\text{H}_5$ ,  $R' = \text{H}$ ,  $Z = \text{CN}$ ) were observed for nitrocyclopropane **96**.



**Scheme 37:** (a) 40% aqueous NaOH, BnEt<sub>3</sub>NCl; 48-74%.

Russell also found that in the case of acrylonitrile using phase transfer catalysis that the Michael addition and subsequent cyclisation could be carried out in one step (Scheme 38).<sup>66</sup> Yields for this reaction were up to 60% (when  $R = \text{Et}$ ).

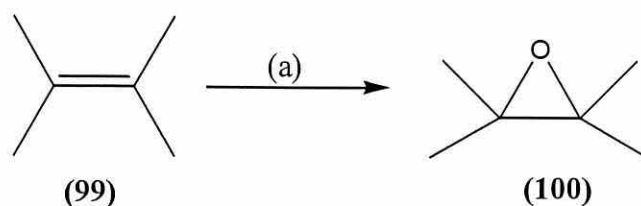


**Scheme 38:** (a) NaOH, BnEt<sub>3</sub>NCl; 60%.

## Epoxidation

### 1) From Alkenes

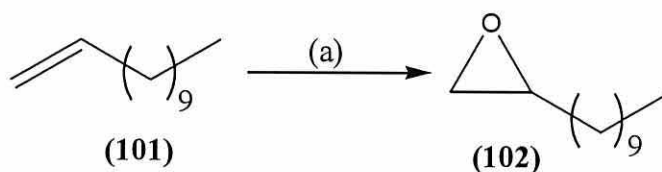
The direct epoxidation of olefins by hydrogen peroxide had been a long-standing goal in oxidation chemistry. Venturello *et al.*<sup>67</sup> found that this could be achieved by the two component association of tungstate and phosphate (or arsenate) ions under acidic conditions (Scheme 39).



**Scheme 39:** (a)  $\text{H}_2\text{O}_2$ ,  $\text{Q}^+\text{X}^-$ ,  $\text{WO}_4^{2-}/\text{PO}_4^{3-}$ ; 71-88%.

Where  $\text{Q}^+\text{X}^-$  is the onium salt which depending on the experiment was either (i) methyltrioctylammonium chloride, (ii) dimethyl(dioctodecyl) (75%) + dihexdecyl (25%) ammonium chloride or (iii) hexadecyltributylphosphonium chloride. The effectiveness of the reaction is a function of the pH of the aqueous phase. The yield observed for the reactions appear to increase as the pH of the aqueous phase decreases, the reaction can however, operate within a large pH range provided the olefin is reactive enough. The cleavage of the oxirane ring was generally avoided due to the relatively short contact times with the aqueous phase (made possible due to the effectiveness of the catalyst and excess olefin used) and the protecting effect of the double phase. Yields of between 71 and 88% were observed with cyclohexene and onium salt (ii) giving the best yield. It should be noted that the unusual activity of the peroxide toward terminal alkenes obtained during this method was only achievable when both tungstate and phosphate ions were present. When used separately they show very little to no catalytic activity.

Curci<sup>68</sup> had previously synthesised 1,2-epoxydodecene in 72% yield with the use of 18-crown-6 as the catalyst. Curci was able to effectively epoxidise the olefin using mild conditions ( $<10^\circ\text{C}$ , pH 7-8) and in a relatively short time (3 h).

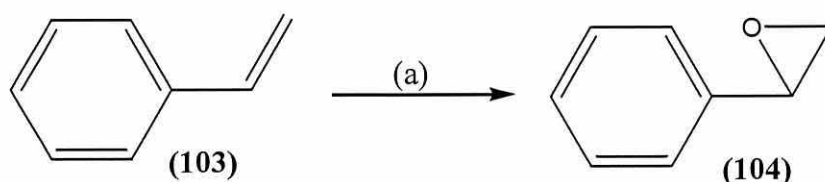


**Scheme 40:** (a)  $\text{H}_2\text{O}_2$ ,  $\text{CH}_3\text{CN}$ , 18-C-6; 72%.

## 2) From Arylalkenes

Whilst Venturello<sup>67</sup> had studied the epoxidation of styrene in a two component association of tungstate and phosphate ions Guilmet and Meunier<sup>69</sup> used sodium hypochlorite in the

presence of a phase transfer catalyst. These reactions were carried out under mild conditions and in the presence of an organometallic complex.



**Scheme 41:** (a) NaOCl, Mn(TPP)OAc; 80%.

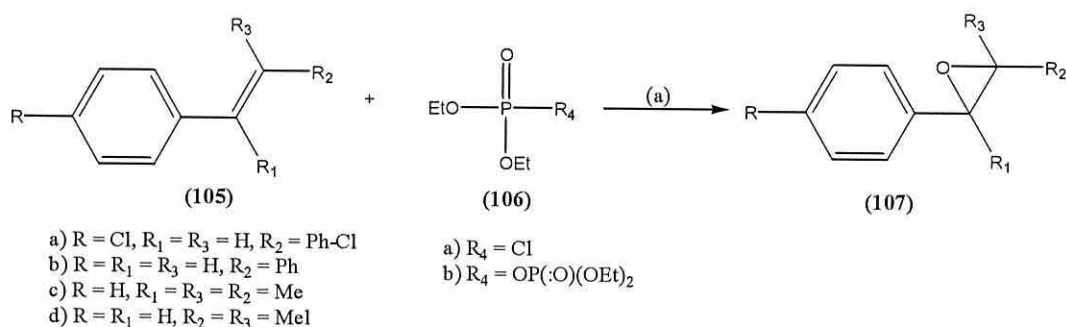
Various tetraphenylporphyrin (TPP) based complexes were used as well as Schiff base complexes. Whilst styrene, **103** was readily oxidized in the presence of both TPP and Schiff base complexes only traces of oxidation are detected without the presence of a catalyst. It should be noted that even though the oxidation of styrene does proceed, various oxidation products are observed along with the epoxide **104**. After 3 hours Mn(III)(TPP)OAc was the best performing catalyst giving 80% conversion of styrene to various oxidation products. Guilmet and Meunier also noted that there was very little variation in the yield of epoxide observed when Mn(III)(TPP)OAc was used under both air and nitrogen atmospheres, suggesting that the oxygen atom for the epoxide arises from the hypochlorite rather than molecular oxygen.

Whilst the yields of epoxide obtained from the oxidation of styrene were relatively poor Guilmet and Meunier studied this area further (concentrating on using Mn(III)(TPP)OAc as the catalyst). They found that the addition of small amounts of pyridine (0.15 eq/ olefin) to the catalytic system the epoxidation of a large variety of olefins is possible in good yields (60-90%).<sup>70</sup> Guilmet and Meunier studied the effect of a variety of substituted pyridines with pyridine, 3,5-dimethylpyridine and 4-methylpyridine performing best converting 80% of **103** to the desired product **104**. The addition of a small amount of these amines to the catalytic system allowed the reaction to complete after 30 mins instead of 5 hours. Guilmet and Meunier proposed that a reason for this is the effect of coordination of pyridine on the manganese porphyrin during the catalytic reaction. This is evident when large substituents are placed on the 2 and 6 position the rate of epoxide formation is slowed, whereas moving the steric groups away from the nitrogen (position 3 and 5) increase the rate again. The rate of reaction is also affected by electronic effects on the pyridine ring. The presence of an electron-donating group (e.g. methyl) at the *para* position increases the rate of reaction whilst



placing an electron-withdrawing group (e.g. cyano) at the *para* position decreases the reaction rate.

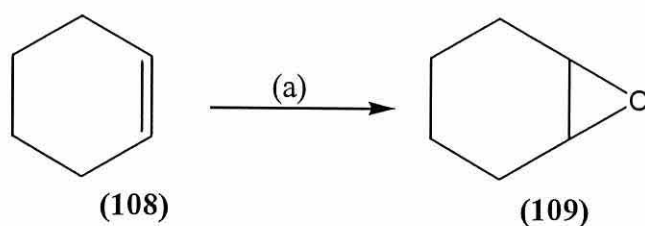
Nojima<sup>71</sup> investigated the synthesis of epoxides from arylalkenes using potassium superoxide and diethyl chlorophosphate **106**, utilising 18-crown-6 ether as the catalyst. The highest yield (45%) for the epoxide **107** was observed with the use of phosphate **106a** and substrate **105a** (Scheme 42).



**Scheme 42:** (a)  $\text{KO}_2$ ,  $\text{Mn}(\text{TPP})\text{OAc}$ ; 45%.

### 3) From Cycloalkenes

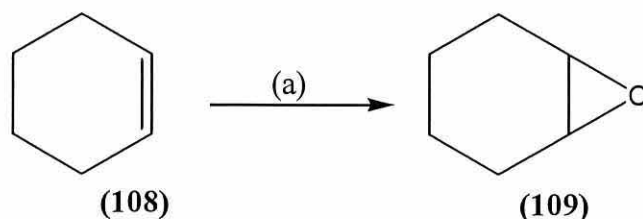
Whilst studying the effect of pyridine on the oxidation of styrene Guilmet and Meunier also studied the effect of 4-substituted pyridines on the phase transfer oxidation of cyclohexene **108**, again using  $\text{Mn}(\text{III})(\text{TPP})\text{OAc}$  as the catalyst.<sup>70</sup> It was shown that the presence of pyridines can greatly improve the yield obtained as a yield of only 22% was observed when no pyridine was used, whilst 72% yield was observed when pyridine was utilized. (Scheme 43).



**Scheme 43:** (a)  $\text{NaOH}$ , pyridine,  $\text{Mn}(\text{III})(\text{TPP})\text{OAc}$ ; 72%.

As has been discussed previously Venturello<sup>67</sup> has investigated the epoxidation of cyclohexene using hydrogen peroxide. Using acidic condition (pH 3) Venturello was able to

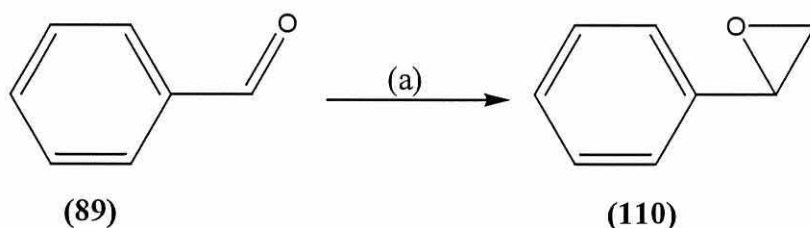
form the desired epoxide in good yields (81-88%) with use of different onium salts (Scheme 44).



**Scheme 44:** (a)  $\text{H}_2\text{O}_2$ ,  $\text{Mn(III)(TPP)OAc}$ ; 81-88%.

#### 4) From Aldehydes

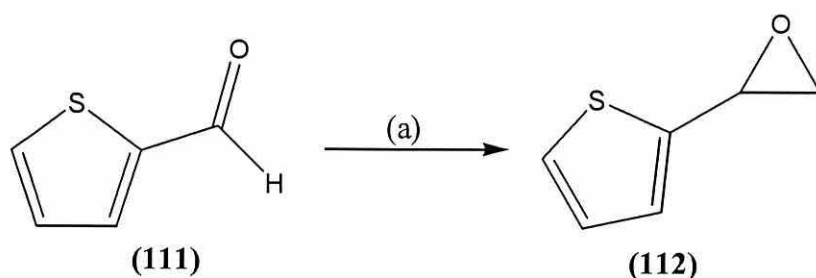
Using benzaldehyde, **89**, Borredon<sup>72</sup> investigated the use of various solvents for the phase transfer epoxidation reaction using trimethyl-sulfonium iodide and catalytic amounts of potassium hydroxide. (Scheme 45)



**Scheme 45:** (a)  $(\text{CH}_3)_3\text{S}^+\text{I}^-$ ,  $\text{KOH}$ ; 85%.

He found that the yield of the reaction could be improved from 40% to 85% if solvents such as 1,4-dioxane or dimethoxyethane were used instead of solvents such as benzene or toluene. The yield of the reaction could be improved further (up to 96%) if solvents such as nitrobenzene or acetonitrile were used.

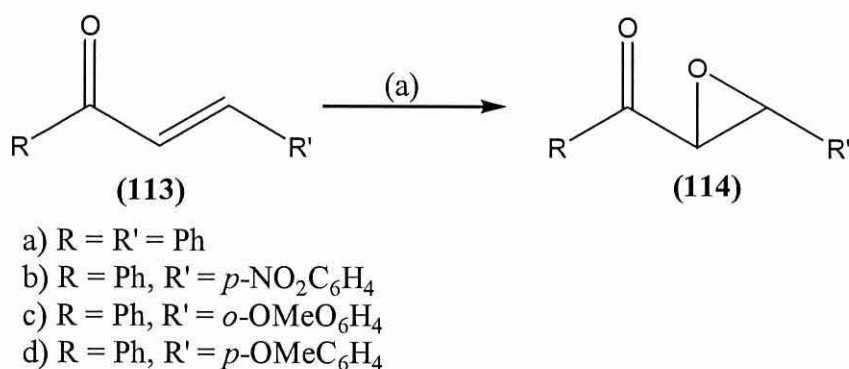
Having optimised the solvent used Borredon<sup>72</sup> studied phase transfer epoxidation of various aryl-aldehydes in the presence of trimethyl-sulfonium iodide and a catalytic amount of potassium hydroxide using acetonitrile as the solvent. High yields >90% were observed for all substrates whilst the highest yield (98%) was observed with thiophene-2-aldehyde **111**. (Scheme 46)



**Scheme 46:** (a)  $(\text{CH}_3)_3\text{S}^+\text{I}^-$ , KOH; 98%.

## 5) From Ketones

Julia *et al.*<sup>73</sup> conducted an extensive investigation of the oxidation of chalcone **113**, to epoxychalcone, **114**. (Scheme 47, Table 7)



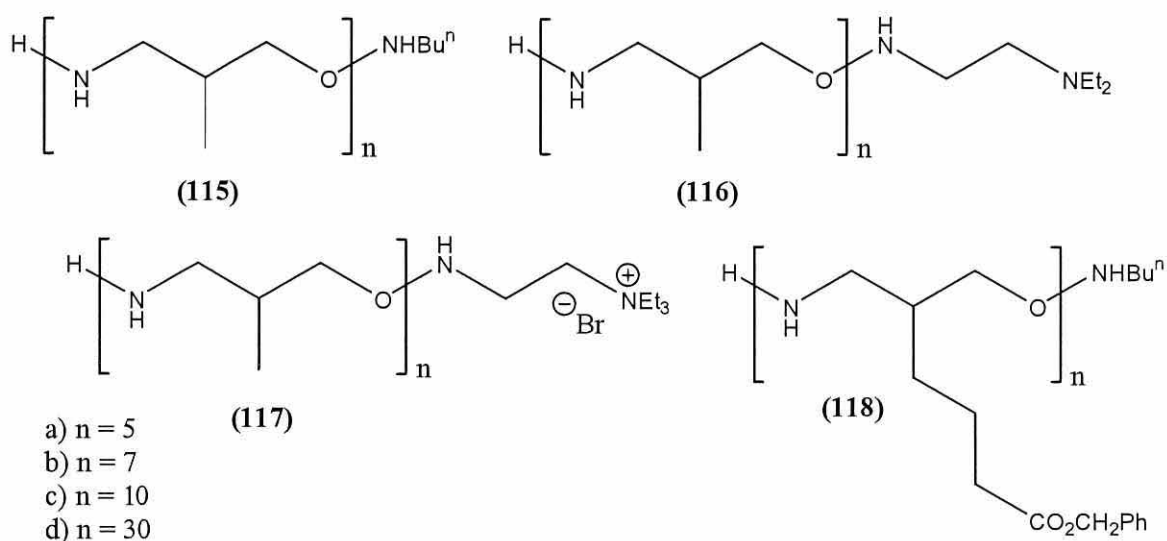
**Scheme 47:** (a)  $\text{I}_2$ ,  $\text{K}_2\text{CO}_3$ , solvent. Conditions used shown in Tables 7 to 11.

**Table 7:** Epoxidation of substituted chalcones **113** in toluene with catalyst **115c**.

Entry	Substrate	Epoxide Yield (%)
1	<b>115a</b>	78-85*
2	<b>115b</b>	83
3	<b>115c</b>	29
4	<b>115d</b>	53

\* Results depend on the purity of the alanine based catalyst **115c**.

The results obtained show that the epoxidation of chalcones **113a** and **113b** proceed in good yields whilst the yields decrease substantially when methoxybenzene was used as a substituent (entries 3 and 4). Along with investigating the effect of different substrates on the chalcones Julia also investigated the effect of different catalysts (Fig. 13, Table 8), solvents (Table 9), reaction temperature (Table 10) and oxidising agents. (Table 11)



**Figure 13:** Catalyst used in the phase transfer epoxidation of chalcone **113a**.

**Table 8:** Epoxidation of chalcone **113a** in toluene with catalyst, **115a-d**, **116c**, **117c** and **118c**.

Catalyst	Reaction Time (h)	Epoxide Yield (%)
none	24	0
<b>115c</b>	24	9
<b>115b</b>	24	18
<b>115c</b>	24	78
<b>115c*</b>	24	100
<b>115d</b>	24	57
<b>115d*</b>	28	96
<b>116c</b>	24	52
<b>117c</b>	24	62
<b>118c</b>	144	12

\* Reaction carried out with no solvent.

As can be seen the reaction does not proceed without the presence of a catalyst. Table 8 also shows that the degree of polymerisation affects the yield observed, as polymerisation increases (from **115a-115d**) so does the yield of epoxide. Julia noted that whilst catalysts **115c** and **115d** could be used the observed yield decreased.

**Table 9:** Solvent effects in the epoxidation of chalcone **113a** with catalyst **115c** at room temperature.

Solvent	Reaction Time (h)	Epoxide Yield (%)
Toluene	24	77
CCl <sub>4</sub>	28	75
Chlorobenzene	48	83
CH <sub>2</sub> Cl <sub>2</sub>	50	78
Cyclohexane	48	92
Hexane	24	95

As can be seen the rate of reaction is highest when hexane is used and is therefore the solvent of choice for racemic reactions. However, for asymmetric phase transfer catalysis toluene and carbon tetrachloride are the solvents of choice as they give the best enantiomeric excess. As can be seen in the table below (10) the best results are observed when the reaction is kept cool.

**Table 10:** Temperature effect in the epoxidation of chalcone **113a** with catalyst **115c**.

Temperature (°C)	Reaction Time (hours)	Epoxide Yield (%)
0	67	86
25	64	77
50	22	36

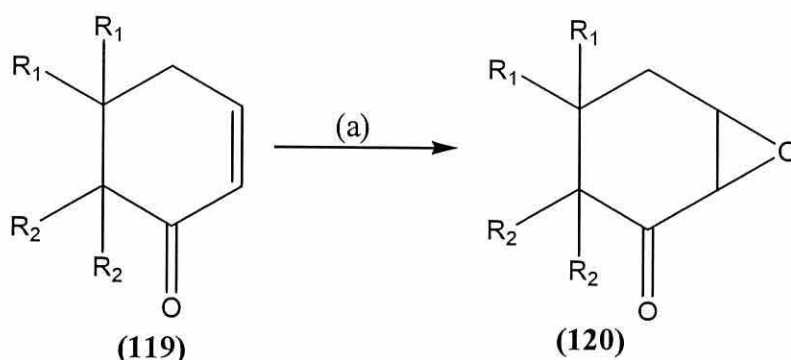
It is assumed that the low conversion at 50 °C is due to the hydrogen peroxide being destroyed at such high temperatures. The table below (11) shows that for a racemic reaction the best oxidant is Bu<sup>t</sup>O<sub>2</sub>H-K<sub>2</sub>CO<sub>3</sub>, however, H<sub>2</sub>O<sub>2</sub>-NaOH should be used as the oxidant if carrying out an asymmetric phase transfer synthesis.

**Table 11:** Effect of the oxidant in the epoxidation of chalcone **113a** with catalyst **115c**.

Oxidant	Yield (%)	e.e. (%)
H <sub>2</sub> O <sub>2</sub> -NaOH	85	88
MCPBA-NaHCO <sub>3</sub> -H <sub>2</sub> O	10	0

Bu <sup>t</sup> O <sub>2</sub> H-NaOH-H <sub>2</sub> O	42	18
Bu <sup>t</sup> O <sub>2</sub> H	0	----
Bu <sup>t</sup> O <sub>2</sub> H-K <sub>2</sub> CO <sub>3</sub>	100	0

Wynberg<sup>74</sup> investigated the phase transfer epoxidation of cyclohex-2-enone derivatives **119** using *tert*-butyl hydroperoxide, quininium benzyl chloride and toluene as the solvent. Yields of 54-60% were observed with the highest yield when R<sub>1</sub> = H and R<sub>2</sub> = CH<sub>3</sub>. (Scheme 48)



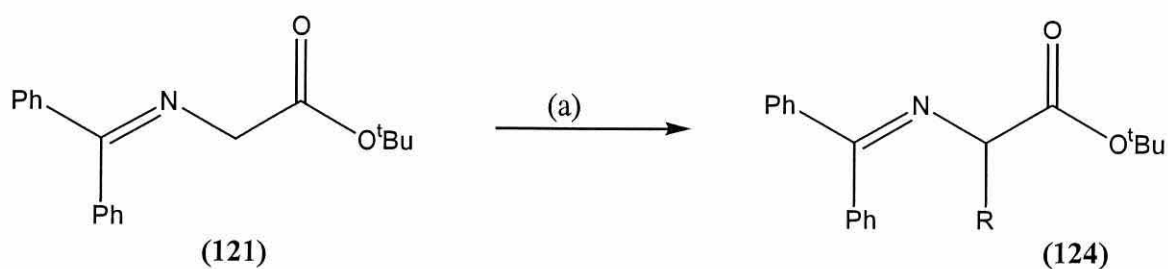
**Scheme 48:** (a) Toluene, quininium benzyl chloride, *tert*-butyl hydroperoxide; 54-60%.

Phase transfer catalysts can also be utilised to facilitate many other reactions including  $\alpha$ - elimination,<sup>75-77</sup> oxidation by KMnO<sub>4</sub>,<sup>25, 78</sup> benzoin condensation,<sup>79</sup> Wittig reaction<sup>80</sup> and reduction by borohydride.<sup>25</sup>

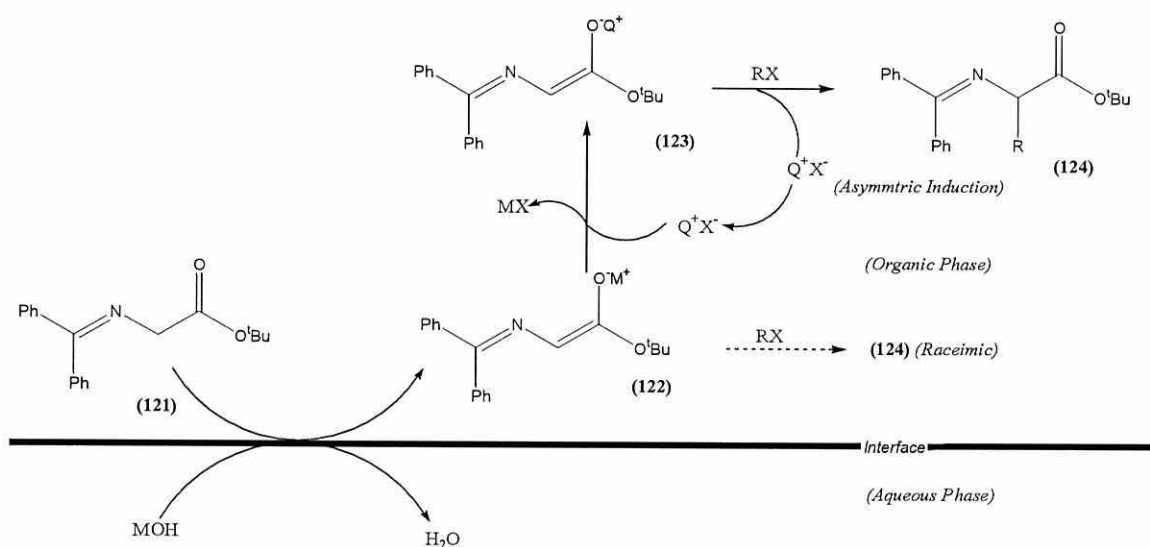
## Asymmetric Phase Transfer Catalysis

The use of phase transfer catalysis in the synthesis of chiral, non-racemic compounds from prochiral substrates using chiral catalysts has had some notable success, but for the most part, the field has been studied far less than achiral phase transfer catalysis. The majority of successful asymmetric phase transfer catalyst reactions occur under basic conditions and involve the functionalisation of active methane or methylene groups. These reactions generally follow an interfacial mechanism.<sup>32, 81</sup>

The alkylation of glycinate Schiff<sup>82-84</sup> base **121** is shown to illustrate both the parameters and key problems associated with such reactions.



**Scheme 49:** (a) Cat.  $\text{Q}^+\text{X}^-$ , Solvent, MOH, R-Br, 25 °C.

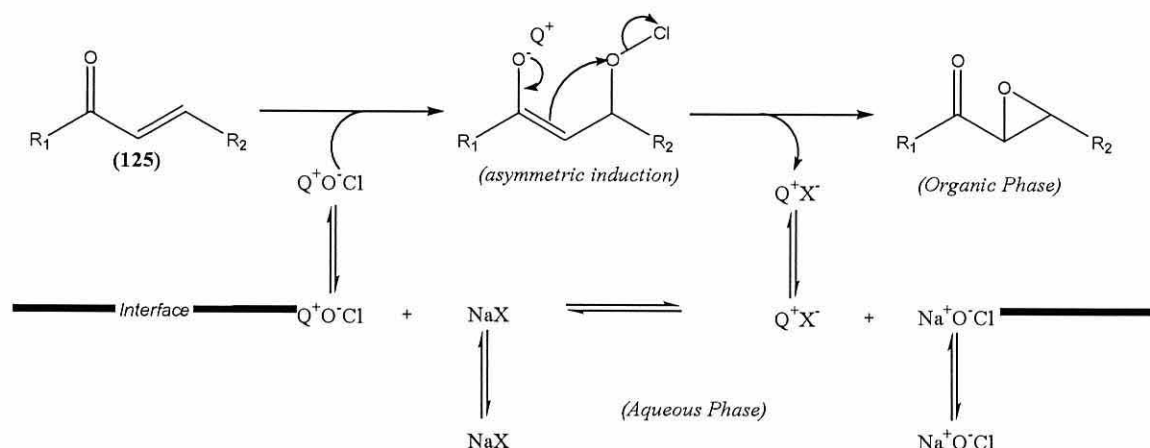


**Figure 14:** Asymmetric alkylation of Schiff base **121**.

As shown above (Fig. 14) the first step is the de-protonation of the  $\alpha$ -proton with base. The corresponding metal enolate **122** stays at the interface whilst the lipophilic chiral onium enolate **123** is formed by the ion-exchange with the catalyst ( $\text{Q}^+\text{X}^-$ ). Thus the enolate goes deep into the organic phase and reacts with an alkyl halide to yield the optically active *mono*-alkylation product **124** with the regeneration of the catalyst. In order for the reaction to be successful the ion-exchange needs to be sufficiently quick so that the chiral onium cation ( $\text{Q}^+$ ) can generate the highly reactive chiral onium enolate **123**, this minimises the direct alkylation of the metal enolate to give racemic **124**. There must also be effective shielding of one of the enantiotopic faces of the enolate anion as this controls the stereochemistry.

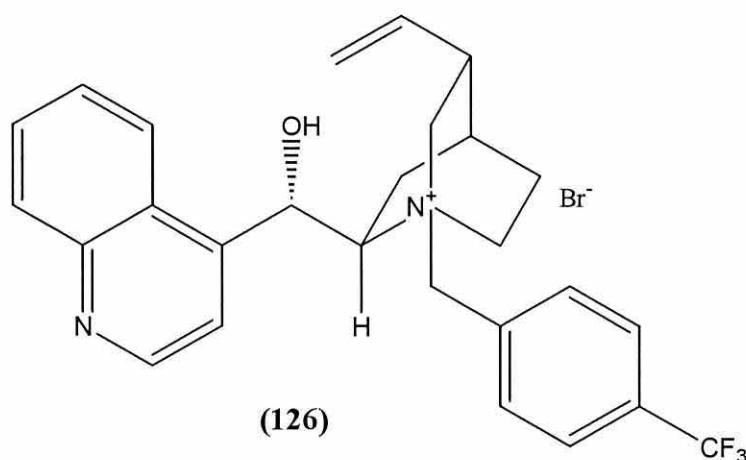
Another system in common use is the nucleophilic addition of an organic or inorganic anion without a pro-chiral centre to pro-chiral electrophile. In these systems the anion can be used either as a solid or its inorganic salt or directly as the aqueous layer. The anion enters the organic layer as a chiral ion pair, exchanging with the catalyst before forming a new stereogenic centre by attacking the pro-chiral electrophile.

A typical example of an asymmetric epoxidation of  $\alpha,\beta$ -unsaturated ketones such as **125** using sodium hypochlorite as the aqueous phase is shown below<sup>85, 86</sup> (Fig. 15).



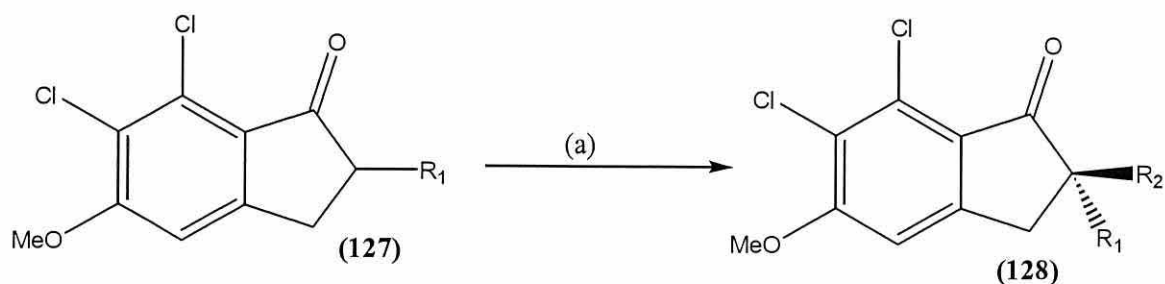
**Figure 15:** Asymmetric epoxidation of  $\alpha,\beta$ -unsaturated ketones using sodium hypochlorite.

Asymmetric alkylation reactions were a long sought after goal of organic synthesis. The first efficient such reaction was in 1984 by Dolling and co-workers<sup>87, 88</sup> who used a cinchonine derived quaternary ammonium salt **126** (Fig. 16) to catalyse the methylation of phenylindanone derivative **127**. (Scheme 50)



**Figure 16:** Cinchonine based quaternary ammonium salt catalyst **126**.

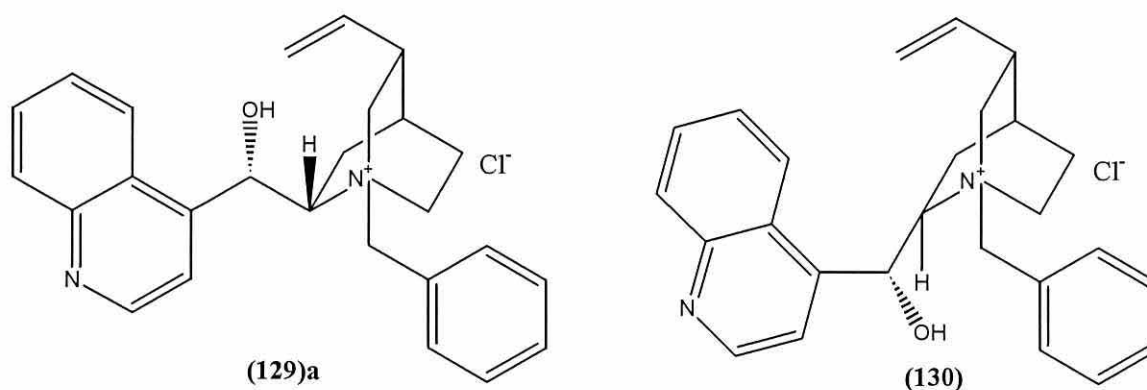




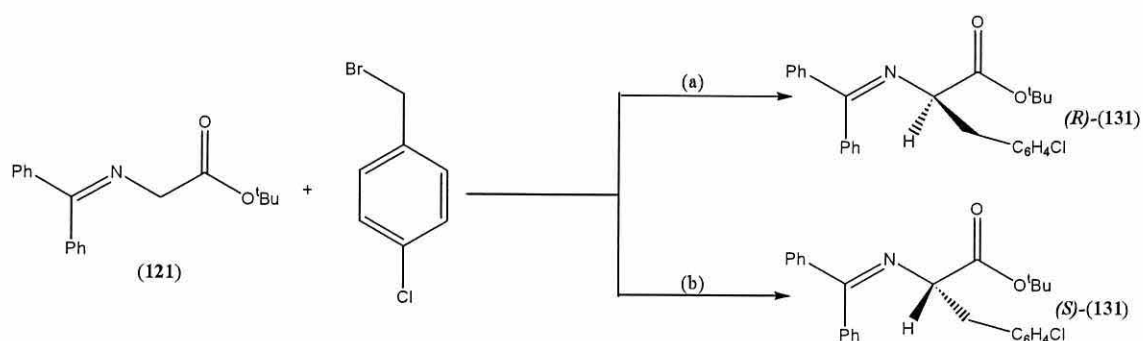
**Scheme 50:** (a)  $R_2\text{Cl}$ , **126** (10% mol), toluene, aq NaOH, 20 °C, 18 h; 99%, 92% e.e.

Previous studies conducted by Segal<sup>89</sup> found that non-polar solvents such as toluene and benzene gave higher e.e.'s than polar solvents such as chloroform or dichloromethane. Dolling investigated the effect of catalyst concentration and found that whilst increasing the concentration (10-50% mol) increased the rate of reaction it had little effect on the e.e. observed. Increasing the concentration of NaOH, with 50% aq being optimal and higher dilution was found to also favour higher e.e. values. Also investigated was the effect of the counter ion used, chloride and bromide provided similar e.e.'s whilst the use of iodide as the counter ion reduced the observed e.e. substantially.

In 1989 a similar cinchona based catalysts **129a** and **130** (Fig. 17) were utilised by O'Donnell *et al.*<sup>84, 90</sup> in the asymmetric synthesis of the  $\alpha$ -amino acid **131**. The  $\alpha$ -amino acid 4-Chloro-D-phenylalanine (*R*)-**131** was synthesised in 81% yield and 66% e.e. when catalyst **129a** was used, however, using the cinchonidine based catalyst **130** produced the opposite enantiomer 4-Chloro-L-phenylalanine (*S*)-**131**. (Scheme 51)

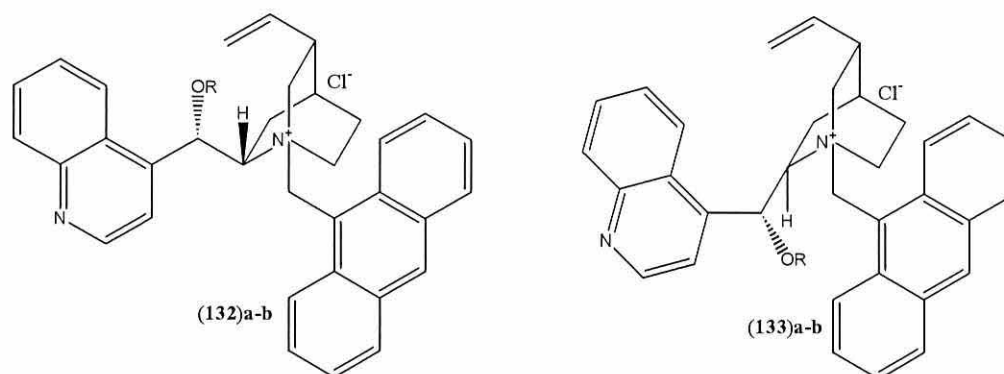


**Figure 17:** Cinchona based catalysts.

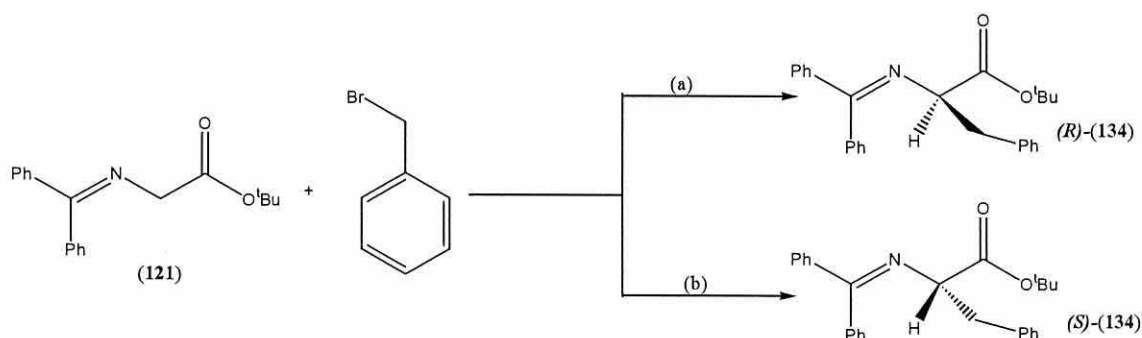


**Scheme 51:** (a)  $\text{CH}_2\text{Cl}_2$ , **129a** (10% mol), 50% aq NaOH, 20 °C. 12 h; 81%, 66% e.e. (b)  $\text{CH}_2\text{Cl}_2$ , **130** (10% mol), 50% aq NaOH, 20 °C. 12 h; 82%, 62% e.e.

In 1997 two independent research groups developed a new class of cinchona alkaloid derived catalysts containing an *N*-anthracenemethyl group. These catalysts announced the dawn of a new era in asymmetric phase transfer catalysis. Two *N*-anthracenylmethyl ammonium salts **132** and **133** were developed by Lygo *et al.*<sup>91</sup> (Fig. 18). These catalysts were subsequently used in the alkylation of Schiff base **121** (Scheme 52).

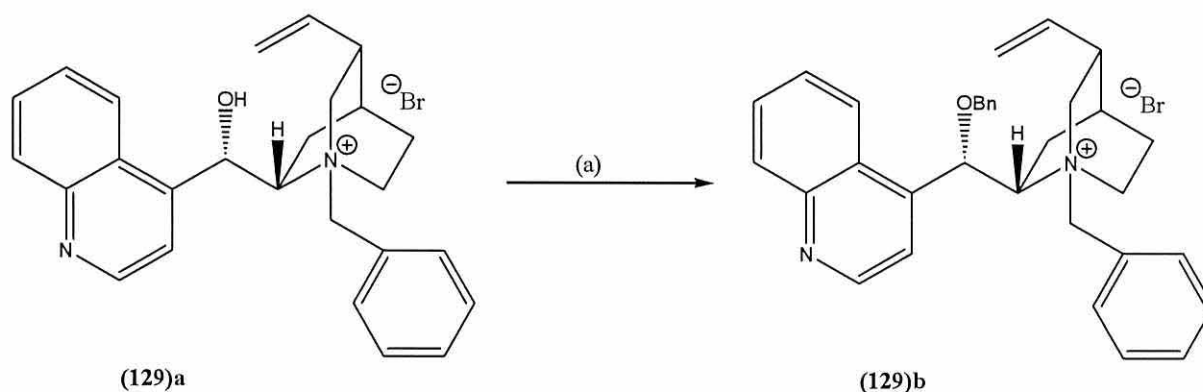


**Figure 18:** *N*-anthracenylmethyl ammonium salts **132/3a**; R = H. **132/3b**: R = Bn.



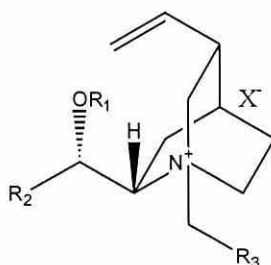
**Scheme 52:** (a) **132a** (10% mol), toluene, 50% aq KOH, 20 °C, 12 h; 63%, 89% e.e. (b) **133a** (10% mol), toluene, 50% aq KOH, 20 °C, 12 h; 68%, 91% e.e.

Lygo's cinchona based catalysts gave enantiomeric excess values ranging from 85% to 90%; a large improvement on the e.e.'s previously observed. Studies found the rate of background uncatalysed reaction was substantially lower when using potassium hydroxide instead of the previously favoured sodium hydroxide. It should be noted that whilst **132a** is named as the catalyst it is known that rapid benzylation of the hydroxyl group occurs resulting in the formation of **132b**. The same observation was made in the work of O'Donnell<sup>92</sup> who used similar reaction conditions to benzylate **129a**. (Scheme 63)



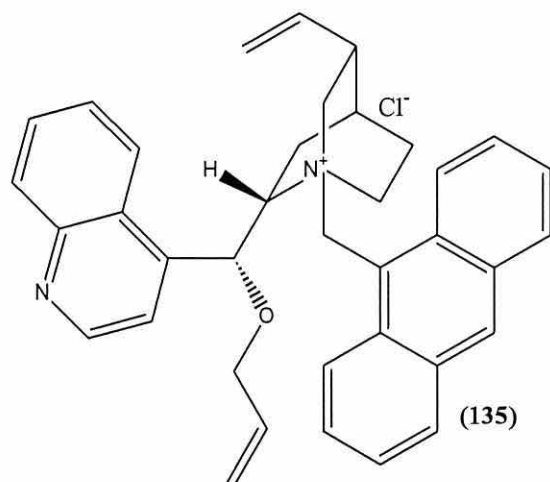
**Scheme 63:** (a) benzyl bromide (2 eq), 50% aq NaOH, stir 4 h.

In 2001<sup>93</sup> efforts were made by Lygo to optimize catalyst **132** by observing the effect of various substituents  $R^1$ ,  $R^2$  and  $R^3$  as well as the effect of the counter ion (Fig. 19). Whilst varying the substituents and counter ion had an impact on both the yield and enantiomeric excess observed it was concluded that the optimum arrangement of substituents was the originally synthesised catalyst **132**.

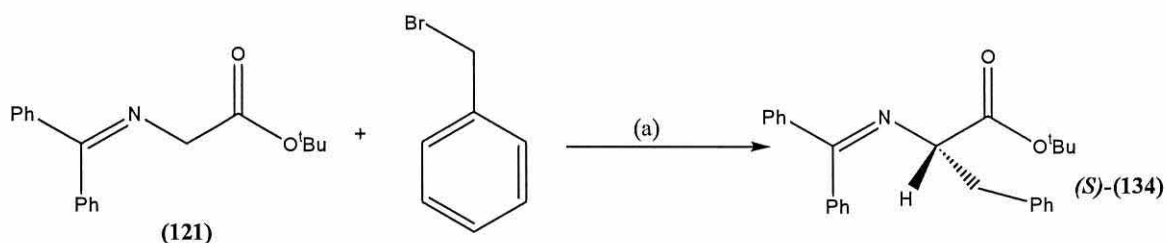


**Figure 19:** Backbone of the cinchona based catalyst.

In 1997 Corey *et al.*<sup>94</sup> also prepared a cinchona alkaloid derived catalyst *O*-allyl-*N*-anthracenylmethyl cinchonidium salt **135** (Scheme 54, Fig. 20).

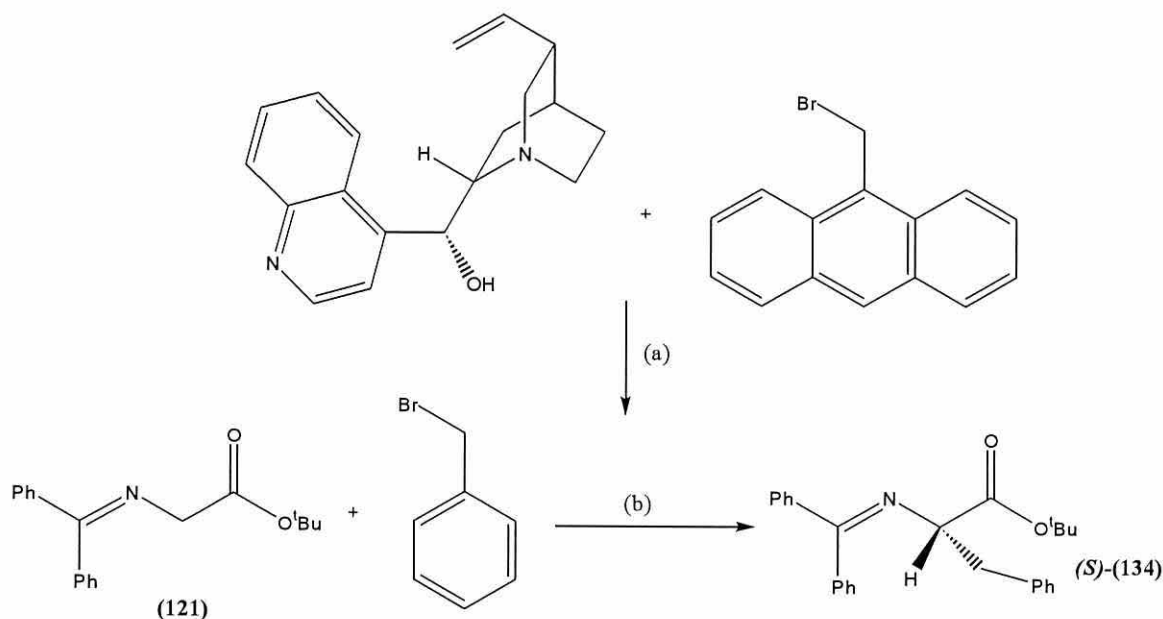


**Fig 20:** *O*-allyl-*N*-anthracenylmethyl cinchonidium salt.



**Scheme 54:** (a) **135** (10% mol), CsOH.H<sub>2</sub>O, CH<sub>2</sub>Cl<sub>2</sub>, -78 °C, 18 h; 84%, 94% e.e.

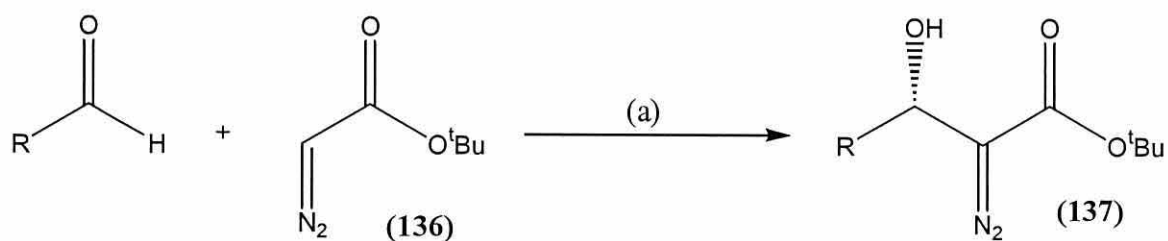
More recently Lygo *et al.*<sup>12</sup> were able to form the chiral quaternary catalyst **132a** *in situ* and subsequently alkylate a Schiff base **121** (Scheme 55).



**Scheme 55:** (a) Toluene, 50 °C, 5 h; (b) **132**, KOH, CH<sub>2</sub>Cl<sub>2</sub>, 20 °C, 18 h; >95%, 93% e.e.

Initially 9-chloromethylantracene was used but it was found that no quaternary ammonium salt formed and none of the desired product **134** was observed. Upon using 9-bromomethylantracene the reaction proceeded and an e.e. of 93% was observed, which is comparable to that obtained if pre-prepared catalyst was used.

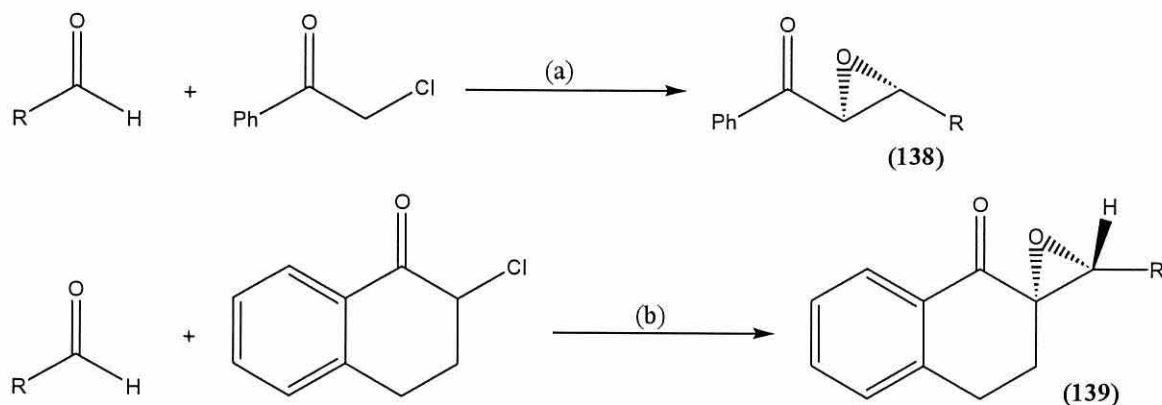
The cinchonine catalyst **132** developed by Lygo was utilised by Arai *et al.*<sup>95</sup> in the investigation of asymmetric aldol reactions of diazoesters **136**. (Scheme 56) With the use of a the base, RbOH the reaction proceeded even at -40 °C. Varying the aldehyde resulted in yields of up to 91% (R = Ph) and e.e.'s as high as 79% (R =  $\alpha$ -Np).



**Scheme 56:** (a) **132** (10% mol), toluene, 50% aq RbOH, -40 °C, 12-94 h; 91%, 79% e.e.

Arai *et al.* also utilised the Dolling developed catalyst **126** in the asymmetric phase transfer catalysed Darzens condensation of phenacyl chloride<sup>96</sup> and chloro ketone<sup>97, 98</sup> with

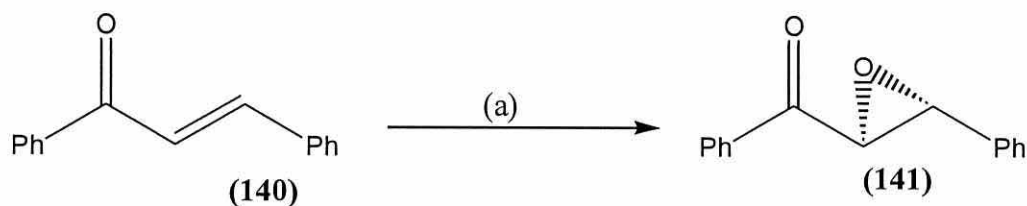
various aldehydes using LiOH as the base. Good yields were observed for both reactions with e.e. as high as 79% (R = Et) achieved for **138** and 69% (R = *i*Pr, cHex) for **139** (Scheme 57).



**Scheme 57:** (a) **126** (10% mol), Bu<sub>2</sub>O, 50% aq LiOH, 4 °C; 83%, 79% e.e.

(b) **126** (10% mol), Bu<sub>2</sub>O, 50% aq LiOH, 4 °C; 99%, 69% e.e..

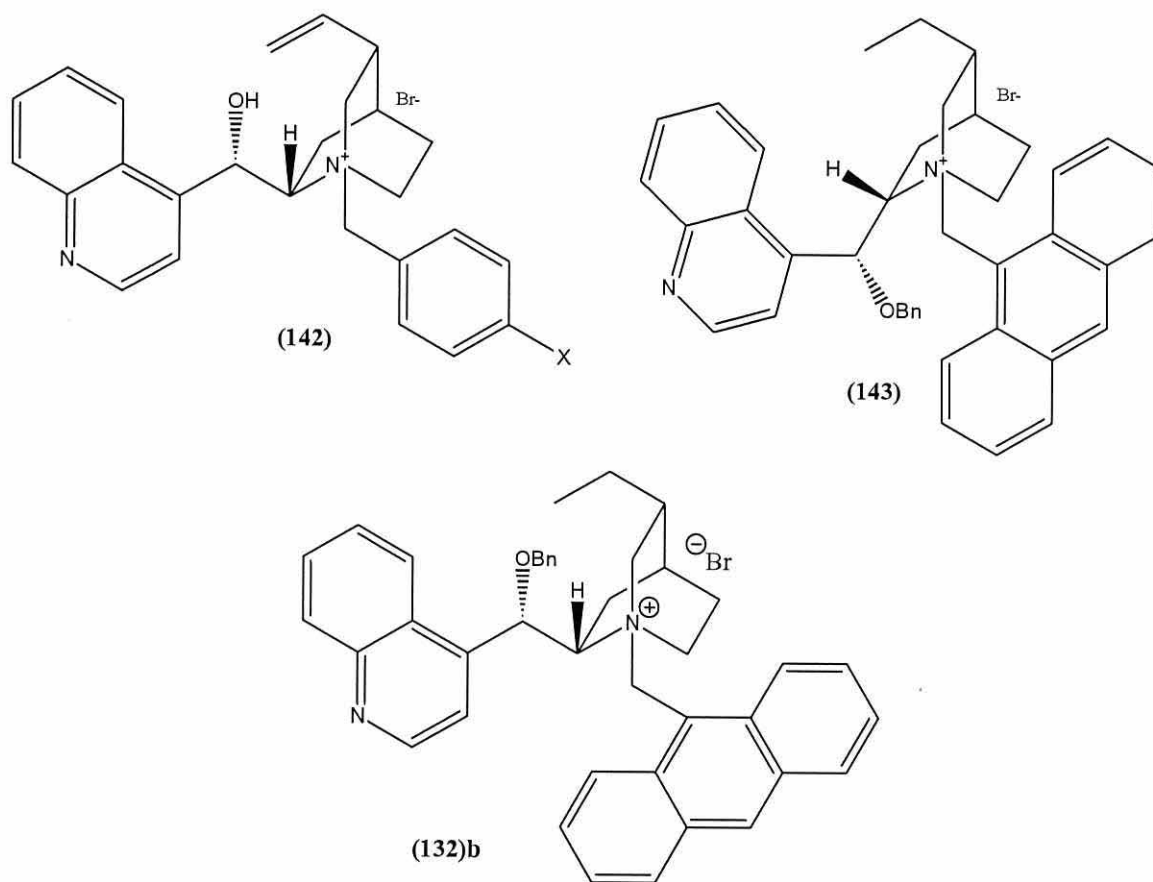
A variety of cinchona derived catalysts have been used in the enantioselective epoxidation of *trans*  $\alpha$ ,  $\beta$ -unsaturated ketones. Arai<sup>99</sup>, Corey<sup>100</sup> and Lygo<sup>101</sup> have all investigated the asymmetric epoxidation of chalcone **140** and its derivatives using varying conditions. (Scheme 58, Table 12).



**Scheme 58:** (a) Catalyst **132b**, **142**, **143** – see table 12.

**Table 12:** Asymmetric epoxidation of chalcone **140**.

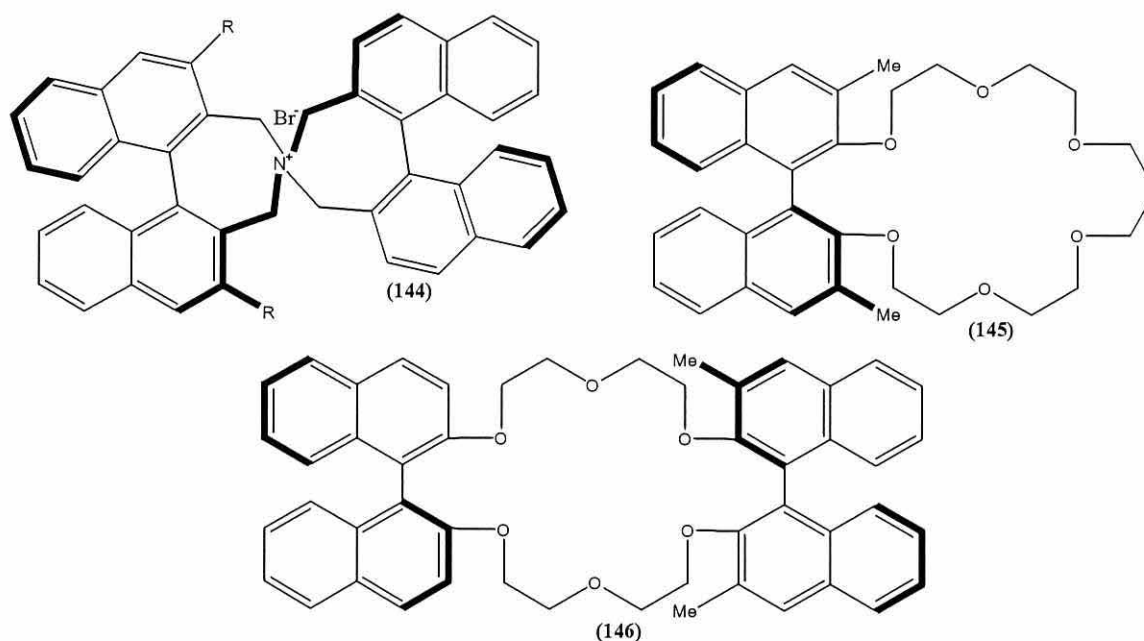
Research Group	Catalyst	Oxidant	Solvent	Temp (°C)	Time (h)	e.e. (%)
Arai	<b>142</b> (5% mol)	H <sub>2</sub> O <sub>2</sub>	Bu <sub>2</sub> O	4	37	84
Corey	<b>143</b> (10% mol)	KOCl	Toluene	-40	12	93
Lygo	<b>132b</b> (10% mol)	NaOCl	Toluene	25	48	81



**Figure 21:** Cinchona derived catalysts synthesised by Arai (**142**) X = H, Hal; Corey (**143**) and Lygo **132b**.

Arai investigated the role of various substituents at the *para*-position and found that the e.e. observed was highly dependent on the substituent ranging from 1% (X = H) to 84% (X = I) (Fig. 21). Lygo's investigations found that by changing the oxidant to H<sub>2</sub>O<sub>2</sub> it was possible to produce the opposite enantiomer to that observed when NaOCl was used. This effect had previously been noted by Wynberg<sup>102</sup> suggesting that two or more competing reaction pathways operate under these conditions. This theory was reinforced by the rate changes observed upon changing oxidant and solvent.

As well as the cinchona based catalyst a wide variety of other catalyst, *e.g.* **144**, developed by Maruoka<sup>103-107</sup> and chiral crown ethers such as **145** and **146** which were utilised by Cram.<sup>108</sup> (Fig. 22)



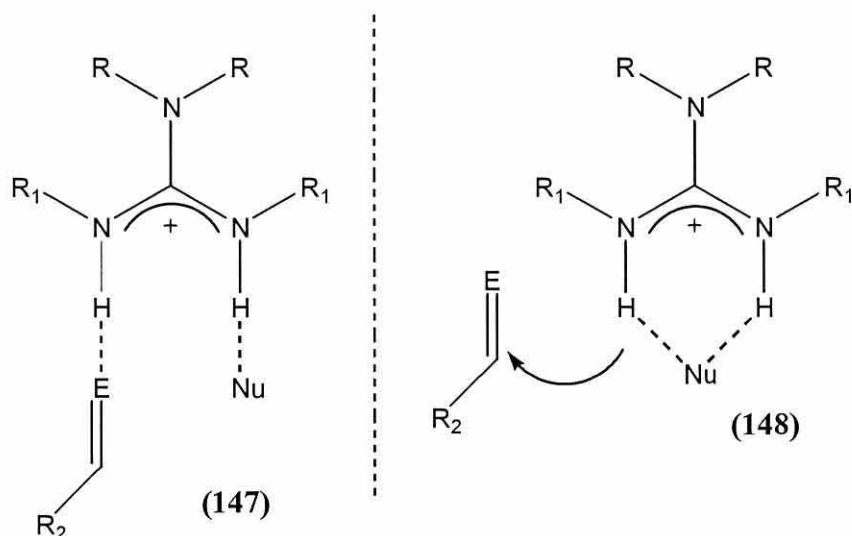
**Figure 22:**

## Guanidines in Organocatalysis

Recently attention has been paid to guanidine organocatalysts because of their ability to mediate a wide variety of organic bimolecular reactions. Guanidine's high basicity ( $pK_a = 13.6$ ), attributed to its delocalisation of the six  $\pi$ -electrons across the symmetric Y-shaped  $CN_3$  unit means that guanidinium salts are ideally suited to use as catalysts.<sup>109</sup> Guanidines also have the ability to act as a Brønsted base to abstract a proton from the substrate forming a guanidinium intermediate. Two mechanisms have been proposed to explain the role of the intermediate. (Fig. 23)

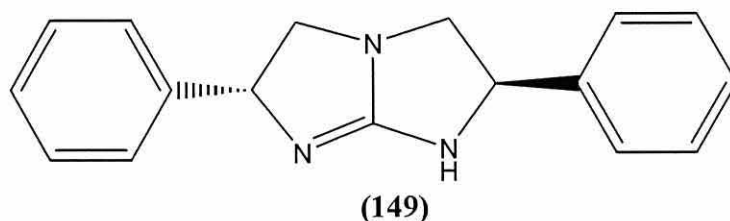
- 1) The intermediate forms a hydrogen bond with the substrate as well as the incoming electrophile to generate the pre-transition-state termolecular complex **147**.<sup>110</sup>
- 2) The intermediate acts as a dual hydrogen bond donor to form a complex **148** with the deprotonated substrate to direct the attack of the electrophile.<sup>111-113</sup>



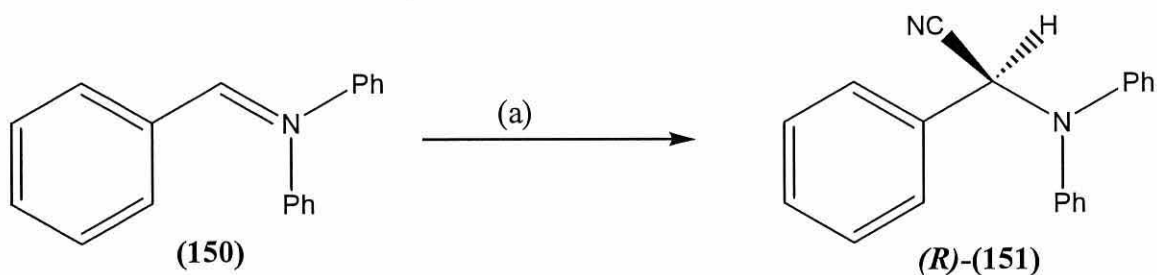


**Figure 23:** Proposed mechanisms explaining the role of the guanidinium intermediate.

C<sub>2</sub>-symmetric guanidines have been developed for use in asymmetric phase transfer catalysis by various researchers such as the Corey, Nagasawa and Murphy groups. In 1999 Corey<sup>110</sup> utilised **149** (Fig. 24) as a bifunctional catalyst for the enantioselective Strecker synthesis of chiral  $\alpha$ -amino acids and  $\alpha$ -amino nitriles such as **151**. (Scheme 59)

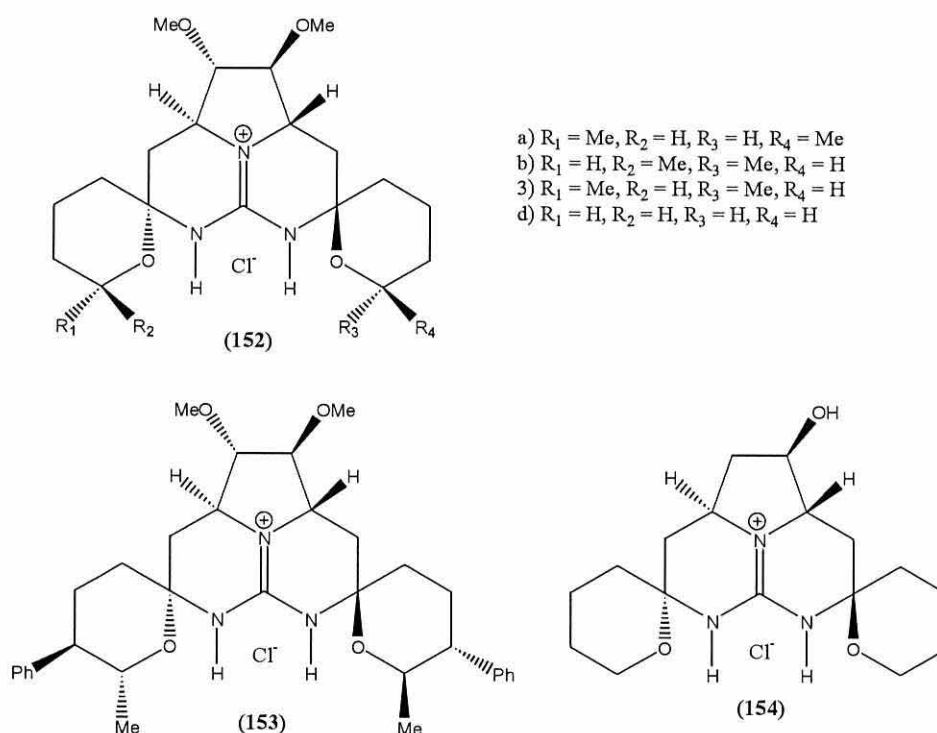


**Figure 24:** C<sub>2</sub>-symmetric guanidine.

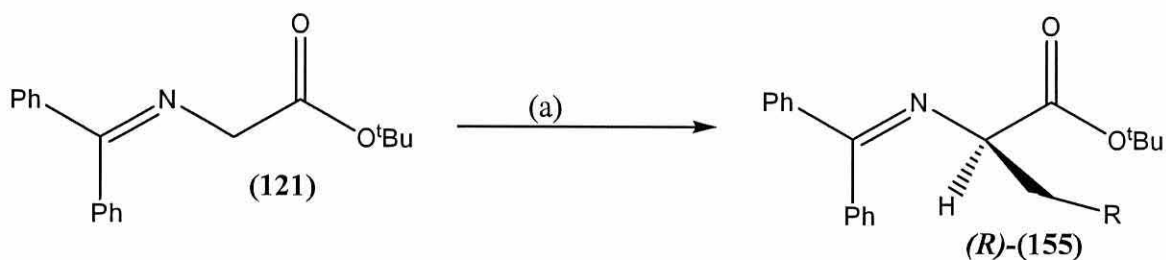


**Scheme 59:** (a) **149** (0.1 eq), toluene, HCN (2 eq), -40 °C, 20 h.

In 2001 Nagasawa *et al.*<sup>114, 115</sup> synthesised five new guanidine based chiral catalysts **152a-d**, **153** and **154** (Fig. 25). These catalysts were later utilised in the asymmetric alkylation of the Schiff base **121** (Scheme 60).<sup>116</sup>



**Figure 25:** Guanidine based chiral catalysts.

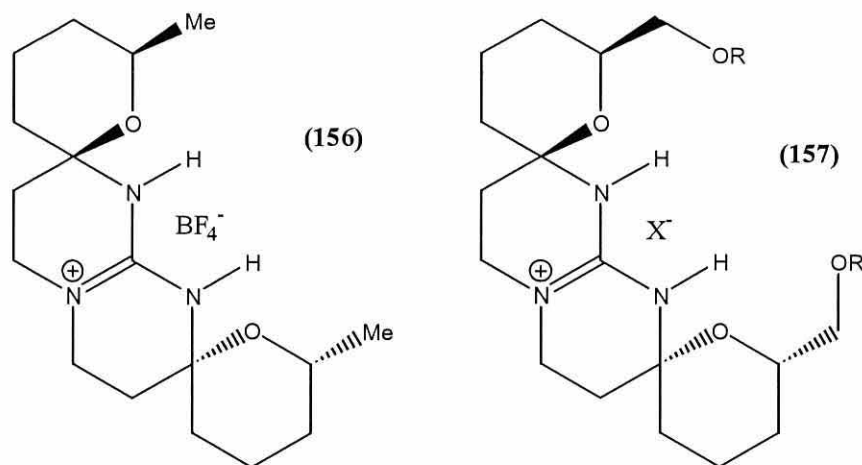


**Scheme 60:** (a) RX, **152**, **153**, **154** (30% mol),  $\text{CH}_2\text{Cl}_2$ , 50% aq KOH; 90%, 90% e.e.

Initially, with **152a** as the catalyst an e.e. of 81% was observed where  $\text{RX} = \text{BnBr}$  and the reaction carried out at room temperature. Reducing the temperature to  $0\text{ }^\circ\text{C}$  reduced the yield to 55% (from 90%) but improved the observed e.e. to 90%. The enantiomeric excess was reduced severely when **152b** and **152c** were used (13 and 12% respectively). A poor e.e. of 7% was also observed with **153**; however, the opposite enantiomer (*S*)-**155** was formed. Catalyst **152a** provided very high level of asymmetric induction because of both the steric hindrance and the “cavity” observed within the structure caused by the methyl groups. The alkylation of the Schiff base **121** was also carried out using **154** as the catalyst again using a variety of substituents (RX). High e.e. (76+%) were observed for all the substituents, however, the highest e.e. (90%) was observed when  $\text{RX} = \text{NpCH}_2\text{Br}$ .

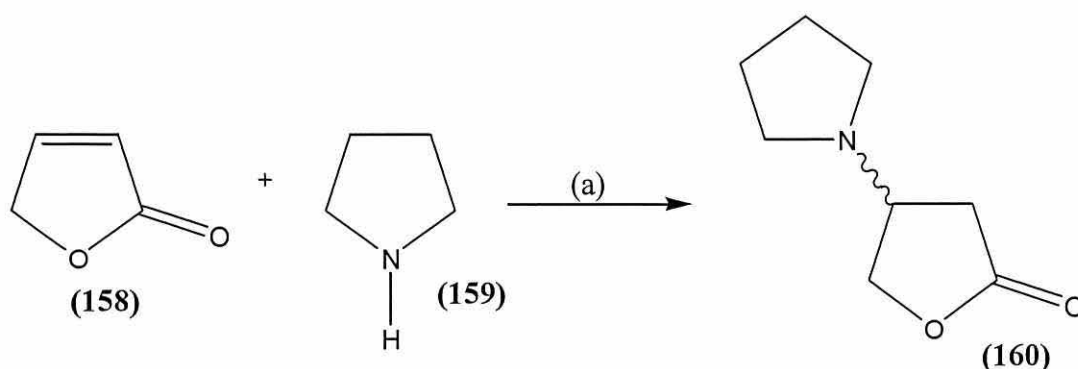
## Aims and Background to the research

There has been great interest in the synthesis and application of  $C_2$ -symmetric guanidine bases within the Murphy group for many years. In 1998 the novel  $C_2$ -symmetric guanidine catalysts **156** and **157** (Fig. 26) were developed.<sup>117</sup>



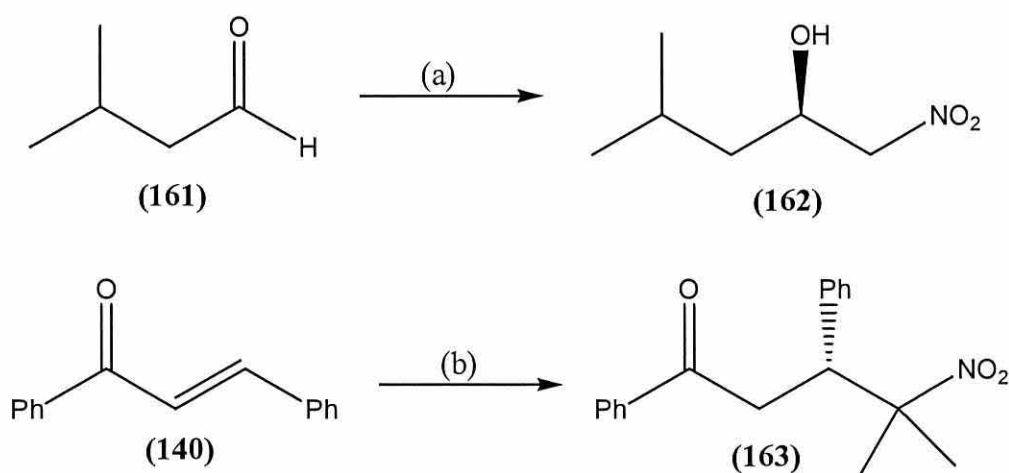
**Fig 26:**  $C_2$ -symmetric guanidine catalysts. **157** (a: R = H, X = Cl; b: R = TBDMS, X =  $BF_4$ ; c: R = TBDPS, X =  $BF_4$ ).

Following this<sup>118</sup> the guanidinium salts **157a-c** were developed and the application of **156** and **157a-c** as a catalyst were tested. Initial studies were aimed at increasing the rate of reaction for the conjugate addition of pyrrolidine **159** to the unsaturated lactone **158** (Scheme 61). The rate of reaction could be improved four fold with **156**·H $BF_4$ , however, a sixteen fold increase was observed when  $^-BPh_4$  was used as the counter-ion and catalyst **157b** also performed well increasing the rate of reaction eleven fold whilst **157c** disappointed only increasing the rate 1.25-fold. The large rate increase found when  $^-BPh_4$  was used as the counter-ion was due the well known lower coordination ability of the tetraphenylborate anion.<sup>119</sup>



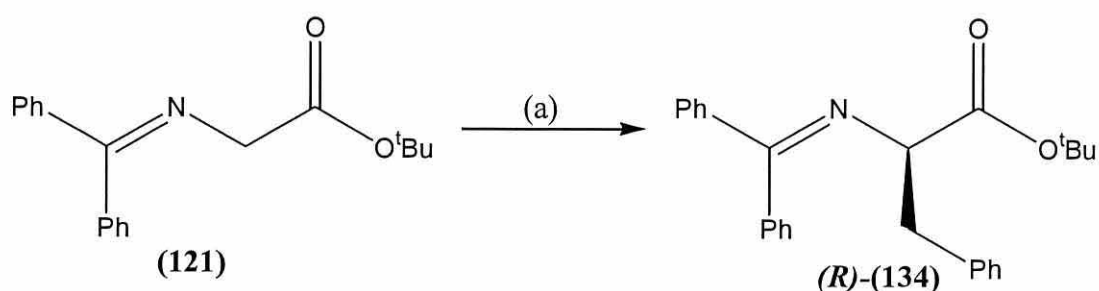
**Scheme 61:** (a) Guanidinium salt, **156**, **157b**, or **157c** (0.1 eq), 0.3 M in  $\text{CDCl}_3$ , rt.

Disappointingly no asymmetric induction was observed in the above reaction, however, asymmetric catalysis of nitro-aldol<sup>120</sup> and nitro-Michael addition<sup>120, 121</sup> was possible using the three catalysts albeit with low e.e. For both nitro-aldol and nitro-Michael addition reactions catalyst **156** was found to give the best e.e.'s; 20% (53% yield) in the synthesis of (*R*)-**162** and 23% (70% yield) when synthesising (*S*)-**163** (Scheme 62).



**Scheme 62:** (a) i) **156**· $\text{HBF}_4$  (0.1 eq.), NaOMe (0.09 eq.), MeOH, 30 min, remove solvent; ii)  $\text{CCl}_4$  rt, **161**  $\text{MeNO}_2$ , 16 h; 53%, 20% e.e. (b) i) **156**· $\text{HBF}_4$  (0.1 eq.), *t*-BuOK, (0.09 eq.), THF,  $(\text{Me})_2\text{CHNO}_2$ , **140**, rt, 24 h; 70%, 23% e.e.

Next it was sought to investigate whether the guanidinium salts could be used as phase transfer catalysts, initially *via* the benzylation of the glycinate Schiff's base **121** (Scheme 63).



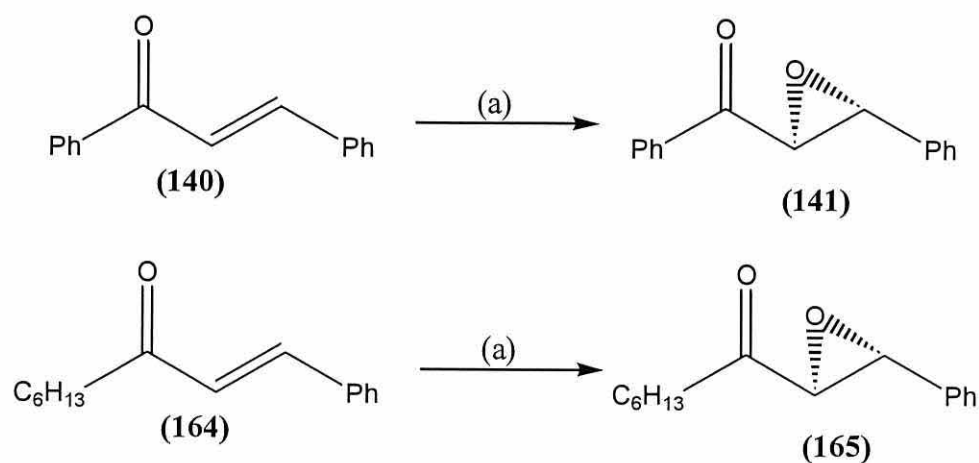
**Scheme 63:** (a) **156/ 157a-c** (0.1 mol), NaOH (0.1 eq.), NaOH (2 M), BnBr (2 eq.), CH<sub>2</sub>Cl<sub>2</sub>, 16 h 0 °C–rt;  
>97%, 86% e.e.

Again catalyst **156** gave the best results (Table 13) obtaining the *R*-isomer in 86% e.e. with almost full conversion of **121** to **134**. The conversion rates when both **157b** and **157c** were utilized could be increased by allowing the reaction to progress for longer or increasing the concentration of NaOH used; however neither increased the amount of enantioselectivity observed.

**Table 13:** Asymmetric epoxidation of Schiff base **121**.

Entry	Catalyst	Conversion (%)	e.e. (%)
1	<b>156</b>	>97	86
2	<b>157a</b>	15	21
3	<b>157b</b>	70	65
4	<b>157c</b>	80	74

The phase transfer epoxidation of chalcones **140** and **164** using **156** as a catalyst was also investigated (Scheme 64). Catalyst **156** was found to be excellent for this transformation; 93% e.e. was observed for **141** and 91% for **165** which compares favourable with existing PTC's used for these processes



**Scheme 64:** (a) 156·HBF<sub>4</sub> (0.05 eq.), NaOCl (aq.), Tol, 16 h 0 °C–rt; 93% e.e.

The aims of this project are two fold. Firstly to develop the methodology for asymmetric phase transfer catalysed epoxidation to other chalcone substrates order to provide medium scale synthesis of commercial quantities of homochiral epoxides. Secondly it is intended that new methodology will be developed for the preparation of new *C*<sub>2</sub> symmetric guanidines and that these can be then applied to similar phase transfer processes.

# Results and Discussion

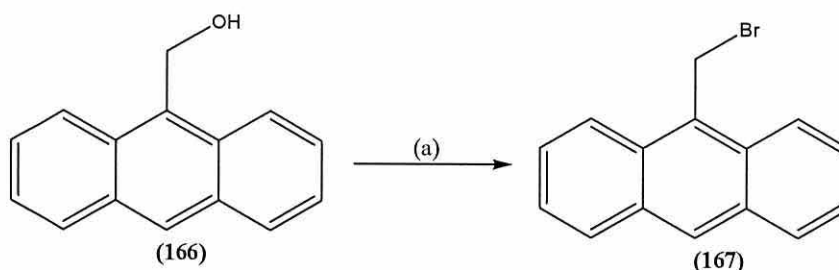
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## Synthesis of catalysts

In order that we might access both enantiomers of the required chalcone epoxides it was necessary to prepare the previously reported catalyst **156** as well as quantities of the previously reported Lygo's catalysts **132a** and **132b**.

## Lygo's catalysts

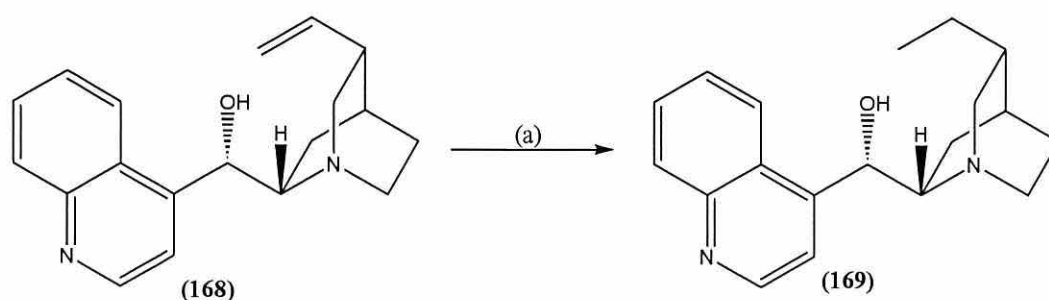
The synthesis of catalyst **132a** was achieved *via* a previously reported 3 step process beginning with the commercially available starting materials 9-Hydroxymethylantracene **166** and Cinchonidine **168**.<sup>122, 123</sup>



**Scheme 65:** (a) i) acetic acid, 33% HBr in acetic acid, ii) 55 °C, stir 3.5 h; 77%.

The bromination of **166** was achieved by addition of HBr in acetic acid to a suspension of 9-Hydroxymethylantracene **166**, in acetic acid and stirring the mixture at 55 °C for 3 h. After work-up 9-Bromomethylantracene **167** was formed as a dark yellow solid in 77% yield melting at 143-145 °C (lit. 147-148 °C).<sup>122</sup> The NMR spectrum of product **167** was similar to the starting material lacking only the OH signal, but confirmation of structure was gained on analysis by mass spectrometry which gave a 1:1 ratio of peaks at 270 and 272 corresponding to the correct isotopic pattern for bromine. The data was in accordance with the literature.<sup>122</sup>

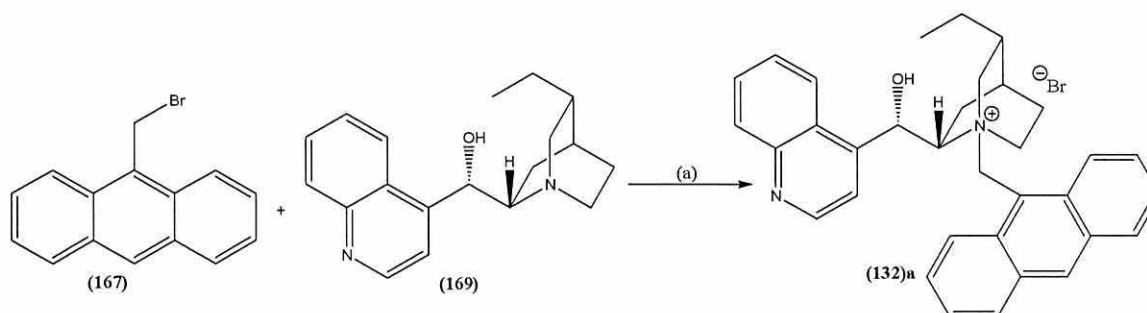
Cinchonidine **168** was hydrogenated with 10% Pd/C in ethanol under a hydrogen atmosphere for 24h. Work-up gave dihydrocinchonidine **169** as a white solid in 53% yield.



**Scheme 66:** (a) ethanol, 10%Pd/C, H<sub>2</sub> gas, stir 24 h; 53%.

The <sup>1</sup>H NMR spectrum of **169** shows the disappearance of two overlapping doublet of doublet signals at 4.88-4.98 ppm (2H) and a triplet of doublet signal at 5.63-5.77 ppm (1H) in the starting material and the appearance of triplet at 0.78 ppm (3H, *J* = 7.3 Hz) and a multiplet signal at 2.48-2.53 ppm (1H) corresponding to the ethyl group. By examining the DEPT spectrum of both the starting material and the product we clearly see the disappearance of a CH<sub>2</sub> signal at 114.5 ppm and the appearance of a methyl signal at 11.8 ppm. Mass spectrometry and melting point comparison also agreed with the required structure.<sup>123</sup>

With the two required starting materials in hand the preparation of *N*-(9-anthracenylmethyl)dihydrocinchonidinium bromide **132a** was achieved by heating a suspension of dihydrocinchonidine **169**, 9-bromomethylantracene **167** and potassium carbonate in toluene for 4 h. Work-up yielded the product **132a** as a yellow solid in 65% yield.

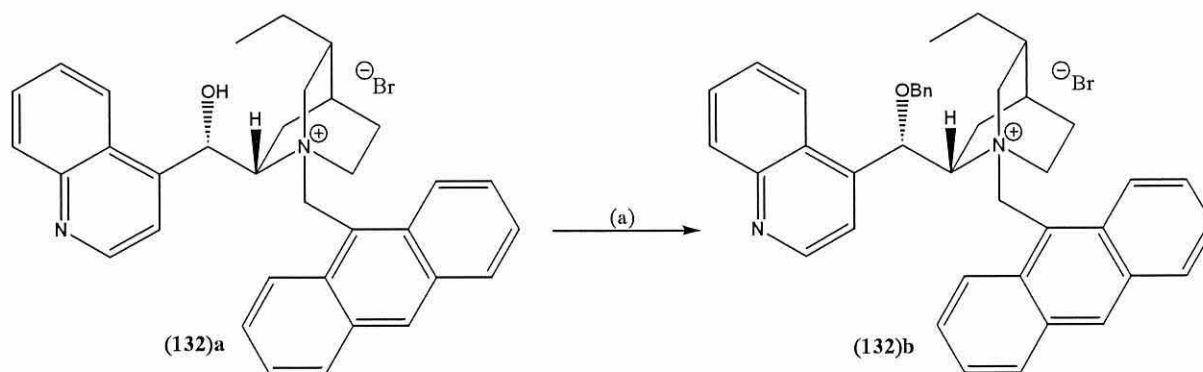


**Scheme 67:** (a) Toluene, K<sub>2</sub>CO<sub>3</sub>, 50 °C, 4 h; 65%.

The structure of compound **132a** was confirmed by <sup>1</sup>H and <sup>13</sup>C NMR as well as mass spectra. The <sup>1</sup>H NMR gave the required signal with the CH<sub>2</sub>N resonances appearing as two doublets at 6.21 (1H, d, *J* = 13.6 Hz, CH) and 6.53 (1H, d, *J* = 13.6 Hz, CH) ppm with the corresponding carbon resonance at 63.8 ppm. Mass spectroscopic analysis gave a molecular



ion at 487.2746 daltons which is close to the required mass of required 487.2744 and a melting point of 168-171 °C (Lit 173-175 °C) and an  $[\alpha]_D^{25}$  of -276 ( $c = 0.518$  in  $\text{CHCl}_3$ ) (Lit -220  $c = 0.7$  in  $\text{CHCl}_3$ ) where also in good agreement with the literature.<sup>91</sup>

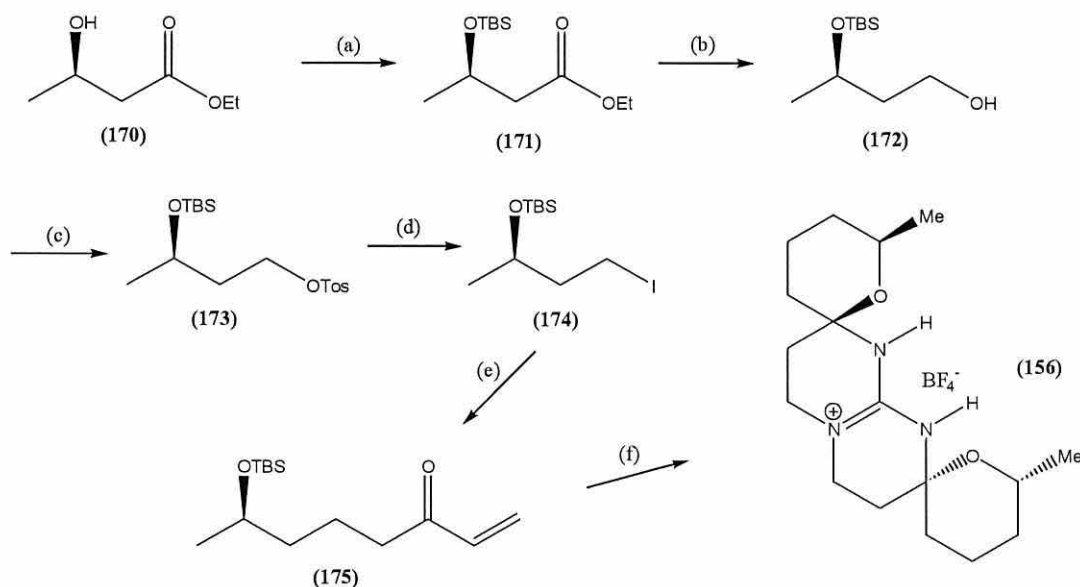


**Scheme 68:** (a) benzyl bromide, 9N NaOH, stir 1.5 h; 83%.

*N*-(9-anthracenylmethyl)dihydrocinchonidinium bromide **132a** was then benzylated *via* the addition of 9N sodium hydroxide to a solution of **132a** and benzyl bromide. The mixture was then stirred vigorously for 1.5 h at room temperature, work-up yielded the desired product **132b** in 83% yield. The structure of compound **132b** was confirmed by  $^1\text{H}$  and  $^{13}\text{C}$  NMR. The  $^1\text{H}$  NMR gave the required signals with the  $\text{CH}_2$  resonances appearing as 4.53-4.64 (2H, m) ppm with the corresponding carbon resonance at 71.3 ppm as well as signals for the phenyl ring within the aromatic region of both spectra. A melting point of 142-144 °C (Lit 137-138 °C) and an  $[\alpha]_D^{25}$  of -204 ( $c = 1.0$  in  $\text{CHCl}_3$ ) (Lit -215  $c = 0.7$  in  $\text{CHCl}_3$ ) were also in good agreement with the literature.<sup>124</sup>

## Murphy's catalyst

The guanidine catalyst **156** had previously been prepared in the group by two workers Howard-Jones<sup>125</sup> and Thomas<sup>126</sup> and has been published in a preliminary communication.<sup>117</sup> The synthetic route is a 6 step process from the commercially available (*R*)-(-)-3-hydroxybutyrate **170** and proceeds in an overall 25% yield, with the lowest yielding step being the addition of guanidine to the enone **175**. (Scheme 69)

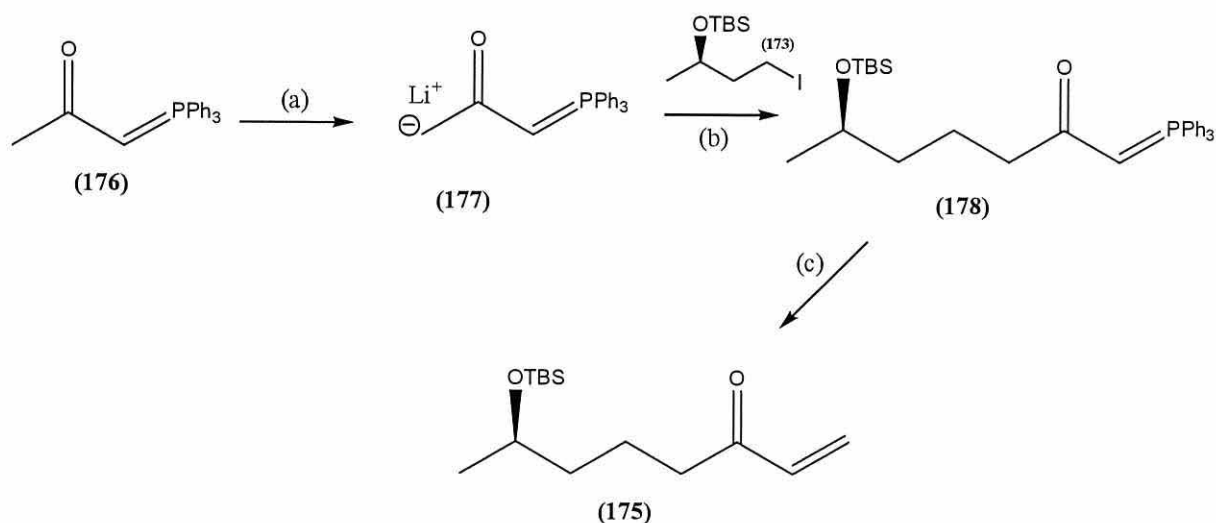


**Scheme 69:** (a) TBDMSCl, Imidazole, DMF (99%). (b) DIBAL-H, hexane -78-0 °C (95%) (c) TosCl, Py, 0 °C (85%) (d) NaI, Acetone (89%). (e) i)  $\text{CH}_3\text{COCHPh}_3$  (**176**), *n*BuLi THF; ii) aq.  $\text{CH}_2\text{O}$  (79%) (f) i) guanidine/DMF, (ii) HCl/MeOH. (iii)  $\text{NaBF}_4$  (aq) (44%).

Reasonable quantities of the catalyst were readily available within the research group, however it was hoped that it might be possible to improve on the synthetic route by optimising the final addition step. We thus treated the alcohol **170** with imidazole and *tert*-butyldimethylsilyl in anhydrous DMF to obtain a near quantitative yield of the silylated ester **171**. This displayed identical spectral data to the literature.<sup>127</sup> Repetition of this reaction gave consistent yields (97-99%, 6 attempts)

The ester **171** was then reduced with an excess of diisobutylaluminium hydride in anhydrous hexane at -78 °C and after stirring overnight and quenching with a solution of Rochelle's salt gave the expected alcohol **172**, in a lower than expected 89% yield. The alcohol gave identical data to that reported previously<sup>128</sup> and the reaction gave reasonably consistent yields on repetition (72-89%, 6 attempts). Tosylation was then effected using *p*-toluenesulphonyl chloride in dry pyridine at 0 °C for 16 hours yielding the tosylate **173** in 82% yield and on repetition yields in the range 78-82% were obtained (5 Attempts). Finally treatment of **173** with an excess of sodium iodide in refluxing anhydrous acetone gave the iodide **174** in 87% yield which on repetition gave yields of 74-87% (5 attempts).

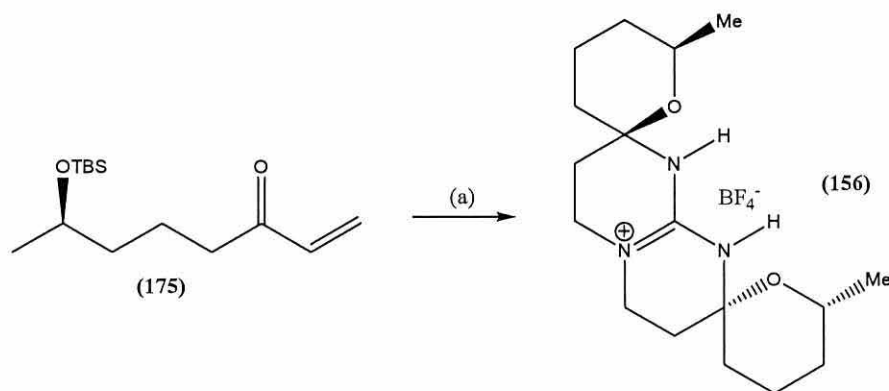
With iodide **174** in hand, its reaction with acetylmethylene phosphorane **176** was attempted. This reaction requires the treatment of **176** with *n*-BuLi in THF to generate the intermediate lithiated species **177** which is then alkylated with the iodide **174**. The crude phosphorane **178** is then treated with formaldehyde leading to the enone **175**. (Scheme 70)



**Scheme 70:** (a) *n*BuLi, THF, -60 °C 1 h; (b) **174**, -78 °C - rt, 16 h.; (c) CH<sub>2</sub>O, CH<sub>2</sub>Cl<sub>2</sub> (79%).

Thus a slight excess of the phosphorane **176** was dissolved in dry THF and cooled to -78 °C ensuring that no precipitation of the phosphorane occurred and *n*-BuLi was then added dropwise. A deep red solution formed which was warmed to -60 °C for 1 hour. The reaction was then cooled (-78 °C) and the iodide **173** was added as a solution in THF and the reaction slowly warmed to ambient temperature overnight. After aqueous work up the phosphorane **178** was treated with formaldehyde to give the enone **175** in 45% yield as evidenced by the ABX pattern of the vinylic group at  $\delta$  5.77 (1H, dd, *J* = 1.5, 10.1 Hz), 6.17 (1H, dd, *J* = 1.5, 17.6 Hz) and 6.31 (1H, dd, *J* = 10.1, 17.6 Hz) ppm. The data was in accordance with the literature.<sup>117</sup>

The yield for this reaction was very low and despite two repetitions this could not be improved upon. The reason for this lower yield is not entirely clear, there was no precipitation of the phosphorane during the lithiation and the solvent and *n*-BuLi were tritruated to ensure the absence of water in the reaction. Despite this the reaction gave access to multigram quantities of **175** which were utilised in the guanidine addition step.

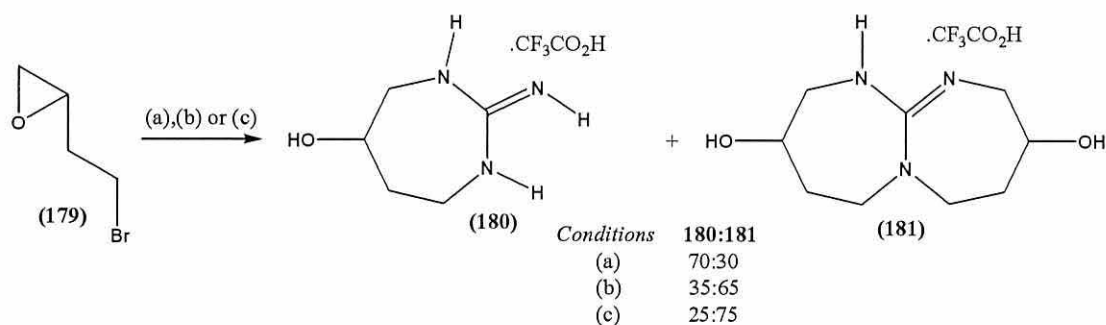


**Scheme 71:** (a) anhydrous DMF, 0 °C, guanidine in DMF, stir 16 h; 38%.

All manipulations using guanidine were carried out under an argon atmosphere and care was taken to keep the reaction vessel under an argon atmosphere. The enone **175** was dissolved in dry DMF, cooled (0 °C) and a solution of freshly prepared guanidine in DMF was added dropwise. The reaction was kept at 0 °C for 15 min before being allowed to warm to ambient temperature and stirred overnight. The reaction was then cooled (0 °C) and an excess of methanolic HCl was added and the reaction stirred for 3 hours. After work up the crude product was ion exchanged by stirring with a saturated solution of NaBF<sub>4</sub>. Column chromatography of the crude product gave the required compound in a disappointingly low yield of 38% repetition twice failed to increase the yield obtained (36-38%). Analysis of the other more polar by-products from the reaction indicated the presence of considerable decomposition possibly by polymerisation. Two further repetitions of this reaction were attempted and on both occasions the guanidine addition stage was kept at 0 °C for longer periods of time (3 and 6 hours) but this did not lead to an improved yield. The data was in accordance with the literature.<sup>117</sup>

## A bicyclic guanidinium catalyst

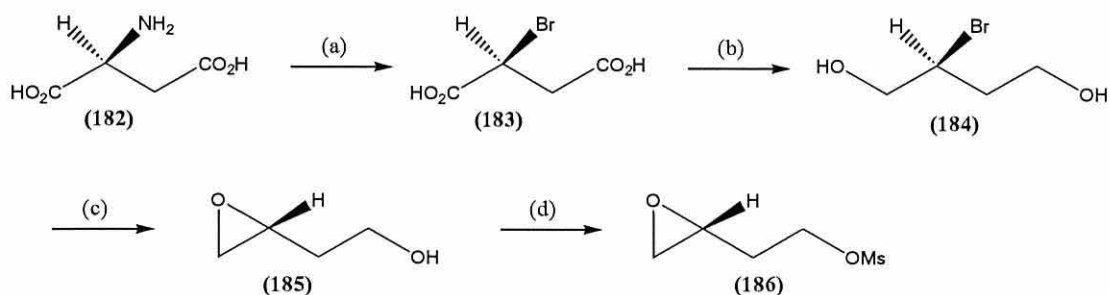
Some previous work in the group had reported that treatment of the bromide **179** with guanidine in *t*-BuOH lead to the synthesis of the 7-membered heterocyclic guanidine **180**.<sup>6</sup> Interestingly a minor by product the bicyclic guanidine **181** was also formed and the reaction could be modified to generate larger quantities of this material (Scheme 72).



**Scheme 72:** (a) i) Guanidine hydrochloride, 1 eq *t*-BuOK, *t*-BuOH, then **179** 16 h, rt. ii) 1 eq *t*-BuOK, 60 °C, 24 h. iii) CF<sub>3</sub>CO<sub>2</sub>H, MeOH. (b) i) Guanidine hydrochloride, 1 eq *t*-BuOK, *t*-BuOH, then **179** 16 h, rt. ii) 1 eq *t*-BuOK, 2 h. iii) epoxide **179**, 22 h. (c) i) Guanidine hydrochloride, 1 eq *t*-BuOK, *t*-BuOH, then epoxide **179** 16 h, rt. ii) 1 eq *t*-BuOK, 2 h. iii) epoxide **179**, 22 h. iv) 1 eq *t*-BuOK, 2 h. v) epoxide **179**, 22 h. vi) 1 eq *t*-BuOK, 60 °C, 24 h. vii) CF<sub>3</sub>CO<sub>2</sub>H, MeOH.

As can be seen the use of multiple additions of the brominated epoxide **179** led to a better yield of the bicyclic guanidine **181** which was easily separated from the monocyclic product **180** in good yield.

From the perspective of generating a homochiral product it would be necessary to use a chiral epoxide and on searching the literature the chiral mesylated epoxide **186** was chosen as a good starting material. This epoxide can be prepared in large quantities from L-aspartic acid **183** as reported by Volkmann<sup>129</sup> and detailed below. (Scheme 73)

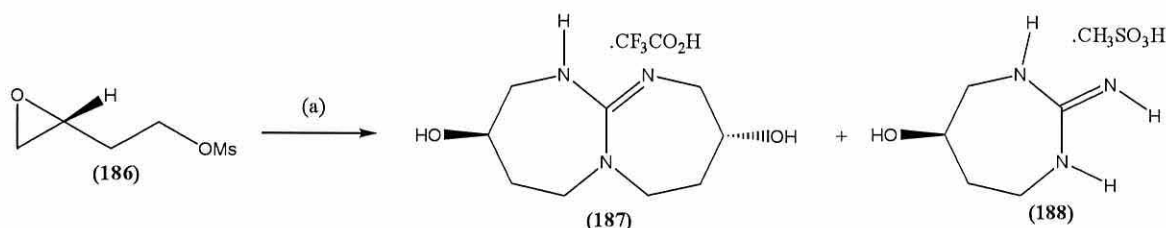


**Scheme 73:** (a) i) NaBr, 6N H<sub>2</sub>SO<sub>4</sub>, ii) L-Aspartic Acid, **182**, iii) 5-10 °C, NaNO<sub>2</sub>, stir 1.5 h; 71% (b) anhydrous THF, -78 °C, BH<sub>3</sub>:Me<sub>2</sub>S, THF, 60 h; 77% (c) anhydrous DCM, cesium carbonate, stir 40 h. (d) -25 °C, triethylamine, methanesulfonyl chloride, stir 2 h; 55%.

Thus, L-aspartic acid was added to a solution of sodium bromide in 6N sulfuric acid, cooled to 5 °C and treated with sodium nitrite to give after work up the bromide **183** in 71% yield. The observed melting point of **183** was 179-181 °C which compares favourably with the

literature value of 185 °C.<sup>129</sup> The bromide **183** was then reduced to the diol **184** in 77% yield using borane-methyl sulphide complex in tetrahydrofuran at -78 °C to rt over 60 h. The formation of **184** was confirmed by comparison with known literature data and specifically by the appearance of the methylene signals at 3.63 (2H, t,  $J = 12.5$  Hz) and 3.84 (2H, d,  $J = 11.0$  Hz) ppm in the  $^1\text{H}$  NMR. The final two stages in the synthesis involve firstly the conversion of diol **184** into the epoxide **185** by reaction with cesium carbonate dissolved in anhydrous dichloromethane which effects the epoxide ring formation. This product was used in the next stage without purification but  $^1\text{H}$  NMR analysis of the crude gave signals at  $\delta$  2.44 (1H, dd,  $J = 2.7, 4.9$  Hz), 2.67 (1H, dd,  $J = 4.7, 8.9$  Hz) and 2.95 (1H, m) indicating the formation of the epoxide. Finally the primary alcohol group in **185** was mesylated using triethylamine and methanesulfonyl chloride at -25 °C in dichloromethane. After work-up the product **186** was isolated in 55% and gave identical data to the literature, specifically the presence of a methyl signal at 3.03 ppm in  $^1\text{H}$  NMR and 37.5 ppm in the  $^{13}\text{C}$  NMR.

With the mesylate **186** in hand the guanidine cyclisation reaction was attempted. Thus guanidine was prepared *in situ* by treating guanidine hydrochloride with potassium *tert*-butoxide in *t*-butanol and after 2 hours a solution the mesylate **186** was added dropwise. After 24 h further potassium *tert*-butoxide was added and after stirring for 2 h, another equivalent of the **186** was introduced as a solution in *t*-butanol. After a further 24 h this two stage procedure was repeated and the reaction heated at 60 °C for 24 h. (Scheme 74)

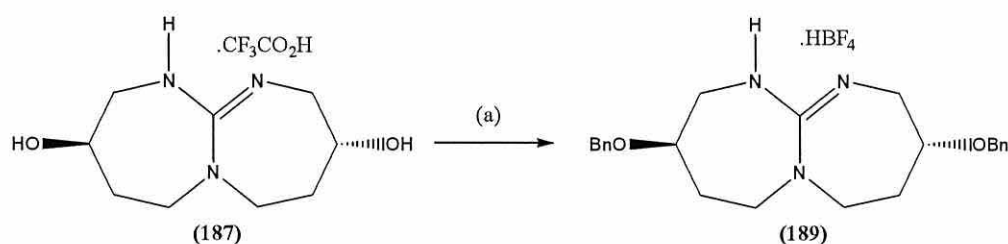


**Scheme 74:** (a) i) guanidine.HCl,  $t\text{BuOK}$ , anhydrous  $t\text{butanol}$ , stir 2 h, ii) **186** in  $t\text{butanol}$ , stir 24 h, iii)  $t\text{BuOK}$ , stir 1 h, iv) **186** in  $t\text{butanol}$ , stir 24 h, 60 °C; 18% (**187**).

The reaction was worked up by the addition of trifluoroacetic acid and the two compounds separated by chromatography. The two compounds were very difficult to separate by chromatography but were separated with care to give pure monocyclic **188** in 35% yield and *ca* 90% pure (as estimated by NMR) bicyclic **187** in 18% yield. These yields were somewhat disappointing and were not surpassed on repeating the reaction on two further occasions.

The structures of the two compounds were confirmed by comparison with the racemic material prepared previously by Jones (née Hall).<sup>130</sup> The proton NMR spectra of both compounds were broad and very similar in nature and not of use for structural identification however significant differences were apparent in the <sup>13</sup>C data to allow identification. In addition, mass spectral data confirmed the structures undisputedly.

The nature of the bicyclic compound was that it was very hygroscopic and required storage over a drying agent to prevent the absorption of atmospheric moisture. It was intended to derivatise the hydroxyl groups within **187** in order that it might act as a phase transfer agent and we thus sought to utilise the benzyl protecting group in combination with sodium hydride to effect this transformation. The general method involved dissolving the bicycle **187** in DMF followed by the addition of an excess of NaH and BnBr followed by stirring under heat for 0-4 h then at rt for 24-48 hrs. (Scheme 75, Table 14)



**Scheme 75** (a) i) anhydrous DMF, 0 °C, NaH, stir 30 min. ii) Benzyl bromide, stir 1 h, heat 60 °C, 4 h; iii) stir rt, 48 h; iv) ion exchange resin, stir 24 h; v) NaBF<sub>4</sub>, 24 h; 33%.

**Table 14:** Conditions used for benzylation of **187**

NaH (eq)	BnBr (eq)	Heat (h)	RT Stir (h)	Yield (%)
4.2	2.3	0	24	22
5.3	2.8	3	48	23
6.4	3.4	4	24	33

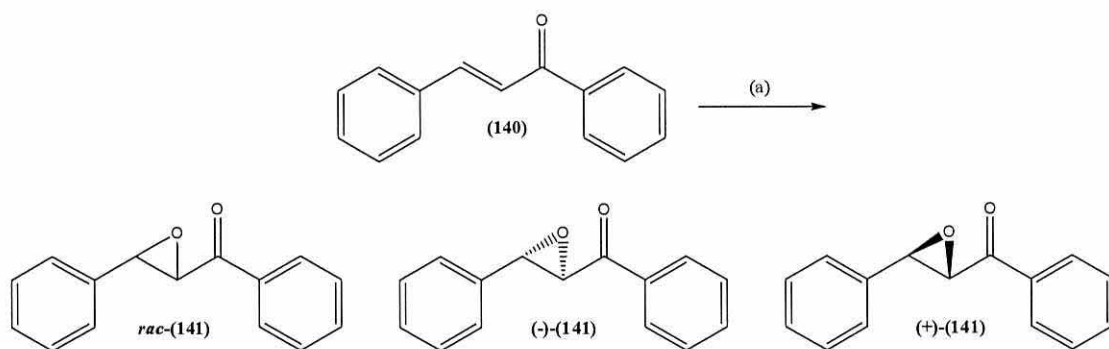
The reaction appears to proceed slowly without heating and does give a better yield on heating for a longer period of time with greater than 3.4 equivalents of BnBr and 6 equivalents of NaH but still gave low yields. These experiments were not optimised further as sufficient **189** as available for use in the phase transfer experiments.

The structure of **189** as confirmed by NMR with the  $^1\text{H}$  NMR appearing much clearer than the unprotected **187** with distinctive signals for each CH environment with the 2 CH's adjacent to the benzyl group appearing at  $\delta$  4.25 (br. t,  $J = 3.5$  Hz) and the  $\text{CH}_2$  of the benzyl at  $\delta$  4.50 (4H, s). The compound was now freely soluble in chloroform and as such signals for the NH protons were observed at  $\delta$  7.62 as a broad singlet. The  $^{13}\text{C}$  NMR gave 4  $\text{CH}_2$  signals at  $\delta$  31.0, 48.2, 55.5 and 70.9 as well as a CH signal at  $\delta$  76.2 and the characteristic guanidine quaternary carbon at  $\delta$  155.5 ppm.



## Epoxidation of Chalcones

With the catalysts available the epoxidation of a range of chalcones was investigated. The chalcones under study were produced at the sponsor company and were available in multi-gram quantities. We first repeated the work performed previously<sup>118</sup> on the epoxidation of chalcone **140** with the catalyst **156** as a standard for comparison purposes and also prepared its enantiomer by utilising the two Lygo catalysts **132a** and **132b**. The general method for all the reaction studied was to dissolve the chalcone and required catalyst in toluene with cooling (0 °C) and vigorous stirring whereupon a solution of sodium hypochlorite (8% aq solution) was added. After 24 h the reaction was quenched and the product obtained by column chromatography. Analysis by proton and carbon NMR was then performed and high resolution MS was used to ensure the integrity of the compounds. Enantiomeric excesses were determined by HPLC and  $\alpha_D$  measurements were taken for comparison. (Scheme 76, Table 15)



**Scheme 76:** (a) i) Catalyst, toluene, 0 °C, ii) 8% NaOCl, stir, 16-24 h; 84%.

**Table 15:**

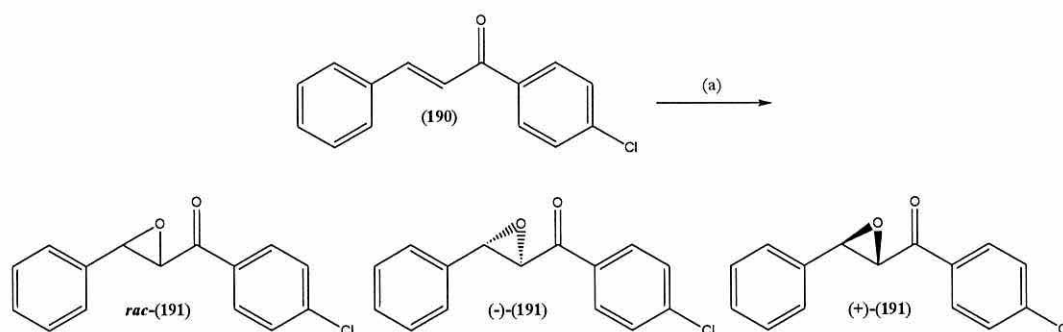
Catalyst	% yield	e.e. (HPLC)	$\alpha_D$	e.e. ( $\alpha_D$ )
$n\text{BuN}_4^+\text{Cl}^-$	84	---	----	---
<b>156</b>	80	91	-185	89
<b>132a</b>	64	37	4	2
<b>132b</b>	74	60	158	76

The results for the chalcone **140** are shown above in table 15 and are as expected for this system. The product can be identified from the diagnostic  $^1\text{H}$  NMR signals for the epoxide which are found at  $\delta$  4.10 ( $J = 1.8$  Hz) and 4.32 ( $J = 1.8$  Hz). In previous work carried out within the group an e.e. of 93% was observed<sup>118</sup> for catalyst **156**

and a comparable e.e. of 91% was obtained on our repetition based on HPLC data. The e.e. obtained with the use catalyst **132a** was again very similar to the previously reported value of 39%,<sup>131</sup> whilst the e.e. previously observed with catalyst **132b** was 86%<sup>101</sup> a somewhat disappointing e.e. of 60% was obtained. The optical rotation data for these two is in reasonable agreement however the HPLC data is more reliable. The values from optical rotation and HPLC support the formation of the **RR-141** when catalyst **156** was used.

As this reaction was known to be well behaved under most conditions this was chosen as a model to test the bicyclic guanidine catalyst **189**. We employed the same conditions as previously discussed and were disappointed to find that no reaction occurred and the chalcone was recovered in quantitative yield. The reaction was repeated with a larger amount of catalyst (0.1 M equivalent) and again no reaction occurred, the reasons for this is not clear.

We next moved to consider other chalcone precursors and the chalcone **190** was then investigated. Again a racemic sample was prepared as a standard and the reaction with  $n\text{Bu}_4\text{N}^+\text{Cl}^-$  as catalyst gave the required compound **rac-191** in 64% yield as evidenced by signals in the  $^1\text{H}$  NMR at  $\delta$  4.10 ( $J = 1.5$  Hz) and 4.25 ( $J = 1.5$  Hz) for the epoxide protons. When the catalysts **156**, **132a** and **132b** were then used the reaction proceeded similarly to give 51%, 79% and 90% yields respectively. (Scheme 77, Table 16)



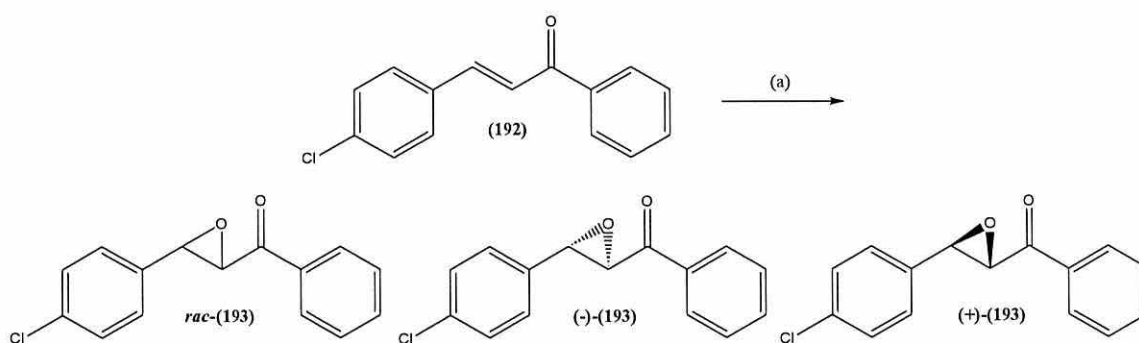
**Scheme 77:** (a) i) Catalyst, toluene, 0 °C, ii) 8% NaOCl, stir, 16 h; 90%.

**Table 16:**

Catalyst	% yield	e.e. (HPLC)	$\alpha_D$	e.e. ( $\alpha_D$ )
$n\text{Bu}_4\text{N}^+\text{Cl}^-$	64	---	----	---
<b>156</b>	51	85	-193	96
<b>132a</b>	79	7	71	35
<b>132b</b>	90	66	143	71

The results for the chalcone **191** are shown above in table 16 and are as expected for this system. Again catalyst **156** gave an e.e. of 85% from HPLC however the yield was low at 51%. The catalyst **132b** gave a higher yield of 90% however the e.e. was only 66%. Finally the hydroxyl catalyst **132a** gave a very low e.e. of 7% from HPLC. The optical rotation data was in broad agreement with the HPLC and both techniques support the formation of the **RR-191** with catalyst **156** with the rotation of -193, which is comparable to the previously reported value of -202.<sup>132</sup>

The chalcone **192** was investigated next and a racemic sample of the epoxide was prepared as a standard by using  $n\text{Bu}_4\text{N}^+\text{Cl}^-$  as catalyst gave the required compound **rac-193** in 96% yield as evidenced by signals in the  $^1\text{H}$  NMR at  $\delta$  4.07 ( $J = 1.2$  Hz) and 4.27 ( $J = 1.2$  Hz) for the epoxide protons. When the catalysts **156**, **132a** and **132b** were then used the reaction proceeded similarly to give excellent yields of 97%, 99% and 92% respectively. (Scheme 78, Table 17)



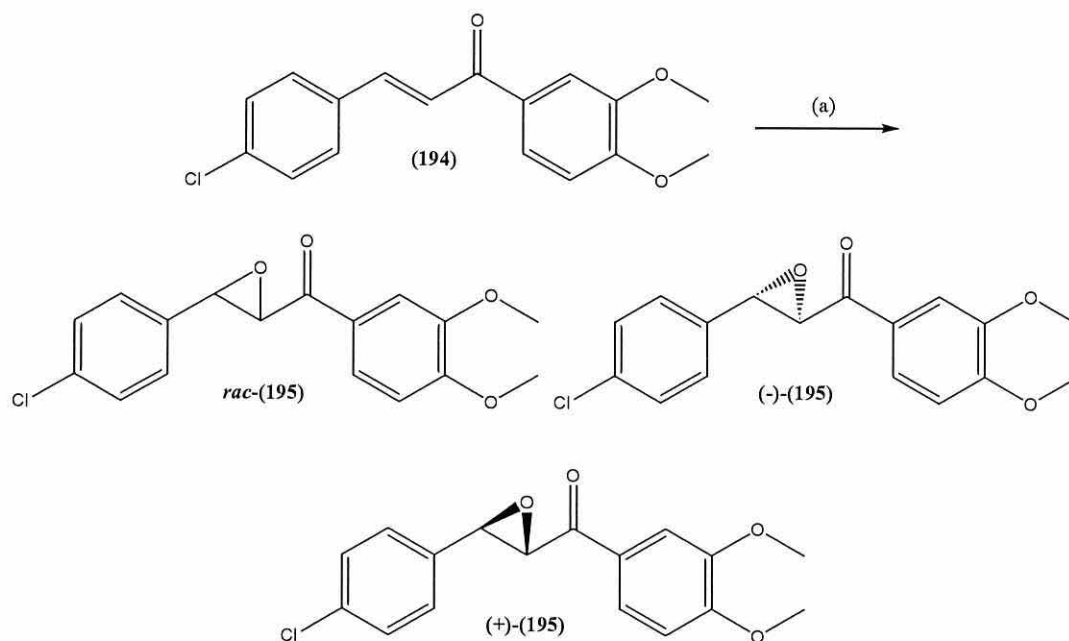
**Scheme 78:** (a) i) Catalyst, toluene, 0 °C, ii) 8% NaOCl, stir, 16 h; 99%.

**Table 17:**

Catalyst	% yield	e.e. (HPLC)	$\alpha_D$	e.e. ( $\alpha_D$ )
$n\text{Bu}_4\text{N}^+\text{Cl}^-$	96	---	---	---
<b>156</b>	97	94	-203	80
<b>132a</b>	99	21	12	5
<b>132b</b>	92	59	150	59

An impressive 94% e.e. was observed when catalyst **156** was used, as evidenced by HPLC which was of the opposite sign of rotation to the product from **132b** which proceeded in 59% e.e. Again the free hydroxyl catalyst **132a** gave a low e.e. of 21%. The optical rotation data was again in broad agreement with the HPLC data and the support the formation of the **RR-193** when catalyst **156** was utilized with a rotation of -203 comparing favourably to the previously reported rotation of -253.<sup>132</sup>

The final enone investigated was **194** and again, a racemic sample was prepared as a standard using  $n\text{Bu}_4\text{N}^+\text{Cl}^-$  as catalyst. This gave the required compound **rac-195** in 89% yield as evidenced by signals in the  $^1\text{H}$  NMR at  $\delta$  4.03 ( $J = 1.5$  Hz) and 4.21 ( $J = 1.5$  Hz) for the epoxide protons. When the catalysts **132a** and **132b** were then used the reaction gave the required product however the yields of 51% and 36% were disappointingly low. When the guanidine catalyst **156** was utilised no reaction was observed when catalyst **156** was used and the starting material was recovered. A second attempt using 10 molar % of the catalyst again failed to give any observable reaction. (Scheme 79, Table 18)



**Scheme 79:** (a) i) Catalyst, toluene, 0 °C, ii) 8% NaOCl, stir, 16 h; 89%.

**Table 18:**

Catalyst	% yield	e.e. (HPLC)	$\alpha_D$
$n\text{BuN}_4^+\text{Cl}^-$	89	---	---
<b>156</b>	0	---	---
<b>132a</b>	51	35	24
<b>132b</b>	36	57	120

## Conclusion

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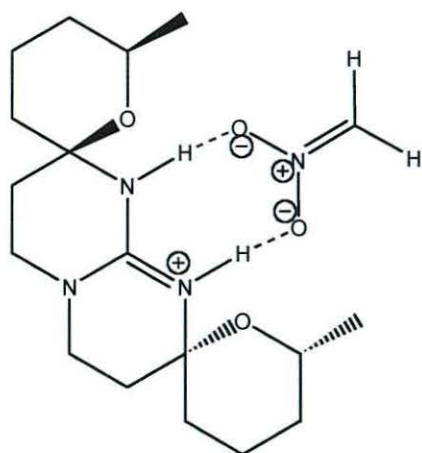
The primary finding from this work is that the optimization of the method for the synthesis of catalyst **156** was more difficult than expected, especially the penultimate step of the synthesis which proved difficult to reproduce literature yields even on repetition. The epoxidation reactions using guanidine **156** however proved to be very efficient with e.e.'s of 85-94% being observed for the three substrates **140**, **190** and **192**, however the reaction of the *bis*-methoxy substituted enone **194** failed to give any product. One possible reason for this might be that the electron donating nature of the methoxy group leads to increased conjugation with the carbonyl group, which in turn might lower the susceptibility of the enone to conjugate addition. Other examples of successful epoxidation of similarly substituted chalcones have been reported.<sup>101</sup> using cinchonine derived catalysts and it might be that the guanidine catalyst is more susceptible to electronic factors in the substrate.

The reactions using Lygo's catalyst **132b** gave lower e.e.'s in all cases and this was somewhat disappointing. Some impurities may have been present in the catalyst however NMR data was in good agreement with the literature. Comparison of the method we utilized, demonstrated that our reactions were run at lower temperature initially and it is possible that uncatalysed background reactivity might play a role in the lower e.e.'s.

Most disappointingly the bicyclic guanidine catalyst **189** was not successful in epoxidating the *trans*-chalcone, however it is possible that it might be used in other phase transfer reactions if the synthesis of **189** could be optimized. Other possibilities are that the catalyst could be improved by utilizing differing functional groups at the benzyl position.

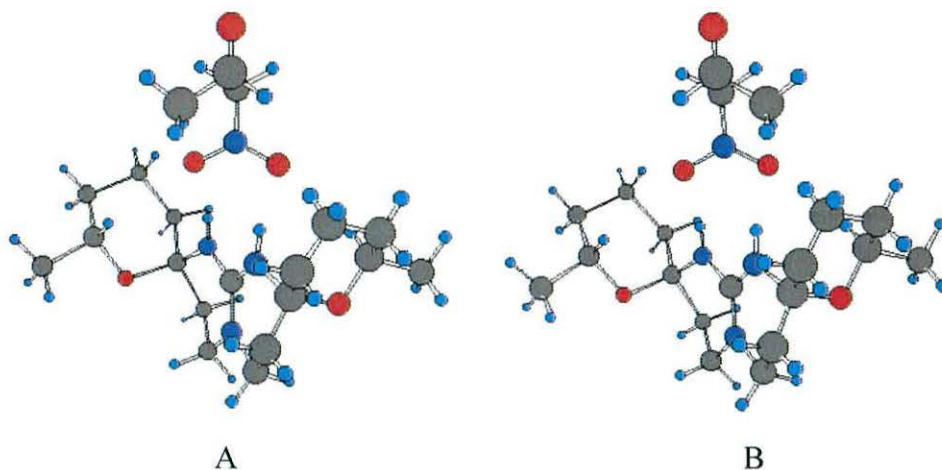
### Mechanism for guanidine base catalysed reactions

Mechanistic studies concerned with the ability of guanidine bases to catalyse phase transfer reactions have been explored by both the Murphy<sup>117</sup> and Nagasawa<sup>114</sup> groups. The Murphy group utilised X-ray structure data<sup>133</sup> and molecular modelling of structure **156** replacing the fluoroborate anion with a nitroenolate (Figure 27)



**Figure 27:**

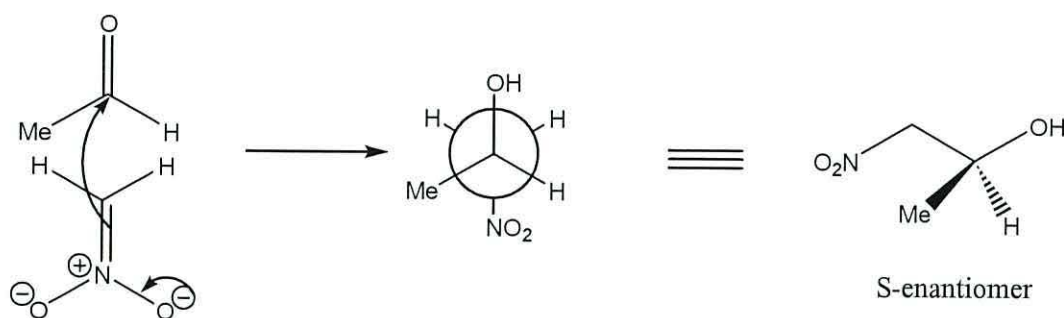
This enabled the study of how an aldehyde such as ethanal approaches and interacts with the guanidine-nitroenolate complex in aldol and Michael reactions. An important factor to note is the distance of the base's chiral centres from the active site. This factor would help explain the lack of selectivity observed during the nitro-Michael reaction studied by Mendoza,<sup>119, 134</sup> Nagasawa<sup>114</sup> and Murphy.<sup>117</sup> (Figure 28)



**Figure 28:** Proposed modes of approach of ethanal toward nitromethane co-ordinated to guanidine base **156**.

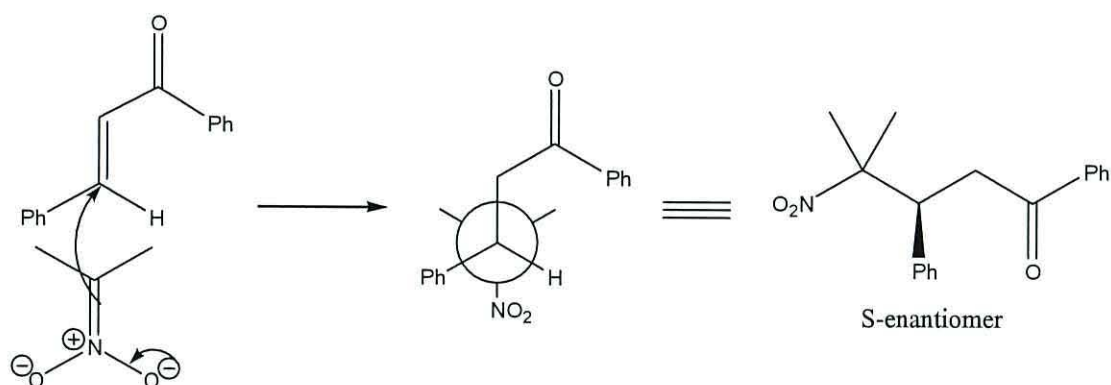
Molecular modelling suggested that the minimised structure A would be favoured over structure B as the approaching aldehyde will be less hindered with this configuration. The modelling was then used to propose a mechanism and predict the stereochemistry expected for the nitro-aldol reaction (Scheme 67, page 62). The modelling undertaken predicts that the aldehyde will approach from above the plane of the guanidine base and that the S-enantiomer will thus be formed. (Figure 29)





**Figure 29:** Proposed mechanism for the guanidine base catalysed nitro-aldol reaction.

Experimental data resulted in the expected *S* selectivity being observed.<sup>a</sup> Efforts were then undertaken to test rigorously the mechanism proposed by synthesising a known compound. The nitro-Michael reaction of chalcone **140** with 2-nitropropane (Scheme 62, page 67) previously studies by Tóke and co-workers<sup>135</sup> was chosen and was carried out utilizing the same conditions as Tóke and co-workers<sup>135</sup> during their studies. The molecular modelling again predicted the synthesis of the *S*-enantiomer with the chalcone approaching from above the plane of the guanidine base (Figure 30). Experimental data confirmed the modelling prediction with **S-163** being formed.



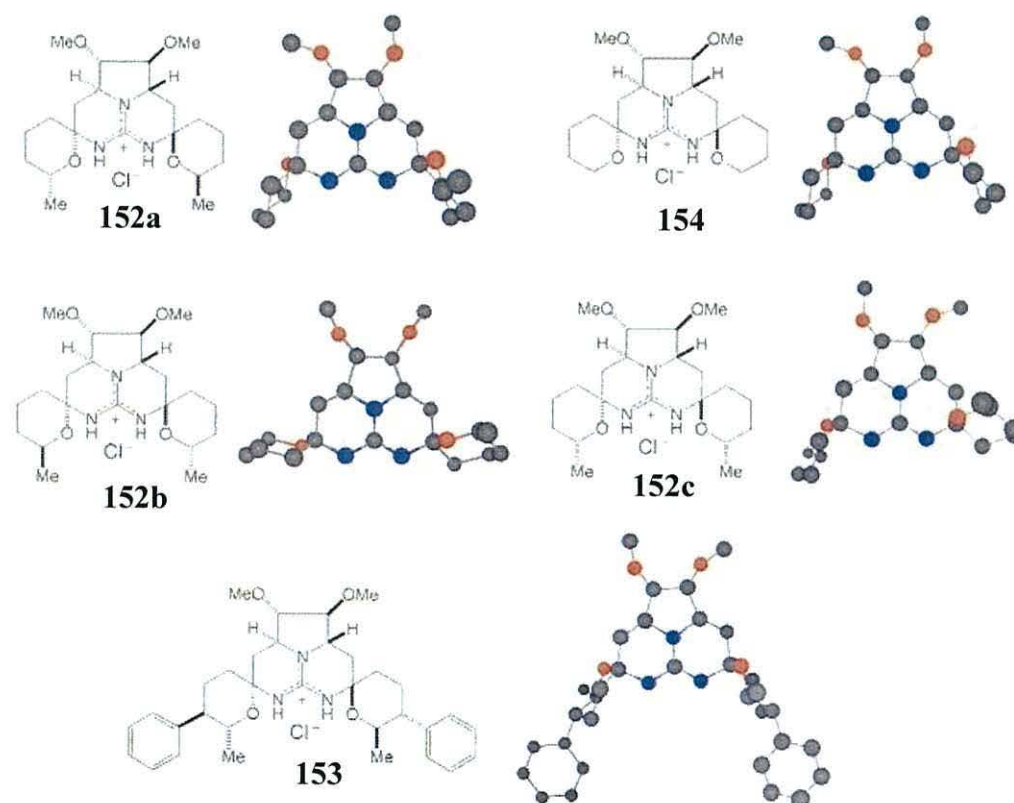
**Figure 30:** Proposed mechanism for formation of **S-163** via a nitro-Michael reaction.

The Nagasawa<sup>111, 114</sup> research group have also utilized molecular modelling to study the mechanism involved in guanidine base catalysed reactions utilizing the guanidine bases discussed previously (Figure 25, page 65).

<sup>a</sup> Whilst the formation of the (*R*)-enantiomer is reported in reference 126, this was in error and it is in fact the (*S*)-enantiomer that is formed and the paper is in error.<sup>126</sup>



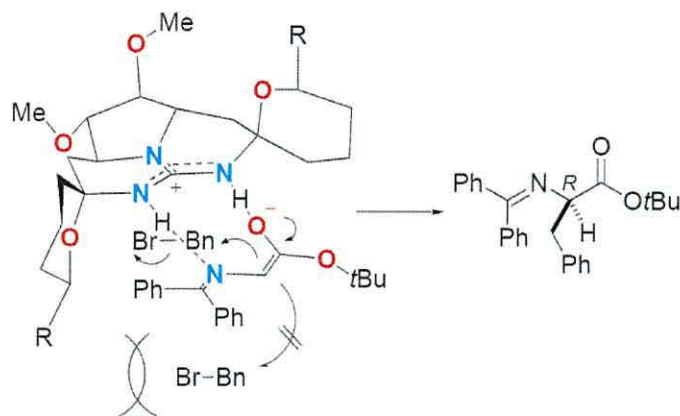
As has been discussed previously Nagasawa found that the “cavity size” caused by the methyl groups within the structure had a substantial effect on both the yield and the selectivity observed. The X-ray structures of **152a** and **152c** (Figure 31) show that with respect to the guanidine plane (side view) the spiro ether rings and methyl substituents on the spiro-rings are orientated in a *trans*-axial arrangement. Nagasawa postulated that this steric hindrance observed at the cavity would enable the base to induce asymmetry into a reaction if the reaction proceeds at the guanidine moiety.



**Figure 31:** Guanidine bases synthesised by Nagasawa and co-workers.

These bases were used to test the asymmetric alkylation of the Schiff base **121** (Scheme 60, page 65). It was noted that the stereochemistry of **155** was controlled by the spirocyclic ether rings of the pentacyclic guanidine core. Furthermore, the ring methyl substituent also plays a large role as can be seen by comparing **153** (forming S-**155**) and

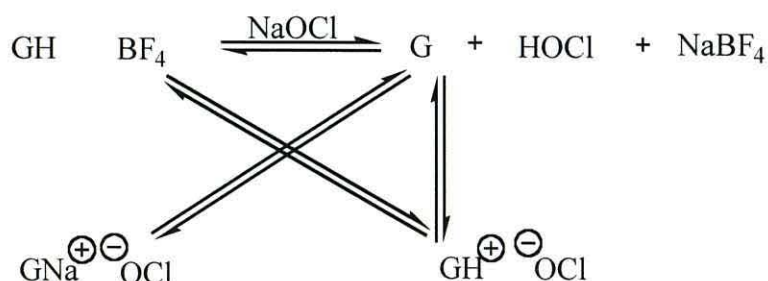
**152a-c/154** (forming **R-155**). The mechanism for this alkylation as proposed by Nagasawa utilizing **152a** is shown in figure 32.



**Figure 32:** Proposed mechanism of alkylation of Schiff base **121** (R = Me).

It was postulated that the transition state shown above is occurring due to *in situ* formation of the guanidine base from its salt in aqueous KOH. This base then forms a complex with the *Z* enolate of the Schiff base **121** via both ionic and hydrogen bonding, the electrophile then approaches from the least hindered face of the complex and thus forming **R-155**. As with previous examples high selectivity was observed and this can be attributed to the ability to control the approach of the electrophile afforded by the steric hindrance due to the methyl groups present.

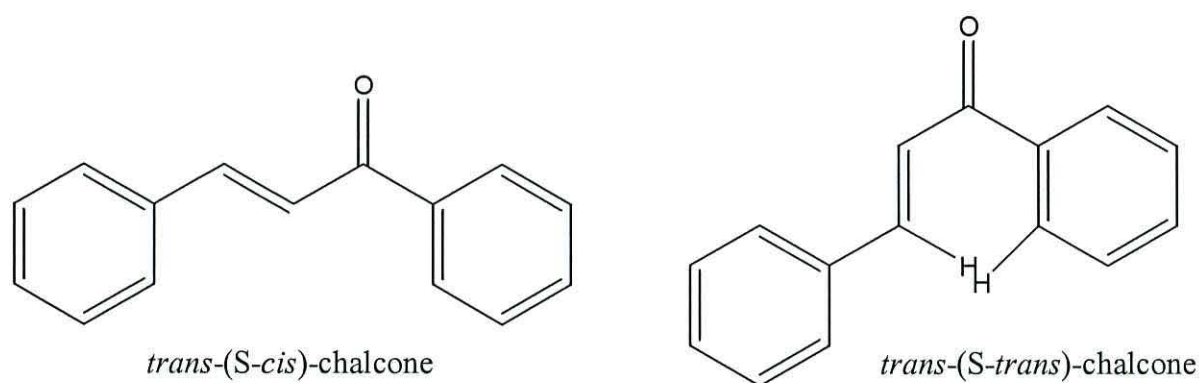
To date the mechanism involved in the transfer of  $\text{OCl}^-$  anions from the aqueous phase to the organic phase has not been studied. Sodium hypochlorite is a strong base (the pH of the solution used in this study was found to be pH 10.6) and thus the complex formed with the guanidine base is intriguing. The exact nature of the guanidinium species formed is unknown although it is probable that a complex equilibrium is in effect. (Figure 33)



G = Guanidine base

**Figure 33:** Predicted equilibrium observed between guanidine base and NaOCl.

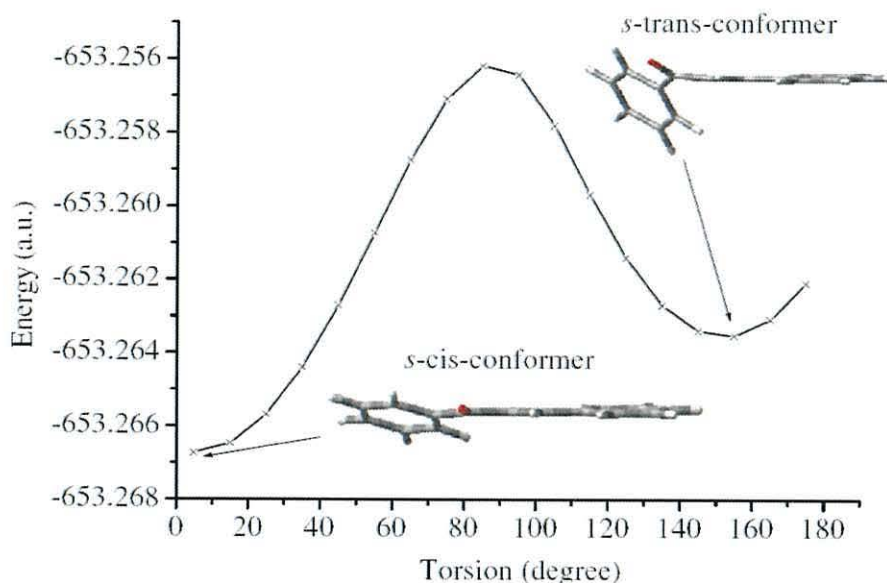
The transfer of hypochlorite with traditional quaternary ammonium salts is easily visualised using the standard phase transfer equilibrium, however with a guanidinium species it is possible that the guanidinium ion is in equilibrium with the free guanidine or is completely deprotonated if the basicity is high. This offers up alternate mechanism in which the guanidine is transferring sodium hypochlorite by coordination of the sodium ion to the guanidine or the oxygen atoms in the spirocycles or indeed a combination of both. Alkali metal complexes of free guanidines have been observed in the literature which adds support to this possibility.<sup>109, 136, 137</sup> The nature of the chalcone species is also undefined as both the *trans*-(*S-cis*)- and *trans*-(*S-trans*)- conformers can exist. (Figure 34)



**Figure 34:** *trans*-(*S-cis*)- and *trans*-(*S-trans*)- conformers of chalcone 140

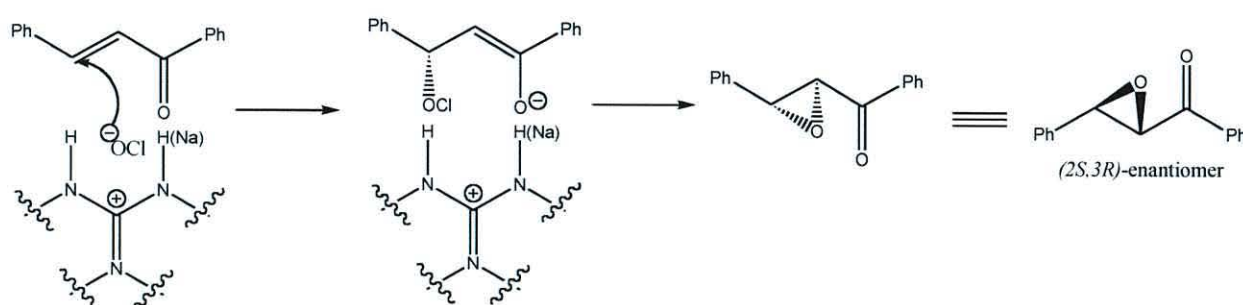
Xue and co-workers<sup>138</sup> found that the *trans*-(*S-cis*)-chalcone was lower in energy due to its planar nature as opposed to the *trans*-(*S-trans*)-chalcone which, due to the steric hindrance caused by the two hydrogen atoms shown in figure XX is non-planar. However, due to the low energy barrier conversion from the *S-cis* to the *S-trans* can take place easily. (Figure 35)





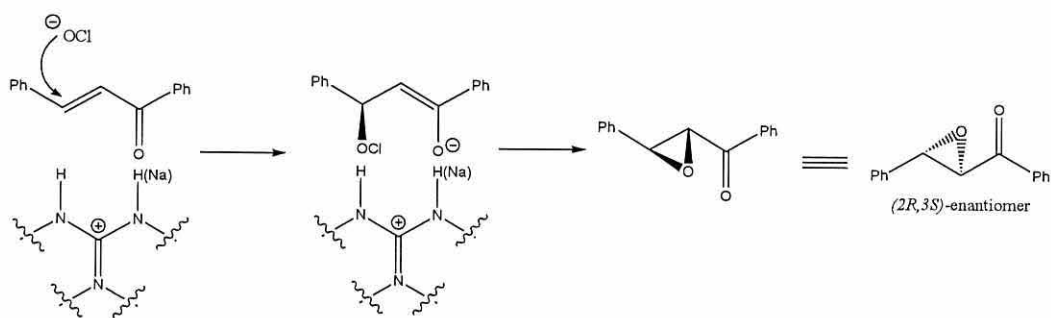
**Figure 35:** Potential curve of the torsion angle in *trans*-chalcone.

Whilst the exact nature of the guanidine species is unknown it can be assumed that the approaching chalcone will be in the *S-cis*- conformation. This conformation is more favourable than the *S-trans* as it enables the stabilisation of the enolate intermediate by the proton/ sodium atom present within the guanidine base. If the reaction proceeds in a similar manner to the nitro-aldol and nitro-Michael reaction, with the approach of the chalcone being from above the plane of the guanidine base, then the formation of the (2*S*,3*R*)-epoxide is predicted which is opposite to that observed. (Figure 36)



**Figure 36:** Proposed mechanism for the epoxidation of chalcone **140**.

An alternate arrangement in which the chalcone associates with the guanidine or guanidinium catalyst initially and then the hypochlorite approaches from the top face of the chalcone would give the required product. (Figure 37)



**Figure 37:** Alternate mechanism for the epoxidation of chalcone **140**.

In conclusion, it is obvious that there is a complex process occurring in this reaction and it might be possible to study this reaction more closely by repeating the work and varying the nature of the reaction conditions. Firstly the use of the free base as a catalyst might give a clue as to the species involved in the reaction as might varying the counter-ion of the hypochlorite by utilising potassium or lithium hypochlorite. Further information might be obtained by determining the  $pK_a$  of the guanidinium species and comparing this with known guanidines and in addition molecular modelling of the process will be useful in determining the approach of the chalcone to a theoretical guanidine-hypochlorite complex and vice versa.

# Experimental

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## REAGENTS

Reagents were obtained from commercial suppliers and were used without further purification. Reactions using *n*-Butyl lithium and diisobutylaluminium hydride refer to the use of these reagents in hexane. Rochelle's salt was prepared by dissolving KOH (10.66 g, 0.27 mol) and NaOH (14.92 g, 0.27 mol) in water (100 ml) before tartaric acid (40.00 g, 0.27 mol) was added.

## SOLVENTS

All solvents used in reactions were purified using methods described in the literature.<sup>139</sup> Using these methods, diethyl ether and tetrahydrofuran were distilled from benzophenone and sodium wire whilst chloroform was distilled from P<sub>2</sub>O<sub>5</sub>. Dichloromethane and Dimethylformamide were dried over CaH and freshly distilled. Methanol was dried by distillation from magnesium and iodine, whereas petrol was distilled and collected between boiling range of 40-60 °C.

## CHROMATOGRAPHY

TLC was performed on glass plates coated with kieselgel 60 F254 (Art. 5554; Merck) with eluent specified in each case. The eluent percentage refers to a solution of the more polar solvent in the least polar solvent. Compounds were visualised using ultraviolet light and/or iodine. Staining reagents were also used, in particular solutions of phosphomolybdic acid (PMA) in EtOH or vanillin in EtOH/H<sub>2</sub>SO<sub>4</sub>, with heating.<sup>140, 141</sup> Column chromatography was performed using Merck 7736 silica gel (particle size 40 – 63 µm) under medium pressure with the eluent specified in each case.

## ANALYTICAL METHODS

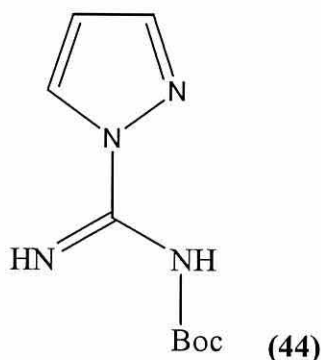
Melting points were recorded with a Gallenkamo MF370 apparatus and are uncorrected. Infrared spectra were obtained on a Perkin-Elmer 1600 FTIR spectrometer as thin film or solution as appropriate with the solvent quoted in each case. Absorption frequencies are reported in wavenumber  $\nu$ , whose unit is the reciprocal centimetre (cm<sup>-1</sup>). Electron impact (EI) and chemical ionisation (CI) were recorded on a VG Masslab Model 12/253 spectrometer and high resolution mass spectra (HRMS) on a VG Analytical ZAB-E

spectrometer at the EPSRC Mass Spectrometry Service Centre at Swansea. Mass measurements are reported in daltons. Optical rotation was determined using a polAAR 2001 machine, where all  $\alpha_D$  values are relative to the solvent, concentration of the sample and temperature, which are specified in all cases. Routine NMR samples were performed on a Bruker AC250 spectrometer,  $^1\text{H}$  at 250 MHz and  $^{13}\text{C}$  at 62.5 MHz, with samples made up in  $\text{CDCl}_3$  solvent unless stated otherwise. Detailed spectra of products were performed on a Bruker Avance-500 spectrometer,  $^1\text{H}$  at 500 MHz and  $^{13}\text{C}$  at 125 MHz, made up in  $\text{CDCl}_3$  solvent unless stated otherwise. HMBC analysis was done by J. Hollingsway at Summit (Wales), Aberystwyth. Chemical shifts are reported as  $\delta$  values (ppm) relative to tetramethylsilane as an internal standard. Spin couplings are denoted as J values (Hz), whilst splitting patterns are reported as singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m), broad (br) or any combination of these.

## MISCELLANEOUS

All non-aqueous reactions were performed using oven dried glassware (250 °C) and were conducted under a positive atmosphere of argon. All new compounds were homogeneous by TLC (unless otherwise stated). Solids were purified by either recrystallisation or chromatography, whilst liquids and oils were purified either by chromatography or distillation. The term 'dried' refers to the treatment of a solution of the compound with anhydrous magnesium sulphate. *n*-butyllithium in hexanes was titrated against diphenylacetic acid in THF immediately before use.<sup>140,141</sup> The term *in vacuo* refers to the reduced pressure of a Büchi rotary evaporator, at water pump pressure (14 mm Hg) at 30-50 °C, or at 1 mm Hg at 25 °C for higher boiling solvents. All yields quoted are for the purified compounds (unless otherwise stated).

### ***N*-Boc-1*H*-Pyrazole-1-Carboxamide **44****<sup>13</sup>

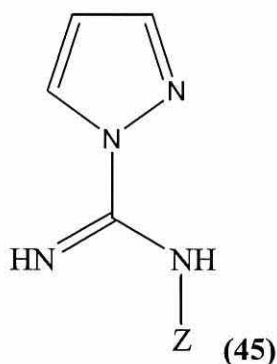


1*H*-Pyrazole-1-carboxamidine **43** (10.0 g, 68 mmol) and di-*tert*-butyl dicarbonate (22.2 g, 102 mmol) were dissolved in anhydrous THF (40 ml) and *N*-diisopropylethylamine (23.6 ml, 136 mmol) was added. After stirring for 16 h, the reaction was diluted with water (50 ml), extracted with dichloromethane (4 x 50 ml) and the combined organic extracts washed with brine (50 ml). After drying (MgSO<sub>4</sub>) the solvent was removed under reduced pressure and the crude product re-crystallised from a minimum volume of warm ether. This gave product **44** as white crystals (11.34 g) in 79% yield.

<b><sup>1</sup>H-NMR: δppm</b>	1.53 (9H, s, <sup>t</sup> Bu), 6.38 (1H, d, J = 1.5 Hz, CH), 7.66 (2H, m, CH, NH), 8.44 (1H, br. d, J = 2.2 Hz, CH), 9.07 (1H, br. s, NH).
<b><sup>13</sup>C-NMR: δppm</b>	28.1 (3 x CH <sub>3</sub> ), 80.1 (C), 108.9 (CH), 128.8 (CH), 143.3 (CH), 155.0 (C), 163.2 (C=O).
<b>FTIR <math>V_{\max}</math> cm<sup>-1</sup> (Nujol)</b>	2967 (C-H), 1667 (C=O), 1635 (C=C), 1454.
<b>Melting Point:</b>	97-99 °C (Lit 98-99 °C) <sup>13, 142</sup>



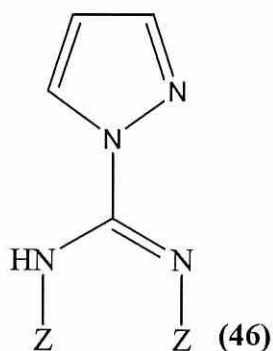
### *N-Z-1H-Pyrazole-1-Carboxamide 45*<sup>13</sup>



1*H*-Pyrazole carboxamidine hydrochloride **43** (5.0 g, 34 mmol) and benzyl chloroformate (8.7 g, 1.5 ml, 51 mmol, 1.5 eq.) were dissolved in anhydrous THF (20 ml) and stirred for 5 minutes. *N*-diisopropylethylamine (8.8 g, 12 ml, 68 mmol, 2 eq.) was then added and the resultant solution stirred overnight. The reaction was diluted with water (200 ml), extracted with dichloromethane (3 x 50 ml) and the organic layers combined and washed with brine (200 ml). After drying (MgSO<sub>4</sub>) the solvent was removed under reduced pressure to yield the crude product **45** which was obtained as a white solid (7.31 g, 88%). This product was not purified but used crude in subsequent reactions.

<b><sup>1</sup>H-NMR: δ ppm</b>	5.23 (2H, br. s, CH <sub>2</sub> ), 6.44 (1H, br. s, CH), 7.40 (5H, m, Ph), 7.70-7.71 (2H, br. s, CH, NH), 8.47 (1H, br. s, CH), 9.06 (br. s, NH).
<b><sup>13</sup>C-NMR: δppm</b>	67.6 (CH <sub>2</sub> ), 109.3 (CH), 128.1 (CH), 128.3 (CH), 128.5 (CH), 128.9 (CH), 136.3 (C), 143.7 (CH), 155.5 (C), 163.9 (C=O).
<b>FTIR <math>\nu_{\max}</math> cm<sup>-1</sup> (CHCl<sub>3</sub>)</b>	3457 (N-H), 3275 (N-H), 3018 (C-H), 1669 (C=O), 1628.2 (C=N).
<b>Melting Point:</b>	106-109 °C (Lit 108-109 °C) <sup>13, 142</sup>

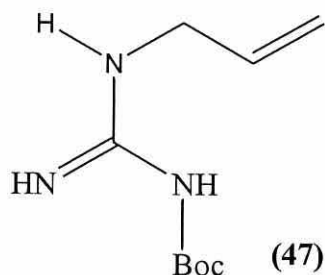
### *N,N'*-bis-*Z*-1*H*-Pyrazole-Carboxamidine **46**<sup>13</sup>



*N*-*Z*-1*H*-Pyrazole-carboxamide **45** (10.0 g, 41 mmol) was dissolved in anhydrous THF (30 ml), cooled (0 °C), and NaH (60% w/w, 5.7 g, 144 mmol) added portion-wise whilst maintaining a nitrogen atmosphere. CbzOSu (15.3 g, 61 mmol) was then added and the mixture stirred overnight. The reaction was then diluted with brine (100 ml), extracted with chloroform (3 x 100 ml) and the combined organic extracts washed with further brine (100 ml), then dried (MgSO<sub>4</sub>). Evaporation under reduced pressure followed by column chromatography (EtOAc/petrol, 0:100 to 50:50 in 10% steps) gave **46** as a white solid (7.06 g, 46%). The product could be recrystallised by dissolving in a small quantity of ethyl acetate and diluted with approximately 4 fold of petrol then cooling in the freezer.

<b><sup>1</sup>H-NMR: δppm</b>	5.25 (4H, s, 2 x CH <sub>2</sub> ), 6.46 (1H, dd, J = 2.7, 1.5 Hz, CH), 7.39 (10H, m, 2 x Ph), 7.64 (1H, br. s, CH), 8.30 (1H, d, J = 2.7 Hz, CH), 9.35 (1H, br. s, NH).
<b><sup>13</sup>C-NMR: δppm</b>	68.4 (CH <sub>2</sub> ), 68.7 (CH <sub>2</sub> ), 110.3 (CH), 128.3 (CH), 128.5 (CH), 128.6 (CH), 128.7 (CH), 128.9 (CH), 134.5 (C), 135.7 (C), 142.9 (CH), 150.6 (C), 158.2 (C).
<b>Melting Point:</b>	88-91 °C (Lit 89-91 °C) <sup>13, 142</sup>

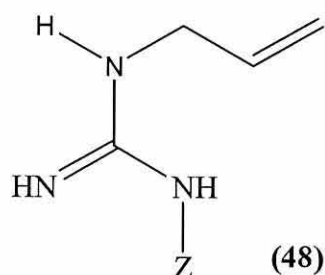
### ***N*-Boc-*N'*-allylguanidine **47****



*N*-Boc-1*H*-Pyrazole-1-Carboxamide **44** (2.0 g, 9.51 mmol) was dissolved in excess allylamine (10 ml) and the mixture refluxed for 2.5 h. The solvent was removed under reduced pressure and recrystallised from dichloromethane/petrol to give **47** (1.51 g, 80%) as a white solid.

<b><sup>1</sup>H-NMR: δppm</b>	1.46 (9H, s, 3 x CH <sub>3</sub> ), 3.83 (2H, d, J = 4.9 Hz, CH <sub>2</sub> ), 5.24 (1H, br. d, J = 10.4 Hz, CH) 5.33 (1H, br. d, J = 17.1 Hz, CH), 5.83 (1H, ddt, J = 17.1, 10.4, 4.9 Hz, CH), 6.34 (1H, br. s, NH), 7.60 (2H, br. s, 2 x NH).
<b><sup>13</sup>C-NMR: δppm</b>	28.4 (CH <sub>3</sub> ), 43.9 (CH <sub>2</sub> ), 78.1 (C), 117.3 (CH <sub>2</sub> ), 133.5 (CH), 162.1 (C), 163.6 (C).
<b>HRMS (ES<sup>+</sup>) <i>m/z</i>:</b>	C <sub>9</sub> H <sub>18</sub> O <sub>2</sub> N <sub>3</sub> ([M+H] <sup>+</sup> ); Requires 200.1394 found 200.1391
<b>Melting Point:</b>	75-78 °C

### *N-Z-N'*-allylguanidine **48**



*N-Z-1H*-Pyrazole-1-Carboxamide **46** (4.0 g, 16.4 mmol) was dissolved in excess allylamine (10 ml) and refluxed for 2.5 h. The solvent was removed under reduced and the crude product purified *via* column chromatography (EtOAc/petrol, 0:100 to 40:60 in 10% steps) to yield **48** as a white solid (2.32 g) in 61% yield.

**<sup>1</sup>H-NMR: δppm** 3.73 (2H, d, J = 4.9 Hz, NCH<sub>2</sub>), 5.07 (2H, s, CH<sub>2</sub>), 5.23 (1H, d, J = 11.3 Hz, CH), 5.25 (1H, d, J = 16.8 Hz, CH), 5.73 (1H, ddd, J = 16.8, 11.3, 4.9 Hz, CH), 7.35 (5H, m, Ph), 7.40 (3H, br. s, 3 x NH).

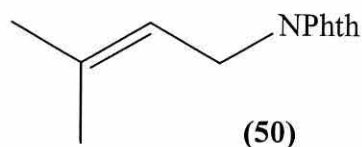
**<sup>13</sup>C-NMR: δppm** 41.9 (CH<sub>2</sub>), 66.2 (CH<sub>2</sub>), 116.4 (CH<sub>2</sub>), 127.8 (CH), 128.0 (CH), 128.4 (CH), 133.6 (CH), 137.3 (C), 162.5 (C), 163.6 (C).

**FTIR  $\nu_{\max}$  cm<sup>-1</sup> (CHCl<sub>3</sub>)** 3018 (C-H), 1629 (C=O), 1580 (C=N).

**HRMS (ES<sup>+</sup>)  $m/z$ :** C<sub>12</sub>H<sub>15</sub>O<sub>2</sub>N<sub>3</sub> [(M+H)<sup>+</sup>]; Requires 234.1243 found 234.1245.

**Melting Point:** 119-121 °C.

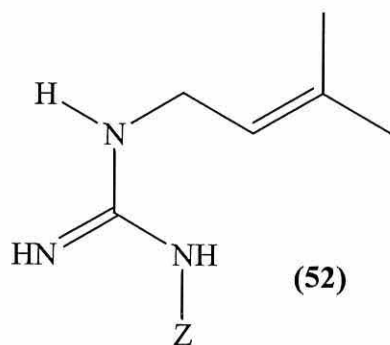
***N*-(3-Methylbut-2-enyl) phthalimide 50<sup>14</sup>**



3,3-Dimethylallylbromide **49** (28.5 g, 0.19 mol) was added to a stirred solution of potassium phthalimide (37.3 g, 0.20 mol) in DMF (200 ml), after which the mixture was stirred for 1 h at room temperature and heated at reflux for 18 h. After cooling to room temperature, the mixture was poured onto ice (115 g) and extracted with dichloromethane (4 x 50 ml). The combined extracts were washed with aqueous KOH (0.2M, 300 ml) and water (300 ml), then dried (MgSO<sub>4</sub>) and evaporated under reduced pressure to give the crude product (28.27 g) as an off-white/yellow solid. The crude product was then dissolved in ether (300 ml), washed with further water (4 x 500 ml) then dried (MgSO<sub>4</sub>) and evaporated under reduced pressure to yield **50** as an off-white solid (26.89 g) in 65% yield.

<b><sup>1</sup>H-NMR: δppm</b>	1.71 (3H, s, CH <sub>3</sub> ), 1.84 (3H, s, CH <sub>3</sub> ), 4.28 (2H, d, J = 7.3 Hz, CH <sub>2</sub> ), 5.28 (1H, t, J = 7.3 Hz, CH), 7.71-7.83 (4H, m, 4 x CH).
<b><sup>13</sup>C-NMR: δppm</b>	17.93 (CH <sub>3</sub> ), 25.64 (CH <sub>3</sub> ), 36.39 (CH <sub>2</sub> ), 123.58 (2 x CH), 132.32 (2 x C), 132.68 (CH), 133.80 (2 x CH), 142.14 (C), 168.29 (2 x C).
<b>FTIR <math>\nu_{\max}</math> cm<sup>-1</sup> (Nujol)</b>	2924 (C-H), 1722 (C=O), 1456 (C=C).
<b>Melting Point:</b>	89-92 °C (Lit 102-105 °C) <sup>143</sup>

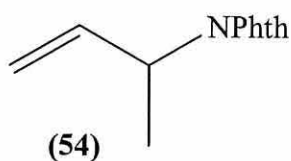
## *N-Z-N'*-(dimethylallyl)guanidine **52**



*N*-(3-methylbut-2-enyl) phthalimide **49** (10.2 g, 46 mmol) was dissolved in 95% methylated spirits (40 ml) and hydrazine hydrate (3.2 g, 51 mmol) was added. The resulting mixture was refluxed for 1.5 h then cooled (0 °C) and treated with HCl (10M, 5 ml). The resulting mixture was filtered under suction through Celite and the precipitate washed with further ethanol (30 ml). Evaporation of the filtrate gave a crude paste which was dissolved in chloroform (50 ml), dried with MgSO<sub>4</sub> and passed through a cotton wool plug to give a solution of dimethylallylamine hydrochloride (40 mmol). Acetonitrile (40 ml), *N-Z-1H*-pyrazole-1-Carboxamide **48** (2.4 g, 10.3 mmol) and triethylamine (6.0 g, 8.2 ml, 60 mmol) were then added to the solution along with MgSO<sub>4</sub> (1-2 g) to dry the reaction solvent. After stirring for 16 h the reaction was filtered and the solvent removed under reduced pressure. The crude product was purified by column chromatography (EtOAc/petrol, 0:100 to 40:60 in 10% steps) to yield **52** as an off-white solid (1.06 g) in 39% yield, along with the recovered starting material, **48** (1.44 g, 60%).

<b><sup>1</sup>H-NMR: δppm</b>	1.58 (3H, s, CH <sub>3</sub> ), 1.69 (3H, s, CH <sub>3</sub> ), 3.63 (2H, d, J = 7.3 Hz, CH <sub>2</sub> ), 5.05 (2H, s, CH <sub>2</sub> ), 5.10 (1H, br. m, CH), 7.31 (5H, m, Ph), 9.0 (3H, br. s, 3 x NH)
<b><sup>13</sup>C-NMR: δppm</b>	17.7 (CH <sub>3</sub> ), 25.5 (CH <sub>3</sub> ), 39.1 (CH <sub>2</sub> ), 66.0 (CH <sub>2</sub> ), 120.0 (CH), 127.5 (CH), 127.7 (CH), 128.2 (CH), 136.2 (C), 137.4 (C), 162.1 (C), 163.5 (C).
<b>FTIR <math>\nu_{\max}</math> cm<sup>-1</sup> (CHCl<sub>3</sub>)</b>	3306 (NH) 3018 (C-H), 1627 (C=O), 1589 (C=C).
<b>HRMS (ES+) <math>m/z</math>;</b>	C <sub>14</sub> H <sub>20</sub> O <sub>2</sub> N <sub>3</sub> [(M+H) <sup>+</sup> ]; Requires 262.1550, found 262.1551.
<b>Melting Point:</b>	81-83 °C.

### ***N*-(1-Methylallyl) phthalimide **54**<sup>14</sup>**



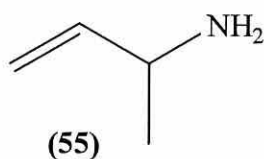
3-Chlorobut-1-ene **53** (19.47 g, 21.6 ml, 215 mmol) was added to a stirred solution of potassium phthalimide (41.7 g, 0.225 mol) in DMF (150 ml). After stirring the solution at room temperature for 16 h the mixture was refluxed for 8 h then cooled to room temperature and poured onto ice (115 g). The aqueous layer was extracted with dichloromethane (4 x 50 ml) and the combined extracts washed vigorously with aqueous potassium hydroxide solution (0.2N, 300 ml) then water (300 ml). The organic extracts were then dried (MgSO<sub>4</sub>) and evaporated under reduced pressure. The resultant oil was dissolved in ether (300 ml) and washed with water (3 x 500 ml) to remove the remaining DMF. The organic phase was dried (MgSO<sub>4</sub>) and evaporated under reduced pressure to give **54** (30.9 g, 71 %) as a waxy solid.

**<sup>1</sup>H-NMR: δppm**      1.58 (3H, d, J = 7.0 Hz, CH<sub>3</sub>), 4.93 (1H, m, CH), 5.16 (1H, d, J = 17.4 Hz, CH), 5.24 (1H, d, J = 10.4 Hz, CH), 6.20 (1H, ddd, J = 17.4, 10.4, 6.4 Hz, CH), 7.76 (4H, m, Ph).

**<sup>13</sup>C-NMR: δppm**      18.2 (CH<sub>3</sub>), 48.9 (CH), 116.3 (CH<sub>2</sub>), 123.1 (CH), 132.0 (C), 132.9 (C), 136.8 (CH), 167.9 (C).

**Melting Point:**      83-85 °C (Lit 85-85.6 °C)<sup>144</sup>

### 1-Methylallylamine **55**<sup>8</sup>

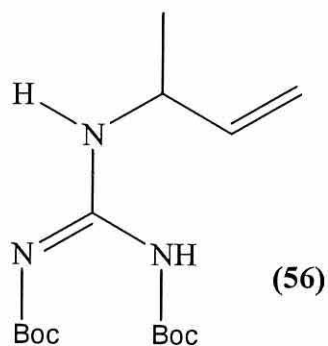


A mixture of *N*-(1-methylallyl) phthalimide **54** (54.5 g, 0.27 mol) and hydrazine hydrate (20.7 ml, aq 85%, 0.36 mol) in 95% ethanol (300 ml) was heated under reflux for 3 h. After cooling in ice, the reaction was treated with hydrochloric acid (32 ml, 12N), filtered to remove phthalhydrazine and the filter pad washed with further water (200 ml). The combined filtrates were evaporated to dryness under reduced pressure, and the solid obtained treated with a solution of potassium hydroxide (26 g, 0.4 mol) in water (50 ml). The resulting solution was extracted with ether (3 x 20 ml) and the combined extracts were dried over KOH pellets and fractionated through a glass-helix packed column to yield **55** as a liquid (11.4 g, Bp. 73-80 °C) which was found to be a 1:1 mixture of the amine and ethanol by <sup>1</sup>H NMR spectroscopy.

<sup>1</sup>H-NMR: δppm      1.15 (3H, d, J = 6.7 Hz, CH<sub>3</sub>), 3.47 (1H, m, CH), 4.95 (1H, d, J = 10.4 Hz, CH), 5.08 (1H, d, J = 17.1 Hz, CH), 5.85 (1H, ddd, J = 17.1, 10.4, 6.1 Hz, CH).

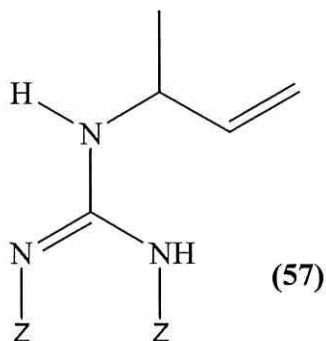


### Attempted synthesis of *N,N'*-Bis-Boc-*N'*-(1-Methyl-allyl)-guanidine **56**



*N,N'*-bis-Boc-1*H*-Pyrazole-Carboxamidine **42** (1.0 g, 3.2 mmol) and 1-methylallylamine **55** (0.5 g, 7.0 mmol) as a 50% solution in EtOH were dissolved in acetonitrile (5 ml) and stirred. After the prerequisite time (see discussion) and purification by column chromatography only the starting material **42** was recovered (0.57 g, 57%).

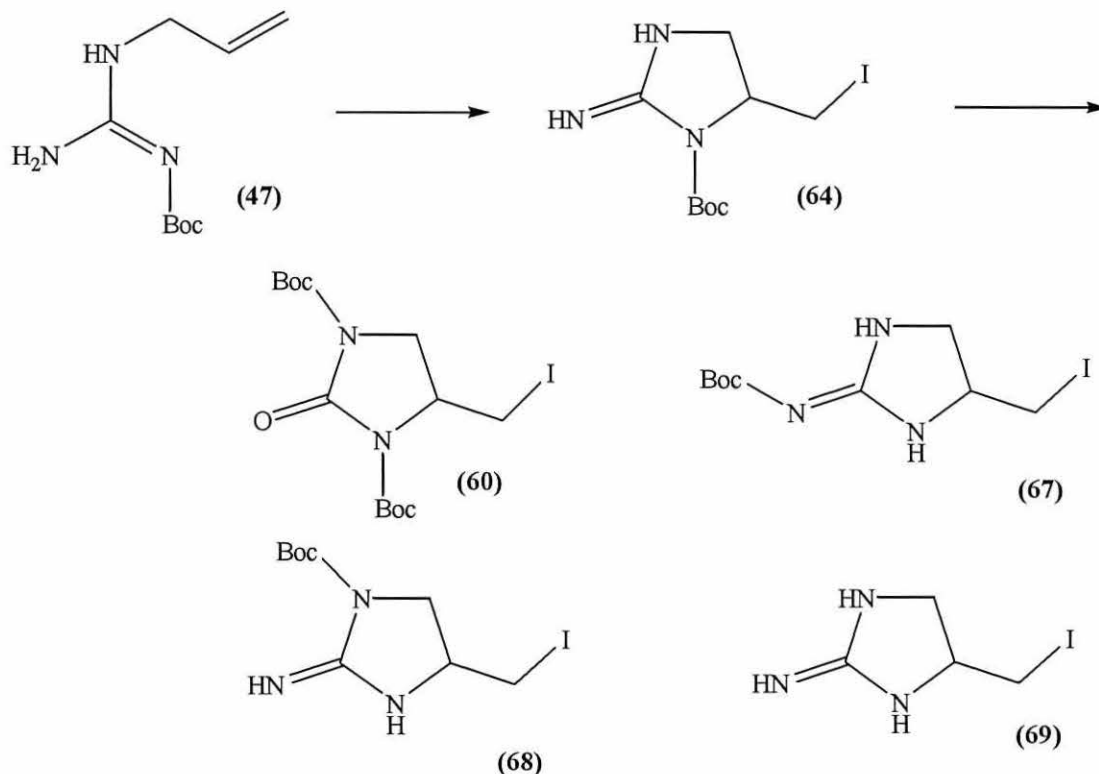
***N,N'*-Bis-*Z*-*N'*-(1-methyl-allyl)-guanidine 57**



*N,N'*-bis-*Z*-1*H*-Pyrazole-Carboxamidine **46** (1.2 g, 3.17 mmol) and 1-methylallylamine **88** (1.0 g, 6.6 mmol), as a 50% solution in EtOH, were dissolved in acetonitrile (5 ml) in a well sealed Carius tube. After 10 days at room temperature the solvent was removed under reduced pressure and the residue purified *via* column chromatography (Ether/petrol, 30:70). The product **97** was obtained as a white solid (0.86 g, 71 %).

<b><sup>1</sup>H-NMR: δppm</b>	1.30 (3H, d, J = 7.0 Hz, CH <sub>3</sub> ), 4.80 (1H, m, CH), 5.16 (6H, m, 2 x CH, 2 x CH <sub>2</sub> ) 5.87 (1H, ddd, J = 17.5, 10.3, 4.6 Hz, CH), 7.38 (10H, m, 2 x Ph), 8.38 (1H, br. d, J = 6.7 Hz, NH) 11.80 (1H, br. s, NH).
<b><sup>13</sup>C-NMR: δppm</b>	20.3 (CH <sub>3</sub> ), 48.5 (CH), 67.4 (CH <sub>2</sub> ), 68.3 (CH <sub>2</sub> ), 114.6 (CH <sub>2</sub> ), 127.9 (CH), 128.1 (CH), 128.4 (CH), 128.5 (CH), 128.7 (CH), 128.98 (CH) 134.5 (C), 136.6 (C), 138.3 (CH), 153.8 (C), 155.0 (2 x C=O).
<b>FTIR <i>V</i><sub>max</sub> cm<sup>-1</sup> (Nujol)</b>	3350 (N-H) 1731 (C=O), 1644, 1638.
<b>HRMS (ES<sup>+</sup>) <i>m/z</i>:</b>	C <sub>21</sub> H <sub>24</sub> O <sub>4</sub> N <sub>3</sub> [(M+H) <sup>+</sup> ]; Requires 382.1767 found 382.1789.
<b>Melting Point:</b>	53-56 °C.

## Cyclisation reaction of *N*-Boc-allylguanidine **47**



*N*-Boc-allylguanidine **47** (0.5 g, 2.5 mmol) was dissolved in acetonitrile (20 ml) and cooled (-15 °C) using an ice/salt bath. Finely powdered potassium carbonate (1.40 g, 10 mmol, 4 eq) was added, followed by iodine (2.55 g, 10 mmol, 4 eq). The mixture was stirred to rt for 16 h before being diluted with water (50 ml). Sodium thiosulphate solution (saturated) was then added until the iodine colour had dispersed and the mixture was extracted with ethyl acetate (3 x 50 ml), dried (MgSO<sub>4</sub>) and evaporated to dryness. This provided crude **64** (0.8 g) which was composed of mainly one isomer as determined by <sup>1</sup>H NMR (see text).

Partial data for **64**

<sup>1</sup>H-NMR: δppm                      1.51 (9H, s, <sup>t</sup>Bu), 3.58 (3H, m, CH, CH<sub>2</sub>), 3.81 (1H, dd, J = 9.3, 12.8 Hz, CH), 4.21 (1H, m, CH).

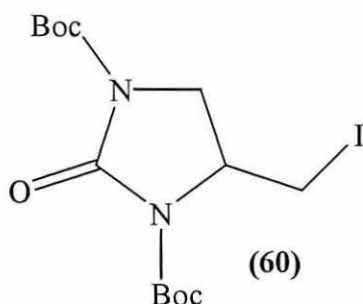
<sup>13</sup>C-NMR: δppm                      9.3 (CH<sub>2</sub>), 28.1 (3 x CH<sub>3</sub>), 53.8 (CH<sub>2</sub>), 57.7 (CH),

The crude **64** (0.74 g) was dissolved in DCM (5 ml) and silica gel (5 g) was added and the resultant slurry (insure sufficient DCM is added) was stirred for 5 days. The slurry was then washed onto a sintered filter and washed with excess DCM to give after evaporation a

crude extract (0.15g, 20% mass recovery). The silica pad was further washed with excess methanol to give after evaporation a crude extract (0.43 g, 57% mass recovery).

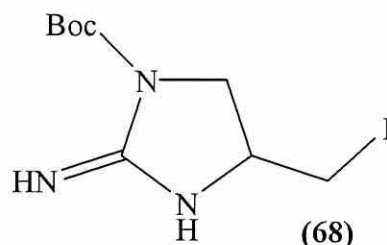
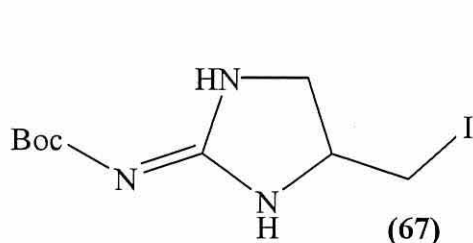
Column chromatography of the DCM extract (EtOAc/petrol, 0:100 to 20:80 in 10% steps) gave the urea **60** (0.015 g, 1.5%). Similarly, chromatography of the methanolic extract gave guanidines **67/68** (0.019 g, 2.5%), **67/68** (0.024 g, 3.5%) and **69** (0.095 g, 13%) as solids.

#### 4-Iodomethyl-2-oxo-imidazolidine-1,3-dicarboxylic acid di-*tert*-butyl ester **60**



<b><sup>1</sup>H-NMR: δppm</b>	1.49, 1.50 (18H, s, 2 x <sup>t</sup> Bu), 3.31 (1H, dd, J = 10.1, 8.5 Hz, CH), 3.45 (1H, dd, J = 10.1, 2.5 Hz, CH), 3.56 (1H, dd, J = 11.1, 3.2 Hz, CH), 3.76 (1H, dd, J = 11.0 Hz, 9.2 Hz, CH), 4.14 (1H, m, CH).
<b><sup>13</sup>C-NMR: δppm</b>	7.7 (CH <sub>2</sub> ), 28.0 ( <sup>t</sup> Bu), 29.7 ( <sup>t</sup> Bu), 45.9 (CH <sub>2</sub> ), 51.2 (CH), 83.7 (C), 84.1 (C), 148.1 (C), 150.0 (C) 150.1 (C).
<b>FTIR <i>V</i><sub>max</sub> cm<sup>-1</sup> (Nujol)</b>	1789 (C=O), 1738 (C=O).
<b>HRMS (ES+) <i>m/z</i>:</b>	C <sub>14</sub> H <sub>23</sub> N <sub>2</sub> O <sub>5</sub> I [(M+H) <sup>+</sup> ]; Requires 427.0724 found 427.0726
<b>Melting Point:</b>	123-125 °C
<b>Rf:</b>	0.21 (5% EtOAc/petrol)

**(4-Iodomethyl-imidazolidin-2-ylidene)-carbamic acid tert-butyl ester and 2-Imino-4-iodomethyl-imidazolidine-1-carboxylic acid tert-butyl ester 67/68**



Higher running fraction, **67**

**<sup>1</sup>H-NMR: δppm (CD<sub>3</sub>OD):** 1.54 (9H, s, <sup>t</sup>Bu), 3.39 (2H, d, J = 4.7 Hz, CH<sub>2</sub>), 3.67 (1H, dd, J = 10.5, 4.7 Hz, CH), 4.02 (1H, m, CH), 4.09 (1H, dd, J = 10.5, 9.4 Hz, CH)

**<sup>13</sup>C-NMR: δppm (CD<sub>3</sub>OD):** 11.4 (CH<sub>2</sub>), 28.8 (<sup>t</sup>Bu), 57.8 (CH<sub>2</sub>), 55.5 (CH), 83.6 (C), 154.6 (C) 165.4 (C).

**Rf:** 0.29 (10% MeOH, CHCl<sub>3</sub>)

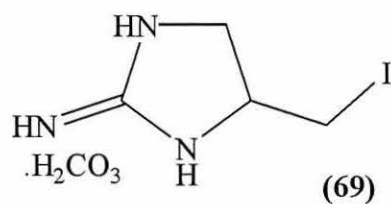
Lower running fraction, **68**

**<sup>1</sup>H-NMR: δppm (CD<sub>3</sub>OD):** 1.56 (9H, s, <sup>t</sup>Bu), 3.38 (1H, dd, J = 10.7, 4.4 Hz, CH), 3.49 (1H, dd, J = 11.1, 1.9 Hz, CH), 3.70 (1H, dd, J = 11.1, 5.4 Hz, CH), 3.87 (1H, dd, J = 10.7, 9.8 Hz, CH), 4.43 (1H, dddd, J = 4.4, 1.9, 5.4, 9.8 Hz, CH).

**<sup>13</sup>C-NMR: δppm (CD<sub>3</sub>OD):** 10.6 (CH<sub>2</sub>), 28.9 (<sup>t</sup>Bu), 49.1 (CH<sub>2</sub>), 59.0 (CH), 88.6 (C), 148.1 (C) 168.9 (C).

**Rf:** 0.26 (50% EtOAc/ petrol)

**4-Iodomethyl-imidazolidin-2-ylideneamine .H<sub>2</sub>CO<sub>3</sub> 69**



**<sup>1</sup>H-NMR:** δppm (CD<sub>3</sub>OD) 3.40 (3H, m, CH, CH<sub>2</sub>), 3.85 (1H, t, J = 10.0 Hz, CH), 4.15 (1H, m, CH).

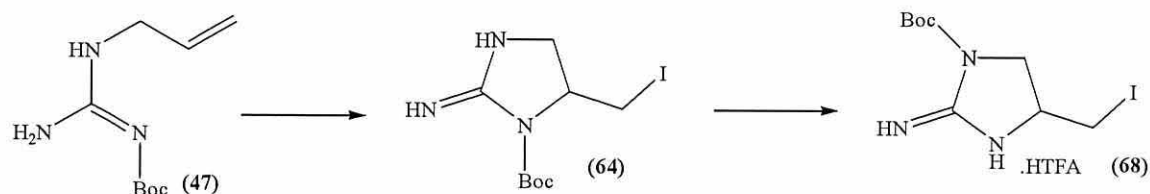
**<sup>13</sup>C-NMR:** δppm 11.5 (CH<sub>2</sub>), 51.0 (CH<sub>2</sub>), 57.2 (CH), 151.5 (C), 161.4 (C).

**FTIR**  $\nu_{\max}$  cm<sup>-1</sup> (Nujol) 3419 (N-H), 1731 (C=O), 1687 (C=N).

**HRMS (ES+) *m/z*** C<sub>4</sub>H<sub>8</sub>N<sub>3</sub>I [(M+H)<sup>+</sup>]; requires 225.9836 found 225.9836

**Rf:** 0.29 (20% MeOH/ CHCl<sub>3</sub>)

## Cyclisation reaction of *N*-Boc-allylguanidine **47** followed by acidic rearrangement



*N*-Boc-allylguanidine **47** (0.30 g, 1.5 mmol) was dissolved in acetonitrile (20 ml) and cooled (-15 °C) using an ice/salt bath. Finely powdered potassium carbonate (0.83 g, 6 mmol, 4 eq) was added, followed by iodine (1.53 g, 6 mmol, 4 eq). The mixture was stirred to rt for 16 h before being diluted with water (50 ml). Sodium thiosulphate solution (saturated) was then added until the iodine colour had dispersed and the mixture was extracted with ethyl acetate (3 x 50 ml), dried (MgSO<sub>4</sub>) and evaporated to dryness. This provided crude **64** (0.498 g) which was dissolved in methanol (5 ml) and trifluoroacetic acid (0.38 ml, 4.9 mmol) was added and the reaction was stirred for 16 h. On evaporation a solid (0.65 g) was obtained which was dissolved in minimum volume of DCM (*ca* 5-10 ml) which was diluted with a small volume of petrol (1-2 ml) and placed in a freezer overnight to give a pale yellow solid. The supernatant liquid was decanted and the solid washed with petrol to give **68** (0.34 g, 70%) as a pale yellow solid.

**<sup>1</sup>H-NMR: δppm (CD<sub>3</sub>OD):** 1.62 (9H, s, <sup>t</sup>Bu), 3.45 (1H, dd, *J* = 10.7, 4.4, Hz CH), 3.55 (1H, br. d, *J* = 10.7 Hz, CH), 3.75 (1H, dd, *J* = 10.7, 5.7 Hz, CH), 3.83 (1H, app. t, *J* = 9.8 Hz, CH), 4.43 (1H, m, CH).

**<sup>1</sup>H-NMR: δppm (CDCl<sub>3</sub>):** 1.56 (9H, s, <sup>t</sup>Bu), 3.35 (1H, dd, *J* = 10.7, 1.8 Hz, CH), 3.47 (1H, dd, *J* = 10.5, 3.4 Hz, CH), 3.53 (1H, dd, *J* = 10.5, 7.0 Hz, CH), 3.87 (1H, app. t, *J* = 10.5 Hz, CH), 4.39 (1H, m, CH), 7.75 (1H, br. s, NH), 11.07 (1H, br. s, NH), 11.88 (1H, br. s, NH).

**<sup>13</sup>C-NMR: δppm (CDCl<sub>3</sub>):** 7.0 (CH<sub>2</sub>), 27.8 (<sup>t</sup>Bu), 46.9 (CH<sub>2</sub>), 56.8 (CH), 87.4 (C), 116.5 (q, <sup>1</sup>*J*<sub>C-F</sub> = 292 Hz, C), 149.9 (C) 156.9, (C), 163.2 (q, <sup>2</sup>*J*<sub>C-C-F</sub> = 35 Hz, C).

**FTIR *V*<sub>max</sub> cm<sup>-1</sup> (Nujol)** 3306 (N-H), 1752 (C=O), 1679 (C=N).

**MS (ES+) *m/z*:** 326 (45%, [M+H]<sup>+</sup>), 270 (100%)

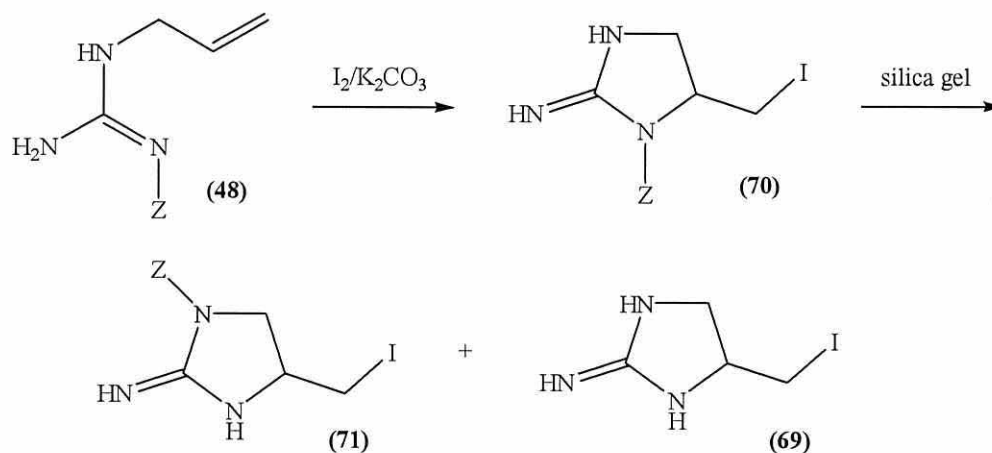
**HRMS (ES+)  $m/z$ :**  $C_9H_{17}N_3IO_2$   $[(M+H)^+]$ ; requires 326.0360 found 326.0363

**Melting Point:** 90-92 °C

**Rf:** 0.29 (10% MeOH/ $CHCl_3$ )



## Cyclisation reaction of *N*-Z-allylguanidine **48**



*N*-Z-allylguanidine **48** (0.5 g, 2.14 mmol) was dissolved in acetonitrile (20 ml) and cooled (-15 °C) using an ice/salt bath. Finely ground potassium carbonate (1.33 g, 9.63 mmol, 4.5 eq) was added, followed by iodine (2.44 g, 8.60 mmol, 4.5 eq) and the mixture was stirred slowly to room temperature overnight before being diluted with water (50 ml). Sodium thiosulphate solution (saturated) was then added until the iodine colour had dispersed and the mixture was extracted with ethyl acetate (3 x 50 ml), dried ( $MgSO_4$ ) and evaporated to dryness. This provided crude **70** (0.913 g) which was composed of mainly one isomer as determined by  $^1H$  NMR (for spectrum in  $CD_3OD$  see text) in  $CDCl_3$

**$^1H$ -NMR:  $\delta$ ppm** 3.28 (1H, dd,  $J = 6.5, 9.8$  Hz, CH), 3.38 (1H, dd,  $J = 4.7, 9.8$  Hz, CH), 3.70 (1H, dd,  $J = 5.7, 10.7$  Hz, CH), 4.05 (1H, dd,  $J = 9.1, 10.5$  Hz, CH) 4.16 (1H, dddd,  $J = 6.5, 4.7, 5.7, 9.1$  Hz, CH), 5.35 (2H, d,  $J = 12.3$  Hz,  $CH_2$ ), 7.5 (5H, m, Ph).

**$^{13}C$ -NMR:  $\delta$ ppm** 9.5 ( $CH_2$ ), 51.7 ( $CH_2$ ), 57.3 (CH), 68.0 ( $CH_2$ ), 128.0 (CH), 128.5 (CH), 134.6 (C), 138.3 (CH), 153.5 (C), 154.6 (C).

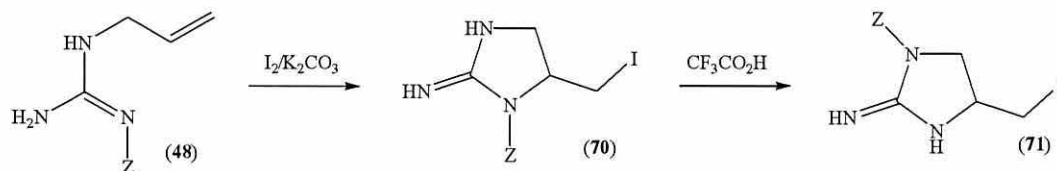
The crude **70** (0.722 g) was dissolved in DCM (5 ml) and silica gel (5 g) was added and the resultant slurry (insure sufficient DCM is added) was stirred for 5 days. The slurry was then washed onto a sintered filter and washed with excess DCM to give after evaporation a crude extract (0.366 g, 51% mass recovery). The silica pad was further washed with excess methanol to give after evaporation a second crude extract (0.262 g, 36% mass recovery). The dichloromethane fraction appeared to contain one major compound and was subject to

chromatography (EtOAc/petrol, 0:100 to 70:30 in 10% steps) gave a solid (61.0 mg, 10 %) compound with spectroscopic data consistent with **71** (see below).

<b><sup>1</sup>H-NMR: δppm</b>	3.03 (1H, app. t, J = 9.8 Hz, CH), 3.12 (1H, dd, J = 9.8, 4.1 Hz, CH), 3.33 (1H, dd, J = 10.1, 5.7 Hz, CH), 3.69 (1H, app. t, J = 9.8 Hz, CH), 3.97 (1H, m, CH), 5.06 (2H, s, CH <sub>2</sub> ), 7.30-7.41 (5H, m, Ph), 8.20 (1H, br. s, NH), 9.20 (1H, br. s, NH)
<b><sup>13</sup>C-NMR: δppm</b>	8.8 (CH <sub>2</sub> ), 48.4 (CH <sub>2</sub> ), 54.6 (CH), 66.7 (CH <sub>2</sub> ), 128.0 (CH), 128.1 (CH), 128.6 (CH), 136.9 (C), (CH), 163.1 (C), 164.7 (C).
<b>FTIR <math>\nu_{\max}</math> cm<sup>-1</sup> (Nujol)</b>	3324 (N-H), 1714 (C=O), 1623 (C=N), 1583 (C=C).

Chromatography of the methanolic extract gave the previously isolated deprotected compound **69** (0.135 g, 22%)

## Cyclisation reaction of *N*-Z-allylguanidine **48** followed by acidic rearrangement



*N*-Z-allylguanidine **48** (0.30 g, 1.3 mmol) was dissolved in acetonitrile (20 ml) and cooled (-15 °C) using an ice/salt bath. Finely powdered potassium carbonate (0.80 g, 5.8 mmol, 4.5 eq) was added, followed by iodine (1.47 g, 5.8 mmol, 4.5 eq). The mixture was stirred to rt for 16 h before being diluted with water (50 ml). Sodium thiosulphate solution (saturated) was then added until the iodine colour had dispersed and the mixture was extracted with ethyl acetate (3 x 50 ml), dried ( $MgSO_4$ ) and evaporated to dryness. This provided crude **70** (0.529 g) which was dissolved in methanol (5 ml) and trifluoroacetic acid (0.32 ml, 4.2 mmols) was added and the reaction was stirred for 16 h. On evaporation a solid (0.69 g) was obtained which was dissolved in dichloromethane (*ca* 5 ml) and diluted with ether (*ca* 1-2 ml) and placed in a freezer. An off white solid (81 mg) initially precipitated which was removed by decanting the mother liquor and proved to be very hygroscopic and gave a complex NMR spectrum. Further dilution of the mother liquor with hexane (*ca* 1-2 ml) and standing overnight in the freezer gave a pale yellow precipitate of **71** (0.222 g, 36%) which was of *ca* 92% purity. A higher purity sample (0.129 g, 21%) was obtained on repeated recrystallisation.

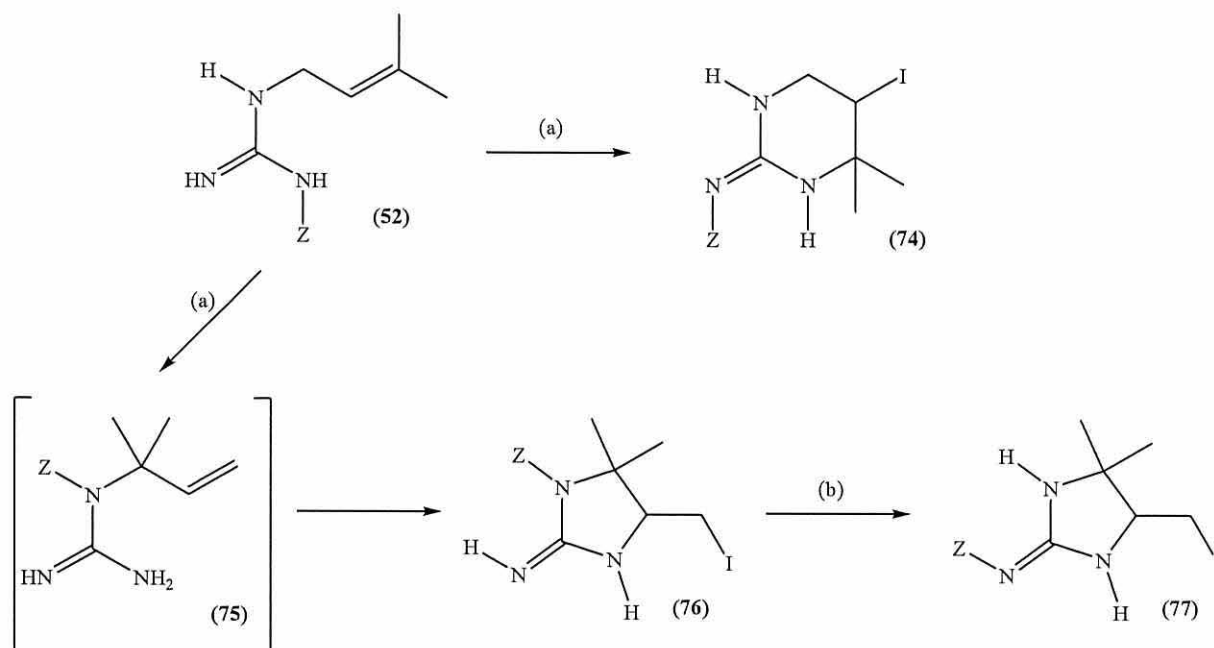
**<sup>1</sup>H-NMR: δppm (CD<sub>3</sub>OD):** 3.45 (2H, m, 2 x CH), 3.64 (1H, dd, *J* = 11.0, 5.5 Hz, CH), 3.88 (1H, dd, *J* = 10.7, 9.8 Hz, CH), 4.53 (1H, m, CH), 5.34 (1H, d, *J* = 12.0 Hz, CH), 5.45 (1H, d, *J* = 12.0 Hz, CH), 7.37-7.47 (5H, m, Ph).

**<sup>1</sup>H-NMR: δppm (CDCl<sub>3</sub>):** 3.32 (1H, br. d, *J* = 10.4 Hz, CH), 3.45 (1H, m, CH), 3.54 (1H, dd, *J* = 10.8, 4.1 Hz, CH), 3.88 (1H, dd, *J* = 10.8, 9.8 Hz, CH), 4.47 (1H, m, CH), 5.31 (1H, d, *J* = 11.7 Hz, CH), 5.40 (1H, d, *J* = 11.7 Hz, CH), 7.38-7.45 (5H, m, Ph), 7.71 (1H, br. s, NH), 11.55 (1H, br. s, NH), 12.48 (1H, br. s, NH).

**<sup>13</sup>C-NMR: δppm (CD<sub>3</sub>OD):** 9.9 (CH<sub>2</sub>), 49.2 (CH<sub>2</sub>), 59.2 (CH), 71.9 (CH<sub>2</sub>), 130.8 (2 x CH), 131.11 (2 x CH), 136.5 (C), 153.4 (C), 158.5 (C).

<b>FTIR <math>\nu_{\max}</math> <math>\text{cm}^{-1}</math> (Nujol)</b>	3324 (N-H), 1714 (C=O), 1623 (C=N), 1583 (C=C).
<b>HRMS (ES+) <math>m/z</math>:</b>	$\text{C}_{12}\text{H}_{15}\text{N}_3\text{IO}_2$ $[(\text{M}+\text{H})^+]$ ; requires 360.0209 found 360.0209
<b>Melting Point:</b>	114-116 °C
<b>Rf:</b>	0.16 (10% MeOH/ $\text{CHCl}_3$ )

## Cyclisation reaction of *N*-Z-*N'*-(dimethylallyl)guanidine **52** followed by acidic rearrangement



*N*-Z-*N'*-(dimethylallyl)guanidine **52** (0.30 g, 1.14 mmol) was dissolved in acetonitrile (20 ml) and cooled (-15 °C) using an ice/salt bath. Finely powdered potassium carbonate (0.71 g, 5.2 mmol, 4.5 eq) was added, followed by iodine (1.31 g, 5.2 mmol, 4.5 eq). The mixture was stirred slowly to rt over 16 h before being diluted with water (50 ml). Sodium thiosulphate solution (saturated) was then added until the iodine colour had dispersed and the mixture was extracted with ethyl acetate (3 x 50 ml), dried (MgSO<sub>4</sub>) and evaporated to dryness to give a solid (0.467 g) which was composed of mainly **74** and **76** in a 67:33 ratio.

Repetition of this reaction using **52** (0.30 g, 1.14 mmol), potassium carbonate (0.95 g, 6.9 mmol, 6 eq) and iodine (1.31 g, 5.2 mmol, 4.5 eq), gave **74** and **76** in a 80:20 ratio.

Repetition of this reaction using **52** (0.30 g, 1.14 mmol), potassium carbonate (0.48 g, 3.4 mmol, 3 eq) and iodine (1.31 g, 5.2 mmol, 4.5 eq), gave **74** and **76** in a 35:65 ratio. Dissolution of this mixture in methanol and cooling (-20 °C) gave **74** (0.1147 g, 26%) as an off white solid and the remaining mother liquor on evaporation gave **76** (*ca* 90% pure 0.302 g, 68% yield) as an oil.

The crude (0.421 g, from reaction 1) was dissolved in methanol (5 ml) and trifluoroacetic acid (0.13 ml) was added and the mixture stirred for 16 h. On evaporation a solid (0.607 g) was obtained (for NMR see text). This solid was dissolved in a small volume of DCM (3 ml) and diluted with ether (*ca* 10 ml) and refrigerated overnight to give a light

yellow precipitate of **77** (0.066 g, 17%) The remaining supernatant liquid was evaporated (0.484 g) and on chromatography (EtOAc/petrol, 0:100 to 80:20 in 10% steps) gave pure **74** (0.0582 g, 15%) as a white solid.

Data for **74**

<b><sup>1</sup>H-NMR (CDCl<sub>3</sub>): δppm</b>	1.35 (3H, s, CH <sub>3</sub> ), 1.37 (3H, s, CH <sub>3</sub> ), 3.43 (1H, dd, J = 9.2, 13.6 Hz, CH), 3.55 (1H, dd, J = 4.6, 13.6 Hz, CH), 3.97 (1H, dd, J = 4.6, 9.2 Hz, CH), 5.02 (2H, s, CH <sub>2</sub> ), 7.30-7.36 (5H, m, Ph), 8.70 (1H, br. s, NH), 9.70 (1H, br. s, NH).
<b><sup>1</sup>H-NMR (CD<sub>3</sub>OD): δppm</b>	1.46 (3H, s, CH <sub>3</sub> ), 1.47 (3H, s, CH <sub>3</sub> ), 3.73 (1H, dd, J = 7.0, 14.2 Hz, CH), 3.94 (1H, dd, J = 4.4, 14.2 Hz, CH), 4.45 (1H, dd, J = 4.4, 7.0 Hz), 5.09 (2H, s, CH <sub>2</sub> ), 7.28-7.40 (5H, m, Ph).
<b><sup>13</sup>C-NMR (CDCl<sub>3</sub>): δppm</b>	27.5 (CH <sub>3</sub> ), 29.2 (CH <sub>3</sub> ), 29.3 (CH), 46.4 (CH <sub>2</sub> N), 52.5 (C), 66.3 (CH <sub>2</sub> ), 128.0 (CH), 128.3 (CH), 128.6 (CH), 137.0 (C), 157.6 (C), 163.1 (C).
<b><sup>13</sup>C-NMR (CD<sub>3</sub>OD): δppm</b>	28.8 (CH <sub>3</sub> ), 30.4 (CH <sub>3</sub> ), 31.3 (CH), 48.9 (CH <sub>2</sub> N), 54.9 (C), 68.3 (CH <sub>2</sub> ), 129.6 (CH), 129.7 (CH), 130.2 (CH), 139.6 (C), 159.2 (C), 165.0 (C).
<b>FTIR <math>V_{\max}</math> cm<sup>-1</sup> (Nujol)</b>	3340 (N-H), 1706 (C=O), 1634 (C=N), 1553 (C=C).
<b>HRMS (ES+) <math>m/z</math>:</b>	C <sub>14</sub> H <sub>19</sub> N <sub>3</sub> IO <sub>2</sub> [(M+H) <sup>+</sup> ]; requires 388.0522 found 388.0522
<b>Melting Point:</b>	160-162 °C
<b>Rf:</b>	0.29 (5% MeOH/CHCl <sub>3</sub> )

Data for **76**

<b><sup>1</sup>H-NMR (CDCl<sub>3</sub>): δppm</b>	1.27 (3H, s, CH <sub>3</sub> ), 1.29 (3H, s, CH <sub>3</sub> ), 3.49 (1H, dd, J = 9.5, 13.6 Hz, CH), 3.60 (1H, dd, J = 4.9, 13.6 Hz, CH), 4.00 (1H, dd, J = 4.9, 9.5 Hz, CH), 4.92 (2H, s, CH <sub>2</sub> ), 7.19-7.28 (5H, m, Ph), 8.70 (1H, br. s, NH), 9.70 (1H, br. s, NH).
<b><sup>13</sup>C-NMR (CDCl<sub>3</sub>): δppm</b>	5.8 (CH <sub>2</sub> ), 19.5 (CH <sub>3</sub> ), 27.9 (CH <sub>3</sub> ), 68.1 (CH <sub>2</sub> ), 69.6 (C), 72.2 (CH), 128.2 (CH), 128.4 (CH), 128.7 (CH), 134.8 (C), 153.1 (C), 161.4 (C).
<b>Rf:</b>	0.15 (10% MeOH/CHCl <sub>3</sub> )

Data for 77

**<sup>1</sup>H-NMR (CD<sub>3</sub>OD): δppm** 1.56 (3H, s, CH<sub>3</sub>), 1.58 (3H, s, CH<sub>3</sub>), 3.39 (1H, dd, J = 7.6, 11.0 Hz, CH), 3.56 (1H, dd, J = 4.4, 11.0 Hz, CH), 3.94 (1H, dd, J = 4.4, 7.6 Hz, CH), 5.42 (2H, s, CH<sub>2</sub>), 7.40-7.51 (5H, m, Ph).

**<sup>13</sup>C-NMR (CD<sub>3</sub>OD): δppm** 3.2 (CH<sub>2</sub>), 20.7 (CH<sub>3</sub>), 28.2 (CH<sub>3</sub>), 66.2 (CH), 69.9 (C), 71.9 (CH<sub>2</sub>), 130.7 (CH), 131.0 (CH), 131.1 (CH), 136.4 (C), 154.1 (C), 158.2 (C)

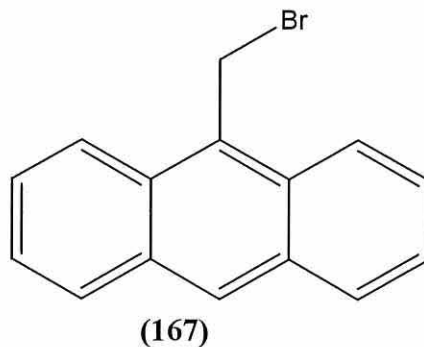
**FTIR  $\nu_{\max}$  cm<sup>-1</sup> (Nujol)** 3335 (N-H), 1716 (C=O), 1611 (C=N), 1515 (C=C).

**HRMS (ES+)  $m/z$ :** C<sub>14</sub>H<sub>19</sub>N<sub>3</sub>IO<sub>2</sub> [(M+H)<sup>+</sup>]; requires 388.0522 found 388.0510

**Melting Point:** 86-88 °C

**Rf:** 0.17 (10% MeOH/CHCl<sub>3</sub>)

## 9-Bromomethylantracene, **167**<sup>122, 124</sup>

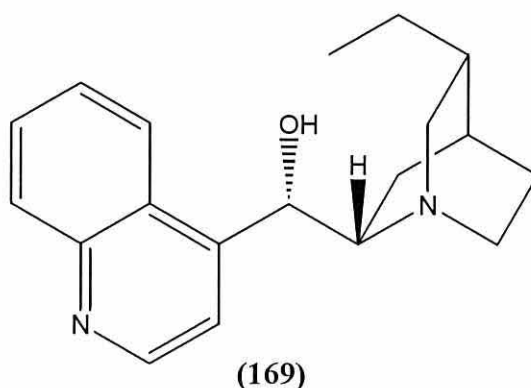


9-Hydroxymethylantracene **166** (10.4 g, 50.0 mmol) was suspended in acetic acid (55 ml) under argon, a solution of 33% hydrogen bromide in acetic acid (50 ml) in acetic acid (35 ml) was then added dropwise. The resulting mixture was stirred at 55 °C for 3.5 hours, then cooled to 5 °C and the yellow precipitate collected. The precipitate was dissolved in chloroform (100 ml) and washed with saturated aqueous sodium hydrogencarbonate until no more CO<sub>2</sub> was produced. The organics were dried over MgSO<sub>4</sub> and then concentrated under reduced pressure to yield the product **167** (10.42 g, 77%) as a yellow solid suitable for use in subsequent reactions.

<b><sup>1</sup>H-NMR: δppm</b>	5.56 (2H, s, CH <sub>2</sub> Br), 7.49-7.55 (2H, m, 2 x CH), 7.63-7.69 (2H, m, 2 x CH), 8.06 (2H, d, J = 8.2 Hz, 2 x CH), 8.32 (2H, d, J = 9.2 Hz, 2 x CH), 8.51 (1H, s, CH).
<b><sup>13</sup>C-NMR: δppm</b>	26.86 (CH <sub>2</sub> Br), 123.52 (2 x CH), 125.36 (2 x CH), 126.77 (2 x CH), 127.90 (2 x C), 129.16 (CH), 129.26 (2 x CH), 129.77 (C), 131.64 (2 x C).
<b>HRMS (ES+) <i>m/z</i>:</b>	C <sub>15</sub> H <sub>11</sub> Br ([M+H] <sup>+</sup> ); Requires 270.0044 found 270.0025
<b>Melting Point:</b>	130-133 °C (Lit 147-148 °C) <sup>122</sup>
<b>Rf:</b>	0.47 (10% ether/petrol).



## Dihydrocinchonidine, **169**<sup>123</sup>



(5-Ethyl-1-aza-bicyclo[2.2.2]oct-2-yl)-quinolin-4-yl-methanol

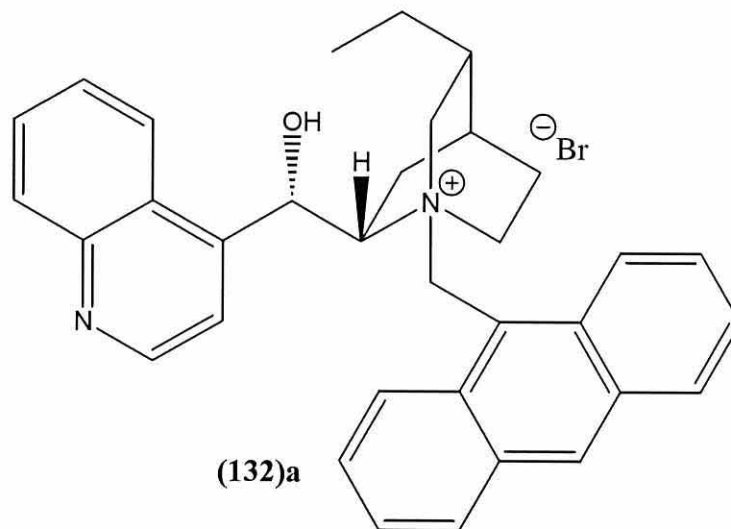
Cinchonidine **168** (6.0 g, 20.4 mmol) was dissolved in ethanol (150 ml), 10%Pd/C (0.5 g) was added and the mixture was stirred under hydrogen at room temperature for 24 hours. The solution was then passed through a pad of Celite and the solvent removed under reduced pressure to yield the product **169** (3.21 g, 53%) as a white solid.

**<sup>1</sup>H-NMR: δppm** 0.78 (3H, d, *J* = 7.3 Hz, CH<sub>3</sub>), 1.19-1.26 (2H, m, 2 x CH), 1.53 (6H, m, 6 x CH), 2.48-2.53 (1H, m, CH), 2.70-2.78 (1H, m, CH), 3.10-3.19 (2H, m, 2 x CH), 3.85 (1H, m, CH), 5.93 (1H, br. s, CH), 8.04 (1H, d, *J* = 8.2 Hz, CH), 8.86 (1H, d, *J* = 4.5 Hz, CH).

**<sup>13</sup>C-NMR: δppm** 11.82 (CH<sub>3</sub>), 20.23 (CH<sub>2</sub>), 25.38 (CH<sub>2</sub>), 27.15 (CH<sub>2</sub>), 27.41 (CH<sub>2</sub>), 37.05 (CH), 43.34 (CH<sub>2</sub>), 57.78 (CH<sub>2</sub>), 60.13 (CH), 69.78 (CH), 118.46 (CH), 122.68 (CH), 126.71 (CH), 128.94 (CH), 130.25 (CH), 148.17 (2 x C), 150.09 (CH).

**HRMS (ES<sup>+</sup>) *m/z*:** C<sub>19</sub>H<sub>24</sub>N<sub>2</sub>O ([*M*+*H*]<sup>+</sup>); Requires 297.1967 found 297.1967

**(1S, 2S, 4S, 5R, 1'R)-1-(Anthracen-9-ylmethyl)-5-ethyl-2-[hydroxy (quinolin-4-yl)methyl]-1-azoniabicyclo[2.2.2]octane bromide, 132a<sup>124</sup>**



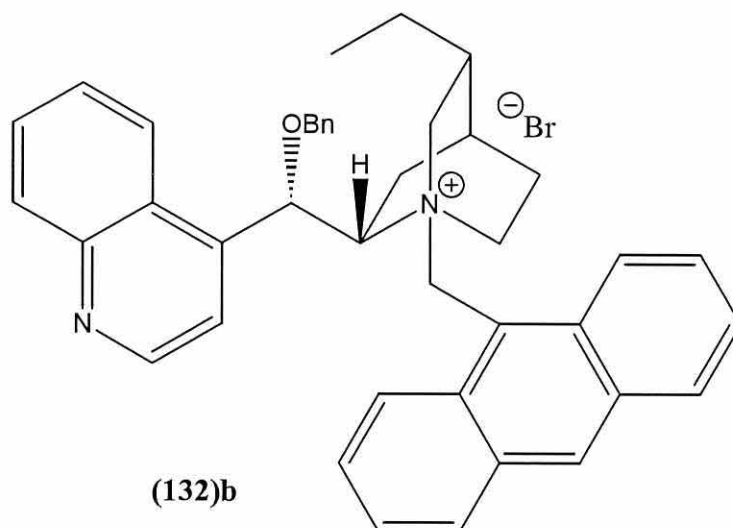
A suspension of dihydrocinchonidine **169** (3.21 g, 10.8 mmol), 9-bromomethylantracene **167** (4.42 g, 16.3 mmol) and potassium carbonate (3.22 g, 23.3 mmol) in toluene (150 ml) under a nitrogen atmosphere was heated at 50 °C for 4 h. The mixture was then allowed to cool to room temperature, poured into ether (300 ml) and the resulting solids collected by filtration. The solids were then extracted with chloroform (4 x 50 ml) and the chloroform extracts concentrated under reduced pressure to give viscous red oil. Ether (100 ml) was then added and the mixture stirred vigorously at room temperature for 2 h. The resulting solid was collected by filtration and dried in vacuum to give the product **132a** as a pale yellow solid (4.00 g, 65%).

**<sup>1</sup>H-NMR: δppm**

0.41 (3H, t, J = 7.3 Hz, CH<sub>3</sub>), 0.87-0.93 (2H, m, CH<sub>2</sub>), 1.04 (2H, m, CH<sub>2</sub>), 1.52 (1H, br. s, CH), 1.72 (2H, m, CH), 2.24 (1H, dd, J = 14.8, 11.6 Hz, CH), 2.47 (1H, dd, J = 12.6, 10.8 Hz, CH), 3.34 (1H, app. q, J = 6.6 Hz, CH), 3.53 (1H, m, CH), 4.55-4.63 (1H, m, CH), 6.21 (1H, d, J = 13.6 Hz, CH), 6.53 (1H, d, J = 13.6 Hz, CH), 6.93 (1H, m, CH), 7.03 (4H, m, 4 x CH), 7.15 (2H, dd, J = 6.1, 7.9 Hz, CH), 7.41 (1H, app. t, J = Hz, CH), 7.50 (2H, m, CH), 7.58 (1H, d, J = 7.9 Hz, CH), 7.89 (1H, d, J = 4.8 Hz, CH), 7.90 (1H, s, CH), 8.58 (2H, d, J = 8.2 Hz, CH), 8.71 (1H, m, CH).

<b><math>^{13}\text{C}</math>-NMR: <math>\delta\text{ppm}</math></b>	11.4 (CH <sub>3</sub> ), 22.9 (CH <sub>2</sub> ), 23.4 (CH), 26.5 (CH <sub>2</sub> ), 37.2 (CH), 51.0 (CH <sub>2</sub> ), 55.3 (CH <sub>2</sub> ), 63.8 (CH <sub>2</sub> ), 66.7 (CH), 67.6 (CH), 118.0 (C), 120.3 (CH), 123.9 (CH), 124.3 (C), 125.0 (CH), 125.6 (CH), 125.9 (CH), 127.3 (CH), 127.9 (CH), 128.5 (CH), 128.5 (CH), 128.8 (CH), 129.6 (CH), 130.4 (2 x C), 130.5 (2 x C), 131.3 (CH), 132.6 (C), 133.3 (C), 145.5 (C), 147.4 (C), 149.6 (CH).
<b>HRMS (ES+) <math>m/z</math>:</b>	$\text{C}_{34}\text{H}_{35}\text{N}_2\text{O}$ ( $[\text{M}+\text{H}]^+$ ); Requires 487.2744, found 487.2746
<b>Melting Point:</b>	168-171 °C (Lit 173-175 °C) <sup>131</sup>
<b>Rf:</b>	0.35 (10% MeOH/ $\text{CHCl}_3$ )
<b><math>[\alpha]_D^{25}</math>:</b>	-276 ( $c = 0.518$ in $\text{CHCl}_3$ ) (Lit -220, $c = 0.518$ in $\text{CHCl}_3$ )

**(1S, 2S, 4S, 5R, 1'R)-1-(Anthracen-9-ylmethyl)-5-ethyl-2-[benzyloxy (quinolin-4-yl)methyl]-1-azoniabicyclo[2.2.2]octane bromide, 132b**



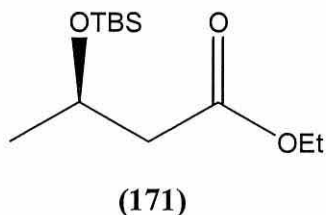
Benzyl Bromide (0.25 ml, 2.12 mmol) was added to a solution of *N*-(9-anthracenylmethyl)dihydrocinchonidinium bromide, **132a** (1.00 g, 1.76 mmol) in dichloromethane (10 ml). The resulting solution was then treated with 9N aqueous sodium hydroxide (0.5 ml) and the mixture stirred vigorously for 1.5 h at room temperature. Water (10 ml) was then added and the aqueous layer extracted with dichloromethane (2 x 10 ml). The combined organic extracts were dried (MgSO<sub>4</sub>) and concentrated under vacuum (bath temperature <30 °C). Petrol (50 ml) was then added and the mixture stirred vigorously for 2 h. The resulting solid was collected by filtration and dried under vacuum to yield the desired product **132b** as a pale yellow solid (0.96 g, 83%).

**<sup>1</sup>H-NMR: δppm**

0.69 (3H, t, *J* = 7.3 Hz, CH<sub>3</sub>), 1.09-1.29 (2H, m, CH<sub>2</sub>), 1.37-1.46 (2H, m, CH<sub>2</sub>), 1.64 (1H, br. s, CH), 1.98-2.00 (1H, m, CH), 2.06-2.13 (2H, m, CH<sub>2</sub>), 2.17-2.28 (1H, m, CH), 3.06-3.16 (1H, m, CH), 4.05-4.16 (2H, m, CH<sub>2</sub>), 4.53-4.64 (2H, m, CH<sub>2</sub>), 4.82 (1H, m, CH), 5.95 (1H, m, CH), 7.36-7.43 (10H, m, 10 x CH), 7.58-7.78 (5H, m, 5 x CH), 7.99 (1H, t, *J* = 6.6 Hz, CH), 8.13 (1H, d, *J* = 8.5 Hz, CH), 8.68 (1H, br. s, CH), 8.97-9.01 (3H, m, 2 x CH), 9.61 (1H, d, *J* = 9.2 Hz, CH).

<b><math>^{13}\text{C}</math>-NMR: <math>\delta\text{ppm}</math></b>	11.4 (CH <sub>3</sub> ), 22.2 (CH), 22.5 (CH), 24.0 (CH), 26.0 (CH <sub>2</sub> ), 26.2 (CH <sub>2</sub> ), 26.3 (CH <sub>2</sub> ), 36.2 (CH), 51.0 (CH <sub>2</sub> ), 55.2 (CH <sub>2</sub> ), 61.4 (CH <sub>2</sub> ), 61.71 (CH <sub>2</sub> ), 71.3 (CH <sub>2</sub> ), 123.2 (C), 124.5 (CH), 126.9 (2 x CH), 128.8 (CH), 129.1 (2 x CH), 129.1 (2 x CH), 129.2 (2 x CH), 129.2 (CH), 130.2 (C), 130.8 (C), 131.3 (C), 133.1 (C), 138.9 (CH), 135.5 (C), 139.9 (C), 148.4 (C).
<b>Melting Point:</b>	142-144 °C (Lit 137-138 °C) <sup>124</sup>
<b>Rf:</b>	0.58 (5% MeOH/CH <sub>2</sub> Cl <sub>2</sub> )
<b><math>[\alpha]_{\text{D}}^{25}</math>:</b>	-204 ( $c = 1.0$ in CHCl <sub>3</sub> ) (Lit -215, $c = 1.1$ in CHCl <sub>3</sub> )

**Ethyl (*R*)-3-((*tert*-butyldimethylsilyl)oxy)butyrate, **171**<sup>127</sup>**

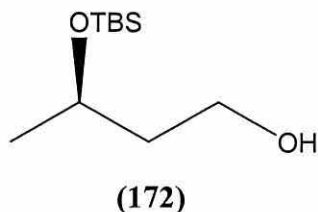


A solution of imidazole (9.76 g, 99.48 mmol) in anhydrous DMF (20 ml) was cooled (0 °C) and ethyl (*R*)-(-)-3-hydroxybutyrate **170**, (5.06 g, 38.26 mmol) was added followed by *tert*-butyldimethylsilyl chloride (7.6 g, 49.74 mmol). The reaction was allowed to warm to ambient temperature and stirred for 3 hours, at the end of this time the solution was extracted with hexane (3 x 60 ml). The organic extracts were combined and washed with aqueous acetic acid solution (2 % v/v, 60 ml) and water (3 x 60 ml) before being dried (MgSO<sub>4</sub>) and the solvent removed by rotary evaporation to give the title compound **171** as a clear oil (9.39 g, 99%). Data was in accordance with the literature.<sup>125</sup>

**<sup>1</sup>H-NMR: δppm**                      -0.05 (3H, s, Me), -0.02 (3H, s, Me), 0.79 (9H, s, 3 x Me), 1.12 (3H, d, *J* = 6.1 Hz, Me), 1.18 (3H, t, *J* = 7.1 Hz, Me), 2.27 (1H, dd, *J* = 5.2, 14.7 Hz, CH<sub>2</sub>), 2.39 (1H, dd, *J* = 7.6, 14.5 Hz, CH), 4.07 (2H, q, *J* = 7.2 Hz, CH<sub>2</sub>) 4.21 (1H, m, CH).

**R<sub>f</sub>:**                                      0.62 (10% ether/petrol)

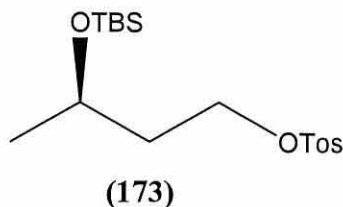
**(*R*)-3-((*tert*-butyldimethylsilyl)oxy)butan-1-ol, **172****<sup>128</sup>



Ethyl (*R*)-3-((*tert*-butyldimethylsilyl)oxy)butyrate **171** (10.21 g, 41.48 mmol) was dissolved in anhydrous hexane, cooled (-78 °C), and diisobutylaluminium hydride (100 ml, 100 mmol) was added dropwise over 30 min. The reaction was allowed to stir overnight, warming slowly to ambient temperature. The reaction was cooled (0 °C) and methanol (6 ml) followed by Rochelle's salt (100 ml) and ether (100 ml) and the mixture stirred until clear. The solution was then separated and the aqueous phase washed with dichloromethane (3 x 100 ml). The combined organic extracts were washed with water (100 ml), dried (MgSO<sub>4</sub>) and the solvent removed by rotary evaporation to yield the product **172** as a pale yellow oil (6.92 g, 89%). Data was in accordance with the literature.<sup>125</sup>

**<sup>1</sup>H-NMR: δppm**                      -0.05, (2H, s, Me) 0.01 (3H, s, Me), 0.82 (9H, s, 3 x Me), 1.11 (3H, d, *J* = 6.4 Hz, Me), 1.50-1.60 (1H, m, CH), 1.63-1.72 (1H, m, CH), 3.14 (1H, br. s, OH), 3.59 (1H, m, CH), 3.75 (1H, m, CH), 4.01 (1H, m, CH).

**(*R*)-3-((*tert*-butyldimethylsilyl)oxy)butan-1-*para*-toluene sulphonate, **173****<sup>127</sup>



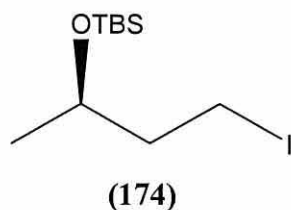
A solution of (*R*)-3-((*tert*-butyldimethylsilyl)oxy)butan-1-ol **172** (8.00 g, 39.18 mmol) in anhydrous pyridine (15 ml) was cooled (0 °C) and treated with a solution of *p*-toluenesulphonyl chloride (8.25 g, 43.19 mmol) in dry pyridine (15 ml) and the reaction stirred overnight. The solution was diluted with hexane (300 ml) and washed with H<sub>2</sub>SO<sub>4</sub> (3 x 200 ml, 2M) and water (2 x 200 ml), dried over MgSO<sub>4</sub> and the solvent removed by rotary evaporator to yield the title compound **173** as an oil (10.91 g, 78%). Data was in accordance with the literature.<sup>125</sup>

**<sup>1</sup>H-NMR: δppm** 0.02 (6H, s, 2 x Me), 0.81 (9H, s, 3 x Me), 1.09 (3H, d, J = 6.1 Hz, Me), 1.63-1.88 (1H, m, CH), 2.46 (3H, s, Ph-Me), 4.10 (2H, t, J = 6.7 Hz, CH<sub>2</sub>), 7.34 (1H, d, J = 7.9 Hz, CH), 7.41 (1H, d, J = 8.2 Hz, CH), 7.78 (1H, d, J = 8.2 Hz, CH), 7.90 (1H, d, J = 8.3 Hz, CH).

**Rf:** 0.28 (5% ether/petrol)



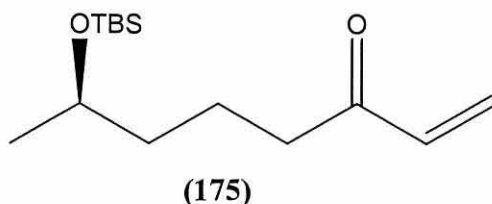
**(*R*)-3-((*tert*-butyldimethylsilyl)oxy)-1-iodobutane, 174<sup>117</sup>**



To (*R*)-3-((*tert*-butyldimethylsilyl)oxy)-butan-1-*para*-toluene sulphonate **173** (6.8 g, 19.00 mmol) in anhydrous acetone (260 ml) was added sodium iodide (15.67 g, 104.5 mmol) and the reaction was refluxed for 4 h. The reaction was then filtered *via* a sinter and the filter pad washed with ether (300 ml), the solvent was removed by rotary evaporator to give a solid residue. The solid was triturated with hexane (5 x 100 ml), and the hexane was filtered and evaporated to give an oil. Purification by column chromatography (ether/petrol, 5:95) yielded the product **174** as a clear oil (3.75 g, 63%). Data was in accordance with the literature.<sup>125</sup>

<b><sup>1</sup>H-NMR: δppm</b>	0.09 (3H, s, Me), 0.10 (3H, s, Me), 0.90 (9H, s, 3 x Me), 1.16 (3H, d, J = 6.1 Hz, Me), 1.92 (2H, t, J = 6.7 Hz, CH <sub>2</sub> ), 3.20 (2H, dt, J = 7.3, 2.45 Hz, CH <sub>2</sub> ), 3.87 (1H, app. sextet, CH).
<b>R<sub>f</sub>:</b>	0.81 (5% ether/petrol)

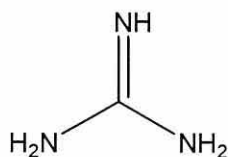
**(*R*)-6-oxo-((*tert*-butyldimethylsilyl)oxy)oct-7-ene 175<sup>117</sup>**



Acetylmethylene triphenylphosphorane (6.1 g, 19.17 mmol) was dissolved in anhydrous THF (120 ml), cooled (-78 °C) and *n*-BuLi (2.5 M, 7 ml, 17.45 mmol) was added dropwise over 5 min. The deep red solution that formed was then stirred at -60 °C for 1 h. The reaction was then cooled (-78 °C) and (*R*)-3-((*tert*-butyldimethylsilyl)oxy)-1-iodobutane **174** (5.48 g, 17.45 mmol) in THF (50 ml) was added and the reaction warmed to ambient temperature by removal of the cooling bath followed by stirring overnight. Water (90 ml) was added and the solution was separated and the aqueous fraction extracted with DCM (3 x 50 ml), dried (MgSO<sub>4</sub>) and the reaction concentrated by rotary evaporation to approximately 50 ml. Formaldehyde solution was then prepared by adding aqueous formaldehyde (96 ml) to DCM (50 ml) and removing the water with excess MgSO<sub>4</sub>. The formaldehyde solution was added to the reaction through a funnel containing a cotton wool plug and stirred overnight. The reaction was diluted with ether (60 ml) and washed with water (2 x 60 ml), dried (MgSO<sub>4</sub>) and the solvent was removed by rotary evaporation. Purification by column chromatography (ether/petrol, 4:96) gave the title compound **175** as a clear oil (2.01 g, 45%). Data was in accordance with the literature.<sup>125</sup>

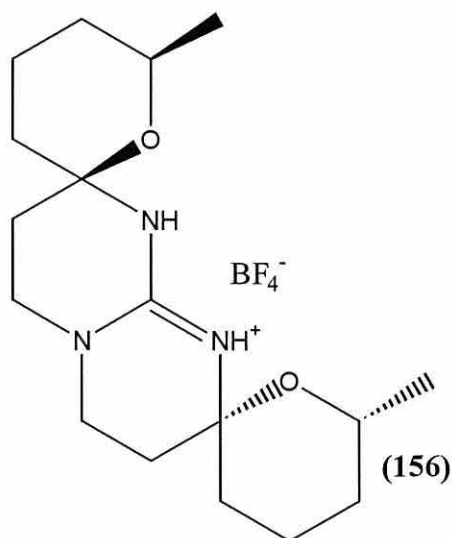
<b><sup>1</sup>H-NMR: δppm</b>	0.04 (6H, s, 2 x Me), 0.88 (9H, s, 3 x Me), 1.12 (3H, d, J = 6.1 Hz, Me), 1.37-1.76 (4H, m, 2 x CH <sub>2</sub> ), 2.58 (2H, t, J = 7.3 Hz, CH <sub>2</sub> ), 3.76 (1H, app. sextet, J = 6.1 Hz, CH), 5.77 (1H, dd, J = 1.1, 10.6 Hz, CH), 6.17 (1H, dd, J = 1.3, 17.7 Hz, CH), 6.31 (1H, dd, J = 10.4, 17.7 Hz, CH).
<b><sup>13</sup>C-NMR: δppm</b>	-4.7 (CH <sub>3</sub> ), -4.4 (CH <sub>3</sub> ), 18.1 (C), 20.2 (CH <sub>2</sub> ), 23.7 (CH <sub>3</sub> ), 25.9 (3 x CH <sub>3</sub> ), 39.1 (CH <sub>2</sub> ), 39.7 (CH <sub>2</sub> ), 68.4 (CH), 127.9 (CH), 136.6 (CH), 200.9 (C).
<b>Rf:</b>	0.19 (2% EtOAc/petrol)

## Guanidine<sup>145</sup>



A static argon atmosphere was maintained throughout this experimental procedure. Sodium methoxide was prepared *in situ* by the addition of small portions of sodium (2.4 g, 104.4 mmol) washed with petrol, to a flask containing dry methanol (200 ml). Once evolution of hydrogen had ceased guanidine hydrochloride (10.0 g, 104.4 mmol) was added and the solution stirred for 4 h. The resulting mixture was filtered to remove precipitated sodium chloride and the solvent evaporated. Under argon the product was dissolved in dry methanol (30 ml) and filtered for a second time. Concentration of the solvent on high vacuum gave free guanidine (4.36 g, 64%).

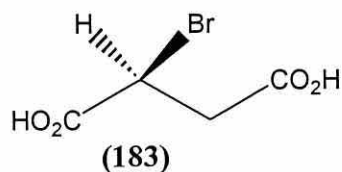
**(6*R*, 6''*R*, 2*R*, 2''*R*)-6,6''-Dimethyldispiro [tetrahydropyran-2,2'-(2,3,4,6,7,8-hexahydro-1*H*-pyrimido[1,2-*a*] pyrimidine)-8',2''-tetrahydropyran]-9'-ium tetrafluoroborate, 156**<sup>117</sup>



All the manipulations using guanidine were carried out under an argon atmosphere and care was taken to keep the reaction vessel under an argon atmosphere. (*R*)-6-oxo-((*tert*-butyldimethylsilyl)oxy)oct-7-ene **175** (1.99 g, 7.77 mmol) was dissolved in anhydrous DMF (35 ml), cooled (0 °C) and a solution of guanidine in DMF (0.229 g, 3.89 mmol) was added dropwise over 5 min. The reaction was kept at 0 °C for 15 min before being allowed to warm to ambient temperature and stirred overnight. The reaction was then cooled (0 °C) and methanolic HCl (40 ml) added (prepared by slowly adding acetyl chloride (4 ml) to cooled (0 °C) methanol (36 ml)). The reaction was warmed to ambient temperature, and stirred vigorously for 3 h. The reaction was then diluted with DCM (200 ml) and washed with water (3 x 100 ml) then a saturated solution of LiBr (3 x 50 ml). The aqueous washings were backwashed with DCM (50 ml) and the combined organic washings were dried (MgSO<sub>4</sub>) and the solvent removed by rotary evaporation until approximately 30 ml of solution remained. The organic phase was then added to a saturated solution of NaBF<sub>4</sub> (30 ml) and stirred overnight. The organic phase was separated and washed with water (3 x 30 ml) and dried (MgSO<sub>4</sub>) and the solvent removed by rotary evaporation. Purification by column chromatography (MeOH/CHCl<sub>3</sub>, 0:100 to 1.5:98.5 in 0.25% steps) gave the title compound **156** as a white solid (0.276 g, 38%). Data was in accordance with the literature.<sup>125</sup>

<b><math>^1\text{H}</math>-NMR: <math>\delta\text{ppm}</math></b>	1.11 (6H, d, $J = 6.1\text{ Hz}$ , 2 x $\text{CH}_3$ ), 1.18 (2H, m, 2 x CH), 1.50 - 2.20 (14H, m), 3.22 (2H, ddd, $J = 1.6, 5.8, 12.5\text{ Hz}$ ), 3.68 (2H, app. dt, $J = 5.0, 12.4\text{ Hz}$ ), 3.84 (2H, ddq, $J = 2.1, 11.8, 6.1\text{ Hz}$ , 2 x CH), 7.50 (2H, br. s, 2 x NH).
<b><math>^{13}\text{C}</math>-NMR: <math>\delta\text{ppm}</math></b>	17.7 (2 x $\text{CH}_2$ ), 21.7 (2 x $\text{CH}_3$ ), 32.1 (2 x $\text{CH}_2$ ), 33.6 (2 x $\text{CH}_2$ ), 33.7 (2 x $\text{CH}_2$ ), 42.7 (2 x $\text{CH}_2$ ), 66.9 (2 x CH), 78.9 (2 x C), 148.4 (C).
<b>Melting Point:</b>	178-180 $^\circ\text{C}$ (Lit 181-182 $^\circ\text{C}$ ) <sup>117</sup>
<b>Rf:</b>	0.39 (5% MeOH/ $\text{CHCl}_3$ )

### (S)-2-Bromosuccinic Acid, **183**<sup>129</sup>

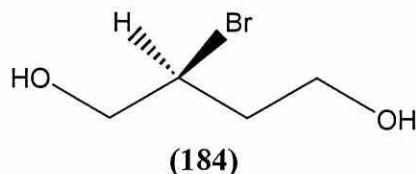


To a solution of sodium bromide (55.64 g, 0.468 mol) in 200 ml of 6 N sulfuric acid under nitrogen was added (15.55 g, 0.117 mol) L-aspartic acid **182**. The resulting solution was cooled to 5 °C. Sodium nitrate (8.07 g, 0.117 mol) was added in portions over a 1.5 hour period while temperature was kept below 10 °C. After the addition was completed, 45 ml of distilled water was added, followed by (3.51 g, 0.059 mol) of urea. The resulting mixture was poured into a separating funnel and extracted with 200 ml of ethyl ether. To the aqueous layer was added sodium chloride (15 g) and the mixture extracted with ether (4 x 100 ml). The combined ether layers were washed with brine (200 ml), dried (MgSO<sub>4</sub>) and the solvent evaporated in vacuum to yield the desired product **183** (16.26 g, 71 %) as a white solid. Data was in accordance with the literature.<sup>129</sup>

<sup>1</sup>H-NMR: δppm                      2.99 (1H, dd, J = 5.8, 17.5 Hz, CH<sub>2</sub>), 3.25(1H, dd, J = 8.9, 17.5 Hz, CH<sub>2</sub>), 4.61 (1H, dd, J = 2.4, 6.5 Hz, CH).

<sup>13</sup>C-NMR: δppm                      11.4 (CH<sub>3</sub>), 22.9 (CH<sub>2</sub>), 23.4

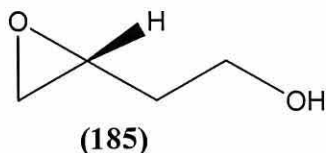
**(S)-2-Bromo-1,4-butanediol, 185<sup>129</sup>**



Under a nitrogen atmosphere (*S*)-2-Bromosuccinic acid **183** (22.57 g, 114 mmol) was dissolved in 180 ml of anhydrous tetrahydrofuran and the mixture cooled to -78 °C. To this solution was added dropwise over 90 minutes a solution of borane-methyl sulphide complex in tetrahydrofuran (137 ml, 0.275 mol). After 15 minutes the cooling bath was removed and the reaction was allowed to warm to ambient temperature and stirred under a nitrogen atmosphere for 60 h. Methanol (70 ml) was then added slowly at 0 °C and the mixture was allowed to stir for 30 minutes before the solvent was removed under reduced pressure. The residue was taken up in methanol (55 ml), and solvent was evaporated under reduced pressure. This procedure was repeated twice to yield (14.92 g, 77%) of diol **184** as an orange oil. Data was in accordance with the literature.<sup>129</sup>

<sup>1</sup> H-NMR: δppm	1.98-2.22 (2H, m, CH <sub>2</sub> ), 3.63 (2H, m, CH <sub>2</sub> ), 3.84 (2H, m, CH <sub>2</sub> ) 4.24-4.31 (1H, m, CHBr).
<sup>13</sup> C-NMR: δppm	37.7 (CH <sub>2</sub> ), 55.3 (CHBr), 60.1 (CH <sub>2</sub> ), 67.2 (CH <sub>2</sub> ).

**(*R*)-(2-Hydroxyethyl)oxirane, **185****<sup>129</sup>

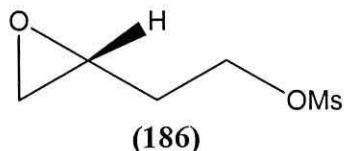


Under a nitrogen atmosphere (*S*)-2-bromo-1,4-butanediol **184** (14.92 g, 89.42 mmol) was dissolved in anhydrous dichloromethane (400 ml) and cesium carbonate (50.14 g, 0.154 mol) was added. The mixture was stirred at room temperature for 40 h and then filtered. The residue was washed with dry dichloromethane (4 x 100 ml). The combined filtrate and wash liquor were used directly for the synthesis of (*R*)-[2-[(Methanesulfonyl)oxyl]ethyl]oxirane **185**. Data was in accordance with the literature.<sup>129</sup>

<sup>1</sup> H-NMR: δppm	1.50-1.59 (1H, m, CH <sub>2</sub> ), 1.75-1.85 (1H, m, CH <sub>2</sub> ), 2.44 (1H, dd, J = 2.7, 4.9 Hz, CH), 2.67 (1H, dd, J = 4.7, 8.9 Hz, CH), 2.94-2.96 (1H, m, CH), 3.62 (2H, t, J = 6.2 Hz, CH <sub>2</sub> ).
<sup>13</sup> C-NMR: δppm	34.9 (CH <sub>2</sub> ), 46.7 (CH <sub>2</sub> ), 50.3 (CH), 59.1 (CH <sub>2</sub> ).



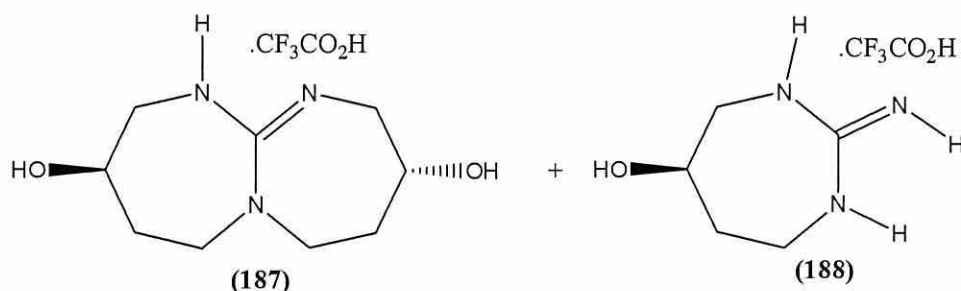
**(R)-[2-[(Methanesulfonyl)oxyl]ethyl]oxirane, 186<sup>129</sup>**



Under a nitrogen atmosphere was added the entire product solution **185**, which was cooled to -25 °C. Triethylamine (15.25 g, 21.0 ml, 0.151 mol) was added followed by slow addition of methanesulfonyl chloride (14.80 g, 0.129 mol, 10.0 ml) over 35 minutes while the reaction temperature was maintained at less than -20 °C. The resulting mixture was allowed to warm to room temperature and stirred for 2 h. The solution was then washed with pH 4 phosphate buffer and the buffer was back-extracted with dichloromethane (4 x 50 ml). The organic extracts were combined and washed with brine solution (50 ml) and the brine back-extracted with dichloromethane (3 x 50 ml). The organic extracts were dried (MgSO<sub>4</sub>) and concentrated under reduced pressure. The crude product was then purified via column chromatography (EtOAc/petrol, 50:50) to yield the product **186** as a red oil (7.98 g, 55%).<sup>129</sup>

<b><sup>1</sup>H-NMR: δppm</b>	1.68-1.75 (1H, m, CH), 1.92-1.98 (1H, m, CH), 2.41(1H, dd, J = 2.8, 4.9 Hz, CH), 2.66 (1H, br. dd, J = 4.4 Hz CH), 3.00-3.18 (1H, t, J = 6.2 Hz, CH), 3.03 (3H, s, CH <sub>3</sub> ), 4.39 (2H, br. dd, J = 5.8 Hz, CH <sub>2</sub> ).
<b><sup>13</sup>C-NMR: δppm</b>	31.6 (CH <sub>2</sub> ), 37.5 (CH <sub>3</sub> ), 45.8 (CH <sub>2</sub> ), 49.8 (CH), 67.4 (CH <sub>2</sub> ).

**(4*R*,8*R*)-3,8-dihydroxy-2,4,5,6,7,8,9,10-octahydro-3*H*-5a,10-diaza-1-azonia-heptalene trifluoroacetate **187** and (5*R*)-5-Hydroxy-[1,3]diazepan-2-ylidene-ammonium methylsulphonate **188**<sup>6</sup>**



Under a nitrogen atmosphere, guanidine hydrochloride (3.98 g, 42 mmol) and potassium *tert*-butoxide (4.69 g, 42 mmol) were dissolved in anhydrous *tert*-butanol (75 ml). The solution was stirred for 2 h then a solution of mesylate **186** (6.92 g, 42 mmol) in *tert*-butanol (20 ml) was added dropwise over 45 min. The reaction mixture was stirred for 16 h at room temperature then potassium *t*-butoxide (4.69 g, 42 mmol) was added. The resulting mixture was stirred for 1 h and then a further solution of **186** (6.92 g, 42 mmol) in *t*-butanol (20 ml) was added dropwise over 45 min. The reaction mixture was stirred for 24 hours then further potassium *t*-butoxide (4.69 g, 42 mmol) was added and further *t*-butanol (40 ml) and the reaction heated to 60 °C for 24 hours. The resulting mixture was cooled and diluted with treated with methanol (20 ml) and trifluoroacetic acid (4 ml) was added. After 5 minutes the solvent was evaporated in *vacuo* and then the solid residue was suspended in a methanol (40 ml) and chloroform (60 ml) mixture which was then filtered through a pad of Celite. The remaining solid and the Celite pad were washed with further methanol/chloroform mixture and the filtrate evaporated in *vacuo* to give the crude product (7.09 g) as a gum. The crude product was purified by column chromatography eluting with MeOH/CHCl<sub>3</sub> (5:95 to 100:0 in 10% steps) to give the monocycle **188** (3.61 g, 35%) and the bicyclic compound **187** (2.37 g, 18%).

Data for **188** (eluting in 30% MeOH/CHCl<sub>3</sub>)

<sup>1</sup>H-NMR: δppm                      2.00-2.40 (2H, m, 2 x CH), 3.30-3.45 (2H, m, CH<sub>2</sub>), 3.50-3.70 (2H, m, CH<sub>2</sub>), 4.50-4.55 (1H, m, CH).

<sup>13</sup>C-NMR: δppm                      35.2 (CH<sub>2</sub>), 47.1 (CH<sub>2</sub>), 57.0 (CH<sub>2</sub>), 71.7 (CH), 118.9 (CF<sub>3</sub>, q, <sup>1</sup>J<sub>C-F</sub> 292 Hz), 157.4 (C), 164.0 (C, q, <sup>2</sup>J<sub>C-F</sub> 35.5 Hz).

**FTIR  $\nu_{\max}$  cm<sup>-1</sup> (Nujol)** 3400 (OH Stretch), 3305 (N-H), 1680 (C=N).

**Rf:** 0.24 (20% MeOH/CHCl<sub>3</sub>)

**Melting Point:** 83-86 °C

Data for **187** (eluting in 40% MeOH/CHCl<sub>3</sub>)

**<sup>1</sup>H-NMR:  $\delta$ ppm** 1.95-2.30 (4H, m, 2 x CH<sub>2</sub>), 3.40-3.75 (8H, m, 4 x CH<sub>2</sub>), 4.45-4.50 (2H, m, 2 x CH-OH).

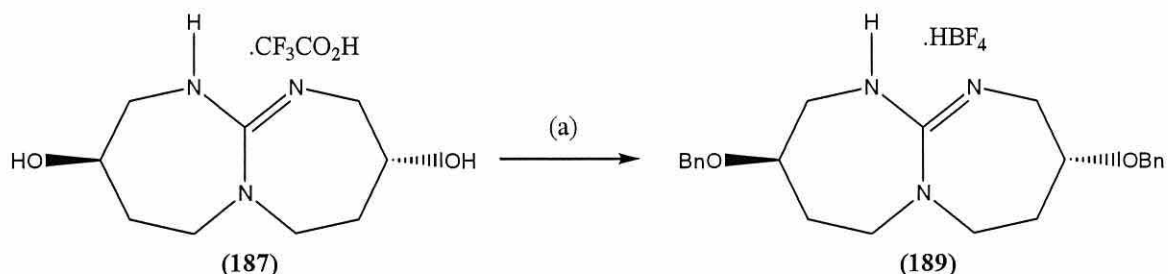
**<sup>13</sup>C-NMR:  $\delta$ ppm** 35.1 (CH<sub>2</sub>), 49.3 (CH<sub>2</sub>), 59.5 (CH<sub>2</sub>), 71.4 (CH), 118.9 (CF<sub>3</sub>, q, <sup>1</sup>J<sub>C-F</sub> 291 Hz), 158.4 (C), 163.9 (C, q, <sup>2</sup>J<sub>C-F</sub> 35.5 Hz).

**FTIR  $\nu_{\max}$  cm<sup>-1</sup> (Nujol)** 3400 (OH Stretch), 3305 (N-H), 1711 (C=N).

**Rf:** 0.25 (20% MeOH/CHCl<sub>3</sub>)

**Melting Point:** 83-86 °C

**(4*R*,8*R*)-3,8-dibenzyloxy-2,4,5,6,7,8,9,10-octahydro-3*H*-5a,10-diaza-1-azonia-heptalene tetrafluoroborate **189****



Under a nitrogen atmosphere diol **187** (776 mg, 2.48 mmol) was dissolved in dry DMF (5 ml) and cooled to 0 °C, NaH (631 mg, 15.78 mmol, 6.4 eq) was added and the solution stirred for 30 minutes. Benzene bromide (1.44 g, 8.40 mmol, 3.4 eq) was added and the resulting mixture stirred at room temperature for 1 h, heated at 60 °C for 4 h and then stirred at room temperature for 48 h. The mixture was then diluted with dichloromethane (25 ml) and extracted with 2N sodium hydroxide solution (25 ml), water (2 x 25 ml) and saturated lithium bromide solution (2 x 25 ml). The organic extracts were then dried (MgSO<sub>4</sub>) and reduced *in vacuo*. The solid was dissolved in methanol (30 ml) and Amberlite ion exchange resin (IRA 400 (OH)) (20 g) was added and the mixture stirred at room temperature for 24 h. After filtration the solvent was removed *in vacuo* and the resultant oil dissolved in dichloromethane (20 ml) and washed with HCl (2N, 20 ml), separated, dried (MgSO<sub>4</sub>) and filtered. A saturated solution of NaBF<sub>4</sub> (20 ml) was added and the mixture vigorously stirred for 24 hours. The solution was then separated and the organic layer dried to give the crude **189** as a viscous red oil (680 mg). Purification by column chromatography (MeOH/CHCl<sub>3</sub>, 0:100 to 5:95 in 0.5% steps) gave **189** as an oil (0.39 g, 34 %).

**<sup>1</sup>H-NMR: δppm** 1.98 (2H, m, 2 x CH), 2.20 (2H, m, 2 x CH), 3.50 (2H, m, 2 x CH), 3.61 (2H, m, 2 x CH), 3.77 (2H, ddd, J = 6.3, 9.8, 11.0 Hz, 2 x CH), 4.05 (2H, dd, J = 3.5, 11.3 Hz, 2 x CH), 4.25 (2H, m, 2 x CH), 4.50 (4H, s, 2 x CH<sub>2</sub>), 7.28-7.36 (10H, m, 2 x Ph), 7.62 (2H, br. s, 2 x NH).

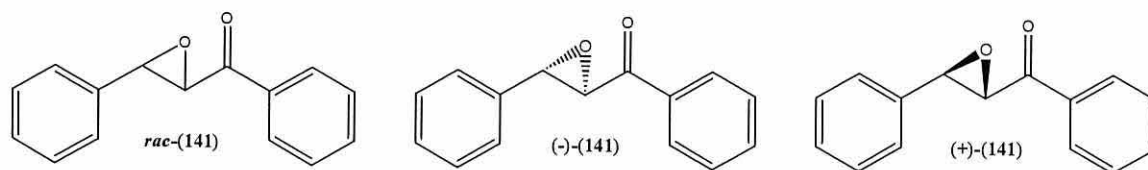
**<sup>13</sup>C-NMR: δppm** 31.0 (2 x CH<sub>2</sub>), 48.2 (2 x CH<sub>2</sub>), 55.5 (2 x CH<sub>2</sub>), 70.9 (2 x CH<sub>2</sub>), 76.2 (2 x CH), 127.7 (4 x CH), 127.9 (2 x CH), 128.5 (4 x CH), 137.5 (2 x C), 155.5 (C).

**FTIR**  $\nu_{\max}$   $\text{cm}^{-1}$  (Nujol) 3305 (N-H), 1716 (C=N), 1590 (C=C).  
**HRMS (ES+)  $m/z$ :**  $\text{C}_{23}\text{H}_{30}\text{N}_3\text{O}_2$  ( $[\text{M}+\text{H}]^+$ ); Requires 380.2333, found 380.2332  
**Rf:** 0.19 (10% MeOH/ $\text{CHCl}_3$ )

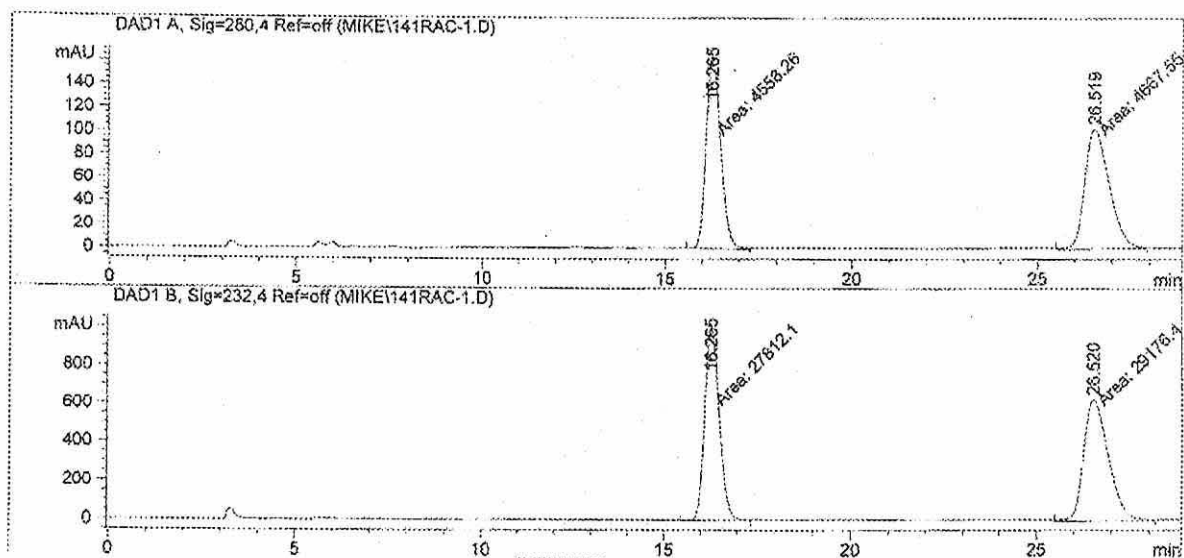
## General method for phase transfer epoxidation.

The catalyst (tetrabutylammounium chloride, **156**, **132a**, **132b** or **189**, 0.04-0.24 mmol) and the required chalcone **140** (1.04-4.8 mmol) were dissolved in toluene (1 ml per mmol chalcone) and the mixture cooled (0 °C) and vigorously stirred. Sodium hypochlorite (1.2 ml per mmol chalcone, 8% aq solution) was then added and the mixture stirred slowly to RT over 16 h. Dichloromethane (30 ml) and brine (20 ml) were added and the organic layer separated, dried (MgSO<sub>4</sub>) and evaporated. The crude product was then purified via column chromatography (ether/petrol) or recrystallisation.

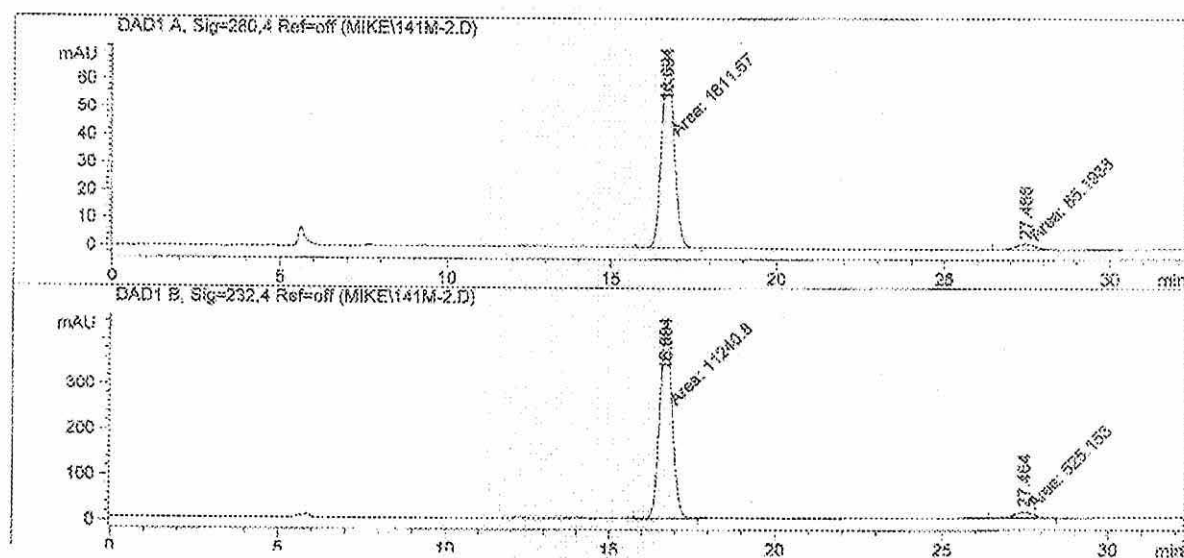
# Phenyl-(3-phenyl-oxiranyl)-methanone, **141**<sup>146</sup>



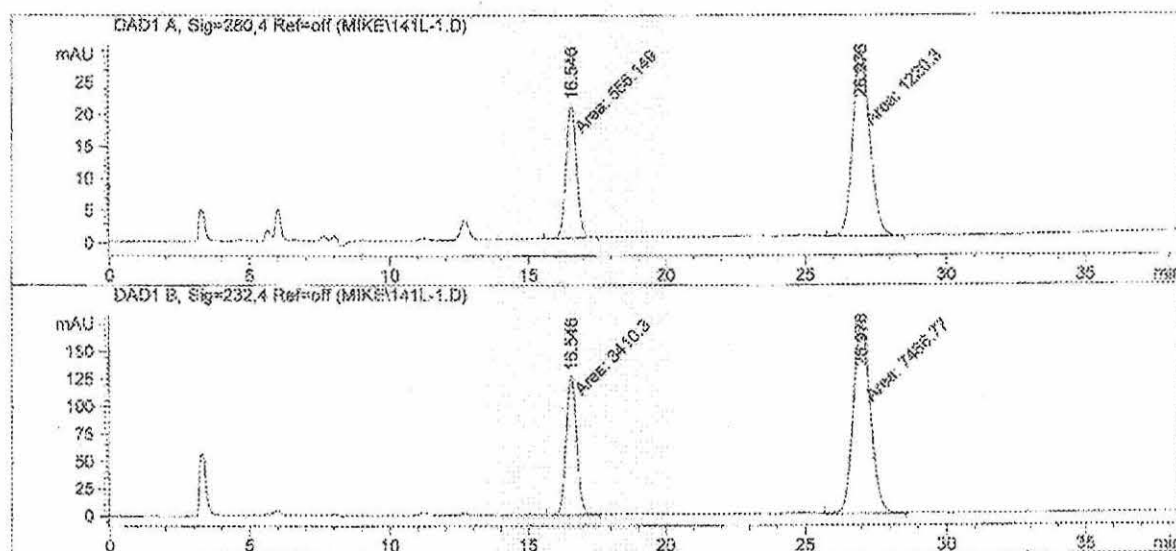
**Rac-141** in 89% yield (0.96 g, from *n*-Bu<sub>4</sub>N<sup>+</sup>Cl<sup>-</sup> (0.06 g, 0.24 mmol) and chalcone **140** (1 g, 4.80 mmol)) **Mp**: 92-94 °C (Lit 96-97 °C)<sup>146</sup>



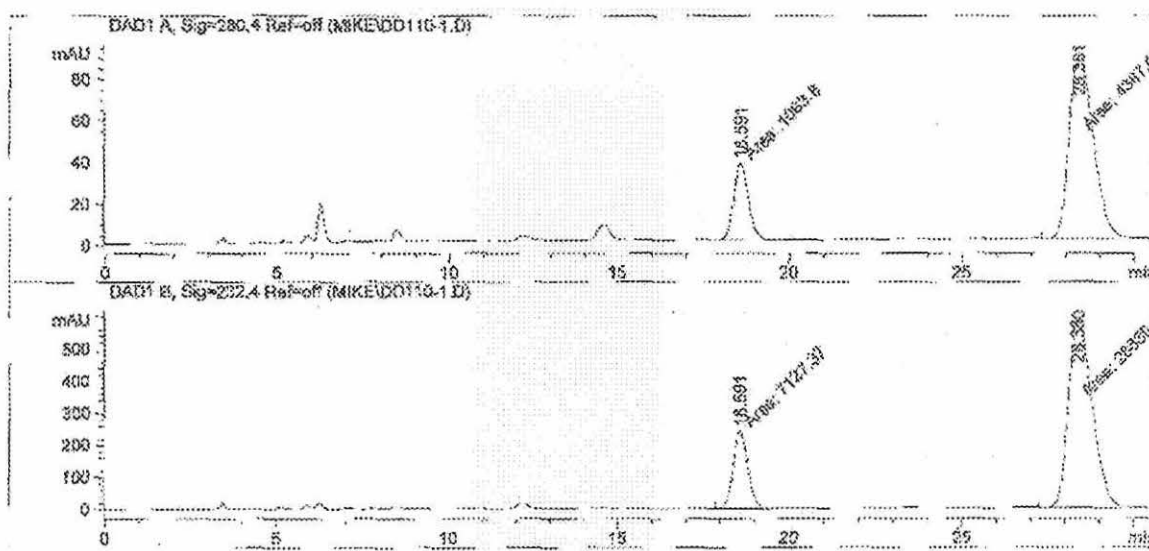
(-)-**141** in 80% yield (0.287 g, from **156** (0.015 g, 0.04 mmol) and chalcone **140** (0.33 g, 1.60 mmol) [ $\alpha$ ]<sub>D</sub><sup>25</sup>: -185 (c 1.0 in CH<sub>2</sub>Cl<sub>2</sub>), e.e. 91% from HPLC, **Mp**: 65-67 °C.



(+)-**141** in 64% yield (0.230 g, from **132a** (0.034 g, 0.06 mmol) and chalcone **140** (0.33 g, 1.60 mmol)  $[\alpha]_D^{25}$ : 4 (c 1.0 in CH<sub>2</sub>Cl<sub>2</sub>), e.e. 37% from HPLC **Mp**: 68-71 °C (Lit 76-77 °C)<sup>131</sup>



(+)-**141** in 74% yield (0.220 g, from **132b** (0.047 g, 0.07 mmol) and chalcone **140** (0.30 g, 1.44 mmol)  $[\alpha]_D^{25}$ : 158 (c 1.0 in CH<sub>2</sub>Cl<sub>2</sub>), e.e. 60% from HPLC **Mp**: 69-72 °C (Lit 76-77 °C)<sup>131</sup>



HPLC data Chiralpak AD column (97.5 : 2.5 Hexane : *i*PrOH) retention times (+)-**141**, 27.5 min: (-)-**141** 16.7 min. Lit  $[\alpha]_D^{25}$  +179 (c = 1.0 THF), 86% e.e.<sup>131</sup>

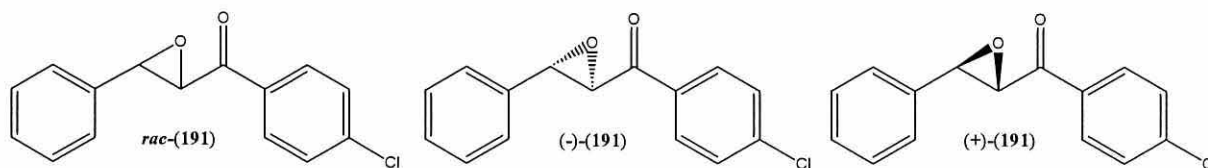
<sup>1</sup>H-NMR:  $\delta$ ppm 4.10 (1H, d, J = 1.8 Hz, CH), 4.32 (1H, d, J = 1.8 Hz, CH), 7.41 (5H, s, Ph), 7.50 (2H, t, J = 7.6 Hz, 2 x CH), 7.64 (1H, t, J = 7.3 Hz, CH), 8.03 (2H, d, J = 7.3 Hz, 2 x CH).



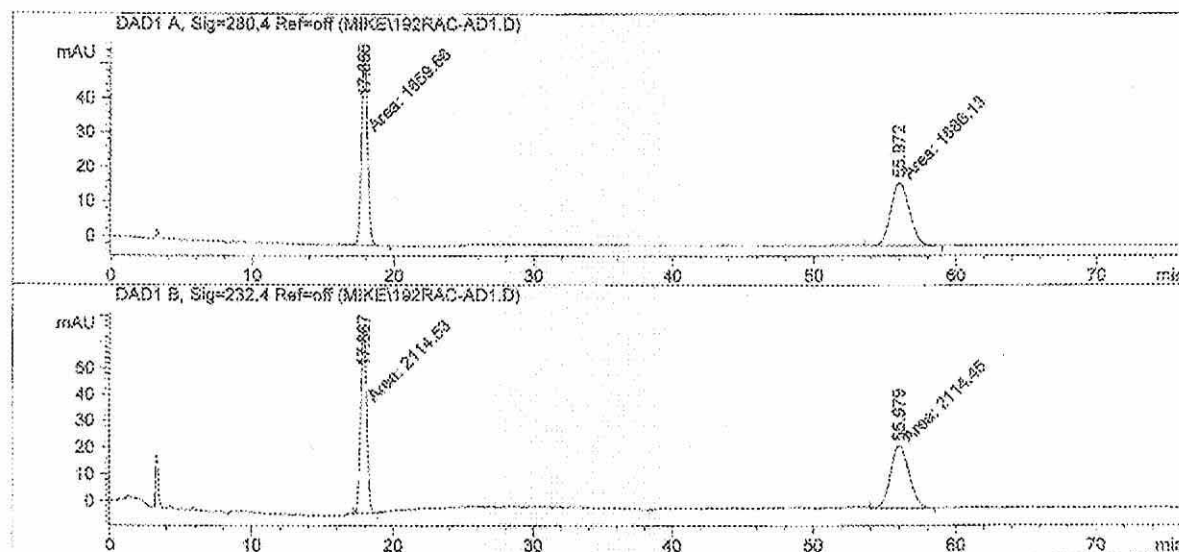
**$^{13}\text{C}$ -NMR:  $\delta\text{ppm}$**  59.4 (CH), 61.0 (CH), 125.8 (CH), 128.4 (2 x CH), 128.8 (CH),  
128.9 (CH), 129.1 (CH), 134.0 (C), 135.5 (C), 193.1 (C).

**Rf:** 0.14 (10% ether/petrol).

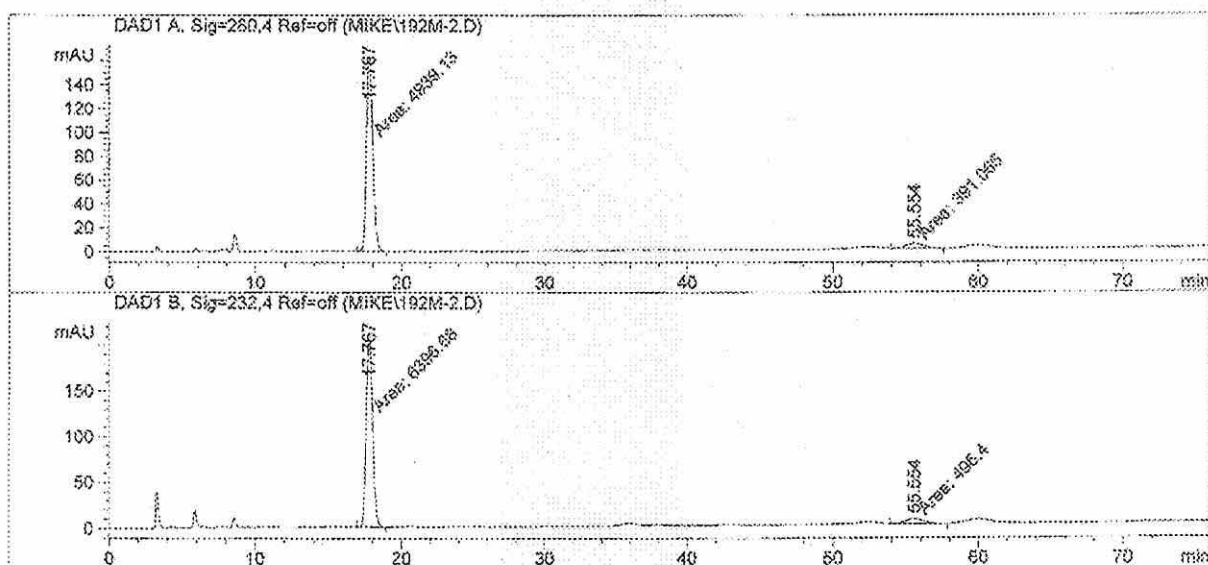
**(4-Chloro-phenyl)-(3-phenyl-oxiranyl)-methanone, 191<sup>147</sup>**



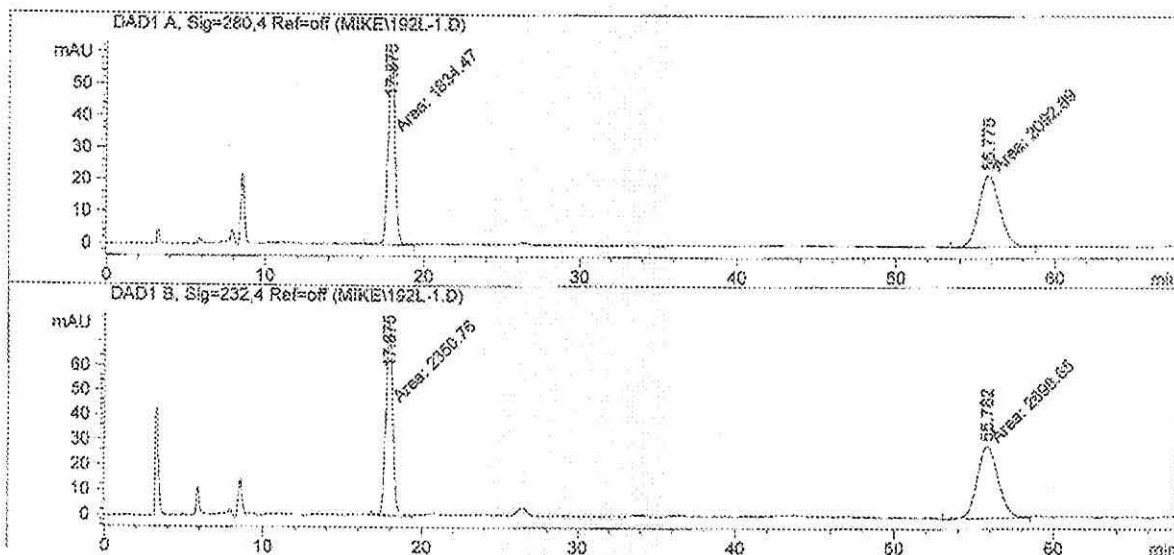
*Rac*-**191** in 64% yield (0.34 g, from  $n\text{-Bu}_4\text{N}^+\text{Cl}^-$  (0.06 g, 0.24 mmol) and chalcone **190** (0.5 g, 2.06 mmol)) **Mp**: 117-120 °C (Lit 118-120 °C)<sup>147</sup>



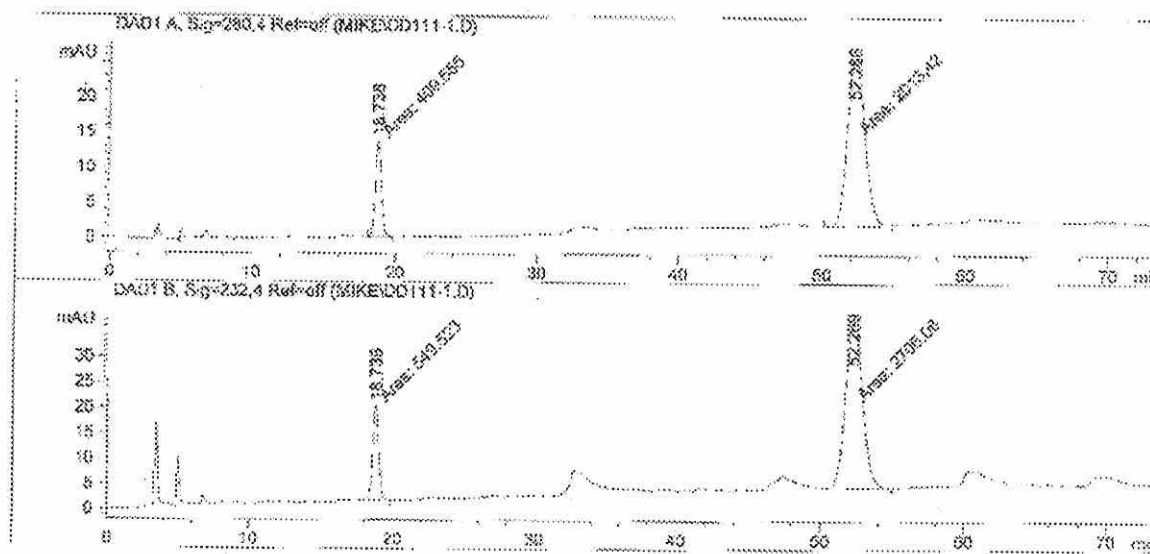
(-)-**191** in 51% yield (0.18 g, from **156** (0.02 g, 0.07 mmol) and chalcone **190** (0.33 g, 1.36 mmol),  $[\alpha]_{\text{D}}^{12}$ : -193 ( $c = 1.0 \text{ CH}_2\text{Cl}_2$ ) 85% e.e. from HPLC **Mp**: 68-70 °C (Lit 67-68 °C)<sup>148</sup>



(+)-**191** in 79% yield (0.262 g, from **132a** (0.04 g, 0.07 mmol) and chalcone **190** (0.33 g, 1.36 mmol) [ $\alpha$ ]<sub>D</sub><sup>12</sup>: 71 (c = 1.0 CH<sub>2</sub>Cl<sub>2</sub>) 7% e.e. from HPLC **Mp**: 76-80 °C.



(+)-**191** in 90% yield (0.288 g, from **132b** (0.04 g, 0.06 mmol) and chalcone **190** (0.30 g, 1.24 mmol) [ $\alpha$ ]<sub>D</sub><sup>21</sup>: 143 (c = 1.0 CH<sub>2</sub>Cl<sub>2</sub>) 66% e.e. from HPLC **Mp**: 75-78 °C.

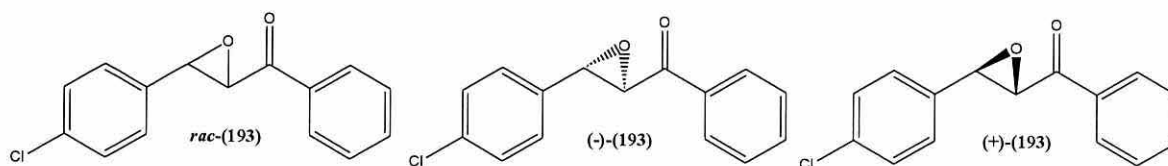


HPLC data Chiralpak AD column (97.5 : 2.5 Hexane : *i*PrOH) (+)-**191** 17.9 min, (-)-**191** 55.9 min. Lit [ $\alpha$ ]<sub>D</sub><sup>25</sup>: -202 (c = 2.0 CH<sub>2</sub>Cl<sub>2</sub>),<sup>132</sup> 99% e.e.

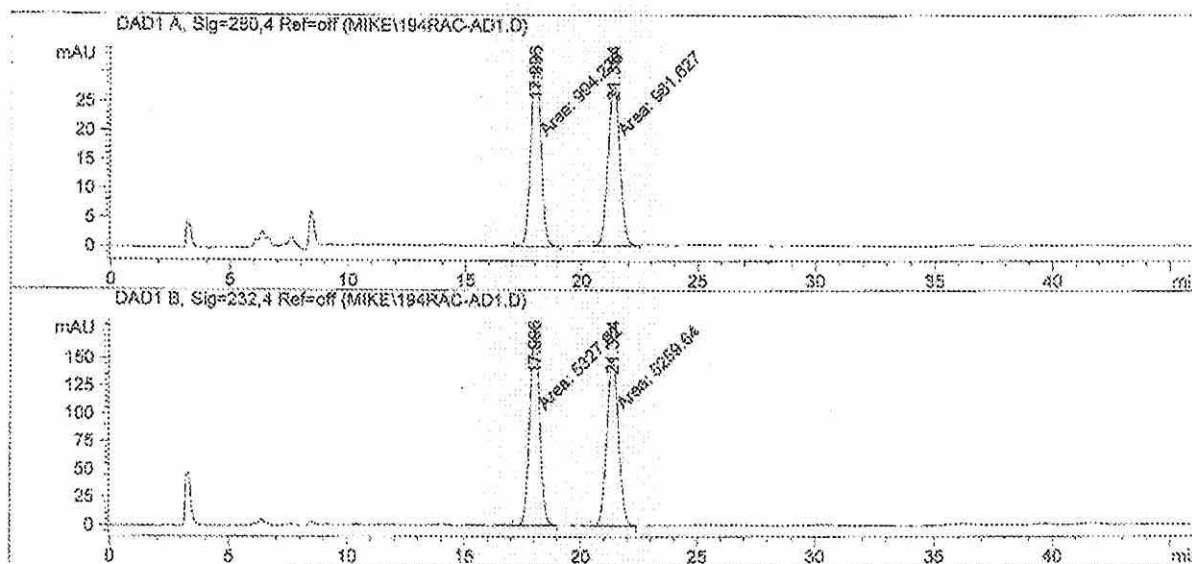
Data

<b><sup>1</sup>H-NMR: δppm</b>	4.10 (1H, d, J = 1.5 Hz, CH), 4.25 (1H, d, J = 1.5 Hz, CH), 7.41 (5H, s, CH), 7.49 (2H, d, J = 8.5 Hz, CH), 8.00 (2H, d, J = 8.3 Hz, CH).
<b><sup>13</sup>C-NMR: δppm</b>	59.3 (CH), 61.1 (CH), 125.8 (CH), 128.8 (CH), 129.2 (CH), 129.3 (CH), 129.8 (CH), 133.8 (C), 135.3 (C), 140.6 (C), 192.1 (C).
<b>HRMS (ES+) <i>m/z</i>:</b>	C <sub>15</sub> H <sub>11</sub> ClO <sub>2</sub> ([M+Na] <sup>+</sup> ); Requires 281.0345 found 281.0327
<b>Rf:</b>	0.11 (10% ether/petrol).

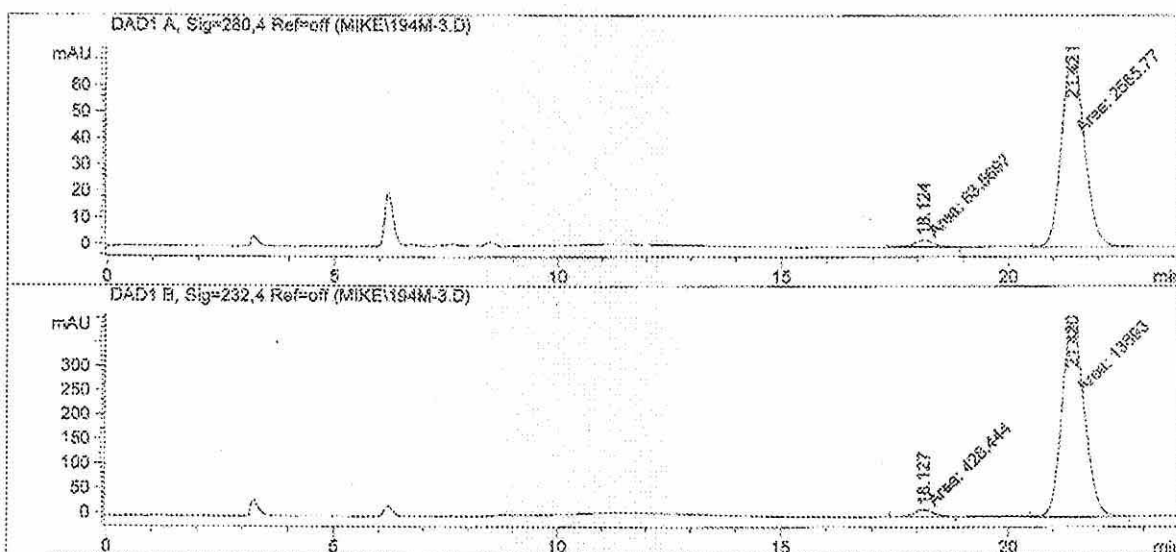
### 3-(4-Chloro-phenyl)-oxiranyl]-phenyl-methanone **193**



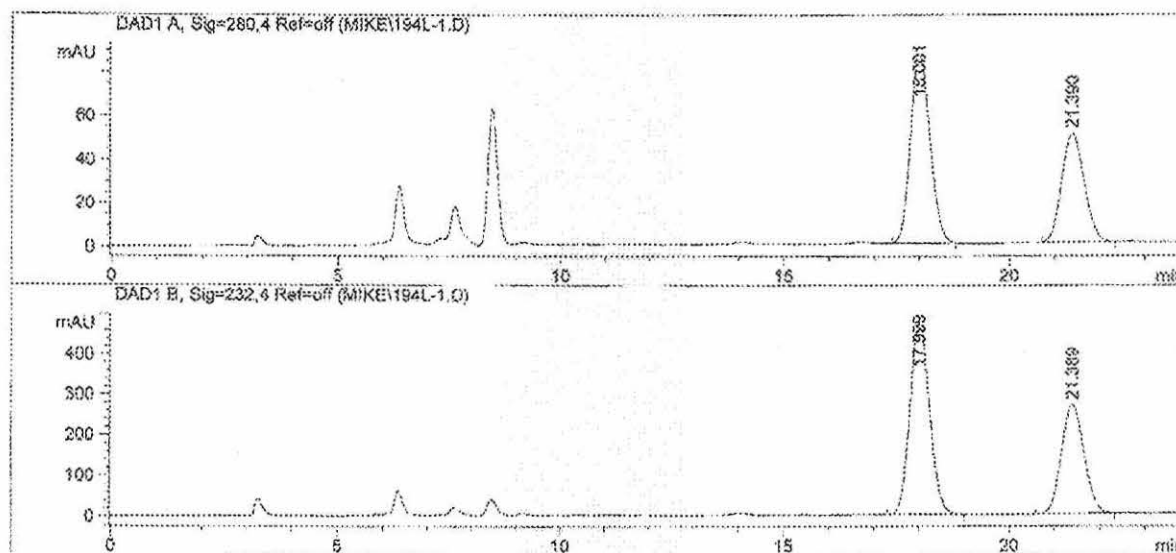
**Rac-193** in 96% yield (0.51 g, from  $n\text{-Bu}_4\text{N}^+\text{Cl}^-$  (0.06 g, 0.24 mmol) and chalcone **192** (0.5 g, 2.06 mmol)) **Mp**: 116-119 °C (Lit 118-120 °C)<sup>147</sup>



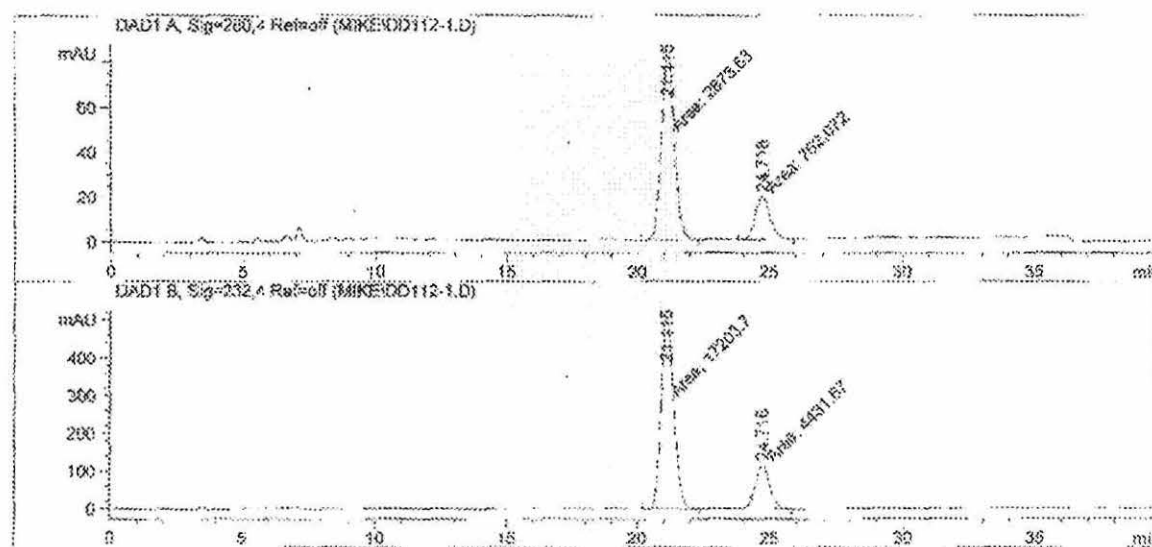
**(-)-193** in 97% yield (0.34 g, from **156** (0.02 g, 0.07 mmol) and chalcone **192** (0.33 g, 1.36 mmol),  $[\alpha]_D^{12}$ : -203 ( $c = 1.0 \text{ CH}_2\text{Cl}_2$ ) 94% e.e. from HPLC **Mp**: 64-66 °C (Lit 69-70 °C)<sup>132</sup>



(+)-**193** in 99% yield (0.35 g, from **132a** (0.04 g, 0.07 mmol) and chalcone **192** (0.33 g, 1.36 mmol) [ $\alpha$ ]<sub>D</sub><sup>12</sup>: 12 (c = 1.0 CH<sub>2</sub>Cl<sub>2</sub>) 21% e.e. from HPLC Mp: 63-66 °C



(+)-**193** in 92% yield (0.29 g, from **132b** (0.04 g, 0.06 mmol) and chalcone **192** (0.30 g, 1.24 mmol) [ $\alpha$ ]<sub>D</sub><sup>21</sup>: 150 (c = 1.0 CH<sub>2</sub>Cl<sub>2</sub>) 59% e.e. from HPLC Mp: 63-66 °C

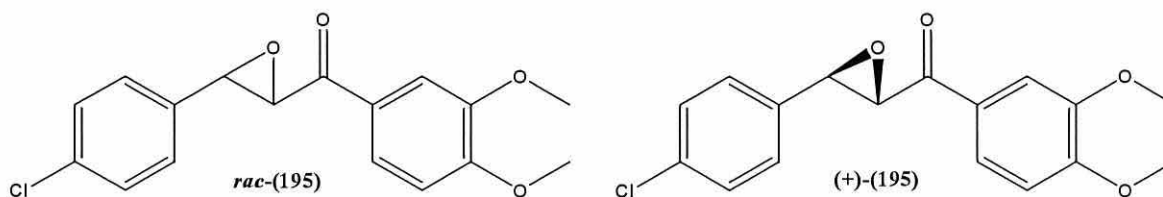


HPLC data Chiralpak AD column (97.5 : 2.5 Hexane : *i*PrOH) (+)-**193** 17.9 min, (-)-**193** 21.3 min. Lit [ $\alpha$ ]<sub>D</sub><sup>25</sup>: -253 (c = 2.0 CH<sub>2</sub>Cl<sub>2</sub>), <sup>132</sup> 99% e.e.

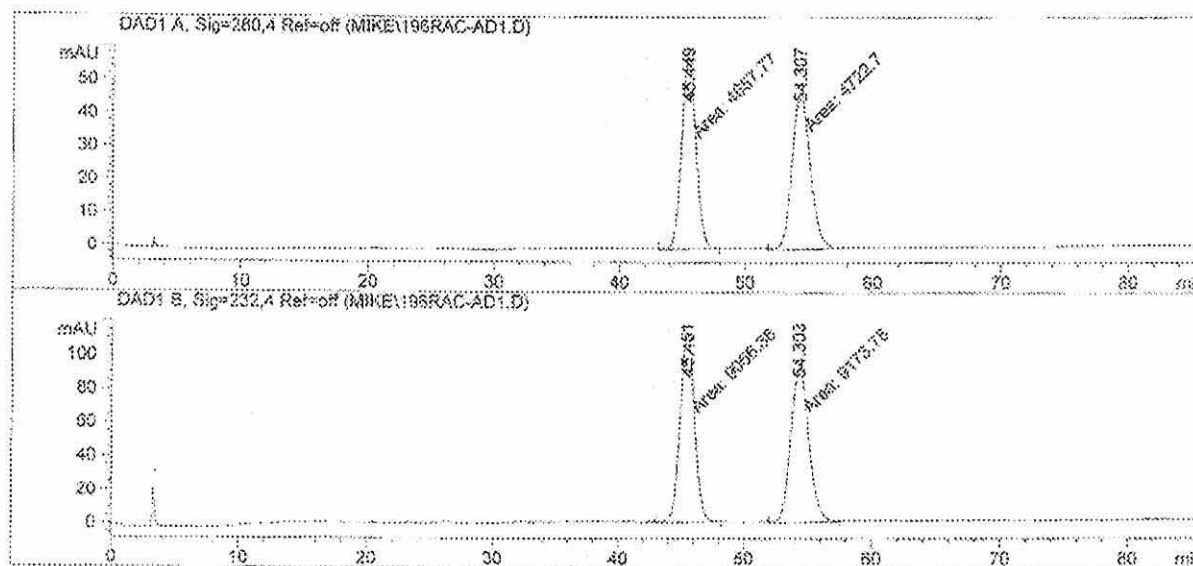
<sup>1</sup>H-NMR:  $\delta$ ppm 4.07 (1H, d, J = 1.2 Hz, CH), 4.27 (1H, d, J = 1.2 Hz, CH), 7.30 (2H, d, J = 8.5 Hz, 2 x CH), 7.38 (2H, d, J = 8.5 Hz, 2 x CH),

	7.51 (2H, t, J = 7.6 Hz, 2 x CH), 7.64 (1H, t, J = 7.6 Hz, CH), 8.00 (2H, d, J = 7.6 Hz, 2 x CH).
<b><sup>13</sup>C-NMR: δppm</b>	58.6 (CH), 61.0 (CH), 127.1 (CH), 128.4 (CH), 128.9 (CH), 129.1 (CH), 134.1 (CH), 134.1 (C), 135.0 (C), 135.5 (C), 192.7 (C).
<b>HRMS (ES+) <i>m/z</i>:</b>	C <sub>15</sub> H <sub>11</sub> ClO <sub>2</sub> ([M+Na] <sup>+</sup> ); Requires 281.0345 found 281.0341
<b>Rf:</b>	0.18 (10% ether/petrol).

### [3-(3-Chloro-phenyl)-oxiranyl]-(2,3-dimethoxy-phenyl)-methanone, 195



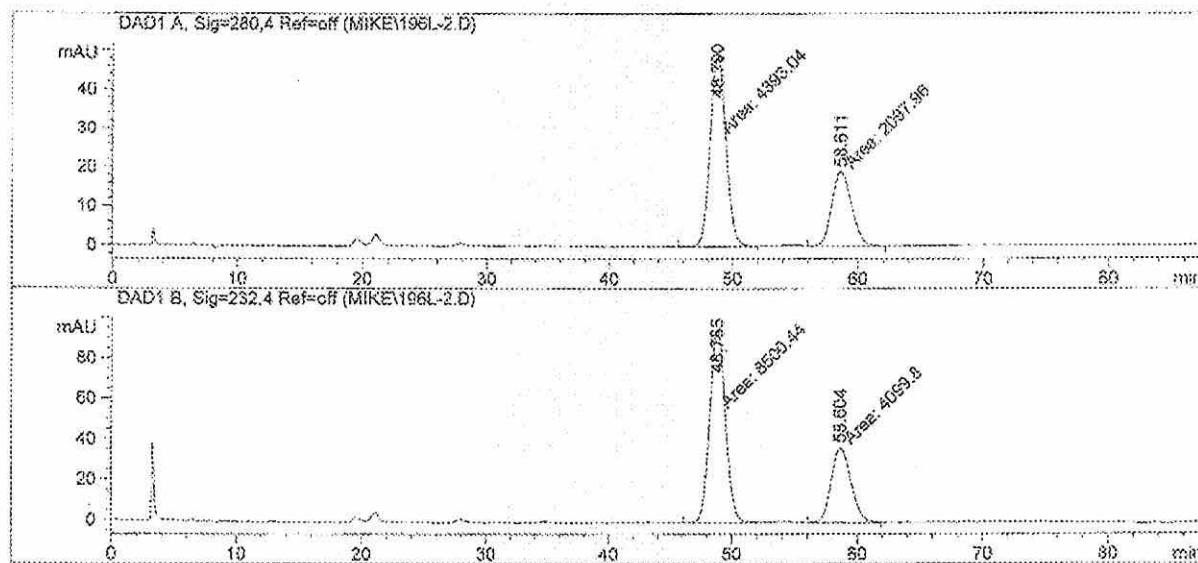
**Rac-195** in 89% yield (0.47 g, from *n*-Bu<sub>4</sub>N<sup>+</sup>Cl<sup>-</sup> (0.06 g, 0.24 mmol) and chalcone **194** (0.5 g, 1.57 mmol)) **Mp**: 125-127 °C



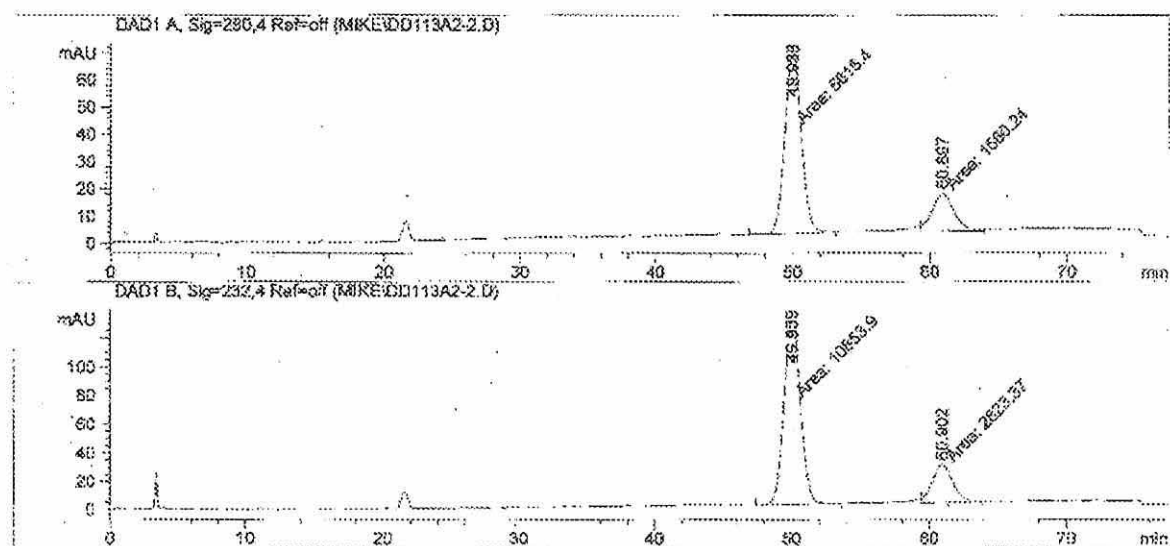
**(-)-195** no reaction (from **156** (0.02 g, 0.06 mmol) and chalcone **194** (0.33 g, 1.04 mmol))



(+)-**195** in 51% yield (0.18 g, from **132a** (0.04 g, 0.07 mmol) and chalcone **194** (0.33 g, 1.04 mmol) [ $\alpha$ ]<sub>D</sub><sup>25</sup>: +24 (*c* 0.059 in THF) 35% e.e. from HPLC **Mp**: 103-106 °C



(+)-**195** in 36% yield (0.11 g, from **132b** (0.03 g, 0.05 mmol) and chalcone **194** (0.30 g, 1.00 mmol) [ $\alpha$ ]<sub>D</sub><sup>25</sup>: +120 (*c* 0.059 in THF) 57% e.e. from HPLC **Mp**: 101-103 °C



HPLC data Chiralpak AD column (97.5 : 2.5 Hexane : *i*PrOH) (+)-**195** 54.3 min, (-)-**195** 45.4 min.

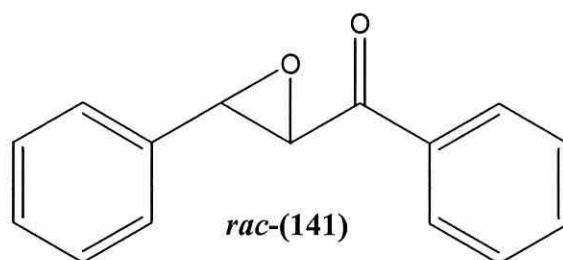
<sup>1</sup>H-NMR:  $\delta$ ppm 3.90 (3H, s, CH<sub>3</sub>), 3.93 (3H, s, CH<sub>3</sub>), 4.03 (1H, d, *J* = 1.5 Hz, CH), 4.21 (1H, d, *J* = 1.5 Hz, CH), 6.88 (1H, d, *J* = 8.6 Hz, CH), 7.26 (2H, app. q, *J* = 8.2 Hz, CH), 7.61 (2H, s, CH), 7.64 (1H, d, *J* = 1.5 Hz, CH).

**$^{13}\text{C}$ -NMR:  $\delta\text{ppm}$**  56.1 ( $\text{CH}_3$ ), 56.2 ( $\text{CH}_3$ ), 58.5 ( $\text{CH}$ ), 60.8 ( $\text{CH}$ ), 110.3, 110.4 ( $\text{CH}$ ), 123.4 ( $\text{CH}$ ), 127.1 ( $\text{CH}$ ), 128.8 ( $\text{C}$ ), 129.0 ( $\text{CH}$ ), 134.3 ( $\text{C}$ ), 134.9 ( $\text{C}$ ), 149.5 ( $\text{C}$ ), 191.0 ( $\text{C}$ ).

**HRMS (ES+)  $m/z$ :**  $\text{C}_{17}\text{H}_{15}\text{ClO}_4$  ( $[\text{M}+\text{Na}]^+$ ); Requires 341.0557 found 341.0558

**Rf:** 0.13 (40% ether/petrol).

### Attempted synthesis of (±)Phenyl-(3-phenyl-oxiranyl)-methanone, **141**<sup>146</sup>



3,8-*bis*-Benzyloxy-2,3,4,5,6,7,8,9-octahydro-1*H*-1,5a,10-triaza-heptalene **183** (0.057 g, 0.12 mmol) and the chalcone (0.5 g, 2.4 mmol) were dissolved in toluene (5 ml) and the mixture cooled (0 °C) along with vigorous stirring. Sodium hypochlorite (6 ml, 8% aq solution) was then added and the mixture stirred to RT over 48 h. Dichloromethane (30 ml) and brine (20 ml) were added and the organic layer separated, dried (MgSO<sub>4</sub>) and evaporated. No reaction occurred.

3,8-*bis*-benzyloxy-2,3,4,5,6,7,8,9-octahydro-1*H*-1,5a,10-triaza-heptalene **183** (0.11 g, 0.24 mmol) and the chalcone (0.5 g, 2.4 mmol) were dissolved in toluene (5 ml) and the mixture cooled (0 °C) along with vigorous stirring. Sodium hypochlorite (6 ml, 8% aq solution) was then added and the mixture stirred to RT over 16 h. Dichloromethane (30 ml) and brine (20 ml) were added and the organic layer separated, dried (MgSO<sub>4</sub>) and evaporated. No reaction occurred.

## References

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# Appendices

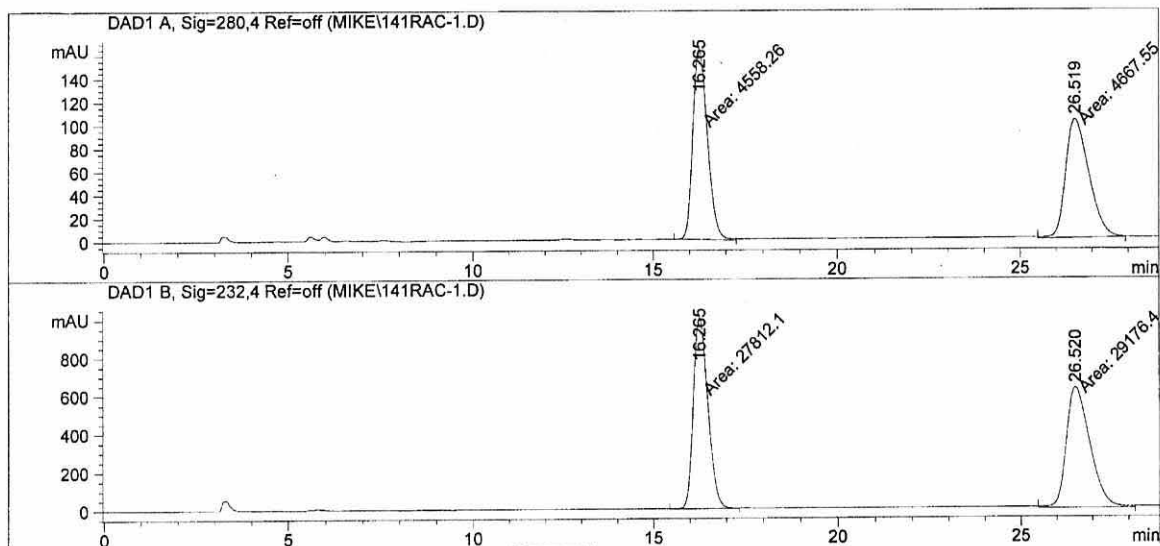
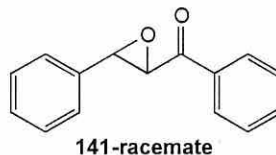
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1.0 ml/min, 21 bar



Signal 1: DAD1 A, Sig=280,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	16.265	MM	0.4620	4558.26025	164.43289	49.4077
2	26.519	MM	0.7576	4667.55078	102.68710	50.5923

Totals : 9225.81104 267.11999

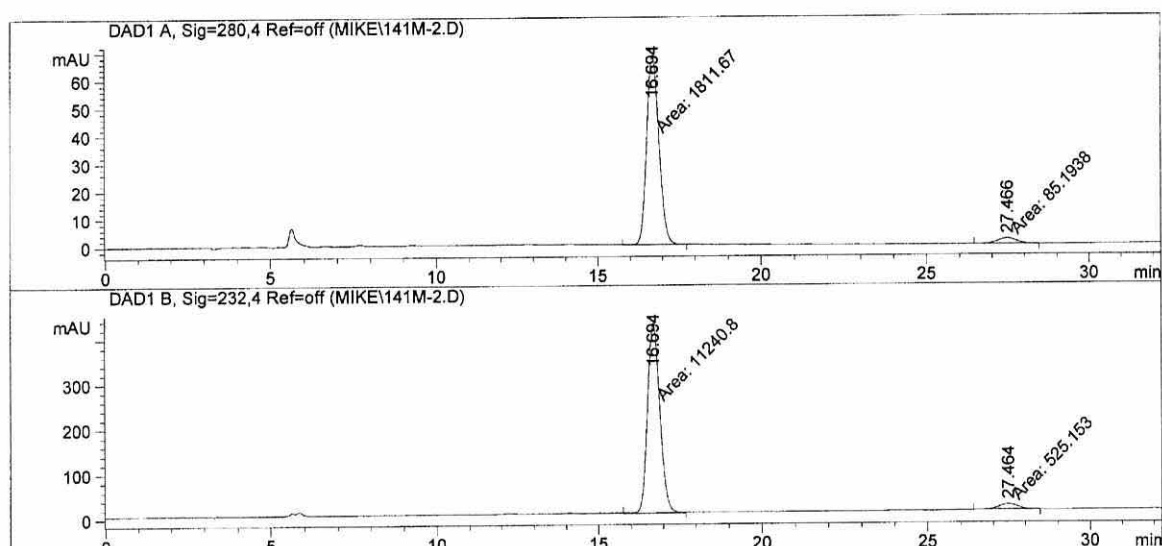
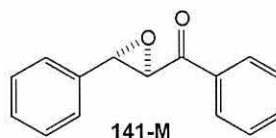
Signal 2: DAD1 B, Sig=232,4 Ref=off

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1	16.265	MM	0.4615	2.78121e4	1004.48657	48.8029
2	26.520	MM	0.7668	2.91764e4	634.14771	51.1971

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                  1.0 ml/min, 21 bar
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Signal 1: DAD1 A, Sig=280,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	16.694	MM	0.4413	1811.66943	68.42260	95.5087
2	27.466	MM	0.6973	85.19376	2.03617	4.4913

Totals : 1896.86319 70.45877

Signal 2: DAD1 B, Sig=232,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
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2	27.464	MM	0.7020	525.15295	12.46782	4.4633

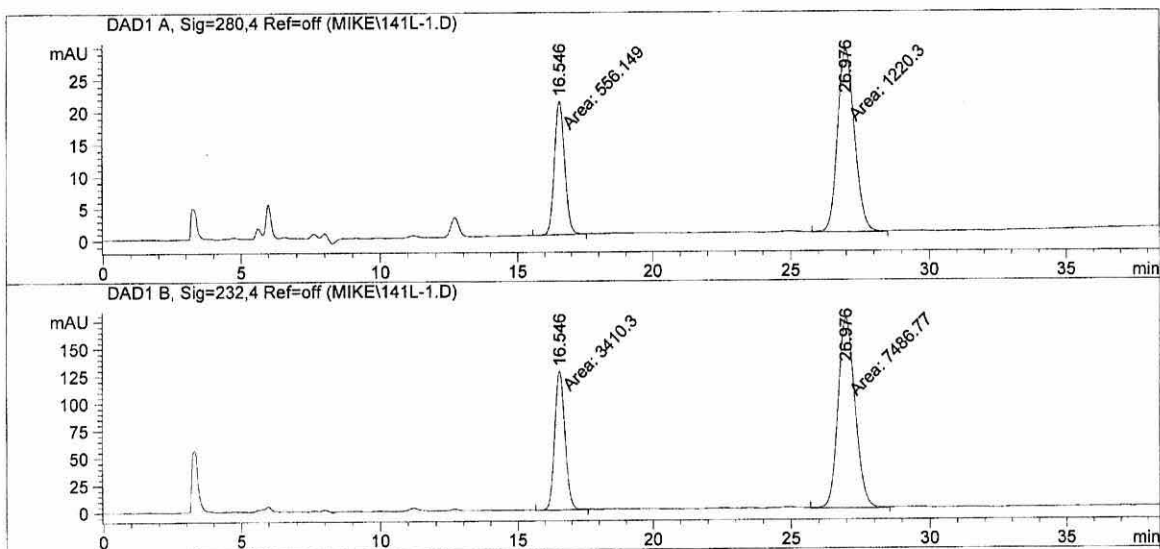
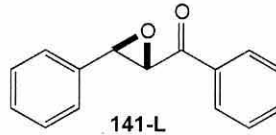
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1.0 ml/min, 21 bar

Location : Vial 0



Signal 1: DAD1 A, Sig=280,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	16.546	MM	0.4461	556.14911	20.77884	31.3068
2	26.976	MM	0.7159	1220.29712	28.41060	68.6932

Totals : 1776.44623 49.18944

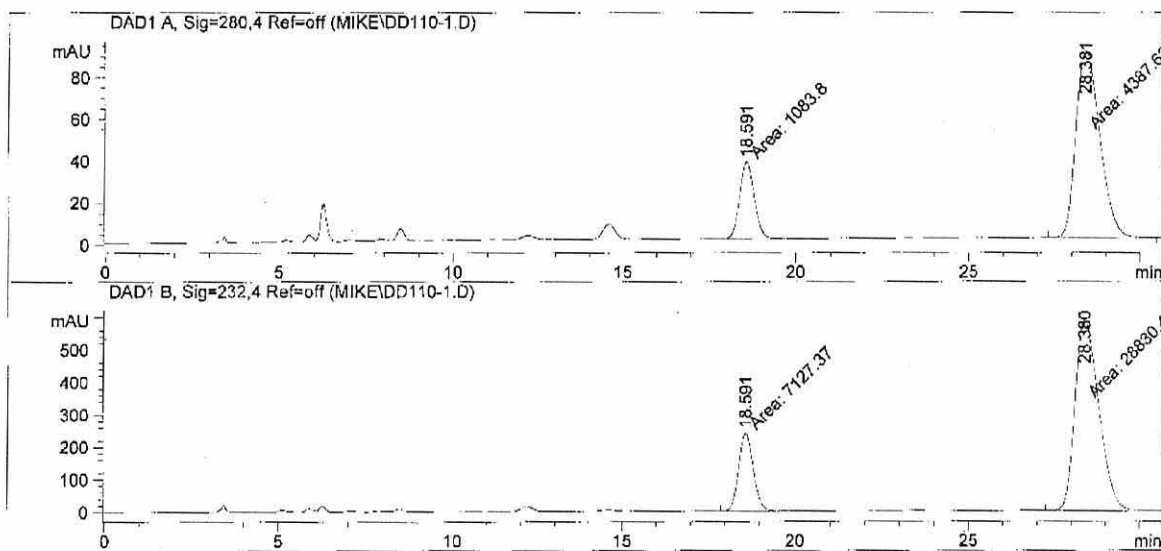
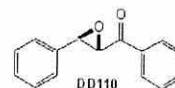
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1	16.546	MM	0.4463	3410.29639	127.34390	31.2956
2	26.976	MM	0.7161	7486.76709	174.25830	68.7044

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Data File C:\CHEM32\1\DATA\MIKE\DD110-1.D  
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Signal 1: DAD1 A, Sig=280,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	18.591	MM	0.4922	1083.80298	36.70182	19.8084
2	28.381	MM	0.8180	4387.61768	89.39573	80.1916

Totals : 5471.42065 126.09755

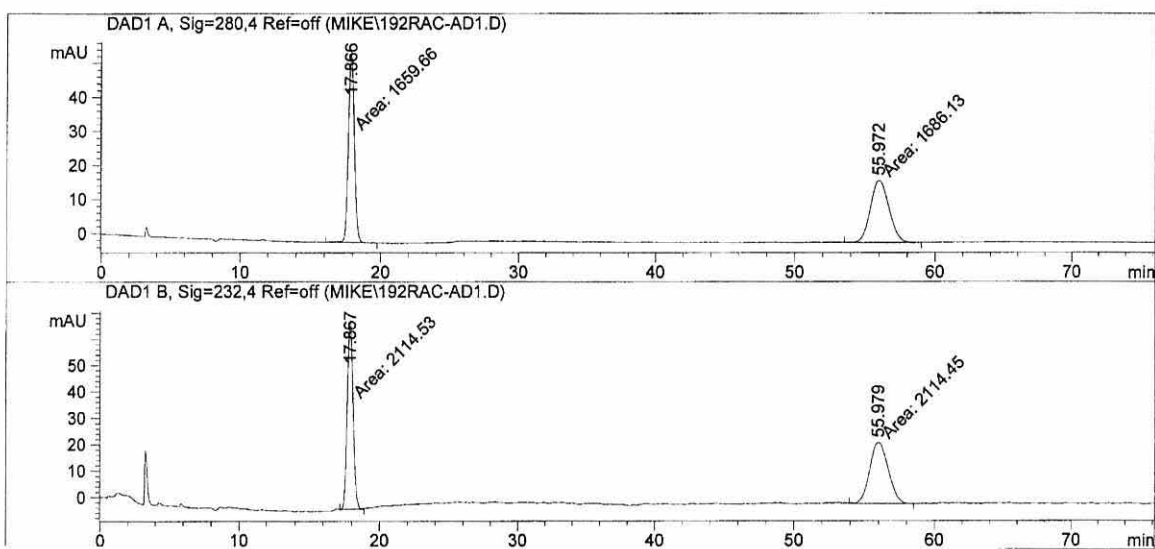
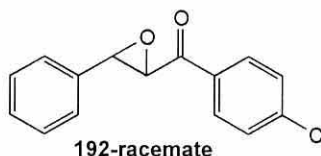
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1	18.591	MM	0.4924	7127.36523	241.23038	19.8215
2	28.380	MM	0.8170	2.88304e4	588.11542	80.1785

Totals : 3.59578e4 829.34579

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                1.0 ml/min, 21 bar
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Signal 1: DAD1 A, Sig=280,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	17.866	MM	0.4951	1659.65527	55.87443	49.6044
2	55.972	MM	1.5422	1686.12964	18.22269	50.3956

Totals : 3345.78491 74.09712

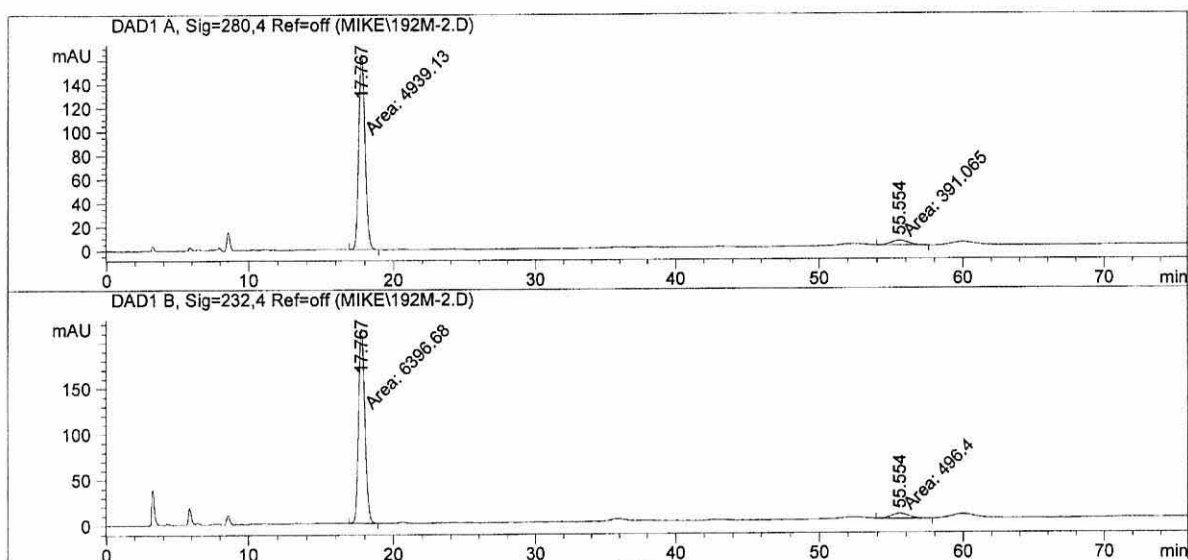
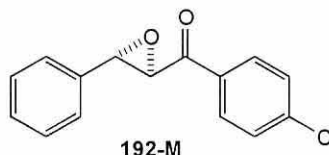
Signal 2: DAD1 B, Sig=232,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	17.867	MM	0.4905	2114.53467	71.85615	50.0010
2	55.979	MM	1.5160	2114.44922	23.24525	49.9990

Totals : 4228.98389 95.10140

Data File C:\CHEM32\1\DATA\MIKE\192M-2.D  
Sample Name: 192M-2

```
=====
Acq. Operator   : Mike
Acq. Instrument : Instrument 1
Injection Date  : 2/3/2009 10:02:23 AM
Acq. Method     : C:\CHEM32\1\METHODS\MIKEC31.M
Last changed    : 2/3/2009 10:00:46 AM by Mike
                  (modified after loading)
Analysis Method : C:\CHEM32\1\METHODS\MIKEC31.M
Last changed    : 2/3/2009 12:25:40 PM by Mike
                  (modified after loading)
Sample Info     : Chiralpak AD
                  90:10 Hexane:EtOH
                  1.0 ml/min, 21 bar
```



Signal 1: DAD1 A, Sig=280,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	17.767	MM	0.5018	4939.12842	164.04933	92.6632
2	55.554	MM	1.5002	391.06476	4.34465	7.3368

Totals : 5330.19318 168.39398

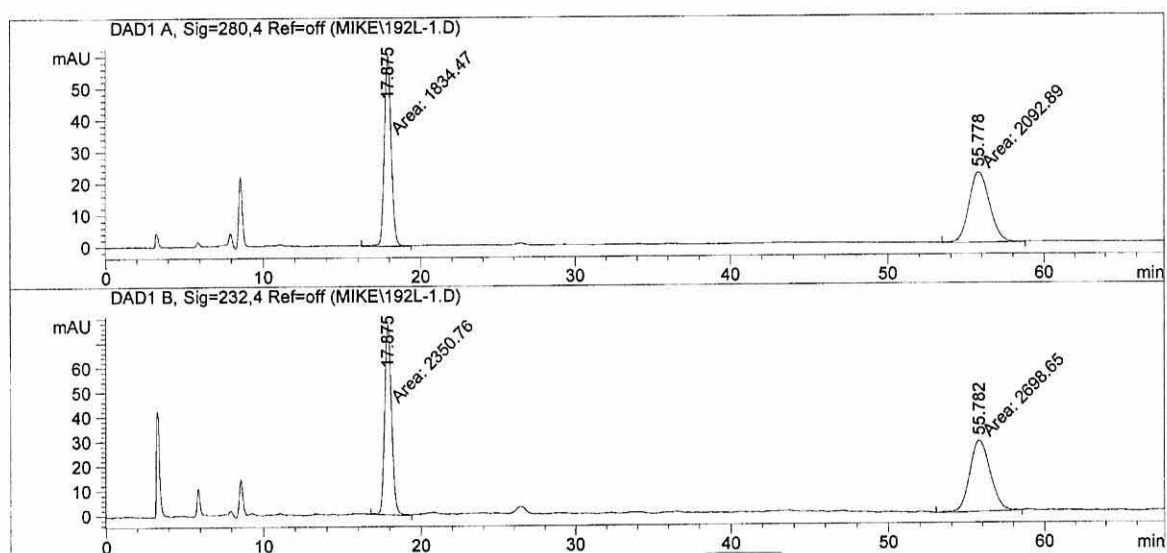
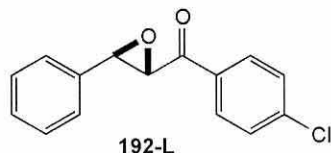
Signal 2: DAD1 B, Sig=232,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	17.767	MM	0.5010	6396.67773	212.79317	92.7986
2	55.554	MM	1.4760	496.40033	5.60510	7.2014

Totals : 6893.07806 218.39827

Data File C:\CHEM32\1\DATA\MIKE\192L-1.D  
Sample Name: 192L-1

```
=====
Acq. Operator   : Mike
Acq. Instrument : Instrument 1
Injection Date  : 2/2/2009 1:42:56 PM
Acq. Method     : C:\CHEM32\1\METHODS\MIKEC31.M
Last changed    : 2/2/2009 1:35:40 PM by Mike
                  (modified after loading)
Analysis Method : C:\CHEM32\1\METHODS\MIKEC31.M
Last changed    : 2/2/2009 5:24:52 PM by Mike
                  (modified after loading)
Sample Info     : Chiralpak AD
                  90:10 Hexane:EtOH
                  1.0 ml/min, 21 bar
```



Signal 1: DAD1 A, Sig=280,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	17.875	MM	0.5091	1834.46948	60.05981	46.7100
2	55.778	MM	1.5591	2092.89258	22.37353	53.2900

Totals : 3927.36206 82.43333

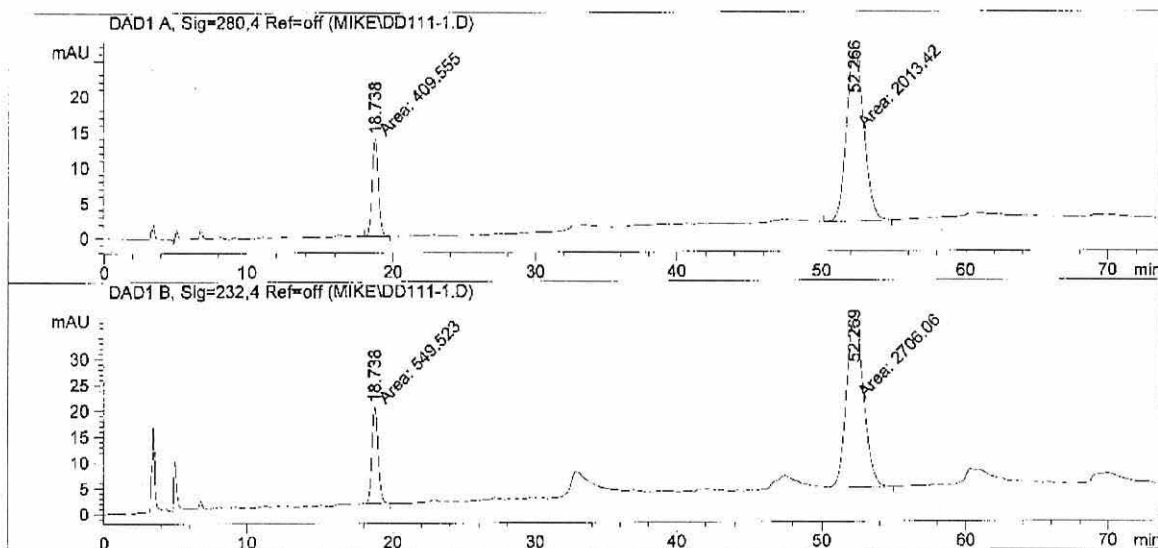
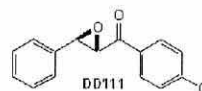
Signal 2: DAD1 B, Sig=232,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	17.875	MM	0.5065	2350.75708	77.35941	46.5551
2	55.782	MM	1.5576	2698.64673	28.87588	53.4449

Totals : 5049.40381 106.23529

Data File C:\CHEM32\1\DATA\MIKE\DD111-1.D  
Sample Name: DD111-1

```
=====
Acq. Operator   : Mike
Acq. Instrument : Instrument 1                Location : Vial 0
Injection Date  : 4/17/2009 3:43:31 PM
Acq. Method     : C:\CHEM32\1\METHODS\MIKEC31.M
Last changed    : 4/17/2009 2:04:12 PM by Mike
Analysis Method : C:\CHEM32\1\DATA\MIKE\DD111-1.D\DA.M (MIKEC31.M)
Last changed    : 4/17/2009 4:57:35 PM by Mike
Sample Info     : Chiralpak AD + guard
                  90:10 Hexane:EtOH
                  1.0 ml/min, 21 bar
```



Signal 1: DAD1 A, Sig=280,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	18.738	MM	0.4978	409.55493	13.71153	16.9030
2	52.266	MM	1.3861	2013.42285	24.21014	83.0970

Totals : 2422.97778 37.92167

Signal 2: DAD1 B, Sig=232,4 Ref=off

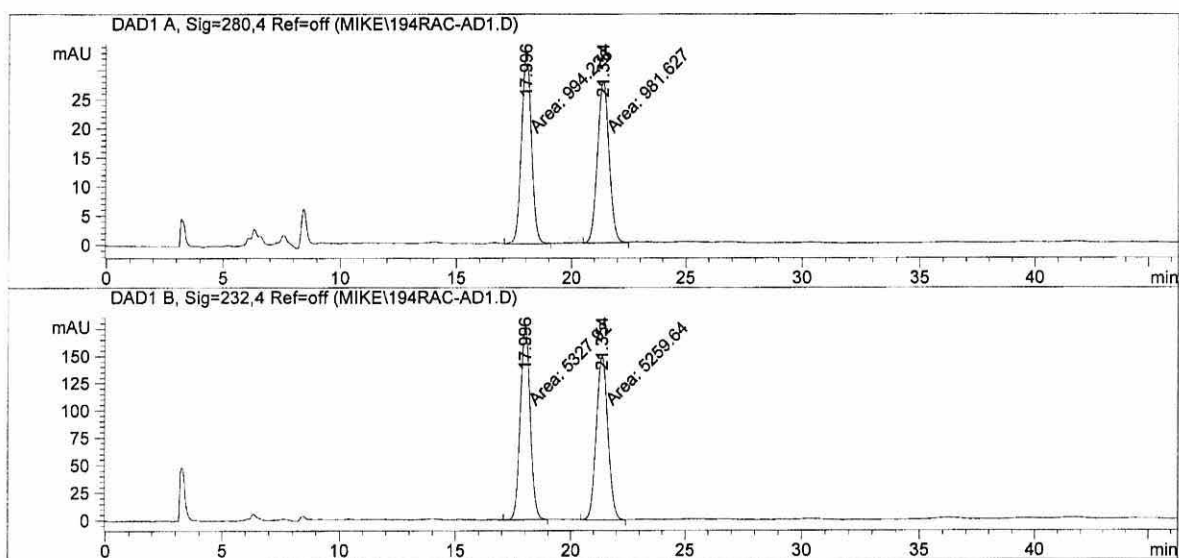
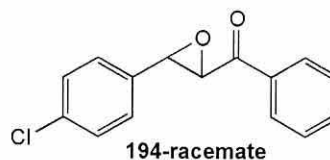
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	18.738	MM	0.4930	549.52289	18.57638	16.8794
2	52.269	MM	1.3794	2706.05737	32.69528	83.1206

Totals : 3255.58026 51.27166



Data File C:\CHEM32\1\DATA\MIKE\194RAC-AD1.D  
Sample Name: 194rac-AD1

```
=====
Acq. Operator   : Mike
Acq. Instrument : Instrument 1
Injection Date  : 2/3/2009 12:39:44 PM
Acq. Method     : C:\CHEM32\1\METHODS\MIKEC31.M
Last changed    : 2/3/2009 12:25:40 PM by Mike
                  (modified after loading)
Analysis Method : C:\CHEM32\1\METHODS\MIKEC31.M
Last changed    : 2/3/2009 2:20:10 PM by Mike
                  (modified after loading)
Sample Info     : Chiralpak AD
                  90:10 Hexane:EtOH
                  1.0 ml/min, 21 bar
```



Signal 1: DAD1 A, Sig=280,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	17.996	MM	0.5048	994.22638	32.82425	50.3188
2	21.354	MM	0.5874	981.62665	27.85413	49.6812

Totals : 1975.85303 60.67837

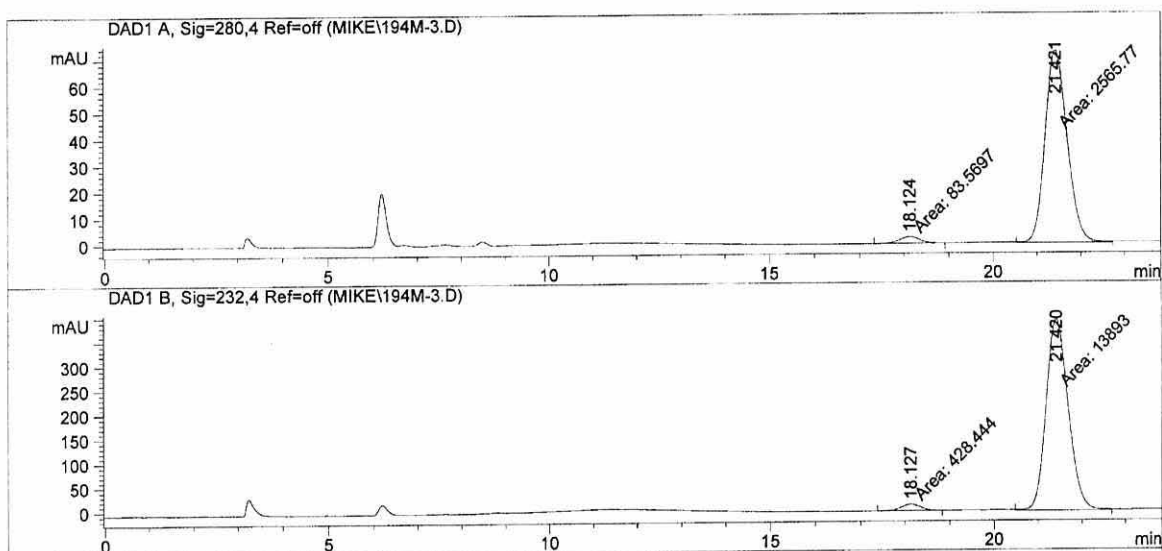
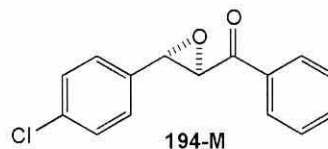
Signal 2: DAD1 B, Sig=232,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	17.996	MM	0.5017	5327.92236	177.00217	50.3225
2	21.354	MM	0.5851	5259.63916	149.83081	49.6775

Totals : 1.05876e4 326.83298

Data File C:\CHEM32\1\DATA\MIKE\194M-3.D  
Sample Name: 194M-3

```
=====
Acq. Operator   : Mike
Acq. Instrument : Instrument 1
Injection Date  : 2/3/2009 3:28:58 PM
Acq. Method     : C:\CHEM32\1\METHODS\MIKEC31.M
Last changed    : 2/3/2009 3:26:21 PM by Mike
                  (modified after loading)
Analysis Method : C:\CHEM32\1\METHODS\MIKEC31.M
Last changed    : 2/3/2009 3:53:25 PM by Mike
                  (modified after loading)
Sample Info     : Chiralpak AD
                  90:10 Hexane:EtOH
                  1.0 ml/min, 21 bar
```



Signal 1: DAD1 A, Sig=280,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	18.124	MM	0.5381	83.56966	2.58846	3.1544
2	21.421	MM	0.5882	2565.77148	72.70225	96.8456

Totals : 2649.34115 75.29071

Signal 2: DAD1 B, Sig=232,4 Ref=off

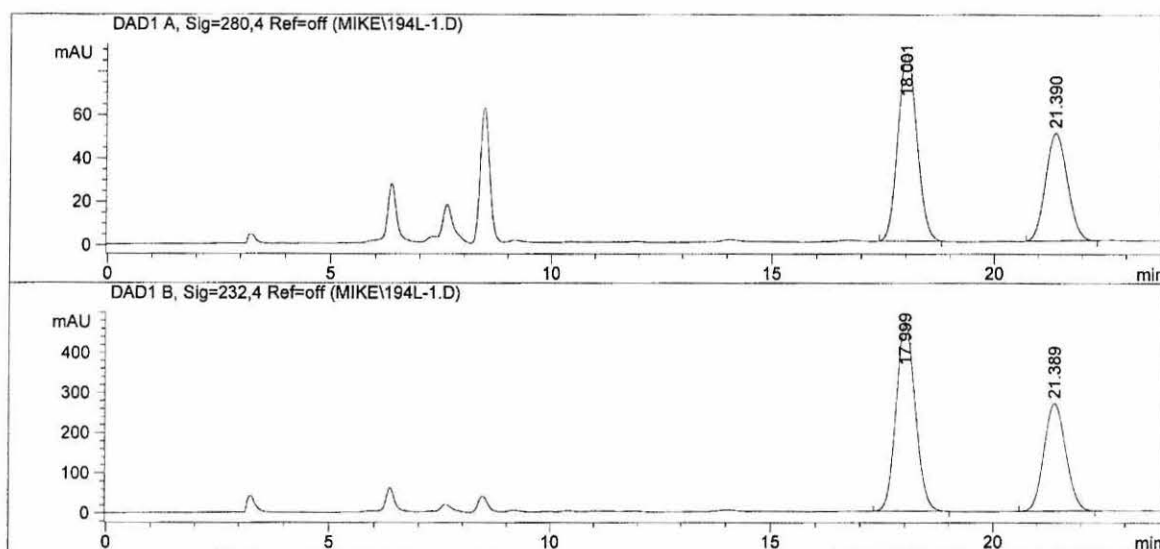
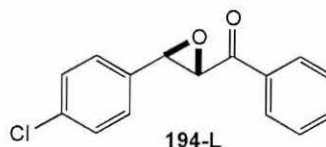
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	18.127	MM	0.5187	428.44394	13.76544	2.9916
2	21.420	MM	0.5867	1.38930e4	394.68756	97.0084

Totals : 1.43214e4 408.45300

Data File C:\CHEM32\1\DATA\MIKE\194L-1.D  
Sample Name: 194L-1

=====

Acq. Operator : Mike  
Acq. Instrument : Instrument 1 Location : Vial 0  
Injection Date : 2/3/2009 1:31:27 PM  
Acq. Method : C:\CHEM32\1\METHODS\MIKEC31.M  
Last changed : 2/3/2009 1:26:38 PM by Mike  
(modified after loading)  
Analysis Method : C:\CHEM32\1\METHODS\MIKEC31.M  
Last changed : 2/3/2009 2:20:10 PM by Mike  
(modified after loading)  
Sample Info : Chiralpak AD  
90:10 Hexane:EtOH  
1.0 ml/min, 21 bar



Signal 1: DAD1 A, Sig=280,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	18.001	BB	0.4673	2607.56787	86.59093	60.4730
2	21.390	BB	0.5432	1704.38538	49.55971	39.5270

Totals : 4311.95325 136.15065

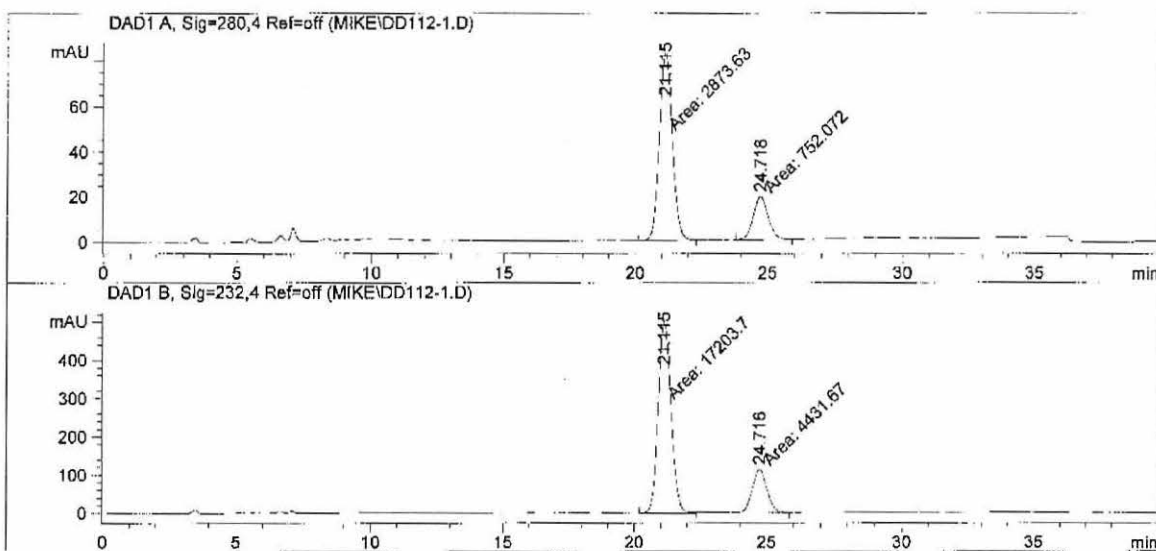
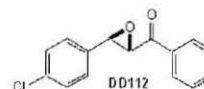
Signal 2: DAD1 B, Sig=232,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	17.999	BB	0.4719	1.43118e4	471.77032	60.7717
2	21.389	BB	0.5381	9238.30469	268.07535	39.2283

Totals : 2.35501e4 739.84567

Data File C:\CHEM32\1\DATA\MIKE\DD112-1.D  
Sample Name: DD112-1

```
=====
Acq. Operator   : Mike
Acq. Instrument : Instrument 1                Location : Vial 0
Injection Date  : 4/20/2009 10:42:42 AM
Acq. Method     : C:\CHEM32\1\METHODS\MIKEC31.M
Last changed    : 4/20/2009 8:44:05 AM by Mike
Analysis Method : C:\CHEM32\1\DATA\MIKE\DD112-1.D\DA.M (MIKEC31.M)
Last changed    : 4/20/2009 11:22:43 AM by Mike
Sample Info     : Chiralpak AD + guard
                  90:10 Hexane:EtOH
                  1.0 mL/min, 21 bar
```



Signal 1: DAD1 A, Sig=280,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	21.115	MM	0.5760	2873.62720	83.14931	79.2572
2	24.718	MM	0.6566	752.07159	19.08970	20.7428

Totals : 3625.69879 102.23901

Signal 2: DAD1 B, Sig=232,4 Ref=off

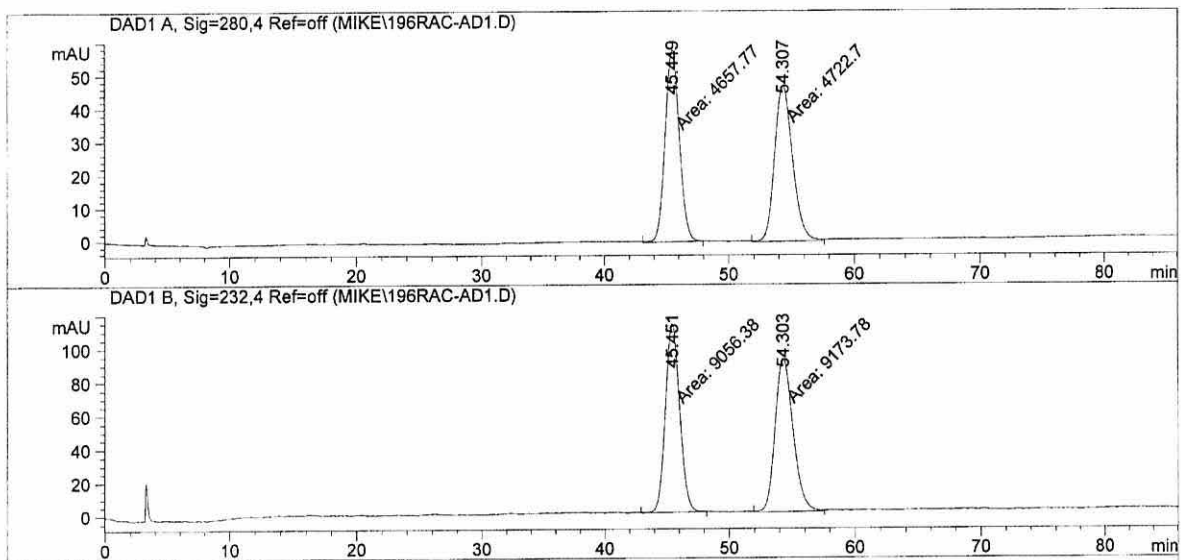
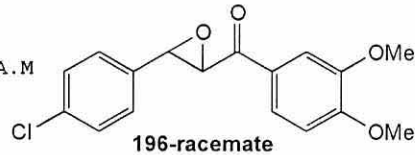
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	21.115	MM	0.5710	1.72037e4	502.13986	79.5165
2	24.716	MM	0.6493	4431.67285	113.75919	20.4835

Totals : 2.16354e4 615.89906

Data File C:\CHEM32\1\DATA\MIKE\196RAC-AD1.D  
Sample Name: 196rac-AD1

=====

Acq. Operator : Mike  
Acq. Instrument : Instrument 1 Location : Vial 0  
Injection Date : 1/30/2009 2:40:05 PM  
Acq. Method : C:\CHEM32\1\METHODS\MIKEC31.M  
Last changed : 1/30/2009 1:42:59 PM by Mike  
(modified after loading)  
Analysis Method : C:\CHEM32\1\DATA\MIKE\196RAC-AD1.D\DA.M  
Last changed : 1/30/2009 4:06:29 PM by Mike  
Sample Info : Chiralpak AD  
90:10 Hexane:EtOH  
1.0 ml/min, 21 bar



Signal 1: DAD1 A, Sig=280,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	45.449	MM	1.3388	4657.77295	57.98561	49.6539
2	54.307	MM	1.6677	4722.70410	47.19674	50.3461

Totals : 9380.47705 105.18235

Signal 2: DAD1 B, Sig=232,4 Ref=off

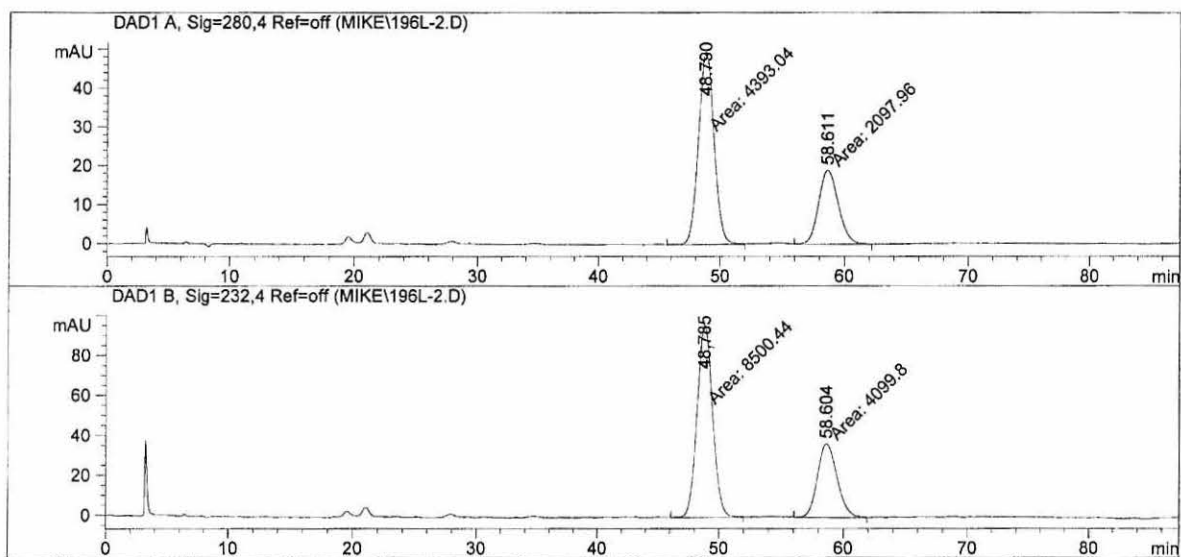
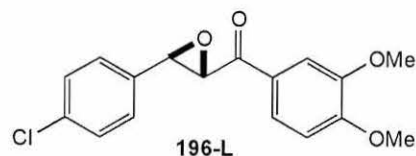
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	45.451	MM	1.3381	9056.38086	112.79877	49.6780
2	54.303	MM	1.6646	9173.77539	91.85265	50.3220

Totals : 1.82302e4 204.65141

Data File C:\CHEM32\1\DATA\MIKE\196L-2.D  
Sample Name: 196L-2

```

=====
Acq. Operator   : Mike
Acq. Instrument : Instrument 1
Injection Date  : 2/2/2009 10:32:56 AM
Acq. Method     : C:\CHEM32\1\METHODS\MIKEC31.M
Last changed    : 2/2/2009 10:03:01 AM by Mike
                  (modified after loading)
Analysis Method : C:\CHEM32\1\METHODS\MIKEC31.M
Last changed    : 2/2/2009 12:00:55 PM by Mike
                  (modified after loading)
Sample Info     : Chiralpak AD
                  90:10 Hexane:EtOH
                  1.0 ml/min, 21 bar
  
```



Signal 1: DAD1 A, Sig=280,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	48.790	MM	1.4741	4393.03955	49.67037	67.6789
2	58.611	MM	1.8368	2097.96216	19.03669	32.3211

Totals : 6491.00171 68.70706

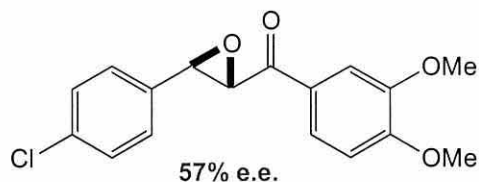
Signal 2: DAD1 B, Sig=232,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	48.785	MM	1.4702	8500.44141	96.36571	67.4625
2	58.604	MM	1.8446	4099.79688	37.04243	32.5375

Totals : 1.26002e4 133.40813

# HPLC Samples run by M. C. McLeod at Nottingham.

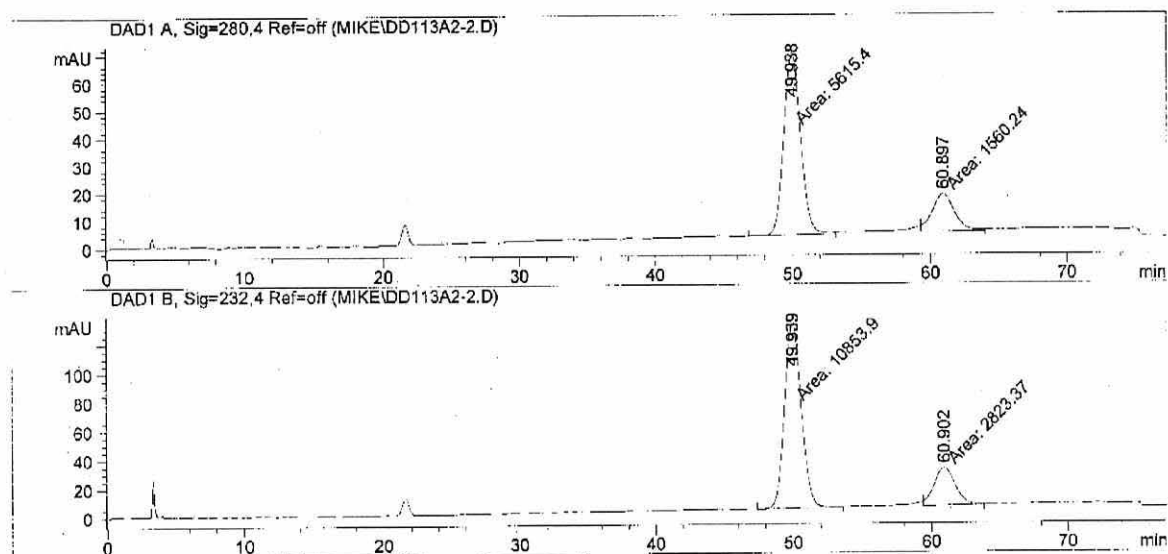
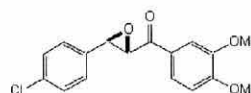
Summary of results:



Data File C:\CHEM32\1\DATA\MIKE\DD113A2-2.D

Sample Name: DD113A2-2

```
=====
Acq. Operator   : Mike
Acq. Instrument : Instrument 1
Injection Date  : 5/12/2009 2:26:53 PM
Acq. Method     : C:\CHEM32\1\METHODS\MIKEC31.M
Last changed    : 5/12/2009 1:52:14 PM by Mike
                  (modified after loading)
Analysis Method : C:\CHEM32\1\DATA\MIKE\DD113A2-2.D\DA.M (MIKEC31.M)
Last changed    : 5/12/2009 3:44:36 PM by Mike
Sample Info     : Chiralpak AD + guard
                  90: 10 Hexane: EtOH
                  1 ml/min, 19 bar
=====
```



Signal 1: DAD1 A, Sig=280.4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	49.938	MM	1.4116	5615.39746	66.29998	78.2564
2	60.897	FM	1.8921	1560.24438	13.74330	21.7436

Totals : 7175.64185 80.04328

Signal 2: DAD1 B, Sig=232.4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	49.939	MM	1.4000	1.08539e4	129.21025	79.3572
2	60.902	FM	1.7838	2823.36914	26.37985	20.6428

Totals : 1.36772e4 155.59010