Some applications and chemistry of (S)-2-(diphenylmethyl)-pyrrolidine

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and

Chemistry

of

(S)-2-(Diphenylmethyl)-Pyrrolidine

A thesis submitted to University of Durham for the degree of Master of Science

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Abstract

The synthetic utility of (S)-2-(diphenylmethyl)-pyrrolidine (**1**) and its amide derivative, (S)-2-(diphenylmethyl)-5-oxo-pyrrolidine (**2**) were examined in two contexts; as chiral auxiliary compounds in asymmetric alkylation reactions and Diels-Alder reactions; as chiral solvating agents (CSAs) for ^{1}H NMR evaluation of chiral acids and alcohols.

In the former case, it was shown that monoalkylation of N-acyl derivatives of (**1**) and (**2**) using lithiated bases led to poor diastereoselectivities (1:1 to 1.12:1) and poor yields (28 to 33 %), while alkylation reactions using HMPA proceeded with modest diastereoselectivities (1.49:1 to 4.25:1). The results of the Diels-Alder study remain premature at present.

In the latter case, (**1**) was an excellent chiral solvating agent (CSA) for chiral carboxylic acids, however it was less effective for chiral alcohols. The amide derivative (**2**) was substantially less effective as a CSA for chiral carboxylic acids and failed completely to resolve chiral alcohols.

Acknowledgement

I would like to thank my supervisor, Dr. David O'Hagan, for his unlimited support, encouragement, and help throughout this work. Otherwise, it would have been so difficult for me to do this work and write this thesis in a foreign language.

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CHAPTER 1

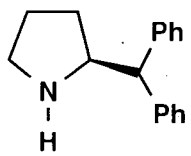
INTRODUCTION

Part 1

1.A. General Introduction

The handedness of a molecule is increasingly acknowledged as an important factor in the development of new organic compounds, particularly in the formulation of new drugs, since both beneficial and detrimental characteristics co-exists in the differently handed forms[1]. Therefore, one of the major objectives in organic synthesis has been the development of general strategies for stereoselective bond construction. In this respect, carbon-carbon bond forming reactions, where chiral molecules are produced in high purity[2], has been a primary focus of activity for many of the leading researchers in academia and the pharmaceutical and fine chemical industries[3].

In this research programme the novel auxiliaries, (S)-2-(diphenylmethyl)-pyrrolidine (**1**) and its amide derivative (S)-2-(diphenylmethyl)-5-oxo-pyrrolidine (**2**) are explored to extend the range of chiral pyrrolidines already reported. An efficient route to (**1**) is exploited and a new route to (**2**) is developed. These auxiliaries have been used to explore asymmetric alkylation and Diels-Alder reactions, and have been tested as chiral solvating agents for NMR analysis. At the outset, it is appropriate to review the current status of chiral pyrrolidines in asymmetric synthesis.



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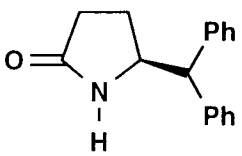

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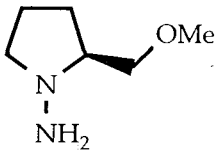
1.B. Chiral Pyrrolidine Auxiliaries

Starting in 1975, enantioselective control of the C-C bond forming process was carried out by transferring chirality to an achiral starting material *via* either (S)- or (R)-1-(amino)-2-(methoxymethyl)-pyrrolidine[4-6] (**3**) or (**4**). These chiral auxiliaries are shown in **Fig. 1.**



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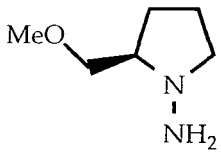
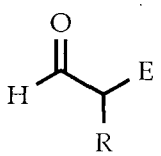


4

Fig. 1

This methodology[7,8], which involves a three-step process, opened up an elegant and economical entry into a variety of important classes of compound with good overall chemical yields and excellent diastereo- and enantio- selectivities. The following stereoselective reactions are relevant: α-alkylation of aldehydes[9] (**5**), ketones[10] (**6**), and ß-keto esters[7] (**7**); diastereo- and enantio- selective aldol reactions[7] (**8**) and (**9**). These are summarised in **Fig. 2**.



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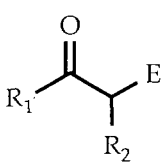

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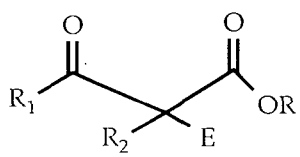

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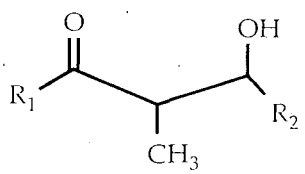

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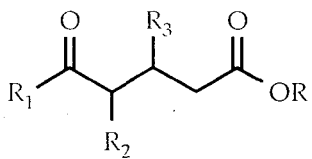
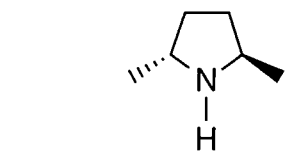


9

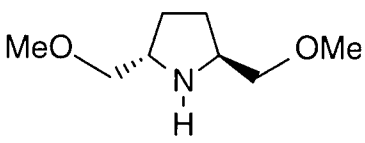
Fig. 2

Additionally C_2-symmetric pyrrolidines have attracted attention as chiral auxiliaries[11], and for instance the 2,5-disubstituted pyrrolidines **(10-12)** are widely recognised as promising chiral auxiliaries for asymmetric synthesis[12].

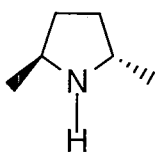
Notable examples include (2R,5R)-2,5-dimethylpyrrolidine[13,14] **(10a)**, and (2S,5S)-2,5-dimethylpyrrolidine[15,16] **(10b)**, (2R,5R)-2,5-bis-(methoxymethyl)-pyrrolidine **(11a)** and (2S,5S)-2,5-bis-(methoxymethyl)-pyrrolidine[12,17] **(11b)**, (2R,5R)-bis-(methoxymethoxymethyl)-pyrrolidine **(12a)** and (2S,5S)-bis-(methoxymethoxy-methyl)-pyrrolidine[12] **(12b)**, the structures of which are shown in **Fig. 3**.



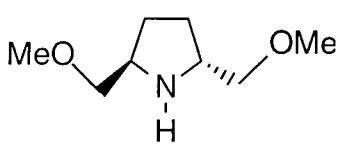
10a



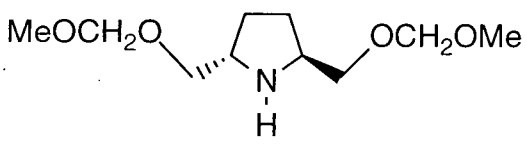
11a



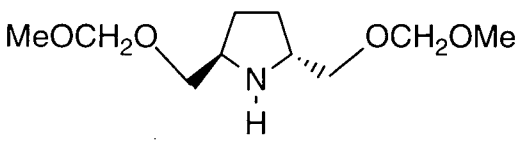
10b



11b



12a

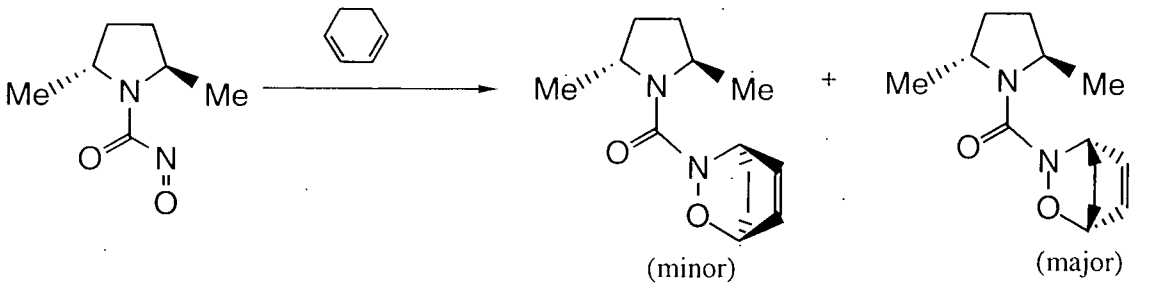


12b

Fig. 3

trans-2,5-Dimethylpyrrolidines[15,16] **(10a)** and **(10b)** are the structurally simplest members of this family of auxiliaries and they have been frequently employed as chiral auxiliaries in enantioselective reactions. The following are some examples: *trans*-2,5-Dimethylpyrrolidine-N-carbamoylnitroso dienophile[18] **(13)** reacts in good yield (81 %) with cyclohexadiene to give the major cycloadduct **(14)** and its minor

diastereoisomer **(15)** with excellent diastereoisomeric excess (ca. 98 % de). **Scheme 1**.



13 **14** **15**

Scheme 1

Intermolecular radical alkyl additions to amide-substituted alkenes[19] **(S)-16** and **(S)-17**, both derived from 2,5-(dimethyl)-pyrrolidine **(10b)**, were also successfully carried out, **Fig.4**.

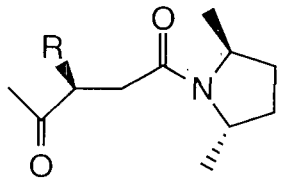
(S)-16 **(S)-17**

Fig. 4

The four products **(18-21)**, shown in **Fig. 5**, were formed as a result of the addition to **(S)-16** of hexyl, cyclohexyl, and tert-butyl radicals.

18 **19**

Fig. 5 continued



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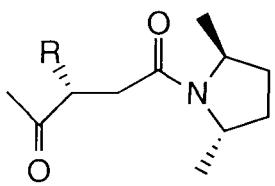
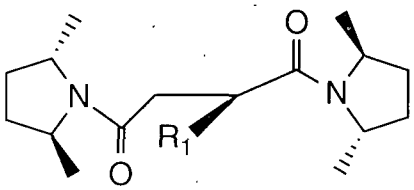


21

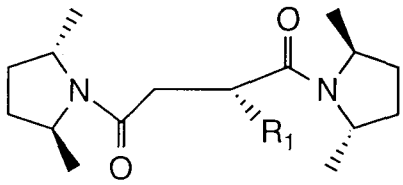
R= n-hexyl, cyclohexyl, t-butyl

Fig. 5

Two stereoisomeric products **(S)-22** and **(S)-23** resulted from the addition of the tert-butyl radical to **(S)-17**, as depicted in **Fig. 6**.



(S)-22



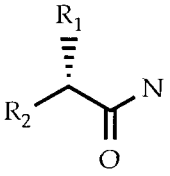
(S)-23

R_1= t-butyl

Fig. 6

Optically active 2,5-*bis*-(methoxymethyl)- and 2,5-*bis*-(methoxymethoxy-methyl)pyrrolidines[12] **(11)** and **(12)** proved effective in a wide variety of applications due to their chelating capability as well as their C_2-symmetry.

The products obtained from monoalkylation[20] **(24)**, double alkylation[21] **(25)**, acylation[22] **(26)** and aldol[23] **(27)** reactions clearly indicates the effectiveness of **(12a)**, when developed as a chiral auxiliary in various situations. [2, 3]–Witting rearangement product[24] **(28)** can also be added to the above catagory. These products **(24-28)** are shown in **Fig. 7**.



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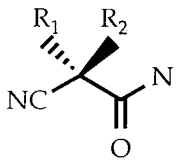

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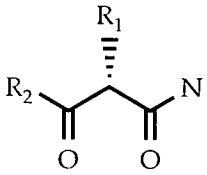

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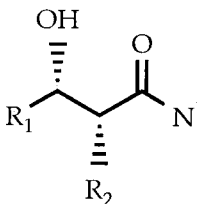

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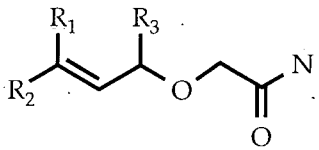

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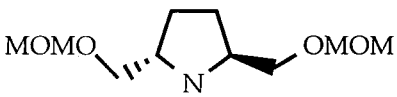
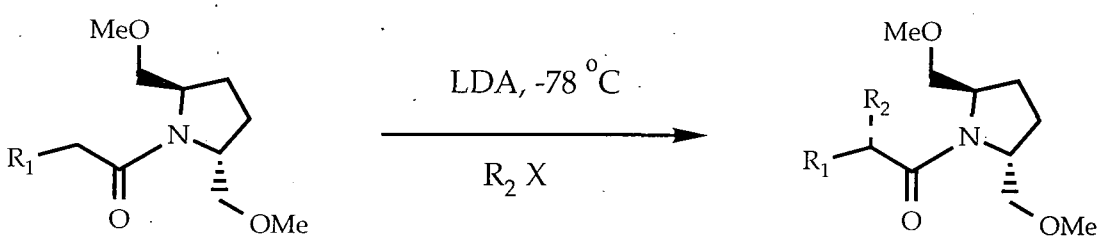


12a

Fig. 7

The following studies are relevant to the use of 2,5-bis-(methoxymethyl)-pyrrolidine (**11b**): The amides[20] (**29**), derived from optically active (**11b**), react in good chemical yields with a variety of combinations of alkyl halides to yield the corresponding alkylation products (**30**) with invariably over 95%de, as shown in **Scheme 2**.



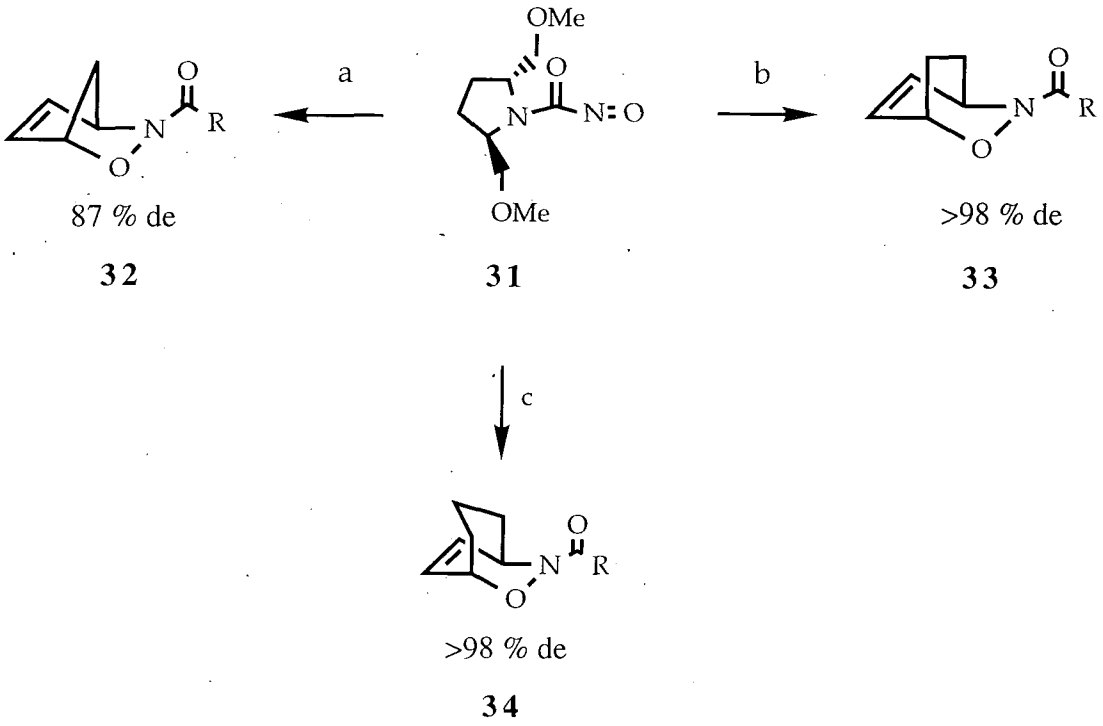
29 **30**

R_1: Me, Et, Bu, Bn.

R_2: Me, Et, Bn, Allyl.

Scheme 2

A carbamoylnitroso compound[25] (**31**), derived from the disubstituted pyrrolidine (**11b**) reacts efficiently with cyclopentadiene, cyclohexadiene and cycloheptadiene to yield the expected Diels-Alder cycloadducts (**32**), (**33**), and (**34**) respectively with excellent diastereoisomeric excess, as illustrated in **Scheme 3**.



a: cyclopentadiene b: cyclohexadiene c: cycloheptadiene

Scheme 3

Thus, the effectiveness of these C_2 symmetric pyrrolidines, derived from amines and amides, have been thoroughly documented in many asymmetric synthetic applications[26].

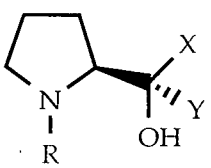
Many methodologies[27] for asymmetric synthesis have been reported and these all involve two essential steps. Transfer of chirality by activation of electronic or steric effects induced by the auxiliary, and then fission of the product-auxiliary adduct to release the product and recover the chiral auxiliary.

1.C. Chiral Amine Ligands

Design of a variety of chiral amine ligands for enantioselective reactions has been an important goal in chemical synthesis[28]. There are many reports of promising enantioselectivity achieved with various chiral amines[29]. For example enantiomerically pure diamines have found widespread use and vicinal diamines having C_2-symmetry have proved especially useful in asymmetric reactions[30]. Therefore the design and synthesis of novel chiral diamines and their application to enantioselective reactions presents a focused challenge of substantial international interest[31a].

Such chiral amine ligands include **(35)-(40)** shown in **Fig. 8**, and some of their applications in enantioselective reactions are discussed. In particular the stereoselective 1,2-addition of Grignard reagents to aldehydes and the enantioselective dihydroxylation of olefins by OsO_4, in the presence of chiral amines **(35)-(40)**, is reviewed.

Soai *et. al.*



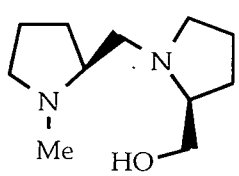
35

a:R= Me, X=Y= Ph

b:R= Me, X=Ph, Y= H

c:R= neo-pentyl, X= Ph, Y= H

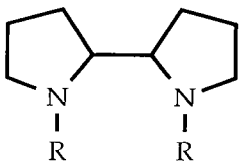
Mukaiyama *et al.*



36

Fig. 8 continued

Hirama *et al.*

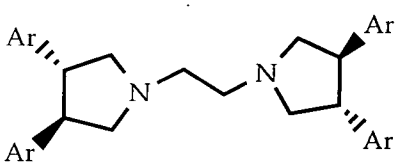


37

a: pentyl

b: neohexyl

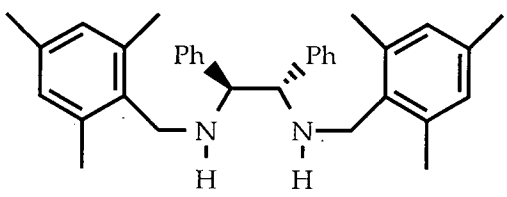
Tomika *et. al.*



38

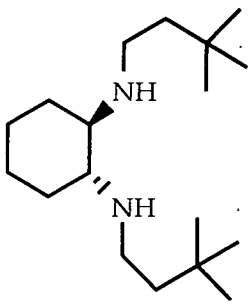
a:Ar= Ph, b:Ar= 3,5-xylyl

Corey *et al.*



39

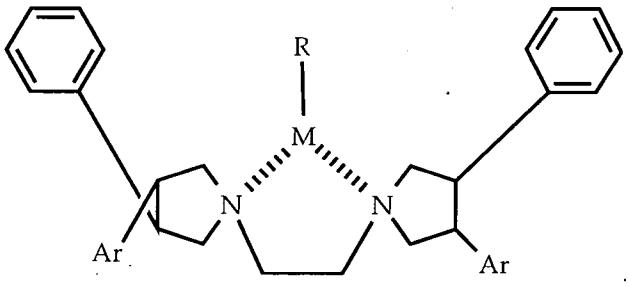
Hanessian *et al.*



40

Fig. 8

Tomika[28] developed an asymmetric environment around a metal chelated with the diamine (**38**) as shown in **Fig. 9**. The bulky aryl groups provided a chiral environment with C_2-symmetry. These metal-coordinated chiral diamines have been widely utilised in the stereocontrol of organo-metallic reactions due to a well-defined asymmetric environment constructed with chiral auxiliaries.



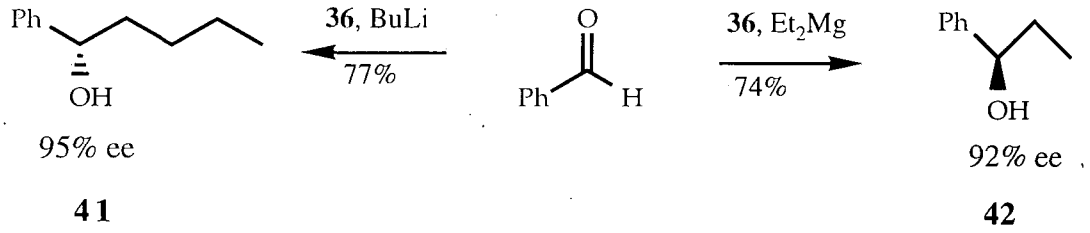
M= Metal

Fig. 9

In order to create the chiral environment, two C_2-symmetric 2,5-disubstituted pyrrolidines were linked together by an ethane linkage *via* the nitrogen atom. This type of auxiliary forms a bidentated metal complexes and provides a well-defined chiral environment around the metal centre[28].

The addition of Grignard reagents to aldehydes in the presence of chiral ligands affords optically active secondary alcohols[32a]. Organo- lithium and magnesium reagents are the most reliable organometallics for 1,2-addition to aldehydes. However organo-zinc or titanium compounds with other asymmetric ligands have also been employed successfully[31b]. In this area of stoichiometric asymmetric catalysis the three most successful methods[32a] have been described by Cram *et al.*, Mukaiyama *et al.* and Seebach *et al.* Recently, several groups have also reported promising enantioselectivity using the amine ligands **(35)**[33], **(36)**[32b], and **(38)**[31a,31b].

For instance, Mukaiyama *et al.* reported the highly enantioselective addition of alkyllithium and dialkylmagnesium to aldehydes in the presence of a lithium salt of the chiral diamine alcohol **(36)**. (S)-1-Phenylpentanol **(41)** with 95% ee and (R)-1-phenylpropanol **(42)** with 92% ee were obtained from the enantioselective addition of butyllithium and diethylmagnesium, respectively, to benzaldehyde[32b], **Scheme 4**.



Scheme 4

Soai[33] *et al.* also reported dialkylzinc reactions with aldehydes using pyrrolidinylmethanols (**35a**), (**35b**), and (**35c**). Optically active alcohols were obtained with up to 100% ee. Some of these results with diethylzinc are summarised in **Table 1**.

Entry	aldehyde	Chiral Ligand	Yield, %	ee, %
1	benzaldehyde	**35a**	100	90(S)
2	benzaldehyde	**35b**	100	72(R)
3	benzaldehyde	**35c**	100	100(R)
4	3-phenylpropanal	**35a**	100	92(S)
5	3-phenylpropanal	**35b**	100	57(R)
6	3-phenylpropanal	**35c**	100	86(R)

Table 1. Diethylzinc reactions with aldehydes using the amine (**35**).

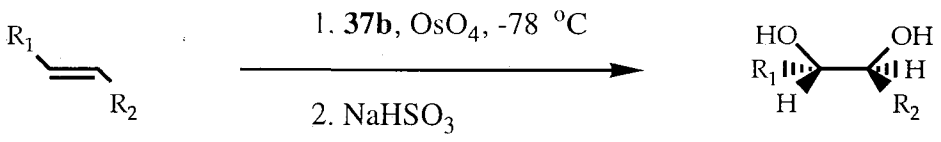
Nakajima[31b] *et al.* have examined 1,2-additions of arylmagnesium bromides to various aldehydes at -100 °C in toluene using the diamine (**38a**) and (**38b**). Both diamines mediated the enantioselective addition of phenylmagnesium bromide to various

aldehydes and the selectivities correlate with the bulkiness of the aldehyde substituent as shown in **Table 2**.

Entry	Chiral Ligand	R in RCHO	Yield, %	ee %, config.
1	**38a**	butyl	73	38, (S)
2	**38a**	isopropyl	68	47, (S)
3	**38a**	hexyl	76	45, (S)
4	**38b**	butyl	87	36, (S)
5	**38b**	isopropyl	90	42, (S)
6	**38b**	hexyl	68	55, (S)

Table 2. Asymmetric 1,2-addition of phenylmagnesium bromide to aldeheydes employing the diamine (**38**).

Over the past decade there have been several reported protocols for the conversion of *trans* and certain *cis* olefins into the corresponding enantiomerically pure or enriched diols, using osmiumtetraoxide in the presence of chiral amine ligand[34]. The following are relevant studies. Although the diamine (**37a**) was found to be a good ligand for asymmetric osmylation of (E)-disubstituted alkenes[35], after considerable effort N,N'-di-neohexyl-2,2'-bipyrrolidine (**37b**) was reported as a chiral ligand[36] superior to (**37a**), which gave excellent enantioselectivities in the OsO_4 oxidation of various olefins at -78 °C as shown in **Table 3**.



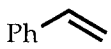
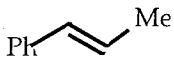
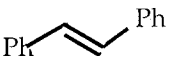
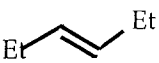
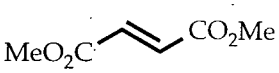
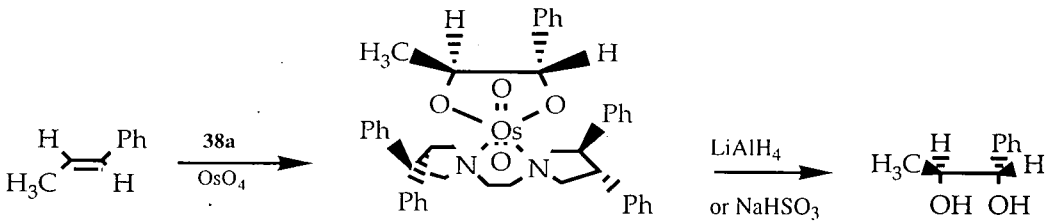
entry	olefin	solvent	% yield	% ee	configuration
1		toluene	90	88	(S)-
2		toluene	95	92	(S, S)-
3		DCM	87	56	(S, S)-
		toluene	96	100	
4		DCM	82	96	(S, S)-
5		DCM	79	98	(R, R)-

Table 3. Enantioselective hydroxylation of olefins with OsO_4 in the presence of (**37b**).

With the use of the D_2-symmetric chiral diamine[37] (**38a**), which consists of two *trans*-3,4-diphenylpyrrolidine units with C_2-symmetry at both ends of the ethylene chain, exceptionally high optical yields were recorded in the production of diols from the dihydroxylation of mono-, *trans*-di, and trisubstituted olefins with OsO4. A typical procedure is exemplified in the reaction of *trans*-1-phenylpropene, **Scheme 5**, and additional examples are given in **Table 4**.



Scheme 5

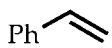
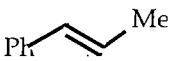
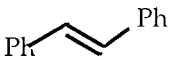
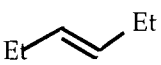
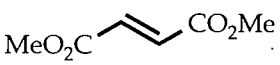
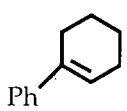
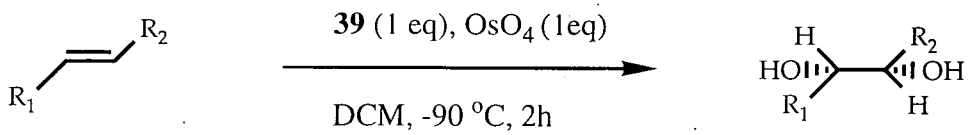
entry	olefin	% yield	% ee	configuration
1		71	90	(S)-
2		73	99	(S, S)-
3		85	97	(S, S)-
4		80	90	(S, S)-
5		67	93	(R, R)-
6		83	83	(S, S)-

Table 4. Enantioselective hydroxylation of olefins with OsO_4 in the presence of (**38a**).

Corey[38] *et al.* have described a system for the enantioselective hydroxylation of *E*-olefins by using the 1:1 mixture of ligand (**39**) and osmium tetraoxide to provide vicinal diols. The system, which occurs in the sense expressed by **Scheme 6**, was unsurpassed in terms of enantioselectivity, ready availability, and recovery of both the

chiral controller ligand and osmium till the discovery of the simplest chiral ligand **(40)** by Hanessian. The results are summarised in **Table 5**.



Scheme 6

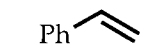
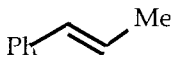
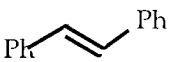
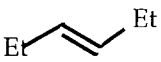
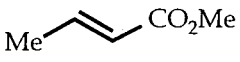
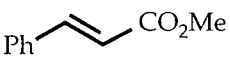
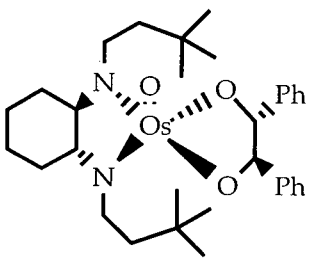
entry	olefin	% yield	% ee	configuration
1		81	92	(S)-
2		95	93	(S, S)-
3		95	92	(S, S)-
4		90	98	(S, S)-
5		82	97	(2R, 3S)-
6		83	92	(2R, 3S)-

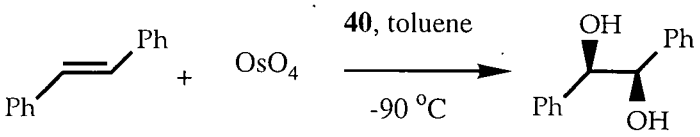
Table 5. Enantioselective hydroxylation of olefins with OsO_4 in the presence of **(39)**.

Hanessian[34] *et al.* demonstrated that the ligand **(40)** or its enantiomer, derived from *trans*-1,2-diaminocyclohexene, is highly effective in the asymmetric *cis*-dihydroxylation of a variety of aromatic and aliphatic olefins under stoichiometric

conditions as shown in **Table 6**. It is noteworthy that the crystalline intermediate (**43**) was observed and isolated for the first time from the reaction of stilbene, **Scheme 7**, suggesting that this osmate ester is readily formed[34].



43



Scheme 7

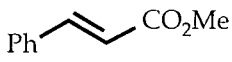
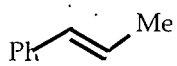
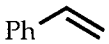
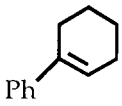
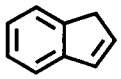
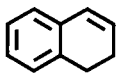
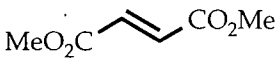
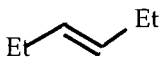
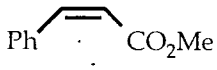
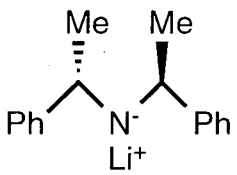
entry	olefin	% yield	% ee	configuration
1		80	99	(2S, 3R)-
2		82	95	(1R, 2R)-
3		70	99	(R)-
4		84	90	(R, R)-
5		70	80	(1R, 2S)-
6		73	70	(1R, 2S)-
7		67	96	(S, S)-
8		78	90	(R, R)-
9		60	87	(2R, 3R)-
10		80	77	(1R, 2S)-

Table 6. Enantioselective hydroxylation of olefins with OsO_4 using (**40**) or its enantiomer.

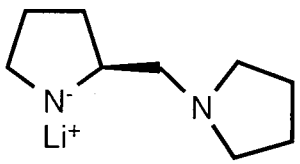
1.D. Homochiral Lithium Amines (HCLAs) as Bases

The use of chiral bases, which function as both a strong base and a chiral auxiliary, has attracted considerable attention in connection with recent progress in stereocontrolled organic synthesis[39]. Although lithium amines have established an important position in organic synthesis and are widely used as strong bases with low nucleophilicity, their homochiral analogues have come into focus more recently as potential stereoselective bases[40]. To date, there have been several reports describing novel asymmetric transformations with homochiral lithium amine (HCLA) bases[41,42].

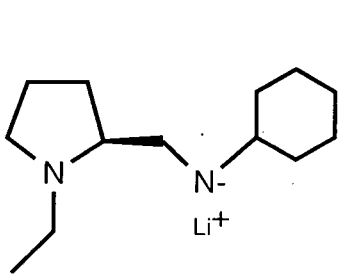
Notable HCLA bases include lithium *(S,S)*-N,N-*bis*(1-phenylethyl)amine[43] (**44**), lithium *(S)*-2-(1-pyrrolidinymethyl)pyrrolidide[44-46] (**45**), lithium cyclohexyl-[*(S)*-1-ethyl-pyrrolidine-2-yl]methylamine[45] (**46**), and chiral lithium amine[47-49] (**47**), as depicted in **Fig. 11.**



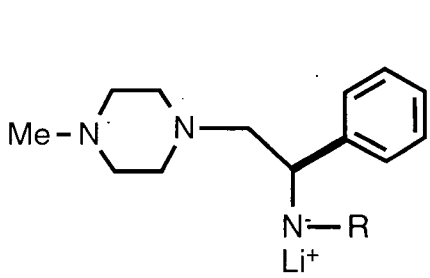
44



45



46



47

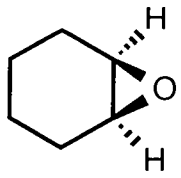
a-) R= i-Pr, **b-**) R= neopentyl

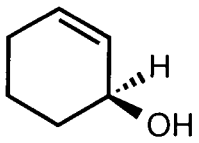
Fig. 11

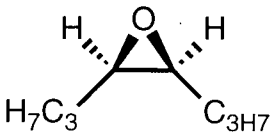
Interests in this area have focused primarily on two asymmetric reactions; the enantioselective asymmetric transformation of symmetrical epoxides to chiral allylic alcohols[43-45] and the conversion of cyclic ketones into optically active products[41,42,48,50]. Other transformations, which have been of more peripheral focus, include the kinetic resolution of both symmetric epoxides[46] and cyclic ketones[41,49]. These reactions will be discussed briefly.

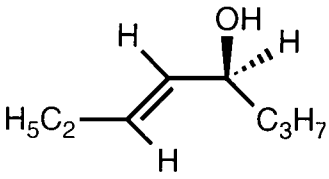
The generation of enantiomerically enriched compounds from asymmetric precursors is attractive[45]. The first example of such a reaction was reported by Whitesell and Felman[43] for the rearrangement of cyclohexene oxide to the corresponding allylic alcohol using a range of mono- and di- alkyllithium amine bases. The highest level of asymmetric induction (31% ee) was observed with the amine **(44),** as depicted in **Entry 1**.

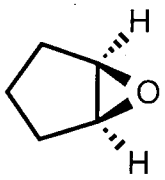
Later work on the asymmetric transformation of cyclohexene oxide was carried out by Asami[44] with the amine **(45)**. It was found when the transformation was carried out in THF as solvent, then **(45)** gave the highest selectivity (92% ee) for cyclohexene oxide, as shown in **Entry 2**. The reaction was further extended to other symmetrical epoxides. Asami[45] also developed a new and efficient HCLA base **(46)**, which shows the opposite selectivity to **(45)**, thus both enantiomers of several optically active allylic alcohols are obtainable from their corresponding symmetrical epoxides, as illustrated in **Entry 4-7**. Epoxide rearrangements using HCLA bases **(44)**, **(45)**, and **(46)** are shown in **Scheme 8** and the results are summarised in **Table 7.**

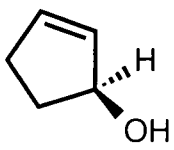
1. 

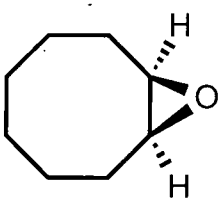
1. **(44)**, or **(45)**, or **(46)**
2. H_3O^+


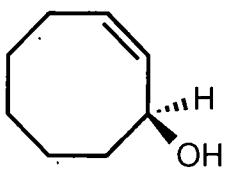
2. 

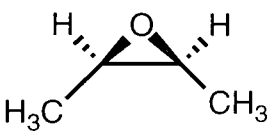
1. **(45)** or **(46)**
2. H_3O^+


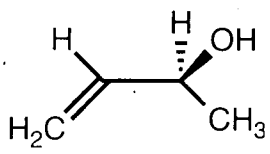
3. 

1. **(45)** or **(46)**
2. H_3O^+


4. 

1. **(45)** or **(46)**
2. H_3O^+


5. 

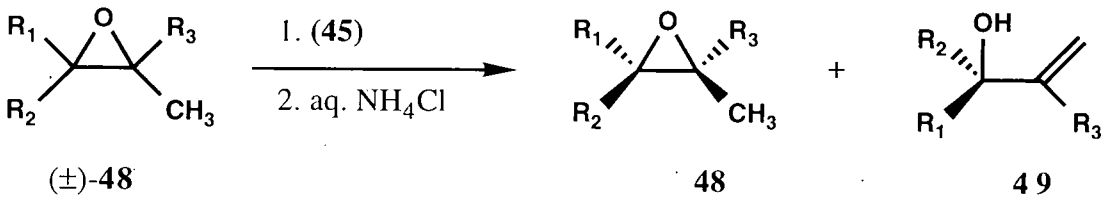
1. **(45)** or **(46)**
2. H_3O^+


Scheme 8

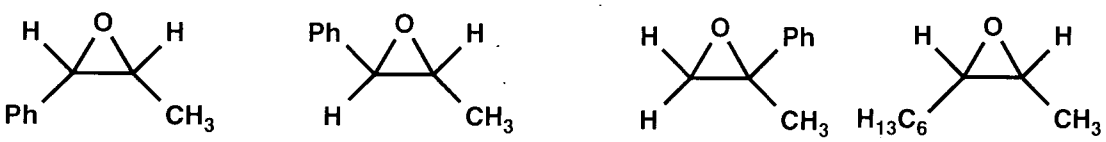
Entry	Reaction	Base	Yield (%)	ee (%), config.
1	1	**44**	65	31, (R)
2	1	**45**	77	92, (S)
3	1	**46**	80	78, (R)
4	2	**45**	66	60, (S)
		46	66	59, (R)
5	3	**45**	49	31, (S)
		46	48	15, (R)
6	4	**45**	45	58, (S)
		46	56	42, (R)
7	5	**45**	60	70, (S)
		46	58	62, (R)

Table 7. Asymmetric transformation of symmetrical epoxides to allylic alcohols using HCLA bases (**44**), (**45**), and (**46**).

In addition to providing optically active products with moderate to high selectivities from acyclic symmetrical epoxides as well as cyclic ones, HCLA bases have been used to generate optically active materials from a kinetic resolution of racemic epoxides[51]. For example, the kinetic resolution of (±)-*cis*-1-phenyl-1,2-epoxypropane (**48a**), (±)-*trans*-1-phenyl-1,2-epoxypropane (**48b**), (±)-2-phenyl-1,2-epoxypropane (**48c**) and (±)-cis-2,3-epoxynonane (**48d**) by the use of chiral lithium amide (**45**) may be given as an example[46], **Scheme 9**. As shown in **Table 8**, chiral lithium amide (**45**) showed high enantiomeric discrimination for *cis*-disubstituted epoxides, while moderate selectivity was observed for *trans*-disubstituted epoxide and terminal epoxide[46].



(±)-48 48 49



48a 48b 48c 48d

Scheme 9

entry	epoxide	base/(±)-(48)	yield (%) for (48)	ee(%) for (48), config.
1	**48a**	3:4	31	95, (1S,2R)
		1:3	67	30, (1S,2R)
2	**48b**	3:4	27	45, (1S,2S)
		1:3	67	11, (1S,2S)
3	**48c**	3:4	11	39, (R)
4	**48d**	3:4	29	95, (2S,3R
		1:3	66	25, (2S,3R)

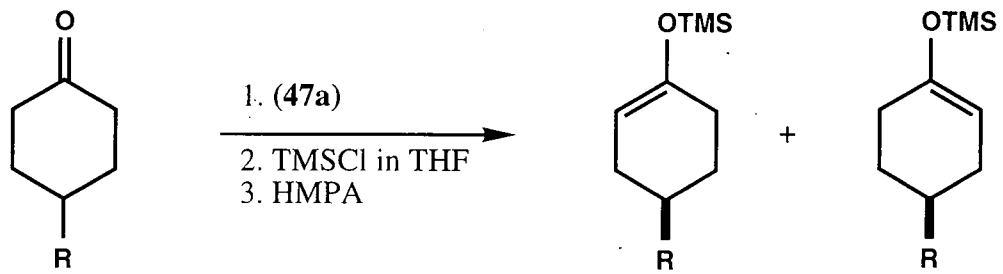
Table 8. Kinetic resolution of epoxides (**48a-d**) with HCLA base (**45**).

The versatility of optically active ketones as chiral synthons in organic synthesis makes their efficient preparations very attractive[49]. Highly selective transformations of enantiotopic groups in prochiral or *meso* compounds are well-known in enzymatic process. Chemical approaches have also been made mainly by diastereoselective

methods. However, enantioselective methods are still limited[47].

The enantioselective deprotonation of prochiral 4-alkyl-cyclohexanones[47] **(50a-c)** and *meso*-3,5-dimethyl-cyclohexanones[48] **(52a-b)** by the use of the chiral amines **(47a)** and **(47b)** are two illustrative examples. In the presence of *in situ* trimethylsilyl chloride (TMSCl), **(50a-c)** and **(52a-b)** gave the corresponding optically active trimethylsilyl enol ethers **(51a-c)** and **(53a-b)** respectively in good enantiomeric excesses (50-97 % ee). The reactions occur as depicted in **Scheme 10** and the results are summarised in **Table 9**.

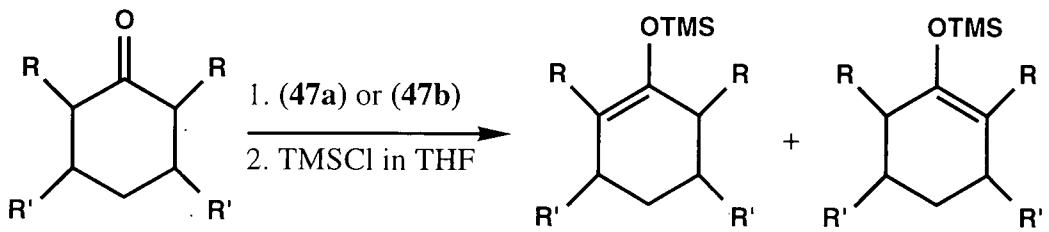
6.



50 **(S)-51** **(R)-51**

R= **a-**) t-butyl, **b-**) i-Pr, **c-**) Me

7.



52 **53** **53**

a:R= Me, R'= H **(S)-53a** **(R)-53a**

b:R= H, R'= Me **(3R,5S)-53b** **(3S,5R)-53b**

Scheme 10

Entry	Base	Ketone	Silyl enol ether	Yield(%)	ee(%)
1	**47a**	**50a**	**(R)-51a**	51	97
2	**47a**	**50b**	**(R)-51b**	85	66
3	**47a**	**50c**	**(R)-51c**	68	50
4	**47a**	**52a**	**(S)-53a**	89	89
5	**47b**	**52a**	**(S)-53a**	73	96
6	**47a**	**52b**	**(3S,5R)-53b**	69	64
7	**47b**	**52b**	**(3S,5R)-53b**	88	90

Table 9. Enantioselective deprotonation of **(50a-c)** and **(52a-b)** using the amines **(47a)** and **(47b)**.

Common to all of these amines is the ability to form a five-membered metal chelate as shown in **Fig 12**, where the nitrogen lone pair has a fixed orientation relative to the sterically bulky groups present and can be used for deprotonation. The generally high levels of asymmetric induction achieved with such bases might be due to this stable conformation, and possibly less to base aggregation[51], as has been suggested.

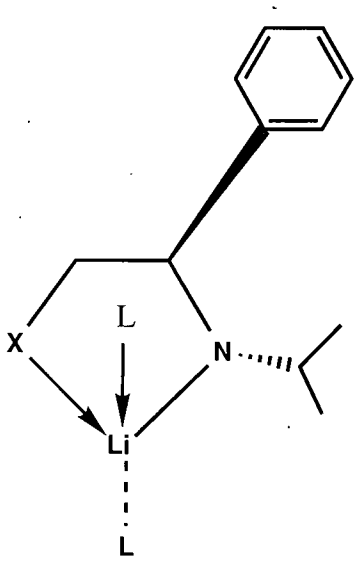
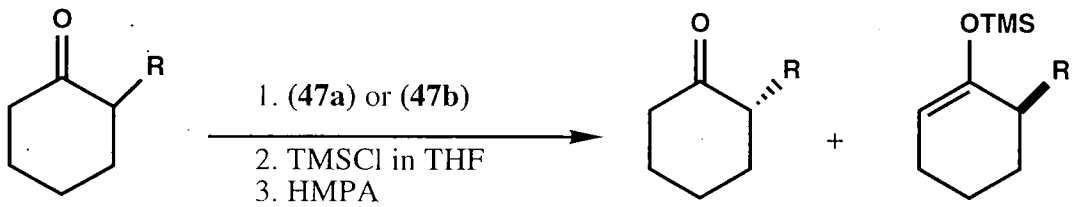


Fig. 12

In addition to providing optically active products from prochiral ketones, HCLA bases have been used to generate optically active materials *via* a kinetic resolution process[51]. An example of this may be found in the kinetic resolution of racemic 2-substituted cyclohexanones[49] (**54a-c**) with the amines (**47a-b**) in the presence of TMSCl to give their corresponding trimethylsilyl enol ethers (**55a-c**), and the unreacted ketones (**54a-c**). The stereochemical course of the reaction can be generalised as depicted in **Scheme 11** and the results obtained in the study are summarised in **Table 10.**



(±)-**54** (S)-**54a-c** (R)-**55a-c**

R= **a-**) t-Bu, **b-**) Ph, **c-**) i-Pr

Scheme 11

Entry	Starting Ketone	Base	Recovered Ketone	Yield(%)	ee(%)	Silyl Enol Ether, (%ee)
1	(±)-**54a**	**47a**	**(S)-54a**	53	27	**(R)-55a**, 37
2	(±)-**54a**	**47b**	**(S)-54a**	45	90	**(R)-55a**, 94
3	(±)-**54b**	**47b**	**(S)-54b**	24	94	**(R)-55b**, 94
4	(±)-**54c**	**47b**	**(S)-54c**	-	18	**(R)-55c**, 94

Table 10. Kinetic resolution of 2-substituted-cyclohexanones **(54a-c)** using the amines **(47a)** and **(47b)**.

Although structurally straightforward lithium amines having C_2 symmetry have proved highly effective, the value of additional coordination sites in HCLA bases has been demonstrated. Efforts have been made to combine the features of C_2 symmetry and an additional coordination site to design new chiral base systems of potential utility[30].

1.E. Chiral Amine Resolving Agents

As a result of an increase in sophistication and versatility in target enantiomerically enriched compounds for industry, there is a need for more accurate and versatile methods for determining the enantiomeric purity and absolute configuration of chiral compounds[52]. Over the past decade, several new techniques have been developed for the determination of the enantiomeric purity of chiral compounds. In general, these methods involve the formation of diastereoisomeric complexes or derivatives for analysis by NMR[53].

NMR spectroscopy is one of the most straightforward and most common methods for determining enantiomeric excess[54]. The method relies on the fact that diastereotopic nuclei are, in principle, anisochronous and should have different chemical shifts and different coupling constants[55]. The determination of the enantiomeric purity using NMR therefore requires the use of a homochiral auxiliary that converts the enantiomers into a diastereoisomeric mixture. Provided this generates a large enough chemical shift non-equivalence to give baseline resolution of the appropriate signals, then integration offers a direct measure of diastereoisomeric composition which can then be related to the enantiomeric composition of the original mixture[56].

Three types of chiral auxiliary have been used to discriminate between enantiotopic groups in enantiomeric mixtures[56,57]; chiral lanthanide shift reagents (CLSRs), chiral solvating agents (CSAs) and chiral derivatizing agents (CDAs). In this section chiral amine derivatizing agents and chiral amine solvating agents will be discussed briefly. CDAs form discrete diastereoisomeric complexes which can be diagnostically characterised by NMR analysis[56]. In order that the ratio of diastereomeric derivatives correctly measures the enantiomeric composition of the substrate the following conditions must be met[57].

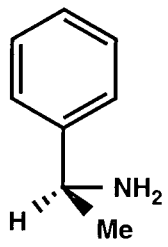
a-) The reagent must be stable to racemization under the conditions of derivatization.

b-) The excess of reagent must be used to avoid from possible kinetic resolution.

c-) There must be no concentration of one diastereoisomer over the other in any purification step.

d-) The reagent must carry an appropriate functional group for NMR signal resolution.

Several chiral amine derivatising agents **(56)-(61)** are depicted in **Fig. 13.**



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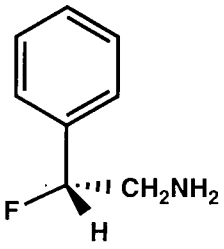

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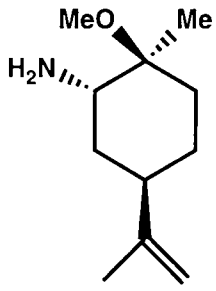

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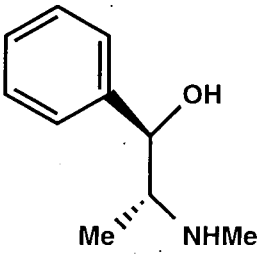

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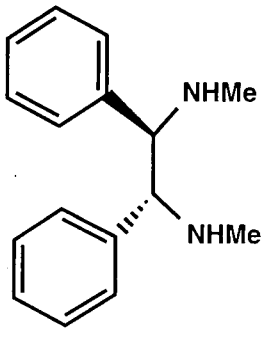

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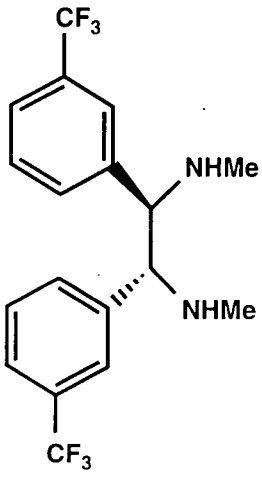
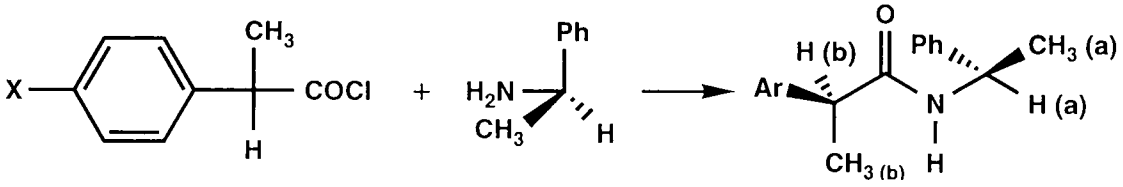
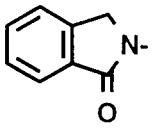


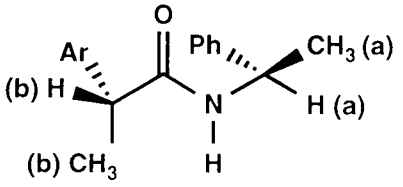
61

Fig. 13

(R)-α-Phenylethylamine[58] (**56**) has been used in the assignment of the absolute configuration of indoprofene (**62**) by exploiting the known configuration of three diastereoisomeric phenylethylamides (**63**), (**64**), and (**65**), as depicted in **Scheme 12**.



Substituent (X):	Amides:
	**62**
H-	**63**
CH_3CONH-	**64**
NH_2-	**65**

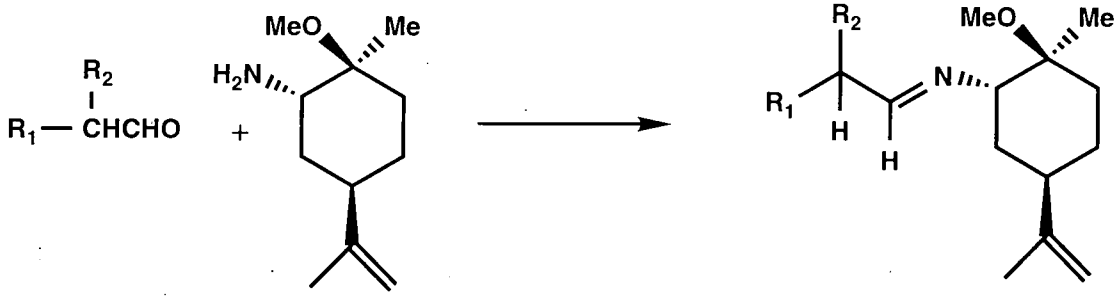


Scheme 12

The characteristic pattern shown by the signals corresponding to CH_3 (a) and H (b) in one diastereoisomer appears in all the four spectra at lower field with respect to the values for the same groups in the alternative diastereoisomer.

2-Fluoro-2-phenyl-1-aminoethane[59] (**57**) has also been used as an effective CDA; amides derived from different chiral acids were distinguished by ^{19}F NMR. It was found that both the H and F atoms give distinct non equivalent chemical shifts for each diastereoisomer when the chiral acid contains a fluorine atom at the stereogenic center. If acids contain -OAc or -OH groups at the chiral center, then F alone gives a distinct chemical shift by ^{19}F NMR. However, H shifts are nearly identical in all cases.

Enantiomeric excess of 2-substituted aldehydes was determined by Meyers[60] and Brich using a simple and reliable method, which involved the straightforward *in situ* formation of a chiral aldimine **(66)** derived from aldehydes and 2-amino-1-methoxymenth-8-ene **(58)** , as shown in **Scheme 13**.

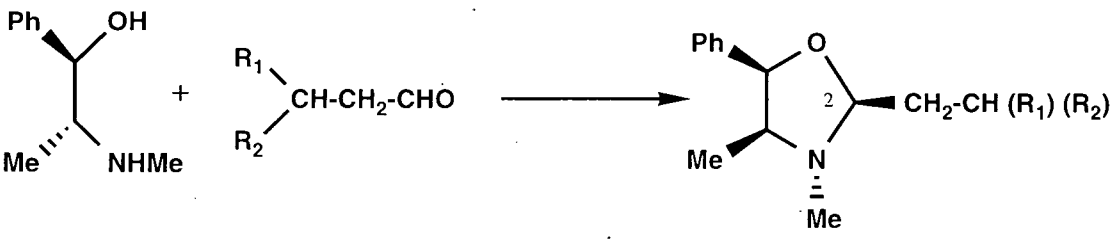


58 **66**

Scheme 13

The observation of a pair doublets originating from the aldimine proton (R-CH=NR) and integration of these signals led to the determination of the enantiomeric purites of aldehydes.

Naturally occuring *(1R,2S)*-ephedrine[61] **(59)** was used to derive oxazolidines **(67)** for the determination of the enantiomeric purity and absolute configuration of 3-substituted aldehydes, as shown in **Scheme 14**.

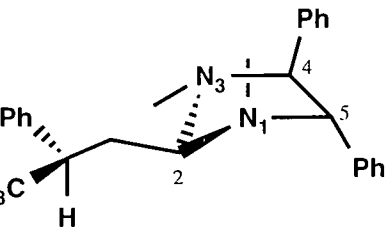


59 **67**

Scheme 14

this study the diastereoisomeric oxazolidines (**67**) were clearly identified by ^{13}C and ^{1}H NMR spectroscopy. The chemical shift of carbon-2 was particularly convenient for easuring the diastereoisomeric ratios and consequently the enantiomeric excesses of e chiral 3-substituted aldehydes. Unlike the ^{13}C NMR method, ^{1}H NMR ectroscopy did not give sufficient resolution for the 3-aryl and 3-alkyl aldehydes.

The enantiomeric purity of aldehydes can be conveniently determined after nverting them into diastereomeric imidazolidines (**68**) and (**69**) by condensation th N,N'-dimethyl-1,2-diphenylethylenediamine[62] (**60**). As illustrated in **Fig. 14**, e more shielded signal for C_4-H or C_5-H belongs to configuration (**68**) because of e bulky phenyl substituent in corresponding aldehyde. For such a configuration the gnal for C_2-H appeared as a pseudo triplet whereas for configuration (**69**) it appears a douplet of doublets. As a result, the diastereomeric imidozolines (**68**) have emical shifts sufficiently different to allow accurate integration of signals for all of the iral aldehydes. Morever the absolute configuration of β-disubstituted aldehydes can deduced from ^{1}H NMR analysis.



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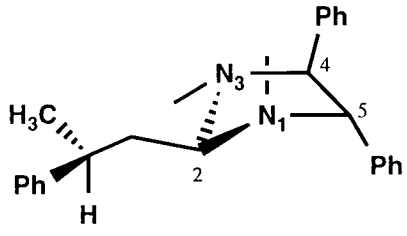


69

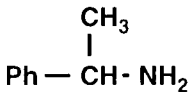
Fig. 14

It was found that this methodology was not always adequate, espicially when e ^{13}C and ^{1}H NMR signals of the aldehyde moiety of the imidazolidine interfere with ose of the diamine unit. Bis-(trifluoromethyl) diamine[63] (**61**), developed to ercome such proplems with aldehydes, is the reagent of choice as it is possible to serve an excellent separation of ^{19}F NMR signals of the diastereoisomers.

In contrast to CDAs which yield stable diastereoisomers as discussed above, CSAs form nonisolable diastereoisomeric complexes that are in fast exchange on the NMR time scale[56]. This phenomenon was proposed by Mislow and Raban, and first experimentally demonstrated by Pirkle[64], stating that enantiomers must be in different average environments when in an optically active chiral solvent[65]. Since that time, several chiral substances have been reported to induce enantiomeric non-equivalence in the NMR spectra of host solutes[64].

Two qualities are essential in the design of CSA-solute combinations[66]. The CSA and the solute should have complementary functionality, which permits their interaction. Both are usually hydrogen bond donors or acceptors such as acids, amines, alcohols, sulfoxides, etc. In nearly every case the CSA contains a group of high diamagnetic anisotropy near its asymmetric centre, a feature that is advantageous in translating the different average spatial environments of solute nuclei into different magnetic environments measurable by the NMR method.

Most widely employed CSAs[64] are 1-phenylethylamine (**70**) and 1-(1-naphthyl)ethylamine (**71**), as shown in **Fig. 15**. Both amines have been used to generate diastereoisomeric complexes of the enantiomers of secondary and tertiary alcohols for NMR analysis[65,68].



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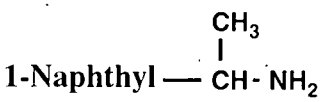


71

Fig. 15

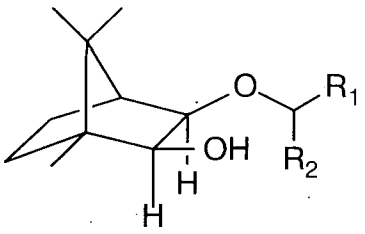
Other chiral amine solvating agents, which have been widely applied for enantiomeric analyses, will be disscussed later.

Part 2

2.A. Asymmetric Diels-Alder Reactions

The efficient construction of enantiomerically pure, structurally complex molecules is a fundamental challenge in organic synthesis. Much of organic chemistry in the last twenty years has focused of methods to induce asymmetry in carbon-carbon bond forming reactions. Among these the Diels-Alder (D-A) reaction merits particular attention. It has been refined to become one of the most powerful tools in organic synthesis since its discovery in 1928. A most attractive feature is the simultaneous, regioselective formation of two bonds leading to the creation of up to four chiral centers, with largely predictable relative stereochemistry[69]. Today, D-A cycloadditions play an ever increasing role in contemporary organic synthesis[70] and they have been widely used as a key step in the synthesis of numerous natural products[71]. Due to the preeminent utility of the D-A reactions in organic synthesis, considerable attention has been given to the exploration of intermolecular asymmetric D-A reactions[72]. Hence, many reports have been published on the preparation of asymmetric alkenes which could be used as useful dienophiles[73].

Asymmetric induction is usually provided by covalently bound auxiliaries, such as the chiral alcohols[74] **(72)**, **(73)**, and **(74)** derived from (S)- and (R)-camphor; the crystalline chiral alcohol[75] **(75)** derived from (+)-camphor-10-sulfonic acid; chiral 2-oxazolidones[76] **(76)** and **(77)**; and (S)-5-(trityloxymethyl)pyrrolidin-2-one[77] **(78)**, as shown in **Fig. 16**.



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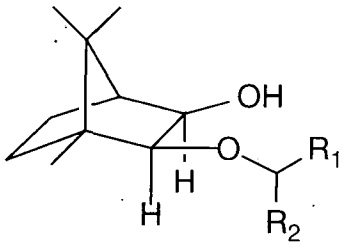
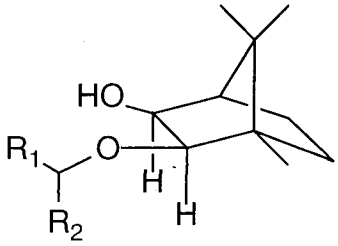


73

a-) R_1= t-Bu, R_2= H **b-)** R_1 and R_2 = Ph



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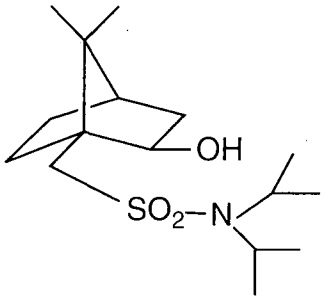
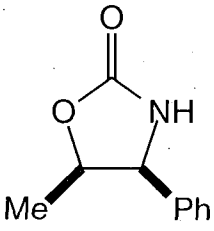


75

a-) R_1= t-Bu, R_2= H

b-) R_1 and R_2 = Ph



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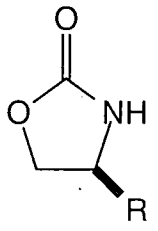

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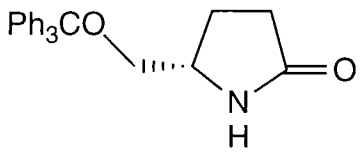


78

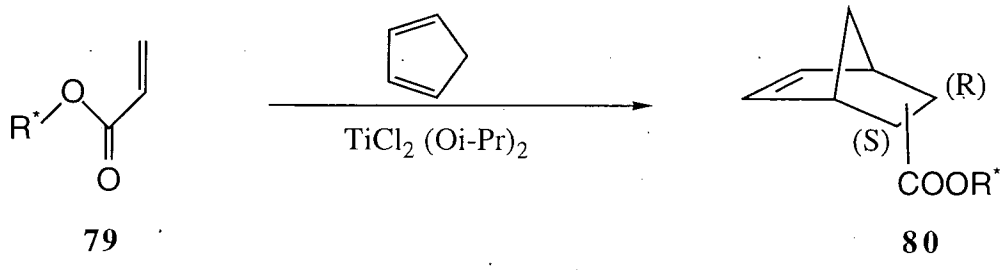
a-) R= i-Pr

b-) R= Bn

Fig. 16

Despite encouraging progress in asymmetric D-A cycloadditions, employing either chiral dienophiles, dienes or Lewis acid catalysts, there is significant scope for improvement[74,78]. Recently, considerable progress has been achieved in accomplishing π-face-stereodifferentiated Diels-Alder additions of prochiral 1,3-dienes to dienophiles which carry a removable chiral auxiliary[69,76].

Oppolzer[74] *et al.* have carried out $TiCl_2(OR)_2$-promoted D-A additions to cyclopentadiene with the acrylates (**79**) prepared from the chiral alcohols (**72**), (**73**), and (**74**), as shown in **Scheme 15**.



79 **80**

R* equal to the chiral alcohols (**72**), (**73**), and (**74**).

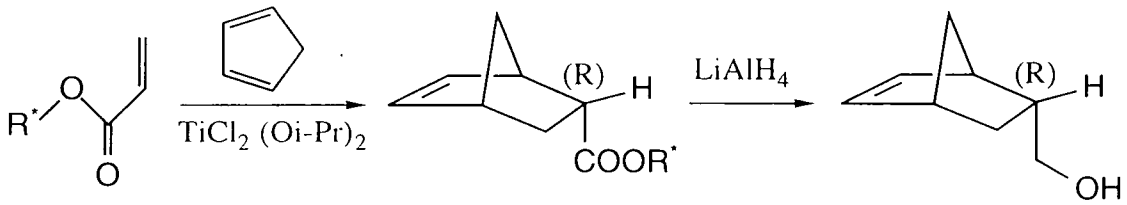
Scheme 15

Such reaction furnished either the (2R)- or the (2S)-cycloadducts (**80**), with up to virtually quantitative asymmetric induction and it was also found that the neopentyl ethers (**72a**), (**73a**) and (**74a**) demonstrate an asymmetric induction ability dramatically superior to the other examples studied to date. These results are summarised in **Table 11**.

Entry	Auxiliary alcohol (R*)	Yield, %	Endo-Adduct d.e.%., config.	endo:exo
1	**72a**	95	97, (S)	96:4
2	**72b**	94	72, (S)	90:10
3	**73a**	96	99.3, (R)	96:4
4	**73b**	74	91, (R)	95:5
5	**74a**	98	99.3, (S)	95:5

Table 11. The assymmetric D-A reactions of acrylates (**79**) derived from the chiral alcohols (**72**), (**73**) and (**74**) with cyclopentadiene.

Oppolzer[75] and co-workers have also focused on the design of the chiral control elements which satisfy the following criteria: (a) Accessible, (b) highly crystalline auxiliary which impose crystallinity to both the dienophiles and adducts, and (c) easily regenerated. In this respect, for instance, the crystalline alcohol (**75**) was prepared starting from (+)-camphor-10-sulfonic acid, and the Lewis-acid-mediated [4+2]-addition of its crystalline acrylate (**81**) to cyclopentadiene was studied. Notably, the crystalline acrylate (**81**) underwent highly *endo*-selective $TiCl_2(Oi\text{-}Pr)_2$-promoted [4+2]-addition to cyclopentadiene at -20 °C and gave efficiently the pure (2R)-adduct (**82**), after two crystallizations. The chiral auxiliary (**75**) was then efficiently regenerated by reducing the (2R)-adduct (**82**) with $LiAlH_4$, as illustrated in **Scheme 16**.

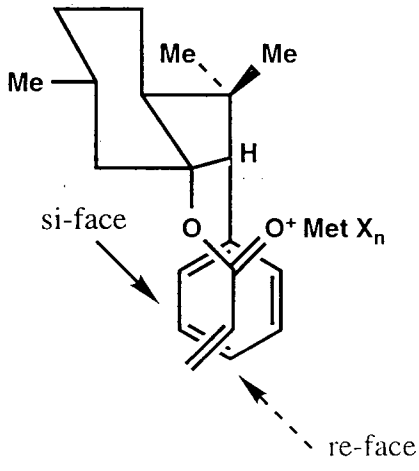


81 **82**

R* equal to the ester of (**75**)

Scheme 16

It has been shown[79] that both diastereofacial selectivity and the direction of the asymmetric induction, depend on the nature of the dienophile and the Lewis acid used as a catalyst. In order to explain the results obtained with Lewis acid, **model 1** can be used. This model was proposed by Oppolzer[80] *et al.* for the acrylates of (-)-8-phenylmenthol where the ester carbonyl group is *anti*-planar with the olefinic C,C-bond and *syn*-planar with the alkoxy-C,H-bond.

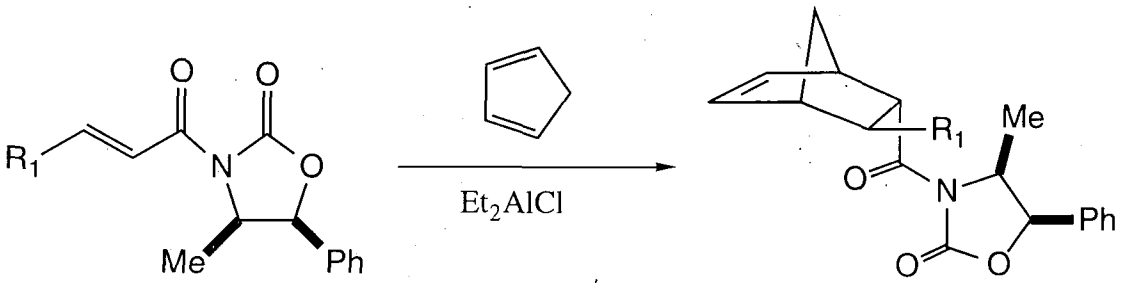


Model 1

It is clearly seen from **Model 1** that the phenyl ring of the ester unit shields the re-face by π,π-orbital overlap, probably even more effectively in the presence of an appropriate Lewis acid, thereby directing the diene addition to the dienophile si-face.

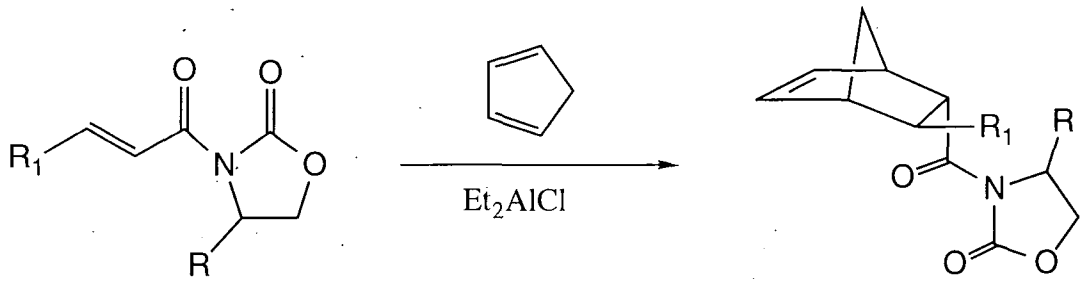
The attainment of absolute stereochemical control in the D-A reaction has been the focus of numerous of investigations. Issues associated with absolute stereochemical control in this reaction remain an important challenge[76].

The acrylates (**83a-85a**) and crotonates (**83b-85b**) derived from chiral 2-oxazolidones[76] (**76**), (**77a**) and (**77b**) are excellent chiral dienophiles showing good π-facial differentiation and high conversions with cyclopentadiene at -100 °C as depicted in **Scheme 17**. These results are summarised in **Table 12**.



83a-) R_1= H

83b-) R_1=Me



84a-) R_1= H, R= i-Pr

85a-) R_1= H, R= Bn

84b-) R_1=Me R= i-Pr

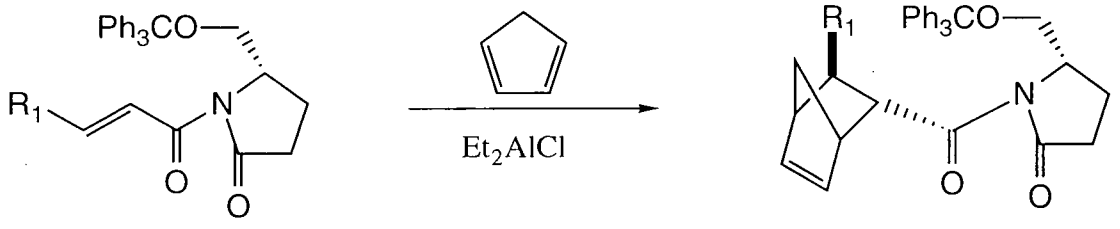
85b-) R_1=Me R= Bn

Scheme 17

Entry	Dienophile	Endo:Exo	Yield(%)	d.e.(%)
1	**83a**	100:1	82	90
2	**84a**	>100:1	81	86
3	**85a**	>100:1	78	90
4	**83b**	60:1	88	96
5	**84b**	48:1	82	90
6	**85b**	55:1	83	94

Table 12. Et_2AlCl-Promoted D-A reactions of dienophiles (**83**), (**84**), and (**85**) derived from chiral 2-oxazolidones (**76**) and (**77**) with cyclopentadiene.

Another option for π-face differentiation in D-A reactions includes the use of (S)-5-(trityloxymethyl)pyrrolidine-2-one[77] (**78**), unique in its ability to control reaction stereochemistry by its characteristic conformation. For instance, almost complete diastereofacial selection was observed in the asymmetric D-A reactions of imide **(86a)** and **(86b)** with cyclopentadiene at -78 C, affording the cycloadducts (**87a**) and (**87b**), as shown in **Scheme 18**.



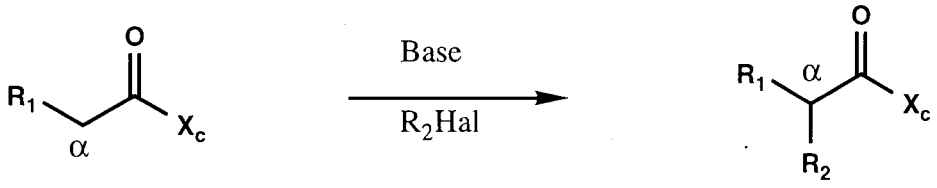
86 **87**

a-) R_1 = Ph **b**-) R_1 = CO_2Me

Scheme 18

2.B. Asymmetric Alkylation Reactions

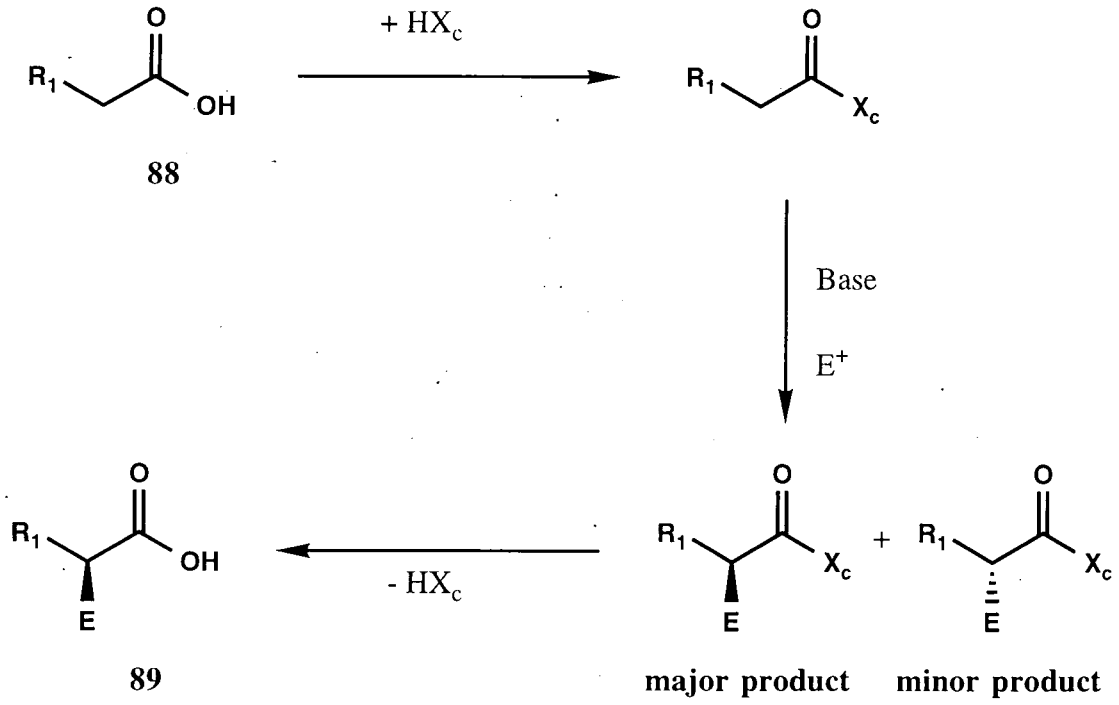
Asymmetric synthesis of carbon-carbon bonds are of considerable importance in synthetic organic chemistry[81]. The development of chiral enolate synthons and their practical utility in bond construction have been the subject of intensive investigation[82]. In recent years, face selective alkylation of chiral enolates rank among the most important methods for asymmetric carbon-carbon bond formation. In particular, the generation of an acyclic stereogenic center α-to a carbonyl group, as shown in **Scheme 19**, has been impressively addressed[83].



X* shows any chiral auxiliaries

Scheme 19

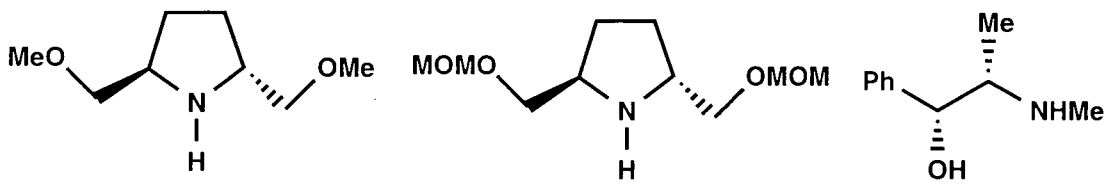
Significant progress has been made towards this objective through the use of asymmetric alkylation of carboxylic acid derivatives[84]. Chirality transfer in enolate alkylations of carboxylic acid derivatives usually occurs in cases where the substrates are covalently bound to a chiral auxiliary. After alkylation the chiral auxiliary is removed to generate a chiral carboxylic acid[85]. A general illustration of this set of chemical operations[86] is depicted in **Scheme 20**.



88 89

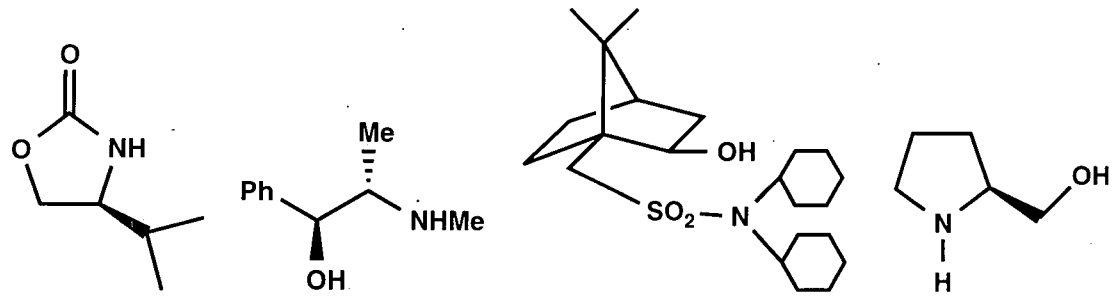
Scheme 20

In this example a carboxylic acid (**88**) is condensed with an optically pure chiral auxiliary (**H-Xc**). Diastereoselective bond construction is then carried out with an electrophile (**El$^+$**), and finally the chiral auxiliary (**H-Xc**) is removed from the system, affording an enantiomerically enriched α-substituted carboxylic acid (**89**). In such cases, chiral auxiliaries are involved to impose absolute stereochemical control on the alkylation step *via* either extra-annular or chelate-enforced intra-annular chirality transfer. Notable examples of such chiral auxiliaries are illustrated in **Fig. 17**.

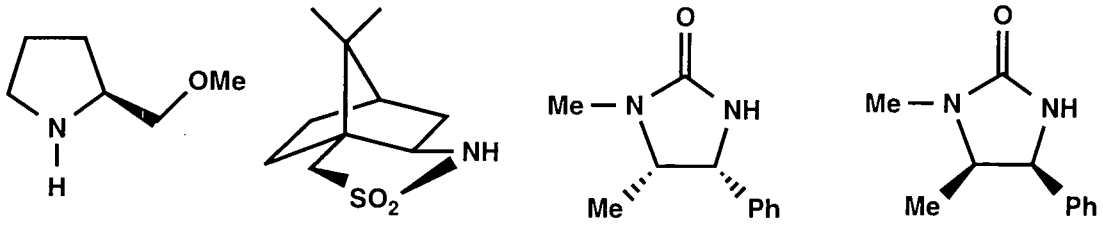


11b **12b** **59**

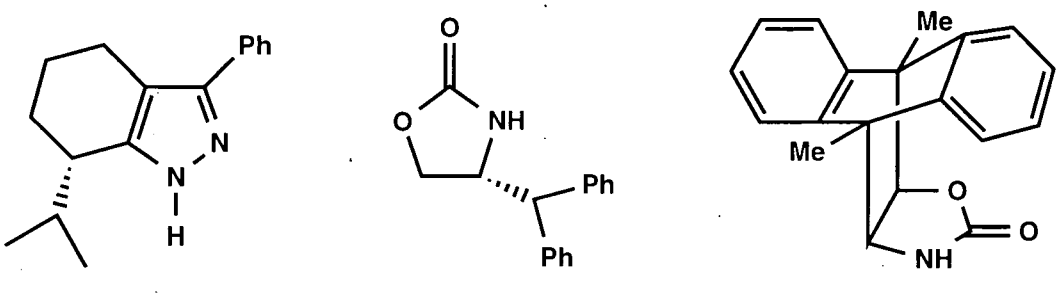
Fig. 17 continued



77a 90 91 92



93 94 95 96



97 98 99

Fig. 17.

Using some of these chiral auxiliaries, the alkylation of propion- amides, imides, and esters with various alkyl halides are shown in **Table 13.** The results obtained from the alkylation reactions illustrate the effectiveness of chiral auxiliaries in controlling the stereospecificity of the enolate alkylations.

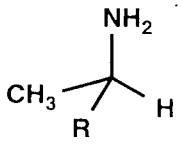
Entry	Chiral auxiliary	Alkyl halide	Base	Yield, %	de, %	Ref. no.
1	**11b**	BnBr	LDA	80	>95 (R)	20
		EtI	LDA	87	>95 (R)	
		n-BuI	LDA	81	>95 (R)	
2	**12b**	BnBr	LDA	81	>99 (S)	20
		EtI	LDA	79	>99 (S)	
3	**77a**	BnBr	LDA	92	>99 (S)	82
		EtI	LDA	36	>98 (S)	
4	**90**	BnBr	LDA	80-99	>99 (S)	84
		MeI				
		EtI				
		n-BuI				
5	**91**	BnBr	LDA	61	98 (R)	87
6	**92**	BnBr	LDA	75	76 (R)	88, 89
		$n\text{-}C_8H_{17}I$	t-BuLi		66 (R)	
7	**94**	BnI	BuLi	89	98.5 (S)	83
8	**95**	$n\text{-}C_8H_{17}I$	LDA	79	94 (S)	90
9	**96**	BnBr	LDA	86	92 (R)	90
10	**97**	EtI	LDA	69	61 (S)	27
11	**98**	BnBr	NaHMDS	81	>98 (S)	91
12	**99**	BnBr	LDA	76	99.98 (R)	92
		EtI		51	99.98(R)	

Table 13. Diastereoselective alkylation reactions with a variety of chiral auxiliaries.

2.C. Chiral Amine Solvating Agents

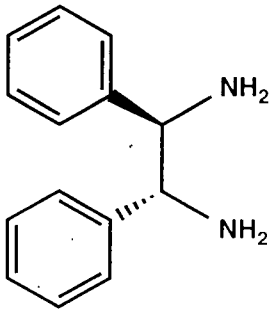
The determination of the enantiomeric purity of chiral alcohols or acids are routinely performed by NMR techniques through the use of chiral derivatising agents[93,99] (CDAs). There are relatively few reports of useful CDAs for carboxylic acids[56] and alcohols[94-96]. The majority of these methods are indirect and involve the formation of the diastereoisomeric derivatives prior to NMR analysis[99]. In addition, the formation and the analysis of these derivatives is often troublesome[93]. An alternative method involves *in situ* NMR analysis with chiral solvating agents (CSAs), which induce anisochrony either through the formation of ion pairing or hydrogen bonding. This emerges as an efficient method for the determination of the enantiomeric composition of acids or alcohols by chemical shift differences in NMR spectroscopy[64].

There are relatively few reports of the use of amines as CSAs for the analysis of carboxylic acids or alcohols. Accompanying structures including 1-phenyl-ethylamine[65] (**70**), 1-(1-naphthyl)ethylamine[68] (**71**), (1R,2R)-1,2-diphenylethane-1,2-diamine[98,99] (**100**) and quinine[100] (**101**) are shown in **Fig. 18**.

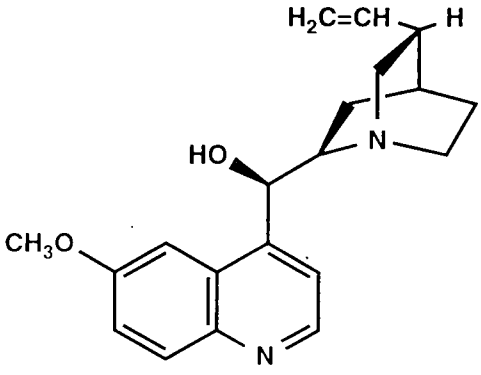


70 : R= Ph

71 : R= 1-Naphthyl



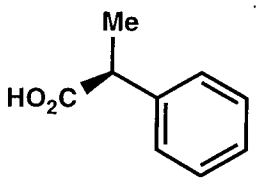
100



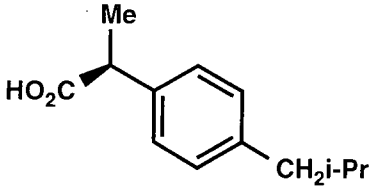
101

Fig. 18

The C_2-symmetric chiral diamine (**100**) has been successfully used as a CSA in the ^1H NMR analysis of the enantiomeric purity of chiral acids[99], including a series of anti-inflammatory agents in the α-arylpropionic acid class and a number of α-halo carboxylic acids. The chiral acids (**102**)-(**110**) examined are shown in **Fig. 19** and the NMR data observed for both the methyl and methine resonances are collected in **Table 14**.

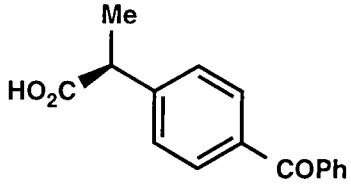


102



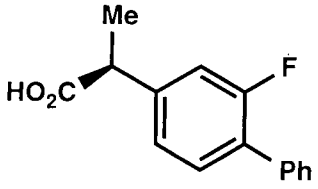
103

Ibuprofen



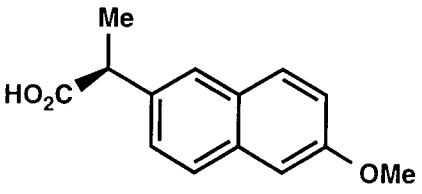
104

Ketoprofen



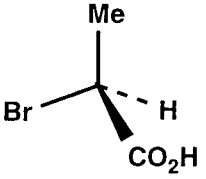
105

Flurbiprofen

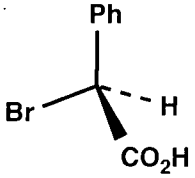


106

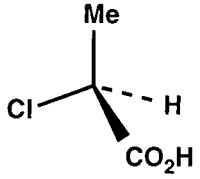
Naproxen



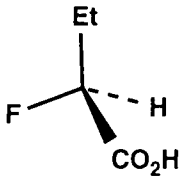
107



108



109



110

Fig. 19

As a result, the enantiomeric purity of samples (**102**)-(**110**) can be measured accurately by integrating either the separate methyl or methine resonances of the diastereoisomeric salt complexes.

Entry	chiral acid	Observed resonance	$\Delta\delta_H$ (ppm) for 1:1 ratio	$\Delta\delta_H$ (ppm) for 2:1 ratio
1	**102**	2-H	-	0.076
		$2\text{-}CH_3$	-	0.027
2	**103**	2-H	0.049	0.099
		$2\text{-}CH_3$	0.016	0.031
3	**104**	2-H	0.014	0.032
		$2\text{-}CH_3$	0.012	0.025
4	**105**	2-H	0.036	0.075
		$2\text{-}CH_3$	0.020	0.039
5	**106**	2-H	0.034	0.068
		$2\text{-}CH_3$	0.018	0.034
6	**107**	2-H	0.086	0.037
		$2\text{-}CH_3$	0.080	0.023
7	**108**	2-H	0.176	0.287
		$2\text{-}CH_3$	-	-
8	**109**	2-H	0.129	0.240
		$2\text{-}CH_3$	0.105	0.269
9	**110**	2-F	-	0.125
		$2\text{-}CH_3$	0.054	0.086

Table 14. NMR shift non-equivalence ($\Delta\delta$) of racemic 2-arylpropionic acids **(102)-(106)** and 2-halocarboxylic acids **(107)-(110)** as their diastereoisomeric salt complexes with the chiral diamine **(R)-100** in $CDCl_3$.

It is interesting to note that diastereoisomeric salts are systems in which there are stronger electrostatic interactions between the components than in the solvates investigated by Pirkle and, therefore, the NMR chemical shift differences are anticipated to be more marked[55]. In the former cases enantiomerically pure CSA and solute enantiomers react by proton transfer to form diastereoisomeric salts. The diastereoisomeric salt complexes may exhibit different NMR spectra in solution under conditions that promote ion pairing between solute conjugate acid and CSA conjugate base counterion[64].

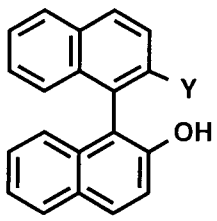
Both the optically active **(70)** and **(71)** have already been pointed out as adequate CSAs for the determination of the enantiomeric excess of secondary and tertiary alcohols. In the presence of optically active[68] **(71)**, the magnitude of $\Delta\delta$ (^{19}F-NMR) for several enantiomeric **R CH (OH) (CF_3)** type alcohols is summarised in **Table 15** to illustrate the effectiveness of **(71)** as a CSA.

Entry	**R in** **R** CH (OH) (CF_3)	$\Delta\delta$ CF_3 (ppm)
1	**Ph**	3.3
2	**m-CH_3-Ph**	3.1
3	**m-CF_3-Ph**	2.6
4	**m-NO_2-Ph**	2.2
5	**m-NH_2-Ph**	3.5
6	**m-F-Ph**	2.9
7	**p-F-Ph**	3.4

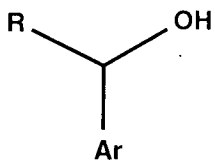
Table 15. Comparison of ^{19}F NMR nonequivalence of enantiomeric RCH(OH)(CF_3) type alcohols in the presense of optically active **(71)**.

The observed non-equivalence ($\Delta\delta$) arises through rapid reversible formation of diastereomeric solvates in which amine-alcohol hydrogen bonding is the principle mode of interaction. The differences in the $\Delta\delta$ values listed in **Table 15** are attributed to varying degrees of amine-alcohol interaction and the conformational preferences of the short lived diastereoisomeric solvates.

Structurally complex, but readily available quinine[100] (**101**) has been reported as a CSA for NMR evaluation of enantiomeric excesses of binaphthyl derivatives (**111**), and simple alkylarylcarbinols (**112**). General formula of both (**111**) and (**112**) solutes are illustrated in **Fig. 20** and typical ^{1}H NMR $\Delta\delta$ values are given in **Table 16**. Diastereoisomeric signal dispersions are obtained in all of the cases examined and these are sufficient to allow one to carry out enantiomeric excess evaluations.



111



112

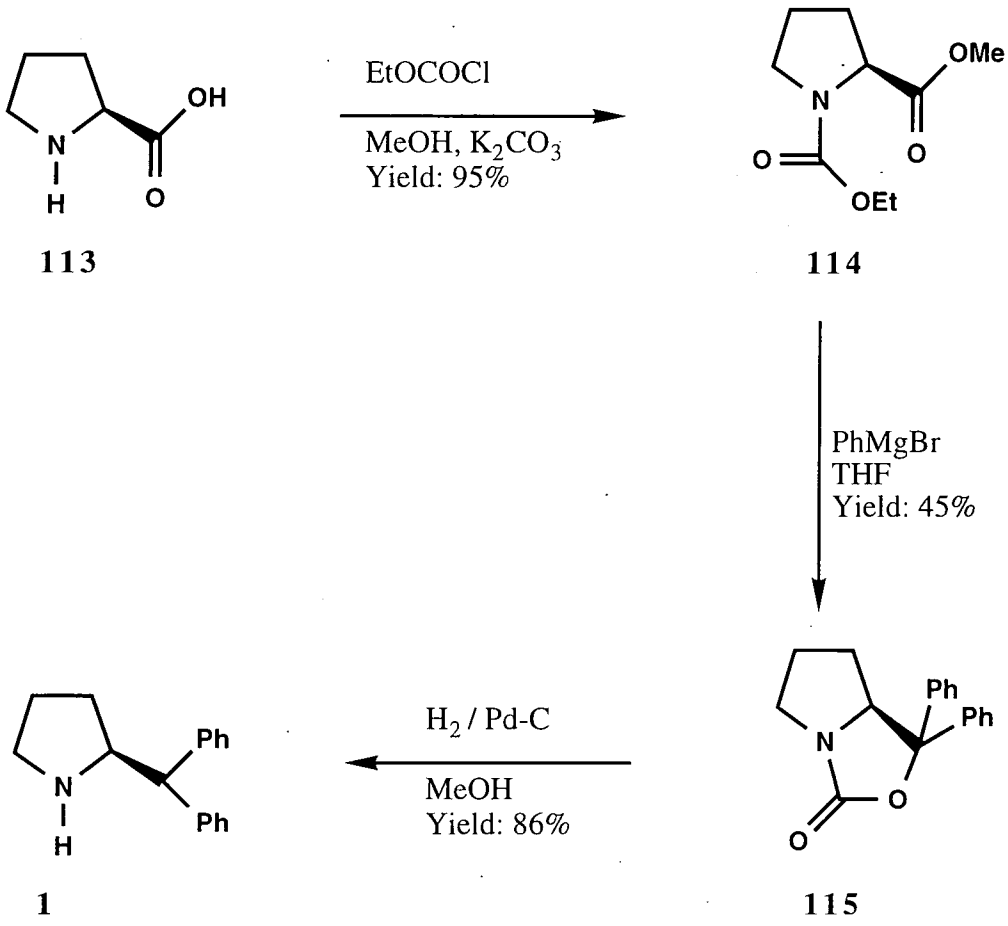
Fig. 20

Entry	Y in (**111**)	R and Ar in (**112**)		Resolved signals	Δδ
		R			
		Ar			
1	OMe			Me	0.07
2	O-iPr			Me	0.04
3	OCOMe			Me	0.01
4	$OCH_2CH=CH_2$			CH_2	0.14
5		Me	Ph	Me	0.01
6		CF_3	9-anthryl	CF_3	0.07

Table 16. Chemical shifts of some NMR signals for diastereomeric adducts formed by racemic (**111**) and (**112**) with quinine (**101**) in $CDCl_3$ at room temperature.

2.D. Aims and Objectives

A new straightforward route to (S)-2-(diphenylmethyl)-pyrrolidine (**1**) has recently been developed in Durham[102], which improves the previous synthesis[4]. The homochiral pyrrolidine (**1**) was prepared in a three step process starting from commercially available L-proline in good overall yield as shown in **Scheme 21**.

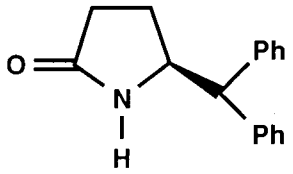


113 **114** **115** **1**

Scheme 21

This pyrrolidine (**1**) is now available in quantity. It has a sterically bulky diphenylmethyl group at the 2-position of pyrrolidine ring system, and clearly offers a novel and useful chiral auxiliary for a variety of asymmetric transformations.

In certain instances (S)-2-(diphenylmethyl)-5-oxopyrrolidine (**2**) may emerge as a more refined chiral auxiliary due to the additional coordination site at the 5-position of pyrrolidine ring system.



2

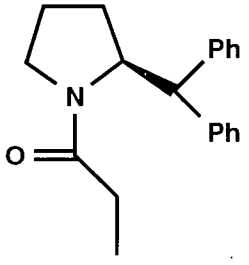
Chiral Auxiliary

The initial aims of this project were to explore the use of the homochiral pyrrolidines (**1**) and (**2**) as chiral auxiliaries in two aspects of asymmetric synthesis;

a) Diels-Alder (D-A) reactions

b) Alkylation reactions.

In this respect the following target molecules (**116**), (**117**), and (**118**) were synthesised and then used in the asymmetric D-A and alkylation reactions to test the effectiveness of pyrrolidines (**1**) and (**2**) at inducing asymmetric transfer.



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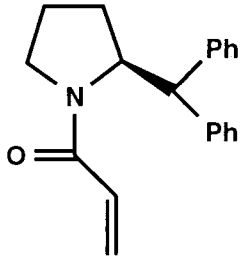

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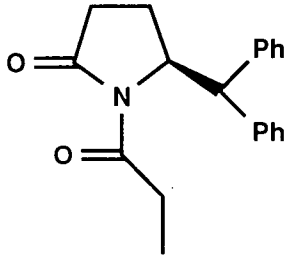


118

NMR Shift Reagents

In view of the ability of various amines to act as chiral shift reagents for NMR analysis, homochiral pyrrolidines (**1**) and (**2**) were also explored in this context.

CHAPTER 2

Results and Discussion

Part 1

1.A. Asymmetric Diels-Alder reactions with cyclopentadiene

1.B. Introduction

The Diels-Alder (D-A) adducts of acrylic acid derivatives constitute an important class of compounds as key intermediates for the total synthesis of a variety of natural products[71]. The vast majority of work on asymmetric D-A reactions deals with additions of 1,3-dienes to chiral, conjugated acrylic acid derivatives[69]. Indeed, high levels of diastereoselectivity have been achieved in the asymmetric D-A reactions of prochiral 1,3-dienes with chiral acrylates[103].

The best diastereofacial selectivities to date were reported by Oppolzer[74] *et al.* in the [4+2]-addition of cyclopentadiene to the acrylates (**79**) derived from chiral auxiliary alcohol (**73a**) and its antipode (**74a**). The reaction was carried out in the presence of mild Lewis acid $TiCl_2(OiPr)_2$ to prevent rapid ether cleavage which occured with $TiCl_4$ and provided (R)-and (S)-endo-cycloadducts (**80**) respectively in excellent yields with 99.3% diastereofacial differentiation (**Table 11**, p. 37).

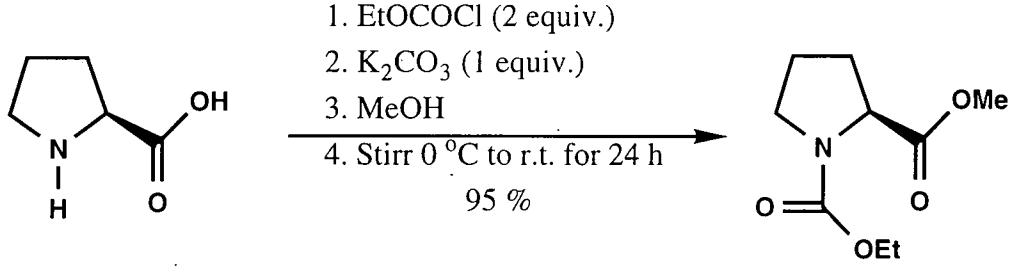
1.C. Results and discussion

To test the effectiveness of homochiral pyrrolidine (**1**) as a chiral auxiliary in D-A reactions, we choose the asymmetric D-A reactions of the N-acrylamide (**119**) and N-crotonylamide (**120**) derivatives of our pyrrolidine with cyclopentadiene. The strategy consists of three steps; the first involves the preparation of the chiral auxiliary,

which is homochiral pyrrolidine (**1**) in this case. The second is the preparation of the N-acrylamide (**119**) and N-crotonylamide (**120**), and finally the Diels-Alder reactions with cyclopentadiene.

Pyrrolidine (**1**) was synthesised from L-proline, following the method[102] which has recently been developed in Durham. The route is highly efficient and involves a three step process allowing the facile preparation of chiral auxiliary (**1**) in multigramme quantities. Pyrrolidine (**1**) is an oil which is stable at room temperature and can be used when required.

The first step in the synthesis of pyrrolidine (**1**) requires the preparation of the N-carboxyamide pyrrolidine ester (**114**), as shown in **Scheme 22**, by simply mixing two equivalent of ethyl chloroformate with L-proline (**113**) and K_2CO_3 in dry and distilled MeOH.

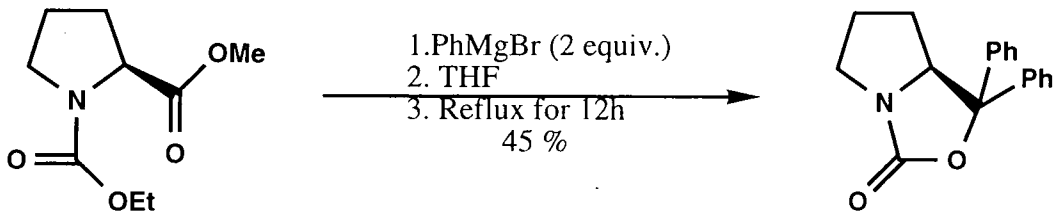


113 **114**

Scheme 22

The reaction described above produces a clear oil, which can be either used directly for further synthesis or, if necessary, can be purified by distillation.

Compound (**114**) is then submitted to a Grignard reaction with a phenyl magnesium bromide, as depicted in **Scheme 23**.

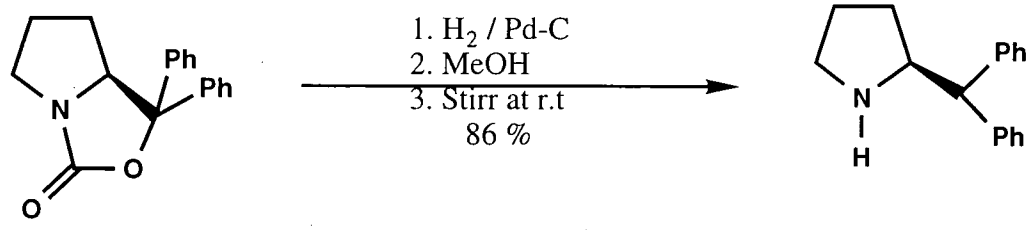


114 **115**

Scheme 23

On work up, this reaction generates either a light-brown solid if excess Grignard reagent is used, or a white solid if a stoichiometric amount of Grignard reagent used. In any case the product can be re-crystallised from ethyl acetate to give (**115**) as a nice white crystalline solid. In order to prevent any side reactions during the Grignard addition, two equivalents of PhMgBr are added.

Compound (**115**) is finally submitted to hydrogenation with palladium catalyst on activated carbon in dry and distilled MeOH, as illustrated in **Scheme 24**.



115 **1**

Scheme 24

This is the key step of the reaction sequence, which removes the elements of carbon dioxide from the cyclic carbamate (**115**) to generate homochiral pyrrolidine (**1**) as an oil. It is noteworthy that evacuation of air from the reaction vessel and filling up with hydrogen are very important process to improve the yield to 86 %. Purification can be achieved either by distillation under reduced pressure or by column chromatography (4:1 ethyl acetate:methanol).

Homochiral pyrrolidine (**1**) as its hydrochloride salt gives a nice crystalline solid. A suitable crystal has allowed us to obtain an X-ray structure. The X-ray structure shows disorder in the pyrrolidine ring between C-3 and C-5, as depicted in **Fig. 23**. It is clear however that the diphenylmethylene group is large enough to dominate one face of the pyrrolidine ring system.

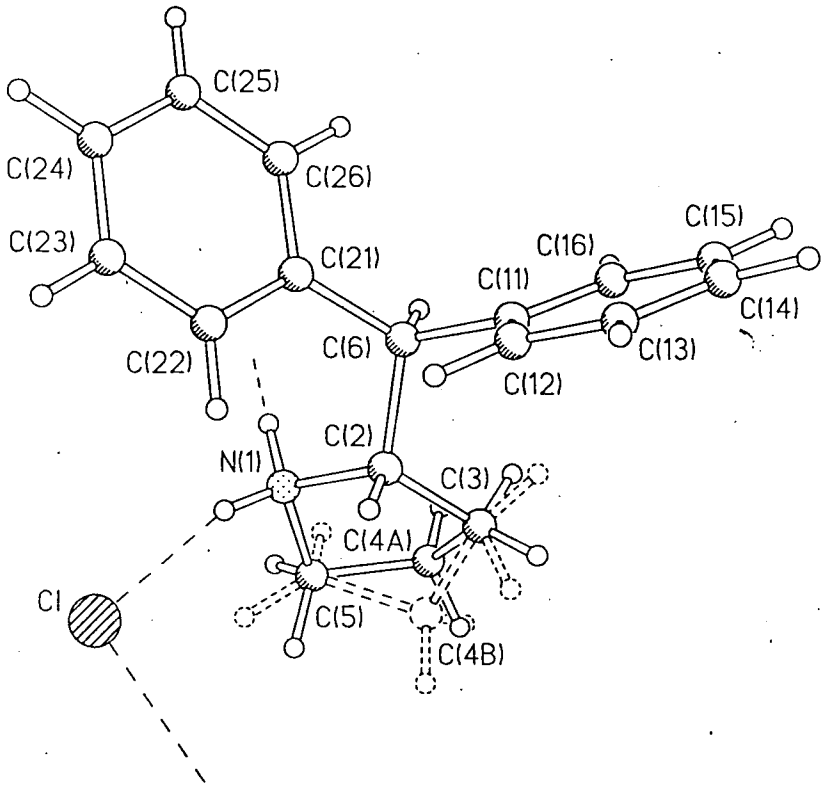
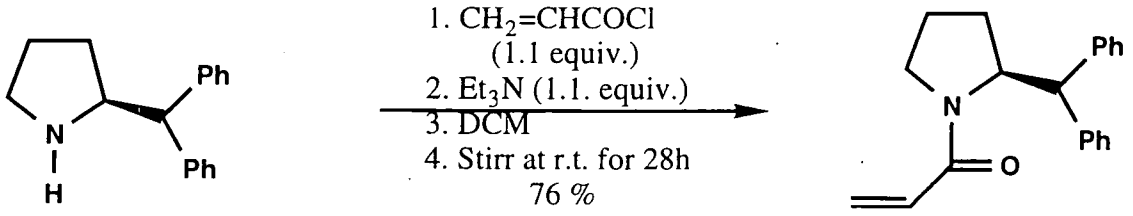


Figure 23. X-ray structure of homochiral pyrrolidine (**1**) as its hydrochloride salt.

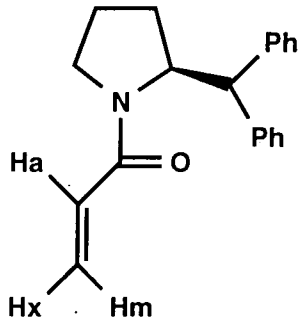
The homochiral pyrrolidine (**1**) was then condensed with acryloylchloride in the presence of triethylamine, as illustrated in **Scheme 25**. Thus, the N-acryloyl derivative (**119**) of the chiral pyrrolidine (**1**) was synthesised as a target dienophile in good yield following the procedure[104] used for the preparation of N-acylpyrazoles. The compound was purified by chromatography and was then re-crystallised from ethyl acetate.



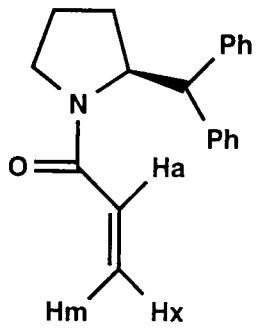
1 **119**

Scheme 25

N-Acrylamide **(119)** is a planar amide derivative which can exist as one of two diastereoisomeric rotamers due to restricted rotation around the N (1)-CO bond. Rotamers **(119a)** and **(119b)** are generally non-isolable but the two populations can be observed by both ^1H and ^{13}C NMR. As can be seen in **Fig. 24**, the dienophile **(119)** was a 1:1 mixture of rotamers **(119a)** and **(119b)**.



119a



119b

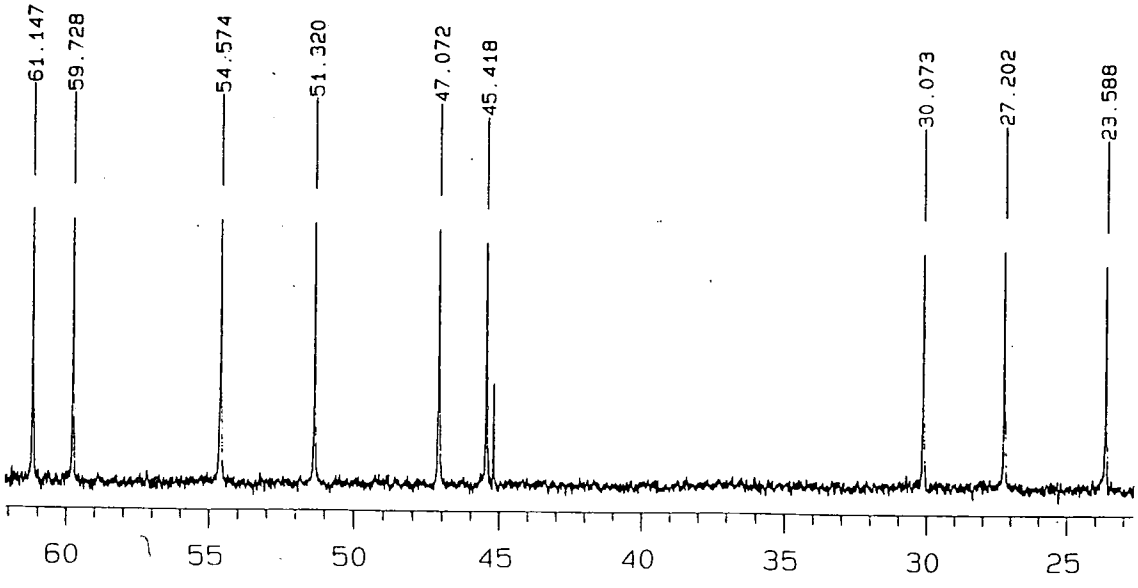
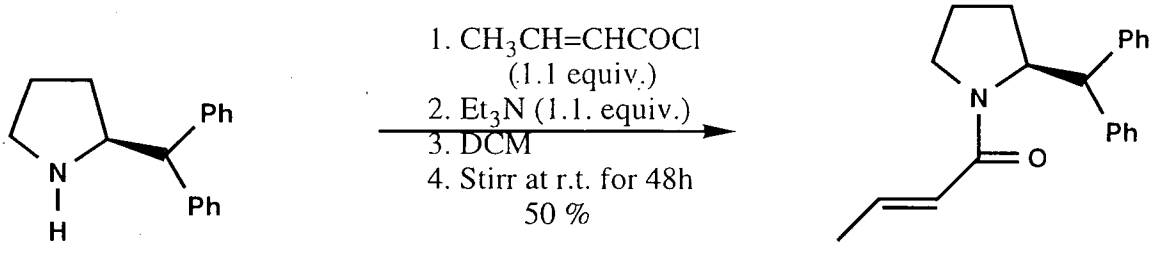


Figure 24. ^{13}C NMR (20-62 ppm) spectrum of the rotamers **(119a)** and **(119b)**.

The anisotropic effect of the aromatic rings clearly influence the chemical shift of the vinylic protons of rotamer (**119b**), which are up-field relative to the vinylic protons of rotamer (**119a**). Two sets of proton signals are observed for the vinylic protons in the region of δ 5.2 and 6.5 ppm, consistent with the presence of two rotamer population. The vinylic protons H_a, H_X and H_m of rotamer (**119b**) gave signals at δ 5.8, 5.2 and 6.0 ppm respectively, whereas those of rotamer (**119a**) occur at δ 6.4, 5.7 and 6.3 ppm.

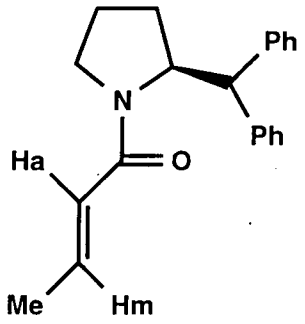
Attention was next turned to the synthesis of the N-crotonylamide derivative (**120**). This offered another Diels-Alder (D-A) dienophile and it was of interest to asses the influence of the additional methyl group on the rotamer populations. Following the literature method[104], N-Crotonylamide (**120**) was prepared by treating the chiral pyrrolidine (**1**) with crotonyl chloride in the presence of triethylamine, as illustrated in **Scheme 26**. The compound was purified by chromatography to remove residual starting material.



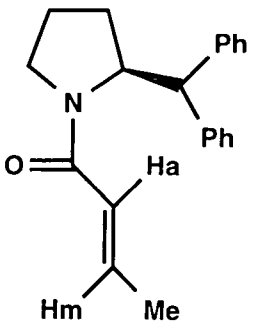
1 **120**

Scheme 26

^1H and ^{13}C NMR analysis indicated two sets of signals, consistent again with the presence of the two diastereoisomeric rotamers. As can be seen in **Fig.26**, rotamers (**120a**) and (**120b**) are also present as a 1:1 mixture and thus extra methyl group does not seem to effect free rotation around the N(1)CO bond. Similar hindered internal rotation about an amide bond was also reported by Nishihara[105] *et al.* for several N-acyl-L-prolines.



120a



120b

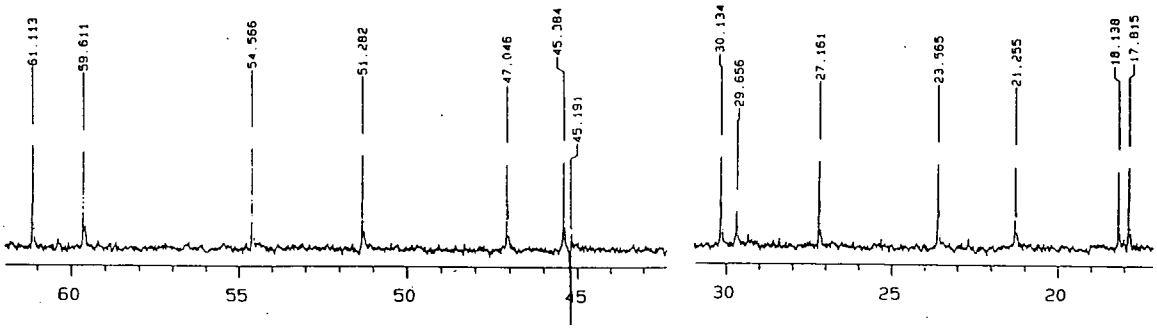
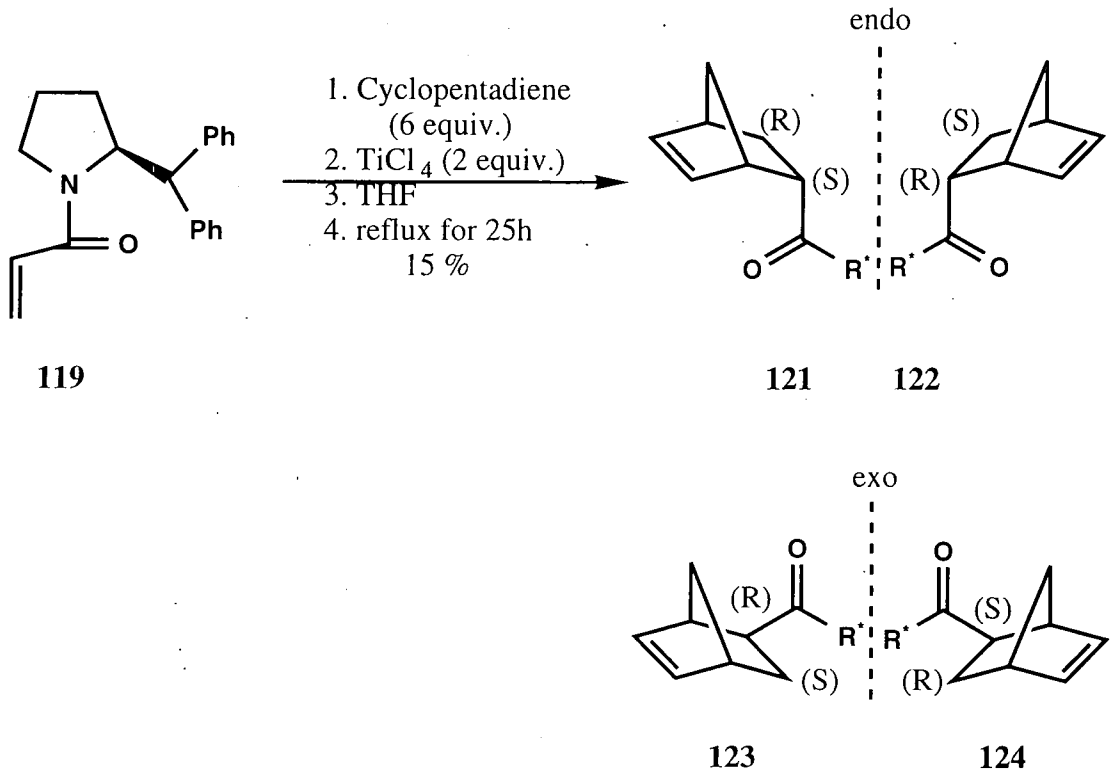


Figure 26. ^{13}C NMR (15-62 ppm) spectrum of the rotamers (**120a**) and (**120b**).

The vinylic protons H_a and H_m in the rotamer (**120b**) gave a doublet and a doublet of quarted at δ 5.5 and 6.6 ppm respectively, whereas the same protons in the other rotamer (**120a**) appeared at δ 6.1 and 6.9 ppm.

It is well known[106] that the best results in asymmetric D-A reactions between prochiral 1,3-dienes and chiral acrylates are obtained in the presence of a Lewis acid catalysts such as $TiCl_4$. In this investigation, both the uncatalyzed and catalyzed reactions of cyclopentadiene with the acrylamide (**119**) were carried out to assess optimal reaction conditions. In the first instance, [4+2]-addition of cyclopentadiene to the acrylamide (**119**) was carried out in the absence of Lewis acid, following the

literature method[107a] with a very slight modification. D-A reaction did not occur in this case, even after heating under the reflux for 24h. However, when acrylamide (**119**) was submitted to $TiCl_4$-mediated Diels-Alder reaction[107b] with cyclopentadiene, a facile cycloaddition followed and a crude mixture of *endo* [(**121**)+(**122**)] and *exo* [(**123**)+(**124**)] cycloadducts were produced, as depicted in **Scheme 27**. To achieve efficient D-A additions of cyclopentadiene to the acrylamide (**119**), the reaction was carried out in DCM at -60 °C for 24h, with a 1:6:0.75 ratio of dienophile:diene:Lewis acid, following the literature[108] for the reactions of cyclopentadiene with N-acryloly derivatives of L-proline, L-phenylalanine, L-alanine and N-methyl-L-alanine esters. There was no addition reaction, even after warming to r.t for another 24h.



119 **121** **122**

123 **124**

Scheme 27

Although t.l.c. analysis of the crude mixture showed two discernible spots, the major component was purified by chromatography. The nature of this component could not be assigned unambigously. It is clearly evident from the ^{13}C NMR spectrum of the

product, as depicted in **Fig. 27**, that this product was a 4:1 mixture of two components, which could be one of the following.

a-) rotamers of one diastereoisomer;

b-) the diastereoisomeric mixtures of *endo* or *exo* cycloadducts, e.g. **(121+122)** or **(123+124)**;

c-) a mixture of one *endo* and one *exo* diastereoisomer, e.g. **(121+123)**.

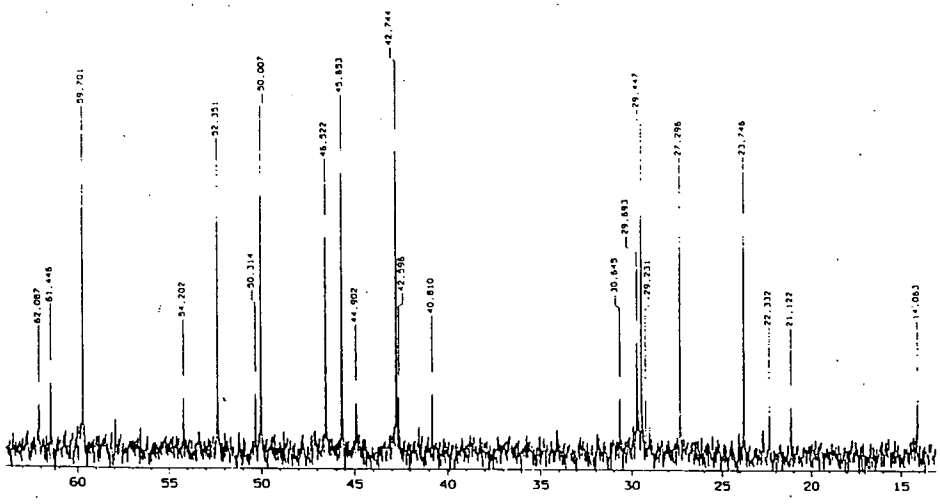


Figure 27. ^{13}C NMR (12-65 ppm) spectrum of the pure compound.

On the three possibilities, (a) is considered most likely. The major component eluted was assumed to be an *endo* diastereoisomer, as depicted in **Fig. 28**, because the *endo* products normally predominant in D-A reactions and assigned using ^{1}H-^{1}H COSY NMR technique. However, the absolute stereochemistry of **(121)** or **(122)** remains ambiguous.

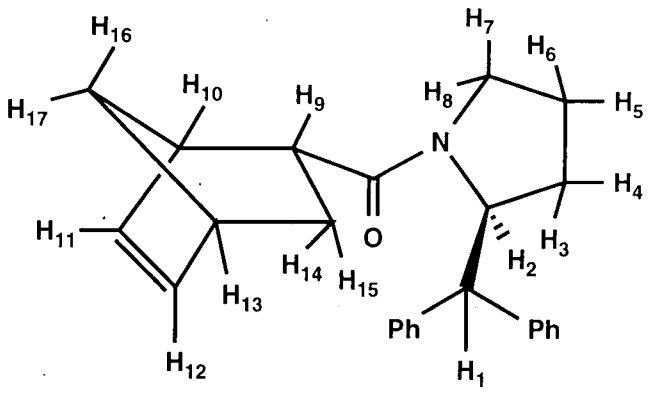


Figure 28

The vinylic protons H_{11} and H_{12} gave signals at δ 5.5 and 6.1 ppm as a doublet of doublets, respectively, with coupling constants 5.6 Hz and 3.2 Hz. The bridge head protons H_{10} and H_{13} gave a broad signals at δ 3.0 and 2.8 ppm due to the small couplings. One of the methylene bridge protons gave a signal at δ 1.3 ppm as a doublet of doublet of doublets with coupling constants 8.0 Hz, 4.5 Hz and 2.0 Hz, whereas the other methylene bridge proton H_{16} gave a signal at δ 1.2 ppm, as a doublet of doublets. The H_9 proton gave a signal at δ 2.9 ppm as a quintet, possibly due to the overlapping patterns of some doublets. The H_{15} proton gave a doublet of doublet of doublets at δ 1.7 ppm with coupling constants 4.0 Hz, 9.2 Hz and 11.6 Hz. The H_{14} proton gave the same signal at δ 1.3 ppm with slightly different coupling constants 2.0 Hz, 4.5 Hz and 8.0 Hz.

As a result, it is too premature to draw firm conclusions at this stage, despite these encouraging results.

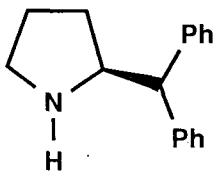
Part 2

2.A. Asymmetric alkylations of chiral N-acyl pyrrolidines

2.B. Introduction

Although there is a large literature dealing with alkylations of chiral enolates, excellent levels of diastereoselectivity (99.98 %) has been observed to date for the alkylation of propionamide enolates of the chiral auxiliary[92] (**99**). Those procedures which generate new centers of chirality in high enantiomeric purity are now the subject of intensive investigations. It is understood that effective asymmetric alkylation is achieved by control of the enolate geometry, coupled with the nature of the chiral auxiliary.

My contribution to this area is to explore our pyrrolidines as novel auxiliaries for asymmetric alkylations of their N-acyl derivatives with various electrophiles. In this context, two chiral auxiliaries have been considered, as illustrated in **Fig. 29**. One of these is (S)-2-(diphenylmethyl)-pyrrolidine (**1**), which has a sterically bulky diphenylmethyl group at the 2-position of pyrrolidine ring system; the other is (S)-2-(diphenylmethyl)-5-oxopyrrolidine (**2**), which is designed with an additional coordination site at the 5-position of pyrrolidine ring system.



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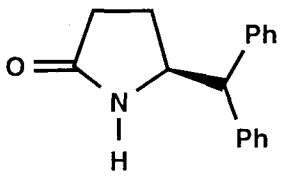


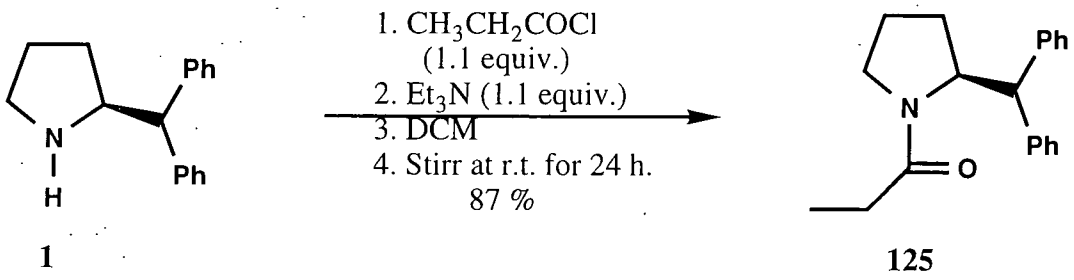
2

Figure 29

2.C. Results and discussion

The chiral auxiliary (**1**) in this research programme was prepared easily from L-proline as indicated before. Initial experiments focused on the synthesis of N-propylamide (**125**) and N-phenylacetylamide (**126**) derivatives of pyrrolidine (**1**).

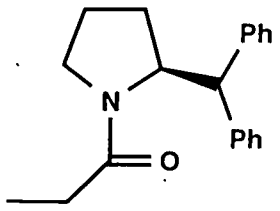
In this respect, the N-propyl derivative (**125**) of pyrrolidine (**1**) was the first target molecule and could be prepared in excellent yield, following the literature[104], by simply mixing pyrrolidine (**1**) with propionyl chloride, in the presence of triethylamine, as depicted in **Scheme 28**. The compound was purified by chromatography to remove residual starting material and was isolated as a white amorphous solid, which could be re-crystallised from ethyl acetate.



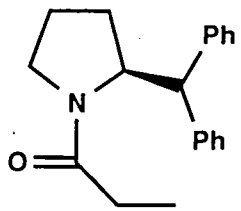
1 **125**

Scheme 28

^1H and ^{13}C-NMR spectra illustrate two sets of signals in this case, consistent with the presence of the two diastereoisomeric rotamers. The rotamers ratio **125a/125b** can be determined from the ^{13}C NMR spectrum as 1.75:1, **Fig. 30**. We assume that rotamer (**125a**) is thermodynamically more stable than rotamer (**125b**). The origin of the preference for rotamer (**125a**) can be explained in terms of interaction between the methyl group and sterically demanding bulky phenyl group. The methyl group in the rotamer (**125a**) is distant from the bulky phenyl group, and thus it is anticipated that interactions between the two substituents will be much less.



125a



125b

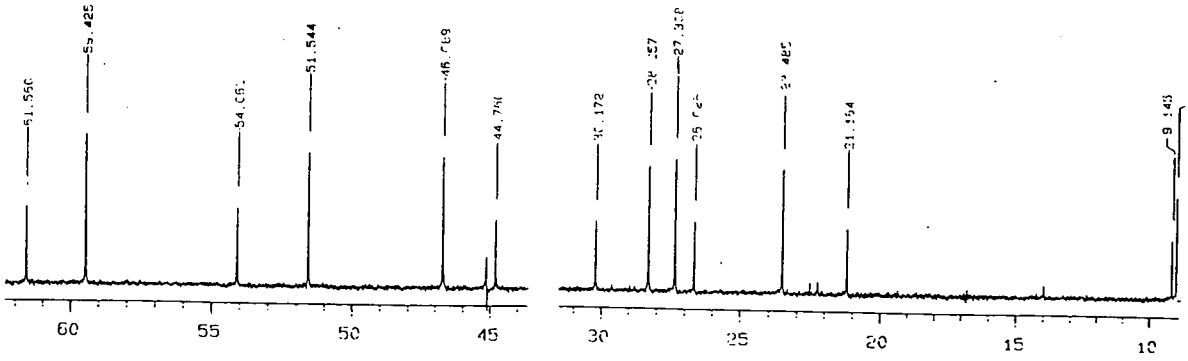


Figure 30. ^{13}C NMR spectrum (8-62 ppm) of N-propylamide (**125**).

The rotamers have been assigned by two-dimensional ^{1}H and ^{13}C NMR spectrum. The signal assigned to the methyl protons in rotamer (**125b**) are shifted up-field when compared to those of rotamer (**125a**). It was also observed that the methylene protons of each of the rotamers were coincident at δ 2.2-2.3 ppm.

We envisage that crystal structure analysis could be helpful in the understanding the steric interactions controlling the rotamer populations. Therefore a suitable crystal of (**125**) was submitted for X-ray analysis. The resultant structure, **Fig. 32**, supported the idea that ethyl group occupies a site *trans* to the bulky phenyl groups, to generate the thermodynamically more stable rotamer (**125a**), the predominant rotamers in the solid state.

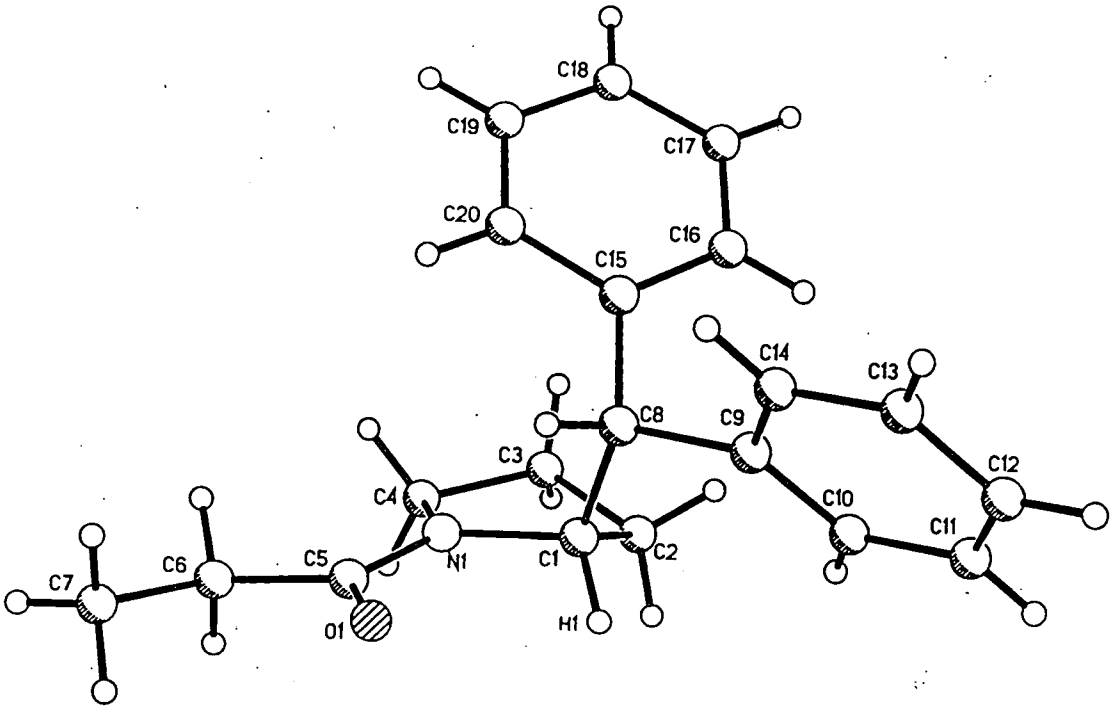
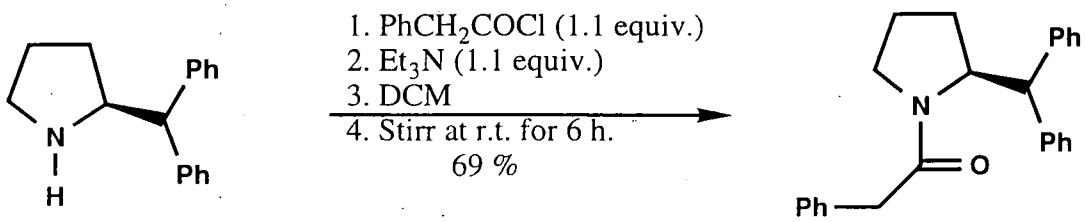


Figure 32. X-ray structure of N-propylamide **(125).**

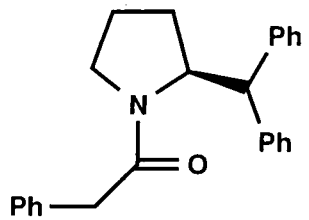
Attention was turned to the synthesis of N-phenylacetylamide. This was of interest to assess further the influence of the more bulky phenyl group on the rotamer populations. Following the literature[104], N-phenylacetylamide (**126**) was prepared by treating the chiral pyrrolidine (**1**) with phenylacetyl chloride in the presence of triethylamine, as depicted in **Scheme 29**. The compound was also purified by chromatography and isolated as a clear oil, which solidified on standing.



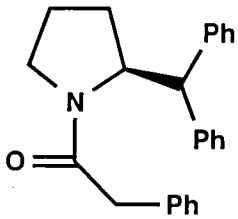
1 **126**

Scheme 29

Again ^{1}H and ^{13}C NMR analysis indicated two sets of signals, consistent again with the presence of the two rotamer populations. As can be seen in **Fig. 33**, rotamers **(126a)** and **(126b)** are present in a 2.33:1 ratio and thus the more bulky phenyl group has an increased steric influence as predicted.



126a



126b

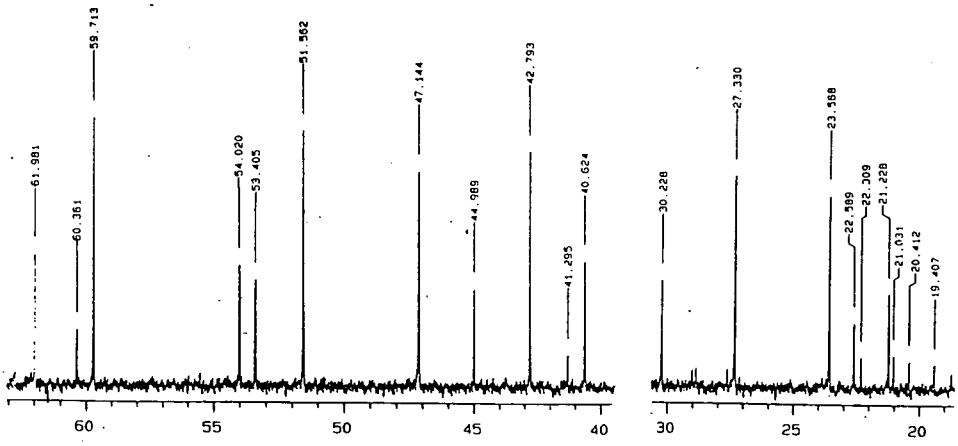
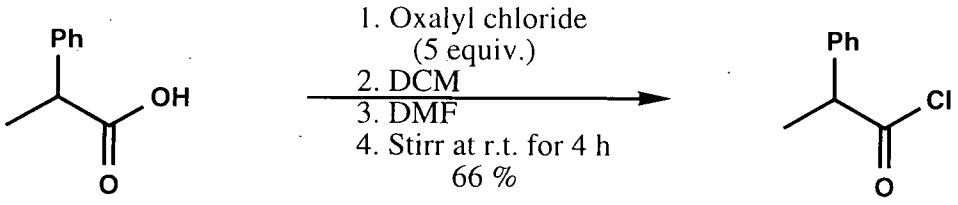


Figure 33. ^{13}C NMR (65-12 ppm) spectrum of N-phenyl acetylamide **(126)**

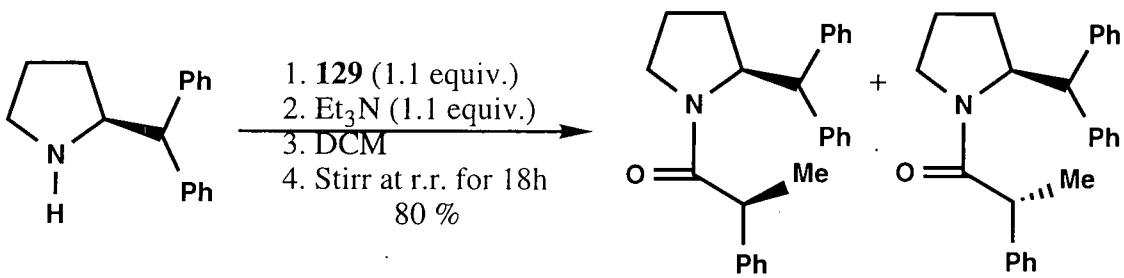
In order to study the stereochemical purity of alkylated products, diastereoisomeric product mixtures were required for reference purposes. Accordingly racemic 2-phenylpropionic acid **(127)** was converted to its 2'-substituted amide derivatives **(2S,8R)-129** and **(2S, 8S)-129**. This was achieved by generating the acid chloride **(128)** with oxalyl chloride[109] in a catalytic amount of DMF, as illustrated in **Scheme 30**. This compound was purified by bulb-to-bulb distillation, and isolated as a clear oil.



127 **128**

Scheme 30

The racemic acid chloride (**128**) was then submitted to the acylation reaction[104] by simply mixing with pyrrolidine (**1**) in the presence of triethylamine, as depicted in **Scheme 31**. The two diastereoisomeric amides **(2S,8R)-129** and **(2S,8S)-129** were separated by chromatography, and isolated as individual oils.



1 **(2S,8S)-129** **(2S,8R)-129**

Scheme 31

The rotamer populations of each diastereoisomer were determined by ^{13}C NMR spectra. It was found that one diastereoisomer, **(2S,8R)-129**, had two sets of signals in a ratio of 1.6:1, consistent with the presence of the two rotamer populations, as shown in **Fig. 34**. On the other hand, the second diastereoisomer, **(2S,8S)-129**, gave only one set of signals, indicating a single predominant rotamer, as depicted in **Fig. 35**. These two spectra, and HPLC analysis, which are illustrated below, were used subsequently to assess the diastereoselectivity of the alkylation reactions.

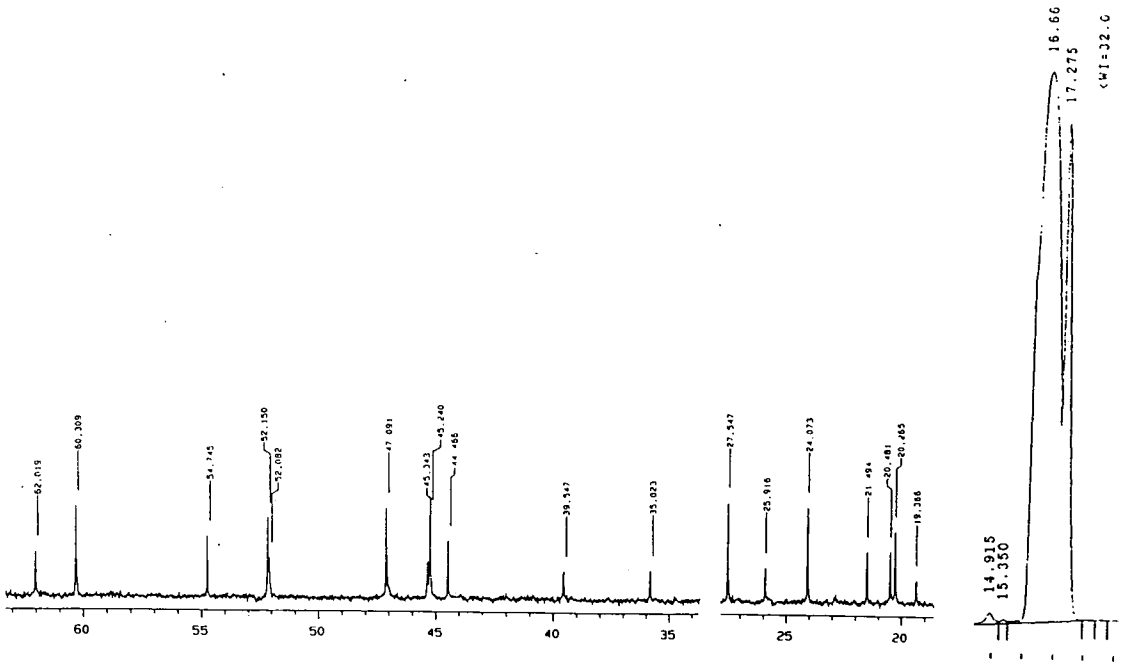


Figure 34. ^{13}C NMR (15-70 ppm) spectrum and HPLC analysis of the diastereoisomeric amide **(2S, 8R)-129**, which exists in two rotamer populations.

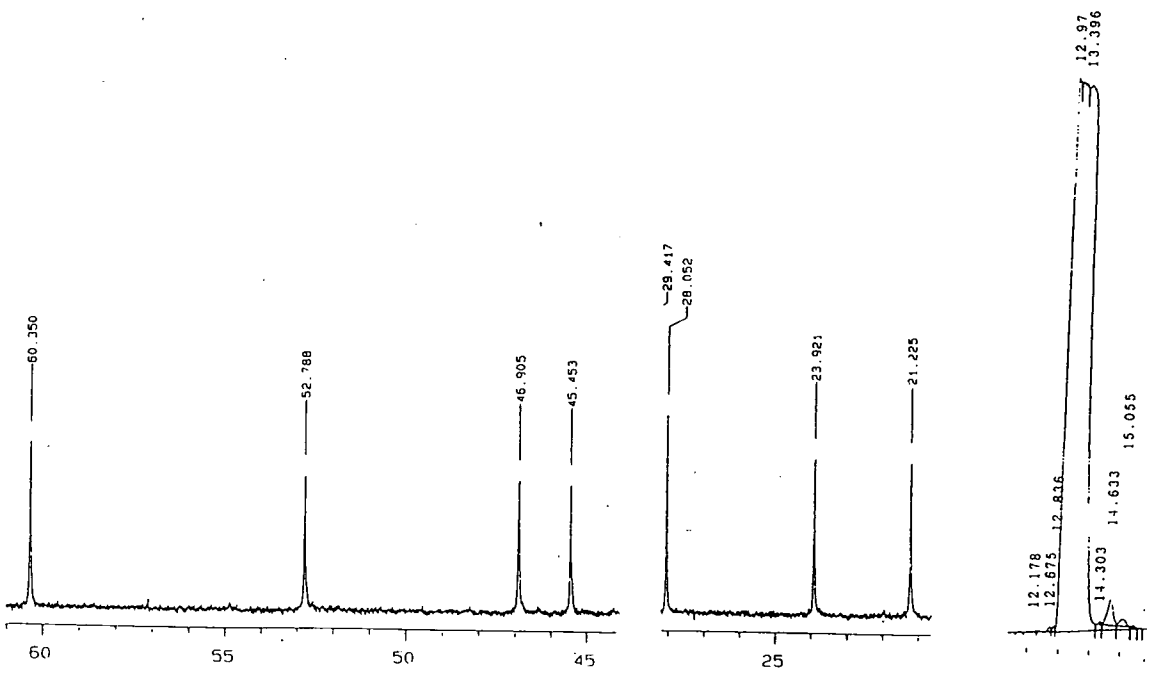
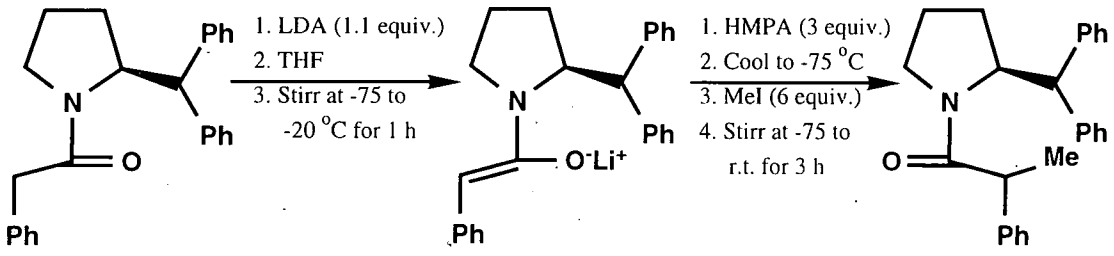


Figure 35. ^{13}C NMR (15-70 ppm) spectrum and HPLC analysis of the diastereoisomeric amide **(2S, 8S)-129**, which exists as a single predominant rotamer.

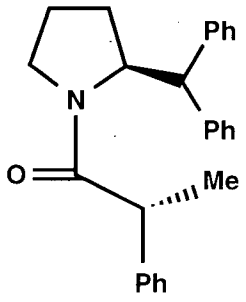
The N-phenylacetylamide enolate (**130**) was generated under standard deprotonation conditions[110] (LDA, -78 °C, THF) and was then subjected to alkylation[20] with methyl iodide in the presence of HMPA[83], as shown in **Scheme 32**.



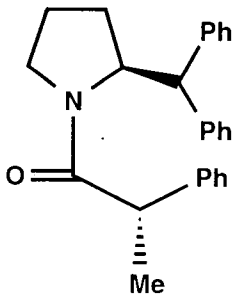
126 **130** **131**

Scheme 32

Two diastereoisomeric amides (**2S, 8R**)-**131** and (**2S, 8S**)-**131** were obtained in the product. The diastereoisomers ratio (**2S, 8R**)-**131**/(**2S, 8S**)-**131** was determined from HPLC analysis as 1.49:1. In the absence of HMPA, the diastereoselectivity ratio decreased to 1.1:1. The diastereoisomeric mixture (**2S, 8R**)-**131** and (**2S, 8S**)-**131** and its HPLC analysis are shown in **Fig. 36**, and thus HMPA improves the stereoselectivity of the alkylation.



(2S, 8R)-131



(2S, 8S)-131

Figure 36 continued

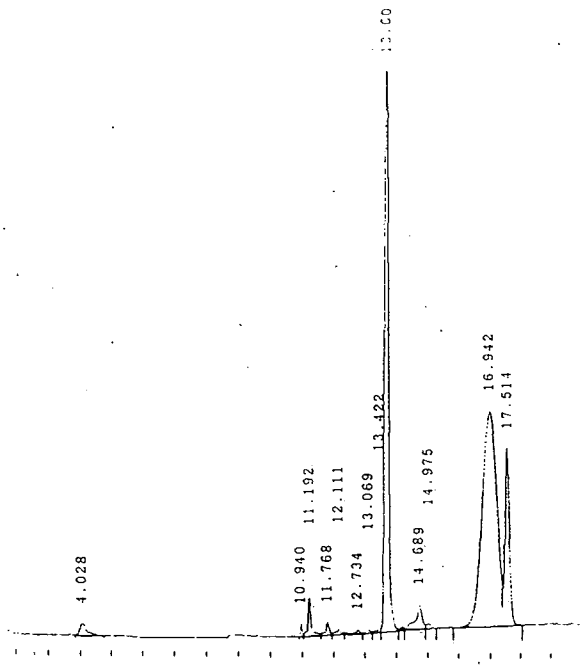
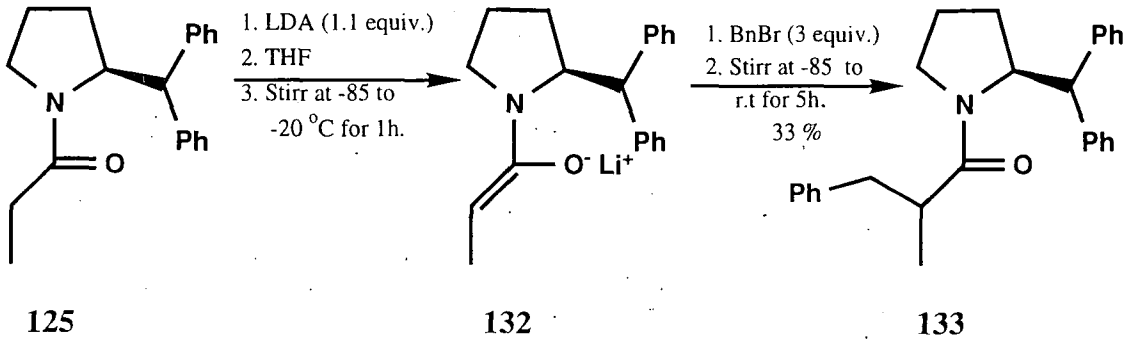


Figure 36. The diastereoisomeric mixture **(2S, 8R)-131** and **(2S, 8S)-131** and its HPLC analysis.

The N-propionylamide enolate (**132**) was also generated under the same standard deprotonation condition[110] (LDA, -78 °C, THF) and was then submitted to an alkylation reaction[20] with benzyl bromide, as illustrated in **Scheme 33**. The resultant diastereoisomers (**133**) were purified by chromatography and individually isolated as a white amorphous solid and a clear oil.

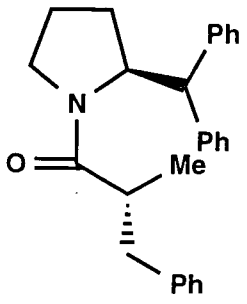


125 **132** **133**

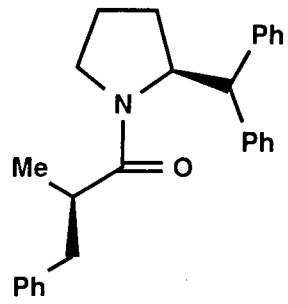
Scheme 33

The diastereoselectivity of the crude reaction mixture was determined from HPLC analysis as 1.12:1. Again when the alkylation reaction[20] was carried out in the presence of HPMA[83], the diastereoselectiviy increased to 2.13:1. ^{1}H and ^{13}C NMR

analysis of one diastereoisomer indicated two sets of signals, consistent with the presence of the two rotamer populations **(2S,8S)-133a** and **(2S,8S)-133b**. The new stereogenic centre is arbitrarily drawn, as shown in **Fig 37** and the rotamer ratio **133a/133b** was determined accurately from the ^{13}C NMR spectrum as 1.28:1.



(2S,8S)-133a



(2S,8S)-133b

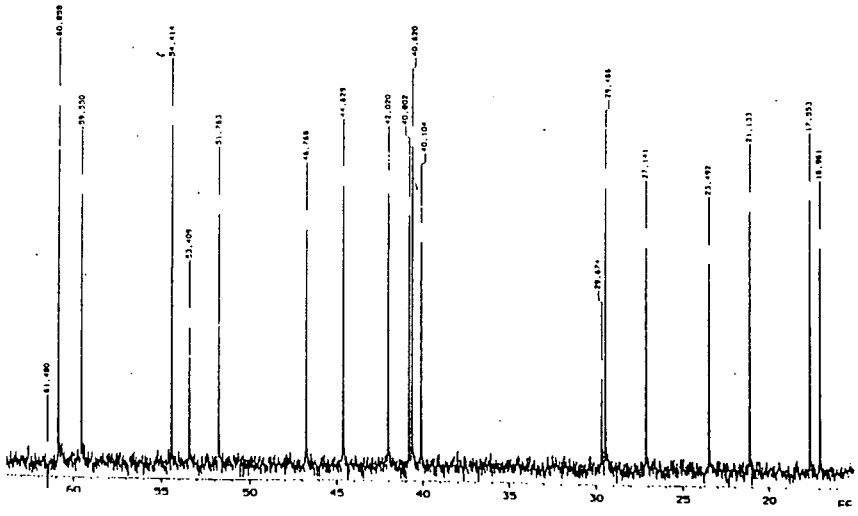


Figure 37. ^{13}C NMR (16-62 ppm) spectrum belonging to **133**. Assignment to diastereoisomer **(2S,8S)-133** or **(2S,8R)-133** could not be made.

Evans has discussed the enolate geometry for alkylation with dialkylamides, and proposes a predominance of the Z-enolate, after deprotonation[86]. In addition, the Z selectivity was quite obvious from the experiment carried out on prolinol amide[20]. These are explained in terms of allylic strain considerations[2]. For instance, the

competitive enolization of dialkylamides can occur from either conformation **A** or conformarion **B**, as shown in **Fig 38**. The transition state for deprotonation from conformation **B** may be destabilized by 1,3-allylic strain interactions between R and methyl substituents. Thus, allylic strain conformational control elements generally give Z-enolates.

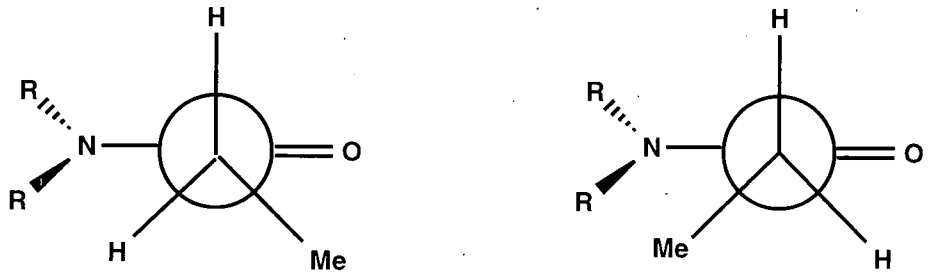


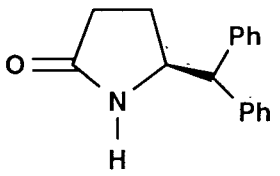
Fig. 38.

These conclusions maybe appropriate to our system, however we must reserve judgement until we assign the absolute stereochemistry of our predominant diastereoisomers.

Each rotamer **(2S,8S)-133a** and **(2S,8S)-133b** can be assigned by two-dimensional ^{1}H-^{1}H and ^{13}C-^{1}H NMR spectra. In this respect, the N-(2'-methy-3'-phenylpropyl) group was examined. The methyl protons from each rotamer gave a doublet at δ 0.4 and 1.1 ppm, with a coupling constant of 6.8 Hz in each case. The methine proton in both rotamers gave dissimilar proton coupling patterns between δ 2.3-2.4 and 2.7-2.8 ppm. One methylene proton gave a doublet of doublets between δ 2.6-2.7 and 2.9 ppm, with coupling constants 7.6 Hz, 10.8 Hz, and 13.2 Hz, whereas the other gave a pair of doublet of doublets at δ 2.5 ppm with a more complex coupling pattern. As a result, it was found that the protons of N-(2'-methyl-3'-phenylpropyl) group in rotamer **(133a)** are shifted down-field when compared to those of rotamer **(133b)**.

Pyrrolidine C-5 oxidation

It is well known that[111] metal ion chelation can play a key organizational role in enolate geometry by establishing a fixed stereochemical relationship between the resident asymmetric center and the enolate system. Therefore, attention was turned to the oxidation of chiral pyrrolidine (**1**) to amide (**2**) to control free rotation about N(1)CO in an effort to impose predictable geometries during the alkylation reaction.



2

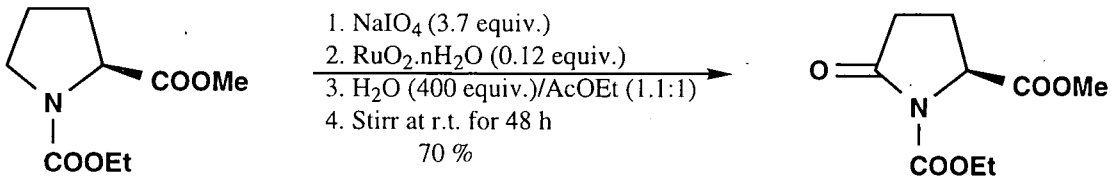
To synthesise the target pyrrolidine (**2**) with an additional coordination site at the 5-position of pyrrolidine ring system, we investigated, in the first instance, the oxidation of carbamate compound (**115**) under three different conditions. The first was the improved Sharpless's oxidation developed by Carlsen[112] *et al.*, which involved the addition of CH_3CN to the traditional CCl_4-H_2O system (**Method A**). The second strategy was the oxidation method reported by Murata[113] *et al.*, which involved the treatment of carbamate compound (**114**) with Fe_2ClO_4-H_2O_2 in CH_3COOH and CH_3CN containing 5 % H_2O (**Method B**), and finally a two-phase oxidation method developed by Yoshifuji[114] *et al.*, which employed a catalytic amount of $RuO_2.H_2O$ and excess of $NaIO_4$ as a co-oxidant in AcOEt-H_2O system (**Method C**), was studied. However, in all of the cases described above the reaction failed, and the carbamate (**115**) was recovered unchanged. These are summarised in **Table 17**.

Entry	Method	Catalyst	Co-oxidant	solvent system	time
1	**A**	$RuO_2.nH_2O$ (0.027 equiv)	$NaIO_4$ (4.1 equiv.)	$CCl_4/CH_3CN/H_2O$ (2:2:3)	192 h
2	**A**	$RuO_2.nH_2O$ (0.031 equiv.)	$NaIO_4$ (4.6 equiv.)	$CCl_4/CH_3CN/H_2O$ (2:2:3)	-
3	**A**	$RuO_2.nH_2O$ (0.37 equiv.)	$NaIO_4$ (4.6 equiv.)	$CCl_4/CH_3CN/H_2O$ (2:2:3)	46 h
4	**A**	$RuCl_3.nH_2O$ (0.090 equiv.)	$NaIO_4$ (4.8 equiv.)	$CCl_4/CH_3CN/H_2O$ (2:2:3)	48 h
5	**B**	$Fe(ClO_4)_2.6HO$ (1 equiv.)	H_2O_2 (5 equiv.)	CH_3CN/CH_3COOH (15 ml:10 equiv.)	96 h
6	**C**	$RuO_2.nH_2O$ (0.15 equiv.)	$NaIO_4$ (10.9 equiv.)	$AcOEt/H_2O$ (1:3)	24 h

Table 17. Attempted oxidation of carbamate **(115)** under three different conditions.

N-Carboxyamide pyrrolidine ester **(114)** is an intermediate in the sythesis of **(1)** and thus we studied the oxidative transformation of **(114)** into the corresponding amide **(134)**. In the first instance, the N-carboxyamide pyrrolidine ester[102] **(114)** was prepared from L-proline **(113)** and purified by distillation as discussed before. The product was then oxidised at room temperature following the method described by Yoshifuji[114] *et al.* as depicted in **Scheme 34**. It is pleasing to report that compound

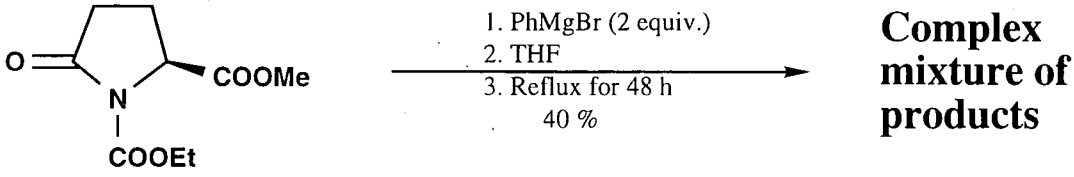
(**134**) was isolated from the organic layer as the only product in high yield and was purified by distillation to give pale-yellow oil.



114 **134**

Scheme 34

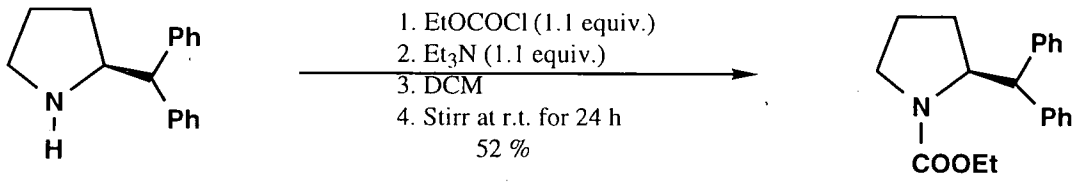
The purified compound (**134**) was then submitted to a Grignard reaction[102] with PhMgBr, as illustrated in **Scheme 35**. However this gave rise to a mixture of unidentifiable products after work up. This route to (**2**) was not developed any further.



134

Scheme 35

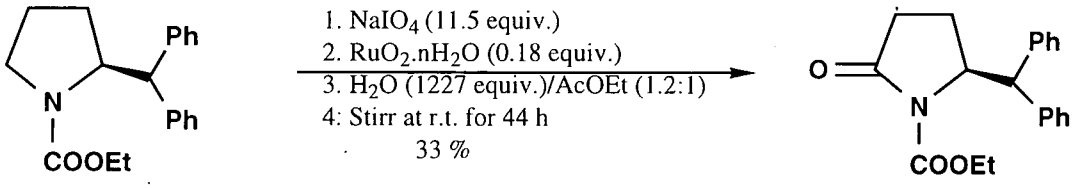
We next focused our attention on the oxidation of N-ethoxycarbamate (**135**) and N-t-butoxycarbamate (**136**) derivatives of pyrrolidine (**1**). In this respect, the N-ethoxycarbmate (**135**) was the first target molecule, and could be prepared in excellent yield following the literature method[104] by simply mixing pyrrolidine (**1**) with ethyl chloroformate, in the presence of triethylamine, as depicted in **Scheme 36**. The resultant compound (**135**) was then purified by chromatography and isolated as a white amorphous solid.



1 **135**

Scheme 36

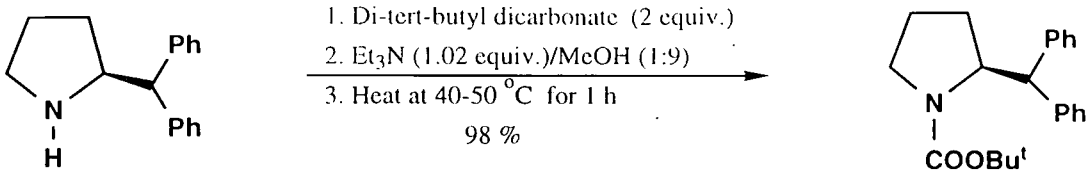
With (**135**) in hand, it was then submitted to oxidation, following the method developed by Yoshifuji[114] *et al.*, with a catalytic amount of $RuO_2.nH_2O$ and excess of $NaIO_4$ in a two-phase system of AcOEt-H_2O, as illustrated in **Scheme 37**. Again the oxidation reaction was successful and compound (**137**) was purified by chromatography and isolated as a white amorphous solid.



135 **137**

Scheme 37

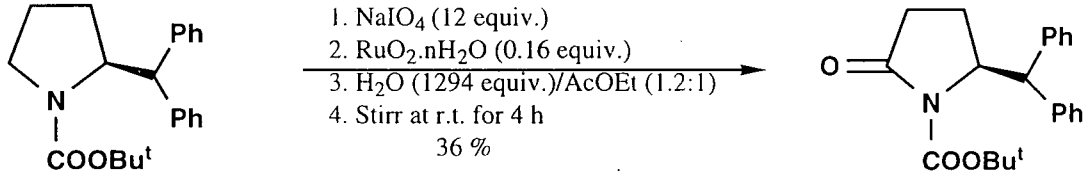
To extend the range of substrates for this oxidation, N-butoxycarbamate (**136**) was prepared as a second target molecule by following the procedure reported by Ponnusamy[115] *et al.* The method involves treatment of pyrrolidine (**1**) with di-tertiary-butyl dicarbonate in a 1:9 mixture of triethylamine-methanol, as shown in **Scheme 38**. Compound (**136**) was then purified by chromatography and isolated as a white amorphous solid.



1 **136**

Scheme 38

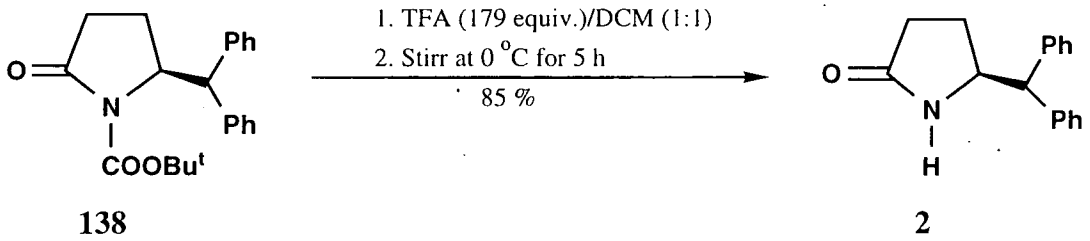
The purified compound **(136)** was then subjected to the Yoshifuji oxidation[114] as depicted in **Scheme 39**. The expected product **(138)** was generated in moderate yield, and was then purified by chromatography and isolated as a white amorphous solid.



136 **138**

Scheme 39

In order to obtain our target amide **(2)** the N-carboxylate esters of **(138)** require to be removed. Although it was reported by Houghten[116] *et al.* that two major problems associated with the use of trifluoroacetic acid (TFA): the high cost of the reagent and the inherent dangers of working with this very volatile and corrosive acid, we decided to use TFA for removal of the N-tertiary-butyloxycarbonyl (Boc) protection group to generate **(2)**. Deprotection of the N-Boc group was achieved by treating **(138)** with a 1:1 mixture of TFA and dichloromethane proceeding smoothly to give **(2)** in good yield, as illustrated in **Scheme 40**.

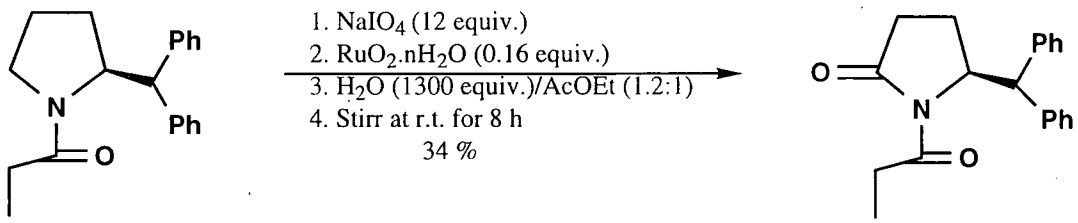


138 **2**

Scheme 40

The target pyrrolidine (**2**) was purified by chromatography and isolated as an oil, which solidified on standing. After removal of colourful impurities by diethyl ether, recrystallisation from ethyl acetate gave (**2**), with its additional coordination site, as a white crystalline solid.

In a final example of this versatile oxidation reaction, N-propylamide (**125**) was treated under the Yoshifuji[114] *et al.* conditions, as shown in **Scheme 41**. The resultant compound (**139**) was purified by chromatography and isolated as a white amorphous solid, which was purified by recrystallisation from ethyl acetate.



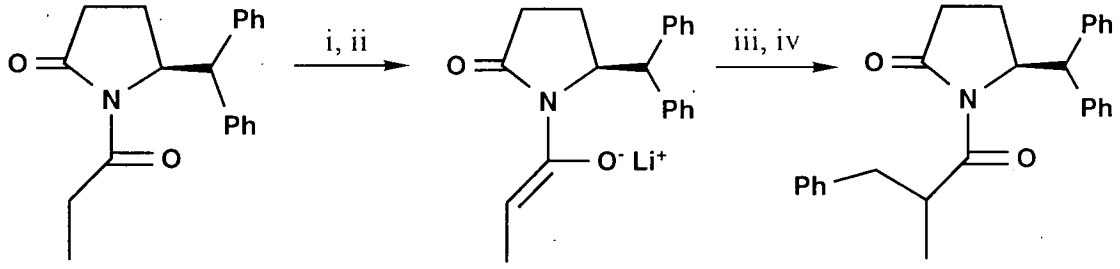
125 **139**

Scheme 40

Alkylation studies with pyrrolidine (139)

One objective of the programme was to assess the pyrrolidine (**2**) as a chiral auxiliary in asymmetric alkylations. Compound (**139**) is a substrate now for direct alkylation and thus the oxidation of (**125**) to (**139**) offers a direct route into the study of

alkylation reactions. Thus, under the standard deprotonation condition[110] (LDA, -78 °C, THF) the amide enolate derivative (**140**) of the purified compound (**139**) was generated, and then this enolate was subjected to an alkylation[20] with BnBr, as illustrated in **Scheme 41**. No alkylation at the C-4 position of (**139**) was observed even with 2 equivalents of LDA.



139 **140** **141**

Reagents: **i-**) LDA (1.1 equiv.), THF); **ii-**) stirr -80 to -20 °C for 1 h; **iii-**) BnBr (3 equiv.), at -80 °C; **iv-**) stirr at -80 °C to r.t. for 3h, 28-33 %.

Scheme 41

Two diastereoisomeric amides were obtained in the product. These amides were purified by chromatography and isolated as individual oils. The diastereoisomeric ratio of the crude mixture was subjected to HPLC and ^{1}H NMR analyses. The HPLC traces of these reactions, with and without HMPA, were complex. However ^{1}H NMR analysis of the HMPA reaction clearly showed two sets of signals in a 4.25:1 ratio, which we tentatively attribute to the alkylated diastereoisomers. In the reaction without HMPA, the HPLC traces are also complex, but ^{1}H NMR suggests a 1:1 mixture of diastereoisomeric products. A re-analysis of the HPLC traces on the basis of the ^{1}H NMR results gives some support to this conclusion, although referencing peaks with pure diastereoisomers is required for a full interpretation of the complex HPLC data.

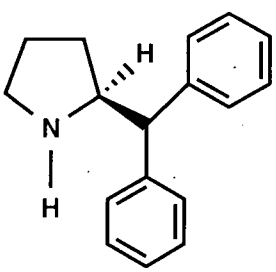
Part 3

3.A. Resolution of racemic acids and alcohols

3.B. Introduction

There are relatively few reports of the use of amines, such as 1-phenyl-ethylamine[65] (**70**), 1-(1-naphthyl)-ethylamine[68] (**71**), (1R, 2R)-1,2-diamino-1,2-diphenylethane[98,99] (**100**) and quinine[100] (**101**), as chiral solvating agents (CSAs) for the analysis of carboxylic acids and alcohols as discussed before. Therefore, there still remains a need for the development of readily available and inexpensive optically pure CSAs for NMR evaluation of acids[117] and alcohols[94]. Bailey and O'Hagan[102] developed a novel and highly efficient route to the homochiral pyrrolidine (**1**) and have used it in a preliminary way as a CSA for the analysis of some acids and alcohols, and this study is now developed further.

In my programme the homochiral pyrrolidine (**1**) and its amide derivative (**2**) were tested as CSAs, and a wider range of chiral acids and alcohols were studied to explore the scope of (**1**) and (**2**) as CSAs for ^{1}H NMR analysis. Also the study was extended to assess the effect of stoichiometry on the resolution of some carboxylic acids and alcohols to contribute a better understanding of the origin of the observed anisochronicity and to optimise the value of the chemical shift non-equivalence.



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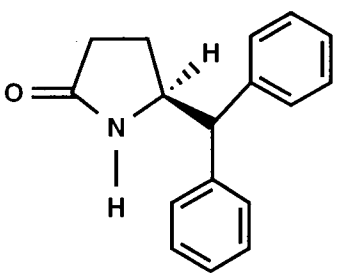

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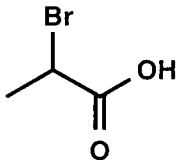
3.C. Results and discussion

In the first part of our programme the ^1H NMR spectra of a series of the diastereoisomeric salts obtained from α-propionic acid derivatives (**142-144**) and optically active pyrrolidine (**1**), or its amide derivative (**2**), was investigated.



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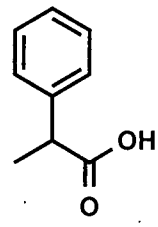

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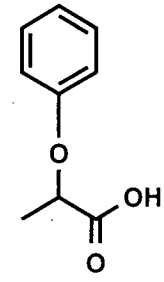
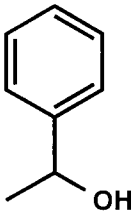


144

In the second part, the ^1H NMR spectra of the diastereoisomeric mixtures obtained from chiral alcohols (**145-148**) and homochiral pyrrolidine (**1**), or its amide derivative (**2**), were recorded.



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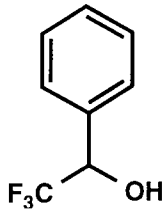

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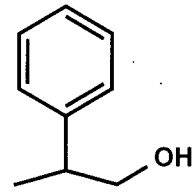
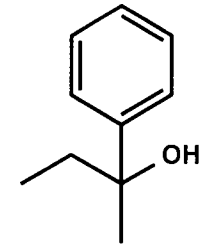


147



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The experimental method for CSA-NMR determination of enantiomeric purity is described below. In a typical experiment standard solutions of both pyrrolidine (**1**) or its amide derivative (**2**) and α-propionic acid derivatives (**142-144**) or alcohols (**145-148**) in $CDCl_3$ were prepared and mixed to give the desired stoichiometric ratio. Then, the ^1H NMR spectrum of the diastereoisomeric mixture was recorded directly at 200 or 250 MHz. The chemical-shift non-equivalence ($\Delta\delta$) of the methyl and

methine resonances in the diastereoisomeric complex was measured to determine the efficiency of (**1**) and (**2**). To determine the optimum chemical shift non-equivalence ($\Delta\delta$), the concentration of CSAs was studied to be up to six times that of the racemic solute.

Resolution of α–propionic acid derivatives

The resolution of α–bromopropionic acid (**142**) was examined as a first example of the acid derivatives, in the presence of homochiral pyrrolidine (**1**) and its amide derivative (**2**). For this purpose, 0.0871 M, 0.5 M, and 0.5 M solutions of (**142**), (**1**) and (**2**) in $CDCl_3$ were prepared, and then the solutions of (**1**) and (**2**) was titrated into the solution of (**142**) respectively. Each titration was monitored by ^1H NMR and the chemical shift non-equivalence ($\Delta\delta$) of the methyl and methine resonances in each diastereoisomeric complex were measured. The $\Delta\delta$ values obtained are summarised in **Fig. 39**.

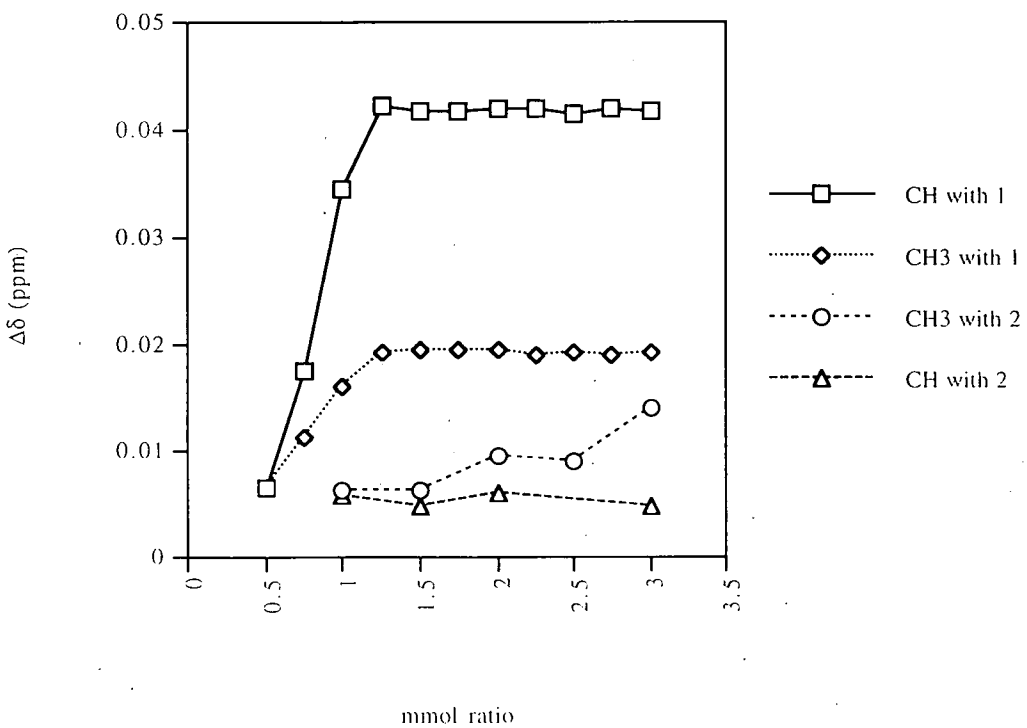


Figure 39. Variation of chemical shift non-equivalence ($\Delta\delta$) for the methyl and methine resonances of (**142**) as a function of (**142**):(**1**) or (**2**) ratio.

In all cases a higher level of chemical shift non-equivalence ($\Delta\delta$) was observed in the presence of (**1**), when compared to (**2**), and the optimum chemical shift non-equivalence was reached when the **142:1** ratio changes from 1:0.5 to 1:1.25. A typical set of ^{1}H NMR spectra are shown in **Fig. 40** for the diastereomeric salt of (**142**) and (**1**), observing the methyl and methine resonances of (**142**).

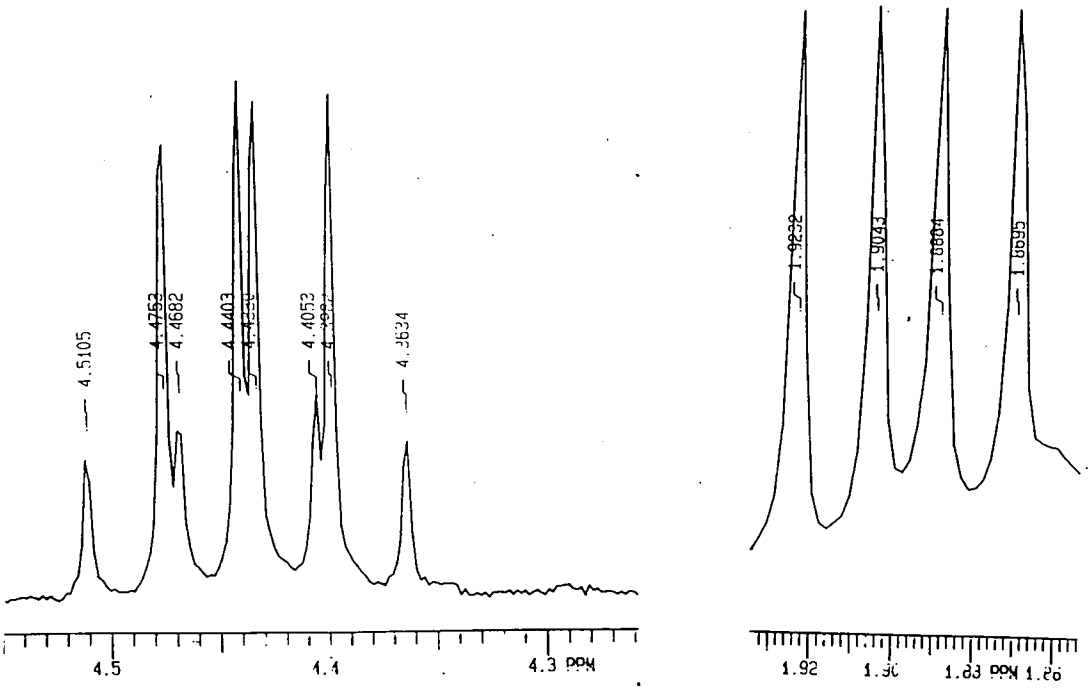


Figure 40. The methyl and methine ^{1}H NMR spectrum of (**142**) in the presence of optically active amine (**1**).

Maximum shift non-equivalences for the methyl ($\Delta\delta$= 0.0192 ppm) and methine resonances ($\Delta\delta$= 0.0421 ppm) were observed at 1:1.25 ratio of (**142**):(**1**). However, above this ratio there was no additional effect of stoichiometry on the chemical shift non-equivalences. Effects of stoichiometry on the chemical shift non-equivalence in the case of (**2**) were not significant. As a result it is clear that amine (**1**) out performs amide (**2**).

As a second example, 2-phenylpropionic acid (**143**) was examined again in the presence of pyrrolidine (**1**) and its amide derivative (**2**). For this purpose, 0.00888 M, 0.4 M, and 0.5 M solutions of (**143**), (**1**), and (**2**) in $CDCl_3$ were prepared, and then the solutions of amine (**1**) and amide (**2**) were titrated into the solution of (**143**) respectively. Each titration was monitored by ^1H NMR, and the observed chemical shift non-equivalences ($\Delta\delta$) are summarised in **Fig. 41**.

Finally, 2-phenoxypropionic acid (**144**) was examined also in the presence of pyrrolidine (**1**) and then its amide derivative (**2**). For this purpose, 0.0802 M, 0.4 M, 0.5 M solutions of (**144**), (**1**), and (**2**) in $CDCl_3$ were prepared, and then the solutions of amine (**1**) and amide (**2**) were titrated into the solution of (**144**) respectively. Each titration was monitored by ^1H NMR and the observed chemical shift non-equivalences ($\Delta\delta$) are summarised in **Fig. 41**.

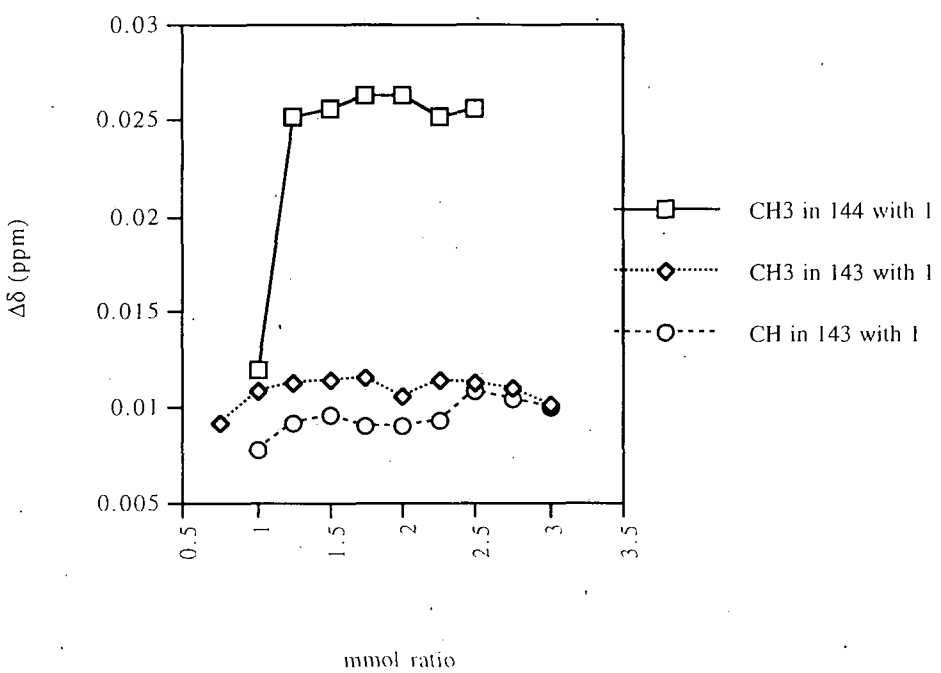
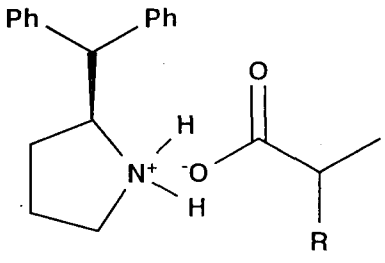


Figure 41. Variation of chemical shift non-equivalence ($\Delta\delta$) for both the methyl and methine resonances of (**143**) and only the methyl resonance of (**144**) as a function of (**143**) or (**144**):(**1**) ratio.

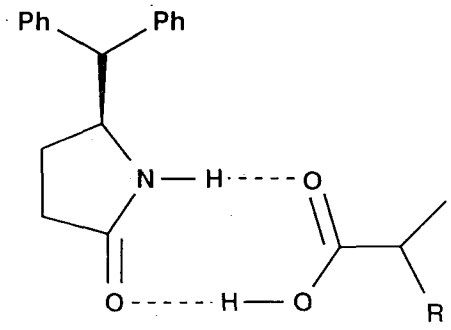
As can be seen in **Fig. 41**, in the series of ^{1}H NMR spectra obtained on titration of (**143**) with (**1**), small chemical shift non-equivalences ($\Delta\delta$) were observed for both the methyl and methine resonances of (**143**). However, there was no significant effect on the observed chemical shift non-equivalences ($\Delta\delta$) beyond one equivalent of (**1**). However in the series of ^{1}H NMR spectra obtained on titration of (**143**) with (**2**), no trace of resolution was observed.

In the case of the titration of (**144**) with (**1**), chemical shift non-equivalences have been observed only in the signals associated with the methyl group of (**144**). The largest shift non-equivalence ($\Delta\delta$= 0.025 ppm) observed during the titration was at a 1:1.25 ratio of (**144**):(**1**), and above this ratio there was no additional effect on varying stoichiometry. In the presence of (**2**), there was no observable enantiomeric separations in both the methyl and methine resonances of (**144**).

The failure of amide (**2**) relative to amine (**1**) as a CSA for the resolution of (**143**) and (**144**) is indicative of a weaker association between the acids and amide. For (**2**) this association must rely on H-bonding. However in the case of amine (**1**) a more effective electrostatic interaction is set up in solution due to the formation of a salt, as shown in **Fig. 42**.



electrostatic salt formation



H-bonding interactions

(intra- or inter-)

Figure 42. Possible interactions between the amine (**1**) and the acid (**144**) or the amide (**2**) and the acid (**144**).

Resolution of alcohols

The resolution of *sec*-phenethanol (**145**) was examined in the presence of pyrrolidine (**1**) and its amide (**2**). For this purpose, 0.109 M, 0.328 M and 0.5 M solutions of (**145**), (**1**) and (**2**) were prepared, and then the solutions of (**1**) and (**2**) were titrated into the solution of (**145**) respectively. Each titration was monitored by ^{1}H NMR and the chemical shift non-equivalencies ($\Delta\delta$) observed are summarised in **Fig. 43**.

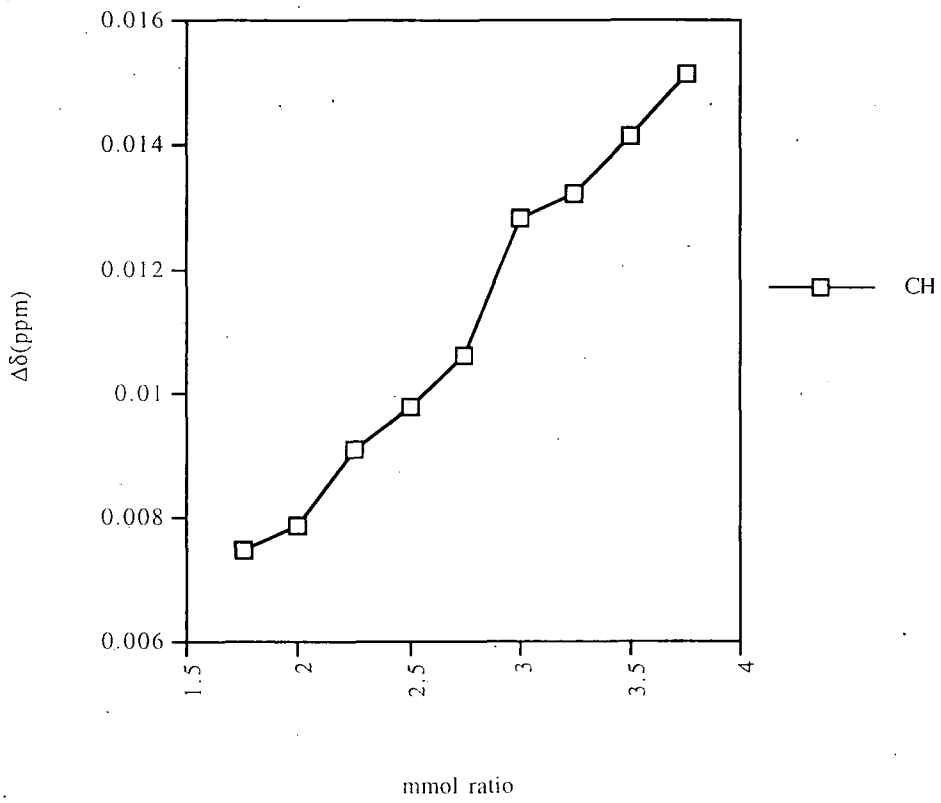


Figure 43. Variation of chemical shift non-equivalencies ($\Delta\delta$) for the methine resonances of (**145**) as a function of (**145**):(**1**) mmol ratio.

In the series of ^{1}H NMR spectra obtained on titration with (**1**) the chemical shift non-equivalencies ($\Delta\delta$) were observed only for the methine resonance of (**145**), as can be seen in **Fig. 43**. Varying the stoichiometric ratio of (**145**):(**1**) from 1:0.25 to 1:3.75 had a two fold effect on the observed chemical shift non-equivalence ($\Delta\delta$).

Unlike the (**1**), in the presence of (**2**) only avery small chemical shift non-equivalence ($\Delta\delta$= 0.00497 ppm) was observed for the methyl resonance of (**145**) and only at a 2:1 ratio of (**145**):(**2**). A typical set of ^{1}H NMR spectrum is shown in **Fig. 44** for the diastereoisomeric complex of (**145**) and (**2**), observing the methyl resonance of (**145**).

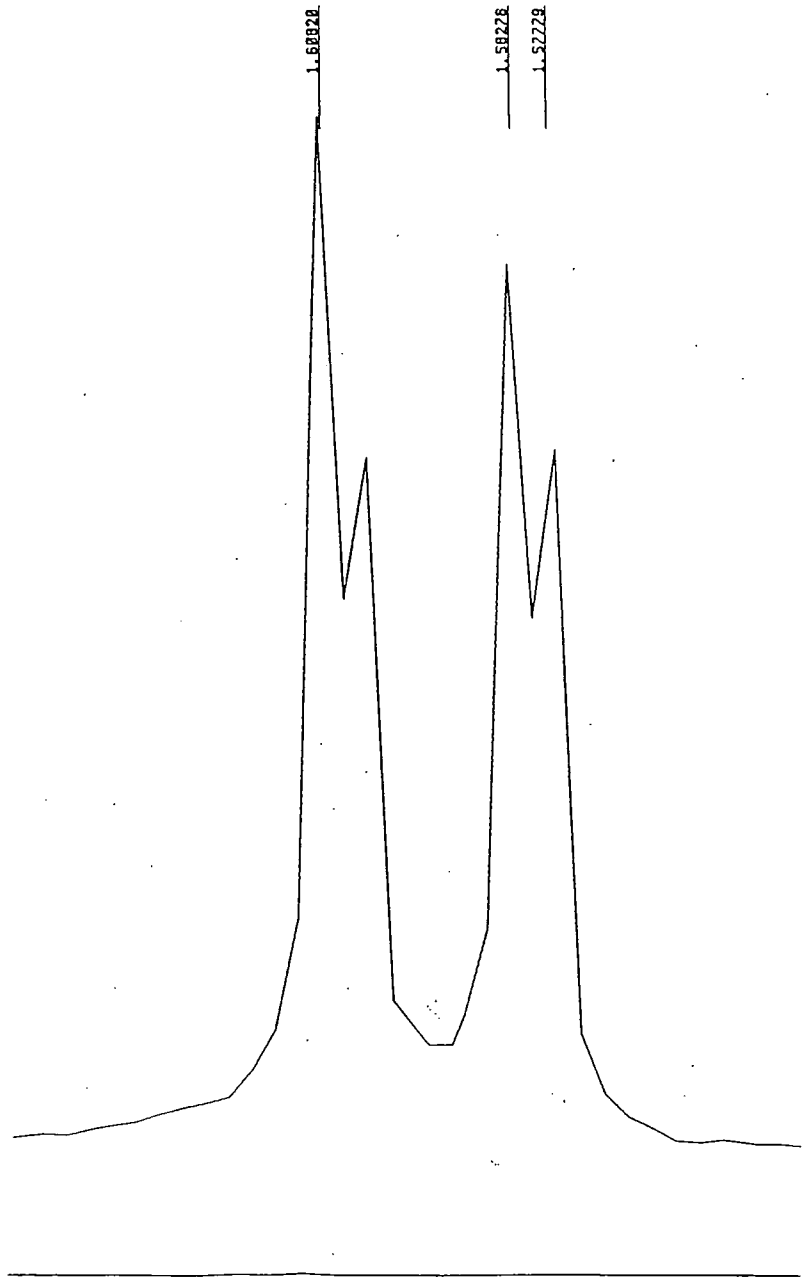
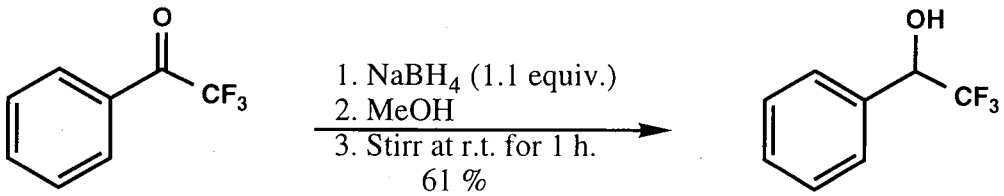


Figure 44. The ^{1}H NMR spectrum between (0-2 ppm) of (**145**) in the presence of optically active amide (**2**).

In order to extend the range of alcohols studied, racemic 2,2,2-trifluoro phenethanol (**146**) was examined in the presence of pyrrolidine (**1**). In this respect, 2,2,2-trifluoroacetophenone (**149**) was converted to the corresponding alcohol (**146**) under standard conditions[118] by simply reducing (**149**) with $NaBH_4$, in the presence of dry and distilled MeOH, as shown in **Scheme 42**. The compound (**146**) was purified by distillation and then directly used for ^1H NMR resolution. However, no trace of resolution was observed for alcohol (**146**) and the others (**147**) and (**148**) in the presence of pyrrolidine (**1**).



149 **146**

Scheme 42

It is clear that (**1**) is an excellent complexing agent for carboxylic acids, however it is less effective for alcohols, presumably as electrostatic complexes are unable to form in the latter case. The amide derivative (**2**) is substantially less effective as a chiral solvating agent for carboxylic acids and fails completely to resolve alcohols.

CHAPTER 3

Experimental

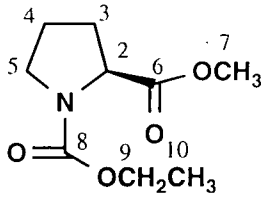
3.A. General experimental

^{1}H and ^{13}C NMR Spectra were recorded on a Varian Gemini-200 operating at 199.977 MHz for ^{1}H and 50 MHz for ^{13}C, a Bruker AC-250 operating at 250.133 MHz for ^{1}H and 62.257 MHz for ^{13}C, and finally a Varian VXR-400 (S) operating at 399.952 MHz for ^{1}H and 100.577 MHz for ^{13}C. Chemical shifts are quoted relative to tetramethylsilane (TMS), $(CH_3)_4Si$ (δ=0) for ^{1}H and ^{13}C, in chloroform-*d* ($CDCl_3$), dimethylsulphoxide-*d6* (DMSO), and acetone-*d6*. IR Spectra were recorded on a Perkin-Elmer F. T. 170X spectrometer using conventional techniques in usually 4 scans. Low resolution mass spectra were recorded on a VG Analytical 7070E organic mass spectrometer operating at 70eV. Melting points were determined using a digital Gallenkamp melting point apparatus and are un-corrected. Flash Chromatography was carried out using Fluka silica gel-60 (35-70 μm). X-Ray crystal data was collected on a Siemens R3m/v diffractometer. High pressure liquid chromatography was carried out on a Perkin Elmer series 410 chromatography using a Hewlett Packard 1040A detection system. All solvents were dried and distilled prior to use unless otherwise stated. Solvents were dried from the following reagents under a nitrogen atmosphere: Tetrahydrofuran (THF) and diethyl ether (sodium benzophenone), dichloromethane (DCM) and triethylamine (calcium hydride), and methanol (magnesium methoxide). Petrol refers to petroleum ether (30-60 °C). Non-aqueous reactions were carried out under nitrogen atmosphere. In general chemicals were used as received from suppliers (Aldrich, Sigma and Jannsen).

3.B. Index to experimental

Entry	Compound number	Related page number in the experimental	Related page number in the text
1	114	91	53
2	115	92	54
3	1	93	54
4	119	94	56
5	120	95	57
6	121-124	97	59
7	125	97	63
8	126	99	65
9	128	100	67
10	129	101	67
11	131	103	69
13	133	105	70
15	134	108	75
16	135	109	76
17	137	111	76
18	136	112	77
19	138	113	77
20	2	114	78
21	139	116	78
22	141	117	79
24	146	120	88

1. Ethyl (S)-1-formyl-2-carboxymethylpyrrolidine[102].



114

Ethyl chloroformate (59.25 g, 0.546 mol) was added dropwise to a solution of L-proline (30 g, 261 mmol) and $K_2CO_3.1^{1/2}H_2O$ (45.1 g, 273 mmol) in dry methanol (330 ml) at 0°C. After addition was complete, the solution was stirred for 24h at room temperature. The solvent was removed under reduced pressure and the residue partitioned between water and chloroform. The layers were separated and the aqueous layer extracted into chloroform (5x30 ml). The combaned organic extracts were washed with brine (2x20 ml) and dried ($MgSO_4$). Filtration and concentration gave the title compound (49.73 g, 94.8%) as a colourless oil. This material was employed directly for further reactions.

δ_H (200 MHz, $CDCl_3$) 1.00-1.25 (2H, p, C-4), 1.70-2.00 (2H, m, C-3), 2.00-2.30 (3H, m, C-10), 3.25-3.50 (2H, m, C-5), 3.60 (3H, s, C-7), 3.95-4.15 (H, m, C-2), 4.15-4.35 (2H, q, C-9).

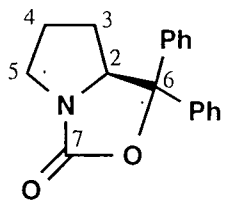
δ_C (50 MHz, $CDCl_3$) 14.6 (C-10), 23.4 (C-4), 24.3 (C-4), 29.8 (C-3), 30.8 (C-3), 46.2 (C-5), 46.6 (C-5), 52.0 (C-7), 52.1 (C-7), 58.7 (C-2), 58.9 (C-2), 61.1 (C-9), 61.2 (C-9), 154.5 (C-8), 155.0 (C-8), 173.2 (C-6), 173.3 (C-6).

Anal. Calcd. for $C_9H_{15}NO_4$: C, 53.70; H, 7.52; N, 6.96. Found: C, 53.41; H, 7.50; N, 7.61.

IR (NaCl disk) υ cm^{-1} : 2981, 2956, 2882, 1749 (C_8=O), 1703 (C_6=O), 1419, 1382, 1349, 1201, 1174, 1121, 1090.

Mass analysis (m/z): EI, 201 (M^+, 5.2 %), 142 (-59, 100 %), 70 (-72, 90.6 %), 41 (-29, 45.7 %).

2. (5S)-[0.3.3]-1-Aza-2-oxo-3-oxa-4,4-diphenylbicyclooctane[102].



115

A solution of ethyl (S)-1-formyl-2-carboxymetylpyrrolidine (37 g, 184 mmol) in THF (60 ml) was added dropwise to a solution of PhMgBr (1M, 380 ml) in THF at 0 °C. The reaction mixture was left to warm to room temperature and was then heated under reflux for 12h. An ice-cold saturated solution of NH_4Cl (500 ml) was added and the layers were separated. The aqueous layer was extracted into ethyl acetate (5x100 ml) and the combined organic extracts were dried ($MgSO_4$). Filtration and concentration gave a pale-yellow solid which was purified by crystallisation in ethyl acetate to yield the product (23.1 g, 45 %) as a white solid. **m.p.** 148.3-148.5 °C (lit. 148-149)[102].

δ_H (200 MHz, $CDCl_3$) 1.00-1.25 (1H, p, C-4), 1.65-2.05 (3H, m, C-3 and C-4), 3.15-3.35 (1H, m, C-5), 3.65-3.80 (1H, m, C-5), 4.50-4.65 (1H, dd, C-2), 7.20-7.45 (8H, m, Ar-H), 7.45-7.60 (2H, d, Ar-H_{AB}).

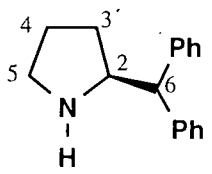
δ_C(62.5 MHz, $CDCl_3$) 24.9 (C-4), 29.0 (C-3), 46.0 (C-5), 69.2 (C-2), 85.8 (C-6), 125.4 (p-Ar), 125.9 (p-Ar), 127.7 (o-Ar), 128.3 (o- and m-Ar), 128.5 (m-Ar), 140.2 (α-Ar), 143.3 (α-Ar), 160.4 (C-7).

Anal. Calcd. for $C_{18}H_{17}NO_2$: C, 77.38; H, 6.14; N, 5.02; Found. C, 77.25; H, 6.16; N, 4.94.

IR (KBr) υ cm^{-1}: 2979, 2905, 1751 (C=O), 1447, 1387, 1345, 1248, 1227, 1056, 1005.

Mass analysis (m/z): EI, 279 (M^+, 13.3 %), 182 (-98, 45.2 %), 105 (-77, 100 %), 77 (-28, 32.4 %); **CI**, 280 (MH^+, 9.1 %), 236 (-44, 15.6 %), 70 (-166, 1.6 %).

3. (S)-2-(Diphenylmethyl)-pyrrolidine[102].



1

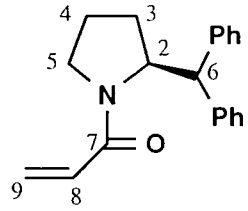
Palladium (4.5 g) on activated carbon was added to a solution of (5S)-[0.3.3]-1-aza-2-oxo-3-oxa-4,4-diphenyl-bicyclooctane (24.0 g, 86 mmol) in dry methanol (300 ml) at room temperature. Upon evacuation/filling procedure, the flask had been charged with hydrogen until the hydrogenation was completed as judged by the consumption of hydrogen gas by volume. Filtration of the catalyst and removal of the solvent gave a residue. Purification either over silica gel (4:1, ethyl acetate/methanol) or by fractional distillation under *vacuo* (preferable in the case of large scale reactions) gave the product (17.53 g, 86 %) as a colourless oil.

δ_H (250 MHz, $CDCl_3$) 1.51-1.62 (1H, m, C-4), 1.83-2.00 (3H, m, C-3 and C-4), 2.28 (1H, s, N-H), 2.92-2.98 (1H, m, C-5), 3.10-3.19 (1H, m, C-5), 3.82-4.01 (2H, m, C-2, C-6).

δC (62.5 MHz, $CDCl_3$) 24.8 (C-4), 30.6 (C-3), 46.2 (C-5), 58.5 (C-6), 62.3 (C-2), 126.4 (p-Ar), 128.3 (o-Ar), 128.7 (m-Ar), 143.7 (α-Ar).

Mass analysis (m/z): EI, 237 (M^+, 0.3 %), 167 (-70, 34.5), 70 (-167, 100 %); **CI**, 238 (MH^+, 100 %), 70 (-168, 22.3).

4. (S)-2-(Diphenylmethyl)-pyrrolidine-N-acrylamide[104].



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Triethylamine (150 mg, 1.48 mmol) and acrylyl chloride (134 mg, 1.48 mmol) were added dropwise to a solution of (S)-2-(diphenylmethyl)-pyrrolidine (289 mg, 1.22 mmol) in DCM (20 ml) at 0 °C. The mixture was stirred overnight at room temperature, was washed with dilute HCl, extracted into DCM (4x30 ml), dried ($MgSO_4$) and concentrated. Purification over silica gel, eluting with ethyl acetate, gave the product (280 mg, 79 %) as an amorphous white solid, which was then crystallised from ethyl acetate. The product has two diastereoisomeric rotamers, A and B, which arise from restricted rotation of the amide bond. **m.p.**125.1-125.3 °C.

A : δ_H (400 MHz, $CDCl_3$) 1.62-1.76 (2H, m, C-4), 1.92-2.18 (2H, m, C-3), 3.40-3.50 (1H, m, C-5), 3.70-3.80 (1H, m, C-5), 4.75-4.80 (1H, d, C-6), 5.08-5.12 (1H, m, C-2), 5.62-5.68 (1H, dd, trans-C-9), 6.30-6.36 (1H, dd, cis-C-9), 6.40-6.46 (1H, dd, geminal-C-8), 7.10-7.38 (10H, m, Ar-H).

A : δ_C (100 MHz, $CDCl_3$) 21.2 (C-4), 27.2 (C-3), 45.4 (C-5), 51.3 (C-6), 59.7 (C-2), 126.0 (p-Ar), 126.1 (p-Ar), 127.4 (o-Ar), 128.0 (o-Ar), 128.1 (m-Ar), 128.7 (m-Ar), 128.9 (C-9), 129.2 (C-8), 140.7 (α-Ar), 141.1 (α-Ar), 164.8 (C=O).

B: δ_H (400 MHz, $CDCl_3$) 1.06-1.20 (1H, m, C-4), 1.50-1.60 (1H, m, C-4), 1.70-1.90 (1H, m, C-3), 1.92-2.18 (1H, m, C-3), 3.15-3.25 (1H, m, C-5), 3.40-3.50 (1H, m, C-5), 4.04-4.10 (1H, d, C-6), 4.60-4.70 (1H, m, C-2), 5.18-5.22 (1H, dd, trans-C-9), 5.78-5.86 (1H, dd, geminal-C-8), 6.00-6.06 (1H, dd, cis-C-9), 7.10-7.38 (10H, m, Ar-H).

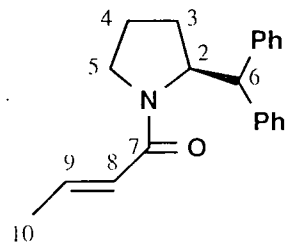
B: δ_C (100 MHz, $CDCl_3$) 23.6 (C-4), 30.1 (C-3), 47.1 (C-5), 54.6 (C-6), 61.1 (C-2), 126.8 (p-Ar), 126.9 (p-Ar), 126.5 (o-Ar), 127.5 (o-Ar), 128.4 (m-Ar), 128.6 (m-Ar), 129.1 (C-9), 129.7 (C-8), 141.9 (α-Ar), 142.1 (α-Ar), 165.1 (C=O).

IR (KBr) υ cm^{-1}: 3023-2881, 1644 (C=O), 1609 (C=C), 1493, 1451, 1422, 1365, 989, 952, 794, 769, 744, 712, 704.

Anal. Calcd. for $C_{20}H_{21}NO$: C, 82.42; H, 7.27; N, 4.81; Found: C, 82.31; H, 7.26; N,4.66.

Mass analysis (m/z): EI, 291 (M^+, absent), 124 (-167, 100 %), 70 (-54, 100 %), 55 (-15, 56.5 %); **CI**, 292 (MH^+, 34.3 %), 124 (-168, 4.1 %), 70 (-54, 10.5 %).

5. (S)-2-(Diphenylmethyl)-pyrrolidine-N-crotonylamide[104].



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Triethyl amine (277 mg, 2.74 mmol) and crotonyl chloride (286 mg, 2.74 mmol) were added dropwise to a solution of (S)-2-(diphenylmethyl)-pyrrolidine (500 mg, 2.11 mmol) in DCM (30 ml) at 0 °C. The mixture was stirred for 48 hours at room temperature

and then washed with dilute HCl. The organics were extracted into DCM (4x30 ml), dried ($MgSO_4$), and concentrated to obtain a light brown solid. Purification over silica gel, eluting with a mixture of ethyl acetate and petrol (1:9), gave the product (321 mg, 50 %) as a white amorphous solid. The product has two diastereoisomeric rotamers, A and B, which arise from restricted rotation of the amide bond. **m.p.** 150-151 °C.

A : δ_H (400 MHz, CDCl3) 1.56-1.60 (3H, dd, C-10), 1.60-1.70 (1H, m, C-4), 1.76-1.86 (1H, m, C-4), 1.92-2.10 (2H, m, C-3), 3.45-3.50 (1H, m, C-5), 3.70-3.80 (1H, m, C-5), 4.75-4.80 (1H, d, C-6), 5.05-6.00 (1H, m, C-2), 6.08-6.12 (1H, d, C-8), 6.86-6.96 (1H, qq, C-9), 7.10-7.38 (10H, m, Ar-H).

A : δ_C (100 MHz, CDCl3) 17.8 (C-10), 21.3 (C-4), 27.2 (C-3), 45.4 (C-5), 51.3 (C-6), 59.6 (C-2), 123.5 (C-9), 126.0 (p-Ar), 126.4 (p-Ar), 128.0 (o-Ar), 128.1 (o-Ar), 128.8 (m-Ar), 128.9 (m-Ar), 129.8 (C-8), 140.8 (α-Ar), 142.0 (α-Ar), 165.3 (C_7=O).

B : δ_H (400 MHz, CDCl3) 1.02-1.12 (1H, m, C-4), 1.62-1.70 (1H, m, C-4), 1.86-1.90 (3H, dd, C-10), 1.92-2.10 (2H, m, C-3), 3.12-3.22 (1H, m, C-5), 3.35-3.50 (1H, m, C-5), 4.05-4.10 (1H, d, C-6), 4.60-4.70 (1H, m, C-2), 5.48-5.56(1H, d, C-8), 6.52-6.60 (1H, qq, C-9), 7.10-7.38 (10H, m, Ar-H).

B : δC (100 MHz, CDCl3) 18.1 (C-10), 23.6 (C-4), 30.1 (C-3), 47.0 (C-5), 54.6 (C-6), 61.1 (C-2), 122.1 (C-9), 126.8 (p-Ar), 126.8 (p-Ar), 128.3 (o-Ar), 128.6 (o-Ar), 129.1 (m-Ar), 129.7 (m-Ar), 139.6 (C-8), 141.2 (α-Ar), 142.2 (α-Ar), 165.5 (C_7=O).

IR (KBr) υ cm^{-1}: 3052-2867, 1657 (C=0), 1597 (C=C), 1443, 1424, 1322, 1205, 969, 757, 703.

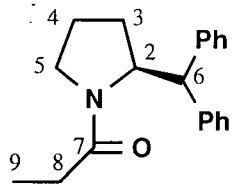
Analysis: $C_{21}H_{24}NO$ (MH^+) requires 306.18579, found 306.18431.

Mass analysis (m/z): EI, 305 (M^+, absent), 138 (-167, 53.3 %), 69 (-69, 100 %) ; **CI**, 306 (MH^+, 1.3 %), 183 (-123, 3.0 %).

6. Synthesis of Diels-Alder adducts (121-124) with cyclopentadiene[107b].

Cyclopentadiene (304 mg, 4.60 mmol) was added to a solution of (S)-2-(diphenylmethyl)-pyrrolidine-N-acryl amide (268 mg, 0.92 mmol) and $TiCl_4$ (350 mg, 1.84 mmol) in toluene (25 ml) at room temperature. The reaction mixture was heated under reflux for 48h and then quenched by addition of water (30 ml). The organic product was extracted into ethyl acetate, the combined extracts were dried ($MgSO_4$), and concentrated. Purification over silica gel, eluting with ethyl acetate, lead to a mixture of cycoadducts. This mixture remains to be characterised.

7. (S)-(Diphenylmethyl)-pyrrolidine-N-propylamide[104].



125

Triethylamine (175 mg, 1.73 mmol) and propionyl chloride (160 mg, 1.73 mmol) were added dropwise to a solution of (S)-2-(diphenylmethyl)-pyrrolidine (340 mg, 1.44 mmol) in DCM (20 ml) at 0 °C. The mixture was stirred overnight and washed with dilute HCl. The organic product was extracted into the DCM (4x30 ml), dried ($MgSO_4$), and concentrated. Purification over silica gel, eluting with ethyl acetate, gave the product (367 mg, 87 %) as an amorphous white solid, which was crystallised from ethyl acetate. The product has two diastereoisomeric rotamers, A and B, which arise from restricted rotation of the amide bond. **m.p.** 97.5 °C.

A: δ_H (400 MHz, $CDCl_3$) 1.05-1.12 (3H, t, C-9), 1.10-1.20 (1H, m, C-4), 1.62-1.72 (1H, m, C-4), 1.92-2.08 (2H, m, C-3), 2.20-2.30 (2H, q, C-8), 3.05-3.15 (1H, tt, C-5), 3.25-3.35 (1H, tt, C-5), 4.65-4.70 (1H, d, C-6), 5.00-5.05 (1H, m, C-2), 7.10-7.38 (10H, m, Ar-H).

A: δ_C (100 MHz, $CDCl_3$) 9.0 (C-9), 23.5 (C-4), 27.3 (C-3), 28.3 (C-8), 46.7 (C-5), 51.5 (C-6), 59.4 (C-2), 125.9 (p-Ar), 126.4 (p-Ar), 127.8 (o-Ar), 128.0 (o-Ar), 128.5 (m-Ar), 129.6 (m-Ar), 141.9 (α-Ar), 142.1 (α-Ar), 172.5 (C_7=O).

B: δ_H (400 MHz, $CDCl_3$) 0.70-0.80 (3H, t, C-9), 0.80-0.90 (1H, m, C-4), 1.20-1.30 (1H, m, C-4), 1.80-1.90 (2H, m, C-3), 2.20-2.30 (2H, q, C-8), 3.40-3.50 (1H, tt, C-5), 3.75-3.85 (1H, tt, C-5), 4.00-4.03 (1H, d, C-6), 4.50-4.55 (1H, t, C-2), 7.10-7.38 (10H, m, Ar-H).

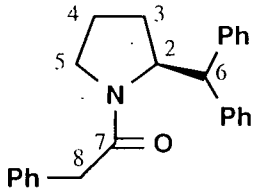
B: δ_C (100 MHz, $CDCl_3$) 9.1 (C-9), 21.2 (C-4), 26.6 (C-3), 28.3 (C-8), 44.8 (C-5), 54.1 (C-6), 61.6 (C-2), 126.7 (p-Ar), 126.8 (p-Ar), 128.3 (o-Ar), 128.5 (o-Ar), 128.8 (m-Ar), 128.9 (m-Ar), 140.7 (α-Ar), 141.4 (α-Ar), 173.1 (C_7=O).

IR (KBr) υ cm^{-1}: 3025-2881, 1641 (C=O), 1493, 1453, 1419, 1299, 1196, 766, 742, 702.

Anal. Calcd. for $C_{20}H_{23}NO$: C,81.91; H, 7.85; N, 4.78. Found: C, 81.81; H, 8.08; N, 4.60.

Mass analysis (m/z): EI, 293 (M^+, absent), 126 (-167, 43.9 %), 70 (-56, 100 %); **CI**, 294 (MH^+, 51.7 %), 126 (-168, 10.1 %), 70 (-56, 19.0 %).

8. (S)-2-(Diphenylmethyl)-pyrrolidine-N-phenylacetamide[104].



126

Triethylamine (555 mg, 5.486 mmol) and phenylacetyl chloride (848 mg, 5.49 mmol) were added dropwise to a solution of (S)-2-(diphenylmethyl)-pyrrolidine (1.0 g, 4.22 mmol) in DCM (40 ml) at 0 °C. The mixture was stirred at room temperature for 6h and was then quenched with dilute HCl (1.27 ml, 1M). Water (100 ml) and brine solution (20 ml) were added and layers were separated. The product was extracted into DCM (4x30 ml), dried ($MgSO_4$), and concentrated on *vacuo*. Purification over silica gel, eluting with a mixture of ethyl acetate and petrol (2:8), gave the title product (1.03 g, 68.8 %) as a colourless liquid, which solidified on standing to give a white amorphous solid. The product has two diastereoisomeric rotamers, A and B, which arise from restricted rotation of the amide bond. **m.p.** 109.5-109.8 °C.

A: δ_H (400 MHz, $CDCl_3$) 1.10-1.30 (1H, m, C-4), 1.40-1.50 (1H, m, C-4), 1.65-1.80 (2H, m, C-3), 2.55-2.65 (1H, d, C-8), 2.75-2.85 (1H, d, C-8), 3.40-3.50 (1H, m, C-5), 3.70-3.80 (1H, m, C-5), 3.90-4.00 (1H, d, C-6), 4.40-4.50 (1H, m, C-2), 6.82-7.30 (3xPh)

A: δ_C (100 MHz, $CDCl_3$) 21.2 (C-4), 30.2 (C-3), 40.6 (C-8), 45.0 (C-5), 54.0 (C-6), 62.0 (C-2), 126.5 (p-Ar), 126.9 (p-Ar), 127.0 (p-Ar), 128.4 (o-Ar), 128.6 (o-Ar), 128.7 (o-Ar), 128.7 (m-Ar), 128.9 (m-Ar), 129.0 (m-Ar), 135.3 (α-Ar), 140.7 (α-Ar), 141.6 (α-Ar), 170.4 (C_7=O).

B: δ_H (400 MHz, $CDCl_3$) 0.90-1.10 (1H, m, C-4), 1.50-1.60 (1H, m, C-4), 1.80-1.95 (2H, m, C-3), 3.00-3.10 (1H, tt, C-5), 3.25-3.35 (1H, tt, C-5), 3.50-3.60 (2H, d, C-8), 4.50-4.60 (1H, d, C-6), 4.90-5.10 (1H, m, C-2), 6.82-7.30 (3xPh).

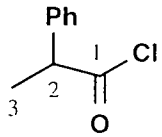
B: δ_C (100 MHz, $CDCl_3$) 23.6 (C-4), 27.3 (C-3), 42.8 (C-8), 47.1 (C-5), 51.6 (C-6), 59.7 (C-2), 126.1 (p-Ar), 126.4 (p-Ar), 126.7 (p-Ar), 127.9 (o-Ar), 128.1 (o-Ar), 128.5 (o-Ar), 128.8 (m-Ar), 129.1 (m-Ar), 129.6 (m-Ar), 134.8 (α-Ar), 141.9 (α-Ar), 142.1 (α-Ar), 169.8 (C_7=O).

Anal. Calcd. for $C_{25}H_{25}NO$: C, 84.46; H, 7.09; N, 3.94 Found. C, 83.86; H, 7.13; N, 3.62.

IR (KBr) υ cm^{-1}: 3446, 3027, 2974, 2920, 2887, 1626 (C=O), 1492, 1447, 1406, 721, 710, 700.

Mass analysis (m/z): EI, 355 (M^+, absent), 188 (-167, 100 %), 91 (100 %), 70 (100 %); **CI**, 357 (MH_2^+, 63.3 %).

9. (RS)-2-Phenylproionyl chloride[109].



128

A solution of racemic 2-phenylpropionic acid (3.0 g, 20.0 mmol) in freshly distilled DCM (5 ml) was added dropwise to a solution of oxalyl chloride (12.9 g, 99.9 mmol) in DCM (10 ml) at room temperature under nitrogen atmosphere. After addition was completed one drop of DMF (dry and distilled) was added to the reaction mixture as a catalyst.and then the entire mixture was stirred for 4 h. Concentration under reduced

pressure gave a crude material as a pale-orangy semi-solid mixture, which was then purified by bulb-to-bulb distillation (50 °C, 0.1-0.01 mm-Hg) under reduced pressure to obtain the product (2.23 g, 66.30 %) as a clear oil.

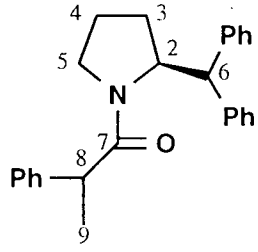
δ_H (200 MHz, $CDCl_3$) 1.60-1.70 (3H, d, CH_3), 4.10-4.30 (1H, q, CH), 7.30-7.50 (5H, m, Ar).

δ_C (50 MHz, $CDCl_3$) 20.8 (C-3), 59.5 (C-2), 130.0 (p-Ar), 130.3 (o-Ar), 131.1 (m-Ar), 139.5 (α-Ar), 177.6 (C=O).

IR (KBr disk) υ cm^{-1}: 1782 (C=0).

Mass analysis (m/z): EI, 170 (M^+, 2.77, 0.9 %), 168 (M^+, 2.77 %), 132 (-36, 14.7 %), 105 (-27, 100 %), 104 (-28, 35.9 %), 27 (-77, 27.5 %).

10. (2S, 8R)- and (2S, 8S)-2-(Diphenylmethyl)-pyrrolidine-N-(2', 2'-methylphenylacetyl)amide[104].



129

A solution of racemic 2-phenyl propionyl chloride (185 mg, 1.1 mmol) in freshly distilled DCM (3 ml) and triethylamine (111 mg, 1.1 mmol) were added to a solution of (S)-2-(diphenylmethyl)-pyrrolidine (237 mg, 1 mmol) in DCM (7 ml) at room temperature. The entire mixture was stirred for 18 h and then washed with dilute HCl. The organic product was extracted into the DCM (4x15 ml), dried ($MgSO_4$) and concentrated. Purification over silica gel, eluting with a mixture of ethyl acetate and petrol

(3:17), gave diastereoisomer (111 mg, 30.10 %) as an oil, whereas the other diastereoisomer (184 mg, 49.80 %) eluted with a 3:7 mixture of ethyl acetate and petrol.

Diastereoisomer 1:

δ_H (250 MHz, $CDCl_3$) 1.27-1.43 (1H, m, C-3), 1.43-1.56 (3H, d, C-9), 1.56-1.73 (2H, m, C-4), 1.92-2.08 (1H, m, C-3), 3.24-3.40 (2H, t, C-5), 3.72-3.88 (1H, q, C-8), 4.72-4.83 (1H, d, C-6), 5.11-5.25 (1H,q, C-2), 7.21-7.54 (15H, m, Ar).

δ_C (62.5 MHz, $CDCl_3$) 20.7 (C-9), 23.4 (C-4), 27.5 (C-3), 45.2 (C-8), 46.4 (C-5), 52.1 (C-6), 59.9 (C-2), 126.1 (p-Ar), 126.5 (p-Ar), 126.7 (p-Ar), 127.5 (o-Ar), 127.7 (o-Ar), 128.2 (o-Ar), 128.7 (m-Ar), 128.9 (m-Ar), 129.6 (m-Ar), 141.3 (α-Ar), 141.9 (α-Ar), 142.2 (α-Ar), 172.3 (C_7=O).

Mass analysis (m/z): EI, 369 (M^+, absent), 202 (-167, 57.5 %), 105 (-97, 66.7 %), 70 (-35, 100 %); **CI**, 370 (MH^+, 5.3 %).

Diastereoisomer 2

A: δ_H (400 MHz, d_6-acetone) 1.9-2.1, 3.4-3.6 (2H, m, C-5), 3.8-3.9 (1H, q, C-8), 5.0 (1H, m, C-2), 4.5-4.6 (1H, d, C-6), 6.6-7.4 (15H, m, Ar).

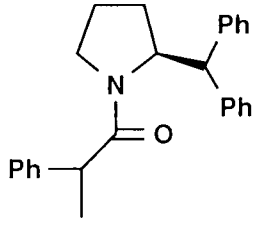
A: δ_C (100 MHz, d_6-acetone) 20.3 (C-9), 24.1 (C-4), 27.6 (C-3), 45.2 (C-8), 47.1 (C-5), 52.2 (C-6), 60.3 (C-2), 126.9 (p-Ar), 127.4 (p-Ar), 127.8 (p-Ar), 128.6 (o-Ar), 128.8 (o-Ar), 129.1 (o-Ar), 129.5 (m-Ar), 129.7 (m-Ar), 130.3 (m-Ar), 143.0 (α-Ar), 143.1 (α-Ar), 143.6 (α-Ar), 172.7 (C_7=O).

B: δ_H (400 MHz, d_6-acetone)

B: δ_C (100 MHz, d_6-acetone) 19.4 (C-9), 21.5 (C-4), 25.9 (C-3), 44.5 (C-8), 45.3 (C-5), 54.8 (C-6), 62.0 (C-2), 126.7 (p-Ar), 127.3 (p-Ar), 127.5 (p-Ar), 128.2 (o-Ar), 128.6 (o-Ar), 129.1 (o-Ar), 129.5 (m-Ar), 129.8 (m-Ar), 130.1 (m-Ar), 142.4 (α-Ar), 143.1 (α-Ar), 143.4 (α-Ar), 174.0 (C_7=O).

Mass analysis (m/z): EI, 369 (M^+, absent), 202 (-167, 86.8 %), 105 (-97, 100 %), 70 (-35, 100 %); **CI**, 370 (MH^+, 40.7 %).

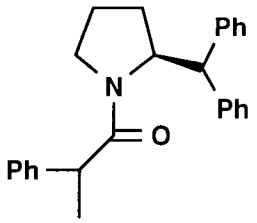
11. (2S, 8R)- and (2S, 8R)-2-(Diphenylmethyl)-pyrrolidine-N-(2', 2'-methylphenylacetyl)amide[20,83,110].



131

Diisopropylamine (31.4 mg, 0.310 mmol) was added dropwise to a 1.6 M solution of butyllithium (21.8 mg, 0.341 mmol) in hexane at room temperature and was then diluted with freshly distilled THF (2 ml). The LDA solution was cooled to -75 °C, a solution of (S)-2-(diphenylmethyl)-pyrrolidine-N-phenylacetylamide (100 mg, 0.282 mmol) in THF (3 ml) was added and the mixture stirred for 1h at -75 to 0 °C. HMPA (151.5 mg, 0.846 mmol) and MeI (240 mg, 1.69 mmol) were added to the mixture at -20 °C and at -75 °C respectively, and the entire mixture was stirred for 3 h and then quenched with aqueous phosphoric acid (5 %, 1 ml). Water (30 ml) was added and the layers were separated. The organic product was extracted into DCM (5x15 ml) and dried ($MgSO_4$). Filtration and concentration gave a crude material as a light-brown liquid.

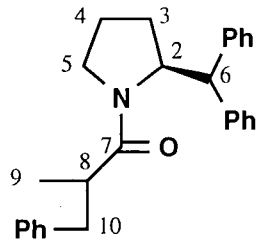
12. (2S, 8R)- and (2S, 8R)-2-(Diphenylmethyl)-pyrrolidine-N-(2', 2'-methylphenylacetyl)amide[20,110].



131

Diisopropylamine (17.1 mg, 0.169 mmol) was added dropwise to a 1.6 M solution of butyllithium (11.9 mg, 0.186 mmol) in hexane at room temperature and was then diluted with freshly distilled THF (2 ml). The LDA solution was cooled to -75 °C, a solution of (S)-2-(diphenylmethyl)-pyrrolidine-N-phenylacetylamide (50 mg, 0.141 mmol) in THF (2 ml) was added and the mixture stirred for 1h at -75 to 0 °C. The reaction was cooled to -75 °C and MeI (240 mg, 1.69 mmol) was added to the mixture. The entire mixture was stirred for 17 h and then quenched with aqueous phosphoric acid (5 %, 1 ml). Water (30 ml) was added and the layers were separated. The organic product was extracted into DCM (5x15 ml) and dried ($MgSO_4$). Filtration and concentration gave a crude material as a light-brown liquid. The spectroscopic analysis were similar to **131**, p. 102.

13. (2S, 8R)- and (2S, 8S)-2-(Diphenylmethyl)-pyrrolidine-N-(2'-methyl-3'-phenylpropyl)amide[20,110].



133

Diisopropylamine (153 mg, 1.51 mmol) was added dropwise to a solution of butyllithium (107 mg, 1.66 mmol) in hexane (1.6 M) and was then diluted with THF (0.5 ml). The LDA solution was stirred for 30 min at room temperature, cooled to -85 °C, and then a solution of (S)-2-(diphenylmethyl)pyrrolidine-N-propylamide (400 mg, 1.37 mmol) in THF (2 ml) was added dropwise. The reaction was stirred for 1h at -20 °C, cooled to -85 °C, and then a solution of benzyl bromide (703 mg, 4.11 mmol) in THF (0.5 ml) was added. The entire mixture was stirred for 5h at room temperature and was then quenched by addition of aqueous phosphoric acid (5%, 1 ml). Water (50 ml) was added and the organic layer separated. The product was extracted into DCM (5x20 ml) and the combined organic extracts were dried ($MgSO_4$). Filtration and concentration gave a crude product as a pale-yellow liquid, which was purified over silica gel, eluting with a mixture of ethyl acetate and petrol (1:1) to give the title compound (172 mg, 33%) as a white crystalline solid. **m.p.** 117.3-117.7 °C.

Diastereoisomer 1

A : δ_H (400 **MHz, CDCl3**) 0.40-0.42 (3H,d, C-9), 0.70-0.90 (2H, m, C-3 and C-4), 1.25-1.35 (1H, m, C-3), 1.40-1.60 (1H, m, C-4), 2.40-2.50 (1H, dd, C-10), 2.55-2.65 (1H, dd, C-10), 2.70-2.80 (1H, sixted, C-8), 2.95-3.05 (1H, m, C-5), 3.20-3.30 (1H, m, C-5), 3.70-3.80 (1H, d, C-6), 3.85-4.95 (1H, m, C-2), 6.60-7.30 (15H, m, Ar-H).

A : δ_C (100 MHz, $CDCl_3$) 17.0 (C-9), 23.5 (C-4), 29.5 (C-3), 40.8 (C-8), 42.0 (C-10), 46.8 (C-5), 54.4 (C-6), 60.9 (C-2), 126.3 (p-Ar), 126.4 (p-Ar), 126.7 (p-Ar), 128.0 (o-Ar), 128.4 (o-Ar), 128.6 (o-Ar), 128.8 (m-Ar), 128.0 (m-Ar), 129.7 (m-Ar), 140.4 (α-Ar), 141.5 (α-Ar), 142.3 (α-Ar), 175.1 (C_7=O).

B: δ_H (400 MHz, $CDCl_3$) 1.00-1.10 (3H, t, C-9), 1.40-1.60 (2H, m, C-4), 1.80-2.00 (2H, m, C-3), 2.30-2.40 (1H, sixted, C-8), 2.40-2.50 (1H, dd, C-10), 2.85-2.95 (1H, dd, C-10), 3.20-3.30 (1H, m, C-5), 3.55-3.65 (1H, m, C-5), 4.40-4.50 (1H, d, C-6), 4.90-5.00 (1H, m, C-2), 6.60-7.30 (15H, m, Ar-H).

B : δ_C (100 MHz, $CDCl_3$) 17.6 (C-9), 21.1 (C-4), 27.1 (C-3), 40.1 (C-8), 40.6 (C-10), 44.6 (C-5), 51.8 (C-6), 59.6 (C-2), 126.0 (p-Ar), 126.3 (p-Ar), 126.7 (p-Ar), 127.9 (o-Ar), 128.4 (o-Ar), 128.5 (o-Ar), 128.8 (m-Ar), 128.8 (m-Ar), 129.3 (m-Ar), 140.2 (α-Ar), 141.1 (α-Ar), 141.9 (α-Ar), 174.5 (C_7=O).

IR (in $CDCl_3$ solution-NaCl disk) υ cm^{-1}: 3054, 3020, 2973, 2958, 2907, 1635 (C=O), 1494, 1435, 1422, 749, 700.

Anal. Calcd. for $C_{27}H_{29}NO$: C, 84.54; H, 7.63; N, 3.74. Found: C, 84.43; H, 7.63; N, 3.74.

Mass analysis (m/z): EI, 383 (M^+, absent), 216 (-167, 21.1 %), 91 (43.4 %), 70 (100 %); **CI**, 385 (MH_2^+, 2.5 %).

<u>Diastereoisomer 2</u>

A: δ_H (400 MHz, $CDCl_3$)

A: δ_C (62.5 MHz, $CDCl_3$) 17.9 (C-9), 23.4 (C-4), 27.4 (C-3), 40.1 (C-8), 40.5 (C-10), 46.4 (C-5), 52.3 (C-6), 59.2 (C-2), 126.0 (p-Ar), 126.5 (p-Ar), 126.8 (p-Ar),

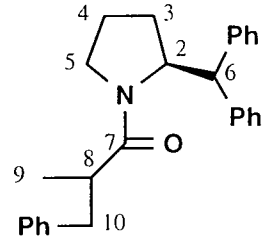
127.9 (o-Ar), 128.1 (o-Ar), 128.6 (o-Ar), 128.9 (m-Ar), 129.0 (m-Ar), 129.5 (m-Ar), 140.3 (α-Ar), 142.0 (α-Ar), 142.1 (α-Ar), 174.6 (C_7=O).

B: δ_H (400 MHz, $CDCl_3$)

B: δ_C (100 MHz, $CDCl_3$) 17.9 (C-9), 21.3 (C-4), 29.4 (C-3), 39.1 (C-8), 40.5 (C-10), 45.4 (C-5), 54.6 (C-6), 60.4 (C-2), 126.0 (p-Ar), 126.5 (p-Ar), 126.8 (p-Ar), 127.9 (o-Ar), 128.1 (o-Ar), 128.2 (o-Ar), 128.9 (m-Ar), 129.3 (m-Ar), 129.5 (m-Ar), 140.3 (α-Ar), 140.5 (α-Ar), 141.7 (α-Ar), 175.0 (C_7=O).

Mass analysis (m/z): EI, 384 (M^+, 0.45 %), 216 (-168, 42.7 %), 91 (67.6 %), 70 (100 %); **CI**, 384 (MH^+, 78.2 %).

14. (2S, 8R)- and (2S, 8S)-2-(Diphenylmethyl)-pyrrolidine-N-(2'-methyl-3'-phenylpropyl)amide[20,83,110].

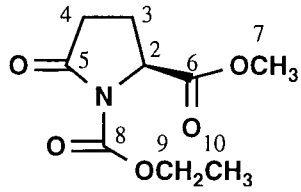


133

Diisopropylamine (20.8 mg, 0.205 mmol) was added dropwise to a 1.6 M solution of butyllithium (14.4 mg, 0.225 mmol) in hexane at room temperature and was then diluted with freshly distilled THF (1 ml). The LDA solution was cooled to -75 °C, a solution of (S)-2-(diphenylmethyl)-pyrrolidine-N-propylamide (50 mg, 0.171 mmol) in THF (1 ml) was added and the mixture stirred for 1h at -75 to 0 °C. HMPA (36.7 mg, 0.205 mmol) and BnBr (87.7 mg, 0.513 mmol) were added to the mixture at -20 °C and

at -75 °C respectively, and the entire mixture was stirred for 9 h and then quenched with aqueous phosphoric acid (5 %, 1 ml). Water (25 ml) was added and the layers were separated. The organic product was extracted into DCM (6x15 ml), washed with brine solution (5x50 ml) to rid of HMPA and dried ($MgSO_4$). Filtration and concentration gave a crude material as a light-brown liquid. The spectroscopic analysis were similar to **133**, p. 105-106.

15. Ethyl (S)-1-formyl-2-carboxymethyl-5-oxopyrrolidine[114].



134

Distilled water (280 ml), sodium meta periodate (31.11 g, 145.45 mmol) and ruthenium dioxide hydrate (550 mg, 4.13 mmol) were added to a solution of ethyl (S)-1-formyl-2-carboxymethylpyrrolidine (7.81 g, 38.86 mmol) in dry and distilled ethyl acetate (260 ml). After addition was complete, the entire mixture was stirred for 48 h at room temperature. The layers were separated and the aqueous layer was extracted into ethyl acetate (4x100 ml). The combined organic extracts were treated with isopropyl alcohol (10 ml) for 3 h to destroy residual RuO_4. Black coloured-RuO_2, which precipitated from the solution, was filtered off and the filtrate was washed with distilled water (300 ml) and dried over anhydrous $MgSO_4$. Filtration and concentration gave a crude product which was purified by distillation in *vacuo* to obtain the product (5.82 g, 69.6 %) as a pale-yellow liquid.

δ_H (200 MHz, $CDCl_3$) 1.04-1.11 (3H, t, C-8), 1.78-1.93 (1H, m, C-4), 2.08-2.50 (3H, m, C-3 and C-4), 3.55 (3H, s, C-10), 3.92-4.14 (2H, m, C-7), 4.44-4.50 (1H, dd, C-2).

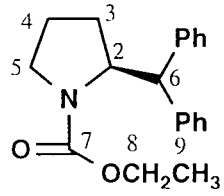
δ_C (50 MHz, $CDCl_3$) 14.4 (C-10), 22.0 (C-3), 31.4 (C-4), 52.9 (C-7), 59.0 (C-2), 63.2 (C-9), 151.3 (C-8), 172.0 (C-6), 173.4 (C-5).

Anal. Calcd. for $C_9H_{13}NO_5$: C, 50.23; H, 6.05; N, 6.51. Found: C, 50.01; H, 6.23; N, 6.17.

IR (NaCl disk) υ cm^{-1} : 2984, 2958, 1796 (C=O), 1750 (C=O), 1719 (C=O), 1373, 1307, 1259, 1213, 1185.

Mass analysis (m/z): EI, 215 (M^+, 2.0 %), 156 (-59, 79.9 %), 84 (-72, 100 %), 41 (-43, 57.5 %).

16. (S)-2-(Diphenylmethyl)-pyrrolidine-N-ethoxycarbamate[104].



135

A solution of triethylamine (796, 5.66 mmol) in DCM (20 ml) and ethyl chloroformate (796 µl, 5.66 mmol) were added to a solution of (S)-2-(diphenylmethyl)-pyrrolidine (1.22 g, 5.15 mmol) in DCM (60 ml) at 0 °C. The reaction mixture was left to warm to ambient temperature and was stirred for 24 h. Ice-cold diluted HCl (55.66 ml, 0.1 M) was added and the layers were separated immediately. The organic product was extracted into DCM (5x30 ml), the combined organic extracts were dried ($MgSO_4$) and concentrated to obtain a crude product. Purification over silica gel, eluting with a mixture of ethyl acetate and petrol (1:4), gave the product (0.830 g, 52 %) as a clear colourless oil, which on standing became an amorphous white solid.

δ_H (400 MHz, 90 °C, d_6-DMSO) 1.00-1.10 (3H, q, C-9); 1.485 (1H, b, C-4); 1.62-1.76 (2H, m, C-3 and C-4); 1.90-2.00 (1H, m, C-3); 2.50 (s, solvent); 3.04 (s, water); 3.06-3.14 (1H, m, C-5); 3.34-3.44 (1H, m, C-5); 3.74 (1H, b, C-2); 3.82-3.92 (1H, b, C-6); 4.26 (1H, b, C-8); 4.62-4.70 (1H, m, C-8)

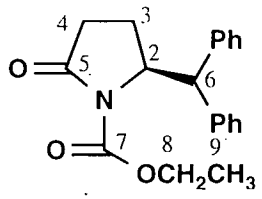
δ_C (100 MHz, d_6-DMSO) 13.9 (C-9), 21.9 (C-4), 28.2 (C-3), 45.2 (C-5), 53.1 (C-6), 59.5 (C-2), 59.8 (C-8), 125.4 (p-Ar), 125.9 (p-Ar), 127.3 (o-Ar), 127.8 (o-Ar), 128.2 (m-Ar), 128.5 (m-Ar), 141.6 (α-Ar), 142.0 (α-Ar), 153.9 (C_7=O).

Anal. Calcd. for $C_{20}H_{23}NO_2$: C, 77.62; H, 7.50; N, 4.53. Found: C, 77.19; H, 7.48; N, 4.62.

IR (NaCl disk) υ cm^{-1}: 3090-2886, 1694 (C=O), 1495, 1451, 1424, 1384, 1337, 1200, 1120, 706.

Mass analysis (m/z): EI, 309 (M^+, absent), 142 (-167, 100 %), 98 (-44, 16.6 %), 70 (-28, 57.2 %); **CI**, 310 (MH^+, 34.6 %), 142 (-168, 6.7 %), 70 (-72, 4.8 %).

17. (S)-2-(Diphenylmethyl)-5-oxo-pyrrolidine-N-ethoxycarbamate[114].



137

Distilled water (36 ml), sodium meta periodate (4 g, 18.70 mmol) and ruthenium dioxide hydrate (39 mg, 0.293 mmol) were added to a solution of (S)-2-(diphenylmethyl)-pyrrolidine-N-ethoxycarbamate (500 mg, 1.62 mmol) in dry and distilled ethyl acetate (30 ml). After addition was complete, the entire mixture was stirred for 44 h until the starting material had disappeared as determined by t.l.c. (1:1,ethyl acetate/petrol). The layers were separated and the organic product was extracted into ethyl acetate (4x30 ml). The combined organic extract was treated with isopropyl alcohol (1 ml) for 2h, to destroy residual RuO_4. Black coloured-RuO_2, which precipitated from the solution, was filtered off, the filtrate was washed with distilled water (100 ml), dried over anhydrous $MgSO_4$, and concentrated to obtaine a crude product. Purification over silica gel, eluting with a 1:1 mixture of ethyl acetate and petrol, gave the product (173 mg, 33 %) as a pale-yellow liquid.

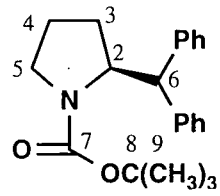
δ_H (200 MHz, d_6-DMSO) 0.80-0.92, 1.20-1.33 (3H, t, C-9), 1.50-1.1.80 (1H, m, C-4), 1.97-2.40 (3H, m, C-3 and C-4), 3.97-4.25 (2H, m, C-8), 4.40-4.50 (1H, d, C-6) , 5.00-5.12 (1H, dd, C-2).

δ_C (50 MHz, d_6-DMSO) 14.7 (C-9), 22.2 (C-4), 31.7 (C-3), 53.6 (C-6), 60.6 (C-2), 63.2 (C-8), 127.3 (p-Ar), 127.8 (p-Ar), 128.9 (o-Ar), 129.2 (o-Ar), 129.2 (m-Ar), 129.8 (m-Ar), 140.5 (α-Ar), 141.3 (α-Ar), 152.3 (C_7=O), 174.8 (C_5=O).

IR (NaCl disk) υ cm^{-1}: 3029, 2981, 1728 and 1715 (C=O), 1371, 1289, 1049, 705.

Mass analysis (m/z): EI, 323 (M^+, 46.5 %), 156 (-167, 64.0 %), 112 (-44, 10.7 %), 84 (-28, 100 %), 56 (-28, 16.3 %); **CI**, 324 (MH^+, 100 %).

18. (S)-2-(Diphenylmethyl)-pyrrolidine-N-t-butoxycarbamate[115].



136

A solution of di-tertiary-butyl dicarbonate (2.25g, 10.31 mmol) in dry and distilled MeOH (20 ml) was added to a mixture of triethylamine (567 mg, 5.60 mmol)) and (S)-2-(diphenylmethyl)-pyrrolidine (1.21g, 5.11 mmol) in dry MeOH (20 ml) at room temperature. The mixture was heated to 50 °C for 10 min., allowed to cool to room temperature and stirred for a further 1h. The reaction was monitored by t.l.c (1:4 ethyl acetate/petrol) until complete and the mixture was cooled to 0 °C and then quenched by addition of diluted hydrochloric acid (10 ml, pH 2.15) and water (40 ml). The product was extracted immediately into ethyl acetate (5x20 ml). The organics were dried ($MgSO_4$), and concentrated to obtain a crude product. Purification over silica gel, eluting with a mixture of ethyl acetate and petrol (1:19), gave the desired product (1.69 g, 98 %) as a pale-yellow liquid.

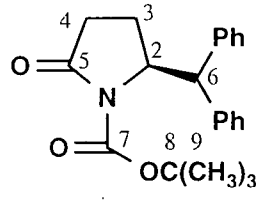
δ_H (400 MHz, d_6-DMSO) 1.12 (1H, s, C-4), 1.26 (9H, s, t-butyl), 1.40-1.50 (1H, b, C-4), 1.60-1.72 (2H, b, C-4 and C-3), 1.85-1.97 (1H, m, C-3), 2.48 (1H, s, DMSO), 2.98-3.08 (1H, m, C-5), 3.30-3.40 (1H, m, C-5), 4.23-4.28 (1H, d, C-6), 4.55-4.65 (1H, dd, C-2), 7.12-7.32 (10H, m, 2xAr)

δ_C (100 MHz, d_6-DMSO) 21.9 (C-4), 27.6 (C-9), 28.2 (C-3), 30.8 (C-8), 45.1 (C-5), 53.1 (C-6), 59.7 (C-2), 125.4 (p-Ar), 125.9 (p-Ar), 127.3 (o-Ar), 127.7 (o-Ar), 128.3 (m-Ar), 128.5 (m-Ar), 141.6 (α-Ar), 142.0 (α-Ar), 153.2 (C_7=O).

IR (NaCl disk) υ cm^{-1}: 3062, 3027, 2978, 2931, 2892, 1808, 1696 (C=O), 1496, 1456, 1392, 1370, 1174, 1124, 1076, 701.

Mass analysis (m/z): EI, 337 (M^+, absent), 282 (-56, 8.9 %), 167 (-115, 22.5 %), 114 (-53, 60.4 %), 70 (-44, 100 %) ; **CI**, 338 (MH^+, absent), 282 (-56, 34.6 %), 238 (-44, 86.5 %), 70 (-168, 100 %).

19. (S)-2-(Diphenylmethyl)-5-oxopyrrolidine-N-t-butoxycarbamate[114].



138

Distilled water (385 ml), sodium metaperiodate (42.43 g, 198.37 mmol) and ruthenium dioxide hydrate (350 mg, 2.63 mmol) were added to a solution of (S)-2-(diphenylmethyl)-pyrrolidine-N-t-butoxycarbamate (5.571 g, 16.53 mmol) in dry ethyl acetate (320 ml). After addition was complete, the entire mixture was stirred for 4 h until the starting material was consumed, as determined by t.l.c. (3:7 ethyl acetate/petrol). The layers separated and the product extracted into ethyl acetate (5x100 ml) and the combined organics were treated with isopropyl alcohol (4 ml) for 3h to destroy residual RuO_4. Black coloured-RuO_2, which precipitated from the solution, was filtered off and the filtrate washed with distilled water (400 ml), and was then dried ($MgSO_4$). The solution was evaporated under reduced pressure to leave a brown residue, which was purified

over silica gel, eluting with a mixture of ethyl acetate and petrol (1:9). Removal of solvents gave the product (2.09 g, 36 %) as a white amorphous solid. **m.p.** 124-125 °C.

δ_H (200 MHz, $CDCl_3$) 1.10-1.75 (1H, m, C-4), 1.44 (9H, s, t-butyl), 1.95-2.33 (3H,m, C-3 and C-4), 4.50 (1H, d, C-6), 5.00 (1H, dd, C-2), 7.10-7.50 (10H, m, 2xAr).

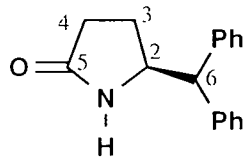
δ_C (50 MHz, $CDCl_3$) 22.0 (C-4), 28.5 (C-9), 30.2 (C-3), 31.8 (C-8), 53.6 (C-6), 60.5 (C-2), 83.5, 127.2 (p-Ar), 127.8 (p-Ar), 129.0 (o-Ar), 129.2 (o-Ar), 129.2 (m-Ar), 129.9 (m-Ar), 140.5 (α-Ar), 141.4 (α-Ar), 152.0 (C_7=O), 175.1 (C_5=O).

Anal. Calcd. for $C_{22}H_{25}NO_3$: C, 75.17; H, 7.17; N, 3.99. Found: C, 75.26; H, 7.41; N, 3.50.

IR (KBr disk) υ cm^{-1}: 3027, 2974, 2927, 1748 (C=O), 1729 (C=0), 1369, 1357, 1345, 1294, 1228, 1168, 1132, 710.

Mass analysis (m/z): EI, 351 (M^+, absent), 167 (-184, 33.9 %), 84 (-83, 100 %); **CI**, 352 (MH^+, absent), 252 (-100, 95.1 %), 84 (-168, 8.3), 58, (-26, 2.2 %).

20. (S)-2-(Diphenylmethyl)-5-oxo-pyrrolidine[116].



2

Distilled trifluoroacetic acid (12ml) was added dropwise to a solution of (S)-2-(diphenylmethy)-5-oxo-pyrrolidine-N-BOC^t (801 mg, 2.28 mmol) in DCM (12 ml) at 0 °C. The mixture was stirred for 5 h and then the solvent was evaporated under reduced

pressure. Purification over silica gel, eluting with a mixture of ethyl acetate and petrol (6:4), gave the title product (487 mg, 85%) as an orangy liquid, which solidified overnight on standing. Removal of pale-yellow impurities, by dissolving in diethyl ether, gave a white amorphous solid, which was then crystallised from ethyl acetate. **m.p.**114.1-114.3 °C.

δ_H (400 MHz, $CDCl_3$) 1.70-1.92 (1H, m, C-3), 2.08-2.30 (1H, m, C-3), 2.30-2.42 (2H, dd, C-4), 3.72-3.83 (1H, d, C-2), 4.33-4.50 (1H, m, C-6), 5.40-5.50 (1H, b, N-H).

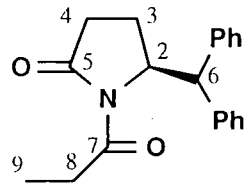
δ_C (100 MHz, $CDCl_3$) 26.4 (C-4), 30.3 (C-3), 57.7 (C-6), 58.3 (C-2), 126.9 (p-Ar), 127.2 (p-Ar), 127.8 (o-Ar), 127.8 (o-Ar), 128.7 (m-Ar), 129.0 (m-Ar), 140.5 (α-Ar), 141.4 (α-Ar), 150.9 (C_5=O).

Anal. Calcd. for $C_{17}H_{17}NO$: C, 81.23; H, 6.82; N, 5.58. Found: C, 80.84 ; H, 6.84 ; N, 5.31.

IR (KBr disk) υ cm^{-1}: 3187, 1692 (C=0), 1496, 1449, 1424, 1283, 1266, 745, 701.

Mass analysis (m/z): EI, 251 (M^+,.absent), 84 (-167, 100 %); **CI**, 252 (MH^+, 7.2 %).

21. (S)-2-(Diphenylmethyl)-5-oxo-pyrrolidine-N-proplyamide[114].



139

Distilled water (200 ml), sodium metaperiodate (21.90 g, 102.40 mmol) and ruthenium dioxide hydrate (181 mg, 1.36 mmol) were added to a solution of (S)-2-(diphenylmethyl)-pyrrolidine-N-propyl amide (2.50 g, 8.53 mmol) in dry ethyl acetate (170 ml). After addition was complete, the entire mixture was stirred for 8 h until the starting material was consumed, as determined by t.l.c. (3:7 ethyl acetate/petrol). The layers were separated, the product extracted into ethyl acetate (8x70 ml) and the combined organics were treated with isopropyl alcohol (3 ml) for 3h to destroy residual RuO_4. Black coloured-RuO_2, which precipitated from the solution, was filtered off and the filtrate washed with distilled water (100 ml), and was then dried ($MgSO_4$). The solution was evaporated under reduced pressure to leave a brown-black residue, which was purified over silica gel, eluting with a mixture of ethyl acetate and petrol (1.5:8.5). Removal of solvents gave the product (0.894 g, 34.1 %) as a pale-yellow liquid, which solidified on standing. Cystallisation from a mixed petrol (40-60 °C)-diethyl ether gave the title product as a white crystalline solid. **m.p.** 67.8-68.4 °C.

δ_H (400 MHz, $CDCl_3$) 1.02-1.05 (3H, t, C-9), 1.40-1.60 (1H, dd, C-3), 2.02-2.22 (3H, m, C-3 and C-8), 2.78-2.90 (2H, m, C-4), 4.50 (1H, d, C-6), 5.20 (1H, m, C-2), 6.90-7.30 (10H, m, 2xAr).

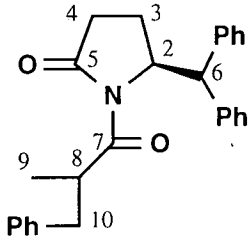
δ_C (100 MHz, $CDCl_3$) 8.3 (C-9), 20.9 (C-4), 30.9 (C-3), 32.0 (C-8), 51.6 (C-6), 58.7 (C-2), 126.5 (p-Ar), 127.2 (p-Ar), 128.3 (o-Ar), 128.6 (o- and m-Ar), 129.6 (m-Ar), 140.2 (α-Ar), 141.0 (α-Ar), 174.8 (C_7=O), 176.0 (C_5=O).

Anal. Calcd. for $C_{20}H_{21}NO_2$: C, 78.13; H, 6.89; N, 4.56. Found: C, 78.10; H, 6.98; N, 4.55.

IR (KBr disk) υ cm^{-1}: 3062, 3028, 2982, 2940, 2882, 1743 (C=O), 1640 (C=0), 1392, 1368, 1238, 703.

Mass analysis (m/z): EI, 307 (M^+, 4.3 %), 140 (-167, 61.8 %), 84 (-56, 100 %), 57 (-27, 33.1 %); **CI**, 308 (MH^+, 9.6 %), 252 (-56, 4.2 %), 84 (-168, 1.5 %), (-35, 100 %).

22. (2S, 8R)- and (2S, 8S)-2-Diphenylmethyl-5-oxopyrrolidine-N-(2'-methyl-3'-phenylpropyl)amide[20,110].



141

Diisopropylamine (149 mg, 1.472 mmol) was added dropwise to a solution of butyllithium (0.960 ml, 1.536 mmol) in hexane (1.6 M) under nitrogen, and then diluted with THF (5 ml), and stirred for 30 min at room temperature. The LDA solution was cooled to -85 °C and then a solution of (S)-2-(diphenylmethyl)-5-oxo-pyrrolidine-N-propyl amide (225 mg, 0.732 mmol) in THF (10 ml) was added dropwise. The reaction was stirred for 1h at -20 °C, cooled to -85 °C, and a solution of benzyl bromide (288 mg, 1.684 mmol) in THF (0.5 ml) was added. The entire mixture was stirred for 3h at -85 °C and was then quenched by addition of aqueous phosphoric acid (5%, 0.5 ml). Water (30 ml) was added and organic product was extracted into DCM (5x30 ml). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated to obtain a crude product

as a colourless oil. Purification over silica gel, eluting with a mixture of ethyl acetate and petrol (1:9), gave the title product (82 mg, 28%) as a colourless oil.

Diastereoisomer 1

δ_H (400 MHz, $CDCl_3$) 1.00-1.10 (3H, t, C-9), 1.65-1.80 (1H, m, C-8), 1.80-1.90 (1H, dd, C-3), 1.95-2.10 (1H, dd, C-3), 2.35-2.45 (1H,dd, C-10), 2.80-2.90 (2H, m, C-4), 2.90-3.00 (1H, dd, C-10), 4.40-4.50 (1H, d, C-6), 5.00-5.10 (1H, dd, C-2), 6.85-7.25 (15H, m, 3xAr).

δ_C (100 MHz, $CDCl_3$) 8.4 (C-9), 27.6 (C-4), 31.1 (3), 36.5 (C-8), 43.4 (C-10), 51.3 (C-6), 56.5 (C-2), 126.4 (p-Ar), 126.5 (p-Ar), 127.3 (p-Ar), 128.2 (o-Ar), 128.5 (o-Ar), 128.6 (o-Ar), 128.6 (m-Ar), 128.6 (m-Ar), 129.6 (m-Ar), 138.3 (α-Ar), 140.4 (α-Ar), 141.0 (α-Ar), 175.0 (C_7=O), 177.0 (C_5=O).

IR (KBr disk) υ cm^{-1}: 3026, 2977, 2936, 1733 and 1695 (C=O), 1495, 1452, 1371, 1224, 734, 699.

Mass analysis (m/z): EI, 399 (MH_3^+, 100 %), 230 (-169, 28.6 %), 174 (-56, 59.6 %), 91 (31.5 %); **CI**, 398 (MH_2^+, 85.7 %), 167 (12.3 %).

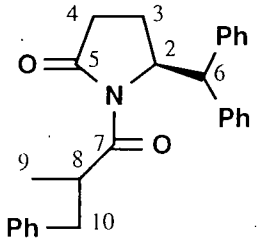
Diastereoisomer 2

δ_H (400 MHz, d_6-Acetone) 1.00-1.10 (3H, d, C-9), 1.26-1.40, 1.48-1.58, 1.74-1.84, 2.00-2.20 (1H, b, C-3), 2.28-2.40 (1H, b, C-3), 2.42-50 (1H, dd, C-10), 2.70-2.80 (2H, b, C-4), 2.80-3.00, 3.06-3.14 (1H, dd, C-10), 4.00-4.10, 4.35-4.45, 4.75-4.80 (1H, b, C-6), 5.05-5.15, 5.25-5.30 (1H, b, C-2), 5.55-5.65, 6.70-6.75, 7.00-7.10, 7.10-7.40.

δ_C (100 MHz, d_6-Acetone)

Mass analysis (m/z): EI, 397 (MH^+, 1.2 %), 230 (-167, 21.3 %), 174 (32.4 %), 91 (62.2 %), 49 (100 %); **CI**, 398 (MH_2^+, 81.6 %), 167 (14.5 %).

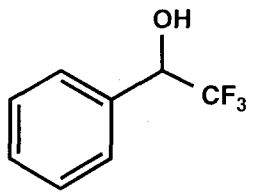
23. (2S, 8R)- and (2S, 8S)-2-Diphenylmethyl-5-oxopyrrolidine-N-(2'-methyl-3'-phenylpropyl)amide[20, 83,110].



141

Diisopropylamine (18.1 mg, 0.179 mmol) was added dropwise to a 1.6 M solution of butyllithium (12.6 mg, 0.197 mmol) in hexane at room temperature and was then diluted with freshly distilled THF (1 ml). The LDA solution was cooled to -80 °C, a solution of (S)-2-(diphenylmethyl)-5-oxopyrrolidine-N-propylamide (50 mg, 0.163 mmol) in THF (2 ml) was added and the mixture stirred for 1h at -80 to 0 °C. HMPA (32.0 mg, 0.179 mmol) and BnBr (83.6 mg, 0.489 mmol) were added to the mixture at -20 °C and at -80 °C respectively, and the entire mixture was stirred for 10 h and then quenched with aqueous phosphoric acid (5 %, 1 ml). Water (40 ml) was added and the layers were separated. The organic product was extracted into DCM (5x15 ml) and dried ($MgSO_4$). Filtration and concentration gave crude material as a light-brown liquid. The spectroscopic analysis was smilar to **141**, p.118.

24. (RS)-2,2,2-Trifluorophenethanol[118].



146

$NaBH_4$ (1.195 g, 31.6 mmol) was added in small portions to a solution of 2,2,2-trifluoroacetophenone (5 g, 28.7 mmol) in dry and distilled methanol (100 ml) over 30 minutes at room teperature. The mixture was stirred for 1h at r.t. and was then quenched with distilled water (20 ml). Organic compound was extracted into diethyl ether (4x100 ml) and dried over $MgSO_4$. Filtration and concentration gave a crude material, which was then purified by distillation (30 °C, 0.1-0.01 mm-Hg) under reduced pressure to give the pure material (3.10 g, 61.3 %) as a colorless oil.

$\Delta\delta_H$ (250 MHz, $CDCl_3$) 2.59 (1H, s, O–H), 5.03 (1H, dq, C-H), 7.43 (5H, m, Ar).

IR (as a film) υ cm^{-1} : 3412 (broad OH peak), 3074, 3038, 1457, 1266, 1206, 1172, 1127, 1062, 866, 834, 760, 705, 632.

Anal. Calcd. for $C_8H_7OF_3$: C, 54.53; H, 4.01. Found: C, 54.17; H, 4.19.

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Colloquia, Lectures and Seminars from Invited Speakers

October 1994 - September 1995

Entry	Speaker's name	Title	Place	Date
1	Dr. M. Block	Large Scale Manufacture of ZD 1542, a Thromboxane Antagonist Synthase Inhibitor	Zeneca Pharmaceuticals, Macclesfield	10.11.94
2	Prof. M. Page	Four Membered Rings and β-Lactamase	University of Huddersfield	16.11.94
3	Dr. Cairns-Smith	Clay Minerals and the Origin of Life	University of Glasgow	17.11.94
4	Dr. J. M. J. Williams	New Approaches to Asymmetric Catalyst	University of Loughborough	23.11.94
5	Prof. P. Parsons	Applications of Tandem Reactions in Organic Synthesis	University of Reading	11.1.95
6	Prof. H. Kroto	C_{60}-The Celestial Sphere that Fell to Earth		16.2.95
7	Prof. R. Bonnett	Chemical Aspects of Photodynamic Therapy	Queen Mary and Westfield College, London	19.1.95
8	Dr. D. A. Roberts	The Design and The Synthesis of Inhibitors of the Renin-Angiotensin System	Zeneca Pharmaceuticals	25.1.995
9	Mrs. S. Owen	Trace Organics in the Environment	Northumberland Water	26.1.95
10	Prof. E. Schaumann	Silicon and Sulphur Mediated Ring Opening of Epoxides	University of Clausthal	22.2.95

October 1995 - September 1996

Entry	Speaker's name	Title	Place	Date
1	Prof. A. Alexakis	Synthetic and Analytical uses of Chiral Diamines	University of Pierre et Madame Curie, Paris	18.10.95
2	Dr. D. M. Davies	Chemical Reactions in Organised Systems: Peracid Reactivity in Surfactant Micelles and Cyclodextrin Hosts	University of Northumbria	25.10.95
3	Prof. W. Motherwell	New Reactions for Organic Synthesis	UCL London	1.11.95
4	Dr. D. Craig	New Strategies for the Assembly of Heterocyclic Systems	Imperial College, London	8.11.95
5	Prof. D. Bergbreiter	Design of Smart Catalyst, Substrates and Surfaces from Simple Polymers	Texas A&M, USA	17.11.95
6	Several Speakers	Perkin Regional Meeting		8.12.95
7	Dr. B. Henderson	Electrospray Mass Spectrometry- a New Sporting Technique	University of Waikato, NZ	10.1.96
8	Dr. R. Whitby	New Approaches to Chiral Catalyst: Induction of Planar and Metal Centred Asymmetry	University of Southampton	6.3.96

Research Conferences Attended

1. Postgraduate Symposium on Bioorganic Chemistry, Durham, 12th December 1994.
2. SCI Novel Organic Chemistry: 6th Graduate Symposium, York, 1st March 1995.
3. One-day Postgraduate Symposium in Bioorganic Chemistry, Southampton, 18th December 1995.
4. North East Universities Postgraduate Chemistry Symposium, Sunderland, 2nd April 1996.