Durham E-Theses

Unusually substituted Fluoroheterocycles

Hall, Christopher W.

UNIVERSITY OF DURHAM

A THESIS

Entitled

UNUSUALLY SUBSTITUTED FLUOROHETEROCYCLES

Submitted by

CHRISTOPHER W HALL B.Sc. (Hons)(Dunelm)
(Trevelyan College)

A candidate for the degree of Doctor of Philosophy

Department of Chemistry

1997

2 1 MAY 1998

We shall not cease from exploration
And the end of all our exploring
Will be to arrive where we started
And know the place for the first time.

Little Gidding from Four Quartets, T. S. Eliot

Acknowledgements

Memorandum

The work described in this thesis was carried out in the University of Durham between October 1994 and May 1997. This thesis is the work of the author, except where acknowledged by reference and has not been submitted for any other degree.

Part of this work has been the subject of the following:

R.D. Chambers, C.W. Hall, J. Hutchinson and R.W. Millar, submitted for publication.

and has been presented by the author at:

ICI Poster Session,
University of Durham,
December 1996.

North East Graduate Symposium,
University of Newcastle,
April 1997.

15 th International Symposium on Fluorine Chemistry,
University of British Columbia,
Vancouver, Canada, August 1997.

and has been presented by Professor R. D. Chambers at:

13 th Winter Fluorine Chemistry Conference,
St Petersburg Beach, Florida, USA, January 1997.

Nomenclature

Throughout this work, an 'F' in the centre of a ring denotes that all unmarked bonds are to fluorine.

Copyright

The copyright of this thesis rest with the author. No quotation from it should be published without his prior written consent and information from it should be acknowledged.

Abstract
Unusually Substituted Fluoroheterocycles
by C W Hall

The research described in this thesis may be divided into five areas:

1, Direct reduction methods involving reactions of pentafluoropyridine with metal hydrides were investigated in order to gain access to unusually substituted fluoro heterocycles. For example, 2,3,5-trifluoropyridine (7) was obtained by reaction of pentafluoropyridine with lithium aluminium hydride.

2, The synthesis of a variety of unusually substituted fluoro heterocycles has been achieved *via* indirect reduction methods. For example, pentafluoropyridine was converted into 2,4,6-tribromo-3,5-difluoropyridine (11), which, following catalytic hydrogenolysis, gave 3,5-difluoropyridine (5). This chemistry was applied to the pyrimidine and quinoxaline ring systems.

3, Reactions of the bromo fluoro heterocycles with a variety of nucleophiles gave fascinating results: hard nucleophiles such as sodium methoxide reacted with 2,4,6-tribromo-3,5-difluoropyridine (11) giving exclusive displacement of fluorine, whilst soft nucleophiles such as sodium thiophenoxide displaced bromine.

4, Palladium mediated coupling reactions of the bromo fluoro heterocycles with alkynes proceeded with ease. The reaction of (11) gave fascinating results with the 2- and 6- position reacting in preference to the 4- position. Also, lithium-bromine exchange of (11) with butyl lithium afforded a stable 4-lithio pyridine derivative.

5, As part of a strategy aimed at synthesising energetic materials, the reactions of 3,5-difluoro-4-nitropyridine-N-oxide (35a) and 3,5-dichloro-4-nitropyridine-N-oxide (36) with ammonia were compared. Interestingly, (35a) gave exclusive displacement of fluorine, whilst (36) gave exclusive displacement of the nitro group. Therefore, the relative order of mobility for this system was found to be $F > NO_2 > Cl$, which is entirely consistent with established data.

Contents

Chapter I

Chapter II

Direct Replacement of Fluorine by Hydrogen from Fully Fluorinated   23
Aromatic Nitrogen Heterocycles

Chapter III

Indirect Replacement of Fluorine by Hydrogen   **39**

Chapter IV

Nucleophilic Substition of Bromofluoroheterocycles 62

Chapter V 84

Metal Mediated Reactions of Bromofluoro-heterocycles 84

Chapter VI   108

Development of Energetic Materials   108

Instrumentation and Reagents   126

Chapter VII

Chapter VIII

Chapter IX

Chapter X

Experimental to Chapter V — 140

Chapter I

I.1 General Introduction

Fluorine is the most abundant of all the halogens and ranks thirteenth in order of abundance of all the elements[1], however, fluorine itself is only present in a handful of naturally occuring organic chemicals[2]. Man obtains fluorine from three principal mineral deposits: fluorospar (CaF_2), cryolite (Na_3AlF_6) and fluoroapatite ($Ca_5(PO_4)_3F$), but only fluorospar is mined for recovery of fluorine. Hydrogen fluoride (HF), which is obtained by reacting sulphuric acid with fluorospar, has often been termed the lifeblood[3] of the fluorochemical industry, because it is necessary for the synthesis of every organofluorine chemical, since both elemental fluorine[4] and metal fluorides such as potassium fluoride, which are so important in the synthesis of fluorine containing compounds, are obtained from HF.

The first reported synthesis of an organofluorine compound is attributed to Dumas and Peligot[4], who in 1836 produced fluoromethane, then in 1883, Paterno and Oliveri[5] synthesised fluorobenzene, the first fluoroaromatic compound. However, it wasn't until 1955 that the first perfluoroaromatic compound was obtained by Desirant[6] who in 1955 synthesised hexafluorobenzene. The first fluoro heteroaromatic compound, 2-fluoropyridine was obtained by Chichibabin and Rjazancev[7] in 1915.

However, it was the work of Swarts[8, 9] between 1890 and 1936 on simple aliphatic fluorine containing compounds and huge efforts by researchers working on the Manhattan project[10] during the Second World War that laid the foundations for fluoroorganic chemistry.

The search for new materials, fine chemicals and drugs has been the driving force behind the development of fluoroorganic chemistry, and some of the uses of fluorine containing compounds are shown here.

Area of Application	Compound
Components of Coolants and Refrigerants	$CFCl_3$, CF_3CH_2F
Anaesthetics	$CF_3CHClBr$ (Halothane)
Artificial Blood	Perfluorodecalin
Pharmaceutically active agents	5-Fluorouracil
Agrochemicals	Trifluralin, Fusilade
Polymers and High Performance Materials	$(CF_2CF_2)_n$ (Polyfluorotetrafluoroethene), $(CF_2CH_2)_n$

The unique chemistry of organofluorine systems is derived from a number of important factors:

1. The high electronegativity of the fluorine atom. The difference between fluorine and chlorine, the closest homologue, is substantially greater than the difference between any other two successive halogens;

2. The strong polarisation of the C-F bond. The difference in electronegativity between the two atoms gradually alters and even inverts the reaction behaviour of adjacent centres;

3. Fluorine has a Van der Waal's radius most like that of hydrogen (F= 1.35, H= 1.10 Å). Thus, the replacement of hydrogen by fluorine does not significantly affect the geometry of the molecule;

4. Fluorine can be readily displaced from fluorocarbons as fluoride ion. This gives fluorine containing compounds a unique and complementary chemistry in comparison with hydrocarbon systems and

5. The C-F bond is very strong (107 Kcalmol^{-1}), which leads to enhanced utility due to thermal stability.

I.2 Synthesis of Fluorine Substituted Nitrogen Aromatic Heterocycles

This thesis is concerned with the synthesis of unusually substituted fluoro heterocycles, or in other words, heterocycles containing C-F bonds at unusual positions. Only systems where fluorine is directly bound to the heteroaromatic ring are discussed.

A large number of fluoroheterocyclic systems are available and these range from monofluorosubstituted heterocycles, such as 2-fluoropyridine through to fully fluorinated heterocycles such as heptafluoroquinoline.

The preparation of fluoroheterocycles has been the subject of many reviews[11-15] and is usually dependent on the availability of certain precursors containing specific functional groups, with amino and chloro substituted compounds being the most notable.

Many of the techniques for the synthesis of fluoroaromatics apply to the synthesis of fluoroheterocycles, therefore, methods for the formation of fluoroheteroaromatics and where appropriate, fluoroaromatics, will be discussed.

The principal methods for synthesising fluorine substituted nitrogen heterocycles falls into five distinct catergories:

1, Halogen exchange (HALEX) reaction;
2, Substitution of hydrogen by fluorine;
3, Substitution of other groups by fluorine;
4, Building block approach and
5, Saturation- rearomatisation.

I.2.1 Halogen- Exchange (Halex)

Halogen exchange or Halex chemistry (for a review see Dolby-Glover[16]) has proven to be one of the most useful and industrially important[17] method for the synthesis of fluoroaromatic and fluoroheteroaromatic compounds.

The method is essentially a nucleophilic substitution reaction of a chloro, bromo or iodo substituted compound with a fluoride ion source to give a fluoro substituted compound and chloro, bromo or iodo ion. The fluoride source is invariably an alkali metal fluoride[16] and may be either sodium fluoride (NaF), potassium fluoride (KF) or caesium fluoride (CsF).

$$NaF \quad < \quad KF \quad < \quad CsF$$

However, as the effectiveness of the reagent increases, so does its price, so in practice potassium fluoride is favoured over sodium fluoride (which is cheaper and less effective) and caesium fluoride (which is more costly but more effective).

Only chloroaromatics activated to nucleophilic attack react sufficiently well, hence electron withdrawing groups (EWG's) such as $-NO_2$, $-SO_3H$ and $-CN$ (which activate *via* mesomeric effects) and halogens and $-CF_3$ (which activate *via* inductive effects) are desirable. Thus chloro heteroaromatic compounds are well suited to the Halex reaction since ring nitrogen is able to activate the ring to nucleophilic attack and stabilises the Meisenheimer intermediate.

X= Cl, Br, I
R= EWG
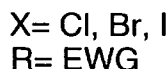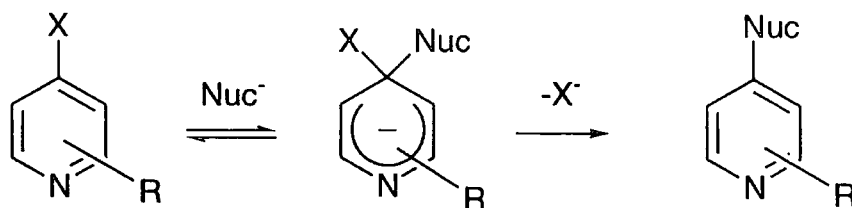
Ever since the pioneering work of Finger[18, 19], who converted 2-chloropyridine (and derivatives) to 2-fluoropyridine (and derivatives),

50 %
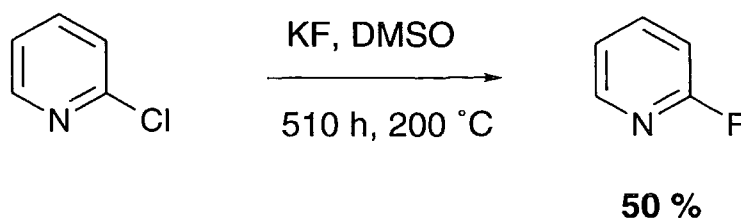
work in the area of Halex reactions has continued to attract interest.

Much research effort has evolved around developing better sources of fluoride ion, usually based around potassium fluoride. Historically, potassium fluoride has been

used with solvents to perform the Halex reaction and Finger and Kruse[20] established the use of polar aprotic solvents in the Halex reaction, with DMSO and DMF being used for the conversion of 2,4-dinitrochlorobenzene to 2,4-dinitrofluorobenzene.

Further work demonstrated that more activated systems reacted well, with 2,3,5,6-tetrachloropyridine yielding 3,5-dichloro-2,6-difluoropyridine[18].

KF, DMSO

24 h, 205 °C

33 %
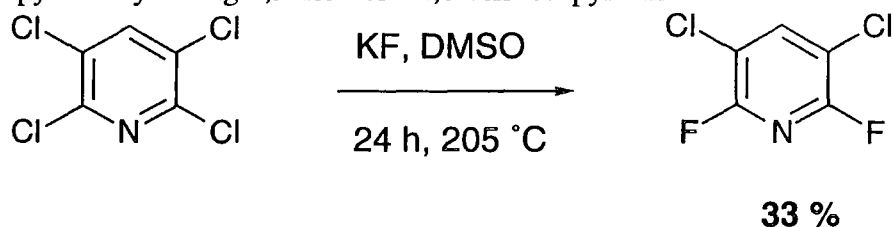
The methodology was then systematically extended to a range of fully chlorinated heteroaromatics (for a review see[11]), for example, pentachloropyridine gave 3,5-dichloro-2,4,6-trifluoropyridine[21].

KF, Sulpholane

190-210 °C

+
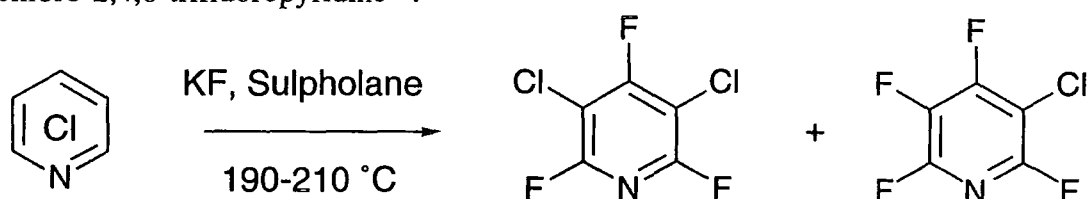
It was also found that if the reaction was performed at elevated temperatures, the solvent could be left out of the reaction and reaction of pentachloropyridine with potassium fluoride gave pentafluoropyridine[21].

KF, autoclave

480 °C

+

68%   **7%**
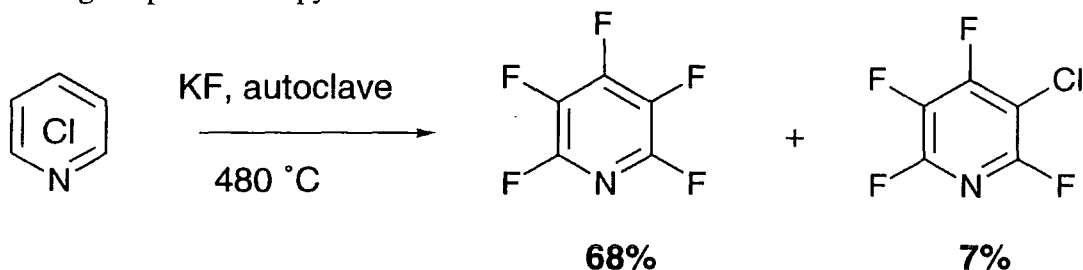
Similarly, other perfluoroheterocyclic systems may be obtained using this technique, for example, hexachloroquinoxaline affords hexafluoroquinoxaline.

The poor reactivity of potassium fluoride in Halex reactions has often been attributed to solvation by water and its poor solubility in solvents. Thus research has continued to find higher performing fluoride sources for the Halex reaction.

I.2.1.a   Potassium Fluoride (KF)
Spray Dried KF[22]

Early workers[21] used anhydrous KF obtained by oven drying KF, however it was found that the surface area of KF may be increased using spray drying techniques. Spray dried KF finds routine application in many Halex processes and has become the standard "bench" form of KF.

I.2.1.b   KF and Phase Transfer Catalysts (PTC's)

KF and Tetraphenylphosphonium bromide (Ph$_4$PBr)

PTC's such as Ph$_4$PBr have enhanced the solubility of KF in organic solvents. Clark[23] found that by measuring the initial rates of reaction of 5-nitro-2-chloropyridine with KF/ Ph$_4$PBr, diethyl ether and acetonitrile performed better than N-methylpyrrolidine (NMP) and sulpholane, whereas for KF alone the order was reversed.
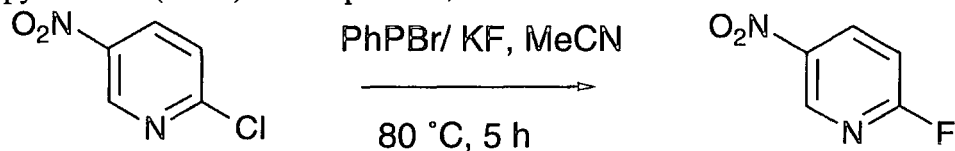
Thus, 5-nitro-2-chloropyridine was converted to 5-nitro-2-fluoropyridine under mild conditions without the need for polar aprotic solvents.

KF, CsF and Ph$_4$PBr

Addition of CsF to a KF/ Ph$_4$PBr mixture lead to an even better fluoride source and 2,3-difluoro-5-chloropyridine was obtained from 2,3,5-trichloropyridine this way[24].
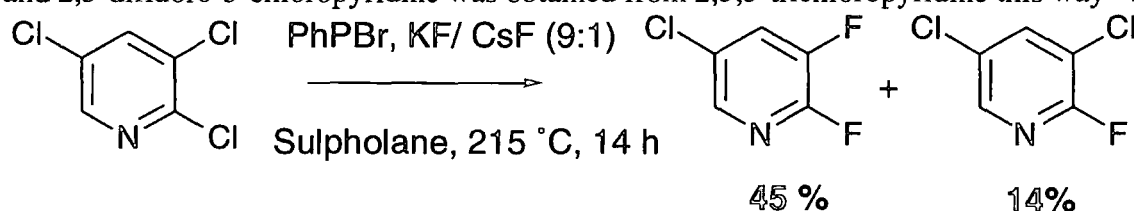
It is interesting to note that the omission of CsF from the reaction results in formation of 2-fluoro-3,5-dichloropyridine.

KF/ n-Hexadecyltrimethylammonium bromide

KF with n-Hexadecyltrimethylammonium bromide as the PTC has been shown recently[25] to work in dimethylformamide (DMF), important owing to the low cost[16] of DMF.
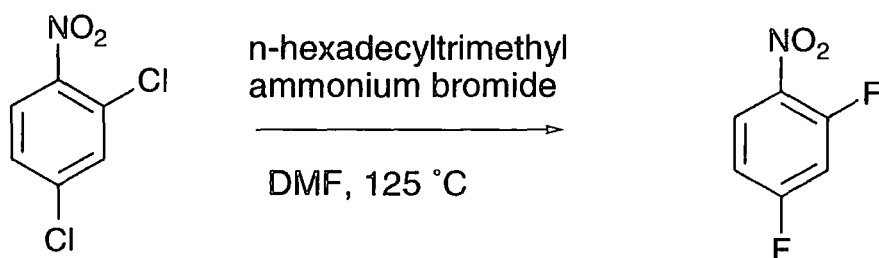
I.2.1.c   KF and Crown Ethers

Crown ethers are able to enhance the performance of KF in two ways. Firstly, they complex the potassium cation making a better fluoride source and secondly they increase the solubility of KF in the solvent.

KF with a catalytic amount of dicyclohexano-18-crown-6 in tetraglyme converted 2,4-dichloropyrimidine into 2,4-difluoropyrimidine[26].

KF, tetraglyme

dicyclohexano-18-crown-6, 150 °C, 12 h
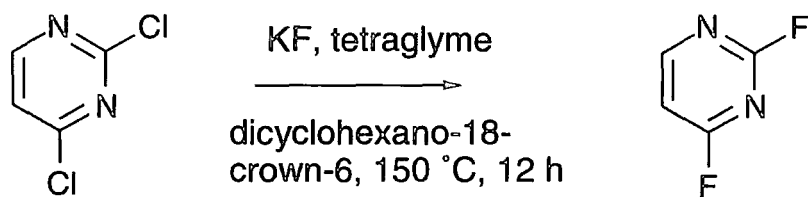
The reactivity of CsF may also be enhanced by the use of crown ethers and although 18-C-6 alone is not able to coordinate the large caesium cation, it is thought that a sandwich type structure is responsible for the enhanced reactivity here.

CsF/ 18-Crown-6

THF

64 %
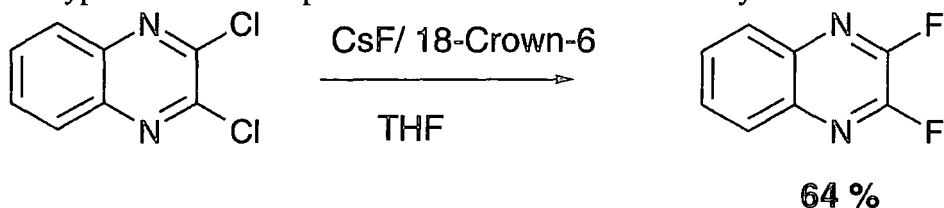
This system is sufficiently reactive (even in THF) for the conversion of 2,3-dichloroquinoxaline to 2,3-difluoroquinoxaline[27].

I.2.1.d   KF and Novel Solvents

KF/ Dimethylpropyleneurea (DMPU)

Reaction of 2,3,5-trichloropyridine with KF with DMPU as solvent and gave 2,3-difluoro-5-chloropyridine[28].

KF, DMPU

220 °C, 4 h

21 %   +   36 %
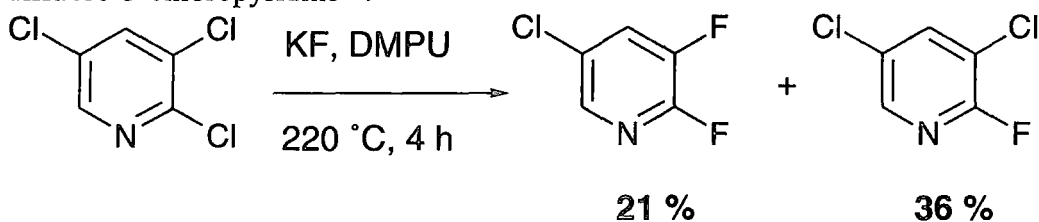
I.2.1.e   Hydrogen Fluoride (HF)

HF offers the attraction of cheapness, although this may be offset by its handling difficulties and lack of reactivity due to H-bonding. However, it may be used to fluorinate very reactive substrates. Trichlorotriazine may be converted to trifluorotriazine[29].

HF, 200 °C
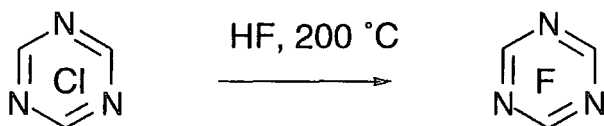
A combination of CsF and HF provides a very reactive fluoride source[30] and has shown faint promise with 3-chloropyridine giving 3-fluoropyridine in a very low yield.

5 CsF, 4 HF

300 °C, 1 h

3 %
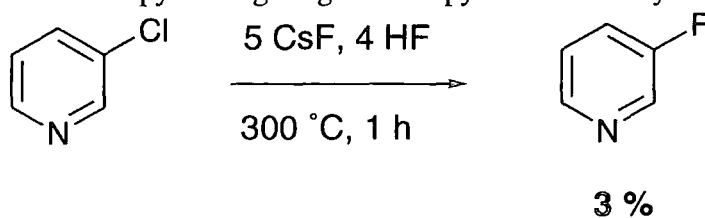
Higher yields were observed when CsF and HF were reacted with 1,3-dichlorobenzene, which gave 1,3-difluorobenzene.

6

97 %
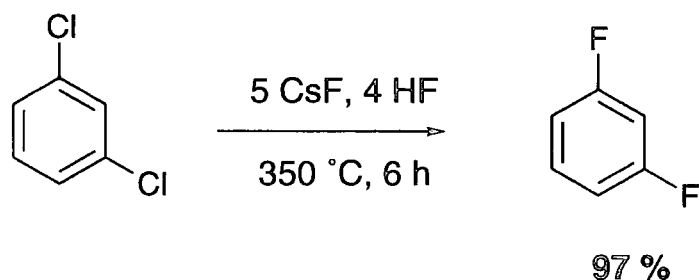
I.2.1.f   Fluorodenitration and Fluorodesulphonylation

Exchange of nitro for fluoro is also a process frequently exploited for the synthesis of fluoroaromatics and may be discussed under the title of Halex chemistry. The nitro group is an excellent leaving group in nucleophilic aromatic substitution reactions and is only surpassed by fluoride as a leaving group[31]. Aromatic nitro compounds are often readily available and sometimes offer an alternative route to the use of chloroaromatics.

Problems encountered in Halex chemistry still persists, namely the fluoride source. One further complication is the tendency for phenols to form, which may be attributed[32] to attack by nitrite on a fluoroaromatic.
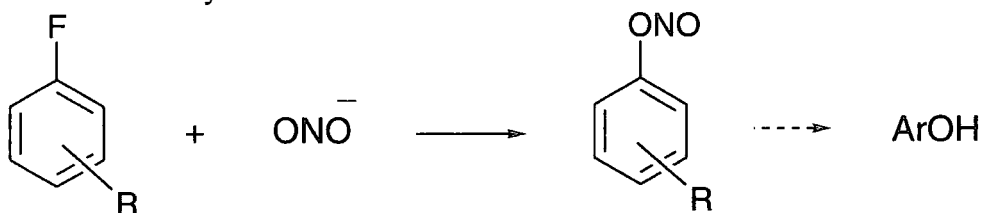
However, high yielding reactions have been encountered, although these are more pertinent to benzenoid, rather than heterocyclic systems.

A rare example[33] of fluorodenitration of a heterocyclic system was provided by 2-nitropyridine, which was converted to 2-fluoropyridine.

60 %
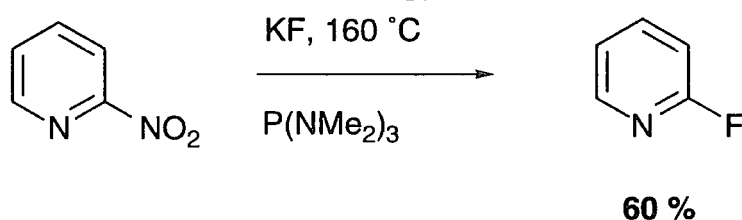
Many of the advances made in the Halex reaction have been applied to fluorodenitration reactions, for example, 3-nitrobenzonitrile reacts with KF and catalytic amounts of Ph_4PBr to give 3-fluorobenzonitrile[34].

86 %

7
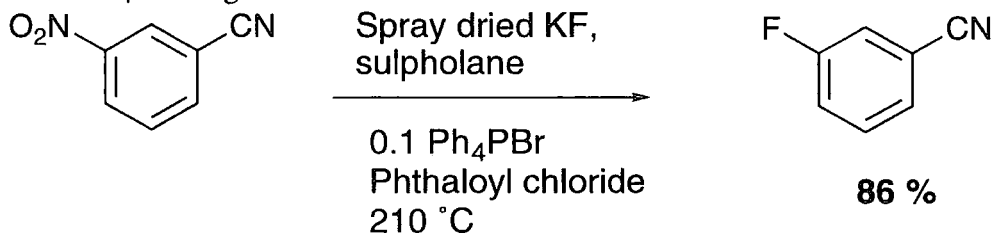
In certain instances, when both chloro and nitro may act as a leaving group, a surprising selectivity of one over the other is observed, for example chloro-2,5-dinitrobenzene was converted to 4-fluoro-3-chloronitrobenzene[35].

NO2 / Cl / NO2   1.2 KF, 0.1 Ph4PBr,
————————————————→
DMSO, 2 h, 90 °C

F / Cl / NO2

100%
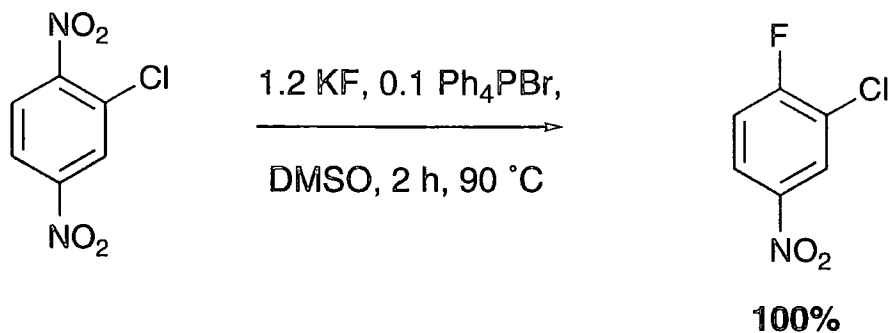
Similarly, fluorodesulphonylation is a viable process[34].

FO2S / SO2F   Spray dried KF, sulpholane
————————————————→
0.1 Ph4PBr
Phthalloyl chloride
210 °C

F / SO2F

74 %
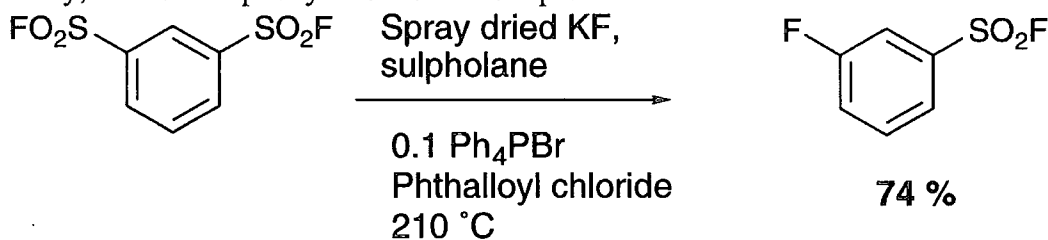
A further example of nitro rather than chloro acting as a leaving group is demonstrated in the reaction of Ph4PHF2[36] with 2-chloro-6-nitrobenzonitrile to give 2-fluoro-6-chlorobenzonitrile.

CN / O2N / Cl   Ph4PHF2, DMSO
————————————————→
2 h, 25 °C

CN / F / Cl

100%
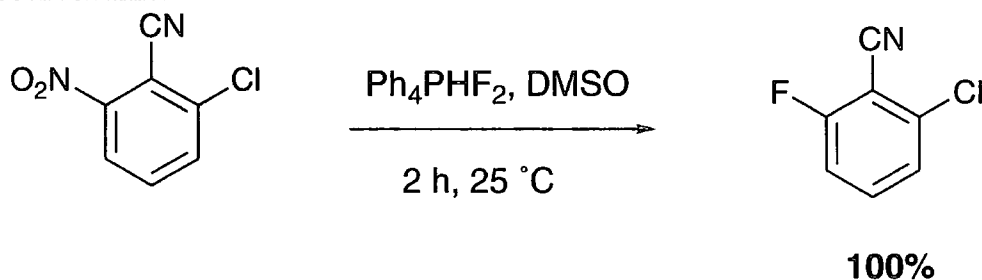
The preference for displacement of nitro rather than chloro has been attributed[36] to the excellent ability of nitro as a leaving group when itself is activated and or twisted out of the plane of the aromatic ring by neighbouring bulky goups.

Tetramethylammonium fluoride (TMAF) has been found to be an effective fluorodenitration reagent[37, 38]. The good selectivity for the fluoroaromatic and not the phenol has been attributed to the stability of ion pairing between nitrite and tetramethylammonium ions. TMAF reacts with 2-nitrobenzonitrile to give a quantitative conversion to 2-fluorobenzonitrile.

CN / O2N   1.2 TMAF, DMSO
————————————————→
80 °C, 1 h

CN / F

100%

8
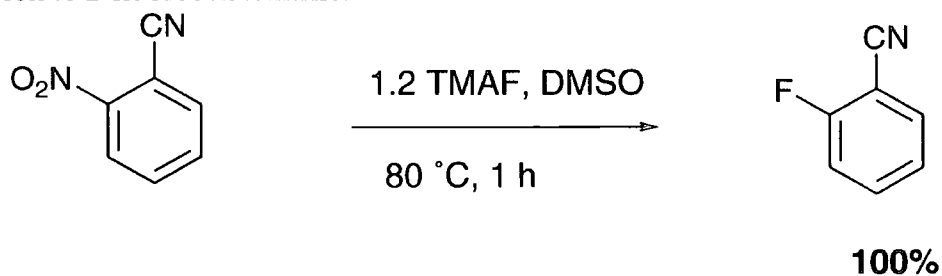
The goal of synthesising fluoro heteroaromatic compounds by directly replacing hydrogen by fluorine is a very desirable target. Thus, a method which employed readily available and cheap heteroaromatics and fluorine gas as primary reagents would be of enormous benefit. However, ring substitution of aromatic systems is typified by electrophilic substitution. Electrophilic aromatic substitution necessarily implies i, the need for an electrophilic source of fluorine, namely "F$^+$" and ii, a sufficiently nucleophilic aromatic substrate.

Heterocyclic aromatics are not particularly activated to electrophilic attack and the generation of the fluoronium ion, "F$^+$" is synthetically challenging[39]. However, significant promise and advances have been made, particularly with benzenoid aromatics.

I.2.2.a   Direct Fluorination with Fluorine (F$_2$) and Related Reagents
I.2.2.a.i   F$_2$

Early reports[40] for the reaction of fluorine with pyridine noted the formation of a solid, which was presumed to be the N-fluoropyridinium salt.
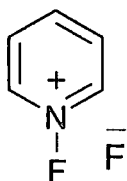
which decomposed violently on warming to temperatures greater than 0 °C, giving some 2-fluoropyridine.

However, a recent study[41] demonstrated that a range of substituted pyridines reacted with fluorine diluted with nitrogen giving 2-fluoropyridine derivatives in acceptable yields. Thus, 2-chloropyridine gave mostly 2-chloro-6-fluoropyridine.
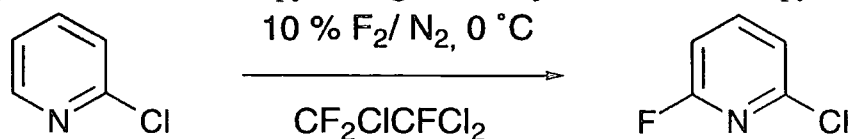
A nucleophilic mechanism has been discounted and a carbene[42] or a radical[41] mechanism may be responsible.

As mentioned, benzenoid systems have shown great promise, for example,
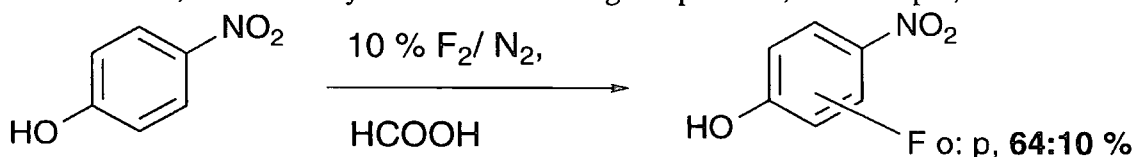
paranitrophenol reacts with fluorine giving ortho and para fluoro derivatives[43] and

79 %
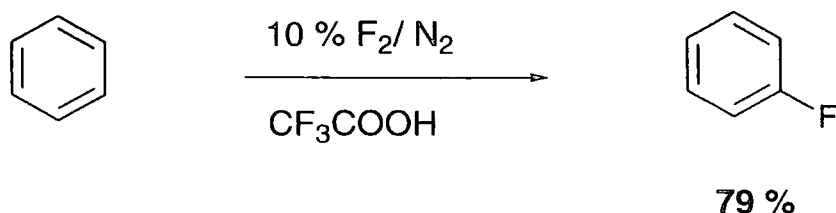
benzene gives fluorobenzene[44]. The critical factor in ensuring good yields appears to be the addition of acids, which encourages an electrophilic mechanism.

Fluorine and Iodine

Much more encouraging is the recent report[45, 46] in which the reactivity of fluorine has been controlled with iodine. Thus, pyridine gave 2-fluoropyridine in good yield. Other heteroromatics gave similar results with, for example, 4,7-dichloroquinoline giving 2-fluoro-4,7-dichloroquinoline and phenanthridine giving 2-fluorophenanthridine.

F_2/ I_2, Et_3N
————————→
$CF_2ClCFCl_2$

88 % (69 % conv.)

F_2/ I_2, Et_3N
————————→
$CF_2ClCFCl_2$

67 % (53 % conv.)
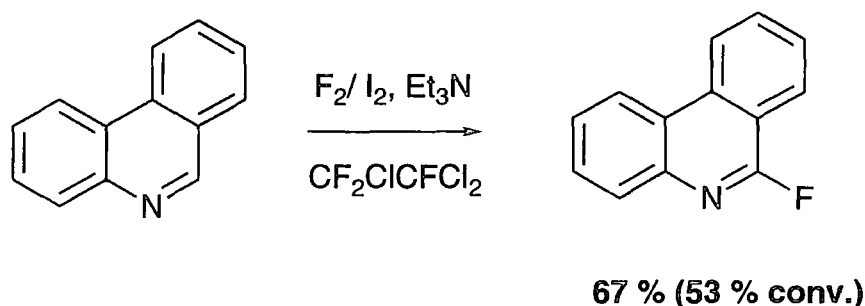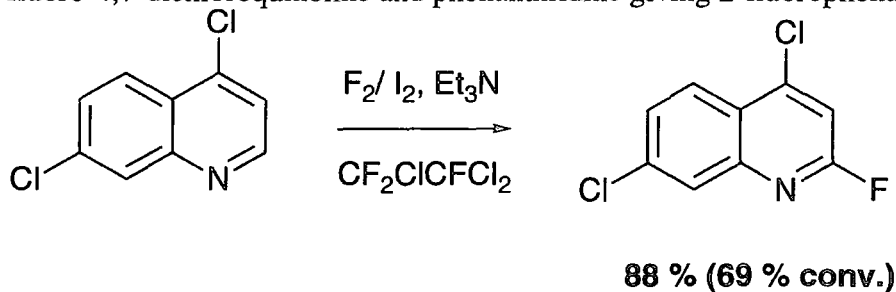
This method provides access to a range of 2-fluorosubstituted heterocycles.

Xenon Difluoride

Xenon difluoride, a costly reagent, has shown[47] surprising promise in the reaction with pyridine and the conversion of pyridine to 2-fluoro, 3-fluoro and 2,6-difluoropyridine has been reported.

XeF_2, -196 °C
————————————→
DCM, warm to RT, 1.5 h

11 %   **35 %**

+

20 %
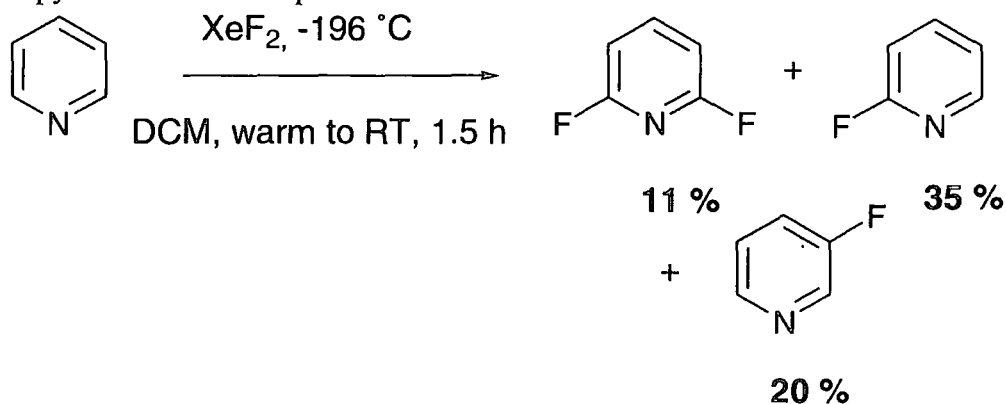
Also, 8-hydroxyquinoline gave 5-fluoro-8-hydroxyquinoline[47].

10

35 %
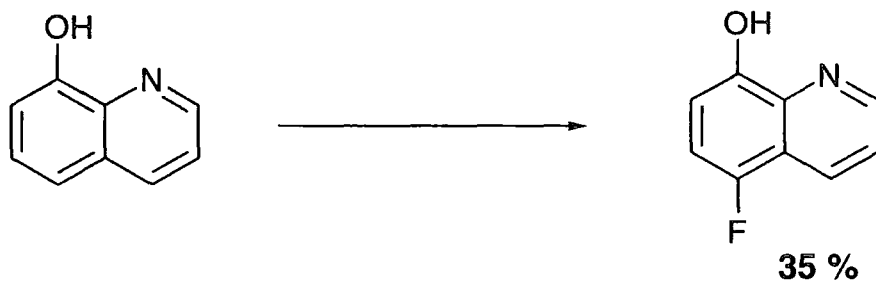
Workers[48] have suggested that the mechanism (which is outlined below) proceeds via single electron transfer from the aromatic substrate to XeF_2.
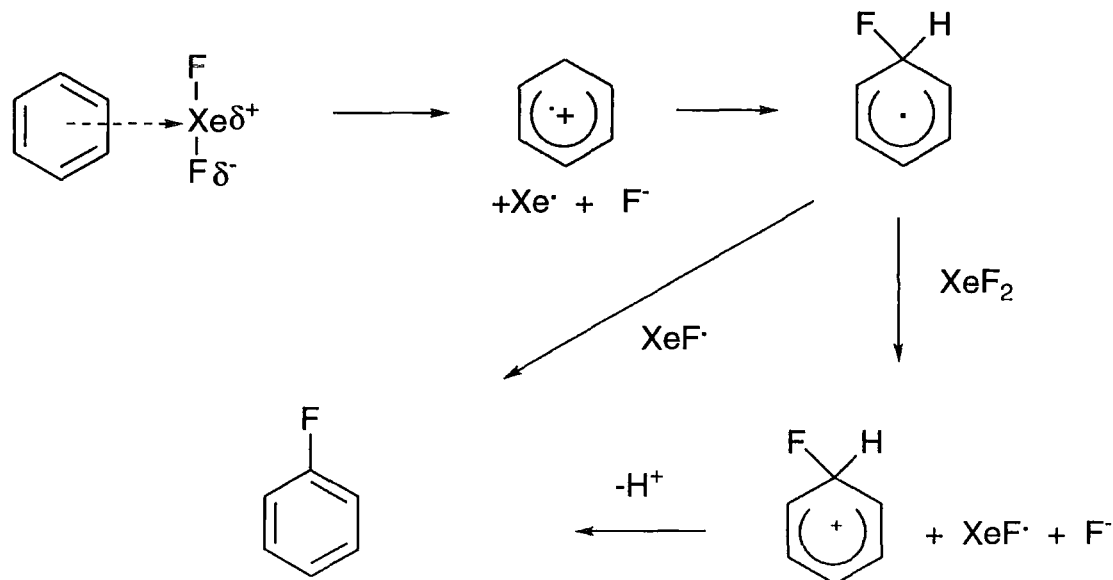
Fluorinated Fullerene

Low conversions of pyridine to 2-fluoropyridine were observed[49] for the reaction of $C_{60}F_{46}$ with pyridine.

10 %
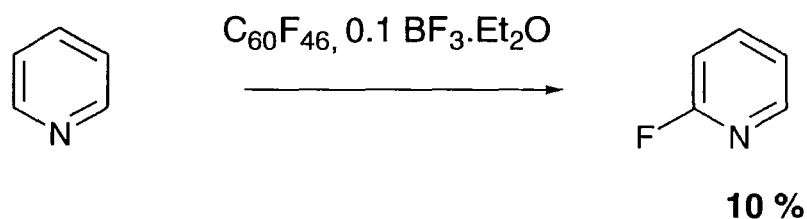
Potassium Tetrafluorocobaltate (III)

Potassium tetrafluorocobaltate (III) ($KCoF_4$) reacts with pyridine to give a complicated product mixture, giving less than 10 % yield of fluoropyridines, along with various side products[50].
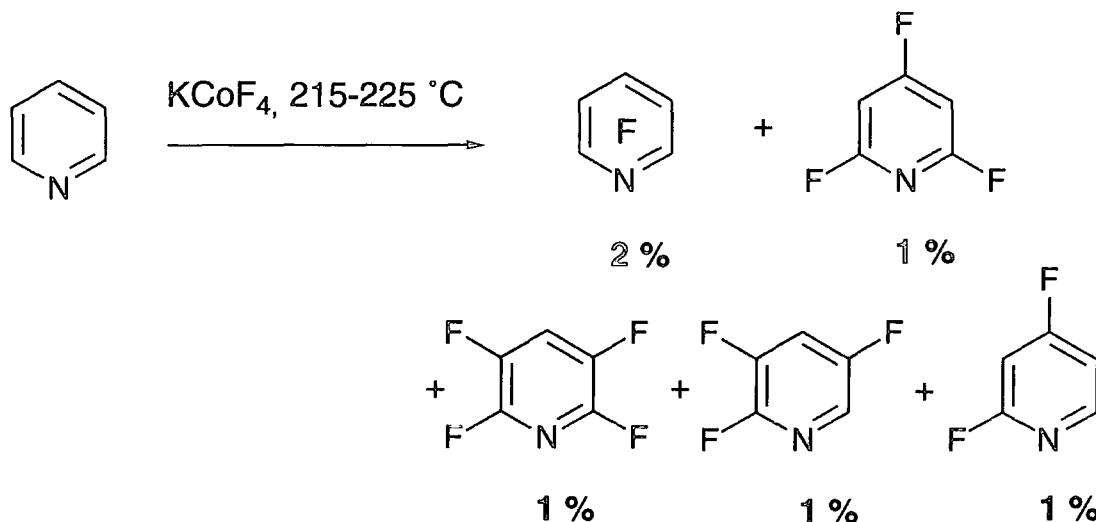
This work was further extended with the use of the milder reagent, caesium tetrafluorocobaltate, however, a similar poor yielding reaction was observed[51].

Electrochemical Fluorination

Mono fluorination of pyridine is possible using electrochemistry and it was demonstrated that pyridine may be converted to 2-fluoropyridine at a platinum anode under suitable redox conditions with tetramethylammonium dihydrogen trifluoride[52].
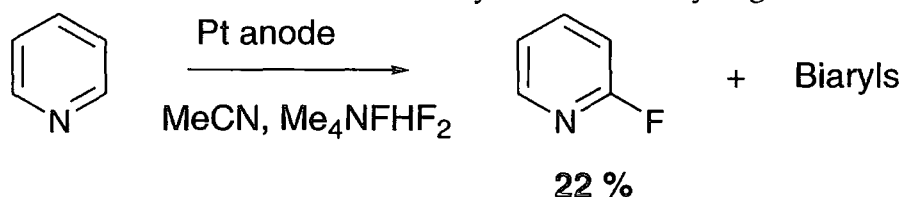
I.2.2.b   Direct Fluorination with Electrophilic Fluorinating Reagents

Numerous so called electrophilic fluorinating reagents have been developed. Such reagents as fluoroxytrifluoromethane, acetyl hypofluorite, caesium fluoroxysulphate, Selectfluor®, N-fluoropyridinium salts and $(CF_3SO_2)_2NF$ were synthesised from suitable precursors and fluorine, with the goal of developing reagents with the ability to deliver F^+[39, 53].

I.2.2.b.i   N-Fluoropyridinium Salts

N-fluoropyridinium salts, which have been used[54] to convert benzene to fluorobenzene, have also found application[42] for the synthesis of 2-fluoropyridine and 2-fluoropyridine derivatives.

12
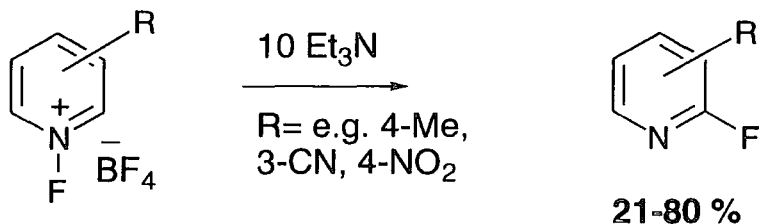
Thus, 2-fluoropyridine and derivatives may be made in good yields. This reaction is of particular mechanistic interest and the authors suggest[42] that a carbene mechanism operates.
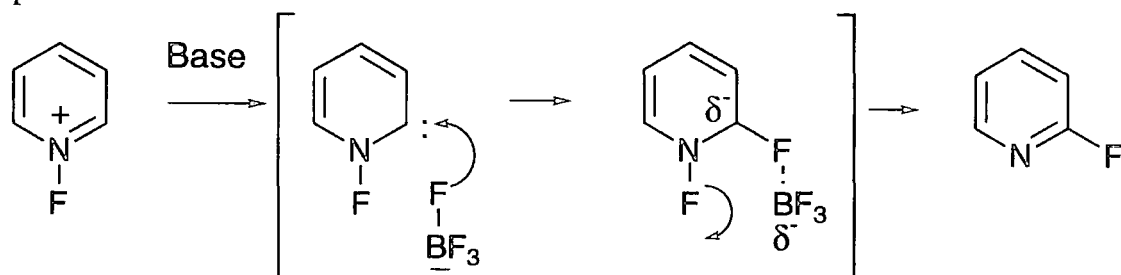
I.2.2.b.ii   Caesium Fluoroxysulphate (CsSO₄F)

$CsSO_4F$ may be used to fluorinate pyridine directly[55], but the reaction is very sensitive to the solvents employed. When solvents such as pentane and diethyl ether were used, 2-fluoropyridine was the major product, but use of nucleophilic solvents, such as methanol gave 2-methoxypyridine.
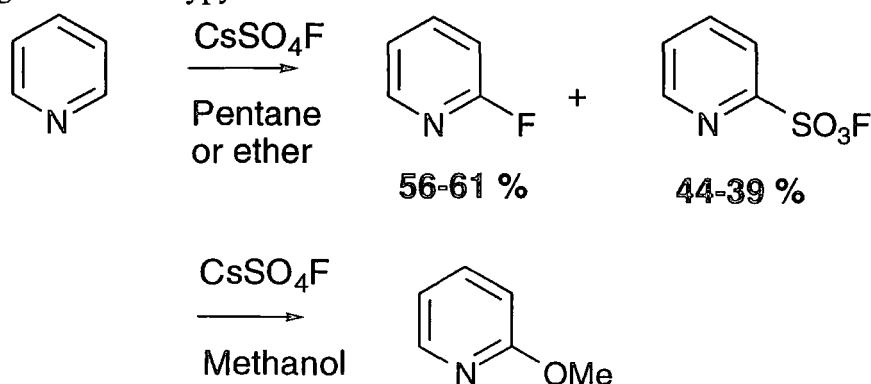
$CsSO_4F$ will also fluorinate alkoxy benzenes[56].

I.2.2.b.iii   Acetyl Hypofluorite (CH₃CO₂F)

CH_3CO_2F has been shown[57] to react with pyridine and quinoline to give 2-acetoxypyridine and 2-acetoxyquinoline.
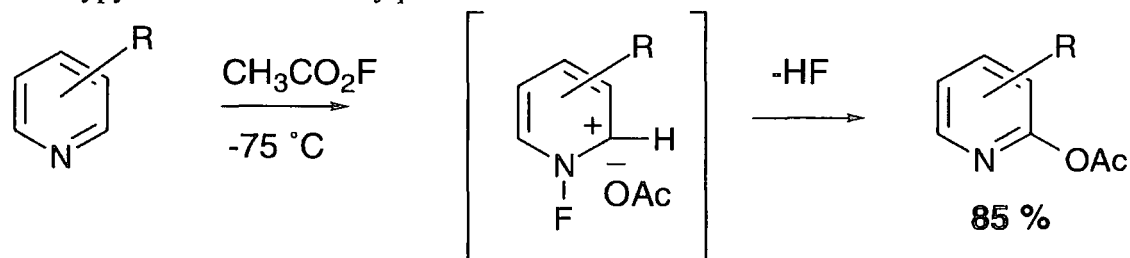
Once again, this reaction is of mechanistic interest and since 2-cyanopyridine failed to react, base abstraction of 2-H appears to be an important step. A mechanism involving a tight ion pair has been proposed[57]. Acetyl hypofluorite will also fluorinate aromatics such as phenol.

I.2.2.b.iv   Other F^+ Reagents: CF_3OF, Selectfluor® amd $(CF_3SO_2)_2NF$.

Fluoroxytrifluoromethane (CF_3OF), Selectfluor® and $(CF_3SO_2)_2NF$ have not been reported as being able to fluorinate heteroaromatic compounds, however, they have shown promise for benzenoid systems.

$$\text{benzene} \xrightarrow[\text{30 min}]{CF_3OF/\ CHCl_3} \text{fluorobenzene}$$

77 %

$$\text{toluene} \xrightarrow[\text{MeCN, reflux}]{\text{Selectfluor}} \text{fluorotoluene} \quad \text{F o: p, 60: 20 \%}$$

$$\text{aniline} \xrightarrow[\text{22 °C}]{(CF_3SO_2)NF} \text{fluoroaniline} \quad \text{F o: p, 69: 24 \%}$$
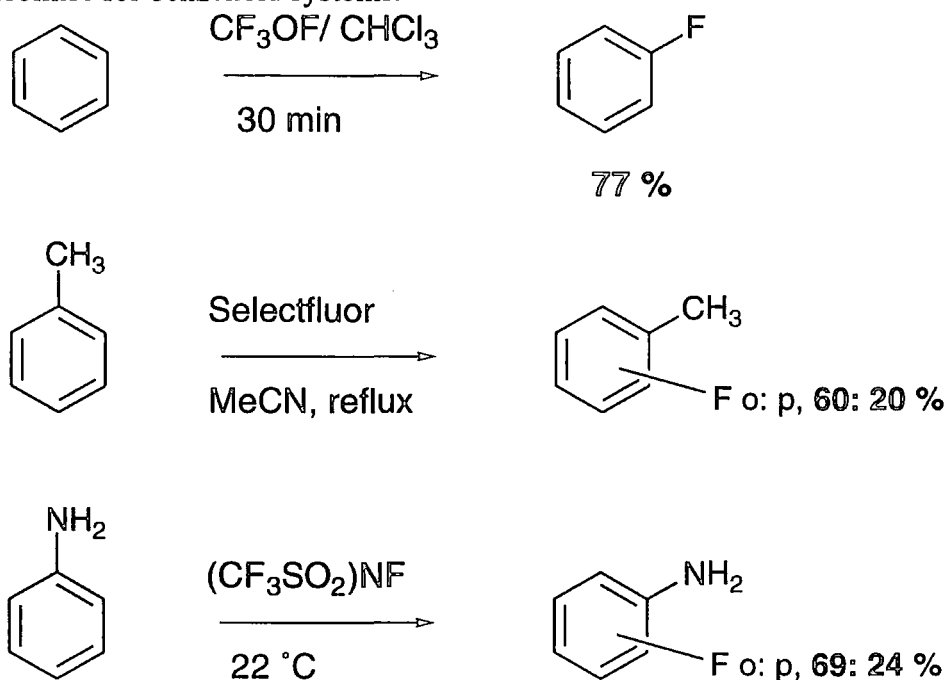
Thus, fluorobenzene[58], fluorotoluene[59] and fluoroanisole[60] respectively may be prepared with these reagents.

I.2.3   Substitution of Other Groups by Fluorine

I.2.3.a   Fluorodemetallation

Fluoro-demetallation has been developed as a method for introducing fluorine (often radio-labelled[61]) into an aromatic compound. this method often offers the benefit of site specificity[62].

The technique has found limited application , with particular use for substituted benzenes. The source of fluorine is much the same as for those discussed in part I.2.2.

Selectfluor®

Selectfluor®, for example, may react with indole-tin derivatives giving a 2-fluoroindole[62].

$$\text{indole-SnMe}_3 \xrightarrow[\text{Selectfluor}]{\text{MeCN}} \text{2-fluoroindole}$$

40 %
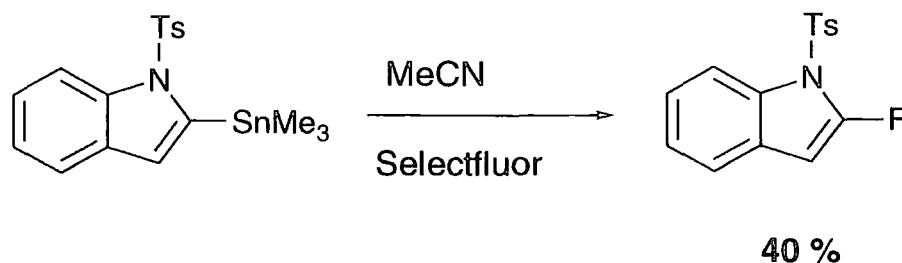
This particular reaction is of benefit, since direct fluorination of the non-metallated indole gave the 3- isomer.

Ts
N → indole with OMe and F products

MeCN
───────────
Selectfluor

48 %
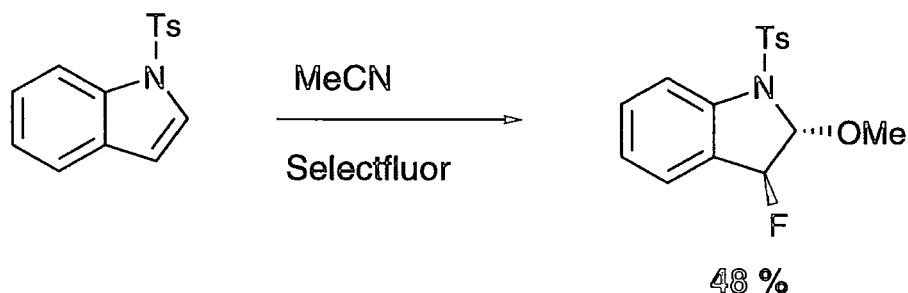
Fluorine

Fluorine itself reacts with a 4-substituted methoxy benzene tin derivative[63] to give 4-fluoroanisole.

OMe ... SnMe$_3$

F_2
───────────
$CFCl_3$, -78 °C

OMe ... F

70 %
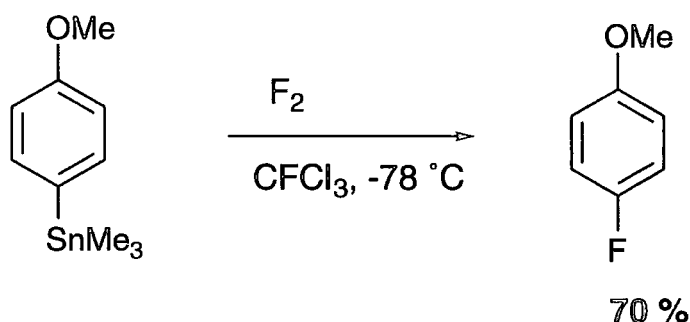
Tetraphenyl tin also affords fluorobenzene under similar conditions[61].

Ph_4Sn
F_2
───────────
$CFCl_3$, -78 °C
ArF

15 %
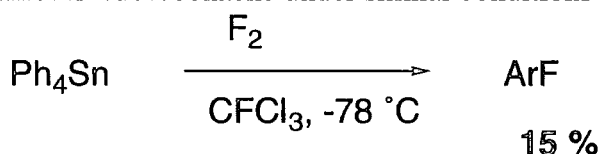
Imidazole tin derivatives have shown[58] limited promise and have reacted with fluorine giving a fluoroimidazole.

Me_3Sn imidazole (N, Me, N-Me)

10 % F_2/ N_2
───────────
$CFCl_3$, -78 °C

F imidazole (N, Me, N-Me)

Not isolated
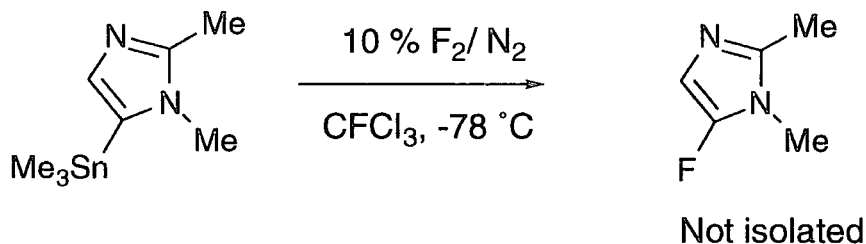
Acetyl Hypofluorite

Acetyl hypofluorite also will fluoro-demetallate benzene derivatives, for example mercury derivatives of phenol[64] gave 4-fluorophenol.

OH ... HgCl

MeCOOF
───────────

OH ... F

47 %
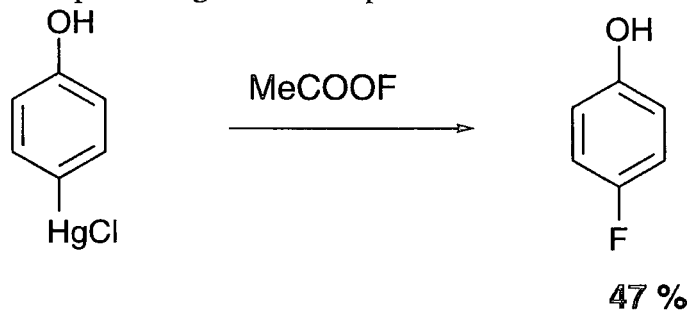
Similarly, silicon and germanium derivatives react adequately[63], for example, tin, silicon and germanium derivatives of methoxy benzene gave 4-fluoromethoxybenzene.

15

OMe / SnMe₃ → MeCOOF / CFCl₃, 0 °C → OMe / F

66 %
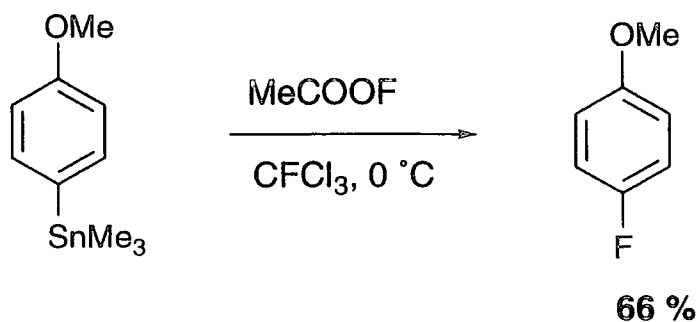
I.2.3.b   Fluorodediazoniation

Fluorodediazoniation refers to the process where an amine group attached to an aromatic or heteroaromatic ring is replaced by fluorine. This reaction, often termed the Balz-Schiemann[65-67] reaction, continues to provoke interest and often provides the only real practical route to fluororomatics and fluoro heteroaromatics.

The reaction proceeds via the initial formation of a diazonium salt, which decomposes in the presence of a fluoride ion source to yield the fluoroaromatic.

$$ArNH_2 \longrightarrow ArN_2^+BF_4^- \xrightarrow{\Delta} ArF + N_2 + BF_3$$
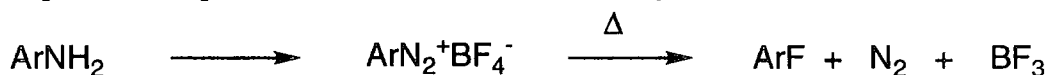
An early example of the Balz-Schiemann reaction is provided by Roe[68], who converted 2-, 3- and 4-aminopyridine to 2-, 3- and 4-fluoropyridine respectively.

NaNO₂ / 40 % HBF₄ / 95 % EtOH

50 %
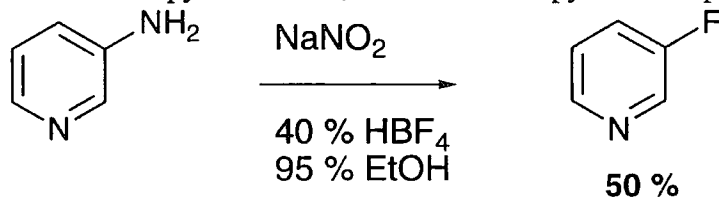
Over the past five decades, the reaction has remained essentially unchanged, for example 3-amino-2,5-dibromopyridine gives 3-fluoro-2,5-dibromopyridine[69], a building block for the synthesis of liquid crystals.

NaNO₂ / HBF₄

29 %
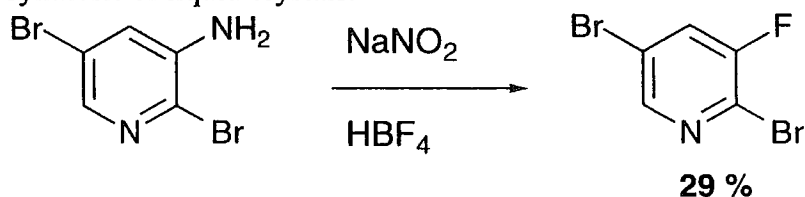
However, the reaction has been modified and the use of hydrogen fluoride (HF), which was used[7] to convert 2-aminopyridine to 2-fluoropyridine (the first synthesis of a fluoroheterocycle), has become common as the fluoride source in these types of reactions.

Boudakian[70] synthesised 2,6-difluoropyridine from 2,6-diaminopyridine using anhydrous hydrogen fluoride (AHF).

NaNH₂ / AHF

62 %

16
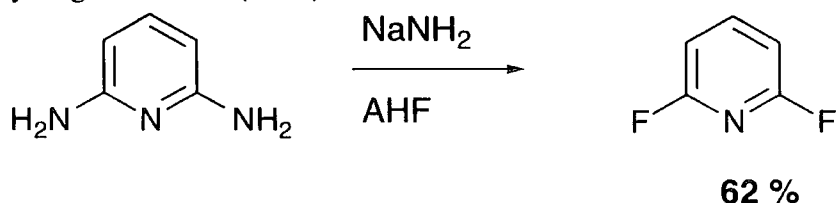
HF techniques have been found to work excellently if used with bases such as pyridine. Workers applied this to the synthesis of a range of fluoroheterocycles[71, 72], for example, 3-fluoropyridine, 2-fluoro-3-nitropyridine and 2-fluoro-4,6-dichloropyrimidine were made in good yield.

91-94 %

97 %

80 %
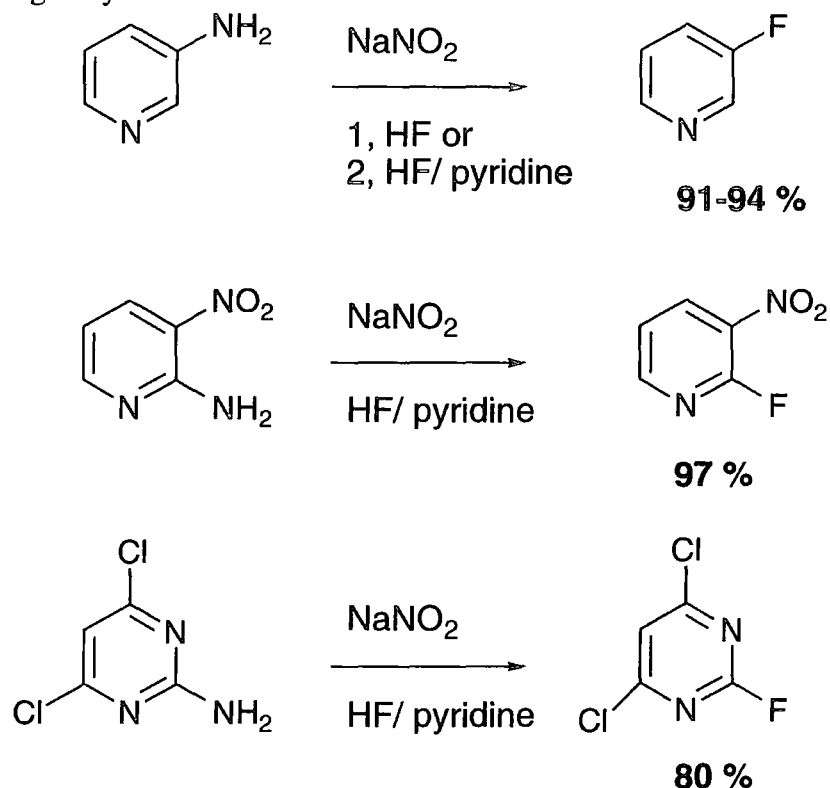
Recent work[72] has suggested that pyridine slows down the rate of decomposition of the diazonium salt and poor yields encountered in the synthesis of fluoroarenes substituted with polar groups (e.g., NO_2, OH) have been improved by photochemical techniques to accelerate the fluorodediazoniation stage.

Other workers[73] claim to have increased selectivity for arenes with polar groups attached such as 4-aminophenol

90 %
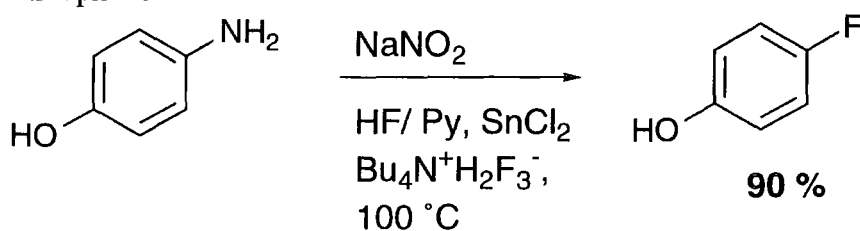
by the addition of tin chloride or tin fluoride and an excess fluoride ion (tetrabutylammonium dihydrogentrifluoride) in an attempt to increase yields. The significance of tin chloride and fluoride will be discussed in chapter II- their relevance is pertinent to hydrodediazoniation- a single electon transfer process which may be improved by the addition of electron donors, such as tin chloride. The merit of adding electron donors to the fluorodediazoniation process is questionable anyway, because the decomposition of fluoro-diazonium salts probably[74] occurs via a heterolytic process (i.e. S_N1 attack of fluoride on the carbocation).

The synthesis of fluoroaromatics by the combination of building blocks usually takes the form of either combination of acyclic precursors (type A),
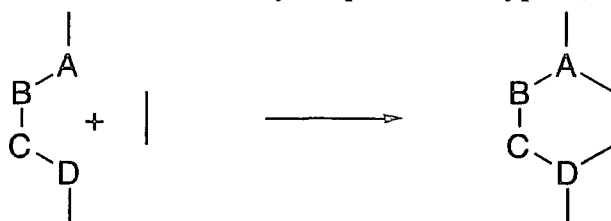
or the reaction of an (often fluorinated) aromatic with an acyclic unit (type B).
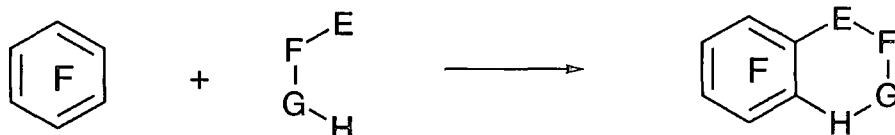
I.2.4.a   Type A

A rare exampleof the synthesis of a fluoropyridine was provided by researchers[75] who prepared a 3-fluoropyridine derivative via a Diels-Alder reaction between 2-fluoro-2-alkenal-N,N-dimethylhydrazones and methyl acrylate.
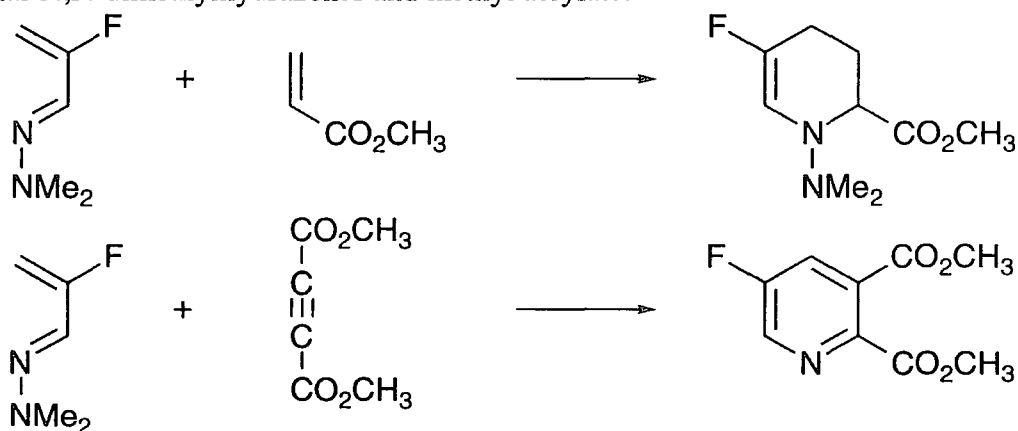
This reaction[75] also provides a route to a 3-fluoroquinoline via reaction with p-benzoquinone.
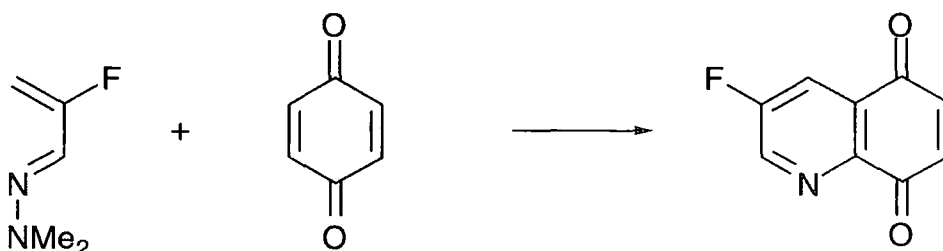
The preparation of fluoropyrimidines via building blocks is a livelier field of study and a variety of substituted 5-fluoropyrimidines may be obtained by reacting ethyl-γ-fluoroacetoacetate or 2-fluorodiethylacetate with amidine and guanidine derivatives, to give, for example, 2,4-dimethyl-5-fluoro-6-hydroxypyrimidine[76] and the 4-keto form of 2-methyl-4,6-dihydroxy-5-fluoropyrimidine[77].

56 %
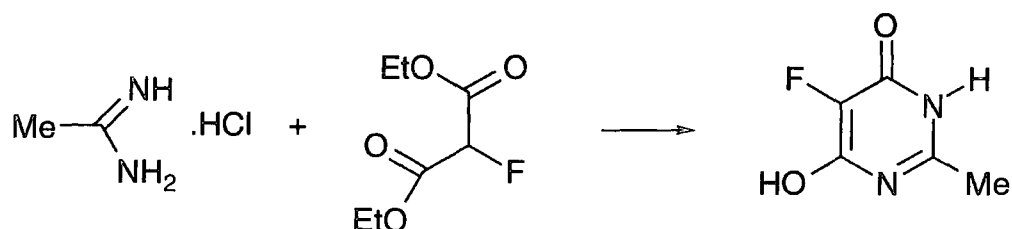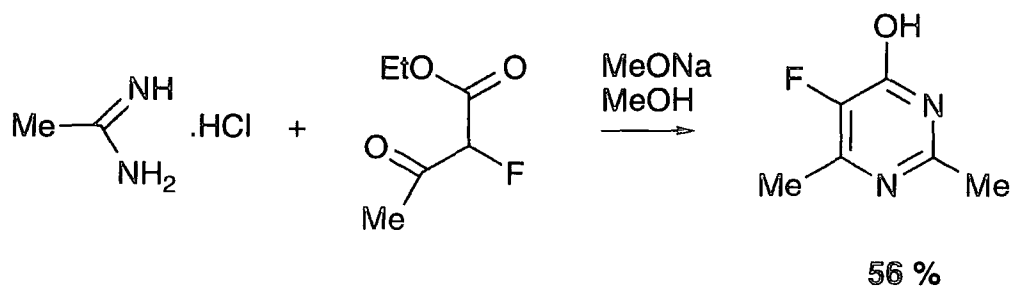
Reichardt[78] provided a route to 5-fluoropyrimidine (and derivatives) by the reaction of 1,1,5,5-tetramethyl-3-fluoro-1,5-diazapentadienium tetrafluoroborate with amidine derivatives.
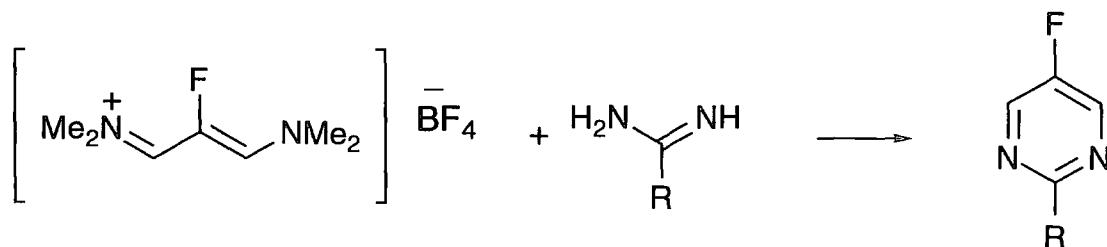
Very similar work by Shi[79] has recently extended this work to a one pot procedure from N-(2,3,3-trifluoro-1-propenyl)trimethylammonium iodide.

Et$_2$NH, MeCN, 70 °C, 3 h

75 %
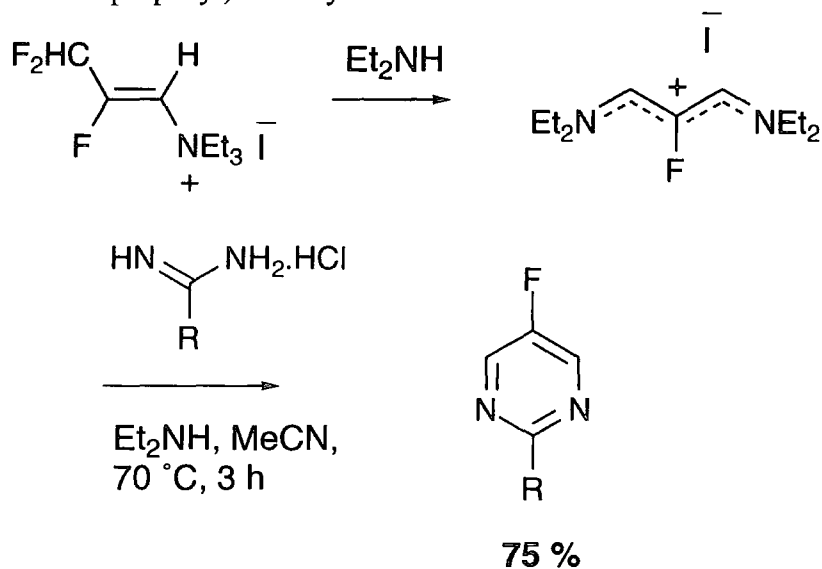
This reaction appears to tolerate a wide range of substituted amidines, from amino to phenyl and provides a route to a variety of 2-substituted-5-fluoropyrimidines.

Ishihara[80] has provided a novel route to 5,6-difluoropyrimidine derivatives *via* the reaction of amidine with 1-substituted F-1-alkenylphosphates.

19

92 %
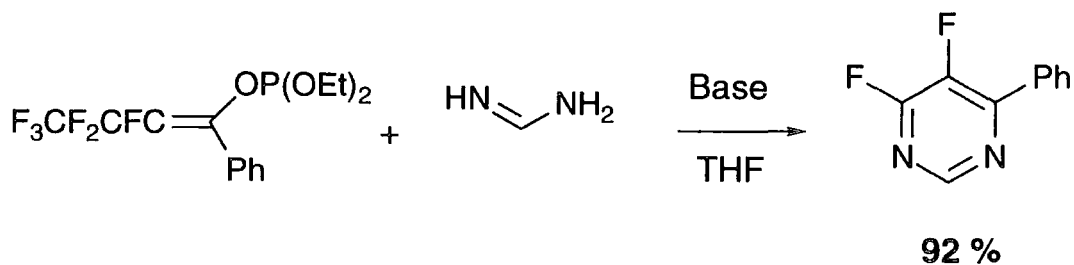
I.2.4.b   Type B

The second type of reaction, where the aromatic ring is already in place provides many interesting routes to fluoroheterocycles.

4-Fluoro-5-nitro-1,2-diaminobenzene may react with oxaldehyde to give a 6-fluoro-7-nitroquinoxaline[81].

50 %
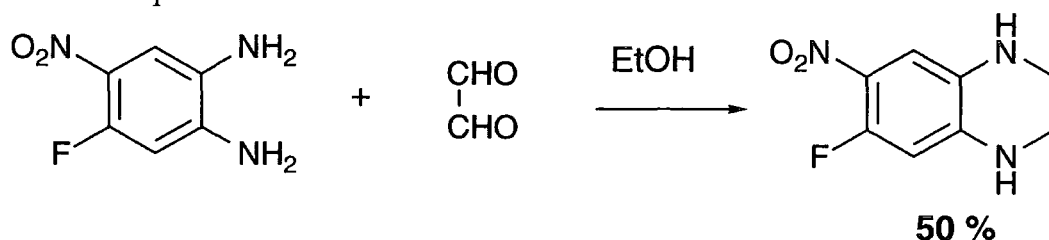
In a similar nucleophilic cyclisation, 5,6,7,8-tetrafluoro-2,3-dihydro-1,4-benzoxazine was made[82] *via* the reaction of hexafluorobenzene with 2-aminoethanol.
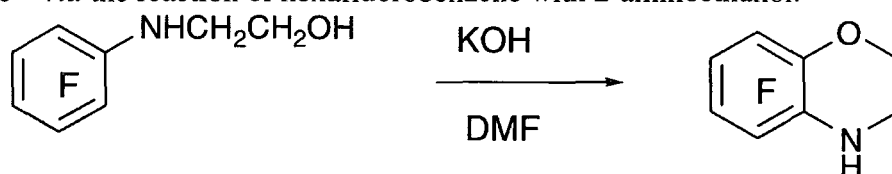
Obviously, though, in these reactions, intramolecular cyclisation must compete with intermolecular reactions[82].

A novel tetrafluorobenzoquinoline was made[83] by the acid catalysed self condensation of 2-(phenylamino)-3,4,5,6-tetrafluorobenzaldehyde.
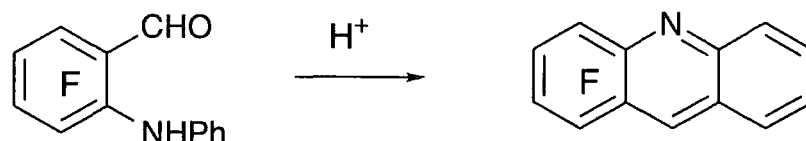
Recently, Brooke[84] synthesised novel fluoroquinoline ring systems *via* cyclisation of thiol substituted fluoroquinolines.

74 %

20
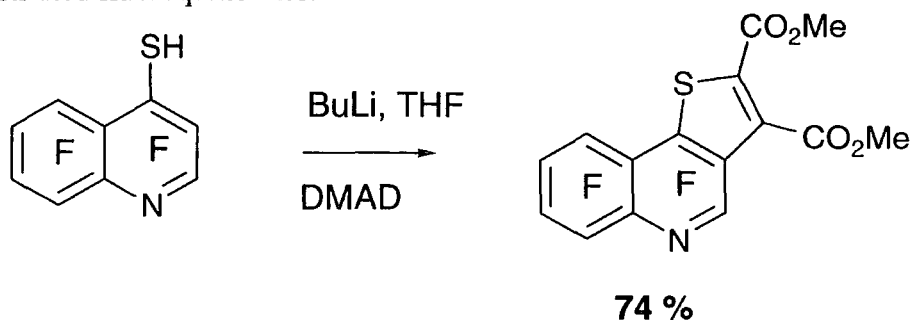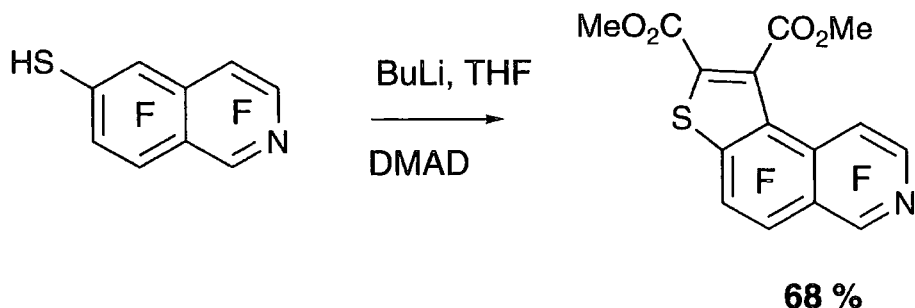
A final type of reaction which warrants mention is a reaction of difluorocarbene to form fluoroaromatics[85].
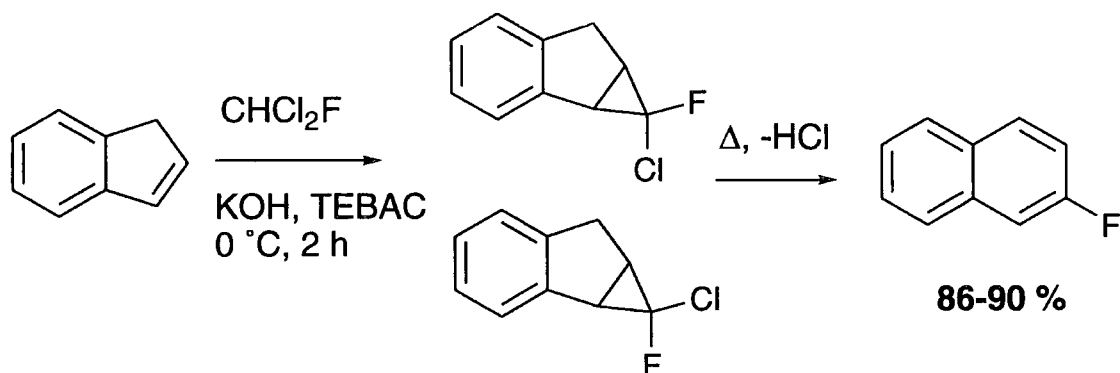
Both fluoronaphthalene and fluorobenzene have been synthesised by ring expansion reactions.
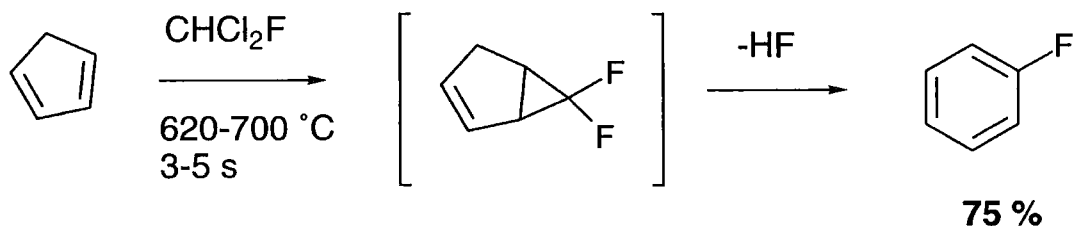
Thus, either low temperature techniques with TEBAC (triethylbenzylammoniumchloride) or pyrolysis at very high temperatures produce good results.

I.2.5   Saturation-Rearomatisation

This method involves the preparation of a fully fluorinated saturated heterocyclic ring from an heteroaromatic precursor followed by defluorination of the saturated ring to give the desired unsaturated fluoroheteroaromatic compound.

For example, pentafluoropyridine may be obtained from pyridine[86] by electrochemical fluorination (ECF) to give perfluoropiperidine followed by defluorination to give pentafluoropyridine.
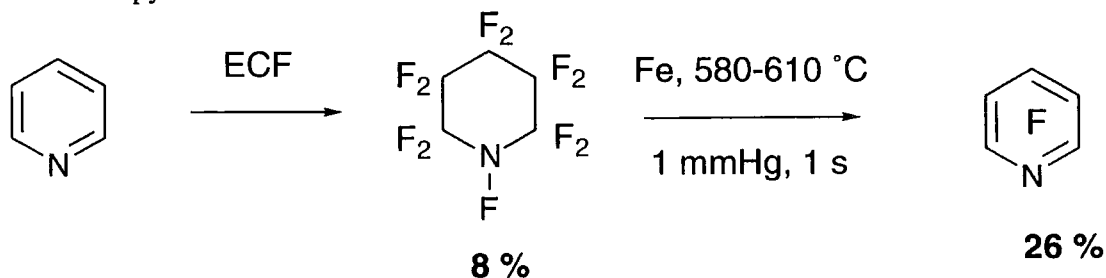
Functional groups may be tolerated to an extent and 4-methylpyridine gives perfluoro-4-methylpyridine[87].
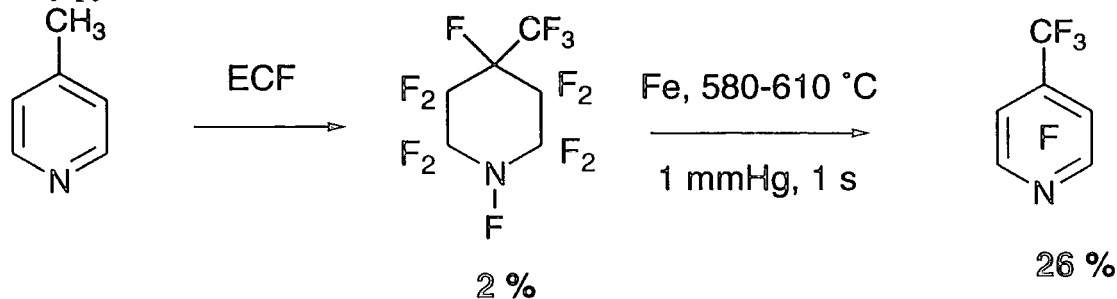
Unfortunately, this method is not a feasible process, owing to the poor yielding reactions involved.

I.2.6   Conclusion

Although many routes to fluoroheterocycles exist, the scope and range of products available are limited.

We were interested in developing new routes to fluoroheterocycles of unusual orientation, in particular we aimed to synthesise 3,5-difluoropyridine.

However, 3,5-difluoropyridine was not obtainable from any of the routes discussed so far, hence, new methodology was required.

Direct Replacement of Fluorine by Hydrogen from Fully Fluorinated Aromatic Nitrogen Heterocycles

The principal reason behind this project was to develop routes to new unusually substituted fluoro heterocycles such as 3,5-difluoropyridine (5).

3   **5**
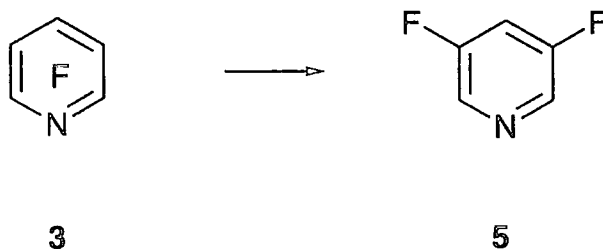
The proposed reaction is shown above and we were interested in developing methodology for the replacement of fluorine by hydrogen in a range of fully fluorinated aromatic heterocycles.

Our first target molecule was 3,5-difluoropyridine (5) and although the use of (5) as a ligand in platinum complexes has been reported[88], details of its synthesis are not available.

We adopted two fundamental strategies for the synthesis of (5):

i, *Direct replacement* of fluorine by hydrogen from highly fluorinated heterocycles, which will be covered in chapter II and

ii, *Indirect replacement* of fluorine by hydrogen from highly fluorinated heterocycles, which will be described in chapter III.

II.1   Methods for the Direct Replacement of Fluorine (F) by Hydrogen (H) from highly fluorinated heterocycles

Several methods concerned with replacing F by H have been described in the literature and a review of these procedures follows.

II.1.1   *via* Metal and Organometallic Reagents

Pentafluoropyridine reacts with zinc in aqueous ammonia giving 2,3,5,6-tetrafluoropyridine[89],

70 %
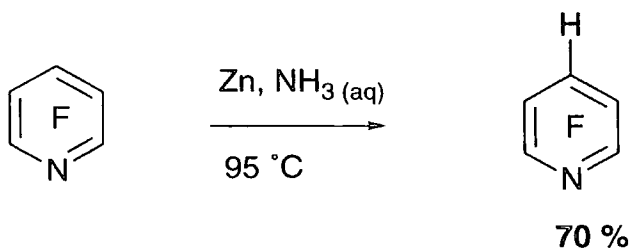
which is surprising since reaction of pentafluoropyridine with ammonia in the absence of zinc, affords 4-aminotetrafluoropyridine[90]. Presumably, in this reaction, electron transfer from zinc to pentafluoropyridine occurs faster than nucleophilic addition of ammonia to pentafluoropyridine.
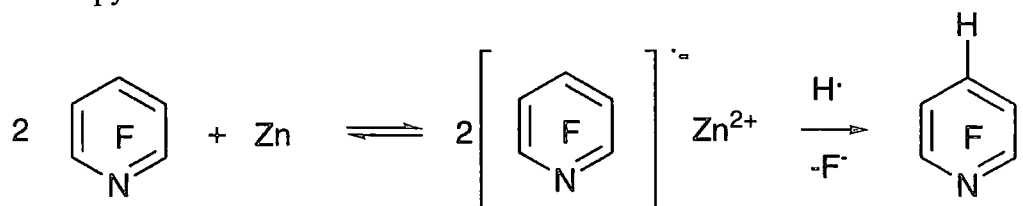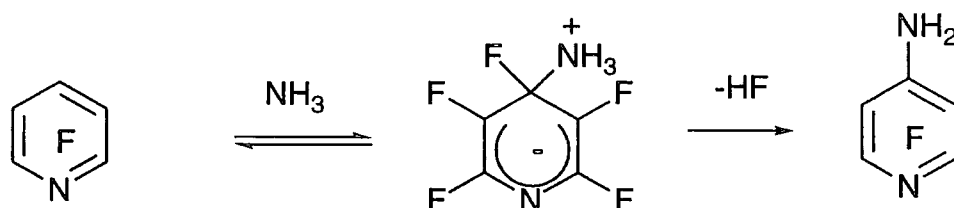
The activation of C-F bonds in perfluoro-1,3-dimethylbenzene by a zinc-copper couple led to the replacement of ring F by H, giving 1,3-bistrifluoromethyl-2,4,5-trifluorobenzene as the major product[91].
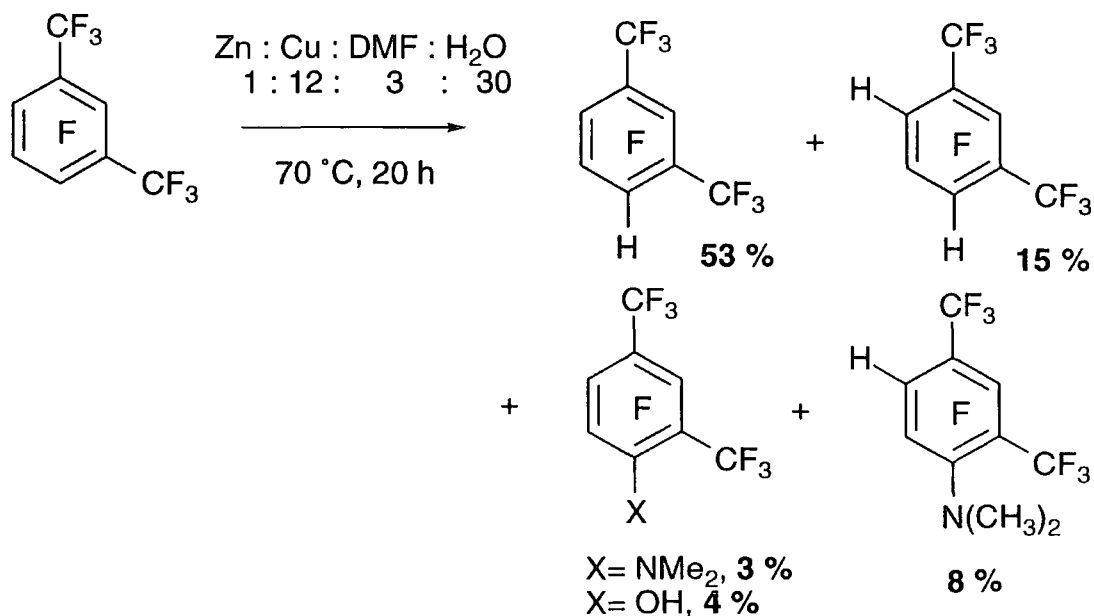
The mechanism for this reaction is likely to be similar to that of pentafluoropyridine with ammonia and will involve electron transfer from the zinc-copper couple to the fluoroaromatic, followed by capture of H and loss of fluoride giving the reduced products.

The other perfluoroxylene isomers also reacted with this reagent, although in the case of *p*-xylene, 4-trifluoromethyl-2,3,5,6-tetrafluorotoluene was the major product.

76 %   7 %
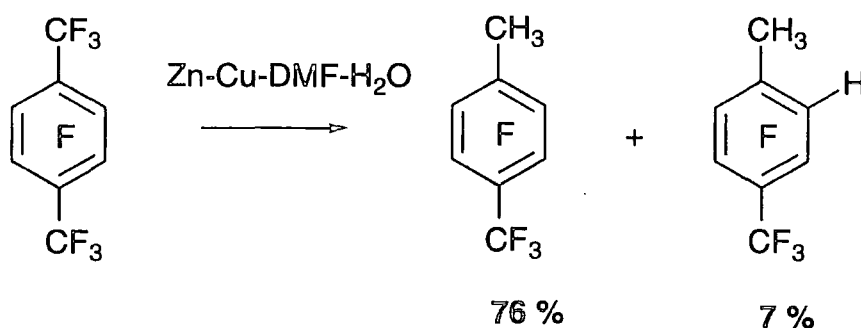
A zirconium complex[92] (biscyclopentadienyl zirconium dichloride) reacts with octafluoronaphthalene and hexafluorobenzene giving 1,3,4,5,6,7,8-heptafluoronaphthalene (97%) and pentafluorobenzene (93%) respectively.
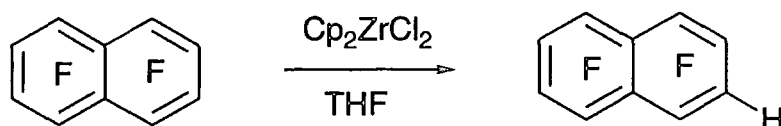
II.1.2 Catalytic Methods

Catalytic reduction of aryl chlorides, bromides and iodides is well documented, however, aryl fluorides do not readily react under these conditions, owing to the strong C-F bond and the high activation barrier to bond breaking. Work in our laboratories[93] showed that at high temperatures, pentafluoropyridine was converted to 2,3,5,6-tetrafluoropyridine using a palladium catalyst.

30 %
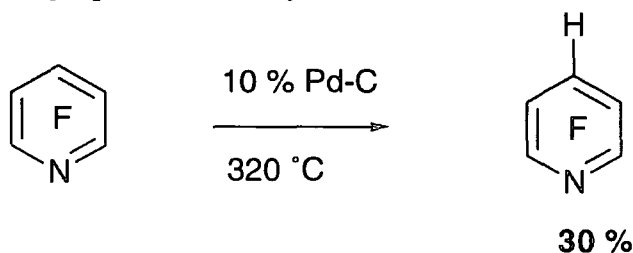
This reaction is, however, a rare example of catalytic hydrogenolysis of C-F bonds.

II.1.3 Electrochemical Methods

In the presence of an H donor (hydroquinone), the pentafluoropyridine radical anion generated from pentafluoropyridine and a mercury cathode was trapped giving 2,3,5,6-tetrafluoropyridine[94].

46 %
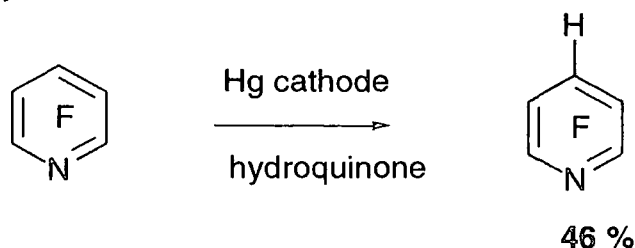
The mechanism shown in scheme (1) probably involves transfer of an electron to give a radical anion

Scheme (1)
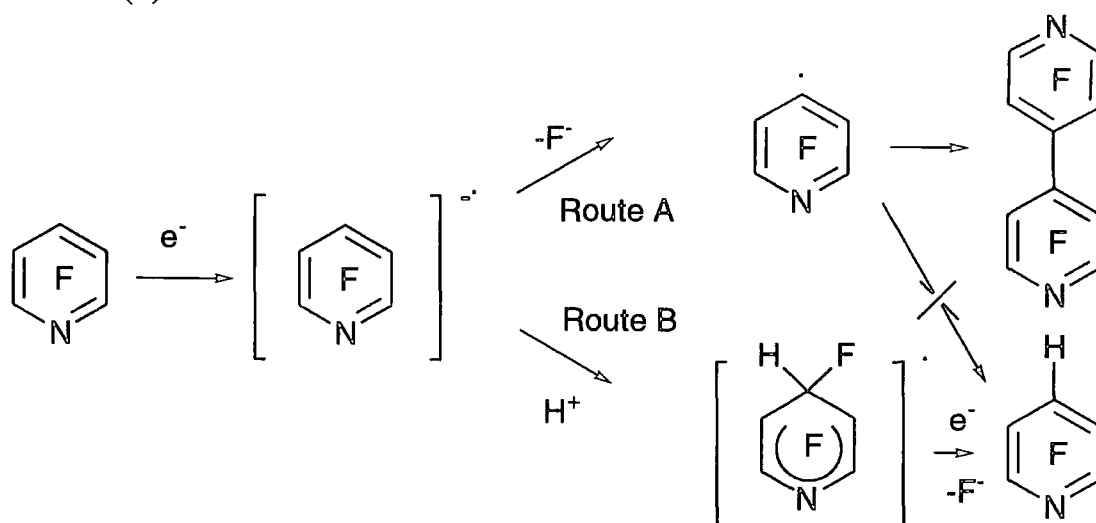
which may either lose fluoride ion to give a radical and then capture H from the solvent (route A) or capture a proton followed by gain of an electron and loss of fluoride ion (route B) to afford the reduced pyridine. Workers in our laboratories preferred route B to route A, because of the necessity of an H-donor, such as hydroquinone to afford 2,3,5,6-tetrafluoropyridine- they argued that the radical produced in route A would abstract H from solvents- but this was not observed: in the absence of hydroquinone, only the bipyridyl was produced, but addition of hydroquinone afforded 2,3,5,6-tetrafluoropyridine.

II.1.4   Nucleophilic Methods

Nucleophilic substitution of highly fluorinated heterocyclic systems has been extensively studied. Pioneering work on the reactions of simple nucleophiles with pentafluoro-pyridine[21, 90] and other perfluoro-heteroaromatic systems such as perfluoro-quinoline[95], perfluoro-isoquinoline[95], perfluoro-quinoxaline[96], perfluoro-pyrimidine[97], perfluoro-pyridazine[98] and perfluoro-pyrazine[99] demonstrated the synthetic versatility of these systems. Research in our laboratories established simple rules for predicting the orientation of attack for nucleophiles and it was shown that nitrogen *para* and *ortho*[100], fluorine *ortho*[101] and *meta*[102,103], and chlorine[104] *ortho* and *meta* to the position of attack are strongly activating. The activating effect of fluorine *ortho* to attack was attributed to initial state effects[101].
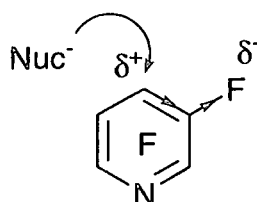
Therefore, a nucleophile attacks a perfluoroheterocycle to maximise the number of activating fluorines and nitrogens. Thus, attack on pentafluoropyridine occurs at the 4-position (2-F *ortho*, 2-F *meta* and 1-N *para*).

Attack here
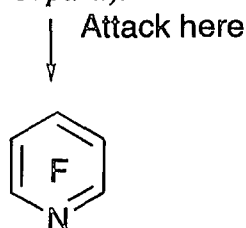
Other factors may influence orientation of attack and lithium hydrazonides[105] and sodium oximates[106] react at 4- *and* 2- positions, an observation which Banks attributed to metal cation participation.

II.1.4.a   Reaction of Highly Fluorinated Heterocycles with Metal Hydrides

Nucleophilic hydride reagents react with perfluoro-aromatic heterocycles and lithium aluminium hydride (LAH) reacts with heptafluoroisoquinoline[95] and tetrafluoropyrimidine[107] giving 3,4,5,6,7,8-hexafluoroisoquinoline and 4,6-difluoropyrimidine respectively. Another report claims that LAH reacts with pentafluoropyridine[108] giving 2,3,5,6-tetrafluoropyridine in high yield.
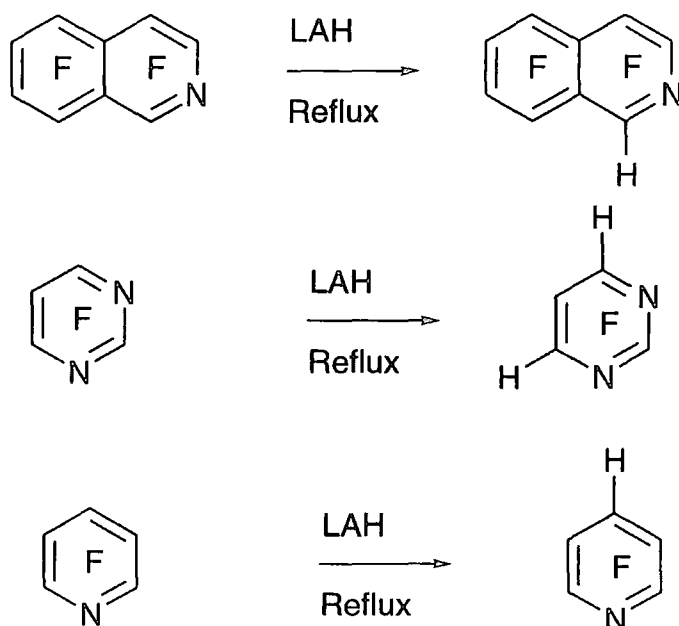
II.1.5   Conclusion for II.1

Following the review of the various procedures available for the direct replacement of F by H, methods outlined in II.1.4.a for replacement of F by H with metal hydrides, were pursued, since this route offered the possibilty of a general synthesis of fluorohydroheterocycles, whereas the other reported procedures appeared limiting.

II.2.1   Diisobutylaluminium hydride (DIBAL)

Work in this laboratory demonstrated that nucleophiles react with 3,5-dichlorotrifluoropyridine (1) giving 4-substituted derivatives[109] of (1). Therefore, we anticipated that (1) would react readily with DIBAL to give the 4-hydro derivative (2).

1   **2, >90 %**
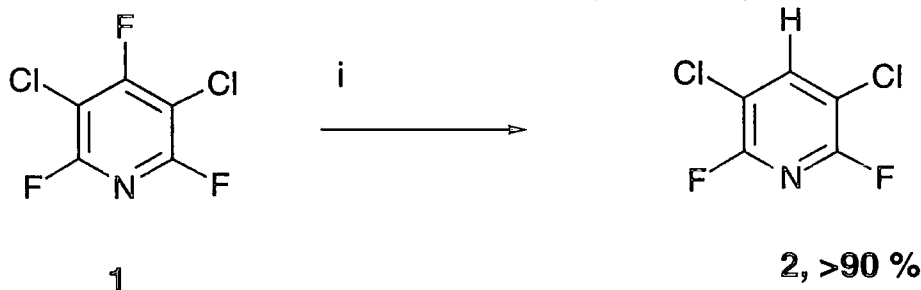
Reagents and conditions: i, 3 equiv DIBAL-H in DCM, 0°C, 68 h

Indeed, simply stirring (1) with DIBAL at room temperature afforded (2) in high yield, as the sole product. (2) was identified by consideration of its mass spectral and nmr spectral data. The mass spectrum of (2) gave a characteristic isotope pattern[110] which may be expected from two chlorine atoms: chlorine exists as two isotopes, ^{35}Cl and ^{37}Cl in a ratio of 3:1, hence two chlorine atoms in a molecule show a characteristic pattern of three lines in the spectrum due to the three possible parent molecular ions.

| ^{35}Cl | ^{35}Cl | ^{37}Cl |
| ^{35}Cl | ^{37}Cl | ^{37}Cl |
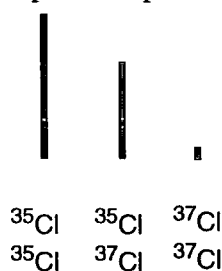
2 chlorine pattern

Fluorine atoms at the 2- and 6- positions are chemically equivalent and gave a doublet due to coupling with 4-H ($^4J_{FH}$ 6.0 Hz) at a chemical shift of -72.32 ppm in the fluorine nmr spectrum. The high field shift is typical for fluorine bound to carbon *ortho* to nitrogen for aromatic heterocyclic systems[111]. Hydrogen at the 4-position gave a resonance at 7.99 ppm in the proton nmr , split into a triplet ($^4J_{HF}$ 7.6 Hz) due to coupling with fluorine at the 2- and 6- position. The carbon nmr gave three resonances which may be assigned as follows: C-2 was readily identified as the peak at 154.5, owing to large coupling with fluorine[112] ($^1J_{CF}$ 247 Hz) and further splitting with fluorine at the 6-position ($^3J_{CF}$ 13.0 Hz). Carbon bound to chlorine at the 3-position was assigned to the resonance at 113.8 ppm, owing to large ^2J coupling to fluorine at the 2- position ($^2J_{CF}$ 37.5 Hz). C-4 gave a triplet due to splitting with fluorine ($^3J_{CF}$ 1.9 Hz) and was assigned to the signal at 143.82 ppm.

28

Pentafluoropyridine (3) is less reactive[109] than (1) towards nucleophiles, therefore, although we expected (3) to react with DIBAL, we were not surprised when at room temperature reaction of (3) with DIBAL in dichloromethane (DCM) at room temperature failed. However, by removing the DCM under vacuum and replacing it with diglyme, then heating in a sealed tube at 100 °C, complete conversion of (3) to 2,3,5,6-tetrafluoropyridine (4) was accomplished.

3   **4, 78%**
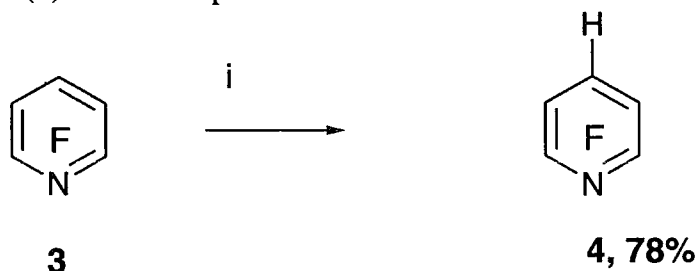
Reagents and conditions: i, 1.5 DIBAL-H, diglyme, sealed tube at 100 °C

Further reaction of (4) was not observed and neither heating (3) in a sealed tube with a two-fold excess of DIBAL at 190 °C nor a three-fold excess at 120 °C proved to be effective. The reaction of (3) with DIBAL now offers a selective synthesis of (4). The nmr spectra for (4) are particularly interesting and although the fluorine spectrum has been discussed by other workers[113], the salient aspects of the fluorine and carbon spectra deserve elaboration.

2,3,5,6-Tetrafluoropyridine contains two sets of chemically equivalent fluorines and the fluorine spectra in fig. (1) shows two resonances of equal intensity at -91.11 and -139.93 ppm.
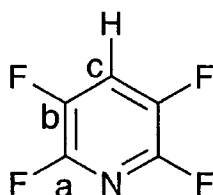
Fluorine at the 3-position typically gives a resonance to high field[111] and F_b may be assigned to the resonance at -139.93 ppm and gives a splitting pattern which is best described as an X part of an AA'MM'X spin system[113, 114]. Thus, F_b does not give a first order spectrum and is strongly second order. Fluorine *ortho* to nitrogen (*i.e.*, at the 2- position) is typically more deshielded than at the 3-position and therefore is found to lower field and F_a may be assigned to the resonance at -91.11 ppm. The proton decoupled carbon spectrum of (4) is shown in fig. (2) and as anticipated, shows three resonances due to the three carbons, C_a, C_b and C_c. Large $^1J_{CF}$ values of 261 and 245 Hz are characteristic[112] of one bond coupling between carbon and fluorine and thus, the doublet of multiplets ($^1J_{CF}$ 261 Hz) and doublet of triplets ($^1J_{CF}$ 245 Hz) at 141.6 and 143.3 may be assigned to C_a and C_b. The closeness of these chemical shifts means that C_a and C_b are essentially indistinguishable, however, C_a may be assigned to 143.3 on account of being *ortho* to nitrogen and would be expected to be shifted more to lower

field than C_b, which is assigned to 141.6 at higher field. Carbon C_c shows a triplet of triplets to high field due to coupling with F_b ($^2J_{CF}$ 20.3) and F_a ($^3J_{CF}$ 3.0 Hz) and may be assigned to the signal at 119.0 and the spectrum has been expanded to show the detail.

II.2.2   Sodium Borohydride (NaBH$_4$)

We anticipated that NaBH$_4$ that would react faster than DIBAL with (1), but, stirring (1) with NaBH$_4$ at room temperature for 68 h gave only a low conversion (<5 %) to (2). Therefore, reactions of this particular reagent with polyhalopyridines were discontinued.

Fig (1). Fluorine Spectrum of (4)

F_a

F_b

Fig (). Carbon Spectrum of (4)

^2J CcFb 20.3 Hz

^3J CcFa 3.0 Hz

C_c

C_b

^1J CbFb 245 Hz

C_a

^1J CaFa 261 Hz

31
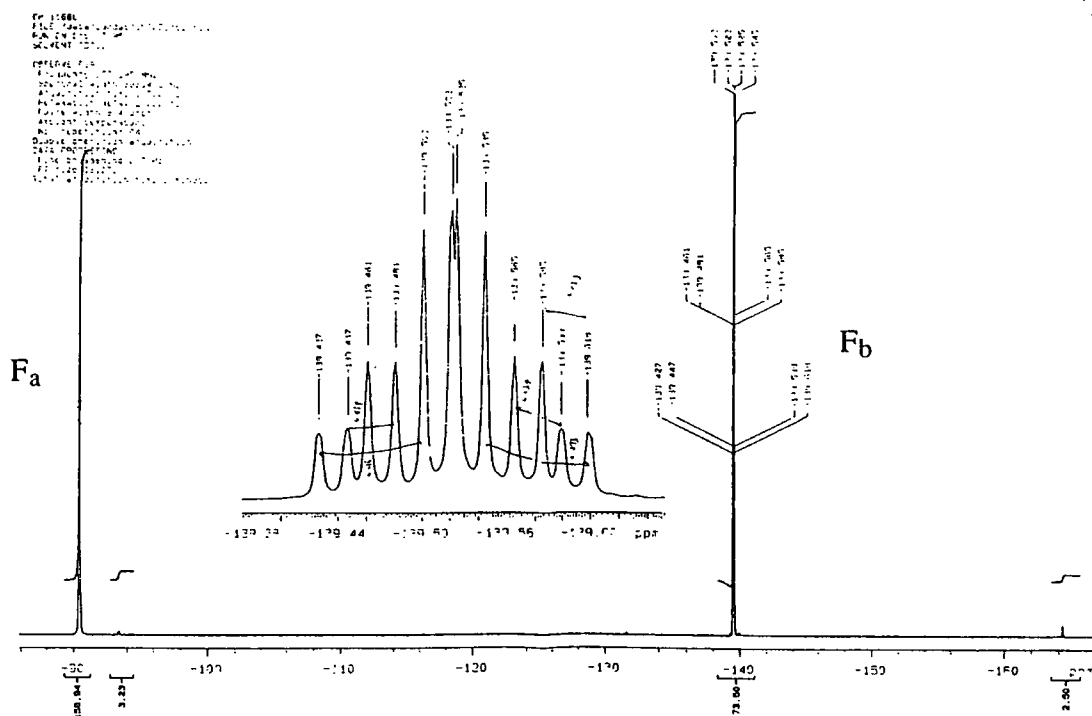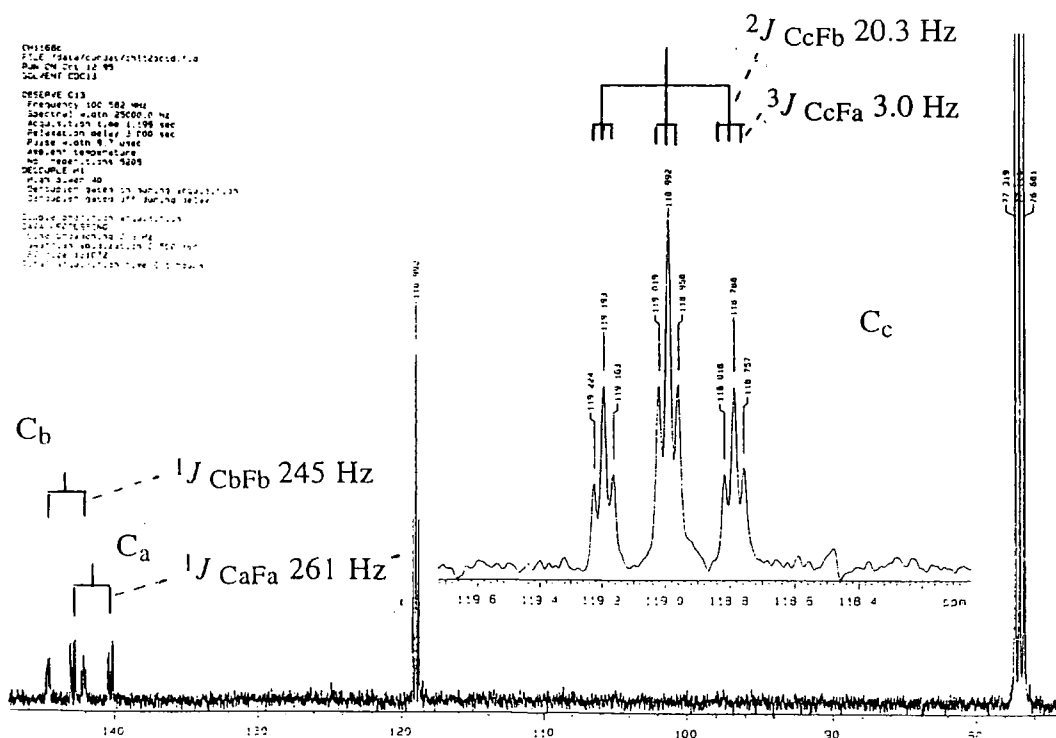
In view of the successful reaction of (3) with DIBAL, we then proceeded to LAH, a stronger reducing agent than DIBAL.

Stirring LAH with (3) in ether at room temperature gave, contrary to the literature[115], three products, 2,3,5,6-tetrafluoropyridine (4), 3,5-difluoropyridine (5) and 3-fluoropyridine (6), which were identified by comparison of their fluorine nmr and GCMS data with authentic samples.
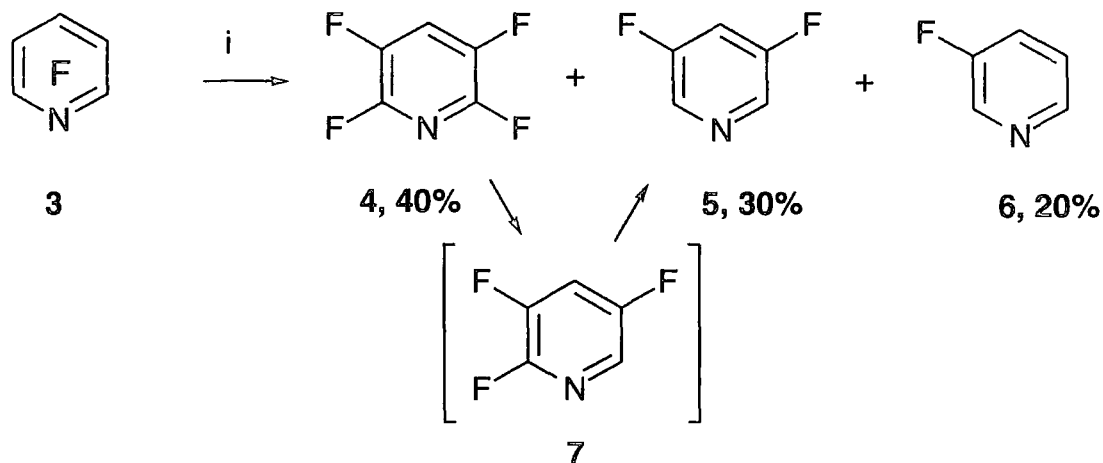
Reagents and conditions: i, 2 equiv LiAlH$_4$ in ether, 0°C, 2 h, RT 28 h

We were intrigued by this result, since the product distribution appeared odd: 2,3,5-trifluoropyridine (7) was not present. This indicates that (7) is more reactive than (4) and as soon as (7) is formed, it immediately reacts with LAH to give (5) and ultimately (6).

A possible explanation for the high reactivity of (7) is that the lithium cation (Li$^+$) plays an important role in determining reactivity. Thus, although (3) and (4) are virtually non-basic[116], removal of F *ortho* to ring nitrogen significantly increases the basicity of nitrogen (in much the same way that F is strongly activating in nucleophilic substitution), and whilst coordination of Li$^+$ to (3) and (4) is unlikely[105], coordination of nitrogen in (7) to Li$^+$ most probably activates (7) to attack by LAH.
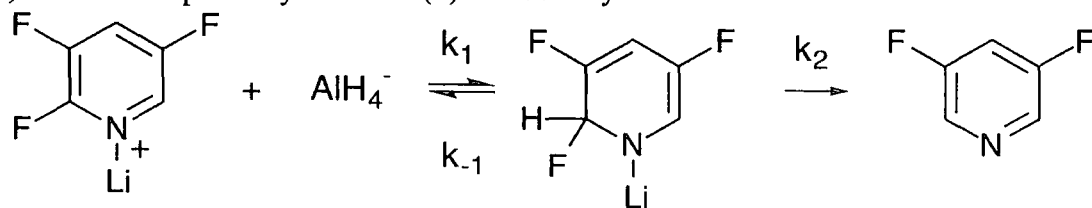
This possibilty was tested with the use of cation complexing agents, which would be able to complex Li$^+$ and thus modify the reactivity the various fluoropyridines to nucleophilic attack by LAH.

Crown poly ethers[117] and macrocyclic rings[118] have been shown to complex Li^+ and 15-Crown-5[117] has been used as a phase transfer catalyst to improve the solubility of LAH in hydrocarbon solvents.

II.2.4.a   12-Crown-4 and LAH

It was anticipated that adding 12-crown-4 to LAH would form the complexed Li^+ and 'free' AlH_4^-. This complexation would have two effects: i, coordination of ring nitrogen in the fluoropyridines would be prevented, thus making them less reactive to attack by AlH_4^- and ii, conversely, complexation of Li^+ would make a more reactive reducing agent, i.e., free AlH_4^-.

Addition of LAH to a solution of 12-crown-4 and (3) in ether gave a crimson coloured precipitate, which after stirring at room temperature led to almost complete conversion of the substrate (3) to (7), with only traces of (4) being detected.

3   **7, 92 %**
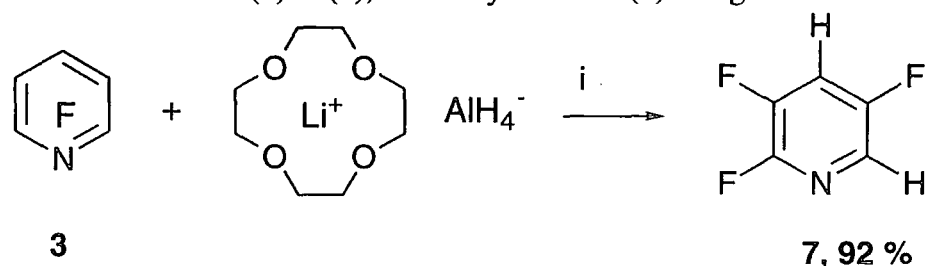
Reagents and conditions; LiAlH₄, Et₂O, 12-Crown-4, RT, 24 h

This was a remarkable reaction, but neither prolonged reaction nor heating to reflux was of synthetic benefit. It is worth noting that this reaction provides a good route to (7), and although it is not a new compound, a previous synthesis by Coe[50] by the direct fluorination of pyridine with potassium tetrafluorocobaltate only gave (7) in a 1% yield Therefore, a full analysis of (7) was performed and the carbon spectra shown in figs (3), (4) and (5) gave particularly interesting data.

Carbons C_a, C_b and C_d may be distinguished from C_a and C_e due to large ^1J coupling with fluorine. C_d is flanked by hydrogens and therefore, in a proton decoupled spectrum, coupling with hydrogen is not observed, consequently, ^2J coupling is not observed and C_d may be assigned to the doublet of triplets at 156.4 ppm (^1J 256 Hz). Carbons *ortho* to nitrogen may be expected to be shifted to lower field[111], thus, C_a was assigned to the doublet of doublets at 148.0 ppm (^1J 236, ^2J 14.1 Hz) and C_b assigned to the doublet of doublets of doublets at 144.7 (^1J 267, ^2J 31.7, ^3J 7.2 Hz). Carbons C_e and C_c were identified by smaller coupling constants and increased intensities, which is to be expected for carbon bound to hydrogen in proton decoupled carbon nmr spectra. C_c may be assigned to the resonance at 115.4 ppm since carbons at the 4- position are generally found to higher field and the similar ^2J coupling with fluorines F_b and F_d (^2J 24.0 and 17.9 Hz) and ^3J coupling with F_a (^3J 3.4 Hz) are consistent with this

assignment. C_e therefore, may be assigned to the lower field shift at 128.5 ppm and is split by fluorines F_d (^2J 26.8 Hz), F_b (^4J 13.7 Hz) and F_a (^3J 5.9 Hz).

Fig (3). Carbon Spectrum of (7)
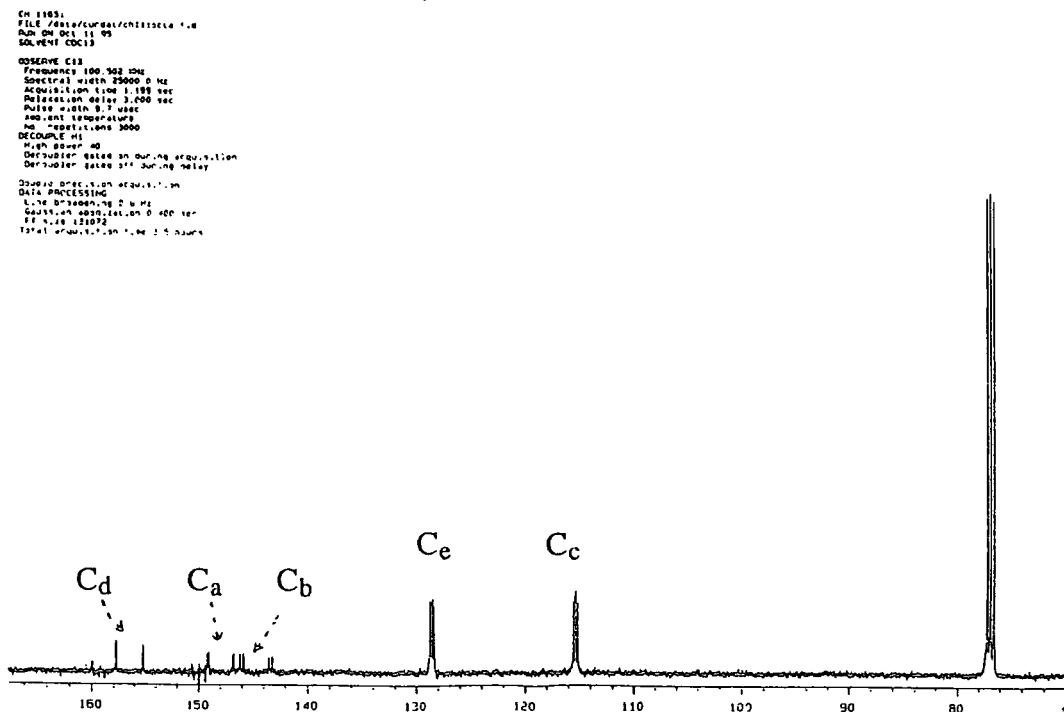
Fig (4). Assigned Carbon Spectrum of (7) with Expansions

Fig (5). Assigned Carbon Spectrum of (7) with Expansions

C_e

C_c

^2J CeFd 26.8 Hz

^3J CeFa 13.7 Hz

^4J CeFb 5.9 Hz

^2J CcFb,d 24.0 and 17.9Hz

$^3J_{CcFa}$

C_e

C_c

36
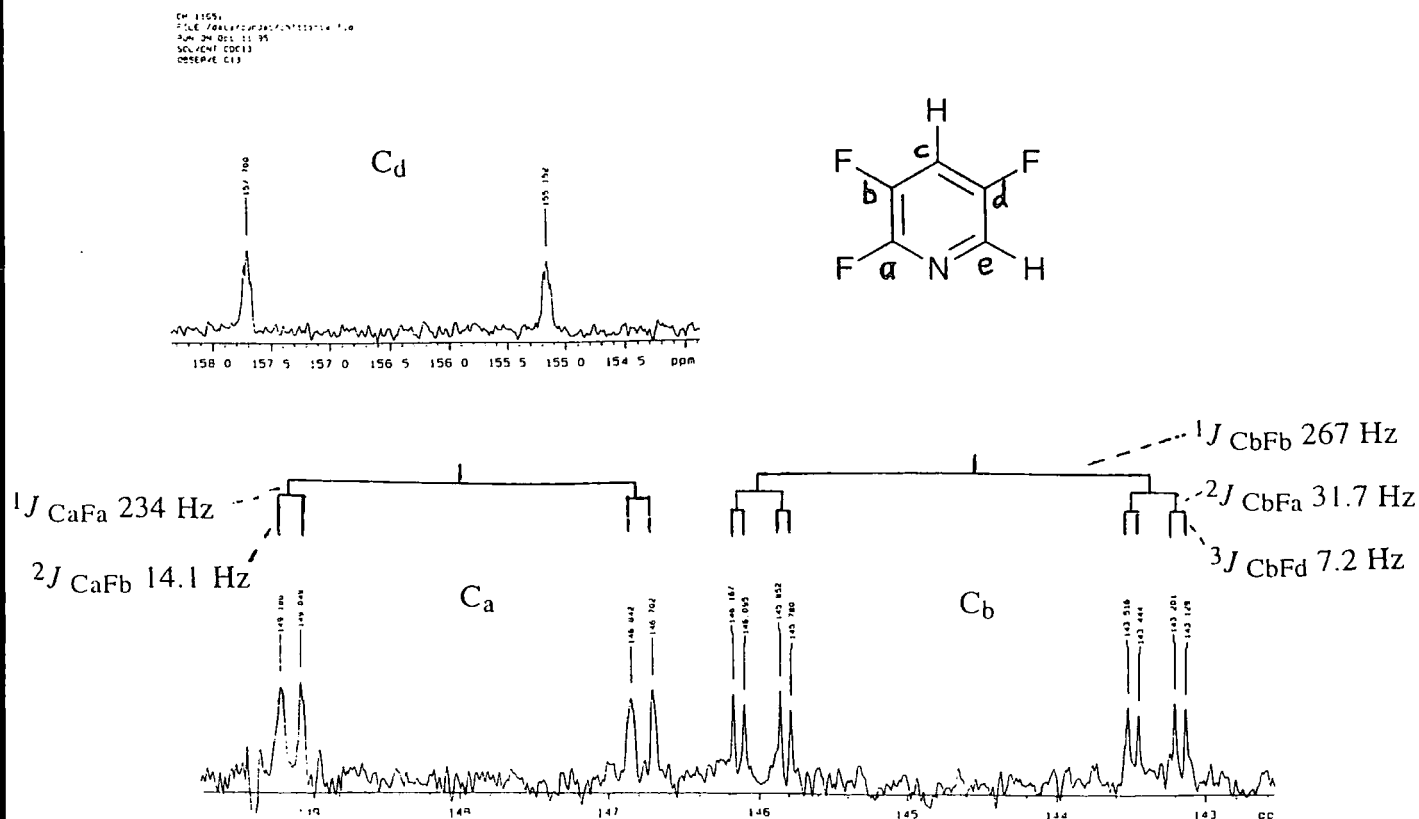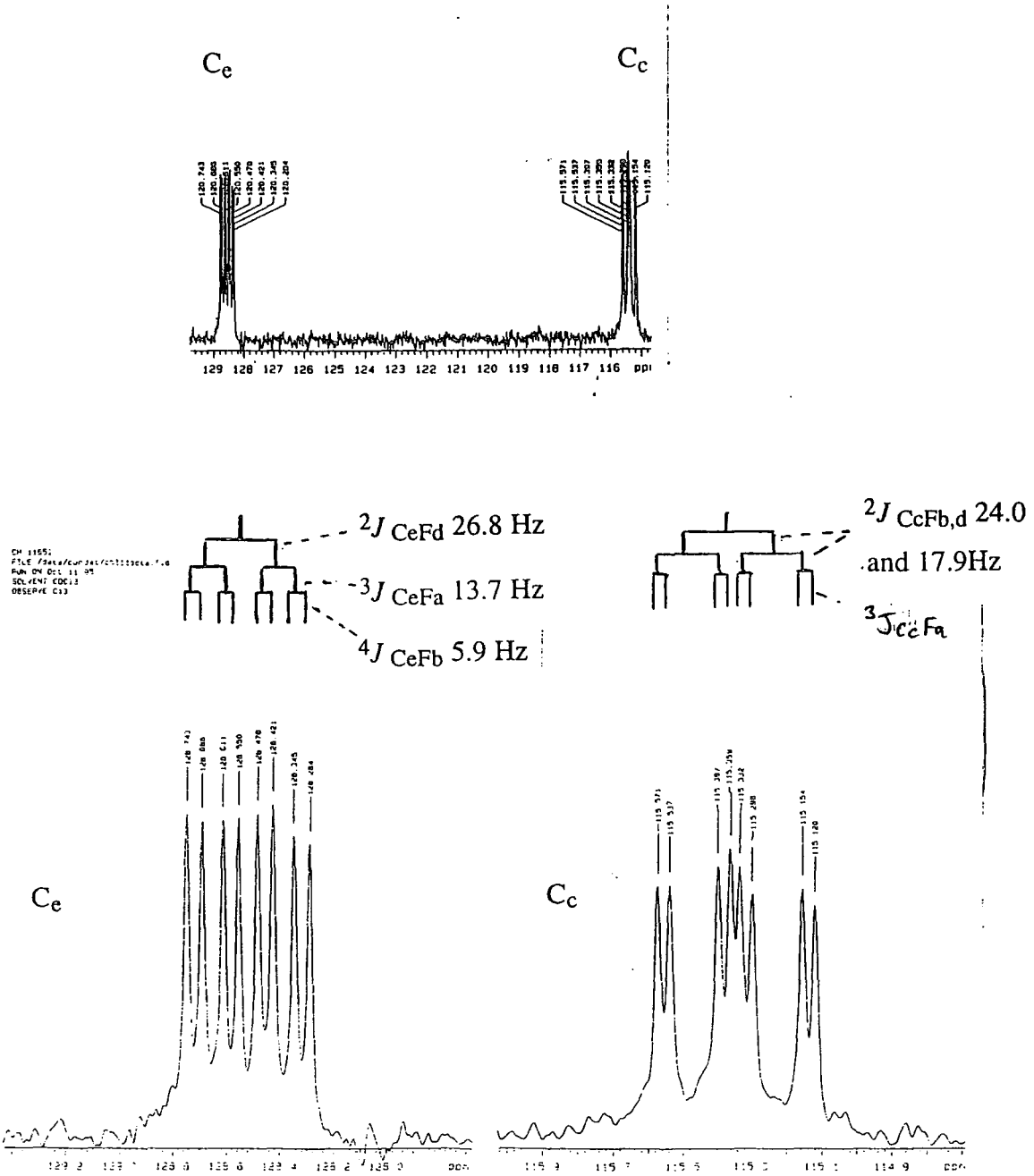
II.2.4.b   Tetramethylethylene diamine (TMEDA) and LAH

It was hoped that by selecting a complexing agent with a lower K_{eq} value than that encountered with 12-crown-4 that a compromise between the reactivity of LAH

$$\text{Complexing Agent} + \text{LiAlH}_4 \underset{}{\overset{K_{eq}}{\rightleftharpoons}} \left[\text{Complex-Li}\right]^+ \text{AlH}_4^-$$
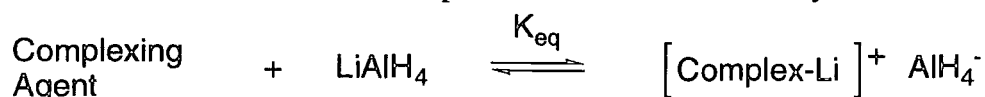
and LAH/ 12-crown-4 would be achieved, with the aim to synthesise (5) directly from (3).

TMEDA, which finds routine application with butyl lithium (it prevents formation of dimers and tetramers of butyl lithium, making a more effective reagent), formed a white suspension when added to LAH in ether.

7, 56%   **5, 36%**
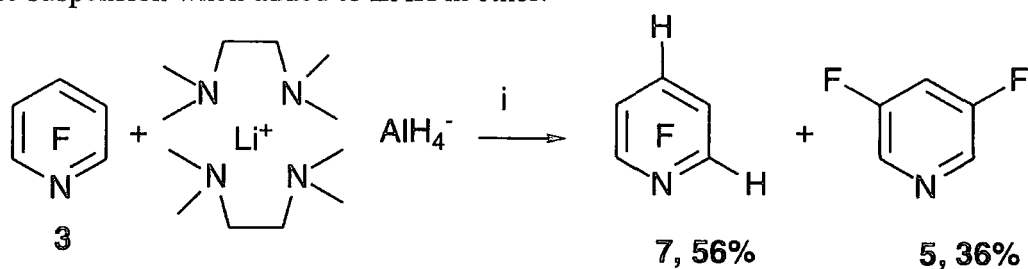
Reagents and conditions: LAH, Et$_2$O, Tetramethylethylenediamine (TMEDA), RT, 25 h

Addition of (3) to this suspension and stirring for 19 h at room temperature gave almost complete conversion to (7) and further reaction gave (7) and (5) as determined by fluorine nmr spectroscopy and GCMS. Neither prolonged reaction nor heating at reflux gave higher yields of (5), but led to side reactions.

The hypothesis outlined in II.2.3 proved to be correct. The lithium cation (Li$^+$) did indeed have an effect in determining reactivity of (3).12-Crown-4, (a powerful cation complexing agent) is able to effectively take Li$^+$ out of the reaction mixture and causes reaction of (3) to give (7), but TMEDA (a weaker complexing agent) was less able to co-ordinate Li$^+$, and reaction of (3) with LAH and TMEDA gave (7) and (5). However, in the absence of any complexing agent, Li$^+$ is able to coordinate to ring nitrogen and LAH reacts with (3) to give (4), (5) and (6) (see scheme (2)).

Scheme (2)
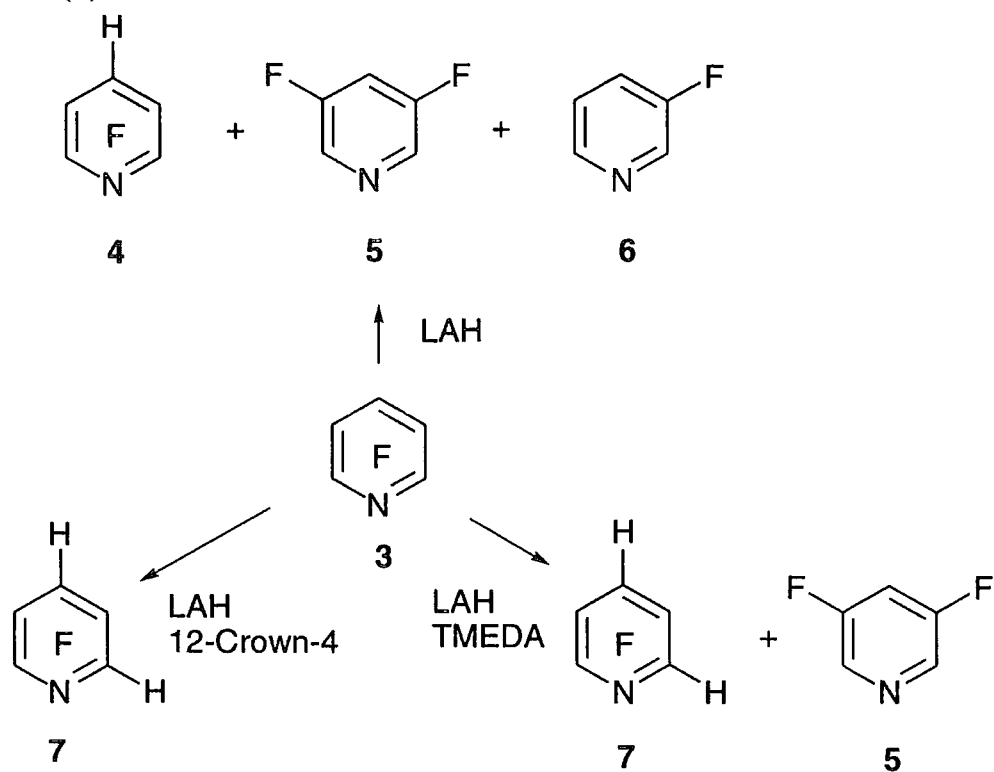
II.3 Conclusion for Chapter II

By reacting metal hydrides with highly fluorinated heterocycles, new selective routes have been developed to 2,3,5,6-tetrafluoropyridine (4), 2,3,5-trifluoropyridine (7) and 2,6-difluoro-3,5-dichloropyridine (2). However, a satisfactory synthesis of 3,5-difluoropyridine (5) was not achieved, therefore, the second part of our strategy for the preparation of (5), namely, the indirect route to (5), was pursued.

Indirect Replacement of Fluorine by Hydrogen

In chapter II methods towards the synthesis of 3,5-difluoropyridine *via* direct replacement of fluorine by hydrogen from a highly fluorinated heterocycle were described.

This chapter is concerned with describing procedures for the indirect replacement of F by H. Thus, we aimed to react pentafluoropyridine with a suitable nucleophile, to give a 2,4,6-trisubstituted-3,5-difluoropyridine, which would undergo reduction affording 3,5-difluoropyridine, as outlined in scheme (3).

Scheme (3)
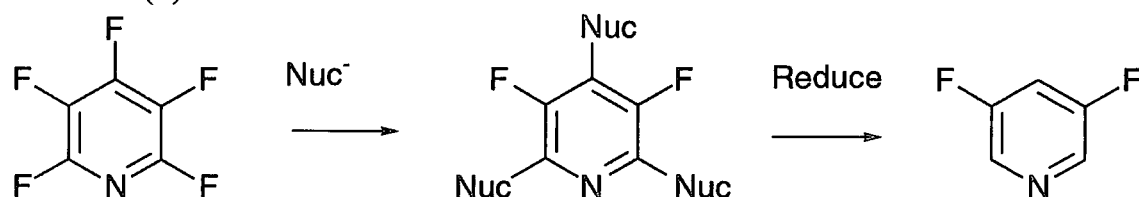
A review of the literature indicated that there were two types of nucleophile which would be suitable for this indirect approach: i, halogens and ii, nitrogen nucleophiles. The various methods for halogenation of highly fluorinated heterocycles and descriptions of the reduction of halofluoroheterocycles will be reviewed. Mention of methods for the replacement of F by H *via* reactions of highly fluorinated heterocycles with nitrogen nucleophiles will also be made.

III.1 Review of Methods for Exchanging Fluorine for Chlorine, Bromine or Iodine in Polyfluoroaromatic Systems

There are principally two approaches for exchanging fluorine (F) by other halogens in highly fluorinated heterocycles: (a) using acid halides (hydrochloric, HCl, hydrobromic, HBr and hydroiodic, HI acid) and (b) using metal halides.

III.1.1 Acid Induced Nucleophilic Substitution of Highly Fluorinated Heterocycles

Nitrogen containing perfluoroheterocycles which are already activated towards nucleophilic attack may be further activated by co-ordination of ring nitrogen to Bronsted and Lewis acids.
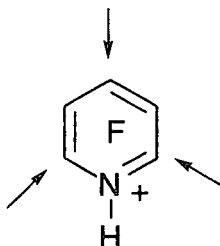
Thus, all positions and particularly those *ortho* and *para* to nitrogen, are more susceptible to attack by nucleophiles when nitrogen is protonated and we may expect pentafluoropyridine to undergo acid-induced nucleophilic substitution as indicated in scheme (4).

Scheme (4)
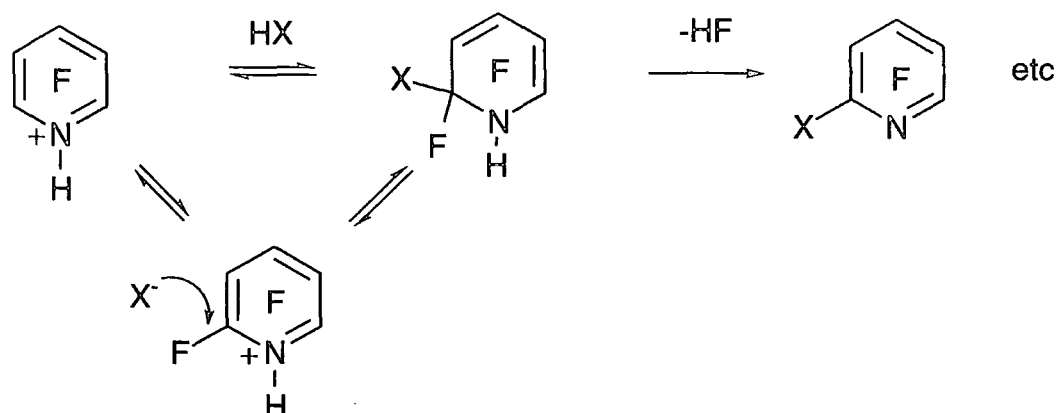
Thus, protonation encourages substitution *ortho* to nitrogen. This principle was excellently demonstrated in work on nucleophilic substitution of tetrafluoropyridazine. Thus whilst nucleophilic substitution of tetrafluoropyridazine by sodium methoxide gives the 4-methoxy isomer, in the presence of sulphuric acid, the 6-methoxy isomer is the favoured product[119].
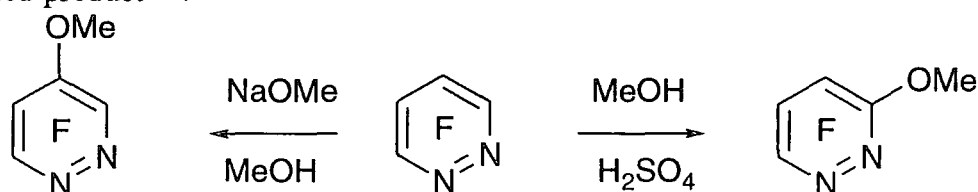
III.1.1.a   Acid Halides

Acid-induced nucleophilic substitution is particularly attractive for the introduction of halogens into highly fluorinated heterocycles.

Both HCl and HBr reacted with heptafluoroquinoline giving 2- followed by 4-substitution and 2,4-dichloro and 2,4-dibromopentafluoroquinoline were made in good yield[120].
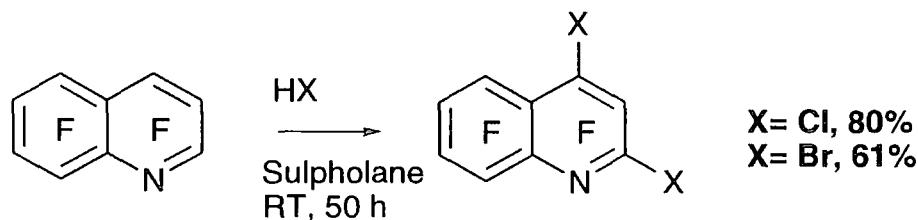
Reacting HI with heptafluoroquinoline gave similar results, affording 2,4-diiodopentafluoroquinoline, but the reaction was complicated by the formation of 2,4-dihydropentafluoroquinoline as a side product[120].

57% 28%
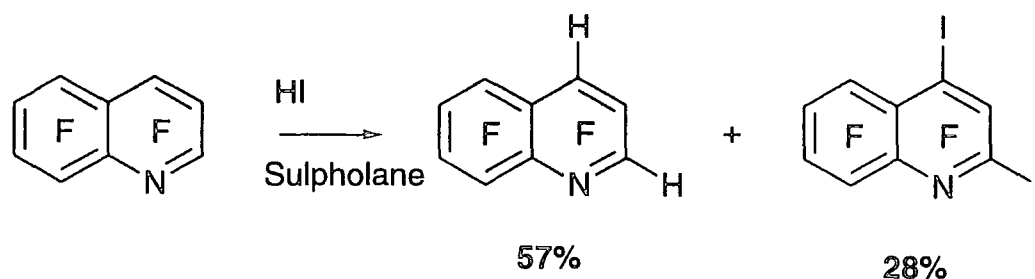
Chambers et. al[120] attributed formation of the dihydro derivative to attack by iodide on the iodo compound, which generated the anion and thus gave the hydro compound.
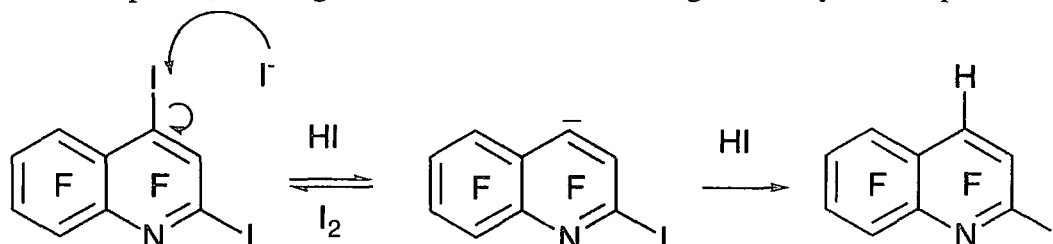
Pentafluoropyridine, which is a very weak base[116], reacts with hydrogen halides, though less readily than heptafluoroquinoline, and reaction with HCl and HBr has been shown to give low yields of the 4-halotetrafluoro and 2,4,6-trihalodifluoropyridines[120].

X= Cl, 7%   X= Cl, 15%
X= Br, 15%   X= Br, 31%
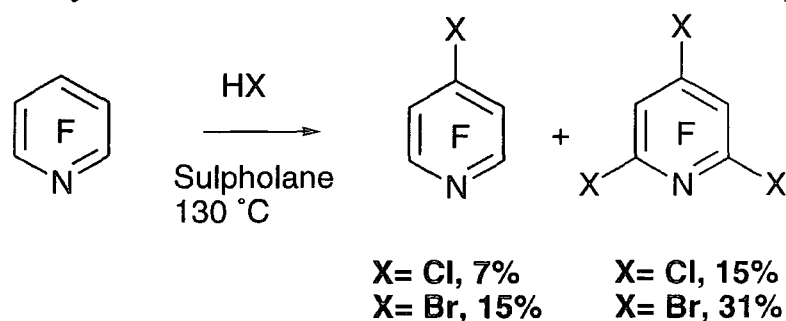
It is interesting to note, that for pentafluoropyridine, reaction with HCl and HBr leads to the 4- position being substituted first. This is probably due to attack of chloride or bromide on the free base, because pentafluoropyridine is only weakly protonated by acids, i.e., considering the equilibrium below, the equilibrium lies to the left (K_{eq} is small).
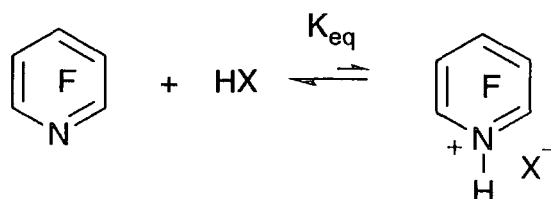
Tetrafluoropyrimidine reacted readily with HCl in the absence of solvent giving a mixture of polychlorofluoropyrimidines[121].

15%   61%   13%

41
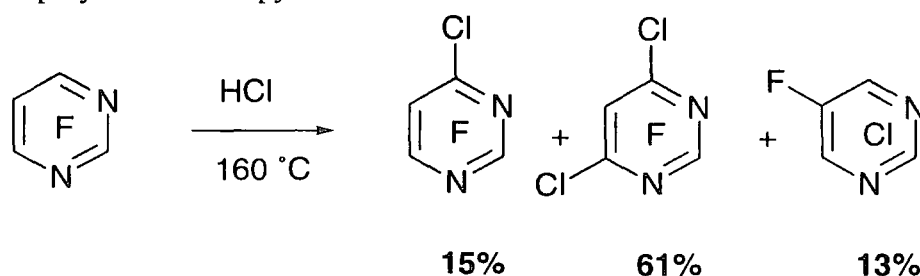
III.1.2 Metal Halides

Compared to powerful nucleophiles such as alkoxides and sulphur nucleophiles, which are known to react well with highly fluorinated heterocycles (see Chambers[122]), halides are weak nucleophiles and a ranking of their relative strengths is shown here[31].

$$NH_2^- > ArS^- > RO^- > R_2NH > ArO^- > OH^- > ArNH_2 > NH_3 >$$
$$I^- > Br^- > Cl^- > H_2O > ROH$$
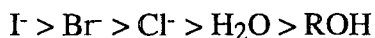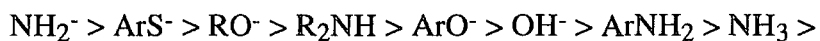
However, they are still able to react with polyfluoro-heterocycles given appropriate conditions.

Tetrafluoropyrimidine reacts with sodium iodide in dimethyl formamide giving replacement of F by I[107]. Interestingly, this reaction gives traces of the 2-hydro derivative, which is formed by nucleophilic attack of I⁻ on the iodofluoroheterocycles.

55%   16%   0.2%
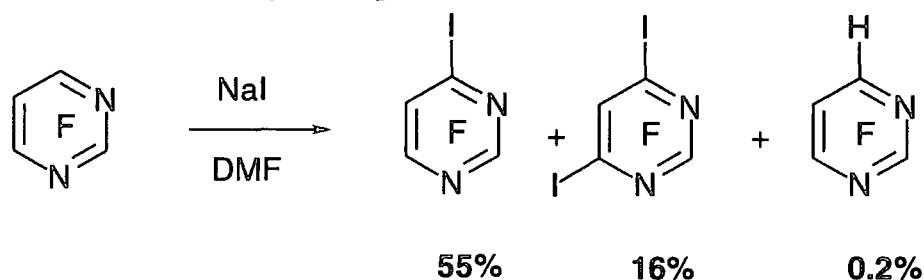
A patent[123] describes reaction of pentafluoropyridine with $CaBr_2$ and $CaCl_2$ and in both cases, 4-halotetrafluoropyridines were made.

X= Cl, 80%
X= Br, 80%
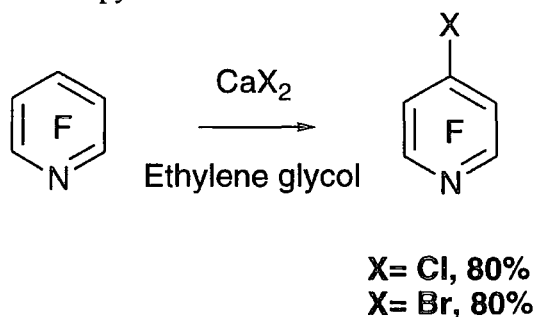
III.2 Methods of Reduction of Halofluoroheterocycles
III.2.1 Catalytic Hydrogenolysis

Catalytic hydrogenolysis, the replacement of halides by hydrogen, is an important process, particularly for dehalogenation of environmentally destructive chloroaromatics (see Cavallaro[124] and Marques[125]).

The technique has also found application in the completely selective removal of bromine and chlorine from bromofluoro and chlorofluoroaromatic systems.

Chambers[93] converted 3,5-dichlorotrifluoropyridine into 2,4,6-trifluoropyridine over a palladium catalyst.

75%
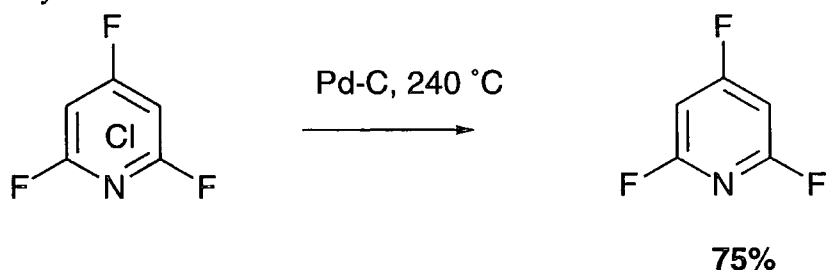
and Baasner[121] demonstrated that catalytic hydrogenolysis of 4,6-dichloro-2,5-difluoropyrimidine gave 2,5-difluoropyrimidine

82%
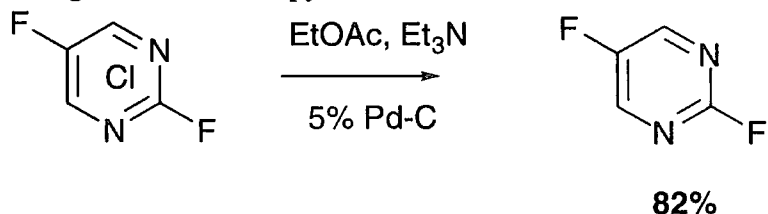
Work on halogenated benzenes has also demonstrated the versatility of this technique and a variety of fluoro-chloro and -bromobenzenes may be de-brominated and de-chlorinated. Two patents[126, 127] describe removal of chlorine from 2,6-dichloro-3,5-difluoronitrobenzene giving 3,5-difluoroaniline,

92%
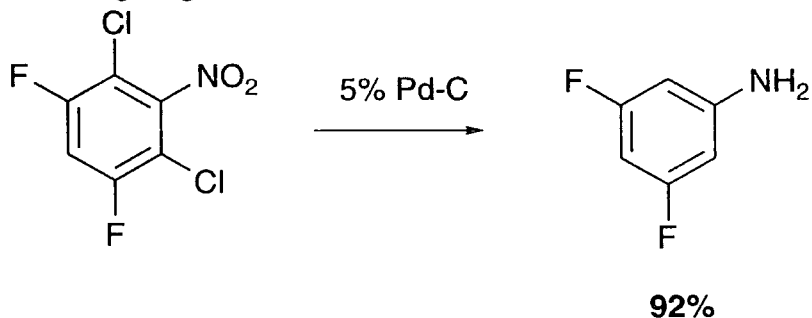
another patent[128] demonstrates that catalytic hydrogenolysis of 2,4-difluorochlorobenzene gives 1,3-difluorobenzene and Yakobson[129] obtained pentafluorobenzene via removal of bromine from bromopentafluorobenzene under catalytic conditions.

51%

43
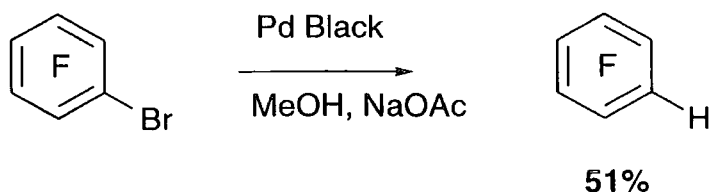
III.2.2   Metal Hydrides and Other Reducing Agents

The use of metal hydrides for the reduction of highly fluorinated heterocyclic systems was described in chapter II. However, their use for the removal of chlorine, bromine or iodine from polyhalofluoroheterocycles is not described in the literature. Nevertheless, their application for the removal of Cl, Br and I from benzene derivatives has been described and will be briefly covered here.

Workers[130] showed that 4-bromochlorobenzene reacts with lithium aluminium hydride (LAH) to afford chlorobenzene in poor yield and went on to demonstrate that irradiation by a mercury lamp gave high yields of chlorobenzene. Interestingly, the same procedure caused reduction of p-fluorotoluene to toluene.

Chung[131] demonstrated that reaction of LAH with o-bromoallyl ether gave phenyl allyl ether and 2,3-dihydro-2-methylbenzofuran.
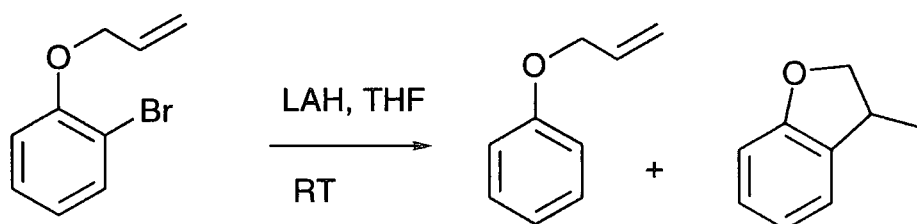
85 : 15

From the above results, the workers attributed the unusual reactivity, and particularly the acceleration of reactivity observed in the presence of the mercury lamp, to the involvement of radical intermediates.

The novel reagent, SmI_2, has found use for the reduction of halo heteroaromatics, however, only monosubstituted examples exist, for example 2-chloropyridine gave pyridine in good yield[132].
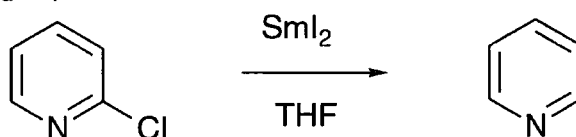
78%

The mechanism, though not fully understood, probably involves single electron transfer from SmI_2 to 2-chloropyridine as the first step, followed by capture of hydrogen from the solvent and loss of chloride ion.

III.3   Replacement of F by H via Reaction of Highly Fluorinated Heterocycles with Nitrogen Nucleophiles

III.3.1   Ammonia

In principle, ammonia could be used to allow indirect replacement of fluorine by hydrogen. Workers in this laboratory showed that pentafluoropyridine reacted with ammonia giving 4-aminotetrafluoropyridine (8).

44

3   **8**
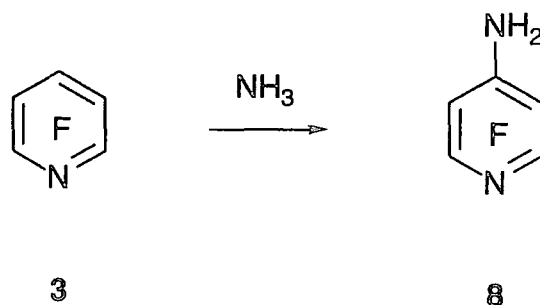
Hydrodediazoniation is a useful method for replacing an aromatic amine by an hydrogen atom and the process is detailed here.
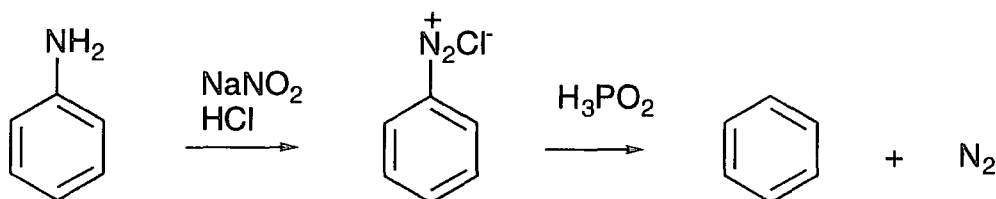
Hypophosphorous acid (H_3PO_2) has become the common source of hydrogen[74, 133, 134] and the mechanism, shown below, is believed to proceed *via* a single electron transfer (SET) process[133, 134].

Initiation $C_6H_5N_2{}^+ \; + \; 2H_3PO_2 \longrightarrow C_6H_5{}^{\cdot} \; + \; N_2$
                                                   $+ \; H_2PO_2{}^{\cdot}$

Propagation $C_6H_5{}^{\cdot} \; + \; H_3PO_2 \longrightarrow C_6H_6 \; + \; H_2PO_2{}^{\cdot}$

               $C_6H_5N_2{}^+ \; + \; H_2PO_2{}^{\cdot} \longrightarrow C_6H_5{}^{\cdot} \; + \; H_2PO_2{}^+$
                                                  $+ \; N_2$

Termination $2\,H_2PO_2{}^{\cdot} \longrightarrow H_2PO_2{}^- \; + \; H_2PO_2{}^+ \; \xrightarrow{H_2O}$

                                                   $H_3PO_3 \; + \; H_3PO_2$
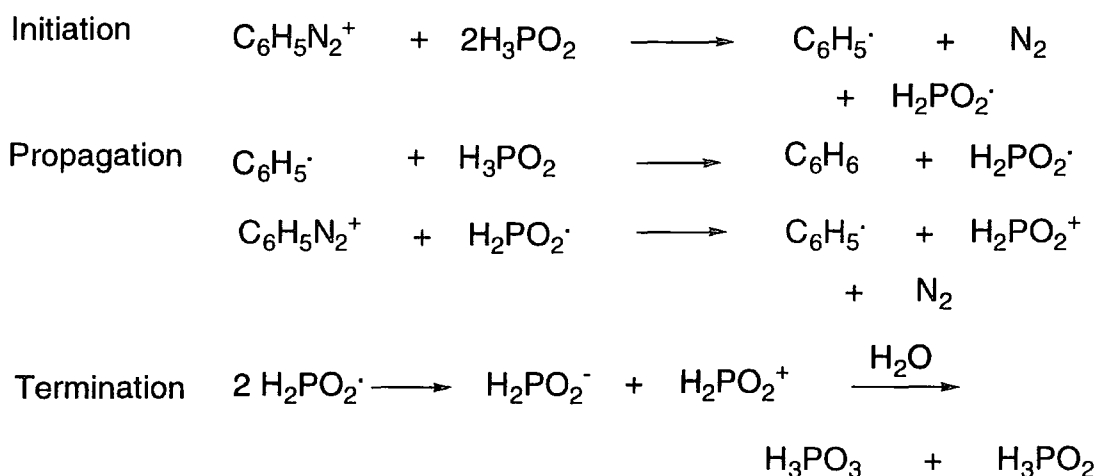
This process continues to attract interest and recent improvements include the addition of electron donors such as ferrocene[135], iron (II) sulphate[136] and trialkylphosphines[137] to decrease reaction times and increase yields by aiding the decomposition of the diazonium salt (see above propagation step). Deuterodediazoniation has been reported[136, 138], whereby deuterium replaces an aromatic amino group.

It also appears that rings bearing nitro groups and halogen atoms[136] are very reactive and work has demonstrated that diazotisation of 4-aminotetrafluoropyridine proceeds smoothly and the subsequent diazo salt may be used in the Sandmeyer reaction[139] (e.g. for the synthesis of 4-bromotetrafluoropyridine) and for the synthesis of azo dyes[140].

Another method of replacing F by H using nitrogen nucleophiles has involved using hydrazino intermediates. Hydrazine reacted with hexafluoroquinoxaline[96] giving 2,3-dihydrazinotetrafluoroquinoxaline, and treatment of this with copper sulphate gave 5,6,7,8-tetrafluoroquinoxaline.
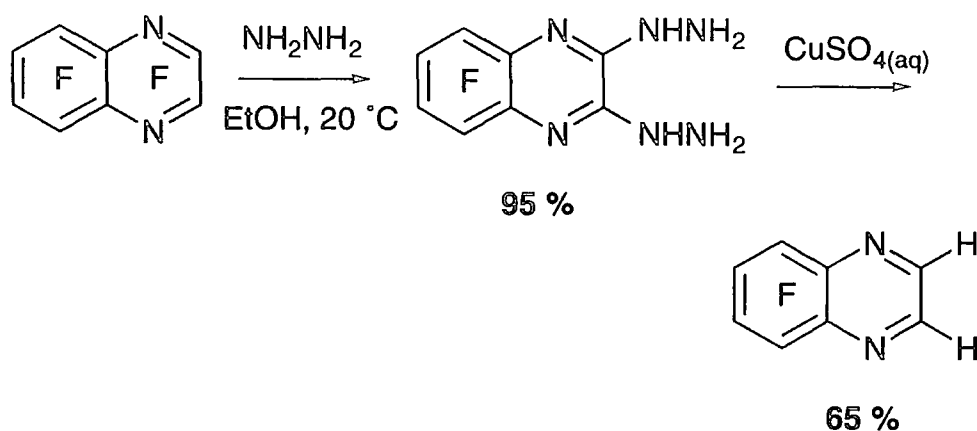
This chemistry was applied to heptafluoroisoquinoline[95] and pentafluoropyridine[115] giving 1-hydrazinohexafluoroisoquinoline and 4-hydrazinotetrafluoropyridine respectively which, following treatment with copper sulphate, gave 5,6,7,8-tetrafluoroquinoxaline[96], 3,4,5,6,7,8-hexafluoroisoquinoline[95] and 2,3,5,6-tetrafluoropyridine[115].
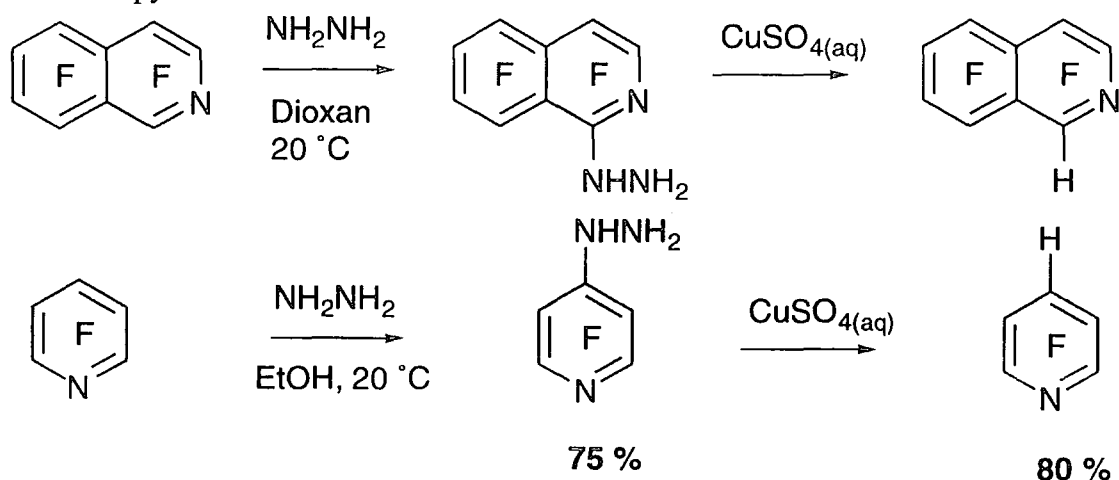
III.4   Conclusion

After reviewing the available methods for *indirectly* replacing F by H from highly fluorinated heterocyclic systems, we chose to develop the methods of i, introducing bromine *via acid-induced nucleophilic substitution* of polyfluoroheterocycles and ii, removing bromine from bromofluoroheterocycles *via catalytic hydrogenolysis*.

Methods involving amination of highly fluorinated heterocycles, followed by diazotisation were also investigated briefly and will be described.

III.5.1   **Pentafluoropyridine.** The reaction of HBr with pentafluoropyridine which was described in the literature[120], gave a poor yield of 2,4,6-tribromo-3,5-difluoropyridine. This reaction was repeated, with identical conditions, except that the temperature was raised in an attempt to achieve a higher yield of 2,4,6-tribromo-3,5-difluoropyridine.

3   **10**   **4, 20%**
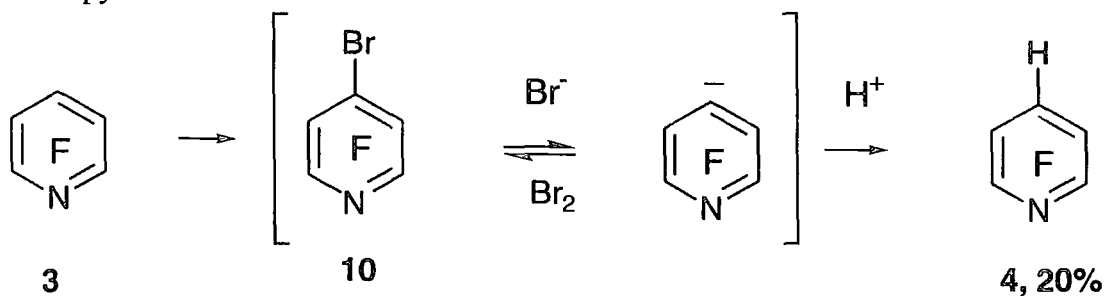
Reagents and conditions: 3 $HBr_{(g)}$, sulpholane, 200°C, autoclave sprayed with PTFE, 48 hrs.

Surprisingly, only 2,3,5,6-tetrafluoropyridine (4) was obtained, which was presumably formed *via* the tetrafluoropyridyl anion. This result is consistent with observations outlined in part III.1.1.a. In the absence of sulpholane, following the above procedure, no conversion of (3) was observed. (4) was identified by comparison of its fluorine nmr and GCMS with an authentic sample.

Combination of HBr and $AlBr_3$ would be expected to give a super-acid ($H^+AlBr_4^-$) and we might anticipate that this would provide a very powerful brominating agent. Indeed it has been shown[99] that tetrafluoropyrazine (which is less basic than pentafluoropyridine[116]) gives tetrabromopyrazine on treatment with $H^+AlBr_4^-$, therefore, we expected that $H^+AlBr_4^-$ would react well with (3). This proved to be the case and reaction of pentafluoropyridine with $H^+AlBr_4^-$ gave 2,4,6-tribromo-3,5-difluoropyridine as a single product in high yield.

3   **11, 77%**
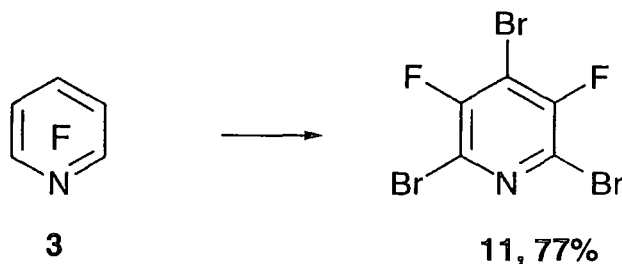
Reagents and conditions: $2AlBr_3$, 3HBr, 150°C, 72 h

(11) was readily identified by considering its nmr and mass spectroscopy data. The fluorine nmr spectrum gave a singlet at -103.2 ppm, which is consistent with literature[120] data and fluorine at the 3- position in pyridine. The carbon nmr spectrum gave three resonances, which is consistent with the symmetrical structure and may be assigned as follows: the resonance at 153.6 ppm gives a large coupling (^1J 264 Hz), which is consistent with carbon bound to fluorine and the chemical shift to low field is

consistent of a highly deshielded nucleus, therefore this peak is assigned to C-3. The shift to higher field (110.1 ppm) with a triplet due to coupling with fluorine at the 3- and 5- position is consistent with C-4. The remaining chemical shift at 122.5 ppm shows an X part of an ABX system and this is consistent with C-2 (see Chapter IV for details).

Fig. (6). Carbon nmr spectrum of (11)

```
CH1166
FILE /data/curdat/chl12octc.fid
RUN ON Oct 12 95
SOLVENT CDCl3

OBSERVE C13
 Frequency 100.582 MHz
 Spectral width 25000.0 Hz
 Acquisition time 1.199 sec
 Relaxation delay 3.000 sec
 Pulse width 9.7 usec
 ambient temperature
 No. repetitions 8192
DECOUPLE H1
 High power 40
 Decoupler gated on during acquisition
 Decoupler gated off during delay

Double precision acquisition
DATA PROCESSING
 Line broadening 0.3 Hz
 FT size 131072
 Total acquisition time 4.5 hours
```

C-3

C-2

C-4
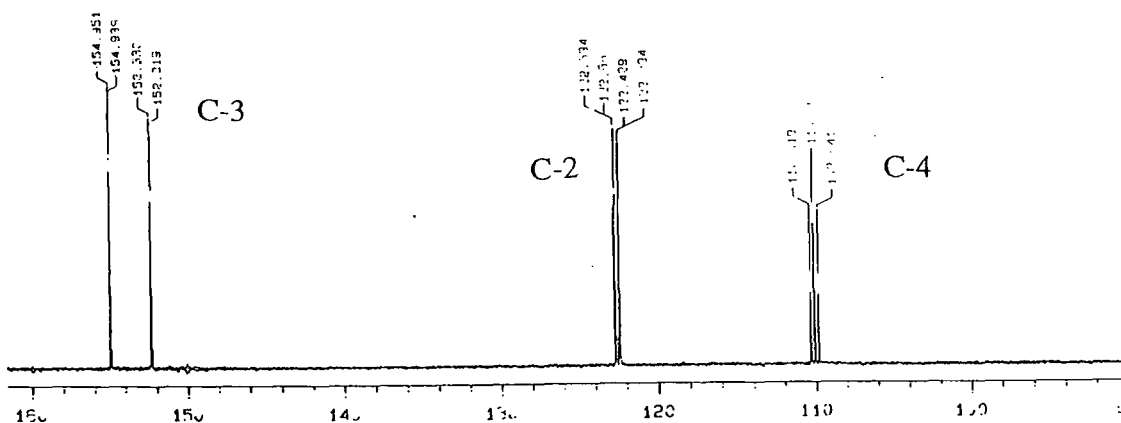
Bromine occurs naturally as two isotopes (^{79}Br and ^{81}Br in a ratio of approximately 1:1) and for a molecule containing three bromine atoms, gives rise to four possible parent ions in the mass spectrum, thus three bromines lead to a characteristic isotope pattern[110] as shown below. (11) gave the isotope pattern characteristic of three bromine atoms.

^{79}Br ^{79}Br ^{79}Br ^{81}Br
^{79}Br ^{79}Br ^{81}Br ^{81}Br
^{79}Br ^{81}Br ^{81}Br ^{81}Br

3 bromine pattern

48
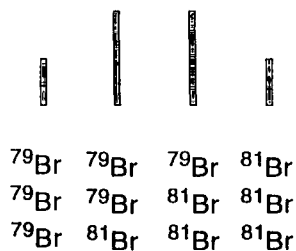
This reaction offers the added benefit of being feasible on a larger scale and may be performed in an Autoclave. It was noticed however, that repeated reaction led to progressively worsening yields of 2,4,6-tribromo-3,5-difluoropyridine (11) and considerable corrosion of the Autoclave, indicating that the surface of the reaction vessel was entering into the reaction. The problem was remedied by applying a thin coat of PTFE to the interior of the container and the high yields were restored. It is possible that glass lined Autoclaves could be used for the same purpose.

III.5.2   Tetrafluoropyrimidine.   This is more reactive[97] than pentafluoropyridine towards nucleophiles and although its relative basicity was not considered in work which determined the relative basicities of a range of highly fluorinated   heterocycles[116], it may be expected to be more basic than pentafluoropyridine, therefore we expected tetrafluoropyrimidine to react readily with $H^{+}AlBr_{4}^{-}$.

12   **13, 79%**
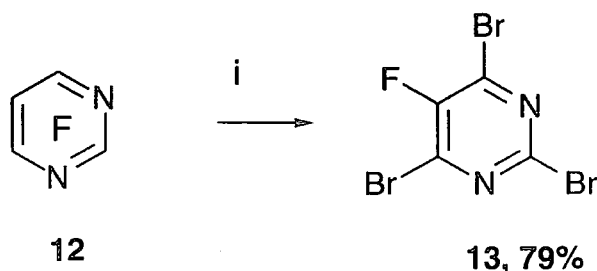
Reagents and Conditions: i, 1.4 HBr, 1.3 $AlBr_3$, 150°C, 43 h

Reaction proceeded smoothly giving 2,4,6-tribromo-5-fluoropyrimidine in high yield, with no traces of other products. 2,4,6-Tribromo-5-fluoropyrimidine (13) gave a single resonance in the fluorine spectrum at -114.9 ppm and its carbon nmr spectrum showed three resonances, indicating the symmetry of (13). The carbon spectrum may be easily assigned: C-5 occurs to low field[111] and gives large one bond coupling to fluorine (^1J 269 Hz), whilst carbons C-2 and C-4, which are highly deshielded are found at 143.4 and 153.5 ppm respectively and may be distinguished by their coupling with fluorine: C-4 is ortho to C-F and gives large ^2J coupling (^2J 23.6 Hz)[112], whilst C-2 is para to C-F and gives smaller coupling (^5J 7.2 Hz).

Fig. (7). Carbon nmr spectrum of (13)

Fig. (7). Carbon nmr spectrum of (13)
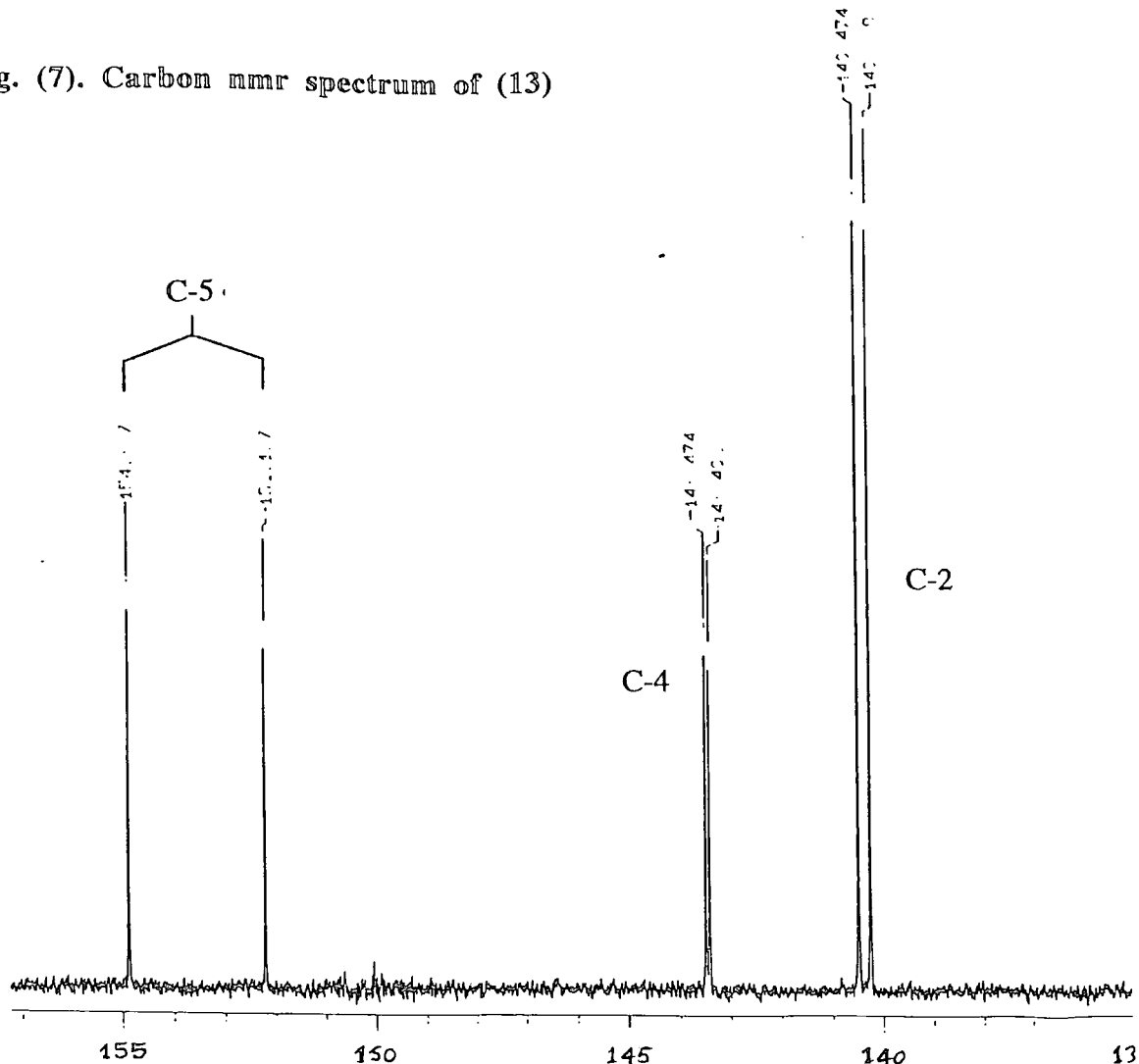
Mass spectroscopy gives a characteristic bromine pattern of four lines which is consistent with a molecule containing three bromine atoms.

III.5.3   Hexafluoroquinoxaline.

This reacts[96] with a variety of nucleophiles, giving mainly 2,3-derivatives, although sodium methoxide gave 2,3,6-trimethoxytrifluoroquinoxaline. Hence, we expected $H^+AlBr_4^-$ to react readily with hexafluoroquinoxaline.

14   **16, 68%**   **15, 13%**
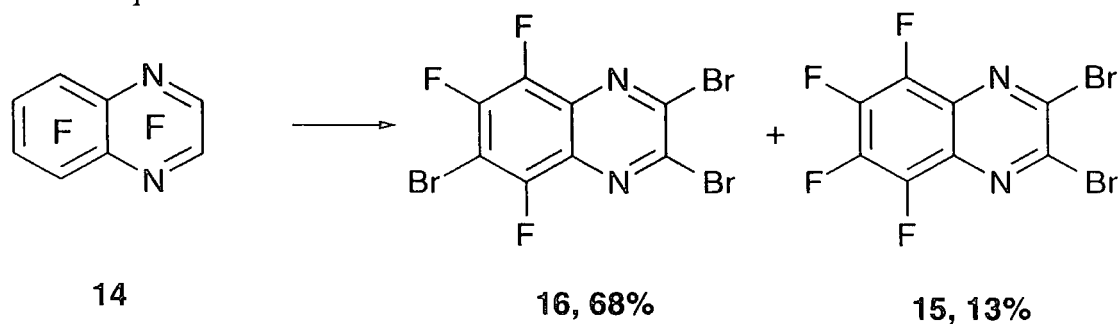
Reagents and Conditions: 2 HBr, 4 AlBr₃, 150°C, 68 h

In fact, reaction gave the di- and tri- bromo substituted compounds (15) and (16) and attempts to push the reaction to obtain complete conversion to (16) led to extensive

50

tar formation. Separation of the two compounds, (15) and (16), by sublimation, crystallisation and column chromatography proved difficult, so this reaction was not pursued. (16) was not fully characterised, however, evidence for its formation was obtained from its GCMS data, which gave a characteristic three bromine pattern.

It is perhaps surprising that 2,3,6,7-tetrabromo-5,8-difluoroquinoxaline was not formed in significant amounts, since one might have thought that (16) would be susceptible to nucleophilic attack, once formed. The formation of (16) may be explained by considering the charge distribution in the following protonated quinoxaline.

-HF   Br⁻

Not formed   16
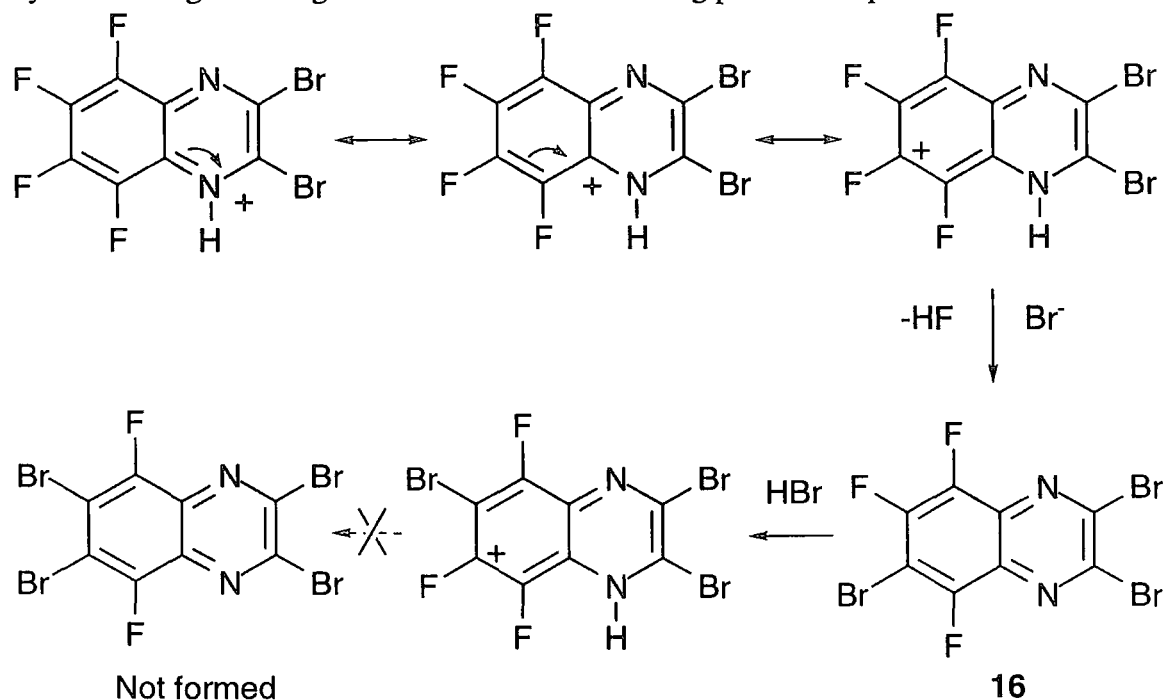
Thus, the 6- (and 7-) position should be activated towards nucleophilic attack and lack of further reaction to give the tetrabromo derivative can only be attributed to steric factors arising from the effect of *peri* fluorine.

In view of the over reactivity experienced with AlBr₃ and HBr, we chose to react hexafluoroquinoxaline (14) with hydrogen bromide alone, and after heating (14) with HBr and acetonitrile in a rotating oil bath at 70 °C, 2,3-dibromotetrafluoroquinoxaline (15) was obtained in good yield.

14   15, 79%
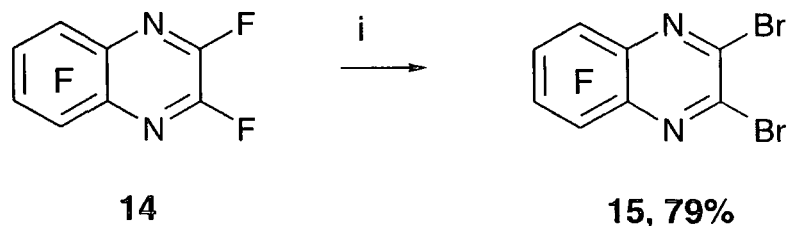
Reagents and Conditions; i, 5HBr, MeCN, rotating oil bath, 70 °C, 42 h

The mass spectrum of (15) showed the isotopic pattern to be expected for a molecule containing two bromine attoms, giving 3 parent ions.

51

^{79}Br ^{79}Br ^{81}Br
^{79}Br ^{81}Br ^{81}Br
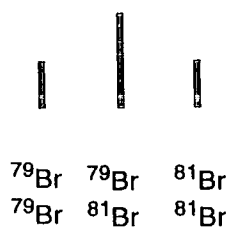
2 bromine pattern

The fluorine nmr spectrum gave two resonances of equal intensity at -149.15 and -149.50 ppm, which indicated that bromination had indeed occurred in the heterocyclic ring (if fluorine had been retained at the 2- position, a shift to lower field would have been obtained) and the carbon nmr spectrum gave four resonances, indicating the symmetry of the molecule. Carbon C-2 is too distant from the fluorinated ring to show coupling with fluorine and gives a singlet at 143.4 ppm. C-5 and C-6 on the other hand, are readily identified and both show large coupling to fluorine (^1J 263 and 258 Hz) and further coupling to the other ring fluorine atoms, thus both C-5 and C-6 give a doublet of multiplets, however, the similarity of the chemical shifts (140.9 and 142.0 ppm) means that they are indistiguishable. The remaining carbon is observed as a multiplet at 127.9 ppm.

Fig. (8). Carbon nmr of (15)

52
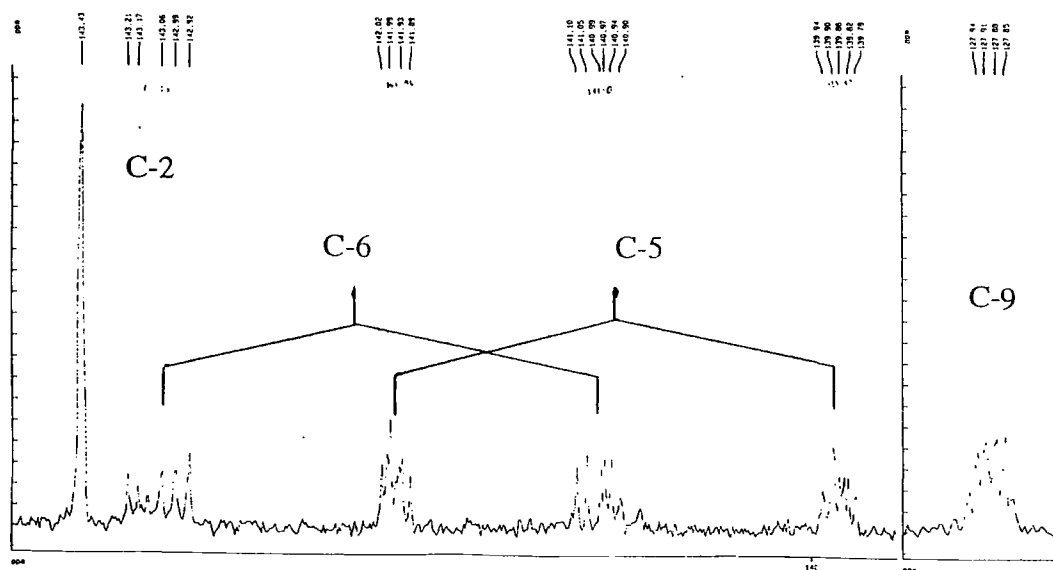
III.6   Reduction of Bromofluoroheterocycles

III.6.1   Catalytic Hydrogenolysis. From the preliminary discussions in part III.2.1, we anticipated that catalytic hydrogenolysis of bromine would occur rapidly to give conversion to the corresponding fluoroheterocycles.

Hydrogenolysis of 2,4,6-tribromo-3,5-difluoropyridine occurred rapidly giving quantitative conversion to 3,5-difluoropyridine (5), with an isolated yield by distillation of 63%.

11   **5, 100% conv.**
                                          63% isolated
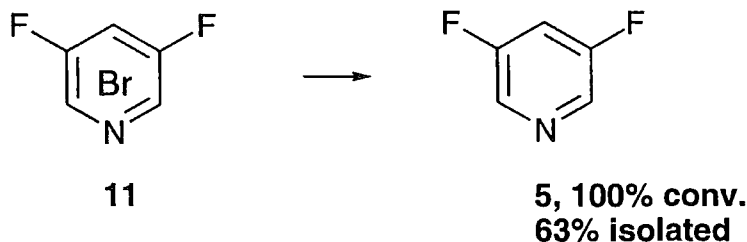
Reagents and conditions: Pd,C H$_2$(g)@4Bar, Et$_3$N, DCM, RT, 22h

The proton nmr spectrum of (11) gave two signals at 7.22 and 8.37 ppm in an intensity ratio of 1:2, which are attributed to 4-H and 2,6-H respectively. The fluorine nmr spectrum showed a single resonance at -124.1 ppm, which is consistent with fluorine at the 3-position[111] and the carbon nmr spectrum showed three resonances, which is consistent with the symmetry of the molecule. Carbon C-2 (134.2 ppm) gave splitting which may be described as an X part of an ABX system, owing to second order effects (see chapter IV.2.1 for other examples). C-3 gave a low field shift (159.1 ppm) and was distinguished by large coupling to fluorine (^{1}J 266 Hz), which was further split by a fluorine atom in the *meta* position (^{3}J 4.5 Hz). C-4 was identified by its high field shift (111.1 ppm) and coupling to fluorine at the 3- and 5- positions and gave a triplet (^{2}J 23.8 Hz).

Fig. (9). Carbon nmr spectrum of (5)
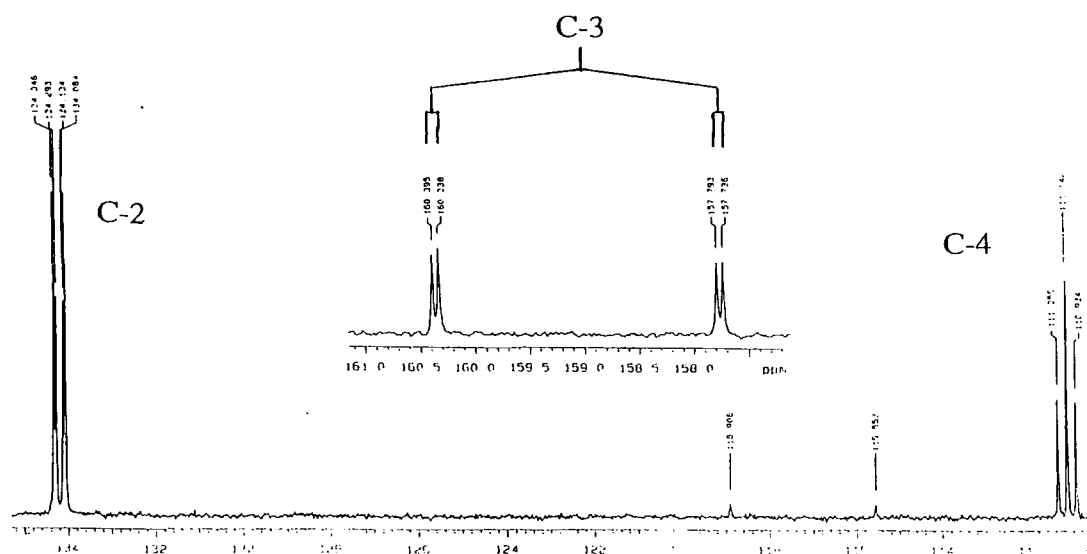
This reaction provides an excellent route to (5) and is suited to larger scale synthesis since very mild conditions are required, both pressure and temperature changes are minimal and there are no undesirable side products.

2,4,6-Tribromo-3-amino-5-fluoropyridine (23c)(see chapter IV for the synthesis of 23c) may be reduced giving 3-fluoro-5-aminopyridine in high yield.

23c   **17, >95%**
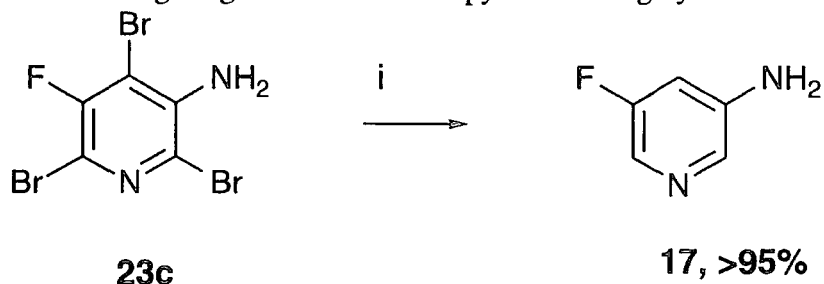
Reagents and conditions: i, Pd,C H_2(g)@4Bar, Et_3N, DCM, RT, 22h

The structure of (17) was easily proved by infra-red, mass and nmr spectral data. The amino group showed a band at 3335cm^{-1} in the IR spectrum which is consistent with an amino group and mass spectroscopy data indicated that there was an even number of nitrogens, since the parent ion had an even mass number (M^+, 114): it is known that an odd number of nitrogen atoms in a molecule leads to an odd mass molecular ion, whilst an even number of nitrogen atoms shows an even mass molecular ion[110]. The fluorine nmr spectrum gave a singlet (-128.34 ppm), which is consistent with fluorine at the 3-position. The carbon nmr spectrum gave five resonances, as would be expected for the unsymmetrical structure. A doublet at 108.2 ppm may be assigned to 4-C since carbon atoms at the 4-position are typically shifted to high field, C-2 which is more deshielded, being *ortho* to C-F and ring nitrogen, gives a doublet at lower field (127.5 ppm). C-5, which is bound to fluorine (^1J 254 Hz) is assigned to the low field doublet at 160.1 ppm. The remaining two resonances at 133.3 (singlet) and 144.0 ppm (doublet, ^3J 6.1 Hz) may be assigned considering the effect of nitrogen and the magnitude of the coupling constant. C-6, which is *ortho* to ring nitrogen may be assigned to the lower field shift (133.3 ppm) and the ^3J coupling of 6.1 Hz is typical of that between carbon at the 3-position and fluorine bound to carbon at the 5-position, thus, C-3 may be assigned to 144.0 ppm.

Fig. (10). Carbon nmr spectrum of (17)
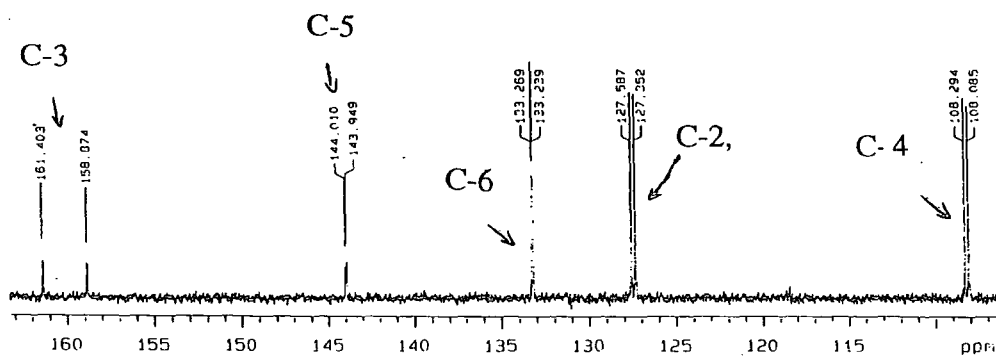
It is apparent from this reaction that this methodology could be used to synthesise a range of novel fluoropyridines (see Chapter IV and scheme (5) for details).

Scheme (5)
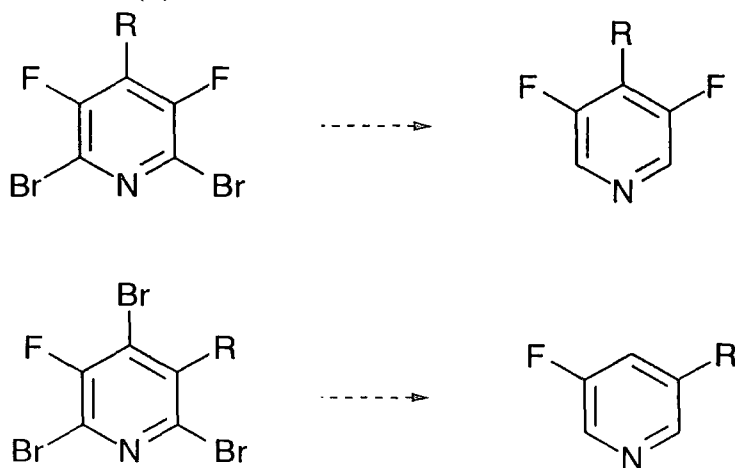
In view of the ready hydrogenolysis of chlorine from 4,6-dichloro-2,5-difluoropyrimidine[121], we anticipated the replacement of Br by H from 2,4,6-tribromo-5-fluoropyrimidine (13) would occur with ease.

55

13   **18, Quant.**
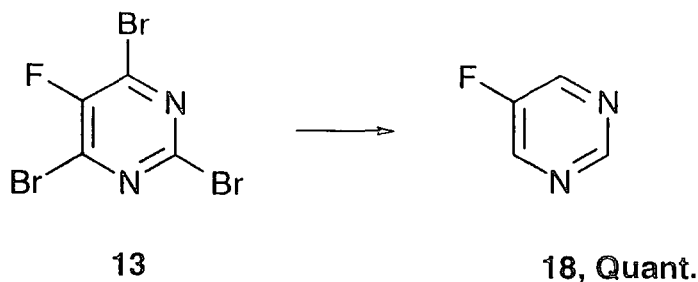
Reagents and Conditions; Pd,C H_2(g)@4Bar, $^nBu_3N$, DCM, RT, 18 h

Indeed, quantitative conversion of (13) to 5-fluoropyrimidine (18) was achieved. (18) was identified by comparison of its fluorine and proton nmr spectra with literature data[78].

We expected hydrogenolysis of 2,3-dibromotetrafluoroquinoxaline would give replacement of Br by H.

15   **19, >95%**
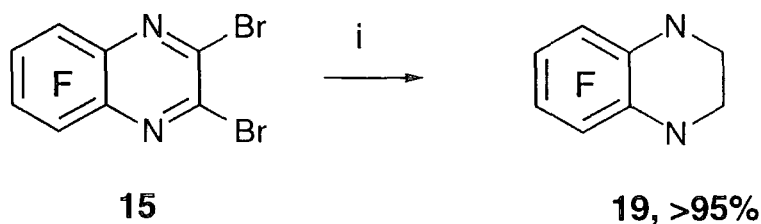
Reagents and conditions: i, Pd,C H_2(g)@4Bar, Et_3N, DCM, RT, 64 h

To our surprise, using palladium on carbon as the catalyst, hydrogenolysis of Br was followed by saturation of the heterocyclic ring to give 1,2,3,4-tetrahydrotetrafluoroquinoxaline (19). 1,2,3,4-Tetrahydrotetrafluoroquinoxaline was identified by its proton nmr spectrum, which indicated that hydrogens at the 2- and 3-positions were bound to sp^3 hybridised carbons (hence evidence for saturation of the heterocyclic ring) and that nitrogen was now bound to hydrogen since two resonances were observed at 3.42 and 3.79 ppm in an intensity ratio of 2:1.

Fig. (11). Proton nmr spectrum of (19)

56
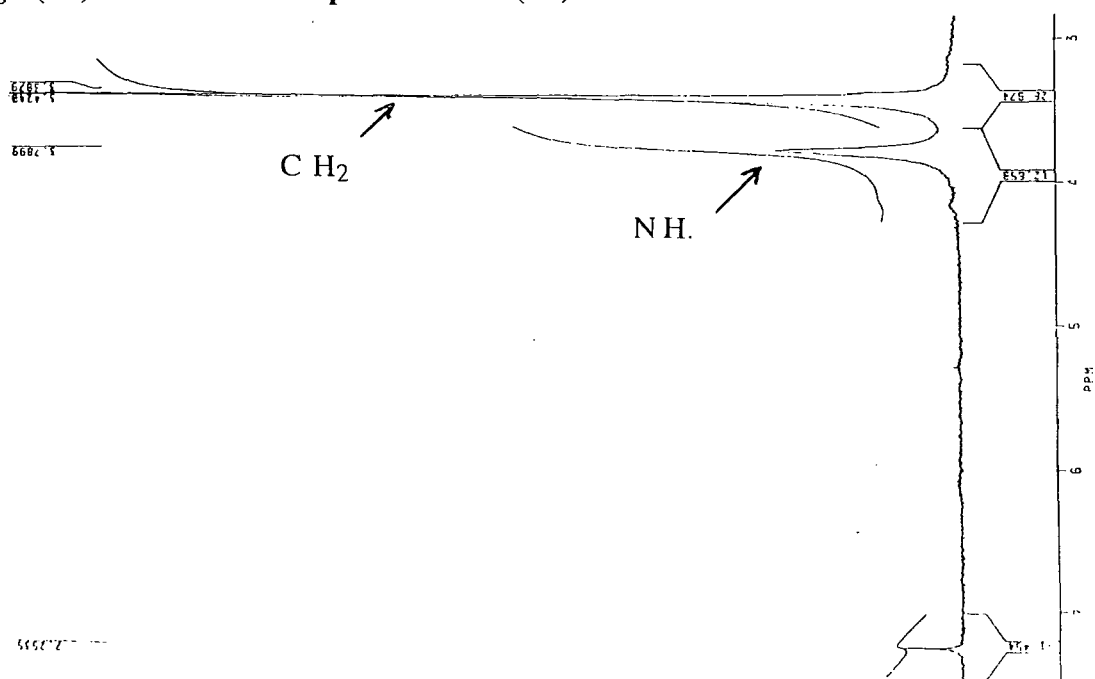
The fluorine nmr spectrum (which gave two resonances of equal intensity at -167.2 and -175.7 ppm) and the carbon nmr spectrum confirmed the symmetrical structure: the resonance at 40.3 ppm was assigned to C-2 since shifts at such high field are indicative of sp^3 hybridised carbon atoms. C-5 and C-6 gave doublets of multiplets with typically large one bond C-F coupling (^{1}J 240 and 241 Hz), however, the similarity of their chemical shifts (133.5 and 136.4 ppm) meant that they were indistiguishable. The remaining carbon atom gave a multiplet at 118.7 ppm due to splitting with ring fluorine atoms.

It was apparent that palladium on carbon was too active a catalyst for this system, so a lower reactivity catalyst, a Lindlar catalyst was chosen.

15   **20, >95%**
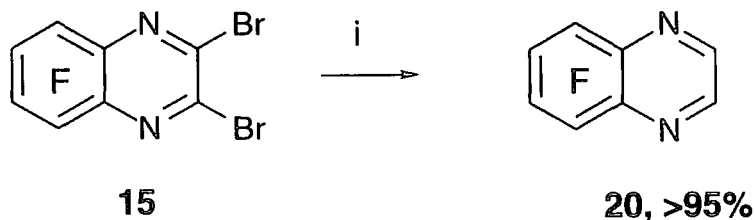
Reagents and conditions: i, Lindlar catalyst, H$_2$(g)@4Bar, Et$_3$N, DCM, RT, 5 d.

The use of the Lindlar catalyst was successful (although the duration of the reaction was longer than with the palladium on carbon catalyst), giving the unsaturated 5,6,7,8-tetrafluoroquinoxaline (20), with no trace of the saturated product (19). Evidence for retention of aromaticity in the heterocyclic ring was shown in the proton nmr spectrum, which gave a doublet at 8.90 ppm. This fact is consistent with chemical shifts for highly deshielded hydrogens and the coupling to fluorine (^{5}J 10.1 Hz) showed that both bromines had been replaced by hydrogen.

Fig. (12). Proton nmr spectrum of (20)
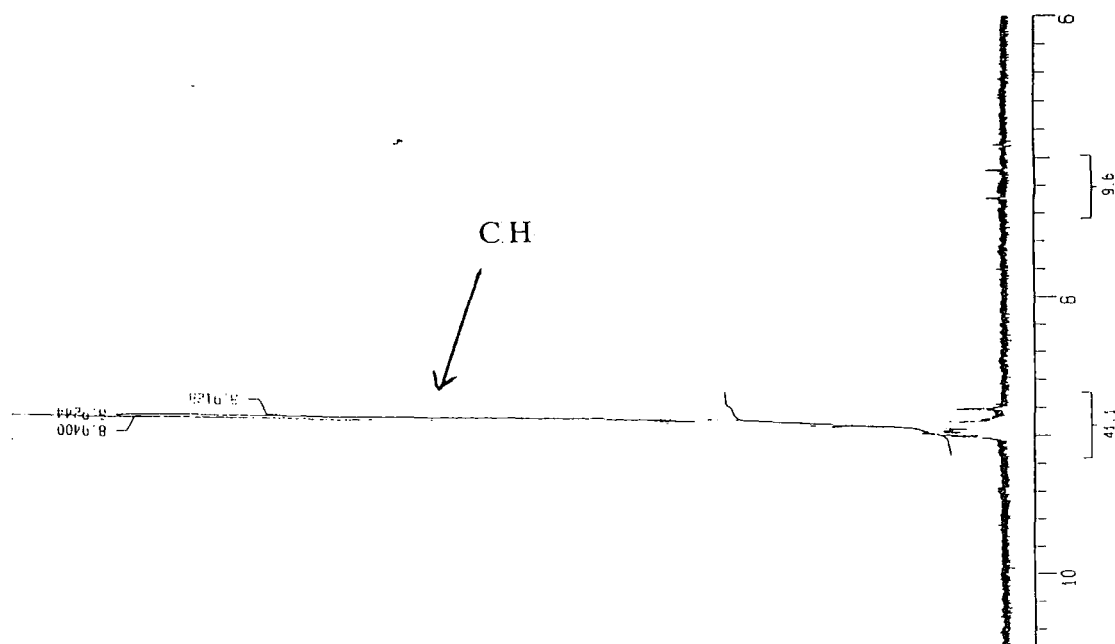
Interestingly, the fluorine nmr spectrum gave only one resonance at -151.65 ppm. Hence, both fluorine atoms in the benzenoid ring have identical chemical shifts. Mass spectroscopy data were consistent with the structure (20) and gave the correct molecular ion (M^+ 202) and the melting point was in agreement with published data. The carbon nmr spectrum was interesting: only three resonances were observed, although four may have been expected. A singlet at low field (145.8 ppm) was attributed to C-2, and the absence of splitting is consistent with carbon bound to hydrogen. Both C-5 and C-6 would have been expected to show separate signals, however, only a complicated doublet of multiplets at 141.4 ppm was seen. The large coupling (^1J 263 Hz) is of course typical of carbon bound to fluorine and it is likely that the chemical shifts of C-5 and C-6 are very similar and appear to coalesce. The remaining carbon atom at the juncture of the two rings was assigned to a singlet at 130.0 ppm.

III.6.2 Metal Hydrides.

Following the successful reaction of pentafluoropyridine and 3,5-dichlorotrifluoropyridine with DIBAL (see Chapter II), we expected (11) to react with DIBAL, so we were surprised when reaction failed.

In view of the success of reactions of pentafluoropyridine (3) with LAH, it was hoped that (11) would readily react with LAH. After ensuring that the temperature remained less than -10 °C (replacement of 3-F occurs at temperatures greater than this), (11) was converted quantitatively to (5), as determined by fluorine nmr spectrosocpy and GCMS.

11   **5, Quant.**
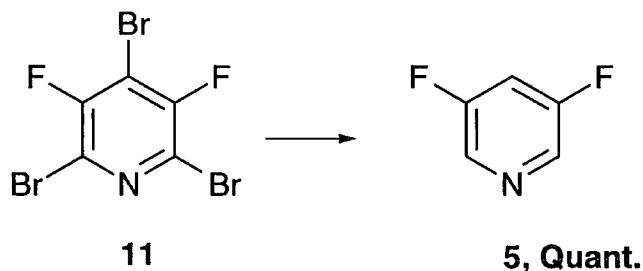
Reagents and conditions: LiAlH₄, Et₂O, -70°C- -10°C, 18 h

We have already observed the control one can achieve by complexing LAH with 12-crown-4, since, whilst reaction of pentafluoropyridine with LAH alone gave a mixture of 2,3,5,6-tetrafluoropyridine, 3,5-difluoropyridine and 3-fluoropyridine, a reaction of pentafluoropyridine with LAH in the presence of 12-crown-4 gave 2,3,5-trifluoropyridine (see scheme (2), Chapter II). Therefore, it was of interest to perform a reaction of (11) with LAH in the presence of 12-crown-4.

11 → **21, >90%**
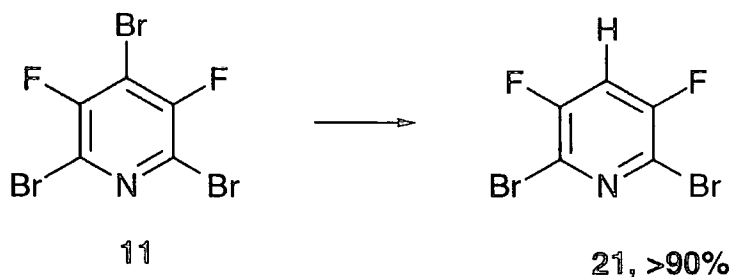
Reagents and conditions: LiAlH₄, Et₂O, 12-Crown-4, RT, 24 h

The reaction gave a fascinating result, giving 2,6-dibromo-3,5-difluoropyridine (21) as the product. Both the single resonance in the fluorine nmr spectrum at -109.10 ppm and three resonances in the carbon nmr spectrum proved the symmetry of the structure and indicated that attack had occurred at the 4-position. C-3 and C-5 gave typical low field shifts at 155.5 ppm and a large ^1J value of 266 Hz due to C-F coupling. C-4 was assigned to a triplet at 113.7 ppm (^2J 23.8 Hz) due to splitting by the fluorines at C-3 and C-5 and carbon atoms at the 2- and 6-position gave a characteristic X part of an ABX system, which is typical for these 3,5-difluoropyridine derivatives. The mass spectrum showed the characteristic three parent ion isotope pattern that a molecule containing two bromine atoms may be expected to give[110]. Proton nmr gave a triplet (7.31 ppm) and coupling with *ortho* fluorine (^3J 6.4 Hz) is consistent with ^3J couplings between F and H for heteroaromatic systems.

This result may be rationalised in scheme (6) by considering the role of Li⁺ in the reaction. In the absence of the crown ether, Li⁺ co-ordinates to ring nitrogen in (11) and activates the 4-, 2- and 6- positions to attack by aluminium hydride, thus (11) gives (5). However, the addition of crown ether prevents co-ordination of Li⁺ to ring N and only the 4- position is sufficiently activated to nucleophilc attack, giving (21).

Scheme (6)

More reactive than

LiAlH₄   LiAlH₄

5   **21**
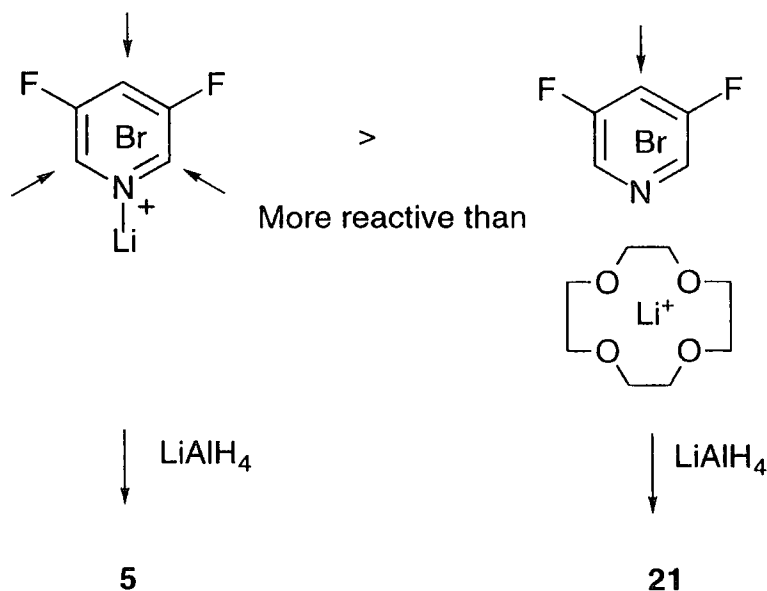
As outlined in chapter II, ammonia readily reacts with perfluoro nitrogen aromatics and the position of substitution is governed by the individual activating influences of F and N. Thus, ammonia reacts with pentafluoropyridine to displace F at the 4- position and it is a relatively easy procedure to synthesise amino substituted fluoroheterocycles.

III.7.1   Reactions of Pentafluoropyridine. 4-Aminotetrafluoropyridine (8) was synthesised from (3) using procedures developed in our laboratories[90], then diazotisation at 0 °C afforded (4) in fair yield. Subsequent amination of (4) gave 2-amino-3,5,6-trifluoropyridine (9), then diazotisation gave (7).

$$NH_2$$

3   8, 91%   4, 47%

9, 67%   7, 40%
                           overall, 11%
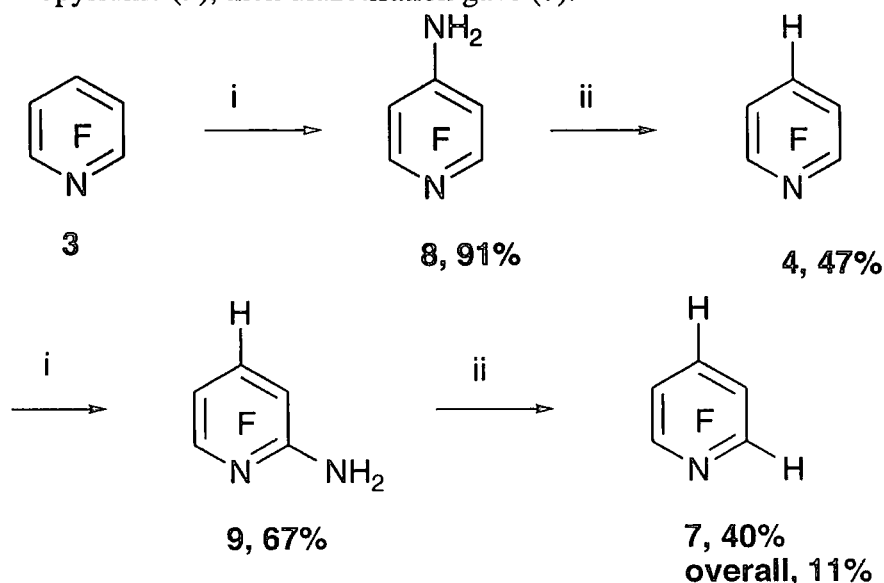
Reagents and Conditions: i, $NH_3(aq)$, 80°C, sealed tube; ii, $6H_3PO_2$, $NaNO_2$, 0°C,3h, RT, 2 h

Pyridines (4) and (7) were identified by comparison of their fluorine nmr spectra and GCMS spectra with authentic samples, whilst (8) and (9) were identified by comparison with literature data.

Although the overall yield here is perhaps disappointing, the methodology provides a step-wise route to (7) and undoubtedly, further effort would have increased yields. For instance, the diazotisations may have been performed in an oxygen free environment (oxygen has been shown to retard the performance of hydrodediazoniation reactions[141], but this paper did not come to our attention until later). However, this step-wise method was not pursued because developments in the bromination/ hydrogenation route showed greater promise.

III.8   Conclusion for Chapter III

Acid-induced bromination of highly fluorinated heterocycles gives a range of bromofluoroheterocycles, which, following catalytic hydrogenolysis, afford various unusually substituted fluoroheterocycles. Particular importance is attached to the

synthesis of 3,5-difluoropyridine, which we are now able to make in high yield and will be used in the development of high energy materials (see chapter VI).

Nucleophilic Substition of Bromofluoroheterocycles

Following the successful synthesis of 2,4,6-tribromo-3,5-difluoropyridine, 2,4,6-tribromo-5-fluoropyrimidine and 2,3-dibromotetrafluoroquinoxaline, it was of interest to explore some of the chemistry of these systems, particularly the reactivity of these bromofluoroheterocycles towards nucleophilics.

IV.1   Nucleophilic Substitution of Polyhaloheterocycles

Reactions of nucleophiles with highly halogenated heterocyclic systems, is of course, not without precedent. The literature contains descriptions of nucleophilic substitution of polyfluoro, polychloro, polybromo and mixed polyhalo heterocycles, therefore, these topics will be expanded on.

IV.1.1   Polyfluoro Nitrogen containing Heterocycles

Of all the halogenated heterocycles, the chemistry of fluorinated heterocycles (and in particular, nucleophilic substitution of fluorinated heterocycles) has been studied the most (see Chambers[11, 122]). Consequently, factors which determine reactivity are well understood. These factors were discussed in Chapter II, but for the sake of clarity, will be described once again.

IV.1.1.1   Pentafluoropyridine

Nucleophilic attack in highly fluorinated heterocycles is determined by the individual activating influences of fluorine and nitrogen. Nitrogen is strongly activating[100] in the order $p > o \gg m$ and fluorine[104] is also activating, in the order $o > m > p$. Particular emphasis must be drawn to the effect of *ortho* fluorine, which, contrary to expectations, is strongly activating and this has been attributed to initial state effects[101].
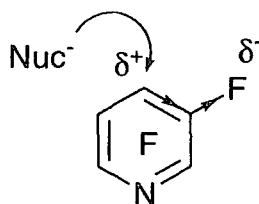
These rules may be used to predict orientation of attack by nucleophiles.

Attack here

pN > oN (activating)
oF > mF (activating)
(pF slightly deactivating)
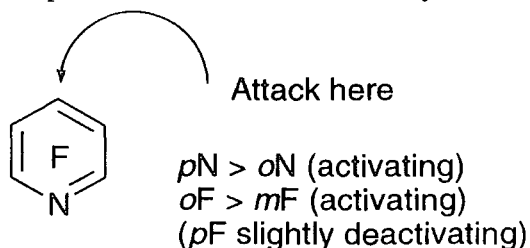
Predictions hold true for almost all nucleophiles and initial attack occurs at the 4-position[90, 109]. There is continual interest in nucleophilic substitution of pentafluoropyridine, and unusual nucleophiles such as trifluoromethylthio[142], imines of hexafluoroacetone[143] and diethylnitroxides[144] have been added to the well established ones. Under certain circumstances, 2- substitution may be observed with lithium hydrazonides[105] and sodium oximates[106] giving significantly increased 2- attack, which workers[105, 106] attributed to metal participation.

IV.1.1.2   Tetrafluoropyrimidine

Rules which rationalise the reaction of pentafluoropyridine with nucleophiles may also be applied to other ring systems.

Banks[97, 145] reacted tetrafluoropyrimidine with a range of nucleophiles and found

Attack here

N
F
N
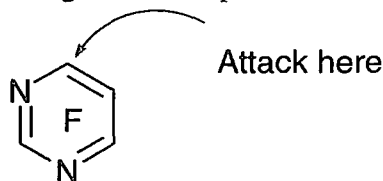
initial attack occurred exclusively at the 4- position.
Thus, the orientation of attack is determined principally by the effect of ring nitrogen.

IV.1.1.3   Hexafluoroquinoxaline

Workers[96] in these laboratories showed that hexafluoroquinoxaline reacted with nucleophiles at the 2- and 3- postions and under forcing conditions, sodium methoxide displaced fluorine from the 6- postion. Attack at the 2- position may be explained by considering the strong activating effects of ring nitrogen in the heterocyclic ring, however, attack at the 6- postion is not easily rationalised and the pseudo *meta* and *para* approach[146] shown in fig. (13), which may be used to explain orientation of attack in polycyclic systems, such as heptafluoroisoquinoline[147], fails here, since both attack at the 5- and 6- position is activated by an equivalent number of *pseudo* fluorines. Attack must therefore, be determined by the activating influences of *ortho* and *meta* fluorine in the benzenoid ring. Work[103] has shown that for highly fluorinated benzenoid systems, the activating effect of fluorine is $m > o > p$ to the position of attack.

Fig. (13)
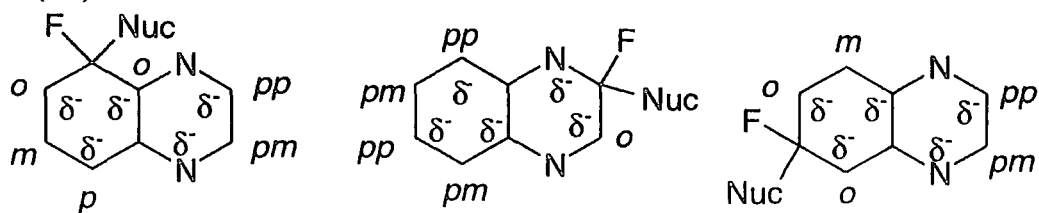
5- attack: 1 *o*F
1 *m*F, 1 *p*F, 1 *pp*F
1*pm* F

2- attack: 1 *o*F
1 *m*N, 1 *o*N, 2 *pp*F
2*pm* F

6- attack: 2 *o*F
1 *m*F, 1 *p*F, 1 *pp*F
1*pm* F

pm = pseudo *meta* (activating)
pp = pseudo *para* (slightly deactivating)

IV.1.1.4   Other Highly Fluorinated Ring Systems

Tetrafluoropyridazine[98], tetrafluoropyrazine[99] and, heptafluoroquinoline[95, 147] and heptafluoroisoquinoline[95, 147] all react with nucleophiles and orientation of attack correlates with the prediction method outlined above.

IV.1.2   Polychloro and Polybromo-heterocycles

Polychloro-heterocycles are primarily of interest as precursors to polyfluoro-heterocycles in the HALEX reaction (see chapter I). Their reactions with other nucleophiles has been studied.

A number of nucleophiles, including methoxide, ammonia, piperidine and diethylamine react with pentachloropyridine[148], giving substitution at the 4- or 2-position.

Nuc=	4- : 2-
NH$_3$/ EtOH	70 : 30
Et$_2$NH/ EtOH	1 : 99
NaOMe/ MeOH	85 : 15
Piperidine/ EtOH	37 : 63
Piperidine/ Benzene	4 : 96
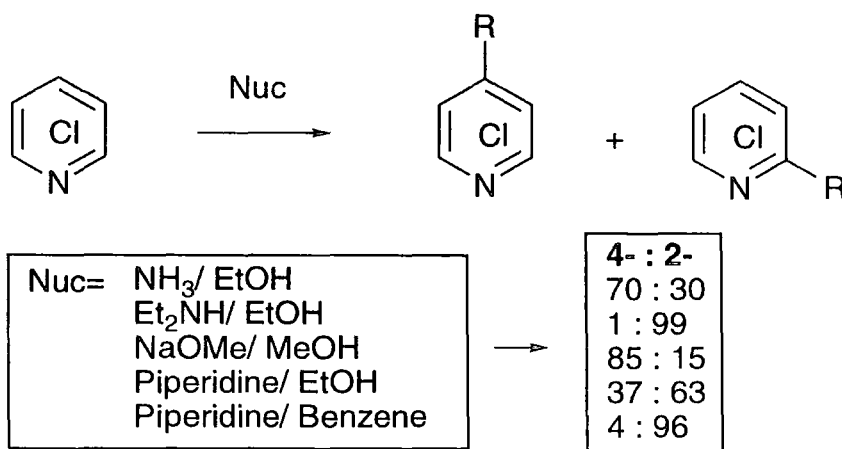
The general rule seems to be that bulky nucleophiles are more likely to attack the less hindered 2- position, whilst small nucleophiles substitute the 4- position. Solvent effects are important too, with solvents such as benzene favouring 2- attack. Thus, the dominating effect for the reaction of pentachloropyridine with nucleophiles is that of ring nitrogen, which encourages 4- and 2- attack.

The reactions[149] of pentabromopyridine with nucleophiles are analogous to those of pentachloropyridine.

Nuc=	NH$_2$NH$_2$/ EtOH	4- : 2-
		66 : 33
	Me$_2$NH/ EtOH	15 : 85
	Me$_2$NH/ Benzene	0 : 100
	NaOMe/ MeOH	66 : 34
	Piperidine/ EtOH	15 : 85
	Piperidine/ Benzene	0 : 100
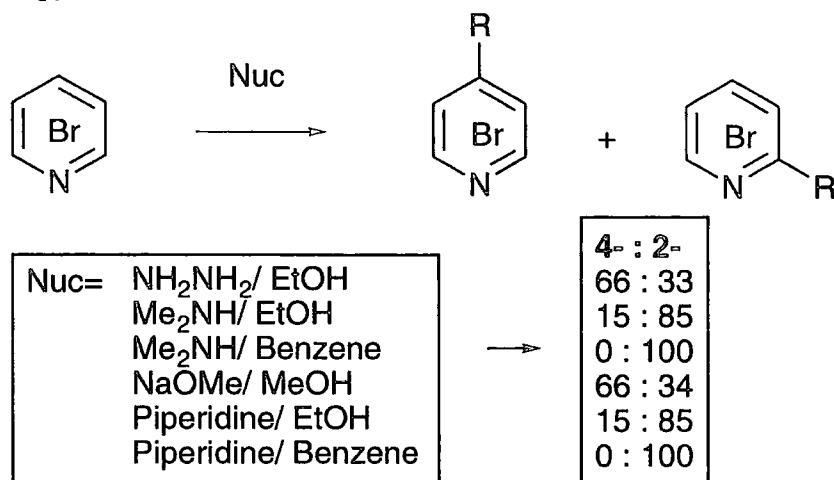
Thus, orientation of attack is determined by ring nitrogen and small nucleophiles prefer to attack the 4-, whilst bulky nucleophiles attack the 2- postion. As in the case of pentachloropyridine, 2- attack may be favoured by the use of a solvent such as benzene.

IV.1.4 Mixed Polyhalosubstituted Heterocycles.
IV.1.4.1 3,5-Dichlorotrifluoropyridine

3, 5-Dichlorotrifluoropyridine has been studied, primarily because of its availability: it is formed by the HALEX reaction of KF with pentachloropyridine and is an intermediate in the synthesis of pentafluoropyridine. Its reactions are, on the whole, the same as pentafluoropyridine with attack occurring at the 4-position[109, 145]. Once again, the individual activating influences of N and F apply and in addition to these, *ortho* chlorine[104] is strongly activating, moreso than *ortho* fluorine, hence 3,5-dichlorotrifluoropyridine is more reactive than pentafluoropyridine.

IV.1.4.2 4-Iodotetrafluoropyridine and 4-bromotetrafluoropyridine

Reaction of 4-Iodotetrafluoropyridine[150] and 4-bromotetrafluoropyridine[139] with a small selection of nucleophiles led to substitution of 2 - fluorine. This was attributed to normal substitution patterns observed for nucleophilic aromatic substitution.

X= I and Br

Nuc=	NH$_{3(aq)}$
	KOH, ^{t}BuOH
	NaOMe/ MeOH
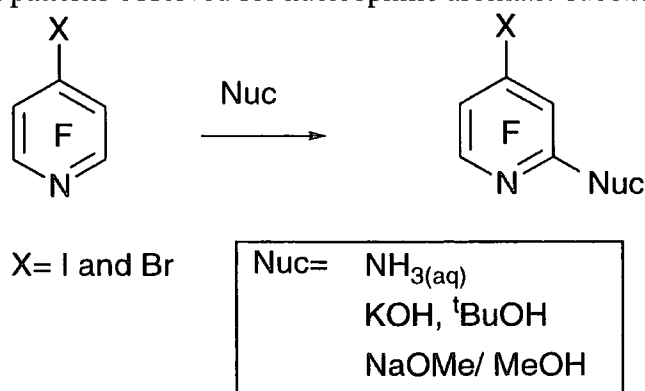
IV.1.4.3 4-Iodotrifluoropyrimidine

Both ammonia and sodium methoxide reacted with 4-iodotrifluoropyrimidine[107] giving exclusive substitution of fluorine, leading to 2-methoxy-4-iododifluoropyrimidine and 2-amino-4-iododifluoropyrimidine.
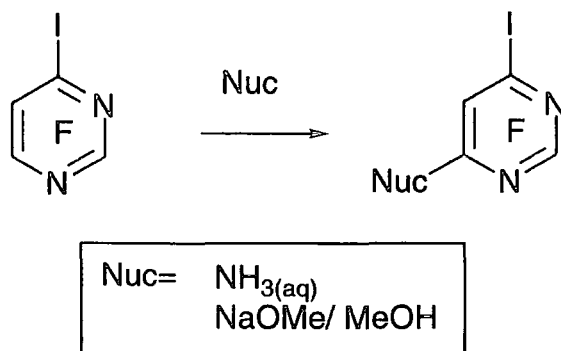
IV.1.5   Conclusion

From an analysis of the behaviour of nucleophiles with various halogenated heterocycles, the outstanding feature determining attack is that of ring nitrogen, which activates the 4- and 2- positions to nucleophilic attack and stabilises the Meisenheimer intermediate (see below).

The mechanism for nucleophilic aromatic substitution is a two step process. The first step (k_1) which is rate limiting (*i.e.*, the slow step), involves attack of the nucleophile on the aromatic ring and formation of the Meisenheimer intermediate.
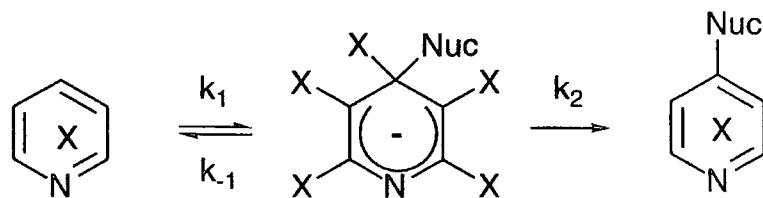
The second step (k_2) involves breaking the carbon-halogen bond and leads to the product.

For each of the cases (X= F, Cl, Br), the halogens play a similar role in activating the system to nucleophilic attack, by withdrawing electron density from the ring on account of their -I inductive effect.

An important difference between the role of *ortho* fluorine and *ortho* chlorine or bromine must be stressed and may be explained in fig. (14). Whilst bromine and chlorine *ortho* to the position of attack are activating on account of their ability to stabilise charge in the intermediate, fluorine *ortho* to attack is strongly activating on account of its strong initial state effect[101], which aids the approach of the nucleophile. Fluorine *para* to the position of attack is also weakly deactivating, whereas *para* chlorine and bromine are activating.

Fig. (14)

X= Cl, Br   C−Cl   C−Br   Stabilising

X= F   C−F   Destabilising (electron pair repulsions)
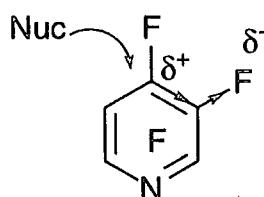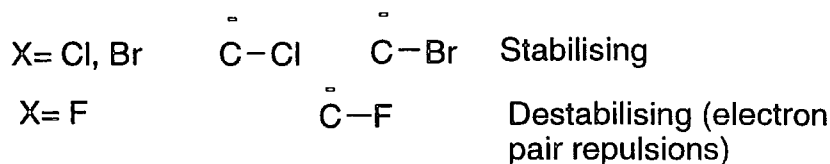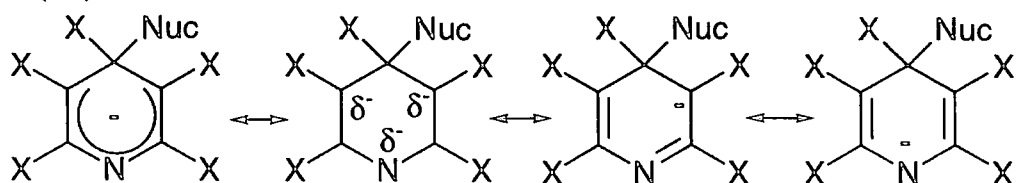
Ortho F- initial state effect

In addition to the fundamental structural differences described above, other effects are important, in particular, steric and solvent effects. Both chlorine and bromine are sterically bulky and tend to encourage substitution *ortho* to nitrogen in polychloro and bromo systems.

vs.
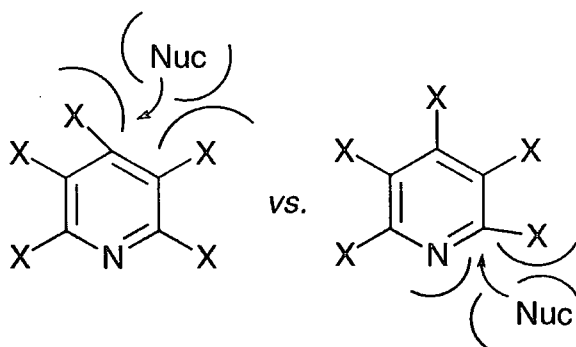
Solvent effects are important in determining whether a nucleophile attacks the 2- or 4- position in pentachloro or pentabromopyridine. Ring nitrogen may form hydrogen bonds with either the solvent or the nucleophile, thus in protic solvents such as methanol, there is considerable H-bonding between the halopyridine and solvent and 4- attack may be encouraged. However, in the absence of protic solvents, the nucleophile may form H-bonds with the halopyridine and 2- attack is encouraged.

vs.
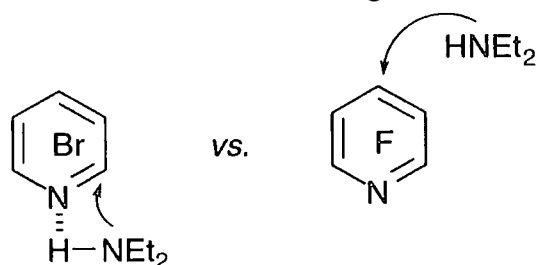
This effect is less relevant for pentafluoropyridine, which is a very weak base[116] and will not form H-bonds with the nucleophile or solvent and 4- attack predominates.

Considering all these arguments, we would anticipate nucleophilic substitution of bromofluoroheterocycles to occur normally, that is orientation of attack determined by nitrogen.

IV.2 Investigation into Nucleophilic Substitution of Bromofluoroheterocycles

IV.2.1 2,4,6-Tribromodifluoropyridine

It was of interest to observe the reactivity of 2,4,6-tribromo-3,5-difluoropyridine towards nucleophiles. In principle, there are three possible positions which a nucleophile may attack. A consideration of the arguments presented in part IV.1, would lead us to predict that 4- attack would be favoured. This is because if all the separate activating influences are considered for each position, the 4- position appears the most activated.
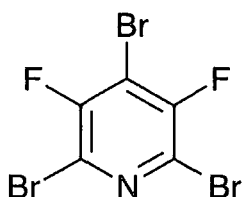
4- attack: 2 *o*F, 2 *m*Br, 1 *p*N

3- attack: 2 *o*Br, 1 *p*Br, 1 *m*N, 1 *m*F

2- attack: 1 *o*F, 1 *p*F, 2 *m*Br, 1 *o*N

Significant attack at the 2- position may also be expected, on account of steric and solvent factors. The interplay of the various factors influencing the orientation of attack was explored by reacting (11) with a variety of nucleophiles.

IV.2.1.1 Phenylthiol, Diethylamine and Piperidine

11   **22a**
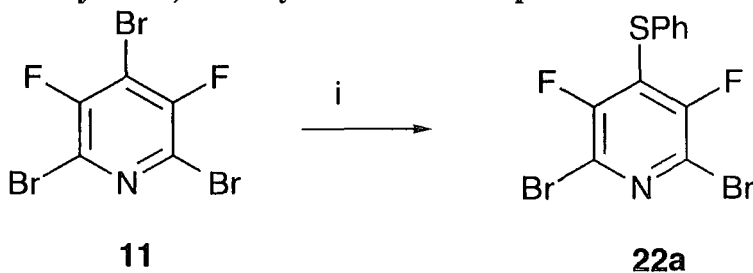
Reagents and conditions; i, PhSH (1.1 equiv.), Na$_2$CO$_3$, MeCN, reflux

Refluxing a mixture of (11) and phenylthiol led to attack at the 4- position giving the 4-thio ether (22a). An excess of thiol led to a polysubstituted mixture, which was not analysed further.

11   **22b**   **22c**
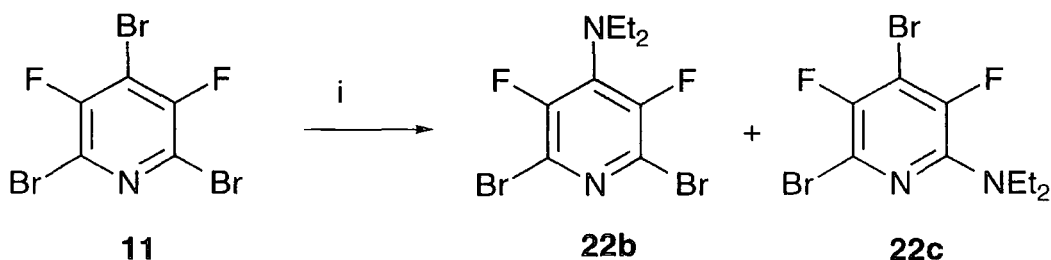
Reagents and conditions; i, Et$_2$NH, MeCN, reflux

Reaction of (11) and diethylamine gave the 4- and 2- derivatives (22b) and (22c), in a ratio of 70: 30 as determined by fluorine nmr. The significant proportion of the 2-

isomer can be attributed to the steric bulk of the nucleophile since attack at the 2-position is less sterically demanding as compared to the 4-position.

Steric Effects

_vs._
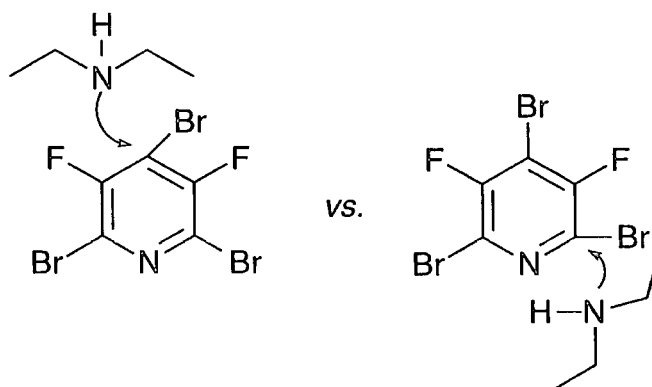
The effect of solvent was found to be significant too, because when the reaction of (11) with diethylamine was repeated without solvent, a higher proportion of the 2-isomer was obtained, which suggests that hydrogen bonding between the nucleophile and (11) was significant.

Solvent Effects

11   **22d**   **22e**
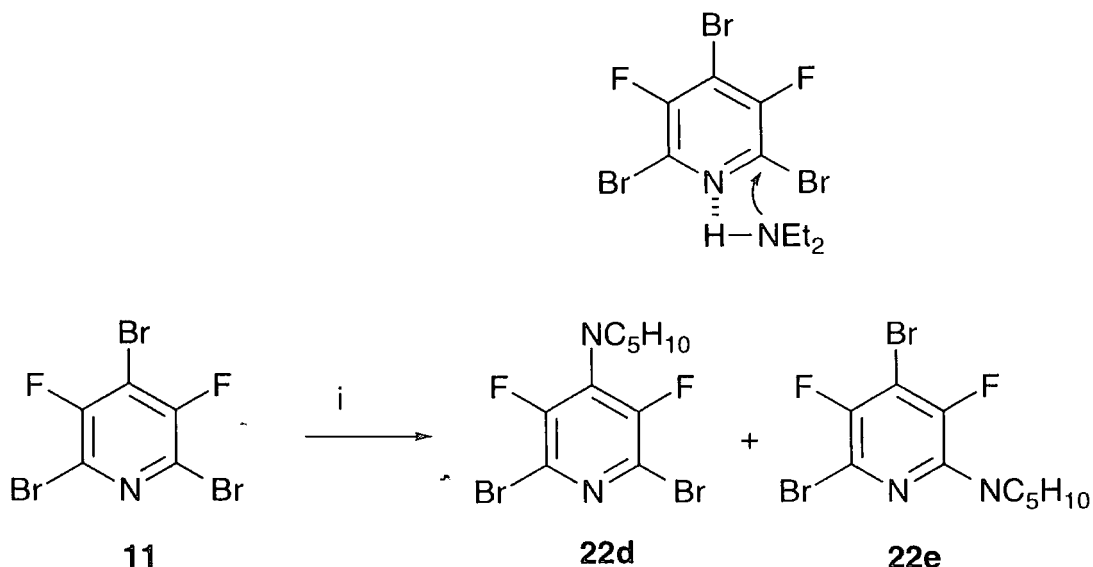
Reagents and conditions; i, Piperidine, MeCN, reflux

Piperidine reacted with (11) giving a similar result to diethylamine. It is interesting that piperidine gave a higher proportion of the 4-isomer (4- : 2-, 80 : 20) than diethylamine, which may be attributed to it being less sterically demanding than diethylamine.

Hence, the nucleophiles phenylthiol, diethylamine and piperidine all displaced bromine from the 4- and 2- positions, as predicted. Displacement of bromine from the 4-position to give (22a,b,d) was confirmed by fluorine and carbon nmr spectroscopy, mass

spectroscopy and elemental analyses. Thus, displacement of bromine from the 4-position led to a singlet in the fluorine nmr spectrum, which was expected since displacement from the 4-position gives a symmetrical molecule and the fluorines in the 3- and 5-position are equivalent. When displacement from the 2- position occurred to give (22c,e), two signals of equal intensity in the fluorine nmr spectrum were observed since fluorine atoms in the 3- and 5- position were now inequivalent. Mass spectroscopy provides compelling evidence for the displacement of bromine from (11). By comparing the bromine isotope patterns in the mass spectra of (22a-e), it was clear that they contained two bromine atoms. Thus, because bromine exists as two isotopes (^{79}Br and ^{81}Br) in a ratio of approximately 1:1, a compound with three bromine atoms would show four parent ion mass fragments[110]. On the other hand, two bromine atoms give three parent mass ion fragments and this was observed.

^{79}Br	^{79}Br	^{81}Br		^{79}Br	^{79}Br	^{79}Br	^{81}Br
^{79}Br	^{81}Br	^{81}Br		^{79}Br	^{79}Br	^{81}Br	^{81}Br
				^{79}Br	^{81}Br	^{81}Br	^{81}Br

<div align="center">
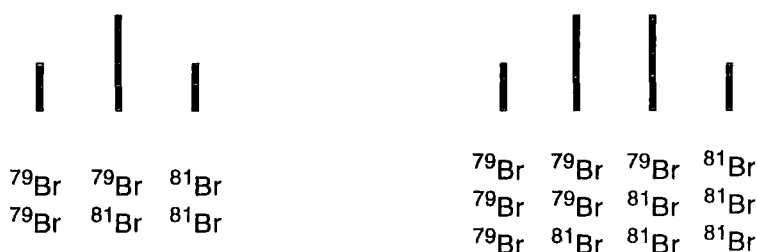
2 bromine pattern   3 bromine pattern

</div>

Further evidence for the structures (22a,b,d) was provided by carbon nmr spectroscopy: compounds (22a,b,d) are symmetrical and give three resonances due to the pyridine ring in the spectrum. The carbon nmr spectra for (22a,b,d) are similar and the principles for the assignment of the spectra shall be discussed in terms of (22d). C-2 may be assigned on the basis of its splitting pattern. Although it may be expected that C-2 would be split by fluorine atoms at the 3- and 5- positions to give a doublet of doublets (*i.e.* a first order spectrum), the observed spectrum is second order (for a thorough discussion see Gunther[114]) and an X part of an ABX spin system is observed. This spin system is typical for substituted 3,5-difluoropyridines and a pattern comprising four or six lines may be observed. The splitting pattern for C-2 (at 123.2 ppm) is shown here.

Fig. (15). Carbon nmr spectrum of (22d)
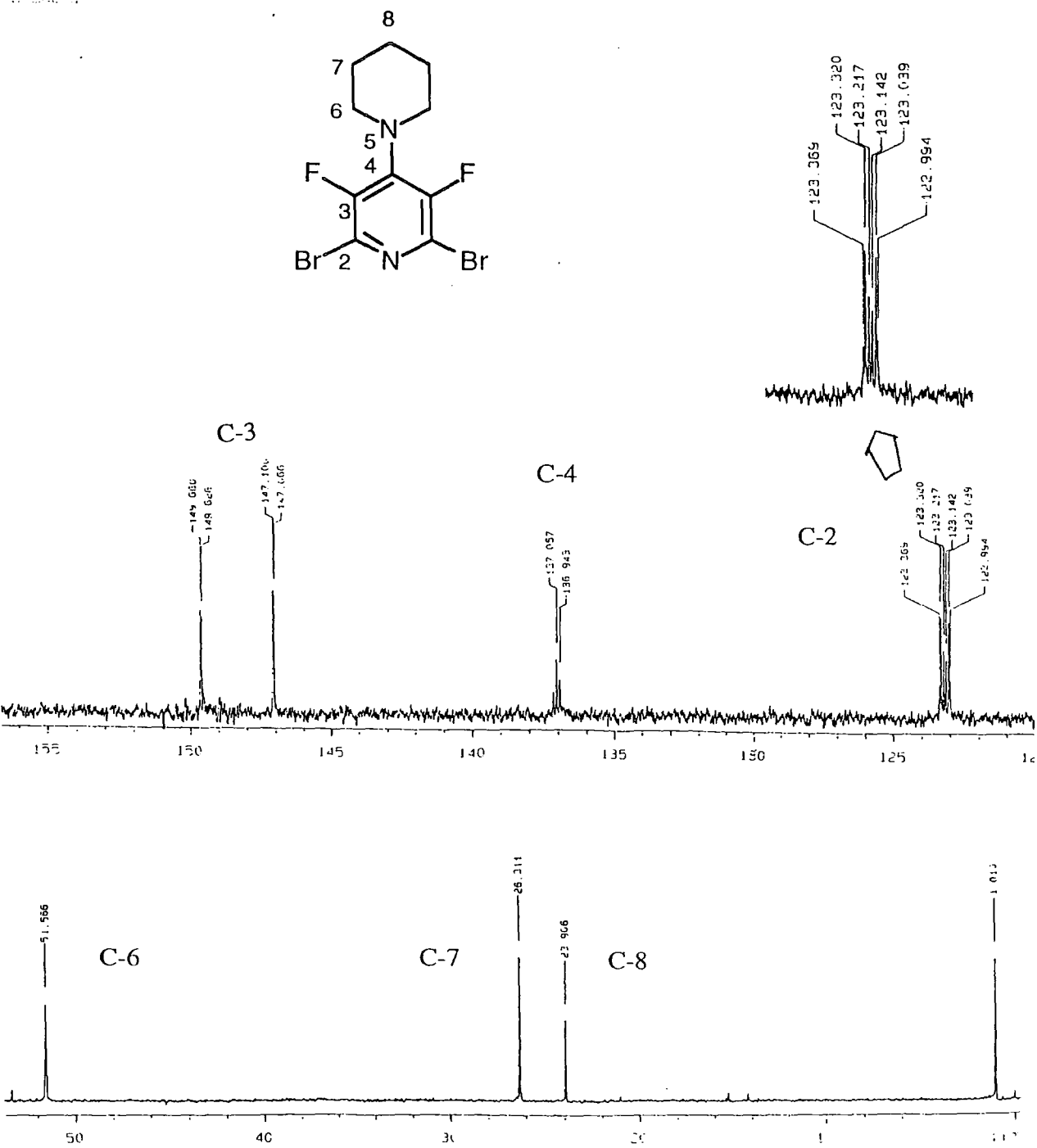
The remaining carbons are readily identified: C-3 is characterised by low field shifts in the region of 150 ppm, but moreover, the large ^1J coupling with fluorine (typically 260 Hz) and smaller ^3J coupling with meta fluorine (typically 3-8 Hz) are indicative of carbon bound to fluorine and C-3 may be assigned to the doublet of doublets at 148.0 ppm. C-4 is easily recognised because coupling with the chemically equivalent fluorines at the 3- and 5- position gives a triplet in the carbon spectrum (^2J 11-20 Hz) and may be assigned to the triplet at 137.1 ppm. The carbon atoms for the piperidine group were assigned by comparison with the free base.

IV.2.1.2 Sodium Methoxide, Potassium Hydroxide, Ammonia and Sodium Phenoxide.

Reaction of (11) with an excess of sodium methoxide led to the displacement of both fluorines giving (23b), whilst one equivalent of sodium methoxide gave the mono ether (23a).
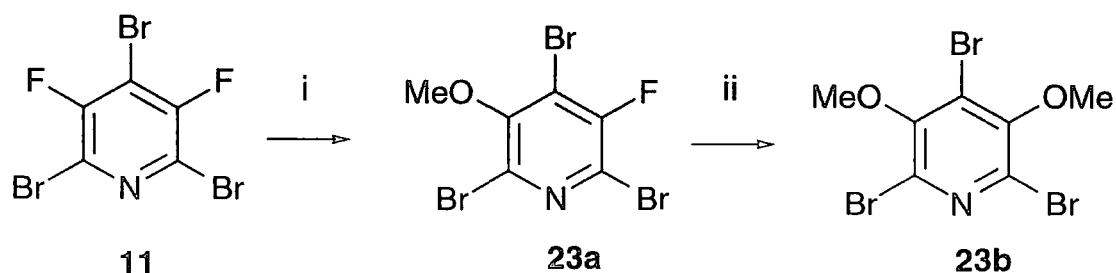
Reagents and conditions: i, 1.2MeONa/ MeOH, RT 60 hrs; ii, xs MeONa, RT, 24 hrs.

Both results were surprising and prompted further reactions of (11) with other nucleophiles.
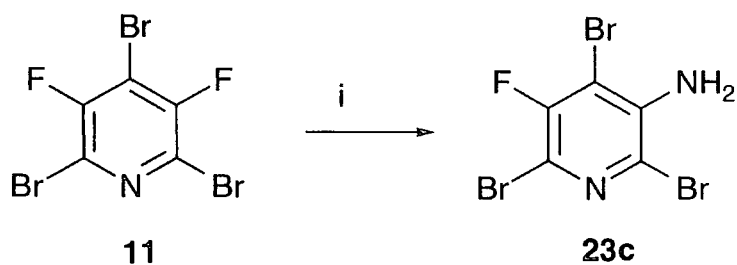
Reagents and conditions: i, $NH_{3(aq)}$, MeCN, 75 °C

Ammonia reacted with (11) giving the 3-amino derivative (23c) in complete conversion, thus displacement of fluorine occurred, which was not anticipated.

Br, F, F, Br, N, Br **11**

i →

Br, F, OH, Br, N, Br **23d**
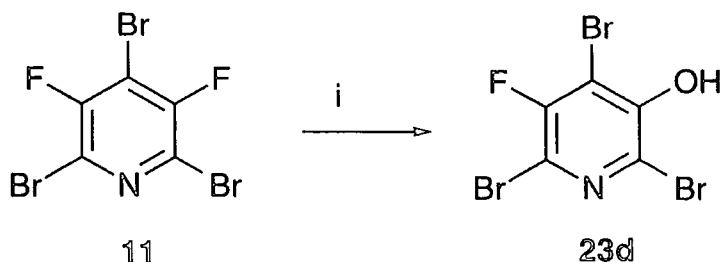
Reagents and conditions: i,KOH, ^tBuOH, reflux

Refluxing potassium hydroxide and butanol with (11) also gave displacement of fluorine, giving the 3-hydroxy derivative (23d).

Br, F, F, Br, N, Br **11**

i →

Br, F, OPh, Br, N, Br **23e**

+

OPh, F, F, Br, N, Br **22f**
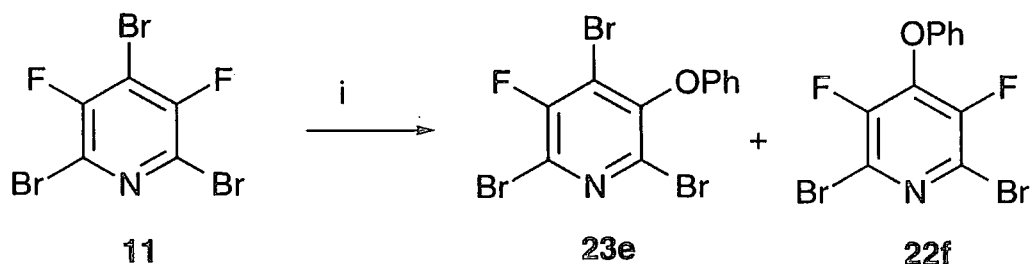
Reagents and conditions: i,PhOH (1.5 equiv.), Na_2CO_3, MeCN, reflux

Reacting (11) with sodium phenoxide in acetonitrile gave both displacement of bromine and fluorine giving (23e) and (22f) in a ratio of 75 : 25 as determined by GCMS. However, separation of these two products by sublimation, crystallisation and column chromatography proved difficult and the reaction was repeated, except the solvent was replaced with ether, and this led to exclusive displacement of fluorine giving the ether (23e).

Br, F, F, Br, N, Br **11**

i →

Br, F, OPh, Br, N, Br **23e**
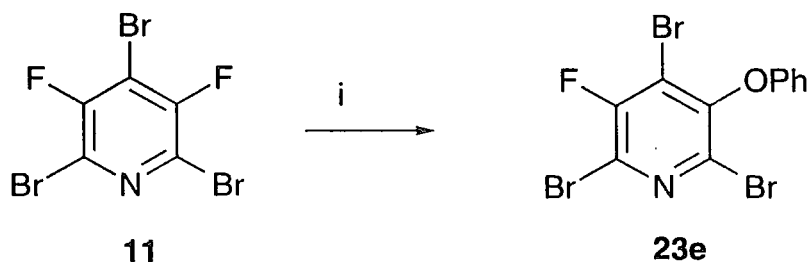
Reagents and conditions: i,PhONa (1 equiv.), ether, reflux

Therefore, the nucleophiles sodium methoxide, potassium hydroxide, ammonia and sodium phenoxide all reacted with (11) displacing fluorine, which was unexpected. Displacement of fluorine (rather than bromine) from (11) was confirmed primarily by fluorine and carbon nmr, mass spectroscopy and elemental analyses. The fluorine nmr spectra for (23a-e) all showed single resonances in the expected region (-100- -106 ppm), except for (23b) which contained no fluorine. Mass spectroscopy was the most important tool because displacement of fluorine from (11) gave compounds containing three bromine atoms and each compound (23a-e) gave a characteristic four line bromine isotope

pattern. Pyridines (23a-e) gave five resonances in the carbon nmr spectrum due to the aromatic ring, except for (23b), which is symmetrical and only gave three resonances. The carbon nmr spectra for (23a,c-e) are similar and the principles for assigning the spectra are essentially the same and thus the spectrum for (23a) shall be discussed.

Fig. (16). Carbon nmr of (23a)

23a
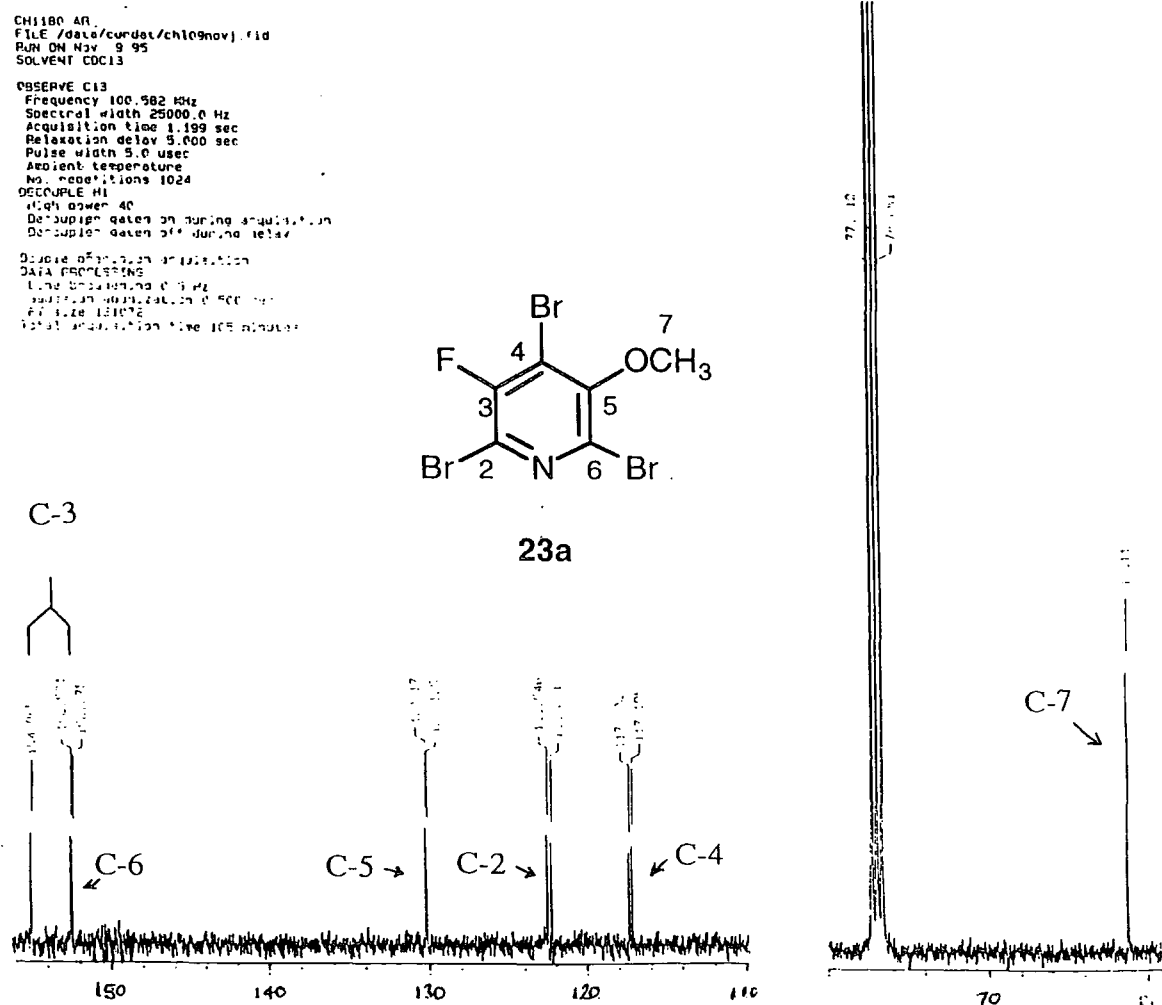
A large doublet at low field (153.7 ppm) may be assigned to C-3 since the large coupling is consistent with carbon bound to fluorine (^1J 250 Hz). A peak at higher field (117.3 ppm) which is split to a doublet (^2J 26.7Hz) is consistent[111] with shifts observed for C-4, and the ^2J coupling observed is typical[112] of two bond C-F coupling. Similarly, a resonance to slightly lower field (122.4 ppm) which gives a doublet (^2J 19.8 Hz) may be assigned to C-2, which also would be expected to be split by fluorine at the 3- position. The two remaining carbons, C-5 and C-6 would both be expected to couple with fluorine to give doublets, however, only one doublet (J 3.8 Hz) at 130.2 ppm and a singlet at 152.4 ppm are observed. Since three bond C-F couplings are typically in the region of 4 Hz, C-5 may be assigned to 130.2 ppm and C-6 to 152.4 ppm.

It appears clear from these results that hard nucleophiles displaced fluorine and soft nucleophiles displaced bromine. By considering (11), this seems a plausible

explanation- the carbon-fluorine bond is a hard centre and reacts with hard nucleophiles (giving the maximium Coulombic interaction[151]) and the carbon-bromine bond provides a soft centre and reacts with soft nucleophiles.

The results for the reaction of (11) with nucleophiles are consistent with observations recorded by Cervera and Bartoli. Cervera[152] observed that whilst sodium methoxide (hard nucleophile) reacted with 3,5-difluoro-4-chloronitrobenzene to displace fluorine, sodium thiophenoxide (soft nucleophile) displaced chlorine.

3%   67%

85%
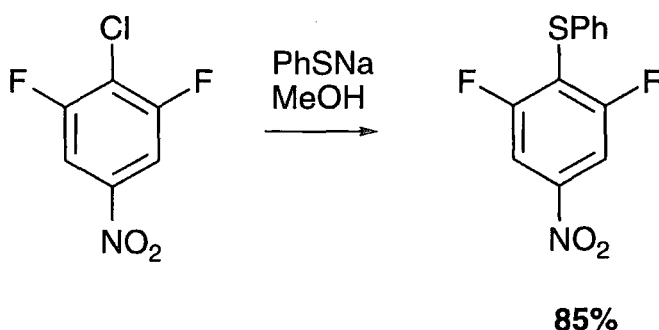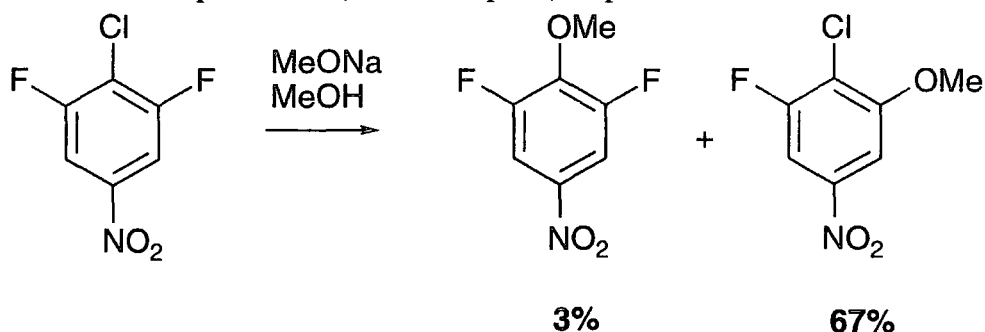
During kinetic studies of nucleophilic reactions of 2,4-dinitrohalobenzenes, Bartoli[153] observed that when X= F, displacement by methoxide (hard nucleophile) occurred 1000 times faster than for X= Cl, Br, but displacement by thiophenoxide (soft nucleophile) displaced fluoride only 10 times faster than the other halides, and even showed a greater rate for the displacement of bromine and iodine over chlorine.

X= F~NO$_2$ 1000x
> Cl > Br > I

X= NO$_2$ > F 10x
> Br > I > Cl
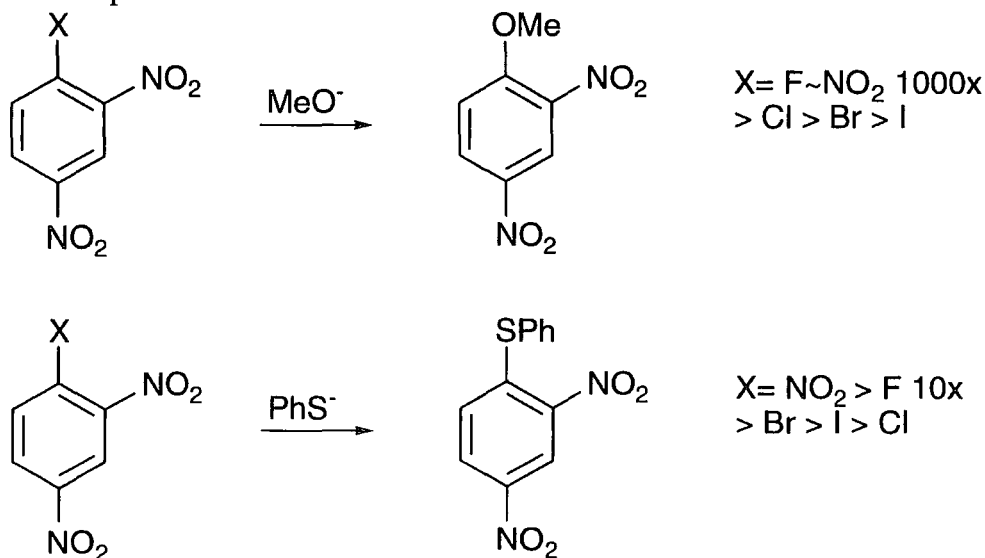
IV.2.1.3 Sodium Amide, Enolate Anions and Lithium Methoxide

In view of the remarkable selectivity observed for the reaction of (11) with hard and soft nucleophiles, it was of interest to react (11) with an ambident nucleophile - one with a hard and a soft attacking centre. For this the following anion was chosen.

Hard   **Soft**
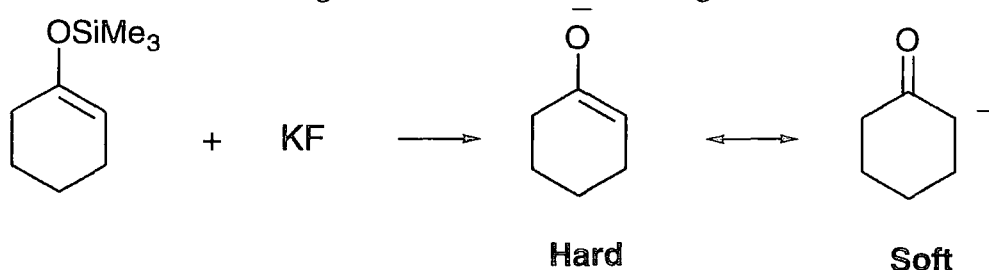
Attack through oxygen would be considered hard, but attack through carbon would be soft. Thus it was anticipated that the enolate would displace fluorine by attack through oxygen or displace bromine by attack through carbon, but surprisingly, reaction of (11) with the enolate anion (24a) gave 2,6-dibromo-3,5-difluoropyridine (21), which was identified by comparison of its fluorine, proton nmr and GCMS spectra with authentic samples.

11   **24a**   **21**
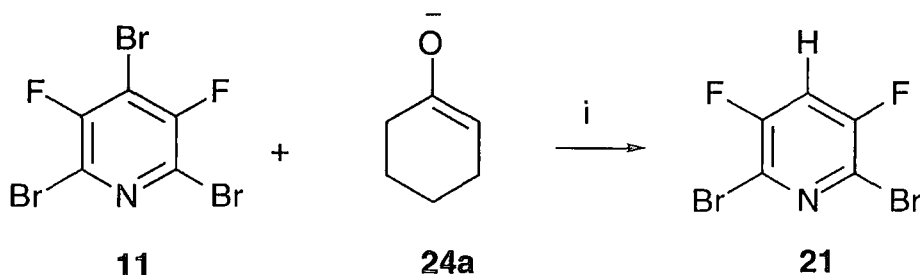
Reagents and conditions; i, 1-Trimethylsilyloxycyclohexene (2.5 equiv.), 3KF, MeCN, RT 16h and 60°C 8h.

This reaction was repeated in an attempt to discover the source of the hydrogen in the product (21), however, reaction of (11) with (24a) using deuterated acetonitrile as the solvent gave (21), (41%). No incorporation of deuterium was observed. Neither the fluorine spectrum (a triplet would have been expected) nor the mass spectrum gave evidence for a deuterated product. Thus the source of the proton in (21) must originate from the starting material, or from wet solvents.

11   **24b**   **21**
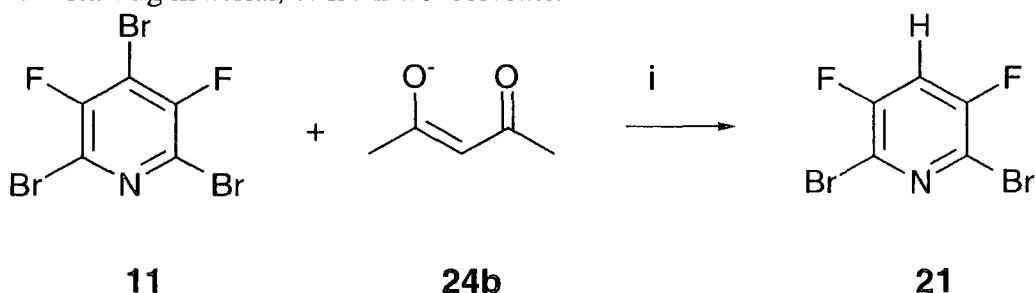
Reagents and conditions; i, 2-Trimethylsilyloxypent-2-ene-4-one (2.5 equiv.), 3KF, MeCN, RT 16h and 60°C 8h.

77

The highly stabilised enolate anion (24b) was also reacted with (11) giving (21), (90%), which was identified by comparison of its fluorine nmr and GCMS spectra with authentic samples. Thus, the enolates (24a and b) showed neither a preference for the hard C-F bond, nor the soft C-Br bond and contrary to expectations, attacked bromine in a halophilic reaction .

11   **21**
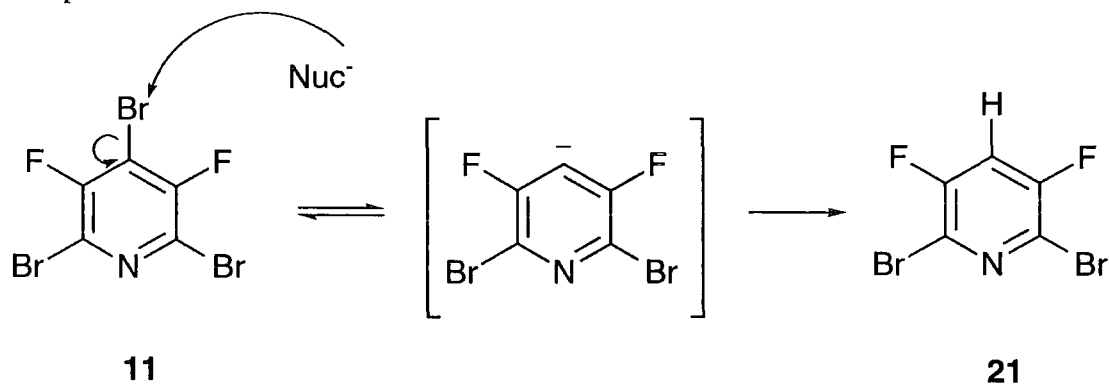
We anticipated that sodium amide would displace fluorine, because sodium amide is a hard nucleophile.

11   **21, 32% conv.**
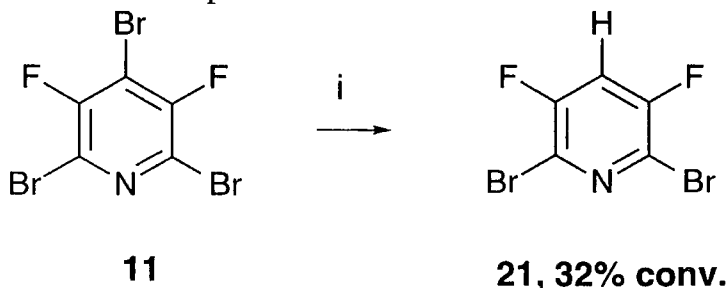
Reagents and conditions: i, $8NaNH_2$, MeCN, 0 °C

However, this was not observed and reaction gave (21), which was identified by comparison of its fluorine and GCMS spectra with an authentic sample. A single electron transfer mechanism was proposed, but then discounted after a reaction in the dark in the presence of dinitrobenzene gave (21). It was also interesting to note that there was no evidence for a pyridyne intermediate, since the 3- or 4- amino derivatives were not observed.

78
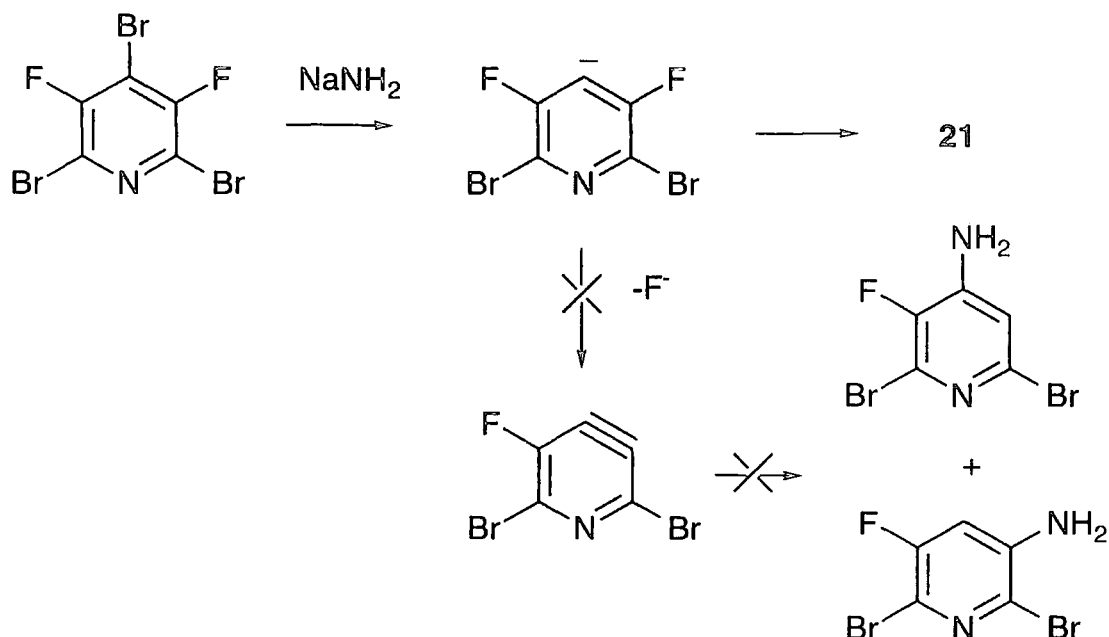
Both the reaction of (11) with enolates and sodium amide are consistent with observations outlined in Chapter III, part III.1.1.a.

It is now known (see IV.2.1.2) that reaction of (11) with sodium methoxide gives exclusive displacement of fluorine to afford 2,4,6-tribromo-3-fluoro-5-methoxypyridine (23a) and 2,4,6-tribromo-3,5-dimethoxypyridine (23b). Other investigations (see Chapter III) into the reaction of (11) with lithium aluminium hydride (LiAlH$_4$) demonstrated that the lithium cation (Li$^+$) played an important role in this reaction, because when (11) was reacted with LiAlH$_4$ alone, 3,5-difluoropyridine (5) was produced, yet in the presence of the cation complexing agent, 12-crown-4, 2,6-dibromo-3,5-difluoropyridine (21) was obtained. Thus, co-ordination of ring nitrogen of (11) to Li$^+$ activates (11) to nucleophilic attack (see Chapter III.6.2.2.a).
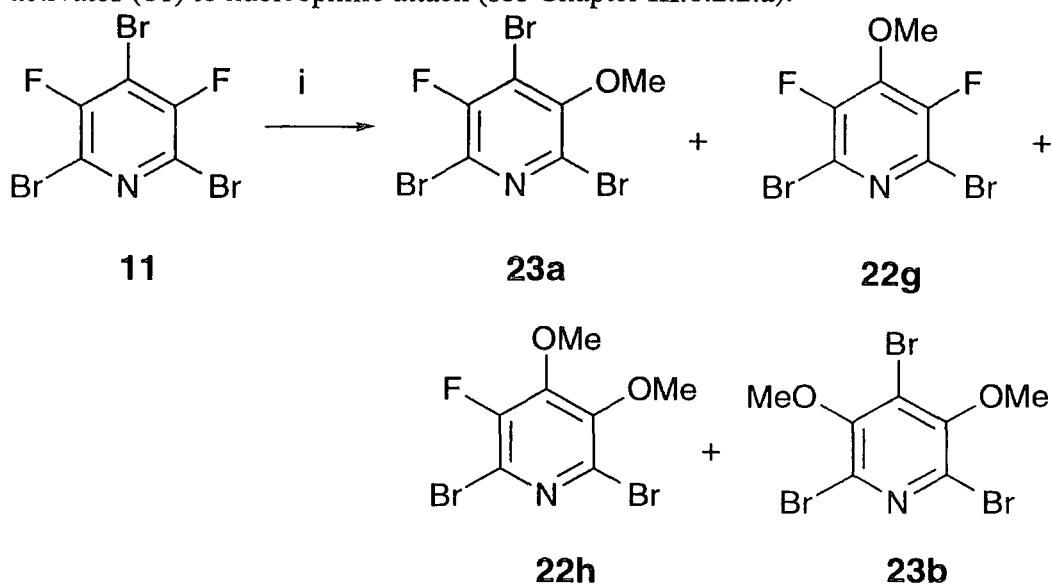
Reagents and conditions; i, LiOMe, MeOH, 67 h, RT

Surprisingly, reaction of (11) with lithium methoxide gave a different range of products when compared to the reaction of (11) with sodium methoxide. Significant quantities of

2,6-dibromo-3,5-difluoro-4-methoxypyridine (22g, 19%) and 2,6-dibromo-3-fluoro-4,5-dimethoxypyridine, (22h, 5%) were obtained, along with (23b, 39%) and (23a, 36%) as determined by GCMS. Another reaction of (11) with lithium methoxide was performed, except that a two fold excess of 12-crown-4 was added to the reaction mixture and this time a different ratio of products was obtained, which are shown below (and the results for the reaction of (11) with sodium methoxide are added for comparison).

Reagent	Product (%)		
	3-attack		4-attack
LiOMe	23a (36)	23b (39)	22g (19)
LiOMe/ 12-Crown-4	23a (71)	23b (18)	22g (9)
NaOMe	23a (100)	-	-

If the minor product (22h) is ignored and a comparison of the ratio of 3-attack to 4-attack is considered, it may be concluded that when lithium methoxide alone was used, 3-attack was favoured over 4-attack in a ratio of 4:1, yet in the presence of 12-crown-4, the ratio was 8:1. Thus, the presence of Li^+ encouraged 4-attack.
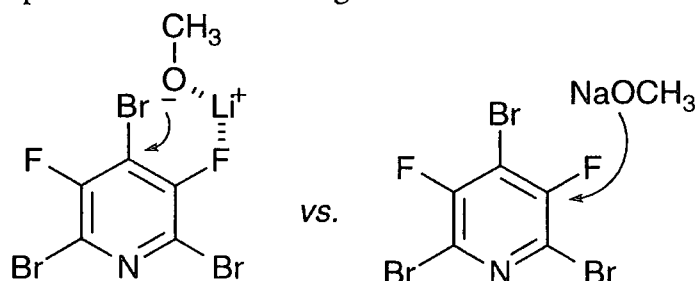
A likely explanation for this result may be deduced if the interaction between Li^+ and fluorine is considered. Co-ordination of Li^+ to a lone pair on fluorine encouraged 4-attack, but when this was hindered (by the complexation of Li^+ by 12-crown-4), 3- attack predominated, as would be expected for a hard nucleophile (which is what is observed for sodium methoxide).

The product mixture for the reaction of (11) with lithium methoxide was purified by column chromatography giving (23b) and a pure mixture of (23a and 22g). Pyridines (23a and b) were identified by comparison of their GCMS and fluorine nmr spectra with characterised samples, however, (22g) was not readily isolated because attempts to purify the mixture of (23a and 22g) by preparative GC failed. Hence a carbon nmr spectrum of the mixture (23a and 22g) was obtained. Due to overlapping of the resonances, C-4 of (22g) was not observed, however, C-2 showed the characteristic four lines of an X part of an ABX system at 123.2 ppm, which is typical for these symmetrical 3,5-difluoropyridines and a large doublet (J 262 Hz) at 147.9 ppm is consistent with C-3 bound to fluorine. Compound (22h) was not isolated, however its GCMS data which showed a characteristic two bromine isotope pattern is consistent with the structure (22h).

IV.2.2   2,4,6-Tribromo-5-fluoropyrimidine

Tetrafluoropyrimidine is more reactive than pentafluoropyridine towards nucleophiles[97], thus 2,4,6-tribromo-5-fluoropyrimidine (13) may be expected to be more reactive than (11) towards nucleophiles. Tetrafluoropyrimidine has been shown to react with a variety of nucleophiles, giving attack at the 4-, 6- and then 2- positions. Hence, a nucleophile attacks *para* (and *ortho*) to nitrogen.

Results for the reaction of (11) with nucleophiles suggested that (13) might react in a similar manner and we anticipated that (13) would react with hard nucleophiles to displace fluorine, and soft nucleophiles to displace bromine.

We reacted (13) with piperidine (soft nucleophile) and sodium methoxide (hard nucleophile).

13   **13a**
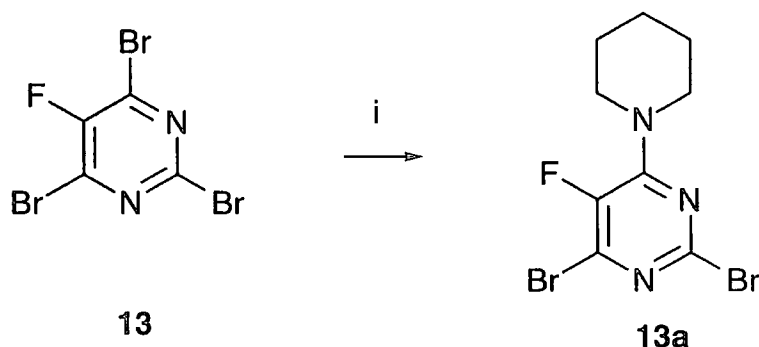
Reagents and Conditions ; i, Piperidine (2 equiv.), MeCN, 88 h, Reflux

Displacement of bromine, rather than fluorine from (13) by piperidine was deduced from consideration of its mass spectrum (which showed an isotope pattern of three lines typical of a molecule containing two bromine atoms), its fluorine nmr spectrum (which gave a single resonance) and its carbon nmr spectrum, which gave four signals in the region expected for pyrimidine carbon atoms. C-5 was readily identified as the resonance at 142.4 ppm, due to large one bond coupling to fluorine (^1J 259 Hz). 4-C(Br) was assigned to the doublet (^2J 24.8 Hz) at 137.4 ppm due to coupling with adjacent C-F. Similarly, the carbon bonded to the piperidine group (C-6) was assigned to the lower field shift at 151.4 ppm, which was also a doublet (^2J 6.5 Hz) due to splitting with an adjacent C-F. C-2 was assigned to the singlet at 142.9 ppm since it would be anticipated that carbon *ortho* to two ring nitrogens would be shifted to lower field. The piperidine carbon atoms were assigned by comparison with the chemical shifts of the free base.

13   **13b**
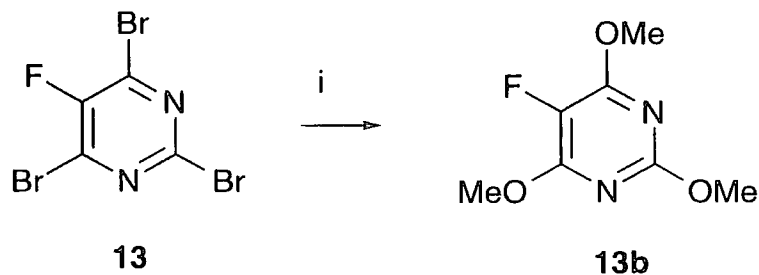
Reagents and Conditions; 9 NaOMe in MeOH, RT 15 h.

81

The formation of the trimethoxy derivative (13b) was identified by comparison of fluorine nmr spectrum, which gave a singlet (-185.4 ppm) as compared with literature[97] data (-110.7 ppm*). Its mass spectrum gave no bromine pattern (thus all the bromine atoms had been displaced) and its carbon nmr, which gave three aromatic resonances due to the symmetrical pyrimidine skeleton.

Thus, both piperidine and sodium methoxide displaced bromine, giving 4-piperidino-2,6-dibromo-5-fluoropyrimidine (13a) and 2,4,6-trimethoxy-5-fluoropyrimidine (13b). Thus, attack is determined by nitrogen in the heterocyclic ring and not the hardness or softness of the nucleophile and bond under attack.

*This chemical shift quoted is -110.7 ppm and is referenced to trifluoroacetic acid (which has a chemical shift of 76.5 ppm relative to $CFCl_3$). Correction to the normal standard of $CFCl_3$, would give a chemical shift of -187.2 ppm.

IV.2.3   2,3-Dibromotetrafluoroquinoxaline

In view of the exclusive displacement of bromine from (13) by both hard and soft nucleophiles, we anticipated that (15) would also react with nucleophiles to give displacement of bromine.

15 → **15b**
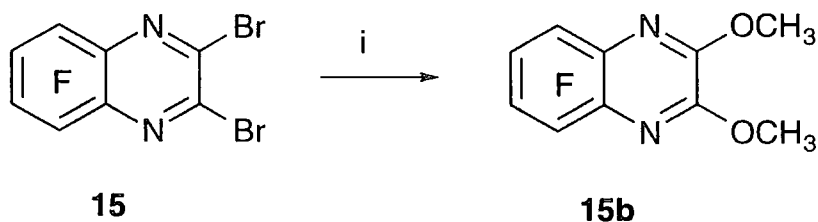
Reagents and conditions; i, LiOMe (1 equiv.), MeOH, RT

15 → **15a**
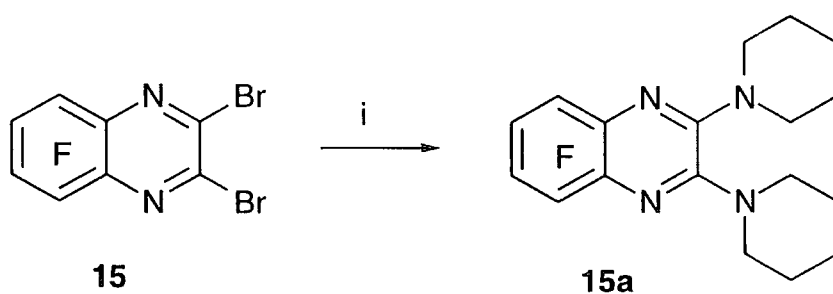
Reagents and conditions; i, Piperidine, MeCN, reflux

Indeed, predictions proved to be correct and both hard (lithium methoxide) and soft (piperdine) nucleophiles displaced bromine giving (15b) and (15a). Evidence for the formation of (15a and b) was provided by the mass spectra, which showed no bromine pattern, thus bromine had been displaced. Fluorine nmr confirmed that the ring fluorines were intact since both derivatives (15a and b) gave two resonances of equal intensity. The carbon nmr spectra for the quinoxaline derivatives were also consistent with the

symmetrical structure and the method for assigning the signals was analogous to the procedure used for 5,6,7,8-tetrafluoroquinoxaline (see Chapter III). Thus, (15) behaved the same as (13) and nucleophilic attack was determined by the orienting effect of the ring nitrogens.

IV.2.4 Conclusion

Nucleophilic substitution of 2,4,6-tribromodifluoropyridine (11) gave unexpected results: hard nucleophiles displaced fluorine and soft nucleophiles displaced bromine. However, reactions of 2,4,6-tribromo-5-fluoropyrimidine (13) and 2,3-dibromotetrafluoroquinoxaline (15) with nucleophiles gave "normal" substitution patterns and both hard and soft nucleophiles displaced bromine at positions *ortho* and *para* to ring nitrogen.

It is well known that ring nitrogen is strongly activating for reactions of nitrogen containing heterocycles with nucleophiles and the behaviour of (11), (13) and (15) may be explained by considering the effect of ring nitrogen, as well as the effect of fluorine.

Thus, because ring nitrogen *para* and *ortho* to attack is activating (to the magnitude of 2.3×10^5 and 6.2×10^4 as compared to C-H^{100}), we would expect the relative reactivity of the heterocycles (11, 13 and 15) to be (13) > (15) > (11) and we would expect nucleophiles to react with (11, 13 and 15) to displace bromine, i.e., at positions *ortho* and *para* to nitrogen. Indeed, this is the case for (13 and 15).

However, when the activating influence of fluorine becomes more important than ring nitrogen, the situation changes. This situation occurs in the reaction of (11) with nucleophiles and because (11) contains only one ring nitrogen, (11) is less reactive compared to (13 and 15). So when (11) reacts with *hard* nucleophiles, the interaction between the *hard* carbon-fluorine centre and the nucleophile is the dominating influence and attack occurs to displace fluorine. On the other hand, when this *hard-hard* interaction is poor (i.e., in the case of reaction of (11) with *soft* nucleophiles), the dominating influence is that of ring nitrogen, which leads to displacement of bromine at the 4- and 2-positions.

Metal Mediated Reactions of Bromofluoro-heterocycles

The synthesis and reduction of a range of bromo substituted fluoroheterocycles were described in chapter III.

The abundance of bromine in the now readily-available bromofluoroheterocycles (2,4,6-tribromo-3,5-difluoropyridine, 2,4,6-tribromo-5-fluoropyrimidine and 2,3-dibromotetrafluoroquinoxaline) suggested that these systems would be particularly attractive in the field of metal mediated chemistry.

Thus, reactions involving palladium, lithium and other metals were of interest and a review of the chemistry involving metal mediated reactions of fluoro-substituted aromatics and heteroaromatics will be presented.

V.1 Palladium Mediated Coupling Reactions

The palladium catalysed arylation or alkenylation of alkenes was discovered by Heck[154] in the late sixties and since this initial report, the reaction has been extended to amongst others, the coupling of aryl halides with alkynes. For a review of the Heck reaction, see deMeijere[155].

Heck Reaction

$$R'—X \quad + \quad \diagup\!\!\!\!= R'' \quad \xrightarrow{Pd(0)} \quad R'\diagup\!\!\!\!=\!\!\!\diagup R''$$
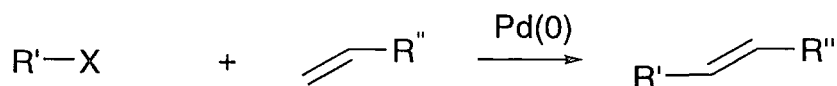
R'= alkenyl, aryl
R"= aryl, alkyl, alkenyl
X= Cl, Br, I, N_2^+, OTf

**Associated Palladium Mediated Coupling Reaction
of Aryl Halide and Alkyne**

$$R'—X \quad + \quad \equiv\!\!-R'' \quad \xrightarrow{Pd(0)} \quad R'—\!\!\equiv\!\!—R''$$
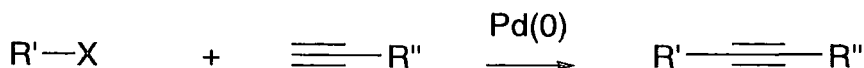
The mechanism is believed to involve oxidative addition of the aryl halide to a Pd(0) catalyst, generating a σ-aryl palladium complex. In the next step, an alkene (or alkyne) molecule is co-ordinated, then inserts into the σ-aryl palladium bond. Elimination of palladium hydride occurs and the coupled product is formed.

-HX

Base

Pd(PPh$_3$)$_2$

R'—X
oxidative
addition

H-Pd(PPh$_3$)$_2$-X

R'-Pd(PPh$_3$)$_2$-X

R'——R"

R'   Pd(PPh$_3$)$_2$X

R"

H   R"

syn-
elimination

syn-
insertion
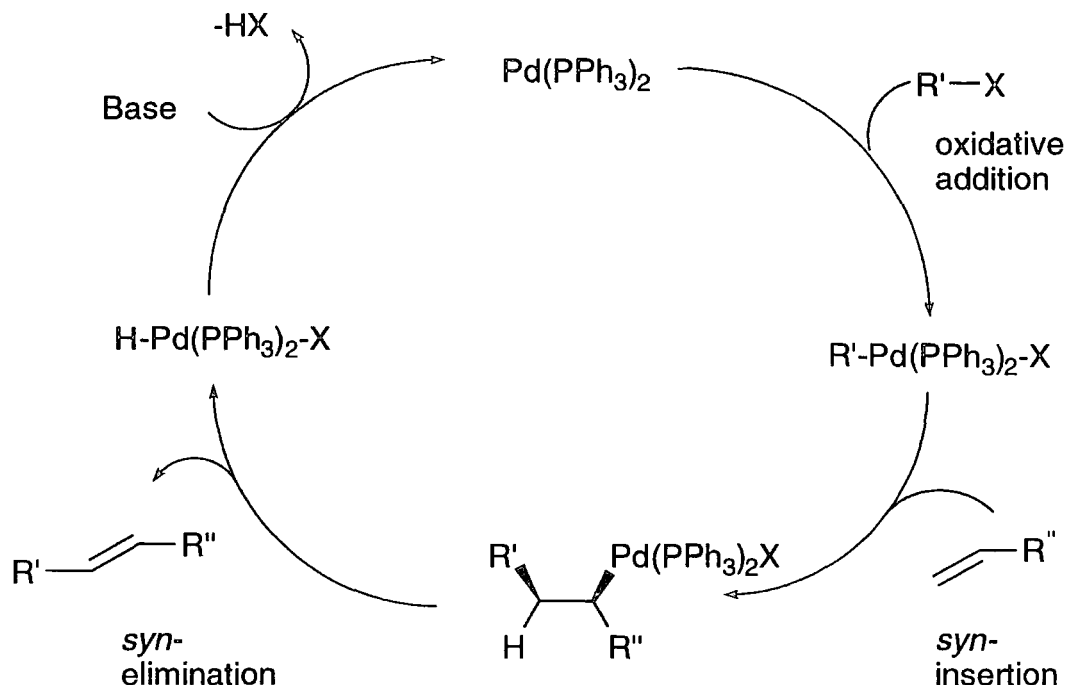
The nature of the leaving group, X, is important since oxidative addition of palladium (O) to the haloarene is considered to be the rate limiting step[155]. In most circumstances, X is a halogen (ArI > ArBr >> ArCl), although diazonium salts, hydroxy arenes and perfluoroalkylsulphonate derivatives of hydroxy arenes may find application[155].

V.1.1   Highly Fluorinated Aryl Halides and Alkynes

Despite the proliferation of reactions involving palladium mediated coupling of aryl and hetaryl halides with alkynes (for a review see Sonagashira[156] and Undheim[157]), coupling of highly fluorinated aryl halides with alkynes and alkenes is scarce, however, some reactions are documented.

Wen[158] showed that pentafluoroiodobenzene coupled with a range of alkynes in good yield.

I

F   +   H———R

(PPh$_3$)$_2$PdCl$_2$

Cul, Et$_3$N

R

F   78-95%

R= Ph, SiMe$_3$
p-NO$_2$C$_6$H$_4$
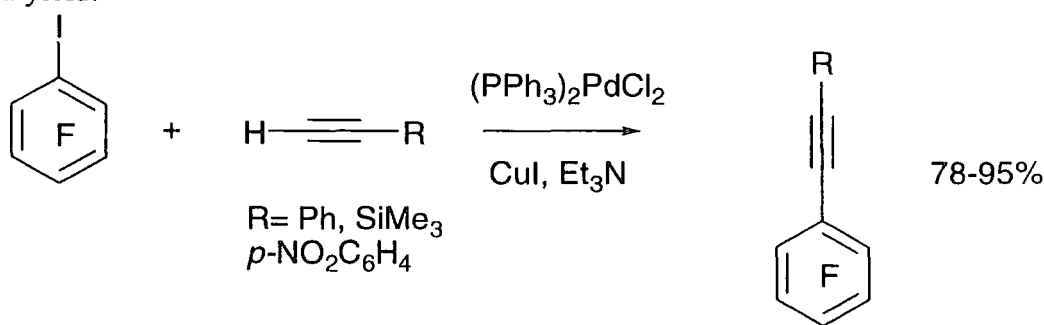
Whitesides[159] found that both 1,4-diiodotetrafluorobenzene and 1,3-diiodotetrafluorobenzene coupled with trimethylsilylethyne giving 1,4- and 1,3-disubstituted tetrafluorobenzenes.

85
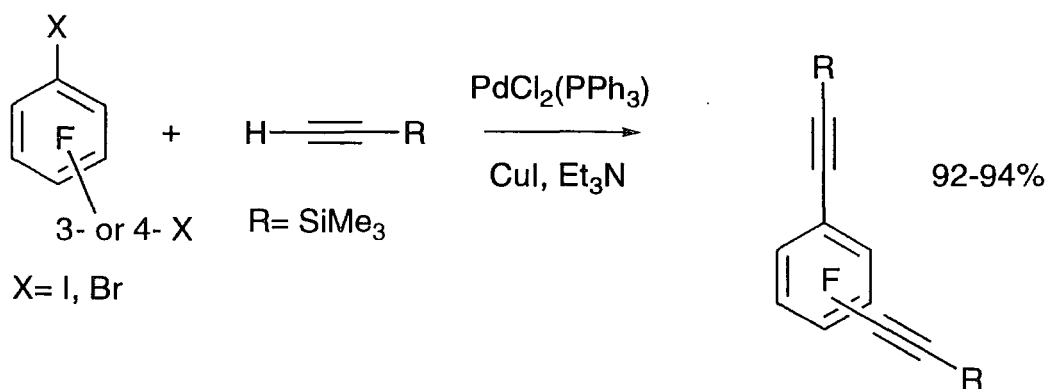
A convenient route to polyfluoroarylsubstituted alkynes has been provided by Chen[160], who coupled polyfluorophenols with alkynes *via* polyfluorophenol perfluoroalkanesulphonates.

X= F, Cl
R_F= CF_3, $CF_2HCF_2O(CF_2)_2$
R= $SiMe_3$, Ph, C_4H_9
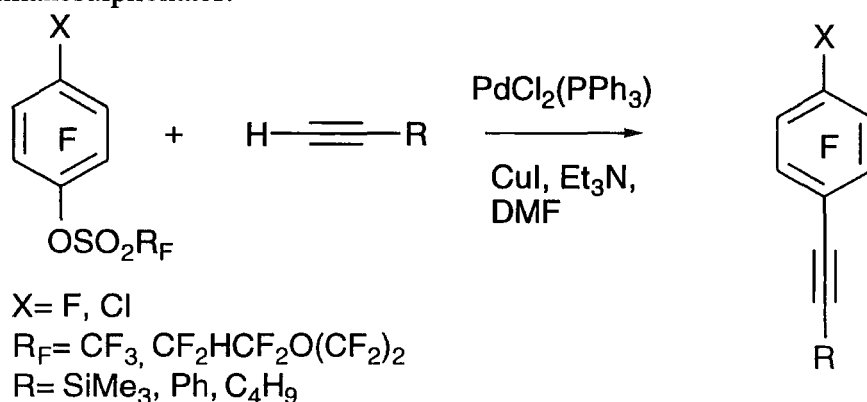
The mechanism is believed to follow the oxidative addition-elimination process outlined in part V.1, however, a charged intermediate is believed to be involved in the reaction pathway.
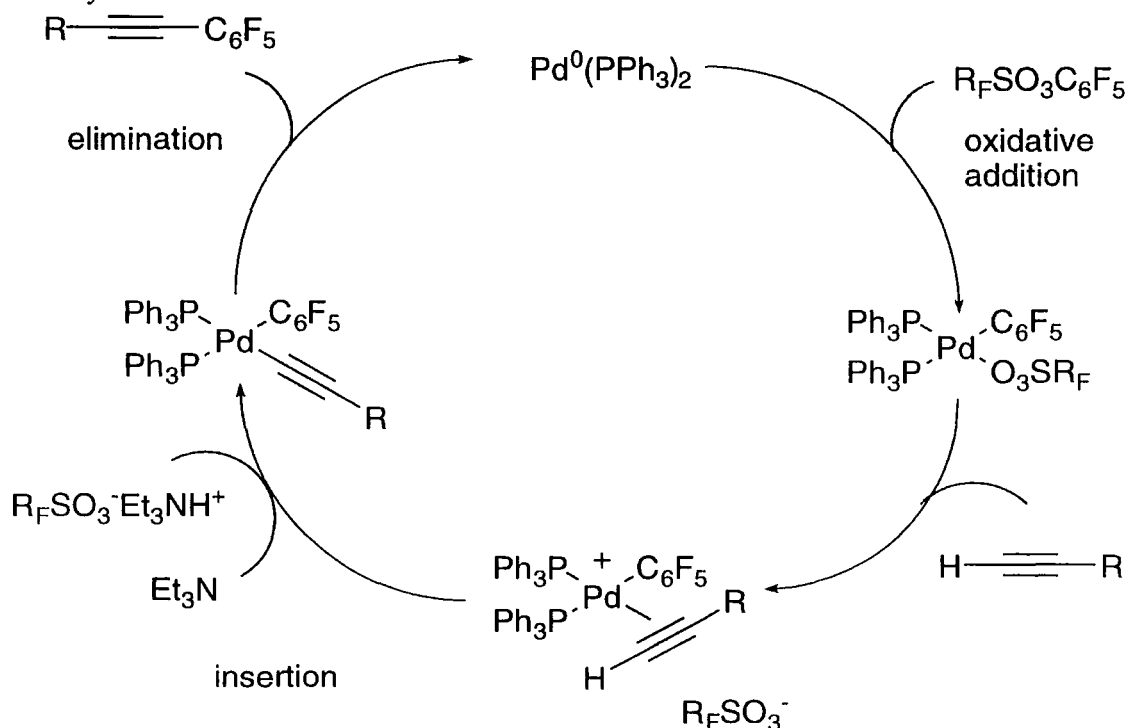
Interestingly, a comparison of the reactivity of polyfluorophenyl perfluoroalkanesulphonate with the non-fluoro analogue indicated that the fluorinated

86

phenol was more reactive. Chen attributed this difference to the stability of perfluorophenylpalladium bromide, with respect to the non-fluoro analogue.

V.1.2   Non-Fluorinated Heteroaromatic Halides

Palladium mediated coupling of alkynes to non-fluorinated aryl and hetaryl halides has been the subject of much attention and numerous examples exist, and a number of positions undergo substitution.

V.1.2.a   Pyridine Trimethylsilylacetylene (TMSA) couples with 2,6-dibromopyridine[161] and 2,5-dibromopyridine[162] to give replacement of all bromines, and it is interesting to observe that for 2,5-dibromopyridine, that the 2-position is more reactive than the 5- position.

$R = SiMe_3$
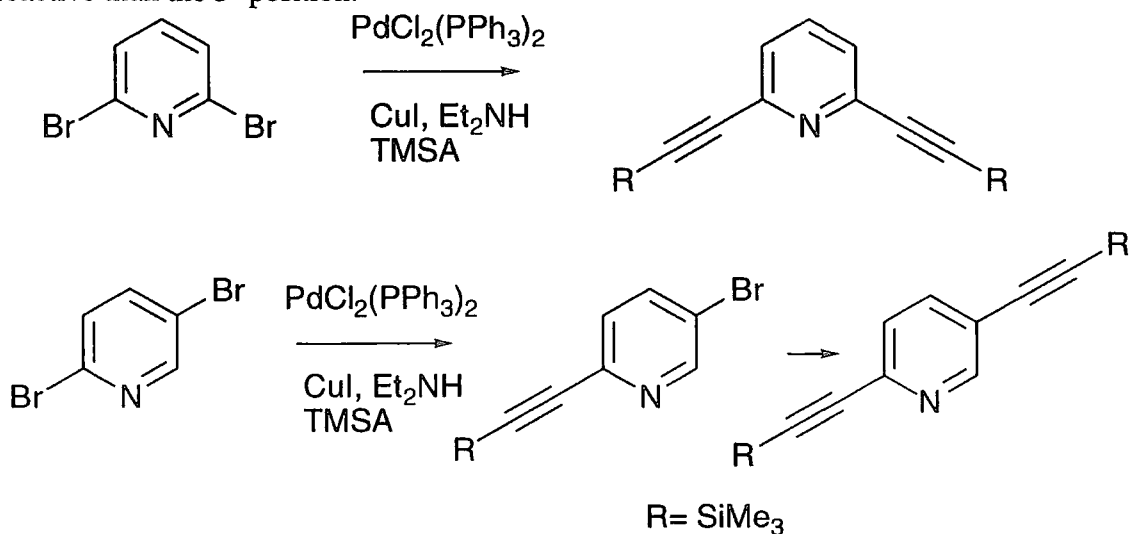
3-Trifluoromethyl-5-chloro-6-iodopyridine[157] shows complete selectivity for the 6-position, arising from the greater lability of C-I over C-Cl.
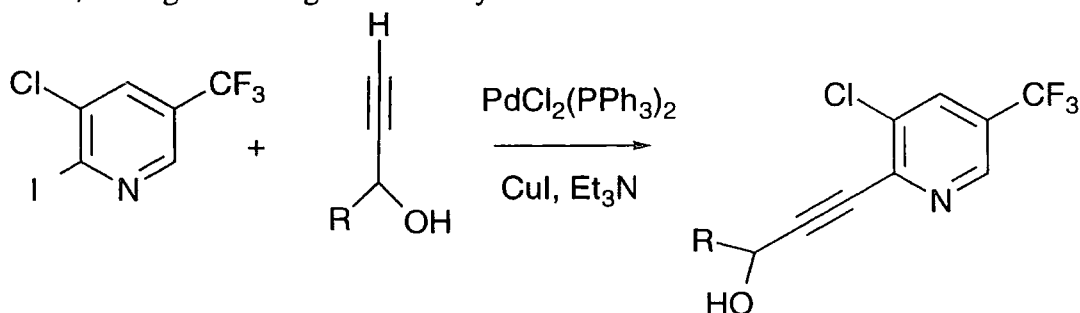
The 4-position of pyridine is also reactive and coupling between 3-cyano-4-chloropyridine[163] TMSA was accomplished.

87
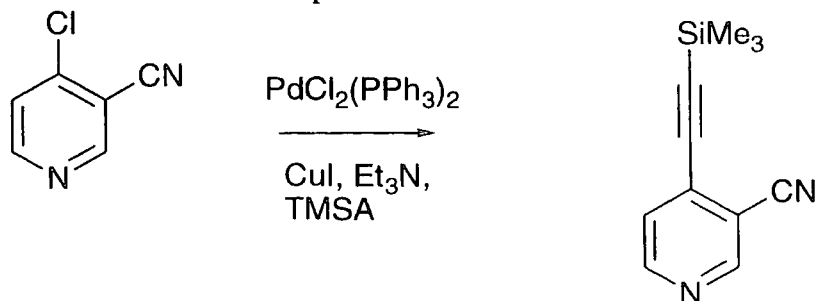
V.1.2.b **Other Heterocyclics** The palladium mediated coupling reaction is very general and may be applied to a wide variety of heterocyclic systems, for example, a 2-bromopyrazine derivative readily coupled with alkynes[164].

R= Ph, alkyl
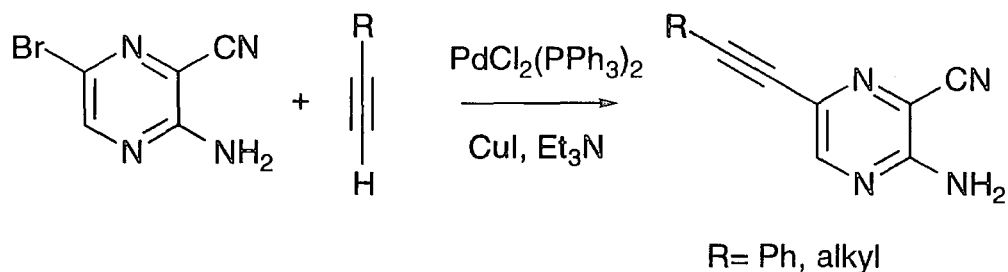
All positions (2-, 4-, 5- and 6-) on pyrimidine appear to be reactive[157] and an example of the coupling of a 4,6-diiodo pyrimidine was given by Edo[165], who coupled 2-methyl-4,6-diiodopyrimidine with butyl- and phenyl-acetylene.

R= Ph, alkyl
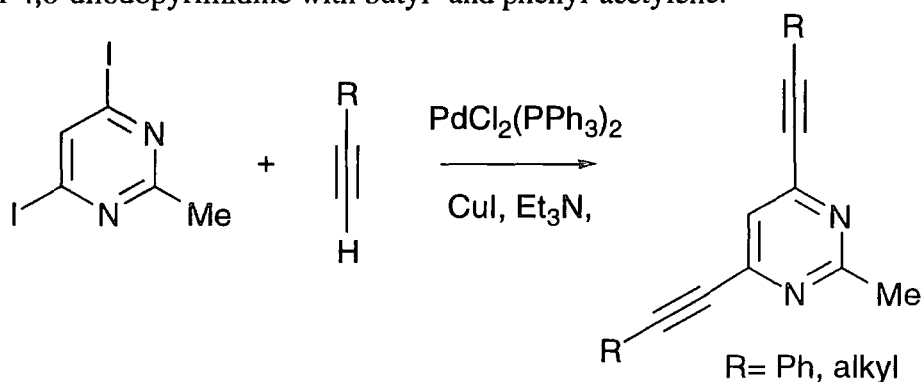
The readily available 2,3-dichloroquinoxaline was shown[166] to react under coupling conditions, although addition of dimethylsulphoxide (DMSO) was required for synthesis of the bis acetylene.
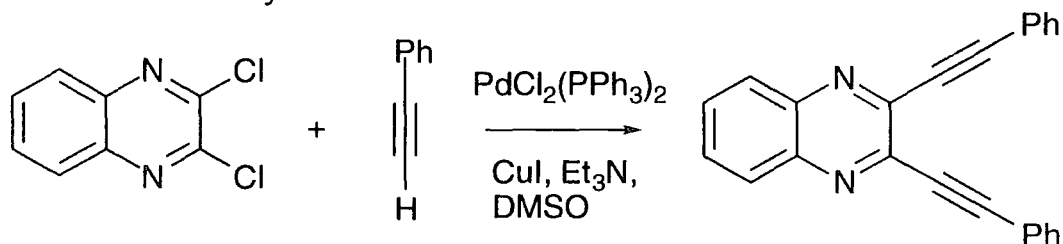
V.1.3 **Other Polyhalo Systems** Both hexabromo- and hexaiodo-benzene were able to undergo a palladium mediated coupling reaction with alkynes to give replacement of all six halogens giving the unusual hexa-alkynyl benzene[167].
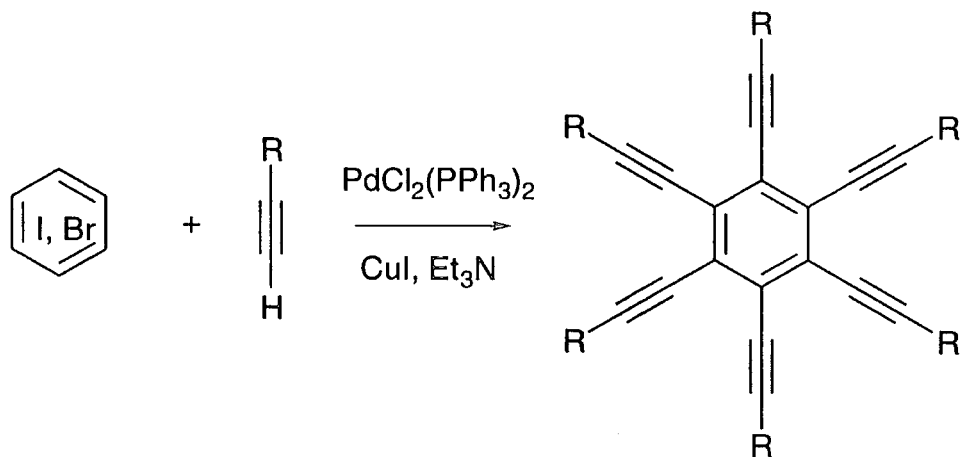
V.2 Lithium Derivatives of Fluoro-Substituted Aromatic Systems

V.2.1 Bromofluoroheterocycles

Reaction of lithium with 4-bromotetrafluoropyridine gave the 4-lithio pyridine[168]. The mechanism presumably involves electron transfer from lithium to the heterocycle, followed by loss of bromide ion.
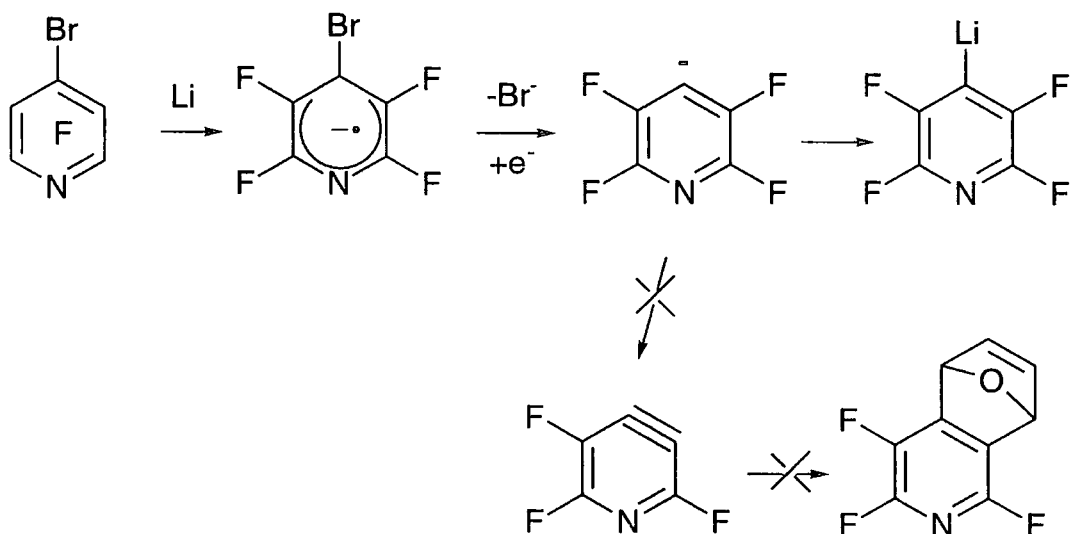
Interestingly, the 4-lithio salt was stable and failed to loose lithium fluoride (and hence no pyridyne) since trapping experiments with furan gave no adduct.

The 4-lithio salt was also prepared[169] *via* reaction of 4-bromotetrafluoropyridine with butyl lithium, and the 4-aldehyde was made by reaction of 4-lithiotetrafluoropyridine with N-methylformanilide. Here, the formation of the 4-lithio compound may be explained by nucleophilic attack at bromine.
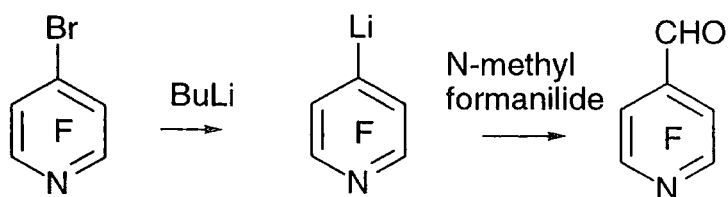
Reaction of 2-fluoro-3-bromopyridine with butyl lithium led to different products, which were dependent on the conditions employed[170]. Whilst short reaction times gave metal-

halogen exchange and hence the 3-substituted product, warming the 3-lithio salt led to 3-products.
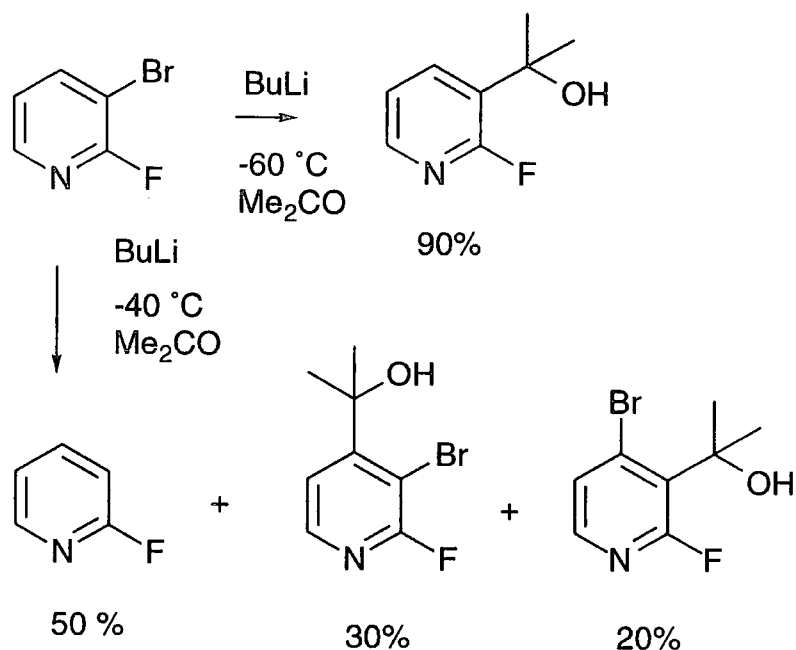
Workers[170] attributed these findings to a series of exchange reactions which are outlined below.
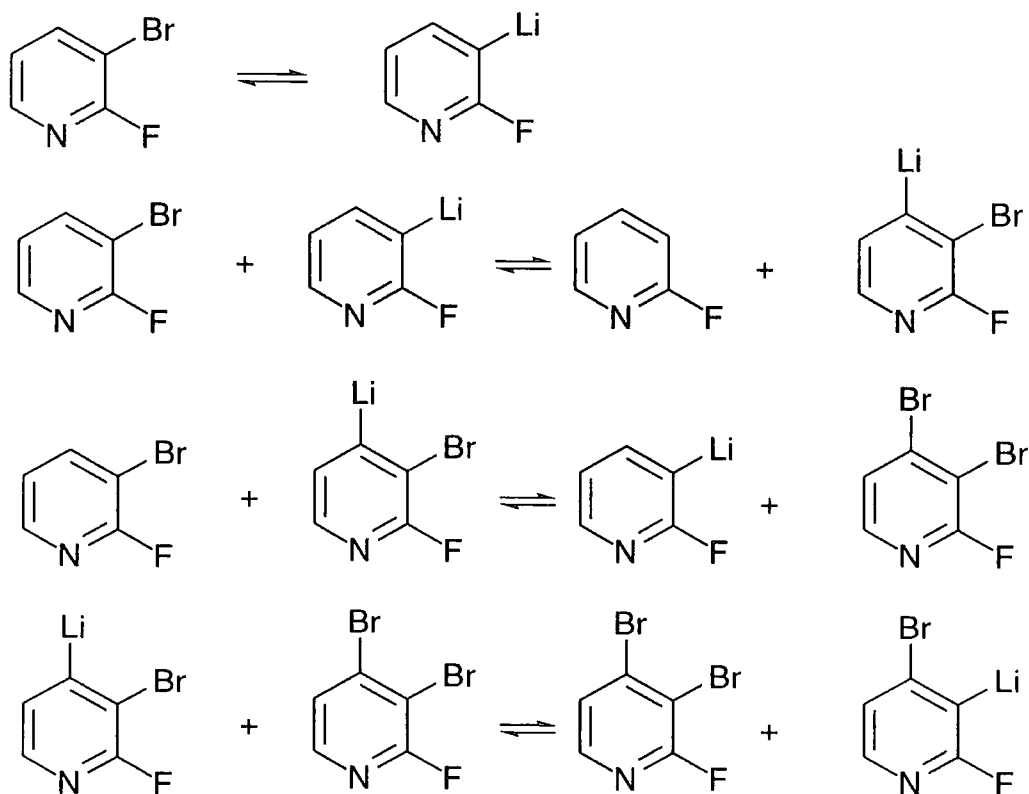
V.2.2   Bromofluorobenzenes Coe[171] observed that reactions of bromofluorobenzenes with metallating agents were very sensitive to the type of solvent and reagent employed. For instance, 2,4-difluorobromobenzene reacted with lithium diisopropylamine (LDA) in THF to give metal hydrogen exchange and hence the 3-lithio-

2,4-difluorobromobenzene, but using butyl lithium in ether gave metal-halogen exchange and the 2,4-difluorolithiobenzene.
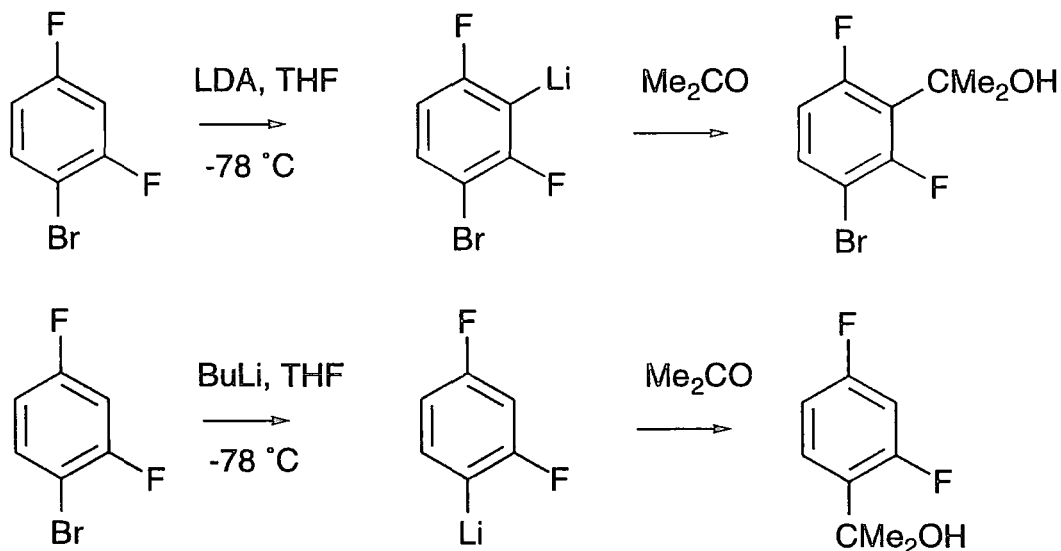
The results were believed to be due to the basic and nucleophilic properties of the metallating agent. LDA, a hindered, non-nucleophilic base, removes the most acidic proton (*i.e.*, the proton flanked by two fluorines), but butyl lithium, a nucleophilic reagent, attacks bromine in a halophilic type reaction giving the 1-lithio salt. Alternatively, the results may be explained by the harder base, LDA, preferring to attack the harder C-H functionality, whereas the softer base, BuLi, prefers to attack the softer C-Br functionality.

V.2.3   **Fluoroheterocycles** The preparation of lithium derivatives of fluoroheterocycles is of interest as a method of functionalising heterocycles and has been discussed in reviews by French workers[170, 172].

The highly fluorinated system, 2,4,5,6-tetrafluoropyridine underwent lithium hydrogen exchange with butyl lithium and reaction with carbon dioxide gave access to a fluorinated nicotinic acid[93].
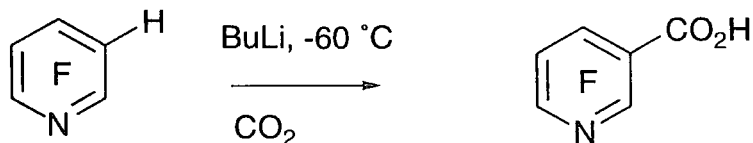
The reactions are often sensitive to reagents and conditions used, thus whilst metallation of 3-fluoroquinoline with butyl lithium led to attack at the 2-position and the formation of the 2-hydro derivative, metallation with LDA led to lithium hydrogen exchange at the 4-position[173].
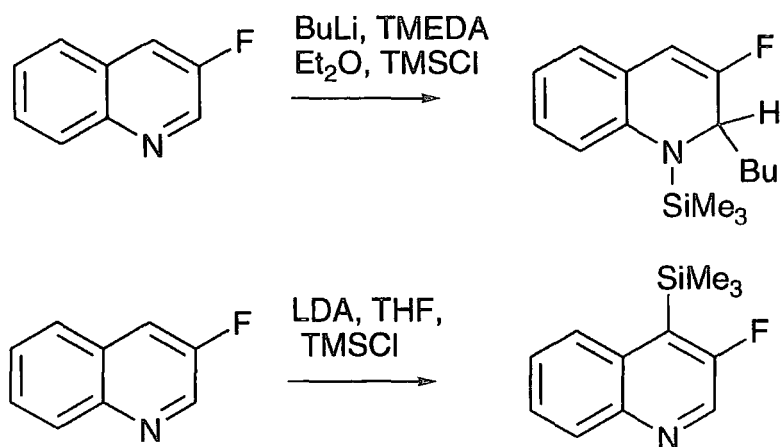
Solvents alone, may affect orientation of metallation and 3-fluoropyridine reacted with butyl lithium in ether giving mainly the 2-isomer (the kinetic product), but using THF gave only the 4-isomer (the thermodynamic product)[174].

Interestingly, both the 2- and 4- lithio salts formed the 3-pyridyne on heating to room temperature and reacted with furan to afford the adduct.

20%

Et$_2$O   10   65%

THF   50   0%
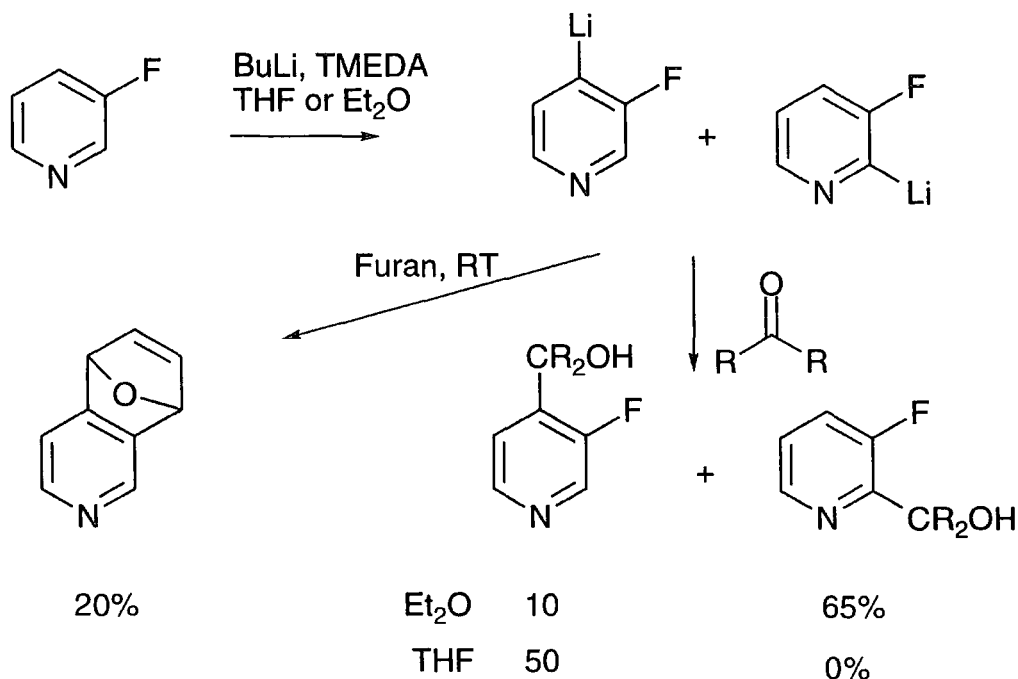
Heterocyclic ring systems even more electron deficient than pyridine react giving lithio salts and 2,4-difluoropyrimidine reacted with LDA giving the 5-lithio salt[175], which gave a keto pyrimidine derivative.

92
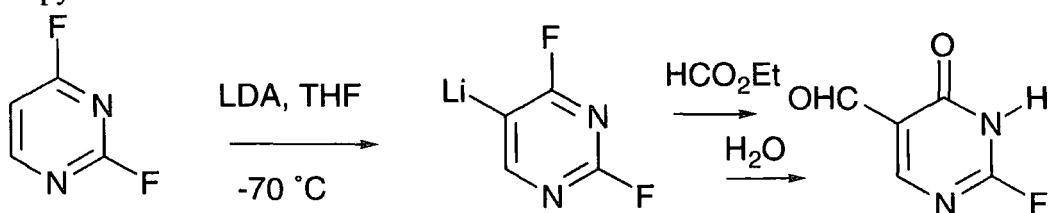
Magnesium, Zinc and Copper Derivatives of Fluoro Substituted Heterocycles

4-Bromotetrafluoropyridine may be used as a synthetic building block for the preparation of magnesium, zinc, cadmium and copper derivatives of fluoroheterocycles. Reaction of ethyl magnesium bromide with 4-bromotetrafluoropyridine gave the 4-magnesium bromide derivative[176]
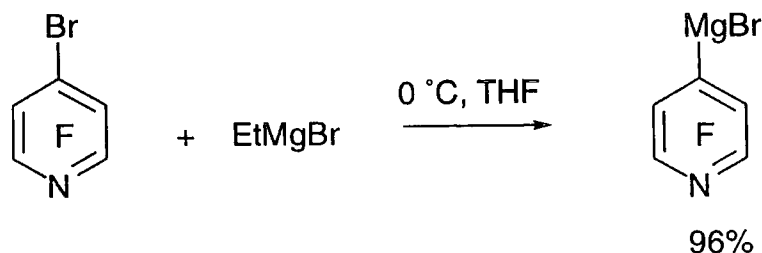
and other workers have demonstrated that the corresponding copper[177, 178], zinc[178] and cadmium[178] derivatives may be prepared from this reagent and a range of 4-substituted tetrafluoropyridines have been synthesised using this methodology.
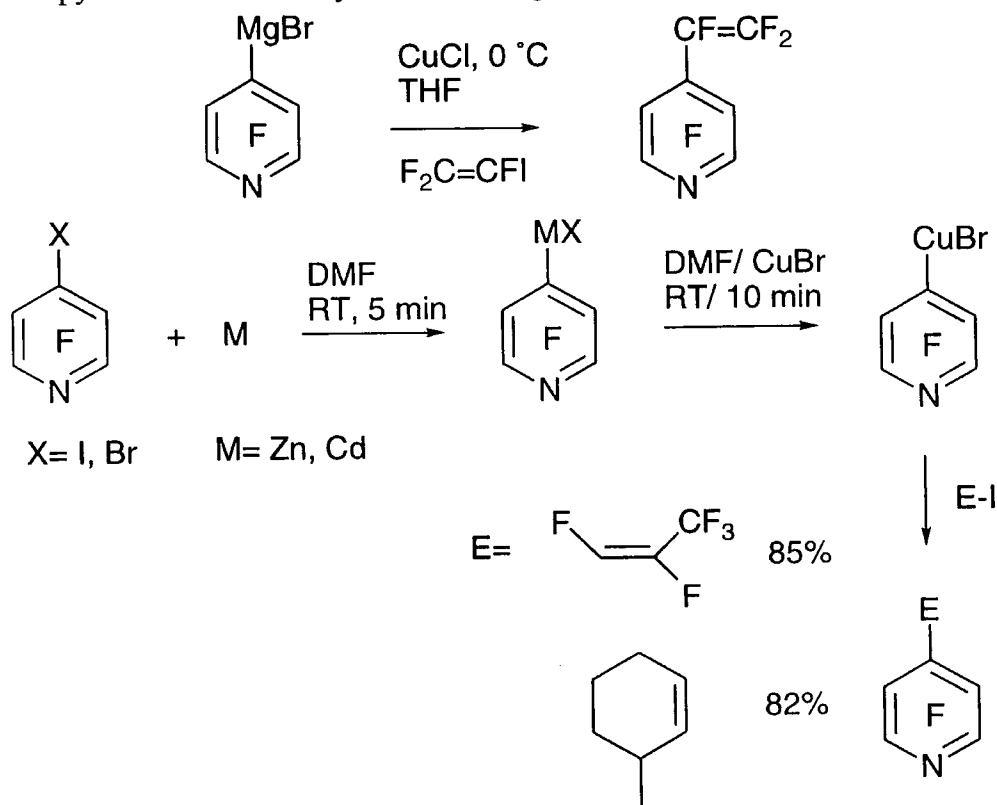
German workers[179] synthesised the 4-zinc and copper derivatives *via* pyrolysis of the zinc and copper salts of 2,3,5,6-tetrafluoronicotinic acid and observed the high stability of the zinc derivatives.

M= Zn, Cu
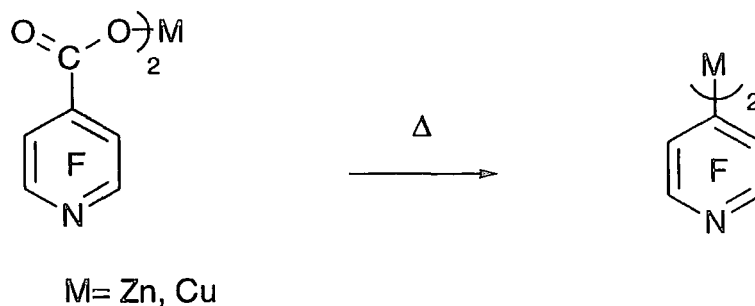
V.4   Conclusion

Bromo substituted aromatic systems react well in a range of metal mediated reactions. It was of particular interest to discover whether 2,4,6-tribromo-3,5-difluoropyridine, 2,4,6-tribromo-5-fluoropyrimidine and 2,3-dibromotetrafluoroquinoxaline would participate in palladium mediated reactions with alkynes. Zinc and lithium derivatives of fluoro and bromofluoroheterocycles were also of interest and will be discussed.

V.5.1   2,4,6-Tribromo-3,5-difluoropyridine We were interested to discover if 2,4,6-tribromo-3,5-difluoropyridine (11) would undergo palladium mediated coupling reactions with alkynes. The 4- position would be expected to be more reactive than the 2- position, since this is the more electrophilic position and insertion of Pd(0) would be favoured in the 4- C-Br rather than the 2- C-Br bond.
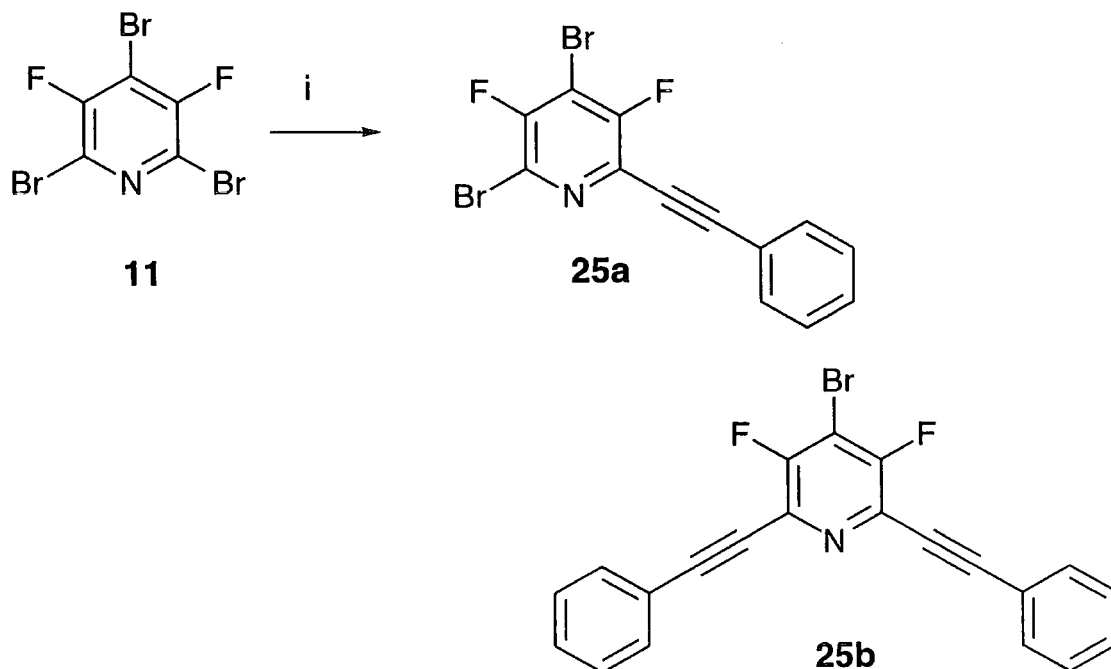
Reagents and conditions; i, Phenyl acetylene (1.8 equivs.), CuI, (Ph₃P)₂PdCl₂, Et₃N, RT, 60 h

Surprisingly, reaction of (11) with phenylacetylene in the presence of a palladium catalyst (PdCl₂(PPh₃)₂) at room temperature gave replacement of bromine by phenylacetylene at the 2- and 6- positions, giving (25a, 38% and 25b, 45%) and a reaction of (11) with a seven fold excess of phenylacetylene gave (25b, 72%).
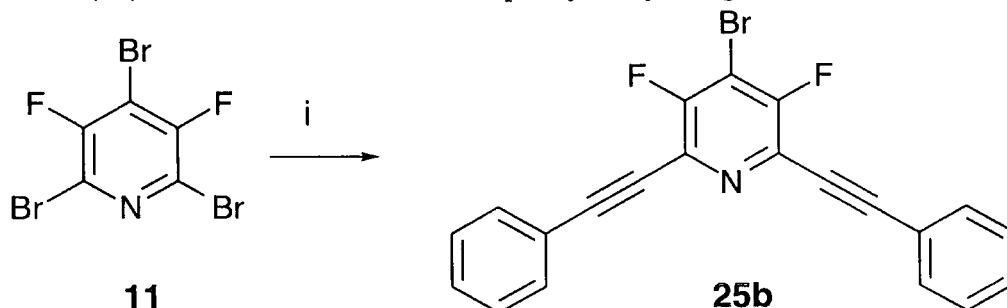
Reagents and conditions; i, Phenyl acetylene (7 equivs.), CuI, (Ph₃P)₂PdCl₂, Et₃N, RT, 88 h
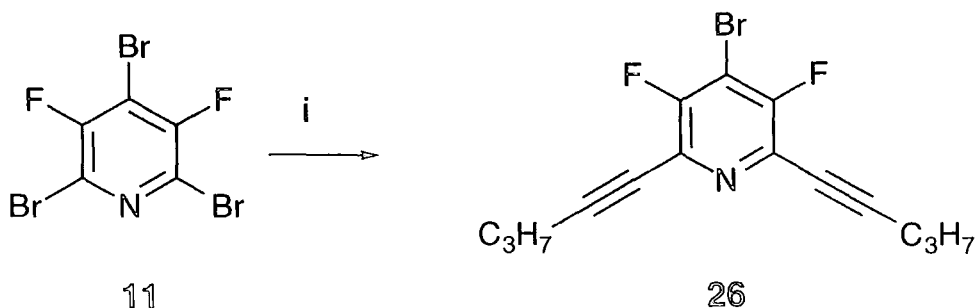
Reagents and conditions; i, 1-Pentyne (2.2 equivs.), CuI, PdOAc$_2$, PPh$_3$, Et$_3$N, RT, 88 h

Reaction of (11) with 1-pentyne also led to the exclusive replacement of bromine at the 2, 6- positions giving (26, 66%).

The preference for substitution of bromine at the 2- position by alkynes was deduced by considering the fluorine and carbon nmr spectra, mass spectra and elemental analyses. Infrared spectroscopy was useful in indicating whether indeed an alkyne had coupled with the pyridine ring (11) because a characteristic band in the region of 2220 cm^{-1} was observed, which is attributable to an alkyne stretch. Mass spectroscopy was vital in indicating how many times bromine had been replaced by an alkyne, thus (25a) gave a characteristic three line, two bromine pattern, whilst (25b and 26) showed only two lines in a ratio of 1:1, which is characteristic of a one bromine pattern[110].
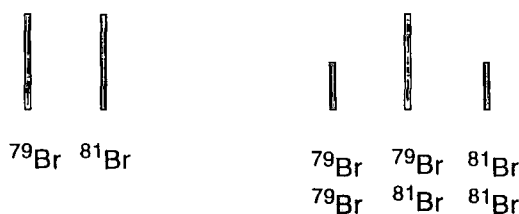
1 bromine pattern   2 bromine pattern

Fluorine nmr spectroscopy indicated whether 2- or 4- attack had occurred, thus displacement of bromine from the 2- position to give (25a) showed two resonances of equal intensity in the fluorine nmr spectrum at -101.3 and -110.4 ppm, whilst displacement from both the 2- and 6- positions to give (25b and 26) showed singlets at -108.2 and -110.5 ppm respectively. The fluorine shifts in the region of -100 to -110 ppm are typical of fluorine atoms at the 3- position in these systems. The carbon nmr spectra for (25a and 26) indicate the symmetry of these structures. Both compounds show almost identical chemical shifts for the pyridine carbon atoms and therefore their spectra will be discussed with respect to (26). C-4 shows a triplet (^{2}J 22.7 Hz) at 108.4 ppm, due to splitting with fluorine atoms at the 3- and 5- positions. C-3 shows a very large one bond coupling with fluorine (^{1}J 269 Hz) and is assigned to a doublet at 156.8 ppm. C-2 shows a characteristic X part of an ABX system at a shift of 128.9 ppm. The carbons atoms for the alkyne group were assigned by comparison with the free alkyne.

Fig. (17). Carbon nmr spectrum of (26)
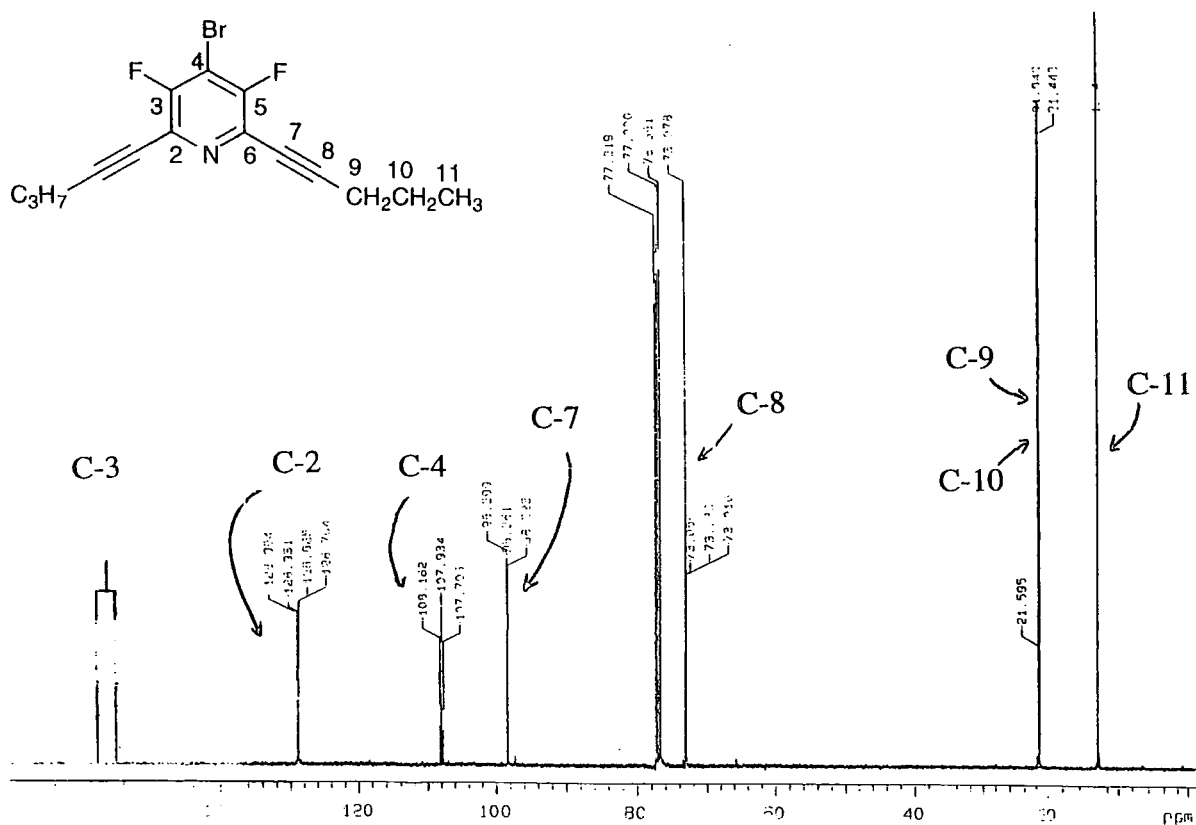
The carbon spectrum for (25a) shows five resonances for the pyridine ring carbon atoms, which would be anticipated for an unsymmetrical structure. Each signal in the spectrum may be readily assigned by its coupling with fluorine atoms and its chemical shift. Thus, C-3 and C-5 may be assigned to the low field shifts at 153 and 157 ppm on the basis of their large one bond coupling with a fluorine (^1J 266 and 267 Hz). C-4 would be expected to show a doublet of doublets due to coupling with fluorine atoms at the 3- and 5- positions, however, a triplet is observed (*i.e.*, the ^2J couplings are comparable) at 109.2 ppm, which is consistent with a carbon atom at the 4- position. The two remaining carbon atoms are attributed to resonances at 123.6 and 128.4 ppm, which both show doublets of doublets. The carbon atoms for the phenyl acetylene group were assigned by comparison with unreacted phenyl acetylene.

97

Fig. (18). Carbon nmr spectrum of (25a)
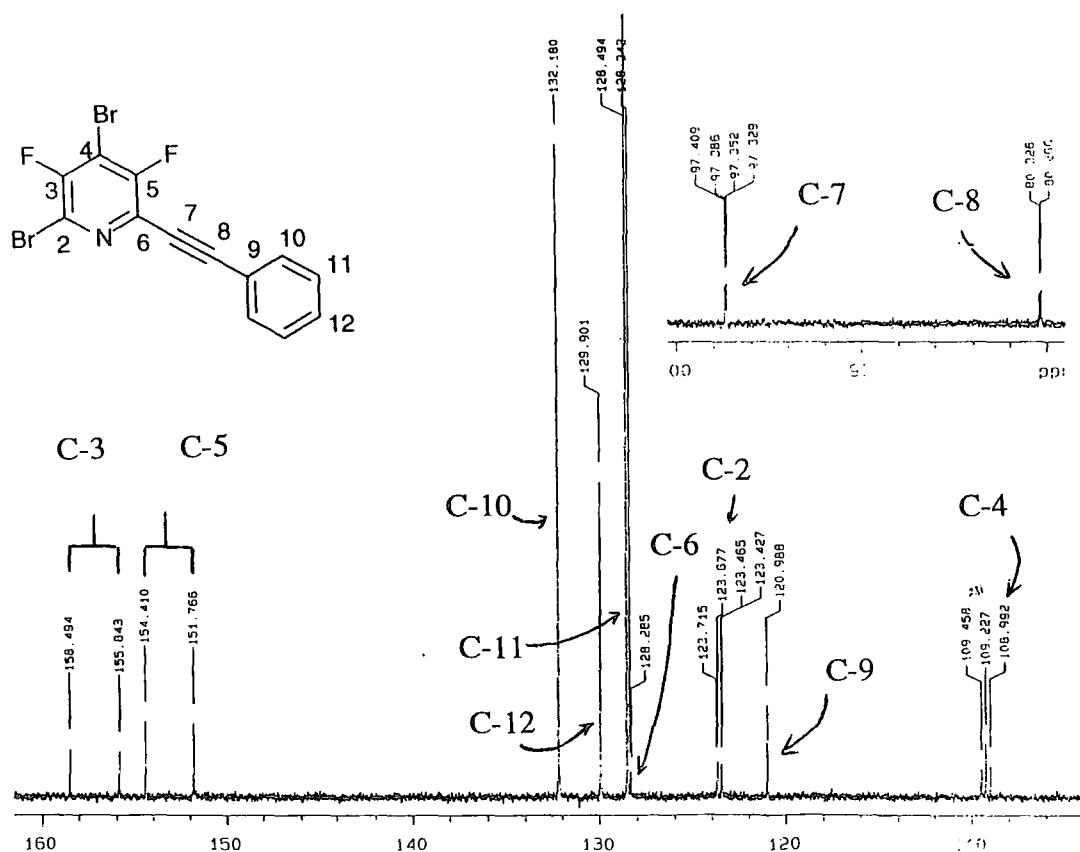
The fact that alkynes substitute bromine at the 2- position rather than the 4- position in (11) may be attributed to either the effect of ring nitrogen or steric factors. Steric factors are unlikely to account for the orientation alone, because it has already been observed (see chapter IV) that bulky nucleophiles such as diethylamine react with (11) at the 2- and 4- positions, however, the 2- position would be expected to less sterically hindered and therefore more favourable for Pd(0) to insert into the C-Br bond than at the 4- position.

Palladium (II) prefers to form four co-ordinate complexes of the type PdL_2X_2, PdL_4^{2+} and PdX_4^{2-}. X is typically a halide, cyanide or thiocyanate and it is interesting to note that fluoro complexes are less prevalent. The ligand L is usually a nitrogen (e.g., ammonia) or heavy atom donor ligand[1].

Thus, taking into consideration these facts which characterise Pd(II) complexes, it is probable that prior to or during oxidative addition of the $Pd(PPh_3)_2$ (0) complex to the carbon-bromine bond, an interaction between ring nitrogen of (11) and palladium occurs, which encourages insertion at the 2- rather than the 4- position.
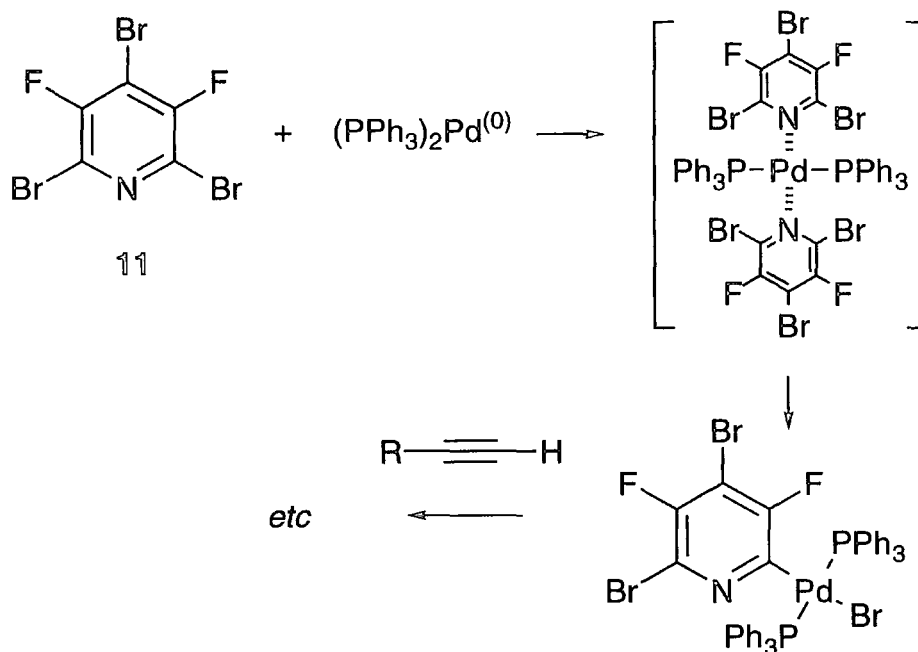
However, a four co-ordinate complex (shown above) is unlikely because the loss of entropy in forming such a complex would more than offset the lowering of the enthalpy term and the interaction probably involves a weak association between (11) and palladium.

V.5.2 **2,4,6-Tribromo-5-fluoropyrimidine** The above result for the reaction of (11) with alkynes suggested that i, systems activated to nucleophilic attack were reactive in palladium mediated reactions and ii, that ring nitrogen had a strong orientating effect for the coupling reaction. Therefore, we anticipated that 2,4,6-tribromo-5-fluoropyrimidine (13), which is very reactive towards nucleophiles (see Chapter IV) and contains C-Br bonds *ortho* to nitrogen, would react well under Pd mediated coupling reactions.
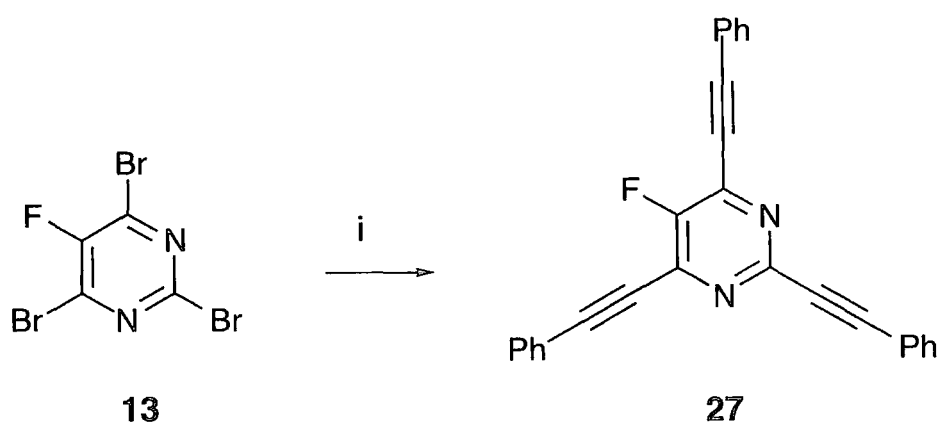
Reagents and conditions; i, Phenyl acetylene (7 equivs.), CuI, (Ph3P)2PdCl2, Et3N, RT 15 h, 37 °C 3 h

Indeed, (13) was very reactive and a reaction of an eight fold excess of phenyl acetylene with (13) under the same conditions as for the reaction of (11) with alkynes gave substitution of bromine from the 2-, 4- and 6- positions, although analysis of the

99

crude mixture by fluorine nmr indicated the presence of the 2,4- coupled product and slight warming was required to obtain higher conversion to the trisubstituted pyrimidine (27). However, only (27, 33%) was recovered following column chromatography. The low isolated yield of (27) may be due to the product adsorbing onto the silica gel.

Identification of (27) was achieved by IR, mass and nmr spectroscopy and elemental analysis. A band at 2217 cm-1 in the IR spectrum is typical of an alkyne stretch and the elemental analysis and mass spectrum (which showed no bromine pattern) were correct for the structure. The fluorine nmr spectrum showed a singlet at -125.09 ppm and the proton nmr spectrum showed two multiplets at 7.67 and 7.43 ppm in a ratio of 2:3 respectively, which is consistent with the structure, although these facts do not aid the identification of the structure. Carbon nmr was the most useful technique for determining the structure. The carbon atoms due to the pyrimidine ring were readily distinguished from the aromatic phenyl carbon atoms by comparison with the carbon nmr spectrum of 2,4,6-tribromo-5-fluoropyrimidine and because they showed shifts at lower field than those for phenyl (as would be expected for electron deficient carbon atoms in a pyrimidine ring) and showed coupling with the fluorine atom at the 5- position.

Fig. (19) Carbon nmr spectrum of (27)
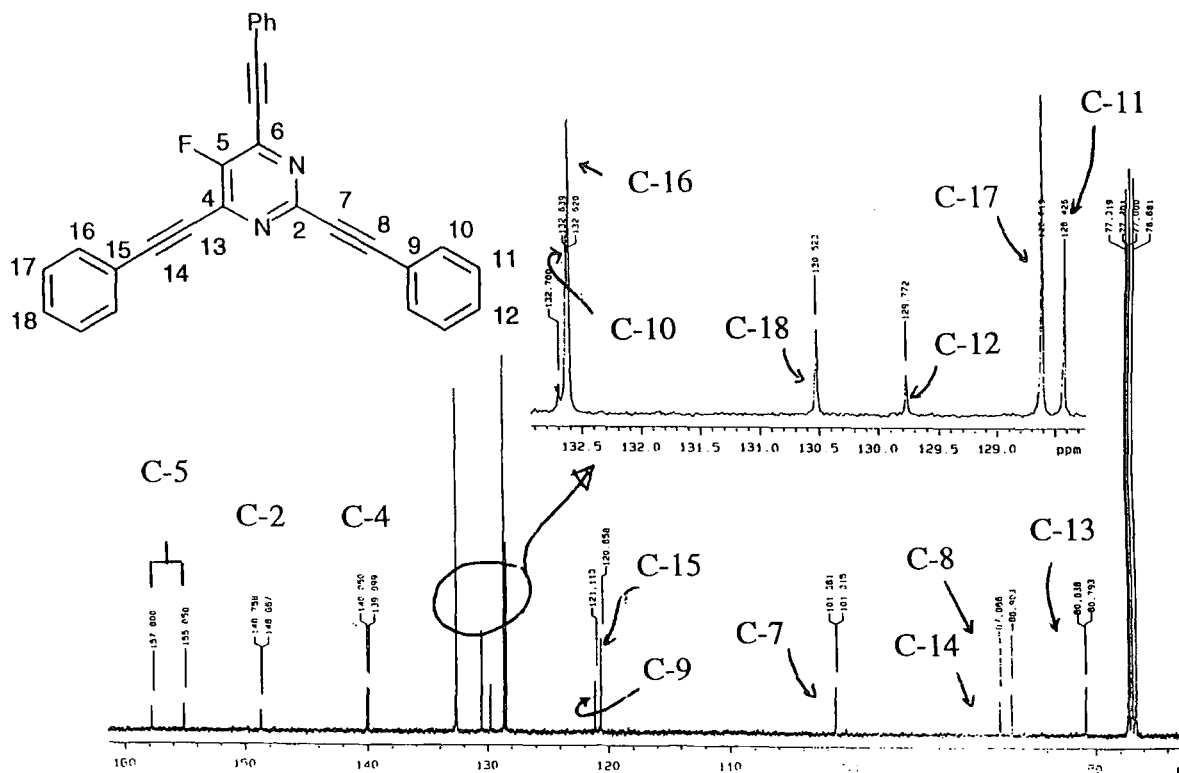
A doublet at 156.4 ppm was assigned to C-5 on account of large one bond coupling with the fluorine atom (^1J 276 Hz), C-4 was assigned to a doublet at 140.0 ppm which showed coupling (^2J 15.2 Hz) which is consistent with a carbon atom *ortho* to C-F. The remaining lower field doublet (^4J 9.2 Hz) at 148.7 ppm was assigned to C-2. The alkynyl carbon atoms were distinguished by their higher field shifts in the region 80-100 ppm. C-7 and C-13 were assigned on the basis of their coupling with the fluorine atom, whilst the other two alkynyl carbon atoms, C-8 and C-14 were not coupled with fluorine. Thus, C-13 was assigned to a doublet (^3J 4.5 Hz) at 80.8 ppm and C-7 was assigned to a doublet (^5J 4.6 Hz) at 101.3 ppm. C-7 was attributed to the shift at 101.3 ppm, rather than that at 80.8 ppm due to its proximity to the ring nitrogens, which may be expected to lead to more deshielding of C-7 than C-13. The remaining alkynyl carbon atoms were assigned to shifts at 87.9 and 86.9 ppm. The phenyl carbon atoms were assigned by comparison with typical phenyl shifts.

V.5.3   2,3-Dibromotetrafluoroquinoxaline

2,3-Dibromotetrafluoroquinoxaline (15) poses none of the orientation problems encountered for the reaction of (11) and (13) with alkynes, that is, both the 2- and 3- carbon - bromine bonds are chemically equivalent.

101

15 → **i** → **28**
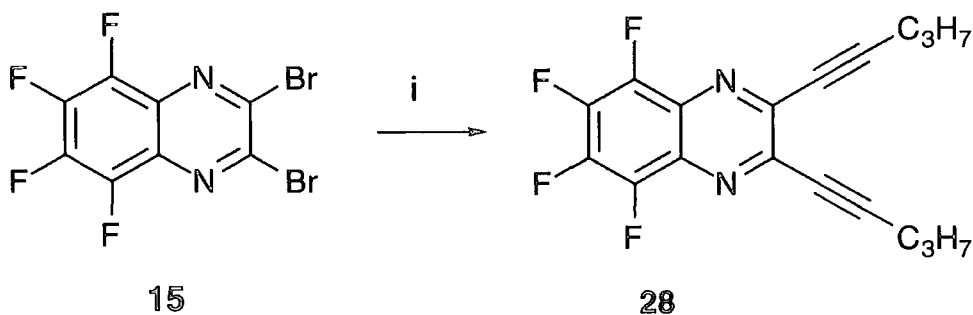
Reagents and conditions; i, 1-Pentyne (5 equivs.), CuI, (Ph₃P)₂PdCl₂, Et₃N, RT 18 h, 40 °C 24 h

Reaction of (15) with 1-pentyne proceeded well and substitution at the 2- and 3-positions occurred giving (28). The product (28) was readily identified: the mass spectrum showed that no bromine was present because there was no bromine pattern, a band at 2221 cm^{-1} in the IR spectrum was typical of an alkyne and elemental analysis was correct. The carbon nmr spectrum showed four signals which would be expected for a symmetrical quinoxaline ring and may be assigned by considering the carbon nmr spectrum of the starting compound (15) and the magnitude of the coupling with fluorine atoms. The carbon atoms of the pentyne group were assigned by comparison with the starting alkyne. Thus, two doublets of doublets at 141.3 and 140.8 ppm both showed large coupling (^{1}J 264 and 285 Hz) which is typical of one bond coupling of carbon to fluorine, thus these were assigned to C-5 and C-6. A smaller doublet at 127.1 ppm was assigned to C-8, since the observed coupling (^{2}J 3.8 Hz) is consistent with a carbon atom *ortho* to C-F. The remaining carbon atom, C-2 may be assigned to a singlet at 142.3 ppm, since a shift in this low field region is consistent with C-2 in compound (15) and the absence of splitting is consistent with a carbon atom distant from the fluorinated ring.

Thus, it is now established that bromo fluoroheterocycles are very reactive in palladium mediated reactions and particular attention is drawn to the effect of ring nitrogen, which is a dominating factor in determining orientation of substitution.

It is also clear from these results and those described in the literature (see V.I.I) that oxidative addition of hetaryl and aryl fluorides to Pd(0) does not occur. The reasons for this have not been presented in the literature, however, a consideration of the various influences affecting the rate of reaction suggest an answer.

Although quantitative data are not available for the palladium mediated coupling reaction , qualitative data do exist and indicates, that for aryl halides, the order of reactivity is iodide > bromide > chloride. It is also interesting to note that diazonium salts and aryl triflates have shown promise[155]. These observations (and in particular the order of halide reactivity) are startingly similar for those observed in S_N2 and S_N1 processes. Thus, for a bimolecular nucleophilic substitution (S_N2) reaction,

$$\overline{\text{Nuc}} + R_3C-X \longrightarrow \text{Nuc}-CR_3 + \overline{X}$$

the reactivity order is X= tosylate > I⁻ > Br⁻ > Cl⁻ and for X=F, the reaction is almost of zero rate.

A similar picture is seen for the S_N1 process.

$$R_3C-X \longrightarrow \overset{+}{C}R_3 \ + \ \overset{-}{X} \ \overset{\overset{-}{Nuc}}{\longrightarrow} \ R_3C-Nuc$$
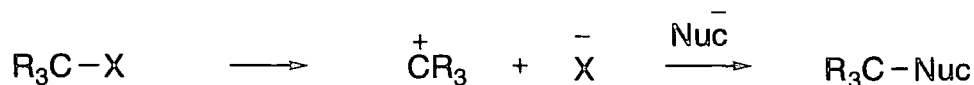
Here the order of reactivity is X= tosylate > I⁻ > Br⁻ > Cl⁻.

Thus, for an S_N2 process, the reaction is first order with respect to nucleophile and first order with respect to substrate (*i.e.*, second order overall)

$$Rate= k[Nuc^-][R_3CX]$$

and for an S_N1 process, the reaction is first order with respect to the alkyl halide.

$$Rate= k[R_3CX]$$

Therefore, for the both the S_N1 and S_N2 processes, breaking of the carbon-halogen bond is involved in the rate determining step, thus the strength of the C-X bond is the major factor in determining the rate of reaction and this reason explains the poor reactivity observed when X=F. Therefore, by extrapolation, the reason for the non-reactivity of aryl fluorides in palladium mediated reactions may be attributed to the rate determining step involving breakage of the C-X bond and because the carbon-fluorine bond is stronger than any of the other carbon-halogen bonds, aryl fluorides are resistant to oxidative addition.

Thus, we may conclude that for these palladium mediated reactions of (11, 13 and 15) with alkynes, the mechanism may considered as a nucleophilic substitution reaction with characteristics of S_N2 and S_N1 processes.

V.6   Lithium Derivatives of Fluoroheterocycles

It was evident from the reactions of butyl lithium with 4-bromotetrafluoropyridine (seeV.2.1) that metal-halogen exchange occurred readily for such systems. Therefore, it was of interest to observe the reactivity of (11) towards butyl lithium.
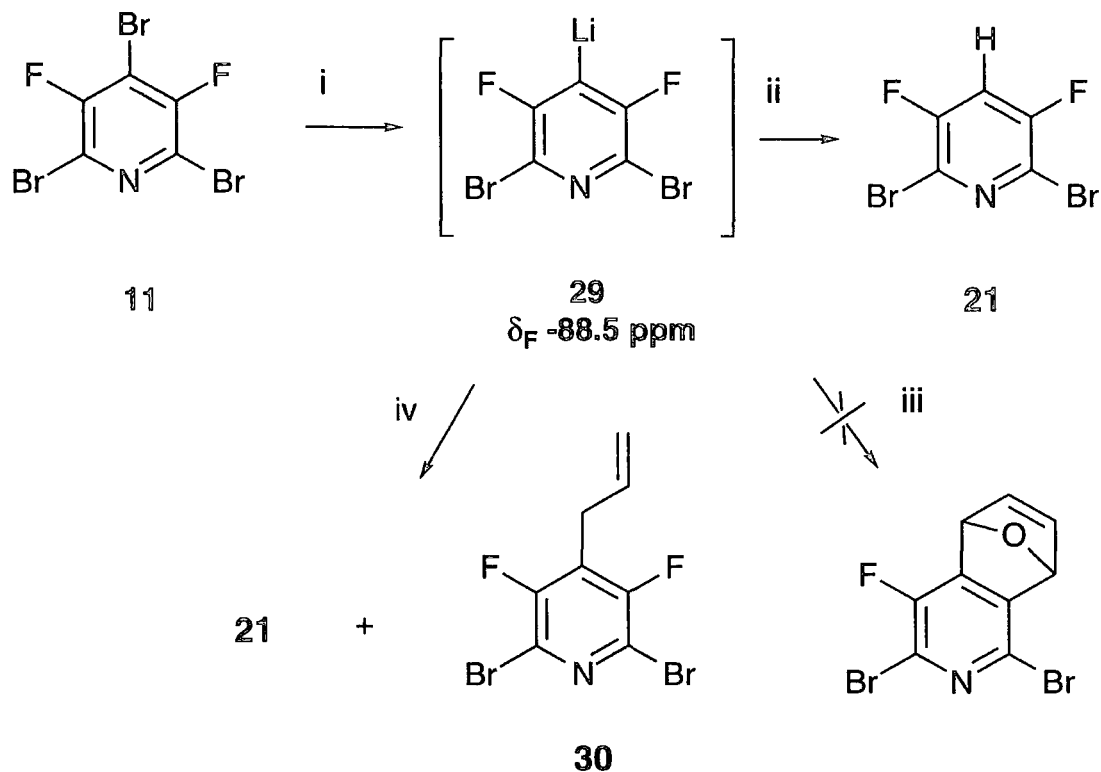
Reagents and Conditions: i, BuLi in Et$_2$O, -78°C, 1 h; ii, H$_2$O room temperature; iii, Furan, reflux; iv, Allyl bromide, RT

Reaction of (11) with butyl lithium or LDA gave the 4-lithio derivative (29), which was stable and was observed by fluorine nmr at room temperature in ether solution giving a chemical shift of -88.5 ppm, as compared to the chemical shift of -103.1 ppm for (11). The identity of the 4- lithio anion was confirmed by reacting it with water to give (21), as determined by comparison of its fluorine nmr spectrum and GCMS with an authentic sample. Reaction with allyl bromide led to the 4-allyl derivative (30). The identity of (30) was shown by its mass spectrum, which showed a pattern characteristic of a molecule containing two bromine atoms and its nmr spectra. The fluorine nmr spectrum showed a singlet at-114.4 ppm, which is typical for these 3,5-difluoropyridine derivatives and shows the symmetry of the molecule. The proton nmr showed three resonances in a ratio of 2:1:2, which is consistent with the allyl group. The carbon nmr spectrum gave further evidence for the structure. C-2 showed a characteristic X part of an ABX system, which is typical of these 3,5-difluoropyridine systems, C-3 showed a large doublet of doublets (^{1}J 262 and ^{3}J 2.6 Hz) at 154.1 ppm, which, again is characteristic of C-3 bonded to fluorine. C-4 gave a triplet at 127.3 ppm, showing coupling with fluorine ion the *ortho* position (^{2}J 20.0 Hz). The carbon atoms attributable to the allyl moiety were easily identified: a high field singlet at 27.7 ppm is characteristic of an sp^3 hybridised carbon atom and was assigned to C-5 and the alkenic carbon atoms were assigned to low field singlets at 118.5 and 131.0 ppm.

δ_F -94.5 ppm
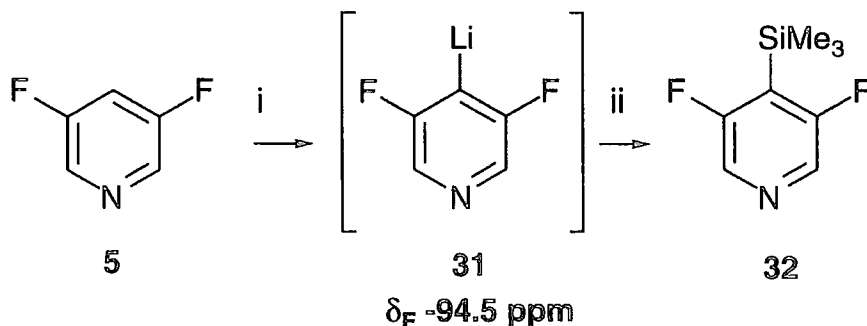
Reagents and Conditions; i, BuLi, TMEDA, Et$_2$O, -78°C, 1.25 h; ii, Me$_3$SiCl, -78°C, 1.5 h, warm to RT, or; i, BuLi, TMEDA, THF, -78°C, 2.0 h*; ii, Me$_3$SiCl, -78°C, warm to RT. (* nmr sample taken and warmed to RT).

Reaction of (5) with butyl lithium afforded the 4-lithio derivative (31) and hence the trimethylsilyl derivative (32). The anion (31) proved to be stable at room temperature and a fluorine nmr spectrum was recorded in THF and a shift was observed at -94.5 ppm, as compared to that of (5) at -124.1 ppm. Interestingly, both solvents, THF and ether, led to formation of the 4-derivative (c.f. lithiations of 3-fluoropyridine, which gave either the 4- or 2- anion, depending on the solvent used[174]). The TMS derivative (32) was identified by a singlet at -113.0 ppm in the fluorine nmr spectrum and the proton nmr spectrum showed two singlets at 0.33 and 8.16 ppm in a ratio of 9:2, which were assigned to C(Me) and C-2 respectively. Carbon nmr spectroscopy showed a spectrum typical of a 4-substituted-3,5-difluoropyridine. C-4 showed a triplet at 122.7 ppm due to splitting with the fluorine atoms (^{2}J 30.5 Hz), C-3 showed a large doublet at 162.8 ppm with coupling (^{1}J 260 Hz) typical of carbon bonded to fluorine and C-2 showed a characteristic X part of an ABX system.

The stability of the anions (29) and (31) indicates the strong stabilising effect of fluorine on anions.

C—C—F   Stabilising

The reluctance to lose lithium fluoride (and hence formation of the pyridyne) is also consistent with the noted stability of 4-lithiotetrafluoropyridine[168] and recent calculations[180] for the stability of the anions of the type C$_6$H$_4$X$^-$, which indicate that for X= F, the anion is far more stable than for X= Cl, Br or I.

33a, b
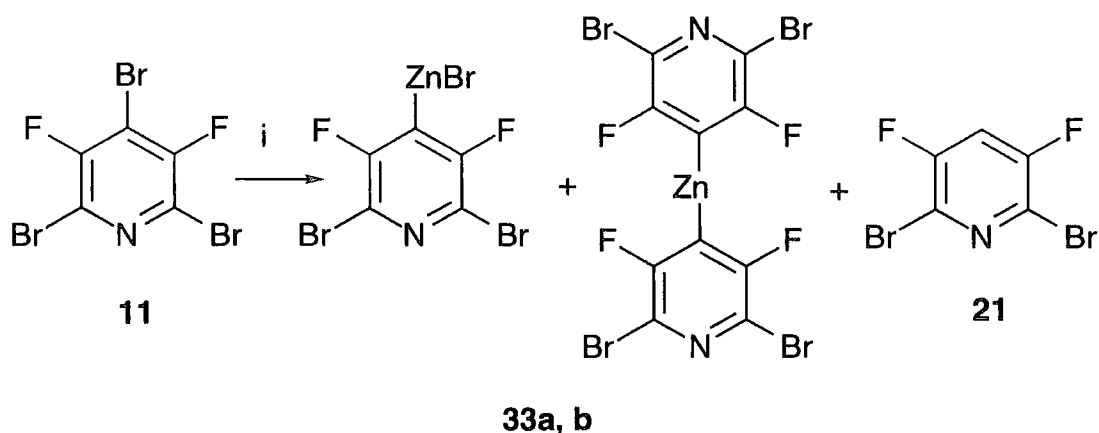
Reagents and Conditions; i, Zinc dust, DMF (dry), stir RT 0.5 h and 40 °C 1h

Simply stirring zinc granules with (11) in dimethyl formamide (DMF) led to the formation of the 4-hydro derivative (21). A fluorine nmr spectrum of the crude reaction mixture before work up indicated the presence of the zinc derivatives (33a, b) and the hydro derivative (21). This reaction was however, of little synthetic benefit, since the product was not readily isolated from the DMF mixture.

33a, b

δ_F **-92.15 (2F, s) and -92.65 (1F, s)**

21, 26%   **30, 74%**
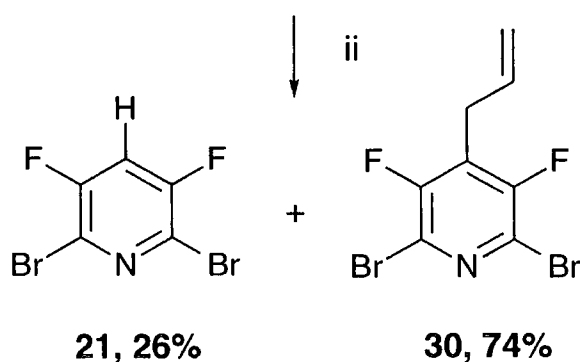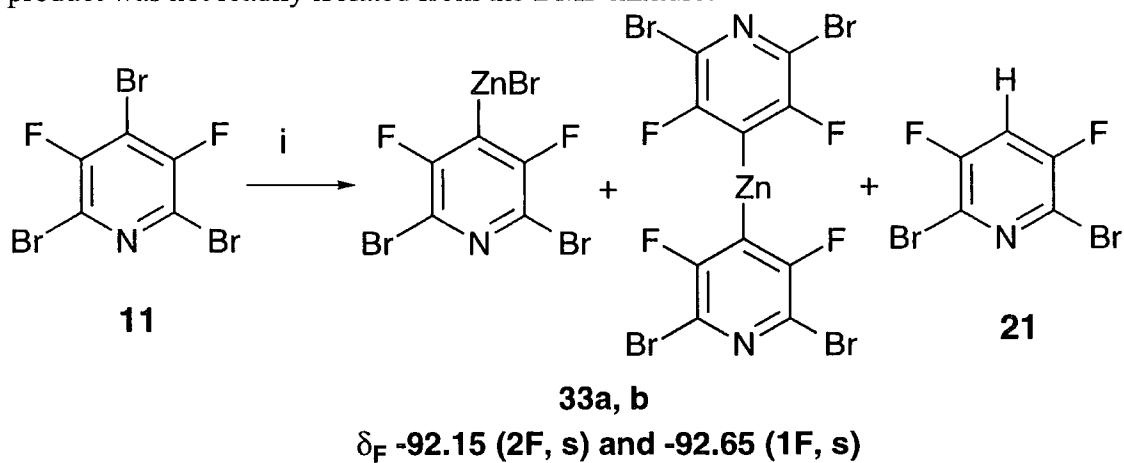
Reagents and conditions; i, Zinc granules, THF, 50 °C, 23 h; ii, Allyl bromide, RT, 0.25 h

However, using THF as the solvent gave a clean reaction and stirring zinc with (11) in THF led to a mixture of the zinc derivatives (33a, b) and the 4-hydro compound (21) in a ratio of 3 : 1, as observed by fluorine nmr, then addition of allyl bromide afforded the

allyl derivative (30), which was identified by comparison of its fluorine nmr spectrum and GCMS with a characterised sample.

V.8   Conclusion

A variety of substituted fluoroheterocyclic compounds have been synthesised *via* metal mediated reactions of 2,4,6-tribromo-3,5-difluoropyridine (11), 2,4,6-tribromo-5-fluoropyrimidine (13) and 2,3-dibromotetrafluoroquinoxaline (15). Particular emphasis is drawn to the palladium mediated reactions of (11) with alkynes, which have established the viability of these highly reactive systems in palladium mediated transformations. The stability of the lithium derivatives of (11) and (5) is also fascinating.

Development of Energetic Materials

"Because of their favourable elemental composition, heteroaromatic nitro compounds represent explosives of high performance (oxygen balance, density, heat of formation and velocity of detonation) as compared to analogous aromatic explosives.[181]"

According to a recent review, explosives may be classed in five categories: 1, heat stable; 2, high performance; 3, melt castable; 4, energetic binders and 5, insensitive high explosives (IHE' s)[181].

A consideration of the various factors which contribute to high performance IHE's would lead us to conclude that the presence of amino groups (which impart thermal stability), a pyridine ring (which decreases impact sensitivity and imparts increased density and hence increased velocity of detonation because VOD is proportional to density squared) and the presence of nitro groups are all necessary as properties of a high performance explosive. Thus, 2,4,6-trinitro-3,5-diaminopyridine-N-oxide (40) appears a likely contender for an energetic material.

| 3 | 5 | 40 |
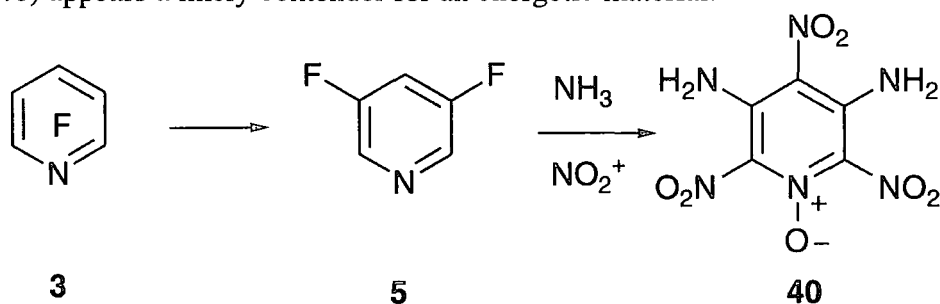
The synthesis of 3,5-difluoropyridine was described in chapter III and it was of interest to develop a route to 2,4,6-trinitro-3,5-diaminopyridine-N-oxide (40) and we thought that by following a series of nitration and amination steps, that 3,5-difluoropyridine (5) may be converted into (40).

VI.1 Electrophilic Aromatic Nitration of Deactivated Aromatics

Electrophilic aromatic nitration is a versatile procedure for the synthesis of aromatic nitro compounds and is reviewed in a recent text[182].

Pertinent to this discussion is however, the nitration of deactivated aromatics such as 3,5-difluoropyridine (5). The nitration of (5) is of course, not described in the literature, however, nitration of pyridine and other derivatives is described and shall be discussed.

VI.1.1 Pyridine and Derivatives. Since the first attempts of the direct nitration of pyridine, attempts have failed to achieve acceptable reactions and even under harsh conditions, pyridine only gives 3-nitropyridine in poor yield[183].
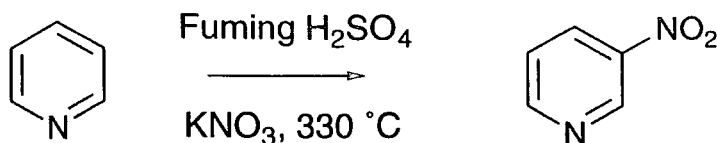
This reaction is perhaps not surprising considering that pyridine is not activated to electrophilic attack and it is probably the pyridinium salt that is present in the reaction mixture, which is even less reactive towards electrophiles than pyridine.
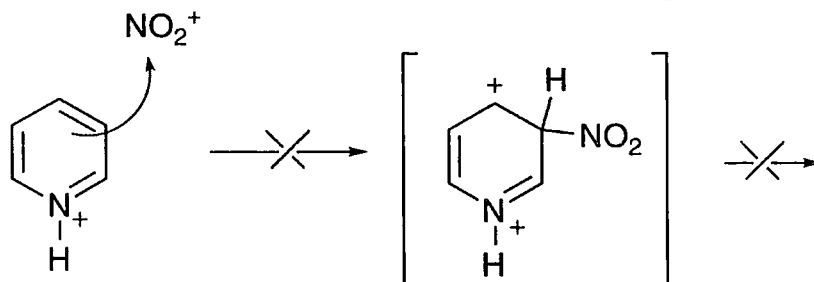
Protonation of pyridine may be avoided by using nitronium tetrafluoroborate and Olah[184] attempted nitration of pyridine with this reagent. However, it was found that the N-nitro and N-nitroso salts were formed with no trace of nitration on the ring carbon atoms.
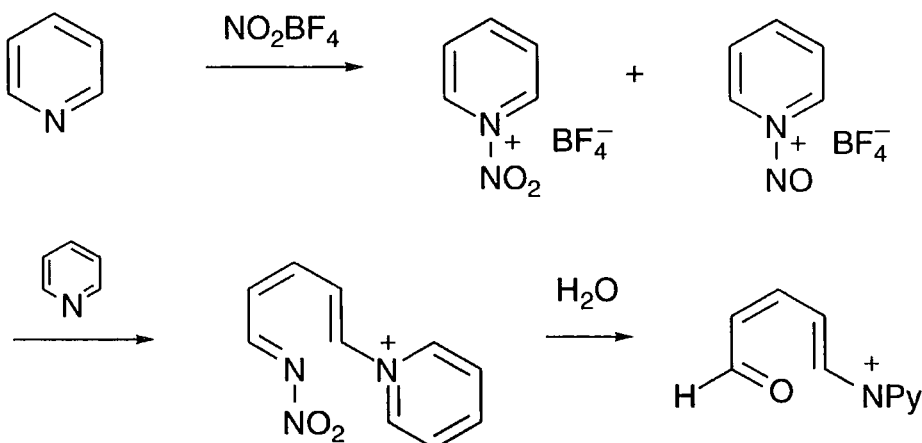
Also, in the presence of excess pyridine, ring opening occurred.

Interestingly, direct nitration of 2-fluoro and 2,6-difluoropyridine with nitronium tetrafluoroborate achieved a degree of success and whilst 2-fluoropyridine gave mostly the N-nitro salt, a 6% yield of 5-nitro-2-fluoropyridine was obtained and 2,6-difluoropyridine gave a 20% yield of 3-nitro-2,6-difluoropyridine[185].

20%
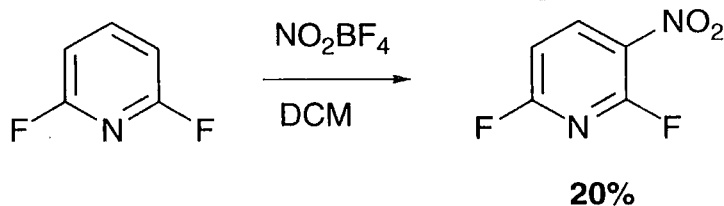
These findings may be attributable to the effect of fluorine which reduces the basicity of ring nitrogen (which prevents the formation of the N-nitro and N-nitroso salts) sufficiently to enable nitration at the carbon atoms.

109

VI.1.2   Pyridine-N-oxides and other Heterocyclic-N-oxides. Although pyridine is reluctant to undergo electrophilic nitration, pyridine-N-oxide is activated to electrophilic attack and nitration gives 4-nitropyridine-N-oxide[186, 187].
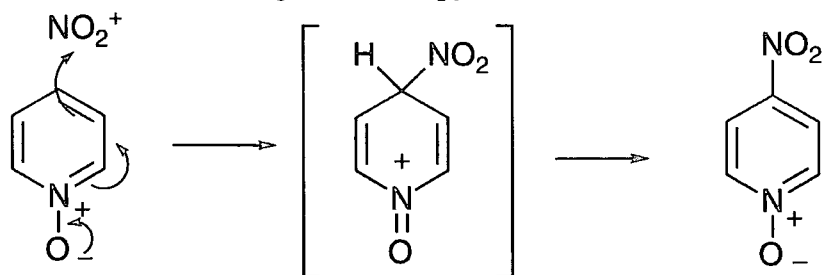
The N-oxide group has a strongly activating influence and its effect may be explained by considering the various canonical forms, thus, charge is delocalised from the N-oxide group onto the aromatic ring making the ring carbon atoms more susceptible to electrophilic attack.
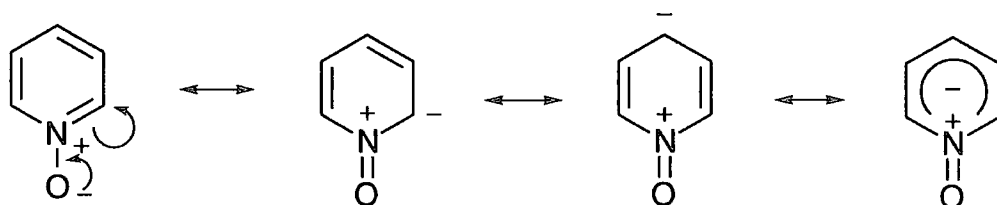
A number of substituted pyridine-N-oxides also undergo nitration at the 4- position, for example, 2,6-dibromopyridine-N-oxide[188] and 2,6-dimethyl-3-fluoropyridine-N-oxide[189] gave the corresponding 4-nitro compounds and 3-fluoroquinoline-N-oxide[190] gave the 4-nitro derivatives. The nitration of 2,6-dimethyl-3-fluoropyridine-N-oxide is particularly interesting because of the similarity between this and 3,5-difluoropyridine (*i.e.*, fluorine at the 3-position). It is also interesting that the directing effect of the N-oxide is greater than of the methyl groups: the methyl groups usually direct electrophilic attack at positions *ortho* and *para* to itself, however, substitution is observed *meta* to the methyl groups.
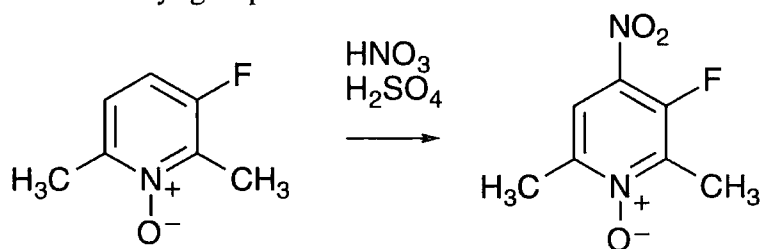
VI.1.3   Fluoro Substituted Benzenes. Benzene is more activated towards electrophilic aromatic substitution than pyridine and the presence of fluorine atoms in the aromatic ring may be expected to deactivate the system to electrophilic substitution on account of their -I inductive effect. On the other hand, the presence of fluorine atoms may stabilise the Wheland intermediate.
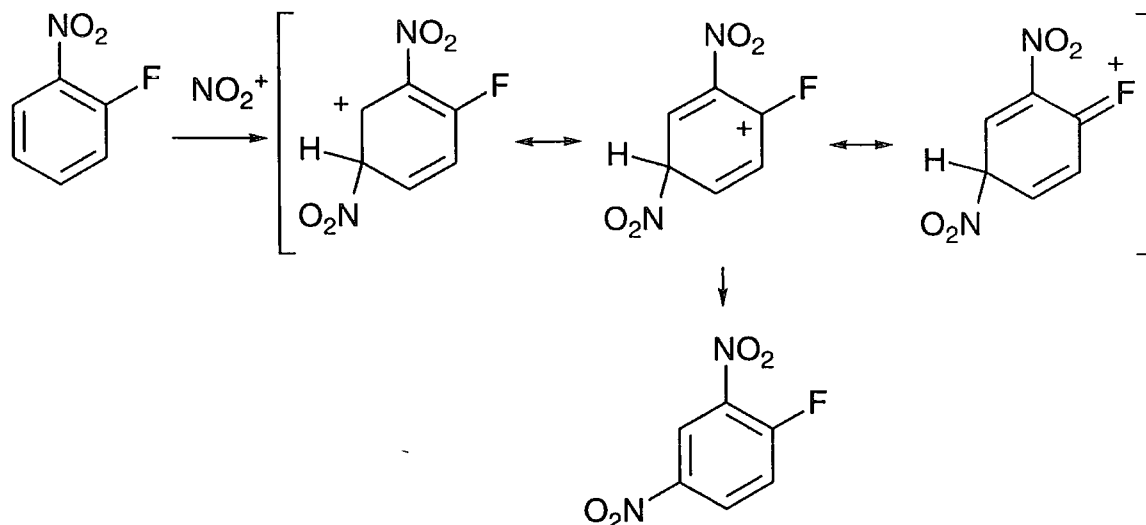
Olah and Sandford[191] found that nitration of 2,4-difluoronitrobenzene, 2,3,4-trifluoronitrobenzene and 1,3,5-trifluorobenzene with nitronium tetrafluoroborate in triflic acid gave 2,4-difluoro-1,5-dinitrobenzene, 2,3,4-trifluoro-1,5-dinitrobenzene and 1,3,5-trifluoro-2,4-dinitrobenzene respectively. These results were compared to the reactivity of nitronium tetrafluoroborate in sulpholane where 1,3,5-trifluorobenzene for example, failed to react. The enhanced reactivity of nitronium tetrafluoroborate in triflic acid was attributed to protonation of the nitronium ion.
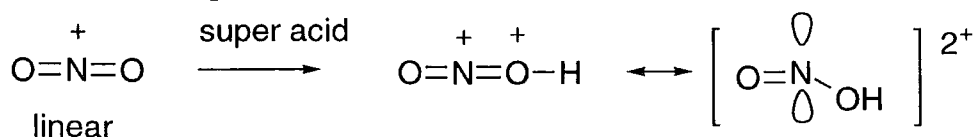
Thus, protonation of oxygen leads to a weakening of the N-O bond (less π character) and to partial electron deficiency at the nitrogen p-orbital making a more reactive nitronium ion.

VI.2 Nucleophilic Substitution of Nitro Activated Aromatics

It is well established[153, 192] that for activated systems, the mobility of the nitro group is comparable with fluorine and for reactions of sodium methoxide with 2,4-dinitro-1-substituted benzenes, the mobility order is $F \sim NO_2 >> Cl > Br > I$. Interestingly, for the reactions of the same substrate with softer nucleophiles such as thiophenolate, the mobility order is $NO_2 > F > Br > I > Cl$. Thus, for hard nucleophiles, fluorine and the nitro group are approximately 1000 times more reactive than the other halogens, yet for softer nucleophiles, the nitro group is 100 times more mobile than fluorine, which in turn is only 10 orders of magnitude more reactive than the other halogens.

Work in these laboratories[193] demonstrated how a nitro group may act as a director and as a leaving group and reaction of 4-nitrotetrafluoropyridine with ammonia led to displacement of fluorine and the nitro group.
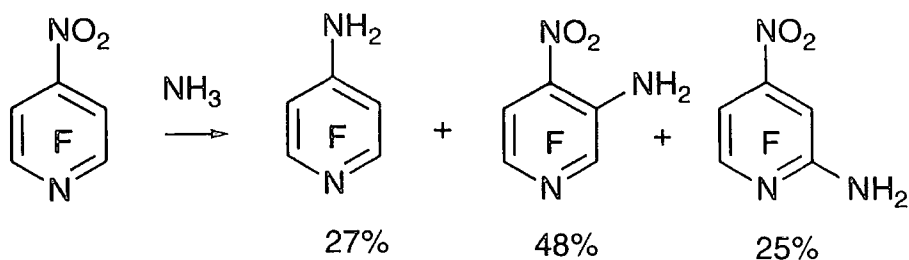
Hence, 4-aminotetrafluoropyridine (27%), 4-nitro-5-aminotrifluoropyridine (48%) and 4-nitro-6-aminotrifluoropyridine (25%) was obtained. If these yields are corrected for statistical factors (i.e., there are two chances to attack at the 2- and 3- positions, but only one chance to attack at 4-), it appears that ammonia shows an equal chance of displacing the nitro group (attack at 4-) and the fluorine atom (attack at 3- and 2-).

Interesting work has demonstrated that the N-oxide group may activate pyridine[194] and quinoline-N-oxides[195] to nucleophilic substitution and increases in rate factors of up to 100 and even 1000 were obtained for the reactions of 4-nitropyridine-N-oxide and 4-chloropyridine-N-oxide as compared to the free bases[194].
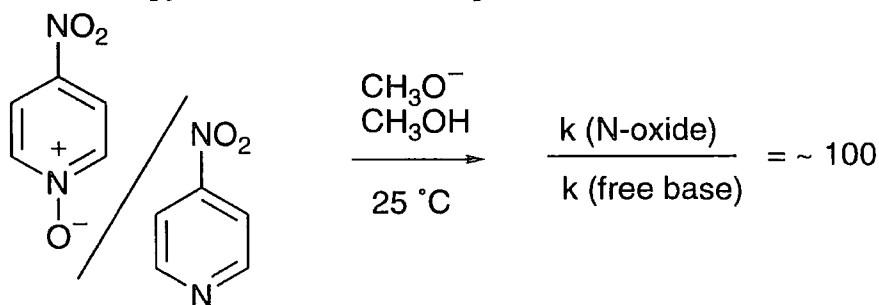
A series of papers by Talik and Talik[189, 196-198] and a patent by Hartman[199] demonstrated the powerful directing effect of the nitro group in a variety of 4-nitro-3-fluoropyridine-N-oxide derivatives and it was found that reaction with a variety of nucleophiles including thiophenolate, sodium methoxide, ammonia and amino acids gave exclusive displacement of fluorine.

VI.3 Discussion
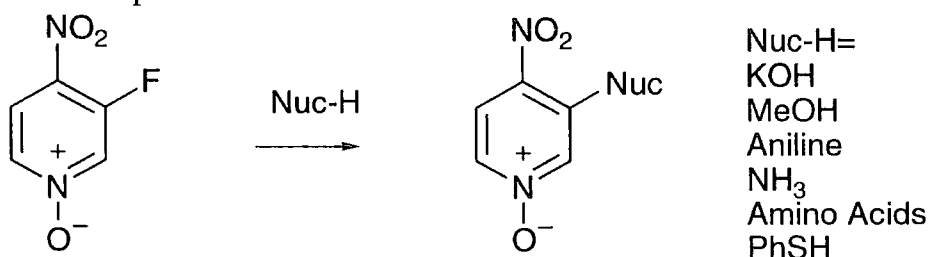
We were interested in investigating and comparing the chemistry of 3,5-difluoropyridine (5) and 3,5-dichloropyridine (34) as potential precursors to the energetic material (40), as described in the proposed scheme.

X= F, **5**
X=Cl, **34**

40
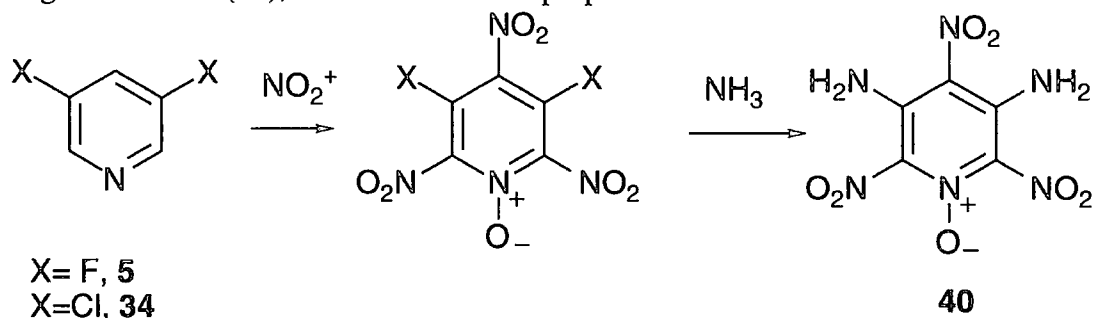
VI.3.1 Nitration of 3,5-difluoropyridine and 3,5-dichloropyridine

It is well established that although pyridine itself is resistant to nitration, pyridine-N-oxide[186, 187] readily undergoes electrophilic substitution.

5a, 71%, X= F
34a, 96%, X= Cl
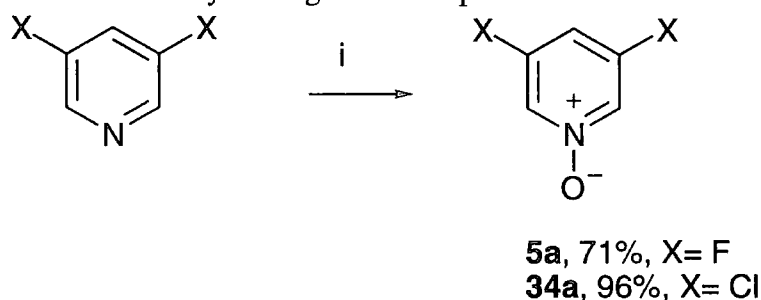
Reagents and Conditions; i, CH_3CO_3H, $CHCl_3$, 50 °C

Therefore the N-oxides of (5) and (34) were prepared to give 3,5-difluoropyridine-N-oxide (5a) and 3,5-dichloropyridine-N-oxide (34a) in essentially quantitative yields. The N-oxides were identified by comparison with the free bases, because, apart from their differing elemental analyses and mass spectra, they presented very similar spectroscopic data.

Nitration of (5a) and (34a) proceeded smoothly at 100 °C using fuming sulphuric and nitric acids as the nitrating medium.

5a, X= F
34a, X= Cl

35a, X= F, 32%
36, X= Cl, 71%

35b, 3%
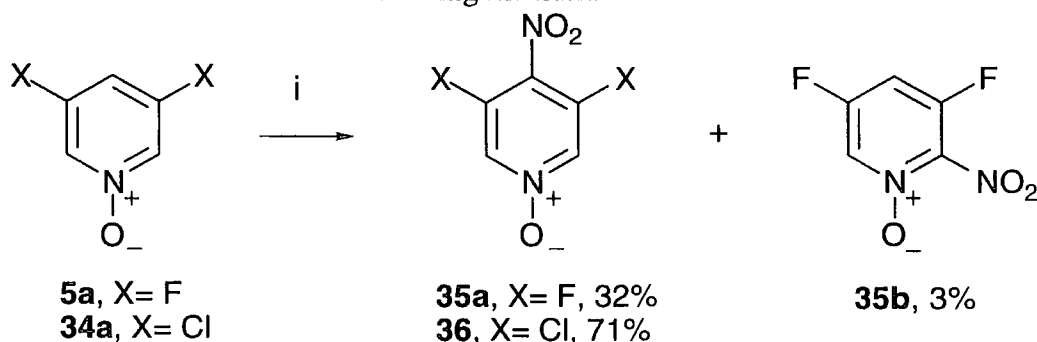
Reagents and Conditions; i, Fuming H_2SO_4, HNO_3, 100 °C

Interestingly, whilst (5a) gave the 4- and 2- isomer in a ratio of 10:1 (as determined by fluorine nmr spectroscopy), the dichloro compound (34a) gave only the 4- isomer (as observed by proton nmr spectroscopy). The disappointing yields of (35a,b) may be attributed to hydrolysis of the nitro compounds, since exhaustive continuous extraction of the neutralised reaction mixture did not improve the yields of (35a,b).

Aqueous work-up
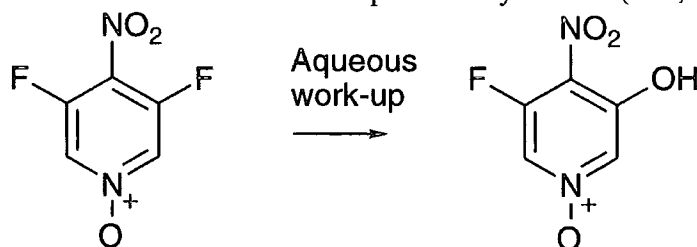
Surprisingly, when reactions of (5a) with nitronium tetrafluoroborate in triflic acid were performed, a media in which the most reticent substrates react[191], reaction failed to occur at all. The reasons for this are intriguing, but lie outside the scope of this project.

It appears that since both (5a and 34a) were nitrated under essentially the same nitrating conditions (the dichloro compound required 5 h at 100 °C, whereas the difluoro compound required 4 h at 100 °C), the effect of the halogens on nitration was negligible. This is perhaps surprising because we may have expected that the halogens, chlorine and fluorine would have exerted differing activating and deactivating effects. Both the halogens would deactivate the system to electrophilic attack on account of their -I inductive effects and this would be particularly important for fluorine, which due to initial state effects, may be expected to deactivate (5a) to attack.
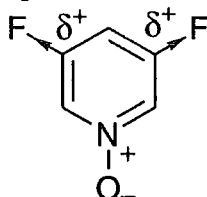
Initial State Effect
(Retards approach of electrophile)

On the other hand, fluorine would stabilise the Wheland intermediate, because of all the halogens, fluorine is able to stabilise α- carbocations the most, which it does via donation of charge through p-p orbital interactions with the carbocation[200].
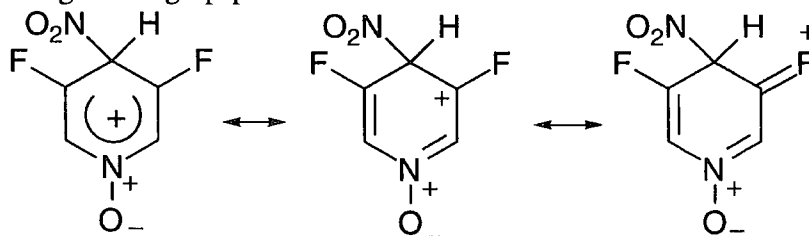
Fluorine stabilising T. S

The nitro compounds were readily identified by conventional techniques, although unambiguous characterisation of (35a) was obtained from its crystal structure.

The dichloro compound (36) was identified by its mass spectrum which showed a typical two chlorine isotope pattern and gave an even mass molecular ion (M^+ 210), which is to be expected for a compound containing an even number of nitrogen atoms. The IR spectrum showed bands at 1549, 1297 and 1353 cm^{-1} which corresponds to the nitro group. Surprisingly, the carbon nmr spectrum showed only two singlets at 125.9 and 138 .8 ppm. It is likely that either this is due to coincident resonances or a very weak resonance of one of the carbon nuclei. Any ambiguity was settled by an elemental analysis. It was interesting to note that (36) appeared sensitive to light and (or) air and its colour rapidly changed from pale yellow to red on exposure to the atmosphere.

The difluoronitro compounds (35a) and (35b) were separated by column chromatography and both structures were easily identified. Their mass spectra showed an even mass molecular ion (M^+ 176) and the IR spectra showed a characteristic band for the nitro group at 1580 and 1335 cm^{-1}. The exact ratio of the 4- : 2- isomer was determined by fluorine nmr spectroscopy: (35a) showed a singlet at -128.12 ppm and (35b) showed two singlets of equal intensity at -111.58 and -115.83 ppm. The carbon and proton nmr spectra were consistent with the structures and were assigned by comparison with (5a).

A crystal structure was obtained for (35a) and unequivocally proved the structure and showed interesting physical characteristics of the molecule.

Fig. (20) Crystal Structure of (35a)
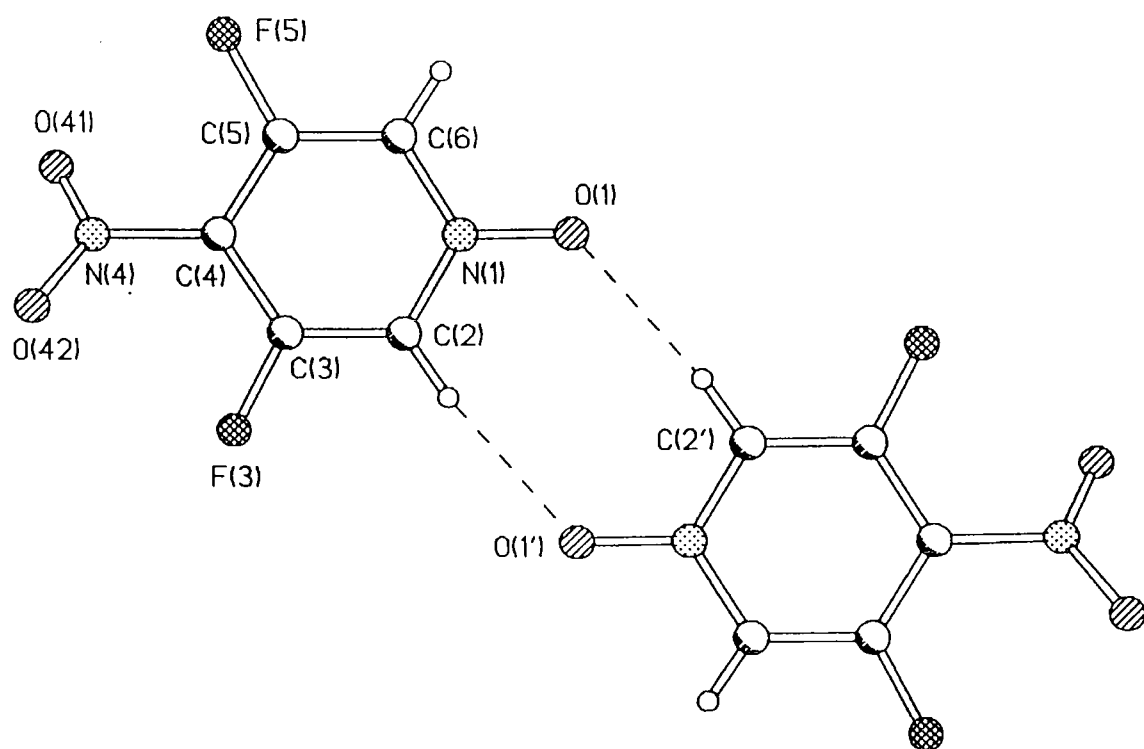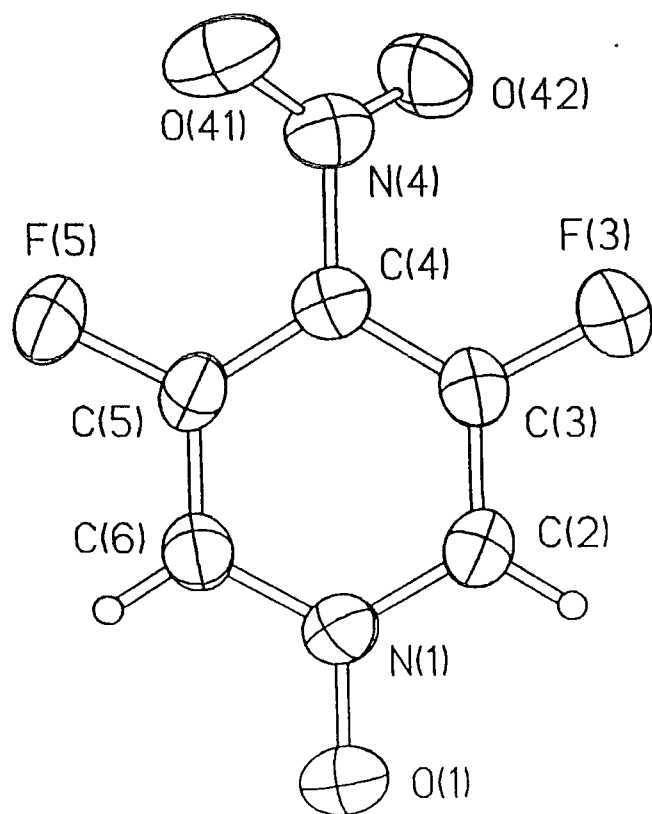
It is fascinating to observe that the molecule crystallises in a dimeric form, with C(2)-H forming hydrogen bonds with the N-oxide group. This fact is remarkable and demonstrates the acidic nature of the proton which is flanked by the electron withdrawing N-oxide and C-F groups. It is also interesting to compare the bond lengths and angles of (35a) with the data for 4-nitropyridine-N-oxide[201].
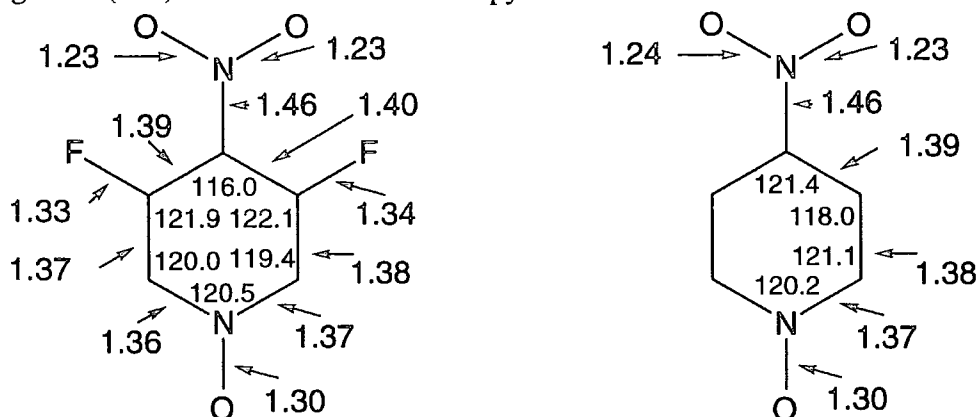
(Bond lengths shown outside ring
Bond angles shown within ring)

The comparison shows no discernible difference in the bond lengths (except of course the difference between C-H and C-F bond lengths), however, the bond angle made by C(3)-C(4)-C(5) for the difluoro compound is significantly more *acute* than for 4-nitropyridine-N-oxide and the C(2)-C(3)-C(4) angle for the difluoro compound is noticably more *obtuse* than for 4-nitropyridine-N-oxide. Thus the molecule (35a) is stretched slightly along its symmetrical axis, which is probably on account of electron pair repulsions between the fluorine atoms and the nitro group.

c.f.
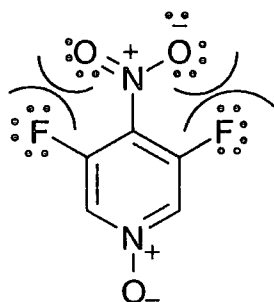
Electron pair
repulsions
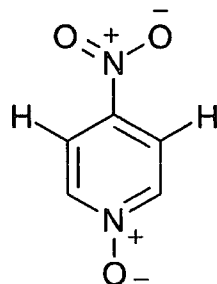
No electron pair
repulsions

VI.3.2   Nucleophilic Amination

It was of interest to observe whether reaction of (35a), (35b) and (36) with ammonia would lead to the displacement of fluoride, chloride or the nitro group.

117

36   **37**
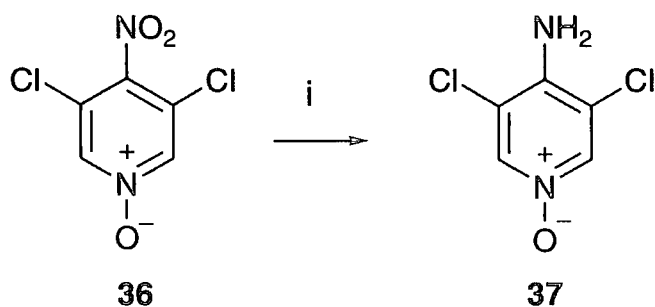
Reagents and conditions; i, NH₃(aq), MeCN, 70 °C

Reaction of (36) with ammonia led to exclusive displacement of the nitro group to give (37). The product was obtained by filtering the reaction mixture and washing with water and the low isolated yield (30%) may be attributed to the solubility of (37) in water, because extraction of the filtrate (*i.e.*, the aqueous washings) gave no material. The amino compound (37) was identified by mass, IR and nmr spectroscopy. The mass spectrum showed that chlorine had been retained because an isotope pattern of two chlorine atoms was observed and the molecular ion had an even mass (M^+ 182), which would be expected for a compound with an even number of nitrogen atoms. A band at 3315 cm^{-1} in the IR spectrum was characteristic of an amino group. The proton and carbon nmr spectra confirmed the structure. The proton nmr spectrum showed two lines in a ratio of 1:1 and the NH₂ group was assigned to a broad singlet at 6.65 ppm and the aromatic protons were assigned to the sharp singlet at 8.26 ppm. The carbon nmr spectrum showed three lines at 114.8, 136.9 and 140.8 ppm which was consistent with the symmetrical structure. C-2 was assigned to the singlet at 114.8 ppm because a shift at high field is consistent with carbon bound to hydrogen. Both C-3 and C-4 were assigned to the lower field shifts on account of them being bonded to chlorine and the nitro group. C-3 was then assigned to the shift at 140.8 ppm and C-4 to 136.0 ppm on account of their relative intensities.

35a, 90% + **35b, 10%** → i

39a, 8% + **39b, 15%** + **38, 57%**
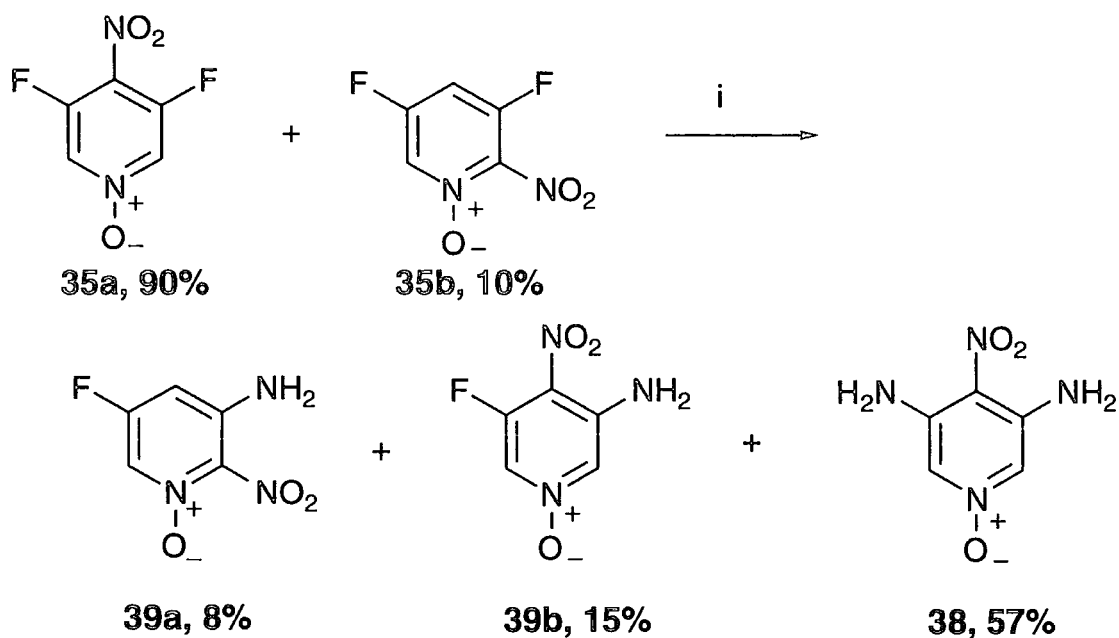
Reagents and conditions; i, $NH_{3(g)}$, MeCN, 70 °C

Reaction of a mixture of the fluoronitro pyridine-N-oxides (35a) and (35b) with ammonia occurred rapidly and afforded a red precipitate which was thought to be ammonium hydrofluoride. The reaction was monitored by thin layer chromatography (TLC) and stopped when all of the starting material had been consumed. Following removal of the ammonium hydrofluoride by washing the mixture with water , column chromatography gave three products which were identified as 3,5-diamino-4-nitropyridine-N-oxide (38, 57%), 3-fluoro-5-amino-4-nitropyridine-N-oxide (39b, 15%) and 3-fluoro-5-amino-6-nitropyridine-N-oxide (39a, 8%). Thus, exclusive displacement of fluorine had occurred.

The compounds (38, 39a and 39b),were identified using the following procedures. 3,5-Diamino-4-nitropyridine-N-oxide: Recrystallisation from methylsulphoxide and water afforded deep red crytals, from which an X-ray crystal structure was obtained as shown below.

Fig. (21). Crystal Structure of (38)
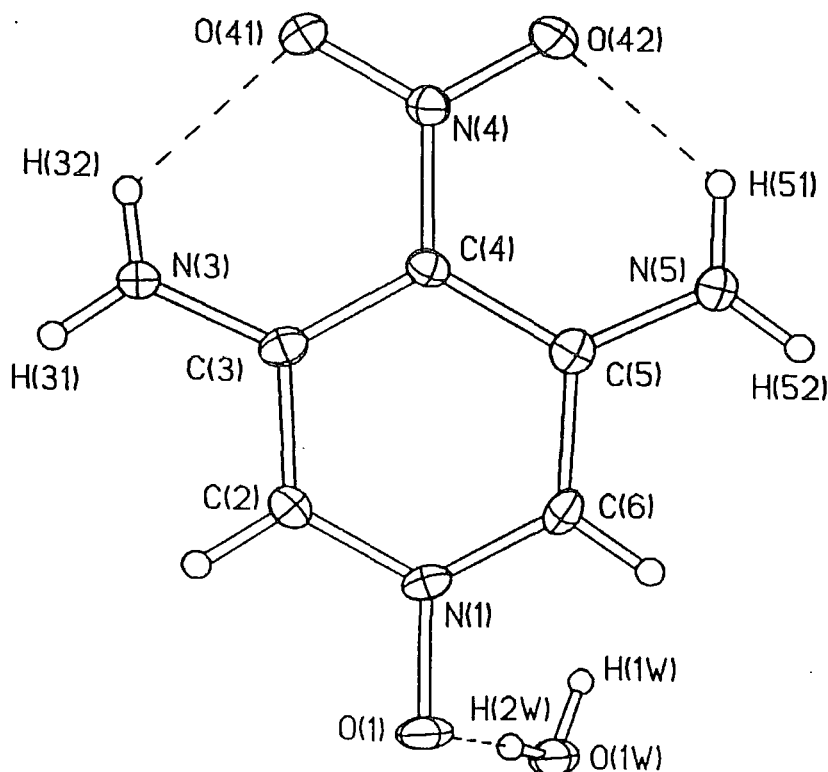
It is interesting to note that there is intramolecular hydrogen bonding between the nitro and amino groups. This is a very useful observation since it is believed that intramolecular hydrogen bonding of this type is necessary for high performance explosives (probably on account of the increase in density this causes)[181]. Also, water of crystallisation is observed, which is consistent with the some-what large O-H band in the IR spectrum. The proton nmr spectrum showed two singlets of equal intensity at 7.39 and 7.11 ppm. Assignment of these signals was made by shaking an nmr sample with deuterium oxide. Deuterium oxide is known to exchange with amino protons and thus, collapse of the singlet at 7.39 ppm meant that we were able to assign this signal to NH_2 and the other signal at 7.11 ppm to the aromatic protons. This very low chemical shift for the amino protons is consistent with results observed for similar systems such as 4-amino-3,5-nitropyridine-N-oxide (NH_2, δ_H 8.41 ppm)[202] and is in agreement with the intramolecular hydrogen bonding, which would lead to deshielding of the hydrogen nucleus.

In addition to the crystal structure, mass , IR and carbon nmr spectroscopy were consistent with the structure.

3-Fluoro-5-amino-4-nitropyridine-N-oxide: Mass spectroscopy gave an odd mass molecular ion (M^+ 173), showing the presence of an odd number of nitrogen atoms. The IR spectrum showed bands typical of an amino group (3430 cm^{-1}) and nitro group

(1567 and 1269 cm⁻¹). The fluorine nmr spectrum showed a doublet at -131.09 ppm and the coupling (^3J 6.4 Hz) was consistent with a fluorine atom in a position *ortho* to a C-H bond. The proton nmr spectrum showed two signals of equal intensity at 7.85 and 7.62 ppm. Examination of the signal at 7.85 ppm showed it was in fact two lines and these were assigned to the aromatic protons, H-2 and H-6, whilst the broader peak at 7.62 ppm was assigned to the amino group.

Fig. (22) Carbon nmr spectrum of (39b)
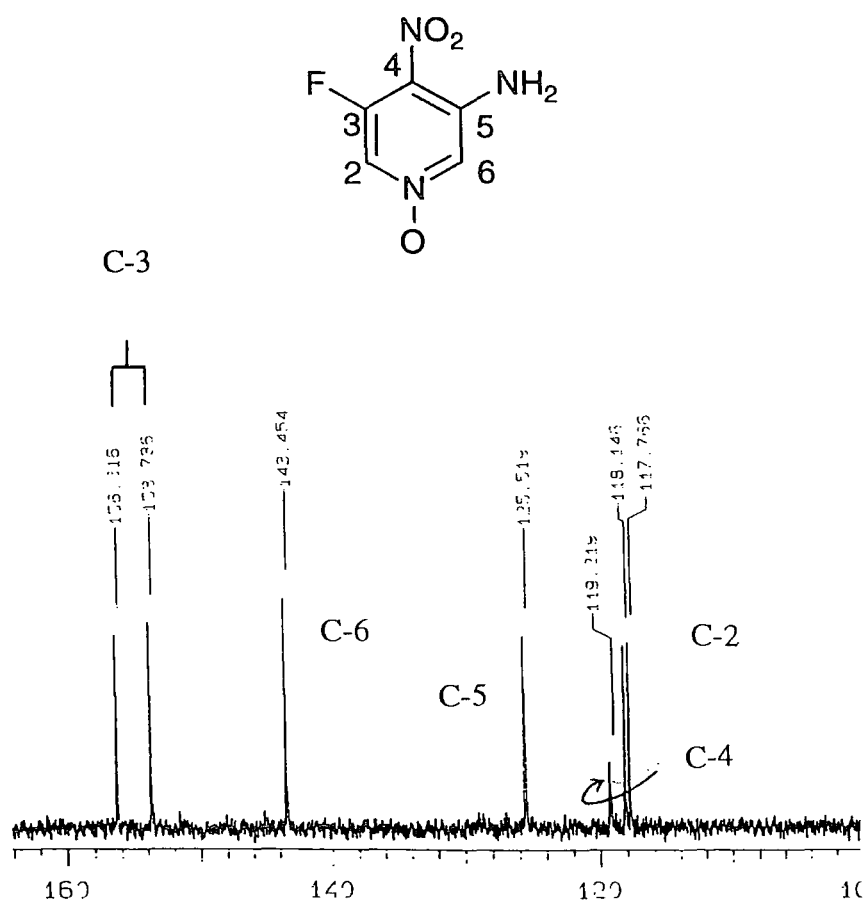
The carbon nmr spectrum gave further evidence for the structure, showing five resonances. A large doublet (^1J 260 Hz) at 155.0 ppm was readily assigned to C-3 on account of the large one bond C-F coupling and a doublet (^2J 38.2 Hz) at 118.0 ppm was assigned to C-2, because coupling of this magnitude is consistent with a carbon atom *ortho* to C-F. The remaining signals were all singlets and were assigned by comparison with (38). A singlet at 119.2 ppm was consistent with C-4 and the other signals were assigned on the basis of their intensities: a singlet at 143.5 ppm was more

121

intense than that at 125.5 ppm, so the former was attributed to carbon bonded to hydrogen (C-6) and the latter to C-5.

3-Fluoro-5-amino-2-nitropyridine-N-oxide: The IR and mass spectra were analogous to its isomer (39b) above.

39a   39c
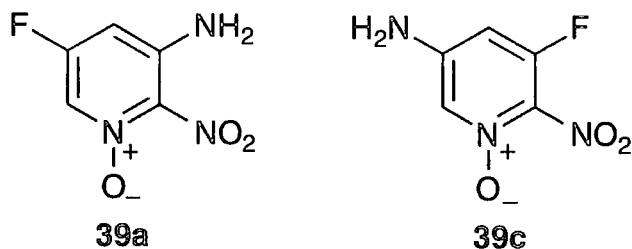
Of course, reaction of (35b) with ammonia could have led to either of the isomers (39a and 39c), however, it is known[194] that for S_NAr processes, the nitro group in the *ortho* position is more activating than in the *para* position due to the -I inductive effect of the nitro group, therefore, we would expect to form the isomer (39a) in preference to (39c). The choice of isomer was confirmed by the fluorine nmr spectrum,
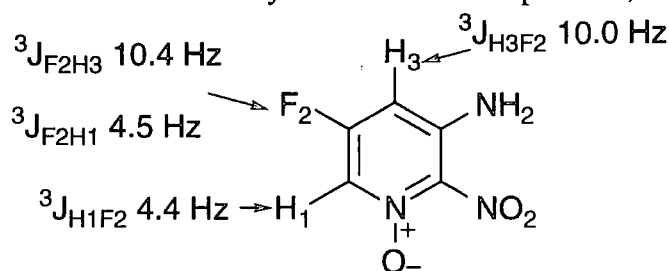
which showed a doublet of doublets, due to coupling of the fluorine atom with H_3 and H_1 (^3J FH 10.4 and 4.5 Hz), which was only consistent with the isomer (39a) because the isomer (39c) would have shown only a doublet due to coupling with H_3. The proton nmr spectrum showed three signals at 8.03, 6.79 and 6.77 in a ratio of 1:2:1. A broad singlet at 6.79 ppm was assigned to the amino protons, a doublet of doublets at 8.03 was assigned to H_1 because the ^3J HF coupling of 4.4 Hz was almost identical to the ^3J FH coupling of 4.5 Hz observed in the fluorine nmr spectrum and hydrogen at the 2-position is typically more deshielded than at the 4- position. H_3 was assigned to the signal at 6.77 ppm, which was partially obscured by the broad NH_2 signal and showed itself as half of the expected doublet of doublets. Full assignment of the proton nmr spectrum was achieved by adding D_2O to the sample in deutero-dimethylsulphoxide (D_6 DMSO), which led to a collapse of the NH_2 resonance. Interestingly, the signal at 6.77 ppm now showed a doublet of doublets (^3J HF 10.0 and ^4J HH 2.0 Hz) and this spliting is consistent with a hydrogen atom in a position *ortho* to a carbon-fluorine bond. Thus, this nmr experiment, the spectra of which are shown in figs. (23 and 24) gave unambiguous proof of the isomer since the ^3J HF coupling of 10.0 Hz is almost the same as the ^3J FH coupling of 10.4 Hz observed in the fluorine spectrum and is consistent with the isomer (39a).

Fig. () Proton nmr spectrum of (39a) in D$_6$ DMSO
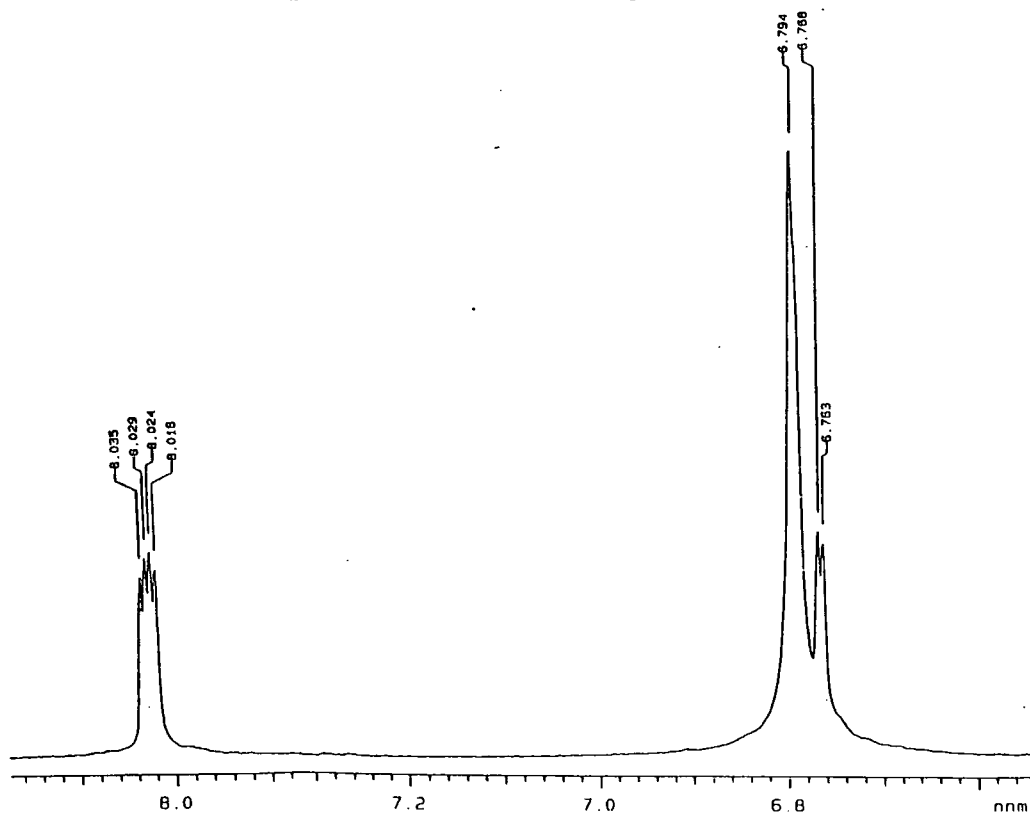
Fig. () Proton nmr spectrum of (39a) in D$_6$ DMSO and D$_2$O
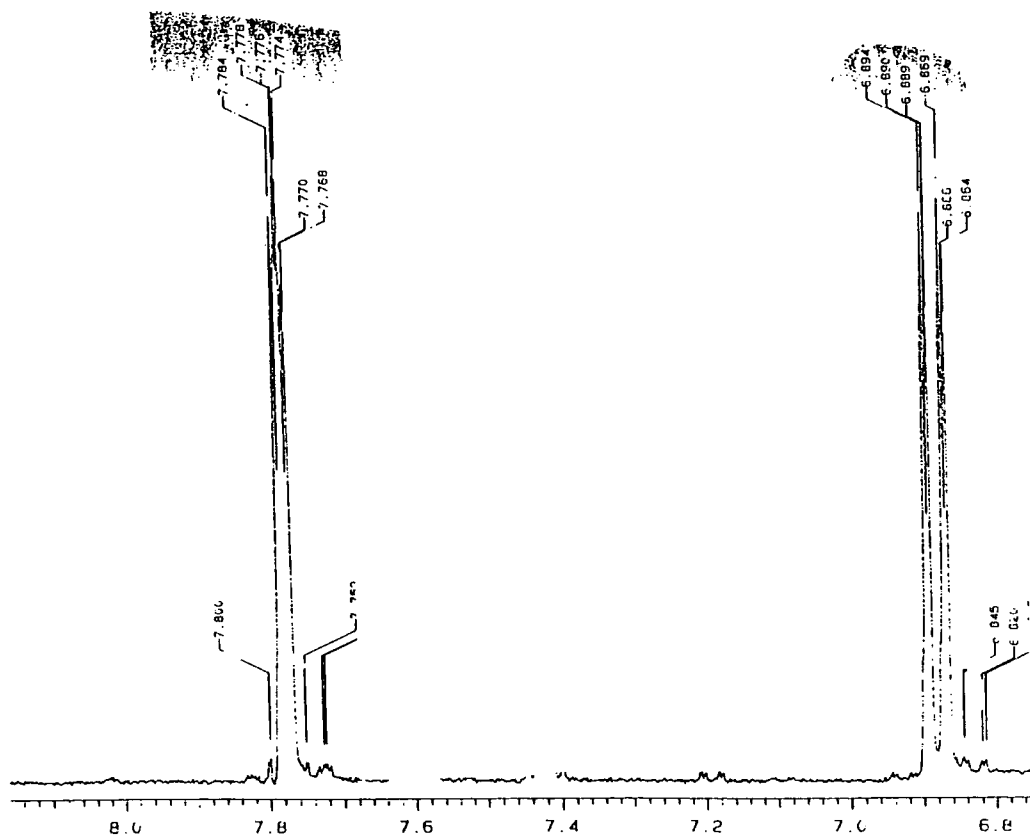
The carbon nmr spectrum was consistent with the structure and showed four doublets and a singlet. The singlet at 138.8 ppm was assigned to C-5 because although we may have anticipated ^3J coupling with the fluorine atom, of the coupling possible (^1J, ^2J, ^3J and ^4J), ^3J is typically of lower magnitude than the others and therefore C-5 was observed as a singlet. A large doublet (^1J 247 Hz) at 159.6 ppm was assigned to C-3 because this large coupling was typical of carbon bonded to fluorine. A doublet (^2J 24.4 Hz) at high field (101.6 ppm) was assigned to C-4 since carbon at the 4- position is typically found at high field. The two remaining doublets at 139.6 and 118.0 ppm were assigned by the magnitude of the coupling constants: C-2 was assigned the former (^2J 39.7 Hz) and C-6 the latter (^4J 15.2 Hz) because carbon *ortho* to C-F should show larger coupling than carbon *para* to C-F.

VI.3.3   **Further nitration reactions.** The final step in the synthesis of (40) was the nitration of (38). Nitrations of amino nitro pyridines do have precedence, for example, Ritter[202] found that nitration of 2-amino-5-nitropyridine gave the 2-nitramino compound and further reaction gave 2-amino-3,5-dinitropyridine.

38
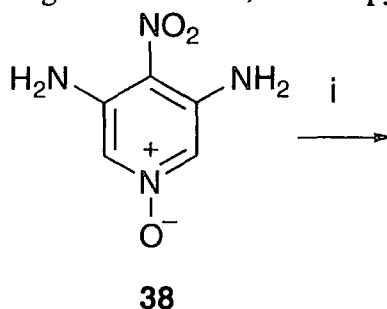
Reagents and conditions; i, Fuming HNO_3, fuming H_2SO_4, 0 °C

However, the results for the nitration of (38) have so far proved inconclusive. Slowly adding (38) to a mixture of fuming nitric and sulphuric acid at 0 °C led to an extremely vigorous reaction. We anticipated that adding the acidic mixture to ice, then neutralisation would lead to the isolation of a solid, because we expected (40) to be insoluble in water. However, no such solid was isolated, but since the compound (38) was insoluble in water, and the reaction product from this nitration *was* soluble in water, we may suggest that reaction had indeed occurred, although as yet the products are unidentified.

VI.3.4   **Conclusion**

     These results for the reaction of 3,5-dichloro-4-nitropyridine-N-oxide (36), 3,5-difluoro-4-nitropyridine-N-oxide (35a) and 3,5-difluoro-2-nitropyridine-N-oxide (35b) with ammonia present fascinating results. Thus, the nitro group was displaced in preference to chlorine for the reaction of (36) with ammonia and fluorine was displaced in preference to the nitro group for the reaction of (35a) and (35b) with ammonia. Considering that the 4- position is known to be more susceptible to nucleophilic attack

it is perhaps not surprising that (36) showed displacement of the nitro group. Similarly, the reaction of (35a) and (35b) with ammonia which showed displacement of fluorine is consistent with the known mobility of fluorine compared to the nitro group. Thus, we may conclude that for this system, the relative mobility order is $F > NO_2 > Cl$.

Instrumentation and Reagents

Gas Liquid Chromatographic Analysis

Analyses were performed on a Fisons Trio 1000 spectrometer linked to a Hewlett Packard 5890 Series II gas liquid chromatograph equipped with a 20m cross-linked methyl silicone capillary column. All GLC-MS mass spectra were generated by electron impact.

Preparative scale GC was performed on a Varian Aerograph Model 920 (catharometer detector) gas chromatograph, fitted with a 3m 10% SE30 packed column.

Elemental Analysis

Carbon, hydrogen, and nitrogen elemental analyses were obtained using a Perkin-Elmer 240 Elemental Analyser or a Carlo Erba Strumentazione 1106 Elemental Analyser.

NMR Spectra

^{1}H NMR spectra were recorded on a Bruker AC250 spectrometer operating at 250.13 MHz, a Varian Gemini VXR200 spectrometer operating at 199.98 MHz, or a Varian VXR400S spectrometer operating at 399.96 MHz. ^{19}F NMR spectra were recorded on the Bruker AC250 spectrometer operating at 235.34 MHz or on the Varian VXR400S spectrometer operating at 376.29 MHz. ^{13}C spectra were recorded on the Varian VXR400S spectrometer operating at 100.58 MHz, or the Varian Gemini VXR200 spectrometer operating at 50.29 MHz. All spectra were recorded with TMS and fluorotrichloromethane as internal references. *J* Values are given in Hz.

FT-IR Spectra

Infrared spectra were recorded on a Perkin-Elmer 1600 FT-IR spectrometer using KBr discs (solid samples) or thin films between two KBr plates (liquid samples), or volatile compounds were run in a sealed gas cell fitted with KBr plates.

Mass Spectra

Mass spectra of solid samples were recorded on a VG7070E spectrometer. Fast atom bombardment (FAB) mass spectrometry was performed on the same machine, with glycerol or glycerol/H_2O as a solvent.

Distillation

Fractional distillation of product mixtures was carried out using a Fischer Spahltroh MMS255 small concentric tube apparatus. Boiling points were recorded during the distillation.

Melting Points

Melting points were carried out at atmospheric pressure, using a Gallenkamp apparatus, and are uncorrected.

Reagents and Solvents

Unless otherwise stated, chemicals were used as received from suppliers (Aldrich, Fluorochem, Fluka, Jansen, BDH). Solvents were dried by standard methods and stored over a molecular sieve (type 4A). A current of dry nitrogen was maintained for removal of the solvent with a syringe.

Experimental to Chapter II

VII.1   Reactions of pentafluoropyridine

VII.1.a   with lithium aluminium hydride

Lithium aluminium hydride pellets (2.0 g, 53 mmol) were added to a solution of (3) (4.2 g, 25 mmol) in ether (40 cm^3) at 0 °C, under nitrogen, with stirring. After stirring at room temperature for 28 h, dilute sulphuric acid was added slowly to the mixture at 0 °C. The mixture was filtered and solvent was removed on a rotavap apparatus to yield a liquid (2.0 g), shown to consist of 2,3,5,6-tetrafluoropyridine (4) (40%), 3,5-difluoropyridine (5) (30%) and 3-fluoropyridine (6) (20%) by comparison of their fluorine nmr spectra and glcms spectra against authentic samples.

VII.1.b   with lithium aluminium hydride and 12-crown-4

A solution of pentafluoropyridine (3) (0.6 g, 3.6 mmol) in tetrahydrofuran (5 cm^3) was added to a mixture of lithium aluminium hydride (5 cm^3, 5 mmol of 1.0 M solution in ether) and 12-crown-4 (1.0 g, 5.7 mmol) in THF (10 cm^3) at 0 °C, with stirring, under an atmosphere of dry nitrogen. The mixture was stirred at 0 °C for 10 min, then at room temperature for 19 h, then iced water added and the mixture extracted into ether. The ether solution was dried (MgSO$_4$), evaporated and the products were isolated by preparative scale GLC (10% SE, 40°C), giving 2,3,5-trifluoropyridine (7, 92%) [50](Found: C, 44.9; H, 1.3; N, 10.5. Calc. for C$_5$H$_2$F$_3$N: C, 45.1; H, 1.5; N, 10.5); IR spectrum no. 2; mass spectrum no. 3; nmr spectrum no. 3.

This reaction was repeated, except that THF was replaced with ether and following work up, 2,3,5-trifluoropyridine (7, 30%) and 2,3,5,6-tetrafluoropyridine (4, 70%); mass spectrum no. 2; nmr spectrum no. 2 were obtained.

VII.1.c   with DIBAL

A Carius tube was charged with pentafluoropyridine (3) (1.0 g, 6 mmol), DIBAL (10 cm^3, 10 mmol of 1.0 M solution in DCM) and diglyme (10 cm^3). The DCM was vac transferred off and the tube was heated at 100 °C for 24 h. The tube was cooled and transfer under reduced pressure gave 2,3,5,6-tetrafluoropyridine (4) [93] (0.7 g, 77%) (Found: C, 39.8; H, 0.6; N, 9.3. C$_5$HF$_4$N requires C, 39.7; H, 0.7; N, 9.3%); mass spectrum no. 2; nmr spectrum no. 2.

VII.2   Preparation of 3,5-dichloro-2,6-difluoropyridine (4a)

3,5-Dichlorotrifluoropyridine (2a) (3.0 g, 15 mmol) was added to a solution of diisobutylaluminium hydride (DIBAL) (30 cm^3, 30 mmol of 1.0 M solution in

dichloromethane) in dry ether (30 cm^3) at 0 °C, under nitrogen, with stirring. After 68 h the mixture was cooled to 0 °C and dilute sulphuric acid added slowly. This was filtered and the product was extracted with dichloromethane (DCM). The DCM solution was dried (MgSO$_4$) and evaporated to dryness giving 3,5-dichloro-2,6-difluoropyridine (4a) [18] (2.4 g, 90%) (Found C, 31.2; N, 7.2; H, 0.39. C$_5$HCl$_2$F$_2$N requires C, 32.6; H, 0.54; N, 7.6%); IR spectrum no. 10; mass spectrum no. 25; nmr spectrum no. 1.

Experimental to Chapter III

VIII.1   Synthesis of bromofluoroheterocycles
VIII.1.a   2,4,6-Tribromo-3,5-difluoropyridine (11)

A hastalloy autoclave (equipped with a copper gasket and an Inconel bursting disc) was charged with aluminium bromide (50.0 g, 187 mmol), (3) (20.0 g, 118 mmol) and hydrogen bromide (25.0 g, 309 mmol). The autoclave was heated at 150 °C for 84 h, cooled, then excess hydrogen bromide was released and passed through a column of soda-lime. The autoclave was opened and ice water cautiously added to the solid mixture, then the mixture extracted into DCM. The DCM solution was evaporated giving 2,4,6-tribromo-3,5-difluoropyridine (11) [120] (38.0 g, 91%), m.p 110-111°C (from DCM-petroleum ether (40-60)(1 : 1) (lit., 105.5-106.5 °C[120]) (Found: C, 17.3; N, 4.1. Calc. for $C_5Br_3F_2N$: C, 17.0; N 4.0%.); IR spectrum no. 3; mass spectrum no. 8; nmr spectrum no. 5.

Reaction of pentafluoropyridine and HBr

An autoclave sprayed with PTFE was charged with pentafluoropyridine (20.0 g, 118 mmol), HBr (32.0 g, 400 mmol) and sulpholane (40 cm^3) and heated at 200 °C for 48 h. The mixture was added to water and extracted into ether. The ether solution was shown to contain pentafluoropyridine (79%) and 2,3,5,6-tetrafluoropyridine (21%) by comparison of their GCMS and fluorine nmr spectra with authentic samples.

VIII.1.b   2,4,6-Tribromo-5-fluoropyrimidine (13)

The above procedure was followed except tetrafluoropyrimidine (12) (10.9 g, 72 mmol), aluminium bromide (25.0 g, 94 mmol) and anhydrous hydrogen bromide (8.0 g, 100 mmol) were used and the vessel heated for 43 h giving a solid. The crude solid was recrystallised from toluene giving 2,4,6-tribromo-5-fluoropyrimidine (19.0 g, 57 mmol, 79%), m.p. 133°C (Found: C, 14.4; H, 0.; N, 7.6 $C_4Br_3FN_2$ requires C, 14.3; H, 0; N, 8.4%); IR spectrum no. 4; mass spectrum no. 9; nmr spectrum no. 6.

VIII.1.c   2,3-Dibromo-5,6,7,8-tetrafluoroquinoxaline (15)

A Carius tube containing hexafluoroquinoxaline (1.1 g, 4.6 mmol), acetonitrile (3 cm^3) and hydrogen bromide (1.8 g, 23 mmol) was heated in a rotating oil bath at 75 °C for 42 h. The mixture was added to dilute sodium bicarbonate (20 cm^3) and extracted into DCM. The DCM solution was dried (MgSO$_4$) and evaporated giving 2,3-dibromo-5,6,7,8-tetrafluoroquinoxaline (1.3 g, 79%), m.p. 96 °C (from DCM), (Found: C, 26.4; N, 7.9. $C_8Br_2F_4N_2$ requires C, 26.7; N, 7.8%); IR spectrum no. 5; mass spectrum no. 10; nmr spectrum no. 27.

A Carius tube containing hexafluoroquinoxaline (0.6 g, 2.5 mmol), aluminium bromide (2.5 g, 10 mmol) and hydrogen bromide (0.5 g, 6 mmol) was heated in a rotating oil bath at 150 °C for 68 h. Work up as in VIII.1.c gave (15, 13%) by comparison of its nmr and mass spectra with an authentic sample, and (16, 68%); mass spectrum no. 39. Separation (and hence isolation the products) by chromatography, sublimation and crystallisation proved difficult, therefore, this experiment was not pursued.

VII.2   Catalytic reduction of bromofluoroheterocycles
VII.2.a   Preparation of 3,5-difluoropyridine (5)

A solution of 2,4,6-tribromo-3,5-difluoropyridine (11) (34.0 g, 97 mmol) in DCM (200 cm^3) was washed with activated carbon and filtered. A palladium catalyst (3.4 g of a 5% Pd/C commercially available product) and triethylamine (45 cm^3, 31.5 g, 312 mmol) were added to the filtrate and the mixture hydrogenated in a Parr apparatus at 4 Bar for 21 h. The mixture was filtered, water (200 cm^3) added and extracted into DCM. Distillation of the DCM solution on Fischer-Spaltrohr apparatus gave *3,5-difluoropyridine* (7.0 g, 61 mmol, 63%), b.p. 92.5 °C (Found: C, 52.2; H, 3.0; N, 12.2. $C_5H_3F_2N_2$ requires C, 52.2; H, 3.0; N, 12.2%); IR spectrum no. 1; mass spectrum no. 1; nmr spectrum no. 8.

VII.2.b   Preparation of 5-fluoropyrimidine (18)

The above procedure was followed except 2,4,6-tribromo-5-fluoropyrimidine (13) (9.7 g, 30 mmol) in DCM (30 cm^3) and tri^{n}butylamine (21 cm^3, 17 g, 90 mmol) and the catalyst (Pd/C, 1.0 g of 5% commercially available product) were hydrogenated at 4 bar for 24 h giving 5-fluoropyrimidine (18) (100% conversion). A sample of 5-fluoropyrimidine was obtained by preparative scale GLC (10% SE, 40 °C) and identified by comparison of its proton and fluorine spectra[78], {lit., δ_H 8.71 (2H, d, ^3J FH 0.8), 9.14 (1H, d, ^5J FH 3.5); δ_F -135.2 (d, ^5J FH 3.5)}; mass spectrum no. 4; nmr spectrum no. 9.

VII.2.c   Preparation of 1,2,3,4-tetrahydro-5,6,7,8-tetrafluoroquinoxaline (19)

A solution of 2,3-dibromo-5,6,7,8-tetrafluoroquinoxaline (15) (1.3 g, 3.6 mmol), palladium catalyst (0.1 g of a 5% Pd/C commercially available product), triethylamine (1 cm^3) and DCM (20 cm^3) were hydrogenated in a Parr apparatus at 4 Bar for 64 h. The mixture was filtered, water (50 cm^3) added and extracted into DCM. The DCM solution was dried (MgSO$_4$), evaporated to dryness and recrystallisation from chloroform gave 1,2,3,4-tetrahydro-5,6,7,8-tetrafluoroquinoxaline (19) [82], (0.9 g, >95%), m.p. 137-138 °C (from chloroform) (lit.,[82] 148-150 °C) (Found: C, 46.3; H,

3.2; N, 12.9. $C_8H_6F_4N_2$ requires C, 46.6; H, 3.2; N, 13.6%); IR spectrum no. 8; mass spectrum no. 7; nmr spectrum no. 28.

VII.2.d   Preparation of 5,6,7,8-tetrafluoroquinoxaline (20)

A solution of 2,3-dibromo-5,6,7,8-tetrafluoroquinoxaline (15) (0.6 g, 1.7 mmol), Lindlar catalyst (0.1 g of a commercially available product), triethylamine (1 cm^3) and DCM (30 cm^3) were hydrogenated in a Parr apparatus at 4 Bar for 120 h. The mixture was filtered, water (50 cm^3) added and extracted into DCM. The DCM solution was dried (MgSO$_4$), evaporated to dryness, sublimed, then recrystallisation from ethyl acetate gave 5,6,7,8-tetrafluoroquinoxaline (20) [96] (0.15 g, 44%), m.p. 89 °C (from chloroform) (lit.,[96] 90-91 °C); IR spectrum no. 7; mass spectrum no. 6; nmr spectrum no. 44.

VII.2.e   Preparation of 3-amino-5-fluoropyridine (17)

A solution of 3-amino-2,4,6-tribromo-5-fluoropyridine (23c) (0.9 g, 2.6 mmol), triethylamine (1.1 cm^3, 7.9 mmol), palladium catalyst (0.1 g of 5% Pd-C catalyst) and DCM (15 cm^3) was hydrogenated on a Parr apparatus for 18 h. Water (20 cm^3) was added and the mixture filtered and extracted into DCM. The DCM solution was dried (MgSO$_4$) and evaporated giving *3-amino-5-fluoropyridine* (0.3 g, >95%), m.p. 86 °C (from DCM) (Found: C, 53.6; H, 4.6; N, 25.0. $C_5H_5FN_2$ requires C, 53.6; H, 4.5 N, 25.0%); IR spectrum no. 9; mass spectrum no. 5; nmr spectrum no. 29.

VII.3   Reaction of Bromofluoroheterocycles with Metal Hydrides
VII.3.a   Lithium Aluminium Hydride

A solution of (11) (0.6g, 1.7 mmol) in ether (5 ml) was added to a solution of lithium aluminium hydride (1.0g, 26 mmol) in ether (15 ml) at -50 °C, with stirring, under an atmosphere of dry nitrogen. The mixture was stirred and warmed to -10°C over 18 h, then ice water added and the mixture extracted into DCM. The DCM solution was dried (MgSO$_4$) and evaporated giving (5) (>99% conv.).

VII.3.b   Lithium Aluminium Hydride and 12-Crown-4

A solution of (11) (1.7 g, 4.8 mmol) in ether (5 cm^3) was added to a solution of lithium aluminium hydride (5 cm^3, 5 mmol of 1.0 M solution in ether) and 12-crown-4 (1.0 g, 5.7 mmol) in ether (10 cm^3) at 0 °C, with stirring, under an atmosphere of dry nitrogen. The mixture was stirred at 0 °C for 10 min, then at room temperature for 18 h, then ice water added and the mixture extracted into DCM. The DCM solution was dried (MgSO$_4$) and evaporated giving a solid, which was recrystallised from DCM giving *3,5-difluoro-2,6-dibromopyridine* (21)(1.1 g, 84%), m.p. 99-100 °C (Found: C, 21.9; H, 0.3; N, 4.8. $C_5HBr_2F_2N$ requires C, 22.0; H, 0.4; N, 5.1%); IR spectrum no. 6; mass spectrum no. 11; nmr spectrum no. 7.

VII.4   **Reactions of Pentafluoropyridine with Nucleophiles/**
              Diazotisation Route

VII.4.a   **Preparation of 4-Amino-2,3,5,6-tetrafluoropyridine (8)**

The procedure of Chambers et al.[90] was followed to afford (8).

VII.4.b   **Preparation of 2,3,5,6-Tetrafluoropyridine (4)**

Hypophosphorous acid (4.3 cm^3, 5.4 g, 40 mmol) was added to 4-aminotetrafluoropyridine (1.1 g, 7 mmol) at 0 °C, with stirring. A solution of sodium nitrite (4.0 g, 60 mmol) in water (30 cm^3) was added dropwise over 10 min. The resultant mixture was stirred at 0 °C for 0.5 h, then at room temperature for 4 h, then neutralised with dilute sodium hydroxide. The mixture was extracted into dichloromethane (DCM). The DCM solution was dried (MgSO$_4$) and evaporated to give (4)[93] (0.5 g, 47%), nmr spectrum no. 2.

VII.4.c   **Preparation of 2-Amino-3,5,6-trifluoropyridine (9)**

An autoclave charged with 2,3,5,6-tetrafluoropyridine (16.0 g, 106 mmol) and concentrated ammonia solution (50 cm^3) was heated at 100 °C for 24 h. Excess ammonia was filtered off to give a white solid (10.5 g, 71 mmol, 67%) which was sublimed (85°C, <5mmHg) yielding colourless needles. These were identified as 2-amino-3,5,6-trifluoropyridine[139](9), nmr spectrum no. 4.

VII.4.d   **Preparation of 2,3,5-Trifluoropyridine (7)**

Hypophosphorous acid (25 cm^3, 255 mmol) was added to (9) (2.4 g, 17 mmol) at 0 °C, with stirring. A solution of sodium nitrite (1.3 g, 18.7 mmol) in water (10 cm^3) was added dropwise over 10 min.

The resultant mixture was stirred at 0 °C for 1.5 h, then at room temperature for 3 h, then neutralised with dilute sodium hydroxide. The mixture was extracted into dichloromethane (DCM). The DCM solution was dried (MgSO$_4$) and evaporated giving (7)[50] (40% estimated by GC); nmr spectrum no. 3.

133

Experimental to Chapter IV

IX.1   Reactions of 2,4,6-tribromo-3,5-difluoropyridine with
         Nucleophiles

IX.1.a   Excess sodium methoxide

A tube containing 2,4,6-tribromo-3,5-difluoropyridine (11) (0.4 g, 1.1 mmol) and a ten-fold excess of sodium methoxide in methanol was sealed and left standing at room temperature for 48 h. Water (20 cm^3) was added and the mixture extracted into DCM. The DCM solution was evaporated to dryness giving a solid and recrystallisation from DCM - petrol (1: 1) gave *2,4,6-tribromo-3,5-dimethoxypyridine* (0.4 g, 100%), m.p. 145-146 °C (Found: C, 22.5; H 1.4; N, 3.3. C$_7$H$_6$Br$_3$NO$_2$ requires C, 22.3; H, 1.6; N, 3.7%); IR spectrum no. 12; mass spectrum no. 13; nmr spectrum no. 10.

IX.1.b   One equivalent sodium methoxide

A solution of (11) (1.0 g, 2.6 mmol) and sodium methoxide (0.184 g, 3.4 mmol) in methanol (3 cm^3) was stirred at room temperature for 60 h. Methanol was evaporated, water (20 cm^3) added and the mixture was extracted into DCM. The DCM solution was dried (MgSO$_4$) and evaporated to dryness. Chromatography on silica gel with DCM - petrol (1: 4) as the eluent yielded *3-fluoro-5-methoxy-2,4,6-tribromopyridine* (0.7 g, 70%), m.p. 116-118 °C (Found: C, 20.0; H 0.8; N, 3.7. C$_6$H$_3$Br$_3$FNO requires C, 19.8; H, 0.8; N, 3.9%); IR spectrum no. 11; mass spectrum no. 12; nmr spectrum no. 11.

IX.1.c   Potassium hydroxide

A mixture of (11) (1.0 g, 2.8 mmol), potassium hydroxide pellets (0.6 g) and tertiary butanol (8 cm^3) was stirred under reflux for 3 h. The mixture was cooled and acidified with dilute hydrochloric acid (30 cm^3). The mixture was extracted into DCM, then the DCM solution was dried (MgSO$_4$) and evaporated to dryness giving *3-hydroxy-5-fluoro-2,4,6-tribromopyridine* (1.0 g, 97%), m.p. 96-97 °C (from DCM) (Found: C, 17.2; H 0.2; N, 4.8. C$_5$HBr$_3$FNO requires C, 17.2; H, 0.3; N, 4.0%); IR spectrum no. 14; mass spectrum no. 14; nmr spectrum no. 14.

IX.1.d   Ammonia

A Carius tube containing (11) (1.0 g, 2.8 mmol), ammonia solution (2 cm^3) and acetonitrile (5 cm^3) was heated in a rotating oil bath at 75 °C for 72 h. Water (20 cm^3) was added and the mixture extracted into DCM, then the DCM solution was dried (MgSO$_4$) and evaporated to dryness giving a solid, which was sublimed and recrystallised from DCM giving *3-amino-5-fluoro-2,4,6-tribromopyridine* (0.9 g, 93%),

m.p. 125.5-126.5 °C (Found: C, 17.3; H, 0.6; N, 7.4. $C_5H_2Br_3FN_2$ requires C, 17.2; H, 0.6; N, 8.0%); IR spectrum no. 13; mass spectrum no. 16; nmr spectrum no. 15.

IX.1.e Sodium phenoxide

Sodium phenoxide was freshly prepared by adding sodium metal to phenol (0.45 g, 4.8 mmol) dissolved in diethyl ether (15 cm^3), under an atmosphere of dry nitrogen. This was refluxed with (11) (1.0 g, 2.8 mmol) for 23 h. Following evaporation of the ether, water (20 cm^3) was added and the mixture extracted into DCM. The DCM solution was dried (MgSO$_4$) and evaporated to give a solid (1.2 g). Fractional sublimation and recrystallisation from acetonitrile gave recovery of 2,4,6-tribromo-3,5-difluoropyridine (0.8 g, 80%) and *3-phenoxy-5-fluoro-2,4,6-tribromopyridine* (0.2 g, 20%), m.p. 100±1 °C (Found: C, 31.3; H, 1.1; N, 2.9. $C_{11}H_5Br_3FNO$ requires C, 31.0; H, 1.2; N, 3.3%); IR spectrum no. 15; mass spectrum no. 15; nmr spectrum no. 19.

Repeating this experiment, but with 2,4,6-tribromo-3,5-difluoropyridine (11) (1.0g, 2.8mmol), phenol (0.4g, 4.3mmol), sodium carbonate (1.0g) and acetonitrile (15ml) gave (23e) and 4-phenoxy-3,5-difluoro-2,6-dibromopyridine (22f); mass spectrum no. 42; nmr spectrum no. 47, in a ratio of 3:1, as determined by GCMS.

IX.1.f Diethylamine

A Carius tube charged with diethylamine (5 cm^3) and 3 (0.5 g, 1.4 mmol) was heated in a rotating oil bath at 50 °C for 95 h. Excess diethylamine was evaporated giving a solid. Water (50 cm^3) was added and the mixture extracted into DCM. The DCM solution was dried (MgSO$_4$) and evaporated to dryness, giving a solid (0.5 g), shown to consist of 4-diethylamino-2,6-dibromo-3,5-difluoropyridine (61% by fluorine nmr) and 2-diethylamino-4,6-dibromo-3,5-difluoropyridine (39% by fluorine nmr). Chromatography on silica gel with DCM - petrol (1: 1) as the eluent yielded

4-diethylamino-2,6-dibromo-3,5-difluoropyridine (0.3 g, 60%), m.p. 41-42 °C (Found: C, 31.4; H 2.9; N, 8.2. $C_9H_{10}Br_2F_2N_2$ requires C, 31.4; H, 2.9; N, 8.1%); IR spectrum no. 17; mass spectrum no. 18a; nmr spectrum no. 12.

and *2-diethylamino-4,6-dibromo-3,5-difluoropyridine* (0.2 g, 30%) (M$^+$ found 341.9179. $C_9H_{10}Br_2F_2N_2$ requires M$^+$ 341.9179); mass spectrum no. 18b; nmr spectrum no. 13.

IX.1.g Sodium thiophenolate

A solution of (11) (1.0 g, 2.8 mmol), phenylthiol (0.33 g, 3.0 mmol), acetonitrile (5 cm^3) and sodium carbonate (0.3 g) was stirred under reflux for 19 h. Water (20 cm^3) was added, then the mixture extracted into DCM. The DCM solution was dried (MgSO$_4$) and evaporated to dryness. Chromatography on silica gel with DCM - hexane (30 : 70) as the eluent yielded *2,6-dibromo-3,5-difluoro-4-thiophenoxypyridine* (0.9 g, 85%), m.p.

65.5-66.5 °C (Found: C, 34.45; H, 1.3; N, 3.2. $C_{11}H_5Br_2F_2NS$ requires C, 34.7; H, 1.3; N, 3.7%); IR spectrum no. 16; mass spectrum no. 19; nmr spectrum no. 16.

IX.1.h   Piperidine

A solution of (11) (1.0 g, 2.8 mmol), piperidine (0.3 cm^3, 0.3 g, 3.0 mmol) and acetonitrile (5 cm^3) was stirred at reflux for 23 h. Water (20 cm^3) added, then the mixture extracted into DCM. The DCM solution was dried (MgSO$_4$) and evaporated to dryness. Chromatography on silica gel with DCM - hexane (1: 1) as the eluent yielded 3,5-difluoro-2,4,6-tribromopyridine (0.6 g, 60%) and *4-piperidino-3,5-difluoro-2,6-dibromopyridine* *(0.4 g, 40%), m.p. 107-109 °C (Found: C, 33.6; H, 3.1; N, 7.1;. $C_{10}H_{10}Br_2F_2N_2$ requires C, 33.7; H, 2.8; N, 7.9%); IR spectrum no. 18a; mass spectrum no. 20a; nmr spectrum no. 17 and *2-piperidino-3,5-difluoro-4,6-dibromopyridine* * mass spectrum no. 20b; nmr spectrum no. 18.

*The ratio of the 4- : 2- isomer was 4 : 1, as estimated from the fluorine nmr spectrum, however, sufficient quantities of the 2-isomer were not recovered for characterisation.

IX.1.i   Sodium amide

A solution of (11) (0.8 g, 2.3 mmol) in acetonitrile (10 cm^3) was added to sodium amide (0.7 g, 18 mmol) at 0 °C, with stirring, under nitrogen, then heated to reflux for 1 h. Water (20 cm^3) was added and the mixture extracted into DCM. The solution was evaporated giving a solid (0.8 g), consisting of (11) (68%) and 2,6-dibromo-3,5-difluoropyridine (21) (32%) by fluorine nmr against an internal standard (2-fluoropyridine).

Sodium amide in the presence of a radical inhibitor

A solution of (11) (0.5 g, 1.4 mmol) and 1,3-dinitrobenzene (0.4 g, 2.4 mmol) in acetonitrile (10 cm^3) was added to sodium amide (0.7 g, 18 mmol) at 0 °C, with stirring, under nitrogen, then heated at 50 °C for 40 h. Water (20 cm^3) was added and the mixture extracted into DCM. The solution was evaporated giving a solid (0.5 g). A fluorine nmr and GCMS showed the solid to contain (21) (100%, 42% conv.) by comparison with an authentic sample.

Sodium amide in the presence of a radical inhibitor in the dark

The above reaction was repeated except (11) (0.5 g, 1.4 mmol) was used, and 1,3-dinitrobenzene (0.4 g) was added. The mixture was stirred for 40 h at 50 °C in the dark. Water (20 cm^3) was added and the mixture extracted into DCM, which was evaporated giving a solid (0.5 g), shown to consist of (11) (58%) and (21) (42%) by fluorine nmr and GCMS.

136

IX.1.j   1-Trimethylsilyloxycyclohexene and potassium fluoride

1-Trimethylsilyloxycyclohexene (0.7 g, 3.9 mmol) was added to a mixture of (11) (0.5 g, 1.4 mmol), dry potassium fluoride (0.5 g) and acetonitrile, at room temperature, with stirring under nitrogen. The mixture stirred at room temperature for 16 h, then at 60 °C for 8 h. Water (20 cm^3) was added and the mixture extracted into DCM. Evaporation of the solution gave *2,6-dibromo-3,5-difluoropyridine* (0.3 g, 79%), m.p. 99-100 °C (from DCM-40/60 petroleum ether, 1 : 1) (Found: C, 21.9; H, 0.3; N, 4.8. C$_5$HBr$_2$F$_2$N requires C, 22.0; H, 0.4; N, 5.1%); IR spectrum no. 6; mass spectrum no. 11; nmr spectrum no. 7.

This reaction was repeated except 1,3-dinitrobenzene (0.4 g, 2.4 mmol) was added to a mixture of (11) (0.5 g, 1.4 mmol), potassium fluoride (3.0 g) and 1-trimethylsilyloxycyclohexene (1.0 g, 6 mmol) in acetonitrile (10 cm^3) and the reaction was carried out in the dark to afford a solid (0.4 g), shown to contain (21) (100% conv., 51% yield).

IX.1.k   2-Trimethylsilyloxypent-2-ene-4-one and potassium fluoride

2-Trimethylsilyloxypent-2-ene-4-one (1.0 g, 5.6 mmol) was added to a mixture of (11) (1.0 g, 2.8 mmol), dry potassium fluoride (1.5 g) and acetonitrile (15 cm^3), at room temperature, with stirring under nitrogen. The mixture was stirred at 60 °C for 18 h. Water (20 cm^3) was added and the mixture extracted into DCM. Evaporation of the solution gave a solid (1.2 g) which was shown to contain (21) (>90%) by comparison of its fluorine and proton nmr spectra and GCMS data with an authentic sample.

IX.1.k   Lithium methoxide

Lithium methoxide (3 cm^3, 3mmol of 1.0M solution in methanol) was added to (11) (1.0 g, 2.8 mmol) in methanol (15 cm^3) at 0 °C, with stirring, under an atmosphere of nitrogen. The mixture was stirred at room temperature for 67 h, then water (20 cm^3) was added and the mixture extracted into dichloromethane (DCM). The DCM solution was dried (MgSO$_4$) and evaporated giving a solid (1.1 g) shown to consist of 4-methoxy-3,5-difluoro-2,6-dibromopyridine (22g) (19%), 2,6-dibromo-4,5-dimethoxy-3-fluoropyridine (22h) (5%), (23b) (39% by comparison with authentic sample) and (23a) (36%). Neither column chromatography (eluting DCM and petrol 7 : 3) nor preparative scale GLC (10% SE30, 140 °C) gave adequate separation of the products. However, a carbon nmr spectrum and GCMS of a mixture of (22g) and (23b) was obtained and the carbon spectra was assigned by comparison with that of (23b).

IX.1.k   Lithium methoxide and 12-crown-4

Experiment IX.1.k was repeated, except that (11) was added to a solution of lithium methoxide and 12-crown-4 (1.4 g, 8 mmol) in methanol. After 48 h, work up gave 4-methoxy-3,5-difluoro-2,6-dibromopyridine (22g, 9%), 2,6-dibromo-4,5-

dimethoxy-3-fluoropyridine (22h, 2%) and (23b, 18%) and (23a, 71%) as determined by comparison with authentic samples.

IX.2   Reactions of 2,4,6-tribromo-5-fluoropyrimidine (13) with nucleophiles

IX.2.a   Piperidine

A solution of 2,4,6-tribromo-5-fluoropyrimidine (13) (1.0 g, 3 mmol), piperidine (0.5 cm^3) and acetonitrile (5 cm^3) was stirred at reflux for 88 h. Water (20 cm^3) was added, then the mixture extracted into dichloromethane (DCM). The DCM solution was evaporated to dryness giving a solid (0.9 g). Chromatography on silica gel with DCM as eluent yielded *2,6-dibromo-5-fluoro-4-piperidinopyrimidine* (0.6 g, 60%), m.p. 107 °C, (Found: C, 31.8; N, 12.2; H, 3.0. C$_9$H$_{10}$Br$_2$FN$_3$ requires C, 31.9; N, 12.4; H, 2.95%); IR spectrum no. 20; mass spectrum no. 21; nmr spectrum no. 31.

IX.2.b   Sodium methoxide

A mixture of sodium methoxide (0.5 g, 13 mmol) and 2,4,6-tribromo-5-fluoropyrimidine (13) (1.0 g, 2.8 mmol) was stirred at room temperature for 1.5 h. Water (30 cm^3) was added and the mixture extracted into DCM. The solution was evaporated to dryness giving 2,4,6-trimethoxy-5-fluoropyrimidine (0.4 g, 71%)[97], m.p. 95 °C (from toluene), (Found: C, 44.6; N, 14.8; H, 4.75. C$_7$H$_9$FN$_2$O$_3$ requires C, 44.7; N, 14.9; H, 4.8%); IR spectrum no. 19; mass spectrum no. 22; nmr spectrum no. 32.

IX.3   Reactions of 2,3-dibromo-5,6,7,8-tetrafluoroquinoxaline (15) with nucleophiles

IX.3.a   2,3-Dipiperidino-5,6,7,8-tetrafluoroquinoxaline (15a)

Piperidine (2 cm^3) was added to (15) (0.6 g, 1.7 mmol) and acetonitrile (15 cm^3) at room temperature, with stirring. The mixture was heated at reflux for 16 h, then water (30 cm^3) was added. The mixture was extracted into DCM, dried (MgSO$_4$), then evaporated to dryness giving a solid (0.7 g). Chromatography on silica gel with DCM-hexane (70 : 30) as the eluent yielded *2,3-dipiperidino-5,6,7,8-tetrafluoroquinoxaline* (0.3 g, 80%), m.p. 146 °C (from hexane), (Found: C, 58.5; H, 5.3; N, 14.8. C$_{18}$H$_{20}$N$_4$F$_4$ requires C, 58.7; H, 4.8; N, 15.2%); IR spectrum no. 21; mass spectrum no. 23; nmr spectrum no. 39.

IX.3.b   2,3-Dimethoxy-5,6,7,8-tetrafluoroquinoxaline (15b)

Lithium methoxide (1 cm^3 of a 1.0 M solution in methanol) was added to (15) (0.34 g, 1.0 mmol) and anhydrous methanol (5 cm^3) at room temperature, with stirring. The mixture was stirred at room temperature for 21 h, then water (40 cm^3) was added. The mixture was extracted into DCM, dried (MgSO$_4$), then evaporated to dryness giving

2,3-dimethoxy-5,6,7,8-tetrafluoroquinoxaline[96] (0.25 g, >95%), m.p. 133 °C (from hexane)(lit., 146-148 °C[96]); IR spectrum no. 22; mass spectrum no. 24; nmr spectrum no. 40.

Experimental to Chapter V

X.1   **Palladium mediated reactions of bromofluoroheterocycles with alkynes**

X.1.a   **Preparation of 2,4-dibromo-3,5-difluoro-6-(phenylacetylenyl)pyridine (25a) and 4-bromo-3,5-difluoro-2,6-di(phenylacetylenyl)pyridine (25b)**

A mixture of (11) (1.0 g, 2.8 mmol), phenylacetylene (0.5 g, 5 mmol), copper (I) iodide (0.01 g, 0.05 mmol)), bis(triphenylphosphine)palladium dichloride (0.04 g, 0.06 mmol) and triethylamine (10 cm^3) was stirred, under an atmosphere of dry nitrogen, at room temperature for 16 h. Water (30 cm^3) was added and the mixture was filtered and extracted into DCM. The DCM solution was dried (MgSO$_4$) and evaporated giving a solid (1.1 g). Chromatography on alumina with hexane as the eluent yielded *2,4-dibromo-3,5-difluoro-6-(phenylacetylenyl)pyridine* (0.4 g, 38%), m.p. 156 °C (from DCM) (Found: C, 42.2; H, 1.3; N, 3.5. C$_{13}$H$_5$Br$_2$F$_2$N requires C, 41.8; H, 1.3; N, 3.8%); IR spectrum no. 32; mass spectrum no. 27; nmr spectrum no. 33 and *4-bromo-3,5-difluoro-2,6-di(phenylacetylenyl)pyridine* (0.5g, 45%), m.p.188 °C (from chloroform) (Found: C, 64.1; H, 2.3; N, 3.4. C$_{21}$H$_{10}$BrF$_2$N requires C, 64.0; H, 2.5; N, 3.6%); IR spectrum no. 33; mass spectrum no. 28; nmr spectrum no. 34.

X.1.b   Preparation of 4-bromo-3,5-difluoro-2,6-di(phenylacetylenyl)pyridine (25b)

A mixture of (11) (1.0 g, 2.8 mmol), phenylacetylene (2.0 g, 20 mmol), copper (I) iodide (0.01 g, 0.05 mmol)), bis(triphenylphosphine)palladium dichloride (0.04 g, 0.06 mmol) and triethylamine (80 cm^3) was stirred, under an atmosphere of dry nitrogen, at room temperature for 88 h. Water (30 cm^3) and dilute sodium dicarbonate solution was added and the mixture was filtered and extracted into DCM. The DCM solution was dried (MgSO$_4$)and evaporated giving a solid (1.7 g). Chromatography on alumina with hexane and DCM (50 : 50) as eluent yielded (25b) (0.8 g, 72%) by comparison of its carbon and fluorine nmr and elemental analysis and 1,4-diphenylbut-1,3-diyne (0.3 g), m.p. 85 °C (lit., 86-87 °C) (Found: C, 94.4; H, 4.95. C$_{16}$H$_{10}$ requires C, 95.0; H, 4.95%), IR spectrum no. 36; mass spectrum no. 41.

X.1.c   Preparation of 2,6-Dipentynyl-3,5-difluoro-4-bromopyridine (26)

1-Pentyne (0.5 cm^3, 6 mmol) was added to a mixture of (11) (1.0 g, 2.8 mmol), copper (I) iodide (0.1 g), palladium (II) acetate (0.04 g), triphenylphosphine (0.08 g) and triethylamine (15 cm^3) at room temperature, under nitrogen, with stirring. The mixture

was stirred at room temperature for 66 h, then added to water (50 cm^3) and extracted into DCM, dried (MgSO$_4$), then evaporated to dryness giving a solid (1.1 g). Chromatography on silica gel with DCM-hexane (50 : 50) as the eluent yielded *2,6-dipentynyl-3,5-difluoro-4-bromopyridine* (0.6 g, 66%), m.p. 84 °C (from hexane) (Found: C, 55.7; H, 4.4; N, 4.4. C$_{15}$H$_{14}$BrF$_2$N requires C, 55.2; H, 4.3; N, 4.3%); IR spectrum no. 35; mass spectrum no. 26; nmr spectrum no. 38.

X.1.d   Preparation of 2,3-Dipentynyl-5,6,7,8-tetrafluoroquinoxaline (28)

1-Pentyne (0.6 cm^3, 7 mmol) was added to a mixture of 2,3-dibromo-5,6,7,8-tetrafluoroquinoxaline (15) (0.45 g, 1.3 mmol), copper (I) iodide (0.06 g), bis(triphenylphosphine) palladium dichloride (0.04 g) and triethylamine (20 cm^3) at room temperature, under nitrogen, with stirring. The mixture was stirred at room temperature for 16 h, then at 40 °C for 24 h, then added to water (30 cm^3). The mixture was filtered, washed and extracted into DCM, dried (MgSO$_4$), then evaporated to dryness giving a solid (0.5 g). Chromatography on silica gel with hexane-DCM (70 : 30) as the eluent yielded *2,3-dipentynyl-5,6,7,8-tetrafluoroquinoxaline* (0.3 g, 69%), m.p. 71-73 °C (Found: C, 64.3; H, 4.3; N, 8.2. C$_{18}$H$_{14}$F$_4$N$_2$ requires C, 64.7; H, 4.2; N, 8.4%); IR spectrum no. 34; mass spectrum no. 30; nmr spectrum no. 46.

X.1.e   Preparation of 2,4,6-Triphenylacetylenyl-5-fluoropyrimidine (27)

Phenylacetylene (0.35 cm^3, 3.2 mmol) was added to a mixture of 2,4,6-tribromo-5-fluoropyrimidine (13) (1.0 g, 3.0 mmol), copper (I) iodide (0.1 g), bistriphenylphosphine palladium dichloride (0.04 g) and triethylamine (15 cm^3) at room temperature, under nitrogen, with stirring. The mixture was stirred at room temperature for 15 h, then at 40 °C for 3 h, then added to water (50 cm^3). The mixture was filtered, washed and extracted into DCM, dried (MgSO$_4$), then evaporated to dryness giving a solid (1.4 g). Chromatography on silica gel with hexane-DCM (50 : 50) as the eluent yielded *2,4,6-triphenylacetylenyl-5-fluoropyrimidine* (0.5 g, 42%), m.p. 234 °C (from chloroform) (Found: C, 83.9; H, 3.7; N, 6.9. C$_{28}$H$_{15}$FN$_2$ requires C, 84.4; H, 3.8; N, 7.0%); IR spectrum no. 37; mass spectrum no. 29; nmr spectrum no. 41 and 1,4-diphenyl-1,3-butadiyne (0.1 g), IR spectrum no. 36.

X.2   Lithiations of 3,5-difluoropyridine (5)
X.2.a   with butyl lithium in ether

A solution of (5) (0.37 g, 3.2 mmol) in ether (5 cm^3) was added to a solution of butyllithium (2.5 cm^3, 4 mmol of 1.6 M soln in hexanes) and tetramethylethylenediamine (TMEDA) (0.8 cm^3, 0.62 g, 5 mmol) in dry ether at -78 °C, with stirring, under an atmosphere of dry nitrogen. After 1.25 h, trimethylsilylchloride (0.8 cm^3) was added and

the mixture stirred at -78 °C for 1.5 h, then at room temperature for 0.5 h. Water (20 cm^3) was added and the mixture extracted into ether. The ether solution was dried (MgSO$_4$) and evaporated to give an oil. Chromatography on silica gel with DCM as the eluent yielded *3,5-difluoro-4-trimethylsilylpyridine* (0.4 g, 65%) (M$^+$ found 187.0629. C$_8$H$_{11}$F$_2$NSi requires M$^+$ 187.0629); mass spectrum no. 40; nmr spectrum no. 20.

X.2.b   with butyl lithium in THF

A solution of (5) (0.45 g, 3.9 mmol) in tetrahydrofuran (5 cm^3) was added to a solution of butyllithium (3.0 cm^3, 4.8 mmol of 1.6 M soln in hexanes) and TMEDA (0.8 cm^3, 0.62 g, 5 mmol) in dry tetrahydrofuran (10 cm^3), at -78 °C, with stirring, under an atmosphere of dry nitrogen. After 2 h, an nmr sample was taken and allowed to warm to room temperature*. Work up of the remaining mixture as above afforded (32) (0.4 g, 100% conversion).

* The initially light colour rapidly darkened on warming. However, the unreacted 4-lithio salt (31) was observed by fluorine nmr at room temperature, nmr spectrum no. 48, with traces (<5%) of the 2-lithio (or 2,4-dilithio) salt, δ_F (235.342 MHz, CFCl$_3$) -101.5 (s) and -113.8 (s).

X.3   Lithiations of 2,4,6-Tribromo-3,5-difluoropyridine (11)
X.3.a   Preparation of 2,6-dibromo-3,5-difluoropyridine (21)

Either a solution of butyllithium (2.2 cm^3, 3.5 mmol of 1.6 M solution in hexanes) or LDA (1.8 cm^3 of 2.0 M solution in THF/ heptane/ ethylbenzene) was added to (11) (1.0 g, 2.8 mmol) in ether (10 cm^3), at -78 °C, with stirring, under an atmosphere of dry nitrogen. After stirring at -78 °C for 3.5 h, water (1 cm^3) was added and the mixture warmed to room temperature and stirred for 1 h. Water (20cm^3) was added and the mixture extracted into DCM. The DCM solution was dried (MgSO$_4$) and evaporated giving a solid (0.8 g), which was shown by fluorine nmr to consist of (11) (10%) and 2,6-dibromo-3,5-difluoropyridine (21) (90%).

X.3.b   4-Lithio-2,6-dibromo-3,5-difluoropyridine (29)

Butyl lithium was reacted with (11) at -78°C as above. After stirring at -78 °C for 1h, the solution was warmed to room temperature and stirred for 3h. A crude fluorine nmr spectrum of the mixture clearly showed the presence of the anion (29), along with the 4-hydro derivative, (21) in a ratio of 3:1; nmr spectra no's. 7 and 37. Hydrolysis with water and work up as above gave (21) (0.6 g, 77%).

X.3.c   Synthesis of 4-allyl-2,6-dibromo-3,5-difluoropyridine (30)

Butyl lithium (1.9 cm^3, 3 mmol of 1.0M solution in ether) was added to a solution of (11) (1.0 g, 2.8 mmol) in ether (15 cm^3) at -78 °C, with stirring, under an atmosphere of dry nitrogen. After 1 h, allyl bromide (0.8 cm^3) was added and the

mixture was stirred for 0.5 h at -78 °C, then warmed to room temperature. Water (40 cm³) was added and the mixture was extracted into DCM. The DCM solution was dried (MgSO₄)and evaporated. Chromatography on silica gel with ethyl acetate and hexane (20 : 80) as eluent yielded *4-allyl-2,6-dibromo-3,5-difluoropyridine* (0.6 g, 71%) (M⁺ found 312.8736. C₈H₅Br₂F₂N requires M⁺ 312.8736); IR spectrum no. 31; mass spectrum no. 38; nmr spectrum no. 35 and (21) (< 0.1 g) by comparison with an authentic sample.

X.3.d   Attempted decomposition and trapping of the lithio anion (29)

A solution of 4-lithio-2,6-dibromo-3,5-difluoropyridine (29) was prepared at -78 °C as above. After 1 h, furan (2 cm³) was added and the solution warmed to room temperature and stirred for 3 h. A crude fluorine nmr spectrum of the mixture clearly showed that the anion (29) had remained predominantly unreacted. Hydrolysis with water and standard work up afforded 2,6-dibromo-3,5-difluoropyridine (21) as the major product (>95%) in a tarry solid (0.6 g).

The experiment was repeated, except that furan (2 cm³) was added to the solution of lithio salt (29) at -78 °C. The mixture was then refluxed for 2 h. Work up gave a tar, which was not shown to contain identifiable products by GCMS and fluorine nmr.

X.4   Zinc derivatives of 2,4,6-tribromo-3,5-difluoropyridine (11)
X.4.a   Reaction of (11) with zinc in DMF

A mixture of DMF (5 cm³), 2,4,6-tribromo-3,5-difluoropyridine (0.8 g, 2.3 mmol) and zinc dust (1.0 g) was stirred at room temperature under an atmosphere of dry nitrogen for 0.5 h and then at 40 °C for 1 h. Three products were characterised by fluorine nmr: (33a and b); nmr spectrum no. 36 and (21); nmr spectrum no. 7 in a ratio of 10 : 1. A few drops of water were added to a nmr tube of the above sample and after 19 h only (21) was observed by fluorine nmr.

X.4.b   Reaction of (11) with zinc in THF

A mixture of zinc granules (0.2 g, 30-100 micron), (11) (1.0 g, 2.8 mmol) and tetrahydrofuran (THF) were stirred under an atmosphere of dry nitrogen at 50 °C for 23 h. A fluorine nmr spectrum of the crude sample clearly showed the presence of the zinc compounds (33a and 33b) (75% (combined mol %)) and the reduced pyridine, (21, 25 mol %); nmr spectrum no's. 36 and 7. Allyl bromide (0.5 cm³) was added and after all the zinc was consumed (0.25 h), water (30 cm³) was added and the mixture extracted into DCM. A fluorine nmr spectrum of the DCM solution showed the presence of (21) (26%) and (30) (74%, by comparison with an internal standard - 2-fluoropyridine).

Chapter XI

Experimental to Chapter VI

XI.1   Preparation of N-oxides
XI.1.a   3,5-difluoropyridine-N-oxide   (5a)

A solution of (5) (0.37 g, 3 mmol), peracetic acid (1.5 cm^3 of 40% solution in acetic acid) in acetic acid (5 cm^3) and chloroform (10 cm^3) was heated at 50 °C, with stirring, for 24 h. The mixture was neutralised by the addition of dilute sodium hydroxide to the chilled mixture, then remaining peroxides were destroyed by the addition of sodium metabisulphite (2 g). Following extraction into DCM, the DCM solution was dried (MgSO$_4$) and evaporated to dryness giving a solid which was recrystallised from DCM - petrol (1:1) to yield *3,5-difluoropyridine-N-oxide* (0.3 g, 71%), m.p. 136.5 °C (Found: C, 45.5; H, 2.3; N, 10.1. C$_5$H$_3$F$_2$NO requires C, 45.8; H, 2.3; N, 10.7%); IR spectra no. 23; mass spectra no. 31; nmr spectrum no. 21.

XI.1.b   3,5-Dichloropyridine-N-oxide   (34a)

3,5-Dichloropyridine (7.5 g, 51 mmol), chloroform (50 cm^3) and peracetic acid (39 cm^3 of 40% solution in acetic acid) were stirred at 50 °C for 67 h. The mixture was neutralised at 0 °C, with dilute sodium hydroxide and peroxides were destroyed with sodium metabisulphite, then the mixture was filtered, extracted into DCM, dried (MgSO$_4$) and evaporated to dryness giving *3,5-dichloropyridine-N-oxide* (8.0 g, 96%), m.p. 111.0 °C (from DCM) (Found: C, 36.3; H, 1.7; N, 8.1. C$_5$H$_3$Cl$_2$NO requires C, 36.6; H, 1.8; N, 8.5%); IR spectra no. 28; mass spectra no. 35; nmr spectrum no. 43.

XI.2   Preparation of nitro-N-oxides
XI.2.a   Nitration of 3,5-difluoropyridine-N-oxide (5a)

3,5-Difluoropyridine-N-oxide (5a) (2.0 g, 15.2 mmol) was added to a mixture of fuming sulphuric acid (15 cm^3) and fuming nitric acid (10 cm^3) at 0 °C, with stirring. The mixture was heated at 100 °C for 4 h, then added to iced water (10 cm^3) and neutralised with sodium bicarbonate solution. The mixture was extracted into DCM using continuous extraction apparatus, then the DCM solution was dried (MgSO$_4$). Column chromatography (eluting DCM/ ethyl acetate) on silica gel afforded recovery of (5a) (0.25 g, 13%), *3,5-difluoro-4-nitropyridine-N-oxide* (0.75 g, 32% based on 87% conversion) m.p. 124 °C (Found: C, 34.2; H, 1.2; N, 15.9. C$_5$H$_2$F$_2$N$_2$O$_3$ requires C, 34.1; H, 1.1; N, 15.9%); IR spectra no. 24; mass spectra no. 32a; nmr spectrum no. 22; crystal structure no. 1 and *3,5-difluoro-2-nitropyridine-N-oxide* (0.07 g, 3% based on 87% conversion); nmr spectrum no. 23.

Nitrations of (5a) were attempted with nitronium tetrafluoroborate as follows: i, (5a, 0.3 g, 2.3 mmol) was added to nitronium tetrafluoroborate (0.4 g, 3 mmol) and sulpholane (10 cm^3) at 0 °C, with stirring, under nitrogen, then heated at 65 °C for 10 h. The mixture was added to water and extracted into ether and a fluorine nmr spectrum of the crude ether mixture showed no conversion of (5a) had occurred. ii, (5a, 0.3 g, 2.3 mmol) was added to nitronium tetrafluoroborate (0.4 g, 3 mmol) and triflic acid (10 cm^3) at 0 °C, with stirring, under nitrogen, then stirred at room temperature over night. Work up with water as above gave only unreacted (5a).

XI.2.b   Nitration of 3,5-dichloropyridine-N-oxide (34a)

3,5-Dichloropyridine-N-oxide (34a) (1.0 g, 6.1 mmol) was added to a mixture of concentrated sulphuric acid (15 cm^3) and fuming nitric acid (10 cm^3) at 0 °C, with stirring. The mixture was heated at 100 °C for 5 h, then added to iced water (10 cm^3) and neutralised with sodium bicarbonate solution. The mixture was extracted into DCM using continuous extraction apparatus, then the DCM solution was dried (MgSO4) and evaporated to dryness giving *4-nitro-3,5-dichloropyridine-N-oxide* (0.9 g, 71%), m.p. 141 °C (from CHCl3) (Found: C, 28.6; H, 0.9; N, 13.1. C5H2Cl2N2O3 requires C, 28.7; H, 1.0; N, 13.4%); IR spectra no. 29; mass spectra no. 36; nmr spectrum no. 42.

XI.3   Preparation of amino-N-oxides
XI.3.a   Reaction of ammonia with (35a) and (35b)

Ammonia gas was bubbled through a solution of (35a) (1.0 g, 5.7 mmol) and (35b) (0.1 g, 0.6 mmol) in acetonitrile, at 70 °C, with stirring for 3 h. The mixture was filtered and washed with acetonitrile. The resulting solid (1.25 g)was added to water (to remove ammonium hydrofluoride) and filtered and dried, then recrystallised from methyl sulphoxide and water, giving *3,5-diamino-4-nitropyridine-N-oxide* (38) (0.55 g, 57%), m.p. decomp. > 300 °C (Found: C, 30.8; H, 3.3; N, 29.2. C5H4FN3O3.H2O requires C, 31.7; H, 4.2; N, 27.5%); IR spectra no. 27; mass spectra no. 34; nmr spectrum no. 24; crystal structure no. 2. The filtrate was evaporated to dryness giving a solid (0.34 g). Chromatography on silica gel with acetonitrile and ethylacetate (50/50) as the eluent gave *3-amino-5-fluoro-2-nitropyridine-N-oxide* (0.07 g, 8%), m.p. decomp. (from ethyl acetate and acetonitrile) (Found: C, 34.6; H, 2.4; N, 24.2. C5H4FN3O3 requires C, 34.7; H, 2.3 N, 24.3%); IR spectra no. 25; mass spectra no. 33b; nmr spectrum no. 25. and *3-amino-5-fluoro-4-nitropyridine-N-oxide* (0.15 g, 15%), m.p. decomp. > 200 °C; (M+ found 173.0237. C5H4FN3O3 requires M+ 173.0237); IR spectra no. 26; mass spectra no. 33a; nmr spectrum no. 26.

145

XI.3.b   Reaction of ammonia with 4-nitro-3,5-dichloropyridine-N-oxide (36)

A sealed Carius tube containing 4-nitro-3,5-dichloropyridine-N-oxide (36) (0.4 g, 1.9 mmol), aqueous ammonia (1 cm³ of 0.88 gl⁻¹ solution) and acetonitrile (1 cm³) was heated in a rotating oil bath at 70 °C for 3 h. The mixture was filtered giving a solid (0.1 g) and a filtrate, which was extracted into DCM, dried (MgSO₄) and evaporated giving a residue (0.0 g). The solid obtained from the filtration was recrystallised from hot methanol giving *4-amino-3,5-dichloropyridine-N-oxide* (0.1 g, 30%), m.p. 210 °C from MeOH) (M⁺ found 177.9701. C₅H₄Cl₂N₂O requires M⁺ 177.9701); IR spectra no. 30; mass spectra no. 37; nmr spectrum no. 45.

XI.4   Further nitrations

3,5-Diamino-4-nitropyridine-N-oxide (0.4 g) was added slowly (over 1.5 h) to a mixture of fuming nitric acid (3 cm3) and fuming sulphuric acid (4.5 cm3) at 0 °C with stirring. The mixture was stirred at room temperature for 4 h, then added to ice and neutralised with aqueous sodium bicarbonate.

1. 3,5-Dichloro-3,5-difluoropyridine (4a)

2. 2,3,5,6-Tetrafluoropyridine (4)

3. 2,3,5-Trifluoropyridine (7)

4. 3,5,6-Trifluoro-2-aminopyridine (9)

5. 2,4,6-Tribromo-3,5-difluoropyridine (11)

6. 2,4,6-Tribromo-5-fluoropyrimidine (13)

7. 2,6-Dibromo-3,5-difluoropyridine (21)

8. 3,5-Difluoropyridine (5)

9. 5-Fluoropyrimidine (18)

10. 2,4,6-Tribromo-3,5-dimethoxypyridine (23b)

11. 2,4,6-Tribromo-3-fluoro-5-methoxypyridine (23a)

12. 2,6-Dibromo-3,5-difluoro-4-diethylaminopyridine (22b)

13. 2,4-Dibromo-3,5-difluoro-6-diethylaminopyridine (22c)

14. 2,4,6-Tribromo-3-fluoro-5-hydroxypyridine (23d)

15. 2,4,6-Tribromo-3-fluoro-5-aminopyridine (23c)

16. 2,6-Dibromo-3,5-difluoro-4-thiophenoxypyridine (22a)

17. 2,6-Dibromo-3,5-difluoro-4-piperidinopyridine (22d)

18. 2,4-Dibromo-3,5-difluoro-6-diethylaminopyridine (22e)

19. 2,4,6-Tribromo-3-fluoro-5-phenoxypyridine (23e)

20. 4-Trimethylsilyl-3,5-difluoropyridine (32)

21. 3,5-Difluoropyridine-N-oxide (5a)

22. 3,5-Difluoro-4-nitropyridine-N-oxide (35a)

23. 3,5-Difluoro-2-nitropyridine-N-oxide (35b)

24. 4-Nitro-3,5-diaminopyridine-N-oxide (38)

25. 3-Fluoro-5-amino-6-nitropyridine-N-oxide (39a)

26. 3-Fluoro-4-nitro-5-aminopyridine-N-oxide (39b)

27. 2,3-Dibromotetrafluoroquinoxaline (15)

28. 1,2,3,4-Tetrahydro-5,6,7,8-tetrafluoroquinoxaline (19)

29. 3-Fluoro-5-aminopyridine (17)

30. 2,6-Dibromo-3,5-difluoro-4-methoxypyridine (22g)

31. 2,6-Dibromo-5-fluoro-4-piperidinopyrimidine (22g)

32. 5-Fluoro-2,4,6-trimethoxypyrimidine (13b)

33. 2,4-Dibromo-3,5-difluoro-6-(phenylacetylenyl)pyridine (25a)

34. 4-Bromo-3,5-difluoro-2,6-di(phenylacetylenyl)pyridine (25b)

35. 2,6-Dibromo-3,5-difluoro-4-allylpyridine (30)

36. Zinc derivatives (33a and 33b)

37. Lithium derivative (29)

Spectrum No. 1
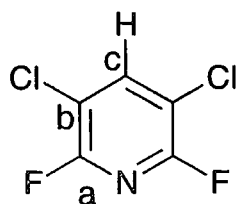
Chemical Shift (ppm)	Multiplicity	Coupling constants (Hz)	Integral	Assignment
^{19}F				
-72.32	d	$^4J_{FH}$ 6.0	-	a
^1H				
7.99	t	$^4J_{HF}$ 7.6	-	c
^{13}C				
154.5	dd	$^1J_{CF}$ 247.0, $^3J_{CF}$ 13.0	-	a
113.8	dd	$^2J_{CF}$ 37.5, $^4J_{CF}$ 2.5	-	b
143.82	t	$^3J_{CF}$ 1.9	-	c

Spectrum No. 2
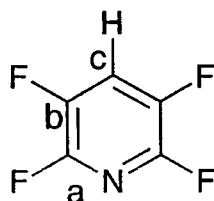
Chemical Shift (ppm)	Multiplicity	Coupling constants J (Hz)	Integral	Assignment
^{19}F				
-91.11	s	-	1	a
-139.93	m	AA'XX'M	1	b
^1H				
7.60	p	$^3J_{FH}$ and $^4J_{FH}$ 7.2	-	c
^{13}C				
141.6	dm	$^1J_{CF}$ 260.5	-	a
143.3	dt	$^1J_{CF}$ 245.1	-	b
119.0	tt	$^2J_{CF}$ 20.3, $^3J_{CF}$ 3.0	-	c

Spectrum No. 3
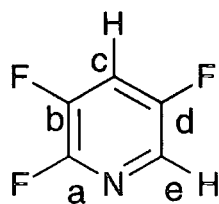
Chemical Shift (ppm)	Multiplicity	Coupling constants J (Hz)	Integral	Assignment
^{19}F				
-89.66	t	$^{3}J_{FaFb}$ 25.6	1	a
-127.37	ddd	$^{5}J_{FdFa}$ 29.4, $^{3}J_{FH}$ 7.2, $^{3}J_{FH}$ 3.0	1	d
-134.16	ddd	$^{3}J_{FbFa}$ 26.0, $^{3}J_{FbHc}$ 8.7, $^{4}J_{FbFd}$ 3.0	1	b
^{1}H				
7.87	s	-	1	e
7.40	ABdd	J_{AB} 15.2, 7.6, $^{4}J_{HF}$ 2.4, $^{4}J_{HH}$ 1.2	1	c
^{13}C				
115.4	ddd	$^{2}J_{CF}$ 17.9, $^{2}J_{CF}$ 24.0, $^{3}J_{CF}$ 3.4	-	c
156.4	dt	$^{1}J_{CF}$ 256.4	-	d
128.5	ddd	$^{4}J_{CF}$ 13.7, $^{2}J_{CF}$ 26.8, $^{3}J_{CF}$ 5.9	-	e
144.7	ddd	$^{1}J_{CF}$ 266.6, $^{2}J_{CF}$ 31.7, $^{3}J_{CF}$ 7.2	-	b
148.0	dd	$^{1}J_{CF}$ 235.9, $^{2}J_{CF}$ 14.1	-	a

Spectrum No. 4
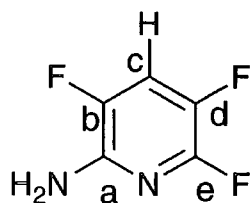
Chemical Shift (ppm)	Multiplicity	Coupling constants J (Hz)	Integral	Assignment
^{19}F				
-152.79	ddd	$^{3}J_{FdFe}$ 23.3, $^{3}J_{FdHc}$ 8.3, $^{4}J_{FdFb}$ 2.6	1	d
-140.99	ddd	$^{3}J_{FbHc}$ 30.9, $^{4}J_{FbFd}$ 8.3	1	e
-94.25	t	$^{3}J_{FF}$ 24.5	1	b
^{1}H				
4.53	brs	-	2	NH$_2$
7.40	ddd	J_{AB} 16.8, $^{4}J_{HF}$ 8.0	1	c
^{13}C				
141.0	t	J_{AB} 13.4	-	a
141.9	dt	$^{1}J_{CF}$ 248.6, $^{3}J_{CF}$ 5.0, $^{4}J_{CF}$ 3.0	-	b
115.2	td	J_{AB} 20.6, $^{3}J_{CF}$ 3.5	-	c
135.8	ddd	$^{1}J_{CF}$ 250.3, $^{2}J_{CF}$ 25.2, $^{3}J_{CF}$ 4.9	-	d
145.3	dd	$^{1}J_{CF}$ 235.4, $^{2}J_{CF}$ 13.5	-	e

Spectrum No. 5
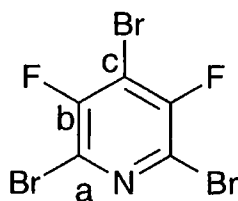
Chemical Shift (ppm)	Multiplicity	Coupling constants J (Hz)	Integral	Assignment
^{19}F				
-103.17	s	-	-	b

151

¹³C

122.5	X part of ABX	-	-	a
153.6	dd	$^1J_{CF}$ 263.6, $^3J_{CF}$ 1.1	-	b
110.1	t	$^2J_{CF}$ 24.0	-	c

Spectrum No. 6
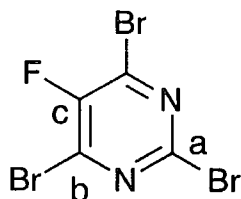
Chemical Shift (ppm)	Multiplicity	Coupling constants J (Hz)	Integral	Assignment
^{19}F				
-114.91	s	-	-	
^{13}C				
140.4	d	$^2J_{CF}$ 23.6	-	b
143.4	d	$^4J_{CF}$ 7.2	-	a
153.5	d	$^1J_{CF}$ 269	-	c

Spectrum No. 7
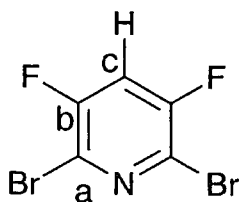
Chemical Shift (ppm)	Multiplicity	Coupling constants J (Hz)	Integral	Assignment
^{19}F				
-109.10	d	$^3J_{FH}$ 6.8	-	b
^1H				
7.31	t	$^3J_{HF}$ 6.4	-	c

^{13}C

122.7	X part of ABX	-	-	a
155.5	dd	$^1J_{CF}$ 265.5, $^3J_{CF}$ 4.5	-	b
113.7	t	$^2J_{CF}$ 23.8	-	c

Spectrum No. 8

Chemical Shift (ppm)	Multiplicity	Coupling constants J (Hz)	Integral	Assignment
^{19}F				
-124.11	s		-	-
^1H				
7.22	tt	$^3J_{HF}$ 8.8, $^4J_{HH}$ 2.3	1	c
8.37	d	$^3J_{HF}$ 2.0	2	a
^{13}C				
111.1	t	$^2J_{CF}$ 21.1	-	c
134.2	4 lines showing X part of ABX	-	-	a
			-	
159.1	dd	$^1J_{CF}$ 261.7, $^3J_{CF}$ 5.7	-	b

Spectrum No. 9
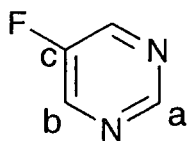
Chemical Shift (ppm)	Multiplicity	Coupling constants J (Hz)	Integral	Assignment
^{19}F				
-137.40	s	-	-	-
^1H				
8.64	s	-	2	b
9.08	d	$^4J_{HH}$ 3.3	1	a

^{13}C

144.8	d	$^2J_{CF}$ 19.5	-	b
154.8	d	$^4J_{CF}$ 6.1	-	a
157.9	d	$^1J_{CF}$ 266.6	-	c

Spectrum No. 10
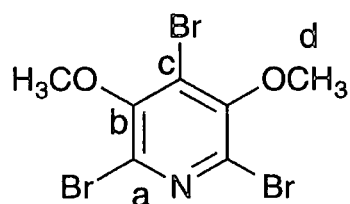
Chemical Shift (ppm)	Multiplicity	Coupling constants J (Hz)	Integral	Assignment
^{1}H				
3.95	s	-	-	d
^{13}C				
61.34	s	-	-	d
125.9	s	-	-	c
130.5	s	-	-	b
153.3	s	-	-	a

Spectrum No. 11
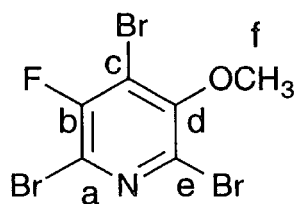
Chemical Shift (ppm)	Multiplicity	Coupling constants J (Hz)	Integral	Assignment
^{19}F				
-103.6	s	-	-	-
^{1}H				
3.97	s	-	-	-

^{13}C

Chemical Shift (ppm)	Multiplicity	Coupling constants J (Hz)	Integral	Assignment
61.21	s	-	-	f
117.3	d	$^2J_{CF}$ 19.8	-	c
122.4	d	$^2J_{CF}$ 26.7	-	a
130.2	d	$^3J_{CF}$ 3.8	-	d
152.4	s	-	-	e
153.7	d	$^1J_{CF}$ 249.8	-	b

Spectrum No. 12

Chemical Shift (ppm)	Multiplicity	Coupling constants J (Hz)	Integral	Assignment
^{19}F				
-121.05	s	-	-	-
^1H				
1.18	t	$^3J_{HH}$ 7.2	3	e
3.39	qt	$^3J_{HH}$ 7.2, $^5J_{HF}$ 1.6	2	d
^{13}C				
13.72	t	$^5J_{CF}$ 1.9	-	e
46.40	t	$^4J_{CF}$ 4.9	-	d
135.9	t	$^2J_{CF}$ 11.5	-	c
148.0	dd	$^1J_{CF}$ 257, $^3J_{CF}$ 4.2	-	b
123.2	6 lines showing X part of ABX	-	-	a

Spectrum No. 13
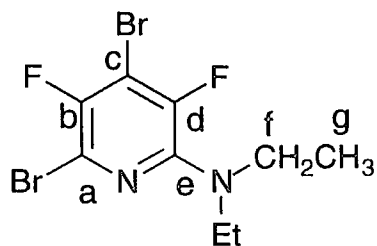
Chemical Shift (ppm)	Multiplicity	Coupling constants J (Hz)	Integral	Assignment
^{19}F				
-122.47	d	$^4J_{FF}$ 4.5	1	d
-125.92	br dt	$^4J_{FF}$ 4.5	1	b
^{1}H				
1.19	t	$^3J_{HH}$ 6.8	3	g
3.47	qd	$^3J_{HH}$ 7.2, $^5J_{HF}$ 2.0	2	f
^{13}C				
13.57	s	-	-	g
44.28	d	$^4J_{CF}$ 5.7	-	f
109.3	t	$^2J_{CF}$ 24.0	-	c
118.4	dd	$^2J_{CF}$ 24.8, $^4J_{CF}$ 3.4	-	a
144.7	dd	$^1J_{CF}$ 249.4, $^3J_{CF}$ 2.7	-	b or d
143.7	dd	$^1J_{CF}$ 260.2, $^3J_{CF}$ 2.3	-	b or d
144.4	br dd	$^2J_{CF}$ 8.8	-	e

Spectrum No. 14
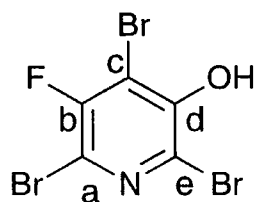
Chemical Shift (ppm)	Multiplicity	Coupling constants J (Hz)	Integral	Assignment
^{19}F				
-104.24	d	1.9	-	-

156

108.5	d	$^2J_{CF}$ 23.6	-	c
117.8	d	$^2J_{CF}$ 27.1	-	a
122.1	d	$^3J_{CF}$ 3.8	-	d
148.3	s	-	-	e
153.7	d	$^1J_{CF}$ 260.2	-	b

Spectrum No. 15
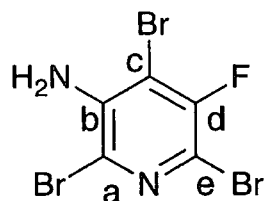
Chemical Shift (ppm)	Multiplicity	Coupling constants J (Hz)	Integral	Assignment
^{19}F				
-106.16	s	-	-	-
^1H				
4.73	br s	-	-	-
^{13}C				
105.1	d	$^2J_{CF}$ 23.9	-	e
113.0	d	$^2J_{CF}$ 27.7	-	c
119.7	d	$^3J_{CF}$ 3.8	-	b
141.0	s	-	-	a
153.4	d	$^1J_{CF}$ 256.5	-	d
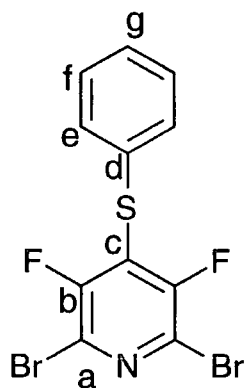
Chemical Shift (ppm)	Multiplicity	Coupling constants J (Hz)	Integral	Assignment
^{19}F				
-104.85	s	-	-	-
^{1}H				
7.33- 7.40	m	-	3	f,g
7.48- 7.50	m	-	2	e
^{13}C				
122.7	6 lines showing X part of ABX	-	- -	a
126.0	t	$^{2}J_{CF}$ 20.0	-	c
129.3	s	-	-	g
132.8	s	-	-	e or f
129.5	s	-	-	e or f
154.1	d	$^{1}J_{CF}$ 263.1	-	b

Spectrum No. 17

Chemical Shift (ppm)	Multiplicity	Coupling constants J (Hz)	Integral	Assignment
^{19}F				
-121.02	s	-	-	-
^{1}H				
1.60	s	-	3	e,f
3.29	s	-	2	d
^{13}C				
123.2	6 lines showing X part of ABX	-	- -	a
137.1	t	$^2J_{CF}$ 11.5	-	c
147.4	dd	$^1J_{CF}$ 257.5, $^3J_{CF}$ 3.4	-	b
23.91	s	-	-	f
26.31	s	-	-	d
51.57	s	-	-	e

Spectrum No. 18
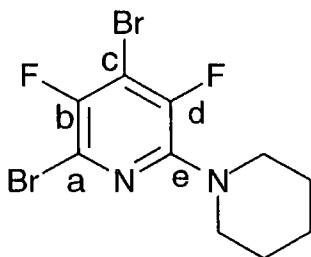
Chemical Shift (ppm)	Multiplicity	Coupling constants J (Hz)	Integral	Assignment
^{19}F				
-119.9	s	-	1	b or d
-120.7	s	-	1	b or d

159

Spectrum No. 19
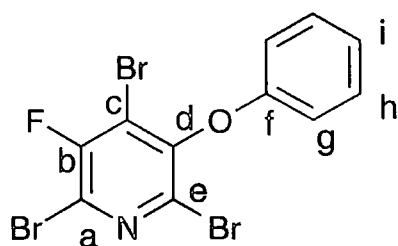
Chemical Shift (ppm)	Multiplicity	Coupling constants J (Hz)	Integral	Assignment
^{19}F				
-104.5	s	-	-	-
^{1}H				
7.34	dd	$^{3}J_{HH}$ 8.4, 7.2	2	h
7.13	t	$^{3}J_{HH}$ 7.2	1	i
6.83	d	$^{3}J_{HH}$ 8.0	2	g
^{13}C				
115.2	s	-	-	g
118.2	d	$^{2}J_{CF}$ 21.3	-	a or c
123.6	s	-	-	i
123.9	d	$^{2}J_{CF}$ 26.4	-	a or c
130.0	s	-	-	h
130.9	d	$^{3}J_{CF}$ 3.8	-	d
147.7	d	$^{4}J_{CF}$ 1.5	-	e
155.5	s	-	-	f
154.0	d	$^{1}J_{CF}$ 262.8	-	b

Spectrum No. 20
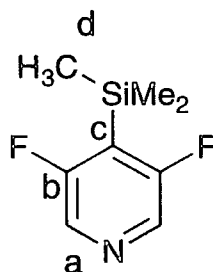
Chemical Shift (ppm)	Multiplicity	Coupling constants J (Hz)	Integral	Assignment
^{19}F				
-113.10	s	-	-	-
^{1}H				
0.33	s	-	9	d
8.16	s	-	2	a
^{13}C				
-0.41	s	-	-	d
122.7	t	$^{2}J_{CF}$ 30.5	-	c
133.5	4 lines showing X part of ABX	-	-	a
162.8	d	$^{1}J_{CF}$ 260.1	-	b

Spectrum No. 21
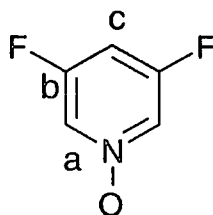
Chemical Shift (ppm)	Multiplicity	Coupling constants J (Hz)	Integral	Assignment
^{19}F				
-118.20	s	-	-	-
^{1}H				
6.95	t	$^{3}J_{HF}$ 7.9	1	c
8.05	s	-	2	a

^{13}C

Chemical Shift (ppm)	Multiplicity	Coupling constants J (Hz)	Integral	Assignment
103.6	t	$^2J_{CF}$ 23.8	-	c
127.0	d	$^2J_{CF}$ 36.9	-	a
160.3	dd	$^1J_{CF}$ 254.1, $^3J_{CF}$ 15.3	-	b

Spectrum No. 22
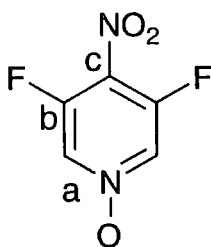
Chemical Shift (ppm)	Multiplicity	Coupling constants J (Hz)	Integral	Assignment
^{19}F				
-128.12	s	-	-	-
^{1}H				
8.14	ddd	$^3J_{HF}$ 3.8	-	a
^{13}C				
152.0	dd	$^1J_{CF}$ 267.8	-	b
128.3	d	$^2J_{CF}$ 34.7	-	a
104.0	t	$^2J_{CF}$ 23.0	-	c

Spectrum No. 23
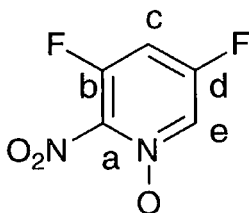
Chemical Shift (ppm)	Multiplicity	Coupling constants J (Hz)	Integral	Assignment
^{19}F				
-111.58	s	-	1	
-115.83	s	-	1	

^{1}H

8.24	d	$^3J_{HF}$ 2.3	1	e
7.55	ddd	$^3J_{HF}$ 8.7, $^3J_{HF}$ 7.2, $^4J_{HH}$ 2.3	1	c

^{13}C

116.1	dd	$^2J_{CF}$ 21.7, 22.1	-	c
132.7	dd	$^2J_{CF}$ 25.9, $^4J_{CF}$ 4.9	-	e
141.8	s	-	-	a
152.5	dd	$^1J_{CF}$ 282.0, $^3J_{CF}$ 8.0	-	b or d
161.8	dd	$^1J_{CF}$ 272.0, $^3J_{CF}$ 4.9	-	b or d

Spectrum No. 24
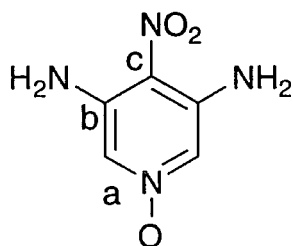
Chemical Shift (ppm)	Multiplicity	Coupling constants J (Hz)	Integral	Assignment

^{1}H

7.39	s	-	2	b
7.11	s	-	1	a

^{13}C

114.8	s	-	-	a
116.9	s	-	-	c
144.4	s	-	-	b

Spectrum No. 25
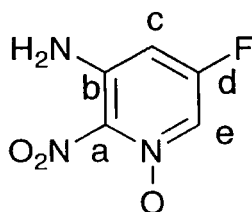
Chemical Shift (ppm)	Multiplicity	Coupling constants J (Hz)	Integral	Assignment
^{19}F				
-120.16	dd	$^3J_{FdHc}$ 10.4, $^3J_{FdHe}$ 4.5	-	-
^{1}H				
8.03	dd	$^3J_{HeFd}$ 4.4, $^4J_{HeHc}$ 2.4	1	e
6.79	br s	-	2	b
6.77	dd	$^3J_{HcFd}$ 10.0, $^4J_{HcHe}$ 2.0	1	c
^{13}C				
101.6	d	$^2J_{CF}$ 24.4	-	c
118.0	d	$^2J_{CF}$ 39.7	-	e
138.8	s	-	-	a
139.6	d	$^3J_{CF}$ 15.2	-	b
159.6	d	$^1J_{CF}$ 246.8	-	d

Spectrum No. 26
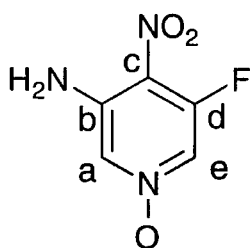
Chemical Shift (ppm)	Multiplicity	Coupling constants J (Hz)	Integral	Assignment
^{19}F				
-131.09	d	$^3J_{FH}$ 6.4	-	-
^{1}H				
7.84	2 lines	-	1	a and e
7.62	s	-	1	b (NH_2)
^{13}C				
118.0	d	$^2J_{CF}$ 38.2	-	e
119.2	s	-	-	c
125.5	s	-	-	a
143.5	s	-	-	b
155.0	d	$^1J_{CF}$ 269.5	-	d

Spectrum No. 27
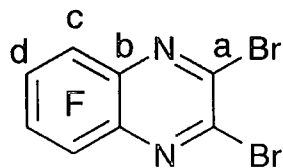
Chemical Shift (ppm)	Multiplicity	Coupling constants J (Hz)	Integral	Assignment
^{19}F				
-149.15	s	-	1	c or d
-149.50	s	-	1	c or d
^{13}C				
127.9	m	-	-	b
140.9	dm	$^1J_{CF}$ 262.9	-	c or d
142.0	dm	$^1J_{CF}$ 257.8	-	c or d
143.4	s	-	-	a

Spectrum No. 28
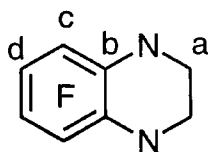
Chemical Shift (ppm)	Multiplicity	Coupling constants J (Hz)	Integral	Assignment
^{19}F				
-167.16	s	-	1	-
-175.72	s	-	1	-
^1H				
3.42	s	-	2	a
3.79	s	-	1	NH_2
^{13}C				
118.7	m	-	-	b
133.5	dm	$^1J_{CF}$ 240.4	-	c or d
136.4	dm	$^1J_{CF}$ 241.4	-	c or d
40.3	s	-	-	a

Spectrum No. 29

Chemical Shift (ppm)	Multiplicity	Coupling constants J (Hz)	Integral	Assignment
^{19}F				
-128.34	s	-	-	-
^1H				
3.84	bs	-	2	NH_2
6.70	ddd	$^3J_{HF}$ 10.3, $^4J_{HH}$ 2.2	1	c
7.87- 7.90	3 lines	-	2	a and e
^{13}C				
108.2	d	$^2J_{CF}$ 21.0	-	c
127.5	d	$^2J_{CF}$ 23.6	-	e
133.3	s	-	-	a
144.0	d	$^3J_{CF}$ 6.1	-	b
160.1	d	$^1J_{CF}$ 254.4	-	d

Spectrum No. 30
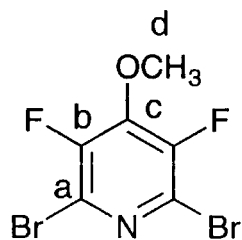
Chemical Shift (ppm)	Multiplicity	Coupling constants J (Hz)	Integral	Assignment
^{19}F				
-128.1	s	-	-	-
^1H				
4.26	s	-	-	-
^{13}C				
61.7	t	$^4J_{CF}$ 4.5	-	d
123.0- 123.3	4 lines showing X part of ABX	-	-	a
147.9	d	$^1J_{CF}$ 261.7	-	b

166

Spectrum No. 31
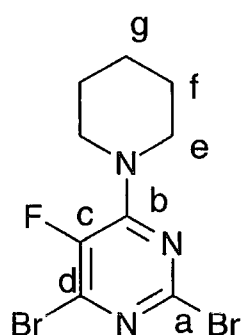
Chemical Shift (ppm)	Multiplicity	Coupling constants J (Hz)	Integral	Assignment
^{19}F				
-136.61	s	-	-	-
^1H				
1.69	m	-	3	f,g
3.76	m	-	2	e
^{13}C				
24.32	s	-	-	g
47.89	s	-	-	e
137.4	d	$^2J_{CF}$ 24.8	-	d
26.01	s	-	-	f
142.4	d	$^1J_{CF}$ 259.4	-	c
142.9	s	-	-	a
151.4	d	$^2J_{CF}$ 6.5	-	b

Spectrum No. 32
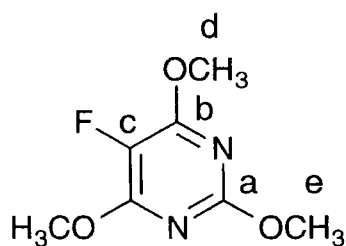
Chemical Shift (ppm)	Multiplicity	Coupling constants J (Hz)	Integral	Assignment
^{19}F				
-185.4	s	-	-	-

¹H

3.95	s	-	1	e
4.02	s	-	2	d

¹³C

54.4	s	-	-	d
54.9	s	-	-	e
128.7	d	$^1J_{CF}$ 247.5	-	c
157.5	s	-	-	a
158.9	d	$^2J_{CF}$ 8.8	-	b

Spectrum No. 33
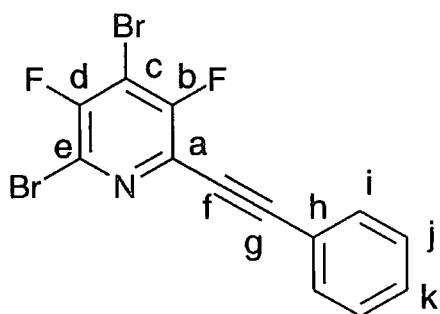
Chemical Shift (ppm)	Multiplicity	Coupling constants J (Hz)	Integral	Assignment
¹⁹F				
-101.27	s	-	1	-
110.36	s	-	1	-
¹H				
7.61	m	-	2	i
7.43	m	-	3	j,k
¹³C				
80.3	d	$^4J_{CF}$ 6.0	-	g
97.4	dd	$^3J_{CF}$ 5.7, $^5J_{CF}$ 2.3	-	f
109.2	t	$^2J_{CF}$ 23.4	-	c
121.0	s	-	-	h
123.6	dd	$^2J_{CF}$ 25.1, $^4J_{CF}$ 3.8	-	a
128.4	dd	$^2J_{CF}$ 21.0, $^4J_{CF}$ 5.7	-	e
128.5	s	-	-	j
129.9	s	-	-	k
132.2	s	-	-	i
153.1	d	$^1J_{CF}$ 265.9	-	b or d
157.2	d	$^1J_{CF}$ 266.6	-	b or d

Spectrum No. 34
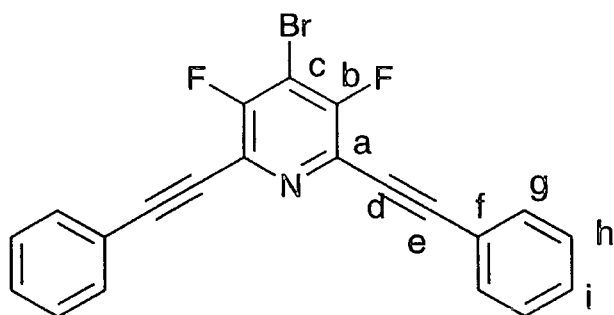
Chemical Shift (ppm)	Multiplicity	Coupling constants J (Hz)	Integral	Assignment
^{19}F				
-108.21	s	-	-	-
^1H				
7.33- 7.44	m	-	3	g,h
7.60- 7.63	m	-	2	i
^{13}C				
81.0	4 lines showing X part of ABX	-	- / -	e
96.3	t	$^3J_{CF}$ 3.8	-	d
108.4	t	$^2J_{CF}$ 22.7	-	c
121.3	s	-	-	f
128.5	s	-	-	h
128.9	4 lines showing X part of ABX	-	-	a
156.8	d	$^1J_{CF}$ 269.0	-	b
129.7	s	-	-	i
132.2	s	-	-	g

Spectrum No. 35

Chemical Shift (ppm)	Multiplicity	Coupling constants J (Hz)	Integral	Assignment
^{19}F				
-114.4	s	-	-	-
^{1}H				
3.53	d	$^3J_{HH}$ 4.8	2	d
5.16	s	-	2	f
5.86	dd	$^3J_{HH}$ 16.0, 8.8	1	e
^{13}C				
27.7	s	-	-	d
118.5	s	-	-	f
122.3	4 lines showing X part of ABX	-	- -	a
127.3	t	$^2J_{CF}$ 20.0	-	c
131.0	s	-	-	e
154.1	dd	$^1J_{CF}$ 262.4, $^3J_{CF}$ 2.6	-	b

Spectrum No. 36
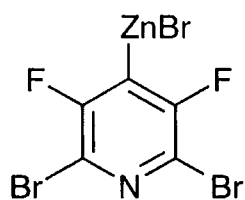
and
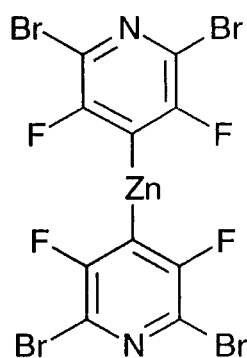
Chemical Shift (ppm)	Multiplicity	Coupling constants (Hz)	Integral	Assignment
^{19}F data				
-92.15	-	-	2	-
-92.65	-	-	1	-

Spectrum No. 37
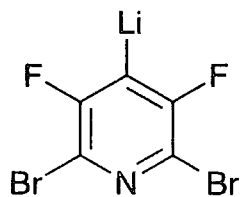
Chemical Shift (ppm)	Multiplicity	Coupling constants (Hz)	Integral	Assignment
^{19}F data				
-87.5	s	-	-	-

Spectrum No. 38
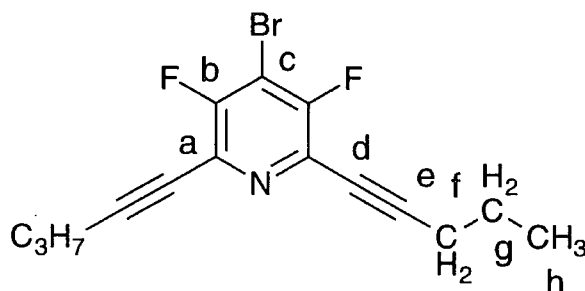
Chemical Shift (ppm)	Multiplicity	Coupling constants J (Hz)	Integral	Assignment
^{19}F				
-110.51	s	-	-	-
^{1}H				
0.96	t	$^{3}J_{HH}$ 7.3	3	h
1.59	q	$^{3}J_{HH}$ 7.2	2	g
2.38	t	$^{3}J_{HH}$ 7.1	2	f

<superscript>13</superscript>C

¹³C

13.46	s	-	-	h
21.44	s	-	-	g or f
21.54	s	-	-	g or f
73.04	s	-	-	e
98.36	s	-	-	d
107.9	t	$^2J_{CF}$ 22.9	-	c
128.9	4 lines showing X part of ABX	-	-	a
156.5	d	$^1J_{CF}$ 267.0	-	b

Spectrum No. 39
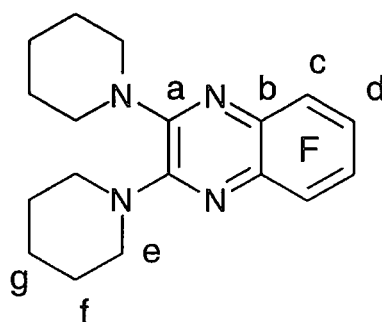
Chemical Shift (ppm)	Multiplicity	Coupling constants J (Hz)	Integral	Assignment
^{19}F				
-157.17		-	1	
-163.17		-	1	
^1H				
1.55	s	-	3	f and g
3.48	s	-	2	e
^{13}C				
24.4	s	-	-	g
25.5	s	-	-	f
47.7	s	-	-	e
138.1	dm	$^1J_{CF}$ 247.0	-	c or d
140.1	dm	$^1J_{CF}$ 249.0	-	c or d
148.6	s	-	-	a
123.8	m	-	-	b

172

Spectrum No. 40
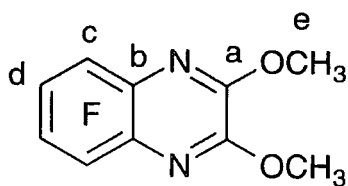
Chemical Shift (ppm)	Multiplicity	Coupling constants (Hz)	Integral	Assignment
^{19}F				
-154.64	d	$^3J_{FF}$ 10.8	1	c or d
-160.18	d	$^3J_{FF}$ 10.8	1	c or d
^1H				
4.19	s	-	-	e
^{13}C				
123.59	dd	$^2J_{CF}$ 7.2, $^3J_{CF}$ 3.8	-	b
139.5	dm	$^1J_{CF}$ 302.7	-	c or d
140.5	dm	$^1J_{CF}$ 267.5	-	c or d
150.6	s	-	-	a
55.0	s	-	-	e

Spectrum No. 41

Chemical Shift (ppm)	Multiplicity	Coupling constants J (Hz)	Integral	Assignment
^{19}F				
-125.09	s	-	-	-

7.67	dd	$^3J_{HH}$ 8.0, $^3J_{HH}$ 1.6	2	g
7.43	m	-	3	h and i

¹³C

80.8	d	$^3J_{CF}$ 4.5	-	j
86.9	s	-	-	k
87.9	s	-	-	e
101.3	d	$^5J_{CF}$ 4.6	-	d
120.7	s	-	-	l
121.1	s	-	-	f
128.4	s	-	-	o
128.6	s	-	-	n
129.8	s	-	-	i
130.5	s	-	-	h
132.6	s	-	-	m
132.6	s	-	-	g
140.0	d	$^2J_{CF}$ 15.2	-	b
148.7	d	$^4J_{CF}$ 9.2	-	a
156.4	d	$^1J_{CF}$ 275.6	-	c

Spectrum No. 42
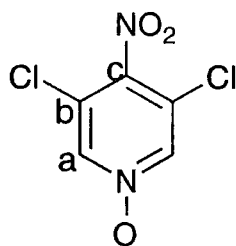
Chemical Shift (ppm)	Multiplicity	Coupling constants J (Hz)	Integral	Assignment
¹H				
8.18	s	-	-	a
¹³C				
125.9	s	-	-	
138.8	s	-	-	

Spectrum No. 43
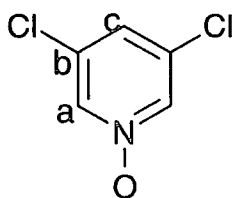
Chemical Shift (ppm)	Multiplicity	Coupling constants J (Hz)	Integral	Assignment
^1H				
8.16	d	$^4J_{HH}$ 1.6	2	a
7.31	t	$^4J_{HH}$ 1.2	1	c
^{13}C				
126.0	s	-	-	a
133.2	s	-	-	c
137.3	s	-	-	b

Spectrum No. 44
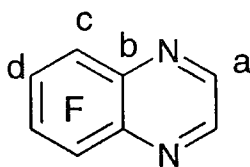
Chemical Shift (ppm)	Multiplicity	Coupling constants J (Hz)	Integral	Assignment
^{19}F				
151.65	m			
^1H				
8.93	d	$^3J_{HH}$ 10.1	-	
^{13}C				
130.0	s	-	-	b
141.4	dm	$^1J_{CF}$ 262.5	-	c and d
145.8	s		-	a

Spectrum No. 45
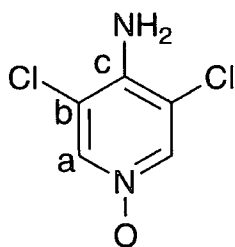
Chemical Shift (ppm)	Multiplicity	Coupling constants J (Hz)	Integral	Assignment
^1H				
8.26	s	-	1	a
6.65	s	-	1	NH_2
^{13}C				
114.8	s	-	-	a
136.9	s	-	-	b
140.8	s	-	-	c

Spectrum No. 46
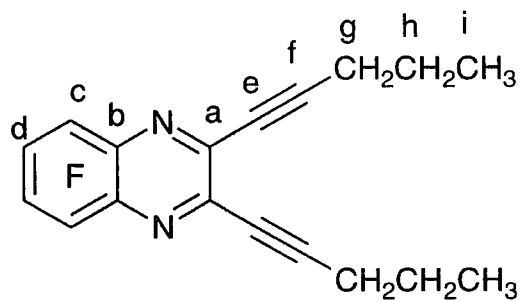
Chemical Shift (ppm)	Multiplicity	Coupling constants (Hz)	Integral	Assignment
^{19}F				
-151.64	AA'XX'	-	1	c or d
-152.39	AA'XX'	-	1	c or d
^1H				
1.12	t	$^3J_{HH}$ 7.4	3	i
1.73	q	$^3J_{HH}$ 7.2	2	h
2.56	t	$^3J_{HH}$ 7.0	2	g

176

13.62	s	-	-	i
21.49	s	-	-	g or h
21.82	s	-	-	g or h
78.34	s	-	-	f
101.03	s	-	-	e
127.10	d	3.8	-	b
141.26	dm	264.0	-	c or d
140.83	dm	284.9	-	c or d
142.26	s	-	-	a

Spectrum No. 47
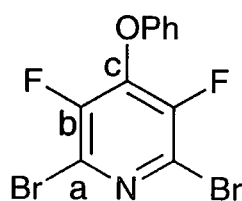
Chemical Shift (ppm)	Multiplicity	Coupling constants J (Hz)	Integral	Assignment
^{19}F				
-124.8	s	-	-	b

Spectrum No. 48
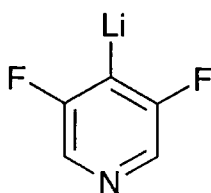
Chemical Shift (ppm)	Multiplicity	Coupling constants J (Hz)	Integral	Assignment
^{19}F				
-94.5	s	-	-	-

Appendix Two

Mass Spectroscopy Data

1. 3,5-Difluoropyridine (5)

2. 2,3,5,6-Tetrafluoropyridine (4)

3. 2,3,5-Trifluoropyridine (7)

4. 5-Fluoropyrimidine (18)

5. 3-Fluoro-5-aminopyridine (17)

6. 5,6,7,8-Tetrafluoroquinoxaline (20)

7. 1,2,3,4-Tetrahydro-5,6,7,8-tetrafluoroquinoxaline (19)

8. 2,4,6-Tribromo-3,5-difluoropyridine (11)

9. 2,6-Dibromo-5-fluoro-4-piperidinopyrimidine (22g)

10. 2,3-Dibromotetrafluoroquinoxaline (15)

11. 2,6-Dibromo-3,5-difluoropyridine (21)

12. 2,4,6-Tribromo-3-fluoro-5-methoxypyridine (23a)

13. 2,4,6-Tribromo-3,5-dimethoxypyridine (23b)

14. 2,4,6-Tribromo-3-fluoro-5-hydroxypyridine (23d)

15. 2,4,6-Tribromo-3-fluoro-5-phenoxypyridine (23e)

16. 2,4,6-Tribromo-3-fluoro-5-aminopyridine (23c)

17. 2,6-Dibromo-3,5-difluoro-4-methoxypyridine (22g)

18a. 2,6-Dibromo-3,5-difluoro-4-diethylaminopyridine (22b)

18b. 2,4-Dibromo-3,5-difluoro-6-diethylaminopyridine (22c)

19. 2,6-Dibromo-3,5-difluoro-4-thiophenoxypyridine (22a)

20a. 2,6-Dibromo-3,5-difluoro-4-piperidinopyridine (22d)

20b. 2,4-Dibromo-3,5-difluoro-6-dipiperdinopyridine (22e)

21. 2,4,6-Tribromo-5-fluoropyrimidine (13)

22. 5-Fluoro-2,4,6-trimethoxypyrimidine (13b)

23. 2,3-Dipiperidinotetrafluoroquinoxaline (15a)

24. 2,3-Methoxytetrafluoroquinoxaline (15b)

25. 3,5-Dichloro-3,5-difluoropyridine (4a)

26. 2,6-Dipentynyl-3,5-difluoro-4-bromopyridine (26)

27. 2,4-Dibromo-3,5-difluoro-6-(phenylacetylenyl)pyridine (25a)

28. 4-Bromo-3,5-difluoro-2,6-di(phenylacetylenyl)pyridine (25b)

29. 5-Fluoro-2,4,6-tri(phenylacetylenyl)pyrimidine (27)

30. 2,3-Dipentynyltetrafluoroquinoxaline (28)

31. 3,5-Difluoropyridine-N-oxide (5a)

32a. 3,5-Difluoro-4-nitropyridine-N-oxide (35a)

32b. 3,5-Difluoro-2-nitropyridine-N-oxide (35b)

33a. 3-Fluoro-4-nitro-5-aminopyridine-N-oxide (39b)

33b. 3-Fluoro-5-amino-6-nitropyridine-N-oxide (39a)

Name:chris hall   Ion Mode:EI+   26-Jan-96 14:35
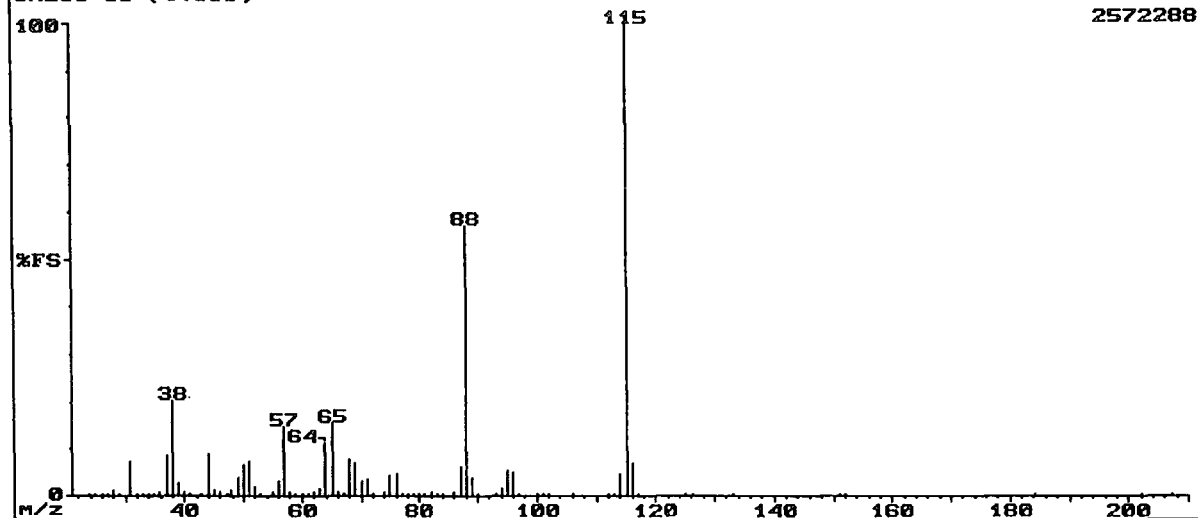
```
----------------------------------------------------------------------------
CH230'93 (1.550)    REFINE                                    255590<
------------------------+-------------------+-------------------+-----------
Mass    Rel Int  |  Mass    Rel Int  |  Mass    Rel Int  |  Mass    Rel Int
------------------------+-------------------+-------------------+-----------
  24      0.10   |   48      1.12    |   70      3.13    |   95      5.41
  25      0.26   |   49      3.69    |   71      3.65    |   96      5.17
  26      0.32   |   50      6.45    |   72      0.16    |   97      0.31
  27      0.34   |   51      7.49    |   74      0.79    |  100      0.08
  28      0.85   |   52      1.88    |   75      4.45    |  101      0.08
  31      7.41   |   53      0.09    |   76      4.61    |  102      0.25
  32      0.29   |   55      0.91    |   77      0.29    |  106      4.09
  33      0.39   |   56      3.17    |   78      0.10    |  112      0.05
  34      0.01   |   57     14.74    |   79      0.03    |  113      0.64
  35      0.01   |   58      0.93    |   80      0.02    |  114      4.65
  36      0.91   |   59      0.08    |   81      0.13    |  115    100.00
  37      8.41   |   60      0.11    |   82      1.03    |  116      6.97
  38     20.19   |   61      0.13    |   83      0.80    |  117      0.25
  39      2.60   |   62      0.70    |   84      0.20    |  125      0.03
  40      0.75   |   63      1.45    |   86      0.65    |  126      0.03
  41      0.11   |   64     11.22    |   87      6.09    |  133     16.35
  43      0.33   |   65     15.38    |   88     57.05    |  184      0.01
  44      8.85   |   66      0.74    |   89      4.01    |  202      0.01
  45      1.02   |   67      0.50    |   90      0.15    |  207      0.01
  46      0.89   |   68      7.77    |   93      0.40    |
  47      0.01   |   69      6.97    |   94      1.63    |
----------------------------+-------------------+-------------------+-------
```
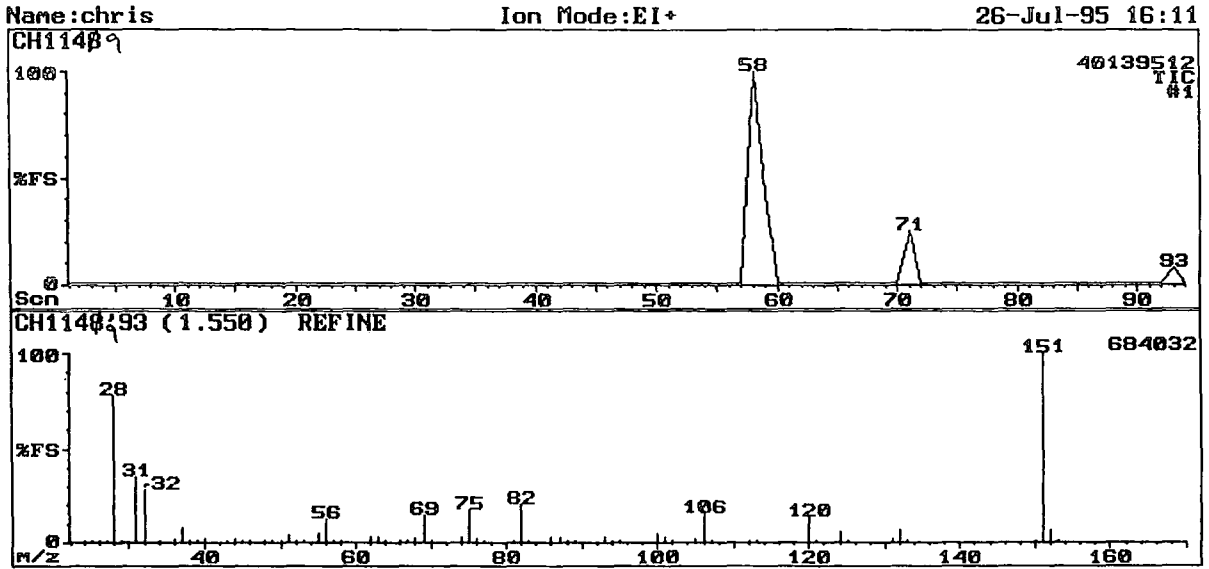
```
CH114  93 (1.550)   REFINE                                    684032

Mass   Rel Int  |  Mass   Rel Int  |  Mass   Rel Int  |  Mass   Rel Int

  24     0.18   |   48     0.56    |   74     3.18    |  106    15.12
  25     0.25   |   49     0.47    |   75    17.51    |  107     1.17
  26     0.14   |   50     1.32    |   76     1.99    |  112     0.25
  27     0.09   |   51     4.15    |   77     0.09    |  113     0.29
  28    77.84   |   52     0.10    |   81     1.27    |  120    13.32
  29     0.87   |   53     0.86    |   82    20.06    |  121     0.68
  31    34.58   |   55     4.38    |   83     0.45    |  124     6.10
  32    28.29   |   56    12.87    |   86     2.69    |  125     0.32
  34     0.10   |   57     1.16    |   87     3.33    |  131     1.52
  36     1.57   |   58     0.20    |   88     0.42    |  132     7.04
  37     7.45   |   62     3.14    |   89     0.07    |  133     0.44
  38     1.42   |   63     2.43    |   93     2.43    |  150     0.50
  39     0.15   |   64     0.13    |   94     0.47    |  151   100.00
  40     2.40   |   66     0.17    |   95     0.07    |  152     6.85
  43     0.53   |   67     0.38    |  100     5.09    |  153     0.12
  44     2.25   |   68     1.54    |  101     2.96    |
  45     0.47   |   69    14.52    |  102     0.17    |
  46     0.94   |   70     0.78    |  105     2.11    |
```

CH11651'107 (1.784) REFINE
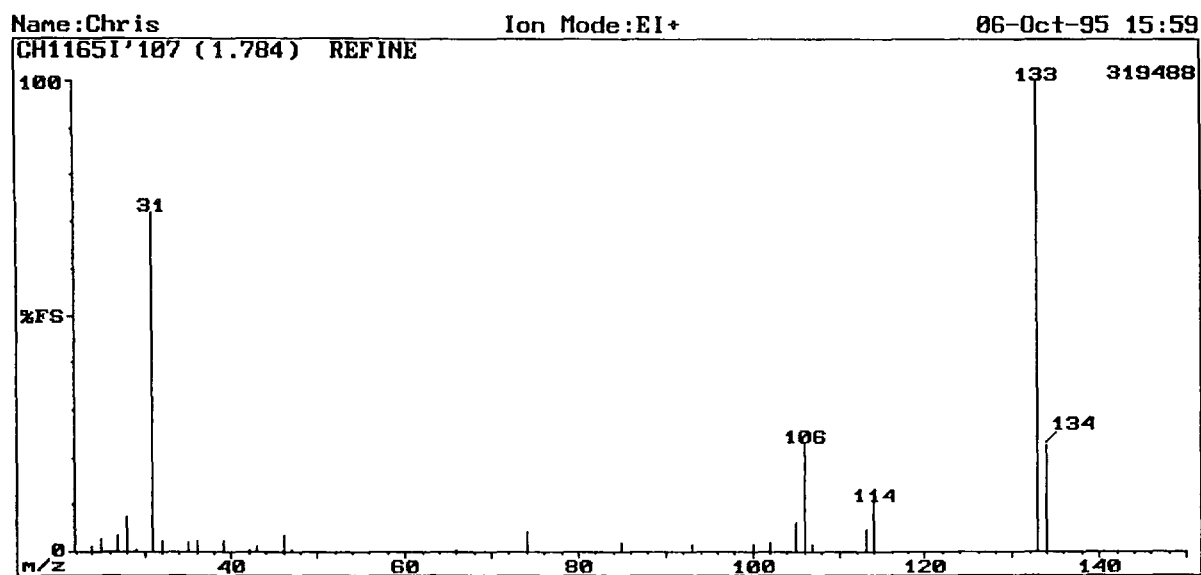
CH11651'107 (1.784) REFINE

Mass	Rel Int	Mass	Rel Int	Mass	Rel Int	Mass	Rel Int
24	1.09	35	1.82	66	0.20	106	23.08
25	2.86	36	2.32	74	4.27	107	1.50
27	3.55	39	2.38	85	1.76	113	4.51
28	7.21	42	0.14	93	1.66	114	10.50
29	0.33	43	1.19	100	1.42	133	100.00
31	72.12	46	3.63	102	1.84	134	22.76
32	2.16	47	0.58	105	6.09		

Name:chris h   Ion Mode:EI+   19-Mar-96 11:39

CH246'84 (1.400) REFINE
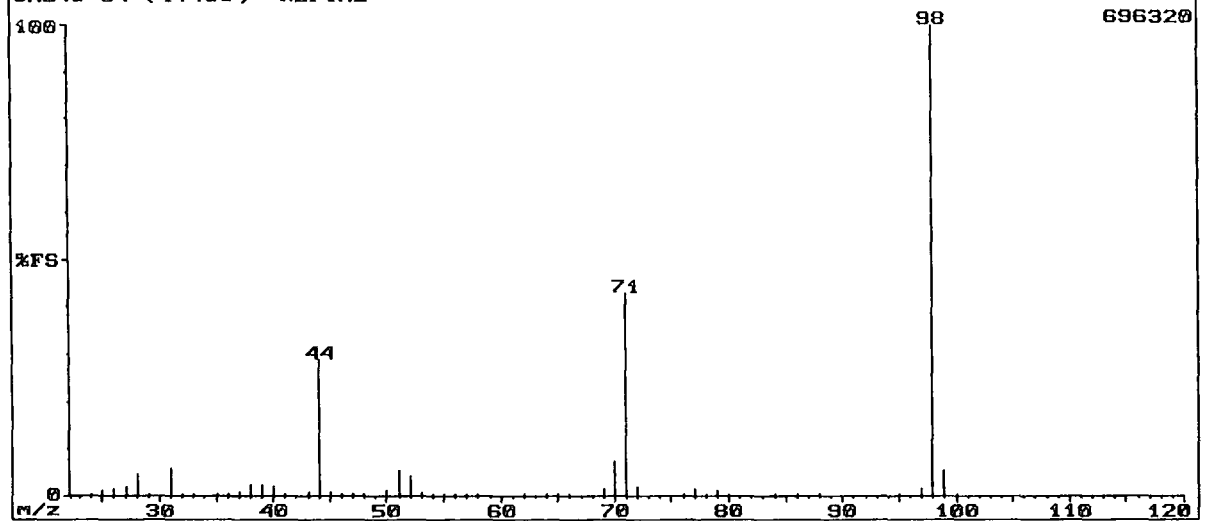
CH246'84 (1.400)   REFINE   6ς

Mass	Rel Int	Mass	Rel Int	Mass	Rel Int	Mass	Rel Int
24	0.41	39	2.43	54	0.05	76	0.28
25	1.36	40	1.77	55	0.07	77	1.73
26	1.42	41	0.11	56	0.12	78	0.13
27	1.94	43	0.63	57	0.31	79	1.18
28	4.63	44	28.68	58	0.14	80	0.08
29	0.08	45	0.95	62	0.05	84	0.11
31	5.66	46	0.36	64	0.06	86	0.07
32	0.30	47	0.02	65	0.04	88	0.02
33	0.09	48	0.04	66	0.13	95	0.04
35	0.11	50	1.23	69	1.42	97	1.70
36	0.34	51	5.26	70	7.39	98	100.00
37	0.83	52	4.23	71	42.94	99	5.59
38	2.32	53	0.87	72	1.83	100	0.17

CH2129B032○   x1   Bgd=31   9-JAN-97 11:55+0:02:46 70E   EI+
8pH=0   I=10v   Hm=113 TIC=173930000   Acnt: Sys:ACE   HAR:
CHRIS HALL   PT= 0°   Cal:PFK8JAN   HASS:
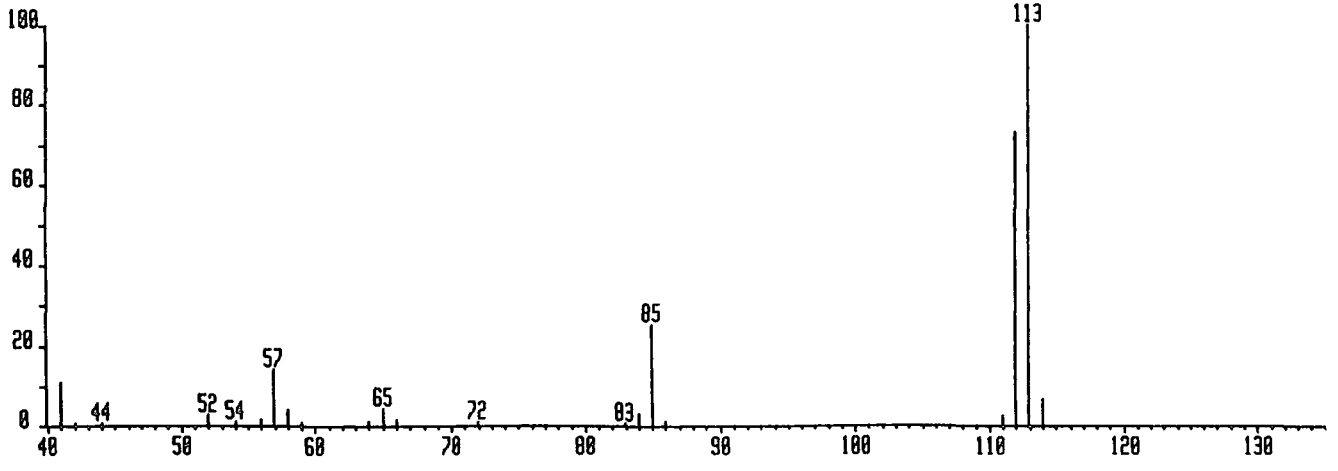
'B#32H   x1   Bgd=31   9-JAN-97   11:55+0:02:46   70E   EI+   2.1
      I=10v   Hm=113   TIC=173930000   Acnt: Sys:ACE
HALL   PT= 0   Cal:PFK8JAN
   Mass   % Base
   41.00   10.56
   42.01   0.37
   43.98   0.47
   51.98   2.46
   54.00   0.69
   55.97   1.36
   56.98   13.77
   57.99   3.65
   58.99   0.80
   63.98   0.90
   64.99   4.10
   66.00   1.41
   71.98   0.65
   82.96   0.48
   83.97   2.70
   84.98   24.97
   85.98   1.16
  110.96   2.53
  111.97   72.86
  112.98   100.00 0
  113.98   6.64

Name:Chris Hall   Ion Mode:EI+   07-Mar-97 15:41

CH2156A
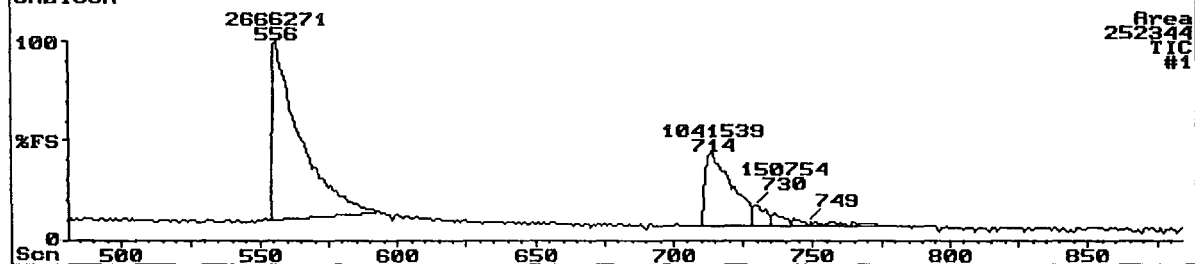
CH2156A 556 (9.267)
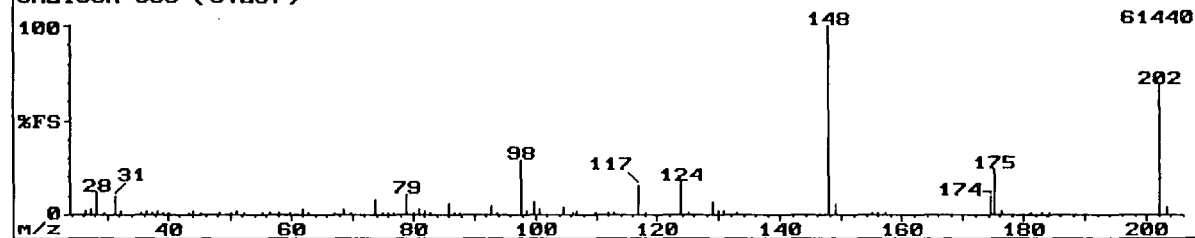
CH2156A 556 (9.267)   6

Mass	Rel Int	Mass	Rel Int	Mass	Rel Int	Mass	Rel Int
26	2.21	55	1.09	87	1.19	130	2.11
27	3.02	56	0.68	88	0.67	131	1.65
28	11.35	58	0.59	93	4.40	133	0.24
29	0.27	60	0.36	94	1.37	148	100.00
31	9.79	62	2.71	98	28.75	149	5.94
32	1.93	63	0.70	99	1.93	155	0.74
35	1.26	67	0.28	100	6.98	156	0.42
36	1.98	69	2.63	101	3.39	157	0.72
37	1.09	70	1.21	105	3.46	174	9.90
38	1.69	74	8.02	106	1.44	175	23.96
39	0.81	75	1.09	107	2.01	176	1.90
40	0.70	76	1.28	110	1.17	181	0.67
43	0.23	77	0.29	112	0.53	183	0.85
44	2.16	79	10.31	113	0.36	184	0.96
45	1.00	80	0.94	117	15.63	202	68.75
48	0.27	81	2.60	118	0.84	203	4.19
50	1.04	82	2.01	124	17.19		
51	2.08	83	0.66	125	0.99		
52	1.34	86	5.63	129	6.77		

CH2147821◊   x1   Bgd=13   5-MAR-97   15:33◊0:01:53   70E   EI+
BpH=0   I=1.4v   Hm=224   TIC=31019000   Acnt: Sys:ACE   HHR:
CHRIS HALL   PT= 0⁰   Cal:PFK4HAR   HASS:
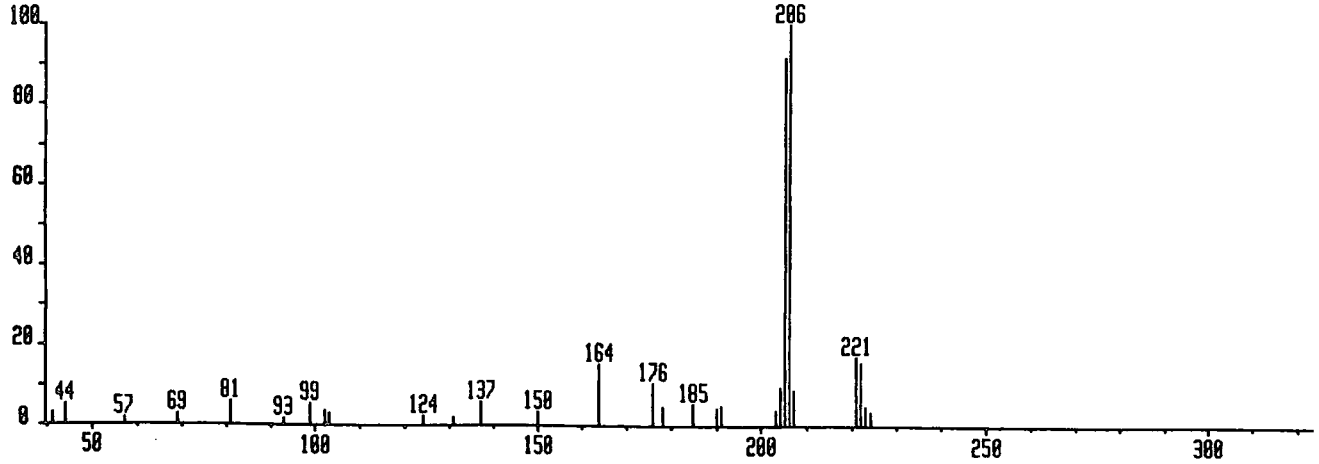
7#21#   x1   Bgd=13   5-MAR-97   15:33+0:01:53   70E   EI+   2.1
      I=1.4v   Hm=224   TIC=31019000   Acnt: Sys:ACE
  HALL   PT= 0   Cal:PFK4MAR
      Mass   % Base
       41.16   2.78
       44.11   4.70
       57.15   1.52
       69.05   2.51
       81.03   5.33
       93.03   1.38
       99.03   5.01
      102.06   3.32
      103.06   2.61
      124.06   1.89
      131.07   1.88
      137.04   5.36
      150.03   3.19
      164.01   14.94
      176.02   10.41
      178.07   4.48
      185.07   5.16
      190.08   4.13
      191.05   4.80
      203.07   3.45
      204.03   9.14
      205.02   91.91
      206.03   100.00
      207.04   8.50
      221.01   16.93
      222.02   15.53
      223.00   4.47
      224.02   2.99

8

Mass	% Base	
41.04	1.29	
43.00	1.08	F
43.05	0.91	F
44.00	0.35	
48.00	2.23	
50.00	1.39	
54.99	11.71	F
55.06	0.70	F
56.00	0.41	
56.06	0.44	
57.00	0.94	F
57.07	1.87	F
62.00	27.22	
63.01	1.50	
67.00	4.97	
68.02	0.31	
69.01	4.33	
73.99	8.24	F
74.04	1.31	F
75.02	0.46	
76.02	0.50	
78.91	9.77	
78.99	0.40	
80.90	8.90	F
81.00	11.69	F
82.00	0.63	
85.99	35.26	
86.99	1.49	F
87.04	0.84	F
90.91	4.62	
92.90	4.80	F
93.00	22.88	F
94.00	1.55	
95.46	0.87	
96.46	0.93	
99.99	1.48	
102.91	0.45	
104.03	0.43	
104.91	1.21	
106.91	0.87	
109.91	0.72	
111.99	63.69	
113.00	4.26	

Mass	% Base	
114.91	2.31	
116.91	2.76	
118.91	0.68	
121.91	8.14	
122.91	7.85	
123.42	0.41	
123.91	8.14	
126.92	0.38	
128.92	1.11	
130.93	0.82	
133.92	2.43	
134.93	1.88	
135.89	6.47	
136.93	1.76	
137.91	0.42	
140.92	3.05	
142.91	3.33	
145.91	2.86	
147.91	2.87	
149.02	4.11	
149.97	0.41	
152.91	1.29	
154.90	1.29	
159.91	6.52	
160.91	0.32	
161.91	6.41	
164.91	6.71	
166.91	6.93	
167.91	0.32	
171.89	1.30	
173.90	1.21	
174.37	1.23	
175.37	3.21	
176.37	3.18	
177.37	1.02	
190.90	60.72	
191.91	3.69	
192.90	59.52	
193.91	3.58	
195.83	0.45	
197.82	0.31	
212.83	0.74	
214.82	1.23	
216.82	0.62	
219.83	0.94	

187

Mass	% Base	
221.83	1.84	
223.83	0.99	
224.83	0.36	
226.82	0.65	
228.83	0.32	
245.83	0.41	
252.84	0.47	
269.82	24.49	
270.81	1.73	F
271.81	46.39	F
272.82	3.31	
273.81	22.83	
274.82	1.85	
276.81	0.39	
348.71	34.83	F
349.68	1.89	F
350.71	100.00	F
351.70	5.89	F
352.71	96.66	F
353.71	5.84	F
354.72	31.78	F
355.73	1.84	

CH2SF56012○   x1   Bgd=1   18-JUN-96 10:21+0:01:17 70E   EI+
8pH=8   I=2.0v   Hₐ=341   TIC=186825000   Acnt: Sys:ACE   HAR:
CHRIS HALL   PT= 0°   Cal:PFK18JUN   HASS:

36F56#12#   x1   Bgd=1   18-JUN-96 10:21+0:01:17 70E   EI+   2.1
=0   I=2.0v   Hm=341   TIC=186825000   Acnt: Sys:ACE
IS HALL   PT= 0   Cal:PFK18JUN

Mass	% Base		Mass	% Base
41.00	100.00		259.78	11.37
42.00	36.51		268.64	3.57
43.01	25.27		269.64	6.88
50.98	2.26		270.64	9.63
51.98	3.08		271.63	6.92
52.99	8.10		272.63	3.84
53.99	9.59		280.64	6.02
55.01	71.48		281.64	11.38
56.00	79.18		282.63	15.32
57.02	33.42		283.63	21.74
67.00	19.24		284.63	9.28
68.00	7.48		285.63	9.73
68.94	7.43 F		293.63	9.06
69.01	25.57 F		295.64	22.33
69.95	14.49 F		296.64	3.92
70.01	10.44 F		297.64	17.47
70.96	4.48 F		299.64	2.64
71.03	11.50 F		307.64	40.78
76.96	5.02		308.65	2.90
79.86	1.33		309.64	84.40
81.00	6.56		310.64	7.11
82.00	6.09		311.63	40.68
83.01	12.00		312.64	1.82
84.01	60.48		323.63	5.23
85.02	9.71		325.61	2.26
94.92	3.67 F		335.63	3.65
95.00	6.31 F		336.64	34.64
95.95	4.61		337.64	13.15
96.93	16.56 F		338.64	69.79
97.01	8.25 F		339.64	11.62
97.96	2.36		340.64	33.01
109.01	3.41		341.64	1.99
109.95	2.69			
111.02	5.16			
121.91	2.97			
122.95	3.23			
123.94	2.58			
125.02	1.25			
147.79	6.83			
148.90	7.97			
149.79	7.18			
149.92	2.45			
152.95	8.37			
174.79	17.78			
176.78	17.83			
177.93	4.04			
189.78	3.62			
191.78	3.57			
201.76	4.45			
203.77	4.83			
229.78	3.48			
230.79	5.12			
231.78	2.66			
232.79	2.55			
253.64	15.20			
254.64	15.45			
255.64	31.75			
256.64	21.00			
257.70	15.09			
258.66	7.77			

BpM=0   I=10v   Hn=424   TIC=857718976   Rcnt: Sys:ACE   HNK
CHRIS HALL   PT= 0°   Cal:PFK13AUG   HASS:

CHRIS HALL   PT= 0   Cal:PFK13A

Mass	% Base		Mass	% Base		Mass	% Base
41.07	6.64		125.10	5.04		363.11	5.55
42.07	2.10		129.01	3.04 F		374.09	2.23
43.04	4.25 F		129.10	4.31 F		376.09	5.58
43.08	6.37 F		130.11	0.85		378.09	3.03
44.03	20.57		131.10	14.23		418.05	1.33
45.06	11.99		132.10	0.71		420.07	4.56
49.02	2.93		136.09	1.45		422.06	4.00
50.04	2.21		139.56	7.20		424.07	0.40
51.02	1.69		140.07	2.56			
55.04	7.53 F		140.56	6.23			
55.10	5.54 F		148.11	21.53			
56.11	2.33		149.14	9.03			
57.12	10.42		150.13	1.87			
59.08	0.58		151.19	7.30			
60.07	3.27		155.12	16.75			
62.06	9.21		156.12	1.42			
67.06	0.94		162.13	4.58			
67.12	1.47		163.14	1.73			
69.06	15.87 F		164.12	0.84			
69.13	4.04 F		169.14	6.61			
70.13	0.89		170.54	0.81			
71.15	2.37		174.13	9.25			
73.10	1.10		175.14	0.75			
74.06	15.23		179.06	3.28			
75.08	1.39		180.05	6.83			
76.07	5.61		181.10	4.15			
78.98	14.38 F		182.15	3.36			
79.06	19.11 F		183.16	2.73			
80.07	1.88		184.00	1.74			
80.98	13.36 F		186.01	0.65			
81.07	9.94 F		200.15	100.00 O			
81.14	1.75 F		201.15	22.37			
82.08	0.81		202.19	0.75			
83.15	1.93		216.14	8.64			
85.17	1.25		217.16	1.09			
86.07	14.04		218.14	2.89			
87.08	1.15		235.14	1.64			
88.08	1.69		260.11	4.25			
90.99	4.02		261.13	2.08			
91.11	1.00		262.12	6.93			
93.06	29.36		263.12	1.86			
94.08	0.71		264.11	1.77			
95.16	1.19		279.13	69.62			
97.17	1.62		280.12	7.65			
98.07	21.79		281.12	70.91			
99.08	1.18		282.13	8.37			
100.08	31.46		295.11	4.63			
101.09	2.29		297.11	5.12			
105.07	23.35		299.14	1.50			
106.06	3.58		339.05	1.54			
107.04	1.79		340.06	1.21			
110.08	3.46		341.07	4.25			
111.20	0.98		342.08	2.34			
112.09	4.35		343.05	2.17			
117.08	15.45		344.09	1.22			
118.07	1.61		358.11	61.81			
119.01	1.59 F		359.11	4.30			
119.10	1.07 F		360.10	96.15			
121.17	2.24		361.10	9.53			
124.10	71.80		362.10	60.57			

CH1178#13♦   x1   Bgd=4   27-OCT-95 15:28+8:01:29 70E   EI+
BpM=8   I=4.9v   Hm=468   TIC=173954000   Acnt   Sys:ACE   HMR:
CHRIS HALL   PT= 8⁰   Cal:PFK19OCT   MASS:
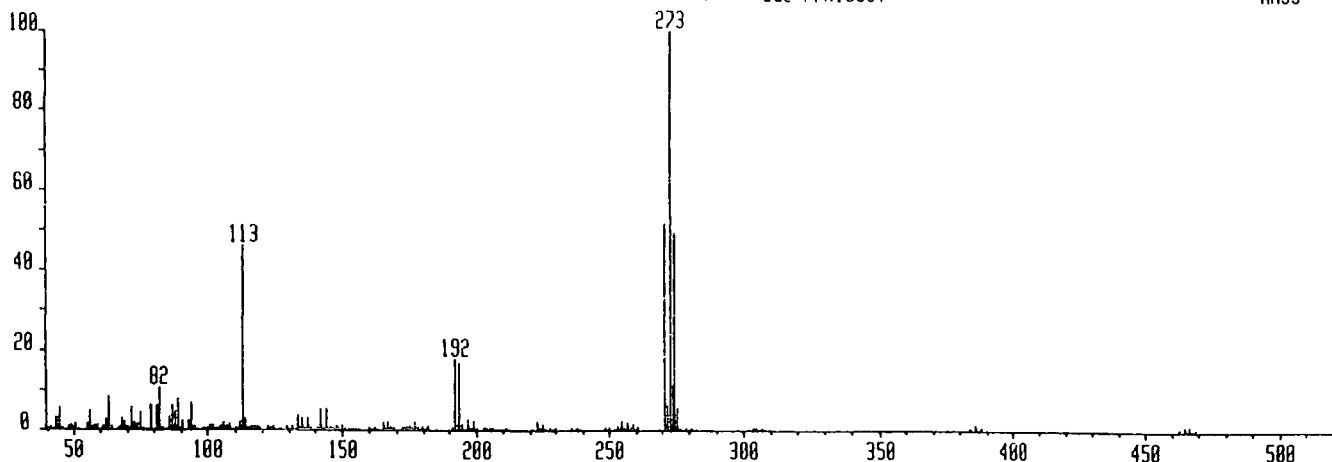
178#13#   x1   Bgd=4   27-OCT-95 15:28+0:01:29 70E   EI+   2.1
=0   I=4.9v   Hm=468   TIC=173954000   Acnt: Sys:ACE
IS HALL   PT= 0   Cal:PFK19OCT

Mass	% Base		Mass	% Base	
43.02	2.72		128.94	0.59	
44.02	2.76		130.96	0.55	
45.04	5.36		133.09	3.53	
48.00	0.56		134.93	2.68	
49.01	0.92		135.93	0.47	
50.01	0.48		136.92	2.86	
51.01	1.26		141.93	5.15	
55.00	1.50		142.93	0.42	
56.01	4.66		143.92	5.13	F
57.03	0.62		144.03	1.90	F
58.04	1.11		144.98	0.40	
59.06	1.17		146.94	0.44	
61.03	0.58		147.93	0.52	
62.01	2.34		148.95	0.47	
63.02	8.11		150.00	1.16	
64.02	0.61		159.93	0.38	
67.00	0.51		161.95	0.43	
68.01	2.69		164.92	1.69	
69.01	2.03		165.93	0.74	
70.04	0.80		166.92	1.58	
71.05	0.38		167.96	0.74	
72.06	5.34		169.01	0.32	
73.03	1.70	F	172.94	0.35	
73.98	0.92	F	173.97	0.61	
74.01	1.38		175.02	0.62	
76.02	4.13		175.99	0.50	
78.02	0.37		177.12	1.58	
78.97	6.19		179.96	0.62	
80.05	5.79		181.94	0.62	
81.04	10.15		191.93	17.50	
81.02	0.35		192.93	1.27	
82.01	3.22		193.93	16.50	
83.04	4.99	F	194.93	1.27	
84.06	5.93	F	196.93	2.34	
86.05	4.62		198.93	2.21	
89.06	7.52		203.92	0.30	
90.07	0.42		205.94	0.39	
90.94	1.97		222.93	1.91	
92.92	2.20	F	224.93	1.43	
93.01	2.13	F	235.96	0.35	
94.01	6.66		237.96	0.39	
95.02	0.76		247.94	0.34	
100.02	0.45		249.94	0.33	
101.06	1.14		252.85	0.57	
102.07	0.95		254.89	2.10	
103.05	0.41		255.86	0.37	
104.04	0.42		256.89	1.76	
104.96	0.61		258.84	1.38	
105.94	1.60		260.84	0.62	
106.93	0.61		270.82	51.85	F
107.93	1.36		271.83	6.00	F
111.99	1.60		272.82	100.00	F
113.01	45.84		273.83	11.23	F
114.02	2.63		274.82	49.21	F
115.92	0.68		275.84	5.39	F
117.01	0.54		383.84	0.46	
117.95	0.65		385.86	0.92	
118.93	0.31		387.87	0.38	
121.93	0.64		462.78	0.35	
123.93	0.73		464.77	0.89	

190

Name:Chris H   Ion Mode:EI+   25-Jul-96 14:00

CH256F89

CH256F89 1312 (21.868)
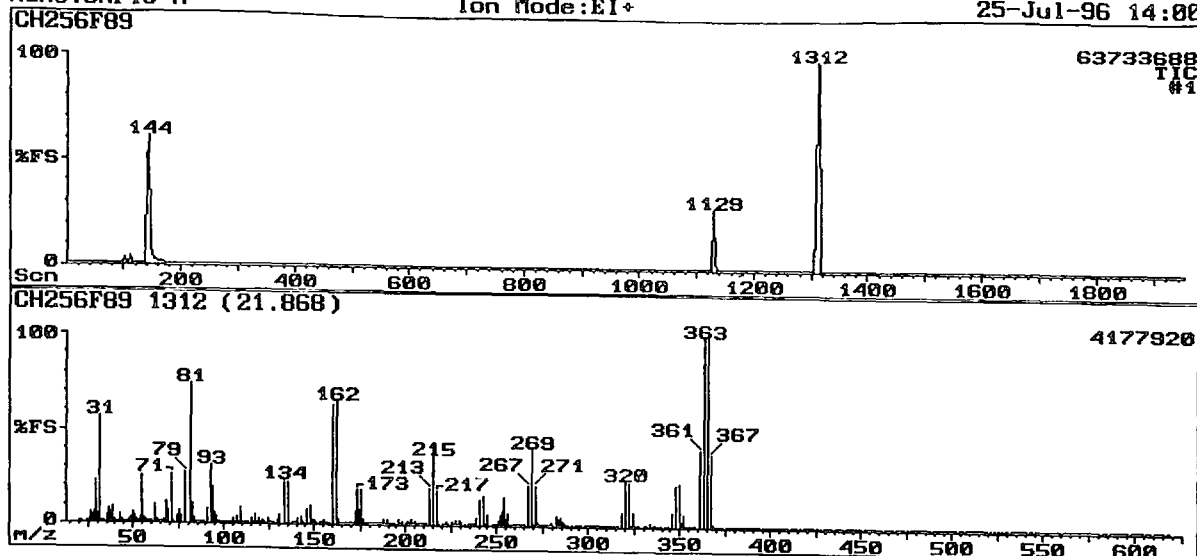
CH256F89 1312 (21.868)   4177920

Mass	Rel Int	Mass	Rel Int	Mass	Rel Int	Mass	Rel Int
275	0.09	339	0.39	403	0.08	463	0.02
276	0.20	340	0.02	404	0.03	464	0.01
277	0.10	341	0.16	405	0.04	465	0.03
278	0.02	342	0.05	406	0.03	467	0.04
280	1.56	343	0.04	407	0.01	469	0.01
281	1.40	344	0.10	408	0.02	469	0.01
282	5.66	346	7.75	409	0.02	471	0.01
283	3.58	348	22.55	411	0.02	472	0.02
284	4.85	350	23.14	412	0.02	473	0.02
285	3.09	351	2.48	413	0.05	473	0.01
286	1.57	352	6.47	414	0.03	475	0.03
287	1.37	353	0.77	416	0.26	476	0.03
288	0.08	354	0.13	418	0.60	477	0.01
289	1.28	355	0.10	419	0.03	478	0.04
291	0.69	356	0.04	420	0.63	480	0.12
292	0.12	357	0.04	421	0.04	481	0.01
293	0.03	358	0.10	422	0.15	482	0.13
294	0.37	361	40.78	422	0.08	482	0.01
295	0.05	363	100.00	423	0.03	484	0.10
296	0.64	365	100.00	425	0.16	485	0.09
298	0.71	367	38.43	427	0.19	486	0.06
299	0.25	368	2.35	428	0.02	487	0.11
300	0.43	369	0.19	429	0.10	488	0.01
301	0.14	370	0.07	430	0.09	489	0.04
302	0.11	371	0.03	431	0.05	491	0.02
303	0.14	372	0.06	432	0.08	491	0.01
304	0.05	373	0.04	433	0.02	492	0.01
305	0.07	375	0.11	434	0.16	493	0.01
306	0.04	376	0.09	436	0.21	495	0.02
307	0.01	377	0.16	437	0.01	496	0.01
308	0.15	378	0.16	438	0.06	497	0.03
309	0.10	379	0.13	438	0.02	498	0.02
310	0.20	380	0.12	439	0.02	499	0.03
311	0.25	381	0.06	440	0.04	500	0.02
312	0.10	382	0.04	442	0.28	501	0.03
313	0.22	383	0.03	443	0.06	502	0.01
314	0.03	384	0.03	444	0.60	503	0.01
315	0.20	385	0.02	445	0.04	505	0.01
316	0.03	386	0.04	446	0.51	506	0.02
318	8.14	387	0.03	447	0.04	508	0.03
320	23.82	388	0.04	448	0.19	509	0.04
322	23.63	389	0.06	449	0.03	509	0.04
323	0.72	390	0.02	450	0.01	511	0.05
324	8.14	391	0.07	452	0.01	512	0.05
325	0.69	392	0.03	453	0.02	513	0.04
326	0.16	393	0.04	454	0.07	514	0.03
327	0.15	394	0.01	455	0.06	514	0.01
330	0.22	395	0.03	456	0.16	516	0.01
332	1.11	396	0.03	457	0.19	517	0.02
334	1.56	397	0.02	458	0.24	518	0.01
335	0.45	399	0.05	459	0.19	519	0.02
336	0.78	400	0.02	460	0.12	519	0.02
337	0.45	401	0.12	461	0.05	521	0.16
338	0.21	402	0.04		0.03	523	0.59

CH1169841ο   x1   Bgd
BpH=0   I=2.0v   Ha=445
CHRIS HALL

13
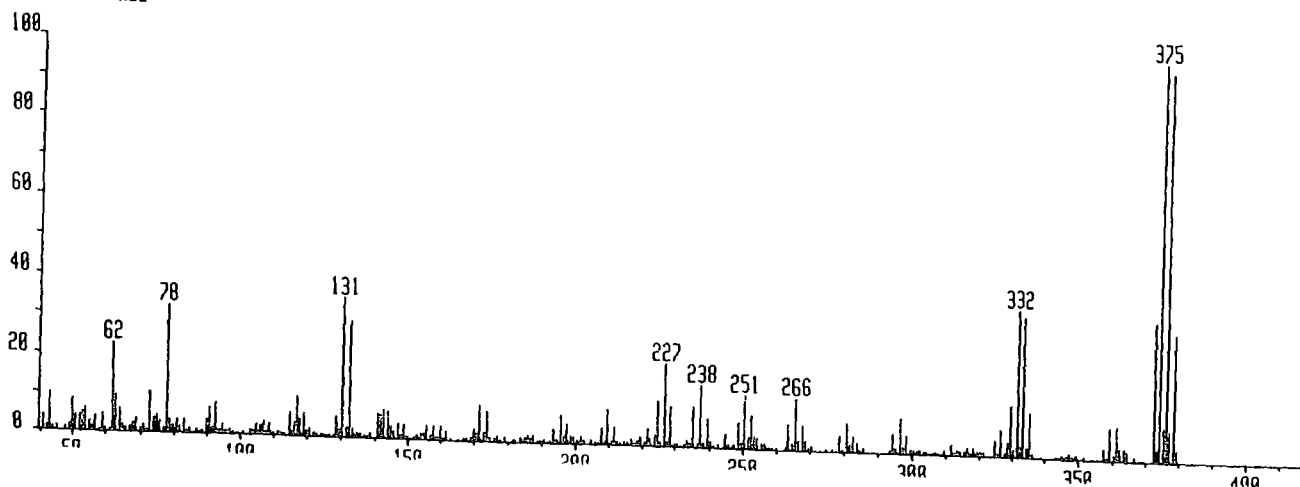
Mass	% Base	Mass	% Base		Mass	% Base	Mass	% Base	Mass	% Base
41.00	3.63	95.98	0.46		153.80	1 40	218.82	0.98	299.64	0.74
41.99	1.05	97.01	0.95		153.95	0.57	219.68	1.90	300.53	0.82
42.98	9.53 F	102.83	1.09		154.79	1.23	220.67	0.74	302.53	0.78
43.02	3.28 F	103.84	0.57		154.95	0.49	221.66	4.20	304.54	0.30
43.97	0.74	103.94	0.51		155.81	3.52	222.66	1.61	306 91	0.43
44.98	1.05	104.84	2.42		156.80	0.93	223.66	2.82	309 65	0.90
47.96	0.84	104.95	0.81		156.93	0.55	224.67	11.40	311.63	2 28
48.96	1.48	105.89	1.98		157.80	3.45	225.67	0.91	312.64	0.49
49.96	8.22	106.85	3.50		158.80	0.85	226.67	20.66	313.60	1.02
50.97	3.76	107.84	0.76		158.93	0.42	227.67	0.93	314.58	0.72
51.95	4 28 F	107.95	0.70		159.92	3 35	228.67	9.87	315 53	0.53
51.98	2.34 F	108.82	2.81		160 79	0.41	229.68	0.40	316.54	1.61
52.96	4.63	108.98	0.54		161 79	2 15	232.78	0.31	316.89	0.42
53.96	5.83	111.00	0.54		168.84	0 68	233.68	1.33	317.53	0.48
54 99	2.35	114.82	5.93		169.78	3.10	234.66	0.57	318.51	1.72
56.01	1.16	114.95	0.63		170 78	2 11	235.65	10.26	319.52	0.71
57 02	3.88	115.83	2.99		171.79	9 38	236.66	0.73	320.51	0.66
58.97	4.52	116.83	9.94		172.77	2 21	237 65	15.50	321 51	0 52
59 97	0.62	117.83	4.10		173.79	7 52	238.65	1.02	324 65	3 82
61.95	22 32	118.82	5.93		174 82	0 99	239.64	7.22	325.64	0.36
62 96	9 32	119.84	1.25		175 79	0 54	240.66	1.27	326.65	6 67
63 96	5 70	120.86	2.03		176 81	1 49	242.65	0.85	327 66	0 68
64.97	1 87	121.84	0.79		178 82	1 00	244.65	0.47	328 61	3 51
65 96	0.91	121.95	0.32		181 69	0 49	244.94	3.34	329.53	12 57
66 98	1.35	122.98	0.41		183 68	1 17	245.95	0.80	330 53	1.70
67 95	1 90	123.96	0.36		183.80	0 34	246 93	0.30	331 52	36 61
68 95	1.91 F	124.97	0.38		184 82	0 95	247.64	0.60	331.91	0 32
69 01	3 18 F	126.81	0.46		185.76	1 61	248.65	6.59	332.53	2 28
70 00	0.74	126.94	0.30		186 80	1 20	249.65	1.38	333 52	34 90
70 93	0 54	127.82	0.47		187 79	1 55	250.64	13.20	334 53	2 07
71 02	1 69	128.82	5.50		189 79	0 44	251.66	2.76	335 52	11 13
72 99	10.38	128.96	0.93		189 79	0 44	252 65	8.08	336 53	0 64
73 94	3 42 F	129 82	1.84		190 92	0 59	253.66	3.00	345 26	0 32
73 98	1 59 F	130.81	35.07		191 90	0 41	254 65	2.78	347 10	0 89
74 95	4 25	131.82	2.30		193 68	2 20	255 67	1.35	347 92	0 42
75 96	2 67	132.80	29.21		194 64	0 67	256.65	1.49	348 48	0 52
76 97	0 92	132.94	1.22		194 96	0 31	258 90	0.38	357 51	2 81
77 93	32.03	133.82	2.08		195 67	7 04	262 65	0.31	358.51	0 38
78 85	3.03	134.82	0.41		196 69	1 65	263 63	6.44	359 51	9 02
78 95	1 97	134.96	1.04		197 67	4 74	264 66	1.25	360 51	1 18
79 86	1 76	135.81	0.81		198 69	1 62	265 63	13.09	361 51	8 24
79 94	1 34	138.95	1.13		198.92	1 02	266 64	2.27	362.51	2.76
80.84	2 93	140.80	6.16		199 75	1 73	267 63	6.53	363 50	2 67
80.97	1.45	140.94	0.52		200 73	0.81	268.64	2.50	364.51	1 98
81.85	1.47	141.81	5.84		201.76	1.62	269.65	0.44	366 50	0.66
81.98	0.53	142.81	7.21		202.74	0 81	270 63	0.98	372.53	34 47
82.96	3.28	143.81	6.73		204.87	0.99	278 63	4.02	373.49	2 88
83.99	0.34	144.80	3.07		205.93	0.40	279 63	0.43	374.51	100.00
85.03	1.08	144.94	0.40		207.67	4 18	280.63	7.26	375.50	8 38
86.96	0.72	145.81	1.86		208.70	0.48	281.65	1.62	376.52	97 69
89.92	3.41	146.80	3.90		208.93	0.48	282.63	3.65	377.53	7 60
90.84	6.61	146.95	2.24		209.66	8.99	283.65	2.53	378.52	31 74
90.94	1.62	147.80	0.63		210.68	0.81	284 65	0.48	379.53	2 65
91.94	1.45	147.95	0.42		211.66	4.43	285.65	1.08	445.85	0 55
92.84	7.94	148.79	2.84 F		212.68	0.62	293.65	0.47		
92 95	0.97	148.91	3.29 F		213.67	0 31	294.66	4.79		
93 91	0.79	149.80	0.36		214 74	0.65	295.66	1.10		
94 85	2 56	149.91	0.49		215 77	0 47	296.66	8.96		
94 98	0 88	151 91	0 47		216.81	1 23	297.66	1.22		
95 86	0.71	152 79	1.15		217.77	0 42	298.66	4.56		

192

Mass spectrum with labeled peaks: 55, 71, 82, 91, 100, 110, 120, 136, 149, 160, 180, 191, 215, 241, 250, 269, 289, 321, 349

CH1184#12*   x1   Bgd=1
BpM=0   I=8.0v   Hm=431   TIC
CHRIS HALL

Mass	% Base	
40.01	0.31	
41.04	4.26	
43.00	2.11	F
43.06	0.73	F
44.01	2.00	
45.02	0.30	
47.00	0.61	
48.00	0.95	
50.01	3.49	
51.01	2.98	
52.01	1.36	
53.01	2.15	
54.00	5.08	
55.00	30.07	F
55.06	1.22	F
56.01	17.24	F
56.06	1.39	F
57.01	3.51	F
57.07	4.27	F
58.03	0.57	
60.01	0.43	
62.01	14.90	
63.01	4.44	
64.02	0.80	
65.03	0.42	
66.01	0.41	
67.01	2.68	
68.01	0.85	
69.01	4.43	
70.02	2.85	
70.99	19.16	
71.09	0.35	
72.00	0.88	
73.03	0.41	
74.00	7.18	

Mass	% Base	
75.00	3.98	
76.01	0.70	
77.99	5.84	
78.91	10.50	F
79.00	0.77	F
79.92	14.72	
80.46	1.25	
80.90	11.25	F
80.99	29.33	F
81.46	1.37	
81.91	14.03	F
82.00	33.16	F
83.00	5.35	
84.00	6.85	
85.00	0.82	
85.99	1.77	
87.03	0.34	
89.99	1.27	
90.91	6.89	F
91.01	1.42	F
91.94	0.75	
92.90	6.64	F
92.99	5.82	F
93.96	0.89	
94.45	0.30	
94.98	0.37	
95.45	0.30	
97.94	0.60	
98.90	0.33	
99.99	5.74	
101.00	2.04	
102.01	0.95	
102.93	0.60	
103.97	0.35	
104.92	1.34	
105.92	3.81	
106.91	1.77	
107.92	3.45	
108.97	5.45	

Mass	% Base	
109.99	8.60	
110.90	1.35	F
111.00	1.71	F
111.97	1.35	
112.90	1.16	F
113.01	1.70	F
114.03	0.35	
114.90	3.77	
115.91	0.85	
116.91	4.81	
117.91	1.36	
118.91	2.10	
119.41	2.67	
119.92	1.90	
120.41	5.07	
120.92	0.86	
121.41	2.36	
121.91	3.39	
122.91	0.39	
123.90	1.85	
128.93	1.41	
129.93	1.27	
130.40	0.30	
130.91	4.42	
131.92	1.33	
132.90	2.65	
133.40	1.26	
133.90	19.29	
134.40	2.56	
134.91	11.96	
135.40	1.41	
135.90	19.95	
136.91	10.34	
137.91	1.04	
140.91	2.30	
141.91	0.92	
142.90	2.54	
143.91	1.22	
144.40	0.33	
144.90	0.42	

145.90	1.41
147.90	1.77
149.00	3.80
149.94	0.79
150.91	0.36
152.89	12.00
153.90	0.47
154.89	11.63
155.91	0.48
157.90	0.73
159.36	0.90
159.90	77.85
160.36	2.59
160.90	6.88
161.36	2.60
161.90	76.21
162.36	0.79
162.91	7.82
163.90	2.26
164.90	1.15
169.88	0.50
171.87	0.91
173.35	0.52
173.87	0.45
174.36	1.56
175.36	1.36
176.35	0.40
178.91	0.30
179.90	5.15
180.90	1.50
181.90	5.23
182.90	1.22
187.89	4.23
188.89	10.39
189.90	6.84
190.89	12.12
191.90	3.11
192.90	1.92
193.83	0.69
194.80	0.57
195.81	1.42
196.80	1.45
197.80	1.22
198.81	1.91
199.81	0.43
200.81	1.21
202.81	0.36
206.95	0.51
207.89	3.93
208.90	1.74
209.89	3.55
210.89	1.53
211.86	0.33
212.81	13.11
213.82	0.49
214.81	25.30
215.82	0.92
216.81	12.36
217.82	0.43
219.82	0.58
221.82	1.30
223.83	0.52
226.88	0.71
228.87	0.41
238.81	6.82
239.81	2.42

240.81	14.23	
241.81	4.59	
242.81	8.35	
243.81	2.23	
244.80	1.04	
249.81	0.52	
258.81	2.61	
259.81	0.65	
260.81	5.03	
261.81	0.50	
262.81	2.33	
264.81	0.30	
266.80	17.61	
267.81	5.79	
268.80	42.34	
269.81	12.72	
270.80	34.50	
271.81	7.29	
272.81	9.64	
273.81	1.20	
277.71	0.45	
279.71	0.49	
284.82	0.79	
286.80	11.18	
287.82	1.51	
288.81	20.95	
289.82	2.68	
290.80	9.68	
291.81	1.22	
317.72	0.32	
318.74	1.70	
319.72	0.95	
320.74	4.91	
321.72	1.05	
322.73	4.76	
323.73	0.40	
324.73	1.46	
344.74	1.20	
346.72	36.53	
347.72	4.33	F
348.71	100.00	F
349.71	11.44	F
350.70	93.31	F
351.71	10.67	F
352.72	30.01	F
353.73	3.34	

```
27#23*      x1     Bgd=11    26-FEB-96  15:08+0:02:22   70E
=0     I=2 Ov  Hm=428   TIC=114598000              Acnt:
IS HALL                                                        PT= 0
```

```
227#23*          x1     Bgd=11
M=0    I=  . /    Hm=428    TI
RIS HALL
```

Mass	% Base	Mass	% Base	Mass	% Base
30 99	34.96	97.09	0.83	242 81	2 79
36 00	2.76	99.01	0.52	244 81	1 06
37 00	3 08	100.00	1.53	250 84	0 57
38 01	12 87	103.04	0.62	252 84	1 50
39 02	48 99	104 01	0.58	254 83	0 87
40 02	2 28	105.00	1.39	263 93	3 02
41 03	5 28	106 00	2.41	264 94	26.26
41 51	0 86	107.03	0.90	265 94	5.45
4 41	4 34	108 02	0.55	266 93	22.50
4 79	0 46	106 99	0.38	267 94	2 81
48	1 33	111.99	10.88	268 83	2 38
5 41	27 35	113.01	1.09	269 82	1.66
5	88 05	114 92	1.03	270 87	1 48
5 5	3 82	116 91	1.71	271 87	2 86
5	1 76	121 90	1.32	271 92	1 23
6 42	6 01 F	123 91	1 15	315 86	0.69
6 29 F		128.92	0 64	317 81	1 97
1 98		130.00	0.76	319 77	3 12
6 41	0 64	131.02	5.77	321 76	3 08
6 79	5 79	132 02	4.13	323 76	0.70
6 90	1 90	133.91	5.29	347 82	0 41
6	15 06	134 92	0 60	343 85	3 39
63 03	13 92	135 90	6.43	344 36	1.91
64 95	5 44	136 91	0.79	345 85	7 38
65 03	24 47	138 02	0.64	346 85	1.53
66 03	1 62	140.92	1.00	347 83	3.57
67.02	2.17	142.91	1.12	348 76	1.99
68.02	1.66	145.90	2.20	349 74	0 86
68.99	2.28 F	147.90	2.79	350 72	4.39
69.07	3.71 F	149.00	0.85	35	4 59
70.07	0.50	152 90	0.94		0 87
70.99	2 42	154.91	0.89	354 64	0 85
71 08	2 31	155.97	1.83	422 76	3 34
73 01	0 84	157.02	5.11	424 77	11 10
74 01	11 08	158.02	18.18	427 76	1 32
75 02	5 99	159.03	1.98	426 78	10 80
76 02	4 74	159.91	9.61	427 79	1.36
77 03	100 00	160.91	0.55	428 76	2.91
78 04	7 41	161.90	9.82		
79 91	3 39	162.90	0.58		
79	0 89	164 90	0.85		
79	1 77	166 90	0.76		
80 00	0 85	171.91	3.98		
81 90	3 82 F	172.92	1.52		
81 90	8 91 F	173 91	2.92		
81 91	1 81	185.01	8.15		
82 00	1 25	186.02	10.20		
82 05	0 93	187.03	1.82		
85 00	0 48	190.90	7.19		
85 10	0 73	192.90	6.77		
85 99	7 11	205.02	0.91		
87 01	1 37	210.94	1.67		
88 01	1 02	212.85	5.71		
89 03	1 58	214.82	10.36		
90 91	2 12	216.82	5.19		
91 05	0 46	235.94	3.07		
92 03	0 85	236.95	1.51		
92 99	17 25	237.94	3.50		
94 00	1 81	238 93	1 47		
95 07	0 93	240 82	2.46		

Mass	% Base
55.02	0.30
63.02	0.30
70.03	1.30
77.02	1.24
79.93	0.31
81.00	1.12
82.01	5.65
83.02	2.88
89.01	0.34
90.03	0.33
90.92	0.42
92.95	0.58
105.94	0.37
107.01	0.45
108.00	1.71
109.02	7.68
110.02	0.41
116.93	0.39
118.93	0.43
120.94	0.33
129.93	0.45
131.93	0.43
133.92	1.21
134.93	1.25
135.92	1.50
136.92	1.20
142.92	0.41
159.92	8.17
160.92	1.83
161.92	7.11
162.92	1.70
163.93	0.92
186.92	1.39
187.93	13.44
188.93	2.53
189.93	14.01
190.92	0.96
198.81	0.33
212.83	5.48
214.82	10.46
215.83	0.32
216.82	5.24
221.83	0.50
239.83	3.82
240.82	0.95
241.83	7.72
242.83	0.76
243.83	3.76
248.83	0.44
265.82	0.31
266.84	7.03
267.83	1.60
268.83	14.14
269.83	2.27
270.83	7.11
271.83	1.11
287.82	0.48
288.83	0.45
345.72	43.25 F
346.74	9.16 F

Mass	% Base
347.73	100.00 F0
348.73	25.20 F
349.73	100.00 F0
350.73	24.31 F
351.74	40.71 F
352.75	7.91
353.74	0.36
534.67	0.58
535.68	0.41
536.67	1.02
537.68	0.68
538.67	0.68
539.68	0.43

CH256F89 1129 (18.818)

100 | 31 | 100 | 303 | 1622016
%FS | | | 301 305
| 5771 81 112 153 162 224
| 124 181 193
m/z 50 100 150 200 250 300 350 400 450 500
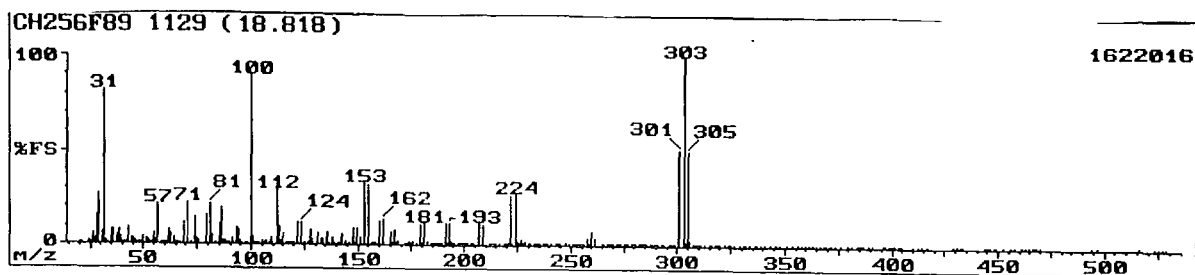
CH256F89 1129 (18.818)   16220   CH256F89 1129 (18.:

Mass	Rel Int	Mass	Rel Int	Mass	Rel Int	Mass	Rel Int	Mass	Rel Int
20	0.57	83	0.32	149	0.30	217	0.26	283	0.01
21	0.01	85	10.23	150	8.90	219	0.07	284	0.05
24	1.47	86	19.44	151	3.93	220	0.22	285	0.05
25	1.01	87	1.55	153	32.83	220	0.06	285	0.28
26	5.87	88	2.19	155	31.82	222	26.26	286	0.33
27	3.17	89	0.52	156	0.80	223	1.18	287	0.49
28	15.21	90	0.09	157	0.03	224	27.02	288	0.59
29	27.53	91	2.87	158	0.07	225	2.00	289	0.34
30	6.38	93	9.15	160	12.75	226	0.08	290	0.26
31	81.82	94	8.02	162	13.13	227	2.48	291	0.16
32	1.53	95	1.80	165	6.88	228	0.05	293	0.06
33	1.15	96	1.12	166	0.24	229	2.24	294	0.02
35	8.02	97	0.18	167	8.08	230	0.10	296	0.12
36	7.95	98	0.21	168	0.42	231	0.02	297	0.01
37	5.11	100	88.89	169	1.47	232	0.05	298	0.20
38	8.14	101	4.23	172	0.73	234	0.06	299	0.02
39	4.23	102	0.47	173	0.54	235	0.01	301	51.52
40	1.06	103	0.51	174	1.47	236	0.10	303	100.00
41	1.40	104	0.09	175	0.33	237	0.22	304	1.89
42	0.64	105	2.04	176	1.88	238	0.14	305	50.25
43	8.40	106	0.34	178	0.76	239	0.14	306	2.54
44	3.11	107	1.83	179	10.61	241	0.14		
45	2.98	109	1.45	180	0.26	243	0.45		
46	1.72	109	1.29	181	11.93	244	0.08		
47	1.33	110	3.95	183	1.63	245	0.02		
48	0.56	112	29.55	184	0.12	248	0.04		
49	0.73	113	9.41	185	0.01	250	0.04		
50	4.17	114	2.08	186	0.06	251	0.05		
51	3.05	115	5.93	187	0.02	252	0.15		
52	2.40	117	1.06	188	0.77	253	0.12		
53	0.54	118	0.06	189	0.31	253	0.17		
54	0.45	119	0.48	190	0.67	254	0.22		
55	5.74	119	0.34	191	11.30	255	0.26		
56	1.48	120	0.11	192	0.88	256	0.11		
57	21.21	122	11.74	193	11.55	258	3.99		
58	1.34	124	11.87	194	1.96	259	0.10		
59	0.44	125	0.56	195	0.28	260	7.51		
60	0.52	127	0.14	196	0.96	262	3.87		
61	0.03	128	7.64	197	0.17	265	0.05		
62	7.45	129	2.48	198	0.10	266	0.01		
63	5.62	131	5.68	199	0.02	267	0.07		
64	3.41	133	2.78	200	0.09	269	0.13		
65	0.88	133	1.01	201	0.15	270	0.36		
66	0.20	134	3.31	202	0.02	271	0.30		
67	1.37	136	6.88	203	0.23	272	0.90		
69	12.12	137	0.37	204	0.05	273	0.38		
71	22.22	138	3.41	205	0.19	274	0.47		
72	1.03	139	0.14	207	11.49	275	0.15		
74	14.20	141	1.31	209	11.11	277	0.04		
75	3.30	142	0.42	212	0.23	277	0.03		
76	1.59	143	5.62	212	0.12	279	0.05		
79	15.97	144	1.80	213	0.19	280	0.01		
81	21.21	146	1.39	214	0.05	281	0.06		
82	4.55	148	8.78	215	0.45	282	0.03		

CH1179'944 (15.735) REFINE

454656
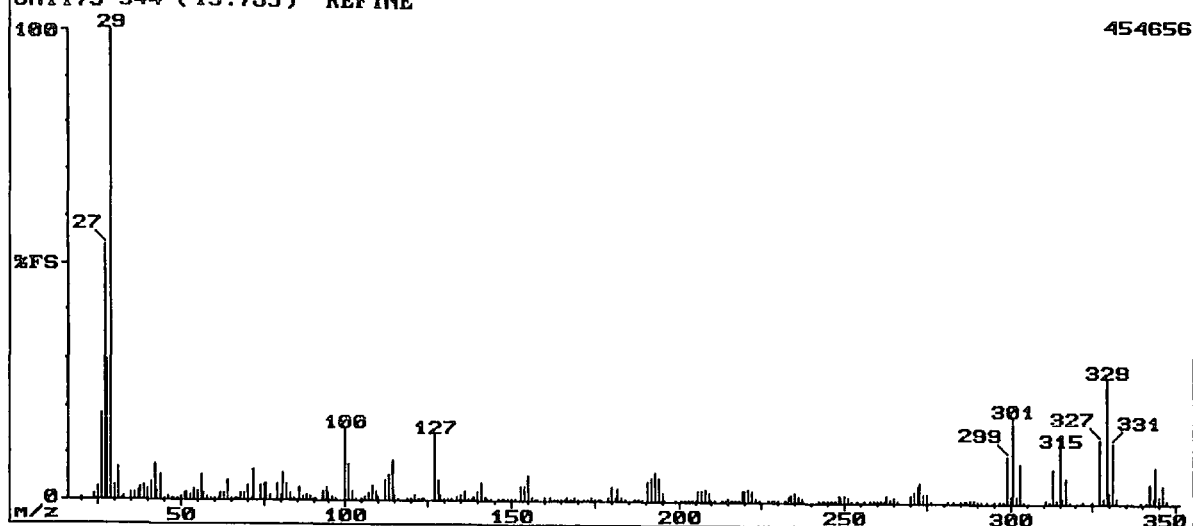
CH1179 944 (15.735)   45875. CH1179 944 (15.73!

Mass	Rel Int	Mass	Rel Int	Mass	Rel Int	Mass	Rel Int	Mass	Rel Int
20	0.47	80	1.40	146	0.20	211	0.10	285	0.16
24	0.99	81	6.08	147	0.23	213	0.23	286	0.45
25	2.57	82	3.33	148	0.29	214	0.35	287	0.56
26	18.30	83	1.51	149	0.48	215	0.69	288	0.75
27	53.57	84	0.45	150	0.27	216	0.42	289	0.62
28	31.25	86	2.57	151	0.11	217	0.57	290	0.26
29	100.00	87	0.73	153	3.19	218	0.20	291	0.28
30	3.17	88	1.14	154	3.00	219	2.13	293	0.12
31	6.92	89	0.76	155	5.25	220	2.41	295	0.21
32	0.54	90	0.29	156	0.85	221	2.85	297	0.45
33	0.93	91	0.29	157	0.28	222	2.37	298	0.24
35	1.70	93	1.91	158	0.17	223	0.85		
36	1.88	94	2.80	160	0.60	224	0.09	299	9.88
37	1.83	95	1.60	162	0.69	227	0.07	300	1.38
38	2.72	96	0.83	163	0.42	228	0.08	301	18.08
39	3.18	97	0.28	164	0.44	229	0.08	302	1.55
40	2.47	100	14.96	165	0.53	230	0.06	303	8.59
41	3.96	101	7.65	166	0.31	232	0.47	304	0.56
42	7.81	102	1.94	167	0.74	233	1.19	311	0.92
43	1.79	103	0.29	168	0.31	234	1.48	312	0.21
44	5.97	105	0.37	169	0.67	235	1.74	313	7.20
45	0.57	106	0.68	170	0.12	236	1.06	314	0.82
46	0.62	107	1.35	172	0.18	237	0.68	315	11.72
47	0.19	108	3.18	173	0.28	242	0.08		
48	0.14	109	1.81	174	0.58	243	0.24	316	1.31
49	0.33	110	0.63	175	0.35	244	0.20	317	5.36
50	0.95	112	4.07	176	0.38	245	0.27	318	0.55
51	1.55	113	5.41	177	0.09	246	0.33	322	0.05
52	1.51	114	8.31	179	0.63	247	0.19	325	0.08
53	1.27	115	0.99	180	2.90	248	1.73	327	13.67
54	2.15	116	0.32	181	0.87	249	1.17	328	1.00
55	1.77	119	0.17	182	2.79	250	1.60	329	25.89
56	5.25	120	0.36	183	0.80	251	1.02	330	2.15
57	1.67	121	1.19	184	0.17	252	0.12	331	12.50
58	0.73	122	0.50	187	0.13	254	0.22	332	1.07
59	0.34	123	0.21	188	0.30	256	0.12		
60	0.12	124	0.22	189	0.21	258	0.20	339	0.08
61	0.21	127	14.01	191	4.30	259	0.21	341	0.37
62	1.73	128	4.24	192	5.19	260	0.37	342	3.96
63	1.72	129	1.28	193	6.19	261	0.45	343	1.05
64	4.41	130	0.42	194	5.08	262	0.37	344	7.25
65	0.50	131	0.23	195	1.93	263	1.44	345	1.31
66	0.36	132	0.20	196	0.20	264	0.61	346	3.54
67	0.24	134	0.75	199	0.23	265	1.28	347	0.56
68	1.44	135	1.27	201	0.47	266	0.45		
69	1.73	136	1.94	202	0.11	270	1.73		
70	3.03	137	0.53	203	0.17	271	2.33		
71	0.55	138	0.29	204	0.10	272	3.57		
72	6.47	139	0.72	205	0.35	273	4.30		
74	3.06	140	1.76	206	2.47	274	2.09		
75	3.47	141	3.74	207	2.40	275	2.11		
76	3.31	142	0.80	208	2.62	276	0.25		
77	1.10	143	0.32	209	2.04	281	0.11		
79	3.79	144	0.24	210	0.44	283	0.05		

CH1179'944 (15.735) REFINE

100 — 29

%FS

27

100   127

299 301 327 329 331
      315

m/z   50   100   150   200   250   300   350

454656

CH1179 944 (15.735)

45   CH1179 944 (15.735)

Mass	Rel Int		Mass	Rel Int		Mass	Rel Int		Mass	Rel Int		Mass	Rel Int
20	0.47		80	1.40		146	0.20		211	0.10		285	0.16
24	0.99		81	6.08		147	0.23		213	0.23		286	0.45
25	2.57		82	3.33		148	0.29		214	0.35		287	0.56
26	18.30		83	1.51		149	0.48		215	0.69		288	0.75
27	53.57		84	0.45		150	0.27		216	0.42		289	0.62
28	31.25		86	2.57		151	0.11		217	0.57		290	0.26
29	100.00		87	0.73		153	3.19		218	0.20		291	0.28
30	3.17		88	1.14		154	3.00		219	2.13		293	0.12
31	6.92		89	0.76		155	5.25		220	2.41		295	0.21
32	0.54		90	0.29		156	0.85		221	2.85		297	0.45
33	0.93		91	0.29		157	0.28		222	2.37		298	0.24
35	1.70		93	1.91		158	0.17		223	0.85			
36	1.88		94	2.80		160	0.60		224	0.09		299	9.88
37	1.83		95	1.60		162	0.69		227	0.07		300	1.38
38	2.72		96	0.83		163	0.42		228	0.08		301	18.08
39	3.18		97	0.28		164	0.44		229	0.08		302	1.55
40	2.47		100	14.96		165	0.53		230	0.06		303	8.59
41	3.96		101	7.65		166	0.31		232	0.47		304	0.56
42	7.81		102	1.94		167	0.74		233	1.19		311	0.92
43	1.79		103	0.29		168	0.31		234	1.48		312	0.21
44	5.97		105	0.37		169	0.67		235	1.74		313	7.20
45	0.57		106	0.68		170	0.12		236	1.06		314	0.82
46	0.62		107	1.35		172	0.18		237	0.68		315	11.72
47	0.19		108	3.18		173	0.28		242	0.08			
48	0.14		109	1.81		174	0.58		243	0.24		316	1.31
49	0.33		110	0.63		175	0.35		244	0.20		317	5.36
50	0.95		112	4.07		176	0.38		245	0.27		318	0.55
51	1.55		113	5.41		177	0.09		246	0.33		322	0.05
52	1.51		114	8.31		179	0.63		247	0.19		325	0.08
53	1.27		115	0.99		180	2.90		248	1.73		327	13.67
54	2.15		116	0.32		181	0.87		249	1.17		328	1.00
55	1.77		119	0.17		182	2.79		250	1.60		329	25.89
56	5.25		120	0.36		183	0.80		251	1.02		330	2.15
57	1.67		121	1.19		184	0.17		252	0.12		331	12.50
58	0.73		122	0.50		187	0.13		254	0.22		332	1.07
59	0.34		123	0.21		188	0.30		256	0.12			
60	0.12		124	0.22		189	0.21		258	0.20		339	0.08
61	0.21		127	14.01		191	4.30		259	0.21		341	0.37
62	1.73		128	4.24		192	5.19		260	0.37		342	3.96
63	1.72		129	1.28		193	6.19		261	0.45		343	1.05
64	4.41		130	0.42		194	5.08		262	0.37		344	7.25
65	0.50		131	0.23		195	1.93		263	1.44		345	1.31
66	0.36		132	0.20		196	0.20		264	0.61		346	3.54
67	0.24		134	0.75		199	0.23		265	1.28		347	0.56
68	1.44		135	1.27		201	0.47		266	0.45			
69	1.73		136	1.94		202	0.11		270	1.73			
70	3.03		137	0.53		203	0.17		271	2.33			
71	0.55		138	0.29		204	0.10		272	3.57			
72	6.47		139	0.72		205	0.35		273	4.30			
74	3.06		140	1.76		206	2.47		274	2.09			
75	3.47		141	3.74		207	2.40		275	2.11			
76	3.31		142	0.80		208	2.62		276	0.25			
77	1.10		143	0.32		209	2.04		281	0.11			
79	3.79		144	0.24		210	0.44		283	0.05			

CHRIS HALL   PT=   S HALL DEK27

Mass	% Base	
43.06	0.30	
44.98	1.77	
50.02	3.89	
51.03	18.11	
52.03	0.91	
56.99	0.54	
57.08	0.56	
57.99	0.88	
59.00	0.40	
61.04	0.39	
62.01	1.38	
62.97	0.87	F
63.03	2.08	F
65.04	19.14	
66.05	1.46	
68.98	7.35	
69.99	0.71	
70.99	0.43	
73.03	0.36	
74.01	1.90	
75.01	1.79	
76.??	1.14	
77.??	22.58	
78.??	1.93	
78.??	0.88	
79.??	1.61	
80.??	0.93	
81.91	1.75	F
81.98	2.08	F
82.99	1.18	
83.99	0.69	
85.99	2.94	
86.97	1.91	
92.99	1.10	
93.97	1.85	
96.99	3.29	
97.49	1.66	
98.98	0.34	
99.99	1.90	
100.49	0.56	
100.98	0.59	
105.99	0.30	
107.01	0.73	
108.00	4.20	
109.00	27.59	
110.00	5.44	
110.49	2.99	
111.00	2.13	
111.99	3.45	
112.99	1.01	
117.96	0.68	
120.02	0.85	
121.00	2.04	
12?.95	0.30	
12?.00	0.31	
1?8.??	0.54	
1?1.01	0.55	
1?2.02	0.61	
1?4.02	0.49	
1??.??	?.51	

Mass	% Base	
137.96	0.45	
143.96	3.21	
144.99	0.46	
148.98	0.74	
149.97	1.69	
150.43	0.37	
150.98	1.78	
152.00	0.69	
152.92	1.10	
154.05	0.37	
154.90	1.18	
157.01	1.13	
158.02	3.05	
159.02	0.40	
159.91	0.30	
161.95	0.36	
162.99	0.52	
164.90	0.63	
166.90	0.67	
169.99	0.86	
170.99	0.41	
174.99	0.31	
176.01	11.44	
177.01	3.35	
178.01	0.38	
186.02	0.44	
187.99	0.66	
189.01	3.18	
189.39	0.51	
189.99	0.91	
190.38	0.92	
190.90	1.53	
191.38	0.45	
191.90	0.45	
192.90	1.48	
193.97	5.47	
194.97	1.53	
195.97	0.37	
196.87	1.47	
198.86	1.53	
200.97	12.19	
201.98	3.69	
202.98	1.44	
203.98	0.53	
217.99	0.45	
218.97	1.07	
219.98	9.84	F
220.97	100.00	F
221.98	10.28	
222.98	5.22	
223.97	0.61	
224.88	0.51	
228.91	0.38	
230.91	0.30	
232.94	0.57	
235.92	0.42	
237.92	0.45	
255.91	0.87	
257.91	0.74	
266.90	0.55	

Mass	% Base	
267 89	0.30	
268 89	0.61	
269.85	0.35	
270 80	0.46	
271 79	0.38	
272 79	0.78	
274.80	0.39	
279 87	7.06	
280 88	4.89	
281 87	7.93	
282 88	4.64	
283 88	0.91	
297 88	0.38	
298 88	2.75	
299 88	4.27	
300 88	4.86	
301 88	4.38	
302 89	2.37	
303 87	0.33	
309 97	0.42	
310.97	0.42	
311 89	0.37	
312 97	0.30	
347 74	0.31	
348 70	0.39	
350 69	0.89	
352 69	0.82	
358 78	2.43	
359 79	1.44	
360 78	4.99	
361 78	2.98	
362 78	2.85	
363 78	1.48	
378 76	35.03	F
379 78	6.29	F
380 77	85.70	F
381 78	10.86	F
382 79	36.52	F
383.80	5.20	
384.79	1.76	
388 88	0.53	
390.89	0.73	
468.79	0.30	
470.79	0.74	
472.79	0.40	

Mass spectrum labeled **20a**, with peaks labeled: 55, 69, 81, 93, 100, 113, 140, 167, 193, 207, 219, 235, 247, 275, 300, 315, 327, 341, 355, 365, 415.

JA#15* x1 Bgd=1 7-DEC-95 11:03+0:01:43 70E
:0 I=7 1v Hm=419 TIC=515314000 Acnt: PT= 0
S HALL

Mass	% Base
168.98	0.40
171.85	0.47
172.89	0.89
173.87	1.02
174.92	1.30
175.93	0.56
176.97	0.72
178.94	0.38
179.95	0.53
180.96	0.55
181.86	0.41
185.07	0.45
190.85	6.18
191.86	5.78
192.85	6.40
193.86	5.62
194.98	3.29
195.99	0.81
196.99	0.90
199.86	0.53
200.87	0.96
201.87	0.41
204.90	0.52
205.86	0.81
206.87	0.97
207.87	0.80
208.86	0.41
213.88	0.45
214.85	0.47
215.87	0.41
216.85	0.55
217.86	0.49
218.85	7.03
219.86	2.59
220.85	6.98
221.85	2.20
222.89	0.60
226.86	0.75
227.89	0.33
228.87	0.58
231.86	0.37
232.86	1.41
233.86	0.95
234.87	1.47
235.92	0.66
244.86	0.50
245.86	0.46
246.87	2.74
247.87	0.72
248.88	2.40
251.76	0.74
253.75	1.51
254.85	0.32
255.84	0.73
256.91	0.35
259.79	0.37
260.85	0.35
269.73	1.70
270.75	0.92
271.73	3.25

Mass	% Base	
272.75	1.56	
273.78	2.14	
274.88	7.11	
275.88	2.29	
276.88	6.99	
277.89	1.24	
278.77	0.74	
280.76	1.00	
282.76	0.46	
283.74	0.95	
284.75	0.38	
285.74	1.98	
286.75	0.63	
287.73	1.46	
288.74	0.48	
289.76	0.40	
296.73	6.57	
297.73	11.42	F
298.73	15.87	F
299.73	21.50	
300.73	13.20	
301.73	10.88	
302.75	3.58	
303.79	0.31	
306.76	0.66	
307.76	0.39	
308.76	0.57	
309.76	0.32	
310.74	1.04	
311.76	0.34	
312.75	12.25	
313.75	1.46	
314.75	22.07	
315.75	2.06	
316.74	10.18	
317.77	0.89	
320.77	0.30	
322.75	0.55	
324.74	2.42	
325.75	0.36	
326.74	3.78	
327.74	0.48	
328.74	1.70	
334.78	0.58	
336.77	1.03	
337.78	0.34	
338.75	1.92	
340.76	2.43	
342.75	0.99	
348.61	0.48	
350.62	1.21	
351.79	1.62	F
352.74	49.71	F
353.76	33.78	F
354.75	100.00	F
355.76	60.98	F
356.74	53.25	F
357.77	29.37	F
358.76	4.35	
359.70	0.65	

CH23A#15* x1 Bgd=1
BpM=0 I=7.1v Hm=419 T.
CHRIS HALL

Mass	% Base
360.67	2.46
361.64	0.52
362.64	2.28
364.63	0.70
412.65	0.77
413.66	0.43
414.66	2.54
415.67	1.11
416.65	2.33
417.67	1.21
418.65	0.81
419.67	0.51

CH23'1092 (18.201) REFINE   20b   212992

CH23'1092 (18.201) REFINE   212

Mass	Rel Int	Mass	Rel Int	Mass	Rel Int	Mass	Rel Int
20	1.98	82	3.70	148	0.83	258	0.39
24	1.04	83	3.79	149	0.47	259	0.31
25	2.88	84	18.99	150	0.22	260	0.17
26	21.27	85	1.55	153	3.52	261	0.66
27	45.19	86	2.46	154	1.49	263	0.29
28	38.94	87	1.27	155	2.19	270	2.70
29	26.20	88	1.58	156	0.32	271	10.58
30	3.40	89	0.55	160	0.81	272	6.25
31	9.98	90	0.38	162	0.38	273	19.11
32	0.69	91	0.22	165	1.39	274	5.68
33	1.98	93	2.49	166	0.47	275	12.98
35	9.13	94	2.49	167	3.37	276	2.46
36	8.89	95	2.31	168	1.58	277	3.40
37	5.68	96	0.81	169	0.57	285	1.05
38	7.42	97	0.20	173	0.37	286	4.99
39	42.31	98	0.11	174	0.61	287	1.27
40	8.77	99	0.94	175	1.35	288	8.65
41	100.00	100	6.85	176	0.93	289	1.42
42	37.02	101	1.59	180	0.91	290	3.64
43	4.93	102	0.49	181	0.38	297	1.07
44	2.25	103	0.21	182	0.83	298	2.79
45	0.56	105	0.38	191	5.77	299	9.38
46	1.01	106	0.50	192	11.66	300	4.84
47	0.52	107	0.93	193	8.05	301	14.78
48	0.47	108	1.01	194	10.46	302	2.73
50	6.10	109	0.28	195	3.79	303	6.40
51	5.68	110	0.28	196	0.58	305	0.38
52	3.34	112	5.86	199	0.45	307	0.82
53	11.54	113	11.30	201	0.81	308	0.23
55	58.65	114	5.53	205	0.78	309	0.57
56	14.06	115	0.41	206	0.63	311	3.70
57	6.52	116	0.25	207	2.01	312	0.63
58	0.50	117	0.26	208	0.77	313	9.38
59	0.40	120	1.04	209	0.89	314	0.85
62	2.25	121	1.56	219	2.94	315	8.05
63	2.76	122	0.56	220	2.13	316	0.71
64	4.72	124	0.55	221	2.67	317	2.28
65	2.19	125	0.20	222	1.40	323	0.32
66	1.78	126	2.46	223	0.39	325	7.63
67	6.94	127	2.94	227	0.76	327	13.82
68	3.97	128	0.98	229	0.56	328	1.01
69	6.88	129	0.60	232	0.56	329	6.73
70	4.45	131	0.32	233	0.55	330	0.60
71	0.49	133	0.24	234	1.16	337	0.29
72	0.17	134	0.38	235	0.60	339	1.31
73	0.33	135	0.38	236	0.47	341	2.07
74	2.22	136	0.34	244	0.35	343	0.85
75	2.28	138	0.45	246	1.49	353	4.30
76	3.79	139	2.19	247	0.89	354	12.86
77	0.53	140	5.02	248	1.98	355	8.77
78	0.91	141	2.46	249	0.48	356	21.63
79	3.37	142	0.65	250	0.95	357	6.64
80	2.04	144	0.33	255	1.47	358	9.38
81	4.66	147	0.68	257	1.44	359	1.16

21

Mass	% Base
41 10	2.15
43 06	3.79 F
43 12	2.08 F
44.06	1.85
48 07	1.31
50.08	11.60
51.09	0.55
52 08	0.84
55 11	2.15
56 15	0.66
57 08	3 26 F
57 15	2 50 F
63 09	0 82
64 10	2 50
67 15	0.44
69 10	96 86
70 11	3 34
71 10	0 89

Mass	% Base
126 09	0 35
127 09	1 07
128 59	0 46
129 09	4 55
131 09	10 81
133 09	5 86
134 09	1 16
139 15	0 73
148 10	46 95
148 12	1 97
150 10	47 46
151 11	1 50
155 11	1 16
157 11	1 17
162 11	0 48
163 11	0 71
166 15	0 96
167 09	2 15
168 09	2 15
169 09	0 43
170 05	0 57
172.05	1.33
174.13	16.25
175.15	0.71
176.13	16.28
177.15	0.53
184.08	0.40
186.07	0.71
201.08	1.43
203.07	3.01
205.08	1.36
208.09	2.32
210.08	4.79
212.09	2.15
219 49	0.34
220.49	0.38
221 50	0.32
253 12	49.52
254 14	2.51
255 12	98 76

Mass	% Base
256 14	4 90
257 12	47 01
258 14	2 15
332 12	34.26
333 12	1 84 F
334 11	100 00 F
335 12	4.97 F
336 12	97 07 F
337 13	5 20
338 12	31 36
339 14	1.37
350 11	0 32
352 12	0 44
446 62	1 97
447 66	0 57

CH296

100 - 53

%FS -

648

0
Scn   200   400   600   800   1000   1200   1400   1600

18714512
TIC
#1

CH296 648 (10.801)

100 -

%FS -

187
188

143 158
142 157 159
70 72   173 189
28 31 42 58   87 100 113

0
m/z   50   100   150   200   250

1441792

CH296 648 (10.801)   1.

Mass	Rel Int	Mass	Rel Int	Mass	Rel Int	Mass	Rel Int
20	0.14	59	6.39	96	0.30	142	14.99
22	0.01	60	6.25	97	1.24	143	42.61
24	0.19	61	0.28	98	3.36	144	5.75
26	2.15	62	0.32	99	6.39	145	4.40
27	4.35	63	0.27	100	12.50	146	0.29
28	24.43	64	0.35	101	1.86	154	0.57
29	18.18	65	0.16	102	1.74	155	2.17
30	9.66	66	0.92	104	1.88	157	10.23
31	14.20	67	2.02	107	0.02	158	45.17
32	1.56	70	34.94	109	0.66	159	17.97
33	2.43	71	2.29	111	3.09	160	1.26
35	0.58	72	17.47	113	10.30	161	0.12
36	1.03	73	5.11	114	2.29	167	0.07
38	1.76	74	1.88	115	5.89	169	1.02
39	0.76	75	0.24	116	3.14	170	1.11
40	1.74	76	0.14	117	1.51	171	0.28
41	2.52	77	0.22	118	2.29	173	12.07
42	10.30	79	0.18	119	0.10	174	0.68
43	9.02	80	0.32	120	0.02	175	0.10
44	3.50	81	0.55	123	0.24	187	100.00
45	4.83	83	6.68	124	0.23	188	82.95
46	2.13	85	11.22	125	0.97	189	9.09
47	4.69	86	7.39	126	1.28	190	0.84
48	0.19	87	13.57	127	7.17	191	0.10
50	0.42	87	5.54	128	3.32	203	0.19
51	0.39	88	6.96	129	3.44	219	0.03
52	2.20	89	0.53	130	1.51	235	0.03
53	1.76	90	0.14	131	0.55	237	0.09
54	5.47	92	0.12	132	0.18	258	0.14
56	6.82	93	0.16	138	0.47	269	0.04
57	7.03	94	0.23	139	0.70		
58	11.65	95	0.43	140	2.34		

Name:Chris Hall   Ion Mode:EI+   26-Mar-97 11:46

Name:Chris Hall   Ion Mode:EI+   26-Mar-97 11:46
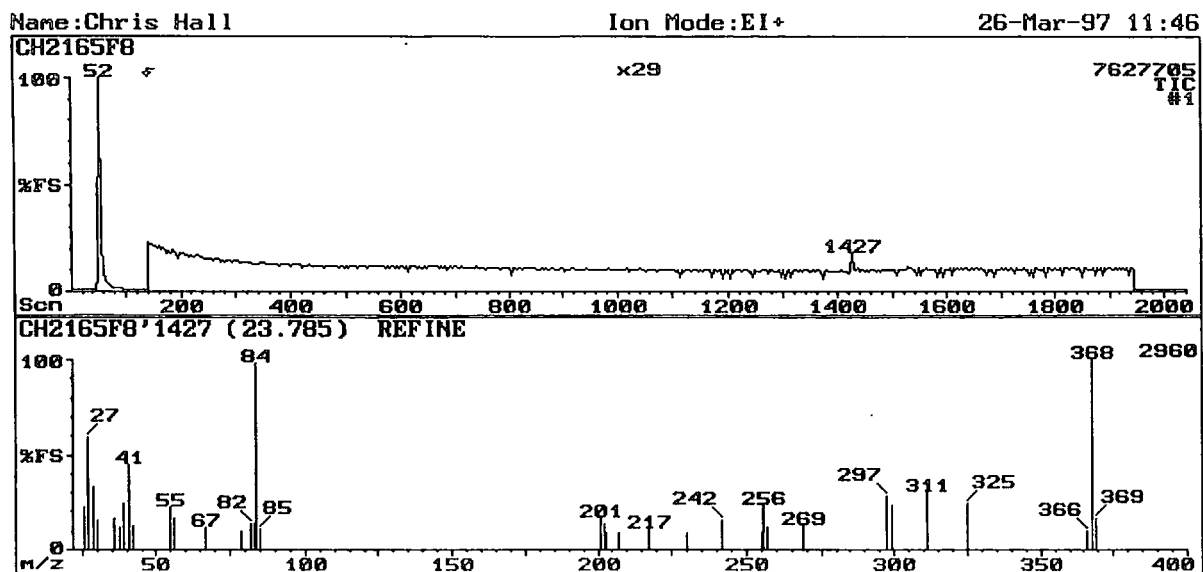
H2165F8'1427 (23.785)   REFINE   2960

ass	Rel Int	Mass	Rel Int	Mass	Rel Int	Mass	Rel Int
26	22.16	55	22.03	202	13.78	269	12.70
27	58.92	56	16.22	203	8.31	297	27.70
29	33.38	67	11.62	207	8.41	299	23.51
30	15.14	79	9.59	217	10.81	311	30.41
36	16.89	82	13.92	230	8.41	325	23.92
38	11.22	83	13.78	242	15.14	366	10.14
39	24.73	84	97.84	255	9.05	368	100.00
41	44.32	85	11.08	256	23.38	369	16.76
42	12.43	201	16.89	257	11.62		
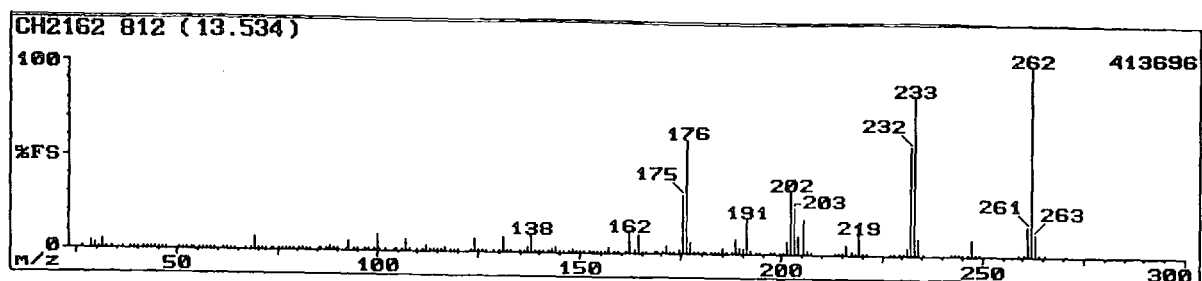
CH2162 812 (13.534)   413696

Mass	Rel Int	Mass	Rel Int	Mass	Rel Int	Mass	Rel Int
26	0.05	85	0.06	142	0.20	193	0.09
28	3.64	86	0.69	143	2.27	194	0.08
29	2.63	87	0.12	144	2.51	197	0.14
30	1.08	88	1.50	145	0.75	198	0.16
31	4.70	89	0.14	146	0.12	199	0.18
32	0.55	90	0.07	147	0.13	200	0.57
33	0.04	92	0.43	148	2.10	201	7.12
36	0.04	93	5.20	149	0.55	202	33.42
38	0.12	94	0.34	150	1.44	203	24.75
39	0.05	95	0.18	151	0.43	204	9.72
40	0.11	97	0.06	152	0.10	205	18.32
41	0.11	98	0.89	153	0.13	206	1.81
42	0.34	99	0.82	154	0.17	207	0.20
43	1.05	100	8.85	155	0.64	213	0.34
44	0.39	101	0.32	156	0.79	214	1.45
45	0.36	102	0.08	157	2.58	215	1.16
46	0.07	104	0.07	158	0.48	216	4.95
47	0.18	105	1.18	159	0.13	217	2.12
50	0.39	106	0.58	161	0.57	218	0.88
51	0.12	107	6.19	162	10.71	219	11.01
52	0.07	108	0.44	163	2.07	220	1.14
53	0.11	110	0.13	164	10.02	221	0.07
54	0.85	111	0.14	165	0.86	227	0.18
55	0.39	112	3.20	166	0.08	228	0.50
56	0.20	113	0.47	168	0.07	229	0.12
57	0.21	114	0.28	169	1.27	230	0.10
58	0.14	115	0.08	170	0.58	231	3.96
59	0.05	116	0.31	171	4.08	232	57.67
61	0.04	117	1.81	172	0.43	233	83.17
62	0.57	118	0.11	173	0.12	234	8.91
63	0.05	119	0.78	174	1.81	235	0.67
64	0.06	120	0.08	175	30.69	242	0.06
67	0.06	123	0.28	176	60.40	243	1.25
68	0.33	124	6.56	177	5.94	244	0.27
69	6.44	125	0.55	178	1.44	245	0.13
70	0.23	126	0.82	179	0.16	246	0.36
71	0.06	127	0.08	180	0.04	247	8.60
72	0.05	129	0.19	181	0.73	248	0.95
73	0.09	130	0.44	182	0.16	249	0.11
74	1.04	131	7.67	183	0.99	259	0.06
75	0.27	132	0.51	184	0.40	260	0.48
76	1.25	133	0.05	185	2.75	261	15.84
77	0.08	135	0.04	186	0.50	262	100.00
78	0.03	136	1.10	187	0.54	263	11.76
79	0.41	137	2.92	188	7.49	264	1.08
80	0.13	138	9.16	189	3.20	265	0.06
81	1.16	139	0.80	190	3.05		
82	0.14	140	0.16	191	18.07		
83	0.03	141	0.61	192	1.69		
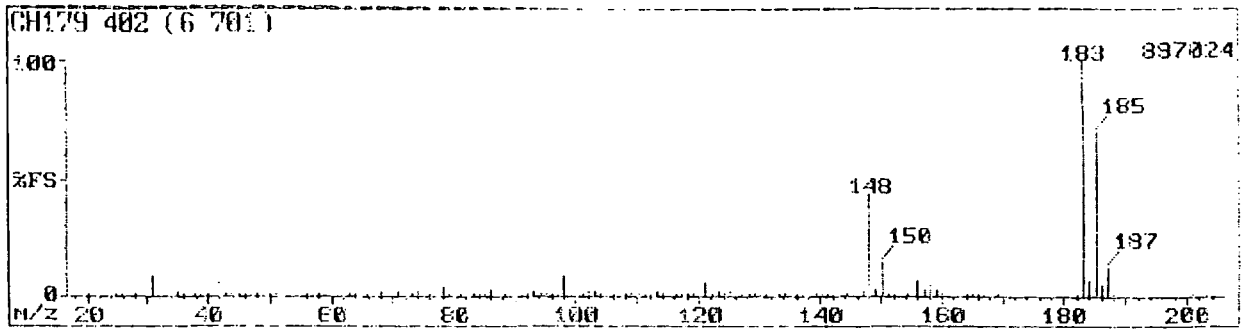
CH179 402 (6 701)

CH179 402 (6.701)

Mass	Rel Int	Mass	Rel Int	Mass	Rel Int	Mass	Rel Int	Mass	Rel Int	Mass	Rel Int	Mass	Rel Int	Mass	Rel Int	Mass	Rel Int
20	0.03	44	0.22	61	0.10	78	3.57	94	1.13	109	1.37	127	1.31	142	0.12	164	1.3
24	0.11	45	0.15	62	0.88	79	1.38	95	0.88	110	0.27	128	0.99	144	0.88	165	0.2
25	0.16	46	0.35	63	0.50	80	0.62	96	0.87	111	0.45	129	0.87	147	1.91	166	0.9
26	0.14	47	2.14	64	0.07	81	0.43	97	0.75	112	1.04	130	0.35	148	43.38	167	0.1
27	0.27	48	0.83	66	0.49	82	1.03	98	8.79	113	1.83	131	0.24	149	3.40	168	0.1
28	0.55	49	1.83	67	0.51	83	0.38	99	0.76	114	0.15	132	0.72	150	14.95	169	0.0
31	9.33	50	1.16	68	2.17	84	0.77	100	3.05	116	1.13	133	0.12	151	0.93	182	0.1
32	0.29	51	1.25	69	0.55	85	0.49	101	0.28	117	0.22	134	0.46	152	0.22	183	100.0
35	2.00	52	0.15	70	0.40	86	3.14	102	1.91	118	0.50	135	0.10	154	0.10	184	6.7
36	1.46	55	1.38	71	1.68	87	0.53	103	2.20	119	0.18	136	0.12	156	6.96	185	69.8
37	1.97	56	0.86	72	0.43	88	0.09	104	0.88	121	5.59	137	0.38	157	3.05	186	4.5
38	0.96	57	0.16	73	0.81	90	1.47	105	0.86	122	0.84	138	1.03	158	4.59	187	12.5
39	0.32	58	0.12	74	1.66	91	1.09	106	1.35	123	1.97	139	0.30	159	2.88	189	0.7
40	0.05	59	0.18	75	0.76	92	1.35	107	0.33	124	0.31	140	0.66	160	0.08	201	0.
42	0.24	60	0.50	76	0.17	93	1.50	108	0.85	125	2.03	141	0.09	163	0.18	203	0.
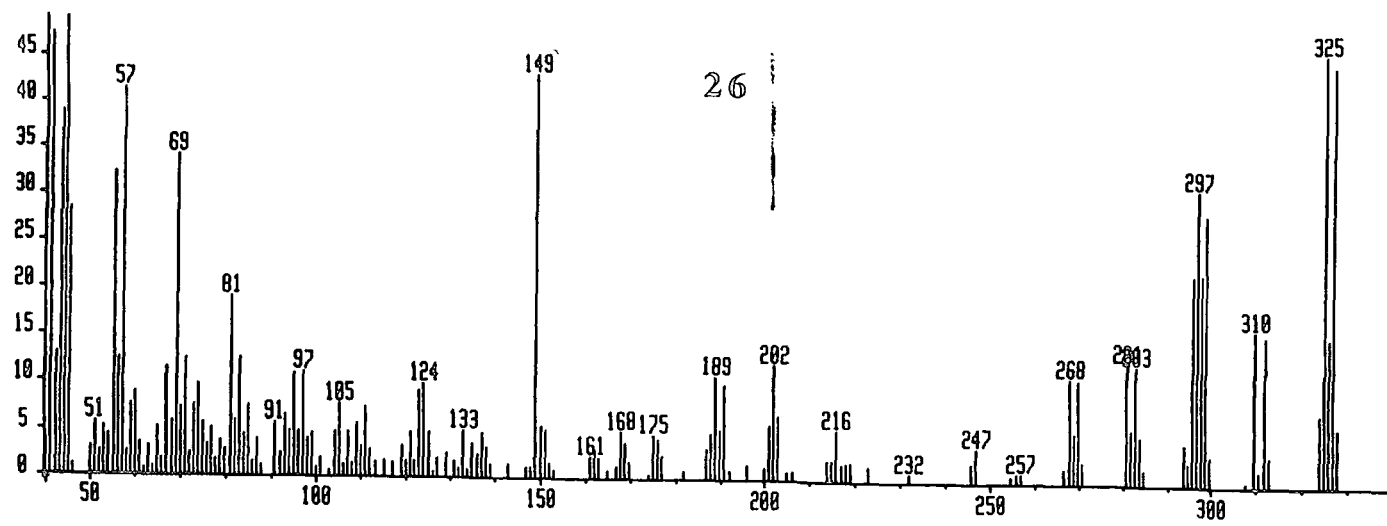
l#11#   x1   Bgd=1   25-MAR-97 18:13+0:01:09 70E
I=3.1v   Hm=327 TIC=251221000   Acnt:
HALL   PT= 0
EI+   1.1 |

l#11#   x1   Bgd=1
I=3.1v   Hm=327   TIC=
HALL

Mass	% Base
40.11	3.67
41.12	47.16
42.11	12.90
43.11	38.83
44.06	100.00
45.09	28.34
46.07	1.00
50.05	2.91
51.05	5.48
52.05	2.50
53.06	5.15
54.06	4.17
55.07	32.24
56.07	12.36
57.08	41.27
58.06	2.49
59.04	7.42
60.02	8.82
61.01	3.31
62.00	0.76
63.01	3.09
63.99	0.93
65.01	5.10
66.00	1.74
67.02	11.41
68.01	5.70
69.01	34.12
70.02	7.14
71.03	12.38
71.99	2.38
72.97	7.45
73.96	9.68
74.95	5.51
75.96	3.16
76.96	4.94
77.96	1.63
78.97	3.62
79.95	2.83
80.98	19.01
81.98	5.80
82.99	12.58
83.98	4.38
85.00	7.41
85.95	1.47
86.94	3.84
87.93	0.95
90.96	5.48
91.95	2.29
92.96	6.35
93.96	4.74
94.99	10.79
95.99	4.74
97.00	10.88
97.97	4.01
98.94	4.59
99.92	0.87
100.94	1.88
102.93	0.63
103.92	4.69
104.93	7.56

Mass	% Base
105.93	1.15
106.94	4.64
107.95	1.35
108.98	5.51
109.97	3.09
110.97	7.34
111.94	2.84
112.98	1.43
114.95	1.65
116.93	1.41
118.93	3.16
119.95	1.63
120.97	4.64
121.97	1.64
122.94	9.09
123.92	9.78
124.96	4.61
125.97	0.50
126.95	1.87
128.96	2.43
130.91	1.59
131.92	0.93
132.93	4.76
133.94	0.79
134.97	3.57
135.96	2.39
136.98	4.72
137.93	3.12
138.96	1.27
142.91	1.27
146.92	1.05
147.89	1.00
148.88	43.22
149.88	5.43
150.91	5.01
151.91	1.48
152.93	0.66
160.88	2.22
161.87	2.95
162.91	2.07
164.95	0.72
166.89	1.20
167.87	4.75
168.87	3.60
169.89	1.62
173.87	0.34
174.88	4.55
175.87	4.13
176.90	2.39
181.87	0.78
186.85	3.10
187.86	4.73
188.87	10.85
189.86	5.16
190.96	9.93
191.95	0.89
195.88	1.42
199.87	1.15
200.85	5.76
201.86	12.17

l#11#   x1   Bgd=1
I=3.1v   Hm=327   TIC=
HALL

Mass	% Base
202.86	6.70
204.88	0.78
205.95	0.93
213.84	2.00
214.85	2.00
215.86	5.29
216.87	1.61
217.87	1.71
218.88	1.96
222.88	1.45
231.85	0.73
245.86	1.96
246.87	3.53
254.71	0.54
255.76	0.84
256.74	0.94
266.69	1.52
267.70	11.14
268.71	5.30
269.70	10.95
270.70	2.13
280.70	12.89
281.69	5.74
282.69	12.60
283.71	4.95
284.82	1.39
293.68	4.29
294.70	2.18
295.71	22.32
296.72	31.52
297.72	22.52
298.72	28.92
299.69	3.05
307.67	0.35
309.70	16.49
310.68	1.51
311.71	15.94
312.78	3.01
323.70	7.55
324.71	46.58 F
325.70	15.82 F
326.72	45.24
327.70	6.14

CH2107A015☆   x1   Bgd=11   21-NOV-96 17:50+0:01:28 70E   EI+
BpM=373 I=562mv Hm=375   TIC=29276000   Acnt: Sys:ACE   HAR:
CHRIS HALL   PT= 0°   Cal:PFK13NOV   HASS:

Mass	% Base
41.04	12.33
43.05	19.22
43.99	55.63
55.06	7.44
57.07	20.53
71.09	8.55
87.02	6.27
103.05	3.83
106.52	9.45
186.03	22.70
187.03	34.70
213.05	82.60
214.05	24.19
215.06	23.68
292.97	81.75
293.97	18.57
294.97	75.59
295.96	5.10
370.88	45.21
372.91	100.00
373.92	7.03
374.90	39.56
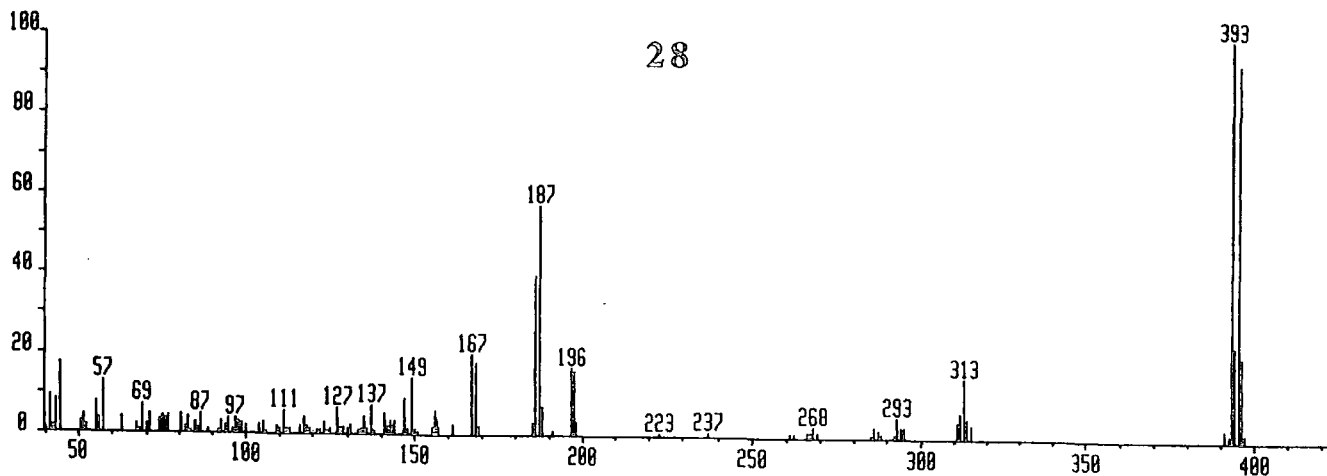
Mass	% Base		Mass	% Base		Mass	% Base
40.15	0.60		131.03	2.01		393.95	23.39 F
41.22	9.05		133.01	0.73		394.96	94.28 F
42.21	1.38		134.00	1.15		395.98	20.79 F
43.21	7.85		134.99	4.13		397.01	1.71
44.15	17.03		135.98	1.16			
50.14	2.29		136.98	6.85			
51.14	4.10		137.97	0.68			
52.15	1.43		140.90	4.93			
55.15	7.40		141.89	1.76			
56.16	3.32		142.88	3.00			
57.16	12.70		143.38	1.93			
63.08	3.80		143.90	3.01			
67.08	1.97		146.43	0.70			
68.08	0.74		146.93	8.52			
69.06	6.82		147.96	0.97			
70.06	1.89		148.96	13.66			
71.04	4.44		150.00	1.18			
73.88	2.97		151.08	0.35			
74.85	4.07		155.05	1.68			
75.82	3.54		156.04	5.96			
76.79	4.25		156.54	3.44			
80.69	4.35		157.06	1.59			
81.69	1.35		161.05	2.38			
82.71	3.81		167.05	19.91			
83.74	0.39		168.05	17.77			
84.67	1.95 F		169.06	1.91			
84.76	2.54 F		185.02	2.77 F			
85.69	1.15		185.22	0.96 F			
86.72	4.35		186.03	39.72			
88.76	0.53		187.04	57.63			
91.78	0.50		188.04	6.84			
92.82	2.61		191.15	0.71			
93.84	1.76		196.49	16.48			
94.89	3.54		197.00	3.55 F			
95.92	0.84		197.49	15.91 F			
96.94	3.55		198.00	3.23			
97.88	2.66		223.12	0.45			
98.90	2.54		237.07	0.66			
99.90	1.88		261.04	0.78			
103.93	1.96		262.06	0.63			
104.95	2.89		266.03	1.12			
105.96	0.49		267.06	1.06			
109.05	1.76		268.05	2.44			
110.01	1.10		269.08	1.04			
111.03	5.38		285.06	0.49			
112.02	0.86		286.06	2.35			
113.04	1.04		287.08	1.87			
116.01	1.85		288.09	0.58			
117.03	4.14		292.06	0.57			
118.04	1.68		293.07	4.70			
119.03	0.90		294.07	2.41			
121.07	0.55		295.08	2.38			
122.04	0.66		311.05	3.74			
123.07	2.76		312.05	6.05			
124.06	0.69		313.05	14.65			
125.12	1.12		314.07	4.67			
127.06	6.08		315.08	2.94			
128.05	1.48		391.00	2.65			
129.04	1.39		391.97	1.47 F			
130.04	0.86		392.97	100.00 F			
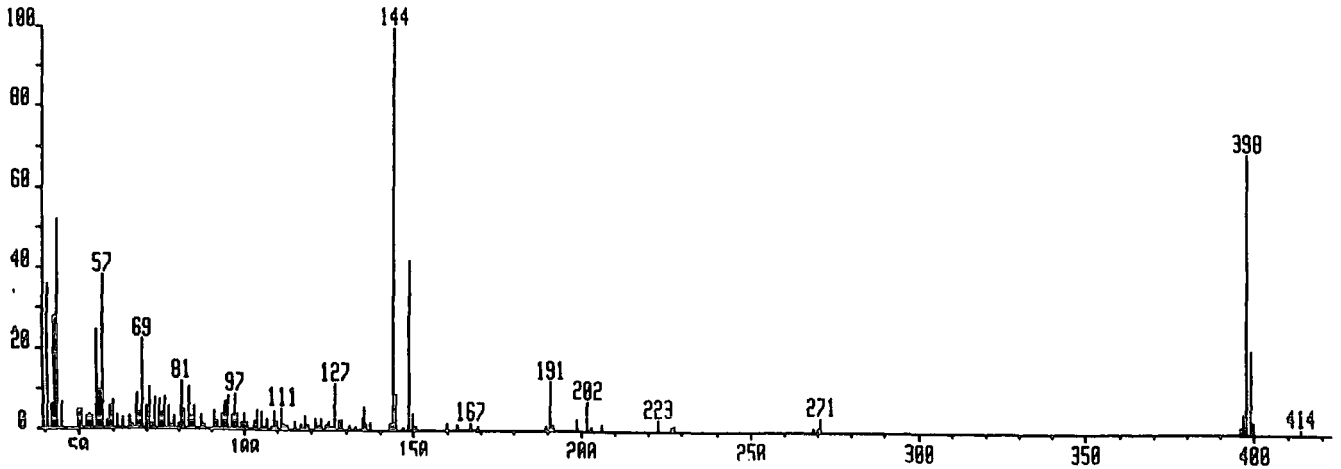
Mass	% Base		Mass	% Base
41.00	35.54		110.00	1.79
42.00	5.76		111.02	4.88
43.01	27.27		112.01	1.07
43.95	51.82		112.98	0.77
44.98	6.31		114.96	1.56
49.97	4.42		116.94	0.93
50.97	4.49		117.92	3.23
51.98	2.77		118.93	1.13
52.99	3.13		120.96	2.38
53.99	2.64		121.97	0.61
55.00	23.98		122.98	2.46
56.01	9.30		123.96	1.00
57.02	37.64		124.99	1.77
58.02	1.86		125.94	0.43
58.99	5.05		126.94	11.10
59.97	6.46		127.94	1.99
60.98	2.97		128.96	1.96
62.97	2.48		130.92	0.69
64.98	2.83		134.97	2.63
65.98	0.71		135.42	5.56
67.00	8.19		135.95	1.25
68.00	3.69		137.00	1.83
68.93	5.15 F		142.92	1.20
69.01	21.54 F		143.92	100.00
70.01	5.16		144.92	8.44
71.02	9.92		146.96	0.50
71.99	1.00		148.90	41.73
72.97	7.10		149.90	3.74
73.96	6.77		150.98	0.83
74.96	3.77		159.87	1.21
75.96	7.59		162.96	0.87
76.97	5.14		166.89	1.23
77.97	0.74		168.85	0.62
78.98	2.69		189.86	0.72
79.98	1.12		190.98	11.72
80.99	11.46		191.97	1.12
82.00	4.31		198.90	2.49
83.01	9.83		201.91	6.88
84.00	2.89		202.91	0.65
85.02	5.07		205.98	1.27
86.96	3.20		222.90	2.24
87.95	0.54		226.88	0.54
90.97	4.04		227.89	0.99
91.94	1.86		268.81	0.57
92.97	3.49		269.83	0.68
93.95	6.48		270.84	3.23
95.00	7.88		395.79	1.22
96.00	3.05		396.82	4.96
97.01	8.33		397.85	69.28
97.97	3.32		398.84	20.58
98.97	1.39		399.82	2.89
99.94	3.38		413.77	1.19
100.95	1.53			
102.95	1.78			
103.93	4.60			
104.94	4.18			
105.96	0.36			
106.97	2.50			
107.97	0.46			
109.00	4.05			

BpA=0   I=2.4v   Ha=352   TIC=193102000   Acnt: Sys:HCL   HAK:
CHRIS HALL   PT= 0°   Cal:PFK23APR   HASS:

Mass spectrum peaks labeled: 213, 291, 334, 148, 319, 305, 277, 51, 64, 77, 89, 98, 115, 130, 164, 185, 195, 229, 241, 265, 350

CH2168#15#   x1   Bgd=11   25-APR-97 10:25+0:01:27 70E   EI+   1
BpM=0   I=2.4v   Hm=352   TIC=193102000   Acnt: Sys:ACE
CHRIS HALL   PT= 0   Cal:PFK23A

Mass	% Base	Mass	% Base
40.18	3.15	273.18	7.65
41.19	20.47	277.16	32.57
42.19	1.84	278.16	23.23
43.20	3.14	279.16	7.33
44.13	67.53	285.17	2.20
50.13	5.25	286.19	1.76
51.14	12.95	287.20	3.67
52.13	2.69	289.17	4.51
53.15	3.04	290.18	45.33
55.16	2.72	291.19	92.27
57.17	2.90	292.19	17.63
63.10	12.60	293.19	13.02
64.09	16.06	294.16	3.10
65.10	15.16	301.21	4.49
66.11	12.23	302.19	1.92
67.11	2.48	303.19	17.77
69.05	2.32	304.20	27.99
74.06	1.39	305.20	49.71
75.06	6.76	306.19	25.25
76.07	8.23	307.17	17.23
77.08	17.02	308.15	3.59
79.09	2.70	309.15	4.81
89.08	3.84	316.23	6.81
91.10	3.09	317.19	4.87
98.05	9.19	318.19	2.53
99.06	2.88	319.21	62.62
103.10	2.28	320.19	13.71
115.11	2.66	321.16	8.09
116.11	1.84	322.16	2.77
117.06	2.35	333.24	3.92
124.07	1.78	334.26	83.17
129.09	3.02	335.24	23.94
130.09	5.36	336.21	1.36
148.07	69.62	337.20	1.39
149.09	9.04	350.21	14.14
164.06	11.18	351.21	1.51
166.05	2.34	352.19	2.94
185.10	9.43		
186.10	1.97		
193.11	2.23		
194.12	3.68		
195.13	5.49		
199.10	3.15		
200.11	3.05		
201.10	1.34		
212.12	3.94		
213.13	100.00		
214.13	10.16		
226.13	3.89		
229.09	12.00		
231.09	3.65		
239.14	1.36		
240.15	1.73		
241.16	5.50		
257.14	1.13		
259.15	3.85		
264.14	2.84		
265.15	4.63		
271.16	1.50		
272.17	4.16		

Mass	% Base		Mass	% Base
44.03	0.59		141.07	1.88
45.04	0.37		156.08	1.95
49.04	0.36		157.10	0.47
50.05	1.36		158.10	1.21
51.04	1.28		210.19	0.36
52.06	0.40		211.20	0.31
53.04	0.31			
56.05	1.50			
57.05	8.23			
58.06	0.74			
59.06	0.60			
61.05	0.49			
62.06	0.52			
63.06	0.89			
64.06	3.34			
65.07	1.09			
68.05	1.70			
69.06	1.34			
70.06	0.65			
71.06	0.44			
73.06	0.34			
74.05	0.67			
75.05	15.13			
76.06	15.28			
77.06	0.97			
80.05	0.37			
81.06	2.43			
82.06	0.97			
83.06	1.33			
84.06	0.89			
85.06	0.59			
87.06	1.27			
88.07	8.08			
89.07	0.65			
91.06	0.46			
93.06	0.31			
94.06	0.97			
95.07	2.27			
96.08	1.16			
99.06	1.06			
100.07	0.61			
101.08	2.07			
102.07	1.13			
103.08	1.95			
104.06	4.16			
105.08	0.54			
110.05	0.88			
111.07	1.90			
112.08	0.81			
113.07	0.97			
114.08	2.44			
115.08	22.48			
116.09	4.55			
117.09	0.39			
128.10	0.41			
131.08	100.00			
132.09	23.49			
133.10	1.44			
139.07	5.16			
140.09	0.85			

32a
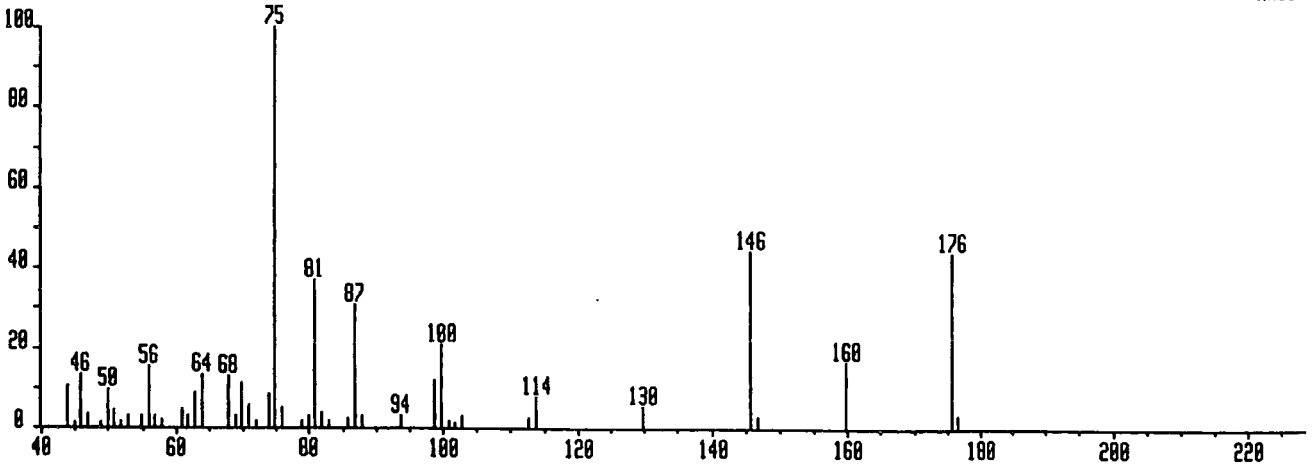
Mass	% Base
43.91	10.27
44.91	1.00
45.89	12.85
46.89	2.96
48.90	1.14
49.90	9.31
50.89	4.08
51.90	1.51
52.89	2.85
54.88	2.60
55.88	15.24
56.88	2.89
57.88	1.68
60.88	4.50
61.88	2.60
62.87	8.53
63.88	12.88
67.86	12.50
68.87	2.89
69.86	11.00
70.86	5.36
71.85	1.52
73.84	8.20
74.84	100.00
75.84	4.83
78.82	1.24
79.83	2.58
80.84	36.56
81.83	3.47
82.83	1.46
85.81	2.13
86.81	30.58
87.82	2.72
93.80	2.88
98.79	11.66
99.80	20.61
100.79	1.52
101.79	1.01
102.78	2.60
112.77	2.37
113.77	7.40
129.74	5.13
145.69	44.27
146.70	2.73
159.68	16.38
175.64	43.67
176.65	2.99

CHRIS HALL
BpM=0   I=1.5v   Hm=173   TIC=70169000   Acnt: Sys:ACE   HMR:
CHRIS HALL   PT= 0⁰   Cal:PFK8JAN   MASS: EI⁺
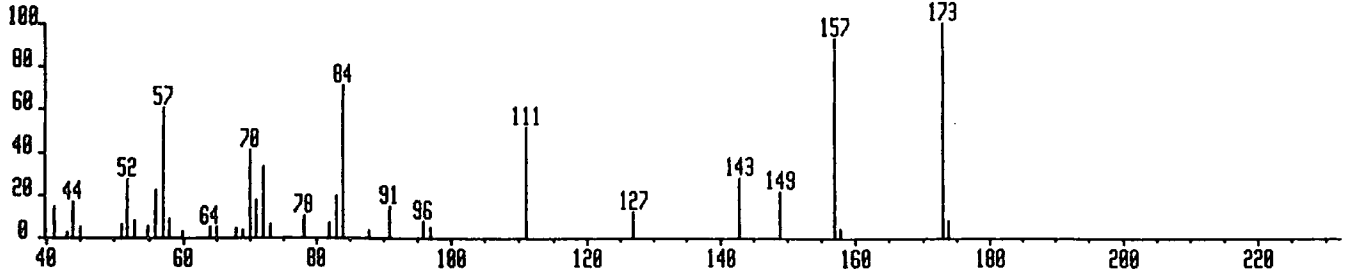
CH2141C#39*   x1   Bgd=22   8-JAN-97   16:38+8:03:14 70E   C1+
BpM=8   I=10v   Hm=173   TIC=301462816   Acnt: Sys:ACE   HMR:
CHRIS HALL   PT= 0⁰   Cal:PFK8JAN   MASS:
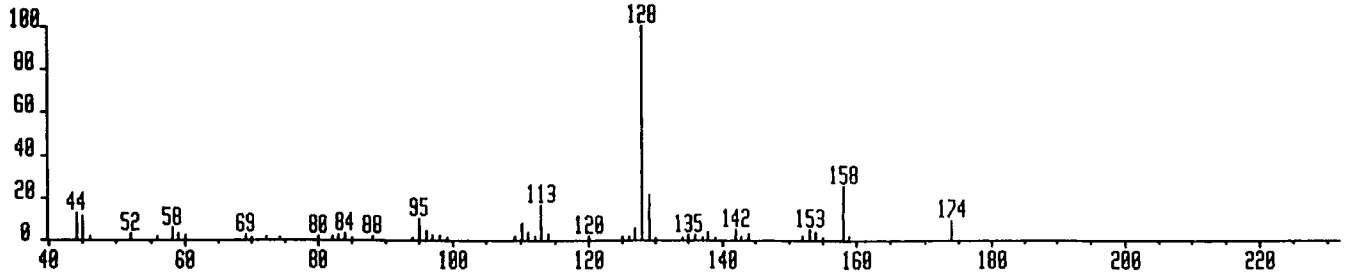
CH2141C#41*   x1   Bgd=27   8-JAN-97   16:38+8:03:23 70E   C1-
BpM=8   I=10v   Hm=220   TIC=530452992   Acnt: Sys:ACE   HMR:
CHRIS HALL   PT= 0⁰   Cal:PFK8JAN   MASS:
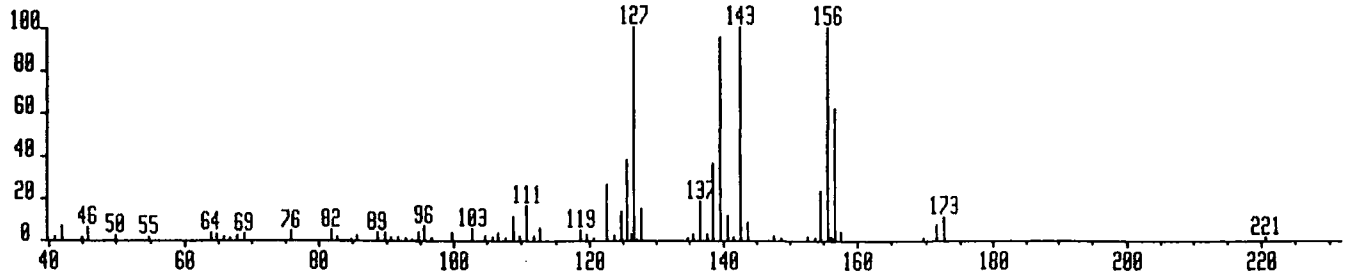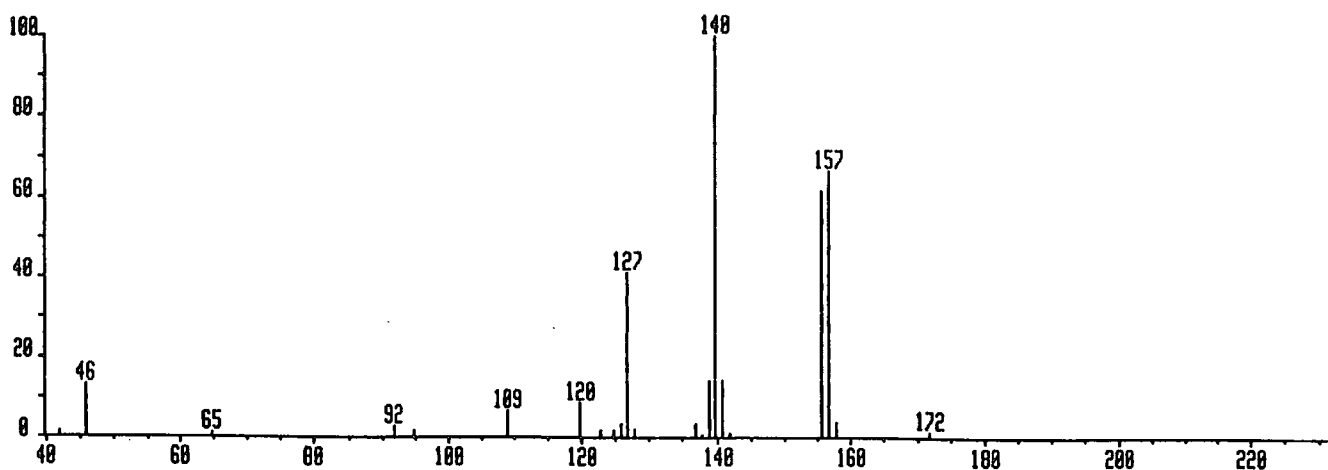
Mass	% Base	
44.01	8.67	
45.01	7.90	
46.03	9.99	
52.05	3.72	
56.00	0.68	
58.02	4.83	
59.02	3.41	
60.01	2.63	
70.01	0.63	
72.02	0.77	
74.04	17.72	
77.01	2.62	
82.99	0.55	
84.00	1.58	
88.01	27.43	
89.01	0.92	
93.98	0.83	
94.98	2.42	
95.98	1.50	
96.99	1.33	
97.98	1.53	
98.98	0.61	
100.02	0.49	
102.01	1.57	
107.99	0.96	
109.98	1.53	
110.98	1.45	
111.96	2.37	
112.96	16.58	
113.95	2.95	
114.94	1.87	
115.97	0.71	
123.96	1.17	
124.98	1.00	
125.95	3.83	
126.96	1.64	
127.96	55.31	
128.95	18.62	
129.94	1.08	F
130.05	2.17	F
137.94	2.97	
138.94	0.72	
139.95	0.49	
140.93	4.37	
141.93	16.12	
142.94	5.12	
143.94	8.27	
151.95	0.78	
152.94	1.13	
153.93	2.13	
157.91	56.41	
158.92	3.41	
173.89	67.63	
174.91	8.38	
175.91	0.65	
190.91	2.19	
446.80	0.84	
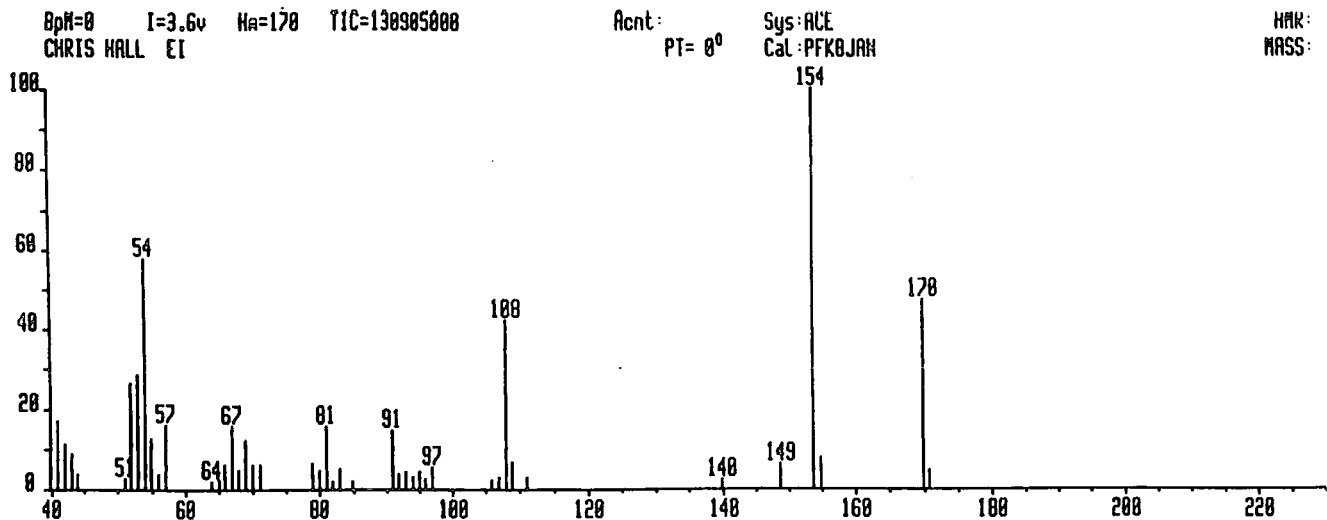
216

Mass	% Base	
40.96	16.92	
41.96	10.92	
42.97	8.42	
43.93	3.51	
50.92	2.48	
51.93	26.29	
52.94	28.26	
53.95	57.43	
54.95	12.32	
55.96	3.55	
56.98	15.83	
63.91	1.84	
64.92	2.04	
65.92	5.67	
66.93	15.49	
67.93	4.52	
68.95	11.83	
69.92	5.74	
70.97	5.90	
78.90	6.10	
79.90	4.53	
80.92	15.30	
81.91	1.74	
82.93	4.67	
84.96	1.88	
90.88	14.52	
91.88	3.48	
92.88	4.01	
93.89	2.65	
94.92	4.16	
95.91	2.23	
96.87	4.85	F
96.94	5.15	F
105.86	2.06	
106.87	2.68	
107.88	42.24	
108.87	6.61	
110.93	2.85	
139.80	1.92	
148.79	5.91	
153.80	100.00	
154.80	7.63	
169.77	47.22	
170.77	4.39	

CH278A#13*   x1   Bgd=11   15-AUG-96 10:32+0:01:22   70E   EI+   1.
BpM=0   I=6.0v   Hm=166   TIC=304886000   Acnt: Sys:ACE
CHRIS HALL   PT= 0   Cal:PFK13AU

Mass	% Base
46.98	5.87
48.00	2.67
49.01	13.92
50.03	25.54
51.02	4.83
52.03	1.52
53.02	6.23
60.00	8.93
61.02	16.57
62.03	28.29
63.04	43.07
64.04	11.31
65.05	0.75
72.00	12.28
73.01	100.00
74.01	8.39
75.01	34.92
76.03	8.60
77.02	0.39
82.97	2.73
84.00	6.59
85.00	10.43
86.00	2.59
87.00	3.48
92.04	0.81
97.01	4.73
98.00	1.13
99.01	2.09
100.02	53.60
101.01	5.97
102.01	16.45
103.01	1.17
106.97	12.19
107.98	13.86
108.97	8.12
109.99	11.43
110.98	1.60
112.02	10.75
114.02	2.19
128.02	2.20
133.00	3.65
135.00	4.17
135.98	4.32
136.99	0.89
137.98	2.16
147.00	12.26
148.00	1.92
149.00	7.51
150.01	0.49
163.00	92.07
164.00	12.50
164.99	57.24
166.00	7.45
166.99	9.05
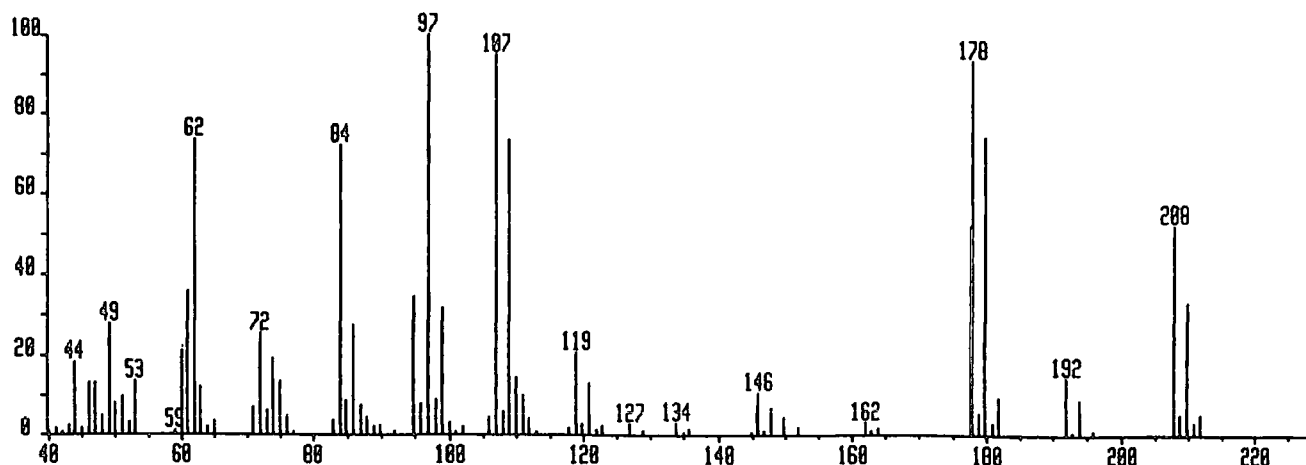
#12#   x1   Bgd=1   12-MAR-97 17:53+0:01:14   70E   EI+   2.1

    I=7.9v   Hm=211   TIC=716533000   Acnt: Sys:ACE

HALL   PT= 0   Cal:PFK910MAR

Mass	% Base		Mass	% Base	
40.00	0.82		122.88	1.91	
41.02	1.41		126.93	2.43	
42.00	0.31		128.93	0.67	
43.00	2.08	F	133.88	2.79	
43.04	0.79	F	134.90	0.46	
43.97	17.69		135.88	1.46	
45.01	1.45		145.78	7.14	F
45.98	12.52		145.90	10.29	F
46.95	12.76		146.87	0.68	
47.98	4.53		147.86	6.47	
48.99	27.51		149.87	4.09	
49.99	7.62		151.87	1.74	
50.99	9.31		161.86	2.61	
52.00	2.73		162.86	0.74	
52.98	12.97		163.86	1.42	
58.95	0.67		177.73	52.50	F
59.96	20.44		177.88	93.64	F
60.98	35.65		178.85	5.00	
61.99	73.30		179.84	74.39	
62.95	11.79		180.85	2.76	
63.99	1.67		181.84	9.19	
64.95	2.96		191.82	13.95	
70.94	6.57		192.82	0.34	
71.94	24.85		193.81	8.42	
72.94	5.83		195.81	0.76	
73.95	18.99		207.80	52.18	
74.97	13.15		208.80	4.81	
75.96	4.37		209.79	32.80	
76.97	0.46		210.80	2.85	
82.93	3.54		211.79	4.85	
83.94	71.88				
84.94	8.14				
85.93	27.12				
86.93	7.14				
87.94	3.95				
88.94	1.69				
89.94	2.21				
91.96	0.76				
94.90	34.40				
95.93	7.42				
96.93	100.00				
97.93	8.61				
98.93	31.66				
99.94	2.89				
100.94	0.36				
101.94	1.69				
105.89	4.24				
106.89	94.99				
107.89	5.50				
108.84	50.18	F			
108.93	73.34	F			
109.91	14.14				
110.89	9.63				
111.92	3.90				
112.94	0.51				
117.90	1.40				
118.88	20.14				
119.89	2.40				
120.88	12.51				
121.90	1.19				
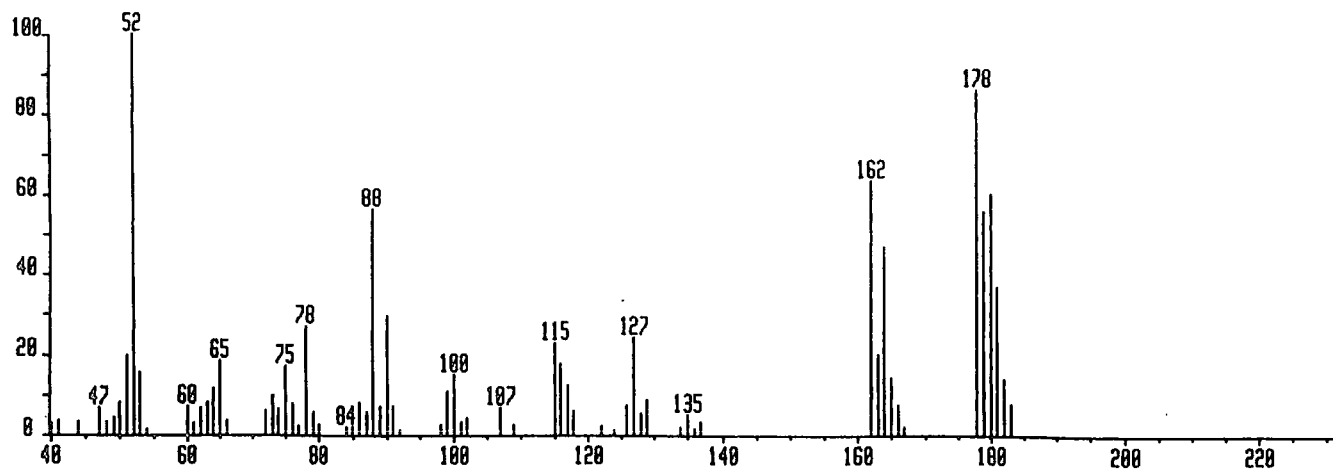
Mass	% Base
40.01	2.81
41.02	3.43
43.98	2.92
46.96	6.41
47.97	3.21
48.98	3.94
50.00	8.01
51.00	19.57
52.01	100.00
53.01	15.41
54.02	1.54
59.97	6.84
60.99	2.85
61.99	6.50
62.99	7.93
64.01	11.34
65.01	18.06
66.02	3.34
71.97	5.87
72.97	9.50
73.97	6.12
74.98	16.65
75.99	.7.67
76.99	2.11
78.01	26.58
79.02	5.45
80.00	2.44
83.96	1.55
84.96	1.84
85.96	8.04
86.96	5.51
87.97	56.26
88.97	6.82
89.97	29.37
91.00	6.71
92.01	0.96
97.96	2.49
98.97	10.52
99.97	14.68
100.97	2.93
101.97	3.95
106.92	6.39
108.92	2.42
114.98	22.55
115.97	17.46
116.98	12.07
117.97	5.97
121.93	2.17
123.93	1.07
125.97	7.10
126.98	23.92
127.98	5.14
128.98	8.64
133.93	1.79
134.93	4.78
135.93	1.24
136.93	3.01
161.93	63.46
162.94	19.73
163.93	46.84

Mass	% Base
164.94	13.88
165.94	7.18
166.96	1.56
177.93	86.13
178.93	55.96
179.93	60.13
180.94	36.90
181.94	13.56
182.96	7.48

Name:Chris Hall   Ion Mode:EI+   16-Sep-96 16:11

CH2105

100
%FS
69
74
0
Scn   100   200   300   400   500   600   700   800
777   9534251
TIC
@1
526

CH2105'777 (12.951)   REFINE   565248

100
39
%FS
27
41
153
313
311   315
126
125   152
234
57
79 99
205
0
m/z   50   100   150   200   250   300   350   400   450   500   550
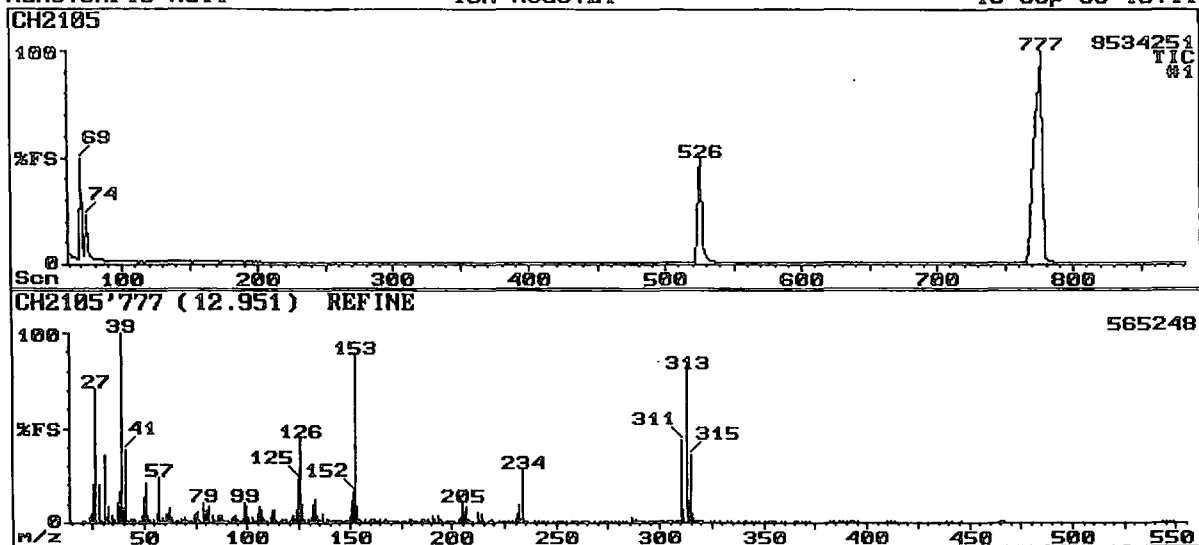
CH2105'777 (12.951)   REFINE   56_

Mass	Rel Int	Mass	Rel Int	Mass	Rel Int	Mass	Rel Int
265	0.06	298	0.31	326	0.04	382	0.02
266	0.10	299	0.27	329	0.03	384	0.02
268	0.07	300	0.23	332	0.06	386	0.05
271	0.22	301	0.18	334	0.06	388	0.06
273	0.50	302	0.08	338	0.03	390	0.05
274	0.13	303	0.04	340	0.03	392	0.08
275	0.09	304	0.04	341	0.03	393	0.03
276	0.06	305	0.03	344	0.08	394	0.06
278	0.13	306	0.05	346	0.08	395	0.05
280	0.19	308	0.13	348	0.04	410	0.05
282	0.09	309	0.21	350	0.10	412	0.04
284	1.29	310	0.35	352	0.29	413	0.03
286	2.90	311	43.48	353	0.11	439	0.07
287	0.54	312	6.57	354	0.14	441	0.04
288	1.63	313	80.43	355	0.03	446	0.04
289	0.27	314	11.23	356	0.05	465	0.10
290	0.13	315	35.87	358	0.09	466	0.04
291	0.19	316	5.07	360	0.09	467	0.06
292	0.26	317	0.36	365	0.07	543	0.04
293	0.34	318	0.06	366	0.03	545	0.08
294	0.39	319	0.07	367	0.07	547	0.09
295	0.28	320	0.05	368	0.08	549	0.04
296	0.31	321	0.07	370	0.08		
297	0.35	324	0.03	372	0.05		

39
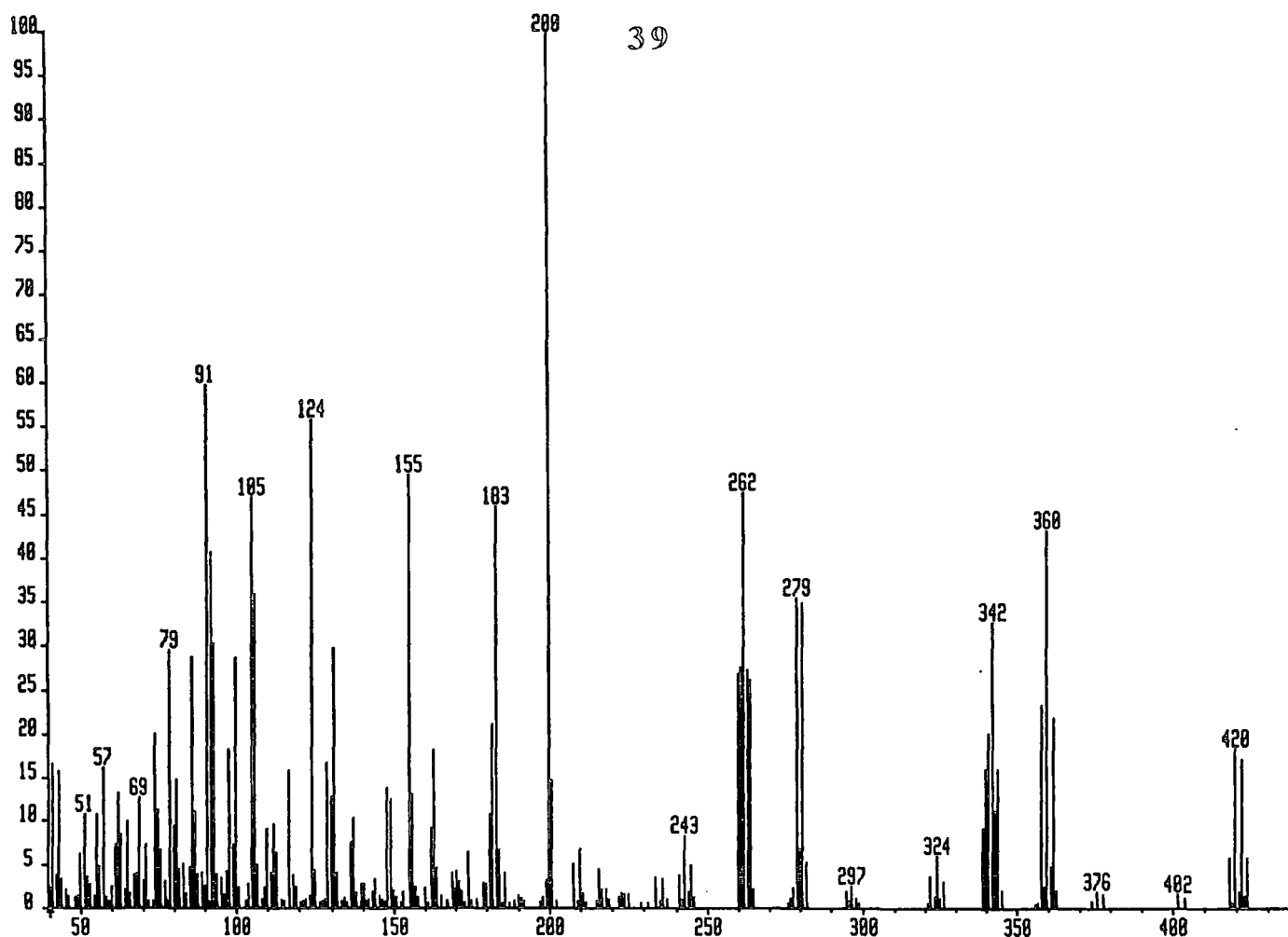
Mass	% Base					
31.00	100.00	71.10	5.31	107.00	3.58	
32.00	2.21	72.05	0.55	108.00	0.62	
35.99	2.13	73.05	0.58	109.08	1.58	
37.01	2.62	74.01	14.74	110.02	6.57	
37.99	4.22 F	75.02	8.22	111.02	2.89 F	
38.02	4.20 F	76.02	4.88	111.15	2.04 F	
39.03	11.00	77.04	2.11	112.02	7.04	
40.03	1.59	77.52	0.80	113.04	4.66	
41.04	12.24	78.05	0.63	114.02	0.63	
42.04	2.66	78.91	13.75 F	115.06	0.55	
43.05	11.60	79.01	21.68 F	117.00	11.70	
44.01	2.42	80.02	6.87	118.01	2.68	
45.03	1.52	80.91	9.59 F	119.01	1.74	
46.03	0.96	81.02	10.94 F	120.07	0.42	
47.99	0.86	82.03	3.25	121.06	0.56	
49.01	1.00	83.09	3.65	122.02	0.64	
50.02	4.52	84.10	1.16	123.11	1.01	
51.02	7.85	85.10	3.39	124.02	41.13	
52.03	2.56	86.01	21.15	125.05	3.17	
53.04	1.97	87.02	8.08	126.11	0.45	
54.05	0.92	88.02	2.82	127.15	0.53	
55.00	6.69 F	89.05	2.95	128.10	0.62	
55.06	7.93 F	90.07	1.85	129.01	12.32	
56.05	3.46	90.91	4.51 F	130.02	9.35	
57.08	11.92	91.07	44.09 F	130.50	0.79	
58.08	0.86	91.52	0.49	131.02	21.94	
59.05	0.58	92.07	29.97	131.50	0.73	
60.01	1.74	93.00	22.21	132.01	2.89	
61.02	5.26	94.03	2.80	133.07	0.58	
62.02	9.75	95.08	2.48	133.93	0.75	
63.03	6.17	96.11	1.10	135.13	0.46	
64.02	1.49	97.12	3.01	136.01	5.47	
65.05	7.22	98.01	13.35	137.04	7.60	
66.05	1.24	99.03	5.25	138.04	1.15	
67.05	2.74	100.01	21.05	139.06	0.44	
68.04	2.82	101.02	1.64	139.49	1.98	
69.01	9.24 F	102.97	0.52	139.99	1.51	
69.09	5.86 F	103.98	1.99	140.48	1.91	
70.07	2.29	105.01	34.57	141.01	0.56	
		106.02	26.48	142.03	0.63	
				143.01	1.30	

222

Mass	% Base		Mass	% Base
144.02	2.42		218.00	1.49
145.10	1.00		219.02	0.65
146.00	0.65		221.94	0.85
147.03	0.57		223.03	1.15
148.01	10.11		223.95	1.08
149.05	9.18		224.98	1.04
150.05	1.45		230.95	0.37
151.09	0.89		233.96	2.48
152.06	0.42		234.99	0.58
152.95	1.25		235.96	2.33
155.02	36.54		236.98	0.64
156.03	9.57		240.98	2.66
157.05	1.70		241.96	0.66
157.93	0.82		242.98	6.04
159.93	1.58		243.99	1.29
160.95	0.33		244.98	3.55
162.02	6.74		246.01	0.83
163.04	13.44		259.97	19.75
164.04	3.32		260.97	20.27
165.05	1.01		261.97	35.00
166.97	0.58		262.98	20.11
167.11	0.53		263.98	19.19
169.02	2.90		264.99	1.53
169.46	1.51		275.93	0.35
169.97	1.03		276.94	0.79
170.45	3.01		277.94	1.63
170.97	2.15		278.96	26.10
171.45	1.40		279.96	4.94
171.97	1.26		280.95	25.65
173.01	0.43		281.97	3.83
174.02	4.61		294.96	1.32
175.04	0.57		295.95	0.57
176.94	0.70		296.95	1.77
178.97	2.07		297.96	0.72
179.96	1.99		298.94	0.35
181.02	7.86		320.97	0.36
182.04	15.51		321.92	2.60
183.06	33.84		322.91	0.87
184.00	4.82		323.91	4.32
185.00	0.32		324.90	0.73
185.93	2.88		325.92	2.17
186.95	0.35		338.90	6.74
189.01	0.58		339.90	11.82
189.99	1.00		340.89	14.84
191.10	0.72		341.90	24.03
191.95	0.55		342.90	8.23
197.01	0.40		343.89	11.82
197.99	0.86		344.90	1.37
199.03	2.28		356.88	0.32
200.03	73.97		357.88	17.22
201.04	10.75		358.89	1.77
202.05	0.52		359.88	31.84
207.95	3.69		360.88	3.41
208.93	0.49		361.89	16.12
209.95	4.94		362.89	1.44
210.93	1.20		373.87	0.54
211.90	0.40		375.88	1.34
214.98	0.55		377.87	1.09
216.00	3.28		401.81	1.05
216.99	1.54		403.83	0.72
			417.81	4.19
			418.78	0.32
			419.82	13.53
			420.83	1.30
			421.81	12.64
			422.82	0.99
			423.82	4.19
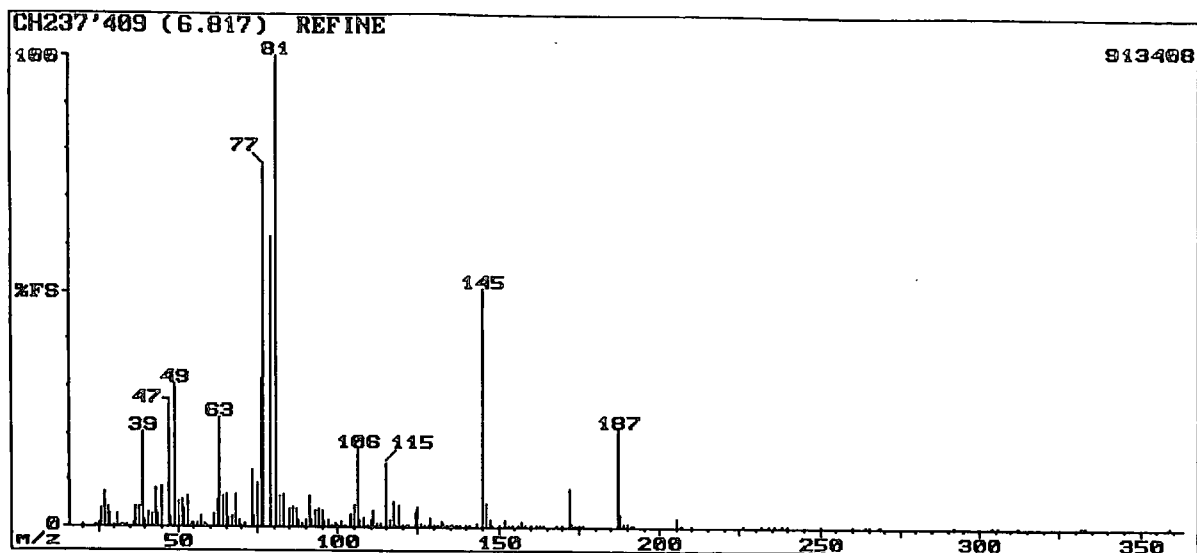
CH237'409 (6.817) REFINE   913

Mass	Rel Int	Mass	Rel Int	Mass	Rel Int	Mass	Rel Int
20	0.10	66	1.82	111	3.39	160	0.02
24	0.34	67	2.21	112	0.67	162	0.07
25	0.76	68	6.98	113	0.63	163	0.16
26	4.06	69	1.58	115	13.68	164	0.08
27	7.40	70	0.48	116	1.42	168	0.14
28	4.20	71	0.74	117	5.30	170	0.49
29	2.58	73	12.11	118	0.53	172	8.07
30	0.22	74	2.19	119	4.60	173	0.67
31	2.58	75	9.42	120	0.47	174	0.26
32	0.19	76	31.39	121	0.26	175	0.06
33	0.52	77	76.23	122	0.40	176	0.18
34	0.04	79	61.43	124	3.03	187	20.85
36	0.86	81	100.00	125	4.46	188	2.77
37	4.37	82	6.70	126	0.76	189	0.83
38	4.40	83	6.81	127	0.28	190	0.71
39	20.18	85	3.84	128	0.28	191	0.07
40	1.51	86	4.12	129	2.07	192	0.03
41	3.11	87	3.84	130	0.58	205	1.85
42	2.55	88	1.49	131	0.27	206	0.19
43	8.07	89	0.83	132	1.32	207	0.07
44	2.77	90	1.39	133	0.64	210	0.09
45	8.74	91	6.47	134	0.25	226	0.05
47	25.90	92	1.52	135	0.11	232	0.09
48	1.76	93	3.62	136	0.09	234	0.22
49	30.49	94	3.95	137	0.12	236	0.31
50	5.33	95	3.39	138	0.20	238	0.03
51	5.66	96	1.17	140	0.10	240	0.08
52	3.90	97	1.69	141	0.50	250	0.16
53	6.75	98	0.32	143	0.71	260	0.02
54	0.81	99	0.68	145	50.67	264	0.16
55	0.88	100	0.58	146	5.18	265	0.06
56	0.62	101	1.00	147	1.74	268	0.36
57	2.52	102	0.43	148	0.19	269	0.06
58	0.74	104	2.80	150	0.11	292	0.02
59	0.37	105	4.76	152	1.37	304	0.03
61	2.89	106	16.82	153	0.17	306	0.06
62	5.86	107	1.60	154	0.06	312	0.03
63	23.43	108	1.85	156	0.26	332	0.31
64	6.75	109	0.42	157	1.31	333	0.07
65	6.95	110	1.53	158	0.27	359	0.14

CH2119F1#12*   x1   Bgd=11   22-NOV-96 16:42+0:01:15   70E   EI+   HMR:
BpM=8   I=10v   Hm=203   TIC=129664000   Acnt   Sys:ACE   MASS:
CHRIS HALL   PT= 0⁰   Cal:PFK22NOV

Mass	% Base
50.07	0.60
51.07	1.18
52.07	0.44
62.99	0.76
73.77	1.08
74.75	2.07
75.72	0.95
76.69	1.36
85.57	0.51
86.59	1.86
87.61	4.66
97.73	1.30
98.75	0.58
99.76	2.11
100.78	7.80
101.28	0.86
104.81	1.56
109.83	0.31
110.84	0.55
121.87	0.72
125.39	1.54
148.77	0.59
149.90	4.13
150.81	1.00
151.83	0.49
160.94	0.41
161.84	0.62
162.85	1.10
173.83	1.86
174.84	1.75
175.84	1.77
198.81	1.62
199.82	19.46
200.82	6.99
201.84	100.00 0
202.83	20.05
203.83	1.38

CH224'1078 (17.968) REFINE
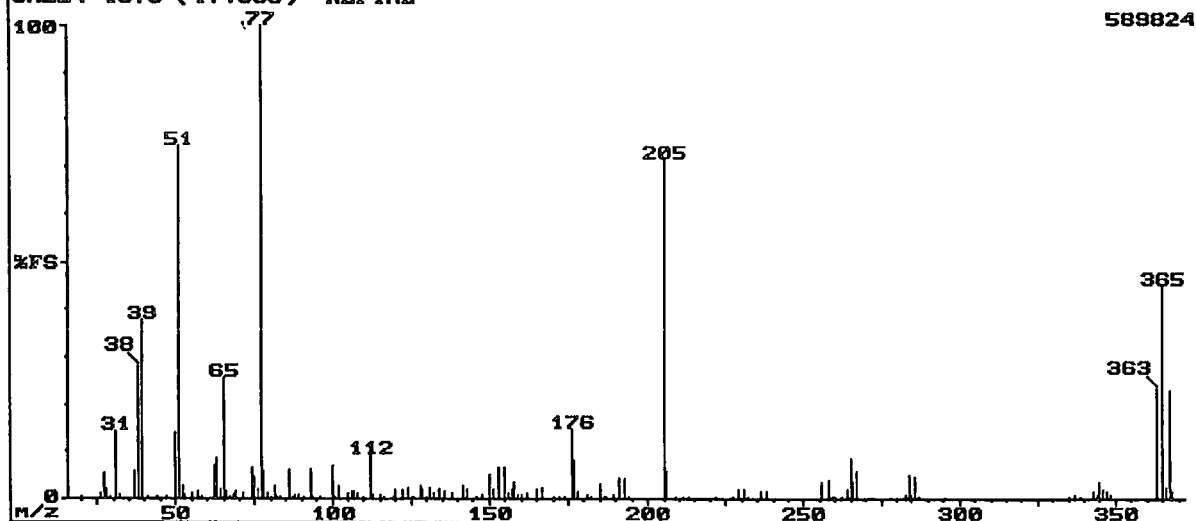
CH224'1078 (17.968)　REFINE

589824

Mass	Rel Int	Mass	Rel Int	Mass	Rel Int	Mass	Rel Int
20	0.03	81	2.57	138	1.10	213	0.28
26	1.09	82	0.36	142	2.82	222	0.12
27	5.47	83	0.18	143	1.90	227	0.16
28	1.97	86	6.16	146	0.47	229	1.93
29	0.12	87	0.36	148	0.88	231	1.96
31	14.41	88	0.91	150	5.03	232	0.30
32	0.93	89	0.68	151	1.84	236	1.39
37	5.86	91	0.41	153	6.55	238	1.41
38	28.13	93	6.08	155	6.73	256	3.52
39	37.85	94	0.57	156	1.12	258	3.86
41	0.28	96	0.19	157	2.11	259	0.50
44	0.31	100	7.03	158	3.34	260	0.52
47	0.09	101	0.33	159	0.59	262	0.40
50	14.06	102	2.91	160	0.84	264	2.04
51	74.31	105	1.07	162	1.14	265	8.38
52	2.82	106	1.40	165	2.13	266	3.34
53	0.90	107	1.44	167	2.21	267	5.73
55	1.32	108	1.22	170	0.11	283	0.68
57	1.74	110	0.55	172	0.22	284	4.95
58	0.10	112	9.24	174	0.58	285	0.59
62	6.90	113	0.86	176	14.76	286	4.69
63	8.72	115	0.80	177	7.99	287	0.40
64	1.96	116	0.43	178	1.45	335	0.45
65	25.87	119	0.30	181	0.97	337	0.80
66	1.42	120	1.97	182	0.39	339	0.42
67	0.26	122	1.78	185	3.13	343	1.73
68	0.81	124	2.25	186	0.53	344	0.60
69	1.40	125	0.18	187	0.51	345	3.65
71	1.15	126	0.47	189	0.74	346	2.11
74	6.68	128	2.73	191	4.30	347	1.49
75	4.82	129	1.78	193	4.25	348	0.92
76	2.09	130	0.44	194	0.27	363	23.26
77	100.00	131	2.45	205	71.53	365	45.14
78	5.95	132	1.01	206	5.69	366	2.27
79	1.00	134	2.02	209	0.05	367	23.09
80	0.20	136	1.52	211	0.32	368	1.74

Appendix Three
Infrared Spectroscopy Data

1.   3,5-Difluoropyridine (5)

2.   2,3,5-Trifluoropyridine (7)

3.   2,4,6-Tribromo-3,5-difluoropyridine (11)

4.   2,4,6-Tribromo-5-fluoropyrimidine (13)

5.   2,3-Dibromotetrafluoroquinoxaline (15)

6.   2,6-Dibromo-3,5-difluoropyridine (21)

7.   5,6,7,8-Tetrafluoroquinoxaline (20)

8.   1,2,3,4-Tetrahydro-5,6,7,8-tetrafluoroquinoxaline (19)

9.   3-Fluoro-5-aminopyridine (17)

10.   3,5-Dichloro-3,5-difluoropyridine (4a)

11.   2,4,6-Tribromo-3-fluoro-5-methoxypyridine (23a)

12.   2,4,6-Tribromo-3,5-dimethoxypyridine (23b)

13.   2,4,6-Tribromo-3-fluoro-5-aminopyridine (23c)

14.   2,4,6-Tribromo-3-fluoro-5-hydroxypyridine (23d)

15.   2,4,6-Tribromo-3-fluoro-5-phenoxypyridine (23e)

16.   2,6-Dibromo-3,5-difluoro-4-thiophenoxypyridine (22a)

17.   2,6-Dibromo-3,5-difluoro-4-diethylaminopyridine (22b)

18.   2,6-Dibromo-3,5-difluoro-4-piperidinopyridine (22d)

19.   5-Fluoro-2,4,6-trimethoxypyrimidine (13b)

20.   2,6-Dibromo-5-fluoro-4-piperidinopyrimidine (22g)

21.   2,3-Dipiperidinotetrafluoroquinoxaline (15a)

22.   2,3-Dimethoxytetrafluoroquinoxaline (15b)

23.   3,5-Difluoropyridine-N-oxide (5a)

24.   3,5-Difluoro-4-nitropyridine-N-oxide (35a)

25.   3-Fluoro-5-amino-6-nitropyridine-N-oxide (39a)

26.   3-Fluoro-4-nitro-5-aminopyridine-N-oxide (39b)

27.   4-Nitro-3,5-diaminopyridine-N-oxide (38)

28.   3,5-Dichloropyridine-N-oxide (34a)

29.   3,5-Dichloro-4-nitropyridine-N-oxide (36)

30.   3,5-Dichloro-4-aminopyridine-N-oxide (37)

31.   2,6-Dibromo-3,5-difluoro-4-allylpyridine (30)

32.   2,4-Dibromo-3,5-difluoro-6-(phenylacetylenyl)pyridine (25a)

33.   4-Bromo-3,5-difluoro-2,6-di(phenylacetylenyl)pyridine (25b)

34.   2,3-Dipentynyltetrafluoroquinoxaline (28)

35.   2,6-Dipentynyl-3,5-difluoro-4-bromopyridine (26)

36.   1,4-Diphenyl-1,3-butadiyne (41)

37.   5-Fluoro-2,4,6-tri(phenylacetylenyl)pyrimidine (27)

Spectrum 1 (bottom left)

Number of Scans= 4 Apodization= Strong
16/05/97 18:44 Res=4 cm-1
Transmittance / Wavenumber (cm-1)
File #1 : YTR1   Kr. di

Peaks: 516.124, 533.704, 718.411, 741.349, 790.897, 895.682, 874.871, 972.725, 1024.48, 1064.85, 1133.41, 1167.83, 1187.18, 1221.16, 1287.31, 1347, 1394.54, 1434.13, 1467.21, 1488.79, 1558.08, 1543.14, 1593.16, 1678.83, 1752.92, 1853.36, 2258.84, 2808.5, 2933.79, 3065.67

Spectrum 2 (top left)

Number of Scans 1   Apodization Si

Peaks: 963.33, 1033.83, 1061.37, 1091.01, 1120.03, 1199.72, 1273.29, 1255.37, 1255.68, 1295.37, 1324.76, 1408.99, 1535.14, 1558.74, 1566.39, 1691.91, 1605.84, 1649.07, 1609.1, 1695.44, 1693.73, 1724.23, 1724.53, 1690.95, 1834.48, 1861.96, 2281.72, 2294.82, 2348.25, 3988.3, 3303.26, 3638.31, 3660.97, 3681.46, 3716.49, 3810.46, 3845.37, 3858.81

Spectrum 3 (bottom right)

Number of Scans= 4   Apodization= Strong
16/05/97 18:24 Res=4 cm-1
Transmittance / Wavenumber (cm-1)
File #1 : YTR1   Kr. di
4,6-TRIBROMO-3,5-DIFLUOROPYRIDINE

Peaks: 547.717, 650.695, 668.771, 699.796, 771.057, 1053.07, 1131.37, 1238.46, 1272.94, 1346.75, 1388.19, 1419.16, 1457.99, 1507.27, 1559.59, 1653.57, 1684.55, 1700.45, 2361.19, 3852.81

Spectrum 4 (top right)

Number of Scans= 4   Apodization=
16/05/97 18:00 Res-
Transmittance / Wavenumber (cm-1)
File #1 : YTR1   Cd 280 ?   Kr. Disc   CH 28.

Peaks: 555.288, 619.258, 676.399, 753.598, 851.696, 1201.26, 1284.37, 1312.94, 1359.02, 1374.47, 1473.01, 1507.59, 1537.57, 2361.4, 3851.83

228

Spectrum 6 peaks:
- 576.838
- 681.334, 668.131, 656.61
- 705.508
- 802.03
- 868.868
- 1093.44
- 1163.1
- 1241.15, 1260.67
- 1346.12
- 1404.72
- 1507.2
- 1540.8
- 1559.37
- 1575.5
- 1636.33
- 1653.58
- 1684.57
- 3056.02

6

Spectrum 8 peaks:
- 783.311
- 858.84
- 925.847
- 969.53
- 1046.88
- 1088.99
- 1141.04
- 1233.83
- 1306.81
- 1335.51
- 1358.32
- 1431.53
- 1465.04
- 1521.21
- 1654.2
- 1684.71, 1662.4
- 2281.27
- 2894.82
- 2946.47
- 3416.72
- 3675.56
- 3853.47

8

Number of Scans= 8   Apodization= Strong

07/03/97 16:42 Res=4 cm-1

rmittance / Wavenumber (cm-1)

147

Spectrum 5 peaks:
- 455.357
- 570.501
- 644.369
- 769.016
- 1005.82
- 1049.1
- 1165.82, 1144.95
- 1249.21
- 1338.35
- 1434.34
- 1485.11, 1505.48
- 1534.2
- 1669.02
- 2361.5

5

Spectrum 7 peaks:
- 422.041
- 462.16
- 668.273
- 741.419
- 802.823
- 843.383
- 866.623
- 911.183
- 966.872
- 980.101
- 1053.86
- 1101.21
- 1194.78
- 1261.52
- 1337.05
- 1395.11
- 1458.13
- 1487.71, 1499.54
- 1540.63
- 1558.99
- 1636.32
- 1646.16
- 1654.56
- 1699.89
- 1717.25
- 1733.92
- 2341.64
- 2360.96
- 3627.54
- 3674.25
- 3836.73
- 3852.18

7

Number of Scans= 4   Apodization= Strong   5 . SNPY

03/04/97 11:02 Res=4 cm-1

ransmittance / Wavenumber (cm-1)

le # 1 : BASELINE

H 2156 SUB REX

229

14

16

13

15

231

Figure 22

421.815
493.333
636.676
667.375 — 644.033
725.438
742.933
803.54
907.543
978.731
1025.37
1046.76
1190.15
1258.85
1289.84
1333.1
1410.04
1433.57
1450.64
1330.71 — 1517.22
1492.99
1560.14
1597.12
1640.03
1660.21
1685.4
2345.73
2380.5
2955.93
3853.56

22

Figure 24

638.67
837.57
1076.24
1188.95
1335
1520.44
1580.11
1633.15
3124.86
3025.41

Wavenumbers (cm-1)

CH2137 F16-23 REX

%Transmittance

90 80 70 60 50 40 30

4000 3500 3000 2500 2000 1500 1000 500

Date: Fri Nov 29 12:14:49 1996
Scans: 32
Resolution: 4.000

24

Figure 21

634.892
643.506
703.85
822 — 869.063
889.91
903.046
916.823
928.153
999.11
1030.18
1110.69
1137.37
1218.5
1237.36
1257.09
1271.25
1378.29
1446.84
1466.07
1506.83
1548.94
1635.84
1653.32
1684.63
2381.23
2839.33
2944.94
3853.09

21

Figure 23

517.42
585.352
607.104
666.084
835.229
869.168
995.788
1018.85
1044.39
1142.99
1181.75
1211.11
1264.88
1371.73
1458.15
1533.18
1574.4
1598.33
1626.67
1637.63
1684.19
2362.22
3042.44
3099.34
3852.78

23

Transmittance / Wavenumber (cm-1)

File # 1 : YTR1

3,5-DIFLUOROPYRIDINE-N-OXIDE   KA dK

Number of Scans= 4   Apodization= Strong

16/05/97 17:09 Res=4 cm-1

233

25

3469.61
3270.72
3104.97
1646.41
1566.85
1540.33
1268.51
1129.28
2369.06
612.15

Date: Thu Dec 05 14:03:21 1996   Thu Dec 05 14:02:38 1996
CH2141 F3-3
Scans: 32
Resolution: 4.000

26

3429.83
3297.24
3118.23
2355.80
1639.78
1566.85
1268.51
1480.56
1182.32
1096.13
532.50
858.56

Date: Thu Dec 05 12:07:07 1996   CH2141 F13-36
Scans: 32
Resolution: 4.000

27

3542.54
3403.31
3131.49
2813.26
2362.43
1626.52
1566.85
1162.43
1109.39
1036.46
1288.51
784.53
651.93

Date: Wed Dec 04 15:21:38 1996   CH2141ss
Scans: 32
Resolution: 4.000

28

3852.27
3109.25
3050.39
3009.52
2403.23
1653.77
1591.69
1559.81
1539.55
1447.87
1403.57
1405.68
1271.46
1131.76
1089.09
1109.11
1044.92
1007.32
969.076
931.184
836.814
821.87
663.209
579.854
557.07
538.779
451.09

Ittance / Wavenumber (cm-1)

Number of Scans= 4   Apodization= Strc

34

430.898
455.006
496.534
656.378
684.196
736.823
766.25
794.315
955.061
1073.96
1107.41
1020.99 1045.28
1164.33
1174.11
1202.69
1224.42
1363.28
1276.63
1339.56 1356.16
1387.33
1419.74
1429.5
1461.36
1499.73
1533.89
1555.07
1576.38
1636.83
1656.52
1684.45
1717.86
2221.1
2343.09
2362.59
2876.65
2936.98
2968.66
3627.53
3852.12

37

423.227
512.921 533.361
545.562
689.356
754.794
784.494
974.546
1024.59
1190.25
1268.72
1393.18
1415.87
1440.49
1507.46 1491.12
1551.68
2217.09

33

417.028
520.939 502.671
528.122
549.03 562.31
669.157
686.622
753.626
864.45
916.492
997.446
1024.28
1069.25
1095.59
1168.7
1234.04 1226.68
1280.84
1312.82
1375.52
1426.66
1436.81
1493.11
1555.13
1571.07
1596.65
1654.44
1878.65
2246.11 2223.05
2344.21
2375.51
3055.05
3451.11
3852.98

35

567.367
667.235
792.357
880.28
1006.06
1172.82
1212.62
1274.04
1317.65
1417.54
1431.34
1447.49
1560.75
2240.39
2342.29
2361.72
2870.76
2932.83
2963.95

236

Appendix Four

Crystal Structure Data

Crystal Structure Data No. 1

Identification code	97srv069
Empirical formula	C5 H2 F2 N2 O3
Formula weight	176.09
Temperature	295(2) K
Wavelength	0.71073 A
Crystal system	Monoclinic
Space group	P2(1)/c
Unit cell dimensions	a = 5.479(1) A alpha = 90 deg.
	b = 10.840(1) A beta = 104.12(1) deg
	c = 11.159(1) A gamma = 90 deg.
Volume	642.74(14) A^3
Z	4
Density (calculated)	1.820 g/cm^3
Absorption coefficient	0.186 mm^-1
F(000)	352
Crystal size	0.35 x 0.25 x 0.20 mm
Theta range for data collection	2.66 to 27.48 deg.
Index ranges	-7<=h<=5, -11<=k<=15, -15<=l<=15
Reflections collected	4314
Independent reflections	1469 [R(int) = 0.0321]
Observed reflections, I>2sigma(I)	1086
Absorption correction	None
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	1424 / 0 / 118
Goodness-of-fit on F^2	1.106
Final R indices [I>2sigma(I)]	R1 = 0.0401, wR2 = 0.0864
R indices (all data)	R1 = 0.0637, wR2 = 0.1102
Extinction coefficient	0.054(5)
Largest diff. peak and hole	0.165 and -0.145 e.A^-3

238

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for 1.   U(eq) is defined as one third of the trace of the orthogonalized Uij tensor

	x	y	z	U(eq)
N(1)	6316(3)	5383(1)	3590(1)	44(1)
C(2)	6757(4)	6103(2)	4624(2)	44(1)
C(3)	5162(3)	7070(2)	4680(2)	42(1)
C(4)	3073(3)	7334(2)	3716(2)	40(1)
C(5)	2710(3)	6569(2)	2687(2)	42(1)
C(6)	4312(4)	5611(2)	2624(2)	45(1)
O(1)	7807(3)	4460(1)	3538(1)	64(1)
F(3)	5652(2)	7743(1)	5714(1)	64(1)
N(4)	1387(3)	8362(2)	3796(2)	49(1)
O(41)	-870(3)	8192(2)	3356(2)	72(1)
O(42)	2333(3)	9317(1)	4290(2)	68(1)
F(5)	801(2)	6767(1)	1706(1)	64(1)
H(2)	8181(43)	5939(20)	5236(22)	61(6)
H(6)	4110(38)	5110(20)	1948(20)	54(6)

Table 4.   Anisotropic displacement parameters (A^2 x 10^3) for 1. The anisotropic displacement factor exponent takes the form:
2 pi^2 [h^2 a*^2 U11 + ... + 2 h k a* b* U12]

	U11	U22	U33	U23	U13	U12
N(1)	45(1)	42(1)	42(1)	3(1)	9(1)	6(1)
C(2)	40(1)	50(1)	39(1)	2(1)	5(1)	0(1)
C(3)	42(1)	46(1)	37(1)	-3(1)	9(1)	-4(1)
C(4)	37(1)	38(1)	46(1)	3(1)	12(1)	-2(1)
C(5)	38(1)	42(1)	40(1)	4(1)	-1(1)	-3(1)
C(6)	51(1)	42(1)	40(1)	-2(1)	5(1)	0(1)
O(1)	66(1)	59(1)	62(1)	-4(1)	6(1)	26(1)
F(3)	64(1)	72(1)	49(1)	-20(1)	2(1)	7(1)
N(4)	49(1)	46(1)	55(1)	7(1)	17(1)	6(1)
O(41)	43(1)	71(1)	101(1)	9(1)	19(1)	10(1)
O(42)	84(1)	45(1)	73(1)	-9(1)	18(1)	5(1)
F(5)	58(1)	64(1)	56(1)	-4(1)	-14(1)	9(1)

Table 3.   Bond lengths [A] and angles [deg] for 1.

N(1)-O(1)	1.301(2)	N(1)-C(6)	1.361(2)
N(1)-C(2)	1.365(2)	C(2)-C(3)	1.376(3)
C(2)-H(2)	0.92(2)	C(3)-F(3)	1.336(2)
C(3)-C(4)	1.396(3)	C(4)-C(5)	1.391(3)
C(4)-N(4)	1.464(2)	C(5)-F(5)	1.334(2)
C(5)-C(6)	1.373(3)	C(6)-H(6)	0.91(2)
N(4)-O(42)	1.227(2)	N(4)-O(41)	1.228(2)
O(1)-N(1)-C(6)	119.9(2)	O(1)-N(1)-C(2)	119.6(2)
C(6)-N(1)-C(2)	120.5(2)	N(1)-C(2)-C(3)	119.4(2)
N(1)-C(2)-H(2)	117.4(14)	C(3)-C(2)-H(2)	123.1(14)
F(3)-C(3)-C(2)	117.3(2)	F(3)-C(3)-C(4)	120.5(2)
C(2)-C(3)-C(4)	122.1(2)	C(5)-C(4)-C(3)	116.0(2)
C(5)-C(4)-N(4)	122.6(2)	C(3)-C(4)-N(4)	121.3(2)
F(5)-C(5)-C(6)	117.6(2)	F(5)-C(5)-C(4)	120.5(2)
C(6)-C(5)-C(4)	121.9(2)	N(1)-C(6)-C(5)	120.0(2)
N(1)-C(6)-H(6)	117.2(13)	C(5)-C(6)-H(6)	122.8(13)
O(42)-N(4)-O(41)	125.5(2)	O(42)-N(4)-C(4)	117.8(2)
O(41)-N(4)-C(4)	116.7(2)		

Crystal Structure Data No. 2

Identification code	97srv070
Empirical formula	C5 H8 N4 O4
Formula weight	188.15
Temperature	150(2) K
Wavelength	0.71073 A
Crystal system	Orthorhombic
Space group	Pna2(1)
Unit cell dimensions	a = 7.000(1) A alpha = 90 deg.
	b = 13.123(1) A beta = 90 deg.
	c = 8.263(1) A gamma = 90 deg.
Volume	759.0(2) A^3
Z	4
Density (calculated)	1.646 g/cm^3
Absorption coefficient	0.143 mm^-1
F(000)	392
Crystal size	0.40 x 0.15 x 0.08 mm
Theta range for data collection	2.9 to 27.5 deg.
Index ranges	-9<=h<=9, -16<=k<=17, -10<=l<=10
Reflections collected	5153
Independent reflections	1682 [R(int) = 0.0461]
Observed reflections, I>2sigma(I)	1486
Absorption correction	None
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	1678 / 1 / 149
Goodness-of-fit on F^2	1.128
Final R indices [I>2sigma(I)]	R1 = 0.0421, wR2 = 0.1015
R indices (all data)	R1 = 0.0524, wR2 = 0.1116
Absolute structure parameter	-1(2)
Largest diff. peak and hole	0.218 and -0.219 e.A^-3

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for 1.   U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

	x	y	z	U(eq)
N(1)	3290(3)	4752(1)	2312(3)	15(1)
C(2)	4013(4)	4297(2)	991(3)	16(1)
C(3)	4198(3)	3231(2)	905(3)	14(1)
C(4)	3529(3)	2649(2)	2259(3)	13(1)
C(5)	2819(3)	3159(2)	3682(3)	14(1)
C(6)	2724(4)	4231(2)	3626(3)	15(1)
O(1)	3121(2)	5764(1)	2305(3)	20(1)
O(41)	4256(3)	1134(1)	994(2)	20(1)
O(42)	2908(3)	1053(1)	3355(2)	23(1)
N(3)	4968(4)	2853(2)	-445(3)	18(1)
N(4)	3573(3)	1567(1)	2198(3)	14(1)
N(5)	2227(3)	2696(2)	5041(3)	19(1)
O(1W)	-784(3)	6063(1)	2584(2)	21(1)

Table 4. Anisotropic displacement parameters (A^2 x 10^3) for 1. The anisotropic displacement factor exponent takes the for $-2 \pi^2 [h^2 a^{*2} U11 + \ldots + 2 h k a^* b^* U12]$

	U11	U22	U33	U23	U13	U12
N(1)	16(1)	11(1)	19(1)	-4(1)	-2(1)	-1(1)
C(2)	17(1)	14(1)	16(1)	2(1)	3(1)	-2(1)
C(3)	11(1)	13(1)	17(1)	-2(1)	-2(1)	2(1)
C(4)	14(1)	12(1)	13(1)	1(1)	-2(1)	0(1)
C(5)	12(1)	16(1)	14(1)	-1(1)	-2(1)	-1(1)
C(6)	16(1)	17(1)	13(1)	-4(1)	3(1)	2(1)
O(1)	27(1)	8(1)	24(1)	-2(1)	-3(1)	1(1)
O(41)	30(1)	13(1)	18(1)	-3(1)	4(1)	1(1)
O(42)	31(1)	13(1)	24(1)	4(1)	-10(1)	-1(1)
N(3)	25(1)	12(1)	17(1)	1(1)	6(1)	2(1)
N(4)	12(1)	13(1)	17(1)	1(1)	1(1)	0(1)
N(5)	24(1)	16(1)	16(1)	0(1)	7(1)	2(1)
O(1W)	29(1)	13(1)	21(1)	-1(1)	-4(1)	1(1)

Table 3.   Bond lengths [A] and angles [deg] for 1.

N(1)-O(1)	1.334(2)	N(1)-C(6)	1.343(3)
N(1)-C(2)	1.343(3)	C(2)-C(3)	1.407(3)
C(2)-H(2)	0.95(3)	C(3)-N(3)	1.335(3)
C(3)-C(4)	1.434(3)	C(4)-N(4)	1.421(2)
C(4)-C(5)	1.441(3)	C(5)-N(5)	1.343(3)
C(5)-C(6)	1.409(3)	C(6)-H(6)	0.91(3)
O(41)-N(4)	1.241(3)	O(42)-N(4)	1.259(3)
N(3)-H(32)	0.79(3)	N(3)-H(31)	0.88(3)
N(5)-H(52)	0.87(4)	N(5)-H(51)	0.92(3)
O(1W)-H(1W)	0.81(5)	O(1W)-H(2W)	0.89(4)
O(1)-N(1)-C(6)	118.9(2)	O(1)-N(1)-C(2)	118.2(2)
C(6)-N(1)-C(2)	122.9(2)	N(1)-C(2)-C(3)	121.1(2)
N(1)-C(2)-H(2)	118(2)	C(3)-C(2)-H(2)	121(2)
N(3)-C(3)-C(2)	116.7(2)	N(3)-C(3)-C(4)	125.9(2)
C(2)-C(3)-C(4)	117.4(2)	N(4)-C(4)-C(3)	119.9(2)
N(4)-C(4)-C(5)	120.0(2)	C(3)-C(4)-C(5)	120.1(2)
N(5)-C(5)-C(6)	117.7(2)	N(5)-C(5)-C(4)	125.3(2)
C(6)-C(5)-C(4)	117.0(2)	N(1)-C(6)-C(5)	121.3(2)
N(1)-C(6)-H(6)	116(2)	C(5)-C(6)-H(6)	122(2)
H(32)-N(3)-H(31)	118(3)	H(32)-N(3)-C(3)	121(3)
H(31)-N(3)-C(3)	121(2)	O(41)-N(4)-O(42)	120.4(2)
O(41)-N(4)-C(4)	119.6(2)	O(42)-N(4)-C(4)	120.0(2)
H(52)-N(5)-H(51)	124(3)	H(52)-N(5)-C(5)	119(2)
H(51)-N(5)-C(5)	116(2)	H(1W)-O(1W)-H(2W)	104(4)

Table 5.   Hydrogen coordinates (x 10^4) and isotropic displacement parameters (A^2 x 10^3) for 1.

	x	y	z	U(eq)
H(2)	4455(44)	4721(23)	143(41)	19(7)
H(6)	2230(43)	4605(23)	4453(38)	14(7)
H(31)	5326(41)	3257(23)	-1238(40)	14(5)
H(32)	5045(47)	2259(24)	-583(42)	14(5)
H(51)	2311(45)	2000(23)	5056(36)	12(7)
H(52)	1898(46)	3066(23)	5867(46)	22(8)
H(1W)	-1223(64)	5502(36)	2753(55)	60(14)
H(2W)	457(64)	5947(31)	2434(59)	58(12)

Distance H..Y
```
    2.069  (0.032)   H31 - O1_$1      2.045 (0.033)   H32 - O41
    2.242  (0.033)   H32 - O1W_$2     1.922 (0.031)   H51 - O42
    1.982  (0.036)   H52 - O1W_$3     2.187 (0.049)   H1W - O42_$4
    1.884  (0.045)   H2W - O1
```

Distance X..Y
```
    2.922  (0.003)   N3 - O1_$1       2.598 (0.003)   N3 - O41
    2.915  (0.003)   N3 - O1W_$2      2.610 (0.003)   N5 - O42
    2.844  (0.003)   N5 - O1W_$3      2.993 (0.003)   O1W - O42_$4
    2.771  (0.003)   O1W - O1
```

Angle XHY
```
163.31 ( 2.70)  N3 - H31 - O1_$1      127.01 ( 3.20)  N3 - H32 - O41
143.57 ( 3.27)  N3 - H32 - O1W_$2     130.44 ( 2.55)  N5 - H51 - O42
171.50 ( 3.12)  N5 - H52 - O1W_$3     173.24 ( 4.25)  O1W - H1W - O42_$4
174.60 ( 4.44)  O1W - H2W - O1
```

Least-squares planes (x,y,z in crystal coordinates) and deviations from ther
(* indicates atom used to define plane)

```
  6.302 (0.004) x + 0.021 (0.018) y + 3.596 (0.010) z = 3.043 (0.003)
*    -0.001 (0.001)  C4        *     0.003 (0.002)  N4
*    -0.001 (0.001)  O41       *    -0.001 (0.001)  O42
Rms deviation of fitted atoms =    0.002
```

```
  6.445 (0.003) x + 0.699 (0.012) y + 3.195 (0.007) z = 3.203 (0.005)
Angle to previous plane (with approximate esd) =   4.23 ( 0.12 )
*    -0.012 (0.002)  N1        *     0.000 (0.002)  C2
*     0.017 (0.002)  C3        *    -0.022 (0.002)  C4
*     0.011 (0.002)  C5        *     0.007 (0.002)  C6
      0.055 (0.004)  N3             -0.089 (0.003)  N4
      0.031 (0.004)  N5             -0.052 (0.003)  O1
Rms deviation of fitted atoms =    0.014
```

```
  6.385 (0.038) x + 0.424 (0.392) y + 3.376 (0.109) z = 3.127 (0.127)
Angle to previous plane (with approximate esd) =   1.80 ( 1.03 )
*    -0.004 (0.003)  C3        *     0.016 (0.013)  N3
*    -0.006 (0.005)  H31       *    -0.006 (0.005)  H32
Rms deviation of fitted atoms =    0.009
```

```
  6.469 (0.062) x + 0.854 (0.447) y + 3.110 (0.131) z = 3.238 (0.172)
Angle to previous plane (with approximate esd) =   2.72 ( 1.79 )
*     0.000 (0.000)  C5        *     0.000 (0.000)  N5
*     0.000 (0.000)  H51             0.076 (0.046)  H52
Rms deviation of fitted atoms =    0.000
```

```
  6.445 (0.003) x + 0.699 (0.012) y + 3.195 (0.007) z = 3.203 (0.005)
Angle to previous plane (with approximate esd) =   0.92 ( 1.46 )
*    -0.012 (0.002)  N1        *     0.000 (0.002)  C2
*     0.017 (0.002)  C3        *    -0.022 (0.002)  C4
*     0.011 (0.002)  C5        *     0.007 (0.002)  C6
Rms deviation of fitted atoms =    0.014
```

Appendix 5.

Requirements of the Board of Studies

The Board of Studies in Chemistry requires that each postgraduate research thesis contains an appendix listing:-

(A)   all research colloquia, seminars and lectures arranged by the Department of Chemistry during the period of the author's residence as a postgraduate student;

(B)   lectures organised by Durham University Chemical Society;

(C)   details of postgraduate induction courses;

(D)   all research conferences attended and papers presented by the author during the period when research for the thesis was carried out.

Colloquia, Lectures and Seminars From Invited Speakers
1994-1997

<u>1994</u>

October 5   Prof. N. L. Owen, Brigham Young University, Utah, USA*
Determining Molecular Structure - the INADEQUATE NMR way

October 19   Prof. N. Bartlett, University of California*
Some Aspects of Ag(II) and Ag(III) Chemistry

November 2   Dr P. G. Edwards, University of Wales, Cardiff
The Manipulation of Electronic and Structural Diversity in Metal Complexes - New Ligands

November 3   Prof. B. F. G. Johnson, Edinburgh University*
Arene-metal Clusters

November 9   Dr G. Hogarth, University College, London
New Vistas in Metal-imido Chemistry

November 10   Dr M. Block, Zeneca Pharmaceuticals, Macclesfield*
Large-scale Manufacture of ZD 1542, a Thromboxane Antagonist Synthase Inhibitor

November 16   Prof. M. Page, University of Huddersfield*
Four-membered Rings and b-Lactamase

November 23   Dr J. M. J. Williams, University of Loughborough*
New Approaches to Asymmetric Catalysis

December 7   Prof. D. Briggs, ICI and University of Durham*
Surface Mass Spectrometry

<u>1995</u>

January 11   Prof. P. Parsons, University of Reading*
Applications of Tandem Reactions in Organic Synthesis

January 18   Dr G. Rumbles, Imperial College, London
Real or Imaginary Third Order Non-linear Optical Materials

244

January 25   Dr D. A. Roberts, Zeneca Pharmaceuticals*
The Design and Synthesis of Inhibitors of the Renin-angiotensin System

February 1   Dr T. Cosgrove, Bristol University*
Polymers do it at Interfaces

February 8   Dr D. O'Hare, Oxford University*
Synthesis and Solid-state Properties of Poly-, Oligo- and Multidecker Metallocenes

February 22   Prof. E. Schaumann, University of Clausthal*
Silicon- and Sulphur-mediated Ring-opening Reactions of Epoxide

March 1   Dr M. Rosseinsky, Oxford University
Fullerene Intercalation Chemistry

March 22   Dr M. Taylor, University of Auckland, New Zealand
Structural Methods in Main-group Chemistry

April 26   Dr M. Schroder, University of Edinburgh
Redox-active Macrocyclic Complexes : Rings, Stacks and Liquid Crystals

May 4   Prof. A. J. Kresge, University of Toronto
The Ingold Lecture Reactive Intermediates : Carboxylic-acid Enols and Other Unstable Species

October 11   Prof. P. Lugar, Frei Univ Berlin, FRG
Low Temperature Crystallography

October 13   Prof. R. Schmutzler, Univ Braunschweig, FRG.
Calixarene-Phosphorus Chemistry: A New Dimension in Phosphorus Chemistry

October 18   Prof. A. Alexakis, Univ. Pierre et Marie Curie, Paris*
Synthetic and Analytical Uses of Chiral Diamines

October 25   Dr.D.Martin Davies, University of Northumbria
Chemical reactions in organised systems.

November 1   Prof. W. Motherwell, UCL London*
              New Reactions for Organic Synthesis

November 3   Dr B. Langlois, University Claude Bernard-Lyon*
              Radical Anionic and Psuedo Cationic Trifluoromethylation

November 8   Dr. D. Craig, Imperial College, London*
              New Stategies for the Assembly of Heterocyclic Systems

November 15   Dr Andrea Sella, UCL, London
              Chemistry of Lanthanides with Polypyrazoylborate Ligands

November 17   Prof. David Bergbreiter, Texas A&M, USA*
              Design of Smart Catalysts, Substrates and Surfaces from Simple
Polymers

November 22   Prof. I Soutar, Lancaster University
              A Water of Glass? Luminescence Studies of Water-Soluble Polymers.

November 29   Prof. Dennis Tuck, University of Windsor, Ontario, Canada
              New Indium Coordination Chemistry

December 8   Professor M.T. Reetz, Max Planck Institut, Mulheim
              Perkin Regional Meeting

1996

January 10   Dr Bill Henderson, Waikato University, NZ
              Electrospray Mass Spectrometry - a new sporting technique

January 17   Prof. J. W. Emsley , Southampton University*
              Liquid Crystals: More than Meets the Eye

January 24   Dr Alan Armstrong, Nottingham Univesity*
              Alkene Oxidation and Natural Product Synthesis

January 31   Dr J. Penfold, Rutherford Appleton Laboratory,
              Soft Soap and Surfaces

246

February 7   Dr R.B. Moody, Exeter University
               Nitrosations, Nitrations and Oxidations with Nitrous Acid

February 12   Dr Paul Pringle, University of Bristol
               Catalytic Self-Replication of Phosphines on Platinum(O)

February 14   Dr J. Rohr, Univ Gottingen, FRG
               Goals and Aspects of Biosynthetic Studies on Low Molecular Weight
               Natural Products

February 21   Dr C R Pulham , Univ. Edinburgh
               Heavy Metal Hydrides - an exploration of the chemistry of stannanes and
               plumbanes

February 28   Prof. E. W. Randall, Queen Mary & Westfield College
               New Perspectives in NMR Imaging

March 6   Dr Richard Whitby, Univ of Southampton*
               New approaches to chiral catalysts: Induction of planar and metal centred
               asymmetry

March 7   Dr D.S. Wright, University of Cambridge
               Synthetic Applications of Me2N-p-Block Metal Reagents

March 12   RSC Endowed Lecture - Prof. V. Balzani, Univ of Bologna
               Supramolecular Photochemistry

March 13   Prof. Dave Garner, Manchester University*
               Mushrooming in Chemistry

April 30   Dr L.D.Pettit, Chairman, IUPAC Commission of Equilibrium Data
               pH-metric studies using very small quantities of uncertain purity

October 9   Professor G. Bowmaker, University Aukland, NZ
               Coordination and Materials Chemistry of the Group 11 and Group 12
               Metals : Some Recent Vibrational and Solid State NMR Studies

October 14   Professor A. R. Katritzky, University of Gainesville,University of
Florida,   USA*
               Recent Advances in Benzotriazole Mediated Synthetic Methodology

247

October 16 Stony   Professor Ojima, Guggenheim Fellow, State University of New York at Brook*
Silylformylation and Silylcarbocyclisations in Organic Synthesis

October 22   Professor Lutz Gade, Univ. Wurzburg, Germany*
and   *Organic transformations with Early-Late Heterobimetallics: Synergism Selectivity*

October 22   Professor B. J. Tighe, Department of Molecular Sciences and Chemistry, University of Aston
Making Polymers for Biomedical Application - can we meet Nature's Challenge?
Joint lecture with the Institute of Materials

October 23 Gutenberg-   Professor H. Ringsdorf (Perkin Centenary Lecture), Johannes Universitat, Mainz, Germany
Function Based on Organisation

October 29 Durham.   Professor D. M. Knight, Department of Philosophy, University of
The Purpose of Experiment - A Look at Davy and Faraday

October 30   Dr Phillip Mountford, Nottingham University
Recent Developments in Group IV Imido Chemistry

November 6   Dr Melinda Duer, Chemistry Department, Cambridge
Solid-state NMR Studies of Organic Solid to Liquid-crystalline Phase Transitions

November 12   Professor R. J. Young, Manchester Materials Centre, UMIST*
New Materials - Fact or Fantasy?
Joint Lecture with Zeneca & RSC

November 13   Dr G. Resnati, Milan*
Perfluorinated Oxaziridines: Mild Yet Powerful Oxidising Agents

November 18   Professor G. A. Olah, University of Southern California, USA*
Crossing Conventional Lines in my Chemistry of the Elements

November 19 Professor R. E. Grigg, University of Leeds*
             Assembly of Complex Molecules by Palladium-Catalysed Queueing
Processes

November 20 Professor J. Earnshaw, Deptartment of Physics, Belfast
             Surface Light Scattering: Ripples and Relaxation

November 27 Dr Richard Templer, Imperial College, London
             Molecular Tubes and Sponges

December 3   Professor D. Phillips, Imperial College, London
             "A Little Light Relief"

December 4   Professor K. Muller-Dethlefs, York University
             Chemical Applications of Very High Resolution ZEKE Photoelectron
                  Spectroscopy

December 11 Dr Chris Richards, Cardiff University*
             Sterochemical Games with Metallocenes

1997

January 15   Dr V. K. Aggarwal, University of Sheffield*
             Sulfur Mediated Asymmetric Synthesis

January 16   Dr Sally Brooker, University of Otago, NZ
             Macrocycles: Exciting yet Controlled Thiolate Coordination Chemistry

January 21   Mr D. Rudge, Zeneca Pharmaceuticals*
             High Speed Automation of Chemical Reactions

January 22   Dr Neil Cooley, BP Chemicals, Sunbury
             Synthesis and Properties of Alternating Polyketones

January 29   Dr Julian Clarke, UMIST
             What can we learn about polymers and biopolymers from computer-
             generated nanosecond movie-clips?

February 4   Dr A. J. Banister, University of Durham

From Runways to Non-metallic Metals - A New Chemistry Based on Sulphur

February 5   Dr A. Haynes, University of Sheffield
Mechanism in Homogeneous Catalytic Carbonylation

February 12   Dr Geert-Jan Boons, University of Birmingham*
New Developments in Carbohydrate Chemistry

February 18   Professor Sir James Black, Foundation/King's College London*
My Dialogues with Medicinal Chemists

February 19   Professor Brian Hayden, University of Southampton
The Dynamics of Dissociation at Surfaces and Fuel Cell Catalysts

February 25   Professor A. G. Sykes, University of Newcastle
The Synthesis, Structures and Properties of Blue Copper Proteins

February 26   Dr Tony Ryan, UMIST*
Making Hairpins from Rings and Chains

March 4   Professor C. W. Rees, Imperial College*
Some Very Heterocyclic Chemistry

March 5   Dr J. Staunton FRS, Cambridge University*
Tinkering with biosynthesis: towards a new generation of antibiotics

March 11   Dr A. D. Taylor, ISIS Facility, Rutherford Appleton Laboratory
Expanding the Frontiers of Neutron Scattering

March 19   Dr Katharine Reid, University of Nottingham
Probing Dynamical Processes with Photoelectrons

* lectures attended

First Year Induction Courses

This course consists of a series of one hour lectures on the services available in the department.

Departmental Organisations -	Dr. E. J. F. Ross
Safety Matters -	Dr. G. M. Brook
Electrical Appliances -	Mr. B. T. Barker
Chromatography and Microanalysis -	Mr. T. F. Holmes
Atomic Absorptiometry and Inorganic Analysis -	Mr. R. Coult
Library Facilities -	Mrs. M. Hird
Mass Spectroscopy -	Dr. M. Jones
NMR Spectroscopy -	Dr. A. Kenwright
Glass-blowing Techniques -	Mr. R. Hart
	Mr. G. Haswell

Research Conferences Attended

April 1995   North Eastern Graduate Symposium, University of Durham.

July 1996   DRA Mini Synposium, DRA Fort Halstead, Sevenoaks, Kent.

April 1997   North Eastern Graduate Symposium, University of Newcastle.

May 1997   21 st Century Heterocyclic Chemistry Conference, Sunderland.

August 1997   15th International Symposium on Fluorine Chemistry, University of British Columbia, Vancouver, CANADA.

Bibliography

1. N. N. Greenwood and A. Earnshaw, *The Chemistry of the Elements*, Pergamon, Oxford, 1984.

2. D. B. Harper and D. O'Hagan, *Nat. Prod. Rep*, 1994, 123.

3. A. K. Barbour, in *Organofluorine Chemicals and Their Industrial Applications*, ed. R. E. Banks, Horwood, Chichester, 1979, p. 44.

4. H. Moissan, *Le Fluor et ses Composes*, Steinheil, Paris, 1900.

5. E. Paterno and V. Oliveri, *Gazzetta*, 1883, 13, 533.

6. Y. Desirant, *Bull. Acad. Roy. Belg., Classe Sci*, 1955, 41, 759.

7. A. E. Chichibabin and M. D. Rajazancev, *J. Russ. Phys. Chem. Soc*, 1915, 46, 1571.

8. F. Swarts, *Bull. Acad. Roy. Belg*, 1892, 24, 474.

9. A. K. Barbour, L. J. Belf and M. X. Buxton, *Adv. Fluorine Chem*, 1963, 3, 181.

10. H. Goldwhite, in *Fluorine: The First Hundred Years (1886-1986)*, ed. R. E. Banks, D. W. A. Sharp and J. C. Tatlow, Elsevier Sequoia, Lausanne and New York, 1986, p. 109.

11. R. D. Chambers and C. R. Sargent, *Adv. Heterocyclic Chem*, 1981, 28, 1.

12. G. M. Brooke, *To be published*, 1997,

13. C. D. Hewitt and M. J. Silvester., *Aldrichimica Acta*, 1988, 21, 3.

14. M. J. Silvester, *Adv. Heterocyclic Chem*, 1994, 59, 19.

15. P. Hradil and S. Radl, *Chemicke Listy*, 1990, 84, 952.

16. L. Dolby-Glover, *Chem. Ind*, 1986, 518.

17. J. S. Moilliet, in *Organofluorine Chemistry. Principles and Commercial Applications*, ed. R. E. Banks, B. E. Smart and J. C. Tatlow, Plenum Press, New York, 1994, p. 195.

18. G. C. Finger, L. D. Starr, D. R. Dickerson, H. S. Gutowsky and J. Hamer, *J. Org. Chem*, 1963, 1666.

19. G. C. Finger and L. D. Starr, *J. Am. Chem. Soc*, 1959, 81, 2674.

20. G. C. Finger and C. W. Kruse, *J. Am. Chem. Soc*, 1956, 78, 6034.

21. R. D. Chambers, J. Hutchinson and W. K. R. Musgrave., *J. Chem. Soc.*, 1964, 3573.

22. S. Fujii and K. Inukai in *Chem. Abs., 86, 5194*; 1977

23. J. H. Clark and D. J. Macquarrie, *Tetrahedron Lett.*, 1987, 28, 111.

24. R. Pfirmann in European Patent No. 0556 737A1, 1993.

25. J. Mason and D. J. Milner, *Synth. Commun*, 1994, 24, 529.

26. P. I. Svirskaya, V. Yedidia, C. C. Leznoff and J. M. Miller, *J. Heterocyclic Chem*, 1985, 22, 149.

27. K. Makino and H. Yoshioka, *Heterocycles*, 1987, 26, 1215.

28. B. Venugopal in European Patent No. 0710649A1, 1996.

29. G. Seifert and S. Staeubli in *Chem. Abs., 90, 23123*, 1979

30. R. E. Fernandez and M. H. Krackov in U.S Patent No. 5315043, 1994.

31. J. March, *Advanced Organic Chemistry,* Wiley, 1992.

32. H. Suzuki, N. Yazawa, Y. Yoshida, O. Furarawa and Y. Kimura, *Bull. Chem. Soc. Jpn,* 1990, 63, 2010.

33. G. Bartoli, A. Latrofa, F. Naso and P. E. Todesco, *J. Chem. Soc., Perkin Trans. 1,* 1972, 2671.

34. N. Yazawa, H. Suzuki, Y. Yoshida, O. Furusawa and Y. Kimura, *Chem. Letters,* 1989, 2213.

35. J. H. Clark and N. Boechat in *Chemistry and Industry*; 1991; 536.

36. S. J. Brown and J. H. Clark, *J. Fluorine Chem,* 1985, **30**, 251.

37. J. H. Clark and D. Wails, *J. Fluorine Chem,* 1995, **70**, 201.

38. A. Boechat and J. H. Clark, *J. Chem. Soc., Chem. Commun,* 1993, 921.

39. J. A. Wilkinson, *Chem. Rev,* 1992, **92**, 505.

40. H. Meinert, *Z. Chem,* 1965, **5**, 64.

41. M. V. D. Puy, *Tetrahedron Lett.,* 1987, **28**, 255.

42. T. Umemoto and G. Tomizawa, *J. Org. Chem,* 1989, **54**, 1726.

43. R. D. Chambers, C. J. Skinner, J. Thompson and J. Hutchinson, *J. Chem. Soc., Chem. Commun,* 1995, 17.

44. L. Conte, G. P. Gambaretto, M. Napoli, C. Fraccara and E. Legnaro, *J. Fluorine Chem,* 1995, **70**, 175.

45. R. D. Chambers and G. Sandford in *Chem. Abs 125, 114513z*; 1994.

46. R. D. Chambers, G. Sandford, C. J. Skinner and M. J. Atherton, *J. Chem. Soc., Perkin Trans. 1, to be submitted,* 1997 (in press),

47. S. P. Anand and R. Filler, *J. Fluorine Chem,* 1976, **7**, 179.

48. S. P. Anand, L. A. Quarterman, H. H. Hyman, K. G. Migliorese and R. Filler, *J. Org. Chem,* 1974, **40**, 807.

49. A. Gakh, A. A. Tuinman, J. L. Adcock and R. N. Compton, *Tetrahedron Lett.,* 1993, **34**, 7167.

50. P. L. Coe, A. G. Holton and J. C. Tatlow, *J. Fluorine Chem.,* 1982, **21**, 171.

51. R. G. Plevey, R. W. Rendell and J. C. Tatlow, *J. Fluorine Chem,* 1982, **21**, 159.

52. J. R. Ballinger and F. W. Teare, *Electrochimica Acta,* 1985, **30**, 1075.

53. G. S. Lal, G. P. Pez and R. G. Syvret, *Chem. Rev,* 1996, **96**, 1737.

54. T. Umemoto, S. Fukami, G. Tomizawa, K. Harasawa, K. Kawada and K. Tomita, *J. Am. Chem. Soc,* 1990, **112**, 8563.

55. S. Stavber and M. Zupan, *Tetrahedron Lett.,* 1990, **31**, 775.

56. S. Stavber and M. Zupan, *J. Chem. Soc., Chem. Commun,* 1981, 148.

57. S. Rozen, D. Hebel and D. Zamir, *J. Am. Chem. Soc,* 1987, **109**, 3789-3790.

58.   M. R. Bryce, R. D. Chambers, S. T. Mullins and A. Parkin, *Bull. Soc. Chim. Fr.*, 1986, 930.

59.   G. S. Lal, *J. Org. Chem*, 1993, **58**, 2991.

60.   S. Singh, D. D. DesMarteau, S. S. Zuberi, M. Witz and H. Huang, *J. Am. Chem. Soc*, 1987, **109**, 7194.

61.   M. J. Adam, J. M. Berry, L. D. Hall, B. D. Pate and T. J. Ruth, *Can. J. Chem.*, 1982, **61**, 658.

62.   H. F. Hodson, D. J. Madge, A. N. Z. Slawin, D. A. Widdowson and D. J. Williams, *Tetrahedron*, 1994, **50**, 1899.

63.   H. H. Coenen and S. M. Moerlein, *J. Fluorine Chem.*, 1987, **36**, 63.

64.   G. W. M. Vissier, B. W. v. Haltern, J. D. M. Herscheid, G. A. Brinkman and A. Hoekstra, *J. Chem. Soc., Chem. Commun.*, 1984, 655.

65.   G. Schiemann, *J. Prakt. Chem*, 1934, **140**, 97.

66.   G. Schiemann, *Chem-Ztg*, 1930, **54**, 269.

67.   G. Balz and G. Schiemann, *Ber*, 1927, **60**, 1186.

68.   A. Roe and G. F. Hawkins, *J. Am. Chem. Soc*, 1947, **69**, 2443.

69.   H. Schlosser in European Patent No. 0573878A1, 1993.

70.   M. M. Boudakian., *J. Fluorine. Chem.*, 1981, **18**, 497.

71.   T. Fukuhara, N. Yoneda and A. Suzuki., *J. Fluorine Chem.*, 1988, **38**, 435.

72.   N. Yoneda and T. Fukuhara, *Tetrahedron*, 1995, **52**, 23.

73.   K. Sasaki, M. Oishi and N. Imaki, *J. Fluorine Chem*, 1996, **76**, 59.

74.   D. S. Wulfman, in *The Chemistry of Diazonium and Diazo Compounds*, ed. S. Patai, Wiley, 1978, 286.

75.   S. Ghosh and M. Schlosser, *J. Fluorine Chem.*, 1994, 53.

76.   E. D. Bergmann, S. Cohen and I. Shahak, *J. Chem. Soc*, 1959, 3278.

77.   I. Takoaka, M. K. Ibrahim, S. R. F. Kagaruki and N. Ishikawa, *Nippon Kagaku Kaishi*, 1985, **11**, 2169.

78.   C. Reichardt and K. Halbritter, *Liebigs Ann. Chem.*, 1975, 470.

79.   X. Shi, T. Ishihara and H. Yamanaka, *Tetrahedron Lett.*, 1995, **36**, 1527.

80.   T. Ishihara, Y. Okada, M. Kuroboshi, T. Shinozaki and T. Ando, *Chem. Letters*, 1988, 819.

81.   R. Nasielski-Hinkens, P. Leveque and D. Castelet, *Heterocycles*, 1987, **26**, 2433.

82.   J. Burdon, V. A. Damodaran and J. C. Tatlow, *J. Chem. Soc*, 1964, 763.

83.   T. N. Gerasimova and N. A. Orlova, *J. Fluorine Chem*, 1985, **28**, 361.

84.   G. M. Brooke and C. J. Drury, *J. Fluorine Chem.*, 1993, **67**, 143.

85.   O. M. Nefedov and N. V. Volchkov, *Russian Journal of Organic Chemistry*, 1994, **30**, 1181.

86.   R. E. Banks, A. E. Ginsberg and R. N. Haszeldine, *J. Chem. Soc*, 1961, 1740.

87.   R. E. Banks, J. E. Burgess and R. N. Haszeldine, *J. Chem. Soc*, 1965, 2720.

88.   D. Craciunescu, V. Scarcia, A. Furlani, C. Ghirvu, L. Ravalico and A. Duadrio, *Acta Pharmaceutica Fennica*, 1987, 96, 157.

89.   S. S. Laev and V. D. Shteingarts, *Tetrahedron Lett.*, 1997, 38, 3765.

90.   R. D. Chambers, J. Hutchinson and W. K. R. Musgrave, *J. Chem. Soc.*, 1964, 3736.

91.   V. I. Krasnov, V. E. Platonov, I. V. Beregovaya and L. N. Shchegoleva, *Tetrahedron*, 1997, 53, 1797.

92.   J. L. Kiplinger and T. G. Richmond, *J. Chem. Soc., Chem. Commun.*, 1996, 1115.

93.   R. D. Chambers, F. G. Drakesmith and W. K. R. Musgrave., *J. Chem. Soc.*, 1965, 5045.

94.   R. D. Chambers, W. K. R. Musgrave, C. R. Sargent and F. G. Drakesmith, *Tetrahedron*, 1981, 37, 591.

95.   R. D. Chambers, M. Hole, W. K. R. Musgrave, R. A. Storey and B. Iddon, *J. Chem. Soc. C.*, 1966, 2331.

96.   C. G. Allison, R. D. Chambers, J. A. H. MacBride and W. K. R. Musgrave, *J. Fluorine Chem.*, 1971, 59.

97.   R. E. Banks, D. S. Field and R. N. Haszeldine, *J. Chem. Soc. (C)*, 1967, 1826.

98.   R. D. Chambers, J. A. H. MacBride and W. K. R. Musgrave, *J. Chem. Soc., (C)*, 1968, 2116.

99.   C. G. Allison, R. D. Chambers, J. A. H. MacBride and W. K. R. Musgrave, *J. Chem. Soc., (C),* 1970, 1023.

100. R. D. Chambers, P. A. Martin, J. S. Waterhouse and D. L. H. Williams, *J. Fluorine Chem.*, 1982, 20, 507.

101. R. D. Chambers, M. J. Seabury, D. L. H. Williams and N. Hughes, *J. Chem. Soc., Perkin Trans. 1*, 1988, 255.

102. R. D. Chambers, J. S. Waterhouse and D. L. H. Williams., *J. Chem. Soc., Perkin Trans. 2*, 1977, 585.

103. R. D. Chambers, D. Close and D. L. H. Williams, *J. Chem. Soc., Perkin Trans. 2*, 1980, 778.

104. R. D. Chambers, D. Close, W. K. R. Musgrave, J. S. Waterhouse and D. L. H. Williams, *J. Chem. Soc., Perkin Trans. 2*, 1977, 1774.

105. R. E. Banks, W. J. Jondi and A. E. Tipping, *J. Fluorine Chem.*, 1996, 99, 87.

106. R. E. Banks, W. Jondi and A. E. Tipping, *J. Chem. Soc., Chem. Commun*, 1988, 1268.

107. R. E. Banks, D. S. Field and R. N. Haszeldine, *J. Chem. Soc. (C)*, 1969, 1866.

108. R. E. Banks, R. N. Haszeldine, J. V. Latham and I. M. Young, *J. Chem. Soc.*, 1965, 594.

109. R. D. Chambers, J. Hutchinson and W. K. R. Musgrave., *J. Chem. Soc., suppl. 1*, 1964, 5634.

110. D. H. Williams and I. Fleming, *Spectroscopic methods in organic chemistry*, McGraw Hill, 1995.

111. J. W. Emsley and L. Phillips, *Prog. Nucl. Magn. Reson. Spectrosc*, 1977.

112. J. W. Emsley, L. Phillips and V. Wray, *Fluorine coupling constants*, Pergammon, 1977.

113. J. Lee and K. G. Orrell, *J. Chem. Soc*, 1965, 582.

114. H. Gunther, *NMR Spectroscopy, Basic Principles, Concepts and Applications in Organic Chemistry*, Wiley, 1992.

115. R. E. Banks, J. E. Burgess, W. M. Cheng and R. N. Haszeldine, *J. Chem. Soc*, 1965, 575.

116. S. L. Bell, R. D. Chambers, W. K. R. Musgrave and J. G. Thorpe, *J. Fluorine Chem.*, 1971, 1, 51.

117. V. Gevorgyan and E. Lukevics, *J. Chem. Soc., Chem. Commun.,1985*, 1985, 1234.

118. J. Pierre and H. Handel, *Tetrahedron Lett.*, 1974, 2317.

119. R. D. Chambers, J. A. H. MacBride and W. K. R. Musgrave, *J. Chem. Soc., (C)*, 1968, 2989.

120. R. D. Chambers, M. Hole, W. K. R. Musgrave and J. G. Thorpe, *J. Chem. Soc., (C)*, 1971, 61.

121. B. Baasner and E. Klauke, *J. Fluorine Chem.*, 1989, 45, 417.

122. R. D. Chambers, *Fluorine in Organic Chemistry*, Wiley and Sons, New York, 1973.

123. R. D. Bowden and R. Slater in U.K Patent No. 1367383, 1974.

124. C. L. Cavallaro, Y. Liu, J. Schwartz and P. Smith, *New J. Chem*, 1996, 20, 253.

125. C. A. Marques, M. Selva and P. Tundo., *J. Chem. Soc., Perkin Trans. 1*, 1993, 529.

126. T. Schach and T. Papenfuhs, in European Patent No. 0598338A1, 1994.

127. T. Schach and T. Papenfuhs, European Patent No. 0667337A1, 1995.

128. T. Schach and T. Papenfuhs, in U.S. Patent No. 5498807, 1996.

129. G. G. Yakobson, V. D. Shteingarts, N. E. Mironova and N. N. Vorozhtsov, *Zh. Obshch. Khim*, 1966, 36, 145.

130. A. L. J. Beckwith and S. H. Goh, *J. Chem. Soc., Chem. Commun*, 1983, 907.

131. S. Chung and F. Chung, *Tetrahedron Lett*, 1979, 27, 2473.

132. Y. Kamochi and T. Kudo., *Heterocycles*, 1993, 36, 2383.

133. N. Kornblum, G. D. Cooper and J. E. Taylor, *J. Am. Chem. Soc*, 1950, 72, 3013.

134. K. H. Saunders and R. L. M. Allen, *Reactions of Diazo Compounds* in *Aromatic Diazo Compounds*, Arnold, 1985.

135. F. W. Wassmundt and W. F. Kiesman, *J. Org. Chem*, 1994, 60, 196.

136. F. W. Wassmundt and W. F. Kiesman, *J. Org. Chem*, 1995, **60**, 1713.

137. S. Yasui, M. Fujii, C. Kawano, Y. Nishimura, K. Shioji and A. Ohno, *J. Chem. Soc., Perkin Trans. 1*, 1994, 177.

138. F. W. Wassmundt and W. F. Kiesman, *J. Labelled Compd. Radiopharm*, 1994, **36**, 281.

139. R. D. Chambers, J. Hutchinson and W. K. R. Musgrave., *J. Chem. Soc.*, 1965, 5040.

140. A. C. Alty, R. E. Banks, A. R. Thompson and H. S. Vellis, *J. Fluorine Chem*, 1988, **40**, 147.

141. D. F. DeTar and M. N. Turetzky, *J. Am. Chem. Soc*, 1955, **77**, 1745.

142. W. Dmowski and A. Haas, *J. Chem. Soc., Perkin Trans. 1*, 1987, 2119.

143. V. A. Petrov and D. D. DesMarteau, *J. Fluorine Chem.*, 1996, **77**, 175.

144. A. J. Adamson, W. J. Jondi and A. E. Tipping, *J. Fluorine Chem.*, 1996, **76**, 67.

145. R. E. Banks, W. J. Jondi and A. E. Tipping, *J. Fluorine Chem*, 1996, **80**, 109.

146. R. D. Chambers, M. J. Seabury and D. L. H. Williams, *J. Chem. Soc., Perkin Trans. 1*, 1988, 251.

147. G. M. Brooke, R. D. Chambers, C. J. Drury and M. J. Bower, *J. Chem. Soc. Perkin Trans. 1*, 1993, 2201.

148. B. Iddon and H. Suschitzky, in *Polychloroaromatic compounds,* ed. H. Suschitzky, Plenum, London and New York, 1974.

149. I. Collins and H. Suschitzky, *J. Chem. Soc. (C)*, 1970, 1523.

150. R. E. Banks, R. N. Hazeldine, E. Phillips and I. M. Young, *J. Chem. Soc. (C)*, 1967, 2091.

151. I. Fleming, *Frontier Orbitals and Organic Chemical Reactions,* Wiley, 1976.

152. M. Cervera, J. Marquet and X. Martin, *Tetrahedron*, 1996, **52**, 2557.

153. G. Bartoli and P. E. Todesco, *Acc. Chem. Res*, 1977, **10**, 125.

154. R. F. Heck, *J. Am. Chem. Soc*, 1968, **90**, 5518.

155. A. d. Meijere and F. E. Meyer, *Angew. Chem., Int. Ed. Engl*, 1994, **33**, 2379.

156. K. Sonogashira, in *Comprehensive Organic Synthesis,* ed. B. M. Trost, Pergammon, Oxford, 1991, vol. 3, p. 521.

157. K. Undheim and T. Benneche, *Adv. Heterocycl. Chem.*, 1995, **62**, 306.

158. Y. Zhang and J. Wen, *J. Fluorine Chem.*, 1990, **47**, 533.

159. T. X. Neenan and G. M. Whitesides, *J. Org. Chem*, 1988, **53**, 2489.

160. Q. Chen and Z. Li, *J. Chem. Soc., Perkin Trans. 1*, 1992, 2931.

161. S. Takahashi, Y. Kuroyama, K. Sonogashira and N. Hagihara, *Synthesis*, 1980, 627.

162. J. W. Tilley and S. Zawoiski, *J. Org. Chem*, 1988, **53**, 386.

163. T. Sakamoto, Y. Kondo and H. Yamanaka, *Chem. Pharm. Bull*, 1985, **33**, 626.

164. E. C. Taylor and P. S. Ray, *J. Org. Chem*, 1987, **52**, 3997.

165. K. Edo, H. Yamanaka and T. Sakamoto, *Heterocycles,* 1978, 9, 271.

166. D. E. Ames and M. I. Brohi, *J. Chem. Soc., Perkin Trans. 1,* 1980, 1384.

167. R. Diercks, J. C. Armstrong, R. Boese and K. P. C. Vollhardt, *Angew. Chem., Int. Ed. Engl,* 1995, 25, 268.

168. R. D. Chambers, F. G. Drakesmith, J. Hutchinson and W. K. R. Musgrave, *Tetrahedron Lett.,* 1967, 1705.

169. R. D. Chambers, C. A. Heaton, W. K. R. Musgrave and L. Chadwick, *J. Chem. Soc. (C),* 1969, 1700.

170. G. Queguiner, F. Marsais, V. Snieckus and J. Epsztajn, *Adv. Heterocyclic Chem.,* 1991, 52, 187.

171. P. L. Coe, A. J. Waring and T. D. Yarwood, *J. Chem. Soc., Perkin Trans. 1,* 1995, 2729.

172. F. Marsais and G. Queguiner., *Tetrahedron,* 1983, 39, 2009.

173. F. Marsais, E. Bouley and G. Queguiner, *J. Organomet. Chem,* 1979, 171, 273.

174. F. Marsais, M. Mallet, G. Queguiner and P. Pastour, *C. R. Acad. Sc. Paris,* 1972, 1535.

175. N. Ple, A. Turck, A. Heynderickx and G. Queguiner, *J. Heterocycl. Chem,* 1994, 31, 1311.

176. C. Tamborski and G. J. Moore, *J. Organomet. Chem,* 1971, 26, 153.

177. E. J. Soloski, W. E. Ward and C. Tamborski, *J. Fluorine Chem,* 1972, 2, 361.

178. B. V. Nguyen and D. J. Burton, *J. Fluorine Chem.,* 1994, 67, 205.

179. P. Sartori and H. Adelt, *J. Fluorine Chem,* 1973/74, 3, 275.

180. M. W. Wong, *J. Chem. Soc., Chem. Commun.,* 1995, 2227.

181. J. P. Agrawal, *Progress in Energy and Combustion Science,* 1997-in press,

182. G. A. Olah, R. Malhotra and S. C. Narang, *Nitration: Methods and Mechanism,* VCH, 1989.

183. F. Friedel, *Chem. Ber,* 1912, 45, 428.

184. G. A. Olah, J. A. Olah and N. A. Overchuk, *J. Org. Chem,* 1965, 30, 3373.

185. J. L. Duffy and K. K. Laali, *J. Org. Chem.,* 1991, 56, 3006.

186. H. J. D. Hertog and W. P. Combe, *Recl. Trav. Chim. Pays-Bas,* 1951, 70, 581.

187. E. Ochiai and M. O. Ishikawa, *Proc. Japan Acad,* 1942, 18, 561.

188. M. V. Ammers and H. J. D. Hertog, *Recl. Trav. Chim. Pays-Bas,* 1958, 77, 340.

189. Z. Talik, T. Talik and A. Puszynski, *Rocz. Chem,* 1965, 39, 601.

190. A. R. Katritzky and J. M. Lagowski, *Chemistry of the Heterocyclic N-Oxides,* Academic Press, 1971.

191. G. A. Olah, K. K. Laali and G. Sandford, *Proc. Natl. Acad. Sci. USA,* 1992, 89, 6670.

192. J. F. Bunnet and R. E. Zahler, *Chem. Rev,* 1951, **49**, 273.

193. R. D. Chambers, J. Hutchinson and W. K. R. Musgrave, *J. Chem. Soc. (C).,* 1966, 220.

194. F. Terrier, *Nucleophilic Aromatic Displacement: The Influence of the Nitro Group,* VCH, 1991.

195. G. Illuminati, *Adv. Heterocycl. Chem,* 1964, **3**, 285.

196. T. Talik and Z. Talik, *Rocz. Chem,* 1966, **40**, 1675.

197. T. Talik and Z. Talik, *Rocz. Chem,* 1966, **40**, 1187.

198. T. Talik and Z. Talik, *Rocz. Chem,* 1966, **40**, 1457.

199. G. D. Hartman In Merck & Co., Lansdale, in U.S Patent No. 399612, 1984.

200. G. A. Olah, Y. K. Mo and Y. Halpern, *J. Am. Chem. Soc,* 1972, **94**, 3551.

201. C. D. Johnson, *Pyridines and their Structure,* Pergammon Press, 1984.

202. H. Ritter and H. H. Licht, *J. Heterocyclic Chem,* 1995, **32**, 585.