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Chiral Hypernucleophilic Acylation Catalysts

and

Synthesis of Bipyridyls *via* Palladium-Catalysed

Reductive Homocoupling of Chloropyridines

By

Richard Pio Lee

A thesis presented to the University of Dublin for the degree of Doctor of Philosophy

December 2000

Trinity College

Dublin

Declaration

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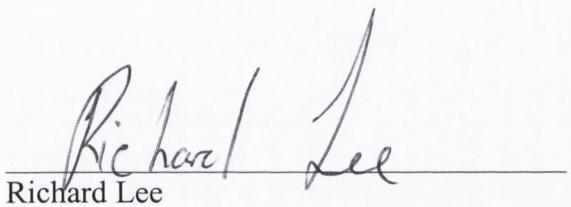

Richard Lee

Summary

Chapter 1 of this thesis discusses the explosion of interest in the non-enzymatic kinetic resolution of secondary alcohols catalysed by chiral derivatives of the hypernucleophilic acylation catalyst, 4-dimethylaminopyridine. Particular attention is drawn to the work of Gregory Fu and Craig Ruble of the Massachusetts Institute of Technology, Kaoru Fuji of Kyoto University and Edwin Vedejs of the University of Wisconsin who have been pioneers in this type of work during the last five years, and who collectively represent the benchmark in terms of non-enzymatic kinetic resolution *via* enantioselective acylation. Also reviewed is the work of other more recent entrants into the field such as Alan Spivey of Sheffield University and Tarek Sammakia of the University of Colorado. Finally, our own tentative steps into this area are discussed as is the structure of the present work, the majority of which has been carried out during the last three years.

Chapter 2 discusses in detail several efficient procedures for the synthesis of 2-halo and 2,6-dihalo-4-dialkylaminopyridines, precursors to the more elaborate compounds discussed in Chapter 3. Also there is a substantial discussion on other synthetic routes to 2-halo-4-dialkylaminopyridines which did not have the desired outcome, particularly the failed conversion of 4-(1'-pyrrolidinyl)-2-pyridone into 2-chloro-4-(1'-pyrrolidinyl)pyridine, and the failure to synthesise 2-amino-4-dimethylaminopyridine in acceptable quantities *via* the generation of a heteroaryne from 3-bromo-4-dimethylaminopyridine.

Chapter 3 describes the synthesis of novel chiral 4-dialkylaminopyridines incorporating the terpene alcohols (–)-menthol and (–)-borneol from 2-bromo-4-dimethylaminopyridine. Thus, (–)-2-bornyloxy-4-dimethylaminopyridine and (–)-2-menthyloxy-4-dimethylaminopyridine proved to be efficient catalysts in the acylation of 1-phenylethyl alcohol but showed no enantioselectivity. Also researched was the ability of heterocyclic *N*-oxides to act as catalysts for the acylation of 1-phenylethyl alcohol in the presence of acetic anhydride. Of particular significance was the fact that 2-dimethylaminopyridine *N*-oxide is an efficient acylation catalyst whereas the free base is inactive. This implied that potential catalysts may not require a 4-dimethylamino substituent to achieve an acceptable rate of reaction. A number of homochiral *N*-oxides were synthesised and indeed they did act as efficient acylation catalysts but showed no enantioselectivity. A detailed kinetic investigation into the acylation of 1-phenylethyl alcohol in deuteriochloroform was undertaken for all compounds showing catalytic activity. It was shown that 4-dimethylaminopyridine was only 1.2 times better than 4-dimethylaminopyridine *N*-oxide as an acylation catalyst. 2-Dimethylaminopyridine *N*-oxide was shown to be almost twice as effective as pyridine under similar conditions.

Chapter 4 deals with an efficient palladium-catalysed synthesis of bipyridines, which is believed to occur *via* a reductive homocoupling reaction. The regeneration of palladium(0) was believed to occur *via* a Wacker reaction involving the alkene present in the reaction mixture although this has not been conclusively demonstrated. Also discussed are initial attempts to synthesise the novel ligand 4,4'-dimethylamino-2,2'-bipyridine from the 2-bromo-4-dimethylaminopyridine synthesised in Chapter 2.

Acknowledgements

First and foremost I would like to take this opportunity to thank my supervisor Dr. David H. Grayson. I greatly appreciate all the encouragement and help he has given me in that time. Thanks to Enterprise Ireland for funding and Olin Corporation for the generous donation of 2-chloropyridine *N*-oxide. Thanks also to Seal Sands Chemicals and to The Reilly Tar & Chemical Corporation for the kind donation of substantial amounts of 4-dimethylaminopyridine.

I would like to thank my parents for indulging me in my pursuit of education and knowledge. Without their financial assistance I would never have travelled so far along this long road of enlightenment. Many thanks to my favourite sisters Margaret and Helen who gave me a bed on the many occasions they found me intoxicated and incapacitated on their doorstep.

I am also grateful to many of the technical staff especially Dr. Martin Feeney for running all my mass spectra so quickly, thanks also to John Kelly for repairing all my broken glassware and Brendan Mulvany for repairing all things electrical. Thanks also to Paul Byrne for loans of various implements over the last three years.

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Special mention is due to the Grayson group both past and present especially Úna, Gilles, Eleonora, Philip, Gillian, Marco, José, David and Guillaume. Also to the many friends I have made in Trinity especially Damien and Anthony, Conor, Elise, Muriel and Fiona.

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God bless us all.

Abbreviations

Ac	acetyl
Aq.	aqueous
b.p.	boiling point
bs	broad singlet
COSY	correlation spectroscopy
d	doublet
dd	double doublet
dt	double triplet
DCM	dichloromethane
DIBAL	diisobutylaluminium hydride
DMA	*N,N*-dimethylacetamide
DMAP	4-dimethylaminopyridine
DMF	*N,N*-dimethylformamide
DMSO	dimethylsulfoxide
g	grams
IPA	isopropyl alcohol
IR	infared
LDA	lithium diisopropylamide
LiTMP	lithium 2,2,6,6-tetramethylpiperidine
mm Hg	millimetres of mercury
m.p.	melting point
ml	millilitre
MHz	megahertz

$MgSO_4$	magnesium sulphate
NBS	*N*-bromosuccamide
Na_2CO_3	sodium carbonate
$NaHCO_3$	sodium hydrogen carbonate
$NaNO_2$	sodium nitrite
NaOH	sodium hydroxide
NMR	nuclear magnetic resonance
ppm	parts per million
PPY	4-(1'-pyrrolidinyl)pyridine
quat.	quaternary
q	quartet
r.t	room temperature
rxn	reaction
s	singlet
TEA	triethylamine
THF	tetrahydrofuran
TMS	trimethylsilyl
T.l.c	thin layer chromatography

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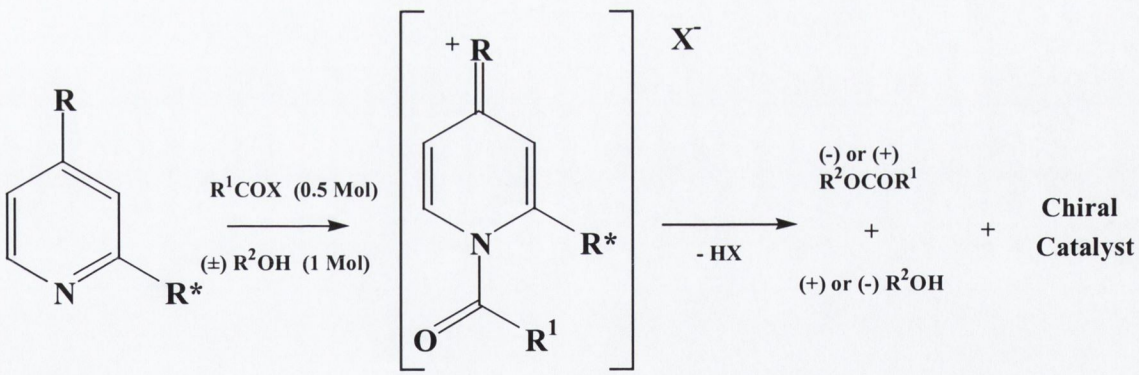
Chapter 1

Introduction

1.1 Aims of this project

The purpose of this project is to synthesise chiral catalysts which will act as enantioselective acyl transfer reagents. Typically, these catalysts will incorporate a pyridine ring bearing a 4-dimethylamino moiety within their structure to confer hypernucleophilicity. When the nitrogen atom of such a pyridine ring exists in an asymmetric environment, it follows that each enantiomer of a racemic alcohol should interact differently with an intermediate *N*-acyl pyridinium ion. In an ideal situation one enantiomer would be selectively acylated leaving the other unchanged. This would provide a simple, straightforward method for the resolution of compounds such as alcohols, thiols and amines (Scheme 1.1). It is the realisation of this hypothesis that is the subject of this project.

Scheme 1.1



Chiral Catalyst

R = NMe_2, NEt_2, Pyrrolidin-1-yl

R* = Chiral substitutent

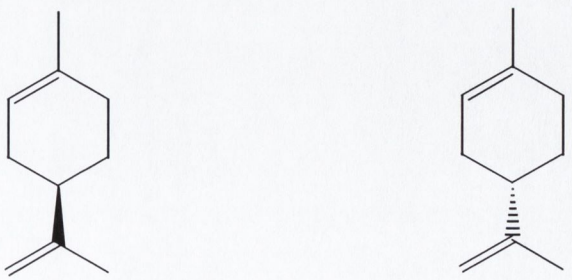
X = Cl, OAc

1.2 Enantiomers

Enantiomers are molecules that possess non-superimposible mirror images (Figure 1.1). Enantiomers have the same physical and chemical properties except that they rotate plane polarised light equally in opposite directions. However, when enantiomers interact with other chiral compounds or with chiral environments different effects are observed due to diastereomeric interactions.

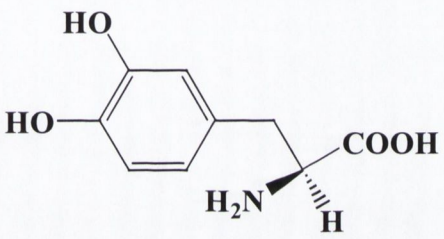
Figure 1.1

Enantiomer recognition is very important in biological processes. In order for an enantiomer to exert a biological action it must fit into a chiral receptor at the target site, into which the other enantiomer will not fit. If however, the other enantiomer fits into a chiral receptor elsewhere in the body there may a severe adverse biochemical reaction to it. An example of enantiomer recognition is limonene which gives orange and lemon skins their characteristic smells. (*R*)-Limonene **1** is found in oranges while the other enantiomer (*S*)-limonene **2** is found in lemons.



1 **2**

A further example of how enantiomer recognition operates in biological systems is 2-amino-3-(3,4-dihydroxyphenyl)propanoic acid (DOPA) which is used in the treatment of Parkinsons' disease. The prodrug DOPA is able to cross the blood brain barrier and reach the site of action where the enzyme dopamine decarboxylase decarboxylates only the (*S*) enantiomer of DOPA **3** to give the achiral therapeutic agent dopamine. Dopamine itself cannot cross the blood brain barrier. It is therefore inadvisable to administer racemic DOPA as there would be an accumulation of (*R*)-DOPA **4** in the body.



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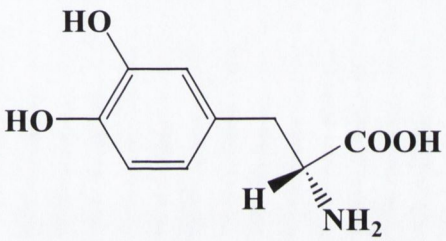

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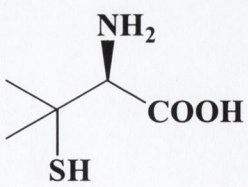
Similarly, (*S*)-penicillamine **5** is an antidote for lead, gold and mercury poisoning while (*R*)-penicillamine **6** can cause atrophy of the eyes, which may lead to blindness.



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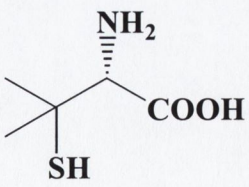

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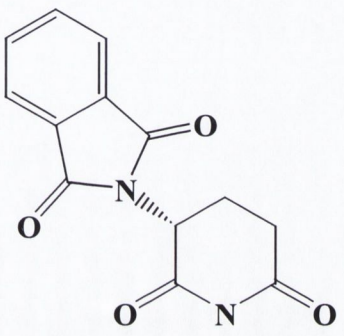
The necessity for enantiopure compounds was highlighted tragically in the 1960's with the drug thalidomide, commercially known as Softenon, which was administered as a sedative. (*R*)-Thalidomide **7** acted as a sedative while (*S*)-thalidomide **8** was teratogenic, inducing malformations in the unborn child.[1] This would have been avoided had the individual enantiomers of thalidomide and the racemate been tested prior to commercialisation.



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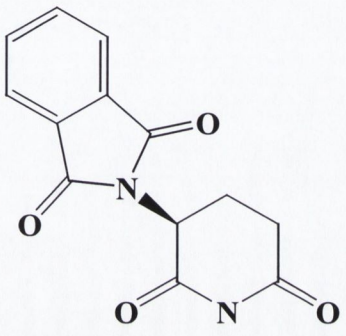

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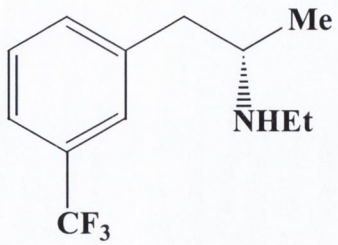
In 1992 the US Food and Drug Administration (FDA) and the European Committee for Proprietary Medicinal Products required manufacturers to research and characterise each enantiomer of all drugs proposed to be marketed as a racemate.[2] Consequently, production of new racemates ceased to be a rational commercial option and instead became a high-risk route for pharmaceutical companies. The regulators also foresaw the redevelopment of existing racemates as single isomer drugs. An example is the anti-obesity drug dexfenfluramine **9** whose racemate was initially developed by Servier.



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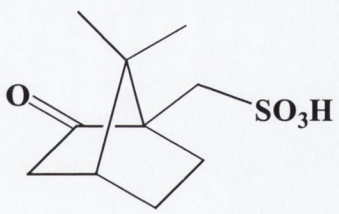
The single isomer drug (Redux) developed by Interneuron Pharmaceutical and manufactured by Wyeth Ayerst received FDA approval in 1996 with the advantage of having reduced side effects. The FDA has announced proposals to extend the market exclusivity for newly approved drugs that are single isomer to five years. Racemates superseded by single isomer drugs are to be withdrawn. Currently, 80% of all drugs entering development are chiral and 75% of all man-made drugs will be single enantiomer by year 2000.[3] It is also estimated that the market for single enantiomer drugs will increase from $73 billion in 1996 to over $90 billion by the year 2000.[4] Therefore, the search for efficient syntheses of enantiomerically pure compounds is an active area of research both in academia and industry. Resolution methods are effective sources of enantiopure compounds, as is the chiral pool and asymmetric synthesis. This project is primarily concerned with kinetic resolution as an effective method for the separation of enantiomers.

1.3 Resolution of enantiomers

Most methods of resolution utilise one basic property of enantiomers: when a pair of enantiomers interact with a chiral reagent, the resulting diastereomers have different properties. Exploitation of this phenomenon allows the enantiomers to be separated. A number of methods have been devised for the resolution of enantiomers.

1.3.1 Classical resolution

The products formed by the interaction of a pair of enantiomers with a chiral reagent are diastereomerically related. The resulting diastereomers will have different properties such as melting points and solubilities, and can often be separated by physical methods such as fractional recrystallisation, distillation, extraction, column chromatography and gas liquid chromatography.[5] Resolution is achieved if the desired enantiomers can be individually regenerated from the separated diastereomers. This represents a convenient method for the resolution of racemic acids, bases, amino-acids, alcohols, aldehydes and ketones. Classical resolution is still the method of choice industrially for the separation of racemates. DSM/Andeno resolve (±)-phenylglycine with (+)–10-camphorsulfonic acid **10** to give (*R*)-(–)-phenylglycine **11,** an intermediate in the synthesis of semi-synthetic penicillins such as ampicillin (Scheme 1.2). The resolving agent is easily recovered and the unwanted enantiomer can be racemised and recycled thus making the process commercially viable.[6]



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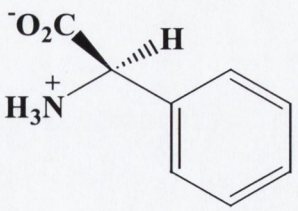

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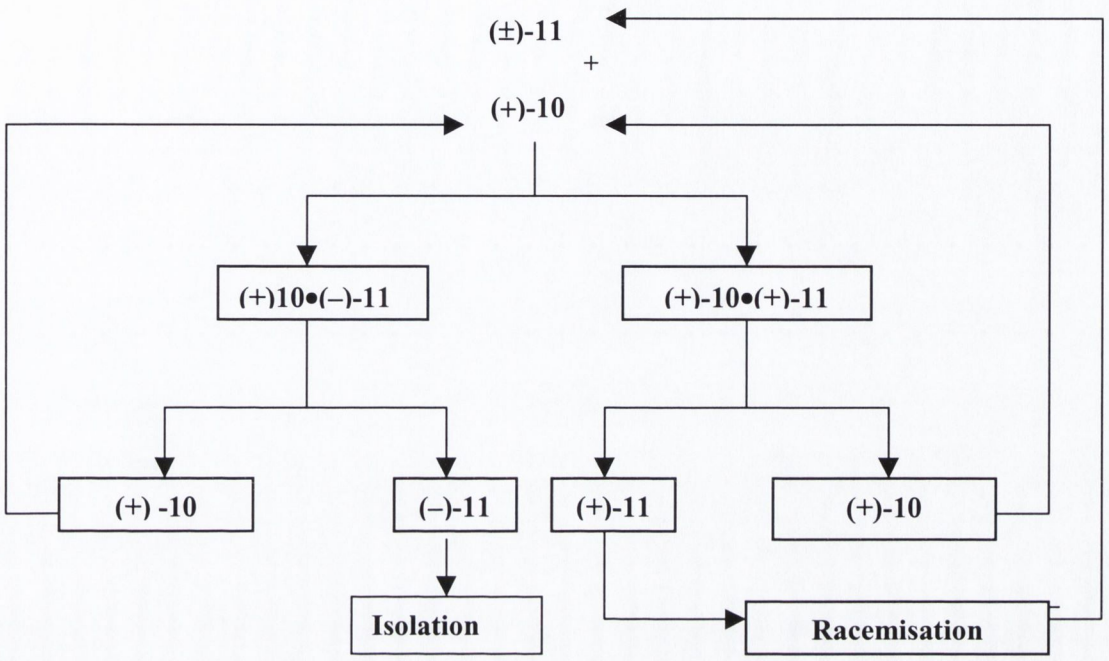
Scheme 1.2



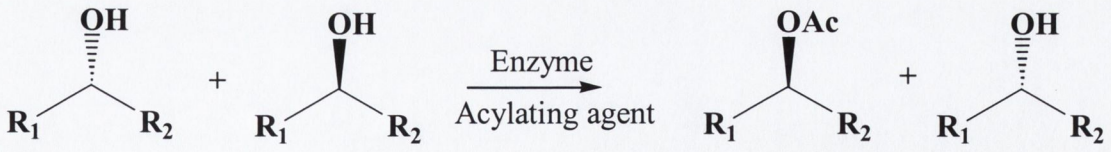
1.3.2 Kinetic resolution

When enantiomers react with a chiral reagent, they will react at different rates because the transition states involved are no longer mirror images of each other; they are diastereomeric rather than enantiomeric. In the case of two enantiomers A and Â interacting with a chiral reagent B, the transition states A.....B and Â.....B will have different internal energies, consequently they will have different activation energies and hence each reaction will have different rates. Kinetic resolution of enantiomers exploits this difference in reaction rates.

1.3.3 Kinetic resolution mediated by enzyme catalysis

Today, kinetic resolution of racemic substrates by enzyme catalysis has become a standard reaction in organic chemistry. More than 2000 enzymes are known, several hundred of these are commercially available from biochemical supply houses such as Sigma and Fluka. When an enzyme is enantiomer specific, one enantiomer of a racemate is selectively transformed to product whereas the other is left unchanged, *i.e.* one enantiomer will fit into the active site of the enzyme and its reaction will be catalysed. The other enantiomer will not bind as well to the active site and its diastereomeric transition state will be less stable, and so its reaction will be very much slower than the other enantiomer and its reaction will be effectively uncatalysed. The magnitude of the energy difference, $\partial\Delta G$ determines the enantiomeric excess. The obvious limitation with this process is that the maximum theoretical yield of product is limited to 50% of the starting material (Scheme 1.3). The unwanted enantiomer must be discarded unless it is possible to recycle it by racemisation.

Scheme 1.3



50%

Enzymes find particular use in effecting the kinetic resolution of secondary alcohols. Secondary alcohols are an important class of readily available derivatizable compounds that can be incorporated into a variety of synthetic strategies. The kinetic

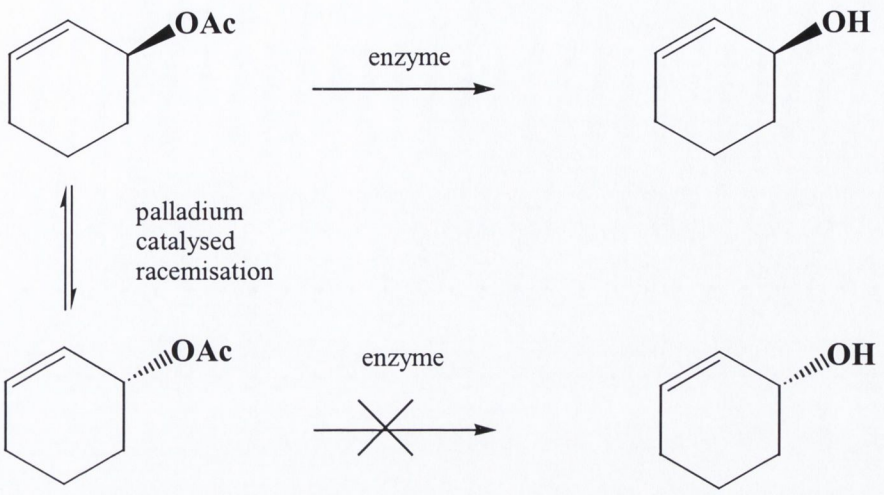
resolution of these compounds or more often their corresponding acetates has traditionally been achieved by esterases with excellent results.[7, 8, 9]

As mentioned earlier enzymatic resolution is limited to a maximum yield of 50%. There are several ways to overcome this problem, (1) use of meso or prochiral substrates,[10] (2) stereoinversion of the remaining enantiomer[11] (*e.g.* Mitsunobu reaction of the remaining alcohol) (3) dynamic kinetic resolution or (DKR).

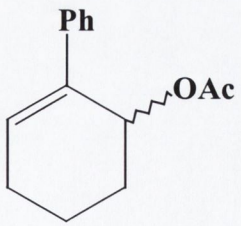
1.3.4 Dynamic kinetic resolution

Both enzymes and transition metal catalysts have been used for the preparation of enantiomerically enriched products. In dynamic kinetic resolution the substrate is continuously racemised during the resolution process and this leads to efficient use of all the starting material. It is therefore possible to obtain in theory a 100% yield of a desired enantiomer. In DKR three criteria must be met. Firstly, an enzyme that is capable of effecting kinetic resolution must be identified. Secondly, a catalyst capable of *in situ* racemisation of the starting material and not the product is required, and thirdly, a system needs to be found where the performance of the enzyme and catalyst are not adversely affected by the presence of each other.[12] This concept was elegantly employed by Allen *et al.*[13] who utilised palladium catalysts in combination with various enzymes to effect the kinetic resolution of allylic alcohols from allylic acetates *via* enzymatic hydrolysis (Scheme 1.4). An enzyme was utilised to hydrolyse one enantiomer of an allylic acetate to give the (*S*)-alcohol and concurrently a palladium catalyst was used to racemise the starting material but not the product, thus the (*S*)-enantiomer favoured by the enzyme was constantly replenished.

Scheme 1.4



The best results obtained were for the allylic acetates **12** and **14**. After 19 days acetate **12** was hydrolysed to the corresponding (*S*)-alcohol **13** with 96% conversion in 96% enantiomeric excess using the enzyme *Pseudomonas fluorescens* lipase (PFL). Allylic acetate **14** gave the (*S*)-alcohol **15** with > 98% conversion and 50 % enantiomeric excess with the same enzyme. The rate determining step is most likely the slow palladium catalysed racemisation of the allylic acetate, since in the former case 50% conversion is achieved after only 2 days.



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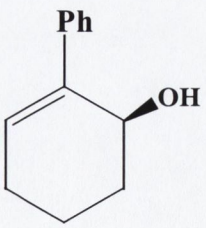

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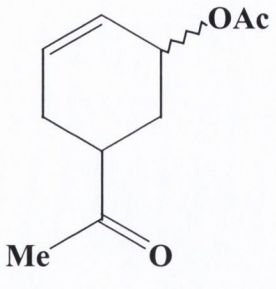
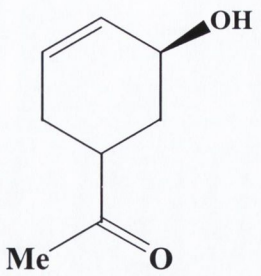
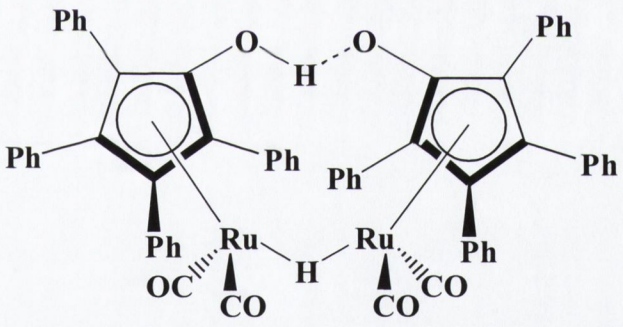




14 **15**

Bäckwell *et al.*[14] report a highly efficient DKR of secondary alcohols in the presence of the ruthenium catalyst **16** using immobilised *Candida antarctica* lipase supported on an acrylic resin. This resin is commercially available under the tradename Novozym 435.

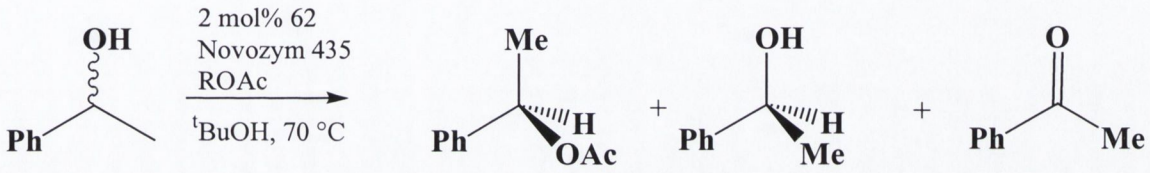


16

Thus, when using vinyl acetate as the acyl donor, racemic 1-phenylethyl alcohol **17** was converted into the (*R*)-acetate **18** in the presence of a catalytic amount of **16** in 50% yield and 99% ee (Scheme 1.5). The rest of the starting material was converted into acetophenone **20** (Table 1.1, entry 1).

When isopropenyl acetate was used as the acyl donor a similar result was obtained, 72% of (*R*)-acetate and 28% acetophenone (Table 1.1, entry 2). The acetophenone formed arises from overall oxidation of the starting material. When 4-chlorophenyl acetate was utilised as the acyl donor, no acetophenone was formed and racemic **17** was converted into (*R*)-acetate **18** in 100% yield and >99% ee. This can be elegantly explained by considering the mechanism involved.

Scheme 1.5



(±)-**17** (*R*)-**18** (*S*)-**19** **20**

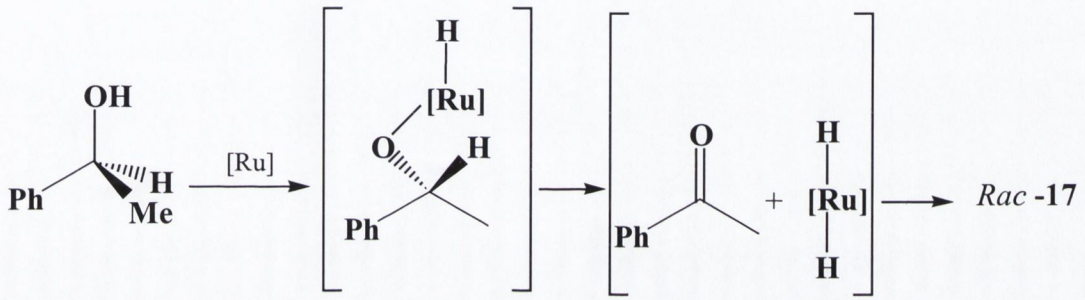
Table 1.1 **Effect of the acyl donor in the dynamic kinetic resolution of (±)-phenylethyl alcohol catalysed by compound 16 as taken from Bäckwell *et al.*[14]**

Entry[a]	ROAc (eq.)	Time (h)	(*R*)-18[b]	(*S*)-19[b]	20[b]	% ee of (*R*)-18
1	Vinyl acetate (5.5)	17	50	0	50	> 99[c]
2	Isopropenyl acetate (5)	24	72	0	28	> 99[c]
3	4-Chlorophenyl acetate (3)	87	100	0	0	>99[c]

[a] Reaction carried out as in scheme 1.5. [b] Conversion and ratio of products were determined by ^{1}H NMR and GC. [c] ee of (*R*) -18 was determined by chiral HPLC.

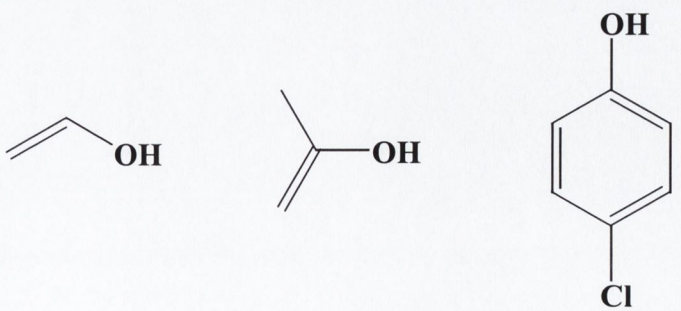
The reaction proceeds through a base-mediated hydrogen abstraction from the substrate to give the ruthenium alkoxy species **21**. Abstraction of the α-proton gives the corresponding ketone (acetophenone) and a ruthenium hydride complex. Subsequent readdition of hydrogen to the acetophenone gives the racemised 1-phenylethyl alcohol, thus replenishing the enantiomer preferred by the enzyme. The formation of the acetophenone in Table 1.1 can be explained by this mechanism.

Scheme 1.6



(*S*)-**17** **21**

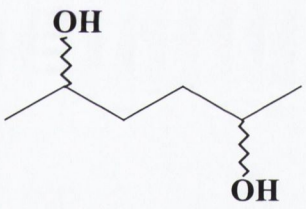
When vinyl or isopropenyl acetates are utilised as acyl donors, transfer of the acyl group to the substrate gives the vinyl alcohols **22** and **23**, which can readily tautomerise to give acetaldehyde and acetone. These carbonyl compounds can both compete with the acetophenone for the intermediate ruthenium hydride complex. This results in consumption of the hydride complex and overall oxidation of the starting material.



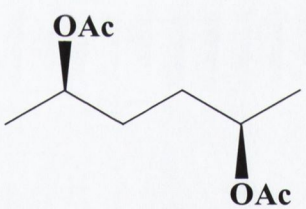
22 **23** **24**

This explains why no acetophenone is produced when 4-chlorophenyl acetate is used as an acylating agent. The 4-chlorophenol **24** produced when the acyl group of 4-chlorophenyl acetate is transferred to the substrate cannot undergo tautomerism and hence cannot accept a hydride from the ruthenium donor. In the event, 1-phenylethyl alcohol was converted into its acetate in 100% yield and > 99% ee. The scope of this reaction was been extended to a range of aromatic and aliphatic secondary alcohols. In all cases impressive yields and levels of selectivities were obtained.

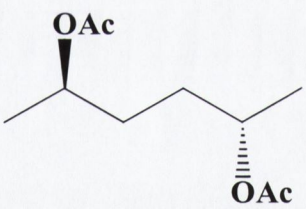
Bäckvell *et al.*[15] have also applied this methodology to the resolution of secondary diols. The meso/dl diol **25** was converted into diacetate **26** in 63% yield as a 86 : 14 mixture of (*R,R*)-**26** (>99% ee) and meso **26**. This was quite impressive considering that the maximum yield in enzymatic kinetic resolution was *circa* 25%.



25



(*R,R*) - **26**



Meso - **26**

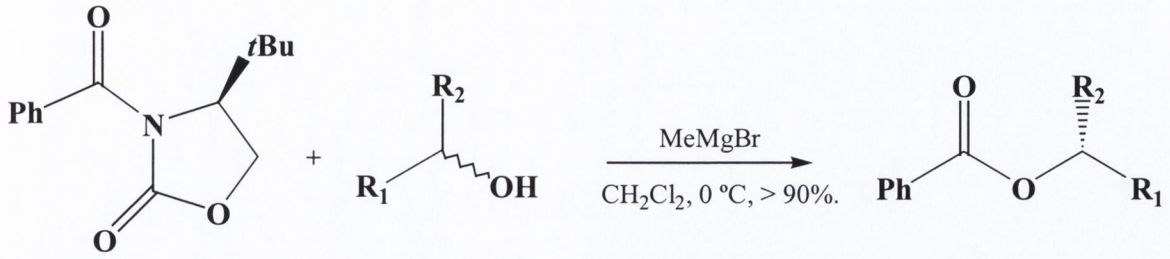
Reetz *et al.*[16] have successfully used DKR to resolve the enantiomers of phenylethylamine with immobilised lipase and ethyl acetate as the acyl donor. The non-acylated (*S*)- enantiomer of the amine was racemised *in situ* by palladium on charcoal. Thus, (*R*)-*N*-acyl-1-phenylethyl amine was isolated in 64% yield and 99% ee.

Latest developments in DKR involve trying to combine two enzymes working in the same reaction vessel but independently of each other. One enzyme for racemisation of the substrate and the other effects the kinetic resolution of the substrate.[17] Stecher *et al.*[18] report that the enzyme *mandelate racemase* FC.51.2.2 from *Pseudomonus putida* strain ACTT 12633 catalyses the racemisation of mandelic acid. The substrate spectrum for the enzyme was found to be very much broader than mandelic acid and was tolerant of a variety of functional groups on the aryl ring. This approach has the advantage of using milder conditions, which would fit synergistically with the conditions required for the enzyme catalysing the kinetic resolution. However, to date there are no reports of an effective two enzyme system capable of a DKR with good yields and high ees. In practice, DKR has become an effective tool in the chemists toolbox to access optically active alcohols, amines and diols.

1.3.5 Non-enzymatic kinetic resolution

The non-enzymatic resolution of secondary alcohols has proved to be more difficult than that catalysed by enzymes alone. The only prominent example is the Sharpless resolution of allylic alcohols.[19] The most straightforward method for the resolution of alcohols is to use a chiral acylating agent such as oxazolidinone **27** (Scheme 1.7).[20] Thus alcohols **28** and **29** were converted to their phenyl esters **30** and **31** with good ee.

Scheme 1.7

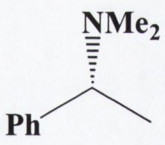


27 (1 eq.) **(2 eq.)**
28 R_1 = Ph, R_2 = Me
29 R_1 = Ph, R_2 = *i*Pr

30 ee = 95%
31 ee = 65%

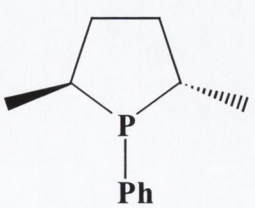
The main drawback with this system is that a stoichiometric amount of the chiral acylating agent must be employed, *i.e.* there is no catalyst turnover.

The activities of certain chiral tertiary amines have also been investigated. 1-Phenylethyl alcohol upon treatment with the chiral amine **32** and acetyl chloride as the acyl donor gave the corresponding acetate of (*S*)-1-phenylethyl alcohol **19** in 68% optical purity. The ratio of alcohol to AcCl to catalyst was 2 : 1 : 1.[21]

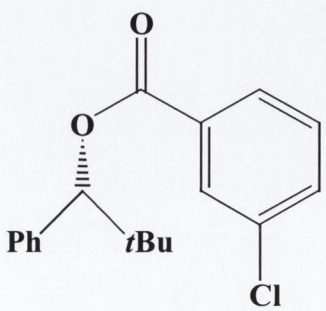


32

(*S*)-15



33

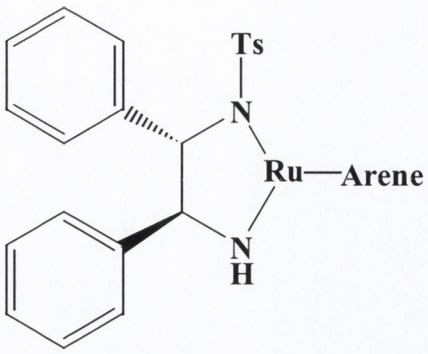


34

The first example of a chiral nucleophilic promoter was described by Vedejs *et al.* [22] The C_2-symmetric phosphine **33** and acetic anhydride gave the acetate of (*S*)-1-phenylethyl alcohol **19** in 44% conversion and 34% ee. The ratio of alcohol : acyl donor : catalyst was 1 : 2.5 : 0.16. Racemic 2,2-dimethyl-1-phenylpropanol was acylated with *m*-chlorobenzoic anhydride under the same reaction conditions to yield ester **34** in 25% conversion, 81% ee, (s = 12-15). *

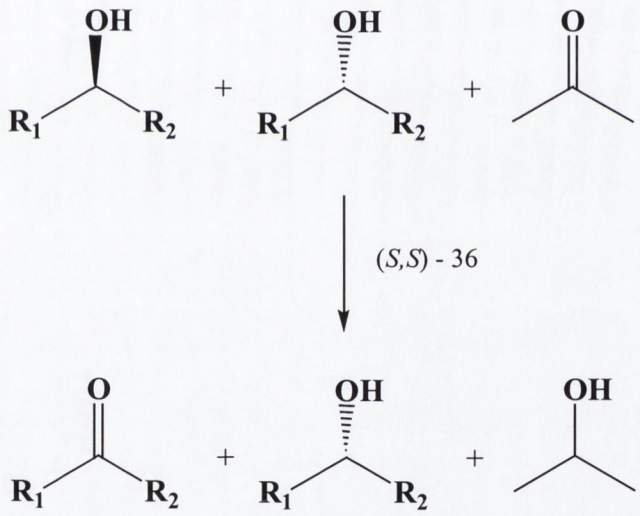
Noyori *et al.*[23] have demonstrated the ability of chiral diamine based Ru(II) complexes as catalysts for the reduction of prochiral ketones to the corresponding alcohols with excellent ee. The hydrogen source in this reaction is isopropyl alcohol which is oxidised to acetone. A major flaw of this reaction is that it is reversible, *i.e.* the reaction is dependent on the reduction potential of the alcohols formed. Alcohols such as 1,2,3,4-tetrahydro-1-naphthol and 1-phenylethyl alcohol cannot be prepared directly by this method since they have high reduction potentials and are readily oxidised back to the ketone again. Bearing this in mind and with the correct choice of catalyst it was proposed that this would provide a simple method for the kinetic resolution of these types of alcohols.[24] Thus, excellent differentiation of enantiomers of racemic alcohols was achieved with the Ru(II) diamine catalysts **35** and **36**. The reaction can be better understood by considering Scheme 1.8. The faster-reacting enantiomer is converted to the ketone while the other remains effectively unchanged, thus providing a mixture consisting of easily separable ketone and alcohol of high optical purity.

*** Stereoselectivity factor s = (rate of fast reacting enantiomer)/(rate of slow reacting enantiomer)**

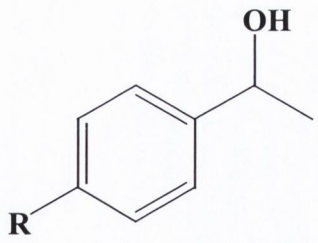


(*S*,*S*)- 35, Arene = *p*-Cymene
(*S*,*S*)- 36, Arene = Mesitylene

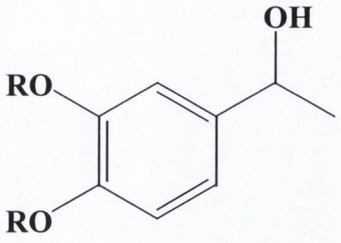
Scheme 1.8



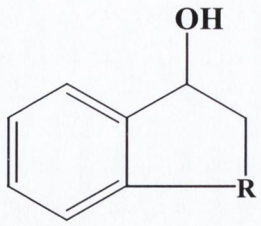
A number of alcohols **37** - **47** were resolved by this methodology in good to excellent ee (Table 1.2). In all cases it was the (*S*)-enantiomer that was converted to the ketone when **35** and **36** were employed as catalysts for the reaction.



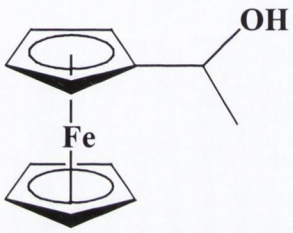
37 R = H
38 R = MeO
39 R = $(CH_3)_2N$



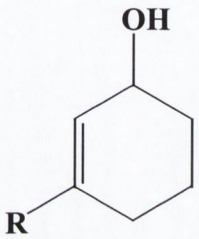
40 R = CH_3
41 R-R = CH_2



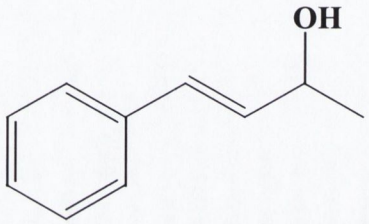
42 R = CH_2
43 R = $(CH_2)_2$



44



45 R = H
46 R = CH_3



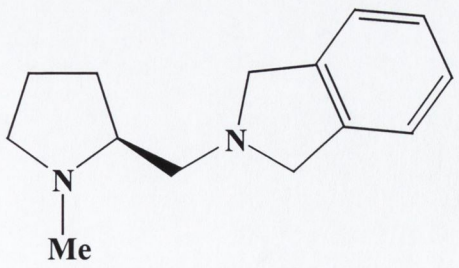
47

An attractive aspect of this methodology is that inexpensive acetone and isopropyl alcohol can be utilised as the hydrogen acceptor and donor respectively. The ketone formed from the substrate can easily be recycled/transformed into desirable products.

Table 1.2 **Resolution of alcohols catalysed by chiral diamine Ru(II) complexes 35 and 36 as taken from Noyori *et al.*[23]**

Alcohol	Catalyst	Mol % of Catalyst	Time h	% Recovery of alcohol	% ee	Configuration	S
37	(*S,S*)-**35**	0.2	36	50	92	*R*	>80
37	(*S,S*)-**36**	0.2	30	51	94	*R*	>100
38	(*S,S*)-**35**	0.2	22	47	92	R	>30
39	(*S,S*)-**36**	0.2	30	44	98	*R*	>30
40	(*S,S*)-**36**	0.2	36	47	97	*R*	> 50
41	(*S,S*)-**36**	0.2	24	47	97	*R*	>50
42	(*S,S*)-**35**	0.2	6	46	97	*R*	>40
43	(*S,S*)-**35**	0.2	6	49	99	*R*	>50
44	(*S,S*)-**36**	0.075	36	51	98	*R*	>100
45	(*S,S*)-**35**	0.2	4.5	43	93	*R*	14

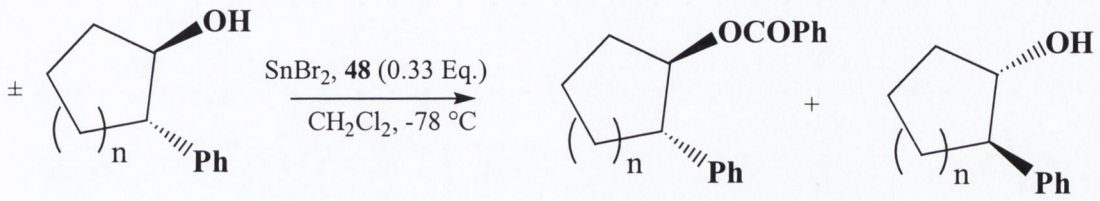
Oriyama *et al.*[25] have resolved a number of secondary alcohols using the chiral diamine **48** derived from (*S*)-proline. In conjunction with a Lewis acid such as $SnBr_2$, 4 Å molecular sieves and an acyl halide as an acyl donor, **48** forms a $SnBr_2$-chiral diamine complex which is effective in promoting asymmetric acyl transfer.



48

Alcohols such as *trans*-2-phenyl-1-cyclohexanol **50** gave benzoate **52** in 44% yield with excellent enantiomeric excess (97%) together with recovered (1*R*, 2*R*)-**50** when such a catalytic system was employed.

Scheme 1.9



49 n = 1
50 n = 2

51 n = 1, ee 86%
52 n = 2, ee 97%

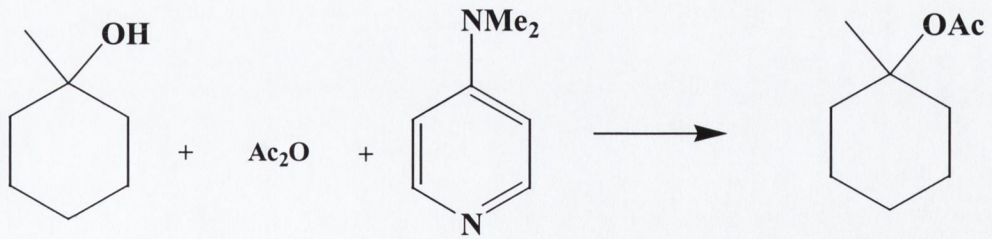
In an investigation with several other alcohols, cyclic substrates generally gave better results than acyclic alcohols. A limitation with this technology was that a high catalyst loading was required (0.33 molar equivalents relative to the alcohol).

The above examples are representative of catalyst systems with low or no turnover. Current thinking into the non-enzymatic kinetic resolution of alcohols involves the synthesis of chiral compounds based around the 4-dialkylaminopyridine structure. The last three years has witnessed an explosion of interest in this area. 4-Dialkylaminopyridines are important catalysts for the acylation of alcohols.

1.4 4-Dialkylaminopyridines

The reaction of acetic anhydride/pyridine with hydroxy compounds is a mild, dependable and general method for the preparation of the corresponding acetates. This was first developed by Verley and Bölsing[26] and was successfully extended by Fischer and Bergmann[27] in their work on carbohydrate chemistry.

Steglich and Höfle[28] found that the addition of 4-dimethylaminopyridine **54** greatly facilitated the acylation of hindered alcohols with carboxylic acid anhydrides. The most useful aspect of this reagent in acylations is that its action is catalytic. The presence of less than 2 mol% of this compound enhances the rate of acylation of a primary or secondary alcohol by a factor of *circa* 10^4. Thus for example 1-methylcyclohexanol **53** was not acylated by acetic anhydride and pyridine or triethylamine, but the addition of 0.05 mol equivalents of 4-dimethylaminopyridine **54** to a mixture of 1-methylcyclohexanol and acetic anhydride led to the formation of 1-methylcyclohexyl acetate **55** in 86% yield.[29]



53 **54** **55**

The superiority of DMAP to other bases is illustrated in Table 1.3. The relative rates of benzoylation of *m*-chloroaniline and benzyl alcohol and the effects of various bases were investigated.[30]

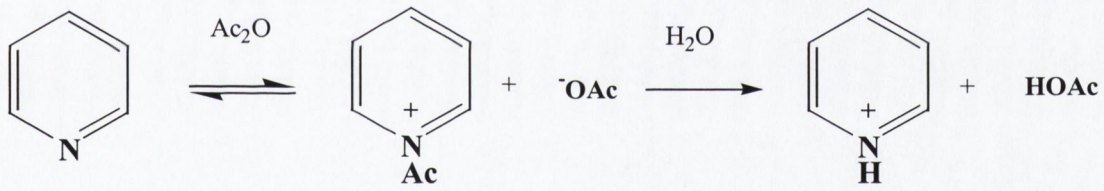
Table 1.3 Effect of various bases on the relative rates of benzoylation of *m*-chloroaniline and benzyl alcohol as taken from Scriven *et al*[30]

		Relative Rate	
Catalyst	**pK_a**	***m*-Chloroaniline**	**Benzyl alcohol**
3-Pyridinecarbonitrile	1.39	14	12
Quinoline	4.87	138	545
Pyridine	5.23	568	9.29×10^3
Isoquinoline	5.40	2.62×10^3	3.39×10^3
2-Methylpyridine	5.96	29	435
3-Methylpyridine	5.63	1.12×10^3	2.29×10^3
4-Methylpyridine	6.04	2.96×10^3	3.98×10^3
4-Phenoxypyridine	6.25	4.80×10^3	7.98×10^3
2,6-Dimethylpyridine	6.72	8	115
DMAP	9.70	3.14×10^6	3.45×10^8
TEA	10.65	21	-

Clearly the use of DMAP has a profound influence on reaction rate of benzoylation of benzyl alcohol and for *m*-chloroaniline. Why is this so?

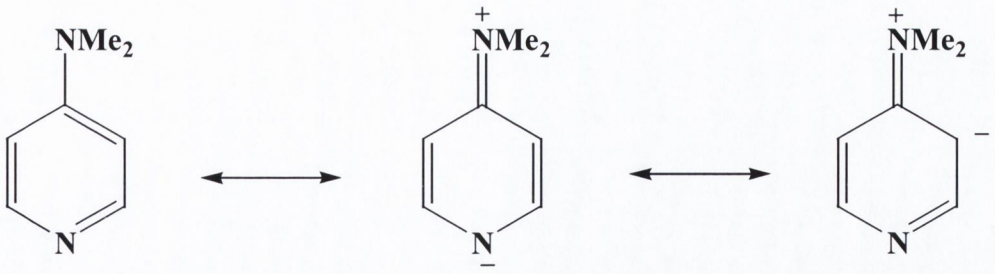
1.4.1 Mechanism of catalysis

To understand the catalytic activity of DMAP one must understand the mechanism of catalysis. On comparing the basicity of pyridine ($pK_a = 5.23$) with that of DMAP ($pK_a = 9.70$) it could be surmised that the increase in reactivity of DMAP is due to the 2.6×10^4 fold increase in basicity. That this is not the case shown by triethylamine ($pK_a = 10.65$) which is about as active as pyridine, therefore catalysis is not truly reflected by consideration of the pK_a alone. The only possible reason for the increase in activity is increased nucleophilic catalysis. For example, the hydrolysis of acetic anhydride in the presence of pyridine has been shown to proceed by nucleophilic catalysis and the unstable acetylpyridinium ion **56** was proposed as an intermediate. The mechanism was formulated on the basis of kinetic analysis.[31]



56

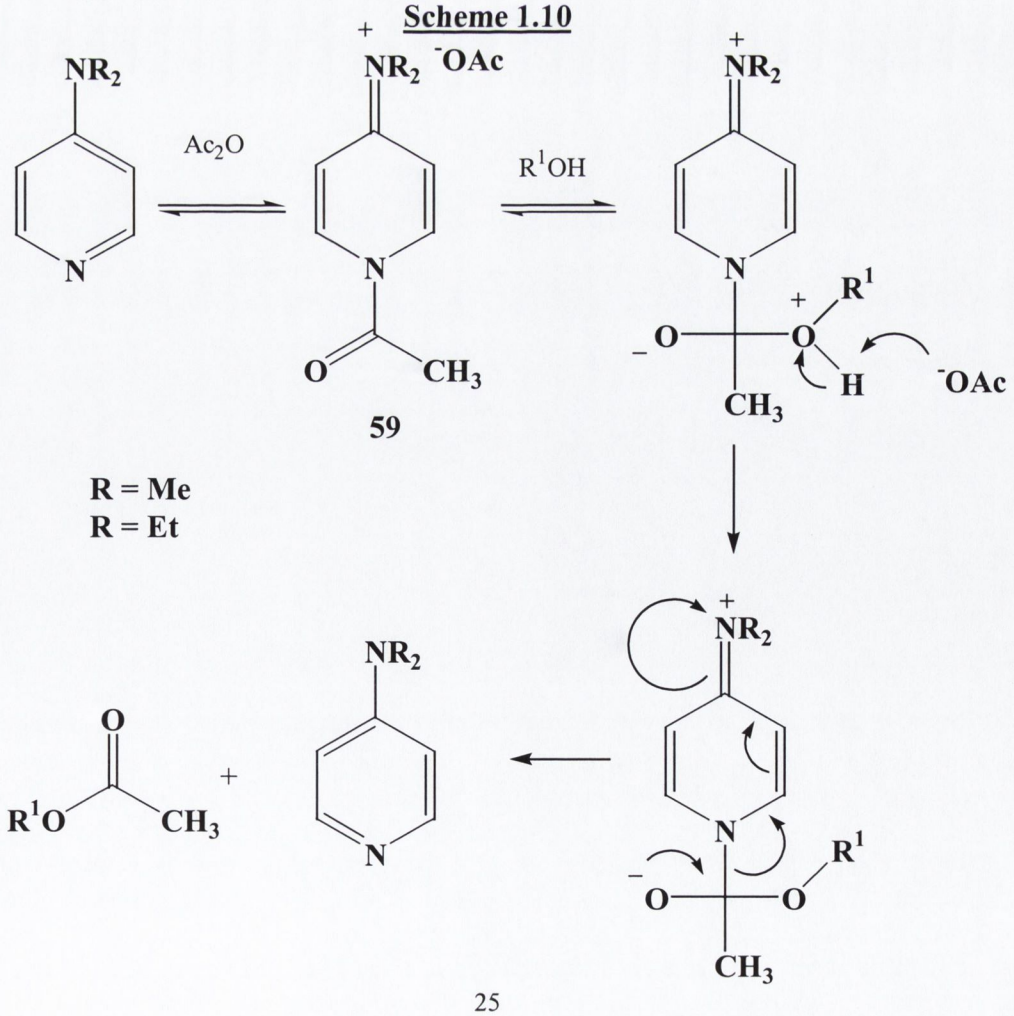
The intermediate salt is most readily formed in the case of the more basic pyridine, DMAP. Unlike the case of pyridine, such salts of DMAP may be isolated and are often quite stable. Another factor is π-π overlap that is possible in the 4-dialkylaminopyridines series to give the canonical structures **57** and **58**. Structures such as **57** greatly increase the nucleophilicity of the ring nitrogen.



57 **58**

Hassner *et al.*[32] recorded the chemical shifts of the β-hydrogens (of the pyridine ring) in a whole series of substituted 4-dialkylaminopyridines. They found that the greatest shielding occurs in the most effective acylation catalyst, 4-(1'-pyrrolidinyl)-pyridine (PPY). They concluded that the catalytic activity is due to a combination of the donor ability of the amine substituent and the stability of the intermediate *N*-acyl-4-dialkylaminopyridinium species **59**. Their results were consistent with the mechanism postulated below (Scheme 1.10).

Scheme 1.10



59

R = Me
R = Et

They also found that the *N*-acyl pyridinium intermediate **59** is sensitive to steric effects since no catalytic activity was observed in the presence of a series of 2-dialkylaminopyridines.

In summary it can be concluded that;

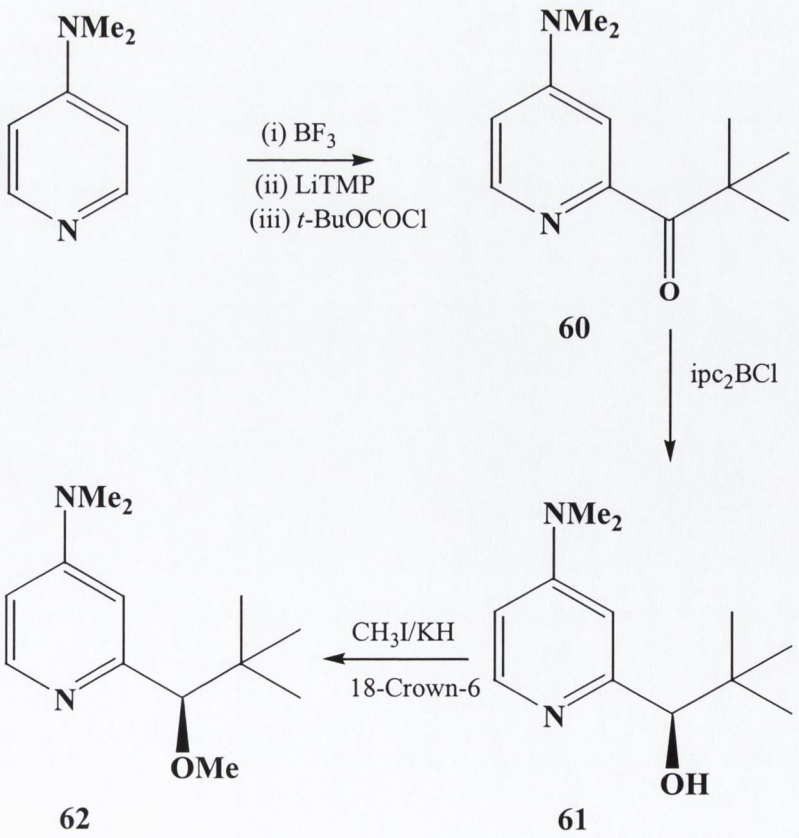
- As a result of their pronounced nucleophilicities bases such as DMAP and 4-(1'-pyrrolidinyl)pyridine (PPY) form high concentrations of *N*-acyl-4-dialkylaminopyridinium salts with acylating agents even in non-polar solvents and are superior to pyridine and amines in this respect.
- Because of charge delocalisation, the *N*-acyl-4-dialkylaminopyridinium salts are present as loosely bound ion pairs, thus greatly facilitating attack of nucleophiles on the activated acyl group with general base catalysis by the neighbouring anion. This effect also explains why carboxylic anhydrides are better suited for these acylations than the corresponding acyl chlorides.

4-Dialkylaminopyridines were soon found to have general applicability in the catalysis of acylations and related reactions including alkylations, halogenations, Criegee rearrangements, cyanylations, dehydrations, oxidations, phosphorylations, silylations and sulphonylations. This coupled with the commercial availability of DMAP in larger quantities for the first time stimulated great interest in its use as a catalyst in organic chemistry, polymers, analytical chemistry and biochemistry.[33]

1.4.2 Chiral 4-dialkylaminopyridines

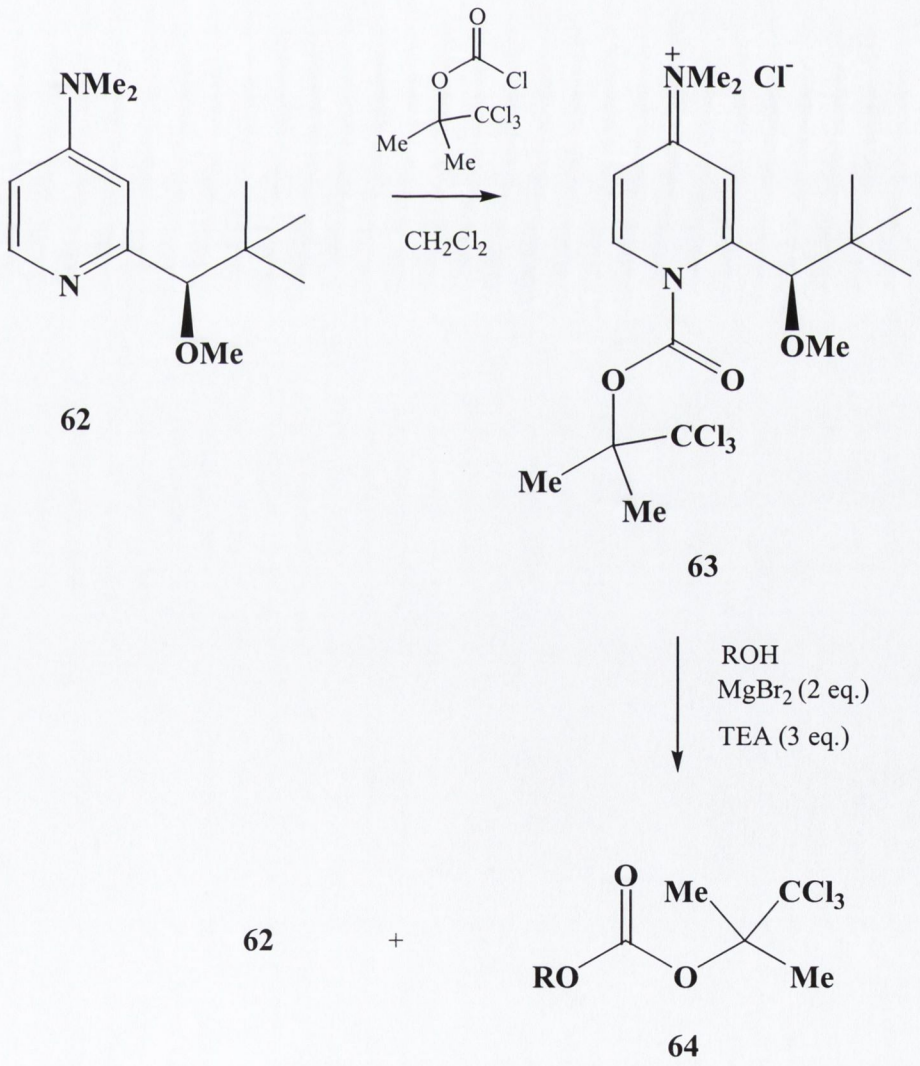
The first chiral 4-dialkylaminopyridine was reported by Vedejs *et al.*[34] who synthesised the chiral acyl transfer reagent **62**. This compound was synthesised from commercially available 4-dimethylaminopyridine (Scheme 1.11). 4-Dimethylaminopyridine was reacted with BF_3 to give the corresponding DMAP-BF_3 adduct in order to increase the acidity of the protons at the 2- and 6- positions, thus increasing the likelihood of abstraction by a strong base such as LiTMP. Metalation at C_2 with lithium tetramethylpiperidine followed by reaction with pivaloyl chloride gave ketone **60** in 61% yield. The ketone was reduced with (–)-*B*-chlorodiisopinocampheylborane (ipc_2BCl) to give the alcohol **61** in 71% yield and 94% ee. Recrystallisation gave material of > 99% enantiomeric purity. Methylation with methyl iodide, potassium hydride and 18-crown-6 gave the catalyst **62**.

Scheme 1.11



This new compound was non-catalytic and was employed in stoichiometric amounts. Reaction of **62** with a commercially available chloroformate generated as expected the corresponding *N*-acyl-4-dimethylaminopyridinium salt **63**. Addition of representative secondary alcohols to **63** did not lead to their acylation. However, the addition of a tertiary amine together with a Lewis acid ($ZnCl_2$ or $MgBr_2$) initiated a slow acyl transfer reaction resulting in the formation of the mixed carbonate **64** (Scheme 1.12).

Scheme 1.12

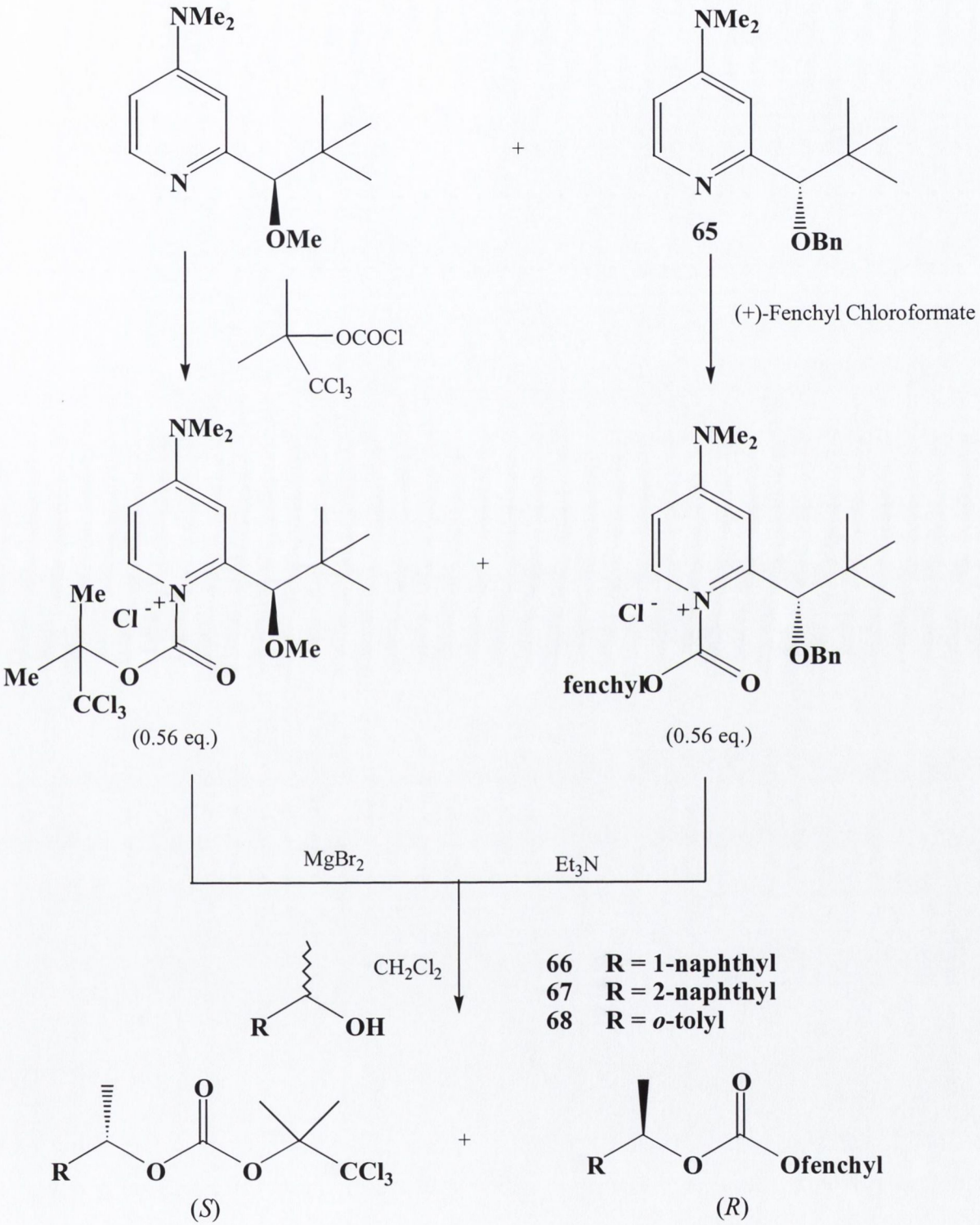


The results of acylating a number of secondary alcohols showed that several of the mixed carbonate esters **64** were formed with > 90% enantiomeric purity at conversions in the range of 20-42%. Catalyst **62** was easily recovered and reused many times without any apparent loss of activity.

An inherent problem with this method for the kinetic resolution of alcohols is that the starting material becomes more and more enriched in the slower reacting enantiomer. Therefore, exceptionally large differences in rates between enantiomers are required to obtain high ee values in product as well as the enriched enantiomer of the starting material, *e.g.* for conversions at 50%, s = 200, ee = 96%; s = 500, ee = 98%. In an attempt to overcome this problem an ingenious protocol known as parallel kinetic resolution (PKR) was developed by Vedejs and Chen.[35]

The underlying principle is of two competing processes run in parallel with similar rates and selectivities but for opposite enantiomers, thus the optimal 1:1 ratio is maintained throughout the experiment. The advantages of this experiment can be appreciated by considering a PKR experiment in which there are two simultaneous reactions with selectivities for opposite enantiomers of the same racemic alcohol and each with s = 49 (100 % conversion); ideally this system would give both products with ee of 96%. By contrast a kinetic resolution would require s = 200 (50% conversion). The chiral DMAP derivatives **62** and **65** were chosen and were expected to behave as quasi-enantiomers and to acylate opposite enantiomers of a racemic secondary alcohol. Thus, when **62** and **65** were treated with representative secondary alcohols **66 - 68** the corresponding carbonates **69 – 71** were formed in good yields and ee. The concept is outlined in Scheme 1.13.

Scheme 1.13

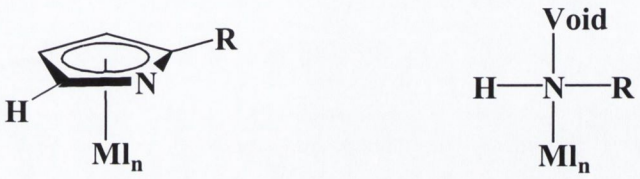


(*S*) - 69 **46%, *ee* = 88%**
(*S*) - 70 **49%, *ee* = 86%**
(*S*) - 71 **46%, *ee* = 83%**

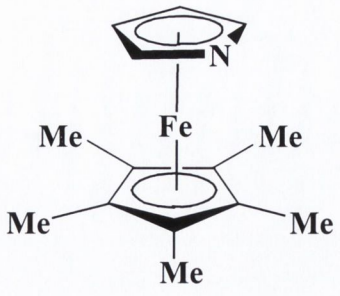
(*R*) - 69 **49%, *ee* = 95%**
(*R*) - 70 **43%, *ee* = 93%**
(*R*) - 71 **46%, *ee* = 94%**

Ruble *et al.*[36] have explored the possibility of π-complexation of a heterocycle to a transition metal as an effective approach to the development of chiral analogues of planar nucleophilic catalysts such as 4-dimethylaminopyridine **54** and imidazole. The resultant complex is chiral by virtue of there being four different substituents on the nitrogen atom (Figure 1.2).

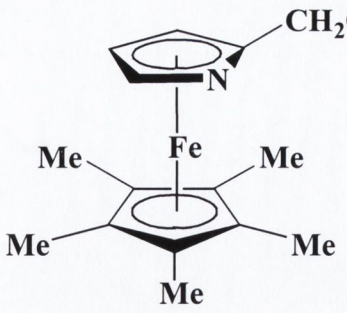
Figure 1.2



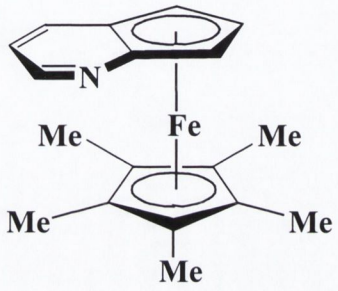
Viewing along the lone pair-nitrogen atom axis, increased differentiation from left to right (H vs R) and from top to bottom (void vs Ml_n) corresponds to a more asymmetric environment around the nucleophilic nitrogen. If either left/right or top/bottom is not differentiated then the complex will be achiral. The compounds 1',2',3',4',5',-pentamethylazaferrocene **72,** 1',2',3',4',5',-pentamethyl-2-trimethyl silyloxymethylaza-ferrocene **73**, pentamethylcyclopentadienylpyrindinyliron **74** and 4-dimethylaminopyrindinyl -pentamethylcyclopentadienyliron **75** were synthesised, **73 - 75** being chiral. The FeCp fragment was chosen as the Ml_n fragment because it was electron-rich, stable and sterically bulky. The pyrindinyl complexes **74** and **75** were chosen to explore the effect of nucleophilicity on five- and six- membered π-bound heterocycles that have different steric and electronic properties. The azaferrocene derivative **73** functioned as an effective acylation catalyst for the kinetic resolution of chiral secondary alcohols.



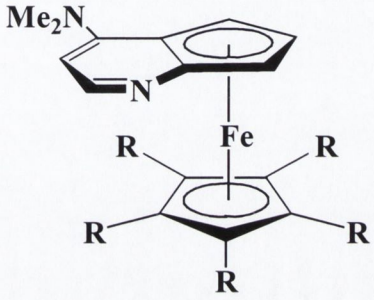
72



73



74

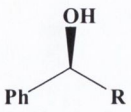
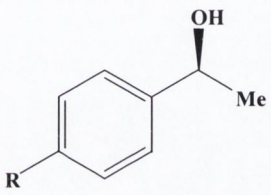
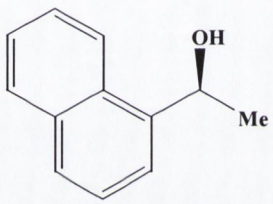
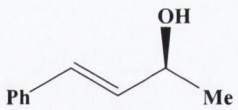
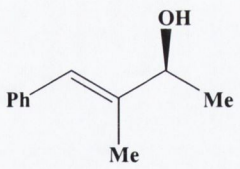


75 R = Me
76 R = Ph

Thus, compound **73** catalysed the acylation of 1-phenylethyl alcohol in benzene employing diketene as the acyl donor to give the corresponding acetate at 58% conversion in 53% ee (s = 3.6). Reaction of 2-naphthylethyl alcohol under the same conditions afforded (*S*)-2-naphthylethyl acetate in 87% ee (s = 6.5) at 67% conversion. Catalyst **75** proved very effective in the acylation of secondary alcohols but showed no enantioselectivity. Modification of **75** by increasing the steric bulk of the cyclopentadienyl fragment (R = Me vs R = Ph) proved highly successful, thus affording **76** which proved a highly enantioselective acylation catalyst.[37]

This catalyst also had the advantage that inexpensive acetic anhydride could be utilised as the acyl donor as opposed to diketene. Thus, in the presence of ether and triethylamine at r.t. a range of racemic alcohols were resolved with high enantioselectivities and good conversions (Table 1.4).

Table 1.4 Catalytic enantioselective acylation of racemic secondary alcohols catalysed by compound 76 as taken from Ruble *et al.* [37]

Entry[a]	Unreacted alcohol major enantiomer	R	% ee of unreacted alcohol (% Conversion)	S (Selectivity)
1		Me	95.2 (62)	14
2		Et	98.8 (62)	20
3		*i*-Pr	97.7 (55)	36
4		*t*-Bu	92.2 (51)	52
5		CH_2Cl	98.9 (69)	12
6		F	99.2 (64)	18
7		OMe	94.5 (60)	15
8			99.7 (63)	22
9			99.1 (67)	14
10			99.0 (61)	22

(a) Alcohol (3.37 mmol), acetic anhydride (2.53 mmol), ether (6 ml), TEA (2.53 mmol)

None of the substrates in Table 1.4 had previously been resolved with a selectivity factor greater than 7 in the presence of a non-enzymatic chiral acylation catalyst. These resolutions were relatively straightforward and were not sensitive to oxygen or moisture. Identical results were obtained for acylations with unpurified reagents

exposed to the atmosphere as opposed to reactions conducted in an inert atmosphere with analytical grade reagents. Finally the catalyst was recovered in >98% yield and reused without any loss of activity.

A wide ranging solvent study into the acylation of (±)-1-phenylethyl alcohol revealed that both the rate and the enantioselectivity were highly dependent on the solvent.[38] In the event, *tert*-amyl alcohol was the solvent of choice for acylations catalysed by **76** (Table 1.5). Interestingly, *tert*-amyl alcohol was not acylated to any great extent under these conditions. When compared to identical reactions run in ether a tripling of selectivites was observed.

This observation had important practical consequences. It had been determined that acylations catalysed by compound **76** conducted at 0 °C in ether led to higher selectivities. Unfortunately, these reactions took several days, whereas when *tert*-amyl alcohol was employed as the solvent acylations proceed at a convenient rate and were typically complete within 24 h.

Table 1.5 Solvent effect on rate and selectivity for the kinetic resolution of 1-phenylethyl alcohol catalysed by 76 from Ruble *et al.* [38]

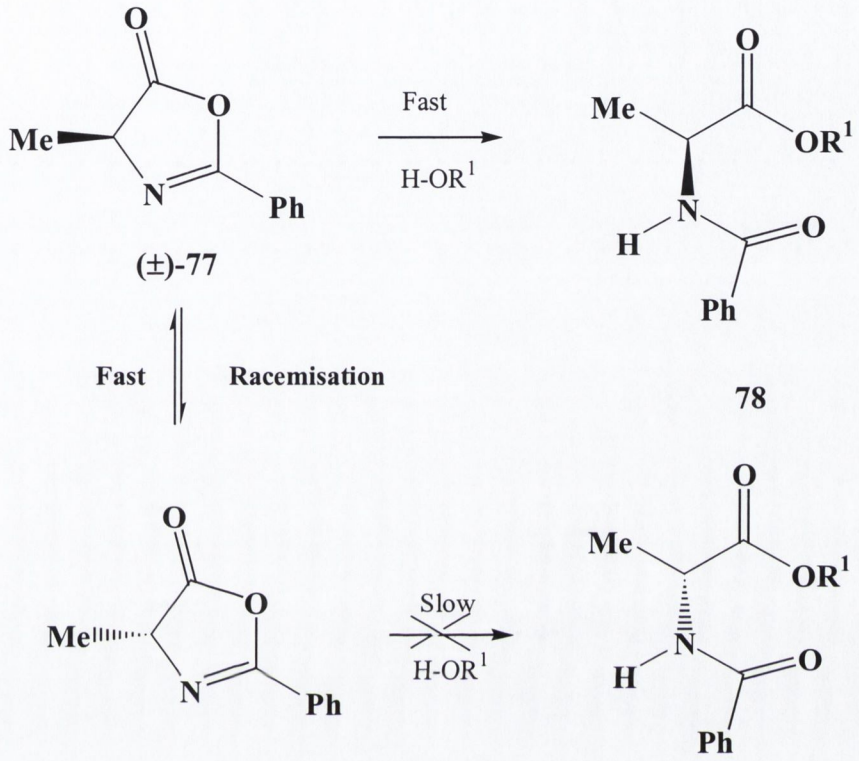
Solvent	% Conversion after 1 h	Selectivity (s)
DMF	6	3.4
CH_3CN	10	3.6
CH_2Cl_2	14	7.0
Acetone	8	8.7
THF	4	9.6
EtOAc	6	11
Toluene	13	11
Et_2O	8	13
***t*-amyl alcohol**	**36**	**27**

The use of *tert*-amyl alcohol as solvent led to general increases in selectivity for a wide range of substrate alcohols. As a result of such a high selectivity factor both alcohol and ester were now accessible in excellent ee. In general selectivities greater than 50, and ee values of 99% are possible. This currently represents the best non-enzymatic asymmetric acylation of arylalkylcarbinols in terms of enantioselectivity and scope. There is a high catalyst turnover and the catalyst is easily recoverable. Also, the reaction conditions permit unpurified reactants to be used without the need for an inert atmosphere.

Ruble *et al.*[39] have also extended the use of this methodology to the synthesis of protected α-amino acids from racemic oxazolidinones with moderately impressive results. Because of their propensity to racemise at room temperature oxazolidinones

such as **77** undergo DKR *via* ring opening by alcohols when subjected to catalysis by **76** to give the protected α-amino acids **78** (Scheme 1.14).

Scheme 1.14



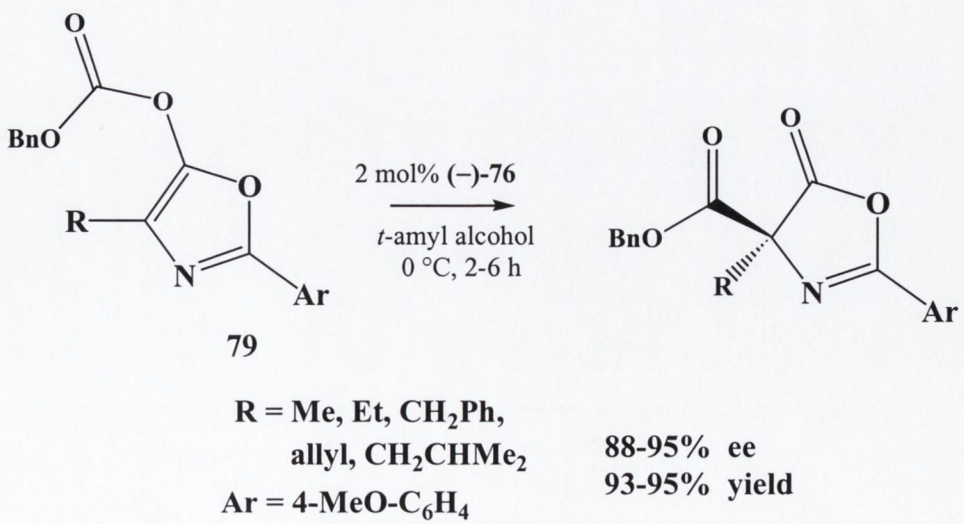
Addition of alcohols to oxazolidinones such as (±)-**77** almost always gives the L-alanine derivatives **78**. The level of selectivity is found to be solvent dependant with toluene affording the best ee (Table 1.6). Stereoselectivity increases with size of alcohol used, *e.g.* use of *i*-PrOH gave an ee of 78% under these conditions. Unfortunately ring opening is very slow ($t_{1/2}$ ~ 1 week).

Table 1.6 **Effect of solvent on enantioselectivity of the ring opening of azlactones catalysed by compound 76 as taken from Ruble *et al.*** [39]

Entry	Solvent	% ee
1	CH_3CN	11
2	$PhNO_2$	17
3	Acetone	20
4	THF	31
5	CH_2Cl_2	33
7	EtOAc	40
8	PhOMe	46
9	Toluene	49

Ruble *et al.*[40] also report that *O*-acylated enol lactones such as **79** undergo an enantioselective rearrangement when subjected to catalysis by compound **76** to form the *C*-acylated isomer thereby generating a new quaternary stereocentre (Scheme 1.15).

Scheme 1.15



79

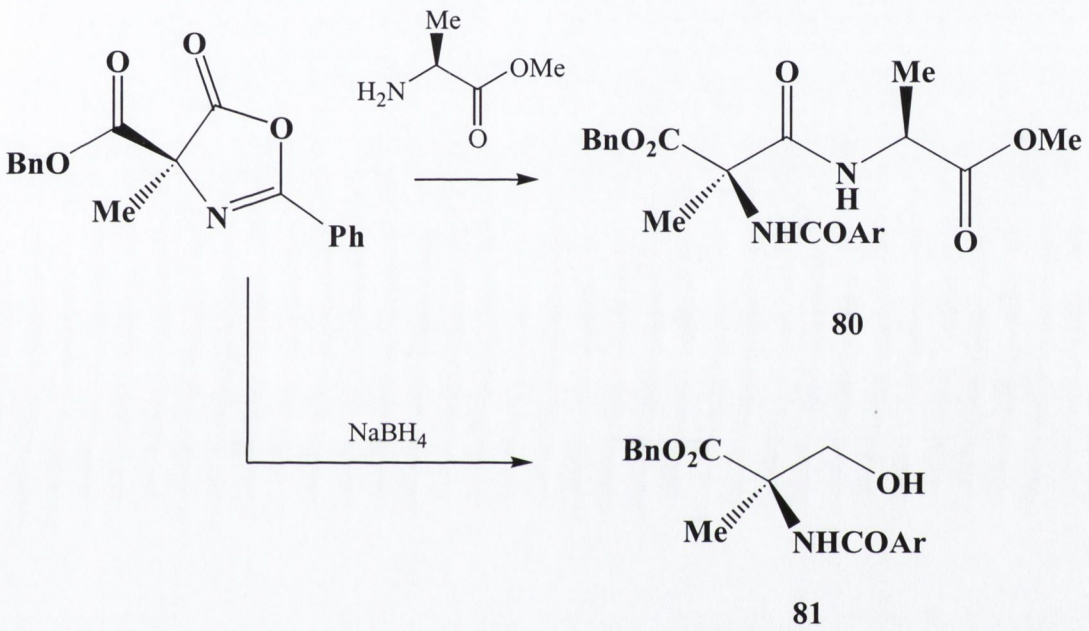
R = Me, Et, CH_2Ph, allyl, CH_2CHMe_2

Ar = 4-MeO-C_6H_4

88-95% ee
93-95% yield

This reaction gave excellent yields and very good selectivity for an array of *O*-acylated enol lactones. The utility of this rearrangement was illustrated by the subsequent conversion of the *C*-acylated oxazolidinone into the dipeptide **80** and into the protected α-methylserine derivative **81** (Scheme 1.16).

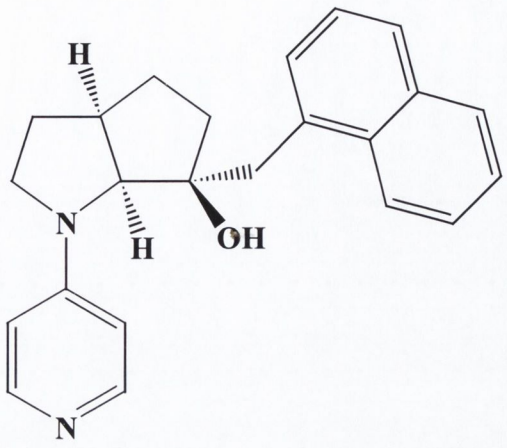
Scheme 1.16



80

81

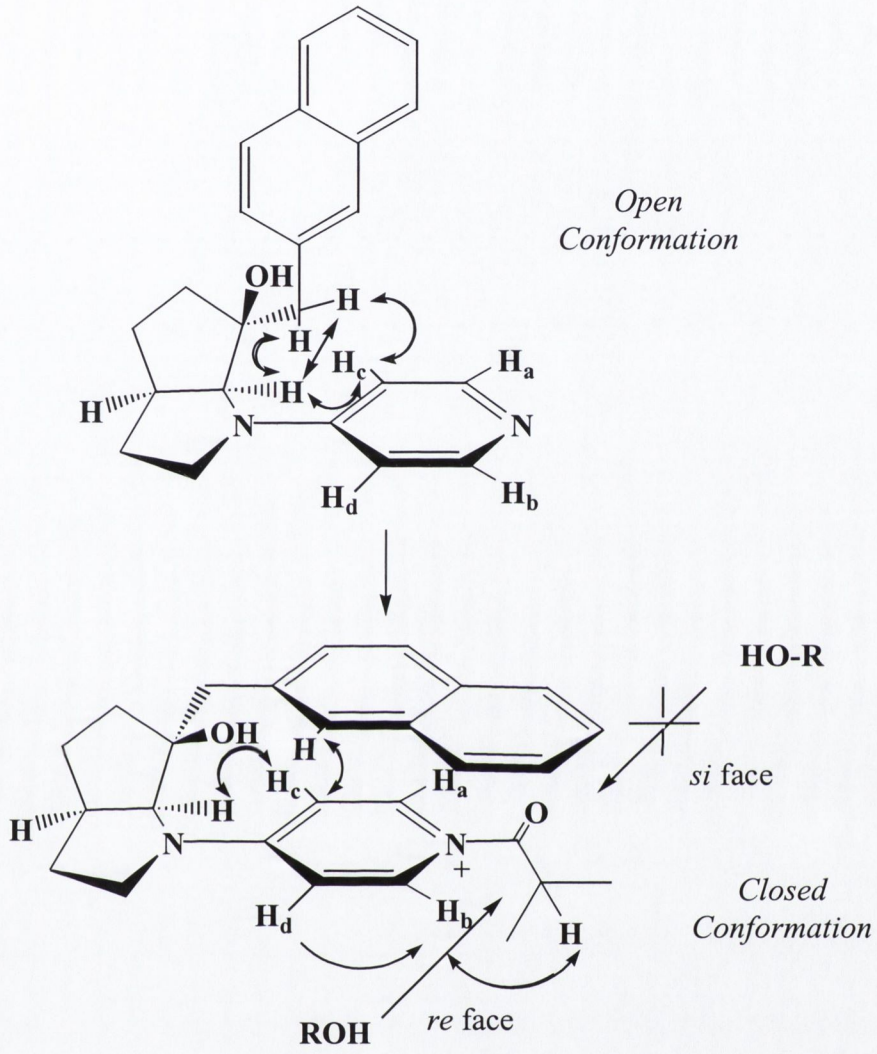
An ingenious approach to the kinetic resolution of secondary alcohols was devised by Fuji *et al.*[41] who prepared the enantiomerically pure pyridine derivative **82**. They assumed that the reduced steric hindrance in the proximity of the nitrogen atom would result in high catalytic turnover and that chiral recognition would be possible by remote asymmetric induction, similar to the "induced fit" mechanism known to operate in enzymes. This method where the stereocontrolling chiral centres are far from the active site overcomes the selectivity-reactivity dilemma, so apparent in the method of Vedejs *et al.*[34]



82

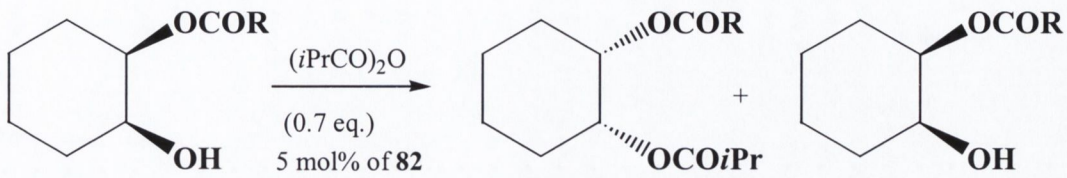
^{1}H NMR NOE experiments in $CDCl_3$ showed that **82** adopts an "open conformation" in the ground state but, upon reaction with an acyl donor such as isobutyric anhydride, this changes to a "closed conformation" in which the naphthyl moiety sits over the pyridine ring of the catalyst (Figure 1.3). In the "open conformation" protons H_a, H_b, H_c and H_d appear as doublets at δ 8.01 and 6.37 ppm respectively. This indicates that there is free rotation about the N(2)-C(1') bond of the molecule and no significant interaction between the naphthalene ring and the pyridine ring. Upon reaction with the acyl donor, protons H_a, H_b, H_c and H_d all appear at different shifts at δ 7.45, 8.93, 5.69 and 6.87 ppm respectively. This dramatic change in chemical shifts indicates that there is π -π interaction between the aromatic rings. Also an NOE was observed between H_b and the proton of the NCOC*H*$(CH_3)_2$ of the acyl group which suggested that the *si* face of the carbonyl moiety is blocked by the naphthalene ring. This in effect prevents approach of the alcohol from the *si* face of the carbonyl group thus leaving the *re* face exposed to attack. This is the enantiodifferentiating event for this catalyst.

Figure 1.3



When the racemic (±)-*cis*-alcohols **83** – **86** were treated with isobutyric anhydride in the presence of a catalytic amount of **82** (5 mol%), the acetates **87** – **90** were formed in good yields (Scheme 1.17). The optical purity of the products was determined by chiral HPLC on the recovered alcohol (Table 1.7).

Scheme 1.17



83 R = *p*-$O_2NC_6H_4$
84 R = Ph
85 R = *p*-$MeOC_6H_4$
86 R = *p*-$Me_2NC_6H_4$

87 R = *p*-$O_2NC_6H_4$
88 R = Ph
89 R = *p*-$MeOC_6H_4$
90 R = *p*-$Me_2NC_6H_4$

Table 1.7 **Resolution of alcohols catalysed by compound 82 as taken from Fuji *et al.*** [41]

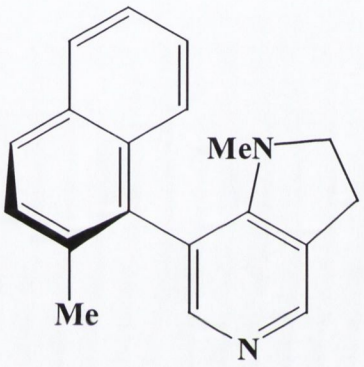
Entry	Substrate	% Conversion	% ee of alcohols 83 -86	Selectivity
1	**83**	73	54	2.4
2	**84**	71	81	4.5
3	**85**	70	85	5.3
4	**86**	72	>99	>10.1

Interestingly, the optical purity of the recovered alcohol is dependent on the electron-donating ability of the aromatic ring in the substrate, possibly indicating that π-π stacking may play a pivotal role in the enantiodifferentiating event (Table 1.7, entries 1 and 4).

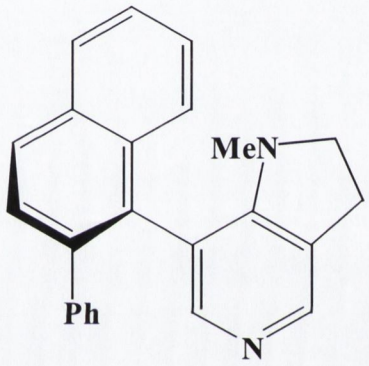
Recent newcomers to the area of non-enzymatic kinetic resolution are Spivey *et al.* [42,43] who have synthesised a number of configurationally stable biaryl analogues of

4-dimethylaminopyridine. The compounds **91** and **92** are configurationally stable at ambient temperature. The chirality of these molecules arises from restricted rotation about the Ar-Py bond.

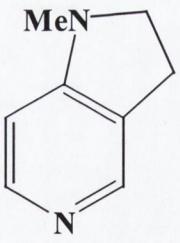
1-Methyl-2-pyrrolidino[3,2-c]pyridine **93** was chosen as the backbone of the catalyst because the C-4-N bond is conformationally rigid and therefore contributes to the barrier of internal rotation about the central biaryl axis. Also, **93** showed catalytic activity on a par with that of DMAP itself.[44]



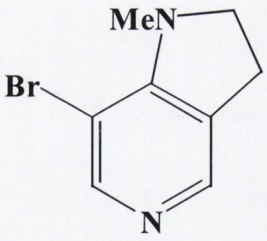
91



92



93

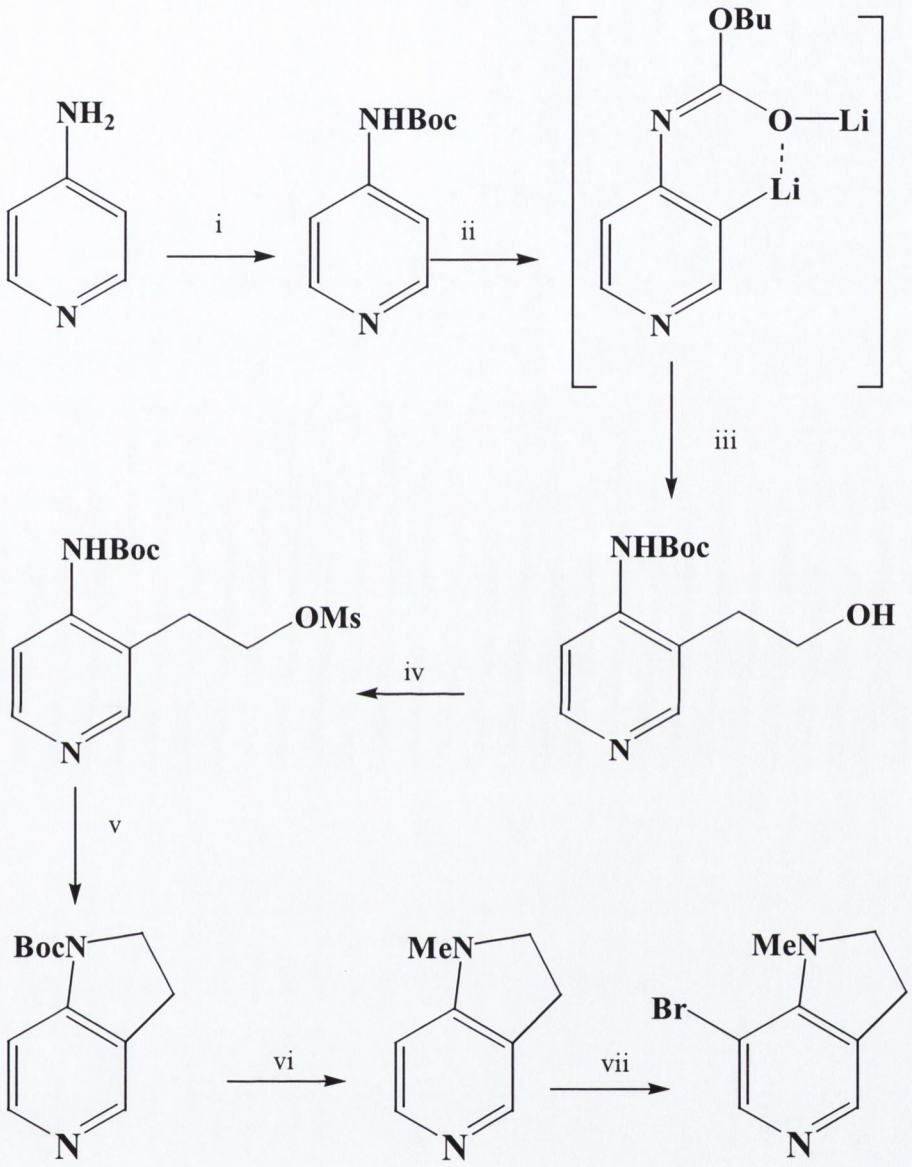


94

Catalysts **91** and **92** were synthesised from the bromo derivative **94** *via* Suzuki cross coupling with arylboronic acids. The bromo compound **94** was synthesised from commercially available 4-aminopyridine (Scheme 1.18). Catalysts **91** and **92** were

designed so that the stereogenic axis was *meta* to the pyridyl nitrogen such that they retained the high nucleophilicity of the parent amine.

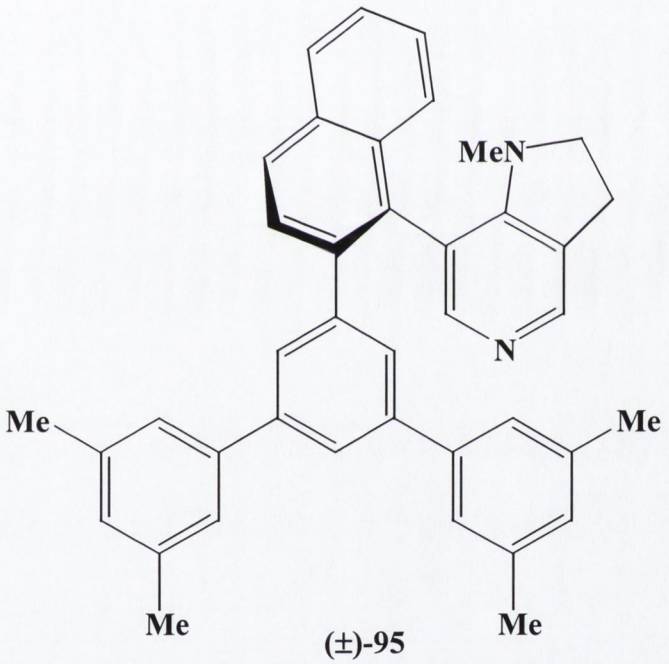
Scheme 1.18



Reagents and Conditions: (i) Boc_2O, DCM, r.t, 45 min, >99 %; (ii) *t*-BuLi, THF, -78 °C, 3.5 h; (iii) ethylene oxide, -78 °C → r.t, 2 h, 75%, (iv) MsCl, Et_3N, DCM, - 10 °C → r.t 2 h, > 99%, (v) LHMDS, THF, -78 °C → r.t → reflux, 95%, (vi) DIBAL, DCM, 0 °C → reflux, 20 h, 55%, (vii) NBS, DMF, 0 °C, 90 min, 81%.

The racemisation of compounds **91** and **92** were sufficiently slow at ambient temperature to allow for the separation of their constituent enantiomers which were

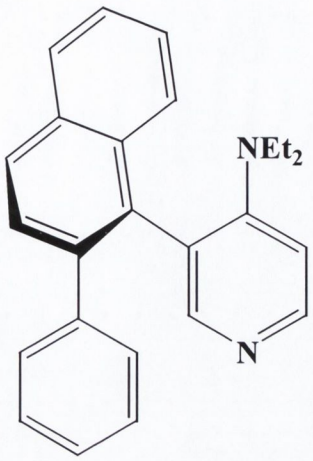
resolved using semipreparative chiral HPLC. In the event catalysts, (+)-**91** and (–)-**92** showed low levels of enantioselectivity (s = 1.3-1.5 and 2.1 depending on solvent respectively) but retained excellent reactivity. The lack of enantioselectivity was attributed to insufficient differentiation between the two faces of the pyridine ring. This differentiation had been elegantly achieved by Fuji *et al.*[41] with the catalyst **82**. In order to overcome this shortcoming compound **95** was chosen by Spivey as the next lead candidate for testing as an enantioselective acylation catalyst. A more sterically demanding substitutent was anticipated to give much better differentiation between the top and bottom faces of the pyridine ring.



(±)-95

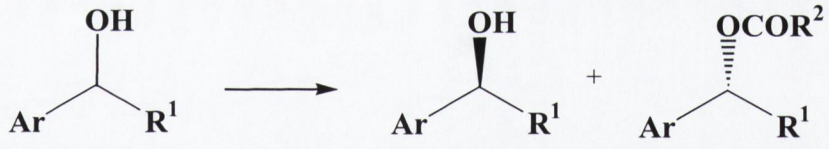
Upon testing, compound (–)-**95** did give a modest increase in enantioselectivity (*s* = 4.7) when 1-(1-naphthyl) ethanol was utilised as the substrate. In order for this process to be practical selectivity factors of > 7 are required.

In order to differentiate the molecule further, a differentiation from left to right was attempted. So, the compound (–)-**96** was synthesised.



(–)-96

A number of secondary alcohols **97** were resolved with good levels of selectivity when (–)-**96** was employed as the catalyst and isobutyric anhydride was used as the acyl donor (Table 1.8).



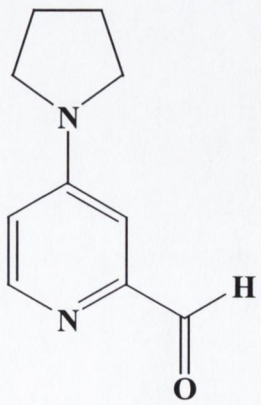
(±)-97 (*S*)-98 (*R*)-99

Although the results obtained were perhaps not as impressive as those obtained by Ruble *et al.*[37] (Table 1.4), they nonetheless were still impressive. Further differentiation of the molecule is still possible by introducing another large biaryl subunit into the 3-position of the pyridine ring which would give the desirable C_2 symmetric compound which may aid further the enantiodiscriminating event.[45] Current work that is ongoing involves further studies into the selectivity-reactivity optimisation.

Table 1.8 **Kinetic resolution of alcohols 97 catalysed by biaryl (–)-96 as taken from Spivey *et al.*[43]**

Entry	Ar	R^1	R^2	Solvent	Time/h	(*S*)-98 % ee	(*R*)-99 % ee	s
1	1- naphthyl	Me	*i*Pr	PhMe	9.0	49.9	78.1	13
2	1- naphthyl	Me	*i*Pr	EtOAc	9.3	76.1	70.9	13
3	Ph	Me	*i*Pr	PhMe	7.6	49.9	78.1	13
4	Ph	Et	*i*Pr	PhMe	9.7	49.9	78.1	13
5	Ph	*i*Pr	*i*Pr	PhMe	10.1	29.8	72.7	8.4
6	Ph	^{t}Bu	*i*Pr	PhMe	10.5	18.8	88.8	20
7	2-Me(C_6H_4)	Me	*i*Pr	PhMe	9.5	60.7	86.0	25
8	2-OMe (C_6H_4)	Me	*i*Pr	PhMe	12.1	40.2	81.5	15
9	2,6-di-Me(C_6H_4)	Me	*i*Pr	PhMe	8.0	21.3	90.7	25

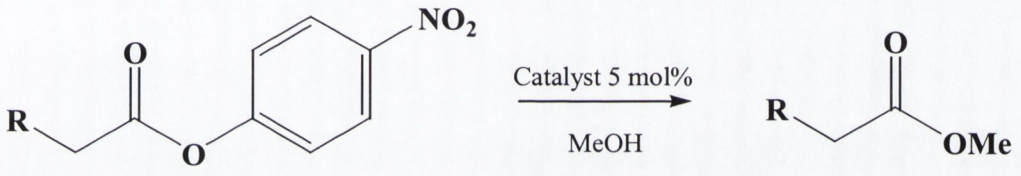
The use of active esters as acyl equivalents for the acylation of alcohols has been well documented. Sammakia *et al.*[46] have developed 2-formyl-4-(1'-pyrrolidinyl)pyridine (FPP) **100** as a catalyst for the hydroxyl-directed methanolysis of hydroxy esters (Scheme 1.19).



100

FPP **100** was designed to have separate binding (2-formyl group) and catalytic (nitrogen of the pyridine ring) sites. The binding site serves two functions, it brings the ester into close proximity with the active site and activates the catalyst upon binding by converting a aldehyde group which is electron-withdrawing into a hemiacetal functionality which is electron-donating. In kinetic studies, the *p*-nitrophenyl (PNP) esters of propionic acid **101**, methoxyacetic acid **102** and glycolic acid **103** were chosen as substrates for methanolysis catalysed by FFP (Scheme 1.19).

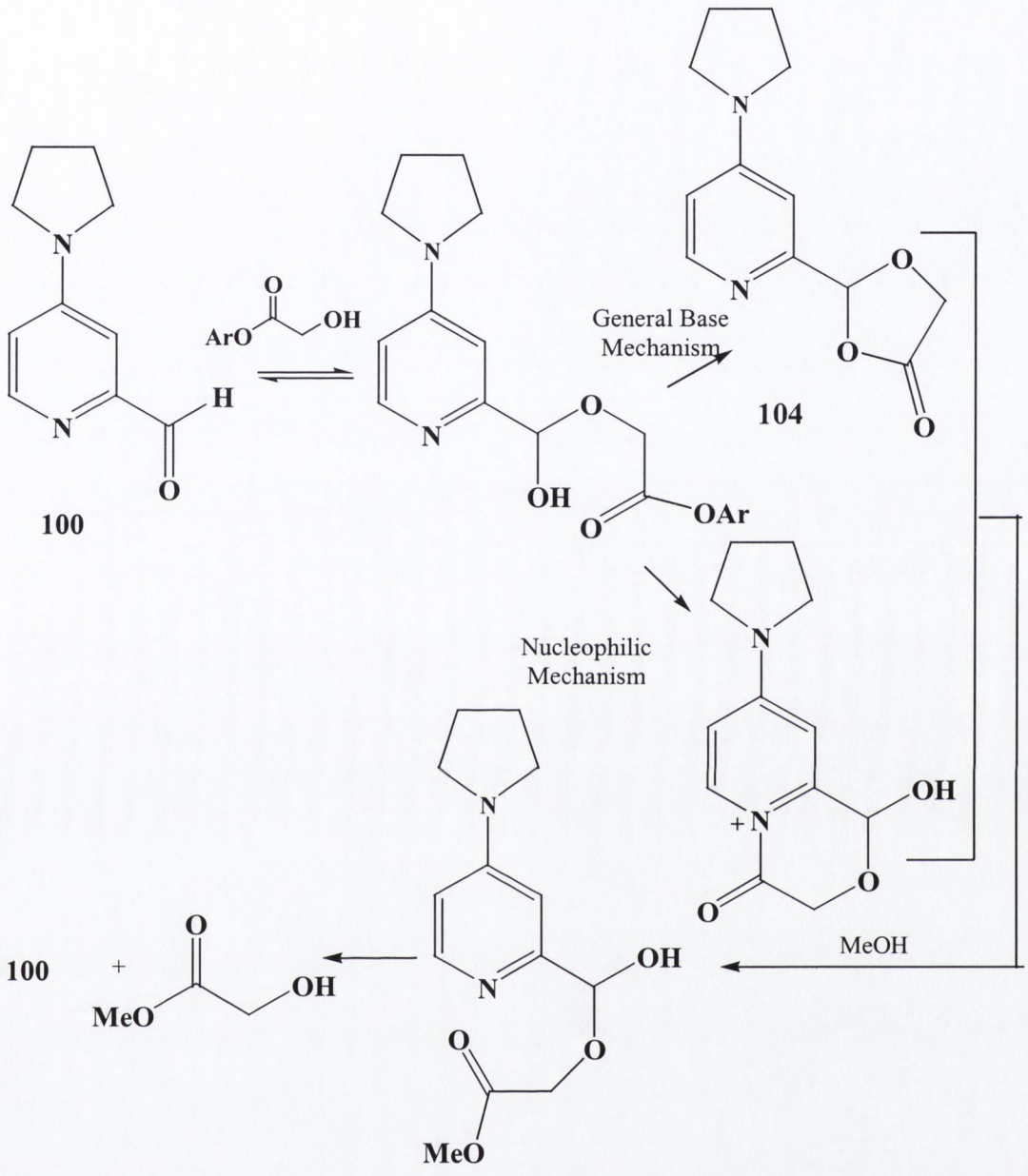
Scheme 1.19



101 **R = Me**
102 **R = OMe**
103 **R =OH**

From these kinetic studies hydroxy ester **103** underwent methanolysis some 96 times faster than the ester **102** and some 511 times faster than the PNP ester of propionic acid **101**. This difference in rate was interpreted as evidence of hydroxyl binding of the alcohol with the binding site as anticipated. However it was uncertain whether the mechanism was nucleophilic or proceeded by general base catalysis (Scheme 1.20).

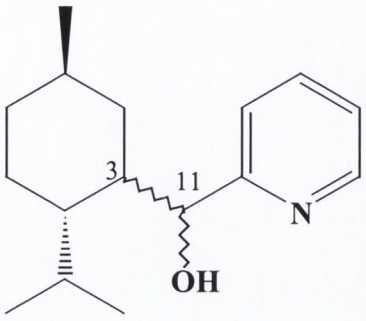
Scheme 1.20

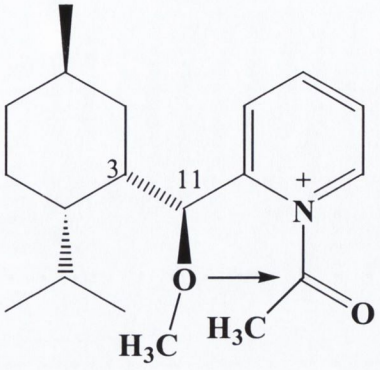


FPP was designed to operate by the nucleophilic mechanism but this was quickly discredited. Use of a range of 6-substituted derivatives of FPP as catalysts served only to speed up the reaction and not hinder it as was observed when Sammakia *et al.* used a range of 2-alkyl-4-dialkylaminopyridnes to catalyse the acylation of alcohols. For example, the introduction of a TMS moiety into the 6-position of FPP increased

the reaction rate by a factor of thirteen relative to FPP itself. This could only mean that the nitrogen of the pyridine ring was more basic and hence a better proton acceptor. If the nucleophilic mechanism were operating, introduction of steric bulk near the vicinity of the pyridine nitrogen would greatly hinder the reaction as is observed in the acylation of alcohols with similar type compounds. This is clearly not the case. Further proof was obtained when the hemiacetal intermediate of the general base mechanism **104** was isolated and characterised by NMR spectroscopy. Current work by Sammakia *et al.* involves attempts to synthesise chiral variants of FPP, which may be capable of kinetic resolution *via* enantioselective ester hydrolysis.

In a model study in this laboratory Storey[47] synthesised the suite of four chiral pyridyl alcohols **105** - **108** and all four of these compounds fulfilled the primary objective of their synthesis in that they catalysed the enantioselective addition of diethylzinc to benzaldehyde. The derived methyl ether **109** did not act as an acylation catalyst and this result was interpreted as evidence of interaction of the ether oxygen electron lone pairs with the strongly electron-deficient carbonyl carbon of the intermediate *N*-acylpyridinium salt. This in turn deactivates the latter towards nucleophilic attack by the substrate alcohol and so acyl transfer does not take place. Vedejs *et al.*[34] also experienced this problem with their chiral 2-subtituted DMAP derivative **62**, hence the requirement of Lewis acids to promote the acyl transfer.

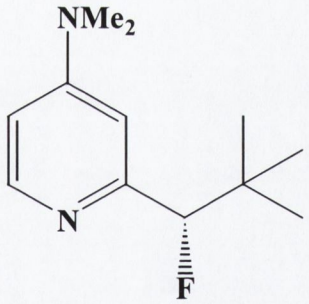




105 3*R*, 11*R*
106 3*S*, 11*S*
107 3*R*, 11*S*
108 3*S*, 11*R*

109

In an effort to circumvent this problem of oxygen lone pair interaction with the *N*-acylpyridinium salt, the fluoro derivative **110** was synthesised by Aubert[48] but this compound also failed to function as an acylation catalyst even under stoichiometric conditions.

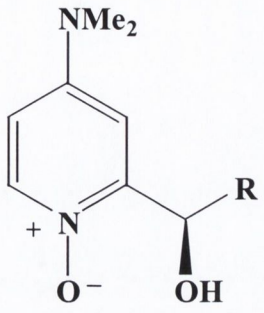


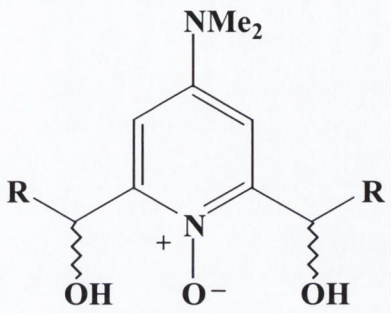
110

1.4.3 Chiral 4-dialkyaminopyridine *N*-oxides

Gallagher[49] discovered that 4-dimethylaminopyridine *N*-oxide is an effective catalyst for the acylation of 1-phenylethyl alcohol with acetic anhydride. This remarkable finding that 4-dimethylaminopyridine *N*-oxide is an acylation catalyst opens up a

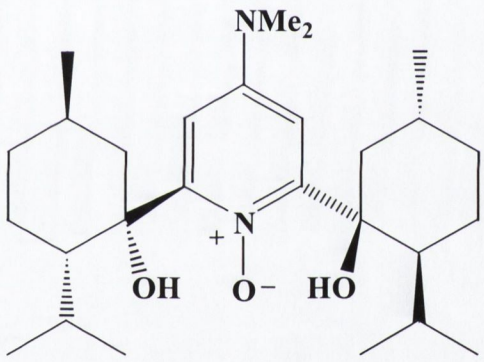
whole new area of research. The following suite of molecules **111** - **115** were synthesised by Aubert[48] and fully characterised.





111 **R = ^{t}Bu**
112 **R = Ph**

113 **R = ^{t}Bu**
114 **R = Ph**

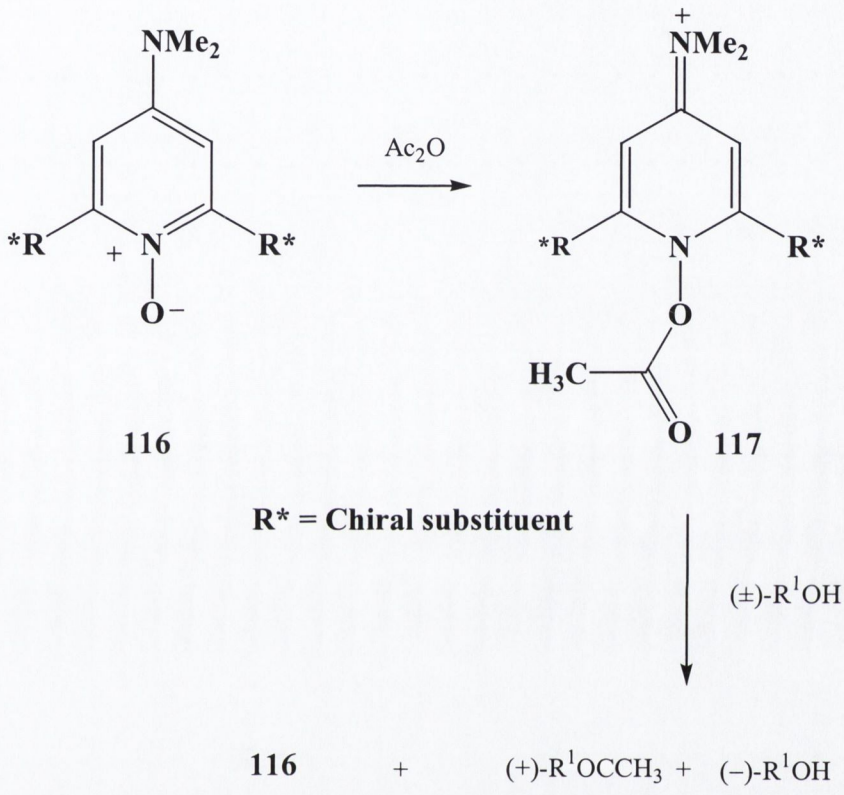


115

Removal of the interactive pendant oxygen atom at the α-carbon of these molecules should allow them to function as hypernucleophilic acylation catalysts. Any steric effects due to bulky substituents at C-2 and/or C-6 should be minimised by the fact that the transferable acyl function should be one atom away from the nitrogen of the pyridine ring. Scheme 1.21 indicates how such an *N*-oxide **116** will react in a truly catalytic manner transferring its acyl group *via* an *O*-acyl intermediate **117** to a

preferred enantiomer of an racemic alcohol leading to a product mixture containing easily separated optically active alcohol and ester (Scheme 1.21).

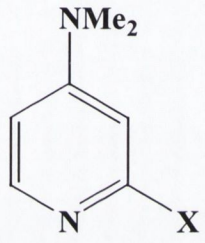
Scheme 1.21



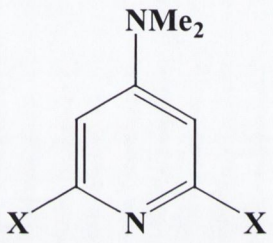
1.5 Detailed Project Description

The initial aims of this project was to synthesis chiral substituted 4-dimethylaminopyridine like compounds that do not have the handicap of oxygen-containing functional groups protruding so close to the catalytic site. As discussed earlier, compounds such as **109**, **111, 112, 113, 114** and **115** cannot function as acylation catalysts due to the oxygen electron lone pair interaction with the intermediate *N*-acyl-4-dialkylaminopyridinium species in the case of **109** and

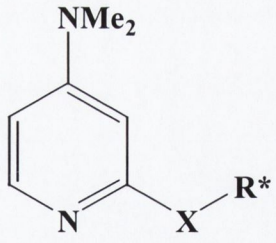
pendent hydroxyl groups in the case of the other compounds **111** - **115**. In order to better facilitate the introduction of suitable chiral groups into the 2- and 6-positions of 4-dimethylaminopyridine, suitable 2- and 2,6-disubstituted 4-dialkylaminopyridines will be required. It was anticipated that the most suitable type of compounds would be 2-halo-4-dimethylaminopyridines **118** and 2,6-dihalo-4-dimethylaminopyridines **119**. Synthesis of these compounds should allow the successful introduction of chiral alkoxides and amines *via* nucleophilic displacement of the halogens to give compounds of type **120, 121** and **122, 123**.

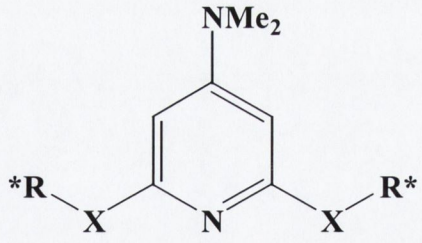


118
X = Cl, Br, I



119
X = Cl, Br, I





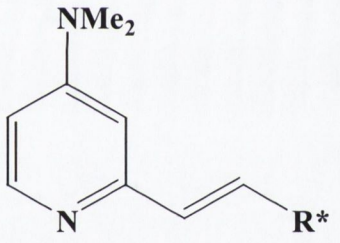
R* = Chiral Substitutent

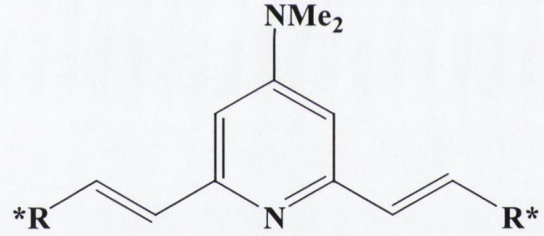
120 X = O
121 X = N

122 X = O
123 X = N

These compounds which are devoid of pendant groups which might interact with the active site of the molecule should function as effective acylation catalysts. Any loss of basicity at the pyridine nitrogen should be offset by the powerfully electron-donating dimethylamino moiety in the 4-position of the aromatic ring.

It was also intended to subject compounds such as **118** to Heck and Stille crosscoupling reactions with certain alkenes embodying a high degree of chiral architecture to give compounds of type **124** and **125**. This would have the effect of introducing into the ring of 4-dimethylaminopyridine, chiral substituents free from heteroatoms, thus increasing the basicity of the ring nitrogen atom and hence the reactivities of these chiral compounds.





R* = Chiral Substitutent

124 **125**

It was also proposed to investigate whether 2-halo-4-dialkylaminopyridines would undergo Ni-catalysed[50] coupling with chiral Grignard reagents derived from chiral pool compounds.

As mentioned earlier, Gallagher had discovered that 4-dimethylaminopyridine *N*-oxide was an effective acylation catalyst.[49] It had not been determined if catalytic

activity was confined only to 4-dialkylaminopyridine *N*-oxides or was characteristic of all *N*-oxides. It was proposed to examine a whole series of *N*-oxides as catalysts for the acylation of alcohols and to examine a series of chiral *N*-oxides as enantioselective acylation catalysts. An important aspect of this methodology is that, unlike their free bases, *N*-oxides are only weakly basic and as such do not require an auxiliary base such as triethylamine to achieve a large number of catalytic cycles per molecule of *N*-oxide. Industrially, for reactions in which catalysts such as DMAP are used, the auxiliary base is sometimes the solvent and is present in considerable excess. Use of DMAP *N*-oxide as a catalyst in conjunction with a cheaper solvent may not require an auxiliary base and thus would result in considerable cost reductions.

It was also intended to undertake a detailed kinetic study into the acylation of 1-phenylethyl alcohol by acetic anhydride catalysed by all compounds synthesised that show catalytic activity. An important reason for doing this was to see how effective each catalyst would be when compared to some reference catalyst such as pyridine. Thus, each new catalyst will have a relative value associated with it which will be indicative of its effectiveness.

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Chapter 2

Synthesis of 2-halo and 2,6-dihalo-4-dialkylaminopyridines

2.1 Introduction

This chapter describes the different avenues explored in the search for a successful synthesis of the title compounds. These compounds were required in order to facilitate the successful introduction of suitable chiral substituents into the 2- and 6- positions of the pyridine ring of 4-dimethylaminopyridine. In the event these compounds were successfully synthesised by several different methods that will now be discussed in more detail.

2.2 Synthesis of 2-chloro- and 2-bromo-4-dimethylaminopyridine *via* diazotisation of 2-amino-4-dimethylaminopyridine

This strategy utilised 2-chloropyridine *N*-oxide **126** as the starting material (Scheme 2.1). This compound is commercially available from Olin Corporation. Due to its unstable nature it is supplied as a 21% w/v solution in water. Extraction of the aqueous solution with DCM afforded 2-chloropyridine *N*-oxide **126** with excellent recovery. 2-Chloropyridine *N*-oxide was easily handled as a solid and was found to be quite stable for prolonged periods at –20 °C. Storage at this temperature during several months revealed no decomposition as revealed by ^{1}H NMR.

2-Chloropyridine *N*-oxide **126** was nitrated according to the procedure of Finger *et al.*[1] to give 2-chloro-4-nitropyridine *N*-oxide **127** in 85% yield. A small amount of the *N*- deoxygenated 2-chloro-4-nitropyridine (<5%) was also present. Recrystallisation from an ethanol : chloroform 70 : 30 mixture afforded 2-chloro-4-nitropyridine *N*-oxide **127** in excellent purity as determined by ^{1}H NMR. The ^{1}H NMR spectrum of **127** revealed that H-3 and H-5 came into resonance at δ 8.37 and

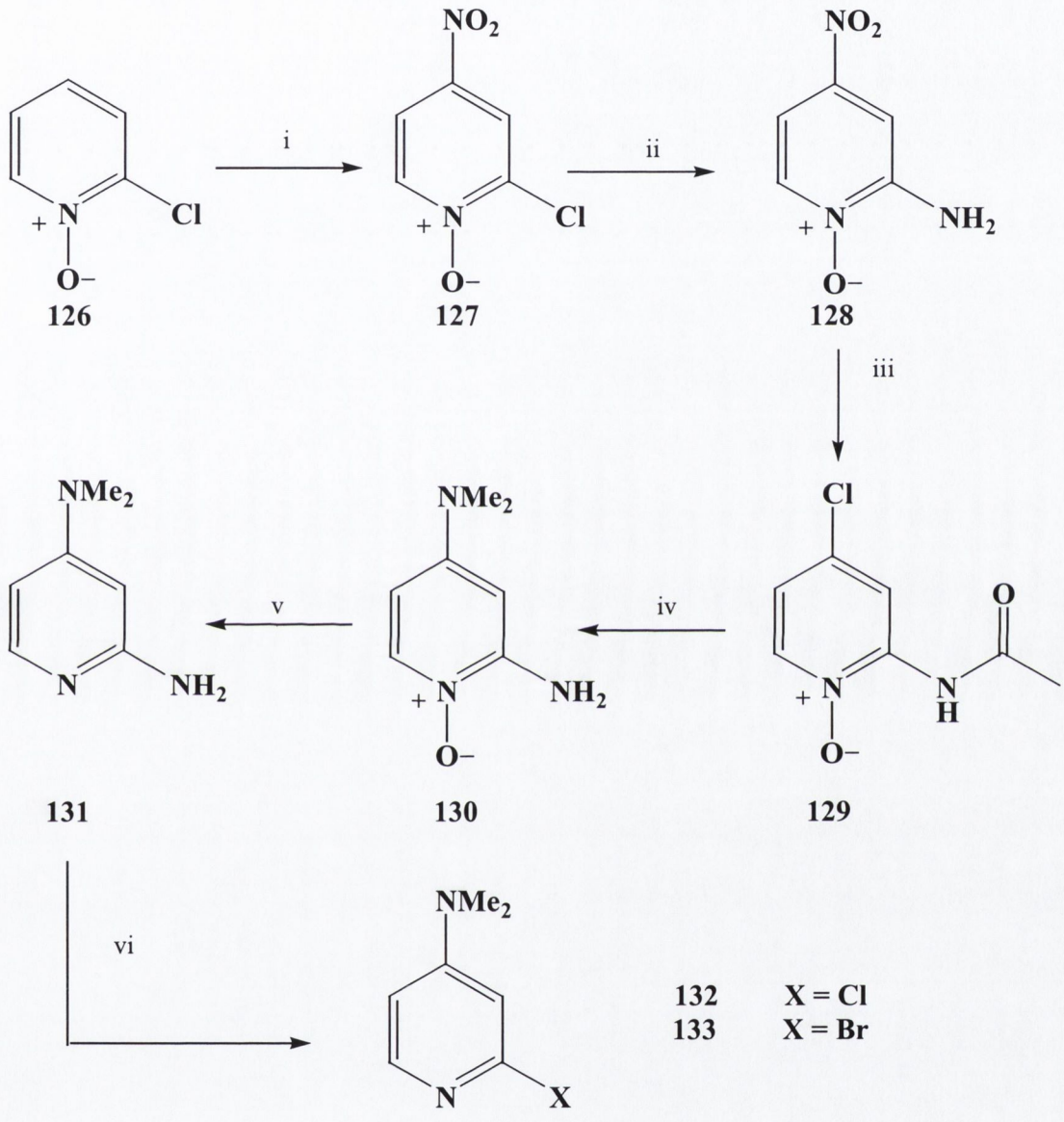
δ 8.04 ppm, respectively. The proton H-5 was split into a double doublet by *ortho* coupling with H-6 and *meta* coupling with H-3. This familiar splitting pattern is characteristic of 2,4-disubstituted pyridines. The chemical shift for H-3 appears significantly downfield at δ 8.37 ppm as a result of the strongly electron-withdrawing nature of the nitro group and of the chlorine *ortho* to it. Also, H-6 came into resonance at δ 8.41 ppm.

The presence of the nitro group in the 4-position of 2-chloro-4-nitropyridine *N*-oxide **127** greatly facilitates nucleophilic displacement of the chlorine at the 2-position by amines.[2] Thus, reaction of 2-chloro-4-nitropyridine *N*-oxide **127** with concentrated ammonia solution in either isopropyl alcohol or *tert*-butyl alcohol gave 2-amino-4-nitropyridine *N*-oxide **128** as expected in excellent yield. Introduction of an amino functionality at the 2-position of the molecule shifts protons H-3 and H-5 upfield by 0.7 and 0.5 ppm to δ 7.64 and δ 7.50 ppm, respectively, when compared to 2-chloro-4-nitropyridine *N*-oxide **127**. The chemical shift for H-6 was moved very slightly upfield by 0.1 ppm to δ 8.20 ppm. The amino protons of **128** came into resonance as a broad singlet at δ 5.93 ppm.

The nitrite anion is a good leaving group from sp^2 hybridised carbon atoms and it is superior to a chloride ion by a factor of *ca.* 1000.[3] The nitro group in 4-nitropyridine *N*-oxides is quite susceptible to displacement by suitable nucleophiles such as alkoxides and halogens.[4] Although the displacement of the nitro group by amines is not well known, there are some literature precedents for this, although it is generally agreed that yields are poor.[5] However, it was still decided to investigate the

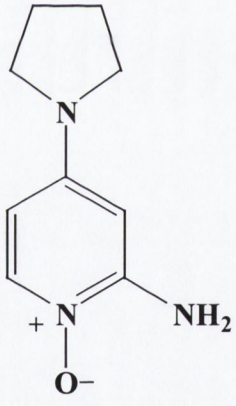
displacement of the nitro group of 2-amino-4-nitropyridine *N*-oxide **128** by amines such as pyrrolidine.

Scheme 2.1

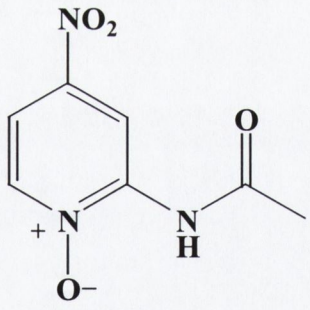


Reagents and Conditions: (i) Fuming HNO_3/H_2SO_4, 90 °C, 3 h, 85%; (ii) aqueous NH_3 (d 0.880), 90 °C, pressure tube, 24 h, >90%; (iii) AcCl, $CHCl_3$, reflux, 18 h, 50%; (iv) aqueous $NHMe_2$, pressure tube, 100 °C, 24 h, 80%; (v) Fe/AcOH, 100 °C, 3 h, >95%; (vi) conc. HCl, $NaNO_2$, -15 °C → 80 °C, 2 h, 60% or HBr, Br_2, $NaNO_2$, -15 °C → 80 °C, 2 h, 70%.

Reaction of **128** with pyrrolidine in refluxing toluene, did give small amounts of 2-amino-4-(1'-pyrrolidinyl)pyridine *N*-oxide **134**. However, isolation of this compound proved very difficult and was hampered by the fact that there appeared to be a considerable amount of non-aromatic material present in the reaction mixture. It was anticipated that the use of 2-acetamido-4-nitropyridine *N*-oxide **135** would facilitate easier displacement of the nitro group from the 4-position. The rationale behind this was that the displacement might be made easier by converting the electron-donating amino group into its amide, thus the lone pair of electrons of the nitrogen in the 2-position would interact with the carbonyl functionality and not the aromatic ring. Successful acylation of the amino *N*-oxide **128** to give the acetamide **135** was easily achieved using acetic anhydride at room temperature with the aid of a catalytic amount of DMAP.



134

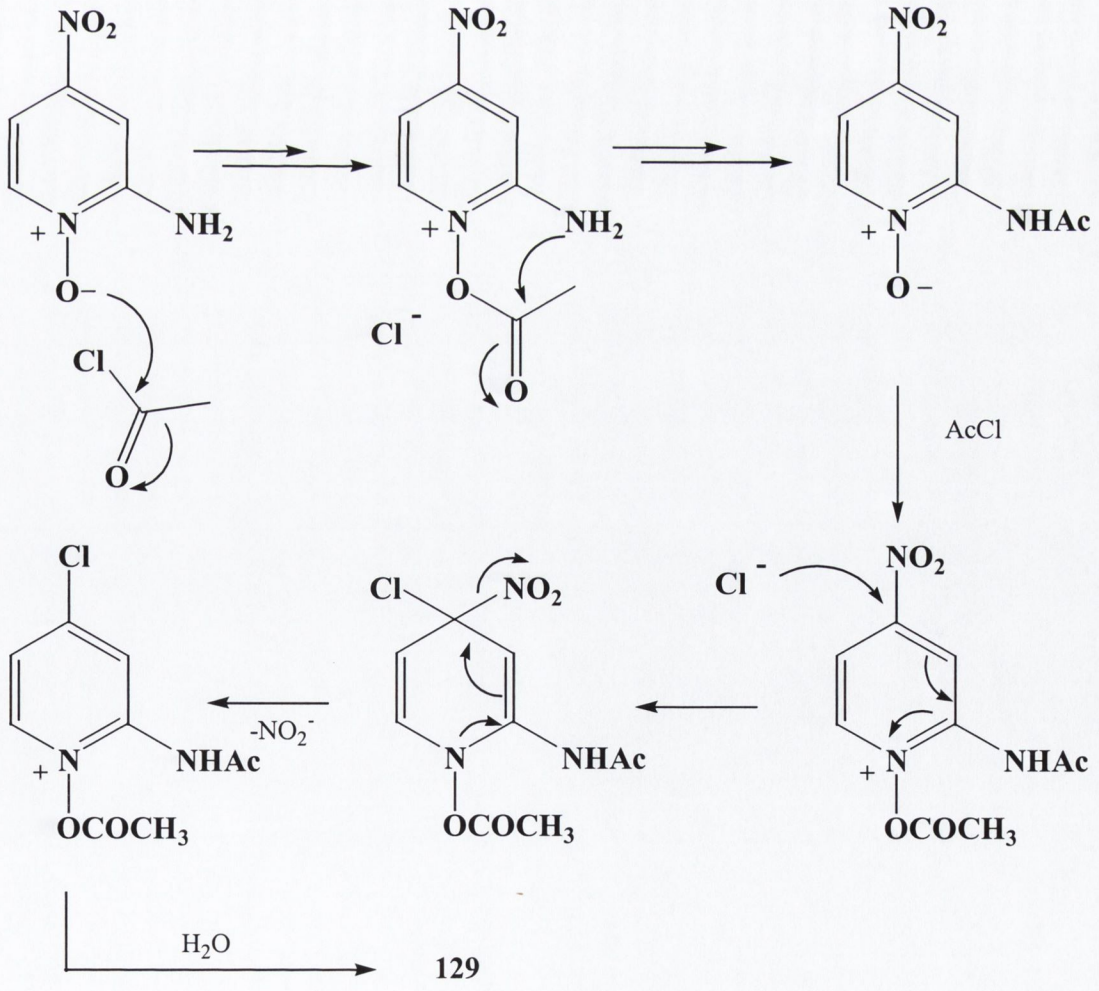


135

Reaction of the acetamide **135** with pyrrolidine in refluxing toluene resulted only in transamidation to give back 2-amino-4-nitropyridine *N*-oxide **128** and a similar result as described above was obtained. It was decided to abandon this route to 2-amino-4-dialkylaminopyridine *N*-oxides since the displacement of the nitro group from **134** and **135** was neither facile nor straightforward, a result that was in agreement with literature observations.[5]

Ochiai *et al.*[6] reported the facile displacement of the nitro group of 4-nitropyridine *N*-oxide by acetyl chloride to give the 4-chloro derivative in almost quantitative yield. Thus, in the present work reaction of 2-amino-4-nitropyridine *N*-oxide **128** with excess acetyl chloride in refluxing chloroform gave 2-acetamido-4-chloropyridine *N*-oxide **129** in moderate yield (50%). Purification was carried out by column chromatography using a DCM : MeOH 90 : 10 mobile phase. The reaction probably proceeds *via* a two step process, the first being a intramolecular transfer of an acetyl group from the acylated *N*-oxide of **128** to the 2-amino substituent (Scheme 2.2), and the second being displacement of the nitro group.

Scheme 2.2



The rate-determining step in this reaction is the displacement of the nitro substituent since complete conversion of 2-amino-4-nitropyridine *N*-oxide **128** into its acetamide **134** is observed after only 2 hours. An interesting aspect of the ^{1}H NMR spectrum of compound **129** is that H-3 is deshielded considerably and appears downfield as a doublet at δ 8.51 ppm, *J* 2.5 Hz, while proton H-5 comes into resonance at δ 7.00 ppm whilst H-6 appears as a doublet at δ 8.16 ppm. The N-H of the acetamide appears downfield at δ 9.96 ppm, and undergoes deuterium exchange in the presence of D_2O.

The displacement of chlorine from the 4-position of 6-membered heterocyclic *N*-oxides is well known.[7] Thus, reaction of 2-acetamido-4-chloropyridine *N*-oxide **129** with aqueous dimethylamine solution resulted in the formation of 2-amino-4-dimethylaminopyridine *N*-oxide **130** in excellent yield. Analysis of the ^{1}H NMR spectrum of 2-amino-4-dimethylaminopyridine *N*-oxide **130** showed that the chemical shifts of H-3 and H-5 had moved considerably upfield to δ 5.87 and δ 6.00 ppm respectively. The proton H-6 came into resonance at δ 7.8 ppm and the amino protons appeared as a broad singlet at δ 5.55 ppm. The dimethylamino moiety came into resonance at δ 2.93 ppm as would be expected, (the chemical shift of the dimethylamino protons in DMAP is δ 3.00 ppm).

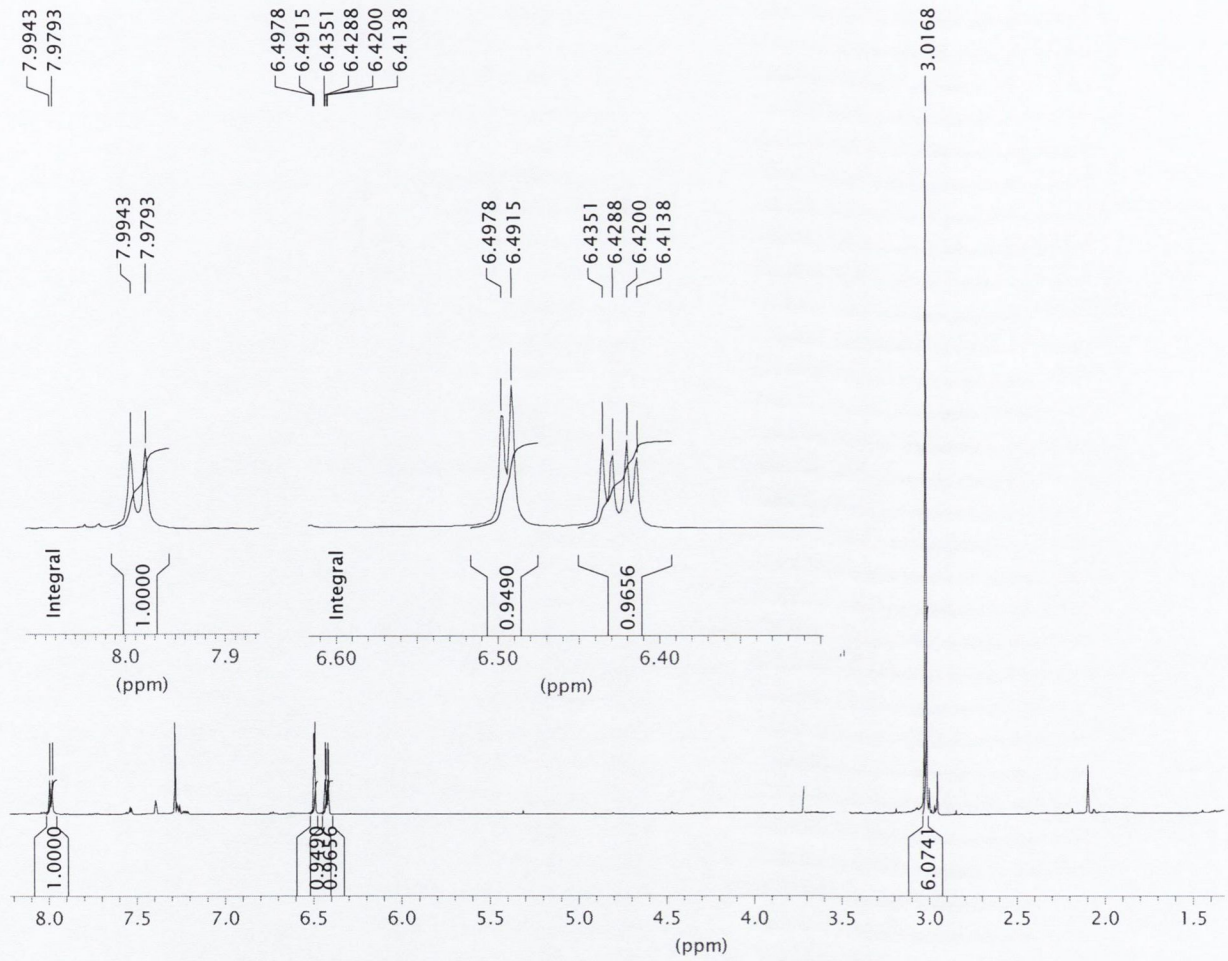
The use of iron to reduce the *N*-oxide functionality is a standard reaction in *N*-oxide chemistry.[8] The *N*-oxide function of 2-amino-4-dimethylaminopyridine *N*-oxide **130** was easily reduced by iron filings in acetic acid to give the free base 2-amino-4-dimethylaminopyridine **131** in quantitative yield. The ^{1}H NMR spectrum of **131** was

not too dissimilar to that of the parent *N*-oxide **130**. Analysis of the spectrum showed that proton H-6 had moved downfield by 0.1 ppm to δ 7.75 ppm upon loss of the *N*-oxide function. Proton H-5 remained unchanged at δ 6.00 ppm while H-3 resonated at δ 5.67 ppm, a difference of 0.2 ppm downfield than in the *N*-oxide **130**. The amino protons resonated at δ 5.65 ppm compared to δ 4.25 ppm in the *N*-oxide. The chemical shift of the dimethylamino protons remained effectively unchanged at δ 2.93 ppm. With this key compound in hand the stage was set for the synthesis of the required 2-halo-4-dimethylaminopyridines.

Aminopyridines are readily diazotised and behave very much like normal aromatic amines. In general, 2- and 4-aminopyridines tend to be resistant to diazotisation in dilute mineral acids and form the corresponding hydroxy or halogeno derivatives when reaction does occur. The use of concentrated acids usually avoids or at best minimises these side reactions.[9]

In the event, 2-amino-4-dimethylaminopyridine **131** underwent diazotization in the presence of concentrated hydrochloric acid and sodium nitrite at –10 °C to yield the expected 2-chloro derivative **132** in 60% yield. This was the only product isolated from this reaction. Analysis of the ^{1}H NMR spectrum of **132** (Figure 2.1) showed H-3 and H-5 very close together at δ 6.49 and δ 6.42 ppm, respectively. H-3 appears further downfield than H-5 since it is adjacent to the electronegative chlorine atom. The chemical shift representing H-6 appears at δ 7.98 ppm and the dimethylamino protons resonate at δ 3.02 ppm. This novel compound was fully characterised by FT-IR, ^{1}H and ^{13}C NMR (Figure 2.2), melting point and MS.

Figure 2.1 ^{1}H NMR spectrum of 2-chloro-4-dimethylaminopyridine 132



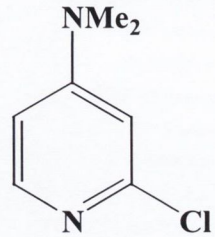
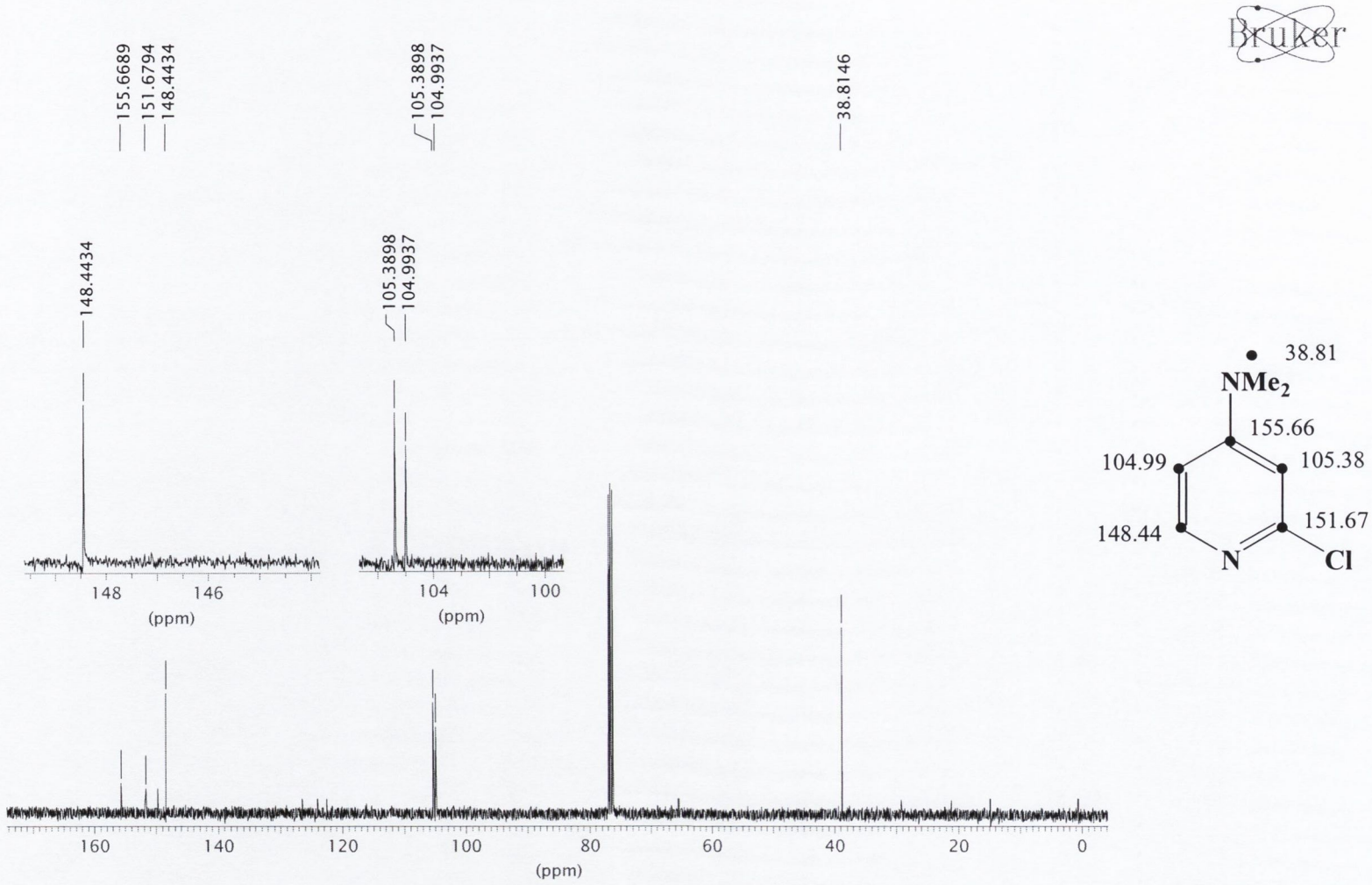


Figure 2.2 ^{13}C NMR spectrum of 2-chloro-4-dimethylaminopyridine 132



The bromo derivative, 2-bromo-4-dimethylaminopyridine **133** was also synthesised similarly from concentrated HBr in the presence of bromine and sodium nitrite. The ^{1}H NMR spectrum of **133** (Figure 2.3) is very similar to that of 2-chloro-4-dimethylaminopyridine **132** except that H-3 is shifted further downfield by 0.2 ppm. Analysis of the ^{13}C NMR spectrum (Figure 2.4) of **133** reveals that C-2 resonates some 10 ppm further upfield than in 2-chloro-4-dimethylaminopyridine **132** as expected because chlorine being more electronegative than bromine pulls electron density from C-2, reduces the shielding effect and shifts resonance to a higher value.

This synthesis of 2-halo-4-dialkylaminopyridines **132** and **133** while successful in achieving the desired outcome, was fundamentally flawed due to the low overall yields (15%) and the number of steps required. Since both 2-chloro-4-dimethylaminopyridine **132** and 2-bromo-4-dimethylaminopyridine **133** were potentially direct precursors to more elaborate compounds, a more desirable synthesis of either which would have fewer steps and a higher yield would be very desirable. This was achieved *via* the use of Fort's base.

Figure 2.3 ^{1}H NMR spectrum of 2-bromo-4-dimethylaminopyridine 133

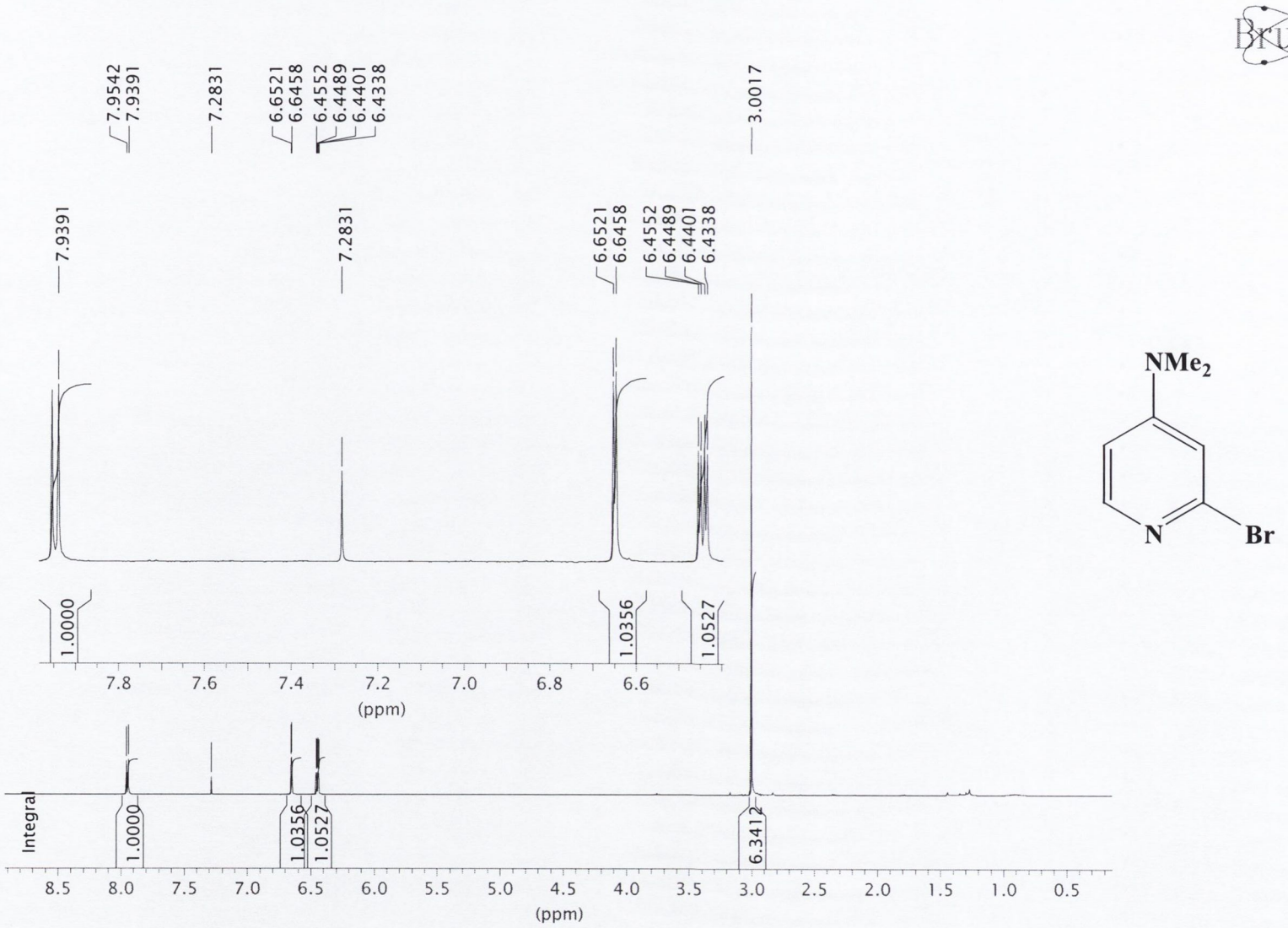
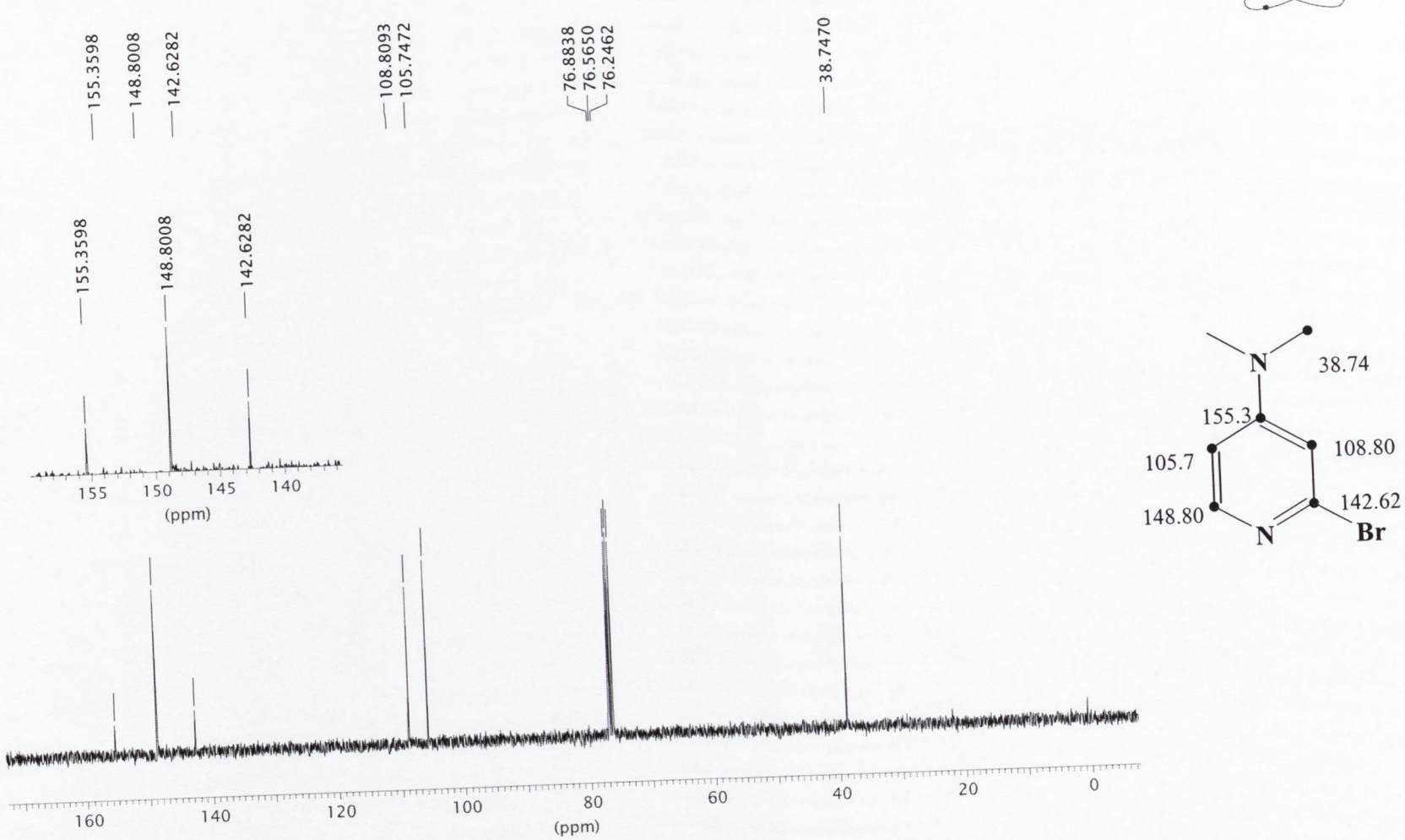


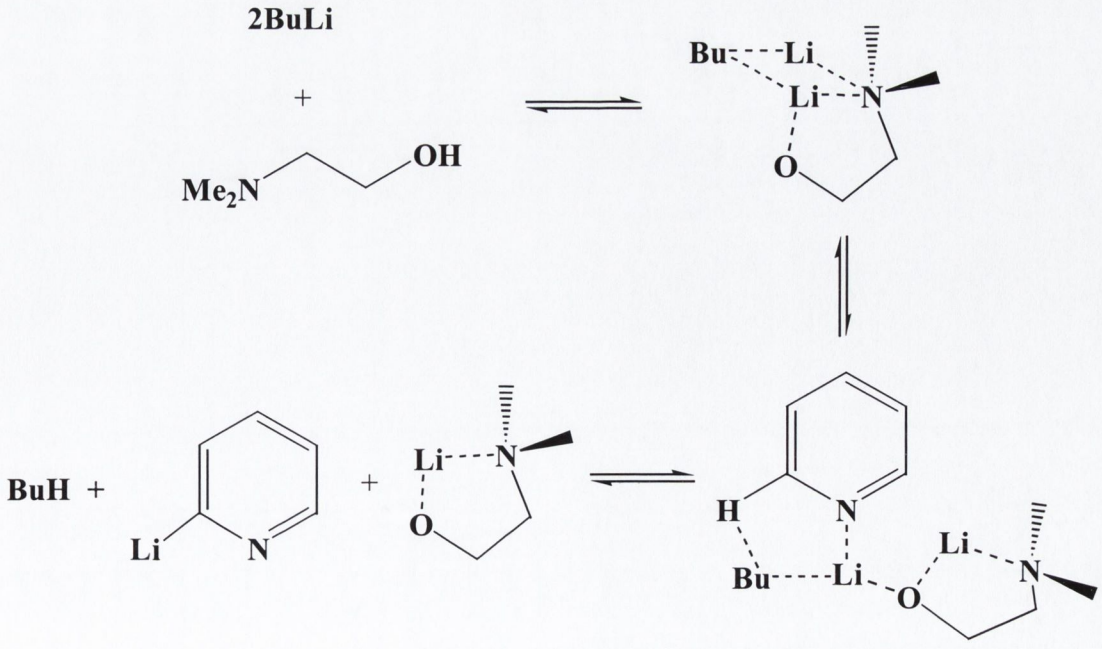
Figure 2.4 ^{13}C NMR spectrum of 2-bromo-4-dimethylaminopyridine 133



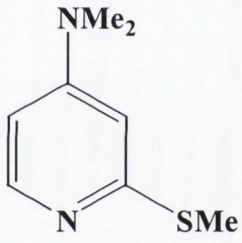
2.3 Synthesis of 2-bromo-4-dimethylaminopyridine 133 using Fort's base

The reaction of pyridines with reagents such as butyllithium and tetramethylethylenediamine (TMEDA) usually results in Chichibabin type reactions, thus limiting their use in the synthesis of functionalised pyridines.[10] This is due in some part to the high nucleophilicity of the reagents. An important aspect to the design and development of strong bases is how to increase basicity without a corresponding increase in nucleophilicity. Fort *et al.*[11] have developed a complex superbase BuLi•LiO$(CH_2)_2NMe_2$ abbreviated BuLi•LiDMAE, which is easily obtained by the reaction of 2 equivalents of butyllithium and 1 equivalent of *N,N*-dimethylaminoethanol in dry hexane. This base can facilitate the functionalisation of pyridines and, to lesser extent, quinolines *via* simple metallation. The base functions by forming an aggregate between the BuLi and the lithiated alcohol which can then form a complex with the pyridine ring to effect the metallation at the 2- and/or 6-position (Scheme 2.3).

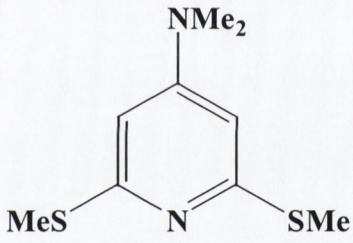
Scheme 2.3



Thus, using BuLi•LiDMAE as the lithiating agent and carbon tetrabromide as the halogenating agent Fort *et al.* [11] synthesised 2-bromopyridine from pyridine in 85% yield. The use of carbon tetrabromide as a halogen equivalent is well known and documented.[12] In a personal communication from Fort it was revealed that the same complex base would metallate more basic pyridines such as 4-dimethylaminopyridine. Thus, 4-dimethylaminopyridine **54** was successfully metallated by Fort and then reacted with dimethyl disulphide as an electrophile to give 4-dimethylamino-2-methylsulfanylpyridine **136** and 4-dimethylamino-2,6-dimethylsulfanyl pyridine **137** in 66% and 24% yields, respectively. This experiment was successfully repeated in our laboratory.



136



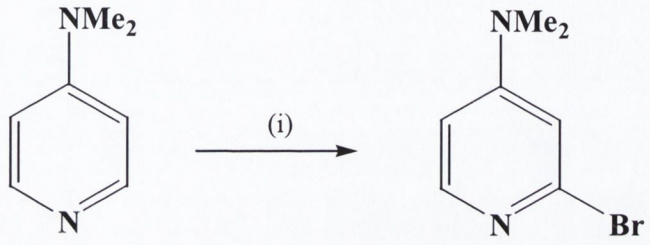
137

It was decided to investigate the application of this technology to the synthesis of 2-bromo-4-dimethylaminopyridine **133** based on the evidence that, (a) 2-bromopyridine had been successfully synthesised in excellent yield by this method and (b) the complex base could metallate the more basic pyridine 4-dimethylaminopyridine.

Thus, treatment of 4-dimethylaminopyridine **54** with this base in dry hexane in the presence of carbon tetrabromide as the halogenating agent (Scheme 2.4) gave 2-

bromo-4-dimethylaminopyridine **133** in 57% yield as the sole reaction product, identical in every respect to the material prepared earlier (Scheme 2.1). There was no evidence to suggest that any 2,6-dibromo-4-dimethylaminopyridine had been formed in this reaction.

Scheme 2.4



54 **133**

Reagents and Conditions: (i) BuLi/DMAE, CBr_4, - 10 °C → 0 °C, 3 h, 57%.

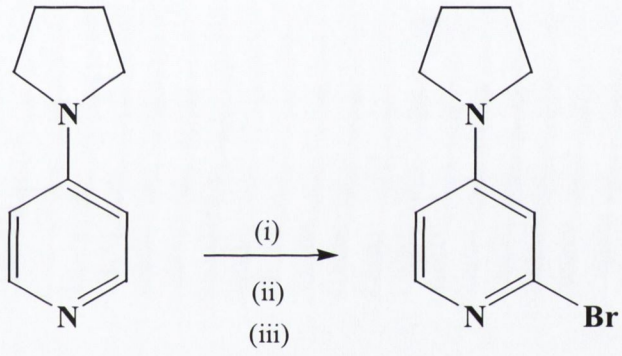
This method affords 2-bromo-4-dimethylaminopyridine **133** from 4-dimethylaminopyridine **54** in workable yield in only one step. When compared to the strategy in Scheme 2.1, there is almost a 3 fold increase in yield and five fewer steps.

While the method of Fort *et al.*[11] did allow access to 2-bromo-4-dimethylaminopyridine **133** the reaction had some major drawbacks. A large amount of an unknown brown solid was invariably present in the crude material after aqueous workup. This resulted in the crude mixture having to be chromatographed (sometimes twice) to obtain material of high purity. Given that the crude material had to be chromatographed and considering that 2 equivalents of butyllithium were required to generate the superbase the process may not have been so economical.

Also the reaction was not amenable to scale up to a level that was synthetically useful (*i.e.* > 1 g).

A recent paper by Sammakia *et al.*[13] describes the synthesis of 2-bromo-4-(1'-pyrrolidinyl)pyridine **139** from 4-(-1'-pyrrolidinyl)pyridine **138** (Scheme 2.5). 4-(1'-pyrrolidinyl)pyridine **138** was complexed with the Lewis acid boron trifluroide diethyl etherate and the resulting adduct was metallated using butyllithium. The metallated species was reacted with elemental bromine to afford 2-bromo-4-pyrrolidinopyridine **139** in good yield.

Scheme 2.5

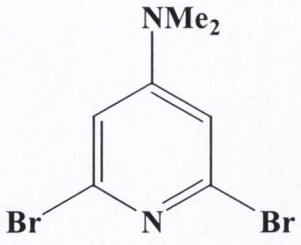


138 **139**

Reagents and Conditions: (i) $BF_3(OEt)_2$, 0 °C, (ii) BuLi, -78 °C, (iii) Br_2, 58%.

Repetition of this experiment with 4-dimethylaminopyridine gave 2-bromo-4-dimethylaminopyridine **133** in, typically, 70% yield. Unlike the method of Fort *et al.*[11] small amounts (5-8%) of the highly desirable 2,6-dibromo-4-dimethylaminopyridine **140** were also obtained from this reaction. Chromatography easily separated the two compounds. The ^{1}H NMR spectrum of **140** was very straightforward. Since the molecule is symmetrical only two signals were observed in the ^{1}H NMR spectrum, at δ 6.63 and 3.00 ppm. These two chemical shifts were

easily assigned to protons H-3 and H-5 and to the dimethylamino protons respectively.



140

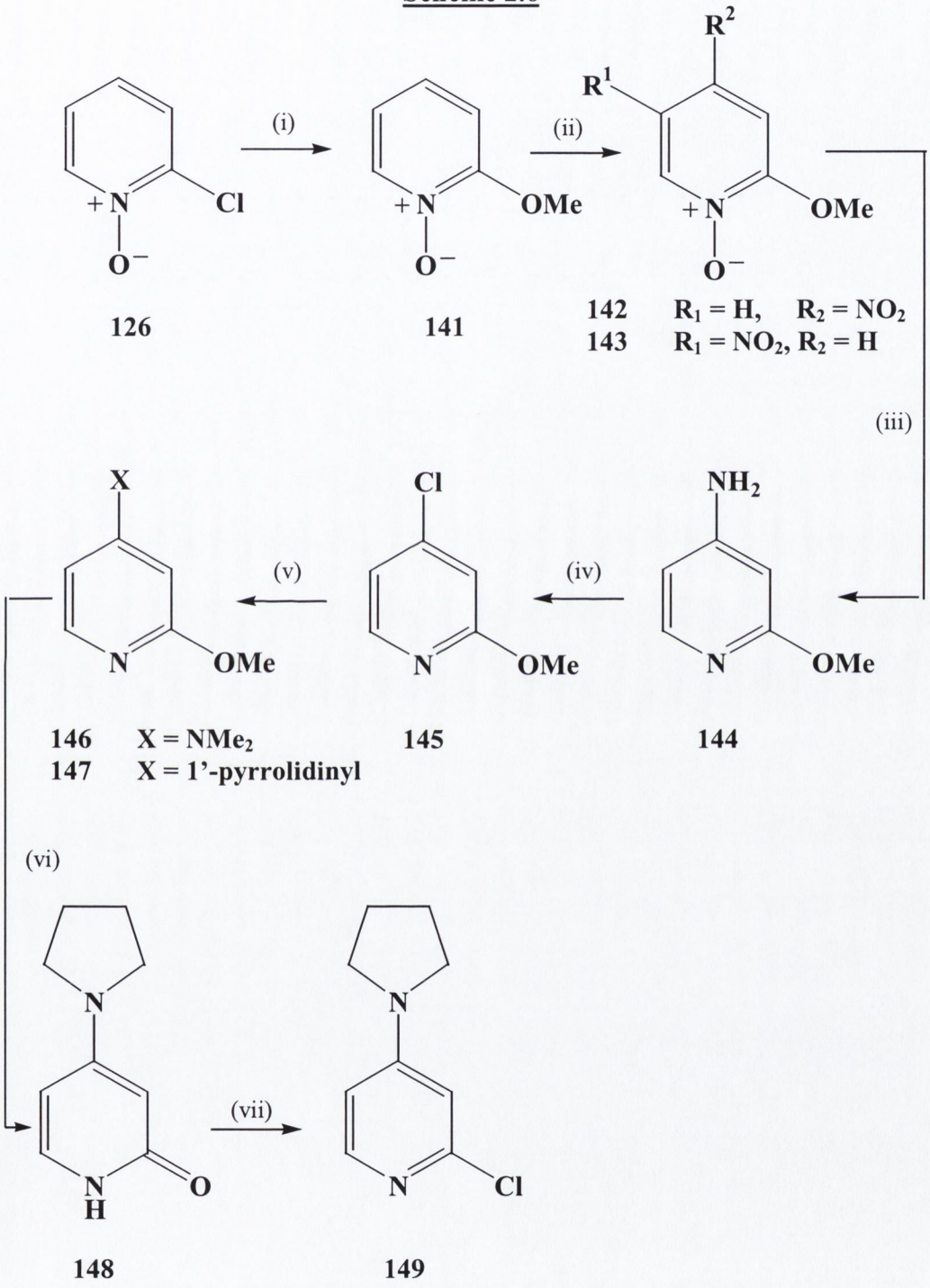
Attempts to make **140** the major product from this reaction by using 2 equivalents of BuLi proved unsuccessful. This methodology developed by Sammakia *et al.*[13] is by and far the method of choice for synthesis of the monobromo derivative **133**. This reaction avoids the need for excessive chromatography and overall uses less butyllithium when compared to the method of Fort *et al.*[11] It has also proved very amenable to scale up (5 g of reactant) without any apparent loss of yield, which cannot be said about the method of Fort *et al.*[11]

2.4 Attempted synthesis of 2-chloro-4-dialkylaminopyridines *via* reaction of 4-(1'-pyrrolidinyl)-2-pyridone with various phosphorus reagents.

The starting point in this synthesis (Scheme 2.6) was again 2-chloropyridine *N*-oxide **126**. The chlorine in the 2-position of this compound underwent facile displacement with methoxide ion to give 2-methoxypyridine *N*-oxide **141** in quantitative yield. The ^{1}H NMR spectrum of **141** showed that protons H-3 and H-5 came into resonance at δ 6.82 and 6.86 ppm. The resonance for H-6 appeared at δ 8.13 ppm. The proton H-4 appears as a distinct double triplet at δ 7.21 ppm. The methoxy methyl appears as a singlet at δ 3.99 ppm. An inherent difficulty with this

compound was its lack of solubility in non-alcoholic solvents. 2-Methoxypyridine *N*-oxide **141** was only partially soluble in chloroform.

Scheme 2.6



126 **141** **142** $R_1 = H$, $R_2 = NO_2$ **143** $R_1 = NO_2$, $R_2 = H$ **144** **145** **146** $X = NMe_2$ **147** X = 1'-pyrrolidinyl **148** **149**

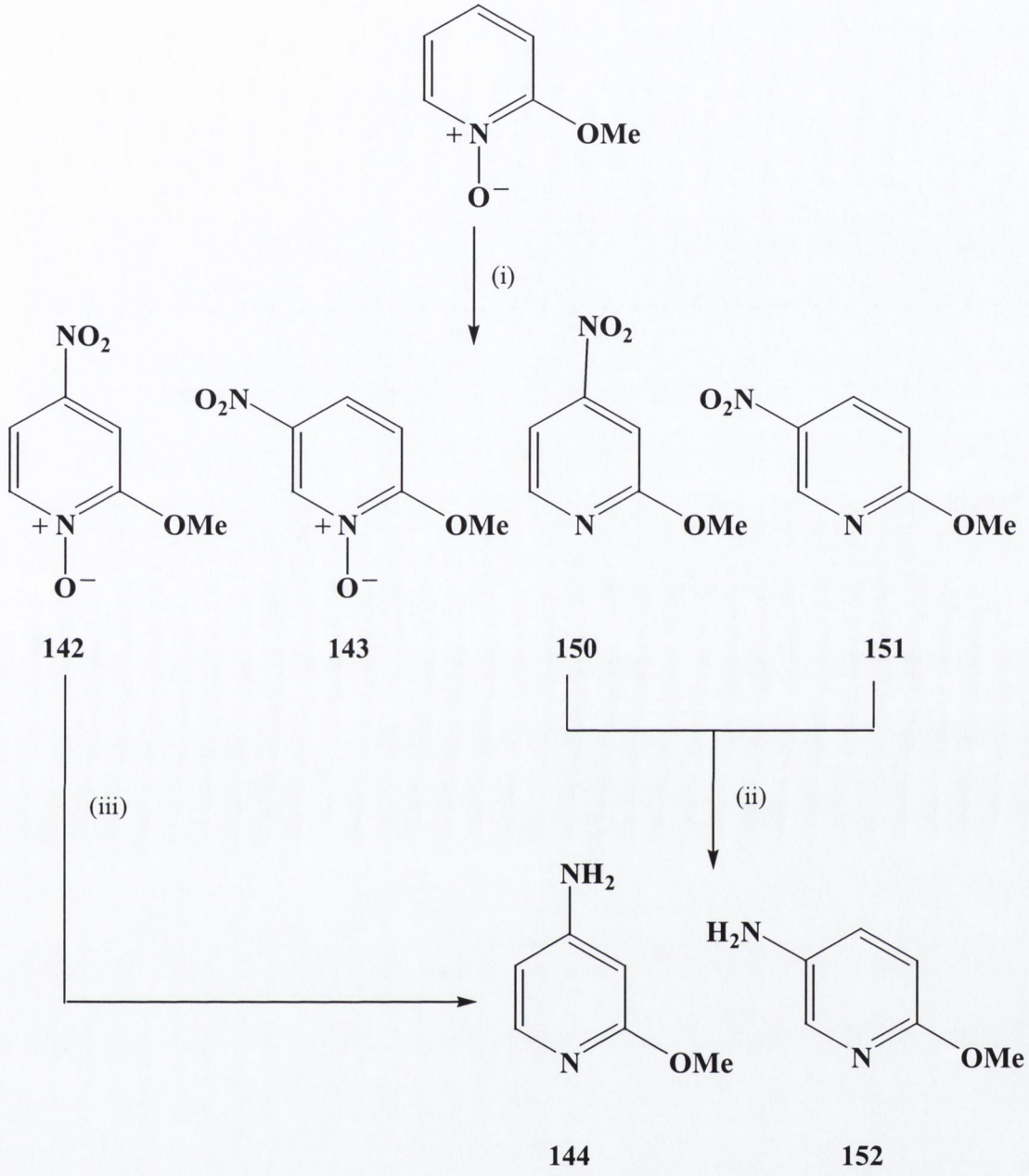
Reagents and Conditions: (i) NaOMe, MeOH, reflux, 95%; (ii) fuming HNO_3/H_2SO_4 75 °C, 3 h 47%; (iii) Fe/AcOH, 100 °C, 2 h, 98%; (iv) conc. HCl, $NaNO_2$, -10 °C → 60 °C, 2 h, 80%; (v) pyrrolidine, *N*-methyl-2-pyrrolidinone, 100 °C, 80%; (vi) BBr_3, DCM, 0 °C, 90%, (vii) $POCl_3/PCl_5$, reflux 4 h.

2-Methoxypyridine *N*-oxide **141** was nitrated according to the procedure of Den Hertog *et al.*[14] to afford a crude mixture whose composition was a 9 : 1 ratio of 2-methoxy-4-nitropyridine *N*-oxide **142** (47% yield overall) and 2-methoxy-5-nitropyridine *N*-oxide **143** (5.2% yield overall), and were separable by chromatography. The formation of the 5-nitro isomer was surprising since Den Hertog *et al.*[14] claimed that the 4-nitro isomer was the sole reaction product. The ^{1}H NMR spectrum of **142** showed 3 aromatic protons at δ 8.36 (H-6), 7.79 (H-3) and 7.74 (H-5) ppm. The methoxy methyl group appeared at δ 4.19 ppm.

The ^{1}H NMR spectrum of 2-methoxy-5-nitropyridine *N*-oxide **143** showed some interesting features. The chemical shift representing H-6 was dramatically shifted downfield to δ 9.16 ppm and showed very fine *meta* coupling with H-4, *J* 2.5 Hz. Proton H-3 appeared as a doublet at δ 7.00 ppm and H-4 at δ 8.10 ppm as a double doublet while the methoxy methyl group resonated as a singlet at δ 4.21 ppm.

Miller *at al.*[15] reported a synthesis of 2-methoxy-4-nitropyridine *N*-oxide **142** which claimed an improvement in yield could be achieved by using a more elevated reaction temperature and a longer reaction time. The formation of 2-methoxy-5-nitropyridine *N*-oxide **143** was observed by Miller *et al.*[15] On repeating this work no apparent increase in yield was observed under these conditions. However, the appearance of another two compounds, the deoxygenated 2-methoxy-4-nitropyridine **150** and 2-methoxy-5-nitropyridine **151** to which Miller *et al.* make no reference, was observed (Scheme 2.7).

Scheme 2.7



Reagents and Conditions: (i) Fuming HNO_3/H_2SO_4, 95 °C, 3 h; (ii) H_2, Pd/C, EtOAc, (iii) Fe/AcOH.

The formation of **151** can be rationalised in one of two ways; (a) initial deoxygenation of 2-methoxypyridine *N*-oxide **141** at the elevated temperature to give 2-methoxypyridine, whose methoxy group directs the nitronium ion to the 5-position of 2-methoxypyridine, or (b) the increased reaction temperature results in larger

amounts of the *N*-oxide **143** being formed which then undergoes deoxygenation to give **151**. The formation of **150** can only be explained by the deoxygenation of 2-methoxy-4-nitropyridine *N*-oxide **142** after nitration has taken place. The formation of deoxygenated products in this reaction parallels the formation of small amounts of 2-chloro-4-nitropyridine in the nitration of 2-chloropyridine *N*-oxide **126** (See page 60, Scheme 2.1).

The formation of 2-methoxy-5-nitropyridine and 2-methoxy-4-nitropyridine were not merely undesirable side-products but constituted a large percentage of the recovered material. The combined mass of compounds **143, 150** and **151** usually equalled that of the desired product **142**. 2-Methoxy-5-nitropyridine *N*-oxide **143** was of no synthetic importance and was discarded after chromatography. Compounds **150** and **151** were not separable from each other by column chromatography. This reaction step represented a severe bottleneck within the overall strategy and limited the amount of the desirable *N*-oxide **142** available for further synthetic steps. Thus, the original nitration conditions of Den Hertog *et al.*[14] were more appropriate under these circumstances.

2-Methoxy-4-nitropyridine *N*-oxide **142** was easily reduced with iron in acetic acid to yield 4-amino-2-methoxy pyridine **144** in excellent yield (98%). Introduction of the amino group at the 4-position shifts protons H-3 and H-5 upfield to δ 5.95 and δ 6.23 ppm respectively. The signal representing H-6 appears as a distinct doublet at δ 7.84 ppm while the amino protons came into resonance as a broad singlet at δ 4.10 ppm. The methoxy group appeared as a singlet at δ 4.90 ppm.

As mentioned earlier, 2-methoxy-4-nitropyridine **150** and 2-methoxy-5-nitropyridine **151** are not separable by column chromatography, so in order to increase the amount of 4-amino-2-methoxypyridine **144** available for subsequent chemistry it was decided to reduce the nitro groups of compounds **150** and **151**, since 2-methoxy-4-nitropyridine **150** is a direct precursor to 4-amino-2-methoxypyridine **144**. Reduction of these compounds was achieved by hydrogenation over palladium on charcoal in ethyl acetate at atmospheric pressure to give a mixture of 4-amino-2-methoxy-pyridine **144** and 2-methoxy-5-aminopyridine **152**, which were separable by chromatography (Scheme 2.7).

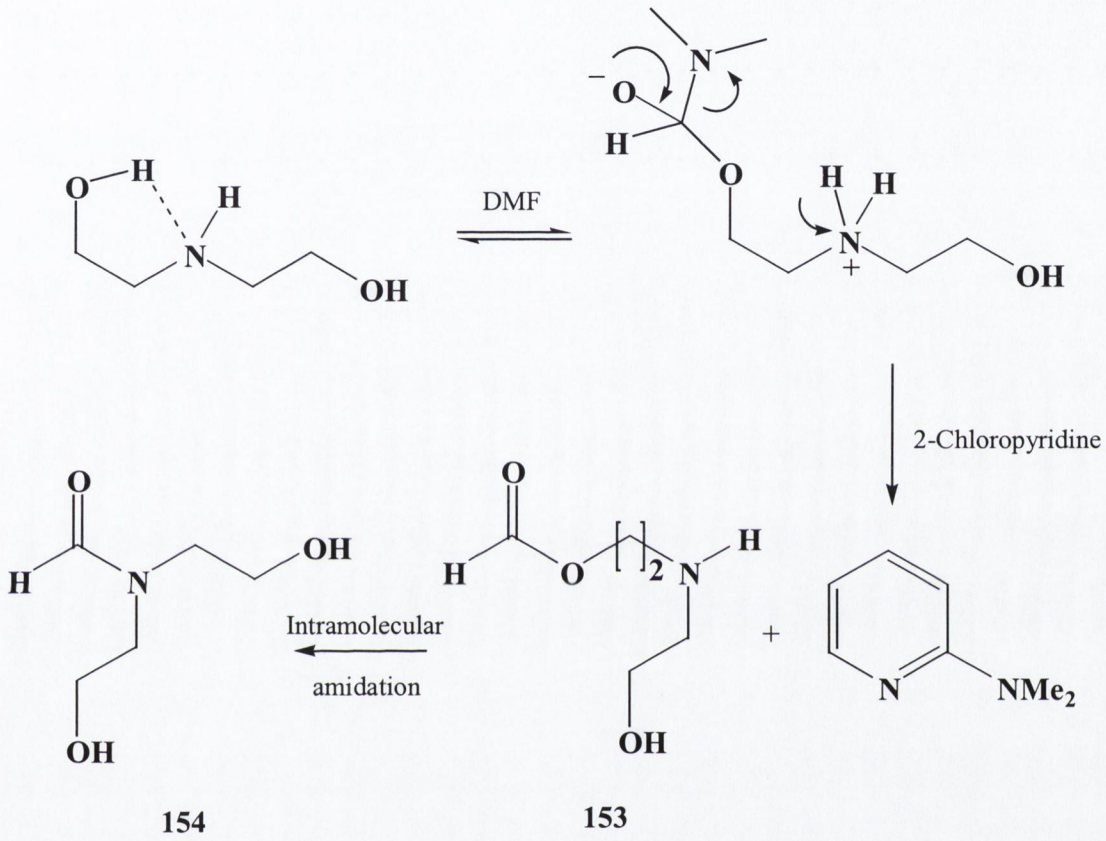
The 4-amino-2-methoxypyridine **144** prepared in this way was identical in every respect with the 4-amino-2-methoxypyridine prepared by the reaction of 2-methoxy-4-nitropyridine *N*-oxide **142** with iron and acetic acid.

2-Methoxy-4-aminopyridine **144** underwent diazotisation with concentrated hydrochloric acid and sodium nitrite at –10 °C, to yield 4-chloro-2-methoxypyridine **145**. This compound was a low-melting point solid and was either a liquid or a colourless solid depending on the temperature in the laboratory. It had a melting point of 24 °C, which was in agreement with literature observations.[16]

The chlorine in the 4-position of **145** was quite resistant to displacement with amines. Initial attempts to displace it with an aqueous solution of dimethylamine at elevated temperature (*ca.* 130 °C) proved to be not very fruitful. A dimethylamino moiety was successfully introduced into **145** using the method of Cho *et al.*[17] who reported a very efficient dimethylamination of activated aromatic halides using DMF

and for example, diethanolamine to give the corresponding dimethylamino derivative in excellent yield. The reaction was very successful with 2-chloropyridine as the aryl halide. A proposed mechanism is outlined below (Scheme 2.8).

Scheme 2.8



154 **153**

An hydroxyl group activated by the neighbouring amino function attacks DMF to produce the intermediate shown. This then delivers a dimethylamino group to the 2-chloropyridine to produce 2-dimethylaminopyridine and the formate **153**. Formate **153** then undergoes *O*-acyl to *N*-acyl migration under the reaction conditions to produce the amide **154**. The amide **154** was isolated and compared to that of an authentic sample prepare by a different route and both were found to be identical.

Since this reaction was successful with 2-chloropyridine as the aryl halide and given that the 2- and 4-positions of pyridine are comparably reactive towards nucleophilic displacement,[18] it was envisaged that this methodology should effect the displacement of the chlorine in 4-chloro-2-methoxypyridine **145** and lead to the successful introduction of a 4-dimethylamino moiety into the molecule to afford 4-dimethylamino-2-methoxypyridine **146**.

Under these conditions 4-dimethylamino-2-methoxypyridine **146** was synthesised in 70% yield. The ^{1}H NMR spectrum of **146** showed three aromatic protons at δ 7.80 (H-6), 6.19 (H-5) and 5.82 (H-3) ppm. The dimethylamino group appeared as a singlet at δ 2.90 ppm and the methoxy methyl also as a singlet at δ 3.85 ppm.

A 4-(1'-pyrrolidinyl) substituent was also introduced into the aromatic ring of **145** by reaction with pyrrolidine in *N*-methyl-2-pyrrolidinone at 130 °C. Under these conditions the chloro-substituent of **145** underwent smooth displacement to afford 2-methoxy-4-(1'-pyrrolidinyl)pyridine **147** in 80% yield. The ^{1}H NMR spectrum of this compound was very straightforward. Aromatic protons H-3 and H-5 had chemical shifts at δ 6.11 and δ 5.76 ppm, respectively, while H-6 came into resonance at δ 7.82 ppm. The methoxy protons appeared as a sharp singlet at δ 3.89 ppm and the α and β hydrogens of the pyrrolidine ring appeared as multiplets at δ 3.28 and δ 2.00 ppm, respectively.

The next step in these syntheses involved cleavage of the methyl ether function of either 4-dimethylamino-2-methoxypyridine **146** and 2-methoxy-4-(1'-

pyrrolidinyl)pyridine **147** with the reagent boron tribromide. Boron tribromide is the reagent of choice to effect the cleavage of ethers under mild conditions without the need for strongly acidic or basic conditions. Another advantage of this reagent is that it can cleave ethers without affecting a large number of other functional groups.[19]

In the event 2-methoxy-4-(1'-pyrrolidinyl)pyridine **147** (**147** was chosen to undergo reaction with boron tribromide since it was felt that **146** might undergo *N*-demethylation) underwent ether cleavage in DCM with boron tribromide by the method of Felix *et al.*[20] to give the title compound 4-(1'-pyrrolidinyl)-2-pyridone **148**. Upon workup it was necessary to reflux the reaction mixture with methanol to decompose complexes formed between the pyridone **148** and boron Lewis acidic species. Alternatively, column chromatography using DCM : methanol 90 : 10 as mobile phase also decomposed the complexes *in situ*.

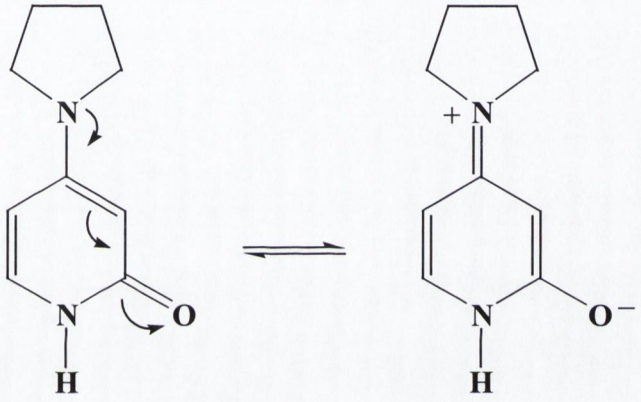
The ^{1}H NMR spectrum (Figure 2.5) of 4-(1'-pyrrolidinyl)-2-pyridone **148** showed a number of chemical shifts which were indicative of structure **148**. Proton H-3 of the molecule appeared at δ 5.41 ppm and H-5 resonated at δ 5.76 ppm. Proton H-6 showed a distinct doublet at δ 7.16 ppm while the N-H of the pyridone appeared far downfield at δ 12.39 ppm, and underwent deuterium exchange in the presence of D_2O. The α and β protons of the pyrrolidine ring had chemical shifts of δ 3.32 and δ 2.01 ppm respectively.

Analysis of the ^{13}C NMR spectrum of **148** showed that there were seven unique carbon atoms present. These resonated at δ 24.80 (β CH_2 of pyrrolidine ring), 46.82

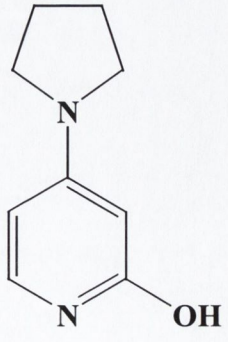
(α CH_2 of pyrrolidine ring), 92.19 (C-3), 96.76 (C-5), 133.87 (C-6), 155.10 (C-4) and 165.57 (C-2) ppm.

The IR spectrum of **148** showed a very strong carbonyl absorption at 1611 cm^{-1}, which was lower than expected for pyridones. This may be because the compound may exist as a vinylogous amide (Figure 2.1).

Figure 2.1

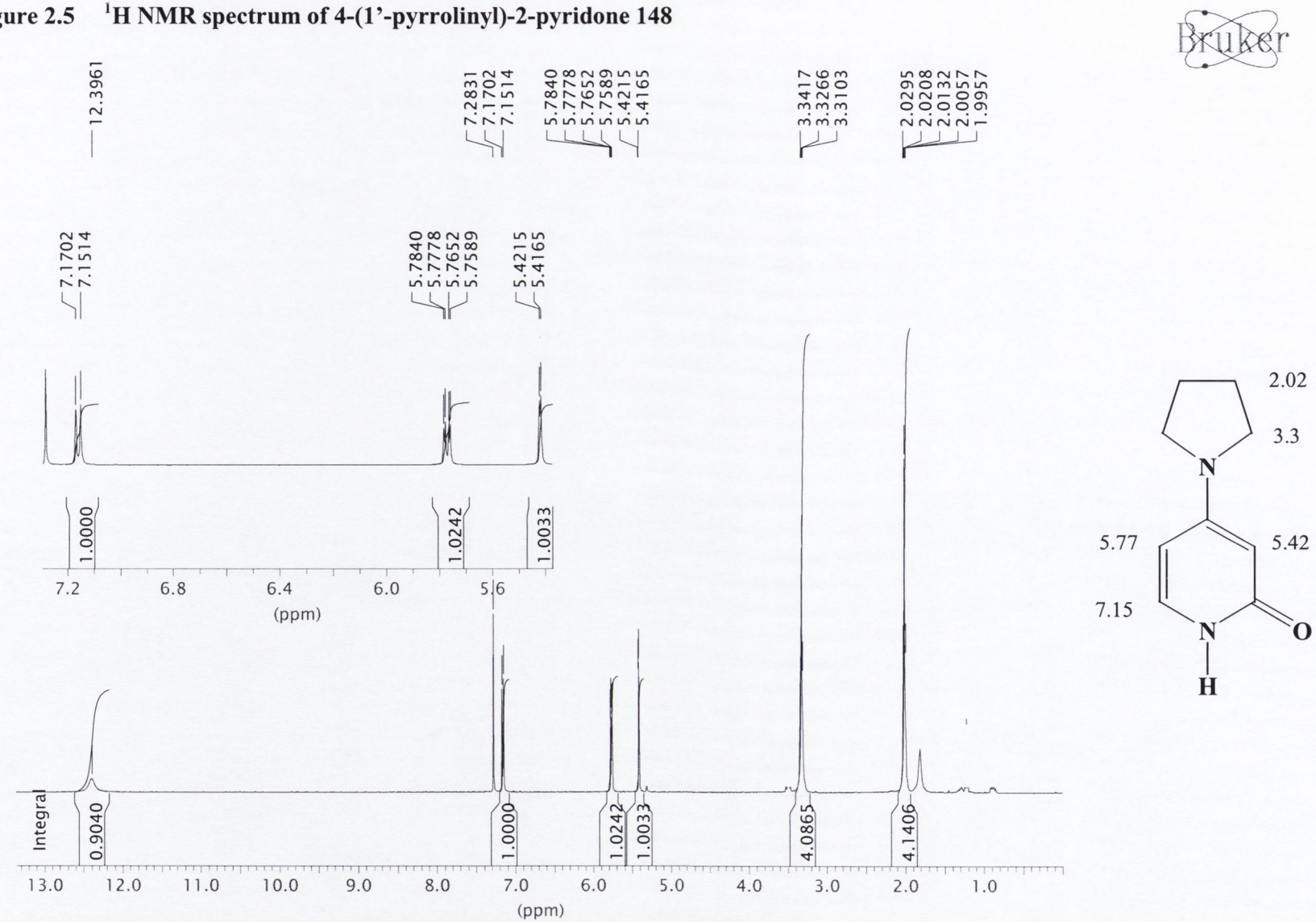


The mass spectrum of **148** gave a nominal mass of 165.1197 calculated for $[C_9H_{12}N_2O + H]^+$ 165.1028. With this data it was concluded that the structure of **148** is indeed represented best by the pyridone form and not by the aromatic alcohol **155**.



155

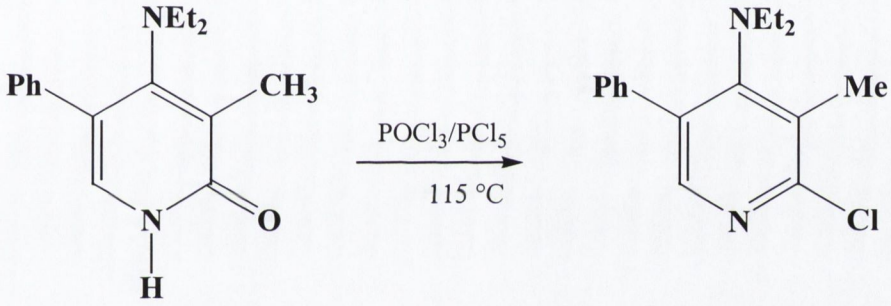
Figure 2.5 ^{1}H NMR spectrum of 4-(1'-pyrrolinyl)-2-pyridone 148



The reaction of phosphorus compounds such as phosphorus oxychloride or phosphorus pentachloride with pyridones is a direct method for synthesis of the corresponding chloropyridines.[21] 2-Pyridone undergoes reaction with phosphorus oxychloride to give 2-chloropyridine in almost quantitative yield.

Fuks *et al.*[22] reported the conversion of 4-diethylamino-3-methyl-5-phenyl-2-pyridone **156** into the corresponding chloro derivative **157** in 75% yield (Scheme 2.9).

Scheme 2.9



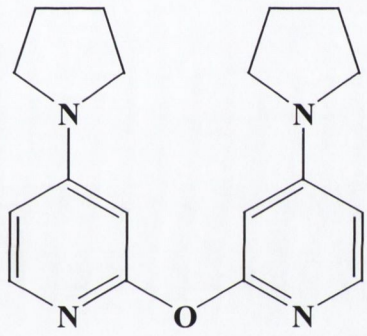
156 **157**

Based on this precedent it was postulated that the pyridone **148** should undergo facile conversion to 2-chloro-4-(1'-pyrrolidinyl)pyridine **149** with phosphorus oxychloride or phosphorus pentachloride or a combination of the two.

Treatment of pyridone **148** with refluxing phosphorus oxychloride afforded two compounds, which were present in the recovered material in almost equal abundance. The identity of the compounds was probed using mass spectrometry. Both compounds were identified by a combination of mass spectroscopy and ^{1}H NMR. One, which had *m/z* of 183.1957 must be 2-chloro-4-(1'-pyrrolidinyl)pyridine **149**

(calculated for $[C_9H_{11}ClN_2 + H]^+$ 183.0689). ^1H NMR provided supporting evidence in conformation of its identity. Based on a knowledge of the chemical shifts of the protons of 2-chloro-4-dimethylaminopyridine **132**, which is chemically similar to **149**, NMR signals could be assigned. Therefore three aromatic resonances at δ 8.02 (H-6), 6.53 (H-3) and 6.47 (H-5) ppm were assigned as indicated. The protons on the pyrrolidine ring resonated at δ 2.21 (β CH_2) and δ 3.46 (α CH_2) ppm.

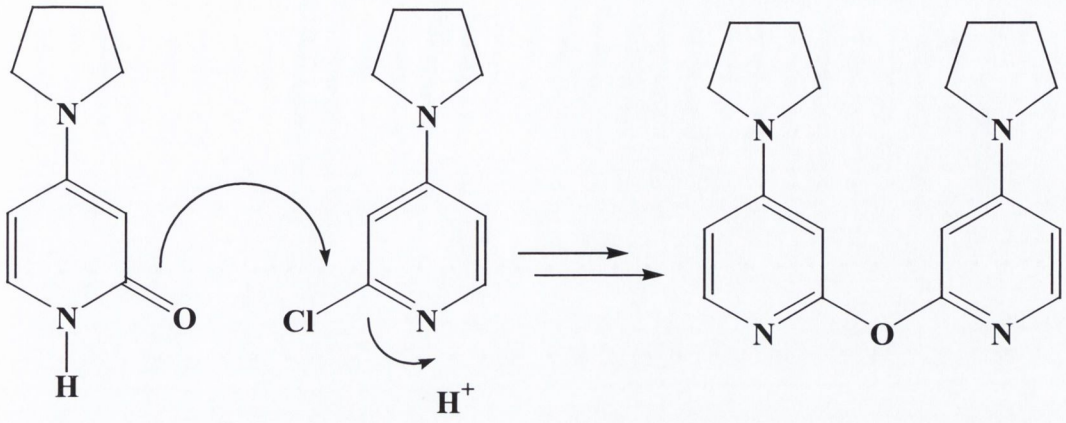
The second compound formed from **148** had *m/z* of 311.1241 (nominal mass) and was deduced to be the ether **158** (calculated for $[C_{18}H_{22}N_4O + H]^+$ 311.1872).



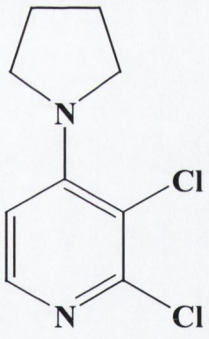
158

^1H NMR signals at δ 8.31 (H-6 + H-6'), 7.39 (H-5 +H-5') and 6.83 (H-3 + H-3') ppm were assigned to the aromatic protons of **158**. The protons on the pyrrolidine rings resonated at δ 2.31 (β CH_2) and δ 3.65 (α CH_2) ppm. The formation of ether **158** can be rationalised by assuming reaction of the 2-chloro-4-pyrrolidinopyridine **149** with the pyridone **148** (Scheme 2.10).

Scheme 2.10



Treatment of the pyridone **148** with a combination of phosphorus pentachloride in phosphorus oxychloride at reflux gave a number of compounds. Only one of the components of the recovered material could be purified by column chromatography and its structure was determined as 2,3-dichloro-4-(1'-pyrrolidinyl)pyridine **159**.



159

The ^{1}H NMR spectrum of **159** revealed four chemical shifts, which were indicative of its structure. Protons H-5 and H-6 came into resonance at δ 7.90 (H-6) and δ 6.49 (H-5) ppm. Both protons were doublets, *J* 7.0 Hz, and were typical of an AB system. The protons on the pyrrolidine ring resonated at δ 2.00 (β CH_2) and δ 3.64 (α CH_2)

ppm. Analysis of the ^{13}C NMR spectrum revealed seven unique carbon atoms, three of which were quaternary carbon atoms. These resonated at δ 25.19 (β CH_2), 50.91 and (α CH_2), 108.76 (C-5), 113.32 (C-3), 143.97 (C-6), 149.51 (C-2) and 152.23 (C-4) ppm.

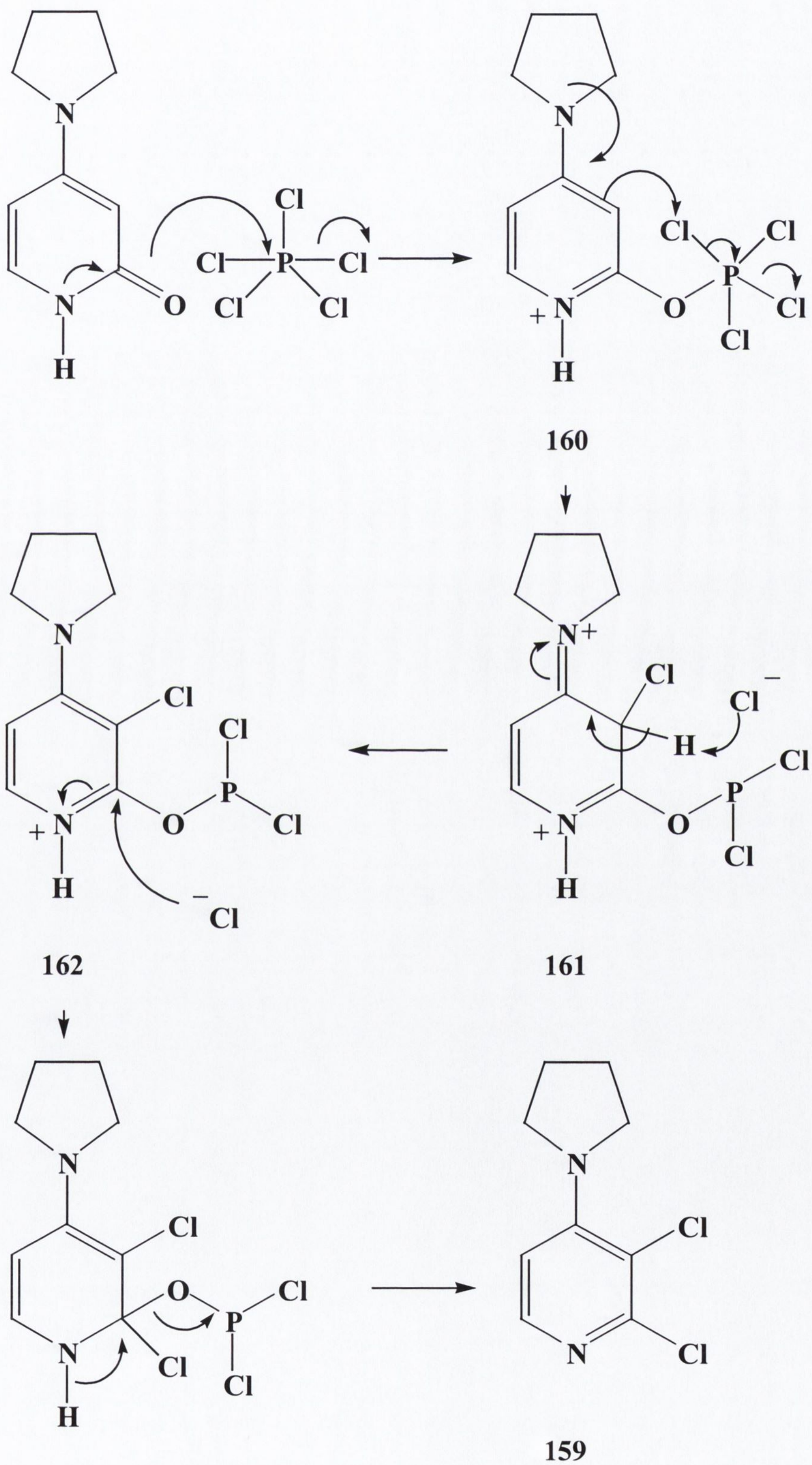
The formation of **159** can be rationalised by activation of the 3-position of the molecule by the 4-(1'-pyrrolidinyl) moiety *via* electron-donation into the aromatic ring, leading to abstraction of a chlorine atom from the intermediate **160** to give **161** (Scheme 2.11). Loss of a proton from **161** results in restoration of aromaticity to give intermediate **162**. Attack by chloride ion at the 2-position of **162** displaces the phosphite to give the 2,3-dihalopyridine **159**. The formation of 2,3-dichloro-4(1'-pyrrolidinyl)pyridine **159** must result from reaction with phosphorus pentachloride since no 2,3-disubstituted derivatives were observed when phosphorus oxychloride was utilised on it own.

^{31}P NMR analysis of the remaining compounds in the product mixture showed that phosphorus was present, and it is thought that they might be compounds of type **163**, a tripyridyl phosphate, or the bipyridyl phosphate **164**. It is well known that the reaction of 2-pyridone with phosphorus oxychloride gives tripyridyl phosphate, which is readily hydrolysed to the bipyridyl phosphate.[23]

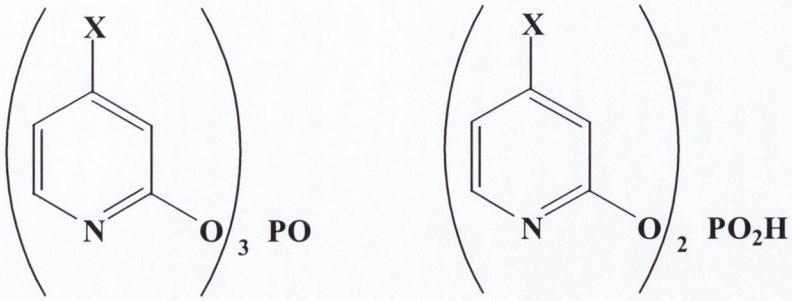
In the event, this synthetic route to 2-chloro-4-dialkylaminopyridines was abandoned since it was too low-yielding and required too many synthetic steps. Also, the last step did not provide 2-chloro-4-(1'-pyrrolidinyl)pyridine **149** cleanly as the only

reaction product and the presence of unwanted side-products severely undermined this synthesis.

Scheme 2.11



X = 1'-pyrrolidinyl

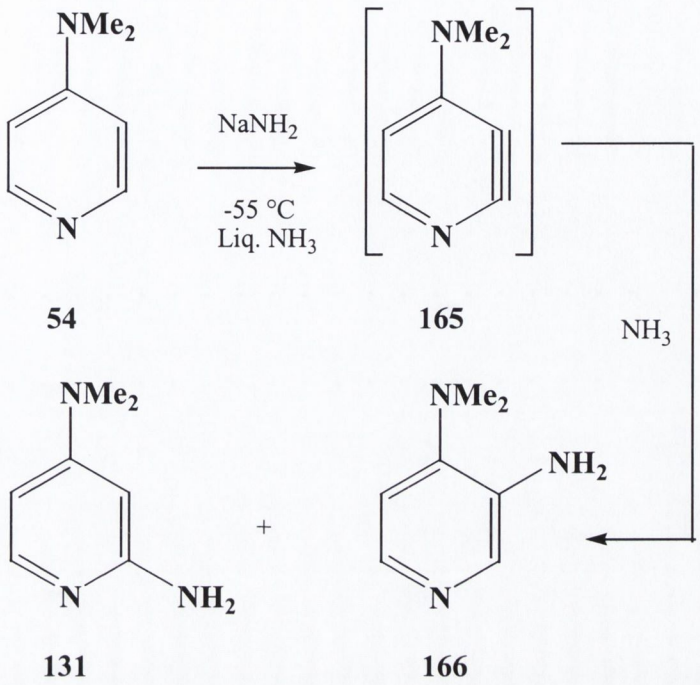


163 **164**

2.5 Attempted synthesis of 2-amino-4-dimethylaminopyridine *via* the trapping of a heteroaryne generated from 3-halo-4-dimethylaminopyridines

Pozharskii *et al.*[24] reported that the amination of 4-dimethylaminopyridine **54** (pK_a 9.37) under the heterogeneous Chichibabin aminating conditions of $NaNH_2$ in refluxing tetralin afforded only trace amounts of 2-amino-4-dimethylaminopyridine **131**, and as such was of no use as a means to prepare this compound. The Reilly Tar and Chemical Corporation report that reaction of DMAP under similar conditions gives only 4-aminopyridine as the sole reaction product.[25] Under the homogeneous aminating conditions of KNH_2 in liquid ammonia, 4-dimethylaminopyridine was inert to amination.[26] In similar conditions the more basic pyridine 4-diethylaminopyridine (pK_a 9.62) underwent partial dealkylation to afford 4-ethylaminopyridine in 75% yield.[27] Based on these literature observations it was felt that direct amination of 4-dimethylaminopyridine **54** was not an option, and therefore initial attempts to synthesise 2-amino-4-dialkyaminopyridines in this laboratory concentrated upon the generation of the pyridyne **165**, the pyridine equivalent of a benzyne (Scheme 2.12).

Scheme 2.12



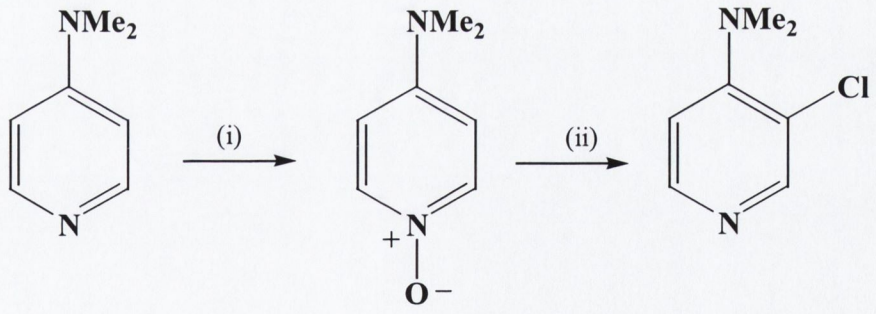
It was presumed that the pyridyne **165**, upon generation from a suitable precursor such as a 3-halo-4-dimethylaminopyridine could be trapped with ammonia to give as a mixture 2-amino-4-dimethylaminopyridine **131** (product of cine-substitution) and 3-amino-4-dimethylaminopyridine **166** (product of normal substitution). It was expected that the 2-amino isomer would predominate over the 3-amino isomer due to the –I inductive effect of the nitrogen alpha to it.

This strategy required the synthesis of 3-halo-4-dimethylaminopyridines. Two alternative routes to 3-halo-4-dimethylaminopyridines were considered. 3-Chloro-4-dimethylaminopyridine **168** was synthesised from 4-dimethylaminopyridine *N*-oxide **167** upon reaction with phosphorus oxychloride (Scheme 2.13). This reaction was discovered by Gallagher[28] in this laboratory and gave yields ranging from 35 –70%. The yield may depend on the state of hydration of the *N*-oxide. When anhydrous 4-

dimethylaminopyridine *N*-oxide **167** was utilised no reaction with phosphorus oxychloride was observed until a catalytic amount of water was added.

4-Dimethylaminopyridine *N*-oxide **167** was synthesised in 75% yield from 4-dimethylaminopyridine **54** *via* oxidation with Caro's Acid (peroxomonosulfuric acid, H_2SO_5) by the method of Robke *et al.*[29] The ^1H NMR spectrum of 4-dimethylaminopyridine *N*-oxide showed a typical aromatic AB system with chemical shifts at δ 6.47 (H-3, H-5) and δ 7.91 (H-6, H-2) ppm, respectively. The introduction of oxygen at the ring nitrogen shifts the resonance due to H-2 and H-6 upfield by 0.3 ppm when compared to 4-dimethylaminopyridine. This is due in part to the *N*-oxide being capable of donating electron density into the aromatic ring as well as withdrawing electron density. The protons H-3 and H-5 remained unaffected by *N*-oxidation and come into resonance at δ 6.47 ppm.

Scheme 2.13



54 **167** **168**

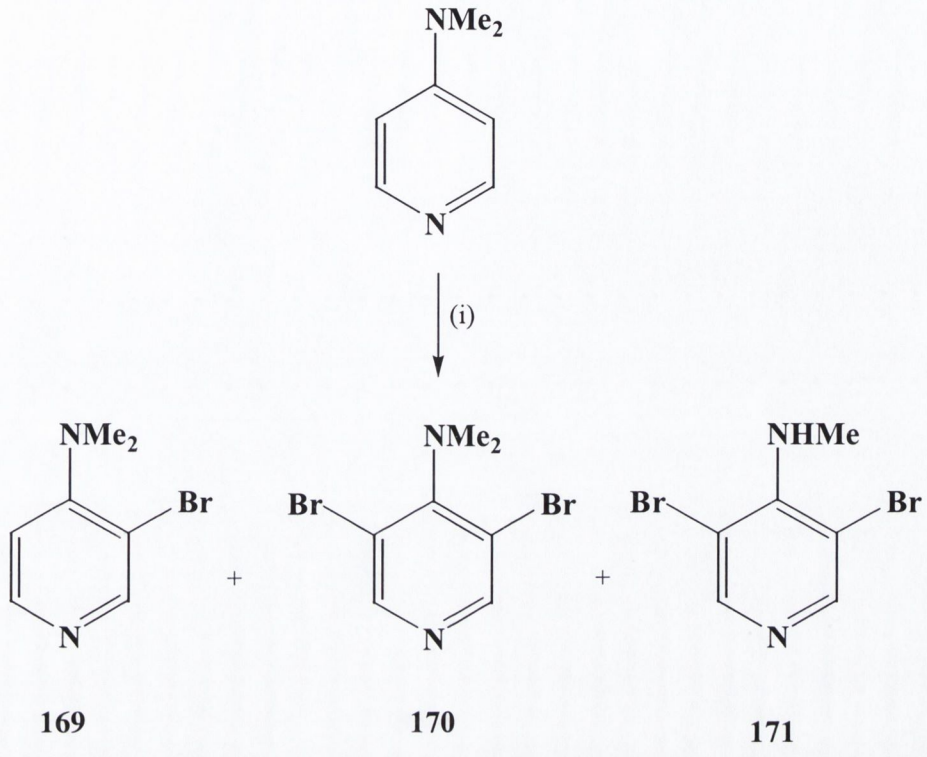
Reagents and Conditions: (i) H_2SO_5, KOH/H_2O, r.t., 24 h, 75% (ii) $POCl_3$, reflux, 10 h, 35%.

The ^{1}H NMR spectrum of 3-chloro-4-dimethylaminopyridine **168** showed three aromatic protons at δ 6.62 (H-5), 8.10 (H-6) and 8.21 (H-3) ppm. The dimethylamino moiety resonated at δ 2.85 ppm. The proton corresponding to H-2 is shifted dramatically downfield since it is alpha to the ring nitrogen and the electron-withdrawing chlorine. It shows no coupling with either H-5 or H-6 and appears as a broad singlet.

Paudler *et al.*[30] described the monobromination of 4-dimethylaminopyridine **54** in good yield by reaction with bromine in the presence of K_2CO_3 in carbon tetrachloride at room temperature. Despite several attempts to carry out this reaction on a synthetically useful scale, this synthesis of 3-bromo-4-dimethylaminopyridine **169** proved ineffective.

However, 4-dimethylaminopyridine **54** was successfully brominated using bromine in acetic acid in the presence of sodium acetate at room temperature to give a mixture of 3-bromo-4-dimethylaminopyridine **169**, 3,5-dibromo-4-dimethylaminopyridine **170**, and 3,5-dibromo-4-methylaminopyridine **171** (Scheme 2.14). Although the yield of 3-bromo-4-dimethylaminopyridine **169** was relatively poor (35%) this reaction was reliable both in small and large scale experiments. The yields of the 3,5-dibromo compounds **170** and **171** were usually of the order of 5% (based on reactant). The formation 3,5-dibromo-4-dimethylaminopyridine **170**, the product of dibromination, is not unusual since the corresponding dibromide is also obtained when 4-aminopyridine is brominated.[31]

Scheme 2.14

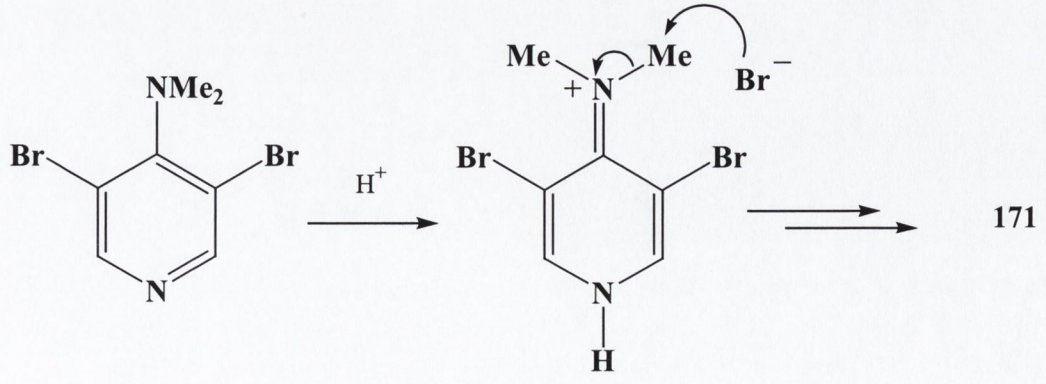


169 **170** **171**

Reagents and Conditions: (i) DMAP, Br_2, NaOAC, AcOH, r.t, 35%.

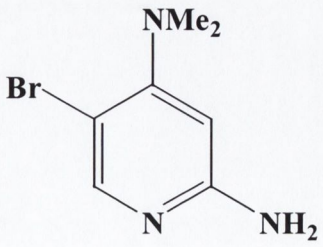
The formation of the dibromide **171** probably arises due to demethylation of the conjugate acid by bromide ion (Scheme 2.15).

Scheme 2.15

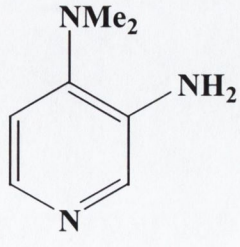


Another procedure for the synthesis of 3-bromo-4-dimethylaminopyridine **169** was reported by Groziak *et al.*[32] where bromination takes place in a biphasic system of water and DCM. With this system, 3-bromo-4-dimethylaminopyridine **169** was synthesised in 75% yield. A small amount of the dibromo compound **170** was present but none of the demethylated dibromide **171** was formed.

Treatment of 3-chloro-4-dimethylaminopyridine **168** or 3-bromo-4-dimethylaminopyridine **169** under heterogeneous conditions with sodium amide in liquid ammonia at –50 °C did not yield the desired 2-amino-4-dimethylaminopyridine **131** or 3-amino-4-dimethylaminopyridine **166**. Unreacted starting material was the only product isolated from the reaction. Groziak *et al.*[32] reported that under homogenous conditions using potassium amide in liquid ammonia that 3-bromo-4-dimethylaminopyridine **169** afforded 6-amino-3-bromo-4-dimethylaminopyridine **172** (5%) and 3-amino-4-dimethylaminopyridine **166** (35%). A substantial amount of 4-dimethylaminopyridine **54** was also in the product mixture. Under heterogeneous conditions the same authors reported that sodium amide in liquid ammonia gave 4-dimethylaminopyridine **54** as the sole reaction product.



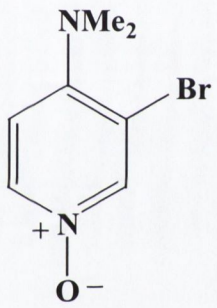
172



166

This observation was not confirmed in this laboratory since 3-bromo-4-dimethylaminopyridine **169** was recovered unchanged from the reaction under similar conditions.

It was presumed that pyridyne generation would be enhanced by use of the *N*-oxide **173**, based on the assumption that the proton in the 2-position would be significantly more acidic due to the strongly electron-withdrawing *N*-oxide functionality. The synthesis of 3-bromo-4-dimethylaminopyridine *N*-oxide **173** was achieved by oxidising the free base **169** with *m*-chloroperoxybenzoic acid in chloroform at room temperature.



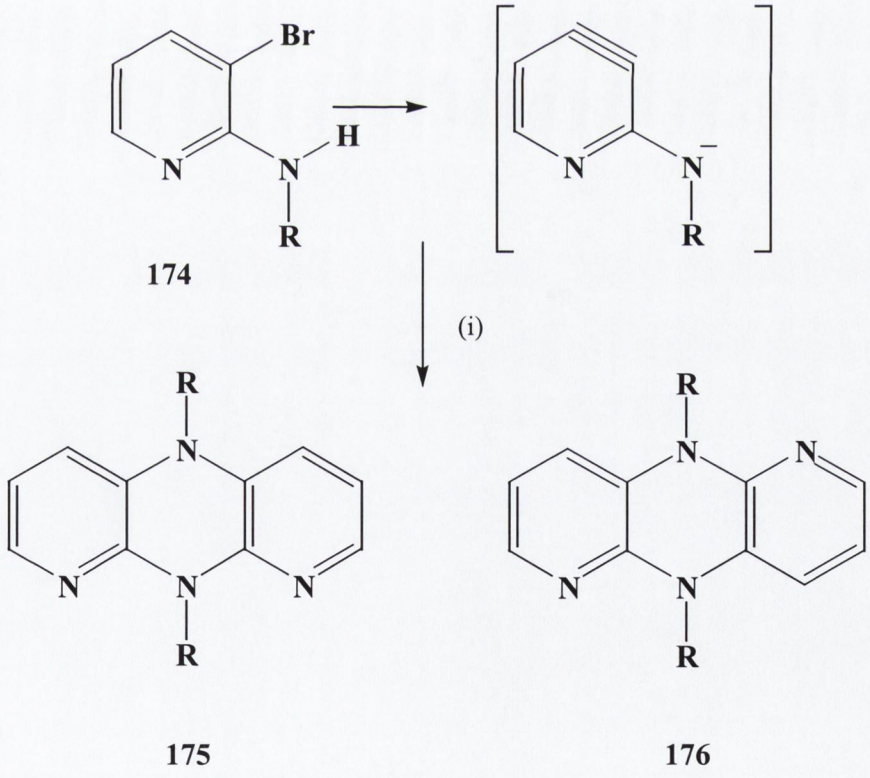
173

The ^{1}H NMR spectrum of 3-bromo-4-dimethylaminopyridine *N*-oxide **173** revealed three resonances at δ 8.32 (H-2), 8.03 (H-6) and 6.77 (H-5) ppm. The dimethylamino protons resonated at δ 2.94 ppm. An interesting aspect of the spectrum is that H-2 couples with H-6 upon introduction of the *N*-oxide functionality. Consequently H-6 is split into a double doublet by *meta* coupling with H-2 and *ortho* coupling with H-5. This fine coupling between H-2 and H-6 was not observed in the free base 3-bromo-4-dimethylaminopyridine **169**.

Reaction of the *N*-oxide **173** under heterogeneous conditions with sodium amide in liquid ammonia again failed to generate any heteroaryne and 3-bromo-4-dimethylaminopyridine *N*-oxide **173** was recovered unchanged from the reaction mixture. It was then decided to investigate the use of a mixed base system to effect heteroaryne generation. This work had its origins in a recent paper by Rodriguez *et al.*[33]

Rodriguez *et al.*[33] reported a very efficient synthesis of dihydropyridopyrazines such as **175** and **176** *via* a dimerization of the heteroaryne derived from a series of 2-alkylamino-3-bromopyridine **174**. The heteroaryne was generated using the mixed base system $NaNH_2$/*tert*-BuONa (Scheme 2.16).

Scheme 2.16



Reagents and Conditions: (i) $NaNH_2$/*t*-BuONa, THF, 0 °C → r.t, 72 h.

This mixed base system was applied to 3-bromo-4-dimethylaminopyridine **169** as the active halide and indeed reaction ensued to yield a number of products. Analysis of the reaction mixture by ^{1}H NMR and t.l.c revealed that the major compound present was in fact 4-dimethylaminopyridine **54** (62%). Also present were 6-amino-3-bromo-4-dimethylaminopyridine **172** (5%), 3-amino-4-dimethylaminopyridine **166** (3%), 3-bromo-4-dimethylaminopyridine **169** (2%) and 2-amino-4-dimethylaminopyridine **131** (28%).

Compounds were identified from the ^{1}H NMR spectrum of the crude mixture and comparison with literature data. The signals observed are summarised in Table 2.1. 2-Amino-4-dimethylaminopyridine **131** was identified by comparison with literature values and the ^{1}H NMR spectrum of a pure sample prepared as shown in Scheme 2.1.

Table 2.1 Structure determination of compounds 54, 131, 166, 169 and 172 by ^{1}H NMR

Compound	^{1}H NMR assignment/ppm	Literature values/ppm
4-dimethylaminopyridine **54**	δ 6.5 (H-3 + H-6), 8.2 (H-2 + H-6) and 3.00 (NMe_2)	δ 6.4 (H-3 + H-6), 8.2 (H-2 + H-6) and 3.00 [34]
2-amino-4-dimethylaminopyridine **131**	δ 7.7 (H-6), 6.0 (H-4), 5.6 (H-3), 4.2 (NH_2) and 2.9 (NMe_2)	δ 7.7 (H-6), 6.0 (H-5), 5.7 (H-3), 4.8 and 2.9 (NMe_2)[32]
3-Amino-4-dimethylaminopyridine **166**	δ 8.1 (H-2), 7.9 (H-6), 6.8 (H-5), 3.7 (NH_2) and 2.7 (NMe_2)	δ 8.0 (H-2), 7.9 (H-6), 6.8 (H-5), 3.7 (NH_2) and 2.7 (NMe_2)[32]
6-amino-3-bromo-4-dimethylaminopyridine **172**	δ 8.0 (H-6), 6.0 (H-3) and 2.8 (NMe_2)	δ 7.98 (H-6), 6.01(H-3) and 2.87 (NMe_2)[32]

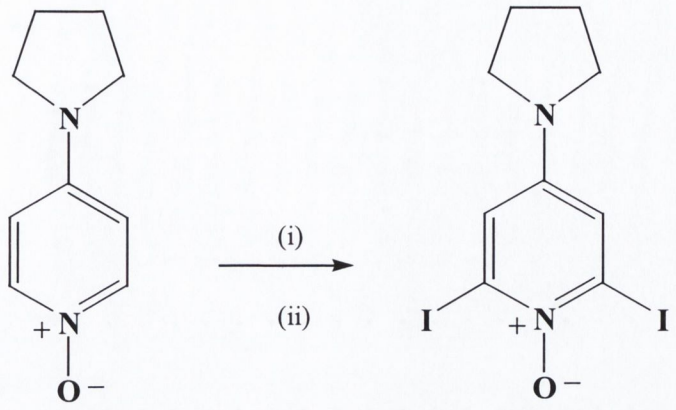
The formation of a considerable amount of 2-amino-4-dimethylaminopyridine **131** (28%) may have come about *via* the pyridyne mechanism, however no trapping experiment were carried out to determine this. Another possible explanation for the formation of **131** would be a Chichibabin type reaction with 4-dimethylaminopyridine **54** formed *in situ* by amide anion attack at the 2-position of the aromatic ring, although this is unlikely giving literature precedents. T.l.c analysis revealed that separation by chromatography of the compounds formed in this reaction was improbable and so it was felt that this did not represent a viable route to 2-amino-4-dimethylaminopyridine **131**. Interestingly, whereas Groziak *et al.*[32] also report the formation of 3-amino-4-dimethylaminopyridine **166,** 4-dimethylaminopyridine **54** and 6-amino-3-bromo-4-dimethylaminopyridine **172** from 3-bromo-4-dimethylamino pyridine **169** under homogenous conditions with potassium amide in liquid ammonia there is no mention of 2-amino-4-dimethylaminopyridine **131** being formed under these conditions.

2.6 Synthesis of 2,6-diiodo-4-dimethylaminopyridine *N*-oxide

This compound was prepared by the method of Sammakia *et al.*[13] These authors reported the synthesis of 2,6-diiodo-4-(1'-pyrrolidinyl)pyridine *N*-oxide **177** from 4-(1'-pyrrolidinyl)pyridine *N*-oxide **178** in 57% yield upon treatment with LDA and iodine (Scheme 2.17).

The reaction was repeated in this laboratory using 4-dimethylaminopyridine *N*-oxide **167** and the same conditions, to give 2,6-diiodo-4-dimethylaminopyridine *N*-oxide **179** in 48% yield. Chromatography afforded material of excellent purity.

Scheme 2.17

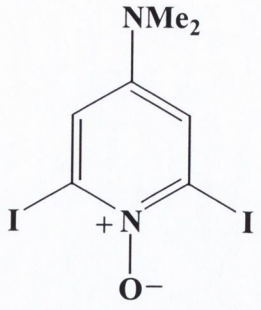


177 **178**

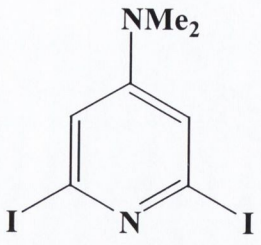
Reagents and Conditions: (i) LDA, -78 °C, (ii) I_2 in THF

The ^1H NMR spectrum of **179** was very simple due to the symmetry within the molecule. Two resonances were observed at δ 2.99 (dimethylamino) and δ 7.11 (H-3 and H-5) ppm. Analysis of the ^{13}C NMR spectrum showed that there were four unique carbon atoms present within the molecule resonating at δ 39.63 (NMe_2), 107.21 (C-2 + C-6), 118.89 (C-3 + C-5) and 146.23 (C-4) ppm.

This reaction allows easy access to 2,6-diiodo-4-dimethylaminopyridine **180** since the *N*-oxide **179** is a direct precursor to the free base by reduction. This compound together with 2,6-dibromo-4-dimethylaminopyridine **140** should allow access to desirable chiral C_2 symmetric compounds *via* nucleophilic substitution or other means.



179



180

2.7 Experimental Section

^{1}H NMR spectra (400.13 MHz) and ^{13}C NMR (100.6 MHz) spectra were measured for solutions in deuteriochloroform or [$^{2}H_6$]-DMSO, using a Bruker DPX-400 spectrometer. Chemical shifts are measured in ppm. J values are given in Hz. Melting points were measured on an Electrothermal melting point apparatus and are uncorrected. FT-IR spectra were measured using a Perkin Elemer FT-IR PARAGON 1000 and a Mattson Genesis II spectrometer. Electrospray mass spectra (ESMS) were recorded on a Micromass LCT electrospray mass spectrometer. T.l.c. was carried out using Merck Kieselgel 60 F_{254} plates and column chromatography was carried out under gravity using Merck Kieselgel 70-230 mesh. Solvents were dried using standard techniques as appropriate.

2-Chloropyridine *N*-oxide 126

2-Chloropyridine *N*-oxide (21% w/v in H_2O; 100 ml) was extracted with dichloromethane (3 × 60 ml). The organic extracts were combined and dried ($MgSO_4$) and concentrated *in vacuo* to give 2-chloropyridine *N*-oxide **126** (19 g; 90%) as a cream solid, m.p. 68.0-68.5 °C, *lit.*[35] 67-68.5 °C.

ν_{max} (N) 3091, 2923, 1467, 1420, 1377, 1276, 1263, 1145, 1083, 1041, 991, 956, 875, 847, 771, and 701 cm^{-1}.

δ_H ($CDCl_3$) 7.18-7.21 (2 H, m, H-4 + H-5), 7.49 (1H, m, H-3) and 8.32 (1H, d, *J* 7.0, H-6) ppm.

δ_C 123.61 (C-5), 125.47 (C-4), 126.67 (C-3), 139.92 (C-6) and 141.10 (quat.,C-2) ppm.

MS (ES): Found *m/z* 152.0343 (nominal mass) calculated for $[C_5H_4ClNO + Na]^+$ 151.9879.

2-Chloro-4-nitropyridine *N*-oxide 127

2-Chloropyridine *N*-oxide **126** (5 g; 3.8×10^{-2} mol) was dissolved in concentrated H_2SO_4 (7.5 ml), which was cooled to 5 °C. Fuming nitric acid (13.5 ml) in concentrated sulphuric acid (5 ml) was added dropwise during thirty minutes. The solution was then heated and stirred at 90 °C for 3 hours. The reaction mixture was then cooled and poured on to an ice/water mixture and neutralised to pH 7 with solid Na_2CO_3 which led to precipitation of the nitro compound. The nitro compound was isolated by filtration, dissolved in hot chloroform and dried ($MgSO_4$). The crude

product was recrystallised from ethanol : chloroform 70 : 30 to give 2-chloro-4-nitropyridine *N*-oxide **127** (5.93 g; 85%), m.p. 153.5 °C, *lit.*[36] m.p. 154 °C.

ν_{max} (N) 2921, 2727, 1592, 1544, 1523, 1461, 1407, 1376, 1275, 1155, 958, 907, 889, 837, 722, 697 and 652 cm^{-1}.

δ_H ($CDCl_3$) 8.04 (1H, dd, J_1 3.0, J_2 7.0, H-5), 8.37 (1H, d, J 3.0, H-3) and 8.41 (1H, d, J 7.0, H-6) ppm.

δ_C ($CDCl_3$) 115.22 (quat., C-2), 118.19 (C-3), 121.61 (C-5), 140.78 (C-6) and 151.79 (quat., C-4) ppm.

MS (ES) Found *m/z* 174.0875 (nominal mass) calculated for $[C_5H_3ClN_2O_3 + H]^+$ 173.9832.

2-Amino-4-nitropyridine *N*-oxide 128

2-Chloro-4-nitropyridine *N*-oxide **127** (1.0 g; 5.7×10^{-3} mol) was reacted with aqueous ammonia (d 0.88; 1.5 ml) in isopropyl alcohol (5 ml) in a pressure tube at 90 °C for 72 hours. Acetone was added to the reaction mixture and ammonium chloride was removed by filtration. The solvent was then evaporated and the concentrated syrup was either left to crystallise or was chromatographed on silica gel using acetone : hexane 65 : 35 as mobile phase to give 2-amino-4-nitropyridine *N*-oxide **128** (0.79 g; 90%), m.p. 167.3-168.5 °C.

ν_{max} (N) 3445, 2923, 1643, 1566, 1527, 1464, 1377, 1350, 1292, 1213, 1125, 1100, 952, 873, 807, 742, 722 and 659 cm^{-1}.

δ_H ($CDCl_3$) 5.93 (2H, bs, NH_2), 7.50 (1H, dd, J_1 3.0, J_2 7.0, H-5), 7.64 (1H, d, J 3.0, H-3) and 8.20 (1H, d, J 7.0, H-6) ppm.

δ_C ($CDCl_3$) 102.39 (C-3), 107.14 (C-5), 137.65 (C-6), 142.28 (quat., C-2) and 149.99 (quat., C-4) ppm.

MS (ES) Found *m/z* 156.1049 (nominal mass) calculated for $[C_5H_5N_3O_3 + H]^+$ 156.0409.

2-Acetamido-4-chloropyridine *N*-oxide 129

2-Amino-4-nitropyridine *N*-oxide **128** (2.6 g; 1.6×10^{-2} mol) was dissolved in dry chloroform (45 ml). Acetyl chloride (15 ml) was then added and the reaction was refluxed with stirring for 24 hours. Upon cooling the contents were then poured onto ice/water and neutralised with Na_2CO_3 and extracted with DCM (3×100 ml). The organic layers were combined and washed with saturated $NaHCO_3$, dried ($MgSO_4$) and the solvent removed. The pure compound was isolated by chromatography over silica gel using DCM : MeOH 95 : 5 as mobile phase to give 2-acetamido-4-chloropyridine *N*-oxide **129** (2.41 g; 50 %), m. p. 181 °C.

ν_{max} (N) 3182, 2221, 1714, 1608, 1561, 1461, 1376, 1280, 1204, 1010, 870, 805, 721 and 664 cm^{-1}.

δ_H ($CDCl_3$) 2.33 (3H, s, CH_3), 7.00 (1H, dd, J_1 3.0, J_2 7.0, H-5), 8.16 (1H, d, J 7.0, H-6), 8.51 (1H, d, J 2.5, H-3) and 9.96 (1H, s, N-H) ppm.

δ_C ($CDCl_3$) 24.48 (CH_3), 114.17 (C-5), 118.47 (C-3), 133.95 (quat., C-2), 136.72 (C-6), 142.19 (quat., C-4) and 164.95 (quat., C-2) ppm.

MS (ES): Found *m/z* 186.1254 (nominal mass) calculated for $[C_7H_7ClN_2O + H]^+$ 186.0196.

2-Amino-4-dimethylaminopyridine *N*-oxide 130

2-Acetamido-4-chloropyridine *N*-oxide **129** (1.05 g; 5.6×10^{-3} mol) was dissolved in aqueous dimethylamine solution (40% w/v; 8 ml) and the reaction was heated in a pressure tube for 24 hours at 120 ° C. Sodium hydroxide (30% w/v; 5 ml) was added and contents were shaken. The reaction was then evaporated to dryness. The salt cake that remained was extracted with boiling chloroform for 24 h. The chloroform extract was dried ($MgSO_4$) and the solvent removed to give 2-amino-4-dimethylaminopyridine *N*-oxide **131** (0.67 g; 83%), m. p. 230 °C.

ν_{max} (N) 3325, 3163, 2978, 2868, 1643, 1435, 1376, 1167, 1063, 972, 895 and 722 cm^{-1}.

δ_H ($CDCl_3$) 2.99 (6H, s, $N(CH_3)_2$), 5.55 (2H, s, NH_2), 5.87 (1H, d, *J* 3.5, H-3), 6.00 (1H, dd, J_1 3.5, J_2 7.5, H-5) and 7.81 (1H, d, *J* 7.5, H-6) ppm.

δ_C (DMSO) 39.66 ($N(CH_3)_2$), 89.51 (C-3), 98.40 (C-5), 136.72 (C-6), 148.66 (quat., C-2) and 150.23 (quat., C-4) ppm.

MS (ES): Found: *m/z* 154.1721 (nominal mass), calculated for $[C_7H_{11}N_3O + H]^+$ 154.0980.

2-Amino-4-dimethylaminopyridine 131

2-Amino-4-dimethylaminopyridine *N*-oxide **130** (1 g; 6.5×10^{-3} mol) was dissolved in acetic acid (10 ml). Iron powder (1g, 17×10^{-3} mol) was added and the reaction

was heated to 100 °C on a steam bath for 3 hours. The solution was allowed to cool and was basified to pH 14 with sodium hydroxide (1 M). The solution was extracted with ether (3 × 80 ml) and the organic layers were combined, dried (Na_2SO_4) and evaporated. The compound was purified by chromatography over silica gel using DCM : MeOH 60 : 40 as mobile phase to give 2-amino-4-dimethylaminopyridine **131** (0.84 g; 95%), m.p. 126 °C, *lit.*,[32] 126-128°C.

δ_H ($CDCl_3$) 2.93 (6H, s, NMe_2), 5.65 (2H, s, NH_2), 5.67 (1H, d, *J* 2.0, H-3), 6.04 (1H, dd, J_1 3.0, J_2 6.0, H-5) and 7.75 (1H, d, *J* 6.0, H-6) ppm.

δ_C ($CDCl_3$) 38.66 ($N(CH_3)_2$), 88.87 (C-3), 99.50 (C-5), 147 (C-6), 155.78 (C-4) and 158.86 (C-2) ppm.

2-Chloro-4-dimethylaminopyridine 132

2-Amino-4-dimethylaminopyridine **131** (1 g; 7.2, × 10^{-3} mol) was dissolved in concentrated HCl (10 ml). The solution was cooled to *circa* –5 °C, to which was added intermittently solid sodium nitrite (3 g; 43 × 10^{-3} mol). After addition of the sodium nitrite the reaction was stirred at 0 °C for a further 30 minutes, then heated to 80 °C for 1 hour. Upon cooling, the reaction mixture was cooled in a ice bath and basified to pH 14 with sodium hydroxide. The solution was extracted with ether (3 × 80 ml). The organic layers were combined, dried (Na_2SO_4) and evaporated. The crude material was chromatographed over silica gel using ether : hexane 50 : 50 as mobile phase to give 2-chloro-4-dimethylaminopyridine **132** (0.67 g; 60%), m.p. 71.5 °C (from hexane).

ν_{max} (N) 2918, 1595, 1461, 1376, 1270, 1223, 1135, 1082, 983, 805 and 721 cm^{-1}.

δ_H ($CDCl_3$) 3.01 (6H, s, $N(Me)_2$), 6.42 (1H, dd, J_1 2.5, J_2 6.0, H-5), 6.49 (1H, d, J 2.0, H-3) and 7.98 (1H, d, J 6.0, H-6) ppm.

δ_C ($CDCl_3$) 38.81 ($N(CH_3)_2$), 104.99 (C-3), 1105.38 (C-5), 148.44 (C-6), 155.35 (C-4) and 149.74 (C-2) ppm.

MS (ES): Found *m/z* 157.0753 (nominal mass) calculated for $[C_7H_{10}ClN_2 + H]^+$ 157.0532.

2-Bromo-4-dimethylaminopyridine 133

2-Amino-4-dimethylaminopyridine **131** (1 g; 7.2, × 10^{-3} mol) was dissolved in concentrated HBr (10 ml). The solution was cooled to *circa* –5 °C, to which was added bromine (1.2 ml, 3 equivalents). Solid sodium nitrite (3 g; 43 × 10^{-3} mol) was added intermittently over 30 minutes. After addition of sodium nitrite the reaction was stirred at 0 °C for a further 30 minutes, then heated to 80 °C for 1 hour. Upon cooling, the reaction mixture was cooled in a ice bath and basified to pH 14 with sodium hydroxide. The solution was extracted with ether (3 × 80 ml). The organic layers were combined, dried (Na_2SO_4) and evaporated. The crude material was chromatographed over silica gel using ether : hexane 50 : 50 as mobile phase to give 2-bromo-4-dimethylaminopyridine **133** (0.80 g; 55%), m.p. 52 °C (from hexane).

ν_{max} (N) 2952, 2925, 2854, 1594, 1515, 1465, 1442, 1378, 1265, 1224, 1132, 1070, 975, 831, 809, 792 and 688 cm^{-1}.

δ_H ($CDCl_3$) 3.00 (6H, s, $N(Me)_2$), 6.44 (1H, dd, J_1 2.5, J_2 6.0, H-5), 6.65 (1H, d, J 2, H-3) and 7.95 (1H, d, J 6.0, H-6) ppm.

δ_C ($CDCl_3$) 39.14 ($N(CH_3)_2$), 105.74 (C-3), 108.80 (C-5), 148.80 (C-6), 155.35 (quat, C-4) and 142.62 (C-2) ppm.

MS (ES): Found *m/z* 200.9602 (nominal mass) calculated for $[C_7H_9{}^{79}BrN_2 + H]^+$ 201.0027.

2-Bromo-4-dimethylaminopyridine 133 by the method of Fort *et al.*[11]

n-Butyllithium (2.3 M; 12.8 ml) was added dropwise to a solution of 2-dimethyl aminoethanol (1.62 ml; 16×10^{-3} mol) in dry hexane (20 ml) at *ca.* –5 °C. During the addition of the butyllithium the temperature was not allowed to rise above 0 °C. After 15 minutes, solid 4-dimethylaminopyridine (0.48 g; 4×10^{-3} mol) was added during 10 minutes and the reaction mixture was stirred at 0 °C for 1 h. Carbon tetrabromide (6.5 g; 20×10^{-3} mol) in THF (40 ml) was added and the solution was stirred for 1 hour 0 °C and 1 h at room temperature. Hydrolysis was performed at 0 °C with water (20 ml). After aqueous work-up the organic layer was dried ($MgSO_4$) and the solvent evaporated. Column chromatography over silica gel using ether : hexane 50 : 50 as eluant to afford 2-bromo-4-dimethylaminopyridine **133** (0.41 g; 52%).

2-Bromo-4-dimethylaminopyridine prepared in this way was identical in every respect to the 2-bromo-4-dimethylaminopyridine prepared from the diazotisation of 2-amino-4-dimethylaminopyridine **131**.

2-Bromo-4-dimethylaminopyridine 133 by the method of Sammakia *et al.*[13]

Boron trifluoride etherate (2.2 ml; 18.0×10^{-3} mol, 1.1 equiv.) was added dropwise to a solution of 4-dimethylaminopyridine (2 g; 16.3×10^{-3} mol) in dry THF (100 ml) at 0 °C. The solution was stirred at 0 °C for 30 minutes and then cooled to –78 °C. *n*-Butyllithium (2.3 M; 13 ml; 26×10^{-3} mol) was added very slowly to the resultant suspension with vigorous stirring. *N.B.* It is essential that the suspension is stirred and the *n*-butyllithium is added very slowly. After addition of the *n*-butyllithium the solution was stirred at –78 °C for a further 30 minutes after which time bromine (1.35 ml; 26×10^{-3} mol) was added slowly. The reaction was maintained at –78 °C for a further 1 h and then allowed to warm to room temperature. Hydrolysis was performed with methanol, then saturated sodium bicarbonate (30 ml) was added. The aqueous solution was extracted with ether (3 × 60 ml). The organic layers were combined, dried (Na_2SO_4) and evaporated to give an orange solid. Chromatography over silica gel using ether : hexane 50 : 50 afforded 2,6-dibromo-4-dimethylaminopyridine **140** (0.22 g; 5%) and 2-bromo-4-dimethylaminopyridine **133** (2.3 g; 70%).

As was the case with the method of Fort *et al.*[11] 2-bromo-4-dimethylaminopyridine **133** synthesised by this method was identical in every respect to previously.

2,6-Dibromo-4-dimethylaminopyridine 140

Side product isolated from the synthesis 2-bromo-4-dimethylaminopyridine **133** by the method of Sammiakia *et al.*[13]

ν_{max} (N) 2956, 1585, 1461, 1376, 1166, 1079, 979, 964, 809, 723 and 599 cm^{-1}.

δ_H ($CDCl_3$) 3.00 (6H, s, $N(CH_3)_2$) and 6.63 (2H, s, H-3 + H-5).

δ_C ($CDCl_3$) 38.98 ($N(CH_3)_2$), 108.49 (C-3 + C-5), 140.31 (C-4) and 156.22 (C-2 + C-6).

MS (ES): Found*: m/z* 278.9459 (nominal mass) calculated for $[C_7H_8{}^{79}Br_2N_2 + H]^+$ 278.0954.

2-Amino-4-(1'-pyrrolidinyl)pyridine *N*-oxide 134

This compound was prepared as nucleophilic displacement of a nitro group from the 4-position of 2-amino-nitropyridine *N*-oxide **128**. Typically procedure is as follows. It did not prove possible to isolate and characterise completely this compound. NMR data shown below was elucidated from the ^1H NMR spectrum of the crude material.

To a pressure tube was added 2-amino-4-nitropyridine *N*-oxide **128** (1.0 g; 6.4×10^{-3} mol) and pyrrolidine (10 ml, 10-12 eq.) and the reaction was heated to 120 °C for 18 h. The reaction mixture was then diluted with chloroform and washed with brine (2 × 20 ml). The organic layer was dried ($MgSO_4$), and evaporated to give the crude mixture.

δ_H ($CDCl_3$) 2.00 (4H, m, H-2' + H-5'), 3.28 (4H, m, H-3' + H-4'), 5.5 (2H, bs, NH_2), 5.7 (1H, d, *J* 3.0), 5.90 (1H, dd, J_1 3.0, J_2 7.5, H-3) and 7.79 (1H, d, *J* 7.5, H-6) ppm.

2-Acetamido-4-nitropyridine *N*-oxide 135

2-Amino-4-nitro-pyridine *N*-oxide **128** (0.56 g; 3.6×10^{-3} mol) was dissolved in acetic anhydride (2.0 ml) to which was added 4-dimethylaminopyridine (0.0175 g; 4 mol%). The reaction mixture was left stirring at room temperature for 28 h. The acetic acid formed and the acetic anhydride were removed *in vauco*. The crude material was diluted with ethanol and heated to dissolve the insoluble acetamide. The solution was then left to crystallise overnight at room temperature and then at -20 °C for 3 h, to afford 2-acetamido-4-nitropyridine *N*-oxide **135** (0.37 g; 52%), m.p. 203-204 °C, *lit.*[37] 206 °C.

ν_{max} (N) 3237, 2951, 1707, 1617, 1526, 1462, 1376, 1345, 1288, 1220, 1077, 1003, 959, 900, 833, 737, 667 and 655 cm^{-1}.

δ_H ($CDCl_3$) 2.37 (3H, s, CH_3), 7.84 (1H, dd, J_1 2.0, J_2 7.0, H-5), 8.35 (1H, d, J 7.0, H-6), 9.27 (1H, d, J 3.0, H-3) and 9.82 (1H, bs, N-H) ppm.

δ_C ($CDCl_3$) 24.43 (CH_3), 108.41 (C-3), 112.23 (C-5), 137.03 (C-6), 143.44 (quat., C-2), 144.46 (quat., C-4) and 168.25 (C=O).

MS (ES): Found *m/z* 220.0683 (nominal mass) calculated for $[C_7H_7N_3O_4 + Na]^+$ 220.0334.

4-Dimethylamino-2-methylsulfanylpyridine 136

This compound was prepared by the method of Fort *et al.*[11] using 4-dimethylaminopyridine (0.48 g; 4.0×10^{-3} mol), 2-dimethylaminoethanol (1.62 ml; 8.0×10^{-3} mol), n-butyllithium (1.6 M; 12.8×10^{-3} mol) and dimethyldisulphide (1.8 ml; 20×10^{-3} mol). Yield 0.43 g (66%).

ν_{max} (N) 2923, 2854, 1591, 1530, 1441.58, 1373.40, 1271, 1223, 1134, 1093, 984, 910, 801 and 705 cm^{-1}.

δ_H ($CDCl_3$) 2.40 (3H, s, SCH_3), 2.80 (6H, s, $N(CH_3)_2$), 6.12 (1H, dd, J_1 2.5, J_2 6.0, H-5), 6.22 (1H, d, J 2.0, H-3) and 7.92 (1H, d, J 6.0, H-6) ppm.

δ_C ($CDCl_3$) 12.79 (SCH_3), 38.42 ($N(CH_3)_2$), 102.29 (C-5), 103.41 (C-3), 148.40 (C-6), 153.69 (quat., C-4) and 159.23 (C-2) ppm.

MS (ES): Found *m/z* 169.1523 (nominal mass) calculated for $[C_8H_{12}N_2S + H]^+$ 169.0799.

4-Dimethylamino-2,6-dimethylsulfanylpyridine 137

This compound was a side product from the synthesis of 4-dimethylamino-2-methylsulfanylpyridine **136** above. Yield 0.20 g (24%).

δ_H ($CDCl_3$) 2.58 (6H, s, $(SCH_3)_2$), 2.96 (6H, s, $N(CH_3)_2$) and 6.23 (2H, s, H-3 + H-5) ppm.

δ_C ($CDCl_3$) 12.79 (SCH_3), 38.42 ($N(CH_3)_2$, 104.41 (C-3 + C-5), 153.69 (quat., C-4) and 159.01 (C-2) ppm

MS (ES): Found *m/z* 215.0995 (nominal mass) calculated for $[C_9H_{15}N_2S_2 + H]^+$ 215.0677.

2-Methoxypyridine *N*-oxide 141

Sodium methoxide (2.51 g; 1.2 equivalents) was added during 20 minutes to a solution containing 2-chloropyridine *N*-oxide **126** (5 g; 38×10^{-3} mol) in methanol (100 ml). The reaction mixture was refluxed until t.l.c analysis revealed complete consumption of 2-chloropyridine *N*-oxide. The mixture was then filtered to remove sodium chloride and the methanol evaporated. To the residue was added ethyl acetate and very sparingly soluble product was then filtered and dried to give **141** as a white a solid (4.45 g; 92%), m.p. 78-79 °C (from ethyl acetate), *lit.*[38] 79 °C.

ν_{max} (N) 2922, 2852, 1647, 1607, 1565, 1507, 1460, 1376, 1315, 1283, 123, 1215, 1180, 1163, 1120, 1054, 1010, 938, 838, 760 and 726 cm^{-1}.

δ_H ($CDCl_3$) 3.97 (3H, s, OMe), 6.82 (1H, t, *J* 9.0, H-5), 6.86 (1H, d, *J* 8.0, H-6), 7.28 (1H, t, *J* 9.0, H-4) and 8.13 (1H, d, *J* 6.0, H-3) ppm.

δ_C ($CDCl_3$) 56.75 (CH_3), 107.70 (C-5), 117.12 (C-3), 127.34 (C-6), 139.67 (C-4) and 158.32 (C-2) ppm.

MS (ES): Found *m/z* 148.1175 (nominal mass) calculated for $[C_6H_7NO_2 + Na]^+$ 148.0375.

2-Methoxy-4-nitropyridine *N*-oxide 142 prepared by the method of Den Hertog *et al.*[14]

2-Methoxypyridine *N*-oxide **141** (1 g; 8×10^{-3} mol) was dissolved at 0 °C in concentrated sulphuric acid (2 ml). To this solution was added a mixture of concentrated sulphuric acid (2 ml) and fuming nitric acid (3 ml) ensuring the temperature was kept below 5 °C. The mixture was heated for 3 h at 75 °C. The

reaction mixture was then poured on to ice and was neutralised to pH 7 with concentrated ammonia solution (d 0.88). The aqueous layer was then extracted with dichloromethane (5 × 20 ml). The organic layers were combined, dried ($MgSO_4$) and evaporated to give a solid whose composition by NMR was 2-methoxy-4-nitropyridine *N*-oxide **142** (90%) and 2-methoxy-5-nitropyridine *N*-oxide **143** (10%). Chromatography over silica gel using chloroform : methanol 90 : 10 as mobile phase gave 2-methoxy-4-nitropyridine *N*-oxide **142** (0.64 g; 47%), m.p. 155.9-156.8 °C, *lit.*[39] m.p. 154-158 °C.

2-Methoxy-4-nitropyridine *N*-oxide 142

ν_{max} (N) 2920, 1654, 1608, 1560, 1508, 1458, 1376, 1345, 1317, 1211, 1179, 114, 1086, 1010, 873, 836, 799, 767 and 721.7 cm^{-1}.

δ_H ($CDCl_3$) 4.19 (3H, s, OMe), 7.74 (1H, d, *J* 3.0, H-3), 7.79 (1H, dd, J_1 3.0, J_2 7.0, H-5) and 8.36 (1H, d, *J* 7.0, H-6) ppm.

δ_C (DMSO) 58.12 (OCH_3), 102.98 (C-5), 112.35 (C-3), 139.97 (C-6), 142.49 (C-2 and 159.10 (C-4) ppm.

MS (ES): Found *m/z* 171.1179 *calculated for* $[C_6H_6N_2O_4 + H]^+$ 171.0406.

2-Methoxy-5-nitropyridine *N*-oxide 143

Side product isolated from the synthesis of 2-Methoxy-4-nitropyridine *N*-oxide 17 above. Yield 0.08 g (6%), m.p. 157.2-158.1 °C, *lit.*[40] 161-162 °C.

ν_{max} (N) 2914, 1615, 1554, 1462, 1376, 1309, 1224, 1138, 1080, 1002, 955, 881, 829, 819,782 and 739 cm^{-1}.

δ_H ($CDCl_3$) 4.21 (3H, s, OMe), 7.00 (1H, d, *J* 9.5, H-3), 8.10 (1H, dd, J_1 2.5, J_2 9.5, H-4) and 9.16 (1H, d, *J* 2.5, H-6) ppm.

δ_C (DMSO) 58.2 (OCH_3), 107.32 (C-3), 121.92 (C-4), 135.46 (C-6), 139.08 (C-5) and 162.74 (C-2) ppm.

MS (ES): Found *m/z* 171.1179 (nominal mass) calculated for $[C_6H_6N_2O_4 + H]^+$ 171.0406.

Synthesis of 2-methoxy-4-nitropyridine *N*-oxide 142 by the method of Millar *et al.*[15]

2-Methoxypyridine *N*-oxide **141** (20 g; 160×10^{-3} mol) was added to concentrated sulphuric acid (60 ml) at 0 °C. A 3 : 1 mixture of fuming nitric acid and concentrated sulphuric acid (110 ml) was added during 40 minutes. The reaction mixture was heated to 90 °C for 3 h. After cooling the mixture was neutralised with concentrated ammonia (d 0.88) to pH 7, ensuring the temperature did not rise above 10 °C. The mixture was extracted with DCM (6 × 100 ml). The extracts were combined and dried ($MgSO_4$) and the solvent evaporated to give the crude mixture. Chromatography over silica gel using DCM : MeOH 90 : 10 as mobile phase gave 2-methoxy-4-nitropyridine **150**, 2-methoxy-5-nitropyridine **151**, 2-methoxy-4-nitropyridine *N*-oxide **142** (5.0 g; 21%) and 2-methoxy-5-nitropyridine *N*-oxide **143** (1.0 g; 4%).

The 2-methoxy-4-nitropyridine *N*-oxide **142** and 2-methoxy-5-nitropyridine *N*-oxide **143** prepared by this procedure were identical in every respect to the 2-methoxy-4-

nitropyridine *N*-oxide **142** and 2-methoxy-5-nitropyridine *N*-oxide **143** synthesised by the method of Den Hertog *et al.*[14]

Compounds 2-Methoxy-4-nitropyridine **150** and 2-methoxy-5-nitropyridine **151** were side products isolated as a mixture from the synthesis of 2-methoxy-4-nitropyridine *N*-oxide **142** by the method of Millar *et al.*[14] above. These compounds were not separable by chromatography.

2-Methoxy-4-nitropyridine 150

Yield 2.9 g (12%, calculated from the ^{1}H NMR spectrum of the crude mixture, which revealed that both isomers were present in almost equal abundance).

δ_H ($CDCl_3$) 4.02 (3H, s, OMe), 7.44 (1H, d, *J* 2.5, H-3), 7.57 (1H, dd, J_1 2.0, J_2 7.0, H-5) and 8.35 (1H, d, *J* 7.0, H-6) ppm.

2-Methoxy-5-nitropyridine 151

Yield 3.1 g (13%).

δ_H ($CDCl_3$) 4.05 (3H, s, OMe), 6.85 (1H, d, *J* 12.0, H-3), 8.40 (1H, dd, J_1 4.0, J_2 12.0 H-4) and 9.07 (1H, d, *J* 4.0, H-6) ppm.

4-Amino-2-methoxypyridine 144

2-Methoxy-4-nitropyridine *N*-oxide **142** (5.18 g; 3.0×10^{-2} mol) was dissolved in acetic acid (40 ml). To this was added iron filings (5 g; 8.9×10^{-2} mol). The reaction mixture was heated on a water bath at 100 °C for 3 h. The reaction mixture was

poured on to ice/water and neutralized to pH 14 with 30% NaOH. The aqueous layer was extracted with ether (5 × 75 ml) The ether extracts were combined, dried (Na_2SO_4) and evaporated to give 4-amino-2-methoxypyridine **144** (3.5 g; 93%), m.p. 89 °C, *lit.* [41] m.p. 88-90 °C.

ν_{max} (N) 3390, 3310, 3179, 1604, 1461, 1377, 1202, 1091, 1040, 974, 843, 801, 770 and 722 cm^{-1}.

δ_H ($CDCl_3$) 3.90 (3H, s, OCH_3), 4.10 (2H, bs, NH_2), 5.95 (1H, d, *J* 2.0, H-3), 6.23 (1H, dd, J_1 3.0, J_2 6.0, H-5) and 7.84 (1H, d, *J* 6.0, H-6) ppm.

δ_C ($CDCl_3$) 52.83 (OCH_3), 93.62 (C-5), 105.14 (C-3), 146.84 (C-6), 154.58 (quat., C-4) and 165.17 (quat., C-2) ppm.

4-Chloro-2-methoxypyridine 145

4-Amino-2-methoxypyridine **144** (3.2 g; 2.6×10^{-2} mol) was added with stirring to concentrated HCl (20 ml) cooled on a ice bath 5 °C. The reaction mixture was then cooled to -10 °C. A solution of sodium nitrite (5.7 g; 8.2×10^{-2} mol) in water (6 ml) was added dropwise. The temperature was not allowed to rise above 5 °C. After addition of the sodium nitrite solution the reaction mixture was stirred at 5 °C for a further 30 minutes then heated to 80 °C for one hour. Upon cooling the mixture was poured onto ice and basified with 30% NaOH, making sure the temperature did not rise above 0 °C. The aqueous layer was extracted with ether (3 × 100 ml), dried (Na_2SO_4) and the solvent removed to give 4-chloro-2-methoxypyridine **145** (2.9 g; 80%), m.p. 25 °C, *lit.* [16]m.p. 26 °C.

ν_{max} (L) 3063, 3011, 2927, 2852, 1587, 1558, 1462, 1387, 1308, 1278, 1258, 1225, 1179, 1103, 1085, 1059, 1034, 985, 863, 855, 805, 710 and 619 cm^{-1}.

δ_H ($CDCl_3$) 3.88 (3H, s, CH_3), 4.14 (2H, bs, NH_2), 5.93 (1H, d, *J* 2.0, H-3), 6.21 (1H, dd, J_1 2.0, J_2 6.0, H-5) and 7.83 (1H, d, *J* 6.0, H-6) ppm.

δ_C ($CDCl_3$) 53.33 (OCH_3), 110.54 (C-5), 117.01 (C-3), 144.84 (C-4), 147.07 (quat., C-4) 164.46 and (quat., C-2) ppm.

4-Dimethylamino-2-methoxypyridine 146

This compound was prepared by the method of Cho *et al.*[17]

Diethanolamine (1.39 g; 13.2×10^{-3} mol, 2.5 equiv.) was added to solution of 4-chloro-2-methoxypyridine **145** (0.760 g; 5.3×10^{-3} mol) in dry DMF (6 ml) and the mixture was heated in a pressure tube at 130 °C for 21 h. Upon cooling, the reaction mixture was poured onto ice/water mixture (10 ml) and extracted with ether (5 × 20 ml). The ether layers were combined and washed with brine (3 × 20 ml), dried (Na_2SO_4) and concentrated *in vacuo*. Chromatography over silica gel using DCM : MeOH 98 : 2 afforded 4-dimethylamino-2-methoxypyridine **146** (0.65 g; 80%) as a colourless oil.

ν_{max} (L) 3407, 2944, 1611, 1543, 1456, 1407, 1376, 1316, 1259, 1156, 1115, 1051, 986, 866, 815, 735 and 664 cm^{-1}.

δ_H ($CDCl_3$) 2.90 (6H, s, $N(CH_3)_2$), 3.85 (3H, OMe), 5.82 (1H, d, *J* 2.5, H-3), 6.19 (1H, dd, J_1 2.5, J_2 6.0, H-5) and 7.80 (1H, d, *J* 6.0, H-6) ppm.

δ_C ($CDCl_3$) 38.66 ($N(CH_3)_2$), 52.57 (OMe), 90.18 (C-5), 102.17 (C-3), 146.13 (C-6), 156.41 (quat., C-4) and 165.17 (quat., C-2) ppm.

MS (ES): Found *m/z* 153.0245 (nominal mass) calculated for $[C_8H_{12}N_2O_1 + H]^+$ 153.1028.

2-Methoxy-4-(1'-pyrrolidinyl)pyridine 147

4-Chloro-2-methoxypyridine **145** (1.00 g; 7.0×10^{-3} mol) was added to *N*-methyl-2-pyrrolidinone (8 ml) in a pressure tube. To this was added pyrrolidine (3 ml; 3.6×10^{-2} mol) and the mixture was heated with stirring at 90 °C for 24 h. The mixture was then poured into water and extracted with ether (3×50 ml), dried ($NaSO_4$) and the solvent removed. The pure compound was isolated by chromatography over silica gel using hexane : ethyl acetate 80 : 20 as mobile phase to give 2-methoxy-4-(1'-pyrrolidinyl)pyridine **147** (1.04 g; 84%), m. p. 56 °C.

ν_{max} (N) 2922, 1609, 1547, 1461, 1413, 1377, 1303, 1276, 1223, 1173, 1109, 1053, 978, 814, 787, 759 and 722 cm^{-1}.

δ_H ($CDCl_3$) 2.00 (4H, m, H-3' + H-4'), 3.28 (4H, m, H-2' + H-5'), 3.89 (3H, s, OCH_3), 5.76 (1H, d, *J* 2.0, H-3), 6.11 (1H, dd, J_1 3.0, J_2 6.0, H-5) and 7.82 (1H, d, *J* 6.0, H-6) ppm.

δ_C ($CDCl_3$) 24.83 (C-3' + C-4'), 46.61 (C-2' + C-5'), 52.64 (OCH_3), 89.97 (C-5), 102.68 (C-3), 146.08 (C-6), 153.72 (quat., C-4) and 164.95 (quat., C-2) ppm.

MS (ES): Found *m/z* 179.1030 (nominal mass) *calculated for* $[C_{10}H_{14}N_2O_1 + H]^+$ 179.1184.

4-(1'-Pyrrolidinyl)-2-pyridone 148

2-Methoxy-4-(1'-pyrrolidinyl)pyridine **147** (1.5 g; 8.4×10^{-3} mol) was dissolved in dry DCM (40 ml), cooled to 0 °C under a N_2 atmosphere. To this solution was added boron tribromide (1.0 M in DCM; 25 ml; 3 eq.). The reaction mixture was stirred for 1 h at 0 °C, 1 h at r.t and finally refluxed for 6 h. The excess boron tribromide was decomposed by careful addition of methanol with intermittent cooling. The solution was then refluxed for a further 2 h, dried ($MgSO_4$) and the solvent removed *in vacuo* to yield 4-(1'-pyrrolidinyl)-2-pyridone **148** (1.24 g; 90%), m.p. >250(d) °C (from DCM).

ν_{max} (N) 3257, 2944, 2880, 1611, 1460, 1377, 1256, 1156, 1046, 973, 924, 797 and 722 cm^{-1}.

δ_H ($CDCl_3$) 2.10 (4H, m, C-3' + C-4'), 3.30 (4H, m, C-2' + C-5'), 5.40 (1H, d, *J* 2.0, H-3), 5.76 (1H, dd, J_1 2.0, J_2 7.0, H-5), 7.16 (1H, d, *J* 7.0, H-6) and 12.6 (1H, bs, N-H) ppm.

δ_C ($CDCl_3$) 24.80 (CH_2), 46.82 (CH_2), 92.19 (C-3), 96.67 (C-5), 133.87 (C-6), 155.10 (quat., C-4) and 165.57 (quat., C-2) ppm.

MS (ES): Found *m/z* 165.554 (nominal mass) calculated for $[C_9H_{12}N_2O + H]^+$ 165.1028.

2,3-Dichloro-4-(1'-pyrrolidinyl)pyridine 159

Phosphorus pentachloride (0.12 g; 5.7×10^{-4} mol) was added to solution of 4-(1'-pyrrolidinyl)-2-pyridone **148** (0.1 g; 6.0×10^{-4} mol) in phosphorus oxychloride (0.5 ml). The temperature was raised to 115 ° with stirring for 3 h. The reaction was then cooled to r.t and poured on to an ice/water mixture (10 ml) and neutralised with solid Na_2CO_3. The aqueous layer was extracted with DCM (3 × 20 ml). The organic extracts were combined, dried (Na_2SO_4) and concentrated *in vaco*. Chromatography over silica gel using DCM : MeOH 90 : 10 afforded 2,3-dichloro-4-(1'-pyrrolidinyl)pyridine **159** (0.060 g; 45%) as the only isolable product.

δ_H ($CDCl_3$) 1.9-2.0 (4H, m, H-3' + H-4'), 3.64 (4H, m, H-2' + H-5'), 6.49 (1H, d, *J* 6.0, H-5) and 7.90 (1H, d, *J* 6.0, H-6) ppm.

δ_C ($CDCl_3$) 25.19 (C-3' + C-4'), 50.91 (C-2' + C-5'), 108.76 (C-5), 113.32 (quat., C-3), 143.97 (C-6) 149.51 (quat. C-2) and 152.16 (quat., C-4) ppm.

MS (ES): Found *m/z* 217.1423 (nominal mass) calculated for $[C_9H_{10}Cl_2N + H]^+$ 217.0299.

4-Dimethylaminopyridine *N*-oxide 167

4-Dimethylaminopyridine **54** (4.88 g; 3.9×10^{-2} mol) was dissolved in KOH (0.5M, 400 ml) and to this solution was added with stirring Caro's acid (peroxymonosulfuric acid, H_2SO_5) (24.59 g; 4.0×10^{-2} mol) during 30 minutes. The resulting solution was stirred slowly for 18 h. The solution was then neutralised to pH 7 with concentrated phosphoric acid. Water was evaporated and the product was extracted from the resulting salt cake with boiling chloroform (3 × 100 ml). The organic layer was then

dried ($MgSO_4$) and evaporated to give 4-dimethylaminopyridine *N*-oxide **167** (4.58 g; 83%), m.p 217-218 °C, *lit.*[29] m.p. 216-218 °C (anhydrous). The *N*-oxide was used without further purification but could be recrystallised from chloroform and ether.

ν_{max} (N) 2922, 1701, 1635, 1455, 1376, 1212, 1168, 1026, 951, 823 and 720. cm^{-1}.

δ_H ($CDCl_3$) 3.00 (6H, s, $N(CH_3)_2$), 6.47 (2H, d, *J* 7.5, H-3 + H-5) and 7.91 (2H, d, *J* 7.5, H-2 + H-6) ppm.

δ_C ($CDCl_3$) 38.69 ($N(CH_3)_2$), 107.48 (C-3 + C-5), 138.84 (C-2 + C6) and 148.76 (quat., C-4) ppm.

MS (ES): Found *m/z* 161.0968 (nominal mass) calculated for $[C_7H_{10}N_2O + Na]^+$ 161.0691.

3-Chloro-4-dimethylaminopyridine 168

To 4-dimethylaminopyridine *N*-oxide **167** (5.0 g; 3.6×10^{-3} mol) was added phosphorus oxychloride (0.33 ml; 8.0×10^{-3} mol, 2 equiv.). HCl gas was given off and the reaction was heated for 10 hours on an oil bath at 90 °C. The reaction mixture was quenched with ice and basified with 10% sodium hydroxide solution and then extracted with ethyl acetate (3 × 50 ml). The organic layers were combined and dried (Na_2SO_4) to yield 3-chloro-4-dimethylaminopyridine **168** as an oil (1.26 g; 22%) which had b.p 108 °C at 0.55 mm Hg.

ν_{max} (L) 3387, 2952, 2881, 2832, 2800, 1582, 1508, 1452, 1438, 1402, 1353, 1294, 1252, 1214, 1180, 1157, 1095, 1058, 1037, 987, 956, 915, 821, 775, 751 and 695 cm^{-1}.

δ_H ($CDCl_3$) 2.85 (6H, s, $N(CH_3)_2$), 6.62 (1H, d, *J* 6.0, H-5), 8.10 (1H, d, *J* 6.0, H-6) and 8.21(1H, s, H-2) ppm.

δ_C ($CDCl_3$) 41.7 (CH_3 × 2), 112.72 (C-5), 121.42 (quat., C-3), 147.98 (C-6), 150.44 (C-2) and 155.15 (quat., C-4) ppm.

MS (ES): Found *m/z* 157.1181 (nominal mass) calculated for $[C_7H_9ClN_2 + H]^+$ 157.0532.

3-Bromo-4-dimethylaminopyridine 169

Bromine (0.84 ml; 0.164 mol) was added to solution containing 4-dimethylaminopyridine **54** (1 g; 8.2×10^{-3} mol) and sodium acetate (2 g; 2.4×10^{-3} mol) in acetic acid (10 ml). The solution was stirred for 4 hours. The reaction mixture was then poured into a beaker of water/ice (20 ml) and basified to pH 10 with 30% NaOH. The solution was then extracted with diethyl ether (3 × 50 ml) to afford the crude product. Column chromatography over silica gel using ether : hexane 60 : 40 as the eluant gave the following; 3,5-dibromo-4-dimethylaminopyridine **170** (0.11 g; 5%), m.p. 56 °C; 3,5-dibromo-4-methylaminopyridine **171** (0.09 g; 5%), m.p 83.5°C and 3-bromo-4-dimethylaminopyridine **169** (0.57 g; 35%), b.p. 113-115 °C at 2.0 mm Hg, *lit.*[42] 82-84 °C at 0.5 mm Hg.

3-Bromo-4-dimethylaminopyridine 169

ν_{max} (L) 3406, 2950, 2875, 2848.6, 2796.9, 1581.2, 1501.9, 1454, 1436, 1399, 1347, 1292, 1208, 1177, 1150, 1088, 1056, 1019 and 954 cm^{-1}.

δ_H ($CDCl_3$) 2.90 (6H, s, $N(CH_3)_2$), 6.67 (1H, d, *J* 5.5 , H-5), 8.23 (1H, d, *J* 5.5 , H-6) and 8.47 (1H, s, H-2) ppm.

δ_C ($CDCl_3$) 42.38 ($N(CH_3)_2$), 112.07 (quat., C-3), 113.56 (C-5), 148.4 (C-6), 153.01 (C-2) and 156.95 (quat., C-4) ppm

MS (ES): Found *m/z* 201.0080 calculated for $[C_7H_9{}^{79}BrN_2 + H]^+$ 201.0027.

3,5-Dibromo-4-dimethylaminopyridine 170

Side product from the reaction above.

ν_{max} (L) 3380, 2921, 2877, 1820, 1734, 1654, 1559, 1498, 1451, 1419, 1396, 1219, 1168, 1136, 1100, 1046, 961, 889, 767, 753, 728, 686 and 652 cm^{-1}.

δ_H ($CDCl_3$) 3.01 (6H, s, $N(CH_3)_2$), and 8.50 (2H, s) ppm.

δ_C ($CDCl_3$) 42.01 ($N(CH_3)_2$), 119.27 (quat., C-3 +C-5), 151.58 (C-2 + C-6) and 154.78 (quat., C-4) ppm.

MS (ES): Found *m/z* 279.0304 (nominal mass) calculated for $[C_7H_8{}^{79}Br_2N_2 + H]^+$ 278.9132.

3,5-Dibromo-4-methylaminopyridine 171

Side product from the reaction above.

ν_{max} (N) 2911, 2361, 1684, 1576, 1540, 1461, 1413, 1376, 1223, 1124, 1067, 1037, 886, 818 and 721 cm^{-1}.

δ_H ($CDCl_3$) 3.31 (3H, d, *J* 5.5, $N(CH_3)$), 4.86 (1H, s, N-H) and 8.31 (2H, s, H-2 + H-6) ppm.

δ_C ($CDCl_3$) 33.91 ($NHCH_3$), 107.05 (C-3 + C-5), 148.98 (C-4) and 150.78 (C-2 + C-6) ppm.

MS (ES): Found: *m/z* 265.0071 (nominal mass) calculated for $[C_6H_6{}^{79}Br_2N_2 + H]^+$ 264.8976.

3-Bromo-4-dimethylaminopyridine *N*-oxide 173

3-Bromo-4-dimethylaminopyridine **169** (1 g; 4.9×10^{-3} mol) was dissolved in distilled chloroform and to this was added *m*-chloroperoxybenzoic acid (1.34 g; 1.1 mol equivalents) and the reaction was stirred at room temperature. The extent of the reaction was monitored by t.l.c. After 18 days the insoluble *m*-chlorobenzoic acid was filtered and the organic layer washed with aqueous sodium hydrogen carbonate to remove any residual *m*-chlorobenzoic acid. The organic layer was then dried ($MgSO_4$) and evaporated. The pure compound was isolated by chromatography over silica using chloroform : methanol 90 : 10 as mobile phase to give 3-bromo-4-dimethylaminopyridine *N*-oxide **173** (255 mg; 24%), m.p. 84.5 °C, *lit.*[30] 83-85 °C.

ν_{max} (N) 3381, 2922, 1612, 1493, 1461, 1421, 1376, 1276, 1218, 1061, 948, 888, 824 and 718 cm^{-1}.

δ_H ($CDCl_3$) 2.94 (6H, s, $N(CH_3)_2$), 6.77 (1H, d, *J* 7.0, H-5), 8.03 (1H, dd, J_1 2.5, J_2 7.0, H-6) and 8.32 (1H, d, *J* 3.0, H-2) ppm.

δ_C ($CDCl_3$) 42.40 ($N(CH_3)_2$, 111.48 (quat., C-3), 113.82 (C-5), 137.51 (C-2), 141.74 (C-6) and 149.76 (quat., C-4) ppm.

2,6-Diiodo-4-dimethylaminopyridine *N*-oxide 179

n-Butyllithium (2 M in hexane; 24 ml; 48×10^{-3} mol) was added dropwise at –78 °C to a solution of diisopropylamine (7.2 ml; $51. \times 10^{-3}$ mol) in dry THF (20 ml). After 30 minutes the mixture was allowed to come to room temperature. The LDA solution was then added to a suspension of 4-dimethylaminopyridine *N*-oxide (1.68 g, $13.75 \times$

10^{-3} mol) in THF (200 ml) in a separate flask at –78 °C under nitrogen. After 1 h, iodine (14 g; 48×10^{-3} mol, 4 equiv.) was added as a solution in THF (20 ml) during 20 minutes. The solution was maintained at –78 °C for a further 2 h and then allowed to warm to room temperature. Hydrolysis was performed with water (20 ml) and the mixture was diluted with DCM (150 ml). The organic layer was washed with sodium thiosulphate solution until all free iodine was neutralised. The organic layer was dried ($MgSO_4$) and concentrated *in vacuo*. Chromatography over silica gel using DCM : methanol 90 : 10 as mobile phase afforded 2,6-diiodo-4-dimethylaminopyridine *N*-oxide **179** (2.01 g, 43%), m.p. 191.7-192.7(d) °C (from DCM/ether).

ν_{max} (N) 2967, 2726, 1712, 1598, 1478, 1376, 1303, 1203, 1168, 1151, 1078, 1060, 966, 890, 819 and 721 cm^{-1}.

δ_H ($CDCl_3$) 2.99 (6H, s, $N(CH_3)_2$) and 7.11 (2H, s, H-3 + H-5) ppm.

δ_C ($CDCl_3$) 39.63 ($N(CH_3)_2$, 107.21 (quat., C-2 + C-6), 118.89 (C-3 + C-5) and 146.23 (C-4) ppm.

MS (ES): Found *m/z* 390.8746 (nominal mass) calculated for $[C_7H_8I_2N_2O + H]^+$ 390.8804.

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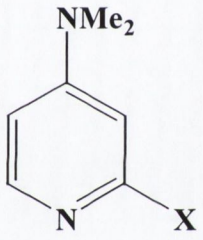
Chapter 3

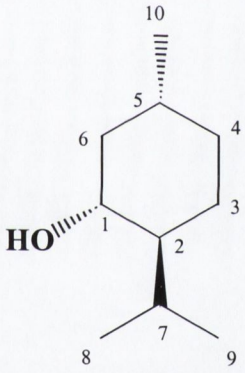
New Chiral Acylation Catalysts

3.1 Synthesis of (–)-2-bornyloxy-4-dimethylaminopyridine and (–)-2-menthyloxy-4-dimethylaminopyridine

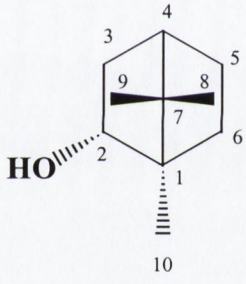
In Chapter 2 several efficient syntheses of the 2-halo-4-dimethylaminopyridines **132** and **133** were reported. It was proposed to exploit these compounds in further chemistry with a view to the introduction of a chiral substituent into the 4-dimethylaminopyridine ring. The chiral handles chosen were the terpenoid alcohols (–)-menthol **181** ((–)-(1*R*, 2*S*, 5*R*)-2-isopropyl-5-methylcyclohexanol) and (–)-borneol **182** ((–)-*endo*-1*S*-1,7,7-trimethylbicyclo[2.2.1]heptan-2-ol).



132 X = Cl
133 X = Br



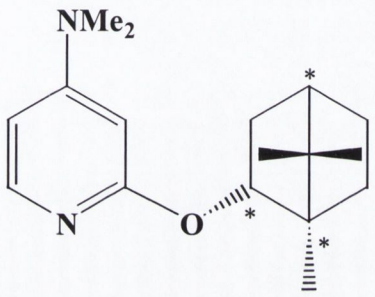
181



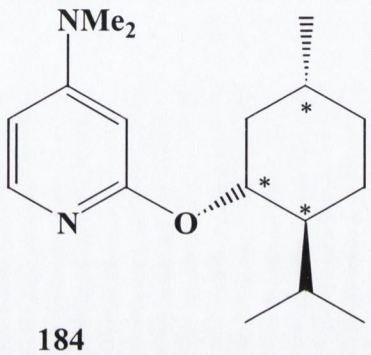
182

Terpenoid alcohols such as **181** and **182** are relatively cheap and are readily available from the chiral pool. Each possesses several asymmetric centres. It was envisaged that reaction of halopyridines **132** and **133** with the sodium salts of **181** and **182** would give the homochiral pyridines, 2-bornyloxy-4-dimethylaminopyridine **183** and 2-menthyloxy-4-dimethylaminopyridine **184**. It was presumed that these chiral groups would provide a sufficiently asymmetric environment about the ring nitrogen to induce enantioselectivity during the catalysis of an acylation reaction.

The displacement of halide anion from the 2-position of pyridines **132** and **133** was not as facile as would be expected. The chloride **132** and the bromide **133** did not undergo nucleophilic displacement upon treatment with the alkoxides derived from the reaction of (–)-borneol or (–)-menthol with sodium hydride in refluxing THF. This result was unusual considering that 2-chloropyridine undergoes easy reaction with the alkoxides derived from (–)-borneol and (–)-menthol.[3]



183



184

* = Chiral centre

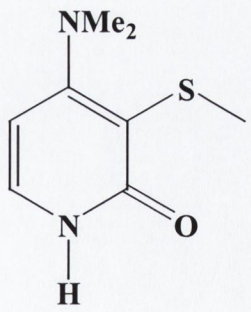
Attention was turned to the use of a higher-boiling solvent and dimethyl sulfoxide was chosen. Reaction of 2-bromo-4-dimethylaminopyridine **133** with the alkoxide of (–)-borneol at 120 °C did result in reaction to give (–)-2-bornyloxy-4-dimethylaminopyridine **183** in 36% yield.

Analysis of the ^{1}H NMR spectrum of (–)-2-bornyloxy-4-dimethylaminopyridine **183** (Figure 3.1) revealed three aromatic protons which resonated at δ 7.84, 6.22 and 5.89 ppm and these were assigned to H-6, H-5 and H-3, respectively. A signal at δ 5.06 ppm was assigned to H-2' (alpha to the ether oxygen). The dimethylamino protons resonated at δ 3.00 ppm. Two singlets at δ 0.91(6H) and 0.99 (3H) ppm were assigned to the 8'-, 9'- and 10'- methyl groups.

Figure 3.1 ^{1}H NMR spectrum of (–)-2-bornyloxy-4-dimethylaminopyridine 183

Analysis of the ^{13}C NMR spectrum of **183** revealed sixteen unique carbon atoms at δ 165.60 (C-2), 156.44 (C-4), 146.48 (C-6), 101.75 (C-3), 91.08 (C-5) 79.66 (C-2'), 48.60 (quat.), 47.16 (quat.), 44. 68 (C-4'), 38.79 (NMe_2), 36.72 (CH_2), 27.68 (C_2), 26.71 (CH_2), 19.39 (Me), 18.63 (Me) and 132.26 (Me) ppm. Subsequent DEPT 90 and 135 experiments confirmed the presence of four quaternary carbon atoms (C-2, C-4, C-1' and C-7'), three methylene carbons (C-3', C-5' and C-6') and five methine carbons (C-3, C-5, C-6, C-2' and C-4'), all consistent with the structure of (–)-2-bornyloxy-4-dimethylaminopyridine **183**.

However, the yield of (–)-2-bornyloxy-4-dimethylaminopyridine **183** was disappointing (36%) and the reaction was investigated further. A second compound was also isolated which constituted the major product of the reaction. Initially its structure could not be determined beyond any reasonable doubt by conventional spectroscopies such as ^{1}H NMR (Figure 3.2), ^{13}C NMR and mass spectroscopy. Eventually, an X-ray crystal structure (Figure 3.3) revealed the unknown compound to be 4-dimethylamino-3-methylsulfanyl-2-pyridone **185**.



185

The ^{1}H NMR spectrum of this compound **185** (Figure 3.2) showed five signals, which are consistent with the above structure. A singlet at δ 2.31 ppm was assigned

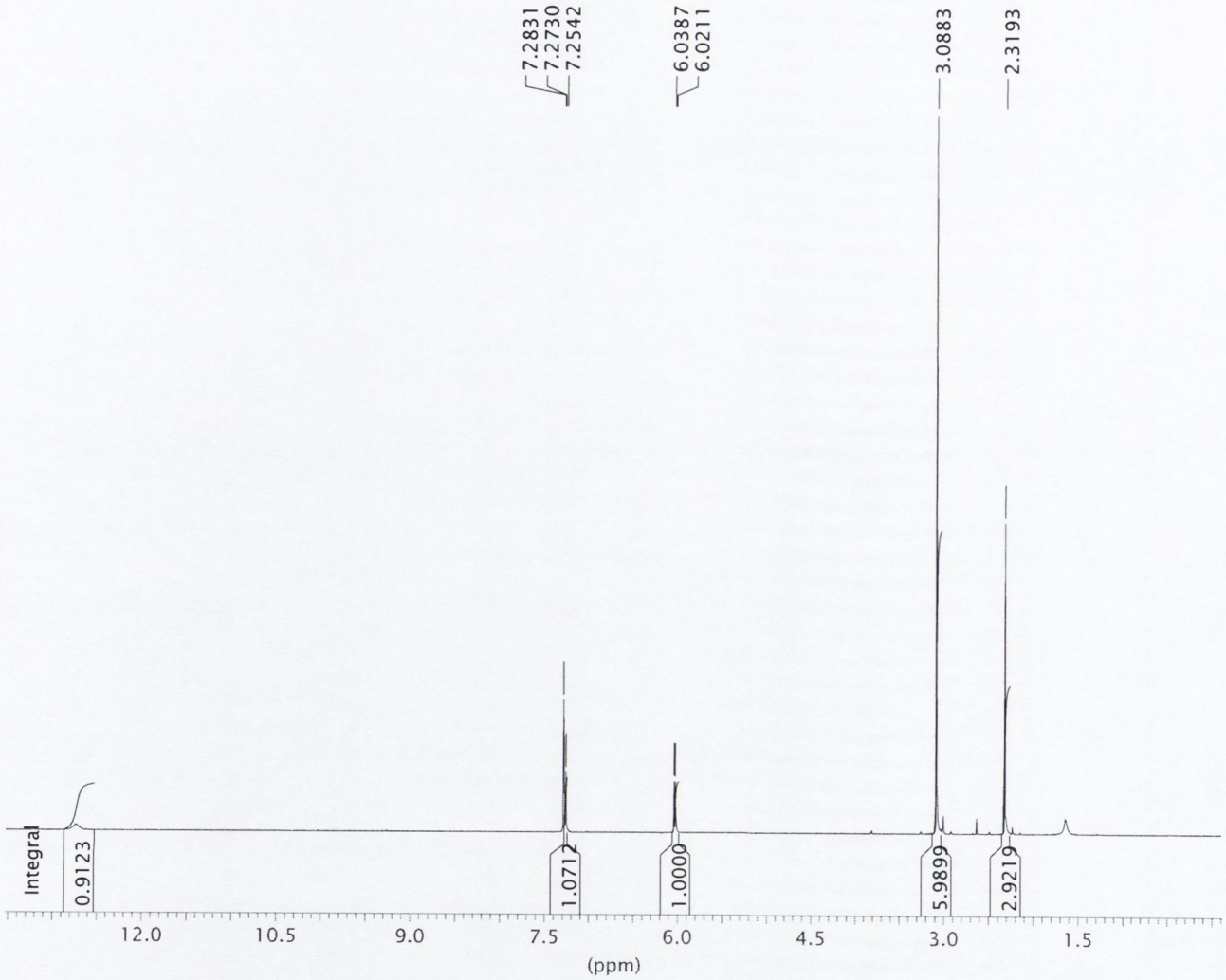
to the methyl group attached to the sulphur atom. The dimethylamino group resonated at δ 3.08 ppm. A ^{1}H doublet at δ 6.02 ppm was assigned to H-5, while H-6 appeared downfield as another doublet (overlapping with the C-H of chloroform) at δ 7.22 ppm.

Analysis of the ^{13}C NMR spectrum of 4-dimethylamino-3-methylsulfanyl-2-pyridone **185** showed seven unique carbon atoms. These resonated at δ 165.43 (C-2), 162.28 (C-4), 132.62 (C-6), 105.58 (C-3), 99.20 (C-5), 40.55 (NMe_2) and 16.70 (SMe) ppm.

Mass spectroscopy gave a nominal mass at 185.0957 (calculated for $[C_8H_{12}N_2OS + H]^+$ 185.0749), a molecular weight in accordance with the structure 4-dimethylamino-3-methylsulfanyl-2-pyridone **185**.

When 2-bromo-4-dimethylaminopyridine **133** was reacted with the alkoxide derived by reaction of sodium hydride with (–)-menthol **181**, the yield of (–)-2-methyloxy-4-dimethylaminopyridine **184** was typically of the order of 5%, while the major product was now 4-dimethylamino-3-methylsulfanyl-2-pyridone **185**. Chromatography easily separated the two compounds and after several reactions a sufficient quantity of (–)-menthyloxy-4-dimethylaminopyridine **184** was isolated for testing as an acylation catalyst.

Figure 3.2 ^{1}H NMR spectrum of 4-dimethylamino-3-methylsulfanyl-2-pyridone 185



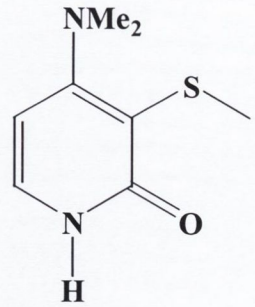
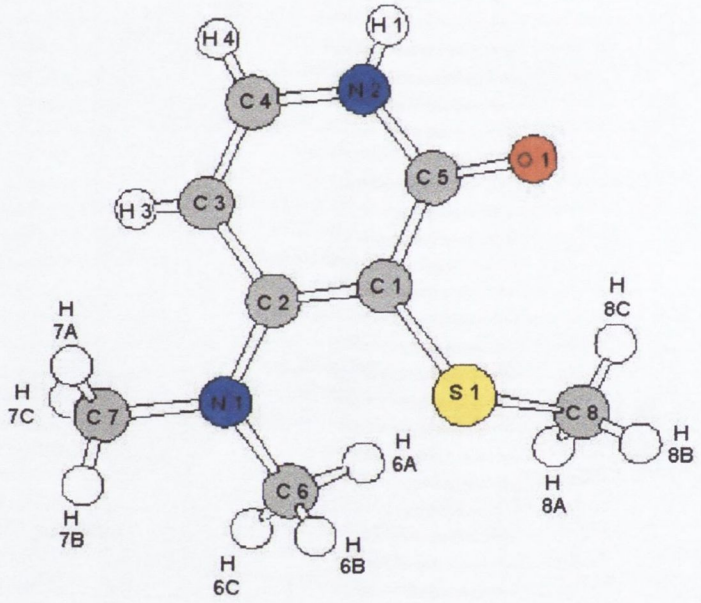


Figure 3.3 X-ray crystal structure of 4-dimethylamino-3-methylsulfanyl-2-pyridone 185



Crystal data: $C_8H_{12}N_2OS$, $M = 184.25$, monoclinic, space group P21/c, $a = 8.5961$ (19), $b = 7.6121$ (16), c = 14.6133 (18) Å, $\alpha = 90$, $\beta = 107.01(14)$, $\gamma = 90°$, $U = 914.4$ (3) $Å^3$, $Z = 4$, $D_c = 1.279$ gcm^{-3}, $T = 293(2)$ K, μ(Mo-Kα) = 0.308 mm^{-1}, $wR_2 = 0.1272$ (1809 reflections collected, 1564 unique), R = 0.056 [I > 2s(I)], ENRAF NONIUS CAD4 diffractometer with graphite monochromator, ω-scans, structure solved by automatic direct methods using SHELXS-86 and refined using full matrix least squares on F^2 using SHELXL-93. All the non-hydrogen atoms were refined anisotropically and the hydrogen atoms were located from subsequent difference Fourier maps.

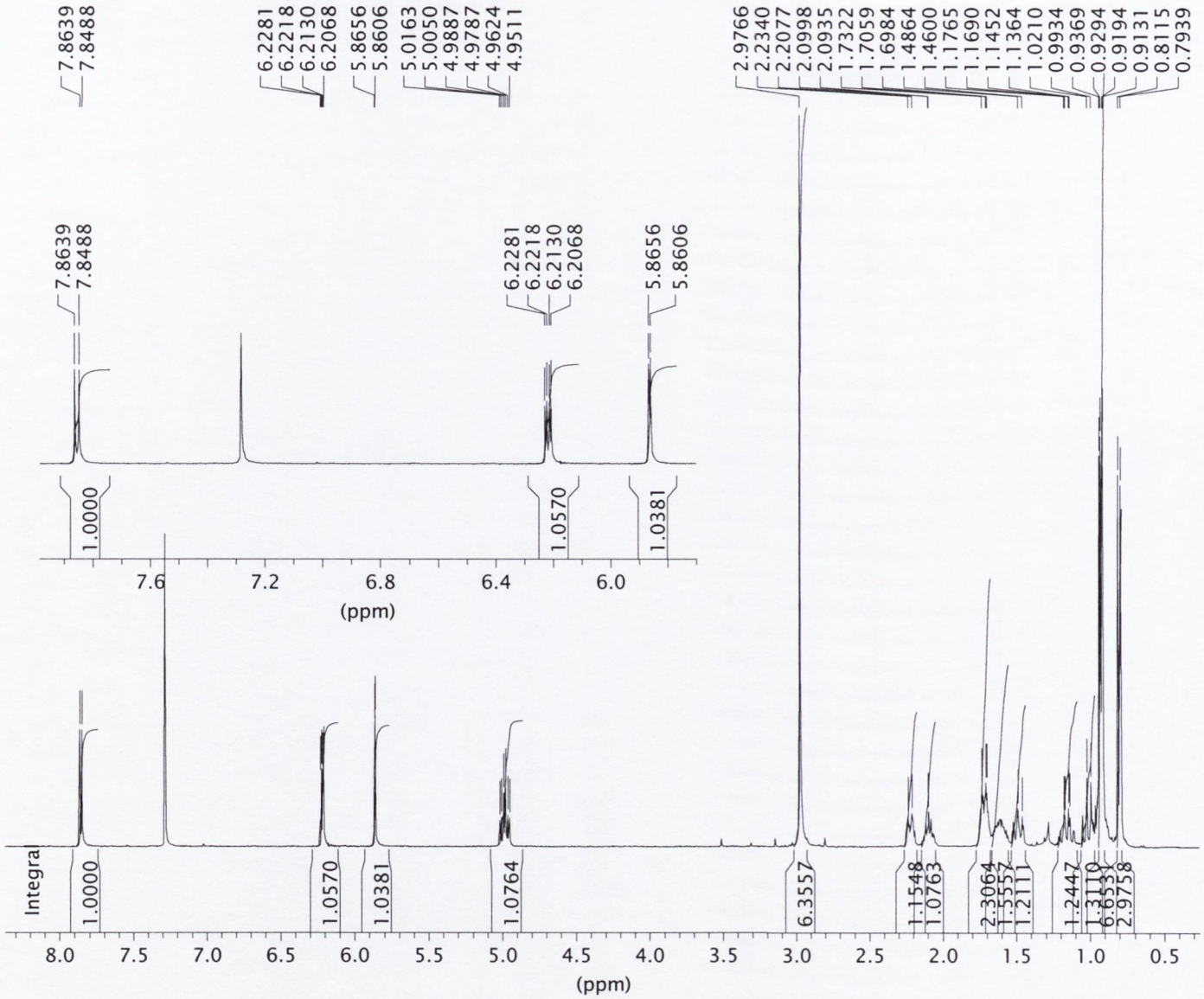
Attempts to improve the yield of 2-menthyloxy-4-dimethylaminopyridine **184** by utilising dry toluene as the solvent and thus avoiding the use of dimethyl sulfoxide met with limited success. Again the yield of **184** was poor, typically 5-8% and the major product from this reaction was 4-dimethylaminopyridine **54**, the product of carbon-halogen bond reduction.

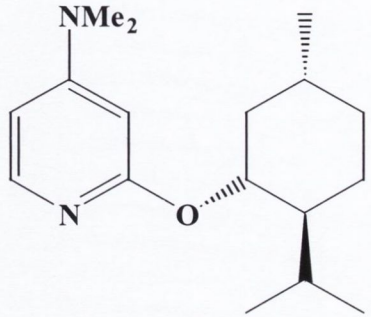
Analysis of the ^{1}H NMR spectrum of (–)-menthyloxy-4-dimethylaminopyridine **184** (Figure 3.4) showed the presence of three aromatic protons at δ 7.85 (H-6), 6.22 (H-5) and 5.87 (H-3) ppm. A double triplet at δ 4.98 ppm was assigned to H-1', a resonance in accordance with its position adjacent to an oxygen atom within the molecule. The dimethylamino protons resonated δ 2.97 ppm. A multiplet at δ 2.09 ppm was assigned to axial proton H-7' of the menthyl group. A triplet at 1.47 ppm was assigned to the proton at H-5'. Two doublets, at δ 0.81 (3H) and 0.92 (6H) ppm, respectively were assigned to the methyl groups attached at C-9' and C-8' and C-10'. These assignments were made in accordance with literature data from the ^{1}H-^{13}C COSY spectrum of (–)-menthol **181**.[1] The formation of the pyridone **185** was unexpected and some preliminary experiments were carried out to probe the mechanism of the reaction.

3.1.1 Possible reaction mechanism for the formation of 4-dimethylamino-3-methylsulfanyl-2-pyridone

Initially it was considered that the alkoxide formed from either of the alcohols **181** and **182** did not play a significant part in the formation of 4-dimethylamino-3-methylsulfanyl-2-pyridone **185** and this was confirmed by simply omitting it from the reaction mixture.

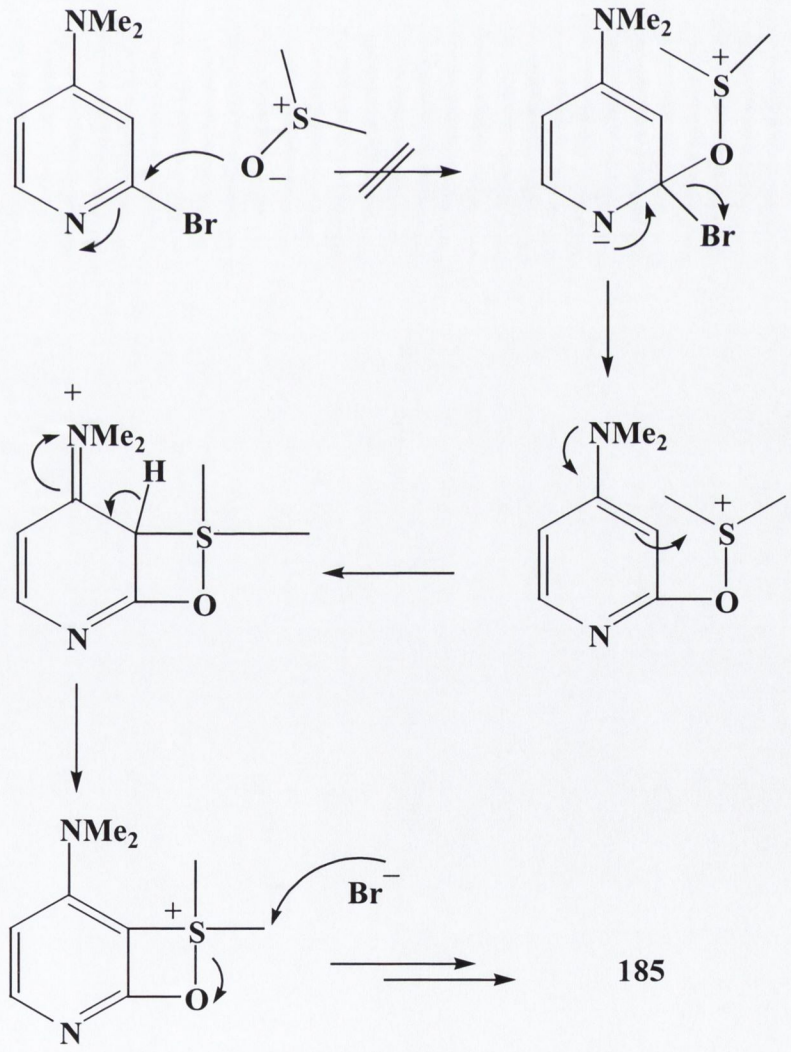
Figure 3.4 ^{1}H NMR spectrum of (–)-2-menthyloxy-4-dimethylaminopyridine 184



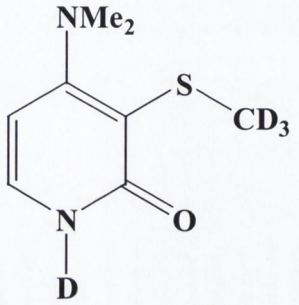


Thus, reaction of 2-bromo-4-dimethylaminopyridine **133** with 1.1 equivalents of sodium hydride in DMSO gave 4-dimethylamino-3-methylsulfanyl-2-pyridone **185** as the sole reaction product. When 2-bromo-4-dimethylaminopyridine **133** was treated with deuteriated DMSO (to facilitate NMR analysis of the reaction mixture) at 120 °C no reaction was observed. This was interpreted as ruling out the possibility that reaction occurs by initial addition of DMSO at C-2, followed by further transformations (Scheme 3.1). Therefore, reaction is dependent on the presence of the base, sodium hydride.

Scheme 3.1



Reaction of 2-bromo-4-dimethylaminopyridine **133** with deuteriated DMSO in the presence of sodium hydride gave the deuteriated pyridone **186** which had a molecular ion of *m/z* 188.0683, (calculated for $[C_8H_8D_4N_2OS + H]^+$ 189.0996). The molecular ion observed is one mass unit less than calculated and this can be accounted for by exchange of the N-D proton to N-H. The proton can come from formic acid, which is used to make up the sample for mass spectroscopy.

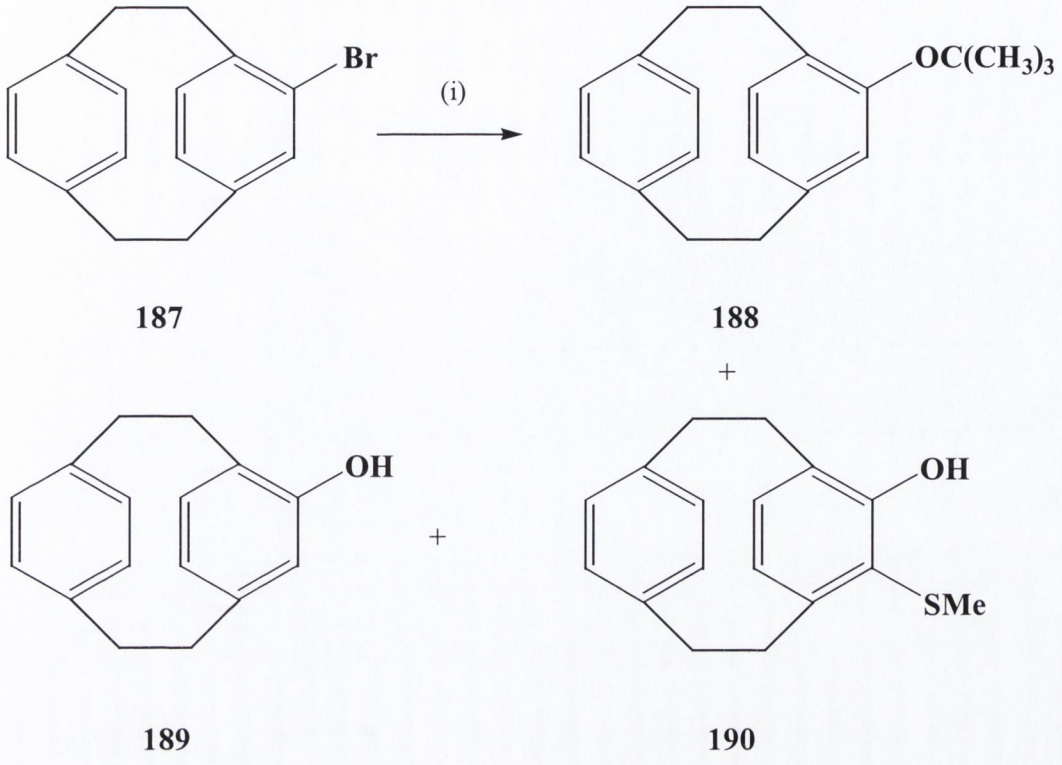


186

It was at this point that a heteroaryne mechanism was suspected to be operating here. Indeed, Cram *et al.*[2] report a similar observation upon treatment of 4-bromo[2.2]paracyclophane **187** with potassium *tert*-butoxide in dimethyl sulfoxide to afford the ether **188**, the phenol **189** and the unexpected thioether **190** (Scheme 3.2).

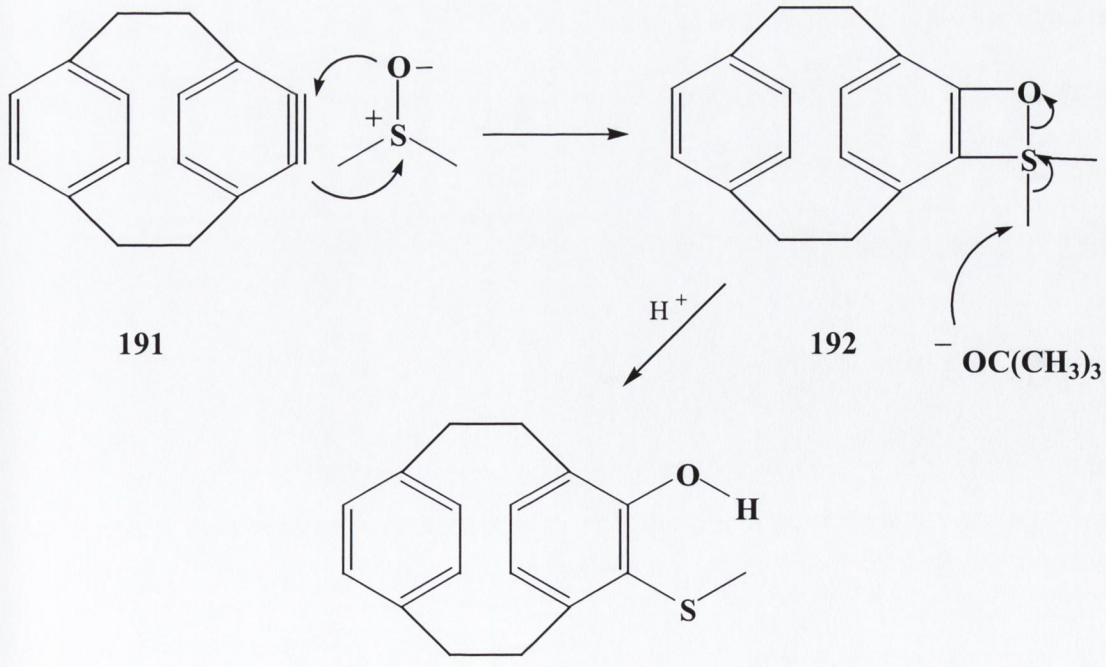
Formation of the thioether **190** was rationalised by initial formation of a heteroaryne **191**, followed by [2 + 2] cycloaddition of a molecule of dimethyl sulfoxide to give the 4-membered intermediate **192**, which then collapses to give the thioether **190** (Scheme 3.3).

Scheme 3.2



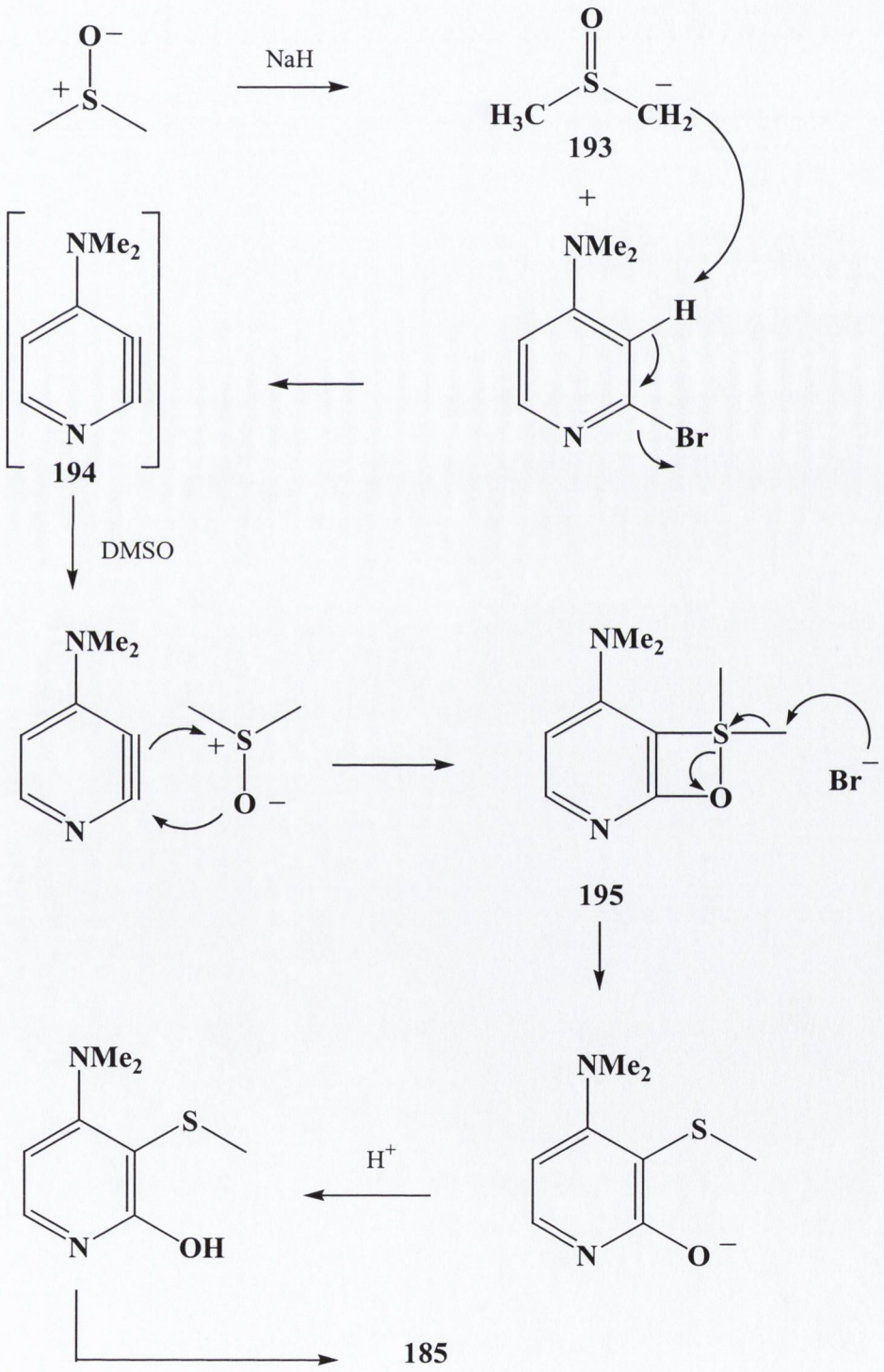
Reagents and Conditions: (i) $(CH_3)_2COK/DMSO$

Scheme 3.3



A similar process is almost certainly involved in formation of 4-dimethylamino-3-methylsulfanyl-2-pyridine **185** from 2-bromo-4-dimethylaminopyridine **133** in the presence of dimethyl sulfoxide and sodium hydride. Thus, a plausible mechanism is depicted in Scheme 3.4.

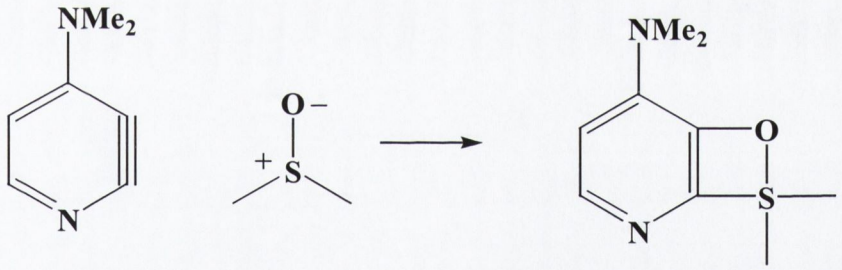
Scheme 3.4



Reaction of sodium hydride with dimethyl sulfoxide results in the formation of the stronger base DIMSYL sodium **193**. Abstraction of H-3 from 2-bromo-4-dimethylaminopyridine **133** leads to the heteroaryne **194**, which almost certainly undergoes [2 + 2] cycloaddition with a molecule of DMSO to give the 4-membered intermediate **195**. Loss of a methyl group from this intermediate gives rise to the collapse of the strained 4-membered ring and formation of 4-dimethylamino-3-methylsulfanyl-2-pyridone **185**.

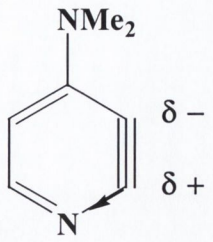
The reaction is regiospecific since each molecule of DMSO adds to the heteroaryne with the oxygen atom entering at C-2 and the sulphur atom at C-3 and not as depicted in Scheme 3.5.

Scheme 3.5



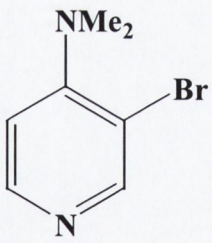
This regiospecificity is due almost totally to polarisation of the triple bond in the heteroaryne **194**. The 2-position of the heteroaryne **194** corresponds to the positive end of the triple bond since it is alpha to the ring nitrogen, which pulls away electron density from this position (Figure 3.5)

Figure 3.5



One way to confirm beyond any reasonable doubt, that a heteroarynic mechanism is leading to the pyridone **185** would be to try and trap the heteroaryne formed *in situ* with a suitable diene such as furan to give the Diels-Alder adduct. However, due to time constraints this experiment was never carried out since the pyridone **185** was not of much synthetic importance in the first place.

Under identical reactions conditions (DMSO and NaH), substitution of 3-bromo-4-dimethylaminopyridine **169** as the aryl halide led only to the formation of 4-dimethylaminopyridine **54**.



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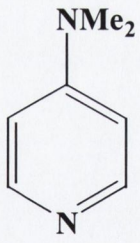

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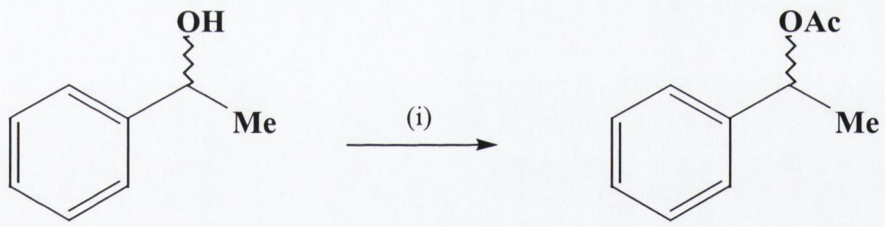
3.1.2 (–)-2-Bornyloxy-4-dimethylaminopyridine 183 and (–)-2-menthyloxy-4-dimethylaminopyridine 184 as acylation catalysts

The acylation of racemic 1-phenylethyl alcohol **17** by acetic anhydride to give ester **196** was investigated using the title compounds as catalysts (Scheme 3.6). 1-Phenylethyl alcohol was chosen as a typical representative secondary alcohol since it has large (phenyl), medium (Me) and small (H) groups at the stereocentre. A number of initial experiments were carried out to ascertain if either of the title compounds were catalysts or not. This simply involved reaction of phenylethyl alcohol with two equivalents of acetic anhydride in the presence of 10 mol% of catalyst (Table 3.1).

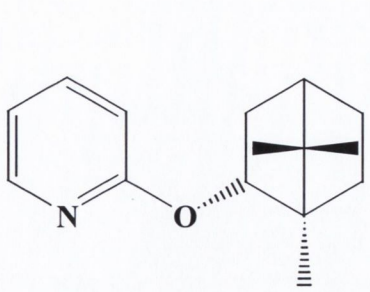
Scheme 3.6



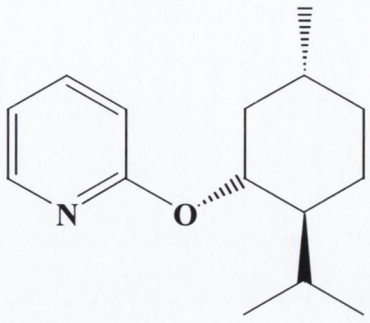
17 **196**

Reagents and Conditions: (i) Phenylethyl alcohol, $(CH_3CO)_2O$ (2.0 eq.), Catalyst 10 mol%

Also tested as acylation catalysts were the compounds (–)-2-bornyloxypyridine **197** and (–)-2-menthyloxypyridine **198**. These compounds had been synthesised previously in our laboratory by Storey[3], however there was no mention of them being used as acylation catalysts.



197



198

Table 3.1 Acylation of 1-phenylethyl alcohol catalysed by compounds 183, 184, 197 and 198

Entry[a]	Catalyst	% Conversion[b]
1	(–)-2-Bornyloxy-4-dimethylaminopyridine **183**	90
2	(–)-2-Menthyloxy-4-dimethylaminopyridine **184**	75
3	(–)-2-Bornyloxypyridine **197**	31
4	(–)-2-Menthyloxypyridine **198**	5
5	None	< 3

(a) 1-Phenylethyl alcohol, acetic anhydride (2 eq.), 18 h, Catalyst 10 mol%; (b) % conversion determined by ^{1}H NMR.

The above table shows that both (–)-2-bornyloxy-4-dimethylaminopyridine **183** and (–)-2-menthyloxy-4-dimethylaminopyridine **184** are efficient catalysts resulting in 90% and 75% conversions of alcohol **17** into ester **196** after sixteen hours. (–)-2-Bornyloxypyridine **197** also shows catalytic activity giving 31% conversion under similar conditions. (–)-2-Menthyloxypyridine **198** is ineffective as a catalyst under these conditions, being no faster than the uncatalysed reaction.

It was hoped that catalysts **183** and **184** would be able to discriminate between the enantiomers of 1-phenylethyl alcohol, thus leading to enantioselective acylation. Accordingly, a number of acylation reactions were carried out which employed 0.5 mol of acetic anhydride per mol of alcohol. The results are given in Table 3.2. *tert*-Amyl alcohol was chosen as the solvent since Ruble *et al.*[4] report that this solvent significantly enhances both rate and enantioselectivity in the acylation of 1-phenylethyl alcohol using catalysts based around the 4-dimethylaminopyridine ring (Chapter 1). This is clearly demonstrated in entries 4 and 5. Under identical conditions 2-bornyloxypyridine **197** gives *ca.* 34% increase in the yield of ester **196** in *tert*-amyl alcohol compared with DCM. Significantly, the *tert*-amyl alcohol is not acylated under these reaction conditions.

As can be seen from entries 1 and 2 (Table 3.2) the presence of triethylamine significantly contributes to the background reaction, thus giving a false impression of the effectiveness of the catalyst. There is a 50% drop in conversion when it is omitted, therefore triethylamine contributes significantly as a catalyst in its own right. This is unusual since both Vedjes[5] and Ruble[4] (as discussed in Chapter 1) utilise this as an auxiliary base in their procedures, which must contribute to the background reaction. Thus, the yield without the auxiliary base is 19% of a maximum of 50%. This was quite impressive considering the amount of **183** used was catalytic (2 mol%).

Table 3.2 Acylation of 1-phenylethyl alcohol catalysed by compounds 183, 184, 197 and 198

Entry[a]	Catalyst	Solvent	Auxiliary Base	Time/h	% Conversion	e.e[c]
1	(–)-2-Bornyloxy-4-dimethylaminopyridine **183** (2 mol%)	*t*-AmOH	Et_3N (50 mol%)	48	37.5	0
2	(–)-2-Bornyloxy-4-dimethylaminopyridine **183** (2 mol%)	*t*-AmOH	-	48	19	0
3	(–)-2-Menthyloxy-4-dimethylaminopyridine **184** (2 mol%)	*t*-AmOH	-	48	14	0
4	(–)-2-Bornyloxypyridine **197** (10 mol%)	*t*-AmOH	-	48	25.4	0
5	(–)-2-Bornyloxypyridine **197** (10 mol%)	DCM	-	48	18.9	0
6	(–)-2-Menthyloxypyridine **198** (10 mol%)	DCM	-	48	9	0
7	None	*t*-AmOH	-	48	0	0

(a) 1-Phenylethyl alcohol (8.2 mmol), acetic anhydride (4.2 mmol), Solvent (5 ml), r.t., 48 h; (b) % conversion determined by ^1H NMR; (c) testing for enantiomeric excess was carried out using polarimetry on both ester and remaining alcohol.

Use of (–)-2-menthyloxy-4-dimethylaminopyridine **184** as catalyst gave a lower yield (14%) under identical conditions (entry 3). Indeed, this trend was also observed when compounds **197** and **198** were utilised as catalysts in the acylation of 1-

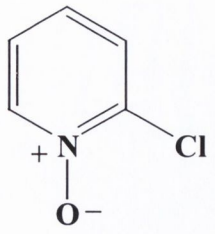
phenylethyl alcohol. (–)-2-Bornyloxypyridine **197** is almost twice as effective as (–)-2-menthyloxypyridine **198** in DCM as solvent. Each of these compounds exhibited moderate activity even at high catalyst concentrations (10 mol%).

Unfortunately, none of the catalysts employed gave material that was optically enriched. Lack of enantioselectivity was attributed to insufficient chiral differentiation around the active site. It was decided that increased differentiation between enantiomers would be possible with molecules containing desirable C_2 symmetry. This will be discussed later on, but the use of *N*-oxides as acylation catalysts will be discussed first.

3.2 Heterocyclic *N*-oxides as acylation catalysts

It had been discovered previously by Gallagher[6] in this laboratory that 4-dimethylaminopyridine *N*-oxide **167** is an efficient acylation catalyst. However, it was not ascertained if this catalytic property was indicative of *N*-oxides as a whole or just confined to the *N*-oxide of 4-dimethylaminopyridine. In order to examine this possibility a whole series of *N*-oxides **126, 141, 167** and **199 - 206** were chosen and studied as catalysts for the acylation of 1-phenylethyl alcohol **17** with two equivalents of acetic anhydride.

2-Chloropyridine *N*-oxide **126** was available commercially from Olin corporation, 4-nitropyridine *N*-oxide **204** and *N*-methylmorpholine *N*-oxide **205** were obtained from Aldrich.



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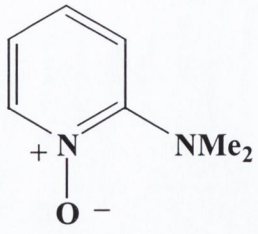

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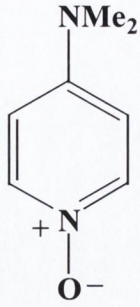

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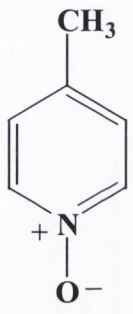

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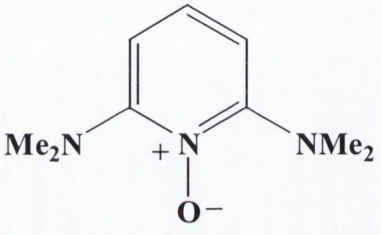

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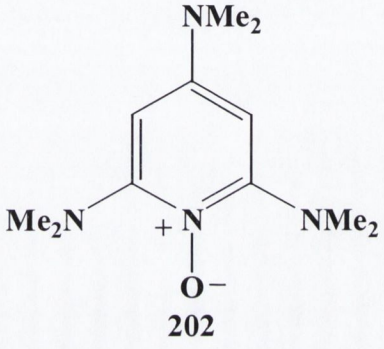

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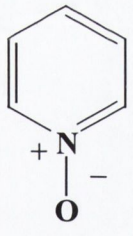

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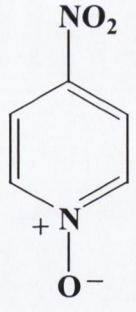

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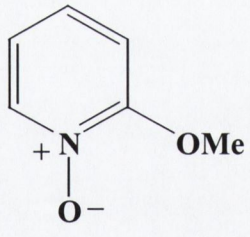

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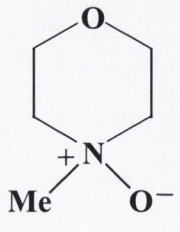

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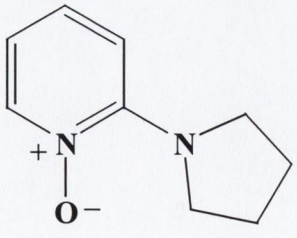


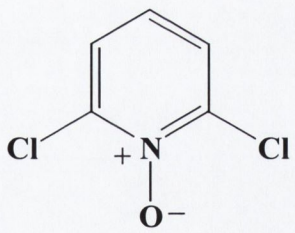
206

2-Dimethylaminopyridine *N*-oxide **199** was synthesised from 2-chloropyridine *N*-oxide **126** by treatment with aqueous dimethylamine solution at 120 °C. Analysis of

the ^{1}H NMR spectrum of 2-dimethylaminopyridine *N*-oxide **199** showed four signals that resonated at δ 8.12 (H-6), 7.17 (H-4), 6.66-6.72 (H-3 + H-5) and 2.90 (NMe_2) ppm. Protons H-3 and H-5 appeared as overlapping multiplets. An unusual aspect of the *N*-oxide **199** is that it is a liquid with boiling point 160 °C at 0.5 mm Hg, which is in agreement with literature observations.[7]

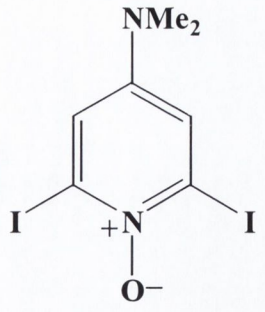
2,6-*bis*(Dimethylamino)pyridine *N*-oxide **201** was synthesised from 2,6-dichloropyridine *N*-oxide **207** by treatment at elevated temperature with an aqueous solution of dimethylamine. 2,6-Dichloropyridine *N*-oxide **207** was synthesised by *N*-oxidation of 2,6-dichloropyridine by the method of Evans *et al.*[8] using trifluoroacetic acid and 30% hydrogen peroxide.

The ^{1}H NMR spectrum of 2,6-*bis*(dimethylamino)pyridine *N*-oxide **201** was very simple and showed three signals with the expected integrals that resonated at δ 7.17 (H-4), 6.48 (H-3 + H-5) and 2.99 (NMe_2) ppm.



207

2,4,6-*tris*(Dimethylamino)pyridine *N*-oxide **202** was obtained from 2,6-diiodo-4-dimethylaminopyridine *N*-oxide **179**, synthesised as described in Chapter 2. Thus, treatment of 2,6-diiodo-4-dimethylaminopyridine *N*-oxide **179** with aqueous dimethylamine in isopropyl alcohol at 130 °C gave **202** in good yield.



179

The ^{1}H NMR spectrum of 2,4,6-*tris*(dimethylamino)pyridine *N*-oxide **202** was again very simple, and showed three signals that resonated at δ 5.20 (H-3 + H-5), 3.04 and 2.97 ppm. A 12H singlet δ 3.04 ppm was assigned to the dimethylamino groups attached at C-2 and C-6 whilst a 6H singlet at δ 2.97 ppm was assigned to the dimethylamino substituent at C-4.

Pyridine *N*-oxide **203** was synthesised from pyridine using the method of Ochiai *et al.*[9] by oxidation with hydrogen peroxide in acetic acid. 4-Dimethylaminopyridine *N*-oxide **167** was prepared by the method of Robke *et al.*[10] while 2-methoxypyridine *N*-oxide **141** had been prepared earlier as described in Chapter 2.

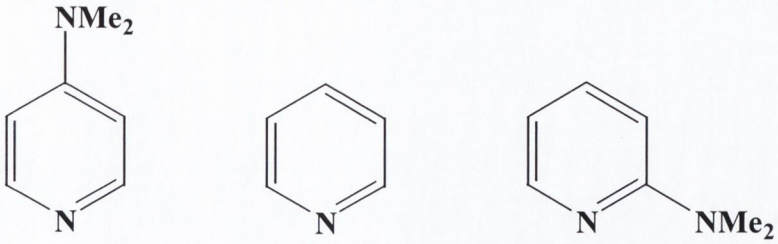
1-Phenylethyl alcohol **17** was reacted with two equivalents of acetic anhydride in the presence of 10 mol% of each of the *N*-oxides listed in order to test for catalytic activity (Table 3.3).

Table 3.3 Acylation of 1-phenylethyl alcohol with acetic anhydride catalysed by the *N*-oxides 126, 141, 1167, 199, 200-205, 208 and 209.

Entry[a]	Catalyst (10 mol%)	% Conversion[b]
1	2-Chloropyridine *N*-oxide **126**	16
2	2,6-*bis*(Dimethylamino)pyridine *N*-oxide **201**	0
3	2-Dimethylaminopyridine *N*-oxide **199**	88
4	4-Dimethylaminopyridine *N*-oxide **167**	100
5	2-Methoxypyridine *N*-oxide **141**	42
6	4-Methylpyridine *N*-oxide **200**	77
7	4-Nitropyridine *N*-oxide **204**	5
8	Pyridine *N*-oxide **203**	60
9	*N*-Methylmorpholine *N*-oxide **205**	11.5
10	2,4,6-*Tris*(Dimethylamino)pyridine *N*-oxide **202**	0
11	None	< 3
12	4-Dimethylaminopyridine **54**	100
13	Pyridine **208**	90%
14	2-Dimethylaminopyridine **209**	15%

(a) 1-Phenylethyl alcohol (1 g, 8.19×10^{-3} mol), acetic anhydride (2 eq.), 16 h, catalyst 10 mol%; (b) % conversion to 1-phenylethyl acetate **196** as determined by ^{1}H NMR.

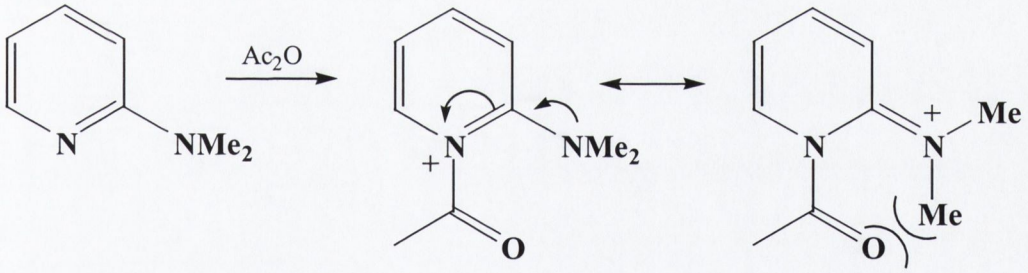
Also tested for comparison were the free bases 4-dimethylaminopyridine **54**, pyridine **208** and 2-dimethylaminopyridine **209** (entries 12 -14). As can be seen from the results obtained, all of the *N*-oxides show catalytic activity when compared to the un-catalysed reaction (entry 11).



54 **208** **209**

At 10 mol% the use of 2-dimethylaminopyridine *N*-oxide **199** results in 88% conversion of the starting alcohol into the corresponding acetate. This result is surprising, since the free base 2-dimethylaminopyridine **209** is essentially ineffective giving only 15% conversion after 16 hours. Schofield[11] reports that the lack of catalytic activity in 2-substituted pyridines is probably due to steric hindrance (Scheme 3.7).

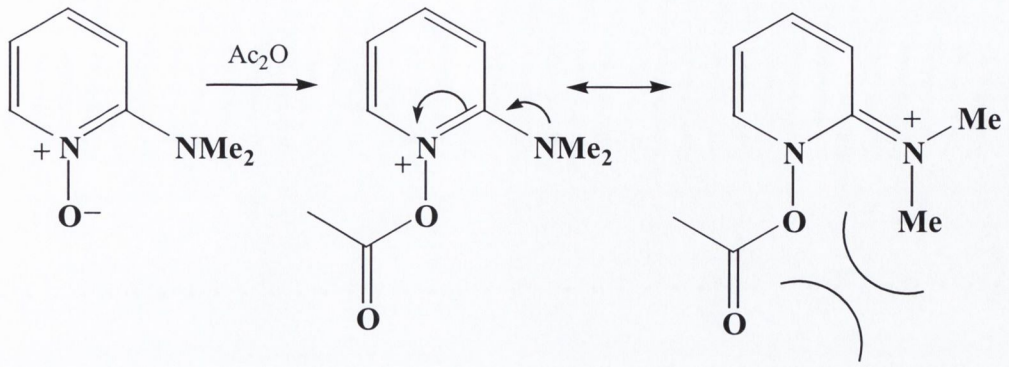
Scheme 3.7



Sterically hindered

This increase in activity in 2-dimethylaminopyridine *N*-oxide **199** can be attributed to the acyl group being one bond further away from any steric constraints the dimethylamino group in the 2-position inflicts on the active site of the molecule (Scheme 3.8).

Scheme 3.8

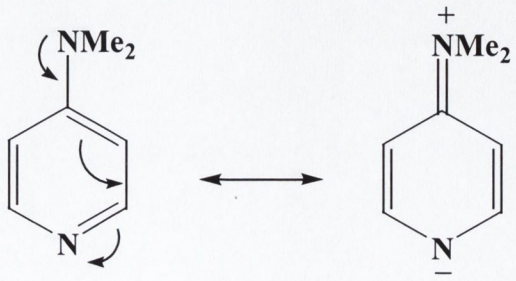


Less steric hindrance

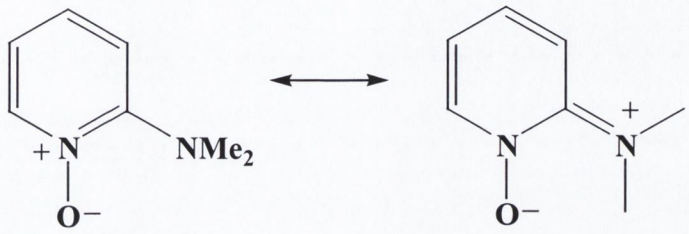
The fact that the *N*-oxide of 2-dimethylaminopyridine **199** is as effective a catalyst as pyridine has important practical consequences. It appears that in order to develop efficient pyridine-based catalysts it may not be necessary to have a dimethylamino substituent in the 4-position to achieve an acceptable rate of reaction.

It is generally accepted that the catalytic effectiveness of 4-dialkylaminopyridines compared to that of pyridine is caused by nucleophilicity.[12] If the resonance structures of 4-dimethylaminopyridine **54** are examined it can be seen that electron drift from the exocyclic nitrogen into the ring nitrogen enhances this nucleophilicity (Scheme 3.9).

Scheme 3.9



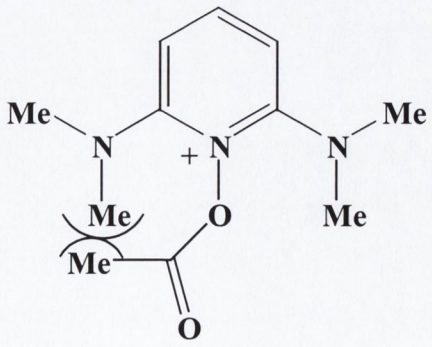
This increased nucleophilicity is also possible with 2-dialkylaminopyridines but steric factors limit this effect. Use of the corresponding *N*-oxide **199** avoids steric constraints while still achieving an acceptable rate of reaction. Thus, the resonance structure **210** represents a more nucleophilic canonical form than **199**.



199 **210**

On this basis it was thought that the catalytic activity of 2-dimethylaminopyridine *N*-oxide **199** might be diminished by steric factors due to the introduction of a second dimethylamino substituent at C-6 to give the C_2 symmetric 2,6-*bis*(dimethylamino)pyridine *N*-oxide **201**. As expected this compound showed no catalytic activity whatsoever, a result that can be rationalised by steric hindrance as shown in Figure 3.6.

Figure 3.6

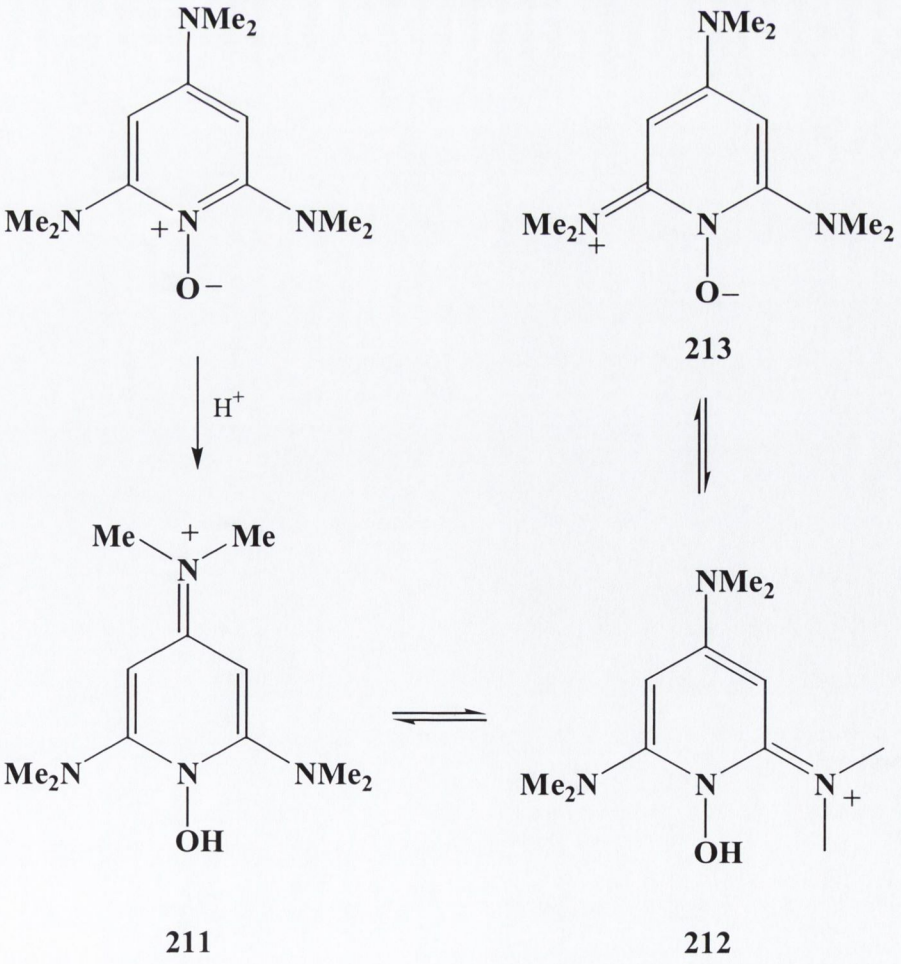


Steric hindrance

It was noticed that this compound was quite unstable with decomposition usually occurring after a couple of days. It also turned an intense blue colour in solution after a period of time (typically 36 h or more).

It was thought that 2,4,6-*tris*(dimethylamino)pyridine *N*-oxide **202** might be a superior hypernucleophilic acylation catalyst, with the 4-dimethylaminopyridine group providing activity *via* the ring nitrogen atom. However, this compound like **201** showed no catalytic activity. It turned an intense red colour in solution after a period of time. The intense red colour of **202** almost certainly arises due to protonation of the *N*-oxide (Scheme 3.10) to give the quinone type species **211** – **213**.

Scheme 3.10



Evidence of this was obtained from ^{1}H NMR spectroscopy and particularly mass spectroscopy. Earlier it was reported that the ^{1}H NMR spectrum of 2,4,6-*tris*(dimethylamino)pyridine *N*-oxide **202** gave three signals that resonated at δ 5.20 (H-3 + H-5), 3.04 and 2.97 ppm. This NMR was recorded shortly after isolation of the compound. A second ^{1}H NMR spectrum obtained some 36 hours later showed that these signals had shifted dramatically. Protons H-5 and H-3 resonated at δ 5.54 whilst the signal corresponding to the dimethylamino protons attached at C-2 and C-6 appeared to switch place with the dimethylamino moiety at C-4 and now resonated at δ 2.91 and δ 3.07 ppm respectively. As mentioned earlier protonation of the *N*-oxide was suspected and this can be accounted for by the slow release of D^+ from $CDCl_3$.

Initially analysis of 2,4,6-*tris*(dimethylamino)pyridine *N*-oxide **202** by MS gave a nominal masses of *m/z* 210.1754 respectively which is fifteen atomic mass units less than the expected accurate mass value of 225.1715. This would indicate that a labile methyl group is being lost before the fragment can reach the detector. Reduction of the cone voltage down to a favourable setting which was a compromise between signal strength and molecule destruction did give a molecular ion of *m/z* 225.1320 consistent with the structure **202** (calculated for $[C_{11}H_{20}N_4O + H]^+$ 225.1715). This would suggest that compound **202** possesses a labile methyl group that is easily lost.

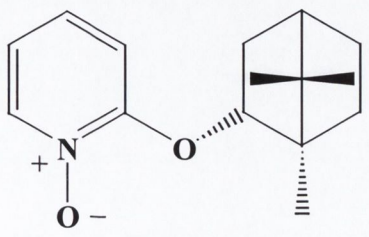
As can be seen from Table 3.3 (above) 4-nitropyridine *N*-oxide **204** is as expected, not an acylation catalyst since the nitro substituent has the opposite effect to the dimethylamino moiety in that it draws electron density away from the catalytic site by virtue of the fact that it is very powerfully electron-withdrawing.

Pyridine *N*-oxide **203** also exhibits catalytic activity, giving a 60% yield of 1-phenylethyl acetate **196** after 18 hours. *N*-Methylmorpholine *N*-oxide **205** showed very poor activity, which suggests that aromaticity is a prerequisite for catalytic activity, or alternatively it may be that the *N*-oxide is too hindered.

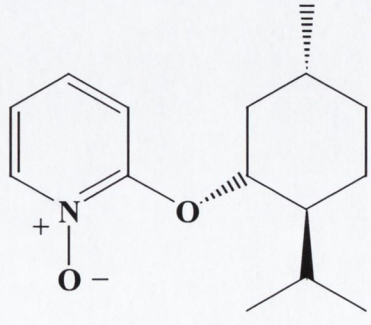
The results above clearly indicate the ability of heterocyclic *N*-oxides to function as acylation catalysts. On foot of these findings it was proposed to synthesise a number of homochiral pyridine *N*-oxides and examine these as potential enantioselective acylation catalysts.

3.2.1 Synthesis of (–)-2-bornyloxypyridine *N*-oxide and (–)-2-menthyloxypyridine *N*-oxide and their evaluation as acylation catalysts

(–)-2-Bornyloxypyridine *N*-oxide **214** and (–)-2-menthyloxypyridine *N*-oxide **215** were synthesised by reaction of 2-chloropyridine *N*-oxide **126** with the sodium salts of the terpene alcohols (–)-menthol **181** and (–)-borneol **182**. Unlike the synthesis of (–)-2-bornyloxy-4-dimethylaminopyridine **183** and (–)-2-menthyloxy-4-dimethylamino pyridine **184** from 2-bromo-4-dimethylaminopyridine **133**, the alkoxides derived from (–)-menthol **181** and (–)-borneol **182** underwent facile reaction with 2-chloropyridine *N*-oxide **126** to afford the title compounds.



214



215

The ^{1}H NMR spectrum of (–)-2-bornyloxypyridine *N*-oxide **214** (Figure 3.7) revealed four aromatic protons at δ 8.22 (H-6), 7.18 (H-4), 6.85 (H-5) and 6.78 (H-3) ppm. A resonance at δ 4.64 ppm was diagnostic of the proton alpha to the ether oxygen. The methyl groups resonated at δ 0.92 (6H) and 0.99 (3H) ppm respectively. Signals between δ 1.23 – 2.40 (7H) were assigned to the skeletal protons of the bicyclo [2.2.1] heptane ring.

The ^{1}H NMR spectrum of (–)-2-menthyloxypyridine *N*-oxide **215** showed the expected aromatic protons at δ 8.22 (H-6), 7.20 (H-4), 6.84 (H-5 + H-3) ppm. Protons H-5 and H-3 appeared as overlapping signals. A resonance at δ 4.50 ppm was diagnostic of the proton alpha to the ether oxygen. Analysis of the high-field area of the spectrum showed that the methyl groups resonated at δ 0.78 (3H) and 0.94 (7H) ppm. The signal at δ 0.94 ppm also contained a proton from the cyclohexane ring, thus explaining the integration for seven protons. Signals resonating at δ 2.33 (1H, H-7'), 2.01 (1H, H-6'$_a$), 1.76 (3H, H-6'$_b$, H-3' and H-4'), 1.45 (1H, H-5') and 1.26 (1H, H-2') ppm were assigned with the help of ^{1}H-^{13}C COSY spectroscopy of **215**. A qualitative correlation was also drawn with literature data for the ^{1}H-^{13}C COSY of (–)-menthol which helped in the assignment of these shifts.[1]

Figure 3.7 ^{1}H NMR spectrum of (–)-2-bornyloxypyridine *N*-oxide 214

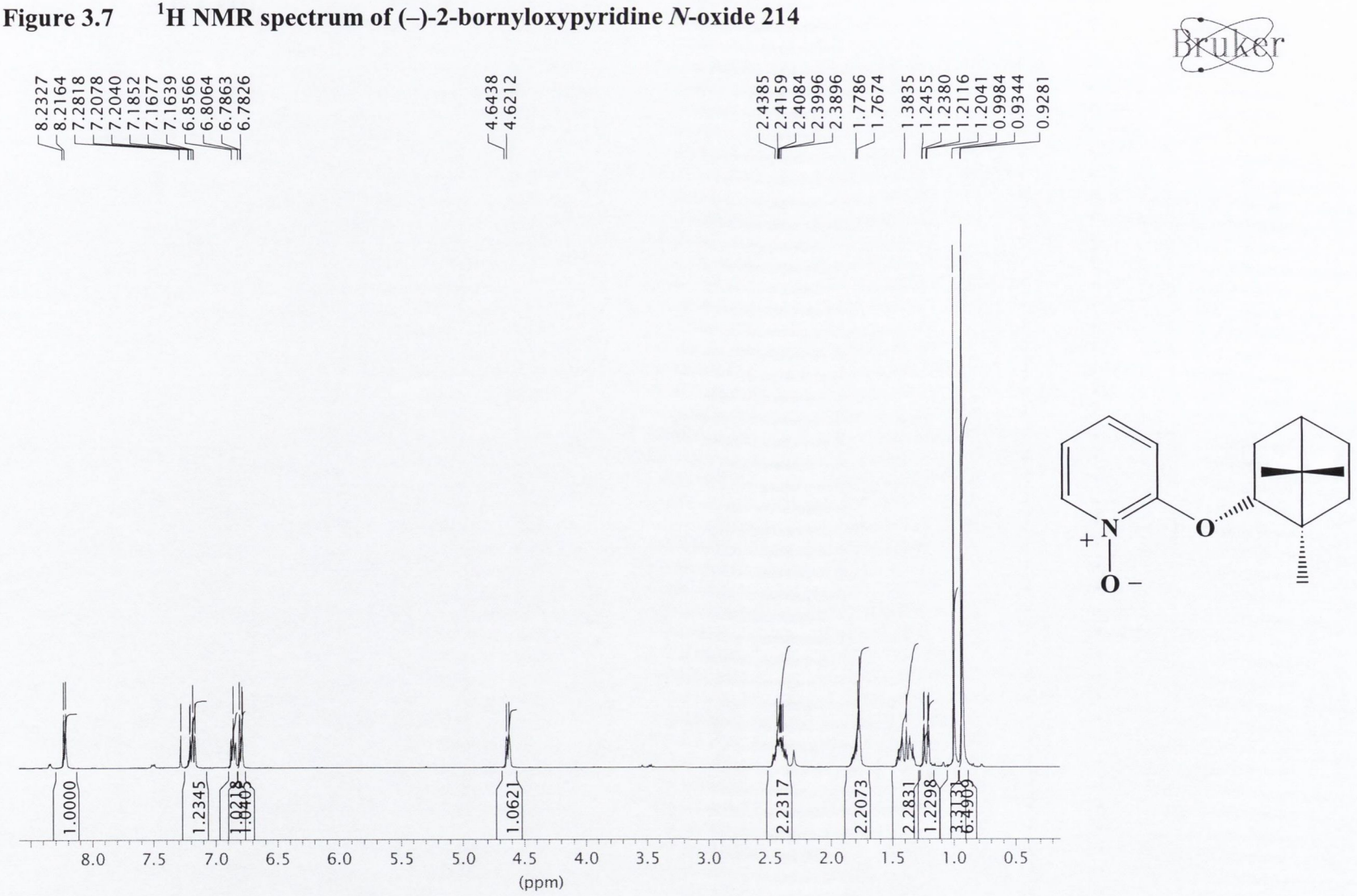
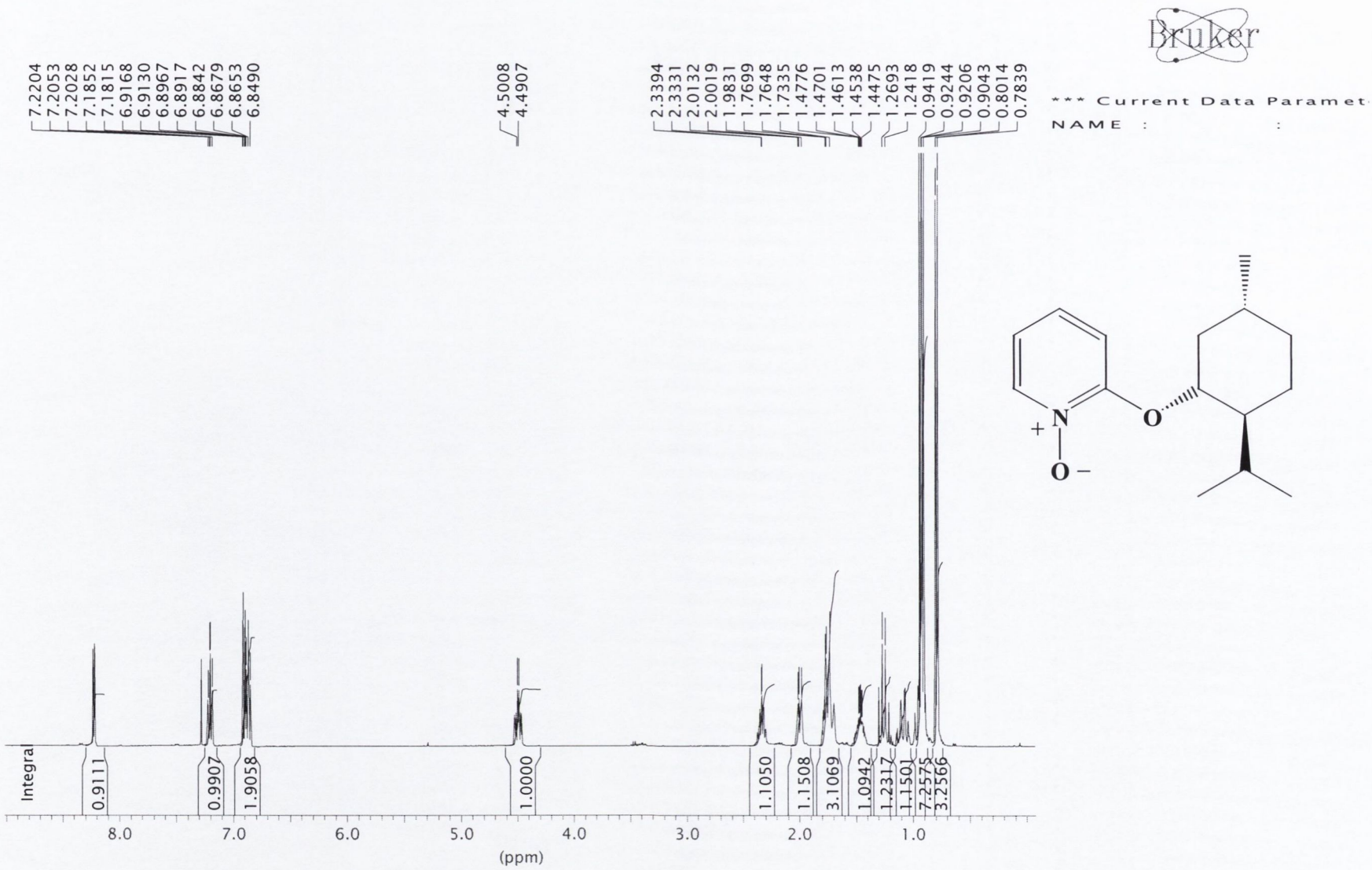


Figure 3.8 ^{1}H NMR spectrum of (–)-2-menthyloxypyridine *N*-oxide 215



As was the case previously these compounds were tested as catalysts for the acylation of 1-phenylethyl alcohol **17** in the presence of two equivalents of acetic anhydride (Table 3.4).

Table 3.4 Acylation of 1-phenylethyl alcohol with acetic anhydride catalysed by the *N*-oxides 214 and 215

Entry[a]	Catalyst (10 mol%)	% Conversion[b]
1	(–)-2-Bornyloxypyridine *N*-oxide **214**	70
2	(–)-2-Menthyloxyoyridine *N*-oxide **215**	36

(a) 1-Phenylethyl alcohol (1 g; 8.19×10^{-3} mol), acetic anhydride (2 eq.), 16 h, catalyst 10 mol%; (b) % conversion determined by ^{1}H NMR.

An interesting aspect of the *N*-oxides **214** and **215** is that they are much more superior as acylation catalysts than are their free bases. In this instance, (–)-2-bornyloxypyridine *N*-oxide **214** is more than twice as effective as (–)-2-bornyloxypyridine **197** under identical conditions. (–)-2-Menthyloxypyridine *N*-oxide **215** is almost six times more effective than the parent base **198**, which is essentially not an acylation catalyst giving only 2% more acetate than in the uncatalysed reaction (Tables 3.1 and 3.4). It should be noted that these reaction conditions do not utilise a solvent. These conditions were used only to ascertain if a particular compound possessed catalytic activity or not.

Thus, compounds **214** and **215** were then tested as enantioselective catalysts for the acylation of 1-phenylethyl alcohol **17** in the presence of 0.6 equivalents of acetic anhydride using DCM or *tert*-amyl alcohol as solvent. The results obtained are tabulated in Table 3.5. Again, as was the case with the free bases (Table 3.2), no asymmetric induction was observed with these catalysts, although they are reasonably efficient catalysts. As was stated earlier, lack of enantioselectivity can be

attributed to insufficient chiral differentiation around the active site. It was decided that increased differentiation between diasteroisomeric transition states might be possible with molecules containing desirable C_2 symmetry.

Table 3.5 Investigation into the enantioselective acylation of 1-phenylethyl alcohol catalysed by *N*-oxides 214 and 215.

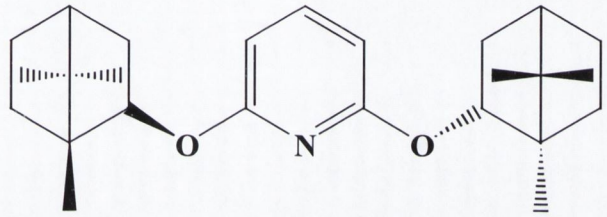
Entry[a]	Catalyst (10 mol%)	Solvent	Time/h	% Conversion	e.e[c]
1	(–)-2-Menthyloxypyridine *N*-oxide **215**	DCM	42	19.8	0
2	(–)-2-Menthyloxypyridine *N*-oxide **215**	*t*-AmOH	42	27	0
3	(–)-2-Bornyloxypyridine *N*-oxide **214**	DCM	42	24	0
4	(–)-2-Bornyloxypyridine *N*-oxide **214**	*t*-AmOH	42	31	0
5	None	*t*-AmOH	42	0	0

(a)1-Phenylethyl alcohol (1 g; 8.19×10^{-3} mol), acetic anhydride (0.6 eq.), catalyst, solvent (5 ml); (b) % conversion determined by ^{1}H NMR; (c) testing for enantiomeric excess was performed using polarimetry.

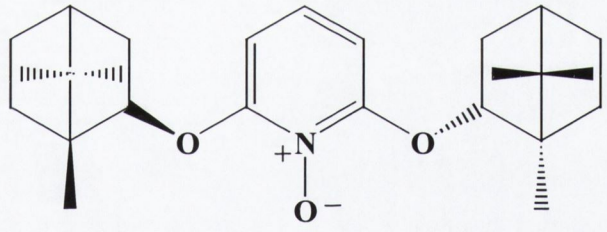
3.3 Synthesis of C_2 symmetric acylation catalysts

The free base (–)-2,6-dibornyloxypyridine **216** was synthesised previously by Storey.[3] The synthesis of the related C_2 symmetric compounds 2,6-dibornyloxypyridine *N*-oxide **217** and 2,6-dibornyloxy-4-dimethylaminopyridine *N*-oxide **218** was achieved using 2,6-dichloropyridine *N*-oxide **207** and 2,6-diiodo-4-dimethylaminopyridine *N*-oxide **179** as precursors. It was anticipated that the halides in the 2- and 6- positions of **207** and **179** would undergo facile nucleophilic

displacement with the alkoxides derived from the reaction of either (–)-menthol **181** or (–)-borneol **182** and with sodium hydride. In the event, (–)-borneol **182** was chosen as the chiral handle to be introduced into these positions since in every instance described above, catalysts such (–)-2-bornyloxy-4-dimethylaminopyridine **183**, (–)-2-bornyloxypyridine **197** and (–)-2-bornyloxypyridine *N*-oxide **214** consistently outperformed their corresponding (–)-menthyl counterparts, (–)-2-menthyloxy-4-dimethylaminopyridine **184**, (–)-2-menthyloxypyridine **199** and (–)-2-menthyloxypyridine *N*-oxide **215** as acylation catalysts respectively.



216



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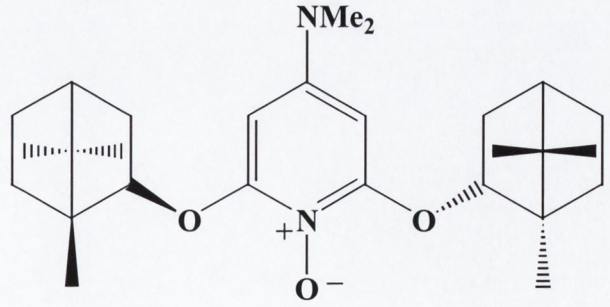


218

The ^{1}H NMR spectrum of (–)-2,6-dibornyloxypyridine *N*-oxide **217** (Figure 3.9) revealed the presence of two aromatic protons as expected at δ 7.06 (1H) and 6.39

(2H) ppm. A signal at δ 4.58 (2H) was again indicative of protons alpha to the ether oxygens. Analysis of the high-field area of the spectrum showed multiplets at δ 2.43 (2H), 2.37 (2H), 1.76 (4H), 1.36 (4H) and 1.23 (2H) ppm. The methyl groups resonated at δ 1.01 (6H) and 0.93 (12H) ppm. The total number of protons was thirty seven which is consistent with the structure proposed.

Compound **218** was synthesised by reaction of the sodium salt derived from (–)-borneol **182** with 2,6-diiodo-4-dimethylaminopyridine *N*-oxide **179**. The ^{1}H NMR of this compound showed that protons H-3 and H-5 came into resonance as a broad singlet at δ 5.55 ppm, whilst the dimethylamino protons resonated at δ 2.98 ppm. The protons of the bornyloxy substituents resonated as multiplets at δ 4.43 (2H, 2'-H), 2.35 (2H), 2.33 (2H), 1.75 (4H), 1.16 (4H) and 1.05 (2H). The methyl groups resonated at δ 0.97 (6H) and 0.81 (12H).

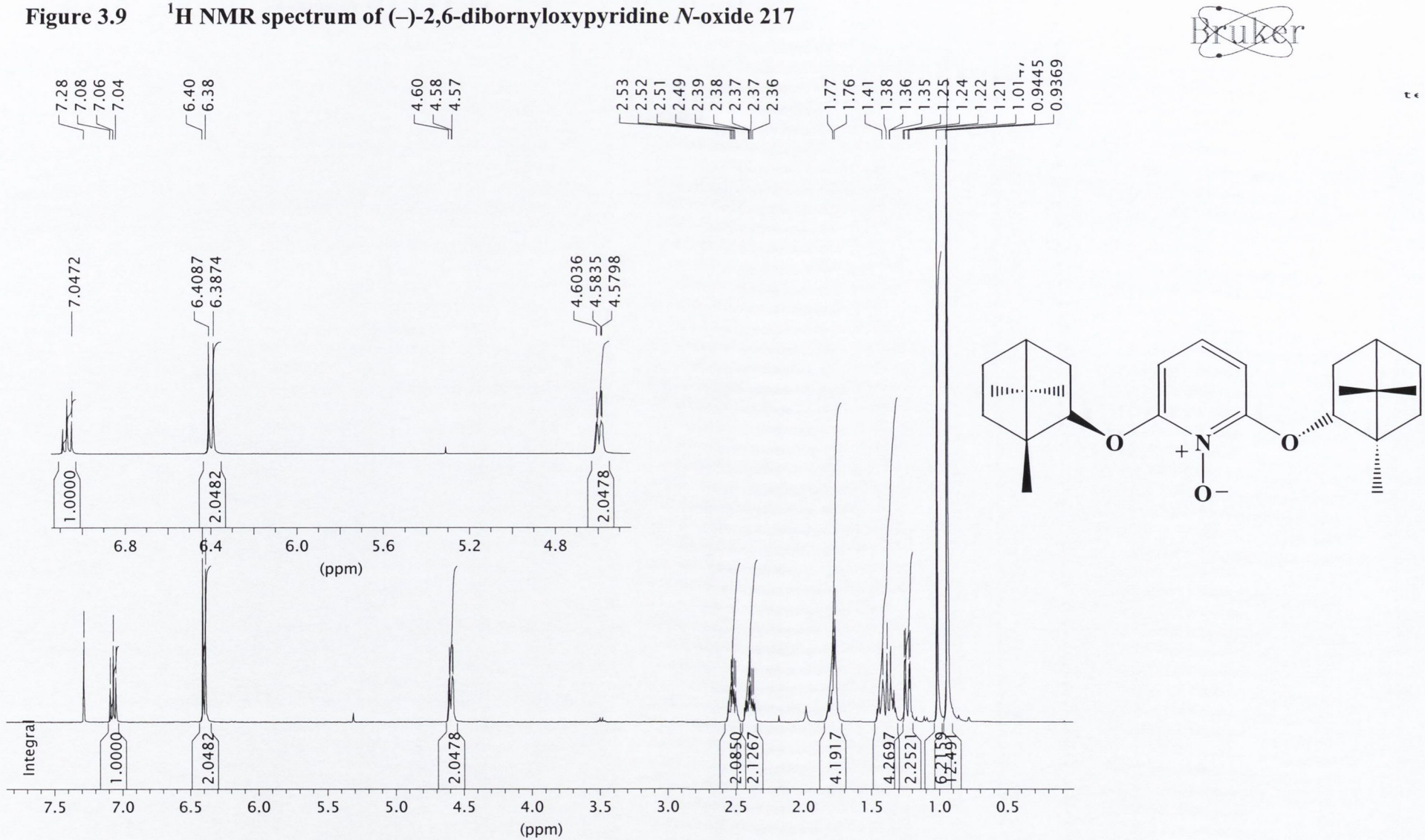
These C_2 symmetric compounds were tested as acylation catalysts and the results are recorded below.

Table 3.6 Acylation of 1-phenylethyl alcohol catalysed by compounds 216, 217 and 218

Entry[a]	Catalyst (10 mol%)	% Conversion[b]
1	(–)-2,6-Dibornyloxypyridine **216**	0
2	(–)-2,6-Dibornyloxypyridine *N*-oxide **217**	48
3[c]	(–)-2,6-Dibornyloxy-4-dimethylaminopyridine *N*-oxide **218**	48

(a) 1-Phenylethyl alcohol (1 g; 8.19×10^{-3} mol), acetic anhydride (2 eq.), 16 h, catalyst 10 mol%; (b) % conversion determined by ^{1}H NMR; (c) 1-phenylethyl alcohol (1 g; 8.19×10^{-3} mol), acetic anhydride (2 eq.), 48 h, *t*-AmOH (0.5 ml), catalyst.

Figure 3.9 ^{1}H NMR spectrum of (–)-2,6-dibornyloxypyridine *N*-oxide 217



As can be seen from Table 3.6 (–)-2,6-dibornyloxypyridine **216** does not act as a acylation catalyst. This may be due to the electron-withdrawing effect of the oxygens at the 2- and 6-positions of the pyridine ring or due to steric hindrance. Interestingly, (–)-2,6-dibornyloxypyridine *N*-oxide **217** is quite an efficient catalyst giving a 48% conversion of 1-phenylethyl alcohol **17** into its corresponding acetate. (–)-2,6-Dibornyloxy-4-dimethylaminopyridine *N*-oxide **218** also gave a 48% conversion of alcohol into acetate but this reaction was done in the presence of a solvent *tert*-amyl alcohol, albeit for a longer period 48 h. Generally the rate of reaction is faster when there is no solvent present.

Compounds **216**, **217** and **218** were then tested as enantioselective acylation catalysts for the acylation of 1-phenylethyl alcohol in the presence of 0.6 mol equivalents of acetic anhydride. It was hoped that the C_2 symmetry possessed by these compounds would provide a more asymmetric environment around the *N*-oxide thus leading to fewer diastereomeric transition states and hence an increase in enantioselectivity.

Table 3.7 Investigation into the enantioselective acylation of 1-phenylethyl alcohol catalysed by *N*-oxides 217 and 218

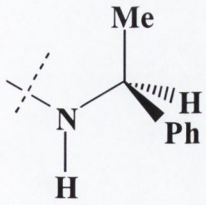
Entry[a]	Catalyst (10 mol%)	Solvent	Time/h	% Conversion	e.e[c]
1	(–)-2,6-Dibornyloxypyridine *N*-oxide **217**	*t*-AmOH	42	11	0
2	(–)-2,6-Dibornyloxy-4-dimethylamino pyridine *N*-oxide **218**	*t*-AmOH	42	20	0
4	None	*t*-AmOH	42	0	0

(a)1-Phenylethyl alcohol (1 g; 8.19×10^{-3} mol), acetic anhydride (0.6 eq.), catalyst, solvent (5 ml); (b) % conversion determined by ^{1}H NMR; (c) testing for enantiomeric excess was performed using polarimetry.

In the event, these compounds did not result in enantioselective acylation. They did prove to be efficient catalysts even with the handicap of two large and bulky substituents at C-2 and C-6.

3.4 Synthesis of 2-(1'-phenylethylamino)-4-dimethylaminopyridine *N*-oxide and (1'*S*)-(–)-2-(1'-phenylethylamino)-4-dimethylaminopyridine and their evaluation as acylation catalysts

This work involved incorporating a (1*S*)-α-methylbenzylamine substitutent **219** into the 2-position of a 4-dimethylaminopyridine ring to give the title compounds 2-(1'-phenylethylamino)-4-dimethylaminopyridine *N*-oxide **220** and (1'*S*)-(–)-2-(1'-phenylethylamino)-4-dimethylaminopyridine **221**. It was envisaged that the nitrogen atom at the 2-position of **220** would not inhibit the activity of this catalyst given that 2-dimethylaminopyridine *N*-oxide was an efficient acylation catalyst. Also, catalytic activity should be enhanced by the presence of a 4-dimethylamino substituent.



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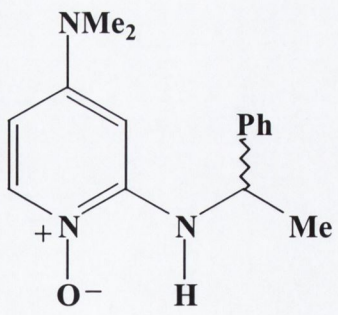
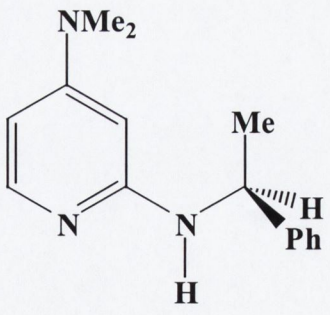


220

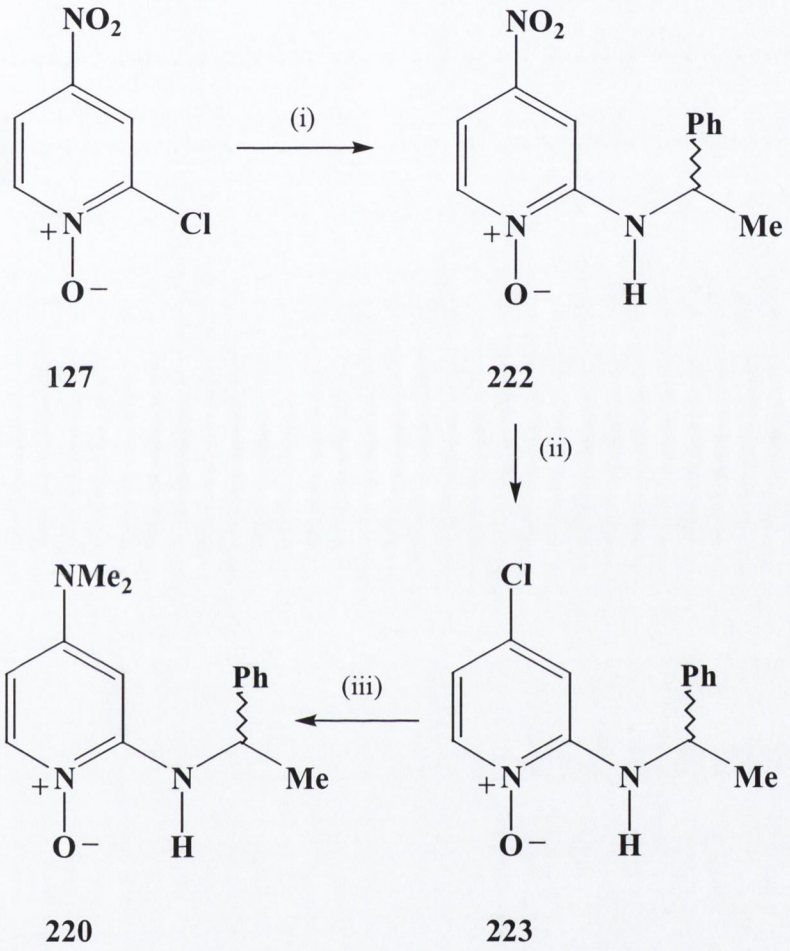


221

One drawback in utilising (1*S*)-α-methylbenzylamine as a chiral handle was that it is quite expensive. It was decided to use the racemic amine, (±)-α-methylbenzylamine

for the synthesis of 2-(1'-phenylethylamino)-4-dimethylaminopyridine *N*-oxide **220** to test for activity. The synthesis of 2-(1'-phenylethylamino)-4-dimethylaminopyridine *N*-oxide **220** was achieved as depicted (Scheme 3.11).

Scheme 3.11



Reagents and Conditions: (i) (±)-PhCH(Me)NH_2, *t*-BuOH, 120 °C, 24 h; (ii) AcCl, $CHCl_3$, 16 h; (iii) aq. 40 % NMe_2, 24 h, 130 °C

4-Nitro-2-(1'-phenylethylamino)pyridine *N*-oxide **222** was synthesised in 90% yield by reaction of (±)-α-methylbenzylamine with 2-chloro-4-nitropyridine *N*-oxide **127**. 2-Chloro-4-nitropyridine *N*-oxide **127** was synthesised as described in Chapter 2.

Analysis of the ^{1}H NMR spectrum of the nitro compound **222** revealed that the protons H-6 and H-3 resonated at δ 8.23 and 7.19 ppm respectively. Proton H-5 appeared to be overlapping with the five aromatic protons of the phenyl substitutent, which resonated at δ 7.31 -7.4 ppm. H-1' resonated at δ 4.68 ppm and was split into a multiplet, presumably due to coupling with the N-H proton and the three protons of the methyl substituent. The methyl protons resonated as a doublet at δ 1.74 ppm, whilst the N-H proton resonated between δ 7.31 -7.4 ppm. This was confirmed by the addition of D_2O where the combined integration's were lowered by 1 as a result.

4-Chloro-2-(1'-phenylethylamino)pyridine *N*-oxide **223** was synthesised in 46% yield by reaction of 4-nitro-2-(1'-phenylethylamino)pyridine *N*-oxide **222** with acetyl chloride in much the same way as 2-acetamido-4-chloropyridine *N*-oxide **129** was synthesised from 2-amino-4-nitropyridine *N*-oxide **128** as described in Chapter 2.

Inspection of the ^{1}H NMR spectrum of 4-chloro-2-(1'-phenylethylamino)pyridine *N*-oxide **223** showed that introduction of chlorine into the 4-position had a dramatic effect on the protons of the pyridine ring when compared to the parent compound. All three pyridine protons were clearly discernible at δ 7.96 (H-6), 6.44 (H-5) and 6.24 (H-3) ppm. The protons of the phenyl substituent resonated at δ 7.24 – 7.44 ppm overlapping with the C-H proton of chloroform. A quartet at δ 4.45 was assigned to H-1'. The methyl protons resonated at δ 1.56 ppm whilst the N-H proton resonated again under the phenyl protons at δ 7.24 – 7.44 ppm. Somewhat surprisingly, no acylation took place at N-H. Under similar conditions 2-amino-4-nitropyridine *N*-

oxide gave the product of mono acylation, 2-acetamido-4-chloropyridine *N*-oxide (Chapter 2).

Treatment of 4-chloro-2-(1'-phenylethylamino)pyridine *N*-oxide **223** with aqueous dimethylamine solution resulted in nucleophilic displacement of the chloride from the 4-position of the molecule to afford 2-(1'-phenylethylamino)-4-dimethylaminopyridine *N*-oxide **220**.

Inspection of the ^{1}H NMR spectrum (Figure 3.10) of **220** reveals that the pyridine protons resonates at δ 7.80 (H-6), 5.88 (H-5) and 5.33 (H-2) ppm. The proton H-3 is shifted to quite a highfield resonance since it is sandwiched between two electron donating groups which shield the nucleus around H-3 thus shifting it to a higher field. The phenyl protons again resonate between δ 7.24 –7.36 ppm and are relatively unchanged due to the introduction of the dimethylamino substituent. Further resonances at δ 6.95 (N-H), 4.50 (H-1'), 2.80 (NMe_2) and 1.63 (Me) ppm can be assigned.

(1'*S*)-(–)-2-(1'-phenylethylamino)-4-dimethylaminopyridine **221** was synthesised from 2-bromo-4-dimethylaminopyridine **133** upon reaction with two equivalents of (–)-(1*S*)-α-methylbenzylamine at elevated temperature.

The ^{1}H NMR spectrum of **221** (Figure 3.11) shows shifts at δ 7.78 (H-6), 7.23-7.40 (5H, Ph), 5.95 (H-5), 5.33 (H-2), 4.69 (N-H), 4.64 (H-1'), 2.82 (NMe_2) and 1.56 (Me) ppm, all consistent with the structure proposed.

Figure 3.10 ^{1}H NMR spectrum of 2-(1'-phenylethylamino)-4-dimethylaminopyridine *N*-oxide 220

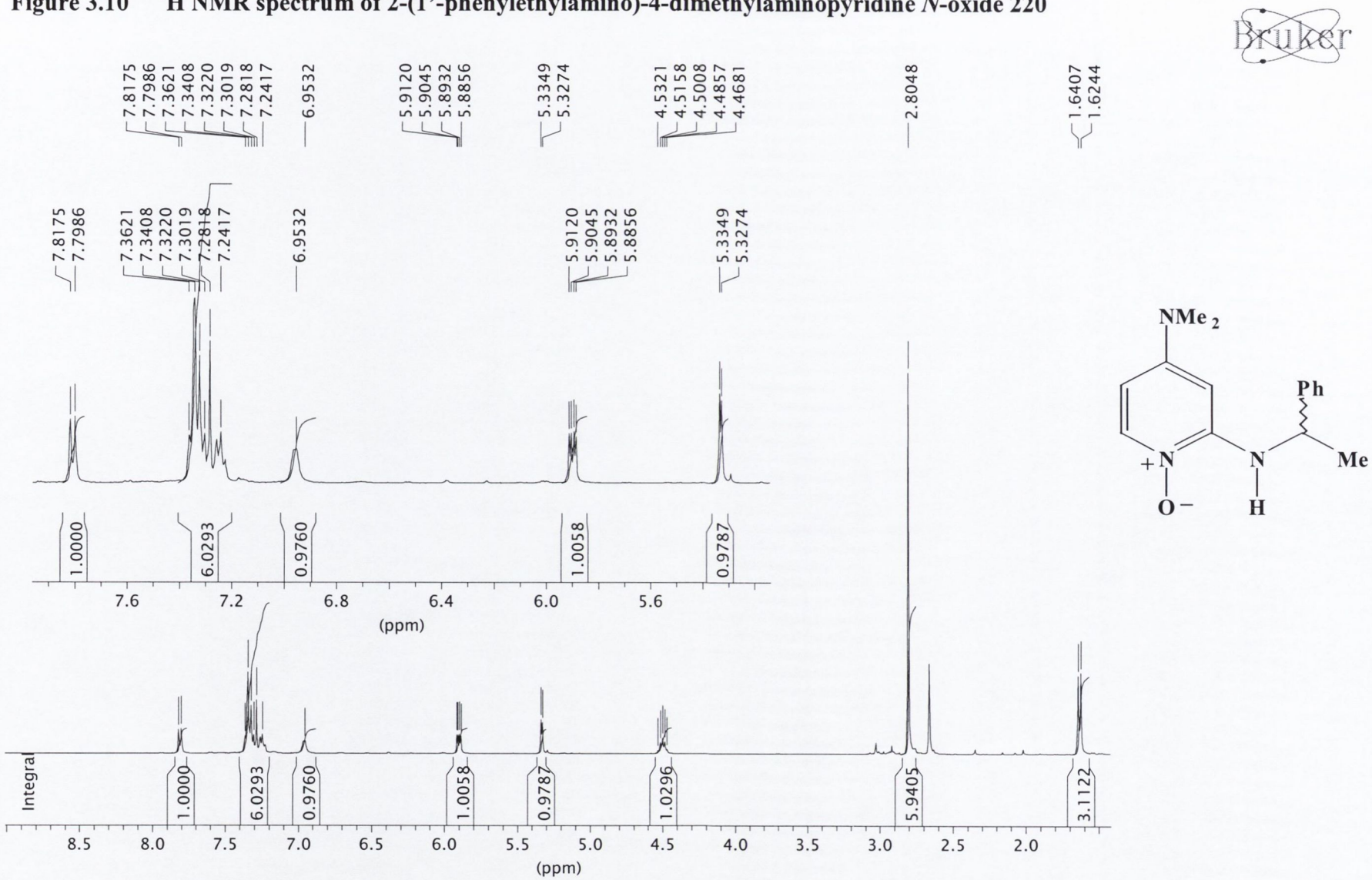
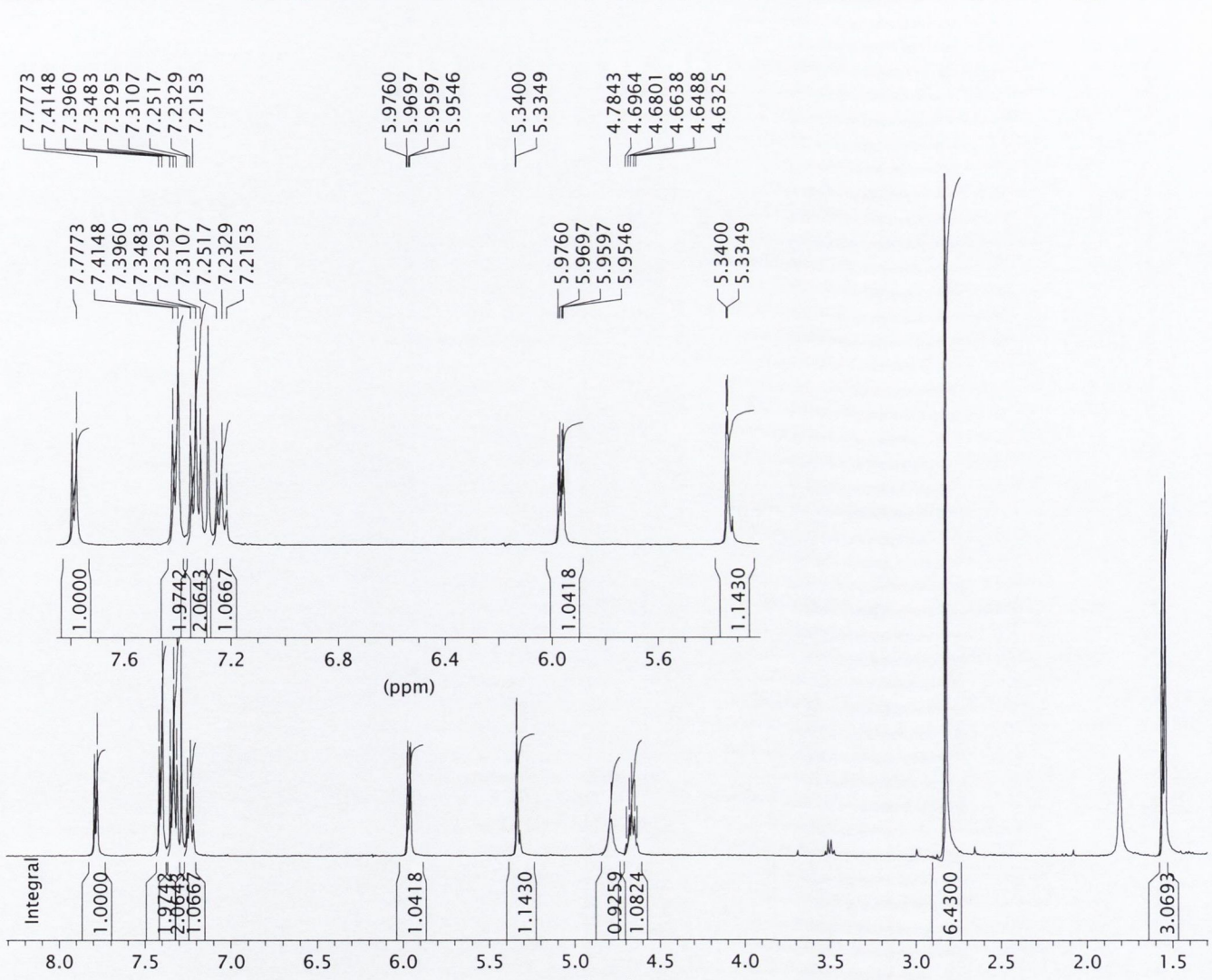
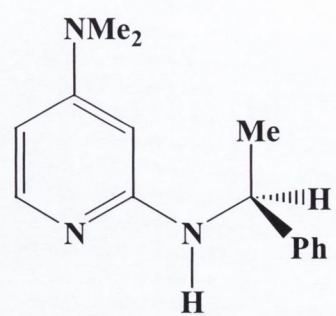


Figure 3.11 ^{1}H NMR spectrum of (1'S)-(–)-2-(1'-phenylethylamino)-4-dimethylaminopyridine 221





2-(1'-Phenylethylamino)-4-dimethylaminopyridine *N*-oxide **220** and (1'*S*)-(–)-2-(1'-phenylethylamino)-4-dimethylaminopyridine **221** were tested as catalysts for the acylation of 1-phenylethyl alcohol **17** in the presence of two equivalents of acetic anhydride (Table 3.8).

Table 3.8 Acylation of 1-phenylethyl alcohol catalysed by compounds 220 and 221.

Entry[a]	Catalyst (10 mol%)	% Conversion[b]
1	2-(1'-Phenylethylamino)-4-dimethylaminopyridine *N*-oxide **220**	100
2[c]	(1'*S*)-(–)-2-(1'-phenylethylamino)-4-dimethylamino pyridine **221**	50
3	None	0

(a) 1-Phenylethyl alcohol (1 g; 8.19×10^{-3} mol), acetic anhydride (2 eq.), 16 h, catalyst 10 mol%; (b) % Conversion determined by ^{1}H NMR; (c) 19 h.

As can be seen from Table 3.8, 2-(1'-phenylethylamino)-4-dimethylaminopyridine *N*-oxide **220** shows excellent catalytic activity for the acylation of 1-phenylethyl alcohol whereas the free base, (1'*S*)-(–)-2-(1'-phenylethylamino)-4-dimethylaminopyridine **221** shows reduced activity giving 50% conversion after nineteen hours. These findings are remarkable considering the number of nitrogens that can be protonated by the acetic acid formed in the reaction. Also the presence of the N-H proton so close to the catalytic site of **221** does not appear to hinder its ability as an acylation catalyst. Amazingly neither of the compounds, **220** and **221** are themselves acylated under these conditions and (1'*S*)-(–)-2-(1'-phenylethylamino)-4-dimethylaminopyridine **227** was recovered from the reaction

unacylated. It was not determined if this compound was still reusable after recovery (presumably it is) and due to time constraints it was not determined if this compound possessed the ability to act as an enantioselective acylation catalyst.

3.5 Measurement of rate constants for the acylation of (±)-1-phenylethyl alcohol in deuteriochloroform catalysed by compounds possessing catalytic activity

All compounds synthesised during this work showing catalytic activity were employed as catalysts for the acylation of (±)-1-phenylethyl alcohol in the presence of acetic anhydride as the acyl donor. No auxiliary bases were employed in these reactions. The reactions were carried out in an NMR tube in $CDCl_3$ and monitored by ^1H NMR spectroscopy. Each reaction mixture was prepared as follows. 500 µl of a 0.41 M solution (2.05×10^{-4} mol) of (±)-1-phenylethyl alcohol and 250 µl of a 1.63 M solution (4.075×10^{-4} mol) of acetic anhydride were added to a NMR tube. After mixing, 25 µl of a 0.328 M solution (8.2×10^{-6} mol, 4 mol%) of each catalyst was added and the time T_0 was recorded. ^1H NMR spectra were recorded at intervals as the reaction proceeded. Using the appropriate equation the second order rate constant for each reaction was obtained from the slope of the graph (Figures 3.12.-3.14).

Equation 3.1

$$\frac{1}{[a]_0 - [b]_0} \ln \frac{[b]_0 ([a]_0 - [x])}{[a]_0 ([b]_0 - [x])} = k_2 t$$

$[a]_0$ =Initial concentration of alcohol in mol L^{-1}, $[b]_0$ =Initial concentration of acetic anhydride in mol L^{-1}, $[x]$ = concentration of ester in mol L^{-1}, k_2 = second order rate constant, t = time

Figure 3.12 **Acylation of (±)-1-phenylethyl alcohol catalysed by 4-dimethylaminopyridine 54 and by 4-dimethylaminopyridine *N*-oxide 167**

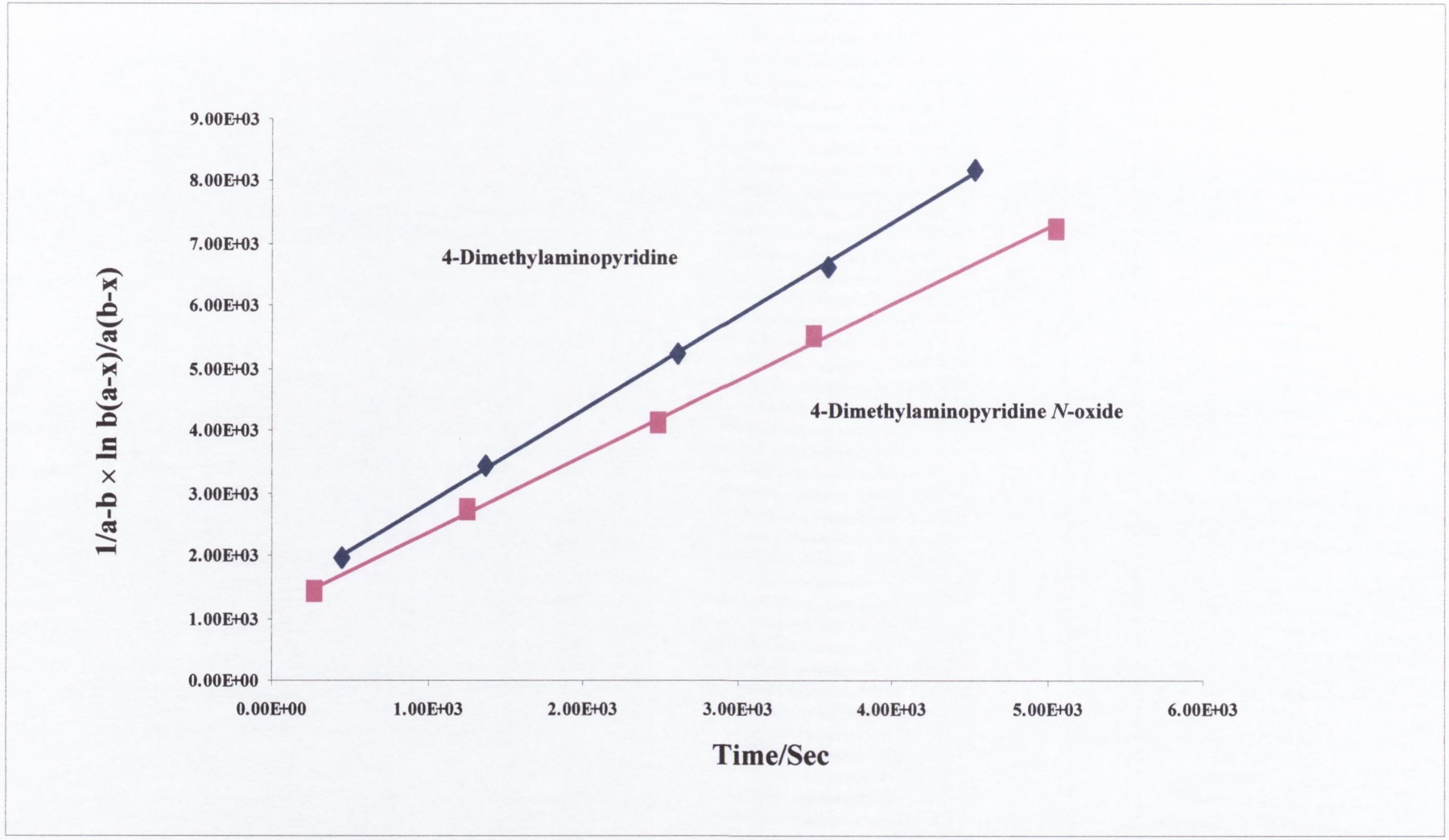


Figure 3.13 Acylation of (±)-1-phenylethyl alcohol catalysed by compounds 200, 201, 204, 207, 209 or 222

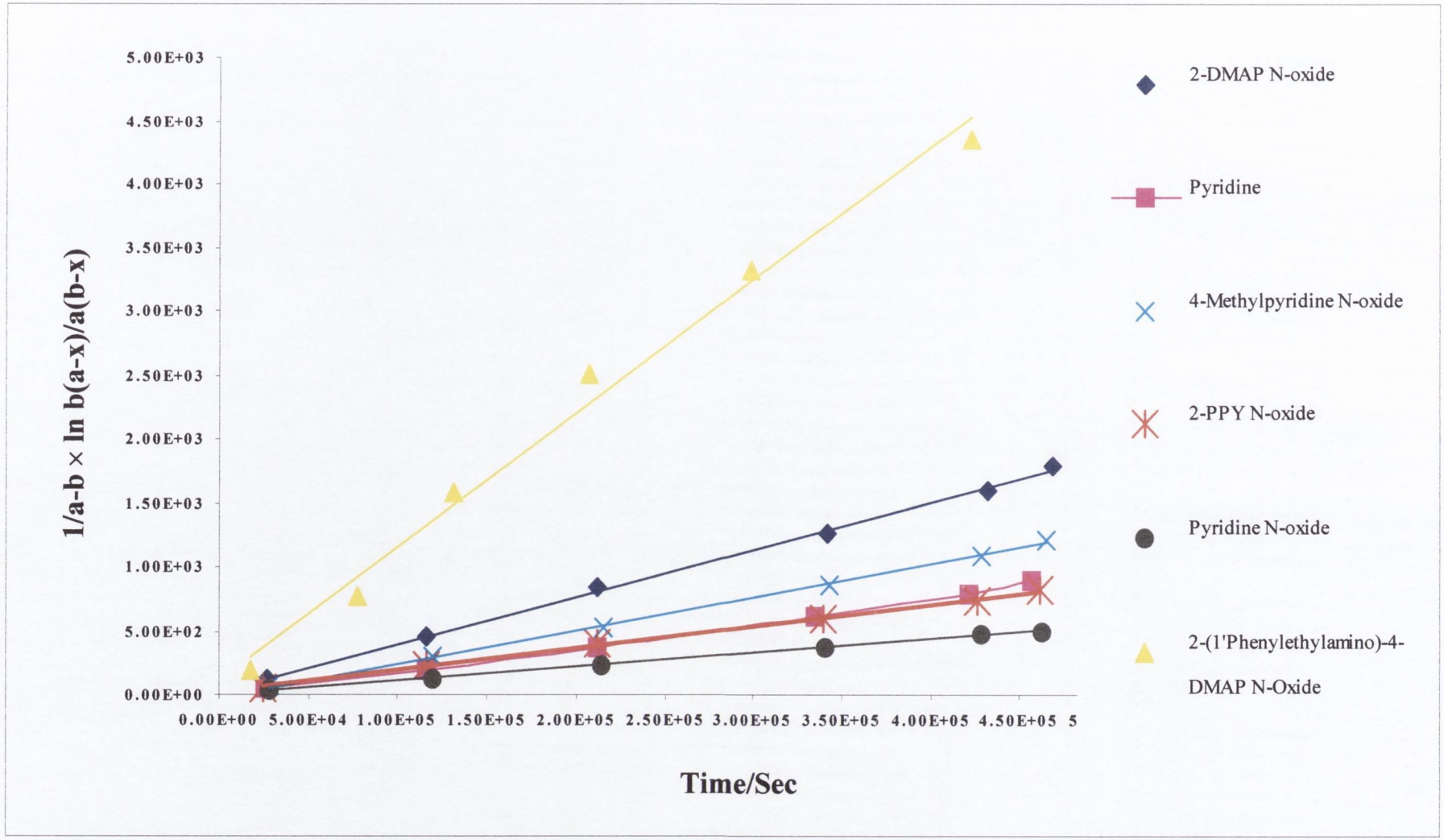
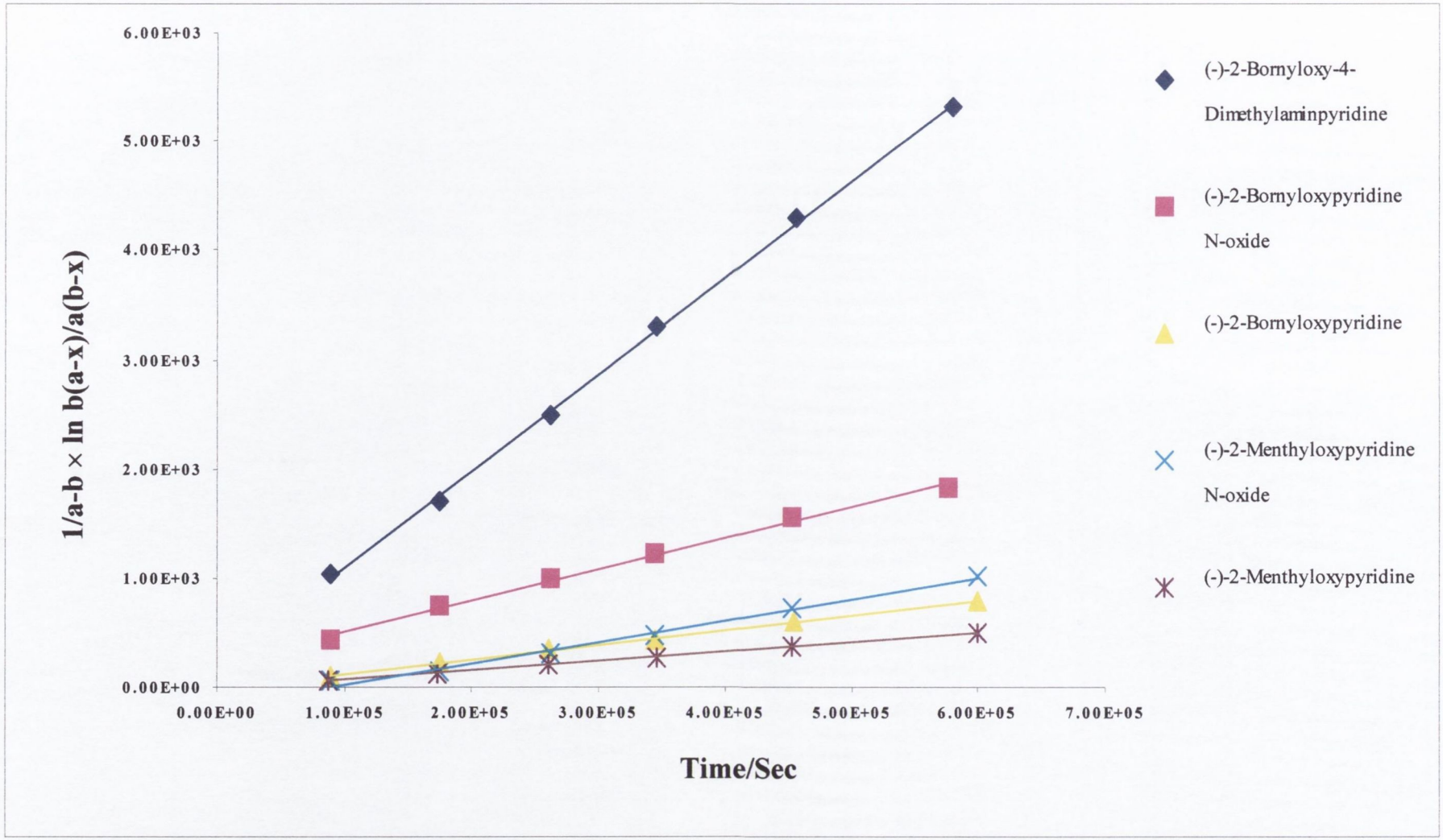


Figure 3.14 **Acylation of (±)-1-phenylethyl alcohol catalysed by compounds 183, 184, 198, 199, 215, 216 and 218**



The rate constants for these reactions are tabulated in Table 3.9.

Table 3.9 Measurement of rate constants for the acylation of (±) 1-phenyl ethyl alcohol in deuteriochloroform catalysed by the compounds listed

Catalyst	Reaction Rate Constant k_2 (mol^{-1} sec^{-1})	k_{rel}
4-Dimethylaminopyridine **54**	1.5038	754.6
4-Dimethylaminopyridine *N*-oxide **167**	1.2193	609.6
4-Methylpyridine *N*-oxide **200**	0.0026	1.3
2-PPY *N*-oxide **206**	0.0017	0.85
Pyridine **208**	0.0020	1
Pyridine *N*-oxide **203**	0.0011	0.55
(–)-2,6-Dibornyloxy-4-dimethylaminopyridine *N*-oxide **218**	0.0026	1.3
(–)-2-Bornyloxypyridine *N*-oxide **214**	0.0028	1.4
(–)-2-Bornyloxypyridine **197**	0.0013	0.65
(–)-2-Menthyloxypyridine *N*-oxide **215**	0.0019	0.95
(–)-2-Menthyloxypyridine **198**	0.0009	0.45
(–)-2-Bornyloxy-4-dimethyaminopyridine **183**	0.0089	4.45
(–)-2-Menthyoxy-4-dimethyaminopyridine **184**	0.0074	3.7
(–)-2,6-Dibornyloxypyridine *N*-oxide **217**	0	0
2-(1'-Phenylethylamino)-4-dimethylamino pyridine *N*-oxide **220**	0.0104	5.2
(1'*S*)-(–)-2-(1'-phenylethylamino)-4-dimethylaminopyridine **221**	0	0

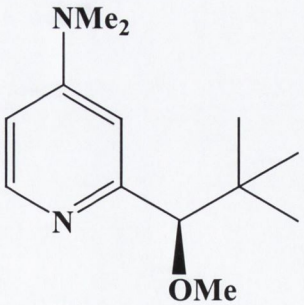
From this data the following can be concluded;

- 4-Dimethylaminopyridine **54** is some 750 times better as an acylation catalyst than pyridine under these conditions.
- 4-Dimethylaminopyridine *N*-oxide **167** is 609 times better as an acylation catalyst than pyridine. Significantly, DMAP is only 1.2 times better then DMAP *N*-oxide as a catalytic acylation catalyst.
- 2-DMAP *N*-oxide **199** is almost twice as effective as pyridine, a surprising result considering the free base is essentially inactive.[11]
- The best non-chiral catalyst is 2-(1'-phenylethylamino)-4-dimethylamino pyridine *N*-oxide **220** which is 5.2 times better than pyridine.
- Significantly (1'*S*)-(–)-2-(1'-phenylethylamino)-4-dimethylamino pyridine **221** did not act as a acylation catalyst under these conditions. However, as has already been demonstrated earlier this compound does possess catalytic activity. The lack of activity may be due to DCl in the chloroform which being a strong acid may totally inactivate the catalyst *via* its deutrochloride salt.
- Of the homochiral catalysts used (–)-2-bornyloxy-4-dimethylaminopyridine **183** exhibits the best activity, being 4.45 times more effective than pyridine. (–)-2-Menthyloxy-4-dimethylaminopyridine **184** is 3.7 time more effective than pyridine under these conditions. (–)-2-Bornyloxypyridine *N*-oxide **214** and (–)-2-menthyloxypyridine *N*-oxide **215** are 1.4 and 0.95 times as effective as pyridine. Significantly, both are better catalysts than the parent free bases.
- Of the C_2 symmetric catalysts synthesized only (–)-2,6-dibornyloxy-4-dimethylaminopyridine *N*-oxide **218** showed any activity in $CDCl_3$. (–)-2,6-Dibornyloxypyridine *N*-oxide did not act as a acylation catalyst under these conditions.

3.6 Discussion

Unfortunately the holy grail of enantiomer discrimination was not achieved with any of the compounds the synthesis of which is described in this Chapter. It should be noted that most of the compounds synthesised show excellent activity as acylation catalysts which are comparable with most of the chiral 4-dimethylaminopyridines discussed in Chapter 1. There are many reasons for lack of enantioselectivity, however the simplest and most straightforward may be that the chiral centres necessary for chiral induction are to far from the catalytic site. For example compounds embodying monoterpene ethers such as (–)-2-bornyloxy-4-dimethylaminopyridine **183** and (–)-2-menthyloxy-4-dimethylaminopyridine **184** have the first chiral centre two atoms away from the active site which may not be close enough. In the case of the *N*-oxides **214**, **215**, **217** and **218** the distance is even greater taking the N–O bond into account.

On this basis it would appear that an ideal catalyst candidate such as **224** should have an asymmetric centre closer to the catalytic site.



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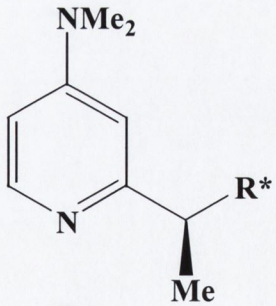
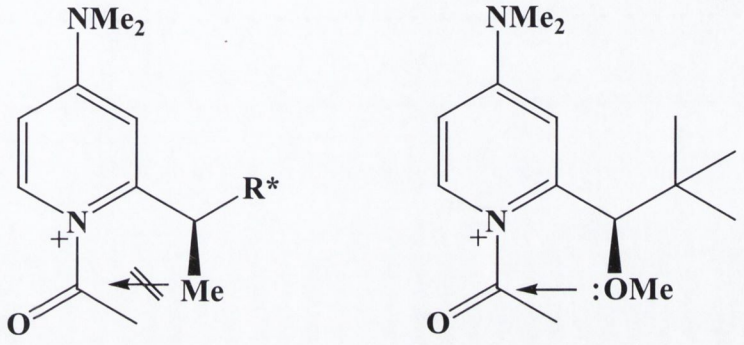


224

Such a compound, while similar to the ether **62** developed by Vedejs *et al.*[13] would be a very efficient catalyst because it is (a) devoid of an ether oxygen thus avoiding electron lone pair interaction with an *N*-acylpyridinium salt (Figure 3.15), and (b)

devoid of a heteroatom at C-2 which would decrease the –I inductive effect, and should reach a optimum balance between reactivity and selectivity.

Figure 3.15



While the synthesis of compounds such as **224** would represent a considerable challenge it would be nonetheless worth investigating.

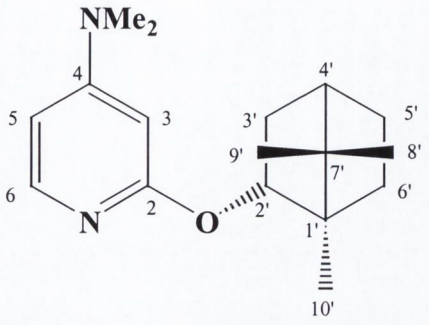
As was stated earlier, there was insufficient time to determine if (1'*S*)-(–)-2-(1'-phenylethylamino)-4-dimethylaminopyridine **221** was an enantioselective acylation catalyst or not. This will have to be investigated further.

2,6-Diiodo-4-dimethylaminopyridine *N*-oxide **179** is a direct precursor to 2,6-diiodo-4-dimethylaminopyridine **180**, a compound which should be exploited further with a view to examining its nickel-catalysed coupling with Grignard reagents derived from the chiral pool.

3.7 Experimental Section

^{1}H NMR spectra (400.13 MHz) and ^{13}C NMR (100.6 MHz) spectra were measured for solutions in deuteriochloroform or [$^{2}H_6$]-DMSO, using a Bruker DPX-400 spectrometer. Chemical shifts are measured in ppm. J values are given in Hz. Melting points were measured on an Electrothermal melting point apparatus and are uncorrected. FT-IR spectra were measured using a Perkin Elemer FT-IR PARAGON 1000 and a Mattson Genesis II spectrometer. Electrospray mass spectra (ESMS) were recorded on a Micromass LCT electrospray mass spectrometer. T.l.c. was carried out using Merck Kieselgel 60 F_{254} plates and column chromatography was carried out under gravity using Merck Kieselgel 70-230 mesh. Solvents were dried using standard techniques as appropriate.

(–)-2-Bornyloxy-4-dimethylaminopyridine 183



(–)-Borneol (0.92 g; 6.0×10^{-3} mol; 1.2 equivalents) was added to DMSO (20 ml) under nitrogen. To this solution was added sodium hydride (60% dispersion; 0.39 g; 1.2 equivalents) and the resultant suspension was stirred for 6 hours or until the evolution of hydrogen gas had ceased. 2-Bromo-4-dimethylaminopyridine (1 g; 5.0×10^{-3} mol) was then added and the reaction was slowly heated to 80 °C for 1 hour and then for 6 hours at 120 °C. Upon cooling, excess sodium hydride was neutralised by careful addition of ethanol and the mixture was acidified with aqueous HCl. The aqueous layer was extracted with ether (3 × 50 ml), basified and re-extracted again with ether (3 × 50 ml). The organic layers were combined, dried (Na_2SO_4) and evaporated. Chromatography over silica gel using hexane : ether 80 : 20 gave 2-bornyloxy-4-dimethylaminopyridine **183** (0.53 g; 36%), m.p. 67.5-68.5 °C, $[\alpha]_D^{20}$ – 52.3 ° (*c* = 0.485, EtOH)

ν_{max} (N) 2912, 2871, 1608, 1544, 1508, 1457, 1376, 1313, 1282, 1261, 1155, 1120, 1052, 1035, 1010, 817 and 723 cm^{-1}.

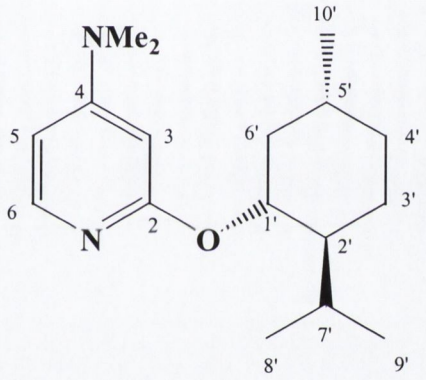
δ_H ($CDCl_3$) 0.91 (6H, s, 2Me), 0.99 (3H, s, Me), 1.07 - 2.48 (8H including multiplets at 1.07 (1H), 1.32 (2H), 1.69 (1H), 1.76 (1H), 2.23 (1H), 2.45 (1H)), 2.98 (6H,

NMe_2), 5.07 (1H, d, *J* 9 Hz, H-1'), 5.90 (1H, d, *J* 2.5, H-3), 6.22 (1H, dd, J_1 2.0, J_2 6.0, H-5) and 7.84 (1H, d, *J* 6.0, H-6) ppm.

δ_C ($CDCl_3$) 13.26 (CH_3), 18.63 (CH_3), 19.39 (CH_3), 26.71 (CH_2), 27.68 (CH_2), 36.72 (CH_2), 38.79 (NMe_2), 44.68 (C-4'), 47.16 (quat.), 48.60 (quat.), 79.66 (C-2'), 91.08 (C-5), 101.75 (C-3), 146.48 (C-6), 156.44 (C-4) and 165.60 (C-2) ppm.

MS (ES): Found *m/z* 275.2668 (nominal mass) calculated for $[C_{17}H_{26}N_2O + H]^+$ 275.2123.

(–)-2-Menthyloxy-4-dimethylaminopyridine 184



This was synthesised as described for (–)-2-bornyloxy-4-dimethylaminopyridine **183** but using 2-bromo-4-dimethylaminopyridine (0.5 g; 2.48×10^{-3} mol), (–)-menthol **181** (0.42 g; 2.72×10^{-3} mol, 1.1 equivalents) and sodium hydride (60% dispersion, 0.109 g; 2.72×10^{-3} mol). Chromatography over silica gel using hexane : ether 80 : 20 gave 2-menthyloxy-4-dimethylaminopyridine **184** (0.068 g; 5%), m.p. 57 °C (from hexane) $[\alpha]_D^{20}$ – 110.4 ° (*c* = 0.521, EtOH).

ν_{max} (N) 2952, 2927, 2867, 1608, 1542, 1509, 1457, 1444, 1376, 1315, 1284, 1259, 1157, 1120, 1097, 1029 and 815cm^{-1}.

δ_H ($CDCl_3$) 0.80 (3H, Me), 0.92 (7H, 2Me + H overlapping), 1.02 – 2.2 (8H, including multiplets at 1.13 (1H), 1.17 (1H), 1.47 (1H), 1.60 (1H), 1.72 (2H), 2.09 (1H) and 2.25 (1H)), 2.97 (6H, s, NMe_2), 4.98 (1H, H-2'), 5.87 (1H, d, *J* 2.0, H-3), 6.22 (1H, dd, J_1 2.5, J_2 6.0, H-5) and 7.85 (1H, d, *J* 6.0, H-6) ppm.

δ_C ($CDCl_3$) 16.25 (C-9'), 20.38 (C-8'), 21.69 (C-10'), 23.33 (C-3'), 25.92 (C-7'), 30.86 (C-5'), 34.21 (C-4'), 38.74 (NMe_2), 40.79 (C-6'), 47.60 (C-2'), 73.47 (C-1'), 91.04 (C-5), 101.70 (C-3), 146.31 (C-6), 156.53 (C-4) and 164.88 (C-2) ppm.

MS (ES): Found *m/z* 277.2499 (nominal mass) calculated for $[C_{17}H_{28}N_2O + H]^+$ 277.2280.

4-Dimethylamino-3-methylsulfanyl-2-pyridone 185

This was the major product isolated from the syntheses of (–)-2-bornyloxy-4-dimethylaminopyridine **183** and (–)-2-menthyloxy-4-dimethylaminopyridine **184**.

Synthesis

2-Bromo-4-dimethylaminopyridine **133** (1 g; 4.9×10^{-3} mol) was added to DMSO (10 ml) under nitrogen. Sodium hydride (60% dispersion; 0.200 g; 1.2 equivalents) was added and the mixture was heated to 120 °C for 4 h. The reaction was allowed to cool to room temperature and ethanol was added cautiously (2 ml) to decompose any excess sodium hydride. Water (10 ml) was then added and the mixture was acidified with aqueous HCl. The aqueous layer was extracted with DCM (3 × 50 ml), basified and re-extracted again with DCM (3 × 50 ml). The second extracts were combined and dried, ($MgSO_4$) and evaporated. Chromatography over silica gel using DCM : MeOH 95 : 10 gave 4-dimethylamino-3-methylsulfanyl-2-pyridone **185** (0.84 g; 92%), m.p. 210 °C (d) (from ether).

ν_{max} (N) 2952, 2854, 2726, 1606, 1461, 1376, 1303, 1261, 1155, 1025, 998, 830 and 723 cm^{-1}.

δ_H ($CDCl_3$) 2.31 (3H, s, SMe), 3.08 (6H, s, NMe_2), 6.0 (1H, d, *J* 7.0, H-5), 7.27 (1H, d, *J* 7.0 Hz, H-6) and 12.72 (1H, bs, N-H exchanges with D_2O) ppm.

δ_C ($CDCl_3$) 16.70 (SMe), 40.55 (NMe_2), 99.20 (C-5), 105.58 (C-3), 132.62 (C-6), 162.28 (C-2) and 165.43 (C-4) ppm.

MS (ES): Found *m/z* 185.0957 (nominal mass) calculated for $[C_8H_{12}N_2OS + H]^+$ 185.0749.

General procedure for the synthesis of the heterocyclic *N*-oxides 199, 201, 202 and 206

2,6-*bis*(Dimethylamino)pyridine *N*-oxide **201** and 2,4,6-*tris*(dimethylamino)pyridine *N*-oxide **202** were synthesised from 2,6-dichloropyridine *N*-oxide **207** and 2,6-diiodo-4-dimethylaminopyridine *N*-oxide **179**, respectively. 2-Dimethylaminopyridine *N*-oxide **199** and 2-(1'-pyrrolidinyl)pyridine *N*-oxide **206** were synthesised from 2-chloropyridine *N*-oxide **126**. A typical procedure is as follows.

To a pressure tube was added either of the halopyridine *N*-oxides **126**, **179** or **207** (3.0 g) and excess 40% dimethylamine solution (5-10 equivalents). When pyrrolidine was utilised as the amine, water (10 ml) was also added to the reaction mixture. The mixture was heated to 130 °C for typically 24 h or until t.l.c revealed complete conversion of starting material. The contents were poured onto ice/water (20 ml) and extracted with DCM (3 × 60 ml). The organic layers are combined, dried ($MgSO_4$) and evaporated. Chromatography over silica gel with DCM : MeOH, 95 : 5 usually afforded material of good quality.

2-Dimethylaminopyridine *N*-oxide 199

Yield 3.1 g (93%), b.p. 160 °C @ 0.5 mm Hg, *lit.*[7] 143-145 @ 0.25 mm Hg.

ν_{max} (L) 3065, 2951, 2860, 1605, 1511, 1440, 1354, 1239, 1144, 1054, 949, 837 and 760 cm^{-1}.

δ_H ($CDCl_3$) 2.90 (6H, s, NMe_2), 6.66-6.72 (2H, m, overlapping, H-3 + H-5), 7.17 (1H, dt, J_1 1.5, J_2 8.0, H-4) and 8.12 (1H, d, J 8.0, H-6) ppm.

δ_C ($CDCl_3$) 39.96 (NMe_2), 114.01 (C-3), 116.50 (C-5), 126.42 (C-4), 139.98 (C-6) and 154.97 (C-2) ppm.

MS (ES): Found *m/z* 161.0968 (nominal mass) calculated for $[C_7H_{10}N_2O + Na]^+$ 161.0691.

2,6-*bis*(Dimethylamino)pyridine *N*-oxide 201

Yield 2.8 g (80%), No melting point was obtained for this compound due to its unstable nature.

δ_H ($CDCl_3$) 2.99 (12H, s, $(NMe_2)_2$), 6.48 (2H, d, J 8, H-3 + H-5) and 7.17 (1H, t, J 8, H-4) ppm.

δ_C ($CDCl_3$) 40.53 (NMe_2), 105.89 (C-3 + C-5), 125.77 (C-4) and 156.30 (C-2) ppm.

2,4,6-*tris*(Dimethylamino)pyridine *N*-oxide 202

Yield 1.12 g (65%).

δ_H ($CDCl_3$) 2.97 (6H, s, 4-NMe_2), 3.04 (12H, s, NMe_2) and 5.20 (2H, s, H-3 + H-5) ppm).

δ_C ($CDCl_3$) 37.66 (4-NMe_2), 41.33 (2,6-*bis*(NMe_2), 78.17 (C-2 + C-6), 87.54 (C-3 + C-5) and 159.24 (C-4) ppm.

2-(1'-Pyrrolidinyl)pyridine *N*-oxide 206

Yield 3.0 g (78%), m.p. 190 °C (from DCM/ether).

ν_{max} (N) 2954, 2923, 2854, 1631, 1579, 1527, 1461, 1376, 1351, 1284, 1253, 1180, 1162, 1132, 1041, and 971 cm^{-1}.

δ_H ($CDCl_3$) 2.05 (4H, m, H-3' + H-4'), 3.89-3.93 (4H, m, H-2' + H-5'), 6.75 (1H, t, *J* 8.0, H-5), 6.88 (1H, d, *J* 8.0, H-3), 7.65 (1H, dt, J_1 1.5, J_2 7.0, H-4) and 8.07 (1H, d, *J* 7.5, H-6) ppm.

δ_C ($CDCl_3$) 24.68 (C-3' + C-4'), 49.51 (C-2' + C-5'), 111.42 (C-5), 113.72 (C-3), 127.00 (C-4), 139.86 (C-6) and 151.54 (C-2) ppm.

MS (ES): Found *m/z* 165.1252 (nominal mass) calculated for $[C_9H_{12}N_2O + H]^+$ 165.1028.

Synthesis of 2,6-dichloropyridine *N*-oxide 207

Hydrogen peroxide (30%; 6 ml) was added to 2,6-dichloropyridine (3 g; 20×10^{-3} mol) in trifluoroacetic acid (30 ml) and the mixture was refluxed for 5 h on a steam bath. The mixture was then diluted with water (300 ml), cooled to –5 °C and filtered to remove insoluble 2,6-dichloropyridine. The filtrate was concentrated *in vacuo* to a volume of 10 ml. To this was added chloroform and solid sodium carbonate. After evolution of carbon dioxide has ceased the mixture was shaken up in a separating funnel and the layers separated. The aqueous layer was extracted with chloroform (2 × 60 ml) and the layers combined, dried ($MgSO_4$) and evaporated to give 2,6-dichloropyridine *N*-oxide **207** (1.94 g; 60%), m.p. 138.5-139.0 °C (from methanol), *lit.*[14] m.p. 139.5-140 °C.

ν_{max} (N) 2952, 2854, 2726, 1711, 1461, 1376, 1304, 1272, 1148, 1077, 966 and 722 cm^{-1}.

δ_H ($CDCl_3$) 7.10-7.15 (1H, t, *J* 8, H-4) and 7.45 (2H, d, *J* 8, H-3 + H-5) ppm.

δ_C ($CDCl_3$) 123.98 (C-3 + C-5), 124.63 (C-4) and 143.14 (C-2 + C-6) ppm.

Pyridine *N*-oxide 203

Hydrogen peroxide (30%; 5 ml) was added to solution of pyridine (4 g; 50×10^{-3} mol) in acetic acid (30 ml) and the mixture was heated on a water bath to 80 °C. After 4 h, hydrogen peroxide (5 ml) was added and the mixture was refluxed for a further 4 h. Water was added (30 ml) and the mixture was concentrated *in vacuo*. Sodium carbonate was added to the residue until the evolution of carbon dioxide had ceased. The aqueous layer was then extracted with chloroform (3 × 60 ml). The organic layers were combined, dried ($MgSO_4$) and evaporated to give pyridine *N*-oxide **203** (3.1 g; 65%), m.p. 65 °C, *lit.*[15] 64-66 °C.

ν_{max} (N) 3373, 2854, 2726, 1604, 1461, 1376, 1240, 1171, 1070, 1015, 836, 767, 722 and 675 cm^{-1}.

δ_H ($CDCl_3$) 7.23-7.24 (3H, m, H-3, H-4 and H-5) and 8.17 (2H, d, H-2 + H-6) ppm.

δ_C ($CDCl_3$) 125.17 (C-3 + C-5), 125.62 (C-4) and 138.88 (C-2 + C-6) ppm.

General procedure for the synthesis of (–)-2-bornyloxypyridine *N*-oxide 214, (–)-2-menthyloxyypyridine *N*-oxide 215, (–)-2,6-dibornyloxypyridine *N*-oxide 217 and (–)-2,6-dibornyloxy-4-dimethylaminopyridine *N*-oxide 218

(–)-2-Bornyloxypyridine *N*-oxide **214** and (–)-2-menthyloxyypyridine *N*-oxide **215** were synthesised from 2-chloropyridine *N*-oxide **126** as described under Method A. (–)-2,6-Dibornyloxypyridine *N*-oxide **217** and (–)-2,6-dibornyloxy-4-dimethylamino pyridine *N*-oxide **218** was synthesised from 2,6-dichloropyridine *N*-oxide **207** and 2,6-diiodo-4-dimethylaminopyridine *N*-oxide **179** as described in Method B.

Method A

2-Chloropyridine *N*-oxide **126** (3 g; 23×10^{-3} mol) was added to a solution under nitrogen containing either of the alcohols (–)-borneol **182** (4.29 g; 27×10^{-3} mol, 1.2 equivalents) or (–)-menthol **181** (4.30 g; 27×10^{-3} mol, 1.2 equivalents) in dry THF (100 ml) and sodium hydride (60% dispersion; 0.90 g; 1.2 equivalents). The mixture was refluxed until t.l.c analysis showed complete conversion of the starting material. Upon cooling ethanol (5 ml) was added to neutralise any excess sodium hydride. The reaction mixture was diluted with DCM (100 ml) and washed with water. The organic layer was dried ($MgSO_4$) and evaporated. Chromatography over silica gel using DCM : MeOH 96 : 4 usually gave product of good purity.

Method B

(–)-Borneol **182** (2.06 g; 13 × 10^{-3} mol, 2.2 equivalents) was added to a solution under nitrogen containing either 2,6-dichloropyridine *N*-oxide **207** (1 g; 6 × 10^{-3} mol) or 2,6-diiodo-4-dimethylaminopyridine *N*-oxide **179** (2.34 g; 6 × 10^{-3} mol) in dry THF (50 ml) with sodium hydride (60% dispersion; 0.436 g; 2.2 equivalents). The reaction was refluxed until t.l.c analysis showed complete conversion of the starting material. Upon cooling ethanol (5 ml) was added to neutralise any excess sodium hydride. The reaction mixture was diluted with DCM (100 ml) and washed with water. Chromatography over silica gel using ether : hexane 90 : 10 as mobile phase was used to purify (–)-2,6-dibornyloxypyridine *N*-oxide **217** whilst DCM : MeOH 96 : 4 was used as eluant for the purification of (–)-2,6-dibornyloxy-4-dimethylaminopyridine *N*-oxide **218**.

(–)-2-Bornyloxypyridine *N*-oxide 214

Yield 2.49 g (44%), m.p. 49.8-50.8 °C (from hexane) $[\alpha]_D^{20}$ – 69 ° (*c* = 0.494, in EtOH)

ν_{max} (N) 2898, 1603, 1555, 1452, 1376, 1300, 1200, 1113, 1032, 980, 889, 869, 827, 750 and 720 cm^{-1}.

δ_H ($CDCl_3$) 0.92 (6H, 2Me), 0.99 (3H, s, Me), 1.20 - 2.40 (7H, including multiplets at 1.21 (1H), 1.37 (2H), 1.75 (2H) and 2.38 (2H), 4.64 (1H, d, *J* 9.0, H-1'), 6.78 (1H, d, *J* 8.0, H-3), 6.84 (1H, t, *J* 7.5, H-5), 7.18 (1H, t, *J* 7.5, H-4) and 8.22 (1H, d, *J* 7.5, H-6) ppm.

δ_C ($CDCl_3$) 13.22 (CH_3), 18.41 (CH_3), 19.22 (CH_3), 26.31 (CH_2), 27.37 (CH_2), 35.75 (CH_2), 44.51 (C-4'), 47.50 (quat.), 49.51 (quat.), 86.17 (C-2'), 110.99 (C-5), 116.85 (C-3), 126.53 (C-4), 139.98 (C-6) and 158.19 (C-2) ppm.

MS (ES): Found *m/z* 248.2345 (nominal mass) calculated for $[C_{15}H_{21}NO_2 + H]^+$ 248.1651.

(–)-2-Menthyloxypyridine *N*-oxide 215

Yield 3.0 g (53%), m.p. 64 °C (from hexane) $[\alpha]_D^{20}$ – 136 ° (c = 0.664 in EtOH).

ν_{max} (N) 2910, 1605, 1555, 1497, 1461, 1376, 1315, 1272, 1202, 1104, 1038, 973, 876, 715 and 719 cm^{-1}.

δ_H ($CDCl_3$) 0.78 (3H, d, *J* 7.0, Me), 0.94 (6H, t, *J* 8.0, 2Me), 1.04 - 2.37 (7H, including multiplets at 1.03 (1H), 1.26 (1H), 1.45 (1H), 1.76 (2H), 2.01 (1H) and 2.33 (1H)), 4.50 (1H, dt, J_1 4.0, J_2 11.0, H-1'), 6.84-6.91 (2H, m, overlapping, H-5 + H-3), 7.20 (1H, dt, J_1 1.5, J_2 8.0, H-5) and 8.22 (1H, dd, J_1 2.0, J_2 7.0, H-6) ppm.

δ_C ($CDCl_3$) 16.04 (CH_3), 20.66 (CH_3), 21.90 (CH_3), 23.13 (CH_2), 25.61 (CH), 31.49 (CH), 34.06 (CH_2), 40.00 (CH_2), 47.41 (CH), 81.10 (C-2'), 112.01 (C-5), 117.50 (C-3), 127.12 (C-4), 140.58 (C-6) and 157.60 (C-2) ppm.

MS (ES): Found *m/z* 250.0142 (nominal mass) calculated for $[C_{15}H_{23}NO_2 + H]^+$ 250.1807.

(–)-2,6-Dibornyloxypyridine *N*-oxide 217

Yield 1.47 g (60%), m.p. 182-183 ° C, $[\alpha]_D^{20}$ – 65 ° (*c* = 0.569, in EtOH).

ν_{max} (N) 2952, 2922, 2853, 1561, 1495, 1462, 1415, 1376, 1346, 1309, 1287, 1230, 1117, 1095, 964, 821, 754 and 721 cm^{-1}.

δ_H ($CDCl_3$) 0.93 (12H, d, *J* 3.0, 4Me), 1.01 (6H, s, 2Me), 1.21 - 2.49 (14H, including multiplets at 1.23 (2H), 1.36 (4H), 1.76 (4H), 2.37 (2H) and 2.43 (2H)), 4.58 (2H, d, *J* 8.0, H-1' + H-1''), 6.39 (2H, d, *J* 8.5, H-3 + H-5) and 7.05 (1H, t, *J* 8.0, H-4) ppm.

δ_C ($CDCl_3$) 13.23 (CH_3), 18.48 (CH_3), 19.23 (CH_3), 26.30 (CH_2), 27.34 (CH_2), 35.79 (CH_2), 44.61 (CH_2), 47.45 (quat.), 49.55 (quat.), 85.73 (C-2'), 101.81 (C-3 + C-5), 125.54 (C-4) and 158.89 (C-2) ppm.

MS (ES): Found *m/z* 400.4326 (nominal mass) calculated for $[C_{25}H_{37}NO_3 + H]^+$ 400.2852.

(–)-2,6-Dibornyloxy-4-dimethylaminopyridine *N*-oxide 218

Yield 1.6 g (60 %), m.p 175(d) °C (from hexane). $[\alpha]_D^{20}$ – 89 ° (*c* = 0.752 in EtOH).

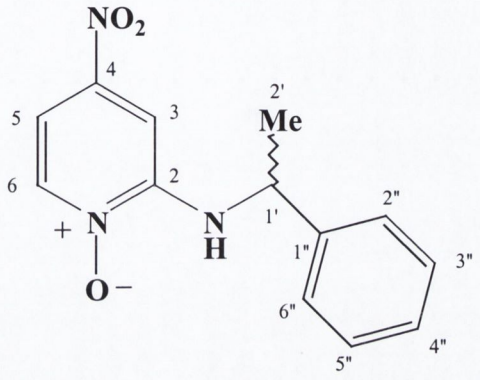
ν_{max} (N) 2952, 2922, 2853, 1561, 1495, 1462, 1415, 1376, 1346, 1309, 1287, 1230, 1117, 1095, 964, 821, 754 and 721 cm^{-1}.

δ_H ($CDCl_3$) 0.81-0.97 (18H, m, 4 overlapping Me), 1.05 - 2.35 (14H, including multiplets at 1.25 (2H), 1.41 (4H), 1.76 (4H), 2.38 (2H) and 2.40 (2H)), 2.98 (6H, s, NMe_2), 4.43 (2H, d, *J* 8.5, H-1' and H-1'') and 5.55 (2H, s, H-3 + H-5) ppm.

δ_C ($CDCl_3$) 13.38 (CH_3), 18.92 (CH_3), 19.50 (CH_3), 26.59 (CH_2), 27.57 (CH_2), 35.75 (CH_2), 37.17 (quat.), 39.03 (quat.), 39.72 (NMe_2), 47.29 (C-4'), 86.53 (C-2'), 111.81 (C-3 + C-5), 156.95 (C-4) and 163.64 (C-2) ppm.

MS (ES): Found *m/z* 443.3943 (nominal mass) calculated for $[C_{27}H_{42}N_2O_3 + H]^+$ 443.3274.

4-Nitro-2-(1'-phenylethylamino)pyridine *N*-oxide 222



2-Chloro-4-nitropyridine *N*-oxide **127** (1 g; 5.7×10^{-3} mol) was added to a solution containing α-methylbenzylamine (1.46 g; 12.0×10^{-3} mol, 2.05 equivalents) in *tert*-butyl alcohol (10 ml) in a pressure tube. The reaction was heated to 120 °C during 18 h. After cooling the reaction mixture was diluted with DCM (20 ml) and was washed with water (2 × 10 ml). The organic layer was dried ($MgSO_4$) and concentrated *in vacuo*. Chromatography over silica gel using DCM : MeOH 96 : 4 as mobile phase gave 4-nitro-2-(1'-phenylethylamino)pyridine *N*-oxide **222** (1.30 g; 88%), m.p 111 – 112 °C.

ν_{max} (N) 3278, 2952, 2927, 1625, 1536, 1506, 1457, 1376, 1344, 1311, 1270, 1230, 1213, 1171, 1083 and 970 cm^{-1}.

δ_H ($CDCl_3$) 1.74 (3H, d, *J* 6.5, Me), 4.68 (1H, multiplet, H-1'), 7.19 (1H, d, *J* 3.0, H-3), 7.31-7.41(7H, m, overlapping, Ph, H-5 and N-H) and 8.23 (1H, d, *J* 7.0, H-6) ppm.

δ_C ($CDCl_3$) 22.83 (CH_3), 51.52 (C-1'), 98.72 (C-3), 104.40 (C-5), 124.11 (C-H, Ph), 126.62 (C-H, Ph), 127.76 (C-H, Ph), 135.93 (C-6), 140.24 (quat., C-1'') and 142.97 (quat. C-4) and 148.40 (C-2) ppm.

4-Chloro-2-(1'-phenylethylamino)pyridine *N*-oxide 223

4-Nitro-2-(1'-phenylethylamino)pyridine *N*-oxide **222** (0.67 g; 25 × 10^{-3} mol) was added to a solution of acetyl chloride (8 ml) in chloroform (30 ml) and the mixture was refluxed for 24 h. Upon cooling the contents were then poured onto ice/water neutralised with Na_2CO_3 and extracted with DCM (3 × 20 ml). The organic layers were combined and washed with saturated $NaHCO_3$, dried ($MgSO_4$) and the solvent removed. Chromatography over silica gel using DCM : MeOH 96 : 4 as mobile phase to give 4-chloro-2-(1'-phenylethylamino)pyridine *N*-oxide **223** (0.31g, 46%), m.p. 111 °C.

δ_H ($CDCl_3$) 1.56 (3H, d, *J* 7.0, Me), 4.45 (1H, multiplet, H-1'), 6.24 (1H, d, *J* 3.0, H-3), 6.44 (1H, dd, J_1 3.0, J_2 7.0, H-5), 7.24-7.44 (6H, overlapping m, Ph, N-H) and 7.96 (1H, d, *J* 7.0, H-6) ppm.

δ_C ($CDCl_3$) 24.04 (CH_3), 52.26 (C-1'), 105.97 (C-3), 111.64 (C-5), 125.09 (C-H, Ph), 127.30 (C-H, Ph), 128.59 (C-H, Ph), 133.81 (C-1''), 136.26 (C-6), 141.88 (quat. C-2) and 149.29 (quat. C-2) ppm.

MS (ES): Found *m/z* 249.0532 (nominal mass) calculated for $[C_{13}H_{13}ClN_2O + H]^+$ 249.0795.

2-(1'-Phenylethylamino)-4-dimethylaminopyridine *N*-oxide 220

4-Chloro-2-(1'-phenylethylamino)pyridine *N*-oxide **223** (0.50 g; 2.0×10^{-3} mol) was added to a pressure tube containing aqueous dimethylamine solution (40%, 10 ml) and the mixture heated to 120 °C for 24 h or until t.l.c analysis revealed consumption of the starting material. The mixture was concentrated *in vacuo* and chromatography over silica gel using DCM : MeOH 96 : 4 afforded 2-(1'-Phenylethylamino)-4-dimethylaminopyridine *N*-oxide **220** (0.36 g; 70%).

δ_H ($CDCl_3$) 1.65 (3H, d, *J* 6.5, Me), 2.80 (6H, s, NMe_2), 4.50 (1H, m, H-1'), 5.33 (1H, d, *J* 3.0, H-3), 5.88 (1H, dd, J_1 3.0, J_2 8.0, H-5), 6.95 (1H, bs, N-H), 7.24-7.36 (5H, overlapping m, Ph) and 7.80 (1H, d, *J* 8.0, H-6) ppm.

δ_C ($CDCl_3$) 24.11 (CH_3), 39.05 (NMe_2), 52.48 (C-1'), 87.27 (C-3), 96.80 (C-5), 125.24 (C-H, Ph), 126.96 (C-H, Ph), 128.40 (C-H, Ph), 136.36 (C-6), 142.91 (quat. C-2'), 148.54 (quat. C-4) and 150.10 (quat. C-2) ppm.

MS (ES): Found *m/z* 258.1582 (nominal mass) calculated for $[C_{15}H_{19}N_3O + H]^+$ 258.1606.

(1'*S*)-(–)-2-(1'-phenylethylamino)-4-dimethylaminopyridine 221

2-Bromo-4-dimethylaminopyridine **133** (0.65 g, 3.25×10^{-3}) in IPA 4 ml containing (–)-α-methylbenzylamine (1.46 g; 12.0×10^{-3} mol, ~ 4.0 equivalents) and the solution was heated to 300 °C in a pressure tube for approximately 96 h. The reaction was diluted with DCM (30 ml) and washed with water (30 ml). The organic layer was washed with a very dilute acidic solution (20 ml, approx. pH 5-6). The organic layer was dried (Na_2SO_4) and concentrated *in vacuo*. (1'*S*)-(–)-2-(1'-

phenylethylamino)-4-dimethylaminopyridine **221** was precipitated by adding hexane (30 ml) which also dissolved any residual α-methylbenzylamine left. The hexane was decanted from the flask. A further portion of hexane (30 ml) was added and the compound filtered. The compound was washed with a hexane (20 ml × 2) to give (1'*S*)-(–)-2-(1'-phenylethylamino)-4-dimethylaminopyridine **221** (0.55 g, 70%), m.p. 117.5 °C. $[\alpha]_D^{20}$ – 58.6 ° (*c* = 0.1 in EtOH).

ν_{max} (N) 3210, 2954, 2923, 2854, 1602, 1567, 1527, 1490, 1373, 1295, 1278, 1211, 1164, 983, 800 and 701 cm^{-1}.

δ_H ($CDCl_3$) 1.55 (3H, d, *J* 6.5, Me), 2.82 (6H, s, NMe_2), 4.56 (1H, m, *J* 6.0, H-1'), 4.69 (1H, bs, N-H), 5.33 (1H, d, *J* 2.0, H-3), 5.95 (1H, dd, J_1 3.5, J_2 6.0, H-5), 7.23 (1H, t, *J* 7.0, H-4''), 7.32 (2H, t, *J* 7.5, H-2'' + H-6''), 7.40 (1H, d, *J* 7.5, H-3'' + H-4'') and 7.78 (1H, d, *J* 6.0, H-6) ppm.

δ_C ($CDCl_3$) 24.09 (CH_3), 38.57 (NMe_2), 51.91 (C-1'), 87.52 (C-3), 98.53 (C-5), 115.28 (quat, Ph), 125.40 (C-H, Ph), 126.35 (C-H, Ph), 128.09 (C-H, Ph), 144.88 (quat. Ph), 147.67 (C-6) and 155.52 (quat. C-2) ppm.

MS (ES): Found *m/z* 242.2283 (nominal mass) calculated for $[C_{15}H_{19}N_3 + H]^+$ 242.1657.

3.8 References

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Appendix

Crystal structure determination of 4-dimethylamino-3-methylsulfanyl-2-pyridine

Crystallography

Data were collected on an Enraf-Nonius CAD-4 diffractometer (Mo-Kα, $\lambda = 0.71073$ Å radiation, graphite monochromator, ω-2θ scan mode) at 20°C. The crystal data and experimental parameters are summarised in **Table 1**. Atomic coordinates, bond lengths and bond angles are found in **Tables 2 and 3**. The final cell parameters were determined using the Celdim routine. It was not found necessary to apply decay or absorption corrections to the data.

The structure was solved by automatic direct methods using SHELXS-86[1] and was refined by full-matrix least-squares anaylsis on F^2 with SHELXL-93.[2] All the non-hydrogen atoms were refined anisotropically. The hydrogen atoms were located from subsequent difference Fourier maps. The diagrams of the structure was drawn using SCHAKAL.[3]

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1. G. M. Sheldrick, *Acta Cryst.*, A46, 467.
2. G. M. Sheldrick, SHELXL-93, *Programme for crystal structure refinement*, University of G□ttingen, Germany, 1993.
3. E. KELLER, University of Freilburg, Germany.

Table 1 **Crystal data and structure refinement for 4-dimethylamino-3-methylsulfanylpyridine**

Empirical formula	$C_8H_{12}N_2OS$		
Formula weight	184.25		
Temperature	293 (2) K		
Wavelength	0.71073 □		
Crystal system	monoclinic		
Space group	P21/c		
Unit cell dimensions	a = 8.5961 (19)	Å	$\alpha = 90$ °
	b = 7.6121 (16)	Å	$\beta = 107.01(14)$ °
	c = 14.613 (18)	Å	$\gamma = 90$ °
Volume	914.4 (3) $Å^3$,		
Z	4		
Density (calculated)	1.279 gcm^{-3}		
Absorption coefficient μ(Mo-Kα)	0.308 mm^{-1}		
wR_2	0.1272		
Reflections collected	1809 (unique 1564)		
R	0.056 [I > 2s(I)]		

ENRAF NONIUS CAD4 diffractometer with graphite monochromator, ω-scans, structure solved by automatic direct methods using SHELXS-86 and refined using full matrix least squares on F^2 using SHELXL-93. All the non-hydrogen atoms were refined anisotropically and the hydrogen atoms were located from subsequent difference Fourier maps.

Table 2 **Atomic coordinates ($\times 10^{-4}$) and equivalent isotropic displacement parameters ($\square^2 \times 10^{-3}$) for 4-dimethylamino-3-methyl sulfanylpyridine**

	X	Y	Z	$U_{(eq)}$
S1	3655(11)	503(13)	5662(6)	43.7(3)
O1	1200(3)	3243(3)	4837(15)	49.2(7)
N1	3450(4)	94(3)	7763(19)	43.6(8)
N2	762(4)	4149(4)	6212(2)	40.2(7)
C2	2624(4)	1446(4)	7231(2)	32.3(7)
C1	2443(4)	1649(4)	6255(2)	32.3(7)
C5	1462(4)	3020(4)	5718(2)	35.8(8)
C4	1017(5)	4034(5)	7167(2)	42.9(9)
C3	1918(4)	2752(5)	7685(3)	40.5(8)
C7	4065(7)	2280(7)	8799(3)	57.8(12)
C8	2203(6)	8330(7)	4822(4)	59.2(12)
C6	3291(8)	1699(6)	7396(4)	62.1(13)
H1	130(4)	4920(5)	5930(3)	44(12)
H3	2000(4)	2650(4)	8300(2)	30(8)
H4	500(4)	4860(4)	740(2)	32(9)
H6A	2340(5)	1810(5)	6780(3)	58(11)
H6B	3230(8)	2470(8)	7810(5)	130(2)
H6C	4130(8)	1930(9)	7200(5)	130(3)
H7A	4340(5)	1360(6)	8940(3)	67(14)
H7B	4930(5)	4800(6)	9020(3)	63(12)
H7C	320(6)	8000(6)	9110(3)	74(14)
H8A	1890(5)	1750(6)	5160(3)	66(14)
H8B	2580(6)	1160(7)	4360(4)	110(2)
H8C	1240(6)	200(7)	4510(4)	900(17)

Table 3 **Bond lengths [□] and bond angles [°] for 4-dimethylamino-3-methylsulfanylpyridine**

S(1)	-	C(1)	1.769(3)
□			
S(1)	-	C(8)	1.790(5)
□			
O(1)	-	C(5)	1.252(4)
□			
N(1)	-	C(2)	1.358(4)
□			
N(1)	-	C(7)	1.454(5)
N(1)	-	C(6)	1.458(5)
N(2)	-	C(4)	1.351(4)
N(2)	-	C(5)	1.369(4)
C(2)	-	C(1)	1.397(4)
C(2)	-	C(3)	1.425(5)
C(1)	-	C(5)	1.424(5)
C(4)	-	C(3)	1.335(5)

C(1)-S(1)-C(8)	102.9(2)
□	
C(2)-N(1)-C(7)	120.8(3)
□	
C(2)-N(1)-C(6)	121.4(3)
C(7)-N(1)-C(6)	114.5(3)
C(4)-N(2)-C(5)	122.7(3)
N(1)-C(2)-C(1)	123.5(3)
N(1)-C(2)-C(3)	119.0(3)
C(1)-C(2)-C(3)	117.5(3)
C(2)-C(1)-C(5)	121.0(3)
C(2)-C(1)-S(1)	122.7(3)
C(5)-C(1)-S(1)	115.5(2)
O(1)-C(5)-N(2)	118.8(3)
O(1)-C(5)-C(1)	124.5(3)
N(2)-C(5)-C(1)	116.8(3)
C(3)-C(4)-N(2)	121.7(4)
C(4)-C(3)-C(2)	120.1(3)

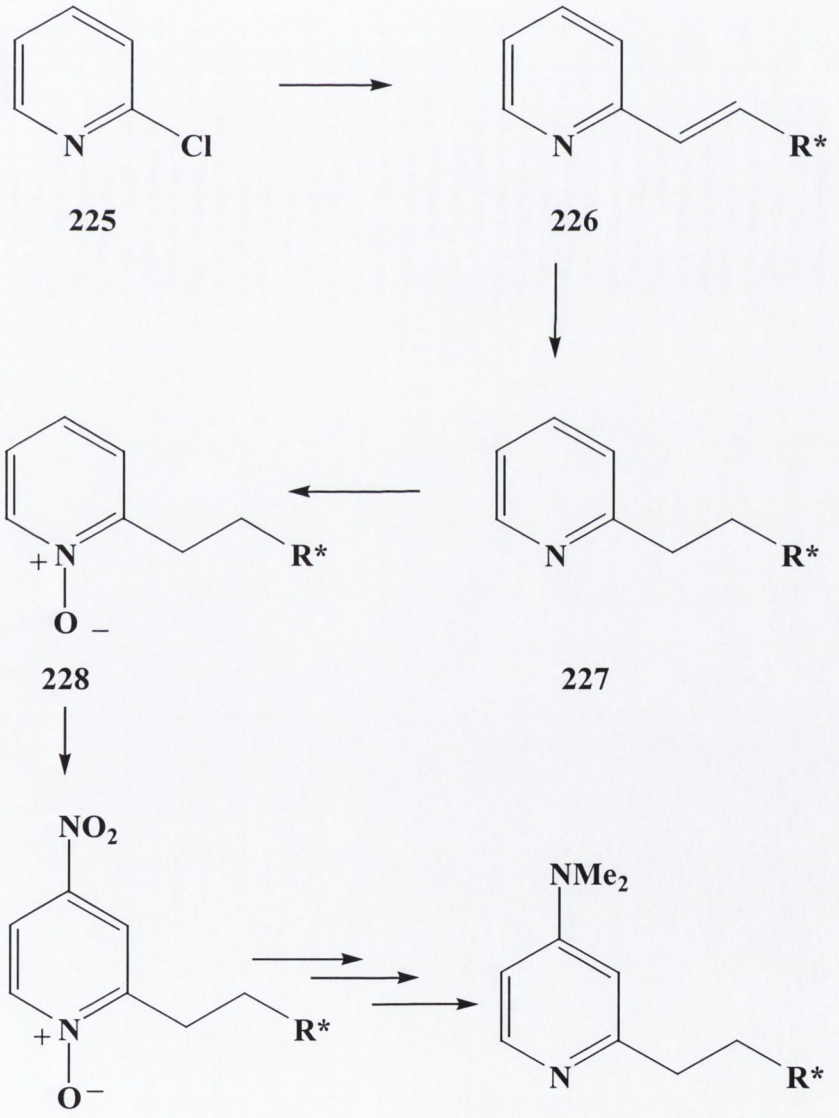
Chapter 4

A novel synthesis of bipyridines

4.1 Introduction

This work had its origins in earlier attempts to synthesise chiral 4-dialkylaminopyridines, the essence of which is described below (Scheme 4.1). It was envisaged that 2-chloropyridine **225** would undergo Heck coupling with a chiral alkene to give a chiral pyridine **226**, which after its reduction and conversion to the *N*-oxide **228**, should undergo nitration to afford the chiral nitro derivative **229**.

Scheme 4.1



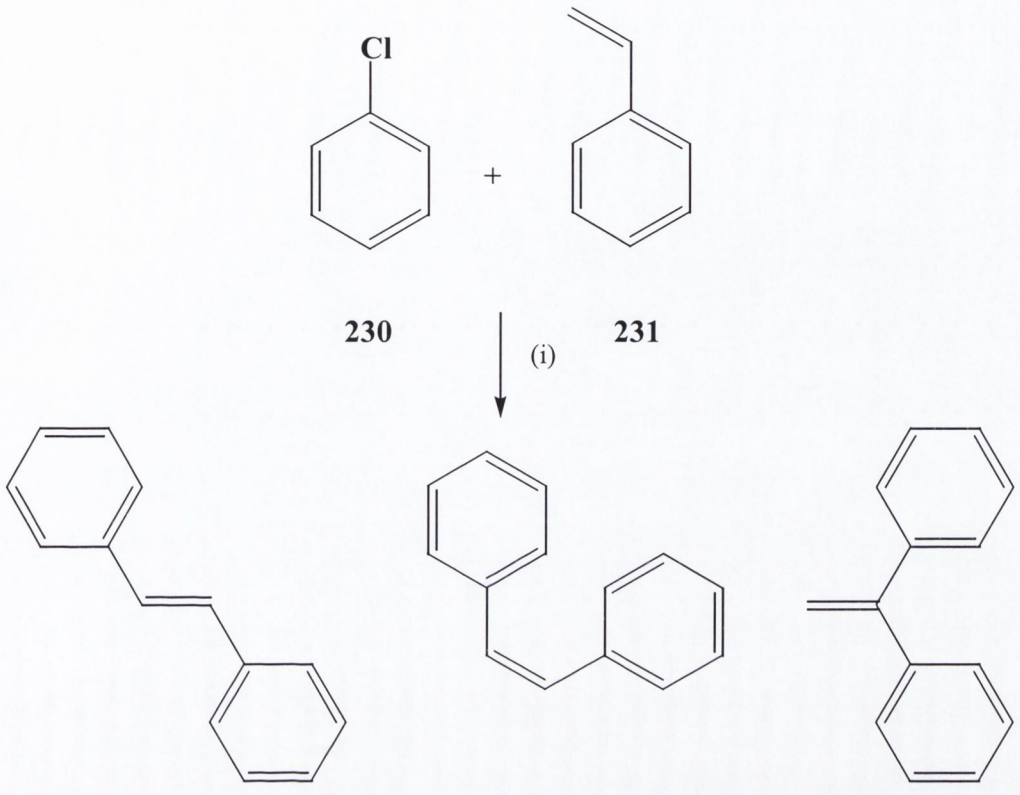
229 **R* = Chiral Substituent**

Subsequent chemistry, would allow the introduction of a 4-dimethylamino substituent and hence given the availability of suitable alkenes from the chiral pool, a whole suite of chiral hypernucleophilic acylation catalysts would ensue.

The coupling of chloroarenes with alkenes *via* a Heck reaction would not normally be possible since chloroarenes are quite unreactive.[1] For example, under classical Heck conditions bromobenzene undergoes palladium-catalysed coupling with ethyl acrylate to give ethyl cinnamate in 78% yield[2] whereas reaction with chlorobenzene gives the lower yield of 4%.[3] However, the advent of new technology devised by Reetz *et al.*[4] has made it possible for the first time to efficiently couple aryl chlorides to alkenes *via* a Heck reaction.

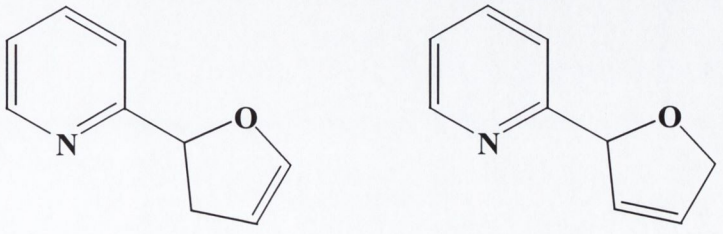
The coupling by Reetz *et al.*[4] of chlorobenzene **230** with styrene **231** was achieved using the catalytic system of $Pd(CH_3CN)_2Cl_2$: Ph_4PCl in DMF with sodium acetate as base to give the Heck products **232**, **233** and **234** (Scheme 4.2). It was found that the use of a small amount of *N,N*-dimethylglycine as an additive resulted in a pronounced improvement in regioselectivity, reducing the proportion of **234** to a negligible amount. In all cases, yields were typically of the order of 90% with *trans*-stillbene **232** having a selectivity factor of typically 85-97 : 1 over the *cis*-isomer. In summary, this represents one of the best catalytic systems for Heck reactions with normally unreactive aryl chlorides.

Scheme 4.2



Reagents and Conditions: (i) $Pd(CH_3CN)_2Cl_2$, Ph_4PCl, CH_3COONa, chlorobenzene, styrene, DMF

In order to model this reaction it was hoped to couple 2-chloropyridine **225** with 2,3-dihydrofuran to give the Heck addition products **235** and **236**. If this reaction were successful, then coupling of 2-chloropyridine **225** with chiral alkenes as envisaged in Scheme 4.1 would be possible.



235 **236**

However, the results of initial experiments using the conditions devised by Reetz[4] involving the use of various catalysts such as $Pd(OAc)_2$ and $Pd(MeCN)_2Cl_2$ gave 2,2'-bipyridine **237** as the only product, albeit in low yield, with no evidence for the formation of the expected addition products **235** and **236** (Scheme 4.3). This unusual result compelled us to review the literature on the synthesis of bipyridyls.

Scheme 4.3

237

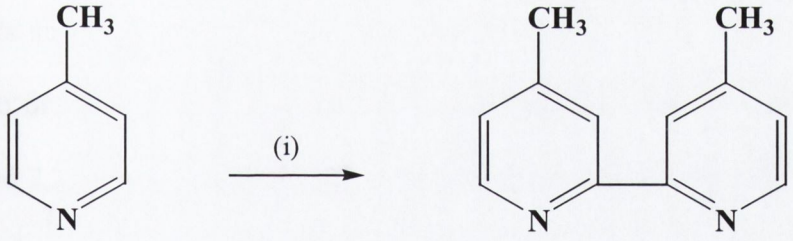
Reagents and Conditions: (i) $Pd(CH_3CN)_2Cl_2$, $(Ph)_3PCl$, *N,N*-dimethylglycine, CH_3OONa, 2,3-dihydrofuran, DMF, N_2, 48 h, 160 °C

4.2 Synthesis of bipyridines

The Ullmann reaction[5] has been used to prepare 2,2'-bipyridine **237** by treatment of 2-bromopyridine with copper powder in a high-boiling solvent.[6] The main drawback with this method is that it requires an equimolar amount of copper and typical yields are quite low (30-40%). The Ullmann reaction has also been adapted for the synthesis of symmetrically substituted bipyridines.[7] In 1956 a considerable improvement in the synthesis of 2,2'-bipyridines was discovered by Sasse *et al.*[8] who simply refluxed pyridine with degassed Raney nickel. This process has now been developed industrially as the method of choice for the synthesis of bipyridines, driven by the commercial use of the herbicide diquat.[9] Other metal

catalysts such as palladium are not nearly as effective as Raney nickel at low temperatures for the synthesis of 2,2'-bipyridine from pyridine.[10] Degassed palladium on charcoal has been used to prepare 6,6'-dimethyl-2,2'-bipyridine from 6-methylpyridine, but in low yield.[11] The limited ability of palladium on charcoal to effect the synthesis of symmetrically disubstituted bipyridines was recently (1998) demonstrated by Polin *et al.*[12] in their efforts to synthesise 4,4'-dimethyl-2,2'-bipyridine from 4-methylpyridine (Scheme 4.4). In this reaction 4-methylpyridine (250 ml) and palladium on charcoal (10% Pd; 10.4 g) afforded only minuscule amounts of product (3% yield), clearly a very unproductive process. More recently, palladium(0) has been used to catalyse the cross-coupling of aryl halides with arylstannanes,[13] arylboronic acids[14] and arylzinc[15] derivatives. While these methods are efficient they require stoichiometric amounts of the organometallic intermediate.

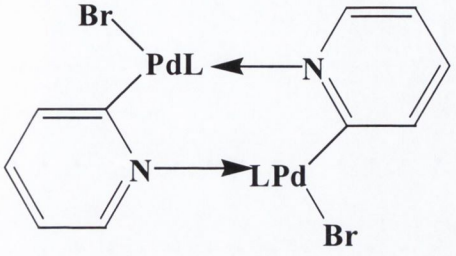
Scheme 4.4



Reagents and Conditions: (i) Pd/C, reflux, 72 h, 3%.

Bozell *et al.*[16] report that under standard Heck conditions, 3- and 4-bromopyridines undergo homocoupling to afford 3,3'-bipyridine and 4,4'-bipyridine respectively at high reactant concentrations. Modification of the reaction conditions did result in Heck cross-coupling between these halopyridines and methyl 2-acetamidoacrylate to

give the expected products. However, 2-bromopyridine did not participate in either a Heck cross-coupling or a homocoupling reaction. This observation was explained by the formation of the complex **238**.[17]



238

The formation of **238** can be explained by oxidative addition of the palladium catalyst to the bromopyridine, which then dimerises to form **238**, thus rendering the catalyst unavailable for further use. When iodopyridines were used instead of bromopyridines homocoupled products were the only products isolated.

These results suggested that the initial aim of coupling 2-chloropyridine with 2,3-dihydrofuran or a chiral alkene would be unsuccessful. However, the formation of homocoupled 2,2'-bipyridine from 2-chloropyridine in our laboratory was surprising, given that this was not observed by Bozell. Based on these literature precedents it was decided that this reaction required further investigation, and efforts concentrated on (a) optimisation of the process, (b) elucidating a possible reaction mechanism and (c) application of this methodology to the synthesis of other functionalised bipyridines.

4.3 Optimisation of the reaction conditions

A number of exploratory reactions were carried out in order to optimise the yield of 2,2-bipyridine **237** (Table 4.1).

Table 4.1 Reductive homocoupling of 2-halopyridines at 150 °C

Entry	Catalyst	Solvent	Time/h	Halopyridine	Alkene	% Yield of 237[b]
1[a]	$Pd(CH_3CN)_2Cl_2$	DMF	24	2-Chloropyridine	Cyclohexene	14
2[a]	$Pd(CH_3CN)_2Cl_2$	DMF	48	2-Chloropyridine	2,3-Dihydrofuran	100
3[a]	$Pd(OAc)_2$	DMF	48	2-Chloropyridine	2,3-Dihydrofuran	100
4[a]	$Pd(CH_3CN)_2Cl_2$	DMF	48	2-Chloropyridine	-	20
5[a]	$Pd(CH_3CN)_2Cl_2$	DMF	48	2-Bromopyridine	-	19
6[c]	$Pd(OAc)_2$	DMF	48	2-Chloropyridine	2,3-Dihydrofuran	60
7[a]	$Pd(OAc)_2$	PhMe	48	2-Chloropyridine	2,3-Dihydrofuran	32
8[a]	$Pd(OAc)_2$	DMA	48	2-Chloropyridine	2,3-Dihydrofuran	23
9[a]	$Pd(OAc)_2$	DMA/1 % H_2O	48	2-Chloropyridine	2,3-Dihydrofuran	11
10[d]	$Pd(OAc)_2$	DMF	48	2-Chloropyridine	2,3-Dihydrofuran	100
11[e]	$Pd(OAc)_2$	DMF	48	2-Chloropyridine	2,3-Dihydrofuran	100
12[e]	$Pd^0(Ph_3P)_4$	DMF	48	2-Chloropyridine	2,3-Dihydrofuran	15
13[e]	$Pd(OAc)_2$	DMF	48	2-Chloropyridine	Vinyl acetate	18
14[e]	$Pd(OAc)_2$	DMF	48	2-Chloropyridine	2,3-Dihydropyran	50

(a) 2-Halopyridine (2 mmol), Pd catalyst (2 mol%), sodium acetate (4 mmol), tetraphenylphosphonium chloride (12 mol%), alkene (6 mmol) and solvent (1 ml); (b) % yield of 2-2'-bipyridine was determined by ^1H NMR of crude product after aqueous workup and extraction with diethyl ether; (c) 2-halopyridine (2 mmol), Pd Catalyst (2 mol%), sodium acetate (4 mmol), alkene (6 mmol) and solvent (1 ml); (d) 2-halopyridine (2 mmol), Pd catalyst (2 mol%), triphenylphosphine (2 mol%), tetrabutylammonium chloride (1 mmol), sodium acetate (12 mmol), alkene (6 mmol) and Solvent (20 ml); (e) 2-halopyridine (2 mmol), Pd catalyst (2 mol%), triphenylphosphine (2 mol%), sodium acetate (12 mmol), alkene (6 mmol) and solvent (20 ml).

From these trial experiments the following were deduced.

- The reaction works best when palladium salts such as $Pd(OAc)_2$ or $Pd(MeCN)_2Cl_2$ are employed.
- A poor result was observed when $[Pd(Ph_3P)_4]$ was employed (entry 12). This may be due to steric hindrance, which may obstruct oxidative insertion of the palladium into the carbon-halogen bond.
- The presence of an alkene is important to the reaction. Without an alkene present the conversion is very poor, with only 20% yield of 2,2'bipyridine **237** observed after 48 h (entries 4 and 5). The more electron-rich alkenes gave the best results. Of the alkenes tried 2,3-dihydrofuran is by far the best, followed by 2,3-dihydropyran, vinyl acetate and, finally, cyclohexene.
- DMF is by far the solvent of choice. Interestingly the chemically similar DMA was particularly disappointing (entries 8 and 9).
- Of the aryl halides there appears to be no significant difference in reactivity when 2-bromopyridine is employed instead of 2-chloropyridine (entries 4 and 5). Therefore, the much cheaper 2-chloropyridine is in fact the aryl halide of choice in this reaction.
- Omission of tetraphenylphosphonium chloride from the reaction results in a reduced yield of 2,2'-bipyridine **237** possibly due to lack of stabilisation of the Ar-Pd-Cl intermediate (entry 6). Aryl phosphonium salts are known to stabilise intermediates in Heck reactions.[20]
- Entries 10 and 11 are refinements to the Heck arylation conditions of O'Neill,[18] which are similar to those of Reetz.

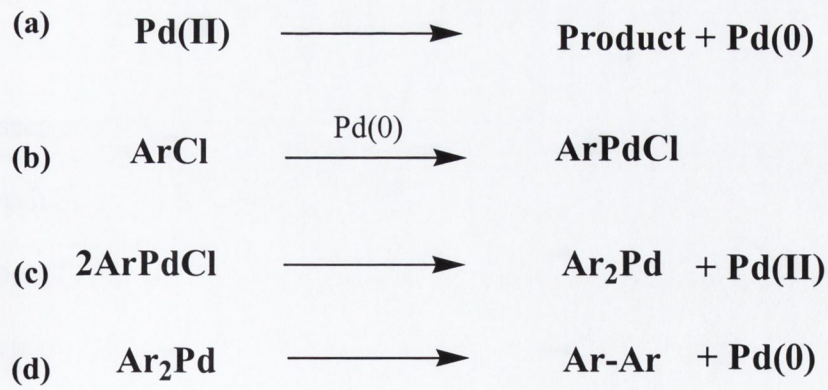
Thus, treatment of 2-chloropyridine **225** with 2,3-dihydrofuran in DMF in the presence of sodium acetate and 2 mol% each of triphenylphosphine and either $Pd(OAc)_2$ or $Pd(CH_3CN)_2Cl_2$ have led to the discovery of what appears to be an entirely new reaction which provides a novel route to 2,2'-bipyridine **237** in 60% yield.*

This reaction can be scaled up by a factor of 20 and the yield is identical with that obtained from the small-scale experiments.

4.4 Possible reaction mechanism

This coupling reaction can be rationalised by a four-step process (Scheme 4.5) which involves (a) reduction of the Pd(II) to Pd(0), (b) oxidative insertion of the catalytic palladium species into the carbon-halogen bond, (c) a disproportionation step with regeneration of Pd(II) and (d) reductive elimination to form the bipyridine and a Pd(0) species.

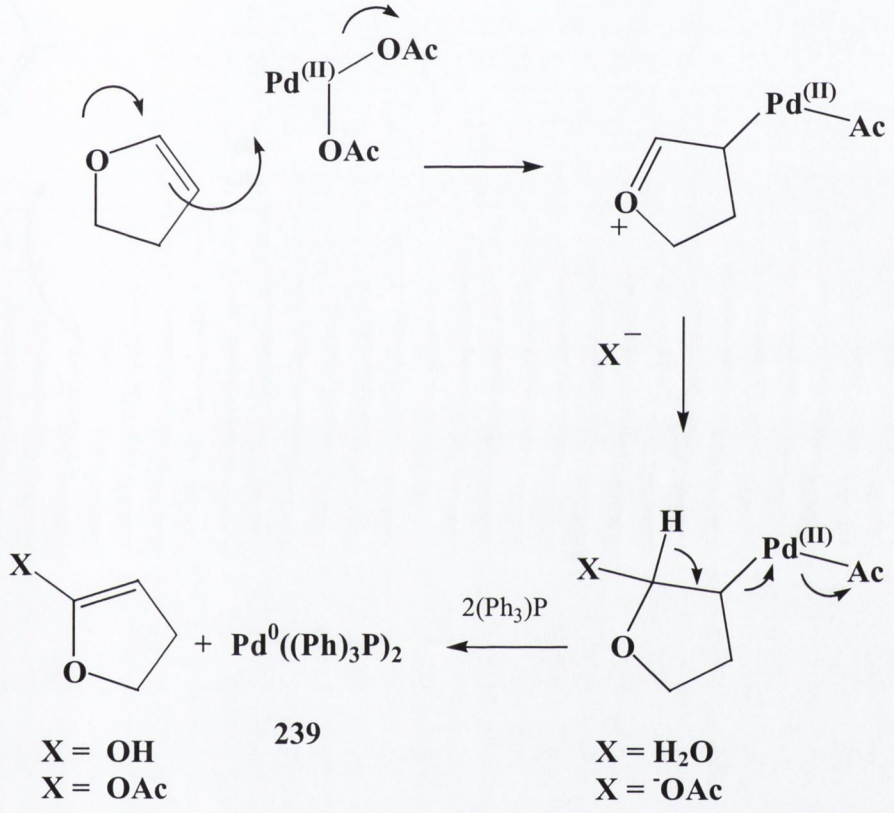
Scheme 4.5



* After column chromatography.

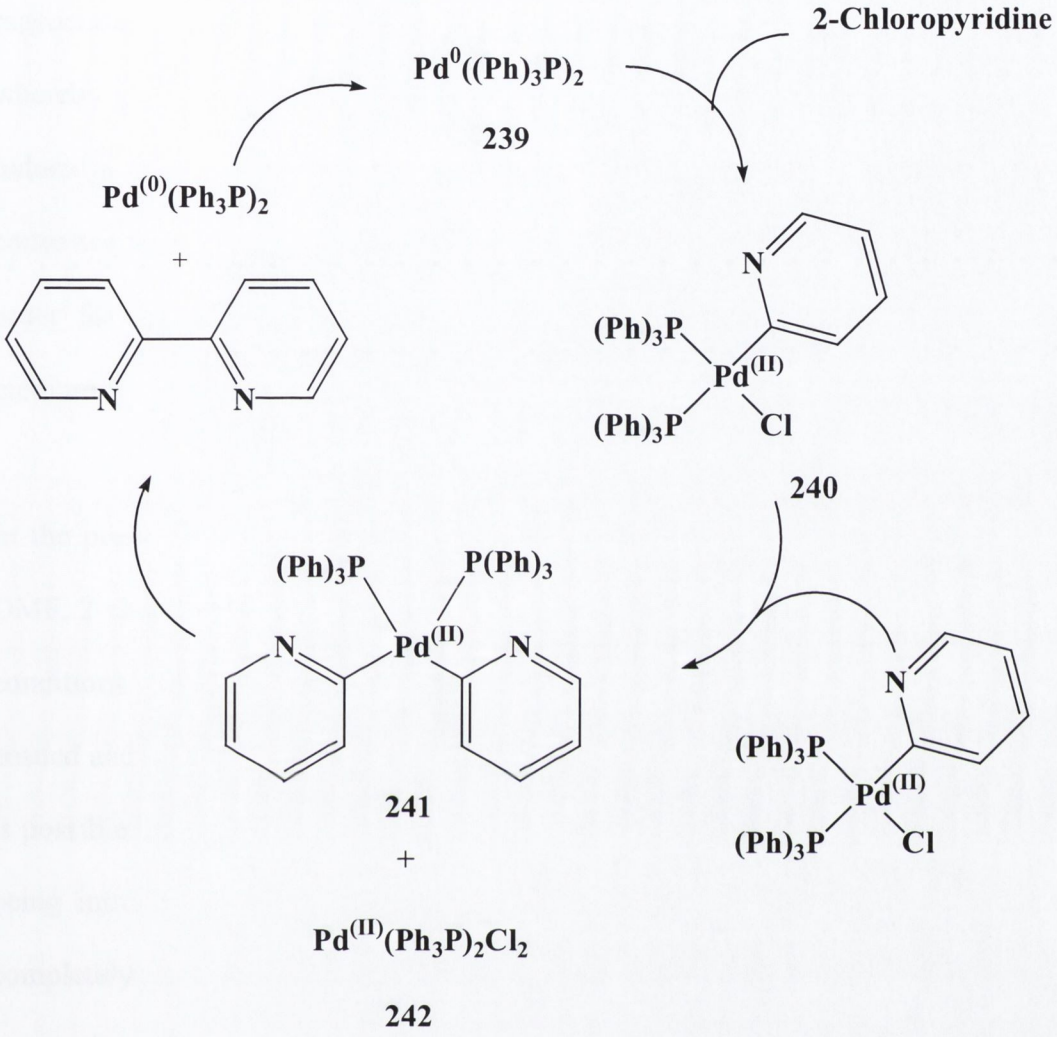
Initially, the palladium(II) which is present as palladium acetate, must be reduced to a palladium(0) species such as **239** and this is most readily achieved by reaction with the activated alkene, 2,3-dihydrofuran (Scheme 4.6). This is generally agreed as being the primary step in the Heck arylation of olefins.[19]

Scheme 4.6



The second step (Scheme 4.7) is an oxidative insertion of palladium(0) into the carbon-halogen bond to give **240** and this species is usually stabilised by solvation or by coordination with electron-donating species such as triarylphosphines.[20] Two molecules of **240** then combine in a disproportionation step to give the intermediate **241** with the elimination of a palladium(II) species **242**. Reductive elimination from **241** of a palladium(0) species **239** then gives 2,2'-bipyridine **237** as the product. The palladium(0) species **239** so produced then is available for another catalytic cycle.

Scheme 4.7



While this mechanism accounts for the formation of 2,2'-bipyridine **237** it does not explain how the palladium(II) is recycled. When the alkene was omitted from the reaction medium a poor yield of 2,2'-bipyridine **237** was observed, and it was concluded that the presence of the alkene was fundamental to the reaction (entries 4 and 5, Table 5.1).

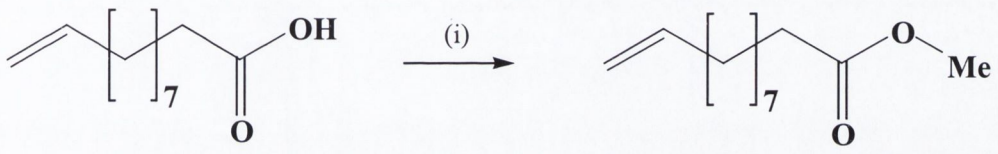
It can be envisaged that a Wacker reaction of 2,3-dihydrofuran runs simultaneously so that the palladium(0) species required for the arylation process is continuously regenerated from palladium(II). The Wacker reaction is a commercial process whereby ethylene is converted to acetaldehyde, and is one of the most important industrial processes that utilises transition metals.[21] In general, terminal olefins are converted to methyl ketones and so olefins can be regarded as masked ketones.[22] In order for the Wacker reaction to occur water must be present in the reaction medium.[23]

In the present work, under dry conditions with anhydrous sodium acetate and dry DMF, 2-chloropyridine **225** did not undergo reaction under reductive homocoupling conditions after 24 h reflux. Upon addition of a catalytic amount of water reaction ensued and 2-chloropyridine **225** was completely converted to 2,2'-bipyridine **237**. It is possible that water was unwittingly present in the experiments listed in Table 5.1, being introduced *via* the sodium acetate or the DMF which may not have been completely dry. In any case as little as 0.5% water in DMF is sufficient for complete conversion to occur. This made it more certain that a Wacker process was at work here.

Despite several attempts, it did not prove possible to isolate the Wacker product from the reaction medium. Thus, with 2,3-dihydrofuran as the alkene, it could not be conclusively shown that a Wacker process runs simultaneously with a Heck reductive homocoupling reaction. The expected Wacker product (γ -butyrolactone) is very water-soluble and more than likely resides in the water layer (if present). It was then decided to replace 2,3-dihydrofuran in the reaction with a more hydrophobic

alkene to maximise the possibility of isolating the Wacker product. The alkene chosen was the methyl 10-undecenoate **244**, which was synthesised from 10-undecenoic acid **243**. 10-Undecenoic acid **243** was converted to its methyl ester since salts of the free acid are essentially detergents and thus aqueous workup would give rise to considerable foaming.

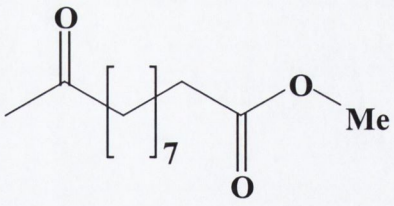
Scheme 4.8



243 **244**

Reagents and Conditions: (i) MeOH, H_2SO_4, 10 h, 100%.

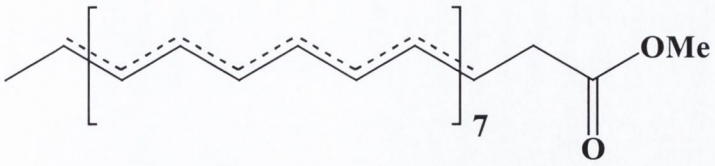
Thus, 10-oxoundecanoic acid **245**, the Wacker product from this reaction has a boiling point of > 200 °C (*lit.*[24] 163-164 @ 13.5 mm Hg) and should be easily separable or at least identifiable from the reaction medium.



245

In the event, appropriate treatment of the reaction mixture separated the neutral products from the basic compounds present. Analysis of the neutral products showed that the methyl 10-undecenoate **244** underwent substantial double bond migration to give a principal product, which was a mixture of isomers of type **246** all having the

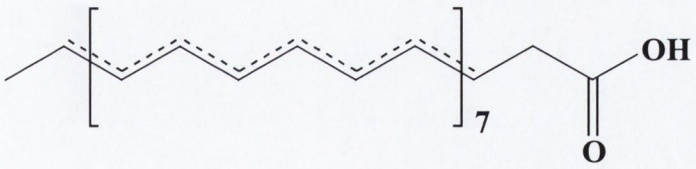
molecular formula $C_{12}H_{22}O_2$. This was borne out by mass spectroscopy which gave a molecular ion of nominal mass 199.0753 (calculated for $[C_{12}H_{22}O_2 + H]^+$ 199.1698).



246

Isomerisation of the long-chain terminal olefin **244** in this reaction was not unusual since this represented for many years the biggest obstacle to the synthesis of methyl ketones from higher α-olefins.[22] This has now been overcome by improved procedures.[25]

A second more polar component was also present which was found to be a mixture of the acids **247**, which had also undergone double bond migration to afford a mixture of isomers. A third more polar compound still which may or may not have been **245** was also identified by t.l.c, however it did not prove possible to separate this by column chromatography.



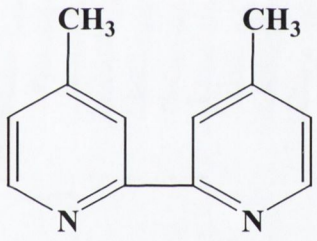
247

Clearly it has not been proved beyond reasonable doubt that a Wacker process is operating here, however the palladium(II) is being regenerated somehow and it is unlikely that that other undefined molecules are capable of this. The dramatic drop in product (2,2'-bipyridine **237**) yield is observed when the alkene is left out of the

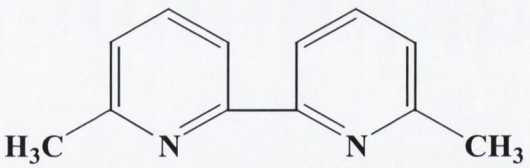
reaction mixture reinforces this point. Although triarylphosphines are capable of regenerating palladium(0),[26] this is unlikely given the small amount (2 mol%) of it in the reaction mixture. Incidentally, triphenylphosphine is oxidised to triphenylphosphine oxide during the reaction process. The elucidation and proof of the mechanism of this novel coupling reaction would be greatly aided by the application of HPLC technology.

4.5 Synthesis of symmetrically substituted bipyridines

The scope of this coupling reaction was extended to the synthesis of some symmetrically substituted bipyridines such as 4,4'-dimethyl-2,2'-bipyridine **248** and 6,6'-dimethyl-2,2'-bipyridine **249** whose direct precursors are 2-chloro-6-methylpyridine **250** and 2-chloro-4-methylpyridine **251**, respectively.



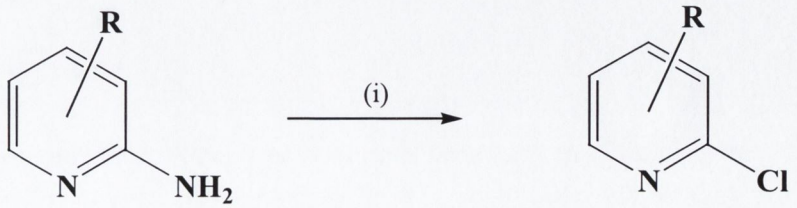
248



249

2-Chloro-6-methylpyridine **250** and 2-chloro-4-methylpyridine **251** were synthesised *via* diazotisation of the corresponding aminopyridines (Scheme 4.9).

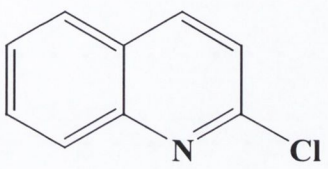
Scheme 4.9



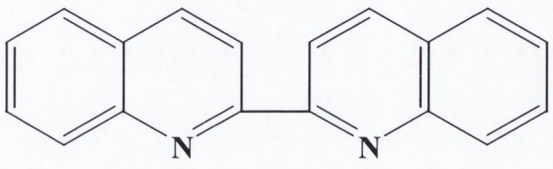
250 R = 6-Me
251 R = 4-Me

Reagents and Conditions: (i) HCl, $NaNO_2$, -10 °C → 80 °C, 57-62%.

Thus, 4,4'-dimethyl-2,2'-bipyridine **248** and 6,6'-dimethyl-2,2'-bipyridine **249** and were obtained in 52% and 61% yield respectively under the reductive homocoupling conditions devised in this laboratory.* Under similar conditions 2,2'-biquinoline **253** was synthesised from 2-chloroquinoline **252** in 48% yield.



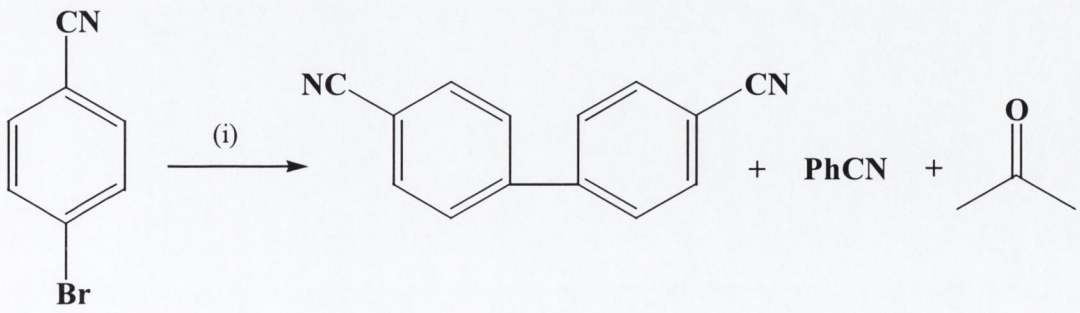
252



253

The potential of palladium acetate to effect the homocoupling of biaryls has been demonstrated recently (1998) by Hassan *et al.*[27] in a reaction which is very similar to the process devised in this laboratory. A catalytic system of palladium acetate and isopropanol in the presence of tetrabutylammonium bromide in DMF was used synthesise a variety of biaryls including biheterocycles. The isopropanol was used as a reducing agent in order to regenerate the palladium(0) required for homocoupling and was oxidised to acetone in the process (Scheme 4.10).

Scheme 4.10



Reagents and Conditions: (i) $Pd(OAc)_2$, nBu_4NBr, Base, DMF, IPA, 160 °C.

* These yields were obtained before it was found that the addition of water favours the reaction.

This catalytic system was also used to synthesise bipyridines with excellent yield (Table 4.2). Although this methodology relies on the use of bromoheteroaryls (except entry 2) rather than the corresponding chloroaryls, this may not be a disadvantage since it has been demonstrated in our laboratory that there is little difference in reactivity between chloro and bromopyridines in this type of reductive homocoupling process. Since this paper[27] was published after our initial work in this area our process cannot be claimed as novel, but certainly is complementary to existing knowledge as will be shown in the next section.

Table 4.2 Synthesis of bipyridines by the method of Hassan *et al.*[27]

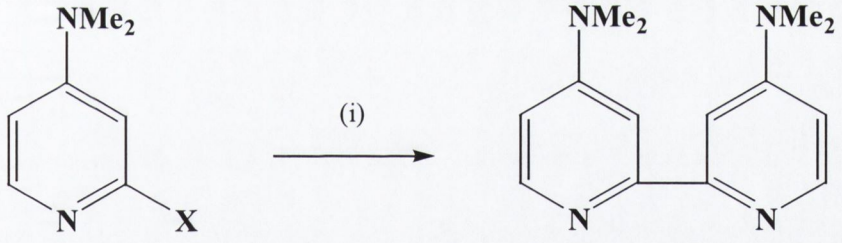
Entry	Substrate	Time (h)	Product	Reduction Yield GC (%)	Coupling yield GC % (Isolated)
1[a]	3-Chloroquinoline	22	3,3'-biquinoline	20	80 (79)
2[a]	2-Chloroquinoline	96	2-2'-biquinoline	11	64 (62)
3[a]	1-Chloro-10-phenyl throline	97	No Product	-	-
4[b]	2-Bromopyridine	45	2,2'-bipyridine	-	92 (92)
5[b]	2-Bromo-5-methyl pyridine	45	5,5'dimethyl-2,2'-bipyridine	-	100 (95)

(a) $Pd(OAc)_2$, K_2CO_3, DMF, IPA; (b) $Pd(OAc)_2$, K_2CO_3, DMF/H_2O, IPA;

4.6 Preliminary investigation into the synthesis of the novel ligand 4,4'-dimethylamino-2,2'-bipyridine

The synthesis of new biaryls, particularly new bipyridines is of the utmost importance considering that these compounds are increasingly finding applications as building blocks in supramolecular components,[28] electrochemistry,[29] photochemistry,[30] non-linear optics[31] and conducting polymers.[32] Since the synthesis of 2-chloro-4-dimethylaminopyridine **132** and 2-bromo-4-dimethylaminopyridine **133** has been achieved in this laboratory (Chapter 2), it was envisaged that these compounds might undergo reductive homocoupling to yield the novel ligand, 4,4'-dimethylamino-2,2'-bipyridine **254** (Scheme 4.11).

Scheme 4.11



132 X = Cl
133 X = Br

254

It was thought that 4,4'-dimethylamino-2,2'-bipyridine **254** might having excellent chelating properties making it the first hypernucleophilic bidente ligand.

A number of coupling reactions were carried out utilising both the conditions devised in our laboratory and those of Hassan *et al.*[27] with varying degree's of success. These results are tabulated overleaf (Table 4.3).

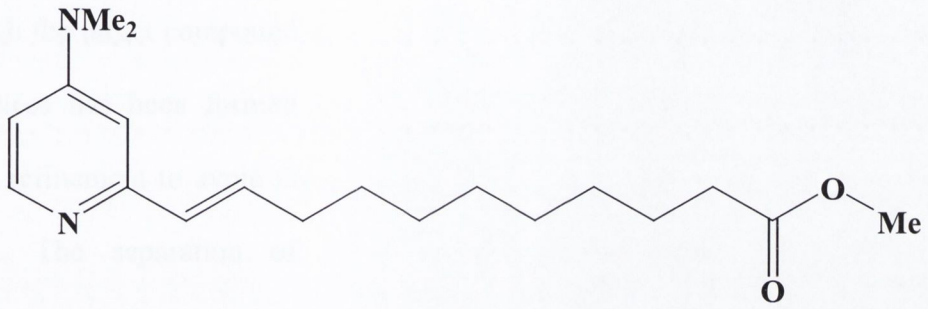
Table 4.3 Palladium-catalysed synthesis of 4,4'-dimethylamino-2,2'-bipyridine from 2-halo-4-dimethylaminopyridines

Entry	Halo-4-DMAP	Alkene	Yield of 31 %[e]	Other products
1[a]	2-Bromo-4-DMAP	10-Undecenoic acetate	50%	**255,256**
2[b]	2-Chloro-4-DMAP	2,3-Dihydrofuran	-	DMAP
3[c]	2-Bromo-4-DMAP	(–)-β-pinene	44	DMAP
4[d]	2-Bromo-4-DMAP	-	20	DMAP

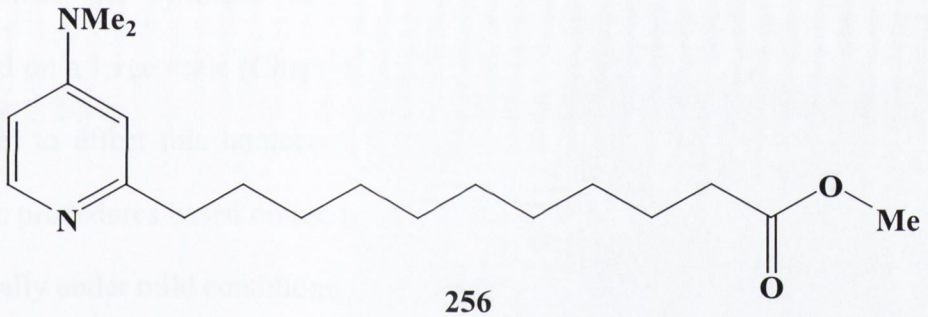
(a) 2-Bromo-4-DMAP (3.1 mmol), $Pd(OAc)_2$ (50 mol%), triphenylphosphine (20 mol%), DMF (20 ml), water (400 μl), sodium acetate (6 mmol), alkene ; (b) 2-chloro-4-DMAP (0.3 mmol), $Pd(OAc)_2$ (12 mol%), triphenylphosphine (20 mol%), DMF (5 ml), water (50 μl), sodium acetate (1 mmol), alkene (500 μl); (c) 2-bromo-4-DMAP (1.5 mmol), $Pd(OAc)_2$ (10 mol%), triphenylphosphine (20 mol%), DMF (20 ml), water (400 μl), sodium acetate (2 mmol), alkene (700 μl); (d) 2-bromo-4-DMAP (2.3 mmol), $Pd(OAc)_2$ (5 mol%), potassium carbonate (2.3 mmol), DMF (4 ml), water (1 ml), *n*-butylammonium chloride (1.25 mmol), isopropyl alcohol (178 μl).

At high palladium concentration (entry 1, Table 4.3) three main products were identified by mass spectroscopy and ^1H NMR of the crude mixture and these were 4,4'-dimethylamino-2,2'-bipyridine **254** which had a nominal mass *m/z* 243.2271 (calculated for $[C_{14}H_{18}N_4 + H]^+$ 243.1610). Signals from the ^1H NMR of the crude mixture were assigned as follow, δ 8.32 (2H, H-6 + H-6'), 7.71 (2H, H-3) and 6.5 (2H, H-5) and 3.12 (12H, NMe_2). Two other compounds whose molecular weights were consistent with structures **255** and **256** had a nominal masses *m/z* 319.3378 (calculated for $[C_{19}H_{30}N_2O_2 + H]^+$ 319.2386) and *m/z* 321.3610 (calculated for $[C_{19}H_{32}N_2O_2 + H]^+$ 321.3610). Assignment of signals for the protons to these

compounds from the ^{1}H NMR of the crude mixture was quite difficult due to overlapping signals and contaminants and so only signals that were clearly discernible are discussed. Signals at δ 3.08 and 3.10 (NMe_2), 3.67 and 3.68 (OMe), 8.10 and 8.12 (H-6) were assigned as indicated.



255



256

Unfortunately, column chromatography did not separate compounds **254**, **255** or **256** and as a result each could not be characterised individually. Structure assignments are based on ^{1}H NMR and mass spectral evidence of the mixture after chromatography which gave three distinct molecular ions. When 2-chloro-4-dimethylaminopyridine **132** was utilised as the aryl halide (entry 2) only 4-dimethylaminopyridine, the product of carbon-halogen bond reduction was observed. Unfortunately this trend was also observed in subsequent experiments with 4-dimethylaminopyridine always being the major product. The best quality of 4,4'-dimethylamino-2,2'-bipyridine **254** was obtained with (–)-β-pinene as the alkene,

(entry 3, Table 4.3). This product mixture showed no Heck crosscoupling. Unfortunately, it proved impossible to separate 4,4'-dimethylamino-2,2'-bipyridine **254** from 4-dimethylaminopyridine by conventional chromatography.

This work was commenced only recently, and clearly presents considerable promise. Although the target compound **254** has not been obtained in good yield and purity it nonetheless has been formed in reasonable yields. The key to this synthesis is method refinement to avoid the formation of 4-dimethylaminopyridine as the major product. The separation of these two compounds should be possible by crystallisation. This would be facilitated by conducting the reaction on a much larger scale. Since the synthesis of 2-bromo-4-dimethylaminopyridine **133** has been achieved on a large scale (Chapter 2) this should be explored. Alternatively, the use of nickel to effect this homocoupling has not been investigated. There are many catalytic procedures based on nickel which are used to effect the synthesis of biaryls and usually under mild conditions.[33]

4.7 Experimental section

^{1}H NMR spectra (400.13 MHz) and ^{13}C NMR (100.6 MHz) spectra were measured for solutions in deuteriochloroform or [$^{2}H_6$] DMSO, using a Bruker DPX-400 spectrometer. Chemical shifts are measured in ppm. J values are given in Hz. Melting points were measured on a electrothermal melting point apparatus and are uncorrected. FT-IR spectra were measured using a Perkin Elemer FT-IR PARAGON 1000 spectrometer. Electrospray mass spectra (ESMS) were recorded on a Micromass LCT electrospray mass spectrometer. T.l.c. was carried out on Merck Kieselgel 60 F_{254} plates and column chromatography carried out under gravity using Merck Kieselgel 70-230 mesh. All solvents that were required dry were dried using standard techniques.

General procedure for the synthesis of bipyridyls 237, 248, 249 and 253

2,2'-Bipyridine **237**, 4,4'-dimethyl-2,2'-bipyridine **248**, 6,6'-dimethyl-2,2'-bipyridine **249** and 2,2'-biquinoline **253** were synthesised from 2-chloropyridine **225**, 2-chloro-4-methylpyridine **251**, 2-chloro-6-methylpyridine **250** and 2-chloroquinoline **252** respectively. Typical procedure is as follows.

To palladium(II) acetate (0.011g; 5.0×10^{-5} mol) in *N,N*-DMF (10 ml) was added triphenylphosphine (0.013g; 5.0×10^{-5} mol), either of the aryl halides **225**, **250**, **251** or **252** (2×10^{-3} mol), 2,3-dihydrofuran (0.43 ml, 6×10^{-3} mol), water (50 μl) and sodium acetate (0.3 g; 3×10^{-3} mol) and the reaction was refluxed for 24 h. The reaction was then diluted up with ether and the ether washed several times with brine (3×25 ml), dried (Na_2SO_4) and evaporated to give the crude product. Chromatography over silica gel using hexane : ethyl acetate 90 : 10 as mobile phase usually gave the corresponding bipyridyl in excellent purity.

2,2'-Bipyridine 237

Yield 0.090 g (60%), m.p. 69.2 °C, *lit.*[34] 69.3 °C.

ν_{Max} (N) 2918, 1582, 1454, 1376, 1038 and 754 cm^{-1}.

$\delta_{(H)}$ ($CDCl_3$) 7.31 (2H, m, H-5 + H-5'), 7.82 (2H, dt, J_1 1.5, J_2 7.5, H-4 + H-4') 8.41 (2H, d, J 8, H-6 + H-6') and 8.6 (2H, d, J 4.5, H-3 + H-3') ppm.

$\delta_{(C)}$ ($CDCl_3$) 120.61 (C-3 + C-3'), 123.20 (C-5 + C-5'), 136.39 (C-4 + C-4'), 148.71 (C-6 + C-6'), 155.74 and (C-2 + C-2') ppm.

MS (ES): Found: *m/z* (nominal mass) 157.0970 calculated for $[C_{10}H_8N_2 + H]^+$ 157.0766.

4,4'-Dimethyl-2,2'-bipyridine 248

Yield 0.11 g, (61%), m.p 170.5-171 °C, *lit.*[6(C)] 171-172 °C.

ν_{Max} (N) 2923, 1734, 1691, 1636, 1591, 1560, 1458, 1376, 1182, 1122, 1094, 1041, 990, 911, 819 and 722 cm^{-1}.

$\delta_{(H)}$ ($CDCl_3$) 2.43 (6H, s, 2Me), 7.13 (2H, dd, J_1 1.0, J_2 5.0, H-5 + H-5') 8.23(2H, d, *J* 2.0, H-3 + H-3') and 8.53 (2H, d, *J* 5.0, H-6 + H-6') ppm.

$\delta_{(C)}$ ($CDCl_3$) 20.66 (CH_3), 121.53 (C-3 + C-3'), 124.12 (C-5 + C-5'), 147.60 (quat., C-4 + C-4'), 148.43 (C-6 + C-6') and 155.62 (quat., C-2 + C-2') ppm.

MS (ES): Found: *m/z* (nominal mass) 185.1187 calculated for $[C_{12}H_{12}N_2 + H]^+$ 185.1079.

6,6'-Dimethyl-2,2'-bipyridine 249

Yield 0.095 g (52%), m.p. 87.5-88.5 °C, *lit.*[35] 88-90 °C.

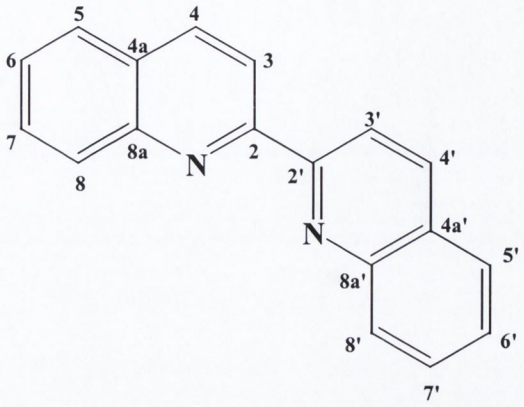
ν_{Max} (N) 2992, 1574, 1462, 1376, 1256, 1150, 1113, 1081, 1034, 993, 898, 779, 722 and 633 cm^{-1}.

$\delta_{(H)}$ ($CDCl_3$)2.64 (6H, s, 2Me), 7.16 (2H, d, *J* 7.5, H-3 + H-3') 7.69 (2H, t, *J* 8.0, H-4 + H-4') and 8.21 (2H, d, *J* 7.5, H-5 + H-5') ppm.

$\delta_{(C)}$ ($CDCl_3$) 24.18, (CH_3), 117.68 (C-3 + C-3'), 122.53 (C-5 + C-5'), 136.47 (C-4 + C-5'), 155.51 (quat., C-2 + C-2') and 157.36 (quat., C-6 + C-6') ppm.

MS (ES): Found: *m/z* (nominal mass) 185.1187 calculated for $[C_{12}H_{12}N_2 + H]^+$ 185.1079.

2,2'-Biquinoline 253



Yield 0.148 g (48%), m.p 193.4 -193.6 °C, *lit.*[36] 193-196 °C. Chromatography over silica gel using hexane : ether 80 : 20 as mobile phase was used.

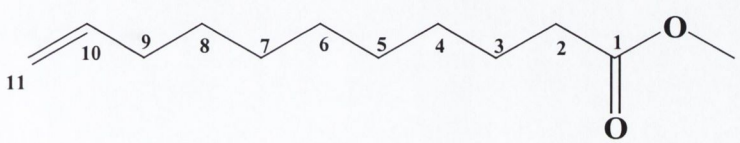
ν_{Max} (N) 2933, 1591, 1460, 1378, 1301, 1157, 953, 830 and 722 cm^{-1}.

$\delta_{(H)}$ ($CDCl_3$) 7.60 (2H, dt, J_1 1, J_2 8, H-6 + H-6'), 7.7 8(2H,dt, J_1 1, J_2 8, H-7 + H-7'), 7.90 (2H, d, *J* 8.0 H-5 + H-5'), 8.25 (2H, d, *J* 8.5, H-4 + H-4'), 8.35 (2H, d, *J* 8.5, H-8 + H-8') and 8.88 (2H, d, *J* 9.0, H-3 + H-3') ppm.

$\delta_{(C)}$ ($CDCl_3$) 118.98 (C-3 + C-3'), 126.46 (C-6 + C-6'), 127.18 (C-5 + C-5'), 128.02 (quat., C-4a + C-4a'), 129.05 (C-7 + C-7'), 129.51 (C-8 + C-8'), 136.24 (C-4 + C-4'), 147.51 (C-8a + C-8a') and 155.81 (C-2 + C-2') ppm.

MS (ES): Found: *m/z* 257.0254 calculated for $[C_{18}H_{12}N_2 + H]^+$ 257.1079.

Methyl Ester of 10-Undecenoic Acid 244



Concentrated H_2SO_4 (10 ml) was added slowly to solution of 10-undecenoic acid **243** (15 g, 8.1×10^{-3} mol) in methanol (150 ml) and the reaction was refluxed until t.l.c analysis revealed complete consumption of 10-undecenoic acid. Upon cooling the reaction was diluted with brine (100 ml) and the aqueous layer was extracted with diethyl ether (3 × 100 ml). The organic layers were combined and washed with saturated sodium hydrogen carbonate (3 × 50 ml) to remove any residual acid. The organic layer was dried ($MgSO_4$) and concentrated *in vacuo*. Vacuum distillation of the product gave 10-undenoic acetate **244** as a colourless liquid (13 g, 81%), b.p. 125 °C at 12 mm Hg, *lit.*[37] 78-80 °C at 0.06 mm Hg.

ν_{Max} (L) 3075, 2975, 2927, 2856, 1741, 1641, 1459, 1436, 1361, 1319, 1319, 1240, 1197, 1172, 1116, 995 and 910 cm^{-1}.

$\delta_{(H)}$ ($CDCl_3$)1.26-1.36 (10H, bs, C_4H_2-C_8H_2), 1.61 (2H, m, C_3H_2), 1.98-2.00 (2H, q, *J* 7.0, C_9H_2), 2.21 (2H, t, *J* 7.5, C_2H_2), 3.63 (3H, s, OMe), 4.87-4.97 (2H, dd, J_1 8, J_2 17, $C_{11}H_2$) and 5.71 (1H, m, $C_{10}H$) ppm.

$\delta_{(C)}$ ($CDCl_3$) 24.41 (C-3), 28.3-28.7 (C-4-C8), 33.24 (C-2), 33.5 (C-9), 50.71 (OMe), 113.59 (C-11), 138 (C-10) and 173.23 (quat, C-1) ppm.

General procedure for the synthesis of 2-chloro-6-methylpyridine 250 and 2-chloro-4-methylpyridine 251

2-Amino-6-methylpyridine or 2-amino-4-methylpyridine (8.57 g, 7.9×10^{-2} mol) was added to concentrated HCl (45.4 ml) which was then cooled on a ice bath to <5 °C. The reaction mixture was then cooled to 0 °C and carefully a solution of sodium

nitrite (14 g; 0.2 mol) in H_2O (30 cm^3) was added ensuring the temperature did not rise above 5 °C. The reaction mixture was stirred at 0 °C for a further 30 minutes, then heated to 80 °C for a further two hours. Upon cooling the contents was poured onto ice, basified with 30% NaOH and extracted with ether (3 × 100 ml), dried (Na_2SO_4) and the solvent removed. The resultant liquid was distilled under reduced pressure to afford the desired compound.

2-Chloro-6-methylpyridine 250

Yield 5.61g (56%), b. p. 68 °C @ 12 mm Hg, *lit.*[38] 58-60 @ 8 mm Hg.

ν_{Max} (L), 3063, 2957, 2925, 1676, 1636, 1587, 1563, 1140, 1409, 1373, 1255, 1238, 1163, 1138, 1108, 1086, 1036, 997, 979, 921, 867, 852, 781, 732, 724 and 679 cm^{-1}.

$\delta_{(H)}$ ($CDCl_3$) 2.42 (3H, s, CH_3), 6.98 (1H, d, *J* 7.5, H-3), 7.00 (1H, d, *J* 8.0, H-5) and 7.43 (1H, t, *J* 7.5, H-4) ppm.

$\delta_{(C)}$ ($CDCl_3$) 23.51 (CH_3), 120.56 (C-3), 121.17 (C-5), 138.29 (C-4), 149.94 (quat., C-2) and 158.87 (quat., C-6) ppm.

2-Chloro-4-methylpyridine 251

Yield 6.27 g (62%), b. p. 72 °C @12 mm Hg, *lit.*[39] 97-99 °C @ 30 mm Hg.

ν_{Max} (L) 3433, 3054, 2922, 2360, 2340, 1593, 1550, 1467, 1444, 1378, 1283, 1237, 1224, 1122, 1085, 1038, 988, 870, 824, 713 and 668 cm^{-1}.

$\delta_{(H)}$ ($CDCl_3$) 2.16 (3H, s, CH_3), 6.88 (1H, dd, *J* 1.5, 5.0, H-5) 6.96 (1H, s, H-3) and 8.00 (1H, d, *J* 5.0, H-6) ppm.

$\delta_{(C)}$ ($CDCl_3$) 20.05 (CH_3), 122.88 (C-5), 124.17 (C-3), 148.59 (C-6), 149.89 (quat., C-4) and 150.81 (quat., C-2) ppm.

4,4'-Dimethylamino-2,2'-bipyridine 254

This compound was synthesised from 2-bromo-4-dimethylaminopyridine **133** using the same procedure for the synthesis of bipyridyls **237**, **248**, **249** and **253**.

$\delta_{(H)}$ ($CDCl_3$) 3.12 (12H, s, $2NMe_2$), 6.51 (2H, dd, J_1 2.5, J_2 8.0 H-5 + H5'), 7.71 (2H, d, *J* 2.5, H-3 + H-3') and 8.31 (2H, d, *J* 8.0, H-6 +H-6') ppm.

MS (ES): Found: *m/z* 243.2271 calculated for $[C_{14}H_{18}N_4 + H]^+$ 243.1610.

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