Palladium catalysed reactions of halogenated heterocycles

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UNIVERSITY OF DURHAM

A Thesis

Entitled

PALLADIUM CATALYSED REACTIONS OF HALOGENATED HETEROCYCLES

Submitted by

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Memorandum

The work presented within this thesis was carried out at the University of Durham between October 1998 and September 2001. This thesis is the work of the author, except where acknowledged by reference and has not been submitted for any other degree. The copyright of this thesis lies solely with the author and no quotation from it should be published without prior written consent and information derived from it should be acknowledged.

Part of this work has been subject of the following:

H. Benmansour, R.D. Chambers, G. Sandford, S. Dahaoui and D.S. Yufit, Arkivoc, 2000, 27.

H. Benmansour, R.D. Chambers, P.R. Hoskin and G. Sandford, J. Fluorine Chem., in press.

H. Benmansour, R.D. Chambers, G. Sandford, G. McGowan, S. Dahaoui, D.S. Yufit and J.A.K. Howard, J. Fluorine Chem., in press.

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Abbreviations

Sulpholane	2,5-Dihydrothiophene-1,1-dioxide
DME	1,2-Dimethoxyethane
DMF	N,N-dimethylformamide
acac	acetylacetonate
dba	dibenzylidene acetone
BINAP	2,2'-bis (bisphenylphosphanyl)-1,1'-binaphtyl
DPPF	1,1'-bis(diphenylphosphino)ferrocene

Note that fluorine in the center of an aromatic ring denotes all of the hydrogen atoms have been replaced by fluorine.

Abstract

Palladium Catalysed Reactions of Halogenated Heterocycles

By H. Benmansour

The research described in this thesis can be divided into four areas:

1-The synthesis of unusually substituted halo-fluoroheterocycles has been achieved. 2,4,6-Tribromo-3,5-difluoropyridine and 4-bromo-2,3,5,6-tetrafluoropyridine were prepared from pentafluoropyridine, aluminium bromide and hydrogen bromide. Reactions with lithium halides allowed the preparation of 4-iodo-2,3,5,6-tetrafluoropyridine, 4-iodo-2,6-dibromo-3,5-difluoropyridine, 4-iodo-2,3,5,6-tetrafluoropyridine and 4-chloro-2,6-dibromo-3,5-difluoropyridine.

2-Reactions of 2,4,6-tribromo-3, 5-difluoropyridine with nucleophiles showed that selective substitution at the C-F centre can be achieved using hard (sodium ethoxide, phenoxide) nucleophiles.

3-Lithium mediated reactions of 2,4,6-tribromo-3,5-difluoropyridine allowed selective functionalisation of the 4-position; lithium-halogen exchange occurred exclusively at this position giving a stable lithium derivative, which was successfully trapped with a range of electrophiles (trimethylsilyl chloride, acid chlorides).

4- Palladium mediated couplings of 2,4,6-tribromo-3,5-difluoropyridine with a range of substituted phenylacetylenes was successful and the 2- and 6-positions were the most activated sites. Coupling with boronic acids gave the disubstituted or trisubstituted products; in the case of trisubstitution, all three positions (2-,4- and 6-) were activated towards coupling. 2,4,6-Tribromo-3,5-difluoropyridine formed a stable zinc derivative, which was coupled with iodoaromatics (iodobenzene, diiodobenzene).

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27. 3,5-difluoro-2,4,6-tris[2-(4-bromophenyl)ethynyl]pyridine **(38)**

28. 2,6-bis[2-(4-chlorophenyl)ethynyl]-4-bromo-3,5-difluoropyridine **(39)**

29. 2-(2-chlorophenyl)ethynyl]-4-bromo-3,5-difluoropyridine **(40)**

30. 4,6-dibromo-6-[2-(2-chlorophenyl)-1-ethynyl]-3,5-difluoropyridine **(41)**

31. 1-(2-{4-bromo-3, 5-difluoro-6- [2-(4- H methoxyphenyl) ethynyl](2-pyridyl)} ethynyl)-4-methoxybenzene **(42)**

32. 4-[4,6-bis (3,3-dimethyl-3-silabut-1-ynyl)-3,5-difluoro (2-pyridyl)]-2,2-dimethyl-2-silabut-3-yne **(43)**

33. 3,5-difluoro-2,4,6-tris(2-phenylethynyl)pyridine **(45)**

34. 3,5-difluoro-(2,4,6-triphenyl)pyridine **(46)**

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Appendix B: Mass Spectra

1.: 2,4,6-tribromo-3,5-difluoropyridine **(1)**

2. 2,6-dibromo-3,5-difluoro-4-chloropyridine **(4)**

3. 2,6-dibromo-3,5,-difluoro-4-iodopyridine **(5)**

4. 2,3,5,6-tetrafluoro-4-iodopyridine **(6)**

5. 2,4,6-tribromo-5-fluoro-3-methoxypyridine **(7)** and **(58)**

6. 2,4,6-tribromo-5-fluoro-3-ethoxypyridine **(8)**

7. 2,4,6-tribromo-3,5-diethoxypyridine **(9)**

8. 2,4,6-tribromo-3,5-diphenoxypyridine**(13)**

9. 4-bromo-3,5-difluoro-2,6-diphenoxypyridine **(17)**

10. 2,3,5,6-tetrafluoro-4-phenoxypyridine **(18)**

11. 3,5,6-trifluoro-2,4-diphenoxypyridine **(19)**

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42. 1,4-diphenyl buta-1,3-diyne

Appendix D: Crystallographic Data

Crystal data, bond lengths and atomic coordinates are given for the X ray structures. Angles, anisotropic displacement parameters and hydrogen coordinates are available on the Cambridge Structural Database (CDS).

List of X Ray structures:

1. 2,4,6-tribromo-3,5-difluoropyridine **(1)**

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CHAPTER I

Synthesis of Fluorine Substituted Nitrogen Aromatic Heterocycles

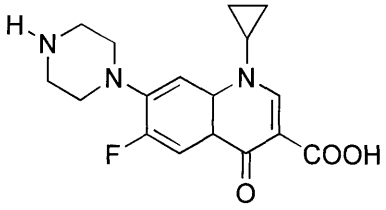
I. 1 General Introduction

Fluorinated compounds have found numerous applications in very diverse areas: agrochemicals, anaesthetics, polymers and high performance materials, the dye industries, coatings, fine chemicals and the pharmaceutical industry. Perfluorinated compounds show exceptionally high chemical and thermal stabilities; in fact liquid inert systems are widely used as refrigerants such as HFC's (in replacement of harmful CFC'S banned since the Montreal protocol); whereas higher boiling inert fluids are able to absorb large quantities of oxygen and can be used as oxygen carriers[1].

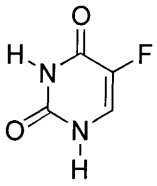
Fluorinated polymers have found use in the aerospace industry[2] as seals, insulating devices and also as lubricants. PTFE (Polytetrafluoroethylene) was accidentally discovered by R. J. Plunkett, a scientist at Du Pont, who found that the contents of a cylinder of tetrafluoroethylene has polymerised[3], obtaining one of the most thermally and chemically resistant perfluorinated polymers; PTFE is now used in gaskets, waterproof clothing, and non stick coating. The surface properties of perfluorinated compounds includes their ability to impart oil repellency to a surface and this property has been used in weatherproof paints, and many items are now protected with a layer of fluorocarbon (e.g. Scotchgard treatment).

Great advances have been made in anaesthesia[4] by the introduction of fluorinated compounds (such as Fluothan $CF_3CHBrCl$), which are safer and easier to handle than the previously used ether and chloroform.

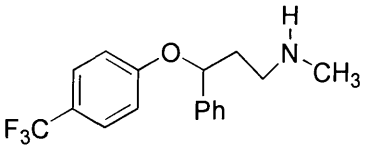
Many fluorinated drugs have been developed since it was found first in 1954 that introducing a fluorine atom in steroids, subsequently used as anti-inflammatory drugs, enhanced the activity compared to the parent non-fluorinated compound. Since then successful fluorinated drugs have been synthesised as antibiotics[5] (Ciprofloxacin), antifungals, antiviral agents, for the treatment of breast cancer (5-Fluorouracil) and as antidepressants (Prozac).



Ciproflaxacin



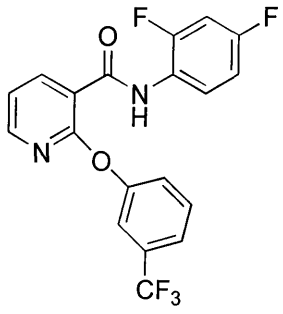
5-fluoro-uracil



Prozac (Eli Lilley)

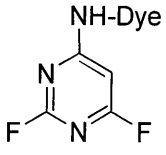
The introduction of fluorine has shown to increase binding to and thus inhibition of the enzyme[6] activity, reducing the rate of metabolism. Fluorine might also facilitate the transport across lipid membranes, since fluorinated compounds can have an increased lipid solubility compared to their hydrocarbon analogues.

Fluorinated agrochemicals are widely used for plant protection as herbicides, fungicides and insecticides; in fact half of the molecules undergoing field trials contain fluorine. For example, Difluphenican is a herbicide active at low doses (65-250 g/Ha) with high selectivity and long action and it acts by inhibiting the biosynthesis of photo pigments, which disrupt the biosynthesis of chlorophyll[5].



Difluphenican

Fluorinated compounds are also used in the dye industry and the liquid crystals industry, and continuous research in developing new bioactive molecules will certainly impart a more and more important place to fluorinated molecules in general use.



Fiber reactive dye

Fluorine is the 13th element in order of abundance in crustal rocks of the earth[7]. Fluorine is obtained from three mineral deposits CaF_2 (Fluorspar), Na_3AlF_3 (Cryolite) and $Ca_5(PO_4)_3F$ (Flouroaspatite) which is the source of the largest amount of fluorine in the earth's crust. In spite of the vast abundance of fluorine, only a handful of naturally occurring molecules contain carbon fluorine bonds. D. B. Harper and D. O'Hagan have listed them in a recent review and, it appears that such molecules are found in a few tropical plants as *Dichapetalum Cymosum* which accumulates the toxic fluoroacetic acid, and some insects such as the moth *Nygmia pseudoconspersa* which concentrates fluoride in its wings.

In consequence, the synthesis of C-F bonds is entirely due to human research. Scheele first in 1717 demonstrated that sulphuric acid liberates a peculiar acid from the metallurgical flux fluorspar which destroys glass. In 1835, Dumas and Peligot synthesised the first organic fluoride, methyl fluoride, by heating dimethyl sulfate with potassium fluoride and this was followed by the synthesis of fluorobenzene in 1883 by Paterno and Oliveri.

In 1886, Moissan produced elemental fluorine for the first time by electrolysing a cooled solution of potassium fluoride in anhydrous hydrogen fluoride in a platinum iridium cell. Later, Swarts (1898) introduced antimony fluoride as a fluorinating agent, which was used to synthesise the first trifluroromethyl-containing compound. His methodology was applied by Midgley and Henne to prepare the coolants fluoromethane and fluoroethane.

The first perfluoroaromatic compound was obtained by Desirant in 1955 who synthesised hexafluorobenzene. It was during the Second World War II[8], within the framework of the Manhattan Project, that the large production of perfluorocarbons through direct or indirect fluorination (via CoF_3) was developed. These perfluorocarbons had the unique properties to resist attack of the corrosive UF_6 used for the preparation of uranium-enriched samples of ^{235}U. After the extensive use of perfluorocarbon materials in the Manhattan Project, organofluorine chemistry attracted the interest of many research groups and industries.

Fluorine possesses particular features that are listed below. These features make the chemistry associated with it display particular mechanistic and reactivity trends.

	H	F	Cl
Electronic configuration	$1s^1$	$2s^22p^5$	$3s^23p^53d^0$
Electronegativity (Pauling)	2.1	4.0	3.0
Ionisation energy (Kcal/gatom)	315.0	403.3	300.3
Electron affinity (Kcal/g mol)	17.8	83.5	87.3
Bond energies C-X (Kcal/g mol)	99.5	116.0	78.0
Bond lengths C-X (Å) in CX_4	1.10	1.32	1.77

- Fluorine has the highest electronegativity of all elements, inducing the strong polarisation of a C-F bond, which influences greatly the reactivity of functional groups,
- Fluorine has three pairs of unshared electrons not involved in any bonding; these pairs can act as a protective sheath that shields the carbon skeleton from chemical attack and accounts for the increased volatility of perfluorocarbons relative to their hydrocarbon analogues,
- High strength of the C-F bond, which imparts some saturated fluorinated compounds great thermal stability,
- Van der Waal's radius of fluorine is close to that of hydrogen and so fluorine introduces only small steric and geometric perturbation relative to the hydrocarbon counterpart.

The aim of this project is to synthesise mixed halofluoroheterocycles, essentially bromofluoroheterocycles, using the different methods available from fluorinated heterocycles. The study of the reactivity of these bromofluoroheterocycles, and the selective functionalisation at the C-F and C-Br centres will be investigated using nucleophilic substitution and to a larger extent metal mediated reactions. Palladium mediated reactions in particular will be more thoroughly investigated using the ring C-Br bonds available.

I. 2 Synthesis of Fluorine Substituted Nitrogen Aromatic Heterocycles

A large number of fluoroheterocycles are now available, ranging from monofluoro-substituted to fully fluorinated heterocycles. Their preparation is essentially dependant on the availability of precursors having certain functional groups such as chloro and amino groups, which may be replaced by fluorine. The various synthetic methods for the preparation of polyfluoroaromatics are generally applicable to polyfluoroheteroaromatics.

The principal methods available fall into the following distinct categories and will be described in the following section:

- Replacement of Halogens by Fluorine,
- Replacement of Hydrogen by Fluorine,
- Replacement of other groups by Fluorine,
- The building block approach.

I. 2. 1 Replacement of Halogens by Fluorine

I. 2. 1. a The Halogen Exchange (HALEX) reaction

The Halex reaction is one of the most useful and industrially[4] used methods for the synthesis of fluoroaromatics and fluoroheterocycles. This method consists of the displacement of a heavier halogen (iodine, bromine, chlorine) from a ring carbon by fluorine using fluoride ion. The fluoride ion source is an alkali metal fluoride and the order of reactivity is as follows, according to their lattice energy:

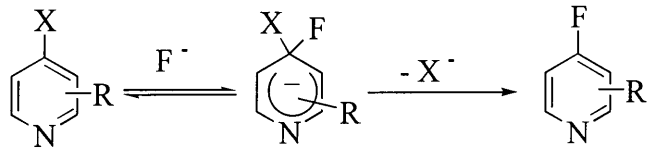
$$CsF > RbF > KF > NaF > LiF$$

Caesium fluoride, the most effective, is too expensive to be used in industrial processes and sodium fluoride can only be used with very activated nitrogen heterocycles[9]. Therefore, in practice potassium fluoride is the most commonly used for its best compromise between cost and reactivity.

In aromatic systems, the leaving group has to be activated by electron withdrawing groups *ortho* or *para* to the halogen being exchanged such as $-NO_2$, -CN, -CHO groups activating through -I and -M effects, or $-CF_3$ and halogens activating through –I effects (in that case more drastic reaction conditions are needed).

The reaction proceeds via the formation of an anionic Meisenheimer intermediate; chlorine is the most easily displaced halogen since there is no bond breaking involved in the rate limiting step; we can therefore use cheap chlorinated substrates for this reaction.

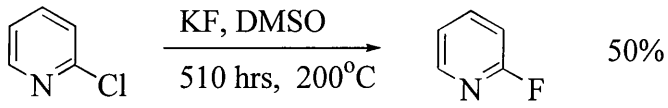
Reactions with chloropyridines are readily performed since ring nitrogen activates the ring to nucleophilic attack and stabilises the Meisenheimer complex:



X: Cl, Br, I

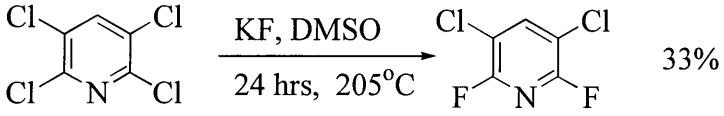
R: EWG

Finger[10] converted 2-chloropyridine to 2-fluoropyridine in DMSO after prolonged heating:

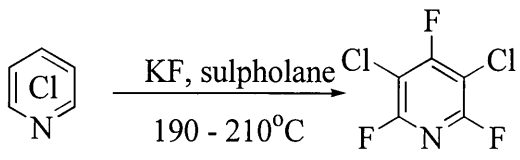


The necessity of using polar aprotic solvents such as DMF, sulpholane or NMP was established; they are able to dissolve alkali metal fluorides sufficiently by acting as electron pair donors to the alkali metal cation, with little solvation of the fluoride ion.

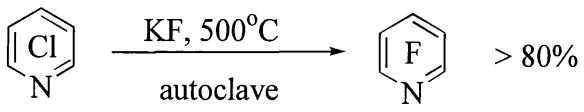
More activated systems reacted well such as 2,3,5,6-tetrachloropyridine gave 3,5-dichloro-2,6-difluoropyridine in shorter reaction times:



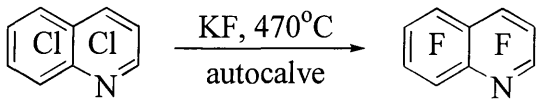
This technique has been extended to fully chlorinated heteroaromatics[11]:



If higher reaction temperatures are necessary the solvent can be left out; pentachloropyridine is converted to pentafluoropyridine under these conditions in good yield [11,4]:



A large number of other heterocycles[12] are fully fluorinated using the Halex process, for example heptafluoroquinoline[13] is prepared from heptachloroquinoline:



The main problem with this synthetic method is the relatively poor solubility of potassium fluoride in the solvents used; improving its performance has been achieved by different techniques[4]:

The use of spray dried KF: The poorly soluble KCl formed during the reaction deposits on KF particles (surface $0.1 m^2/g$) and diminishes its reactivity. Increasing the surface area of the KF by using spray dried KF (surface $1.5 m^2/g$) reduces this undesirable effect.

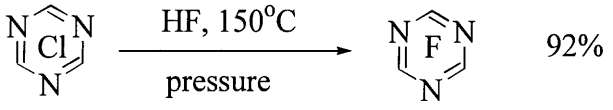
The use of phase transfer catalysts: Addition of quaternary ammonium and phsophonium salts increases the mobility of F^- from the solid phase to the solution phase. Cetyltrimethylammonium bromide $[(CH_3)_3C_6H_5N^+Br^-]$ is effective up to decomposition temperature (150°C) whereas tetraphenylphosphonium bromide $[(C_6H_5)_4P^+Br^-]$ was more effective at reaction temperatures up to 220°C.

The use of crown ethers: They provide a better fluoride source by complexing the potassium cation; this technique found application in the laboratory, but is too expensive to be used in industrial processes.

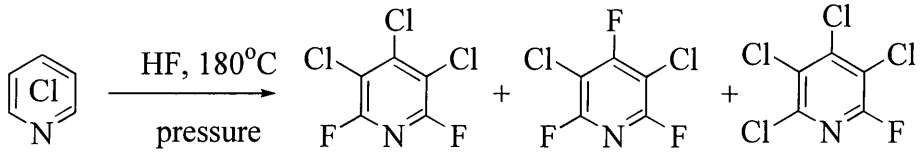
Complexes of tertiary amines with hydrogen fluoride or 'Proton Sponge' hydrofluoride can be valuable sources of fluoride ion for the Halex exchange. They have the advantages of being recyclable and usable in homogeneous conditions.

I. 2. 1. b Using Hydrogen Fluoride

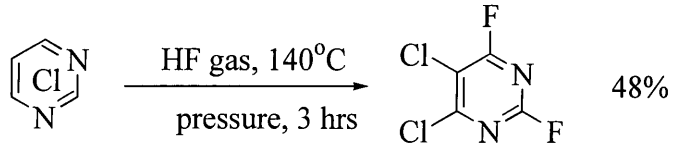
Only a few examples of fluorination of heterocycles using HF are available, because of the necessity of using very activated substrates and the difficulty to handle hydrogen fluoride. However, trichloropyrazine was converted to trifluoropyrazine in high yield:



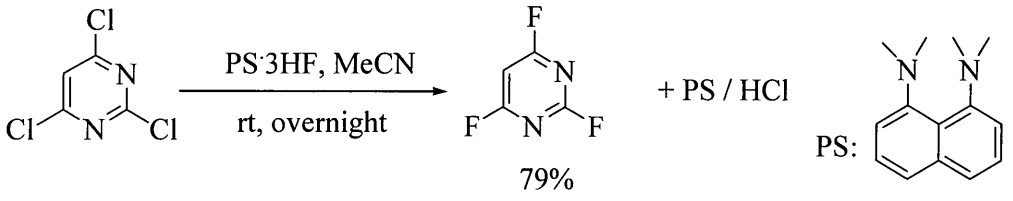
Pentachloropyridine afforded a mixture of polyfluoropyridines:



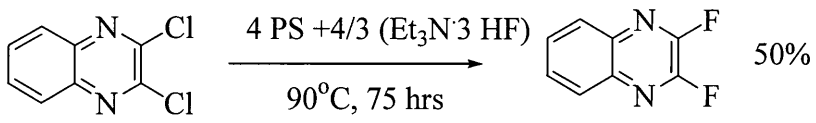
Acceptable yields were obtained with tetrachloropyrimidine by substitution at the most activated 2- and 4-positions[9,14]:



Chambers[15] showed that this fluoride source was useful for the fluorination of trichloropyrimidine at room temperature:

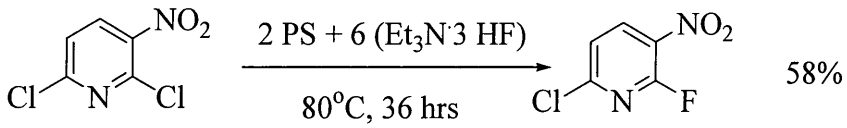


Later, other workers[16] generated this fluorination reagent in situ in the presence of triethylamine and chlorobenzodiazines were partially or completely fluorinated:



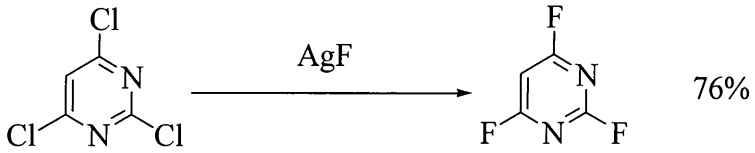
The yields obtained are higher than with the procedure where the fluoride ion source is synthesised prior to reaction.

Among pyridines, only chloronitropyridines underwent the exchange and the yields were lower than when potassium fluoride is used (76%):



I. 2. 1. c Use of metal fluorides

Metal fluorides were used to exchange chlorine for fluorine; 2,4,6-trichloropyrimidine reacted with silver fluoride to afford 2,4,6-trifluoropyrimidine[14] in good yield:



Using antimony pentafluoride, which acts as a Lewis acid, afforded good yields of difluorotriazines from trichlorotriazines[14]. When the less reactive antimony trifluoride was activated by bromine, chloride or antimony pentachloride, similar results were obtained[17].

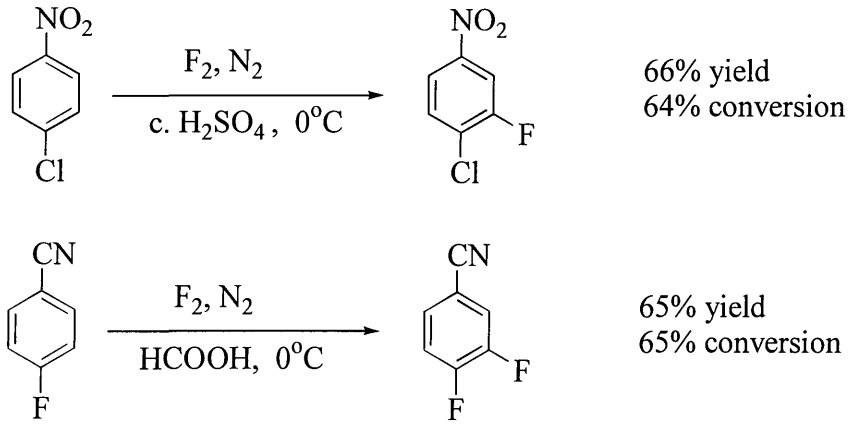
I. 2. 2 Replacement of hydrogen by fluorine

I. 2. 2. a Direct fluorination with F_2 and related reagents

I. 2. 2. a. i Direct fluorination with F_2

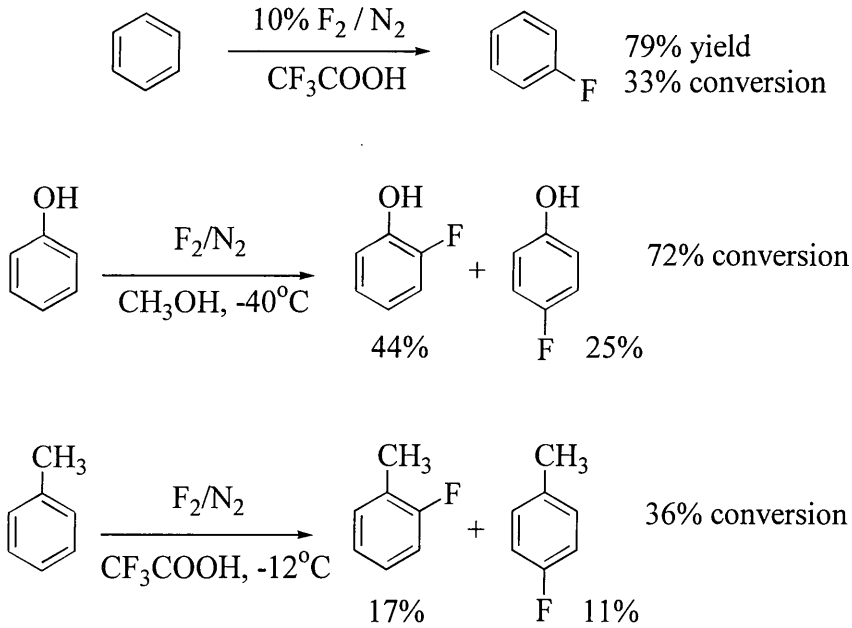
Reactions of elemental fluorine were believed for a long time to be hard to control and complicated to perform and therefore, not synthetically very useful. Nowadays, it is possible to fluorinate a range of aromatics and few heterocyclic compounds under controlled conditions, and in good yields.

A number of substituted aromatics have been selectively fluorinated in good yields in concentrated sulphuric acid or formic acid[18].

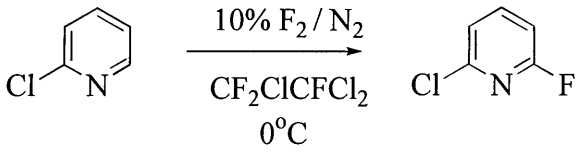


Fluorination could occur by either a single electron transfer mechanism or an electrophilic substitution process; using the above solvent favours the electrophilic process, which interacts with fluorine and makes it more susceptible to nucleophilic attack.

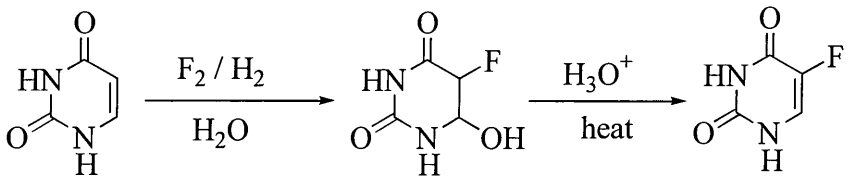
Fluorination of benzene, phenol and toluene afforded a mixture of *ortho* and *para* fluoroaromatics[19] but the selectivity was never very high:



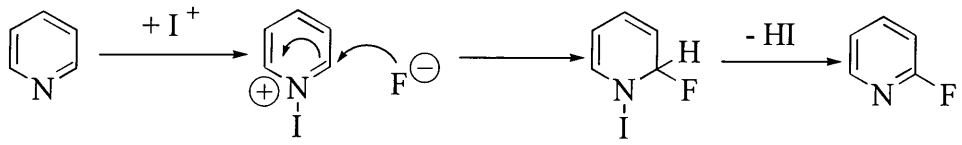
Substituted pyridines reacted with fluorine diluted in nitrogen to give 2-fluoro pyridines derivatives in acceptable yields[20]:



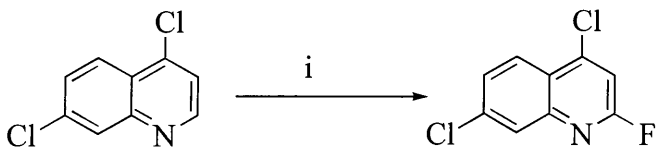
The products formed in the fluorination of 2-chloropyridine are consistent with attack by an electrophilic reagent at the most electron rich C=N bond. The compound 5-fluoroacil is synthesised on industrial scale using F_2:



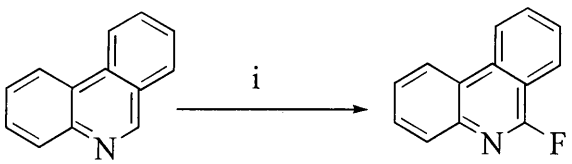
Several heterocycles where successfully fluorinated using F_2 assisted by iodine through the following mechanism[18]:



Good yields of 2-fluoroquinoline derivatives were obtained:



69% conversion
88% yield

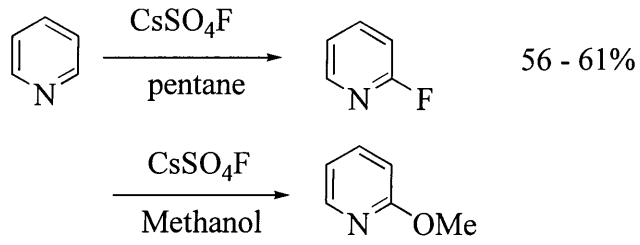


53% conversion
67% yield

i: F_2, I_2, Et_3N, $CF_2ClCFCl_2$, rt.

I. 2. 2. a. ii Using caesium fluoroxysulphate $CsSO_4F$

2-Fluoropyridine[21] was obtained in acceptable yields from pyridine under mild conditions in non-polar solvents using caesium fluoroxysulphate but repeating the reaction in methanol afforded 2-methoxypyridine only.

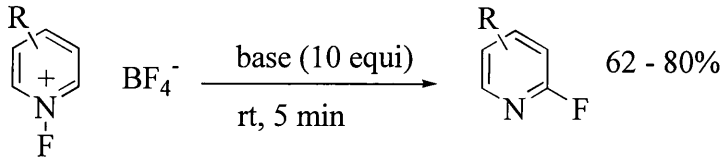


I. 2. 2. a. iii Using fluoroxytrifluoromethane CF_3OF

This reagent is a useful for the synthesis of partially fluorinated compounds, and has been very widely used in the electrophilic fluorination of aromatics[12]; it has also allowed the fluorination of uracil leading to 5-fluorouracil[22] in good yields.

I. 2. 2. b Using N-fluoropyridinium salts

Umemoto[23] prepared 2-fluoropyridine via base induced decomposition of N-fluoropyridinium salts with BF_4, SbF_5 or PF_6 counter ion in triethylamine:



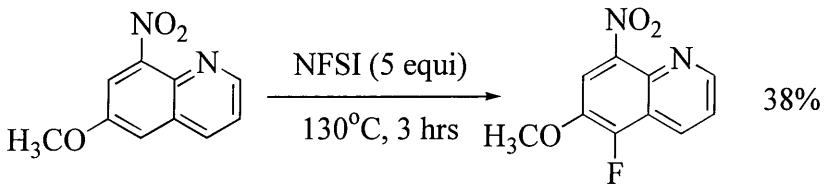
R: methyl, dimethyl, methoxy, chloro, dichloro

This method does not require the presence of activating groups or drastic reaction conditions and is believed to proceed via a carbene mechanism.

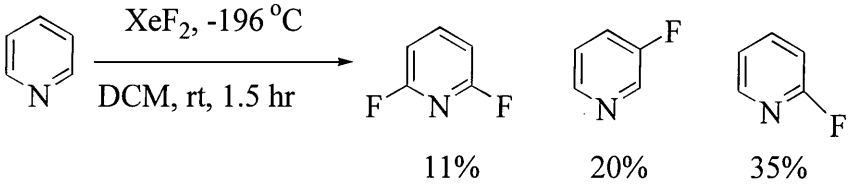
I. 2. 2. c Use of other reagents

A wide range of new F^+ reagents are now available such as Selectfluor® (1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis (tetrafluoroborate)) and new N-fluoropyridinium salt reagents, but they are mainly used in the direct fluorination of aromatics.

However, the synthesis of a fluoroquinoline derivative[24] has been recently reported via direct fluorination with NFSI (N-fluorobenzenesulfonimide) in moderate yields:

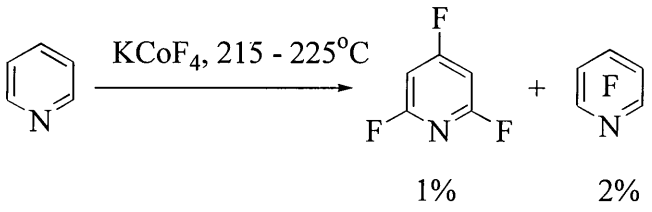


Using xenon difluoride XeF_2: Zupan and co-workers[25] have extensively studied the fluorination of dibenzofuran using xenon difluoride, which yielded a mixture of 1-, 2- and 3-fluorobenzofuran in moderate yields (30-40%). Fluorination of pyridine using XeF_2 occurred under mild conditions, affording a mixture of 2-, 3-fluoropyridine and 2,6-difluoropyridine[26]. This result was not expected since pyridine is relatively deactivated compared to benzene, which required the addition of a catalyst (HF, $BF_3.OEt_2$...)[27].



The product distribution cannot be attributed to a simple electrophilic process and the amount of 3-fluoropyridine formed is not consistent with nucleophilic substitution. Zupan has previously proposed that the similar product distribution obtained during the fluorination of dibenzofuran can be explained by a competitive process between ionic attack leading to 2-fluorobenzofuran and the formation of an ion radical intermediate affording 3-fluorobenzofuran[25].

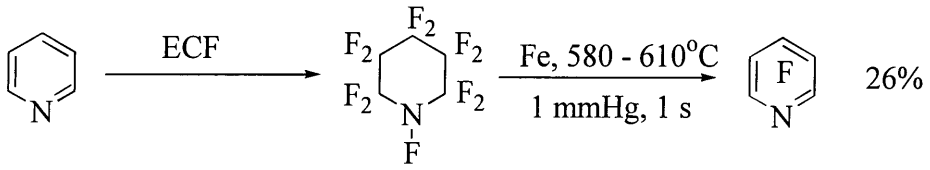
Using potassium tetrafluorocobalt ($KCoF_4$): The fluorination of pyridine with $KCoF_4$ afforded a complex mixture where polyfluoropyridines represent less than 10% of the composition of the mixture[28]:



Most of the remaining products consist of fluorinated imines resulting from ring opening reactions. A cation-radical mechanism[29] has been proposed in the early stages of the reaction producing fluoropyridines followed by rearrangement and ring openings. When the reaction was repeated using cobalt trifluoride CoF_3, widely used in the fluorination of aromatics[14], fewer products were recovered indicating a much greater decomposition.

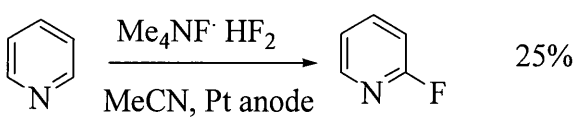
I. 2. 2. d Saturation–Rearomatisation

This process involving formation of fully fluorinated-saturated fluorocarbons followed by defluorination (over iron for example) to afford the unsaturated compound has been successful for the synthesis of aromatics[13]. However, defluorination of perfluoropiperidine gave poor yields of pentafluoropyridine[12]:



I. 2. 2. e Electrochemical fluorination

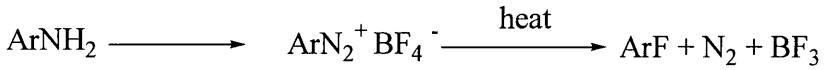
Pyridine was converted into 2-fluoropyridine using dilute tetramethylammonium dihydrogen trifluoride at a platinum anode[30]. The conversion and yields were relatively low (31% and 25% respectively); this yield is, however, greater than that obtained with pyridine / HF system.



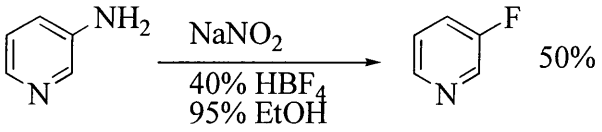
I. 2. 3 Replacement of other groups by fluorine

I. 2. 3. a Diazotization reactions: The Balz -Schiemann process

A diazonium salt formed from an aromatic or heteroaromatic amine is decomposed in the presence of a fluoride ion source:

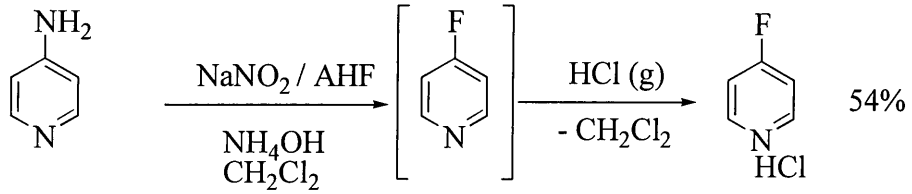


2-, 3- and 4-aminopyridine are converted to 2-,3- and 4-fluoropyridine respectively:

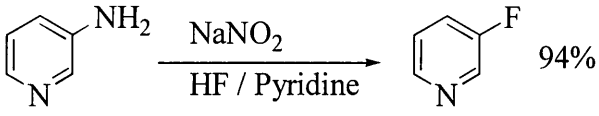


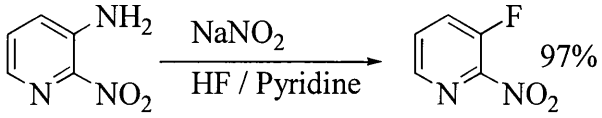
The reaction yields are improved by the addition of other fluoride ion sources such as PF_6^-, SiF_6^- and F^- (from anhydrous HF), the last affording the best results[31]; the low yields obtained by the traditional diazotisation stem from the necessity of isolating the diazonium salt but using HF makes this unnecessary.

4-Fluoropyridine, which is unstable and undergoes facile self-condensation, has been isolated as the hydrochloride salt[31] from fluorodiazotization of 4-aminopyridine:

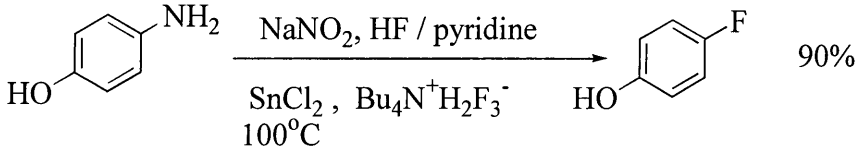


The use of pyridine as a solvent afforded even better results[32 33]:





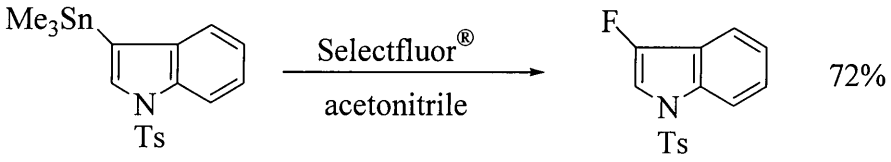
In general, aromatics bearing *ortho* and *para* polar groups afforded poor yields and low selectivity when HF/pyridine alone was used. Sasaki[34] postulated that the addition of a reductant (such as $SnCl_2$) would promote a homolytic cleavage of the diazonium salt under mild conditions. By this method high yields and great selectivity of 4-fluorophenol has been obtained from 4-aminophenol:



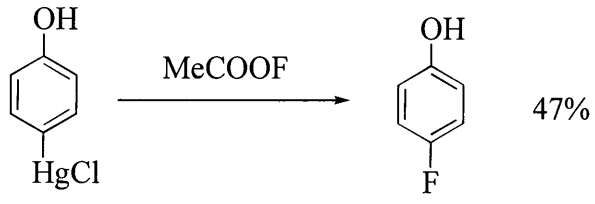
I. 2. 3. b Fluorodemetallation

The stabilising *ipso* directing effect of an organometallic can be used with electrophilic reagents to specifically fluorinate a number of activated aromatics; this method is generally used for isotope labelling.

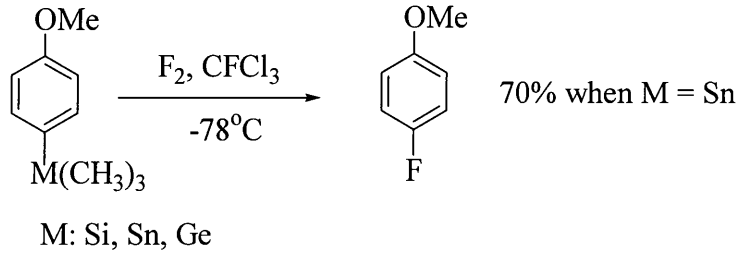
Using Selectfluor® in the synthesis of fluoroindoles[35] from trimethylstannylindole:



Using acetyl hypofluorite in the synthesis of substituted fluorobenzenes from their mercury[36] derivatives:



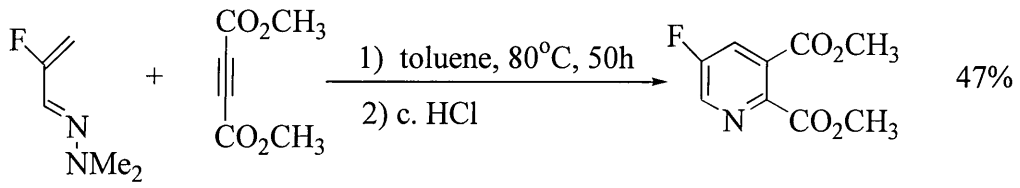
Using elemental fluorine from tin, germanium and silicon[37] aromatic derivatives:



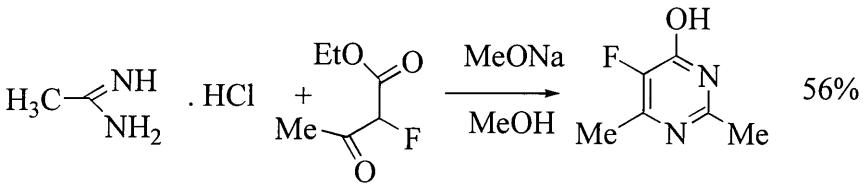
I. 2. 4 The building block approach

I. 2. 4. a From fluorinated acyclic precursors

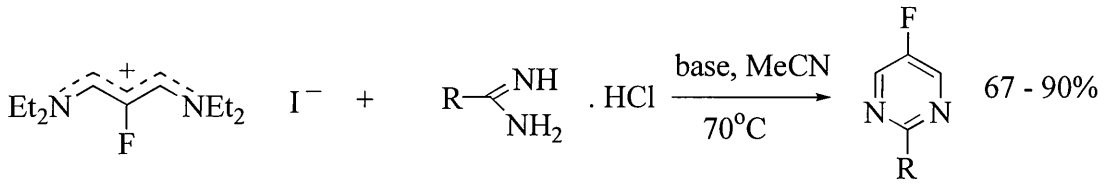
3-Fluoropyridine was prepared via the Diels-Alder condensation of a fluorinated hydrazone and dimethyl acetylenedicarboxylate[38]:



A large number of fluoropyrimidines have been prepared using a 'building block' approach, generally by reacting a 1,3-dicarbonyl with bifunctional nitrogen nucleophiles[39]. 5-Substituted pyrimidines may be prepared by reacting ethyl-γ-fluoroacetate with amidine or gaunidine derivatives:

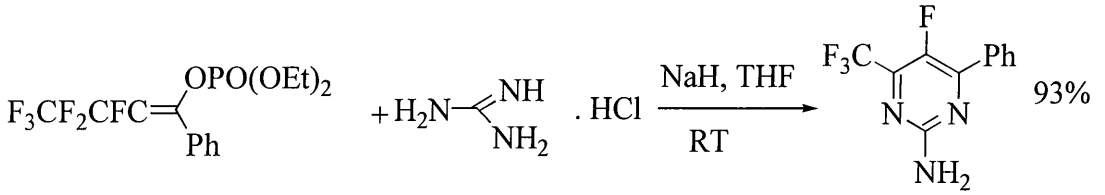


A similar synthesis afforded a range of 2-substituted-5-fluoropyrimidines using 1,1,5,5-tetraethyl-3-fluoro-1,5-diazapentadienium iodide[40] generated in situ:



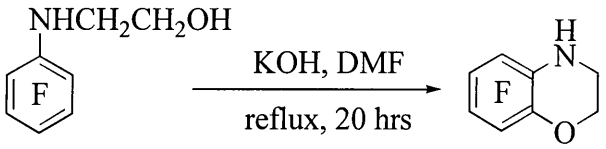
R: Ph, Me, H, NH_2, NHMe

The use of 1-F-substituted alkenyl phosphate precursors synthesised from F-alkyl ketones also provided a range of disubstituted fluoropyrimidines[41]:

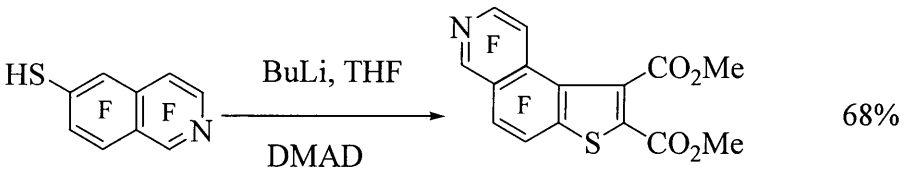


I. 2. 4. b Cyclisation

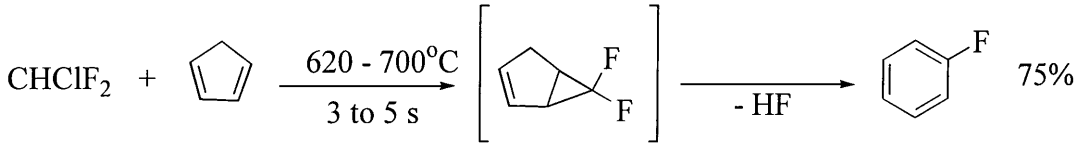
The first example of intramolecular cyclisation in polyfluoroaromatics was obtained by Burdon[42] by heating ethylene glycol and hexafluorobenzene; the same route using 2-aminoethanol gave 5,6,7,8-tetrafluoro-2,3-dihydro-1,4-benzoxazine:



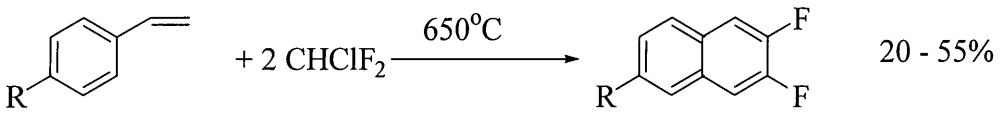
Later, the cyclisation of a thiol substituted fluoroquinoline, using BuLi and dimethylacetylene dicarboxylate (DMAD), was achieved[43]:



Fluorocarbenes are also useful to synthesise fluoroaromatics; difluorocarbenes react with cyclopentadiene to give fluoroaromatics and derivatives of cyclopentadiene afforded substituted fluorobenzenes[44]:

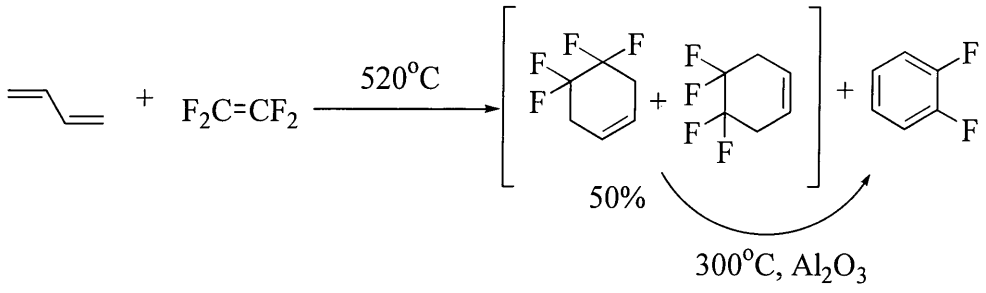


This methodology was also efficient to synthesise difluoronaphthalenes:



R: H, CH_3, F, Cl

The thermal cycloaddition of polyfluorinated olefins and 1,3-dienes gave difluorobenzenes in moderate yields:



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CHAPTER II

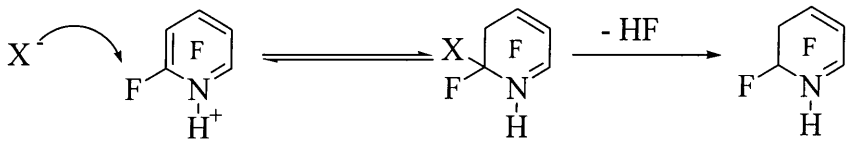
Synthesis and nucleophilic substitution reactions of halofluoroheterocycles

II.1 Synthesis of halofluoroheterocycles

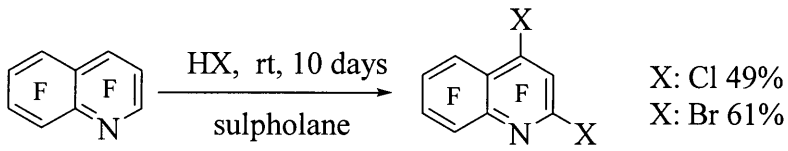
There are two methodologies available for the replacement of fluorine by other halogens: using acid halides and using metal halides.

II.1.1 Using Acid Halides

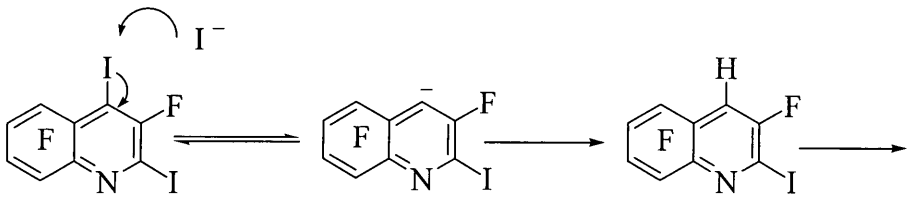
Early work on hexafluoroquinolin-2-ol showed that N-perfluoroheterocycles, which are in general relatively weak bases, could be further activated to nucleophilic attack by protonation of the ring nitrogen by coordination to a Lewis or Bronsted acid. *Ortho* attack is favoured on the protonated species; this was attributed to the large base weakening effect of the fluorine at that position. The reaction proceeds through the following path:



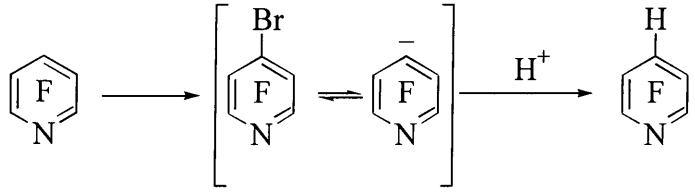
Heptafluoroquinoline[1] reacted in goods yields with HCl and HBr to give the substitution products at the 2- and 4-position.



Reaction with hydrogen iodide afforded 3,5,6,7,8-pentafluoroquinoline in addition to 2,4-diiodopentafluoroquinoline; the formation of the dihydroadduct was explained by the attack of iodine on 2,4-diiodohexafluoroquinoline compound and subsequent formation of the hydro compound.

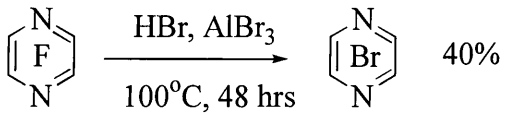


With pentafluoropyridine[1], no reaction occurred with HI and poor yields of the bromo and chloro derivatives were obtained and when the temperature was raised only 2,3,5,6-tetrafluoropyridine was formed presumably via the pyridyl anion.

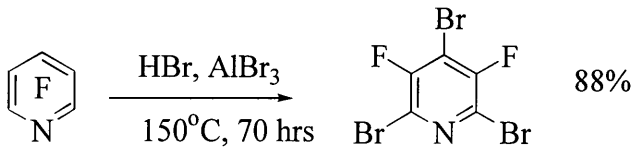


In pentafluoropyridine, attack occurs at the 4-position first because pentafluoropyridine, a weak base (pKa 5.23), is weakly protonated.

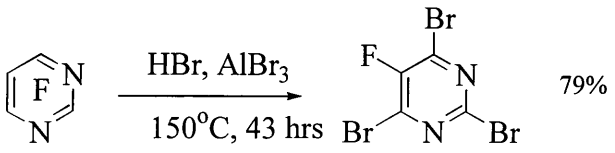
Tetrafluoropyrazine[2], a weaker base, was successfully brominated using a mixture of HBr and $AlBr_3$, which produces the strong brominating agent $H^+AlBr_4^-$:



This methodology was extended to pentafluoropyridine[3] and good yields of 2,4,6-tribromo-3,5-difluoropyridine were obtained:

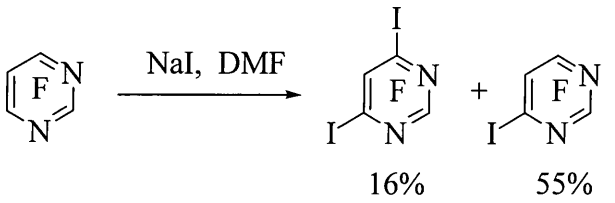


Tetrafluoropyrimidine also reacted readily with $H^+AlBr_4^-$ giving 2,4,6-tribromo-5-fluorpyrimidine:

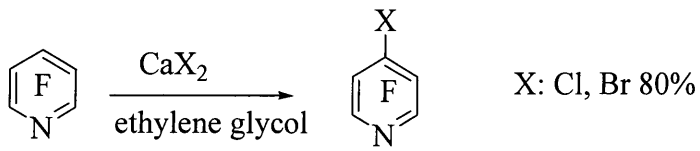


II. 1. 2 Using Metal Halides

Despite their weak nucleophilicity, metal halides (for a review see [4]) react with polyfluoroheterocycles, and metal iodides are the strongest halogenating reagents. Tetrafluoropyrimidine reacts with sodium iodide in DMF to afford iodotetrafluoropyrimidine in 55% yield:



Pentafluoropyridine reacts with $CaBr_2$ and $CaCl_2$ to afford 4-halotetrafluoropyridines:



II. 1. 3 Conclusion

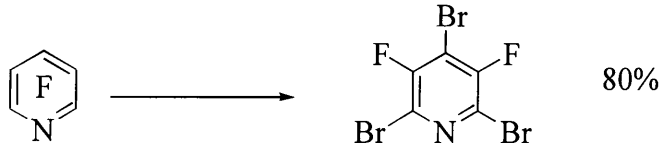
As shown by the review above, there are many methods available for the synthesis of fluoroheterocycles and mixed halofluoroheterocycles, we will therefore use these available methods for the synthesis of mixed bromofluoroheterocycles that are interesting substrates for the selective functionnalisation of the pyridine ring.

II. 2 Synthesis of mixed halofluoroheterocycles derived from pentafluoropyridine

With the aim of synthesising and studying the reactivity of halofluoroheterocycles, we decided to investigate an efficient methodology for the synthesis of such compounds, using the different methods provided by the literature.

II. 2. 1 Using haloacids

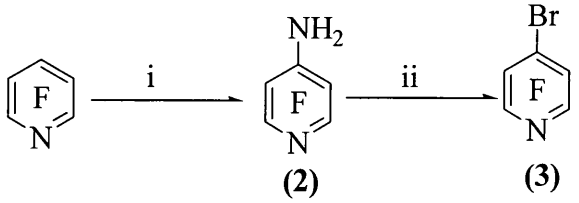
The use of the super acid $H^+AlBr_4^-$ is a suitable route for the large scale synthesis of 2,4,6-tribromo-3,5-difluoropyridine, which was subsequently used as a model compound to investigate the chemistry of bromofluoroheterocycles.



(1)

Reagents and conditions: 3 HBr, 2 $AlBr_3$, 150°C, 62 hrs.

Among other bromofluoroheterocycles of interest, 4-bromotetrafluoropyridine is a potentially useful substrate. The synthesis of 4-bromotetrafluoropyridine was previously achieved[5] from decomposition of the diazonium salt of 4-aminotetrafluoropyridine; this reaction gave moderate yields in a two steps process. Repeating the reaction afforded 4-bromotetrafluoropyridine (55% GC yield) and no further purification was attempted; the product was identified by comparison with an authentic sample.



(2) **(3)**

Conditions and reagents: i NH_3 aq, rt, 30 mn.
ii H_3PO_4 (50% i water), 0°C, 30 mn; $NaNO_2$, 15 mn;
CuBr in hydrobromic acid, 0°C, 15mn; warm rt.

Using the appropriate conditions (excess of pentafluoropyridine and aluminium bromide relative to HBr) in an autoclave during a relatively short reaction time, the product **(3)** was isolated by distillation or vacuum transfer in 54% conversion and 91% yield.

(3)

54% conversion
91% yield

Conditions and reagents: $AlBr_3$ 1.4, HBr 0.8, 150 °C, 20 hrs.

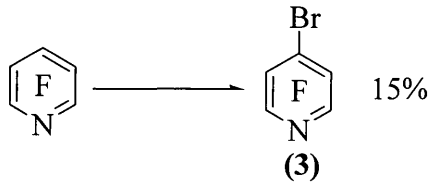
Using an excess of HBr afforded 2,4,6-tribromo-3,5-difluoropyridine. However, a 1:1 ratio of HBr and $AlBr_3$ with an excess of pentafluoropyridine afforded a mixture of 2,4,6-tribromo-3,5-difluoropyridine and 4-bromotetrafluoropyridine. Scaling up the reaction (40 g pentafluoropyridine) and increasing the reaction time (to 48 hrs) lowered the yield of 4-bromotetrafluoropyridine formed.

II. 2. 2 Using Lithium halides

II. 2. 2. a Synthesis of 4-bromotetrafluoropyridine using LiBr

A patent[6] describes a process for the bromination of perfluoroaromatic compounds such as octafluoronaphthalene using LiBr as nucleophilic bromide source in a polar aprotic solvent giving good results (e.g. 55% yield of bromoheptafluoronaphthalene).

The same methodology was applied to pentafluoropyridine and afforded a complex mixture, containing only low yields (15%) of 4-bromotetrafluoropyridine and traces of 2,4,6-tribromo-3,5-difluoropyridine. The remainder consisted of unidentified products of higher molecular weights and attempted purification was inefficient. However, 4-bromotetrafluoropyridine could be easily recovered in low yield by distillation.



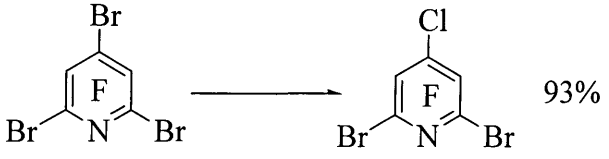
(3)

Conditions and reagents: LiBr 1 equi, sulpholane, 225 °C, 24 hr, Carius tube.

Repeating the reaction using a large excess of LiBr led to the formation of a black solid only slightly soluble in dichloromethane.

II. 2. 2. b Using LiCl with 2,4,6-tribromo-3,5-difluoropyridine

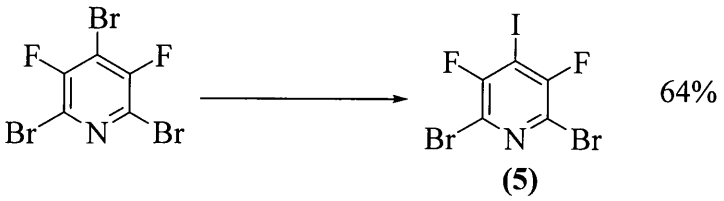
Reaction of **(1)** with lithium chloride afforded 2,6-dibromo-3,5-difluoro-4-chloropyridine **(4)** in excellent yields. Compound **(4)** was identified by ^{19}F NMR (singlet at -110.5 ppm) and the isotopic pattern of the GCMS analysis. This is a useful procedure to exchange halogens as it can be conducted at reasonable temperatures.



Conditions and reagents: LiCl 1 equiv, DMF, 92 °C, 20 hrs.

II. 2. 3 Synthesis of 4-iodotetrafluoropyridine and 4-iodo-2,6-dibromo-3,5-difluoropyridine

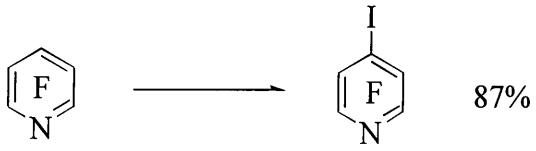
2,4,6-Tribromo-3,5-difluoropyridine reacts with sodium iodide to give 4-iodo-2,6-dibromo-3,5-difluoropyridine **(5)** in good yields. First attempts using acetone or monoglyme as the solvent were disappointing, but the use of DMF[7] instead resulted in a dramatic increase of the conversion and the yield of the reaction.



(5)

Reagents and conditions: 5 NaI, dry DMF, 150°C, 20 hrs.

Reaction of pentafluoropyridine with NaI afforded 4-iodotetrafluoropyridine **(6)** also in good yields, and the product was isolated by column chromatography or by distillation as a low melting solid; increasing the reaction time increased the proportion of by-products formed.



(6)

Conditions and reagents: NaI 4.5 equiv, dry DMF, 110 °C, 15 hrs.

The methods used provided an entry to different halofluoroheterocycles obtained in good yields via relatively straightforward procedures.

II. 3 Nucleophilic substitution reactions of highly fluorinated heterocycles

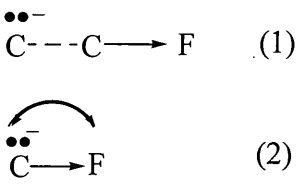
Nucleophilic attack on fluorinated heterocycles is well documented[8,9,4]. Here we will describe the factors governing nucleophilic substitution in such systems, starting from pentafluoropyridine as a good model for rationalising the effects of fluorine and the role of the ring nitrogen.

Nucleophilic substitution in fluoroheterocycles occurs readily; pentafluoropyridine being converted quantitatively to tetrafluoro-4-aminopyridine by stirring it at room temperature with aqueous ammonia, whereas the amination of pyridine takes place at 110°C with sodamide in toluene[10].

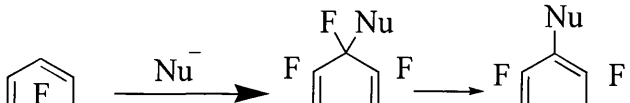
The role of fluorine atoms at the position *ortho*, *meta* and *para* has been estimated[11,12] from the rate constants of the attack of ammonia in dioxane-water in comparison with a hydrogen at the same position: the requirement is to maximise the number of activating fluorines in the Meisenheimer intermediate.

It has been discovered that the order of activation of fluorine relative to the position of nucleophilic attack is[4]:

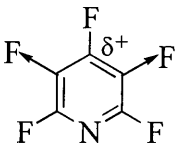
Ortho > Meta >> Para



These effects have been explained by the fact that a fluorine in position (1) is strongly carbanion stabilising, but in (2) the electron withdrawal is offset by the electron pair repulsion and the fluorine is overall destabilising.

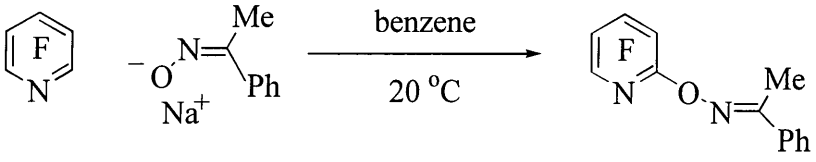


The activating effect of *ortho* fluorine is surprising at the first sight since we would expect it to be slightly deactivating, for the same reasons that a fluorine *para* is deactivating (see fig above). This has been rationalised on the basis that if the reaction proceeds via an early transition state, meaning initial state-like, the carbon is made harder and facilitates the approach of a relatively strong nucleophile[13,9]; on the other hand studies on fluorobenzene systems[11] reveal that the total charge is greater at the *ipso* site of attack when an *ortho* fluorine is present; therefore, activation effect of *ortho* fluorine is the combination of 'initial state effect' and the ability to stabilise ionic complexes.

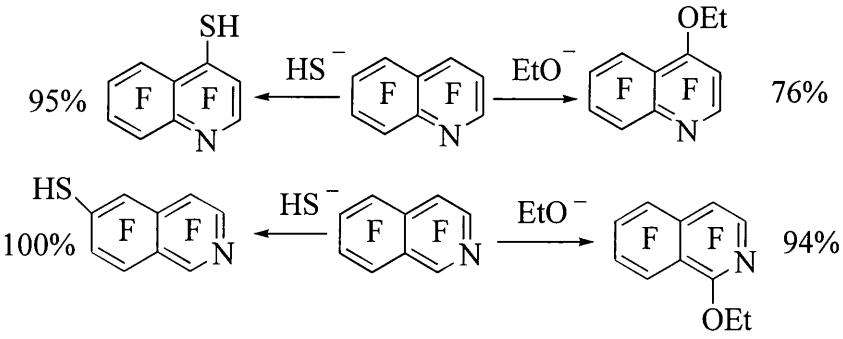


Ring nitrogen activates attack at the 2- and 4- position which maximise charge density at the nitrogen atom; but there is some discrimination between the two positions, 4-chloropyridine is more reactive than 2-chloropyridine towards attack by methoxide ion[14]. Attack at the 4-position is activated by four fluorines, two *ortho* and two *meta* whereas at the 2-position there are only three activating fluorines: therefore nucleophilic attack occurs exclusively at the 4-position and a large number of examples of nucleophilic attack on pentafluoropyridine have been reviewed in the literature[4,8,9].

Only one example in which a significant proportion of substitution at the 2-position was obtained along with the 4-substitution has been reported[8], when pentafluoropyridine was reacted with the anti ketooximate salt $Ph(Me)=NO^- Na^+$; the formation of a complex involving the ring nitrogen and the salt accounts for the formation of the 2-derivative.



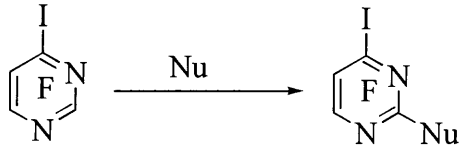
In other fluorinated heterocycles the same factors govern substitution; in tetrafluoropyrimidine attack occurs at the 4-position, while in perfluoroisoquinoline at the 2- and 4- positions. In these systems the directing effect of ring nitrogen is stronger than electron pair repulsions. When there is no *para* fluorine available, such as in tetrafluoropyrazine[2] and perfluoroisoquinoline, attack occurs *ortho* to the ring nitrogen. A study on heptafluoroquinoline and heptafluoroisoquinoline showed that the nature of the nucleophile influences the site of attack[15]:



The activated positions in perfluoroquinoline are the 2- and 4- positions that are attacked by oxygen nucleophiles, and the activated one in perfluoroisoquinoline is the 6-position attacked by sulphur nucleophiles, whereas oxygen nucleophiles attack the 1-position. The hardness of the nucleophile has been used to account for the orientation pathways observed.

II. 4 Nucleophilic substitutions of mixed halofluoroheterocycles

In mixed polyhalosusbtituted heterocycles such as 3,5-dichlorotrifluoropyridine, 4-iodotetrafluoropyridine and 4-iodotrifluoropyrimidine, the substitution is governed by the directing effect of nitrogen, and substitution occurs at the 2-position rather than the 4-position for steric reasons.



Nu: $NH_{3(aq)}$, NaOMe/ MeOH

The mechanism proposed for the nucleophilic substitution is a two step process, the formation of the Meisenheimer intermediate being the rate limiting step; *ortho* bromine and chlorine are activating on account of their I- inductive effect which stabilises the intermediate, and fluorine activates through its initial state effect; the mobility of the halogens is in the order F >> Cl, Br, I.

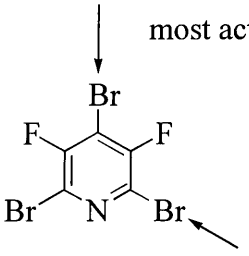
Para chlorine and bromine are activating and *para* fluorine slightly deactivating; in bromo and chloroheterocycles, ring nitrogen may form hydrogen bonds with the

nucleophile or the solvent and change the orientation of the substitution and this effect is non-existent in pentafluoropyridine, which is a very weak base.

II. 5 Nucleophilic substitutions reactions on 2,4,6-tribromo-3,5-difluoropyridine

Our aim is to investigate the chemistry of a model bromofluoroheterocycle, and the reactivity toward nucleophilic substitution is the first obvious type of reaction to investigate.

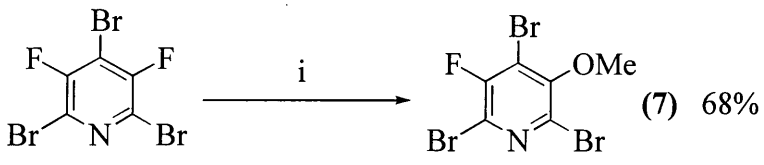
Taking into account the activating effects of fluorine and the directing effect of ring nitrogen, the 4-position appears to be the most activated position; however, we can expect some substitution at the 2-position on account of steric effects.



most activated position: 2 *o* F, 2 *m* Br, 1 *p* N

second most activated position: 1 *o* F, 1 *p* F, 2 *m* Br, 1 *o* N

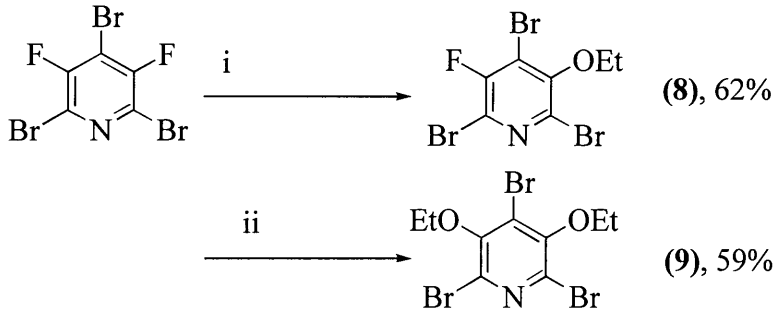
Reaction with **sodium methoxide** led exclusively to the displacement of fluorine:



(7) 68%

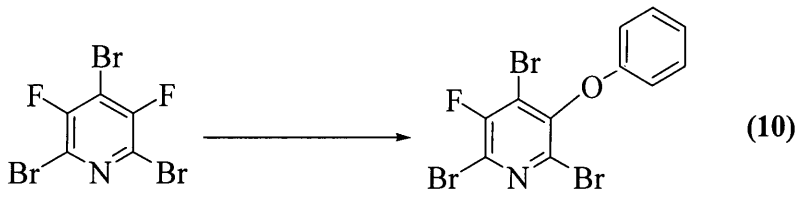
Reagents and conditions: i: 1.2 MeONa / MeOH, rt, 55 hrs.

Reaction with **sodium ethoxide** in refluxing ethanol, in the presence of 18-crown-6-ether, led again to the displacement of fluorine and an excess of sodium ethoxide displaced of both fluorine atoms.



Reagents and conditions: i: 1.2 EtONa/EtOH, 1.2 18-crown-6 , reflux, 48 hrs.
ii: 4 EtONa/EtOH, 4 18-crown-6, reflux, 25 hrs.

Phenol and sodium metal in refluxing tetrahydrofuran reacted with **(1)** to give 3-phenoxy-2,4,6-tribromo-5-fluoropyridine **(10)**:

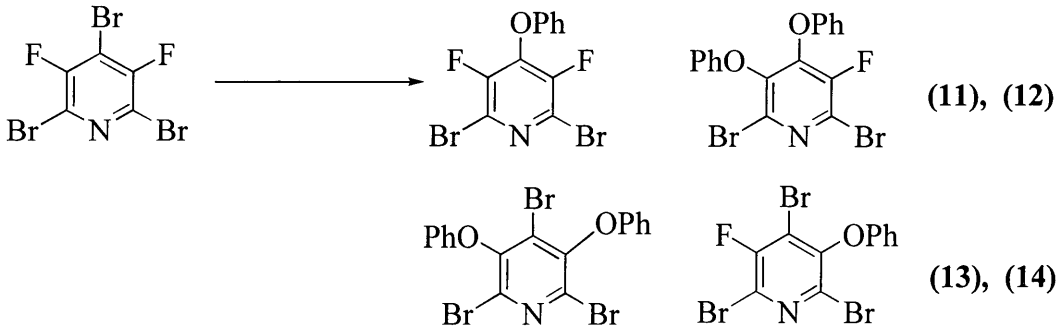


(10)

Reagents and conditions: 1.2 PhONa, THF, reflux, 16 hrs.

All these products were purified by column chromatography and analysed by GCMS, NMR and elemental analysis and **(10)** was identified by comparison with previous literature data[3]. In all cases, a small amount (<10%) of the product corresponding to the displacement of bromine was observed, but was not significant enough to allow recovery.

Buchwald[16] reported that the synthesis of diaryl ethers from aryl iodides and bromides can be successfully accomplished via a copper catalysed reaction using caesium carbonate as a base, without the necessity to form the alkoxide and using lower boiling solvents such as toluene. The copper catalysed nucleophilic substitution is believed to proceed via the formation of the active cuprate-like intermediate $[(RO)_2Cu]^- Cs^+$. We used this methodology to promote substitution at the C-Br centre rather than the C-F centre. The reaction was carried out in different conditions, varying the ration of **(1)** to phenol.



(11), (12)

(13), (14)

Reagents and conditions: 2 PhOH, 2 Cs_2CO_3, 2.5% CuBr, 5 mol% EtOAc, toluene, reflux, 36 hrs.

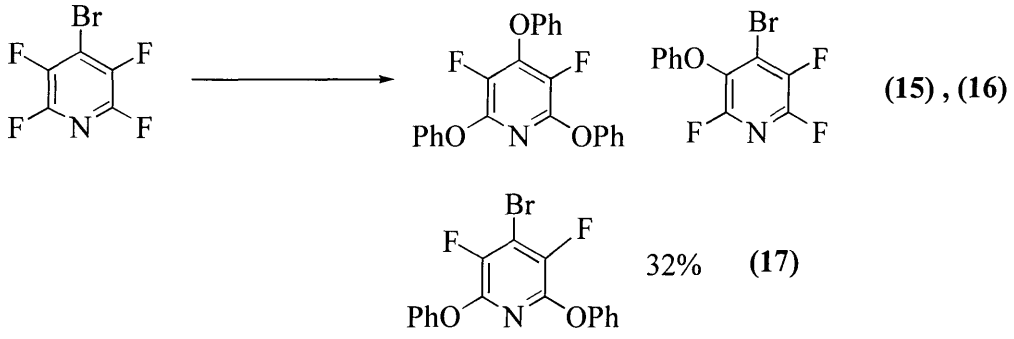
We report in the table below the results obtained using the copper catalysed and uncatalysed coupling of **(1)** with phenol. These results are compared to the ones obtained via nucleophilic substitution using sodium phenoxide in ether:

Exp	Ratio (1)/C_6H_5OH	(11)	(12)	(13)	(14)
1[a]	0.5	27	24	34	4
2[a]	0.7	30	5	19	33
3[a]	1	30	9	19	33
4[b]	**1**	**28**	**10**	**20**	**38**
5[c]	**1**	**-**	**-**	**-**	**100**

a): 2.5% copper; b): no copper added; c): sodium phenoxide, ether, reflux.
All yields reported are GC yield.

Comparing the results obtained in experiment **5** with experiments **1**, **2**, **3**, and **4** show that the conditions used modify the selectivity of the reaction, and substitution at the C-Br centre (from **(11)** and **(12)**) accounts for 35 to 50 % of the products formed, while in **5** no substitution at the C-Br bond has occurred. On the other hand, comparing experiment **4** (without copper) to experiments **1**, **2**, **3** (with copper) show that similar ratios and yields of substitution at the C-F and C-Br centre are obtained and, copper does not clearly promote substitution at the C-Br centre. Presumably, the reaction does not proceed via a cuprate intermediate, but the use of the weak base caesium carbonate in ether promotes substitution at the 4-position.

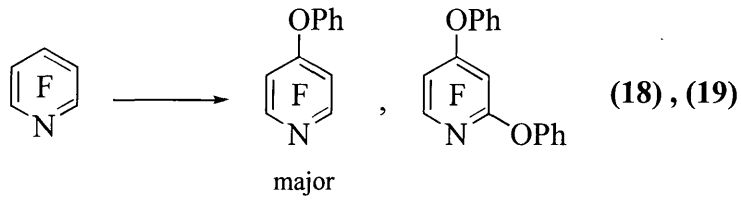
When the same procedure was applied to 4-bromotetrafluoropyridine, it afforded a mixture of 4-bromo-2,3,6-trifluoro-5-phenoxypyridine **(16)**, 4-bromo-3,5-difluoro-2,6-diphenoxypyridine **(17)** and 3,5-difluoro-2,4,6-triphenoxypyrdine **(15)**:



Reagents and conditions: 1 PhOH, 1Cs_2CO_3, 2.5% CuBr, 5 mol% EtOAc, toluene , reflux, 55 hrs.

Here we also observe the low selectivity of the reaction and the preferential attack at the hard fluorine-carbon bond via a nucleophilic substitution rather than a copper catalysed coupling at the bromine-carbon bond. The separation of the ethers was difficult, only **(13)** and **(17)** were recovered by column chromatography and fully characterised.

The reaction of pentafluoropyridine with phenol confirms the fact that the discrimination between the C-Br soft centre and the hard C-F one is responsible for the orientation of substitution; in fact substitution on pentafluoropyridine occurs rapidly at the most activated 4-position first **(18)**, which undergoes a second substitution to afford 2,4-diphenoxy-3,5,6-trifluoropyridine **(19)**:



Reagents and conditions: 1.2 PhONa, THF, rt, overnight.

Cervera and co workers[17] obtained similar results from nucleophilic substitution on 3-fluoro-4-chloronitrobenzene and 3,5-difluoro-4-chloronitrobenzene using soft and hard nucleophiles. From mechanistic and kinetic data as well as from theoretical calculations, they observed that:

- Soft nucleophiles (sulphur) attack *para* to the nitro group as expected displacing chlorine, while hard nucleophiles (oxygen) attack *meta* to the nitro group displacing fluorine,
- This behaviour is not the result of a change of mechanism from an electron transfer mechanism (such behaviours are reported in related photochemical S_NAr reactions) to a polar one,
- Both reactions proceed through a second order reaction, the first step being rate-limiting,
- Lower values of entropies observed with sulphur nucleophiles compared to oxygen nucleophiles suggest that the formation of the Ar-Nu bond is more advanced in the transition state with sulphur nucleophile and therefore contributes largely to the stability of the energy of interaction: it is an orbitally controlled reaction,
- On the other hand, reactions with oxygen nucleophiles proceed via an early transition state with a less advanced formation of the new Ar-Nu bond, the energy of the transition state depends of the electrostatic interaction of the nucleophile with the nucleofuge: it is a charge controlled reaction.

These results agree with Bartoli's[18] that demonstrate that fluorine will react faster in these types of reactions with hard nucleophiles since the rate of reaction depends linearly on the polarizability of the nucleofuge.

Previous work in our laboratory has also shown that soft nucleophiles attack 2,4,6-tribromo-3,5-difluoropyridine at the 4-position (at the C-Br bond) only. This inversed regioselectivity has already been observed[15] when heptafluoroquinoline and heptafluoroisoquinoline were reacted with oxygen and sulphur nucleophiles as mentioned earlier (section II. 3)

Other fluorinated heterocycles such as 2,4,6-tribromo-5-fluoropyrimidine displayed the normal pattern of substitution at the 4-position regardless of the nature of the nucleophile. This is probably due to the fact that in this more activated heterocycle, the directing effect of nitrogen is stronger than the C-F interaction with the hard nucleophile.

II. 6 Conclusion

Our methodologies provided an efficient method for the synthesis of halofluoroheterocycles in good yields. Reaction of 2,4,6-tribromo-3,5-difluoropyridine with nucleophiles demonstrate that selective functionalisation can be achieved using either strong or weak nucleophiles, since they selectively attack at the C-F or C-Br centre. In the particular case of phenol, it has been demonstrated that using different condition reactions, namely nature of the base and solvent used, the selectivity of the nucleophilic attack can be modified.

II. 7 References

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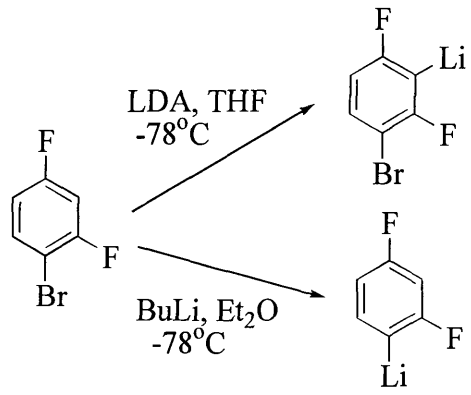
CHAPTER III

Lithium-mediated reactions of bromofluorobenzenes, fluoroheterocycles, and bromofluoroheterocycles

The lithium mediated reactions of fluoroaromatics or fluoroheterocyclic systems provides an entry to useful functionalisation, through the selective replacement of a proton or a bromine; the site of attack and the yield of the reactions are highly dependent upon the solvent, the nature of the base used and the temperature of the reaction, as illustrated by the examples below.

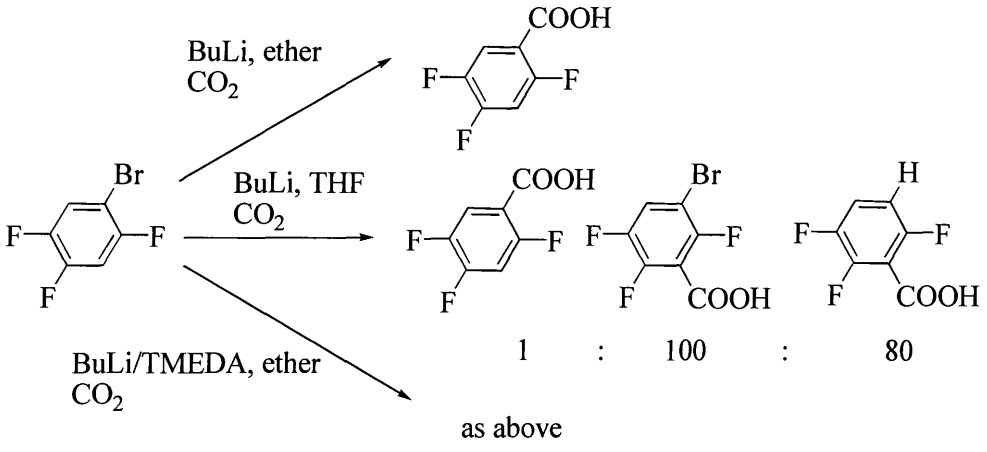
III. 1 Bromofluorobenzenes

Metalation reaction of bromofluorobenzenes showed that the site of metalation is sensitive to the type of solvent and the nature of the base employed; Coe[1] observed that 2,4–difluorobromobenzene reacted with LDA (lithium diisopropylamide) in THF to give the 3-lithio-2,4-difluorobenzene by abstraction of the more acidic proton, whereas using BuLi (butyllithium) in ether gave the bromine-lithium exchange product:



The same phenomenon was observed when 1,5-dibromo-2,4-difluorobenzene, 2,3,4-trifluorobromobenzene, 3,4-difluorobromobenzene, 3,4-difluoro-1,2-dibromobenzene and 2,3,5,6-tetrafluorobromobenzene were employed.

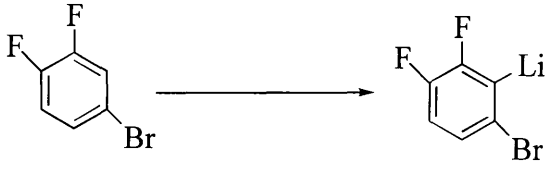
Bridges[2] obtained similar results with 2,4,5-trifluorobromobenzene; in addition he observed that using a mixture of BuLi and TMEDA in ether afforded the same results as BuLi in THF.



This was explained by the fact that in ethereal solutions alkylithium species exist as oligomeric aggregates, which are too inert to promote hydrogen-lithium exchange. Good lithium chelator additives such as TMEDA or DABCO are strong enough to break up these tight aggregates to the more reactive dimers or even monomers and enhance the basicity of butyllithium; tetrahydrofuran has the same depolymerising effect.

The above results and those obtained by Schlosser[3] with bromofluoro-substituted arenes showing facile LDA demetalation shows the strong activating effects of a fluorine atom on neighbouring C-H bonds.

Nevertheless, bromine atoms do enhance proton mobility at neighbouring centres:

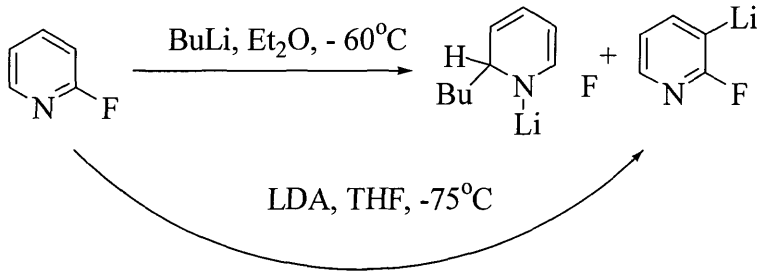


However, *ortho*-litihated halobenzenes undergo rapid benzyne formation at temperatures below -50°C.

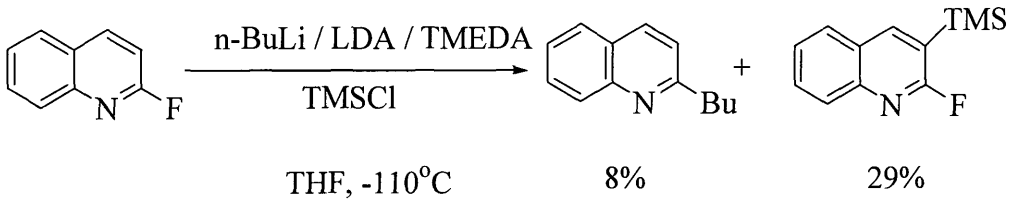
III. 2 Fluoroheterocycles

Chambers[4] first demonstrated *ortho*-metalation processes on polyfluoropyridines. Among the halogens fluorine is the most useful *ortho*-director in metalation reactions, whereas other halogens such as bromine and iodine favour halogen-metal exchange[5].

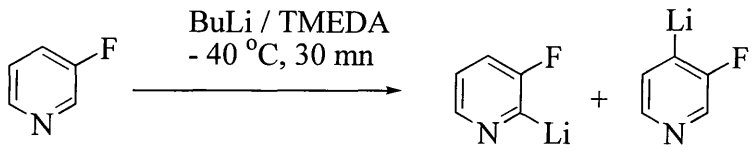
Directed *ortho*-metalation chemistry in heterocyclic chemistry is valuable because halogens can undergo functionalisation via addition-elimination, metal-halogen exchange, nucleophilic substitution and cross coupling reactions. When metalation of 2-fluoropyridine[5] was carried out using butyllithium, the lithio derivative was obtained along with the addition product; complete chemoselectivity was achieved with the more selective LDA:



The "soft" character of n-BuLi favours nucleophilic reactivity, whereas the "hard" LDA leads to protophilic attack. The same results were obtained with 2,5,6,7 and 8-fluoroquinoline[5]:



Metalation of 3-fluoropyridine[6] with n-BuLi afforded low yields and poor regioselectivity, treatment with n-BuLi / TMEDA complex afforded 2- or 4-substituted products; the 2-lithio species predominates in ether while the 4-lithio intermediate is obtained in THF:

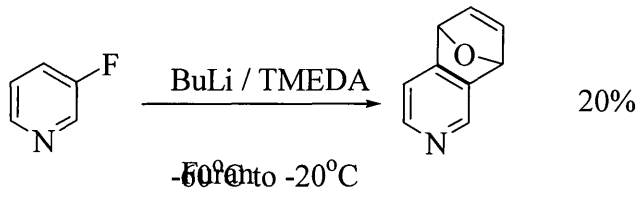


Et_2O (%)	68	3
THF (%)	0	75

In ether, coordination of the base with ring nitrogen is favoured and lithium-nitrogen chelation increases the acidity of the 2-proton; both effects lead to C-2 proton abstraction. At higher temperatures or with longer reaction times the 2-lithio derivative equilibrates with the thermodynamically more stable 4-lithio derivative. In free 3-fluoropyridine, the proton at the 4-position is more acidic. This has been rationalised on the basis of the electrostatic repulsion between the nitrogen unshared electron pair and the C-Li bond of the developing 2-lithiated species. Proton abstraction in THF occurs at the most acidic 4-position since the base/pyridine chelate is dissociated and the metalation is kinetically controlled at the most acidic 4-position.

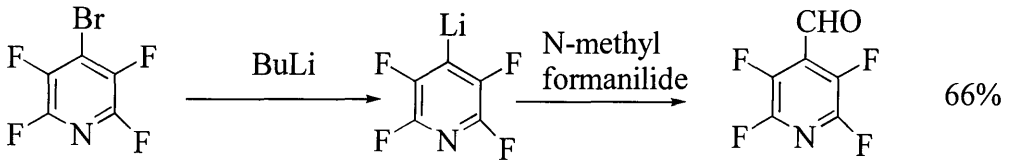
Complete regioselectivity at the C-2 position was never observed with TMEDA; using DABCO (-75°C, 1 hr, Et_2O) and trapping with TMSCl afforded the 2-silylated derivative in 80% yield, with less than 1% of the 4-adduct.

This might result from the poor solubility of the 2-lithio species in the DABCO solution, slowing down the isomerisation from the 2- to the 4-lithio derivatives; the use of LDA as a base afforded the 4-lithio derivative exclusively[7]. The lithio-derivative was stable up to - 20°C and was successfully trapped with furan:



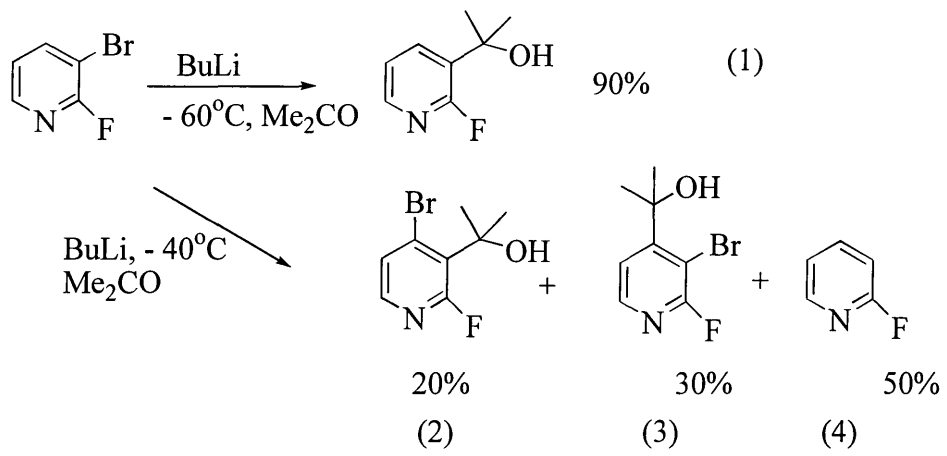
III. 3 Bromofluoroheterocycles

Metalation of 4-bromomtetrafluoropyridine[8] afforded the 4-lithio derivatives by nucleophilic attack on bromine, which was trapped with N-methylformanilide to afford the 4-aldehyde in good yield:



Subsequent oxidation of the aldehyde afforded tetrafluoroisonicotinic acid in good yields (79%).

Metalation of 2-fluoro-3-bromopyridine gave different results depending on the temperature and reaction times[5]:

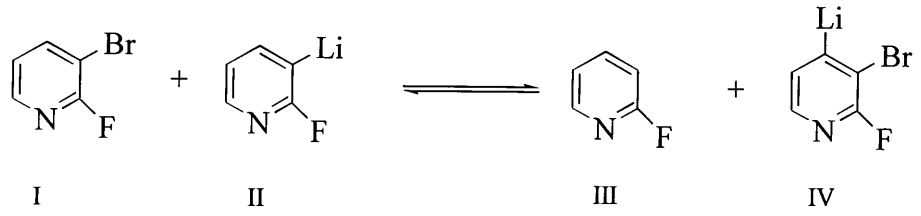


Formation of (2), (3) and (4) were rationalised by a series of Halogen Scrambling and Metal-Halogen exchange reactions outlined below:

Bromo-lithium exchange: with butyllithium (0.5 equiv):

I II

Homotransmetalation: (II) undergoes equilibrium transmetalation with the starting material (I):

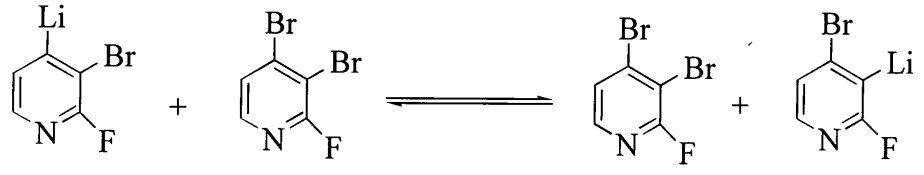


I II III IV

Formation of catalytic amounts of 3,4-dibromopyridine:

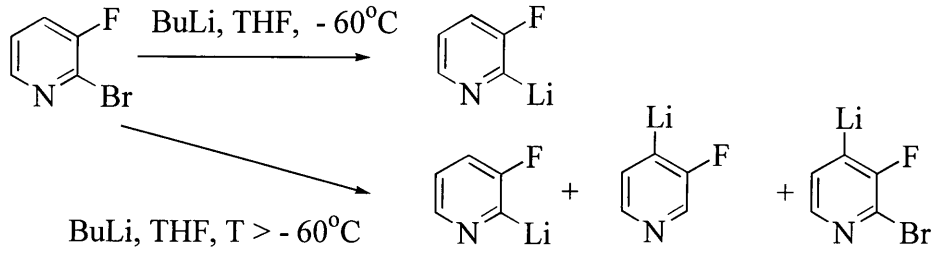
I IV V VI

Bromo migration: formation of the stabilised intermediate (VII) and regeneration of (VI), via a halogen dance reaction[9]:



IV VI VI VII

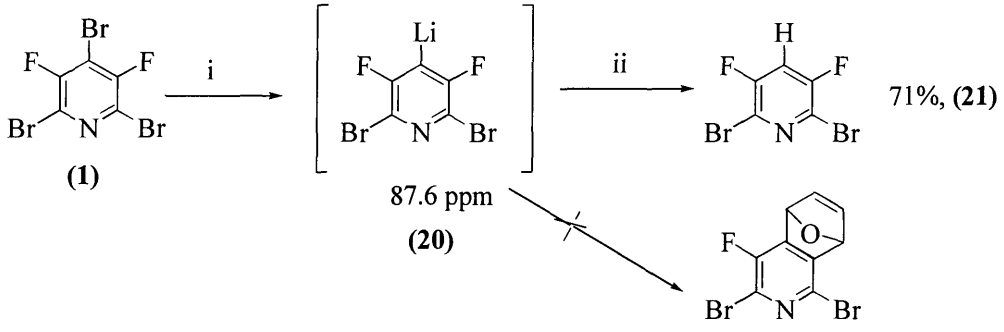
The metalation of 2-bromo-3-fluoropyridine is dependent upon the temperature of the reaction[10]:



III. 4 Lithium mediated reactions of 2,4,6-tribromo-3,5-difluoropyridine

The results above demonstrate that bromo substituted aromatic systems are good substrates for lithium mediated reactions, we were therefore interested in exploring the reactivity of halogenofluoroheterocycles such as 2,4,6-tribromo-3,5-difluoropyrdine **(1)** in lithium mediated reactions.

Reaction of **(1)** with BuLi in dry ether (or THF) afforded 2,6-dibromo-3,5-difluoropyridyllithium **(20)** exclusively; its formation is indicated by the change of colour from colourless to yellow and if the temperature rose above -65°C or moisture was present during the dropwise addition of butyllithium, the solution turned to a black tar.



Reagents and conditions: i 1.2 BuLi in dry ether, -78 °C, 90 mn; ii H_2O, RT.

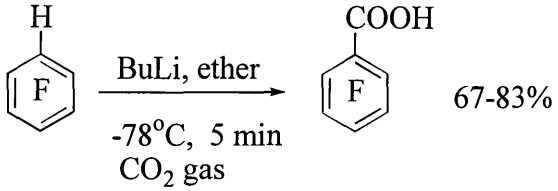
2,6-Dibromo-3,5-difluoropyridyllithium **(20)** was stable at room temperature, ^{19}F NMR gives a singlet at -87.6 ppm (compared to -103.7 for **(1)**) and the nature of the intermediate was further confirmed by trapping with water to afford 2,6-dibromo-3,5-difluoropyrdine **(21)**. The structure of **(21)** was confirmed by ^{19}F NMR, which gives a doublet at -109.2 ppm ($^3J_{HF}$ 6.8) typical of these 3,5-difluoropyridine derivatives and shows the symmetry of the molecule. GCMS analysis shows a characteristic three line, two bromine pattern.

The 4-lithioderivative was reluctant to lose LiF since attempts of trapping the resulting pyridyne with furan at different temperatures (-30°C to room temperature) failed and only the 4-hydro derivative was recovered after work up; 4-bromotetrafluoropyridine[4] also failed to lose LiF.

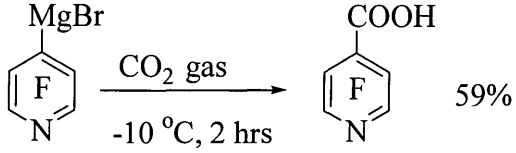
The stability of the 4-lithioderivative can be explained by the stabilising effect of the two ortho fluorines to the site of attack. The stable 2,6-dibromo-3,5-difluoropyridyllithium derivative was subsequently trapped with a range of electrophiles as described below.

III. 4. 1 Carbonation of 2,4,6-tribromo-3,5-difluoropyridine

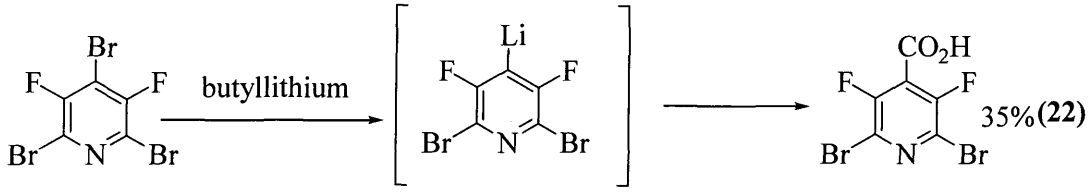
Solid carbon dioxide and 4-lithiotetrafluoropyridine gave moderate yields of the isonicotinic acid derivative; the solution of 4-lithioderivative was therefore poured onto solid carbon dioxide and allowed to react for two hours. The yield obtained was still low. In fact, the crude product contained large amounts of the hydrolysis product 2,6-dibromo-3,5-difluoropyridine. Tamborski[11] showed that the carbonation of pentafluorobenzene by bubbling CO_2 gas gave very good yield of the acid derivative:



Chambers[12] also obtained good results for the carbonation of 2,3,5,6-tetrafluoropyridiylmagnesium bromide when dry CO_2 was bubbled through the solution:



This alternative method was used and CO_2, dried by passing down a calcium chloride tube, was bubbled into the solution for 3 hours while the temperature was allowed to rise to room temperature and stirred overnight with stirring.



-87.6 ppm

(20)

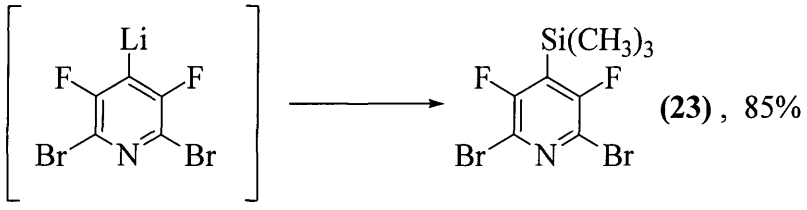
Reagents and conditions: CO_2 gas, -65 °C, 3 hrs, RT overnight

The yield of 2,6-dibromo-3,5-difluoroisonicotinic acid **(22)** obtained was slightly better, and the presence of some 2,6-dibromo-3,5-difluoropyridine was detected. Increasing the reaction time did not improve the yield of **(22)**.

III. 4. 2 Reaction of (1) with alkylated group IV electrophiles

III. 4. 2. a With trimethylsilyl chloride

When **(1)** was trapped with trimethylsilyl chloride, the 4-silylderivative was obtained in high yield and was purified by column chromatography and sublimation.

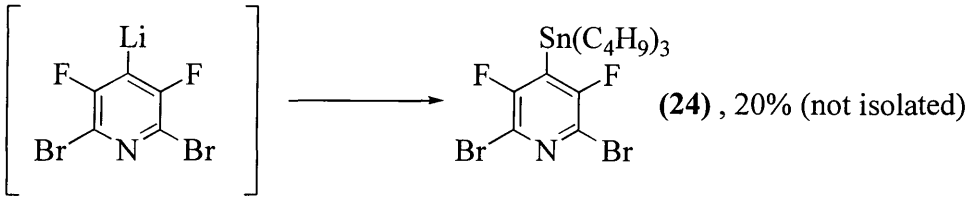


Reagents and conditions: 1.2 $Si(CH_3)_3Cl$, -78 °C, 75 min, RT overnight

Using a two-fold excess of butyllithium and trimethylsilyl chloride resulted, according to GCMS analysis, in a mixture of the mono and the disilyl derivative. These two products were difficult to separate since the disilyl derivative degraded on the chromatography column.

III. 4. 2. b With tributyltin chloride

Trapping of **(20)** with tributyltin chloride gave low yields of **(24)**; which was not expected since tributyltin chloride is more reactive towards nucleophiles compared to the silyl analogue.



(24) , 20% (not isolated)

Reagents and conditions: 1.2 $Sn(C_4H_9)_3Cl$, -78 °C, 2 hrs, RT overnight

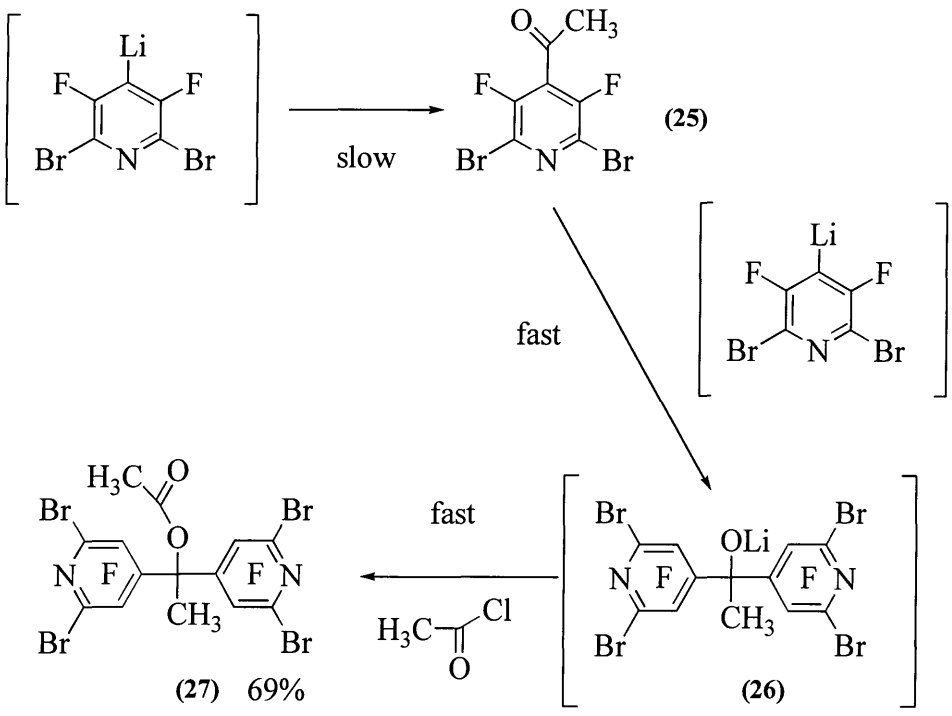
A number of fluorinated compounds were present in the crude mixture. The reaction was repeated using a non-aqueous work up since we suspect that the addition of water during the hydrolysis of the crude mixture might provoke the decomposition of the stannate and formation of the 4-hydro compound. In ethereal solution, the work up was modified; potassium fluoride was added to the crude mixture to precipitate the remaining tributyltin chloride in the form of tributyltin fluoride. Nonetheless, analogous low yields were obtained.

Tin is much larger than silicon and it bulkiness may account for this low reactivity with 2,4,6-tribromo-3,5-difluoropyridine. However, in comparison, 2,3,4,6-tetrafluoropyridine[13] was reported to react in good yield with both silyl and tin derivatives; tributyltin chloride afforded better yields.

III. 4. 3 Reactions of (1) with acid chlorides

III. 4. 3. a With acetyl chloride

When 2,6-dibromo-3,5-difluoropyridyllithium **(20)** was trapped with acetyl chloride, the GCMS analysis indicated the presence of the expected methyl ketone **(25)** (23%), the 4-hydrocompound **(21)** (30%) and another unknown brominated product (37%). The ^1H NMR spectrum of this unknown species showed the presence of two methyl groups, one at δ 2.34 ppm and the second one at 2.16 ppm. The mass spectrum indicated a molecular weight of 630, consistent with an even number of nitrogen atoms in the molecule. The singlet obtained in the ^{19}F NMR (-108 ppm) confirmed the symmetrical nature of the compound while elemental analysis confirmed the empirical formula $C_{14}H_9O_2N_2Br_4F_4$. All these data suggest that the structure of the unknown product is **(27)**, and a mechanism of its formation is shown below:

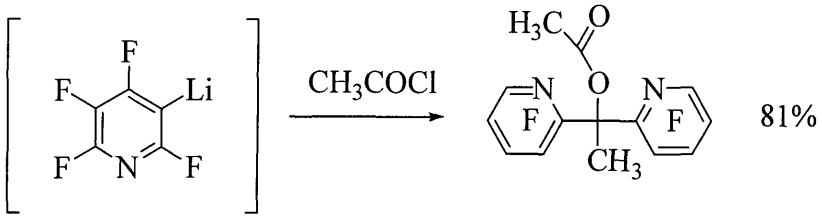


Reagents and conditions: 1.2 CH_3COCl; -78 °C; 2 hrs; -15 °C, 1hr; 0°C, 1 hr; RT overnight

The 2,6-dibromo-3,5-difluoro-4-pyridiyl methyl ketone **(25)** is produced first, but is more reactive than acetyl chloride towards the 4-lithiocompound; a second reaction takes place to give 1,1,-bis-(2,6-dibromo-3,5-difluoro-4-pyridyl)ethoxide **(26)**. This salt reacts further with acetyl chloride, and ester formation occurs to give the corresponding 1,1-di(2,6-dibromo-3,5-difluoro-4-pyridyl)ethyl acetate **(27)**.

When the reaction was repeated with an equimolar ration of acetyl chloride (with respect to 2,4,6-tribromo-3,5-difluoropyridine), the ester **(27)** was formed almost exclusively in high yields (69 % isolated). The second reaction occurs much faster than the first step, otherwise the 2,6-dibromo-3,5-difluoro-4-pyridiyl methyl ketone only would have been formed and the third stage also, since we did not obtain a mixture of 2,6-dibromo-3,5-difluoro-4-pyridiyl methyl ketone and 1,1,-bis-(2,6-dibromo-3,5-difluoro-4-pyridyl)ethanol upon aqueous work up. We can conclude that 2,6-dibromo-3,5-difluoro-4-pyridyl group is more electron withdrawing than chlorine, despite its bulkiness compared to acetyl chloride.

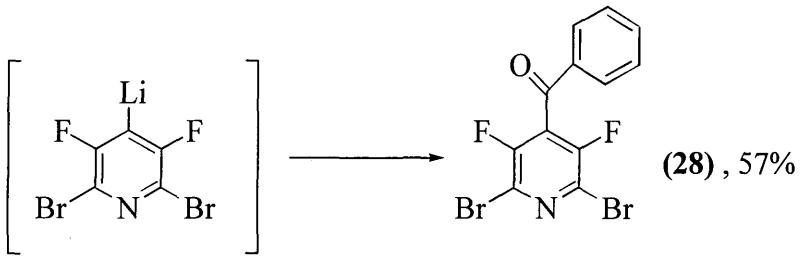
Reaction of 2,3,4,6-tetrafluoropyridine with acetyl chloride gave similar results as reported by Coe[13] during the course of this work:



Reagents and conditions: - 70°C, 30 min; warm RT, 1hr; stir RT, 1hr.

III. 4. 3. b With benzoyl chloride

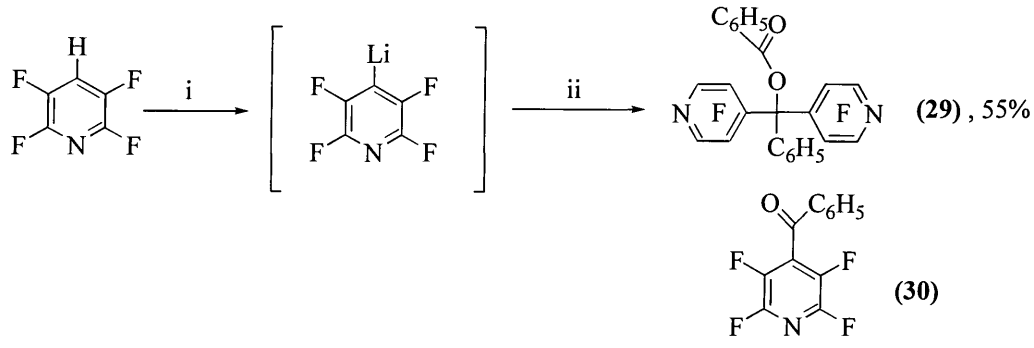
2,6-Dibromo-3,5-difluoropyridyllithium was trapped with benzoyl chloride to form the ketone derivative and after optimisation of the experimental conditions, 2,6-dibromo-3,5-difluoro-4-pyridyl-phenylmethanone **(28)** was obtained in reasonable yield (57%).



Reagents and conditions: 1.2 C_6H_5COCl; -78 °C; 3 hrs; -15 °C, 1hr; 0°C, 1 hr; RT overnight

The structure of **(28)** was elucidated without ambiguity by ^{19}F NMR, which showed a singlet at -112.2 ppm (**(1)** at -103.7 ppm); ^{13}C NMR showed the expected downfield chemical shift of the carbonyl group at -184.5 ppm. Microanalysis and mass spectroscopy were also consistent with the proposed structure.

In contrast, reaction of 2,3,5,6-tetrafluoropyridine with benzoyl chloride surprisingly afforded a mixture of **(29)** and **(30)** in the ration (3.6: 1), and the ester was isolated in 55% yield.

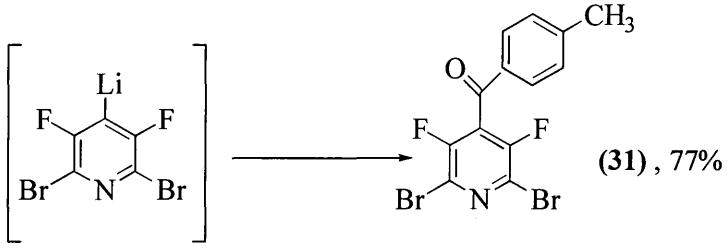


Reagents and conditions: i 1.2 BuLi in dry ether, -78°C, 45 mn;
ii 1.2 C_6H_5COCl; -78 °C; 30 mn; RT 2 hrs.

The ester **(29)** formation probably goes through the same mechanism of formation of 1,1,-bis-(2,6-dibromo-3,5-difluoro-4-pyridyl)ethoxide **(27)**. **(30)** is still more reactive (more electron withdrawing) than benzoyl chloride towards 2,3,5,6-tetrafluoro-4-pyridyllithium in spite of its bulkiness.

III. 4. 3. c With *p*-toluyl chloride

p-Toluyl chloride was reacted in the same way with 2,6-dibromo-3,5-difluoropyridyllithium, and **(31)** was exclusively formed. Complete conversion was observed, and only traces of the 4-hydro-compound were detected. ^{19}F NMR analysis gave a singlet at -112.3 ppm corresponding to the two equivalent fluorines of the symmetric molecule and X ray analysis confirmed the structure (see fig 1).



Reagents and conditions: 1.5 $CH_3C_6H_4COCl$, - 78°C, 3 hrs; - 15°C, 1hr; RT overnight.

X ray analysis of (31)

X ray analysis of a crystal of **(31)** showed that the pyridine rings are arranged in a parallel fashion, whereas the benzene rings are arranged in an edge to face **(ef)** configuration (Fig 2). Two neighbouring molecules are related by an inversion centre,

which results in a reverse arrangement of the pyridyl rings (Fig 1). The distance between two neighbouring pyridyl planes is 3.638 Å and the dihedral angle between the aromatic carboxyl group and the pyridyl group is 118.74(19)°.

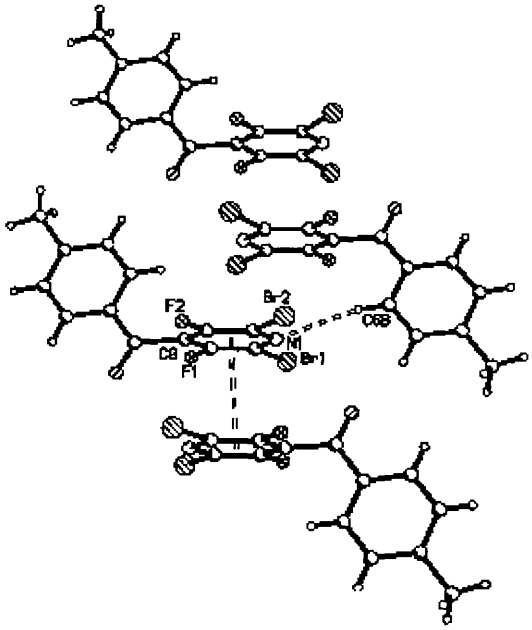


Fig 1: two neighbouring molecules of **(31)**

The arrangement of the benzene rings in **(31)** is similar to the most favourable **(ef)** arrangement observed in the crystal structure of the isolated benzene molecule. This arrangement corresponds to the local minimum repulsion[14] arising from the coulombic attraction between hydrogen atoms and carbon atoms from neighbouring molecules, although crystal arrangement in benzene crystal molecule has also been rationalised on the basis of interactions between electric quadrupole moments.

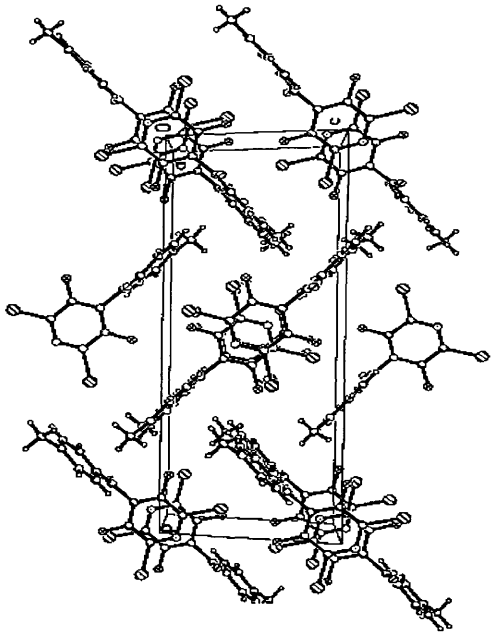


Fig 2: Packing Arrangement of **(31)**

The crystal structures of many arene-fluoroarene compounds have been studied and they generally display an alternate face-to-face stacking of arene and perfluorarene molecules. The first example of such arrangement was provided by the crystal structure of a (1:1) mixture of benzene and hexafluorobenzene[15]. This directing effect has been utilised for the synthesis of self-organised aggregates of polymeric or oligomeric materials for electronic and optoelectronic devices[16-18], and to orient olefinic molecules in the solid state and induce topochemical [2+2] photocycloaddition reactions[19]. This alternate packing observed in arene-fluoroarene complexes is thought to result from the electrostatic interaction of electric quadrupole moments of opposite signs, which determines the overall structure of the solid, even if a network of weakly polarised hydrogen bonds might also contribute to stabilising the lattice[20,21]. However, recent calculations estimating the intermolecular energies in such systems suggest that van der Waals interactions are the major contribution to the total energy, and that electrostatic interaction (quadrupolar interactions) represent less than 15% of the total energy[22]. The study of this interaction has not been extensively investigated for mixed fluoroheteroaromatic-aromatic compounds, but the example of 4-(4-biphenyl)-2,3,5,6-tetrafluoropyridine has been reported[23] and the alternate parallel packing has also been observed with other fluorinated aromatic rings.

In the case of **(31)**, non alternate packing is observed and this is probably due to the low level of fluorination of the pyridine ring, in fact no alternate stacking has been observed in the literature with rings containing less than four fluorine atoms, whether this is the result of electrostatic or van der Waals interactions is beyond the scope of the present discussion. The distance between two parallel pyridine planes in **(31)** is larger than the typical length of a π-π interaction, therefore the configuration observed probably results from the most energetically favourable arrangement of the pyridine rings, in other words the best way to 'fill the space'.

We studied the solid state structure of 4-phenoxy-2,3,5,6-tetrafluoropyridine **(18)** (Fig 3), containing a more highly fluorinated pyridine moiety. We observed in that case a **partial** overlapping (Fig 4) between the benzene and the pyridine rings, and the calculated distance between the two rings is 3.4 Å, which might indicate the occurrence of aromatic interactions. The lone pair of the oxygen atom might participate in hydrogen bond interactions or contribute to offset the parallel stacking via electrostatic repulsion.

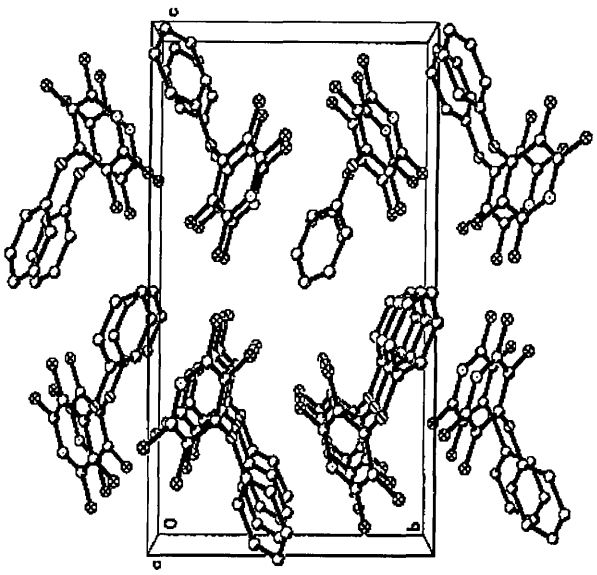


Fig 3: packing arrangement of **(18)**

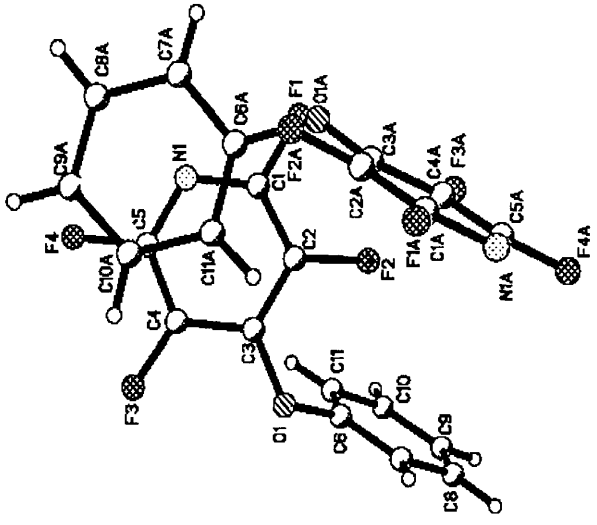
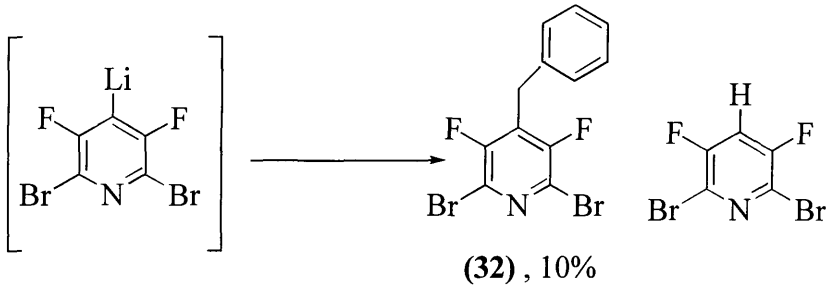


Fig 4: Partial overlapping in **(18)**

III. 4. 3. d With benzyl bromide

Trapping of 2,6-dibromo-3,5-difluoropyridyllithium with benzyl bromide afforded low yields (10 %) of the expected 4-benzyl-2,6-dibromo-3,5-difluoropyridine **(32)**, along with the 4-hydro compound, as identified by GCMS analysis. No starting material

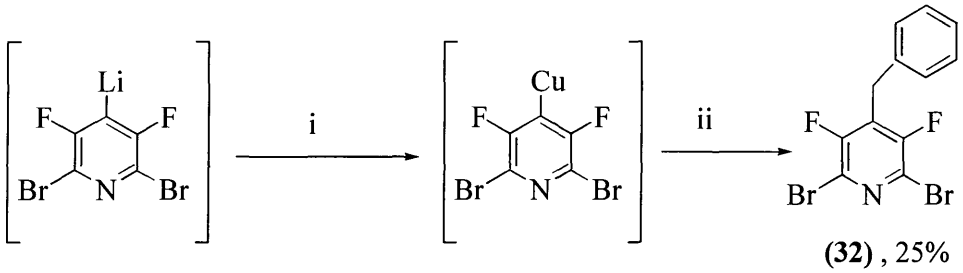
(1) remained in the crude mixture; we suspect the formation of polymeric material to account for the low yield.



(32), 10%

Reagents and conditions: 1.2 $C_6H_5CH_2Br$, - 78°C, 1 hr; - 15°C, 1hr; RT overnight.

Heating the solution to reflux after addition of benzyl bromide did not improve the yields, but some nucleophilic substitution product appeared. Better yields (25%) were obtained via the formation of the copper intermediate[24], achieved by the addition of copper iodide to the solution of 2,6-dibromo-3,5-difluoropyridyllithium at low temperature. However, separation by column chromatography failed. In general, this reaction was very unreliable, and the reproducibility of the results difficult to reach.



(32), 25%

Reagents and conditions: i 2 CuI; -78°C, 4 hrs; ii 1.2 $C_6H_5CH_2Br$, -78°C, 1 hr; -15°C, 1hr; RT 16 hrs

III. 5 Conclusions

The results obtained demonstrate that 2,4,6-tribromo-3,5-difluoropyridine undergoes exclusive metal halogen exchange at the 4- position from the most stable carbanion due to the presence of the two *ortho* fluorine atoms. The lithio-derivative formed is stable and can be trapped by a variety of electrophiles (e.g. TMSCl, acid

chlorides), and therefore lithium-mediated reactions are a useful methodology for the selective functionalisation of **(1)** at the 4-position.

III. 6 References

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CHAPTER IV

Palladium Catalysed Cross Coupling Reactions

IV. 1 General introduction

Cross coupling reactions of organometallic reagents with organic halides (or triflates) is one of the most straightforward and elegant methods for carbon-carbon bond formation, since the polarity of the carbon-metal in these reagents confers a nucleophilic character to the carbon bound to the metal and allows a variety of reactions with carbon-centred electrophiles which would be otherwise impossible.

Until the late 1960's, only Grignard and lithium reagents were used to accomplish these couplings but they were mostly limited to alkenyl halides and characterised by their low chemoselectivity. In 1972, Kumada[1] and Coriu reported that the reaction of Grignard reagents with alkenyl or aryl halides could be catalysed by nickel. Murahashi[2] reported later the palladium catalysed version of Kumada-Coriu reaction of Grignard reactions, demonstrating the high stereoselectivity of the reaction:

$$PhHC{=}CHBr + RMgX \xrightarrow{\text{cat. } Pd(PPh_3)_n} PhHC{=}CHR \quad 86\text{-}100\%$$

R: Me, $CH_2{=}CH$, *p*-MePh

It was discovered afterwards the higher sterospecificity and therefore superiority of palladium over nickel in these reactions. Further studies established the feasibility of Palladium-Catalysed Cross-Coupling reactions of organometallic complexes with vinyl and aryl halides, triflates and even diazonium salts[3-5]. Palladium catalysed cross coupling reactions may utilise a variety of metals such as Mg, Zn, B, Al, Sn and Cu as counterions; even organosilanes can be successfully used despite the low ionic nature of the C-Si bond.

Historically the Heck-Mori[6-8] reaction discovered in the late 1960's simultaneously by American and Japanese groups, was the first palladium catalysed reaction designed and relatively well understood from the mechanistic point of view; the process enabled the effective coupling of aryl and alkenyl halides (or triflates) with alkenes.

Nowadays, palladium catalysed coupling reactions display a broad scope of reactions with respect to the two carbons to be coupled, in fact reaction with alkynyl nucleophiles, hydrometallation, tandem processes[9] and aryl aryl coupling[10,11] have been achieved successfully. Therefore palladium catalysed coupling is a powerful method for the synthesis of complex molecules and is in consequence used in many industrial processes[12-14].

IV. 2 General features

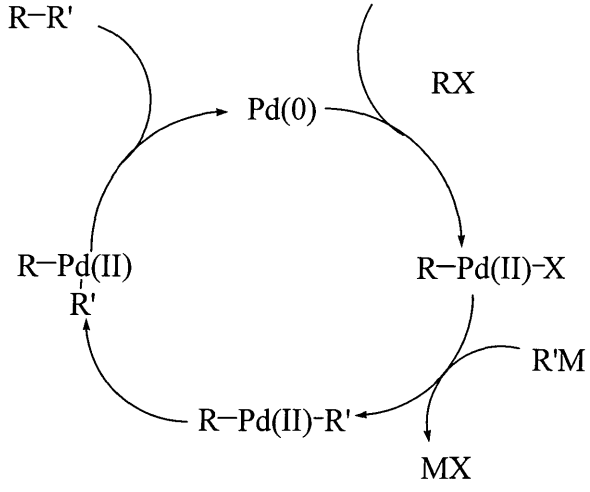
Organotransition metals enjoy the presence of partially filled d orbitals, which gives access to new reaction pathways unavailable for main group organometallics[15]. In consequence these elements have a number of stable oxidation states, geometries and coordination numbers; their reactivity towards organic reagents is directly related to these features. This diversity has the advantage to make them highly stereospecific but at the same time inconveniently sensitive to small changes in the substrate that can turn an efficient reaction into a reaction that does not proceed; this obstacle is generally overcome by the fine tuning of the reactivity through the choice of appropriate spectator ligands coordinated to the transition metal.

Palladium exists in two stable oxidation states +2 (d^8) and zerovalent (d^{10}) state and participates in two types of bonding: σ donor bonds which are formed by overlap of the filled sp^3 hybrid orbitals of the ligands with vacant dsp orbitals of the metal and back donating bonds which are formed by the filled d orbitals of the metals back donating density to the ligand by overlap with vacant antibonding π^* orbitals. Therefore, the electronic density of the metal can be modulated by varying the nature of the ligand L (L: PPh_3, RCN, OAc) at the metal centre[16]. Pd(II) complexes such as $Pd(PPh_3)_2Cl_2$ are electrophilic and react with electron- rich organic compounds; they are generally catalyst precursors for Pd(0) catalysed processes. Pd(0) complexes are on the other hand strong bases and nucleophiles; the most common ones are $PdP(Ph_3)_4$, $Pd(dba)_2$ or $Pd_2(dba)_3.CHCl_3$. The sources of Pd(0) necessary for catalysed reactions

shown below represent only a tiny part of the large spectrum of catalysts available today, which are often synthesised to suit the requirements of a particular type of coupling.

IV. 3 General mechanism of the Palladium-Cross-Coupling reactions

Palladium-Cross-Coupling reactions are generally accepted as proceeding through the following simplified mechanism:



Scheme 1: General mechanism of a Metal Mediated Cross-Coupling reaction

IV. 3. 1 Oxidative addition

The first step that involves the addition of Pd(0) complexes to organic halides and related electrophiles; the coordinatively unsaturated transition metal (Pd) in a low valence state (therefore electron-rich and prone to oxidation) formally inserts into a carbon-halogen bond and is oxidised to Pd(II) to form the thermodynamically favoured (from the equilibrium with the cis-complex)[17] **trans**-σ-Pd(II) complex; the metal is being oxidised and the substrate reduced, therefore electron-deficient substrates are more reactive than the electron-rich ones. The substrates should be halides (or triflates) lacking β-hydrogens since β-hydride elimination occurs very fast.

Good σ donor ligands at the transition metal generally facilitate the oxidation and π acceptors suppress it. If Pd(II) complexes are used as source of Pd(0), they are reduced in situ by triphenylphosphine or the nucleophile itself. Three mechanisms are

possible for the oxidative addition step and depend on the nature of the reaction partners: a) a concerted associative one step insertion, best known for non polar reactants such as oxidative addition into C-H bonds (hydrocarbon activation); b) electron transfer radical chain mechanism; and c) ionic two step S_N2 process, most often observed with strongly nucleophilic low valent metals and S_N2 substrates, the rate law is second order, and polar solvents accelerate the rate of oxidative addition; this latter mechanism is the more likely to occur when the transition metal used is palladium.

The mechanistic studies conducted by C. Amatore[18-21] have established many important facts:

-When a general source of Pd(0) such as the tetrakis triphenylphosphine complex $Pd(PPh_3)_4$ is used, the active species in solution is the low ligated complex $Pd(0)(PPh_3)_2$ 14-electron species formed by spontaneous deligation of $Pd(PPh_3)_4$; even if it exists at low transient concentration because of the uphill character of the equilibrium by which it is formed.

-When a Pd(II) complex is used, at least three Pd(0) complexes are formed in solution, the more reactive species is the anionic $Pd(0)(PPh_3)_2Cl^-$ complex in equilibrium with a dimeric species $Pd(0)_2(PPh_3)_4Cl_2^{2-}$. The ligation / deligation process being very fast, $Pd(0)(PPh_3)_2$ does not exist in solution.

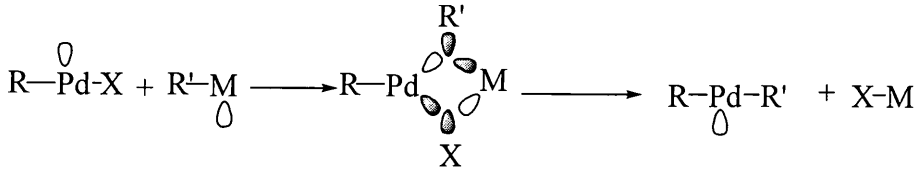
-Addition of cations as Li^+, Zn^{++} accelerated the rate of the reaction through the formation of ion pairs and subsequently more naked Pd(0) complex, which is evidence of the formation of anionic species derived from R-X.

IV. 3. 2 Transmetallation step

This step is generally believed to be rate limiting, even if in some particular cases the oxidative addition has been shown to be the slowest one[20]. It consists of the transfer of the electrophile to the transition metal complex to form a trans-dialkyl-palladium(II) complex.

The main group organometallic (M) has to be more electropositive that palladium; and both metals involved must benefit from the process energetically. For example transmetallation from organosilanes occurs only with addition of fluoride ion (from added tetrabutylammonium fluoride TBAF) that aids the cleavage of the Si-C bond and the formation of the stable Si-F bond.

The transmetallation is more likely to involve a four-centred σ bond metathesis promoted by an empty orbital on each metal involved:



Scheme 2: Mechanism of the transmetallation step

It generally occurs with retention of configuration. When there is more than one group attached to M, the order of rate of transmetallation for different substituents is:

Alkynyl > vinyl > aryl > allyl ~ benzyl >> alkyl.

IV. 3. 3 Reductive Elimination

The rearrangement of the **trans**-dialkyl-palladium(II) complex occurs rapidly to afford the **cis** isomer, which undergoes reductive elimination, reverse of the oxidative addition, affording the coupled product R-R' and regenerating Pd(0). Anything reducing the electronic density at the metal such as electron-acceptor ligands will facilitate this step.

IV. 3. 4 Leaving groups on R-X

The reactivity of a substrate coincides with the order of their reactivity in oxidative addition with palladium (II) complexes:

I > OTf > Br > Cl.

For aryl, alkenyl and alkynyl halides, palladium coupling reactions almost always involves iodides or reactive bromides and this is one of the major limitations of this type of reactions. N-containing heterocycles are activated towards oxidative addition at the α and γ positions through the activating effect of nitrogen; even α and γ-chloroheterocycles are sufficiently activated for palladium-catalysed reactions whereas chlorobenzene requires hindered electron rich ligands.

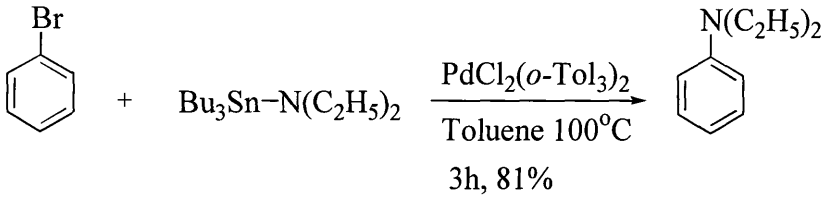
In conclusion; palladium-catalysed cross-coupling reactions are a very versatile method to realise complex organic transformations. We do not intend to cover the

whole area of palladium catalysed chemistry, but we will limit our scope to cross coupling types of reactions involving the use of aryl and heteroaryl halides (including the more rare fluorinated ones) as substrates and reagents.

IV. 4 The Buchwald-Hartwig C-N and C-O bond formation reactions

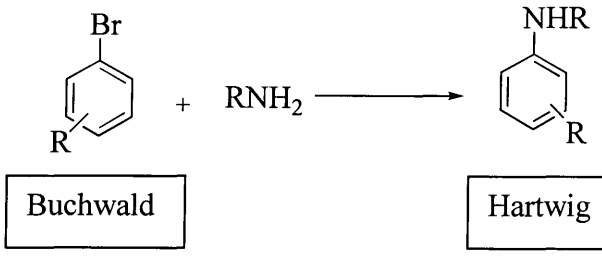
IV. 4. 1 C-N bond formation reactions

The Migita group performed the first aryl C-N bond formation catalysed by palladium in 1983 using organostannanes, but this was not really satisfying because of the use of toxic aminostannane substrates:



Later, palladium-catalysed reactions were performed without organostannanes by Boger[22] but the use of a large amount of the expensive $Pd(PPh_3)_4$ (1.5 equivalent) and the competing oxidative addition of liberated HBr, made it of a limited use.

Buchwald[23] and Hartwig[24] simultaneously realised the catalytic amination of aryl bromides with free amines using P(*o*-Tolyl)$_3$ ligand in the presence of a stochiometric amount of base. However, these reactions afforded low yields when no *ortho* or *para* electron withdrawing groups where present on the aryl group. This method was further improved by the use of different catalysts and ligands providing a high yielding methodology for the catalytic formation of a C-N bond:

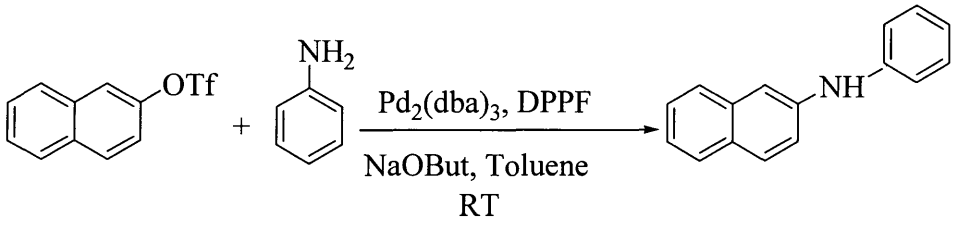


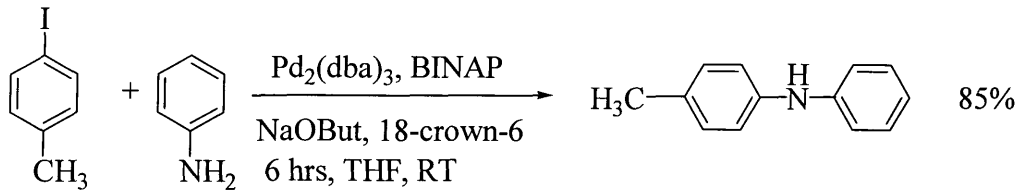
Buchwald	Hartwig
$Pd(dba)_2$ 5%, BINAP	$PdCl_2(DPPF)$ 5%, DPPF
NaOBut or Cs_2CO_3	NaOBut
Toluene, 80°C	THF, reflux
98%	94%

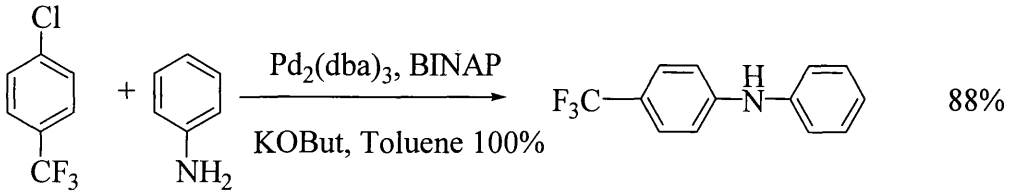
This methodology involved the use of bis-phosphine intermediates; sterically hindered ligands were not necessary to obtain high yields in intermolecular amination of aromatics, a weak base such as caesium carbonate promoted the reaction and, finally this methodology tolerated a variety of functional groups such as esters, aldehydes, enolisable ketones and nitro groups.

The use of bidentate ligands such as BINAP or DPPF is necessary to promote reductive elimination over β-hydride elimination from the amido-palladium intermediate by its bidentate chelating ligand. When pyridines were involved, these ligands also prevented the formation of bis-phenyl complexes that terminate the catalytic cycle[25], whereas a monodentate ligand can sometimes facilitate amination of bromopyridines.

A variety of aryl halides were coupled in good yields, sometimes at room temperature:

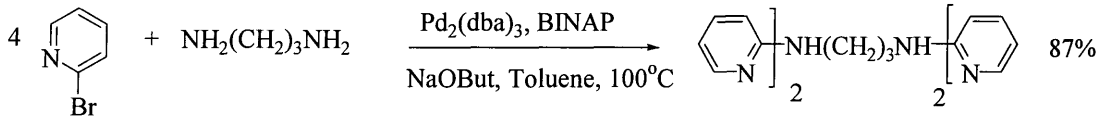


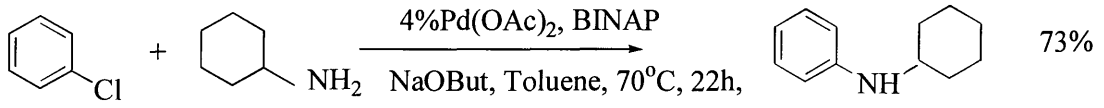




This is an efficient process to selectively couple a primary amine in the presence of a secondary one to allow the synthesis of peptide analogues[26], and triarylamine dendrimers where it was found to be a superior method to the copper mediated Ullman coupling.

Coupling using pyridine substrates was possible without using harsh conditions or activated substrates. The following examples showed that primary amines and anilines were arylated and the protocol worked for both chloro and bromopyridines:

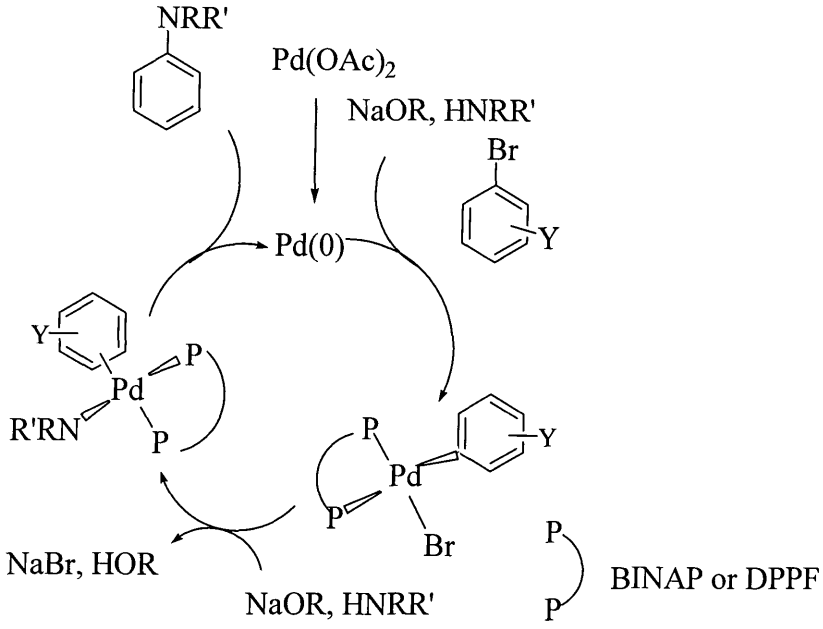




The limitation of this method is its inability to cross couple halopyridines with acyclic dialkylamines.

Mechanism of the reaction[27,28]

The mechanism consists in oxidative addition to the aryl halide to form a palladium complex, ligand exchange and deprotonation by the base, reductive elimination that competes with elimination if there is a β-hydrogen present, and finally formation of the aminoaryl and regeneration of the catalyst.

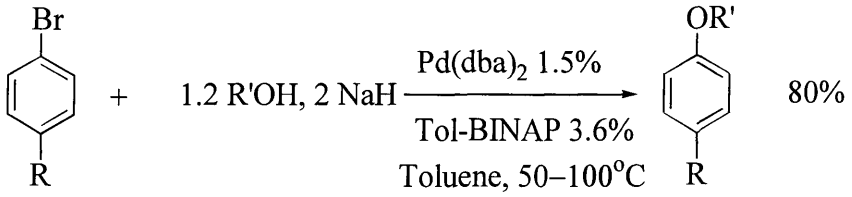


Scheme 3: General mechanism of the palladium mediated amination of bromobenzenes.

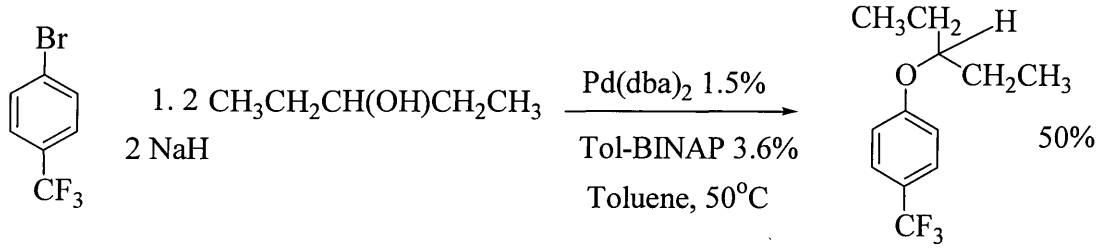
IV. 4. 2 C-O bond formation reactions

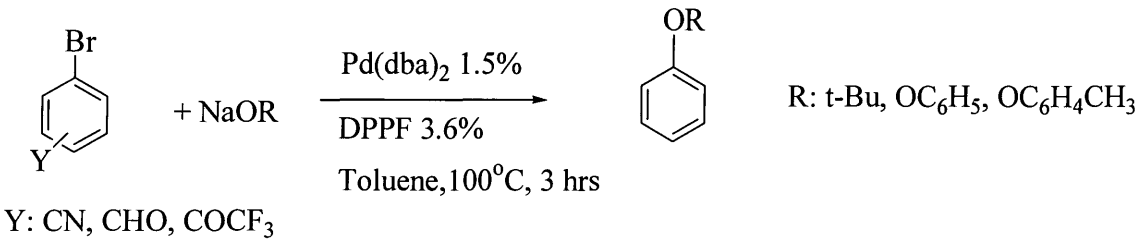
Compared to their nitrogen and sulphur counterparts, alkoxides are less nucleophilic, and so reductive elimination to form C-O bond is much slower; however, Buchwald's[29,30] successfully realised the intermolecular Pd catalysed synthesis (using BINAP as a ligand) of aryl cyclic ethers from *o*-haloaryl-susbtituted-alcohols. Previous methods for the synthesis of aryl ethers required harsh and restrictive conditions: use of an excess of freshly prepared sodium alkoxides (4 equivalents for aryl bromides), high temperature reactions, and high boiling solvents such as DMF, DMSO or HMPA.

Good yields of mono and diaryl ethers[31,32] were obtained from the reaction of electron deficient aryl halides with tertiary alcohols[33]:



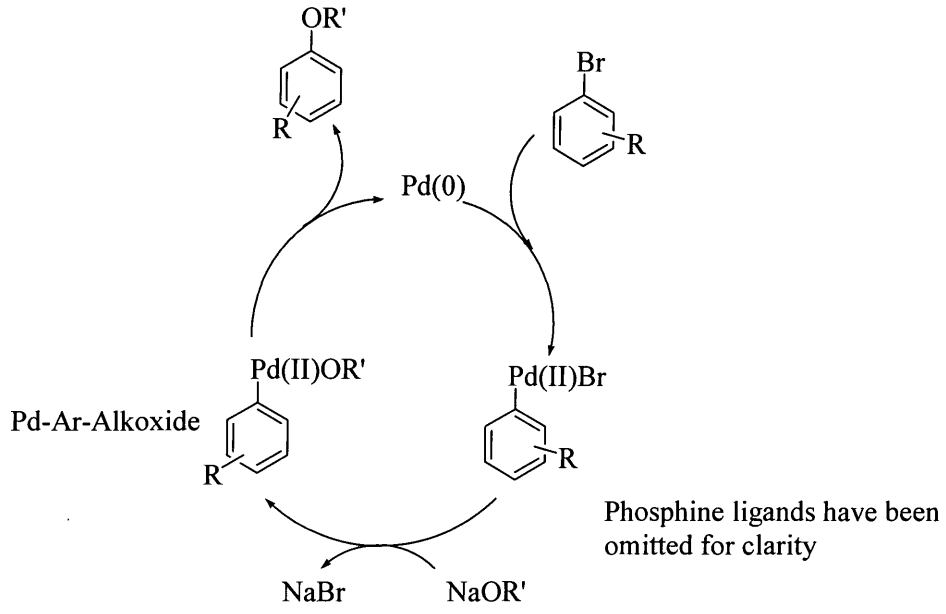
R: CN, CF_3, t-Bu
R': $PhCH_2$-, CH_3-, t-Bu-





Mechanism of the reaction

This process was the first to form a C-O bond through a reductive elimination, via an insertion mechanism[34] as in the C-N formation process, bulky ligands and weaker electron donating groups favour reductive elimination[31] over β-hydride elimination.



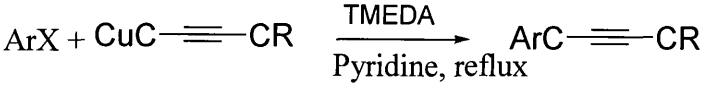
Scheme 4: General mechanism of the palladium mediated C-O bond formation.

No reaction occurred when no catalyst was present in solution. When unactivated aryl halides were substrates, the use of hindered trialkylphosphines (such as $P(t\text{-}Bu)_3$) accelerated oxidative addition[32]. However, this method did not find many applications

in heterocyclic chemistry, since SnAr displacements involving many heteroaryl halides occur readily without the aid of palladium.

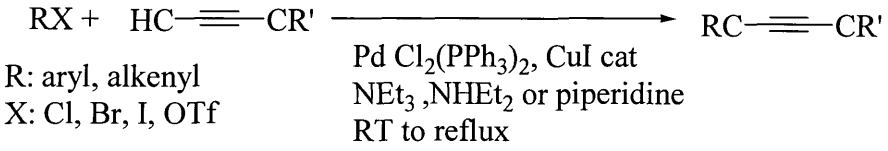
IV. 5 The Sonogashira reaction

The Sonogashira coupling is the palladium catalysed version of the Stephen-Castro[35] coupling of alkynyl copper reagents with aryl halides for the preparation of internal acetylenes:



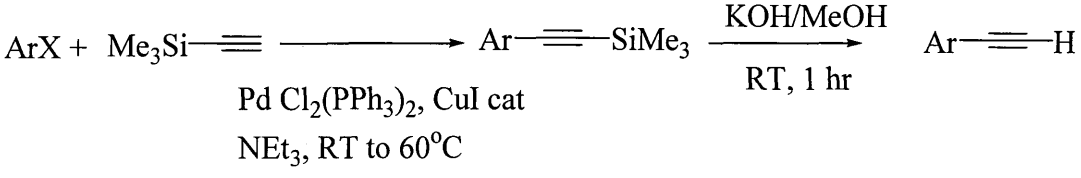
Although this method was efficient for vinyl and allenic halides, it required the isolation of the alkynylcopper(I) and vigorous reactions conditions.

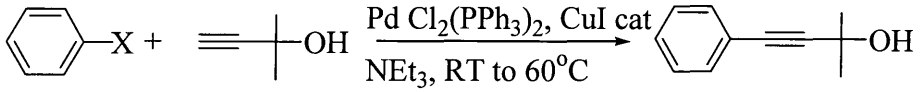
Sonogashira[36-38] successfully coupled terminal alkynes with vinyl and aryl halides in the presence of a palladium catalyst, an aliphatic amine and catalytic CuI under mild conditions:



The synthesis of terminal acetylenes using acetylene gas gave only internal acetylenes because of the higher reactivity of the monosubstituted acetylene compared to acetylene gas.

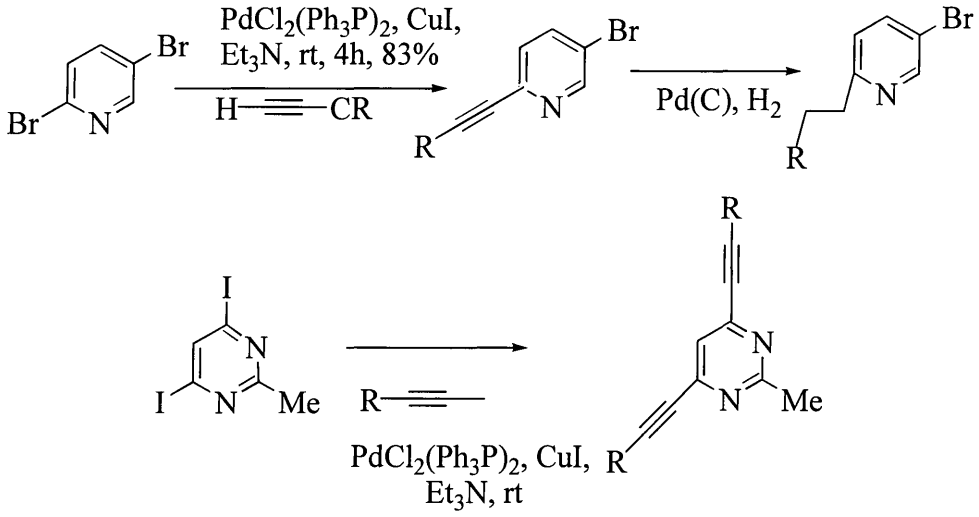
However, protection of the acetylenes by the trimethylsilyl group or by alcohols[39,40] followed by hydrolysis afforded the desired product in good yields:



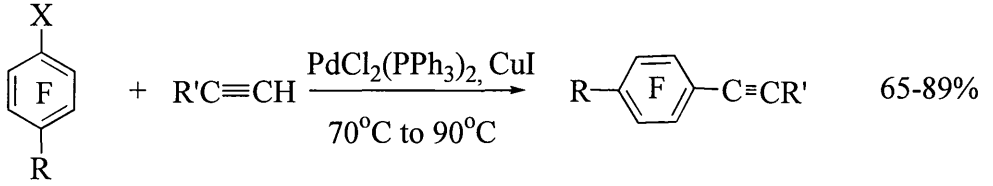


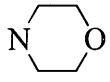
X: Br, I

Sonogashira couplings with aryl groups were achieved at room temperature when bulky highly reactive ligands were used[41]. A variety of heterocycles[42,43] were efficiently coupled with terminal acetylenes under Sonogashira conditions:



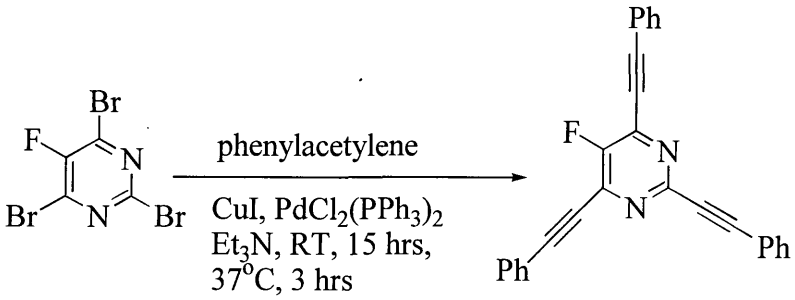
Many examples exist in the literature using highly fluorinated substrates participating in Sonogashira couplings[44], however Nguyen[45] reported the coupling of substituted tetrafluorophenyl halides with terminal acetylenes in good yields and under mild conditions:



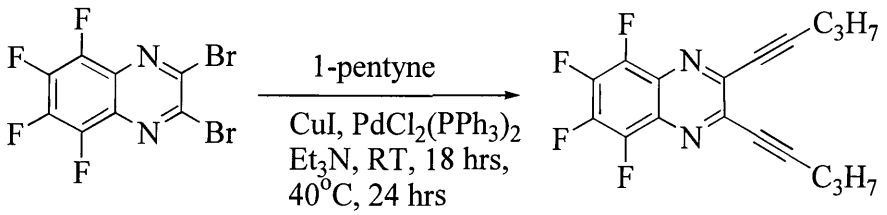
R: OMe, $N(Me)_2$, Br, 

X: I, Br

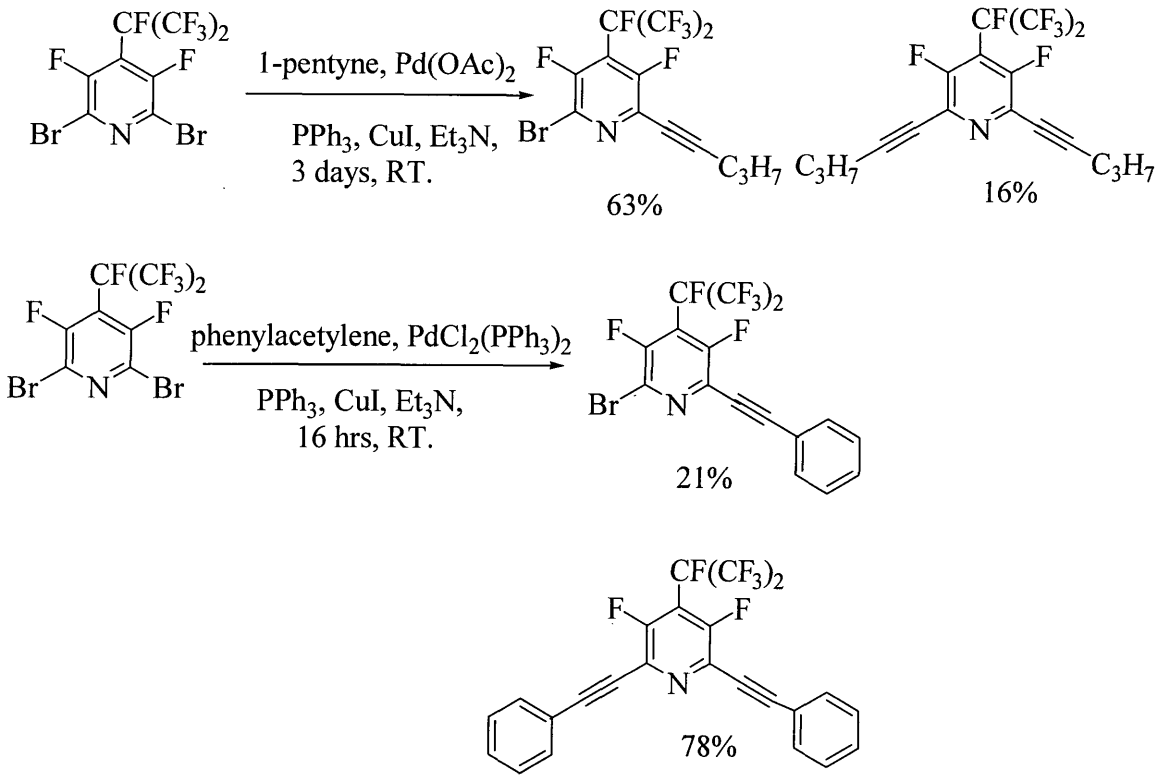
Early work in our laboratories has showed that mixed bromofluoroheterocycles will react with acetylenes in an efficient manner; in fact 2,4,6-tribromo-5-fluoropyrimidine coupled with phenylacetylene to afford the trisubstituted adduct:



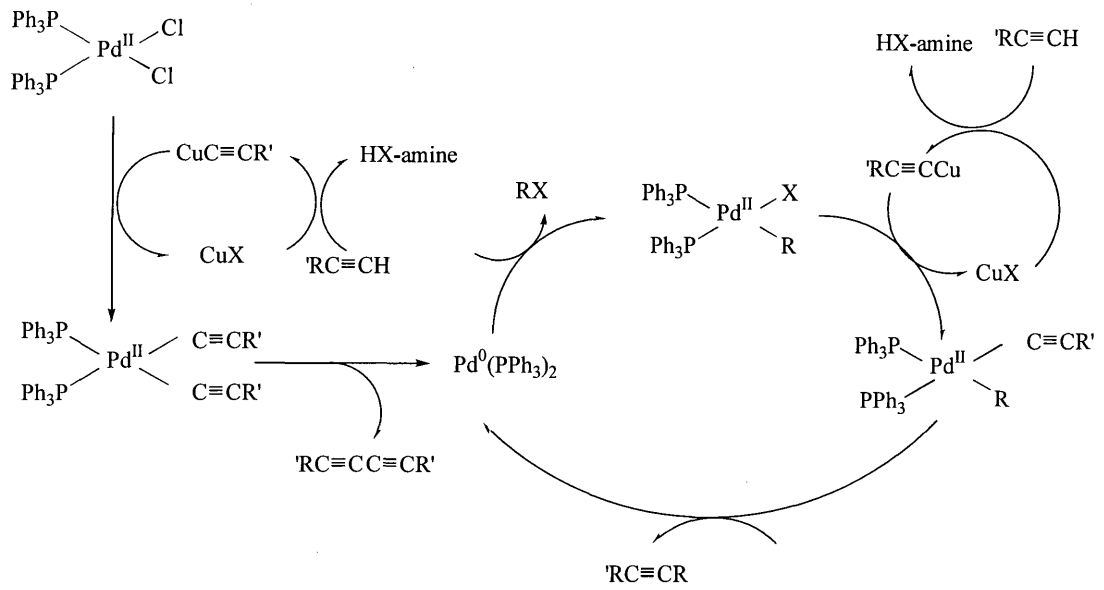
Furthermore, 2,3,-dibromotetrafluoroquinoxaline reacted with 1-pentyne substituting at both the 2- and 3- carbons :



Substituted bromopyridines containing perfluoroalkyl groups were also reactive enough to undergo palladium catalysed reactions under Sonogashira conditions:



IV. 5. 1 Mechanism of the reaction



Scheme 6: General mechanism for the Sonogashira coupling

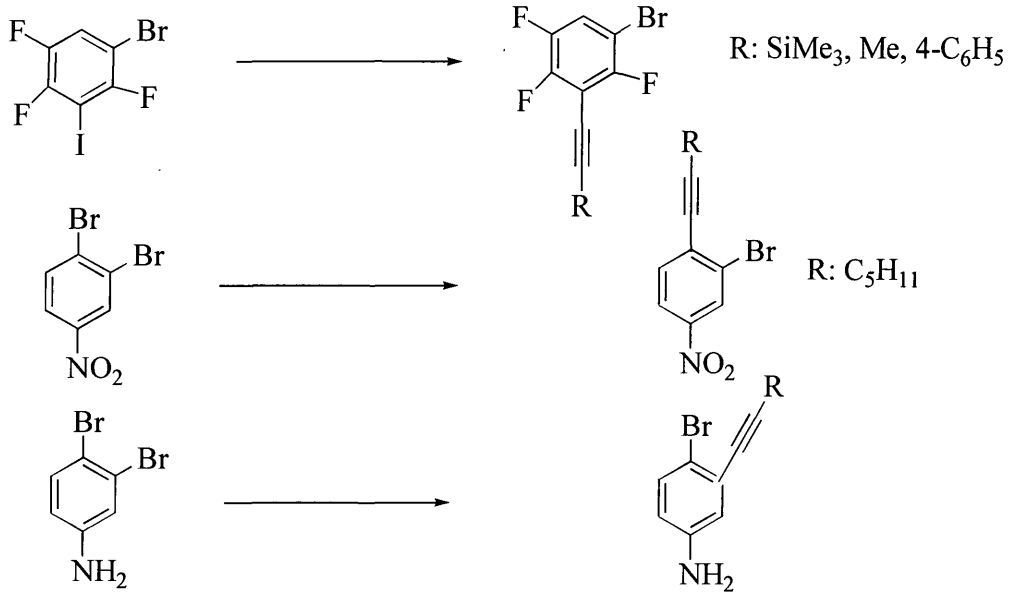
The mechanism of the reaction is believed to go via a copper intermediate that undergoes transmetallation more readily. The coordinatively unsaturated 14 e^- complex

$Pd(0)(PPh_3)_2$ (or a similar species) is produced by reductive elimination of a Pd-acetylide complex. Tetrakis (triphenylphosphine)Pd can also be used. The active species are generated after the loss of excess triphenylphosphine, Pd on C (10%) can also be used for couplings with aryl bromides. The amine plays a role in the formation of the copper intermediate and can act as a reducing agent to generate Pd(0); excess of triphenylphosphine slows down the reaction .

IV. 5. 2 Reactivity of substrates[46]

Vinyl iodide > vinyl bromide > aryl iodide > aryl bromide > aryl chloride

Reaction with aryl bromides and triflates proceeds only if activated by substituents and high temperatures, while excess triphenylphosphine provokes deposition of inactive Pd metal. Aryl chlorides react only if electron-withdrawing groups are present (eg NO_2) that weaken the C-Cl bond; however, chlorinated N-heterocycles react better if the nitrogen is in an activating position relative to chlorine[47]. One halogen can be selectively coupled by difference in reactivity or activation:

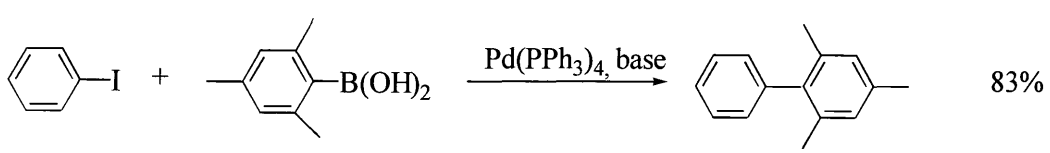


IV. 6. The Suzuki coupling reaction

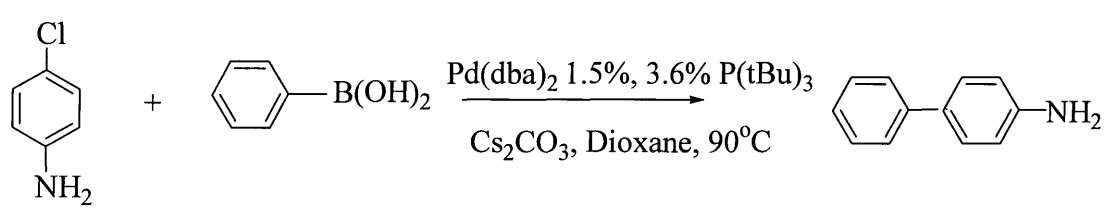
Cross coupling of aryl or vinylic halides (or triflates)[48] with organoboron reagents seems very improbable at first sight; boron is relatively highly electronegative making the carbon-boron bond almost covalent and transmetallation of an organoboron reagent to transfer an organic group should be too slow too be useful. However, after coordination of a hydroxy base or F^- anion to the boron atom, it is possible to allow transfer to the adjacent positive centre via a 1,2-migration. Therefore coupling with organoboron reagents is made possible, and is an attractive method for heterorayl and biaryl synthesis (for a review see A. R. Martin and Y. Yang[49]) even in large scale setting for the following reasons:

- Organoboron reagents are thermally stable and easy to handle,
- They are inert to water and oxygen, and show no toxicity.
- Tailor-made organoboron reagents can be synthesised for the needs of a particular reaction.

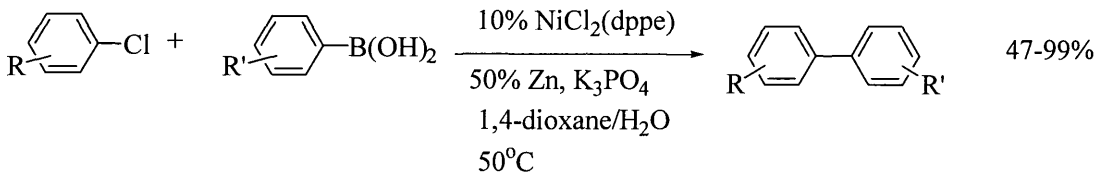
The Suzuki coupling has been used to synthesise a range of sterically hindered biaryls[50] used in natural product synthesis[51]:



Although chlorobenzenes have low reactivities, in the presence of electron-rich phosphines such as $P(tBu)_3$ coupling occurs:

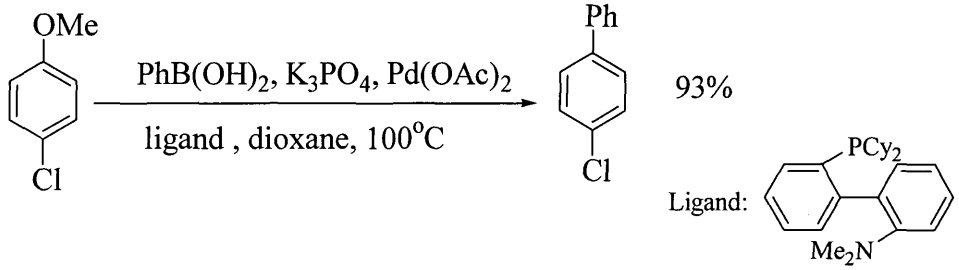


Deactivated chloroaryls usually failed to react with palladium catalysis but many examples of the use of the more active nickel catalyst allowed coupling to proceed [52,53]:

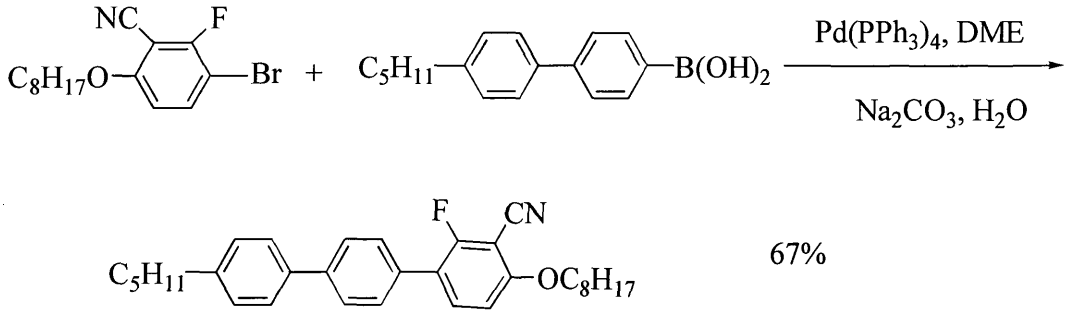


R: Ac, $COCH_3$, CF_3, CHO
R': H, F, NH_2, CH_3

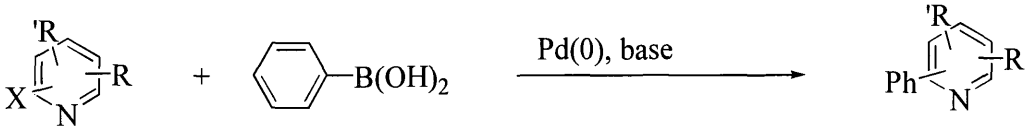
Lately[54], a few examples have been reported of successful Suzuki coupling reactions with palladium catalyst involving deactivated aryl chlorides via the use of very particular ligands as shown in this example[55]:



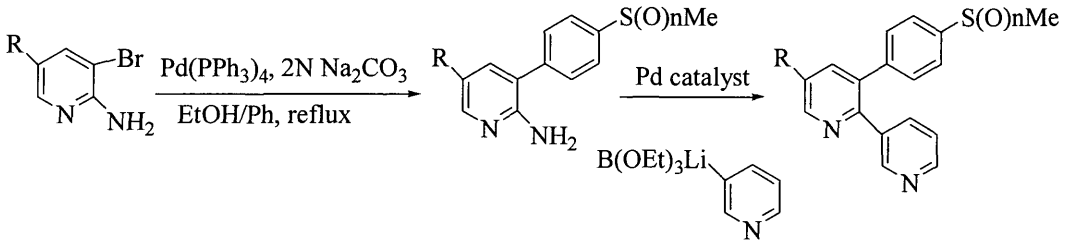
Fluorinated benzenes used in the synthesis of liquid crystals[56,57] underwent coupling with organoboron reagents:

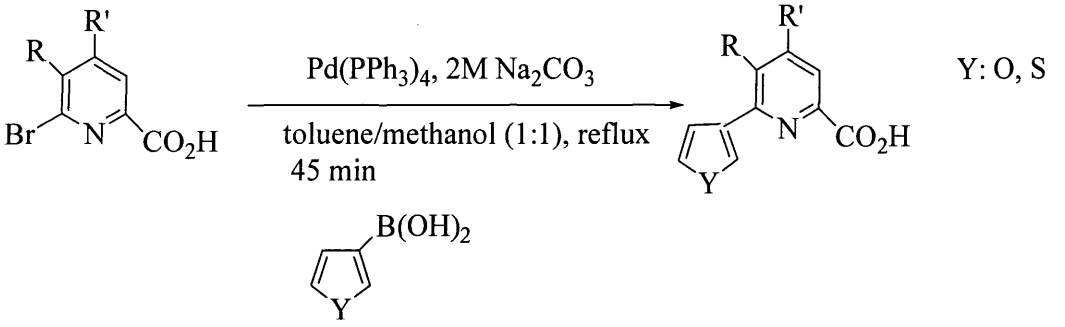


Halopyridines have also been coupled also with phenyl[58], substituted phenyl[59], pyridyl and other heterocycles[60]:

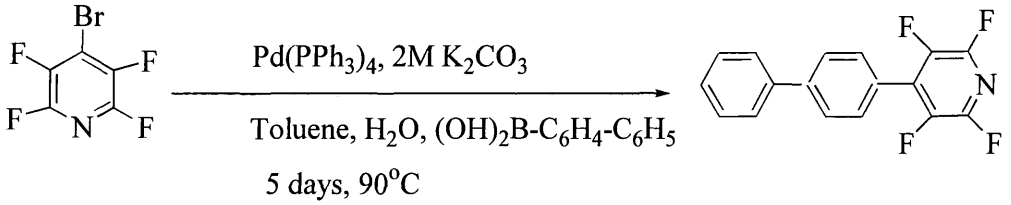


X: Br, Cl, I
R:H, OCH_3, OH, NH_2, NO_2
R': H, CH_3

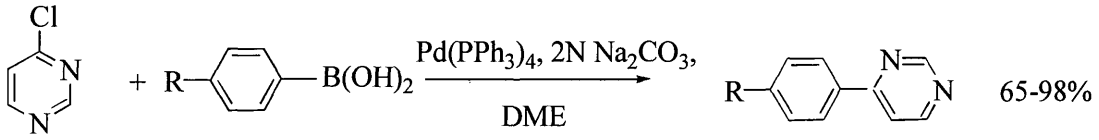




Fluorohalopyridines were coupled to obtain materials used in light emitting diodes[61]:

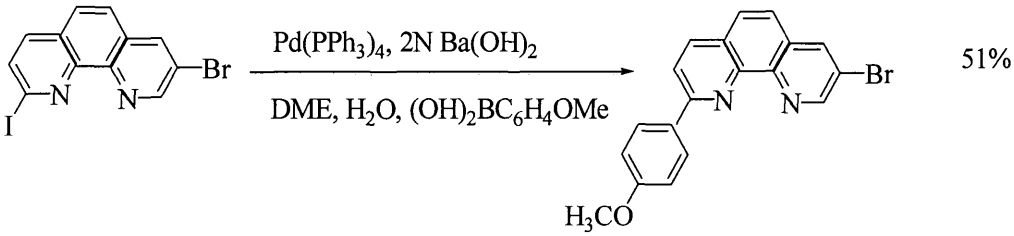


Chloropyrimidines react with a range of boronic reagents[62,63]:

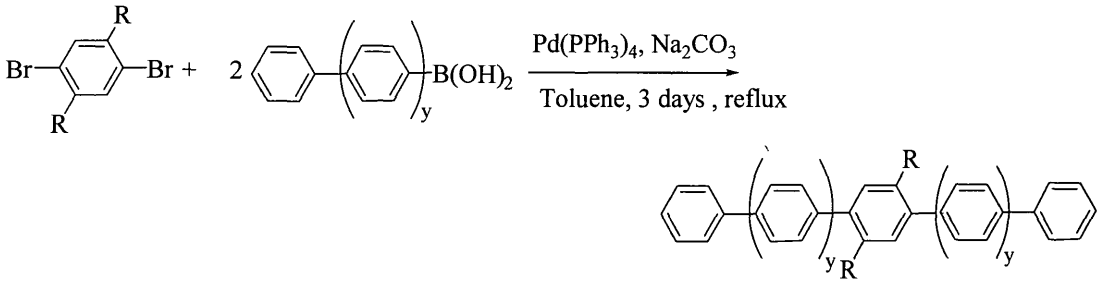


R: H, F, CN, CH_3, CH_3O, NO_2

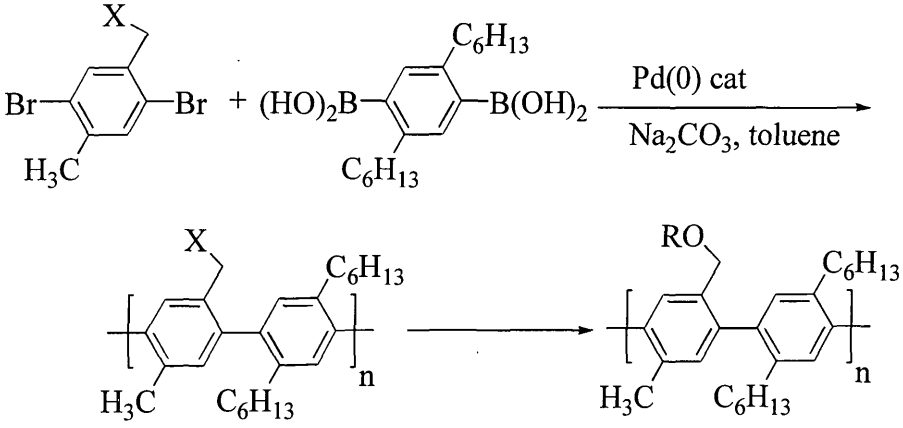
Unsymmetrical phenanthrolines[64] were synthesised:



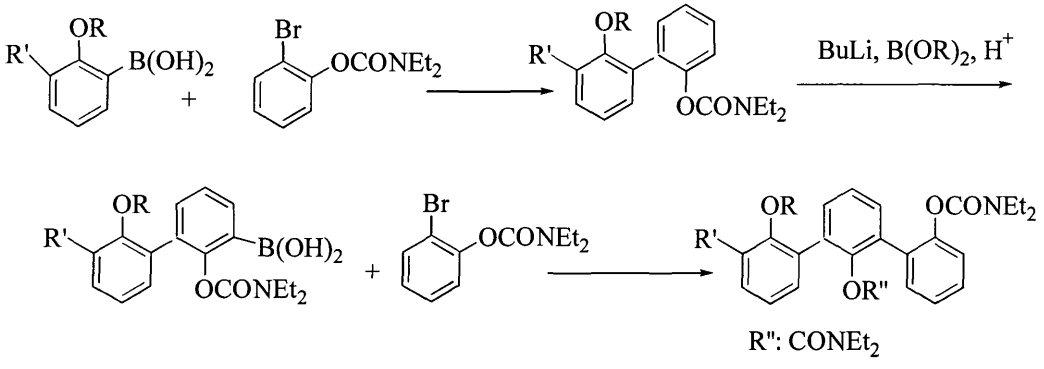
The Suzuki coupling has also been used for the palladium-catalysed polymerisation of benzene derivatives for the synthesis of oligo-*p*-phenyls[65,66]:



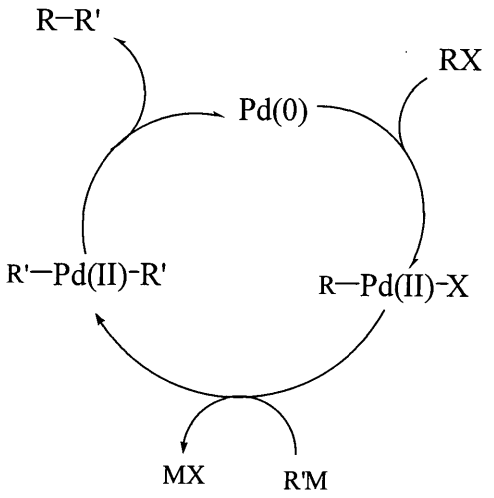
A broad range of dendrimers have also been prepared using poly(*p*-phenylene)-(PPP) derived cores using the Suzuki polycondensation:



One pot multiaryl coupling was also achieved via Suzuki coupling affording a range of polyaryls, and Snieckus[49] developed an iterative *ortho*-metallation transition metal-catalysed-cross-coupling strategy to construct terphenyls and quaterphenyls:



IV. 6. 1 Mechanism of the reaction

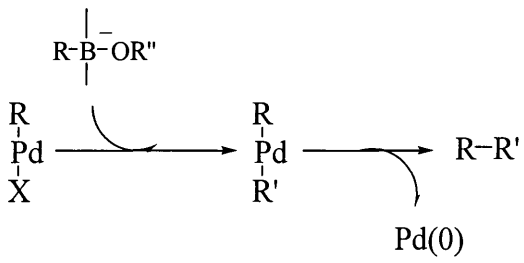


Scheme 7: General mechanism of the Suzuki coupling

The mechanism goes through the classical cycle of palladium-catalysed cross-coupling process: Oxidative addition of alkenyl, alkynyl, allyl, benzyl and aryl halides to Pd(0) complexes to give a stable trans σ-Pd(II) complex with retention of configuration; the oxidative addition is very slow and the competing β-hydride elimination might fail the reaction; aryl and alkyl halides are activated by electron withdrawing groups. The reaction proceeds with the presence of a base that can be used in aqueous solution in toluene or tetrahydrofuran, or in suspension in dioxane or dimethylformamide. Whereas $RB(OH)_2$ is not nucleophilic enough, the quaternized $RB(OH)_3^-$ is able to transmetallate. In fact, acid halides at pH 7 are slower to react than at pH 11. Hydroxide bases such as Na_2CO_3, K_3PO_4 or fluoride ions sources such as CsF are generally used.

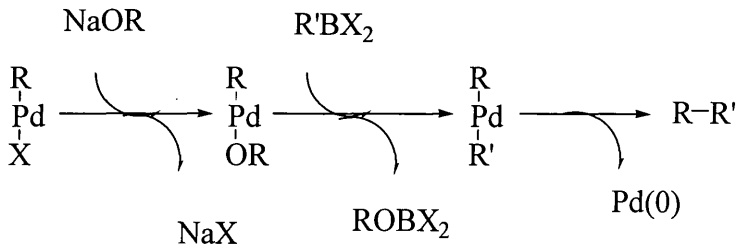
Little is known about the transmetalation step, it is highly dependant on the type of organometallics used; however, it has been proposed to proceed through one of the following processes[67,68].

The nucleophilicity of the organic group on the boron atom is enhanced by the quaternization of the boron with the base to afford the ate complex:



Alternatively, a mechanism involving the formation of palladium-alkoxy complexes has been proposed for the reaction of 1-alkenylboron compound and a 1-

alkenyl halide[65], and the possibility of the formation of such an intermediate has been proposed in the catalytic cycle of the aryl-aryl coupling reaction[65]:

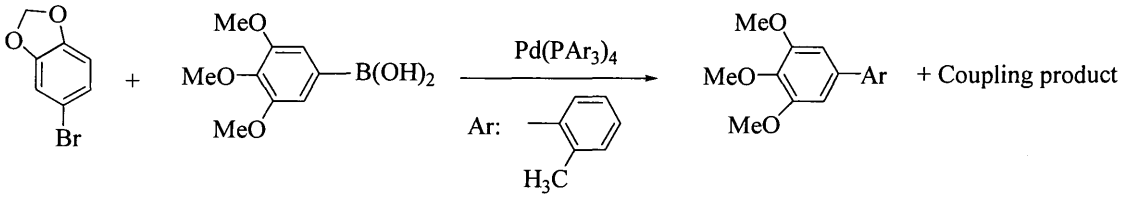


Reductive elimination occurs from the cis RPd(II)R'complex to afford the coupled product. The most commonly used palladium catalysts are $Pd(PPh_3)_4$, $Pd(PPh_3)_2Cl_2$ and $Pd(OAc)_2$ with triphenylphosphine. The order of reactivity of the R' group is:

diaryl > alkyl-, aryl- > dipropyl- > diethyl

This order of reactivity suggests the participation of the aryl π electrons (if R' is an aryl group) in the formation of the cis-diaryl Pd(II) complex which directly eliminate the organic partners from the four coordinated complex.

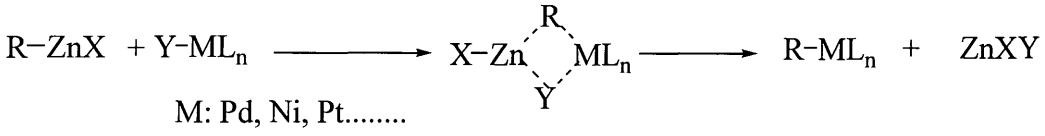
One of the problems encountered in Suzuki coupling is the aryl-aryl exchange between palladium and triphenylphosphine which is enhanced by electron-donating groups on the aryl group. The use of sterically hindered ligands such as the bulky *o*-MeC_6H_5[69] increased the yield of the coupled product:



The coupling of sterically hindered arylboronic acids with halopyridines requires the use of strong bases such as sodium t-butoxide[70]. The nucleophilicity of the boronate formed is enhanced and it will react faster with the aryl-palladium(II) complex and therefore the rate of transmetallation is increased.

IV. 7 The Negishi Coupling

The Negishi[71] reaction is the palladium-catalysed cross-coupling reaction between organozinc reagents and organic halides or triflates. Organozinc reagents have been known for about 150 years, but have been replaced by lithium and Grignard reagents for their higher reactivity. It is this low reactivity which allows for the presence of many functional groups. Organozinc reagents, although unreactive with most organic electrophiles, undergo smooth transmetallations with transition metal complexes. The resulting organometallic reacts with a range of electrophiles:



Scheme 8: Metal mediated reactions of organozinc reagents

Whereas unsaturated alkyl halides undergo smooth cross-coupling with organozinc reagents (C_{sp2}-C_{sp2} coupling), the coupling of the corresponding saturated alkyl halides (C_{sp3}-C_{sp3}) is inefficient because of the slow reductive-elimination step from the palladium complex.

Since this step is slow, exchange of the ligands might compete leading to the homocoupled products. However, using nickel in conjunction with a promoter ligand (such as *p*- or *m*-trifluoromethylstyrene)[72] instead of palladium made C_{sp3}-C_{sp3} coupling possible; the reductive elimination was accelerated by removing electron density from the metal centre through coordination of the double bond of the ligand to the metal centre which acts as a σ donor but also as π acceptor. Triflates are more reluctant to react with zinc reagents unless DPPF ligands are used. The Negishi coupling is compatible with ketones, esters, amines and nitriles. Optimal reaction conditions are provided by the use of $Pd(dba)_2$ (4%) and TTP(16%) which allow coupling in a few hours at room temperature.

Preparation of Organozinc reagents[73,74,75]

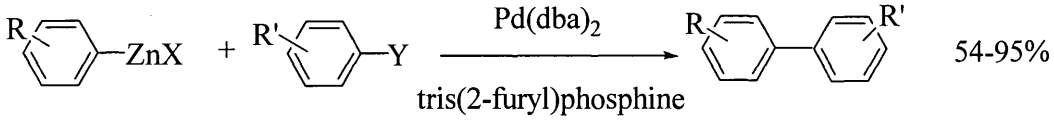
Many methods are available for the preparation of organozinc reagents:

- Preparation by direct insertion of zinc metal: used to prepare organozinc iodides bearing almost all possible organic functionalities with the exception of the nitro and hydroxy groups. The zinc dust is activated by treatment with 1,2,-

dibromoethane and TMSCl. For primary alkyl halides, the reaction occurs at 40°C in THF; secondary alkyl iodides react at room temperature, whereas benzylic bromides undergo insertion at 0°C. Insertion into a Csp^2-I bond is less straightforward, and requires longer reaction times, higher temperatures or the use of polar solvents,

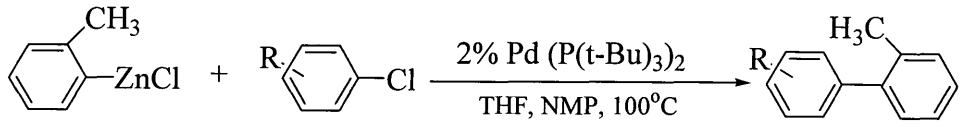
- Rieke's zinc: More activated zinc is prepared by the reduction of zinc halides, used for reactions with less reactive aryl iodides or bromides and also secondary and tertiary alkyl bromides. Zinc chloride is treated with finely cut lithium in the presence of an electron carrier such as naphthalene to produces a highly reactive zinc which reacts with various π deficient heterocycles at room temperature for few hours to give the corresponding heteroaryl zinc iodide,
- Ultrasound: has led in some cases to more efficient and faster zinc insertions than by conventional methods,
- By iodine–lithium exchange: performed on functionalised alkenyl or aryl iodides followed by a transmetallation with zinc bromide,
- By boron-zinc exchange: This method is used for the preparation of dialkylzinc compounds, which are more reactive than organozinc halides. Functionalised olefins are hydroborated with Et_2BH and treated with diethylzinc or diisopropylzinc. The exchange proceeds under mild conditions in few minutes; the driving force of the reaction is the formation of the stable dialkylzinc compounds and in some cases the formation of volatile organoboranes such as BEt_3.

The formation of biaryls was achieved in good yields using the Negishi reaction[11]:

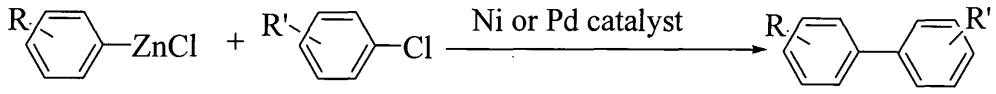


R: H, Cl, Me, CN, CO_2Me, CO_2Et, $CONMe_2$
R': OMe, CHO, CN, CO_2Me, NO_2, CO_2Et
Y; I, Br, OTf, OSO_2F
X: Cl, Br, I

Preparation of unsymmetrical biaryls from activated and deactivated aryl chlorides was also achieved[76,77]:

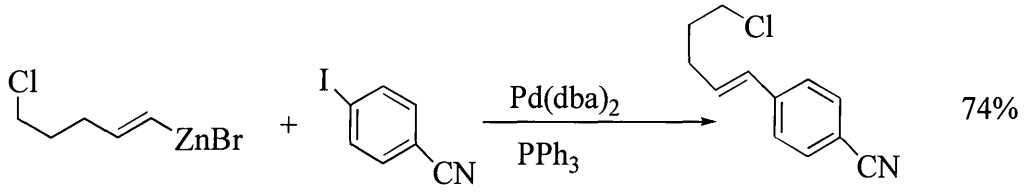


R: OCH, n-Bu, CH_3, H 88-94%%

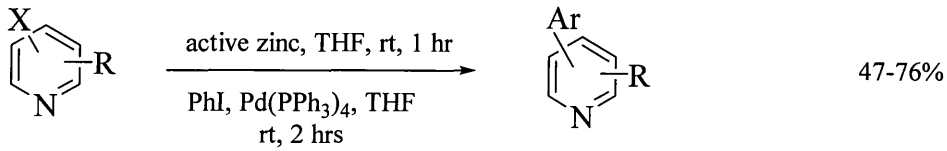


R: C_6H_5, p-CH_3-C_6H_5 63-89%
R': CN, CO_2Me, COEt

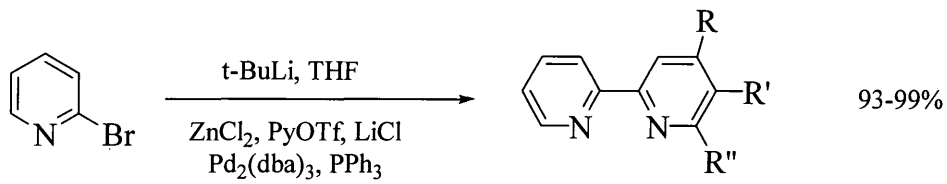
Coupling of aryl or alkenyl zinc iodides generated by lithium-iodide transmetallation with various unsaturated iodides[78] and some bromides is reported:



Cyanation of aryl triflates[79] was achieved via the organozinc intermediates, using $Pd(PPh_3)_4$. Pyridines were functionalised through the synthesis of their organozinc derivative via deprotonation-transmetallation[80-83], or the use of active Rieke's zinc[84,85]. Subsequent coupling with aryl or heteroaryl afforded unsymmetrical bisheteroaryls or bipyridines in good yields:

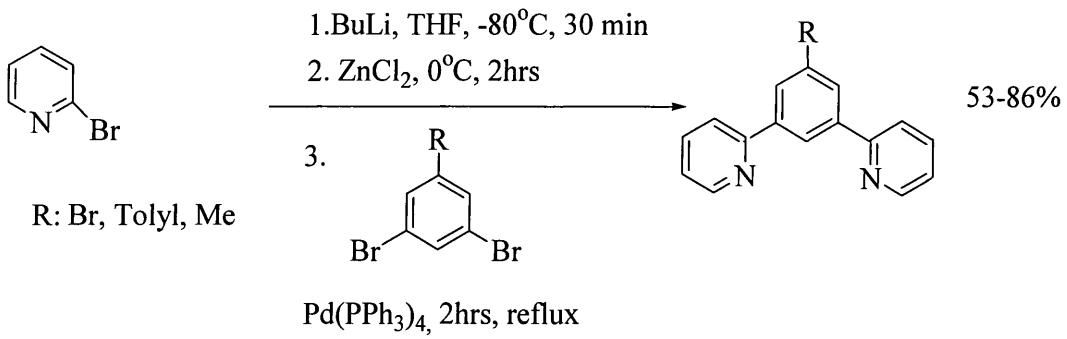


R: H; 2,6-diMe
X: 2-Br, 3-I, 4-I



R, R', R": H, Me

Terpyridines, analogues for cyclometallated luminescent cyclodextrins were efficiently synthesised by this route[86]:



R: Br, Tolyl, Me

Other heterocycles were functionalised via the Negishi reaction such as thiazoles[87], pyrazolopyridines[88], pyrazoles[89,90] that were coupled with aryl groups at the 5-position. 6-Pyridinyl-2-quinolines[91] were also synthesised in moderate to high yields.

IV. 8 The Stille coupling

The Stille reaction is the palladium catalysed coupling between an organostannane and an electrophile to form a new C-C bond[92]. It is regarded as one of the most versatile methods used in palladium-catalysed cross-coupling reactions. Organostannanes are prepared by a number of routes and are not oxygen or moisture sensitive. On the other hand, tin tolerates a wider variety of functionalities compared to organozinc reagents for example. The pitfall of this reaction is the toxicity of the

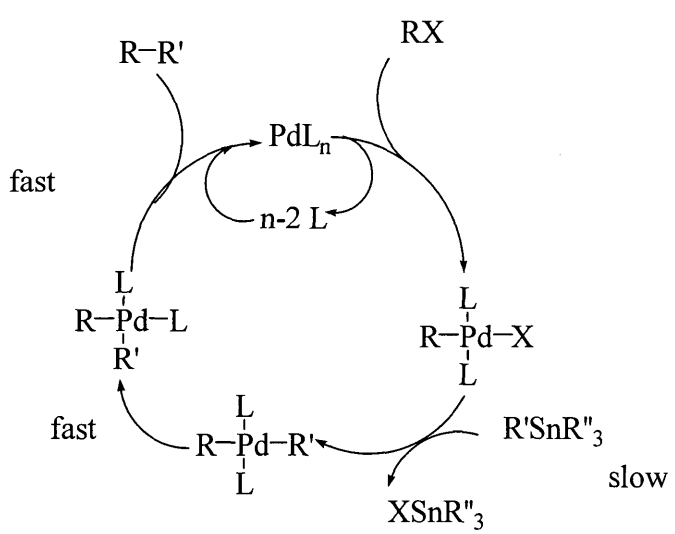
stannanes used, which makes them not suitable for large-scale synthesis; nevertheless this process may be used for the preparation of natural products and medicinal agents. In this reaction, essentially only one of the groups on tin enters into the coupling reaction and different groups are transferred at different rates from tin (alkynyl groups are the slowest).

$$RX + R'SnR''_3 \xrightarrow{PdL_n} RR' + XSnR''_3$$

Thus, an unsymmetrical organotin reagent containing three alkyl groups (usually methyl or butyl) is chosen; the fourth group which undergoes transfer is usually an alkynyl , alkenyl, aryl , benzyl or allyl group.

IV. 8. 1 Mechanism

The Stille reaction occurs under mild conditions, in high yields and allows coupling with acid chlorides, benzyl, vinyl, aryl halides and vinyl triflates, and transmetallation is the rate-limiting step:



Scheme 8: General mechanism of the Stille coupling

Sometimes co-catalysts are used, such as cuprous iodide[93] which act as a ligand scavenger to facilitate the formation of the unsaturated Pd(II) intermediate and react with organostannanes to form a more reactive organocopper reagent in highly polar solvents, similarly to the Sonogashira coupling.

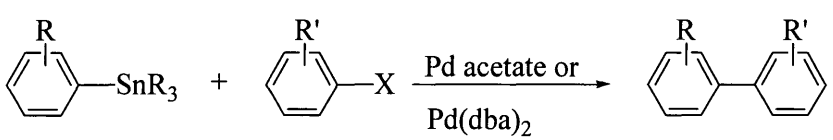
Difficulties in purification, the cost and toxicity issues associated with the use of stochiometric amounts of organotin reagents are a serious limitation to the use of this process. One of the solutions to this problem is to develop a Stille cross coupling protocol catalytic in tin[94]. This protocol reported recently allows in one pot to: a) generate the vinyltin from a terminal alkyne using trimethyltin chloride as a tin source, b) couple it with the electrophilic partner and c) recycle the organtin by product back to the organotin hydride. High yields are maintained (up to 90%) and 94% less tin has been used.

Preparation of organotin reagents

Many routes are available of organotin reagents; below are briefly listed the most used ones:

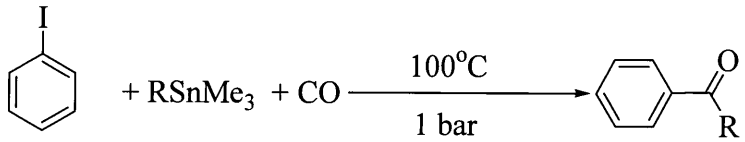
- From electrophilic and nucleophilic organotin compounds: reaction of an organotin halide with an organometallic compound,
- Addition of a complex containing a tin-copper bond across a triple bond,
- From tin amides or oxides: weak acidic proton are replaced by tin in a reaction with tin amides or oxides,
- Tin hydride addition to alkenes and alkynes, through the regiospecific free radical addition of organic hydrides to olefins.

Arylstananes possessing a tributyltin or trimethyltin moiety are the most used biaryl precursors; the coupling partner is an aryl halide or trifalte; when triflates are used addition of LiCl is necessary as co-reagent[11]:

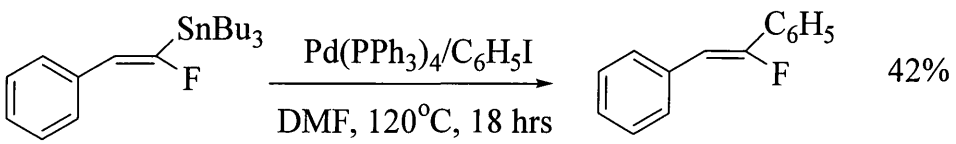


R: H, Cl, Me, OMe, CHO R': Ph, Bu, Me
X: Br, $N_2^+BF_4^-$, I, OTf, OMs

Carbonylative coupling has also been achieved:



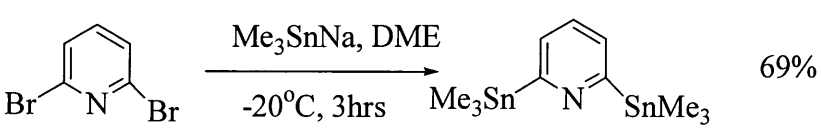
Coupling of fluorovinylstannanes with aryl and vinyl iodides provide good yields of stereoisomerically pure substituted fluoroolefins with retention of the double bond geometry[95]:



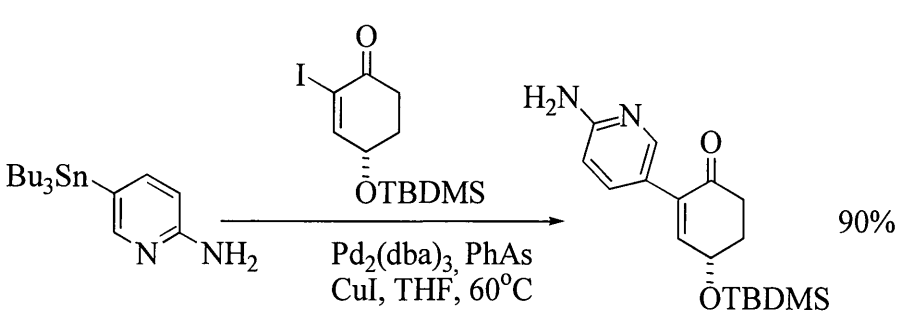
Heteroarylstannanes are more prevalent than their heteroarylboron counterparts; consequently innumerable aryls and heteroaryls take part in Stille couplings with halopyridines. In a Stille coupling reaction, the pyridine ring can act as a nucleophile (pyridylstannane), or an electrophile (pyridyl halide or triflate).

IV. 8. 2 Pyridine as a nucleophile

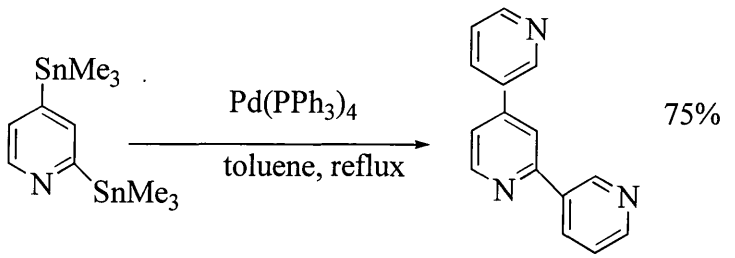
Pyridylstannanes are prepared by regioselective metalation, *ortho* lithiation of halopyridines and halogen exchange of halopyridines. Another less used method is the displacement of a halogen with sodium trimethylstannane:



Pyridiylstannanes are coupled with aryls, heteroaryls and other electrophiles:

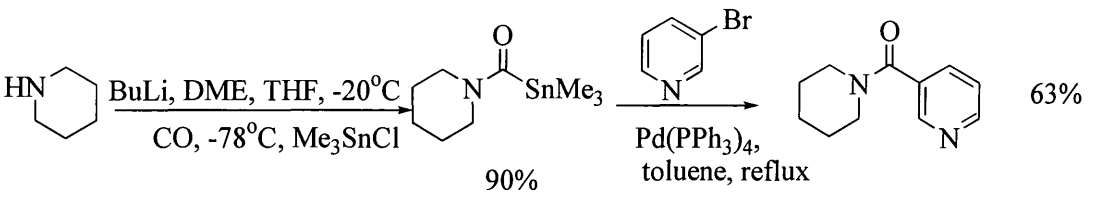


This route has been used for the synthesis of bipyridines, tetrapyridines, terpyridines and other oligomers[96,97]:



IV. 8. 3 Pyridine as an electrophile

Stille coupling of carbamoylstannane and 3-bromopyridine provides a unique entry to amide products:



The Stille strategy was used in the synthesis of a large number of natural products such as the synthesis of Lavendamycin analogues, an antitumour antibiotic[98]. A Stille coupling of a bromopyridine on solid support was described[99] which has a potential for application in combinatorial chemistry and high throughput screening.

IV. 9 Palladium Catalysed Cross Coupling reactions involving fluorinated compounds

Few examples of palladium-catalysed cross-coupling reactions involving fluorinated substrates or reagents are found in the literature, however Burton's group[100]developed a useful methodology for the cross coupling of aryl iodides and vinyl halides with perfluorovinylzinc derivatives.

Stable perfluorovinyl zinc derivatives were obtained by direct insertion of zinc in the corresponding fluorinated vinyl iodides or bromides[44]:

$$R_fFC{=}CFX \xrightarrow[RT]{\text{Zn metal, DMF}} R_fFC{=}CFZnX$$

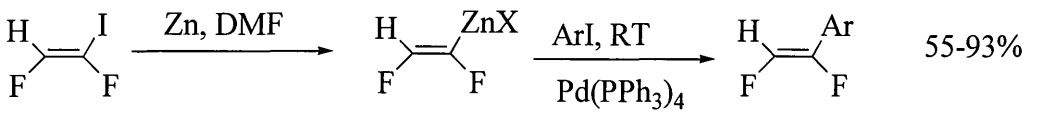
R_f: F, CF_3 cis and trans, CF_3CFCF *Z* and *E*

X: Br, I

Coupling with aryl iodides was performed in good yields:

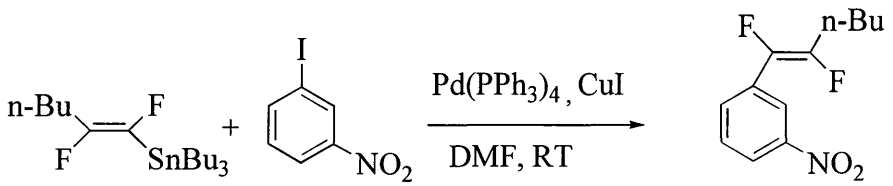
$$F_2C{=}CFZnX \xrightarrow[60 \text{ to } 80^{\circ}C,\ 1 \text{ to } 10 \text{ hrs}]{Pd(PPh_3)_4,\ 1\text{-}3\%} F_2C{=}CFAr \qquad 61\text{-}81\%$$

The zinc reagent of *cis* 1,2-difluoro-olefin precursors coupled with aryl iodides stereoselectively to give the (Z)-α–β-difluorostyrenes:



55-93%

1,2-difluorovinylstannanes prepared from 1,2-difluorovinylsilyls readily participated in palladium catalysed cross coupling reactions:



87%

IV. 10 References

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CHAPTER V

V Palladium mediated reactions of 2,4,6-tribromo-3,5-difluoropyridine

Palladium chemistry is a potential versatile methodology that might be used with halogenopyridines, however, few examples involving fluoroheterocycles are found in the literature (see section IV-5). 2,4,6-tribromo-3,5-difluoropyridine **(1)** will be used as a model compound to investigate the reactivity of fluorohalogenoheterocycles in palladium mediated reactions.

V. 1 The Sonogashira coupling

The Sonogashira coupling is one of the more powerful methods for the coupling of aryl or heteroaryl halides with acetylenic substrate owing the high yields obtained and the versatility of the substrates tolerated, the reactivity of the alkynes depends upon the electronic character of the acetylenic substituent. 2,4,6-tribromo-3,5-difluoropyridine is activated towards palladium coupling and should react smoothly under Sonogashira conditions.

V. 1. 1 Coupling with substituted phenylacetylenes

We studied the coupling of **(1)** with phenylacetylenes bearing electron donating and withdrawing groups. The acidity of the acetylenic proton in such phenylacetylenes is dependent on the nature of the substituted group on phenyl group as shown in the table below which lists the relative acidities of the substituted phenylacetylenes by comparing their respective rates of detritiation in an alkaline buffer solution[1]:

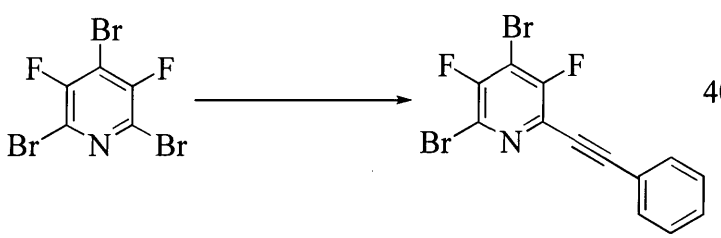
X	10^4 $k^{a)}$ (min^{-1})	$K^{b)}_{rel}$
H	**250**	**1**
p-OMe	156	0.62 (least acidic)
p-F	270	1.08
p-Cl	360	1.44
o-Cl	685	2.74 (most acidic)
p-Br	380	1.52

Table 1: Rates of detritiation of X-C_6H_4CCH compounds in buffered 20% -water methanol (pH~8.05) at 25°C.
a): Pseudo first order rate constants.
b): Relative rates to that of phenylacetylene.

The objectives are to study the reactivity of **(1)** with such substituted phenylacetylenes and the regioselectivity of the reaction, and also the possible correlation between the CH-acidity of the phenylacetylene and the reactivity with **(1)**.

V. 1. 1. a (1) with phenylacetylene

Under mild conditions, reaction of **(1)** with phenylacetylene gave the 2-mono-substituted product in moderate yields:

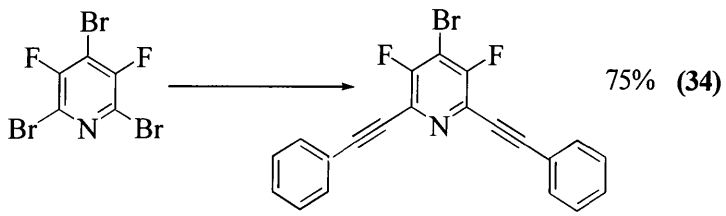


40% **(33)**

Reagents and conditions: Phenylacetylene (1.2 equivs), CuI, $PdCl_2(PPh_3)_2$, Et_3N, rt, 12 h

GCMS analysis confirmed that monosubstitution leading to **(33)** had occurred (m/z 373) and the site of substitution was elucidated without ambiguity by ^{19}F NMR analysis; the spectra displayed two peaks indicating the non-symmetrical nature of the molecule.

Using an excess of phenylacetylene (5 equivs) afforded **(34)** in good yield, and disubstitution was confirmed by GCMS analysis, which gave the parent ion corresponding to the diadduct (m/z 393) only and two lines in a ratio 1:1 characteristic of a one bromine pattern. ^{19}F NMR, which displayed one signal at -108.2 ppm, demonstrated that substitution occurred at the 2- and 6-positions and not at the 2- and 4-positions that should give two signals for the two non-equivalent fluorine atoms. Using a larger excess of the substrate (7 equi) under forcing conditions afforded only the diadduct **(34)**.



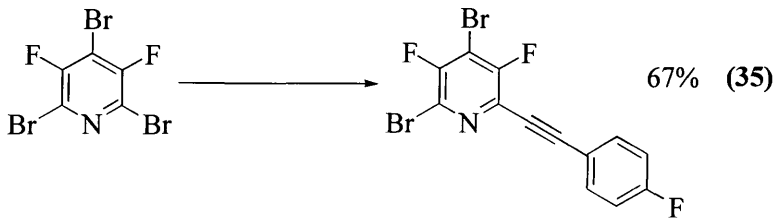
Reagents and conditions: Phenylacetylene (5 equivs), CuI, $PdCl_2(PPh_3)_2$, Et_3N, rt, 22 h

Consistent with the results above, when 4-bromo-tetrafluoropyridine was reacted with phenylacetylene, no coupling occurred, and even at increased temperature (100°C) the starting material **(1)** was recovered. These results indicate that palladium catalysed coupling does not parallel nucleophilic aromatic substitution (4-position most activated towards nucleophilic aromatic substitution in 4-bromo-tetrafluoropyridine[2,3] and in **(1)**).

When reaction of **(1)** with phenylacetylene was conducted without added copper catalyst, the reaction did not proceed at all and the starting material was recovered along with phenylacetylene dimer; this confirms the crucial role of copper (as underlined in scheme (6)) in the transmetallation step via the formation of the copper acetylide intermediate probably.

V. 1. 1. b (1) with 1-(1-ethynyl)-4-fluorobenzene

Reaction with 1-(1-ethynyl)-4-fluorobenzene afforded the 2-susbtituted adduct **(35)** in good yields. In this case, the weaker base caesium carbonate was used rather than triethylamine:



67% **(35)**

Reagents and conditions:1-(1-ethynyl)-4-fluorobenzene (1.2 equivs), CuI, $PdCl_2(PPh_3)_2$, toluene, Cs_2CO_3, 60°C, 24 h.

The structure of **(35)** was elucidated by ^{19}F NMR which gave three signals, two of them corresponding to the 3 and 5- fluorine atoms on the pyridine ring (-108.1 and -110.4 ppm) and the third one to the benzenoid fluorine (-100.9 ppm), GCMS, elemental analysis, and X ray analysis (see Fig 5) confirmed the structure. In the solid state, **(35)** adopts a totally flat conformation. The packing arrangement shows that the pyridine rings pack in a slightly offset head to tail arrangement.

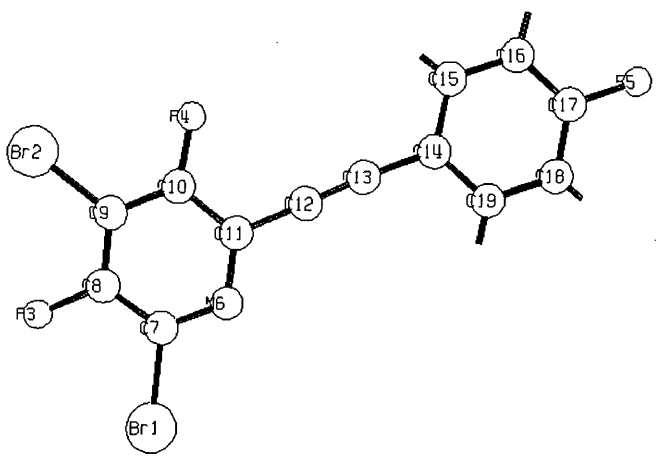


Fig 5: Single molecule of **(35)**

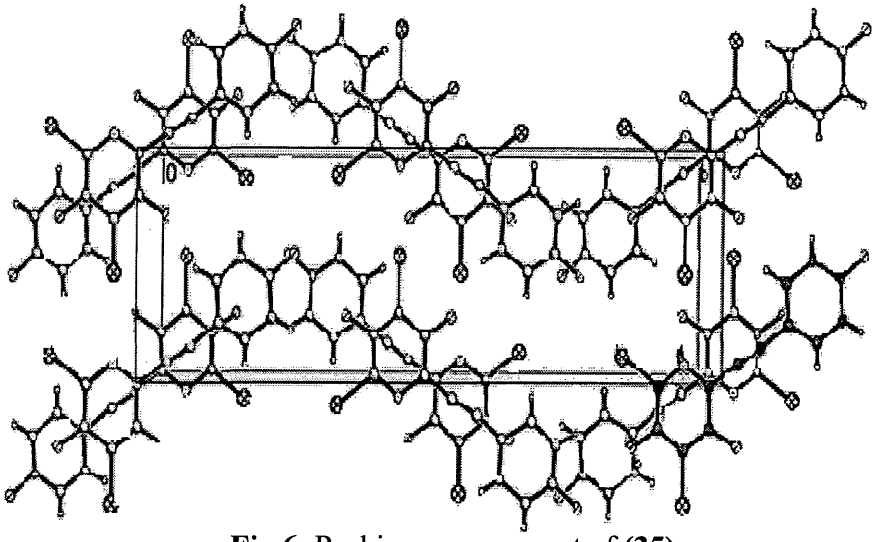
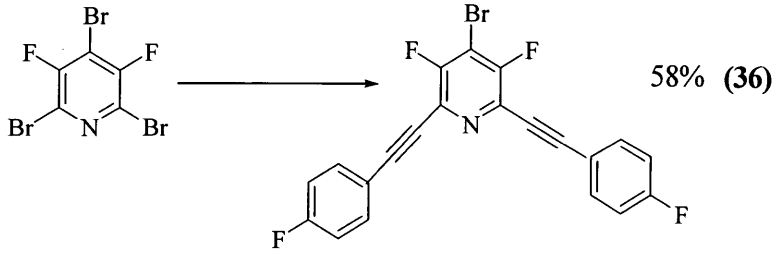


Fig 6: Packing arrangement of **(35)**

Reaction of **(1)** with excess of 1-(1-ethynyl)-4-fluorobenzene gave **(36)**. The ^{19}F NMR (Fig 7) of **(30)** consisted of one sharp singlet corresponding to the two equivalent fluorines on the pyridine ring, and a broad multiplet corresponding to the benzenoid fluorines. ^{13}C NMR (Fig 8) displayed two large $^{1}J_{CF}$ couplings (163 and 269 Hz) at 163.4 and 158.6 ppm corresponding to pyridine and aromatic **C**-F carbons respectively (Fig 8).



Reagents and conditions: 1-(1-ethynyl)-4-fluorobenzene (4 equivs), CuI, $PdCl_2(PPh_3)_2$, toluene, Cs_2CO_3, 60°C, 19 hrs.

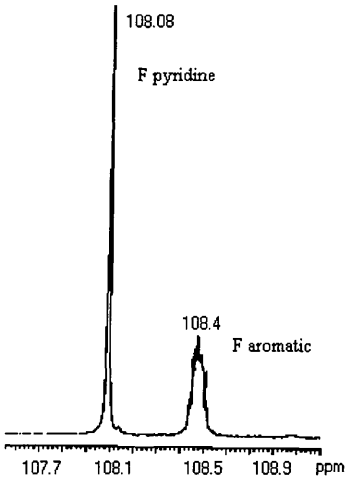


Fig 7: ^{19}F NMR of **(36)**

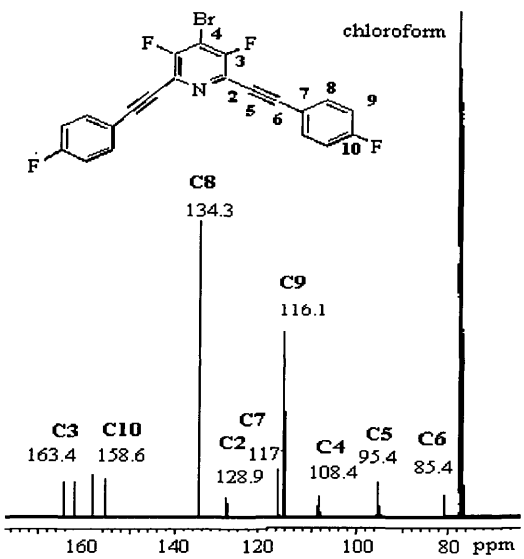


Fig 8: ^{13}C NMR of **(36)**

X ray analysis also confirmed the structure of **(36)**, and in this case the molecule is not planar (Fig 9), one benzenoid group makes an angle of 38.4° with the pyridine ring, whereas the second one an angle of 16.5° with the pyridine ring and the pyridine rings are stacked on top of each other (Fig 10).

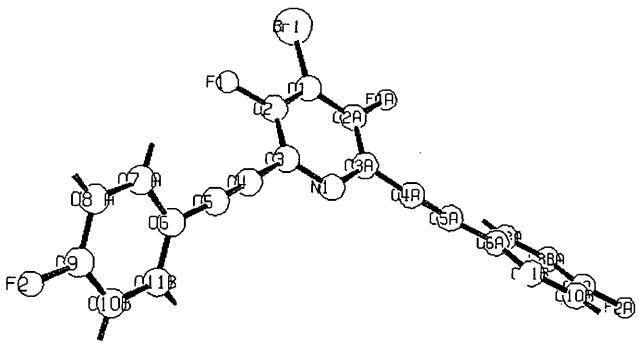


Fig 9: Single molecule of **(36)**

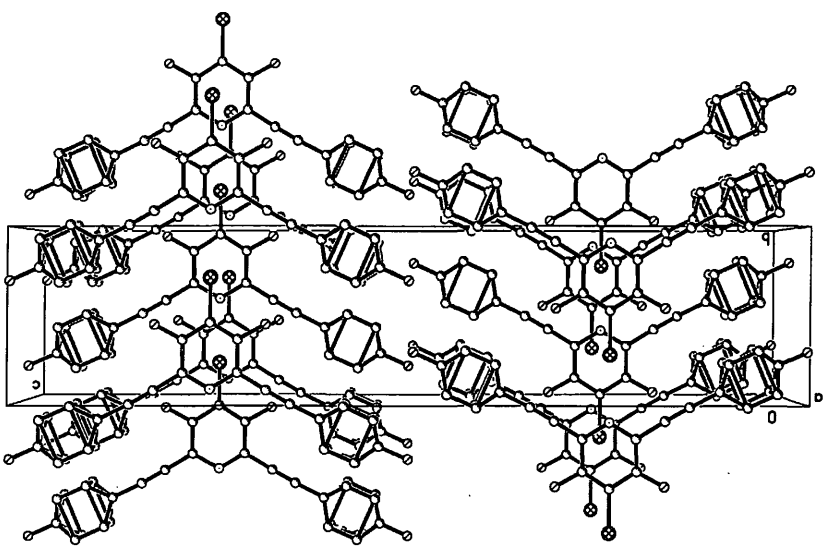


Fig 10: Packing arrangement of **(36)**

A relatively large amount of 1-(1-ethynyl)-4-fluorobenzene dimer was formed as identified by GCMS (m/z 238). According to the catalytic cycle described in scheme 4 only traces of the dimer are expected. The reaction was repeated under more rigorous conditions (argon), and in that case only traces of the dimer were detected. The formation of large amounts of the homocoupled product is, therefore, related to the presence of oxygen in the reaction media.

A qualitative experiment (using the more available phenylacetylene) was carried out to rationalise the formation of the diyne. A mixture of phenylacetylene (1 equiv) and CuI (1 equiv) were exposed to air for 3 minutes, and the mixture stirred at room temperature over night. The solution turned to a yellow paste, which was showed to consist by GCMS in 72% phenylacetylene dimer (m/z 202). This observation confirms that terminal alkynes undergo oxidative homo coupling in the presence of copper and oxygen , known as the Glaser reaction[4]:

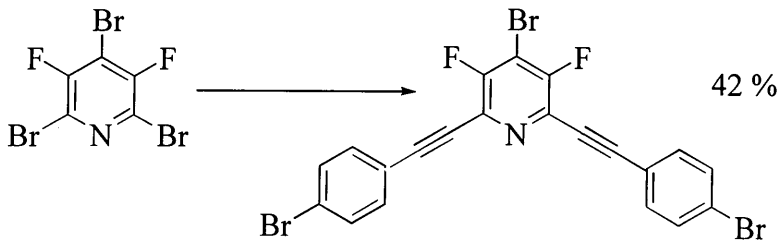
$$RC{\equiv}CH + 2\,Cu(II) \longrightarrow RC{\equiv}{-}{-}{\equiv}CR + 2H^+ + 2\,Cu(I)$$

$$Cu(I) + 1/2\,O_2 + H_2O \longrightarrow 2\,Cu(II) + 2\,OH^-$$

Previous workers[5] demonstrated in a qualitative manner that this process is catalytic and is accelerated by the presence of palladium catalyst. Therefore, palladium coupling reactions with terminal alkynes have to be carried out in the total absence of oxygen to avoid homocoupling of the alkynes.

V. 1. 1. c (1) with 1-bromo-4-(1-ethynyl)benzene

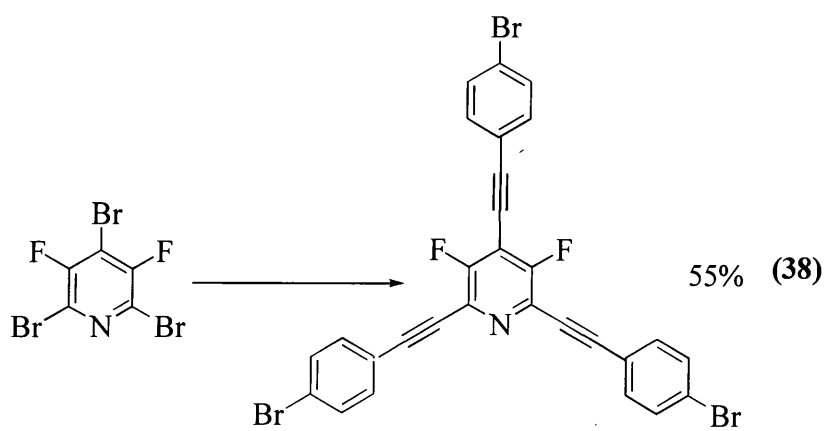
When **(1)** was reacted with one equivalent of 1-bromo-4-(1-ethynyl)benzene, the reaction mixture gave after work up and purification a white solid, which by ^{19}F NMR gave a singlet at -107.5 ppm; microanalysis showed that **(37)** was formed.



42 % **(37)**

Reagents and conditions: 1-bromo-4-(1-ethynyl)benzene (1.2 equiv), CuI, $PdCl_2(PPh_3)_2$, Et_3N, 100°C, 48 h

Coupling with a five fold excess of the substrate gave total conversion after 24 hrs, and a mixture of **(37)** and **(38)**. Purification afforded **(38)** in moderate yield; a single peak in the ^{19}F NMR, microanalysis and GCMS confirmed that **(38)** was formed.



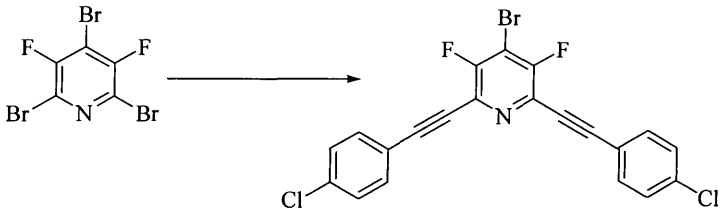
55% **(38)**

Reagents and conditions: 1-bromo-4-(1-ethynyl)benzene (4 equivs), CuI, $PdCl_2(PPh_3)_2$, Et_3N, 100°C, 17 h

We note that no further coupling with 1-bromo-4-(1-ethynyl)benzene occurs at the C-Br bond of the benzenoid ring in **(37)** and **(38)**.

V. 1. 1. d (1) with 1-chloro-4-(1-ethynyl)benzene

The reaction was conducted under the standard Sonogashira conditions, the product formed was identified as **(39)** only and no traces of the monoadduct were detected; the yields were relatively disappointing and when the reaction was repeated at longer reactions times, no significant increase of the yield was observed.



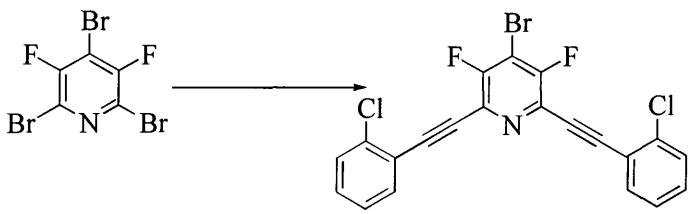
38 % **(39)**

Reagents and conditions: 1-chloro-4-(1-ethynyl)benzene (1.2 equivs), CuI, $PdCl_2(PPh_3)_2$, Et_3N, rt, 22 h

However, repeating the reaction with a 5-fold excess of substrate, gave after 12 hrs at room temperature better yields of **(39)** again (79%). Purification of the crude product in both cases was difficult, which resulted in a lowering of the isolated yields obtained.

V. 1. 1. e (1) with 1-chloro-2-(1-ethynyl)benzene

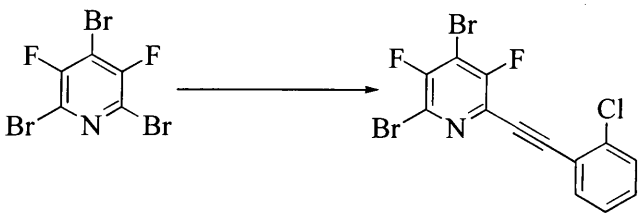
Coupling with 2-chlorophenylacetylene using an equimolar ratio or an excess of substrate afforded **(40)** in both cases. The solution turned to white after 1 hour, but the reaction was left to proceed to completion. The crude yields were high but repeated purifications contributed here again to decrease the yields.



37% **(40)**

Reagents and conditions: 1-chloro-2-(1-ethynyl)benzene (4 equivs), CuI, $PdCl_2(PPh_3)_2$, Et_3N, rt, 72 h

Using an excess of 2,4,6-tribromo-3,5-difluoropyridine, the monoadduct **(41)** was eventually obtained:



21% **(41)**

Reagents and conditions: 1-chloro-2-(1-ethynyl)benzene (0.6 equivs), CuI, $PdCl_2(PPh_3)_2$, Et_3N, 90°C, 18 h

The ^{13}C NMR (Fig 11) shows five resonance peaks for the pyridine ring carbon atoms, which is anticipated for the unsymmetrical molecule. C3 and C5 may be assigned to the low field shifts at 153 and 157 ppm on the basis of the large one bond coupling with a fluorine (214 Hz); C4 would be expected to show a doublet of doublet due to the coupling with fluorine atoms at the 3- and 5- positions but we observe a triplet instead (the ^2J couplings are comparable) at 108 ppm, the two other carbons were attributed to resonances at 122.8 and 128.5 ppm. The carbon atoms of 1-chloro-2-(1-ethynyl)benzene were readily assigned. The structure of **(41)** was also confirmed by X ray analysis (Fig12).

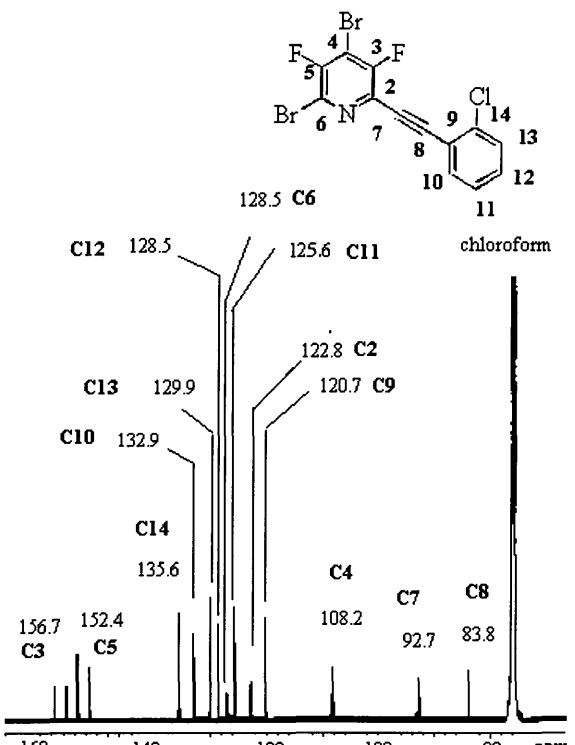


Fig 11: ^{13}C NMR of **(41)**

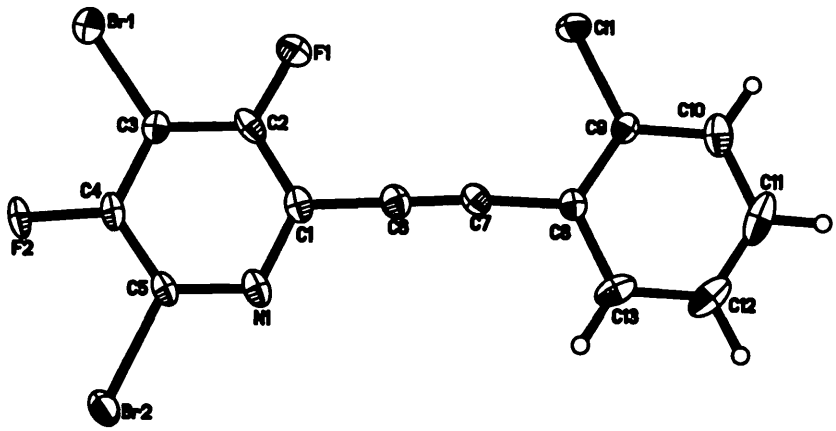


Fig 12: Single molecule of **(41)**

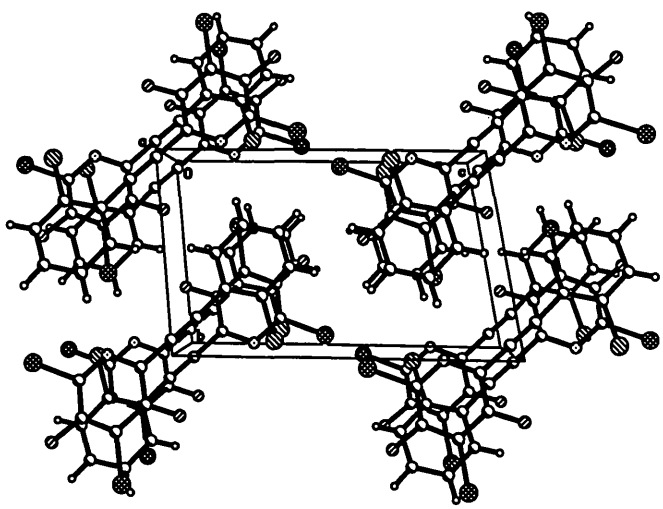


Fig 13: Packing arrangement of **(41)**

Two polymorphic form of **(40)** were revealed by the X-ray analysis of two samples obtained from two distinct reactions. The most common factors leading to polymorphism in organic compounds are the nature of the solvent of crystallisation, cooling and stirring rates, presence of impurities and the temperature of crystallisation. One form was recrystallised from toluene and the other from dichloromethane, but the rate and the temperature of crystallisation were not controlled. At a given temperature and pressure, only one polymorphic form of a substance is thermodynamically stable, but since the rate of transformation of metastable polymorphs to the stable one can be slow, it is not surprising that we obtained two polymorphs of **(40).**

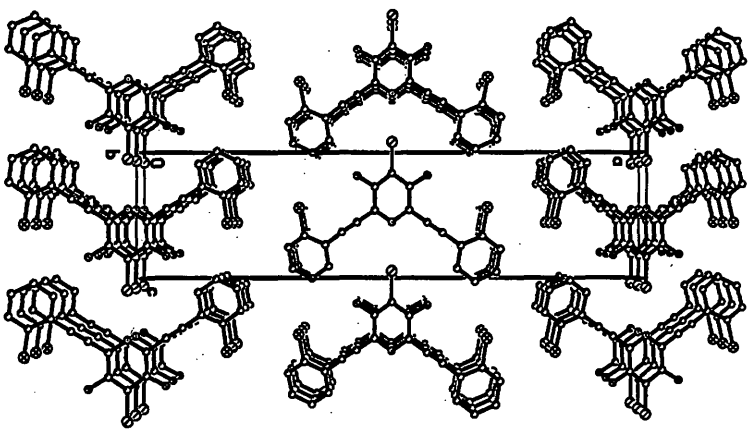


Fig 14: Packing arrangement of polymorph (I) of **(40)**

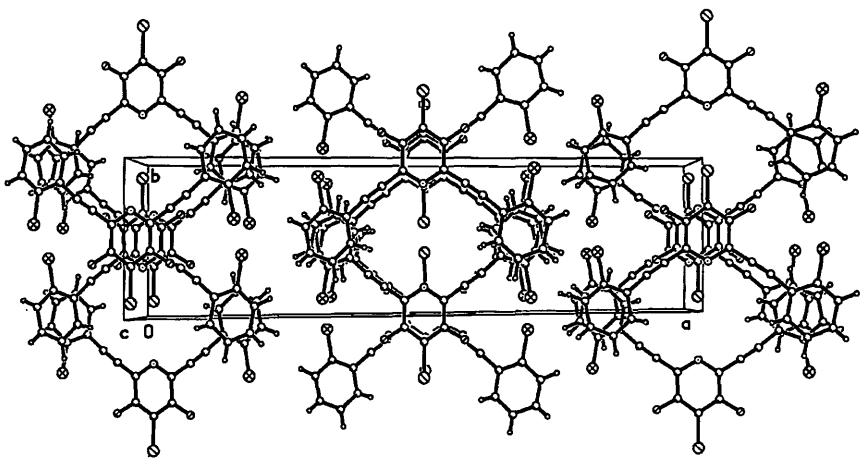
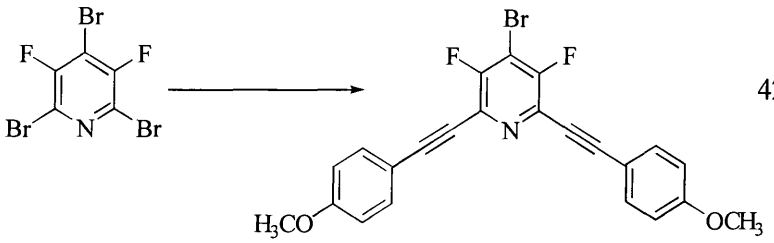


Fig 15: Packing arrangement of polymorph (II) of **(40)**

V. 1. 1. f (1) with 1-(1-ethynyl)-4-methoxybenzene

Coupling led to the formation of **(42)** only which was easily separated by column chromatography; ^{19}F NMR gave a singlet at -109.3 ppm and confirmation of the structure was achieved by X-ray analysis. Substitution occurred at the 2- and 6-position, although this substrate bears the least acidic proton of the series of substituted acetylenes.



42 % **(42)**

Reagents and conditions: 1-(1-ethynyl)-4-methoxybenzene (1.2 equivs), CuI, $PdCl_2(PPh_3)_2$, Et_3N, rt, 48 h

Examination of the solid state structure showed that the methoxy groups are distorted in the solid state and occupy two positions corresponding to two electronic densities, giving rise to two residual peaks.

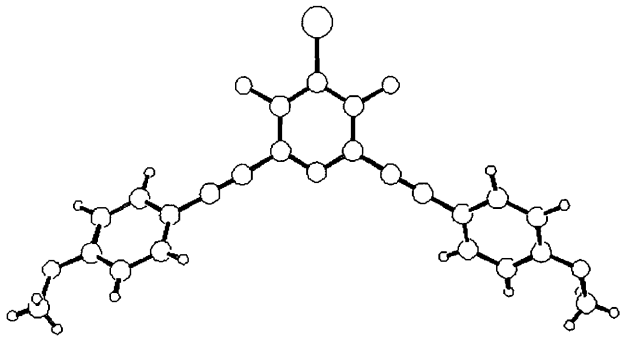


Fig 16: Single molecule of **(42)**

V.1. 2 Conclusions

The coupling reactions of **(1)** with different substituted phenylacetylenes under Sonogashira conditions led to the observations that:

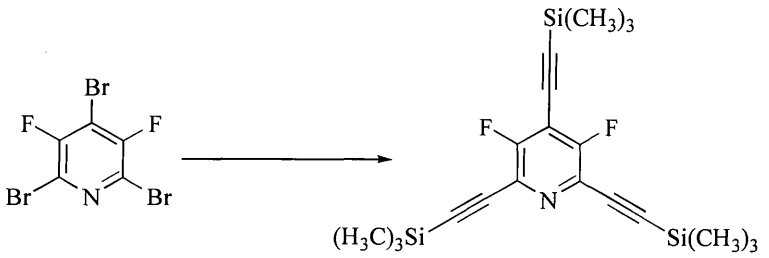
- The 2-and 6-positions are the most reactive positions in all cases,
- The 4-bromo substituted phenylacetylene is the most reactive, and also the most acidic (in the series of *para* substituted phenylacetylenes) (see section V. 1. 1. c and table 1), in this system attack at the 4-position occurs to give the trisubstituted product,
- Steric factors are important in these reactions, the most acidic substrate, namely *o*-chlorophenylacetylene, did not give the trisubstituted product. As a result, the 2- and 6-positions are the most reactive positions
- The nature of the Pd(0) active species might play a role in the regioselectivity of the reaction. The exact structure of the Pd(0) active complexes is not identified and the more bulky dimeric species $Pd(0)_2(PPh_3)_4Cl_2^{2-}$ in equilibrium with the anionic $Pd(0)(PPh_3)_2Cl^-$ complex might contribute to the structure of the active Pd(0) species.

V. 1. 3 (1) with trimethylsilylacetylene

The Sonogashira coupling reaction is a very efficient method for the synthesis of terminal acetylenes (as an alternative to the halogenation-dehalogenation of vinyl aromatics for example). The use of trimethysilylacetylene[6] is advantageous since it will afford a crystalline and readily manipulated trimethysilsyl–protected ethynyl fluorinated pyridine derivative.

Coupling of 2,4,6-tribromo-3,5-difluoropyridine **(1)** conducted using the standard catalyst ($PdCl_2(PPh_3)_2$) and CuI, gave a brown insoluble powder. Microanalysis of the powder revealed the presence of nitrogen (7.9 % N) and the formation of polymeric material and ring opening of the pyridine may have occurred.

Alternatively, we used another catalytic system ($Pd(OAc)_2$, PPh_3)[7], which afforded **(43)** after reaction at room temperature. In this case the use of 1.2 equivalents of the substrate was sufficient to afford the trisubstituted product only.

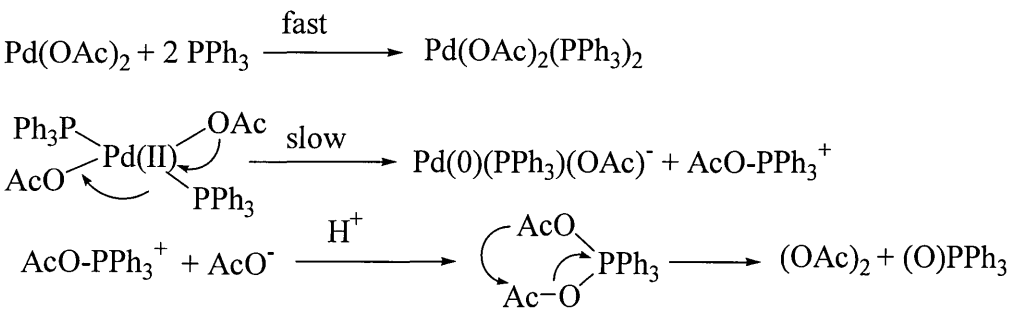


29 % **(43)**

Reagents and conditions: trimethysilyl acetylene (1.2 equivs), CuI, $Pd(OAc)_2$, PPh_3, Et_3N, rt, 48 h

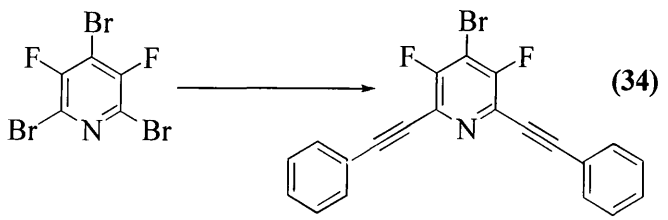
The compound **(43)** is fairly sensitive to air and moisture (mp 96.3-96.8°C), although it did not degrade with time.

When $Pd(OAc)_2$ was used in combination with PPh_3 as a catalytic system, we observed the formation of the phosphine oxide (GCMS-^{31}P NMR), in fact one equivalent of triphenylphosphine is oxidised to triphenylphosphine oxide during the reduction of palladium acetate to Pd(0):



Two unexpected results were obtained in the above coupling: a) ($PdCl_2(PPh_3)_2$, CuI) is inactive for this system, whereas ($Pd(OAc)_2$, n PPh_3, CuI) promotes coupling; b) all three 2, 4, and 6- positions are activated. When palladium dichloride is used, another process might compete efficiently with the transmetallation or the reductive elimination step of the reaction, because either the copper acetylide is not formed or transmetallation into the Pd (II) complex is too slow. Whereas with palladium acetate, transmetallation and reductive elimination proceed normally. In order to probe the role of the structure Pd(II) complexes in the coupling on the site of substitution, reaction of 2,4,6-tribromo-3,5-difluoropyridine**(1)** with phenylacetylene using $Pd(OAc)_2$, PPh_3 as a catalytic system was undertaken.

The reaction was performed in a NMR tube and the only coupled product observed by ^{19}F NMR and GCMS was **(34),** and no substitution at the 4-position was observed:

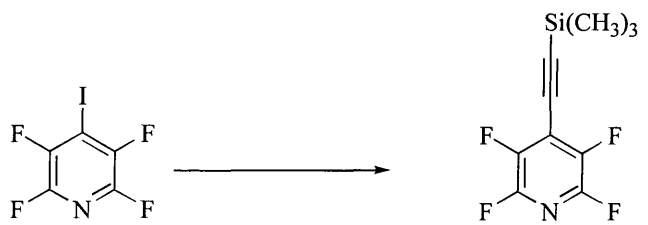


(34)

Reagents and conditions: Phenylacetylene (1.3 equivs), CuI, $Pd(OAc)_2$, PPh_3, Et_3N, sonic bath, 3 hrs

It is difficult to rationalise the results obtained above, as many factors such as the nature of the Pd(0) active species and intermediate formed and the bulk of the active Pd(0) species involved may play a role in the reactivity and regioselectivity of the reaction.

Coupling of trimethylsilylacetylene with 4-iodotetrafluoropyridine afforded **(44)** as a mixture with the trimethylsilyl acetylene dimer (m/z 194). The reaction proceeded slowly and after 5 days at room temperature the conversion was 81%. Separation by column chromatography (on silica or alumina) or preparative gas chromatography did not allow the isolation of highly pure samples of **(44)**.



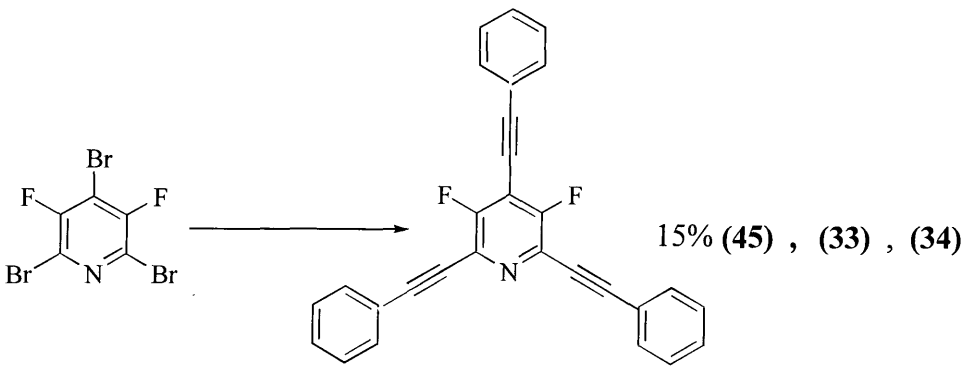
70 % GC yield **(44)**

Reagents and conditions: trimethysilyl acetylene (1.2 equivs), CuI, $Pd(OAc)_2$, PPh_3, Et_3N, rt, 5 days

V. 1. 4 (1) with trimethylsilylphenylacetylene

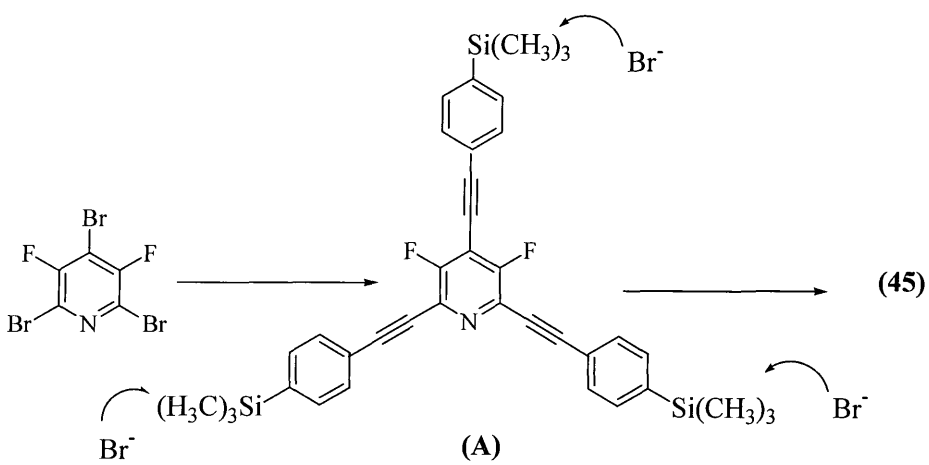
Coupling was relatively slow since no reaction occurred after 28 hrs at room temperature; the reaction was allowed to proceed by increasing the temperature to reflux, affording three products corresponding to **(33)**, **(34)** and **(45)** as a minor product.

The structure of **(33)** and **(34)** were established by comparison with authentic samples previously prepared.



Reagents and conditions: trimethylsilylphenylacetylene (7 equivs), CuI, $PdCl_2(PPh_3)_2$, Et_3N, reflux, 56 h

The formation of **(45)** results from the deprotection of the Ar-TMS product **(A)** with the bromide anion Br^- formed in situ:



Use of the alternate catalytic reagent ($Pd(OAc)_2$, PPh_3) under milder conditions (room temperature) failed to afford the coupled product. Here again, as with trimethylsilylacetylene, we observed that substitution occurs at the 4-position, which confirms the fact that the nature of the nucleophile is also important in the regioselectivity of the reaction.

V. 1. 5 Conclusions

2,4,6-Tribromo-3,5-difluoropyridine **(1)** is activated towards palladium induced cross coupling reactions under Sonogashira conditions, the 2- and 6- positions are the most active positions and in some cases substitution at all three positions is observed. The interplay of different factors such as the nature of the Pd(0) species formed, the nature of the nucleophile and steric factors give rise to different patterns of substitution. Electronic and steric effects of the substituted groups on phenylacetylene induce different arrangements and packing in the solid state.

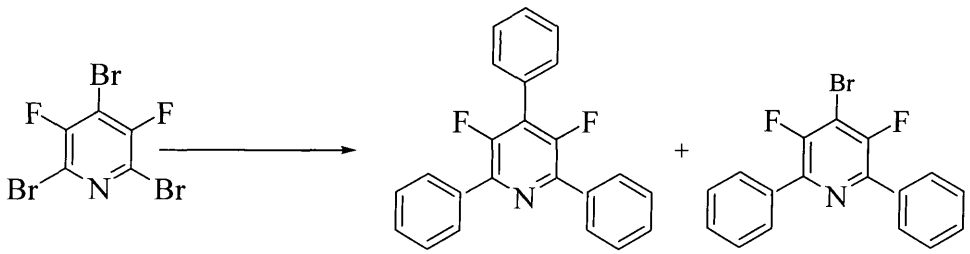
V. 2 The Suzuki Coupling

The Suzuki coupling is a versatile and efficient palladium mediated coupling method for the substitution on 2,4,6-tribromo-3,5-difluoropyridine **(1)** using substituted aryl boronic acids. The wide range of commercially available boronic acids, the relatively low toxicity of the by products formed and the possibility to work under aqueous conditions can be exploited to perform coupling with various aryl boronic acids.

The original conditions as first reported by Suzuki ($Pd(PPh_3)_4$, Cs_2CO_3/H_2O, toluene) applied for the synthesis of biaryls showed that electron rich arene boronic acids were prone to deboronation under these conditions but, Gronowitz[8] demonstrated that such deboronations can be suppressed by using glycol dimethyl ether (DME) as the solvent. Gronowitz[9,10] conditions ($Pd(PPh_3)_4$, Cs_2CO_3/H_2O, DME) have been used during our coupling reactions.

V.2. 1 (1) with benzeneboronic acid

Gronowitz conditions were used for this coupling using $Ba(OH)_2$ as a base, one equivalent of benzeneboronic acid afforded a mixture of the monosubstituted, disubstituted and trisubstituted 2,4,6-tribromo-3,5-difluoropyridine; using an excess of benzeneboronic acid gave 3,5-difluoro-2,4,6-triphenylpyridine **(46)** as a major product in good yields:

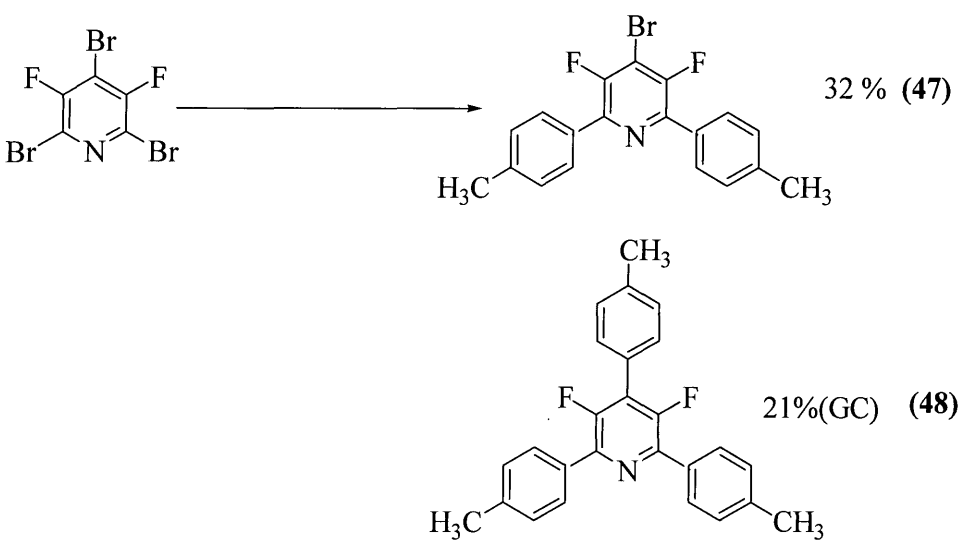


43% **(46)** 18% (GC)

Reagents and conditions: 3 equivs benzeneboronic acid, 4 equivs $Ba(OH)_2$, $Pd(PPh_3)_4$, DME/H_2O, 93°C, 48 hrs.

V. 2. 2 (1) with *p*-tolylboronic acid

Using one equivalent of *p*-tolylboronic acid afforded a mixture **(47)** and **(48)** after total conversion of the starting material, ^{19}F NMR proved the symmetrical nature of the two molecules (respectively at -117 and -127 ppm). Using an excess of the nucleophile afforded **(48)** as a major product:



32 % **(47)**

21%(GC) **(48)**

Reagents and conditions: 1.2 equivs *p*-tolylboronic acid, 2 equivs $Ba(OH)_2$, $Pd(PPh_3)_4$, DME/H_2O, 93°C, 24 hrs.

Single crystal X-ray analysis of **(47)** showed a disordered arrangement, where interestingly four single molecules (A), (B), (C), (D) have different bond angles and bond lengths. Fig 17 show two of the four different arrangements of the single molecules. The benzene rings (with their hydrogens) in (B) for example are disordered

with equal probability between two positions (I) and (II). The order in the sublattice (a/2, b, c) is violated by different orientations of the benzene rings in (C) and (D).

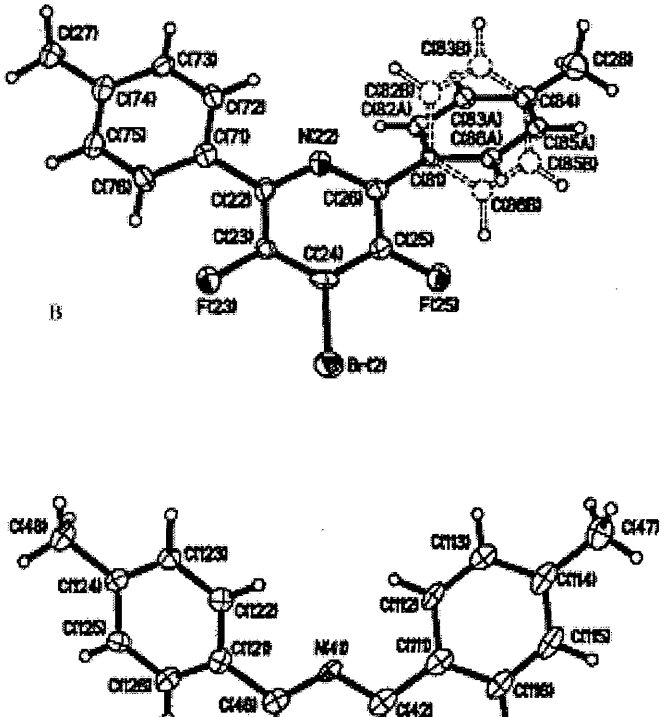


Fig 17: Two different types of single molecules in **(47)**

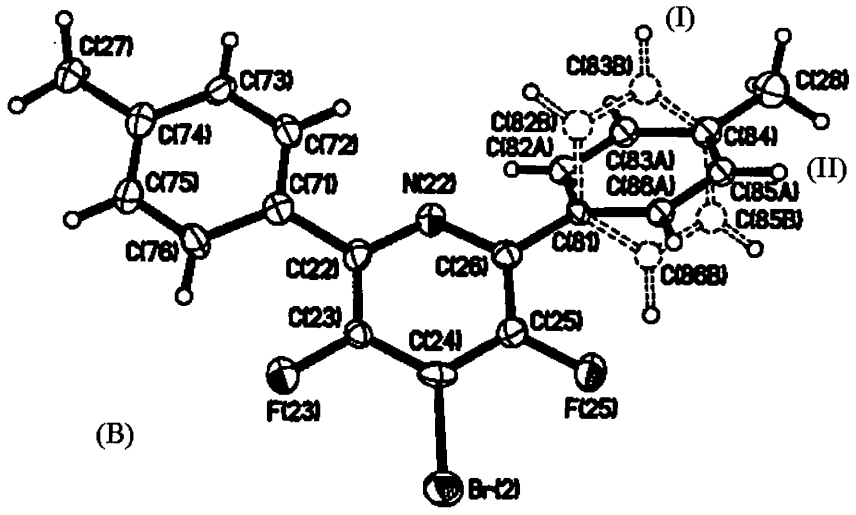
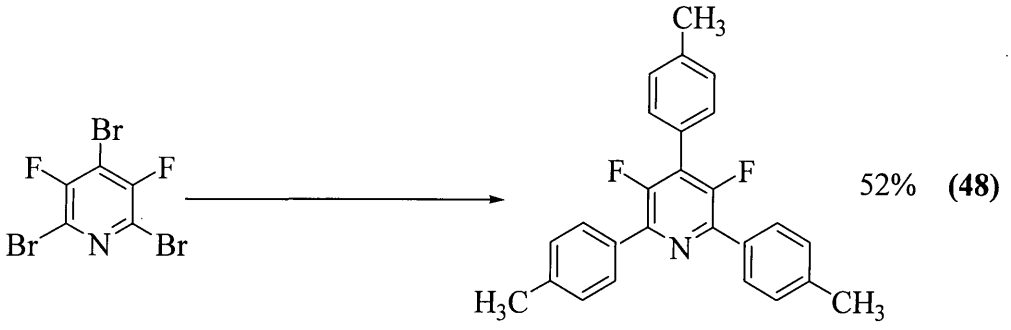


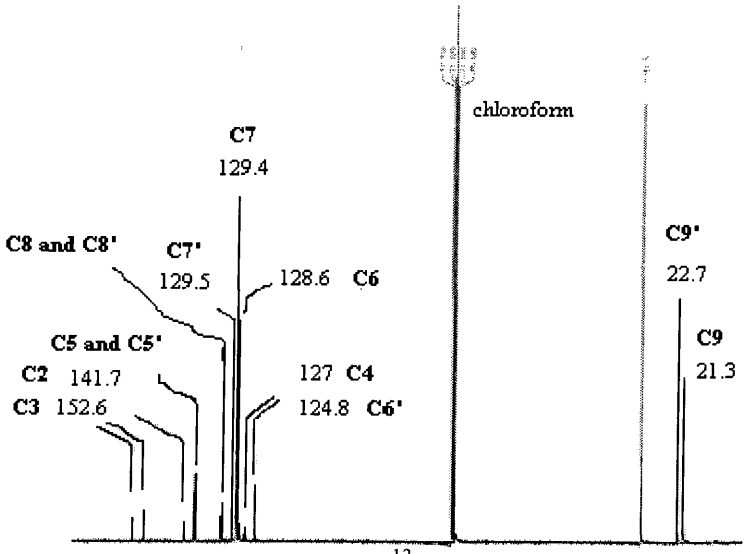
Fig 18: Disorder of the benzene ring in (B).

This unexpected packing in the solid state might result from the steric bulk introduced by the methyl groups on the benzene rings, and more surprisingly we also observe partial overlapping of the pyridine moiety with the aromatic rings.



Reagents and conditions: 3 equivs *p*-tolylboronic acid, 3 equivs $Ba(OH)_2$, $Pd(PPh_3)_4$, DME/H_2O, 93°C, 18 hrs.

^{13}C NMR of **(48)** showed that the aromatic carbons of the rings at the 2-C and 4-C of the pyridine ring are not identical and the NMR spectra displayed 13 resonances, three of them corresponding to the symmetrical pyridine ring carbon atoms, a low field large doublet at 152.6 ppm corresponding to C-3 and C-5. C-4 shows a triplet (rather than a doublet of doublet) at a lower shift (127 ppm) than expected due to the presence of the *p*-tolyl group instead of the bromine atom.



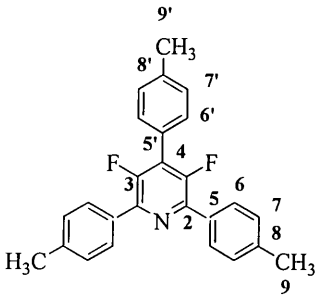
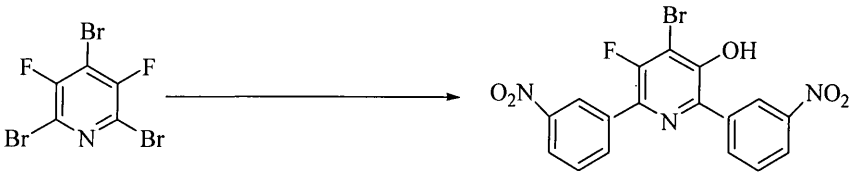


Fig 19: ^{13}C NMR of **(48)**

V.2. 3 (1) with 3-nitrobenzeneboronic acid

Coupling with 3-nitrobenzene boronic acid afforded unexpected results, since when both equimolar and excess amounts of the nucleophile were used we observed the exclusive formation of **(49)**. The structure of **(49)** was confirmed by GCMS, NMR and microanalysis.



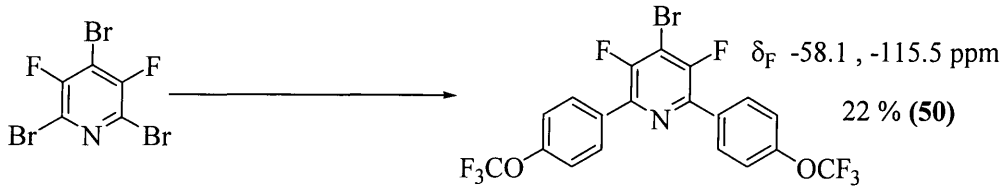
54%, **(49)**

Reagents and conditions: 1.2 or 3 equivs 3-nitrobenzeneboronic acid, $Ba(OH)_2$, $Pd(PPh_3)_4$, DME/H_2O, 93°C, 20 hrs.

We can explain the formation of **(49)** by the fact that the introduction of the strongly electron withdrawing group at the 2 and 6-positons activates the pyridine ring towards nucleophilic substitution, and attack at the C-F center by the free base (OH^-) present in solution occurs. The nucleophilic substitution occurs even if the amount of base present is the amount strictly necessary (2 equivalents) for the palladium catalysed coupling, which accounts for the moderate yields obtained. We could also envisage that attack of the free base occurs prior to palladium catalysed coupling, however, this is improbable since no similar behavior is observed with other substituted boronic acids.

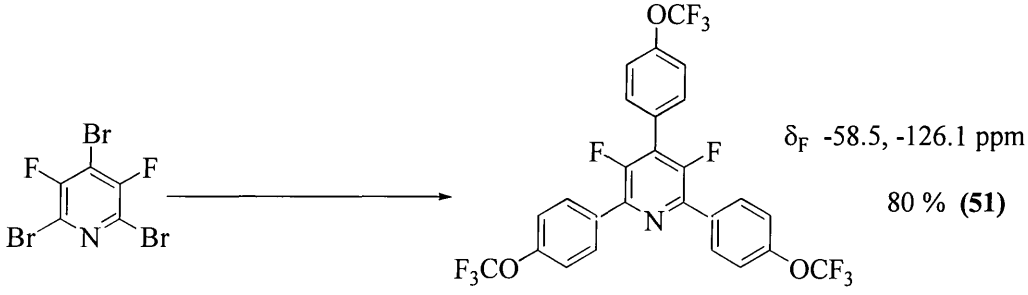
V. 2. 4 (1) with 4-trifluoromethoxybenzeneboronic acid

Coupling with *p*-trifluoromethoxybenzene boronic acid afforded a mixture of 4-bromo-3,5-difluoro-2,6-di(4-trifluoromethoxyphenyl)pyridine **(50)** and 3,5-difluoro-2,4,6-tri(4-trifluoromethoxyphenyl)pyridine **(51)**:



Reagents and conditions: 0.8 equivs 4-trifluoromethoxybenzeneboronic acid, $Ba(OH)_2$, $Pd(PPh_3)_4$, DME/H_2O, 93°C, 21 hrs.

An excess of 4-trifluoromethoxybenzeneboronic acid afforded 3,5-difluoro-2,4,6-tri(4-trifluoromethoxyphenyl)pyridine **(51)** in good yields:



Reagents and conditions: 3 equivs 4-trifluoromethoxybenzene boronic acid, $Ba(OH)_2$, $Pd(PPh_3)_4$, DME/H_2O, 93°C, 12 hrs.

In the course of these experiments we made some observations that are worth to noting and rationalising:

-When coupling with 4-methoxybenzeneboronic acid was performed, lower yields of the expected substituted products were obtained and the mixture was contaminated with the dimerised product 1-methoxy-4-(4-methoxyphenyl)benzene (m/z 214, compared to authentic samples). The formation of the biphenyl has been generally observed only when the cross coupling is very slow, and the rate of homocoupling is increased in the presence of oxygen[11,12].

-We also observed in the course of all the coupling reactions that various amounts of triphenylphosphine oxide (TPPO) **(B)** are present as soluble phosphorous species in solution. TPPO was separated and identified by ^{31}P NMR, ^{13}C NMR and GCMS. Although TPPO might be formed by the oxidation of triphenylphosphine in the presence of oxygen, and commercial palladium tetrakis triphenylphosphine contains TPPO in small amounts, it cannot account alone for the amounts observed, since the reactions are carried out under nitrogen and the same batch of palladium catalyst was used for all the coupling reactions. The formation of TPPO occurs during the regeneration of the catalyst by reduction of Pd(II) back to Pd(0). The reduction of Pd(II) intermediates at elevated temperatures with PPh_3 under basic conditions is a well known[13,14] process.

Studies on the reaction of palladium(II) complexes in alkali solution in the presence of iodobenzene gives TPPO and a phenyl palladium dimer with two hydroxo bridges only; these species were identified by ^{31}P NMR and single crystal X-ray crystallography, and almost no Palladium metal was formed:

$$2[(PPh_3)_2PdCl_2] + 2PhI + 6KOH \longrightarrow [PPh_3Pd(Ph)(OH)]_2 + 2\,PPh_3O + 2\,KI + 4KCl + 2H_2O$$

The palladium phosphine complexes proceeding in the presence of alkali are reduced to a Pd(0) species by their own coordinated phosphine ligands which are oxidised to phosphine oxides, OH^- playing the role of a specific promoter. Even if we are unable to identify the precise Pd species involved, this process may account for the regeneration of the active palladium catalyst in our reaction. In fact, the stoichiometry used (1:2) provides more than enough base to complex the boron reactants and form the hydroxy-palladium complex, leaving free OH^- to take part in the reduction of Pd(II) back to Pd(0). However, that catalytic regeneration can also occur through the reduction of Pd(II) by the organoboron substrate must not be completely ruled out[15].

V. 3 Palladium catalysed reactions of 2,4,6-tribromo-3,5-difluoropyridine(1) with amines and ethers

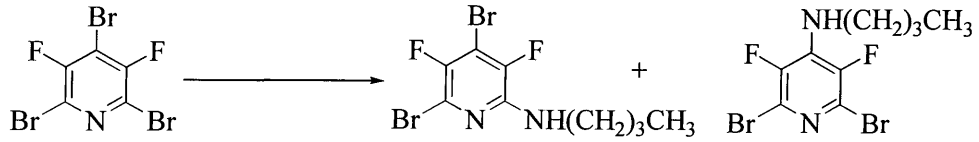
V. 3. 1 (1) with butylamine

The palladium catalysed amination reaction has emerged as a useful methodology for the amination of aryl halides as an alternative route to nucleophilic aromatic substitution. The nucleophilic substitution reactions of 2,4,6-tribromo-3,5-difluoropyridine with amine nucleophiles led to different products arising from substitution at the C-F and / or C-Br bond; these patterns of substitution are dependent on the nature of the amine (hard or soft). Ammonia led to exclusive substitution at the C-F bond, whereas piperidine and diethylamine to substitution at the 2- and 4- positions. Coupling with a primary amine (butylamine) was performed under catalytic and non-catalytic conditions to investigate the effect of palladium on selectivity, which we expect to direct substitution at the C-Br centre.

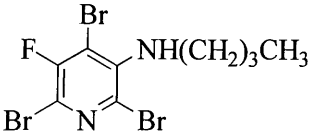
For the coupling of 2,4,6-tribromo-3,5-difluoropyridine with butylamine we used a bis-chelating phosphine ligand such as DPPF (1,1'-bis(diphenylphosphino)ferrocene) (BINAP can also be used) which inhibit side reactions such as β-hydride elimination from the amidopalladium complex and the formation of the debrominated product (otherwise observed with non chelating ligands such as P(*o*-tolyl)$_3$ ligand)[16,17].

The presence of electron-withdrawing groups on 2,4,6-tribromo-3,5-difluoropyridine should accelerate the reaction rate by accelerating the reductive elimination step. The amido complexes containing the chelating phosphine DPPF are stable and facilitate reductive elimination to form the aminopyridine expected. The reductive amination is believed to occur from a cis four coordinate palladium amido complex although it has been proposed that an additional pathway involving the formation of a dipyridineamido complex, more stable than the monopyridineamido complex, might occur and slow down the catalytic cycle.

The same reaction was conducted without palladium catalyst in the same conditions (solvent, temperature, reaction time). The results obtained in both reactions are summarised in the table below:



(53)



(54)

	Yield of **(53)** [c] (%)	Yield of **(54)** (%)
Catalytic conditions [a]	42	40
Non-catalytic conditions [b]	20	57

a): butylamine (1.2 equivs), $Pd_2(dba)_3$, DPPF, Cs_2CO_3, toluene, 90°C, 20 hrs.
b): butylamine (1.2 equivs), toluene, 90°C, 20 hrs.
c):combined GC yields of the two isomers.

The purification of **(53)** was not attempted and **(54)** was identified by GCMS and NMR spectroscopy (Fig 20).

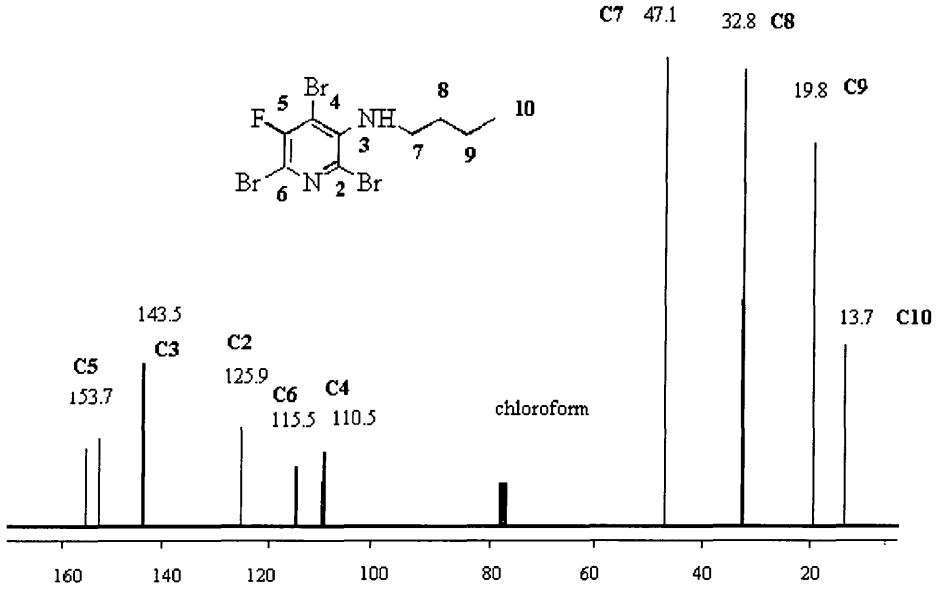


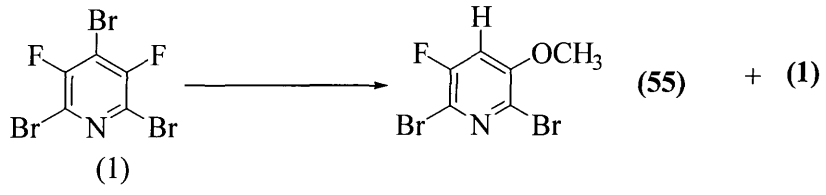
Fig 20: ^{13}C NMR of **(54)**

We expect that the use of a harder amine would direct substitution towards the C-F centre even more.

V. 3. 2 (1) with sodium methoxide

A similar approach was used to probe the ability of palladium coupling methodology to direct coupling at the C-2 and C-4 carbons in the formation of aryl ethers. Although reduction through β-hydrogen elimination cannot occur when aryl alcohols (or oxides) are used, the use of bis-chelating ligand is still necessary because it will accelerate reductive elimination and the use of preformed oxides is preferable to caesium carbonate.

Coupling with sodium methoxide performed in toluene in the presence of palladium catalyst, proceeded only after addition of a phase transfer catalyst to give 2,6-dibromo-3-fluoro-5-methoxypyridine **(55)** only; GCMS analysis showed a typical three line two bromine pattern and the structure was confirmed by ^{13}C NMR (fig 21).



Reagents and conditions: sodium methoxide (2 equivs), $Pd_2(dba)_3$, DPPF, Cs_2CO_3, benzyldimethyltetradecylammonium chloride dihydrate toluene-THF (1: 9), 80°C, 60 hrs.

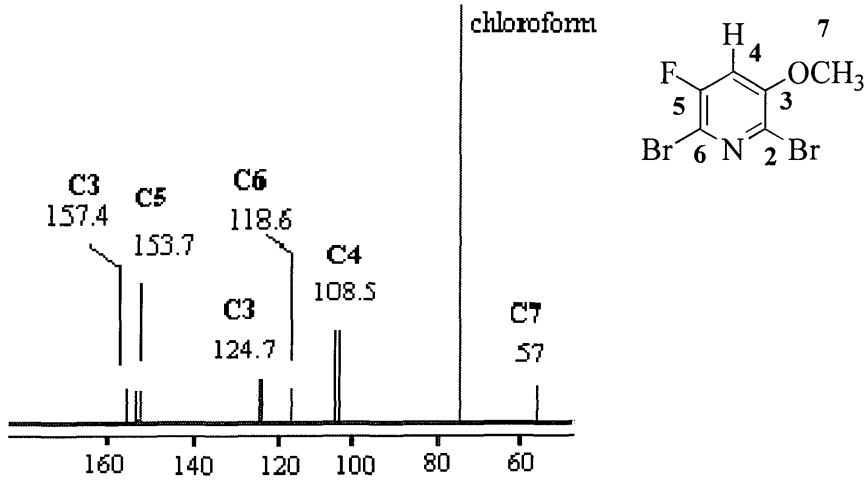
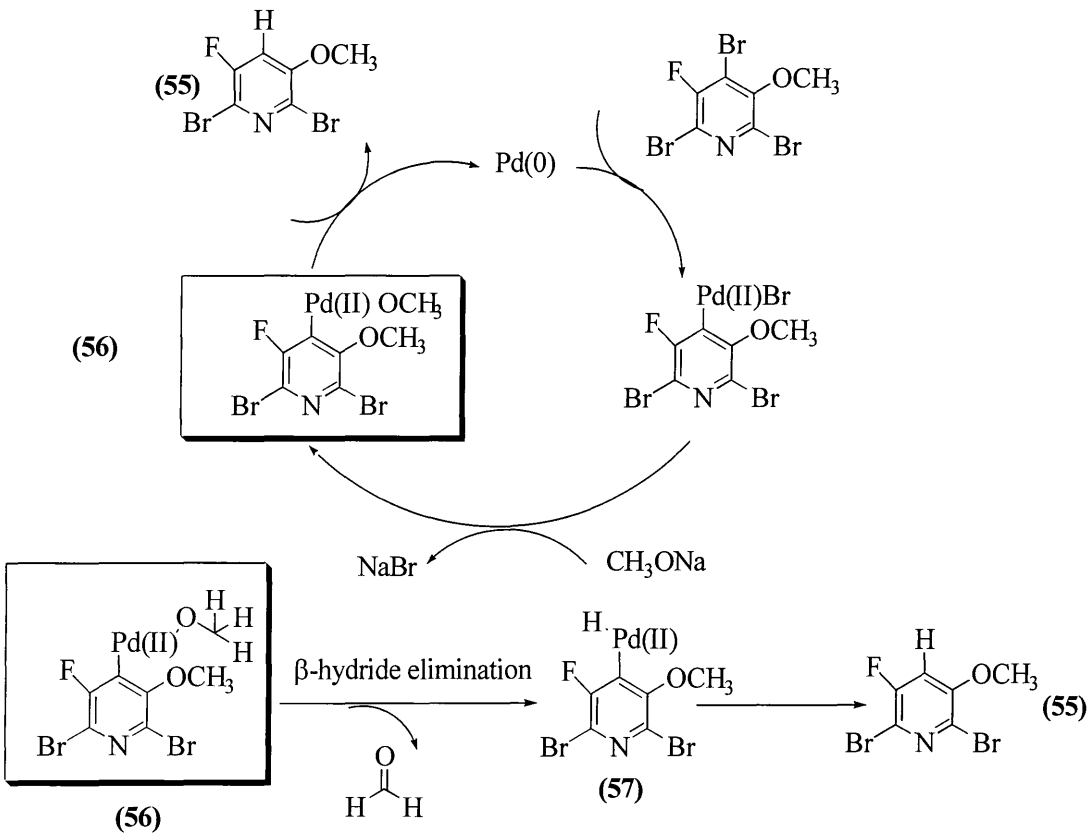


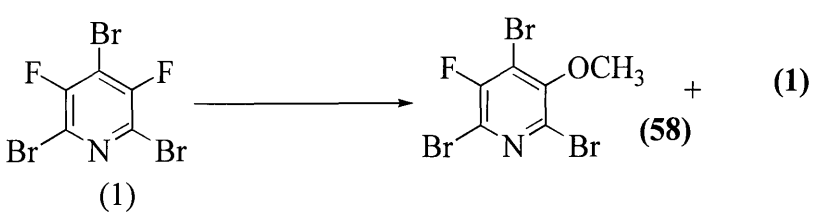
Fig 21: ^{13}C NMR of **(55)**

The formation of **(55)** results probably from the generation of the β-hydride elimination product, which is formed due to the faster nucleophilic substitution of the hard methoxide anion at the C-F centre compared to the slower C-O reductive elimination from the palladium complex **(56)**. The bis-chelating ligand effect favouring the reductive elimination over β-hydride elimination is not sufficient to counterbalance the reactivity of sodium methoxide towards the C-F centre.



Scheme 10: Mechanism of the formation of **(55)**

The same reaction without palladium catalyst afforded the expected 2,4,6-tribromo-3-fluoro-5-methoxypyridine **(58)**, as identified by comparison with previous authentic samples of **(7)**.



Reagents and conditions: sodium methoxide (2 equivs), toluene-THF (1:9), rt, 20 hrs.

V. 3. 2 Conclusion

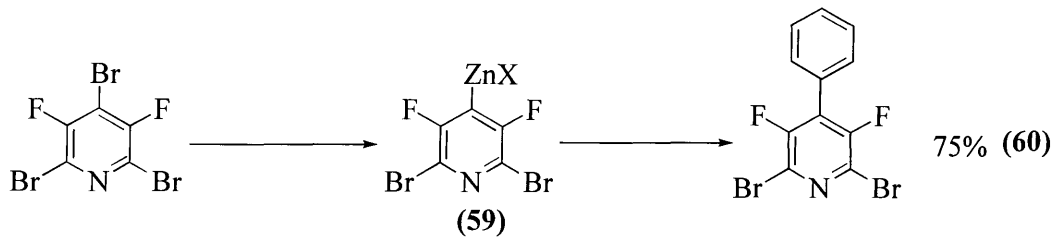
These experiments demonstrate that reactions of 2,4,6-tribromo-3,5-difluoropyridine towards oxygen and nitrogen nucleophiles are mostly governed by the directing effects of fluorine and bromine through their interaction with hard and soft nucleophiles, and this pattern of reaction is not significantly affected by the directing effect towards the C-Br introduced by the use of palladium catalysis. However, the reduction of bromine to hydrogen when sodium methoxide was used is observed.

V. 4 The Negishi coupling

The Negishi coupling could be a useful approach for the synthesis of aryl-heteroaryl compounds from 2,4,6-tribromo-3,5-difluoropyridine **(1)** using aryl halides and the zinc derivative prepared from **(1)**. We first investigated the possible ways to prepare the desired zinc derivative. Direct insertion of zinc (15 hours, Zn granules, DMF), active Rieke's zinc (lithium, naphthalene, $ZnCl_2$) and chemical activation (Zn granules, dibromethane, trimethylsilyl chloride) failed to afford a zinc derivative. However, the more straightforward directed halogen-metal exchange at low temperature with butyl lithium followed by transmetalation with (Li-Zn) provided access to the organometallic zinc intermediate in a quantitative manner. Therefore, the synthesis of the 4-aryl substituted 2,6-dibromo-3,5-difluoropyridine is a possible via a one pot synthesis in a three step sequence.

V. 4. 1 (1) with iodobenzene

This methodology was applied for the arylation of 2,4,6-tribromo-3,5-difluoropyridine and afforded the coupled product 2,6-dibromo-3,5-difluoro-4-phenylpyridine **(60)** in good yields after heating at 50°C for 17 hours, and the product was easily purified by column chromatography:

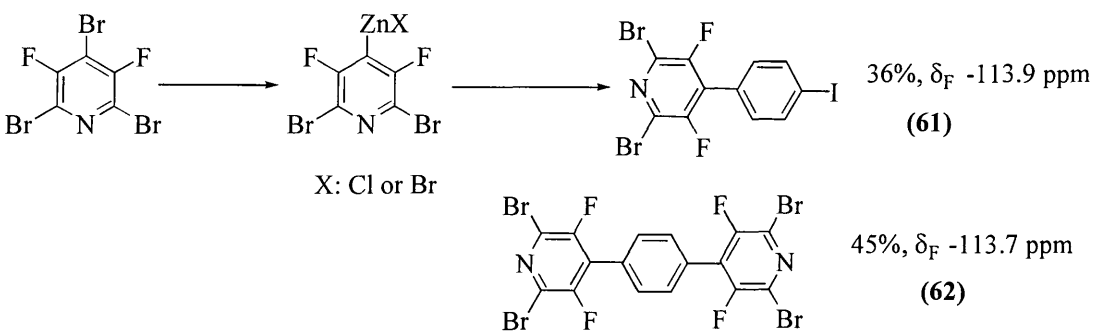


(59)

Conditions and reagents: BuLi (1.2 equivs), -78°C, THF, 1 hr; ZnX_2 (1M, 2.5 equivs), rt, 30 mn; iodobenzene (0.6 equivs), $Pd_2(dba)_3$, TPP, 50°C , 17 hrs.

V. 4. 2 (1) with 1,4-diiodobenzene

Trapping of the zinc derivative with an excess of diiodobenzene (0.3 equivalents respective to the zinc derivative) failed to afford the desired product **(61)**; however **(61)** was obtained by using a larger amount of diiodobenzene (0.6 equivalents respective to the zinc derivative) and 2,6-dibromo-3,5-difluoro-4-(4-iodophenyl)pyridine **(62)** was also formed and isolated:



Conditions and reagents: BuLi (1.2 equivs), -78°C, THF, 1 hr; ZnX_2 (1M, 2.5 equivs), rt, 30 mn; diiodobenzene (0.6 equivs), $Pd_2(dba)_3$, TPP, rt, 5 hrs.

Single crystal X-ray analysis confirmed the structure of **(62)**:

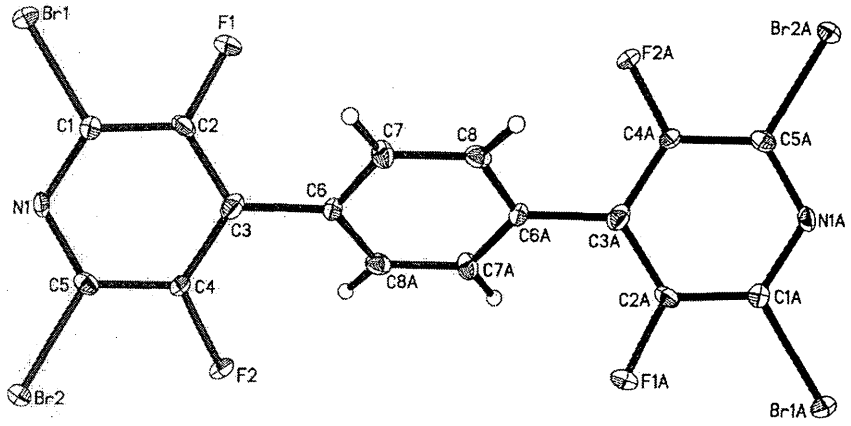


Fig 22: Single molecule of **(62)**

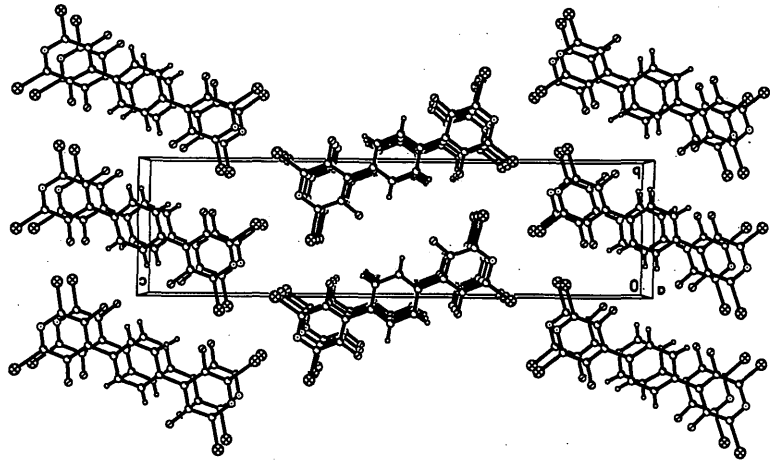
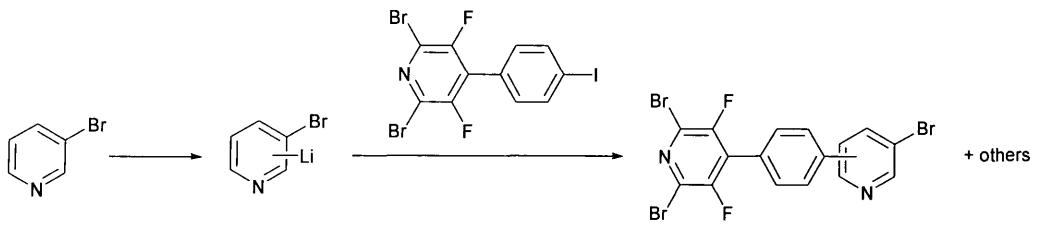


Fig 23: Packing arrangement of **(62)**

The stepwise synthesis of **(62)** via the formation and isolation of **(61)** first did not afford better yields of **(62).**

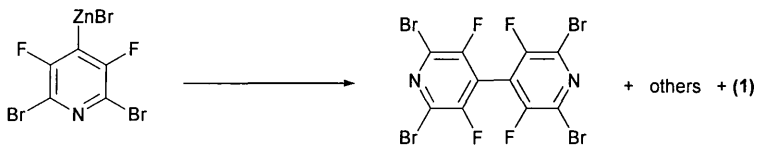
Attempted coupling of 2,6-dibromo-3,5-difluoro-4-(4-iodophenyl)pyridine **(61)** with 3-bromopyridine (via metal-halogen exchange and transmetalation with zinc) failed when tetrahydrofuran was used as solvent but the reaction proceeded with dimethylformamide, affording a complex mixture that was not analysed further.

The mixture contained amounts of **(63)** as identified by GCMS analysis (m/z 505) and a three line pattern characteristic of a three bromine containing molecule indicating that deprotonation rather than metal halogen exchange of the 3-bromopyridine might have occurred also:



Coupling with acid chlorides (acetyl chloride, benzoyl chloride) using this methodology failed to give satisfying results, and 2,6-dibromo-3,5-difluoropyridine was exclusively formed; it is possible that these results are the consequence of the presence of some free acid in the acid chloride. Only low yields of the acylheteroarenes have been previously reported in the literature[18]. The uncatalysed process gave high yields of the desired products ((**28**) and (**31**)) and is therefore a superior method for the formation of the corresponding acylheteroarenes.

We also attempted to prepare **(64)** by this methodology, as an alternative to the Ullman coupling, which was previously unsuccessful. 65% conversion was observed after 48 hrs, the reaction mixture contained the title product, but here again the mixture was too complex to allow separation of high purity samples of **(64)**. The zinc derivative of 2,4,6-tribromo-3,5-difluoropyridine might not be reactive enough to undergo efficient coupling.



m/z 544 **(64)**

Reagents and Conditions: 1.2 equivs. **(1)**, $Pd_2(dba)_3$, TPP, THF, 50°C, 48 hours

V. 4. 3 Conclusions

These results demonstrate that the zinc mediated cross coupling reactions allows the preparation of aryl-heteroaryl coupled products derived from 2,4,6-tribromo-3,5-difluoropyridine and aryl iodides. We can anticipate that a range of bis-heteroaryls can also be attained via coupling with the very reactive substituted iodopyridines, rather than the less reactive bromo counterparts.

V. 5 Conclusions

The use of palladium-mediated reactions with **(1)** allowed the synthesis of a range of substituted heterocycles in an efficient manner via coupling at the C-Br centres. The coupling reactions with substituted phenylacetylenes under Sonogashira conditions showed that the 2- and 6-positions were the most reactive ones, the use of boronic acids as coupling partners gave the disubstituted and trisubstituted products and in that case all three positions were activated towards coupling. A stable zinc derivative of **(1)** was obtained which can be coupled with different aryl iodides, allowing functionalisation at the 4- position only. Palladium mediated cross coupling is a viable methodology for the functionalisation of halogenated heterocycles such as **(1)**, and a wide range of substrates can efficiently take part in these reactions.

CHAPTER VI

Experimental section

INSTRUMENTS AND REAGENTS

Gas Liquid Chromatographic analysis

Chromatography was performed on a Hewlett Packard 5890 Series II gas liquid chromatograph equipped with a 25 m cross-linked methyl silicone or 5% phenyl methyl silicone capillary column.

NMR spectra

NMR spectra were recorded in deuteriochloroform on either a Brucker AC 250, a Varian Gemini 200, a Varian Mercury 200, a Varian VXR 400S or a Unity Inova 500 NMR spectrometer using trimethylsilane as internal standard. Coupling constants are given in Hertz (Hz) and in ^{19}F NMR upfield shifts are quoted as negative.

Mass Spectra

Mass spectra were recorded on a Fisons VG Trio 1000 spectrometer coupled with a Hewlett Packard 5890 series II gas chromatograph. Accurate mass measurements were determined on a Micromass autospec mass spectrometer or at the EPSRC Mass Spectrometry Service Centre, Swansea.

Elemental Analyses

Elemental analyses were carried out on an Exeter Analytical CE-440 elemental analysis machine.

Reagents and solvents

All chemicals were used as received from the suppliers unless otherwise stated. Solvents were dried using standard methods and stored over molecular sieves when appropriate.

Melting points

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

Boiling points

Boiling points were either recorded during distillation or determined at atmospheric pressure (Siwoloboff's method) using a Gallenkamp apparatus and are uncorrected.

FT-IR Spectra

IR spectra were recorded on a Perkin-Elmer 1600 FT-IR spectrometer using thin films between KBr plates as either neat liquids or as Nujol mulls.

VI. 1 EXPERIMENTAL TO CHAPTER I

VI.1. 1 Synthesis of 2,4,6-tribromo-3,5-difluoropyridine (1)

A Hastalloy autoclave (equipped with a copper gasket and an Inconel bursting disc,) charged with aluminium bromide (50.0 g, 0.187mol), pentafluoropyridine (20 g, 0.118 mol) and hydrogen bromide (25 g, 0.31 mol). The autoclave was heated at 150°C for 63 hours then cooled and excess gaseous hydrogen bromide was neutralised by release through a column of soda lime. The autoclave was opened and ice water added to the solid contents. This mixture was extracted with DCM, washed with water, and dried over $MgSO_4$ and the remaining DCM was removed giving *2,4,6-tribromo-3,5-difluoropyridine* (34.0 g, 81%) as white crystals, m.p. 114-115 °C (from DCM-petroleum ether 940-60)(1: 1) (Found: C, 17.10; N, 3.8. $C_5Br_3F_2N$ requires C, 17.07; N, 3.9); nmr spectrum no. 1; mass spectrum no. 1, ir spectrum no 1.

VI. 1. 2 Synthesis of 4-bromo-2,3,5,6-tetrafluoro-pyridine (3)

VI. 1. 2 a Using aluminium bromide and hydrogen bromide:

The reaction was carried out in a 160 ml Hastalloy autoclave equipped with a copper gasket and an Inconel bursting disc. The autoclave was charged with aluminium bromide (13.0 g, 49.31 mmol), pentafluoropyridine (5 g, 29.5 mmol) and hydrogen bromide (2 g, 24.65 mmol) and heated at 150°C for 20 hours. After cooling, the excess gaseous hydrogen bromide was neutralised by release through a column of soda lime. The autoclave was opened and ice water added to the solid contents. This mixture was extracted with DCM, washed with water, and dried over $MgSO_4$. The crude mixture was purified by vacuum transfer, to afford *4-bromo-2,3,5,6-tetrafluoro-pyridine* (1.4 g, 44%) as a white liquid, b.p. 136-138°C, (Found: C, 25.8; N, 5.9. C_5F_4NBr requires C, 25.6; N, 6.15). nmr spectrum no. 2.

VI. 1. 2. b From 2,3,5,6-tetrafluoro-4-pyridinamine (2)

In a round bottomed flask, a solution of pentafluoropyridine (5 g, 29.58 mmol) was vigorously stirred at room temperature with liquid ammonia; after 30 min a white precipitate was formed in the organic layer, water was added, the solution was extracted with ether, dried over $MgSO_4$ and evaporated to give *2,3,5,6-tetrafluoro-4-pyridinamine*

(2) (4.9 g, 100%) as a white solid, m.p. 76-78°C, (Found: C 35.8,1; H, 1.13; N, 17. $C_5H_2N_2F_4$ requires C, 36.1; H, 1.2; N, 17.05). nmr spectrum no. 3.

To a stirred solution of the amine (3 g, 18 mmol) was added hydrophosphorous acid (20 ml, 50% in water) at 0°C over 30 min, then sodium nitrite was added dropwise to the solution which turned to yellow over 15 min. CuBr (11.3 g) in hydrobromic acid (18 ml) was added at 0°C over 15 min and the solution was allowed to warm to room temperature. The mixture was diluted with water, extracted with ether, dried over $MgSO_4$ and the solvent removed giving a yellow oil (1.65 g). The crude solution consisted in a mixture of *4-aminotetrafluoropyridine* and *2,3,5,6-tetrafluoro-4-bromopyridine* (in 55% yield). No further purification was attempted.

VI. 1. 2. b. c From pentafluoropyridine and lithium bromide

In a carius tube was added pentafluoropyridine (2 g, 11.83 mmol), lithium bromide LiBr (0.3 g, 11.83 mmol) and dried sulpholane. The carius tube was heated at 225°C for 24 hours, cooled down and DCM was added and stirred for 12 hours at room temperature. Distillation under reduced pressure afforded *2,3,5,6-tetrafluoro-4-bromopyridine* (15%). The product was identified by comparison with analytically pure samples.

VI. 1. 3 Synthesis of 2,6-dibromo-3,5-difluoro-4-chloropyridine (4)

In a round bottomed flask was mixed 2,4,6-tribromo-3,5-difluoropyridine (0.5 g, 1.42 mmol) and lithium chloride LiCl (60 mg, 1.42 mmol) in DMF, the mixture was heated at 92°C for 20 hours. Water was added; the mixture extracted in DCM, dried over $MgSO_4$ and the solvent evaporated. Chromatography on silica gel with hexane as the eluant afforded *2,6-dibromo-3,5-difluoro-4-chloropyridine* (93 %, 0.41 g) as a white solid, m.p. 76.2-76.5°C. (Found 304.8058. $C_5F_2Br_2ClN$ requires 304.8054), nmr spectrum no. 4, mass spectrum no. 2, ir spectrum no 2.

VI. 1. 4 Synthesis of 2,6-dibromo-3,5-difluoro-4-iodopyridine (5)

In a round bottomed flask was mixed 2,4,6-tribromo-3,5-difluoropyridine (3 g, 8.54 mmol), sodium iodide NaI (6.4 g, 42.7 mmol) in DMF, the mixture was heated at 150°C for 20 hours. The mixture was extracted with a mixture of water and ether (50:50 % volume) then washed with sodium metabisulfite and with water again; it was then dried over $MgSO_4$ and the solvent evaporated. The crude was product was washed with

hexane and chromatography on silica gel with DCM-hexane (1:1) as the eluant afforded *2,6-dibromo-3,5-difluoro-4-iodopyridine* (64%, 2.2 g) as a white solid, m.p. 154-155°C (Found 398.7391. $C_5F_2Br_2IN$ requires 398.7389). nmr spectrum no. 5, mass spectrum no. 3, ir spectrum no 3.

VI. 1. 5 Synthesis of 2,3,5,6-tetrafluoro-4-iodopyridine (6)

In a round-bottomed flask was mixed pentafluoropyridine (20 g, 118.354 mmol) and sodium iodide NaI (100 g, 532 mmol) in DMF, and the mixture was heated at 150°C for 15 hours. The mixture was extracted with a mixture of water and ether (50:50 % volume) then washed with sodium metabisulfite and with water again; it was then dried over $MgSO_4$ and the solvent evaporated. Chromatography on silica gel with DCM-hexane (10:1) as the eluant afforded *2,3,5,6-tetrafluoro4-iodopyridine* (87%, 28 g) as a white solid, m.p. 64-66°C (Found 276.901015. C_5F_4IN requires 276.901164). nmr spectrum no. 6, mass spectrum no. 4, ir spectrum no 4.

VI. 2 EXPERIMENTAL TO CHAPTER II

VI. 2.1 Synthesis of 2,4,6-tribromo-3-fluoro-5-methoxypyridine(7)

A solution of **(1)** (1 g, 2.84 mmol) and sodium methoxide (0.184 g, 0.34 mol) in methanol was stirred at room temperature for 55 hours. Methanol was evaporated water added and the mixture was extracted into DCM, then dried over $MgSO_4$ and evaporated to dryness. Chromatography on silica gel column with DCM as the eluent afforded *2,4,6-tribromo-3-fluoro-5-methoxypyridine* (68%, 0.66 g), m.p. 109-110°C, (Found : C 20.0, H 1.10, N 3.8. $C_6H_3Br_3FNO$ requires C, 19.78; H, 0.82; N 3.65). nmr spectrum no. 7, mass spectrum no. 5, ir spectrum no 5.

VI. 2. 2 Synthesis of 2,4,6- tribromo-5-fluoro-3-ethoxypyridine (8)

In a round-bottomed flask equipped with a condenser and a drying tube, a solution of 2,4,6-tribromo-3, 5-difluoropyridine **(1)** (1 g, 2.84 mmol) and 18-crown-6 (0.75 g, 2.84mmol) in ethanol (10 ml) was stirred at room temperature until dissolution of **(1).** Sodium ethoxide (0.24 g, 3.55 mmol) was added and after stirring for one more hour, the solution was heated to 78°C for 84 hours. Water (20ml) was added and the mixture extracted into DCM. The DCM solution was dried over $MgSO_4$ and evaporated to dryness. Column chromatography on silica gel with DCM-hexane (1:2) as the eluent afforded *2,4,6-tribromo-5-fluoro-3-ethoxypyridine* (62%, 0.65 g), m.p. 95-96°C (Found: C, 22.4; H, 1.5; N, 3.6. $C_7H_5Br_3FNO$ requires C, 22.1; H, 1.3; N, 3.7%). nmr spectrum no. 8, mass spectrum no. 6, ir spectrum no 6.

VI. 2. 3 Synthesis of 2,4,6- tribromo-3,5-diethoxypyridine (9)

In a round bottomed flask equipped with a condenser and a drying tube, a mixture of 2,4,6-tribromo-3,5-difluoropyridine **(1)** (1.5 g, 4.26 mmol) and 18-crown-6 ether (1.12 g, 4.26 mmol) in ethanol (10 ml) was stirred at room temperature until dissolution of **(1)**, then sodium ethoxide (1.74 g, 25.56 mmol) was added and stirred for one more hour, the solution was heated to 78°C for 48 hours, water (20 ml) was added and the mixture extracted into DCM. The DCM solution was dried over $MgSO_4$ and evaporated to dryness. Chromatography on silica gel with DCM-hexane (1:2) as the eluent yielded to *2,4,6-tribromo-3,5-diethoxypyridine* (59%, 0.67g), m.p. 99-100°C (Found: C, 26.9;

H, 2.3; N, 3.4. $C_9H_{10}Br_3NO_2$ requires C, 26.8; H, 2.5; N, 3.5%). nmr spectrum no. 9, mass spectrum no. 7, ir spectrum no 7.

VI. 2. 4 Synthesis of 2,4,6-tribromo-3-fluoro-5-phenoxypyridine (10)

In a round-bottomed flask equipped with a condenser and a drying tube, sodium metal Na (0.33 g, 14.34 mmol) was added under nitrogen to a solution of dry tetrahydrofuran. Phenol (1.02 g, 11.48 mmol) was added and the solution stirred at reflux temperature (78^oC) until dissolution of the sodium was complete. The solution was cooled and 2,4,6-tribromo-3,5-difluorpyridine (0.8 g, 2.46 mmol) added. After 16 hours the solution was cooled down, water added and the solution extracted into DCM, dried over $MgSO_4$ and evaporated to dryness affording *2,4,6-tribromo-3-fluoro-5-phenoxypyridine* (54%, 0.67 g). A fluorine NMR (single peak at -104.1 ppm) and GCMS was consistent with literature.

VI. 2. 5 Synthesis of 2,4,6-tribromo-3,5-diphenoxypyridine(13)

In a three neck flask previously dried equipped with a condenser and a drying tube, was dissolved under nitrogen 2,4,6-tribromo-3,5-difluoropyridine (1 g, 2.84 mmol) in dry toluene (10 ml), cesium carbonate Cs_2CO_3 (1.85 g, 5.68 mmol), CuBr (0.02 g, 0.142 mmol), 1-naphthoic acid (0.98g, 5.68 mmol), ethyl acetate (0.5 mmol, 5.0 mol%) and molecular sieves 5A (650 mg). The solution was refluxed for 36 hours then was cooled; filtered and washed with 5% aqueous NaOH and extracted three times with DCM. The combined organic layers were washed with brine. The organic layer was dried over $MgSO_4$ and concentrated under vacuum. Purification by column chromatography on silica gel using DCM-hexane (1:4) as the eluent afforded *2,4,6-tribromo-3,5-diphenoxypyridine* (32%, 0.43 g), m.p. 142-144 ^oC (Found: C, 40.4; N, 2.4; H, 2.4. $C_{17}H_{10}Br_3N$ requires C, 40.8; N, 2.8; N, 2.0%). nmr spectrum no. 10, mass spectrum no. 8, ir spectrum no 8.

VI. 2. 6 Synthesis of 4-bromo-3,5-difluoro-2,6-diphenoxypyridine (17)

To a solution of 4-bromo-2,3,5,6-tetrafluoropyridine (0.5 g, 2.17 mmol) in toluene (10 ml) was added phenol (2.17 mmol, 0.2g), caesium carbonate Cs_2CO_3 (2.17 mmol, 1.54 g), CuBr (2.5 mol%, 0.11 mmol, 20 mg), ethyl acetate (0.125 mmol, 5 mol %), 1-naphthoic acid (2.17 mmol, 0.37 g) and molecular sieves. The solution was heated to

reflux for 55 hours, cooled down and extracted into DCM. The combined organic phases were washed with 5% aqueous NaOH, the aqueous layer extracted with DCM, and the extracts washed with brine. The crude was dried over $MgSO_4$, and the solvent evaporated. Purification by column chromatography with silica gel, using DCM as the eluent afforded *4-bromo-3,5-difluoro-2,6-diphenoxypyridine* (32%, 0.26 g) as a white solid, m.p.148-149°C (Found C, 53.4; H, 3.0; N, 3.4. $C_{17}H_{10}F_2NBrO_2$ requires C, 53.9; H, 2.6; N, 3.7%). nmr spectrum no. 11, mass spectrum no. 9, ir spectrum no 9.

VI. 2. 7 Synthesis of 2,3,5,6-tetrafluoro-4-phenoxypyridine (18) and 3,5,6-trifluoro-2,4-diphenoxypyridine (19)

In a three neck flask equipped with a condenser and a drying tube was added Na metal (1.22 g, 53.28 mmol) under nitrogen to a solution of phenol (6 g, 64.6mmol) in dry tetrahydrofuran. The solution was stirred at room temperature for 45 min until total dissolution of the sodium metal. Pentafluoropyridine (7.3 g, 43 mmol) was added and the reaction was very exothermic and after 10 mn a white solid was precipitated indicating the formation of sodium fluoride. The solution was stirred at room temperature overnight. The sodium fluoride was filtered, the solution was extracted with DCM,dried over $MgSO_4$ and the DCM was evaporated. Column chromatography on silica gel with DCM-hexane (1:6) as the eluent afforded *2,3,5,6-tetrafluoro-4-phenoxypyridine* (21%, 2.1 g) as a yellow liquid, b.p. 114-116°C, (Found: C, 54.6; N, 2.2; H, 5.7. $C_{11}H_5F_4NO$ requires C, 54.3; N, 2.0; H, 5.75). nmr spectrum no. 12, mass spectrum no. 10, ir spectrum no 10.

The other product was identified as *3,5,6-trifluoro-2,4-diphenoxypyridine* (6.5 g, 52%) as a white solid, m.p. 69-70°C (from hexane), (Found: C, 64.3; N, 4.5; H, 3.10. $C_{17}H_{10}F_3NO_2$ requires C, 64.3; N, 4.4; H, 3.1%). nmr spectrum no. 13, mass spectrum no. 11, ir spectrum no 11.

VI. 3 EXPERIMENTAL TO CHAPTER III

VI. 3. 1 General procedure: Preparation of 4-lithio-2, 6-dibromo-3, 5-difluoropyridine (20)

A three necked flask equipped with a low temperature thermometer, a drying tube and flushed with dry nitrogen, was charged with 2,4,6-tribromo-3, 5-difluoropyridine (1 g, 2.84 mmol) and diethyl ether. The mixture was cooled to -78°C before n-butyllithium (1.6M in hexanes) (1.9 ml, 3.55 mmol) was added. The resulting solution, which gradually turned to yellow, indicating the formation of the lithio anion was stirred at -78°C for 90 min.^{19}F analysis of the crude mixture indicated complete of the starting material to 4-lithio-2,6-dibromo-3, 5-difluoropyridine; δ_F -89.7 ppm (s). nmr spectrum no. 14.

VI. 3. 2 Synthesis of 2,6-dibromo-3,5-difluoropyridine (21)

A solution of the 4-lithio-2,6-dibromo-3,5-difluoropyridine was prepared at –78°C as above. Water was added (20 ml); the solution turned to white and was extracted into DCM. The DCM solution was dried over $MgSO_4$ and evaporated to dryness. The crude product was sublimed to give *2,6-dibromo-3,5-difluoropyridine* (71%, 0.55 g) as a white solid, m.p. 98.4-98.9°C (Found : C, 22.2; N, 5.0; H, 0.4; Br, 58.3; F, 13.7. $C_5HF_2Br_2N$ requires C, 22.2; N, 5.1; H, 0.3; Br, 58.6; F 13.9%). nmr spectrum no. 15, mass spectrum no. 12, ir spectrum no 12.

VI. 3. 3 Attempted decomposition and trapping of the lithio anion with furan

A solution of the 4-lithio-2,6-dibromo-3,5-difluoropyridine was prepared at -78°C as above, furan (0.95 g in 5 ml ether) was added slowly at -78°C and the solution was stirred and warmed to room temperature overnight. After work up of the reaction, the crude ^{19}F NMR and GCMS showed that 2,6-dibromo-3,5-difluoropyridine was the major product. The experiment was repeated except that furan was added at -15°C, after work up the crude product consisted in a mixture of 2,6-dibromo-3,5-difluoropyridine and other non identifiable products of high molecular weight.

VI. 3. 4 Synthesis of 2,6-dibromo-3,5-difluoroisonicotinic acid (22)

A solution of the 4-lithio-2,6-dibromo-3,5-difluoropyridine was prepared at -78°C as above; the temperature was allowed to warm to -65°C and carbon dioxide was bubbled into the solution. A white precipitate began to form; carbon dioxide was passed in the solution for 2 hours. A solution of sodium hydrogencarbonate was added and the ethereal layer was extracted into DCM. The aqueous layer was acidified and extracted with ether; combined etheral layers were dried over $MgSO_4$. The solution was filtered and the solvent evaporated to afford *2,6-dibromo-3,5-difluoroisonicotinic* (35%, 0.12 g), m.p. 154-156°C (Found: C, 22.8; N, 4.1; H, 0.3. $C_6HBr_2F_2O_2N$ requires C, 22.7; N, 4.4; H, 0.3%). nmr spectrum no. 16, mass spectrum no. 13, ir spectrum no 13.

VI. 3. 5 Synthesis of 2,6-dibromo-3,5-difluoro-4-trimethylsilylpyridine (23)

A solution of the 4-lithio-2,6-dibromo-3,5-difluoropyridine was prepared at -78°C as above. Chlorotrimethylsilane (0.38 g, 3.5 mmol) was added and the mixture stirred for 1 h 30 min, warmed to room temperature overnight and water was added (2 x 20 ml). The solution was extracted into DCM; dried over $MgSO_4$ and evaporated giving a brown liquid. Chromatography on silica gel with ethyl acetate-hexane (1:1) as the eluent yielded *2,6-dibromo-3,5-difluoro-4-trimethylsilylpyridine* (85%, 0.82 g), m.p. 86-88°C (Found: C, 27.8; H, 2.6; N, 3.4. $C_8H_9Br_2F_2NSi$ requires C, 27.8; H, 2.60; N, 4.05%). nmr spectrum no. 17, mass spectrum no. 14, ir spectrum no 14.

VI. 3. 6 Attempted synthesis of 2,6-dibromo-3,5-difluoro-4-tributyltinpyridine (24)

A solution of the 4-lithio-2,6-dibromo-3,5-difluoropyridine was prepared at -78°C as above; tributyltinchloride (2 ml, 7.36 mmol) was added; the solution turned to brown and was stirred for 2 hours and warmed to room temperature overnight. Water was then added (2x20 ml) and extracted into DCM; the extract was dried over $MgSO_4$ and evaporated giving a brown liquid, which showed to consist by GCMS in a *2,6-dibromo-3,5-difluoro-4-tributylpyridine* (20%) and other products. The reaction was repeated as previously except that after stirring overnight, the mixture was filtered, potassium fluoride (KF) added, stirred for 1 hour and filtered again. GCMS showed the same results previously observed.

VI. 3. 7 Synthesis of 1,1-di(2,6-dibromo-3,5-difluoro-4-pyridyl)ethyl acetate (27)

A solution of the 4-lithio-2,6-dibromo-3,5-difluoropyridine was prepared at -78°C as above. Acetyl chloride (0.22 g, 2.84 mmol) was then added and the solution maintained at -78°C for further 90 min; warmed to -15°C for 45 min and to 0°C for 1 hour and to room temperature overnight to form a white solution. Water was poured into the solution, which was extracted into DCM, dried over $MgSO_4$ to give a white solid. Chromatography on silica gel with DCM-hexane (1:3) as the eluent afforded *1,1-di(2,6-dibromo-3,5-difluoro-4-pyridyl)ethyl acetate (*69%, 1.23 g) as a white solid, m.p. 158-160°C (Found C, 27.0; H, 1.2; N, 4.2. $C_{14}H_9Br_4F_4N_2O_2$ requires C, 26.6; H, 1.42; N, 4.4%). nmr spectrum no. 18, mass spectrum no. 15, ir spectrum no 15.

VI. 3. 8 Synthesis of 2,6-dibromo-3,5-difluoro-4-pyridyl-phenylmeyhanone (28)

A solution of the 4-lithio-2,6-dibromo-3,5-difluoropyridine was prepared at -78°C as above. Benzoyl chloride (0.61 g, 4.32 mmol) was then added and the solution maintained at -78°C for further 90 min; warmed to -15°C for 45 min, to 0°C for 1 hour and to room temperature overnight to form a white solution. Water was poured into the solution and extracted into DCM. The organic phase was dried over $MgSO_4$. Chromatography on silica gel with DCM-hexane (1: 4) as the eluent afforded *2,6-dibromo-3,5-difluoro-4-pyridyl-phenylmeyhanone* (57%, 0.61 g) as a white solid. m.p. 130-132°C (from hexane) (Found: C, 38.2; N, 3.6; H, 1.4. $C_{12}H_5NOF_2Br_2$ requires C, 38.2; N, 3.7; H, 1.3%). nmr spectrum no. 19, mass spectrum no. 16, ir spectrum no 16.

VI. 3. 9 Synthesis of bis (2,3,5,6-tetrafluoro(4-pyridyl))phenylmethyl benzoate (29)

In a dry three neck flask was dissolved under nitrogen 2,3,5,6-tetrafluoropyridine (1 g, 6.62 mmol) in dry ether (15 ml); the solution was cooled at -78°C, butyllithium in 1.6M hexanes (5.17 ml, 8.28 mmol) was then added and the solution was stirred under nitrogen for 1 hour. The solution turned from white to yellow indicating the formation of the lithio derivates. Benzoyl chloride (1.15 ml, 9.93 mmol) was added and the solution maintained at -78°C for further 30 min; warmed to room temperature overnight to form a white solution. Water was added (15 ml) to the mixture; the solution extracted into DCM and dried over $MgSO_4$. Recrystallisation in acetonitrile-petrol ether and sublimation afforded *bis (2,3,5,6-tetrafluoro(4-pyridyl))phenylmethyl benzoate* (55%, 1.75 g), m.p. 145-147°C (Found: C, 56.6; N, 5.6; H 2.0. $C_{24}H_{10}F_8N_2O_2$ requires C, 56.4; N, 5.5; H, 2.0%). nmr spectrum no. 20, mass spectrum no. 17, ir spectrum no 17.

VI. 3. 10 Synthesis of 2,6-dibromo-3,5-difluoro(4-pyridyl)-4-methylphenylketone (31)

A solution of the 4-lithio-2,6-dibromo-3,5-difluoropyridine was prepared at -78°C as above. *p*-Toluyl chloride (0.66 g, 4.26 mmol) was then added and the solution maintained at -78°C for further 90 min; warmed to -15°C for 45 min and to 0°C for 1 hour and to room temperature overnight to form a white solution. Water was poured into the solution and extracted into DCM, dried over $MgSO_4$ to give a yellow solution. Crystals of *2,6-dibromo-3,5-difluoro(4-pyridyl)-4-methylphenylketone* (77%, 0.85 g) crystallised out of solution, m.p. 145-146°C (Found: C, 39.9; H, 1.8; N, 3.6, $C_{13}H_7Br_2F_2NO$ requires C, 39.9; H, 1.7; H, 4.0%). nmr spectrum no. 21, mass spectrum no. 18, ir spectrum no 18.

VI. 4 EXPERIMENTAL TO CHAPTER V

VI. 4. 1 General procedure for the reaction of 2,4,6-tribromo-3, 5-difluoropyridine with phenylacetylenes

All reactions were carried out under a nitrogen atmosphere; fresh triethylamine (Aldrich) was used as a solvent, unless otherwise stated. All reagents were commercially available and used without further purification. The reactions were carried out in three necked round bottom flasks previously dried overnight in the oven and flushed with nitrogen for 1 hour prior to reaction.

2,4,6-tribromo-3,5-difluoropyridine (1 g, 2.84 mmol) was added under nitrogen to a solution of triethylamine and stirred until dissolution. The appropriate palladium catalyst, CuI and the reactant were then added. The reaction was stirred at room temperature, and analysed periodically by ^{19}F NMR analysis. The reaction was then filtered and water was added to the filtrate, which was extracted into DCM (3x30 ml). The organic extracts were dried (Mg_2SO_4) and evaporated to give a crude product, which was purified by column chromatography on silica gel unless otherwise stated.

V. 4. 1. a Synthesis of 2,4-dibromo-3, 5-difluoro-6-(phenylethynyl)pyridine (33)

A mixture of 2,4,6-tribromo-3,5-difluoropyridine (1 g, 2.84 mmol), phenylacetylene (0.5 g, 0.05 mmol), $Pd(PPh_3)_2Cl_2$ (2%, 40 mg) and CuI (1%, 5.4 mg) in triethylamine (20 ml) was stirred at room temperature for 12 hours. Chromatography on silica gel with hexane as the eluent afforded *2,4-dibromo-3, 5-difluoro-6-(phenylethynyl)pyridine* (76%, 0.8 g) as a white solid, m.p. 156-158°C, (Found: C, 42.2; H, 1.3; N, 3.5. $C_{13}H_5Br_2F_2N$ requires C, 41.8; H, 1.3; N, 3.8%). nmr spectrum no. 22, mass spectrum no. 19, ir spectrum no 19.

VI. 4. 1. b Synthesis of 2,6-bis(2-phenylethynyl)-4-bromo-3, 5-difluoropyridine (34)

A mixture of 2,4,6-tribromo-difluoropyridine (1 g, 2.84 mmol), phenylacetylene 2.0 g, 20.0 mmol), $Pd(PPh_3)_2Cl_2$ (2%, 40 mg) and CuI(1%, 5.4 mg) in triethylamine (20 ml) was stirred at room temperature for 12 hours. Chromatography on silica gel with hexane-DCM (1:1) as the eluent afforded *2,6-bis(2-phenylethynyl)-4-bromo-3,5-difluoropyridine* (82%, 0.87g) as a white solid, m.p. 186°C, (Found C, 64.1; H, 2.6; N,

3.6. $C_{21}H_{10}BrF_2N$ requires C, 64.0; H, 2.5; N, 3.4%). nmr spectrum no. 23, mass spectrum no. 20, ir spectrum no 20.

VI. 4. 1. c Synthesis of 2,4-dibromo-3,5-difluoro-6-[2-(4-fluorophenyl)ethynyl]pyridine (35)

A mixture of 2,4,6-tribromo-3,5-difluoropyridine (0.58 g, 1.66 mmol), 1-ethynyl-4-fluorobenzene (0.24 g, 2 mmol), caesium carbonate as a base (2.32 mmol, 0.75 g), was added $Pd(PPh_3)_2Cl_2$ (2%, 23.1 mg) and CuI(1%, 3.2 mg) in dry toluene (20 ml) was heated at 60°C for 24 hours. Vacuum sublimation afforded *2,4-dibromo-3,5-difluoro-6-[2-(4-fluorophenyl)ethynyl]pyridine* (87%, 0.56 g) as a white solid, m.p. 216-218°C, (Found: C, 39.66; H, 1.02; N, 3.54. $C_{13}H_4Br_2F_3N$ requires C, 39.93; H, 1.31; N, 3.58%). nmr spectrum no. 24, mass spectrum no. 21, ir spectrum no 21

V. 4. 1. d Synthesis of 4-bromo-3,5-difluoro-2-(4-fluorophenyl)-6-[2-(4-fluorophenyl)ethynyl]pyridine (36)

A mixture of 2,4,6-tribromo-difluoropyridine (0.18 g, 0.52 mmol), 1-ethynyl-4-fluorobenzene (0.25 g, 2.08 mmol), caesium carbonate (0.24 g, 0.73 mmol), $Pd(PPh_3)_2Cl_2$ (2%, 7.3 mg) and CuI (1%, 1 mg) in dry toluene (20 ml) was heated at 60°C for 24 hours. Chromatography on silica gel with DCM-Hexane(1:2) as the eluent afforded *4-bromo-3,5-difluoro-2-(4-fluorophenyl)-6-[2-(4fluorophenyl)ethynyl]pyridine* (58%, 0.63 g) as a white solid, m.p. 225-227°C, (Found: C, 58.4; H, 1.8 ; N, 3.2. $C_{21}H_8BrF_4N$ requires C, 58.6; H, 1.8; N, 3.25). nmr spectrum no. 25, mass spectrum no. 22, ir spectrum no 22.

V. 4. 1. e Synthesis of 4-bromo-2,6-di[2-(4-bromophenyl)-1-ethynyl]-3,5-difluoropyridine (37)

A mixture of 2,4,6-tribromo-difluoropyridine (1 g, 2.84 mmol), 1-ethynyl-4-bromobenzene (0.5 g, 2.84 mmol), triethylamine (20ml), $Pd(PPh_3)_2Cl_2$ (2%, 40 mg), CuI (1%, 5.4 mg) was stirred at 100°C for 48 hours. Chromatography on silica gel with DCM-hexane (1:3) afforded *4-bromo-2,6-di[2-(4-bromophenyl)-1-ethynyl]-3,5-difluoropyridine* (56%,0.72 g) as a white solid, m.p. 270-272°C, (Found: C, 45.7; H, 1.4; N, 2.5. $C_{13}H_4Br_3F_2N$ requires C, 45.5; H, 1.4; N, 2.5%). nmr spectrum no. 26, mass spectrum no. 23, ir spectrum no 23.

VI. 4. 1. f Synthesis of 3,5-difluoro-2,4,6-tris[2-(4-bromophenyl)ethynyl]pyridine (38)

A mixture of 2,4,6-tribromo-3,5-difluoropyridine (0.25 g, 0.7 mmol), 1-ethynyl-4-bromobenzene (0.47 g, 2.84 mmol), triethylamine, $Pd(PPh_3)_2Cl_2$ (2%, 9.7 mg) and CuI (1%, 1.33 mg) was heated at 100°C for 17 hours. Chromatography on silica gel with DCM-hexane (1:4) and DCM as the eluents afforded *3,5-difluoro-2,4,6-tris[2-(4-bromophenyl)ethynyl]pyridine* (55%, 0.25 g) as a white solid, m.p. 173-174°C, (Found: 648.8488. $C_{29}H_{12}Br_3F_2N$ requires 648.8482). nmr spectrum no. 27, mass spectrum no. 24, ir spectrum no 24.

VI. 4. 1. g Synthesis of 2,6-bis[2-(4-chlorophenyl)ethynyl]-4-bromo-3,5-difluoropyridine (39)

2,4,6-tribromo-3,5-difluoropyridine (0.31 g, 0.88 mmol), 1-ethynyl-4-chlorobenzene (0.15 g, 1.10 mmol), $Pd(PPh_3)_2Cl_2$ (2%, 12 mg) and CuI (1%, 1.67 mg) in triethylamine (20 ml) were reacted at 80°C for 10 hours. After work up, recrystallisation in DCM and sublimation *2,6-bis[2-(4-chlorophenyl)ethynyl]-4-bromo-3,5-difluoropyridine* (42.5%, 0.17 g) was isolated as a white solid, m.p. > 250°C, (Found C, 54.5; H, 1.6; N; 3.00. $C_{21}H_8BrF_2Cl_2N$ requires C, 54.4; H, 1.7; N, 3.0%). nmr spectrum no. 28, mass spectrum no. 25, ir spectrum no 25.

Repeating the reaction using 2,4,6-tribromo-3,5-difluoropyridine (0.16 g, 0.46 mmol), 1-ethynyl-4-chlorobenzene (0.25 g, 1.83 mmol), $Pd(PPh_3)_2Cl_2$ (2%,6.4 mg) and CuI (1%, 0.87 mg) in triethylamine (25 ml), the solution was stirred at room temperature for 12 hours and after sublimation and column chromatography gave *2,6-bis[2-(4-chlorophenyl)ethynyl]-4-bromo-3,5-difluoropyridine* again, as compared to a previously characterised sample.

VI. 4. 1. h Synthesis of 2,6-bis[2-(2-chlorophenyl)ethynyl]-4-bromo-3,5-difluoropyridine (40)

A mixture of 2,4,6-tribromo-3,5-difluoropyridine (0.32 g, 0.915 mmol), 1-ethynyl-2-chlorobenzene (0.5g. 3.66 mmol), $Pd(PPh_3)_2Cl_2$ (2%, 12.7 mg) and CuI (1%, 1.74 mg) in triethylamine was stirred at room temperature for 3 days. After recrystallisation (dichloromethane), afforded 2,6-bis*[2-(2-chlorophenyl)ethynyl]-4-bromo-3,5-difluoropyridine* (37%, 0.15 g) as a white solid, m.p. 196.4-197.6 (from DCM), (Found: M^+ 462.918. $C_{21}H_8BrCl_2F_2N$ requires M^+ 462.916). nmr spectrum no. 29, mass spectrum no. 26, ir spectrum no 26.

When the reaction was repeated using a equimolar ratio of starting material and substrate, **(40)** was obtained again, as a white solid, m.p. 145.2-145.8°C (from toluene).

VI. 4. 1. i Synthesis of 2,4-dibromo-6-[2-(2-chlorophenyl)-1-ethynyl]-3,5-difluoropyridine (41)

A mixture of 2,4,6-tribromo-3,5-difluoropyridine (0.50 g, 1.42 mmol), 1-ethynyl-2-chlorobenzene (0.11 g. 0.85 mmol), $Pd(PPh_3)_2Cl_2$ (2%, 18.72 mg) and CuI (1%, 2.55 mg) in triethylamine was stirred at 90°C for 18 hours. Chromatography on silica gel with DCM-hexane (3:1) as the eluent, sublimation and second column with DCM-hexane (1:4) afforded *2,4-dibromo-6-[2-(2-chlorophenyl)-1-ethynyl]-3,5-difluoropyridine* (21%, 0.12 g) as a white solid, m.p. 179.1-181.6°C (Found: C, 38.5; H, 1.2; N; 3.1. $C_{13}H_4Br_2ClF_2N$ requires C, 38.3; H, 0.9; N, 3.4%). nmr spectrum no. 30, mass spectrum no. 27, ir spectrum no 27.

VI. 4. 1. j Synthesis of 1-(2-{4-bromo-3, 5-difluoro-6- [2-(4- H methoxyphenyl) ethynyl](2-pyridyl)} ethynyl)-4-methoxybenzene (42)

A mixture of 2,4,6-tribromo-3,5-difluoropyridine (0.83g, 2.36 mmol), 1-ethynyl-4-methoxybenzene (0.39g, 2.95 mmol), $Pd(PPh_3)_2Cl_2$ (2%, 32.8 mg) and CuI (1%, 4.5 mg) in triethylamine (20 ml) was stirred at room temperature for 48 hours. Chromatography on silica gel with DCM-hexane (1:3) as eluent and DCM-hexane (1:1) afforded *1-(2-{4-bromo-3, 5-difluoro-6- [2-(4- H methoxyphenyl) ethynyl](2-pyridyl)} ethynyl)-4-methoxybenzene* (42%, 0.44 g) as a white solid, m.p. 198-200°C, (Found: C, 60.5; H, 2.8; N, 3.1. $C_{23}H_{14}BrF_2NO_2$ requires C, 60.8; H, 3.10; N, 3.08%). nmr spectrum no. 31, mass spectrum no. 28, ir spectrum no 28.

VI. 4. 1. k Synthesis of 4-[4,6-bis (3,3-dimethyl-3-silabut-1-ynyl)-3,5-difluoro (2-pyridyl)]-2,2-dimethyl-2-silabut-3-yne (43)

A mixture of 2,4,6-tribromo-3,5-difluoropyridine (1.0 g, 2.84 mmol), trimethysilyl acetylene (0.49ml, 3.55 mmol), Pd acetate (2%, 0.057 mmol, 13 mg), PPh_3 (4%, 30.4 mg) and CuI (1%, 3.4 mg) in triethylamine (25 ml) was stirred at room temperature for 48 hours. Chromatography on silica gel with DCM-hexane (1:8), DCM-hexane (1:4) as eluants afforded *4-[4,6-bis (3,3-dimethyl-3-silabut-1-ynyl)-3,5-difluoro (2-pyridyl)]-2,2-dimethyl-2-silabut-3-yne* (29%, 0.49 g) as a white solid, m.p. 96.3-96.8°C, (Found $[M+H]^+$, 404.14. $C_{21}H_{27}1F_2N$ requires M^+, 403.20). nmr spectrum no. 32, mass spectrum no. 29, ir spectrum no 29.

When the reaction was carried out with an excess of trimethylsilylacetylene, the same results were obtained.

VI. 4. 1. l Synthesis of 3,5-difluoro-2,4,6-tris(2-phenylethynyl)pyridine (45)

A mixture of 2,4,6-tribromo-3,5-difluoropyridine (1g, 2.84 mmol), 4-trimethylsilylphenylacetylene (3.46, 19.88 mmol), $Pd(PPh_3)_2Cl_2$ (2%, 40 mg) and CuI (1%, 5.4 mg) in triethylamine (20 ml) was heated at 100°C for 56 hours. Chromatography on silica gel with DCM-hexane (1:3) as the eluent afforded *3,5-difluoro-2,4,6-tris(2-phenylethynyl)pyridine* **(45)**, *2,6-bis(2-phenylethynyl)-4-bromo-3,5-difluoropyridine* **(34)**, and 2,*4-dibromo-3,5-difluoro-6-(phenylethynyl)pyridine* **(33)**. *3,5-difluoro-2,4,6-tris (2-phenylethynyl) pyridine)* m.p. 156-159°C, (Found $[M]^{+,}$ 416.1258. $C_{29}H_{15}F_2N$ requires 416.1251). nmr spectrum no. 33, mass spectrum no. 30, ir spectrum no 30.

VI. 4. 1. m Control experiment with phenylacetylene in the presence of air

To a solution of phenylacetylene (2.55 g, 0.025 mmol) in triethylamine was added CuI (4.71 g, 0.025 mmol) and stirred at 80°C for 15 hours. The solution was exposed to air for 2 min, the solution turned yellow, and a solid precipitated that was filtered. GCMS analysis and comparison with literature data confirmed that confirmed that *1,4-dipheny-1,3-butadiyne* **(A),** nmr spectrum no. 44, was formed.

VI. 4. 2 General procedure for the reaction of 2,4,6-tribromo-3, 5-difluoropyridine with boronic acids

2,4,6-tribromo-3,5-difluoropyridine (1 g, 2.84 mmol) was dissolved in monoglyme (5 ml) under a nitrogen atmosphere, then tetrakis triphenylphosphine palladium Pd $(PPh_3)_4$ was added (6%), the boronic acid (1.25 or 3 equiv), and finally barium hydroxide (2 equi) dissolved in water. The solution turned to a solid that dissolved upon heating to 93-94°C. After completion of the reaction monitored by ^{19}F NMR, the crude mixture was filtered on a celite pad, the filtrate recovered, and the celite thoroughly washed with dichloromethane. To the mixture was added water, and the products were extracted in DCM (3x30 ml), dried over Mg_2SO_4 and the solvent evaporated. The products were separated using column chromatography on silica gel; further sublimation, recrystallisation, or second columns were performed when necessary.

VI. 4. 2. a Synthesis of 3,5-difluoro (2,4,6-triphenyl)pyridine (46)

To a solution of 2,4,6-tribromo-3,5-difluoropyridine (1 g, 2.84 mmol) in monoglyme was added benzeneboronic acid (3 equiv, 8.52 mmol, 1.04 g), $Ba(OH)_2$ (2 equi, 17.1 mmol, 2.82 g) in water, and the Pd catalyst (6%, 119.7mg) and the mixture was heated for 48 hours. Chromatography on silica gel with DCM-hexane (1:1) as the eluent afforded *3,5-difluoro (2,4,6-triphenyl)pyridine* (0.42 g, 43%) as a white solid, m.p. 135-137°C, (Found 343.117393. $C_{23}H_{15}F_2N$ requires 343.117256). nmr spectrum no. 34, mass spectrum no. 31, ir spectrum no 31.

VI. 4. 2. b Synthesis of 2,6-bis(4-methylphenyl)-4-bromo-3,5-difluoropyridine (47)

To a solution of 2,4,6-tribromo-3,5-difluoropyridine (1 g, 2.84 mmol) in monoglyme was added *p*-tolylboronic acid (1.25 equiv, 0.48 g, 3.55 mmol), $Ba(OH)_2$ (2 equiv, 7.10 mmol) in water, and the Pd catalyst (6%, 197 mg), and the mixture was heated for 24 hours. Chromatography on silica gel with hexane-DCM (3:1) as the eluent afforded *2,6-bis(4-methylphenyl)-4-bromo-3,5-difluoropyridine* (32%, 0.35 g) as a white solid, m.p. 150-151.2°C (from chloroform), (Found C, 59.8; H, 3.8; N, 3.7. $C_{19}H_{14}BrF_2N$ requires C, 60.9; H, 3.7; N, 3.7%). nmr spectrum no. 35, mass spectrum no. 32, ir spectrum no 32.

VI. 4. 2. c Synthesis of 3,5-difluoro-2,4,6-tris (4-methylphenyl)pyridine (48)

To a solution of 2,4,6-tribromo-3,5-difluoropyridine (0.3 g, 0.855 mmol) in monoglyme was added (b) (0.34 g, 256 mmol), $Ba(OH)_2$ (2 equiv, 0.36 g) in water, and the Pd catalyst (6%, 59.3 mg) and the mixture heated for 18 hours. Chromatography on silica gel with hexane-DCM (2: 1) as the eluent afforded *3,5-difluoro-2,4,6-tris(4-methylphenyl)pyridine* (52%, 0.17 g), as a white solid, m.p. 152-154°C, (Found C, 80.7; H, 5.5; N,3.6. for $C_{26}H_{21}F_2N$ requires C, 81.0 ; H, 5.5; N, 3.6%). nmr spectrum no. 36, mass spectrum no. 33, ir spectrum no 33.

VI. 4. 2. d Synthesis of 4-bromo-5-fluoro-2,6-di(3-nitrophenyl)-3-pyridinol (49)

To a solution of 2,4,6-tribromo-3,5-difluoropyridine (0.8 g, 2.28 mmol) in monoglyme was added 3-nitrobenzeneboronic acid (1.25 equi, 2.85 mmol, 0.48 g), $Ba(OH)_2$ (2 equi, 4.56 mmol, 0.76 g) in water, and the Pd catalyst (6%, 158.5 mg). After heating for 48 hours, the mixture was worked up and chromatography on silica gel with pet-ether-ethyl acetate (1:1) as the eluent followed by a second column on hexane afforded *4-bromo-5-fluoro-2,6-di(3-nitrophenyl)-3-pyridinol* (54%, 0.53 g) as a white solid, m.p. 145.1-

145.8°C, (Found: [M+H] 432.9708, $C_{17}H_9BrFN_3O_5$ requires 432.9709). nmr spectrum no. 37, mass spectrum no. 34, ir spectrum no 34.

VI. 4. 2.e Synthesis of 4,6-bis(4-methylphenyl)-2-bromo-3,5-difluoropyridine (50)

To a solution of 2,4,6-tribromo-3,5-difluoropyridine (1 g, 2.84 mmol) in monoglyme was added 4-trifluoromethoxybenzeneboronic acid (0.8 equi, 2.27 mmol, 0.47 g), $Ba(OH)_2$ (2 equi, 4.54 mmol, 1.19 g) in water, and the Pd catalyst (6%, 155 mg) and the mixture heated for 21 hours. Chromatography on silica gel with hexane as the eluent afforded *4,6-bis(4-methylphenyl)-2-bromo-3,5-difluoropyridine* (22%, 0.32 g) as a white solid, b.p. > 300°C (Found: [M+H] 513.9689, $C_{19}H_8F_8O_2Br$ [M+H] requires 513.9693). nmr spectrum no. 38, mass spectrum no. 35, ir spectrum no 35.

VI. 4. 2. f Synthesis of 3,5-difluoro-2,4,6-tris(4-trifluoromethoxyphenyl)pyridine (51)

To a solution of 2,4,6-tribromo-3,5-difluoropyridine (0.15 g, 0.43 mmol) in monoglyme was added 4-trifluoromethoxybenzeneboronic acid (3 equi, 1.31mmol, 0.27 g), $Ba(OH)_2$ (2 equi, 0.86 mmol, 0.144 g) in water, and the Pd catalyst (6%, 30.14 mg) and the mxiture heated for 12 hours. Chromatography on silica gel with ethyl acetate-pet ether 40-60°C (1:10) as the eluent afforded *3,5-difluoro-2,4,6-tris(4-trifluoromethoxyphenyl)pyridine* (80%, 0.21 g) as a orange thick oil, b.p. 209-211°C , (Found: C, 52.2; H, 2.2; N, 2.1. $C_{26}H_{12}F_{11}NO_3$ requires C, 52.5; H, 2.0; N, 2.3%). nmr spectrum no. 39, mass spectrum no. 36, ir spectrum no 36.

VI. 4. 2. g Reaction with 4-methoxybenzeneboronic acid

To a solution of 2,4,6-tribromo-3,5-difluoropyridine (0.18 g, 0.52 mmol) in monoglyme was added 4-methoxybenzeneboronic acid (1.56 mmol, 0.24 g), $Ba(OH)_2$ (2 equi, 0.17 g, 104 mmol) in water, and the Pd catalyst (6%, 35.5 mg), the mixture was heated for 3 hours. Recrystallisation from DCM followed by chromatography on silica gel with DCM-hexane (2:1) as the eluent afforded 1-methoxy-4-(4-methoxyphenyl)benzene, nmr no. 47, which was identified by comparison with the literature.

VI. 4. 3 Palladium catalysed and non-catalysed reactions of 2,4,6-tribromo-3,5-difluoropyridine with oxygen and nitrogen nucleophiles:

VI. 4. 3. a Palladium catalysed reactions of 2,4,6-tribromo-3,5-difluoropyridine with butylamine

To a solution of 2,4,6-tribromo-3,5-difluoropyridine (1 g, 2.84 mmol) in toluene was added butylamine (1.25 equi, 3.40 mmol, 0.25 g, 0.34 ml), $Pd(dba)_2$ (2%, 0.056 mmol, 51 mg), DPPF (4%, 0.2056 mmol, 60 mg) and Cs_2CO_3 (4 mmol, 1.3 g) under an atmosphere of nitrogen, and the mixture was heated for 36 hours. The crude mixture consisted in *N3-butyl-2,4,6-tribromo-5-fluoro-3-pyridinamine* **(54)** and a mixture of *N4-butyl-2,6-dibromo-3,5-difluoro-4-pyridinamine* and *N2-butyl-4,6-dibromo-3,5-difluoro-2-pyridinamine* **(53)**. mass spectrum no. 37. No separation of the isomers was attempted.

VI. 4. 3. b Non-catalysed reactions of 2,4,6-tribromo-3,5-difluoropyridine with butylamine (54)

In a round bottomed flask containing 2,4,6-tribromo-3,5-difluoropyridine (1g, 2.84 mmol) in dry toluene was added butyl amine (1.2 equiv., 3.4 mmol, 0., 0.25 g, 34 ml) and heated at 96°C for 14 hrs, the reaction was cooled. Water was added, and the solution was extracted with DCM, dried over $MgSO_4$ and the solvent evaporated. Chromatography on silica gel with DCM-hexane (1:3) as the eluent afforded *butyl (2,4,6-tribromo-5-fluoro-3-pyridyl) amine* (48%, 0.55 g) as thick brown oil, m.p. 236-238°C (Found: C 27.0, H 2.6, N 6.9. $C_9H_{10}Br_3FN_2$ requires C, 26.8; H, 2.5; N, 7.2%). nmr spectrum no. 40, ir spectrum no 37.

VI. 4. 3. c Palladium catalysed reactions of 2,4,6-tribromo-3,5-difluoropyridine with sodium methoxide (55)

In a round bottomed flask containing 2,4,6-tribromo-3,5-difluoropyridine (1 g, 2.84 mmol) in toluene-THF(1:9) was added sodium methoxide (2.0 equi, 5.68 mmol, 0.30 g), Pd(dba) (5%, 80 mg, 0.14 mmol), DPPF (5%, 130 mg, 0.16 mmol), Cs_2CO_3 (4 mmol, 1.3 g) and benzyldimethyltetradecylammonium chloride dihydrate under an atmosphere of nitrogen, and the solution was heated at 80°C for 60 hours. The reaction was cooled; water was added, and the solution extracted with DCM, washed with saturated brine, extracted again and dried over $MgSO_4$ and the solvent evaporated. Chromatography on silica gel with DCM-hexane (1:1) as the eluent afforded *2,6-dibromo-3-fluoro-5-*

methoxypyridine (0.46g, 48%) as a white solid, m.p. 101-102.5°C (Found: C 25.5, H 1.4, N 4.7. $C_6H_4Br_2FNO$ requires C, 25.2; H, 1.4; N, 4.9. nmr no 41, mass spectrum no. 38, ir spectrum no 38.

VI. 4. 3. d Non-catalysed reactions of 2,4,6-tribromo-3,5-difluoropyridine with sodium methoxide (58)

In a round bottomed flask containing 2,4,6-tribromo-3,5-difluoropyridine (1 g, 2.84 mmol) in toluene was added sodium methoxide (1.2 equi, 3.55 mmol, 0.24 g) and the mixture was stirred at room temperature for 55 hours. Toluene was evaporated water added and the mixture was extracted into DCM, then dried over $MgSO_4$ and evaporated to dryness. Chromatography on silica gel column with DCM-hexane (1:3) as the eluent afforded *2,4,6-tribromo-3-fluoro-5-methoxypyridine* (48%, 0.46 g), which was identified by comparison with analytically pure samples of **(7),** nmr no 7.

VI. 4. 4 Zinc-mediated reactions of 2,4,6-tribromo-3,5-difluopyridine

VI. 4. 4. 1 Preparation of the zinc derivative of 2,4,6-tribromo-3,5-difluopyridine (59)

Under an atmosphere of dry nitrogen 2,4,6-tribromo-3,5-difluoropyridine (1 g, 2.84 mmol) was added to a solution of dry THF (15 ml) and cooled to -78°C; BuLi (1.6M hexanes) (1.2 equi, 3.41 mmol, 1.9 ml) was added over 15 min and stirred at -78°C for 30 min, the solution turned red. A solution of $ZnBr_2$ 1M (2.5 equi, 7.1 mmol, 6.4 ml) was added over 10 min. The solution was maintained at low temperature for 1 hour and allowed to warm to room temperature and the solution became colourless. ^{19}F NMR of the crude mixture showed the presence of **(59)**. nmr spectrum no. 42, mass spectrum no. 39.

VI. 4. 4. 2 Synthesis of 2,6-dibromo-3,5-difluorophenylpyridine (60)

To a solution of the zinc derivative of 2,4,6-tribromo-3,5-difluoropyridine (0.2 g) was added iodobenzene (0.6 equi, 0.42 mmol, 84 mg), $Pd(dba)_2$ (4%, 0.0168 mmol, 15.4 mg) and triphenylphosphine (16%, 0.0672, 17.6 mg). The mixture was heated to 50°C for 17 hrs, allowed to cool to room temperature, water was added and the mixture extracted in DCM (3x30 ml). The DCM solution was dried over $MgSO_4$ and evaporated. Chromatography on silica gel with DCM- hexane (1:2) as the eluent afforded *2,6-dibromo-3,5-difluorophenylpyridine* (75%, 0.2 g) as a white solid, m.p. 151.7-152.1°C. (Found C, 38.0; H, 1.4; N, 3.9. $C_{11}H_6Br_2F_2N$ requires C, 37.9; H, 1.4; N, 4.1%). nmr spectrum no. 43, mass spectrum no. 40, ir spectrum no 39.

VI. 4. 4. 3. Synthesis of 2,6-dibromo-4-(4-iodophenyl)-3,5-difluoropyridine (61)

To a solution of the zinc derivative of 2,4,6-tribromo-3,5-difluoropyridine (0.5 g) was added 1,4-diiodobenzene (0.6 equi, 0.84 mmol, 280 mg), $Pd(dba)_2$ (4%, 0.0168 mmol, 30.8 mg) and triphenylphosphine (16%, 0.0672, 35.2 mg). The mixture was stirred at room temperature for 23 hours, water added and the mixture was extracted in DCM (3x30 ml). The DCM solution was dried over $MgSO_4$ and evaporated. Chromatography on silica gel with DCM-hexane (4:1) as the eluent yielded *2,6-dibromo-4-(4-iodophenyl)-3,5-difluoropyridine* (36%, 0.24 g) as a white solid, m.p.145-147°C (Found M^+ 472.7721. $C_{11}F_2Br_2H_5IN$ requires 472.7723). nmr spectrum no. 44, mass spectrum no. 41, ir spectrum no 40.

VI. 4. 4. 4 Synthesis of 2,6-dibromo-4-[4-2,6-dibromo –3,5-difluoro-4-pyridyl)phenyl] 3,5-difluoropyridine (62)

To a solution of the zinc derivative of 2,4,6-tribromo-3,5-difluoropyridine (1.5 g) was added 1,4-diiodobenzene (0.6 equi, 2.56 mmol, 850 mg), $Pd(dba)_2$ (4%, 0.102 mmol, 184 mg) and triphenylphosphine (16%, 0.41, 106.5 mg). The mixture was stirred at room temperature for 5 hours, water was added and the mixture was extracted in DCM (3x30 ml). The DCM solution was dried over $MgSO_4$ and evaporated. Chromatography on silica gel with DCM-hexane (1: 2) and then methanol as the eluents yielded *2,6-dibromo-4-[4-2,6-dibromo–3,5-difluoro-4-pyridyl)phenyl]-3,5-difluoropyridine* (45%, 1.2 g) as a white solid, m.p. 286-287°C, (Found C, 29.8; H, 0.6; N, 4.3. $C_{16}H_4Br_4F_4N_2$ requires C, 30.1; H, 0.6; N, 4.5%). nmr spectrum no. 45, mass spectrum no. 42, ir spectrum no 41.

(4-Phenylbuta-1,3,-diynyl)benzene: mass spectrum no 44, ir spectrum no 42

Triphenylphosphine oxide (TPPO): nmr spectrum no 46, mass spectrum no 43.

methoxypyridine (0.46g, 48%) as a white solid, m.p. 101-102.5°C (Found: C 25.5, H 1.4, N 4.7. $C_6H_4Br_2FNO$ requires C, 25.2; H, 1.4; N, 4.9. nmr no 41, mass spectrum no. 38, ir spectrum no 38.

VI. 4. 3. d Non-catalysed reactions of 2,4,6-tribromo-3,5-difluoropyridine with sodium methoxide (58)

In a round bottomed flask containing 2,4,6-tribromo-3,5-difluoropyridine (1 g, 2.84 mmol) in toluene was added sodium methoxide (1.2 equi, 3.55 mmol, 0.24 g) and the mixture was stirred at room temperature for 55 hours. Toluene was evaporated water added and the mixture was extracted into DCM, then dried over $MgSO_4$ and evaporated to dryness. Chromatography on silica gel column with DCM-hexane (1:3) as the eluent afforded *2,4,6-tribromo-3-fluoro-5-methoxypyridine* (48%, 0.46 g), which was identified by comparison with analytically pure samples of **(7),** nmr no 7.

VI. 4. 4 Zinc-mediated reactions of 2,4,6-tribromo-3,5-difluopyridine

VI. 4. 4. 1 Preparation of the zinc derivative of 2,4,6-tribromo-3,5-difluopyridine (59)

Under an atmosphere of dry nitrogen 2,4,6-tribromo-3,5-difluoropyridine (1 g, 2.84 mmol) was added to a solution of dry THF (15 ml) and cooled to -78°C; BuLi (1.6M hexanes) (1.2 equi, 3.41 mmol, 1.9 ml) was added over 15 min and stirred at -78°C for 30 min, the solution turned red. A solution of $ZnBr_2$ 1M (2.5 equi, 7.1 mmol, 6.4 ml) was added over 10 min. The solution was maintained at low temperature for 1 hour and allowed to warm to room temperature and the solution became colourless. ^{19}F NMR of the crude mixture showed the presence of **(59)**. nmr spectrum no. 42, mass spectrum no. 39.

VI. 4. 4. 2 Synthesis of 2,6-dibromo-3,5-difluorophenylpyridine (60)

To a solution of the zinc derivative of 2,4,6-tribromo-3,5-difluoropyridine (0.2 g) was added iodobenzene (0.6 equi, 0.42 mmol, 84 mg), $Pd(dba)_2$ (4%, 0.0168 mmol, 15.4 mg) and triphenylphosphine (16%, 0.0672, 17.6 mg). The mixture was heated to 50°C for 17 hrs, allowed to cool to room temperature, water was added and the mixture extracted in DCM (3x30 ml). The DCM solution was dried over $MgSO_4$ and evaporated. Chromatography on silica gel with DCM- hexane (1:2) as the eluent afforded *2,6-dibromo-3,5-difluorophenylpyridine* (75%, 0.2 g) as a white solid, m.p. 151.7-152.1°C. (Found C, 38.0; H, 1.4; N, 3.9. $C_{11}H_6Br_2F_2N$ requires C, 37.9; H, 1.4; N, 4.1%). nmr spectrum no. 43, mass spectrum no. 40, ir spectrum no 39.

VI. 4. 4. 3. Synthesis of 2,6-dibromo-4-(4-iodophenyl)-3,5-difluoropyridine (61)

To a solution of the zinc derivative of 2,4,6-tribromo-3,5-difluoropyridine (0.5 g) was added 1,4-diiodobenzene (0.6 equi, 0.84 mmol, 280 mg), $Pd(dba)_2$ (4%, 0.0168 mmol, 30.8 mg) and triphenylphosphine (16%, 0.0672, 35.2 mg). The mixture was stirred at room temperature for 23 hours, water added and the mixture was extracted in DCM (3x30 ml). The DCM solution was dried over $MgSO_4$ and evaporated. Chromatography on silica gel with DCM-hexane (4:1) as the eluent yielded *2,6-dibromo-4-(4-iodophenyl)-3,5-difluoropyridine* (36%, 0.24 g) as a white solid, m.p.145-147°C (Found M^+ 472.7721. $C_{11}F_2Br_2H_5IN$ requires 472.7723). nmr spectrum no. 44, mass spectrum no. 41, ir spectrum no 40.

VI. 4. 4. 4 Synthesis of 2,6-dibromo-4-[4-2,6-dibromo –3,5-difluoro-4-pyridyl)phenyl] 3,5-difluoropyridine (62)

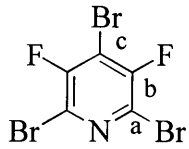
To a solution of the zinc derivative of 2,4,6-tribromo-3,5-difluoropyridine (1.5 g) was added 1,4-diiodobenzene (0.6 equi, 2.56 mmol, 850 mg), $Pd(dba)_2$ (4%, 0.102 mmol, 184 mg) and triphenylphosphine (16%, 0.41, 106.5 mg). The mixture was stirred at room temperature for 5 hours, water was added and the mixture was extracted in DCM (3x30 ml). The DCM solution was dried over $MgSO_4$ and evaporated. Chromatography on silica gel with DCM-hexane (1: 2) and then methanol as the eluents yielded *2,6-dibromo-4-[4-2,6-dibromo–3,5-difluoro-4-pyridyl)phenyl]-3,5-difluoropyridine* (45%, 1.2 g) as a white solid, m.p. 286-287°C, (Found C, 29.8; H, 0.6; N, 4.3. $C_{16}H_4Br_4F_4N_2$ requires C, 30.1; H, 0.6; N, 4.5%). nmr spectrum no. 45, mass spectrum no. 42, ir spectrum no 41.

(4-Phenylbuta-1,3,-diynyl)benzene: mass spectrum no 44, ir spectrum no 42

Triphenylphosphine oxide (TPPO): nmr spectrum no 46, mass spectrum no 43.

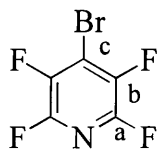
APPENDIX A

Spectrum no 1



Chemical shift (ppm)	Multiplicity	Coupling constant (Hz)	Integral	Assignment
^{19}F				
-103.7	s	-	-	b
^{13}C				
122.5	4 lines showing X part ABX	-	-	a
153.6	dd	$^{1}J_{CF}$ 263.5, $^{3}J_{CF}$ 11.5	-	b
110.09	t	$^{3}J_{CF}$ 24.0	-	c

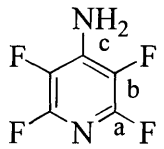
Spectrum no 2



Chemical shift (ppm)	Multiplicity	Coupling constant (Hz)	Integral	Assignment
^{19}F				
-89.0	m	-	-	a
-134.7	m	-	-	b
^{13}C				
114.4	tt	$^{3}J_{CF}$ 7.04, $^{2}J_{CF}$ 41.5	-	c
141.5	dm*	$^{1}J_{CF}$ 260.7	-	b
143.8	dm*	$^{1}J_{CF}$ 247.6	-	a

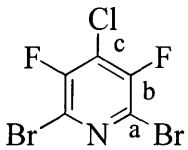
*) X part of an AA'BB'X

Spectrum no 3



Chemical shift (ppm)	Multiplicity	Coupling constant (Hz)	Integral	Assignment
^{1}H				
4.9	bs	-	-	c
^{19}F				
-94.2	s	-	-	a
-164.8	m	-	-	b
^{13}C				
130.5	dm*	$^{1}J_{CF}$ 246.9	-	b
137.4	tt	$^{2}J_{CF}$ 12.9, $^{3}J_{CF}$ 6.4	-	c
143.6	dm*	$^{1}J_{CF}$.232.50	-	a

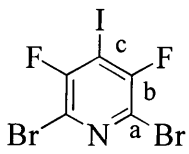
*) X part of an AA'BB'X



Spectrum no 4

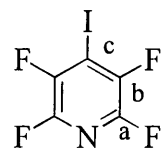
Chemical shift (ppm)	Multiplicity	Coupling constant (Hz)	Integral	Assignment
^{19}F				
-110.9	s	-	-	b
^{13}C				
122.0	4 lines showing X part ABX	-	-	a
101.4	t	$^{2}J_{CF}$ 28.5	-	c
151.6	d	$^{1}J_{CF}$ 266.5	-	b

Spectrum no 5



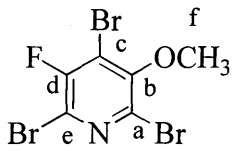
Chemical shift (ppm)	Multiplicity	Coupling constant (Hz)	Integral	Assignment
^{19}F				
-91.9	s	-	-	b
^{13}C				
88.8	t	$^{2}J_{CF}$ 25.5	-	c
121.5	4 lines showing X part ABX	-	-	a
156.8	d	$^{1}J_{CF}$ 242.9	-	b

Spectrum no 6



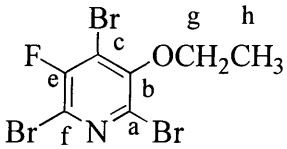
Chemical shift (ppm)	Multiplicity	Coupling constant (Hz)	Integral	Assignment
^{19}F				
-89.8	m	-	-	a
-123.1	m	-	-	b
^{13}C				
88.8	tt	$^{2}J_{CF}$ 25.5, $^{3}J_{CF}$ 2.3	-	c
142.0	ddd	$^{1}J_{CF}$ 241.0, $^{2}J_{CF}$ 35, $^{3}J_{CF}$ 4.2	-	b
143.7	dddd	$^{1}J_{CF}$ 281.6, $^{2}J_{CF}$ 35.5, $^{3}J_{CF}$ 21.4, $^{4}J_{CF}$ 9.85	-	a

Spectrum no 7



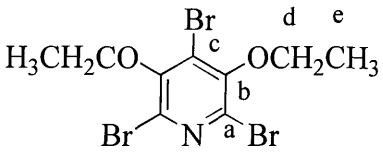
Chemical shift (ppm)	Multiplicity	Coupling constant (Hz)	Integral	Assignment
^{19}F				
-103.6	s	-	-	b or c
^{1}H				
3.96	-	-	-	f
^{13}C		-	-	
61.0	s			f
117.3	d	$^{2}J_{CF}$ 19.7	-	c
122.4	d	$^{2}J_{CF}$ 26.7	-	e
130.1	d	$^{3}J_{CF}$ 3.8	-	b
151.9	s	-	-	a
153.1	d	$^{1}J_{CF}$ 260.5	-	d

`Spectrum no 8



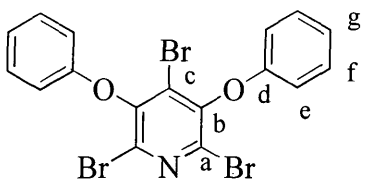
Chemical shift (ppm)	Multiplicity	Coupling constant (Hz)	Integral	Assignment
^{19}F				
-104.1	s	-	-	b
^{1}H				
1.4	t	-	3	h
4.1	q	-	2	g
^{13}C		-	-	
15.0	s			h
70.6	s	-	-	g
117.3	d	$^{2}J_{CF}$ 21.2	-	c
122.4	4 lines showing X part ABX	-	-	f
130.7	d	$^{3}J_{CF}$ 3.4	-	b
151.9	s		-	a
153.1	d	$^{1}J_{CF}$ 260.5	-	e

Spectrum no 9



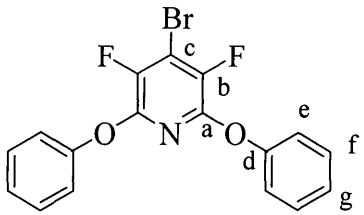
Chemical shift (ppm)	Multiplicity	Coupling constants (Hz)	Integral	Assignment
^1H				
1.5	t	$^3J_{HH}$ 6.8	6	e
4.1	q	$^3J_{HH}$ 6.8	4	d
^{13}C				
30.8	s	-	-	e
70.2	s	-	-	d
125.6	s	-	-	c
130.2	s	-	-	b
151.6	s	-	-	a

Spectrum no 10



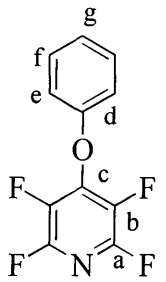
Chemical shift (ppm)	Multiplicity	Coupling constants (Hz)	Integral	Assignment
^{1}H				
6.8	d	$^{3}J_{HH}$ 8.0	2	f
7.1	t	$^{3}J_{HH}$ 7.4	1	g
7.3	m	-	2	e
^{13}C				
115.0	s	-	-	c
123.4	s	-	-	e
126.8	s	-	-	g
129.9	s	-	-	a
132.3	s	-	-	f
147.8	s	-	-	d
155.5	s	-	-	b

Spectrum no 11



Chemical shift (ppm)	Multiplicity	Coupling constants (Hz)	Integral	Assignment
^{19}F				
-139.3	s	-	-	b
^{1}H				
7.0	bm	-	2	e
7.1-7.2	bm	-	1	g
7.3-7.5	bm	-	2	f
^{13}C				
112.3	t	$^{2}J_{CF}$ 26.1	-	c
119.9	s	-	-	g
125.0	s	-	-	e
130.2	s	-	-	f
140.1	dd	$^{1}J_{CF}$ 256.2, $^{3}J_{CF}$ 36.5	-	b
144.4	dm	$^{2}J_{CF}$ 168.2	-	a
153.9	s	-	-	d

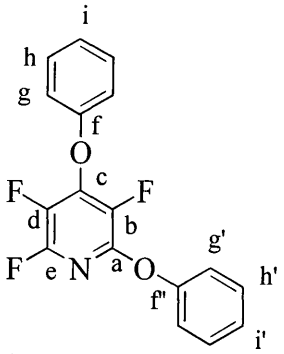
Spectrum no 12



Chemical shift (ppm)	Multiplicity	Coupling constants (Hz)	Integral	Assignment
^{19}F				
-89.1	s	-	-	a
-157.4	s	-	-	b
^{1}H				
6.98	d	$^{3}J_{HH}$ 8	2	e
7.1	t	$^{3}J_{HH}$ 7.2	1	g
7.3	dd	$^{3}J_{HH}$ 8.3, 7.1	2	f
^{13}C				
116.6	s	-	-	e
125.1	s	-	-	g
130.0	s	-	-	f
136.3	dm*	$^{1}J_{CF}$ 241.4	-	b
144.4	dm*	$^{1}J_{CF}$ 216.2	-	a
144.6	tt	$^{2}J_{CF}$ 10.3, $^{3}J_{CF}$ 5.3	-	c
155.0	s	-	-	d

*): as an X part AA'BB'X system.

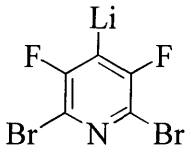
Spectrum no 13



Chemical shift (ppm)	Multiplicity	Coupling constant (Hz)	Integral	Assignment
^{19}F				
-89.1	s	-	1	e
-153.1	s	-	1	b or d
159.3	s	-	1	b or d
^{1}H				
6.9	d	$^{3}J_{HH}$ 8.0	2	g or g'
7.1	d	$^{3}J_{HH}$ 8.1	2	g or g'
7.17	t	$^{3}J_{HH}$ 7.1	1	i or i'
7.18	t	$^{3}J_{HH}$ 7.2	1	i or i'
7.31	dd	$^{3}J_{HH}$ 8.4, 7.2	2	h or h'
7.35	dd	$^{3}J_{HH}$ 8.3, 7.1	2	h or h'
^{13}C				
116.7	s	-	-	g'
121.0	s	-	-	g
124.9	s	-	-	i'
125.7	s	-	-	i
129.9	s	-	-	h'
130.0	s	-	-	h
134.6	dd	$^{1}J_{CF}$ 259.5, $^{2}J_{CF}$ 30.5	-	e
138.0	dd	$^{1}J_{CF}$ 262.0, $^{3}J_{CF}$ 7.2	-	d
143.4	td	$^{2}J_{CF}$ 10.8, $^{3}J_{CF}$ 5.3	-	c
144.8	ddd	$^{1}J_{CF}$ 238.3, $^{3}J_{CF}$ 13.5, $^{4}J_{CF}$ 3.4		b

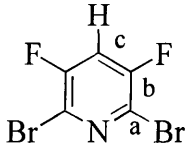
144.9	ddd	$^{2}J_{CF}$25.2, $^{2}J_{CF}$11.6, $^{5}J_{CF}$ 3.01		a
152.7	s	-	-	f'
156.1	s	-	-	f

Spectrum no 14



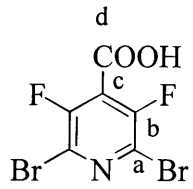
Chemical shift (ppm)	Multiplicity	Coupling constant (Hz)	Integral	Assignment
^{19}F				
-87.7	s	-	-	-

Spectrum no 15



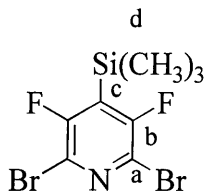
Chemical shift (ppm)	Multiplicity	Coupling constant (Hz)	Integral	Assignment
^{19}F				
-109.1	d	$^{3}J_{HF}$ 6.8	-	b
^{1}H				
7.31	t	$^{3}J_{HF}$ 6.8	-	c
^{13}C				
122.7	4 lines showing X part ABX	-	-	a
113.7	t	$^{2}J_{CF}$ 23.8	-	c
155.5	dd	$^{1}J_{CF}$ 265.5, $^{3}J_{CF}$ 4.5.	-	b

Spectrum no 16



Chemical shift (ppm)	Multiplicity	Coupling constant (Hz)	Integral	Assignment
^{19}F				
-110.6	s	-	-	b
^{1}H				
6.26	bs	-	-	d
^{13}C				
106.4	t	$^{2}J_{CF}$ 24.2	-	c
123.4	4 lines showing X part of ABX	-	-	a
152.6	d	$^{1}J_{CF}$ 270.4	-	b
159.1	s	-	-	d

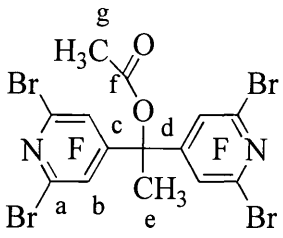
Spectrum no 17



Chemical shift (ppm)	Multiplicity	Coupling constant (Hz)	Integral	Assignment
^{19}F				
-99.7	s	-	-	b
^{1}H				
0.36	s	-	-	d
^{13}C				
0.66	s	-	-	d

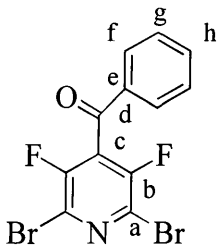
122.4	t	$^{2}J_{CF}$ 32.7	-	c
127.4	4 lines showing X part ABX	-	-	a
159.5	d	$^{1}J_{CF}$ 257.0	-	b

Spectrum no 18



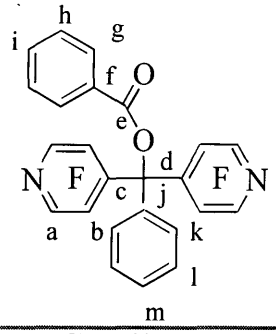
Chemical shift (ppm)	Multiplicity	Coupling constant (Hz)	Integral	Assignment
^{19}F				
-108.1	s	-	-	b
^{1}H				
2.2	s	-	-	g
2.3	s	-	-	e
^{13}C				
21.4	s	-	-	g
26.9	s	-	-	e
78.1	s	-	-	d
124.3	4 lines showing X part of ABX	-	-	a
128.5	m	-	-	c
153.1	d	$^{1}J_{CF}$ 267	-	b
168.5	s	-	-	f

Spectrum no 19



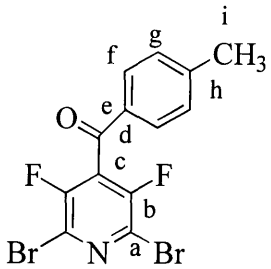
Chemical shift (ppm)	Multiplicity	Coupling constant (Hz)	Integral	Assignment
^{19}F				
-112.2.	s	-	-	b
^{1}H				
7.54-7.57	m	-	2	f
7.6	t	$^{3}J_{HH}$ 7	1	h
7.71-7.74	m	-	2	g
^{13}C				
123.3	4 lines showing X part ABX	-	-	a
126.2	t	$^{2}J_{CF}$	-	c
129.5	s	-	-	g
131.3	s	-	-	h
134.6	s	-	-	f
135.6	s	-	-	e
152.1	d	$^{1}J_{CF}$ 264.7	-	b
184.5	s	-	-	d

Spectrum no 20



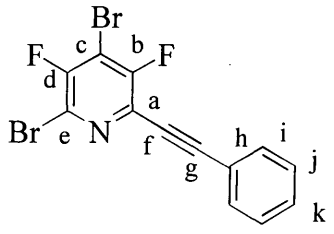
Chemical shift (ppm)	Multiplicity	Coupling constant (Hz)	Integral	Assignment
^{19}F				
-89.7	m	-	-	a
-136.9	m	-		b
^{1}H				
7.4-7.6	m		-	All rest hydrogens
8.00-8.02	m		2	g
^{13}C			-	
124.6	s	-	-	h
125.2	s	-	-	m
128.2	s	-	-	c or j
128.8	m	-	-	c or j
129.1	s	-	-	l
129.6	s	-	-	g
130.04	s	-	-	f
130.1	s	-	-	k
131.8		-	-	
132.02	m	-	-	j
134.6	s	-	-	i
139.5	dm	$^{1}J_{CF}$ 225.0	-	a
144.5	dm	$^{1}J_{CF}$ 227.1	-	b
165.1	s	-	-	e

Spectrum no 21



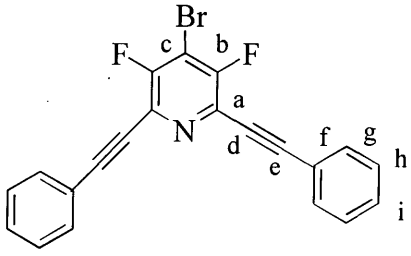
Chemical shift (ppm)	Multiplicity	Coupling constant (Hz)	Integral	Assignment
^{19}F				
-112.3	s	-	-	b
^{1}H				
1.4	s	-	-	i
7.3	d	$^{3}J_{HH}$ 8.4	2	f
7.6	d	$^{3}J_{HH}$ 8.0	2	g
^{13}C				
22.0	s	-	-	i
123.3	4 lines showing X part ABX	-	-	a
126.5	t	$^{2}J_{CF}$ 29.2	-	c
129.9	s	-	-	g
130.0				f
132.3	s	-	-	e
147.2	s	-	-	h
153.0	dd	$^{1}J_{CF}$ 258.0, $^{3}J_{CF}$ 1.9	-	b
184.0	s	-	-	d

Spectrum no 22



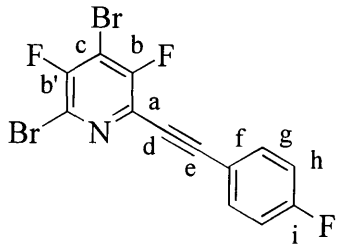
Chemical shift (ppm)	Multiplicity	Coupling constant (Hz)	Integral	Assignment
^{19}F				
-108.1	s	-	-	b
^{1}H				
7.30-7.36	m	-	2	i
7.55-7.57	m	-	3	j, k
^{13}C				
81.0	4 lines showing X part of ABX	-	-	g
96.3	t	$^{3}J_{CF}$ 3.8	-	f
121.0	s	$^{2}J_{CF}$ 22.7	-	c
123.6	dd	$^{2}J_{CF}$ 25.1, $^{4}J_{CF}$ 3.8	-	a
128.5	s	-	-	j
129.8	s	-	-	k
132.2	s	-	-	i
153.1	d	$^{1}J_{CF}$ 265.9	-	b or d
157.2	d	$^{1}J_{CF}$ 267	-	b or d

Spectrum no 23



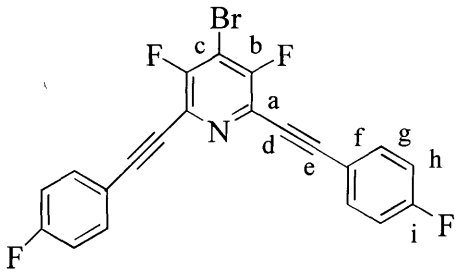
Chemical shift (ppm)	Multiplicity	Coupling constant (Hz)	Integral	Assignment
^{19}F				
-108.1	s	-	-	b
^{1}H				
7.30-7.36	m	-	3	g,h
7.55-7.57	m	-	2	i
^{13}C				
81.0	4 lines showing X part of ABX	-	-	e
96.3	t	$^{3}J_{CF}$ 3.8	-	d
108.4	t	$^{2}J_{CF}$ 22.7	-	c
121.0	s	-	-	f
128.5	s	-	-	h
128.9	4 lines showing X part of ABX	-	-	a
129.7	s	-	-	i
132.2	s	-	-	g
156.8	d	$^{1}J_{CF}$ 269	-	b

Spectrum no 24



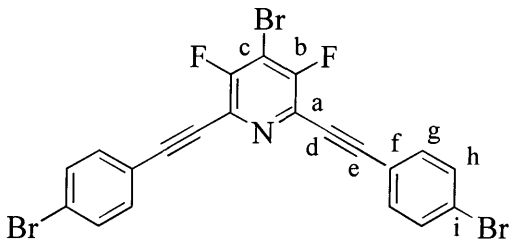
Chemical shift (ppm)	Multiplicity	Coupling constant (Hz)	Integral	Assignment
^{19}F				
-108.1	s	-	-	b or d
-100.9	s	-	-	i
-110.4	s	-	-	b or d
^{1}H				
7.58-7.61	m	-	2	g
7.08-7.11	m	-	2	h
^{13}C				
80.3	4 lines showing X part of ABX	-	-	d
94.5	t	$^{3}J_{CF}$ 3.4	-	e
109.5	t	$^{2}J_{CF}$ 23.3	-	c
115.8	d	$^{2}J_{CF}$ 22.1	-	f
123.9	dd	$^{4}J_{CF}$ 3.4, $^{2}J_{CF}$ 24.1	-	h
128.6	4 lines showing X part of ABX	-	-	a
134.3	d	$^{3}J_{CF}$ 8.34	-	g
153.4	d	$^{1}J_{CF}$ 265.5	-	b or b'
157.4	d	$^{1}J_{CF}$ 266.3	-	b orb'
164.7	d	$^{1}J_{CF}$ 252	-	i

Spectrum no 25



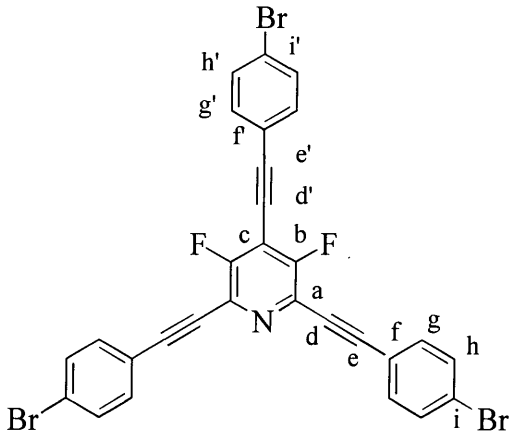
Chemical shift (ppm)	Multiplicity	Coupling constant (Hz)	Integral	Assignment
^{19}F				
-108.08	s	-	-	b
-108.4	m	-	-	i
^{1}H				
7.36	m	-	2	g
7.50	m	-	2	h
^{13}C				
80.7	4 lines showing X part of ABX	-	-	e
95.2	t	$^{3}J_{CF}$ 3.8	-	d
108.7	t	$^{2}J_{CF}$ 22.9	-	c
116.1	s	-	-	h
117.4	s	-	-	f
128.8	4 lines showing X part of ABX	-	-	a
134.3	s	-	-	g
156.5	d	$^{1}J_{CF}$ 268.9	-	i
163.3	s	$^{1}J_{CF}$ 251.4	-	b

Spectrum no 26



Chemical shift (ppm)	Multiplicity	Coupling constant (Hz)	Integral	Assignment
^{19}F				
-107.5	s	-	-	b
^{1}H				
7.18-7.23	m	-	4	g, h
^{13}C				
80.9	4 lines showing X part of ABX	-	-	e
94.1	s	-	-	d
108.8	s	-	-	c
119.1	s	-	-	f
123.5	s	-		i
128.9	4 lines showing X part of ABX	-	-	a
132.1	s	-	-	g
133.8	s	-	-	h
155.9	d	$^{1}J_{CF}$ 269.4	-	b

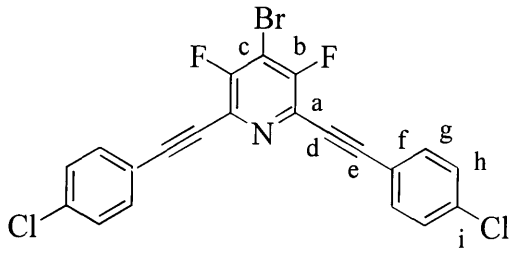
Spectrum no 27



Chemical shift (ppm)	Multiplicity	Coupling constant (Hz)	Integral	Assignment
^{19}F				
-110.84	s	-	-	b
^{1}H				
7.22	m	-	-	All hydrogens
^{13}C				
82.5	4 lines showing X part of ABX	-	-	e
94.9	4 lines showing X part of ABX	-	-	e'
104.0	m	-	-	d
105.6	m	-	-	d'
110.0	m	-	-	c
120.2	s	-	-	i
120.6	s	-	-	i'
124.5	s	-	-	f
125.1	s	-	-	f'
129.1	4 lines showing X part of ABX		-	a
132.1	s	-	-	g
132.2	s	-	-	g'
133.7	s	-	-	h
133.9	s	-	-	h'

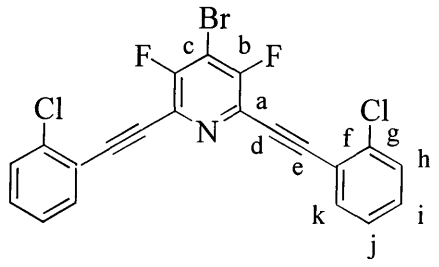
158.4	d	$^{1}J_{CF}$ 274	-	b

Spectrum no 28



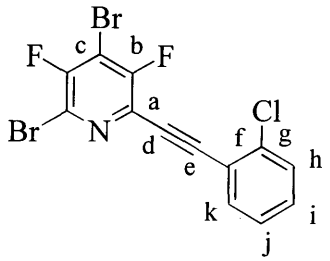
Chemical shift (ppm)	Multiplicity	Coupling constant (Hz)	Integral	Assignment
^{19}F				
-107.6	s	-	-	b
^{1}H				
7.37	dt	$^{3}J_{HH}$ 8.4, $^{3}J_{HH}$ 1.6	2	g
7.54	dt	$^{3}J_{HH}$ 8, $^{3}J_{HH}$ 1.6	2	h
^{13}C				
81.7	4 lines showing X part ABX	-	-	d
95.1	t	$^{3}J_{CF}$ 3.8	-	e
108.5	t	$^{2}J_{CF}$ 22.5	-	c
119.7	s	-	-	f
128.6	4 lines showing X part ABX	-	-	a
128.9	s	-	-	h
133.4	s	-	-	g
136.0	s	-	-	i
157.0	d	$^{1}J_{CF}$ 269	-	b

Spectrum no 29



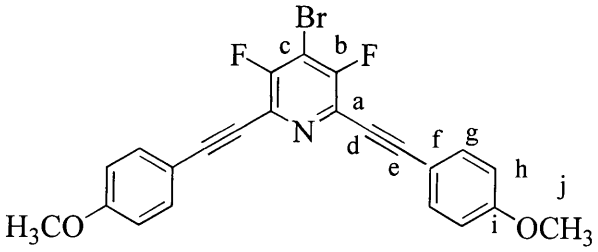
Chemical shift (ppm)	Multiplicity	Coupling constant (Hz)	Integral	Assignment
^{19}F				
-106.7	s	-	-	b
^{1}H				
7.28	dt	$^{3}J_{HH}$ 7.6, $^{3}J_{HH}$ 1.2	1	i
7.35	dt	$^{3}J_{HH}$ 7.6, $^{3}J_{HH}$ 1.6	1	k
7.40	d	$^{3}J_{HH}$ 7.6	1	j
7.60	dd	$^{3}J_{HH}$ 7.6, $^{3}J_{HH}$ 1.6	1	h
^{13}C				
85.7	4 lines showing X part ABX	-	-	d
93.0	t	$^{3}J_{CF}$ 3.8	-	e
108.8	m	-	-	c
121.7	s	-	-	f
126.6	s	-	-	j
126.8	s			i
129.0	4 lines showing X part ABX	-	-	a
129.7	s	-	-	h
131.1	s	-	-	k
134.2				g
157.7	d	$^{1}J_{CF}$ 270.4	-	b

Spectrum no 30



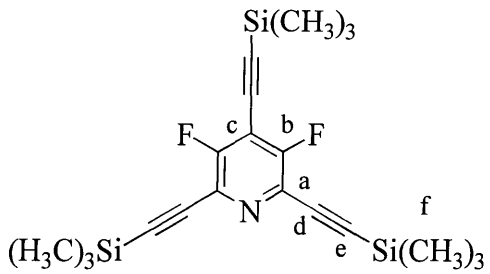
Chemical shift (ppm)	Multiplicity	Coupling constant (Hz)	Integral	Assignment
^{19}F				
-109.4	s	-	-	b
^{1}H				
7.21-7.26	m	-	1	i
7.29-7.33	m	-	1	k
7.37-7.42	m	-	1	j
7.55-7.58	m	-	1	h
^{13}C				
85.7	4 lines showing X part ABX	-	-	d
93.0	t	$^{3}J_{CF}$ 3.8	-	e
108.8	m	-	-	c
121.7	s	-	-	f
126.6	s	-	-	j
126.8	s			i
129.0	4 lines showing X part ABX	-	-	a
129.7	s	-	-	h
131.1	s	-	-	k
134.2				g
157.7	d	$^{1}J_{CF}$ 270.4	-	b

Spectrum no 31



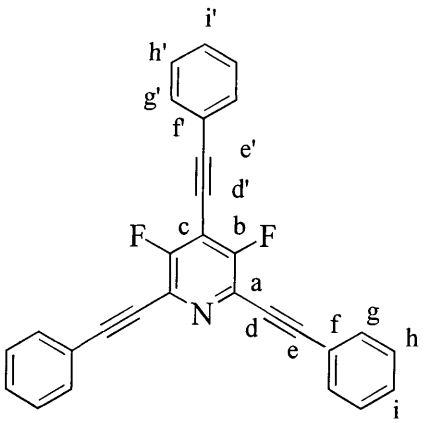
Chemical shift (ppm)	Multiplicity	Coupling constant (Hz)	Integral	Assignment
^{19}F				
-109.3	s	-	-	b
^{1}H				
3.86		-	-	j
7.21	sd	$^{1}J_{HH}$ 8.37	1	g
7.54	d	$^{1}J_{HH}$ 8.37	1	h
^{13}C				
55.2	s	-	-	j
80.3	4 lines showing X part ABX	-	-	e
96.6	t	$^{3}J_{CF}$ 3.5	-	d
108.5	t	$^{2}J_{CF}$ 23.1	-	c
113.5	s	-	-	f
114.1	s	-	-	g
129.4	4 lines showing X part ABX	-	-	a
134.0	s	-	-	g
156.5	d	$^{1}J_{CF}$ 267.8	-	b
160.6	s	-	-	i

Spectrum no 32



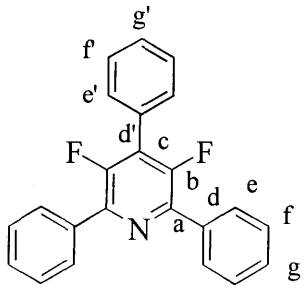
Chemical shift (ppm)	Multiplicity	Coupling constant (Hz)	Integral	Assignment
^{19}F				
-107.5	s	-	-	b
^{1}H				
0.26	s	-	-	f
^{13}C				
0.54	s	-	-	f
95.4	4 lines showing X part ABX	-	-	e
103.5	t	$^{3}J_{CF}$ 3.8	-	d
108.5	t	$^{2}J_{CF}$ 22.4	-	c
128.4	4 lines showing X part ABX	-	-	a
157.3	d	$^{1}J_{CF}$ 269.3		b

Spectrum no 33



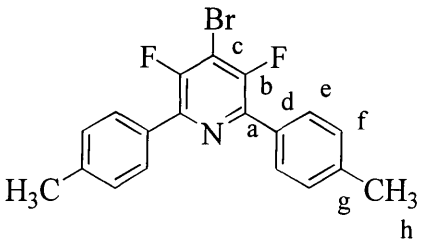
Chemical shift (ppm)	Multiplicity	Coupling constant (Hz)	Integral	Assignment
^{19}F				
-111.45	s	-	-	b
^{1}H				
7.30-7.40	m	-	4	g, h, g', h'
7.60-7.70	m	-	2	i, i'
^{13}C				
81.6		-	-	e
95.9				e'
104.8				d
105.0				d'
110.7	m	-	-	a
121.2	-	-	-	f
121.8	s	-	-	f'
128.7	s	-	-	i
128.8	s	-	-	i'
129.8	s	-	-	h
130.4	s	-	-	h'
132.2	s	-	-	g
132.4	s	-	-	g'
158.1	d	$^{1}J_{CF}$ 273	-	b

Spectrum no 34



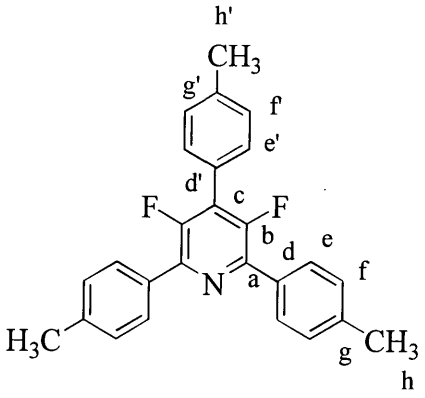
Chemical shift (ppm)	Multiplicity	Coupling constant (Hz)	Integral	Assignment
^{19}F				
-126.4	s	-	-	b
^{1}H				
2.1	m	-	4	g, g',f, f'
7.47-7.49	m	-	2	e'
7.95-7.97	m	-	2	e
^{13}C			-	
127.6	m	-		c
128.4	s	-	-	g
128.5	s	-	-	g'
128.8	bs	-		e'
129.1	s	-	-	f
129.3	s	-		f'
130.1	bs	-	-	e
135.4	m	-	-	d
139.3	m	-	-	d'
144.4	X part of an ABX system	-	-	a
152.8	d	$^{1}J_{CF}$ 226.8	-	b

Spectrum no 35



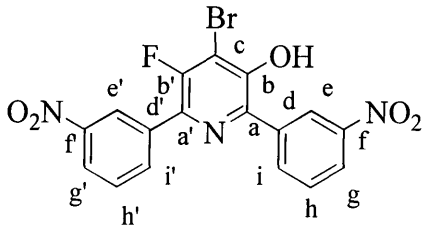
Chemical shift (ppm)	Multiplicity	Coupling constant (Hz)	Integral	Assignment
^{19}F				
-117.5	s	-	-	b
^{1}H				
2.1	s	-	-	h
7.21-7.24	m	-	2	f
7.80-7.830	m	-	2	e
^{13}C				
21.2	s	-	-	h
109.7	t	$^{2}J_{CF}$ 23.2	-	c
128.8	m	-	-	e
129.5	s	-	-	f
131.9	d	$^{3}J_{CF}$ 7.03	-	d
139.8	s	-	-	g
141.9	X part of an ABX system	-	-	a
153.1	d	$^{1}J_{CF}$ 271.5	-	b

Spectrum no 36



Chemical shift (ppm)	Multiplicity	Coupling constant (Hz)	Integral	Assignment
^{19}F				
-127.0	s	-	-	b
^{1}H				
2.1	s	-	-	h, h'
7.30-7.49	m		4	f, f'
7.47-7.49	m	-	2	e'
7.95-7.97	m	-	2	e
^{13}C				
21.3	s	-	-	h
21.4	s	$^{2}J_{CF}$ 23.2	-	h'
125.0	s	-	-	e
127.4	t	$^{3}J_{CF}$ 23.4		c
128.9	s	-	-	f
129.0	s	-	-	f'
129.4	s	-		g
129.5	s	-	-	g'
130.2	t	$^{4}J_{CF}$ 1.9		e'
132.9	t	$^{3}J_{CF}$ 3.4	-	d'
139.1	d	-	-	d
141.7	X part of an ABX system	-	-	a
152.7	d	$^{1}J_{CF}$ 264.7	-	b

Spectrum no 37

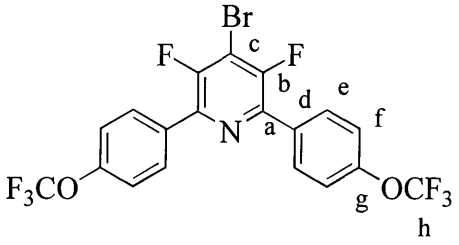


Chemical shift (ppm)	Multiplicity	Coupling constant (Hz)	Integral	Assignment
^{19}F				
-119.9	s	-	-	b'
^{1}H				
7.726	t	$^{3}J_{HH}$ 8.0	1	h or h'
7.720	t	$^{3}J_{HH}$ 8.0	1	h or h'
8.33	d*	$^{3}J_{HH}$ 7.5	2	g and g'
8.40	d	$^{3}J_{HH}$ 7.5	1	e or e'
8.48	d	$^{3}J_{HH}$ 7.0	1	e or e'
8.90	bs	-	1	i or i'
9.02	bs	-	1	i or i'
^{13}C				
110.5	d	$^{2}J_{CF}$ 22.1	-	c
123.6	s	-	-	e'
124.0	s	-	-	e
124.1	s	-	-	g'
124.4	s	-	-	g
129.9	s	-	-	f
134.3	s	-		h'
134.4	s	-	-	h
135.2	s	-	-	i
136.1	s	$^{3}J_{CF}$ 6.9		d'
136.2	d	$^{4}J_{CF}$ 2.3	-	i'
137.7	s	-		d
139.3	d	$^{3}J_{CF}$ 5.0	-	b

148.4	d	$^{4}J_{CF}$ 1.6	-	a
148.8	d	$^{2}J_{CF}$ 73.6	-	a'
157.7	d	$^{1}J_{CF}$ 261.5	-	b'

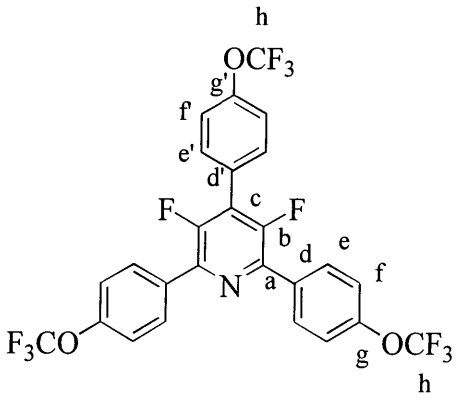
*: the two doublets superpose.

Spectrum no 38



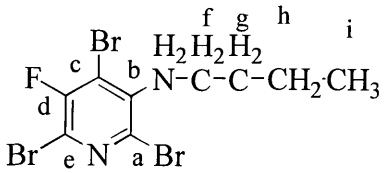
Chemical shift (ppm)	Multiplicity	Coupling constant (Hz)	Integral	Assignment
^{19}F				
-58.1	s	-	-	h
-115.5	s	-	-	b
^{1}H				
7.3	bd	$^{3}J_{HH}$ 8.2	2	f
8.03	bd	$^{3}J_{HH}$ 8	2	e
^{13}C				
110.0	m	-	-	c
120.3	q	$^{1}J_{CF}$ 257.8		g
120.8	bs	-	-	f
121.6	s	-	-	i
130.3	m	-	-	e
132.6		-	-	d
140.5	X part of an ABX system	-	-	a
150.1	bs	-	-	g
153.5	d	$^{1}J_{CF}$ 267.5	-	b

Spectrum no 39



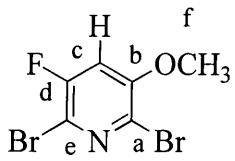
Chemical shift (ppm)	Multiplicity	Coupling constant (Hz)	Integral	Assignment
^{19}F				
-58.8	s	-	-	h
-126.1	s	-	-	b
^{1}H				
7.22-7.30	m	-	4	f
7.32-7.35	m	-	2	f'
7.48-7.57	m	-	2	e'
7.95-8.03	m	-	4	e
^{13}C				
120.7	bs	-	-	f
120.9	bs			f'
121.5	q	$^{1}J_{CF}$ 258.1	-	h
126.2	t	$^{2}J_{CF}$ 19.1		c
130.3	m	-	-	e
130.7	t	$^{3}J_{CF}$ 3.4		d
131.7	m	-	-	e'
134.2	m	-	-	d'
140.8	X part of an ABX system	-	-	a
149.3	bs	-	-	g
150.1	bs	-	-	g'
153.4	d	$^{1}J_{CF}$ 270.5	-	b

Spectrum no 40



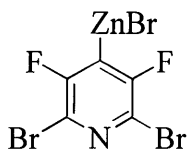
Chemical shift (ppm)	Multiplicity	Coupling constant (Hz)	Integral	Assignment
^{19}F				
-104.4	s	-	-	b
^{1}H				
0.85	t	-	-	i
1.32	sext	$^{3}J_{HH}$ 7.6	2	h
1.48	quint	$^{3}J_{HH}$ 7.66	2	g
3.36	t	$^{3}J_{HH}$ 7.2	2	f
4.15	bs	-	-	NH
^{13}C				
13.7	s	-	-	i
21.4	s	$^{2}J_{CF}$ 23.2	-	i
19.8	s	-	-	h
32.8	s	-		g
47.1	s	-	-	f
110.5	d	$^{2}J_{CF}$ 21.7		c
115.5	d	$^{2}J_{CF}$ 27.7	-	e
125.9	d	$^{4}J_{CF}$ 3.1	-	a
143.5	X part of an ABX system	-	-	b
153.7	d	$^{1}J_{CF}$ 256.0	-	d

Spectrum no 41



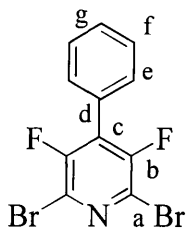
Chemical shift (ppm)	Multiplicity	Coupling constant (Hz)	Integral	Assignment
^{19}F				
-112.4	d	$^{3}J_{HF}$ 4	-	d
^{1}H				
3.86	s	-	-	f
1.32	t	$^{3}J_{HF}$ 4	1	c
^{13}C				
57.0	s	-	-	f
108.6	d	$^{2}J_{CF}$ 24.4		c
116.7	d	$^{2}J_{CF}$ 26.1	-	e
124.7	d	$^{4}J_{CF}$ 3.0	-	a
153.7	s	-	-	b
156.1	d	$^{1}J_{CF}$ 261.0	-	d

Spectrum no 42



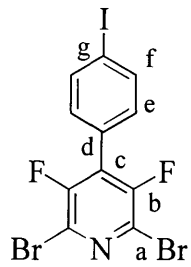
Chemical shift (ppm)	Multiplicity	Coupling constant (Hz)	Integral	Assignment
^{19}F				
-93.0	s	-	-	-

Spectrum no 43



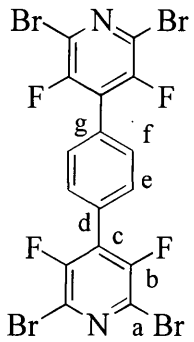
Chemical shift (ppm)	Multiplicity	Coupling constant (Hz)	Integral	Assignment
^{19}F				
-114.0	s	-	-	b
^{1}H				
7.47-7.50	m	-	3	e and g
7.50-7.53	m	-	2	f
^{13}C				
123.7	X part of an ABX system	-	-	a
124.2	s	-	-	e
125.2	s	-	-	g
125.8	t	$^{3}J_{CF}$ 28.6	-	c
130.4	s	-	-	f
131.9	bs	-	-	d
152.6	d	$^{1}J_{CF}$ 261.5	-	b

Spectrum no 44



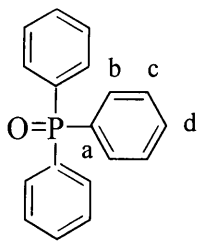
Chemical shift (ppm)	Multiplicity	Coupling constant (Hz)	Integral	Assignment
^{19}F				
-113.8	s		-	b
^{1}H				
7.51-7.52	m	-	2	e
7.87-7.89	m	-	2	f
^{13}C				
97.1	s	-	-	g
123.4	X part of an ABX system	-	-	a
125.2	s	-	-	e
125.5	t	$^{2}J_{CF}$ 18.0	-	c
131.3	t	$^{3}J_{CF}$ 2.3	-	d
138.1	s	-	-	f
152.3	d	$^{1}J_{CF}$ 264.0	-	b

Spectrum no 45



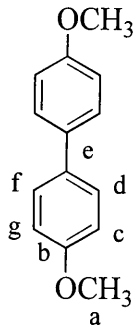
Chemical shift (ppm)	Multiplicity	Coupling constant (Hz)	Integral	Assignment
^{19}F				
-113.6	s	-	-	b
^{1}H				
7.66	m	-	4	e, f
^{13}C				
123.8	X part of an ABX system	-	-	a
127.4	t	$^{2}J_{CF}$ 23.0	-	c
128.3	s	-	-	e, f
130.6	s	-	-	d
152.7	d	$^{1}J_{CF}$ 211.2	-	b

Spectrum no 46



Chemical shift (ppm)	Multiplicity	Coupling constants (Hz)	Integral	Assignment
^{31}P				
28	s		-	-
^{1}H				
7.43-7.46	m	-	1	d
7.50-7.53	m	-	2	c
7.63-7.68	m	-	2	b
^{13}C				
127.4	d	$^{3}J_{CP}$ 11.9		c
130.9	d	$^{4}J_{CP}$ 2.9	-	d
131.0	d	$^{2}J_{CP}$ 9.9	-	b
156.6.	d	$^{1}J_{CP}$ 104.1	-	a

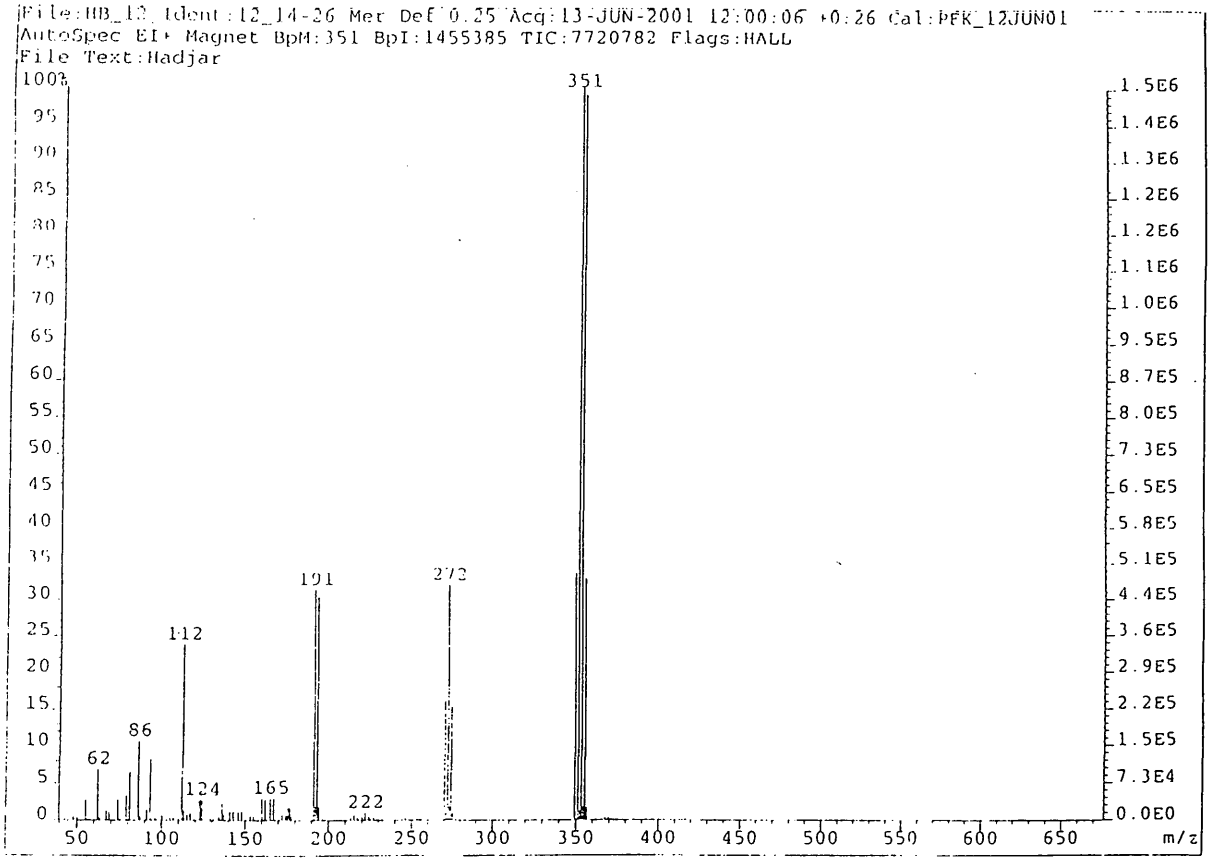
Spectrum no 47



Chemical shift (ppm)	Multiplicity	Coupling constant (Hz)	Integral	Assignment
^{1}H				
3.8	s	-	-	a
6.87-6.95	m	-	2	c , g
7.61-8.10	m	-	2	d , f
^{13}C				
55.4	s	-		a
113.8	s	-	-	e
135.5	s	-	-	d
137.7	s	-	-	c
163.4	s	-	-	b

APPPENDIX B

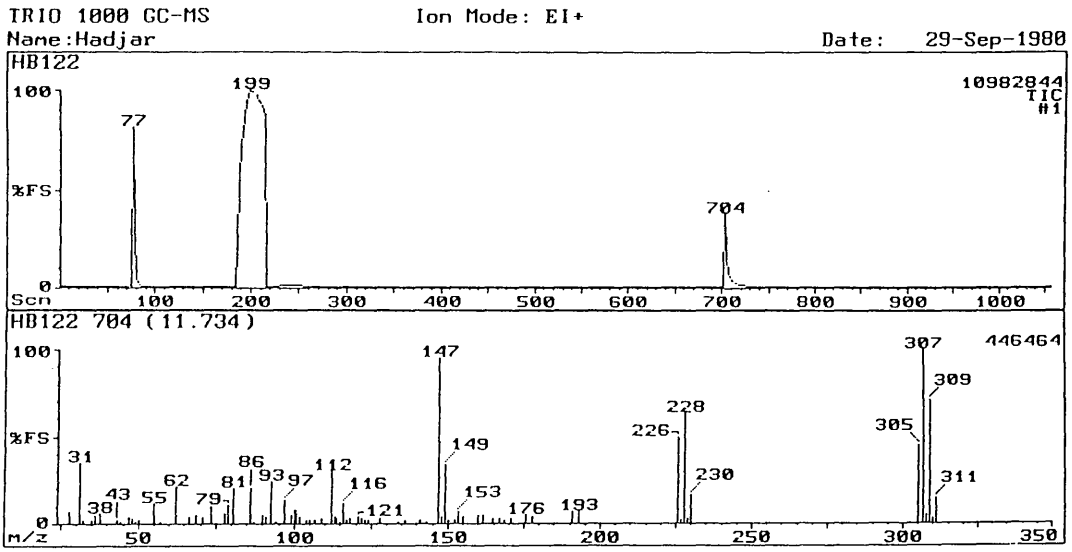
1.: 2,4,6-tribromo-3,5-difluoropyridine (1)




```
! MS_USER:SPE_DEFAULT.LIS  13-JUN-2001  12:01
! Listing of raw data for -
!       data file HB_12
!       data identifier 12_14-26 Mer Def 0.25
! Axis display range       X_MASS (40.00, 676.35)
! Normalising intensity  1.45539E+06
! Data threshold 0.30% of normalising intensity
!
```

ABS MASS	REL (%) HEIGHT	ABS MASS	REL (%) HEIGHT	ABS MASS	REL (%) HEIGHT	ABS MASS	REL (%) HEIGHT
48.0602	0.57	112.1598	23.90	160.1711	2.97	224.2416	0.53
50.0675	0.39	113.1643	1.40	162.1725	2.87	227.2307	0.40
55.0654	2.80	115.0941	0.81	165.1725	3.05	246.2950	0.33
62.0803	6.95	117.0972	1.04	167.1745	3.00	270.2886	16.43
63.0904	0.32	122.1039	2.78	172.1745	0.80	271.2937	0.97
67.0845	1.30	123.1040	2.79	174.1954	0.68	272.2900	32.11
69.0918	1.11	124.0911	2.83	174.7421	0.67	273.3057	1.78
74.0972	2.80	129.1310	0.46	175.7045	1.82	274.2913	15.52
79.0264	3.38	131.1331	0.37	176.6915	1.70	275.3193	1.02
81.0662	6.64	134.1197	0.97	177.6802	0.58	349.3738	33.79
86.1047	10.80	135.1388	0.76	191.2184	31.51	351.3721	100.00
87.1166	0.50	136.1257	2.40	192.2233	1.88	352.2880	1.29
91.0400	1.53	137.1102	0.80	193.2203	30.48	353.3691	99.03
93.1217	8.41	141.1288	1.29	194.2231	1.83	354.3104	1.82
94.1406	0.49	143.1323	1.26	213.2214	0.35	355.3435	32.99
95.6036	0.32	146.1373	1.19	215.2253	0.67	356.4407	1.74
100.1437	0.69	148.1413	1.28	217.2263	0.34	367.4242	0.34
105.0750	0.57	153.1678	0.66	220.2357	0.50	369.3865	0.40
107.0801	0.41	155.1745	0.66	222.2250	1.01		

2. 2,6,-dibromo-3,5-difluoro-4-chloropyridine (4)

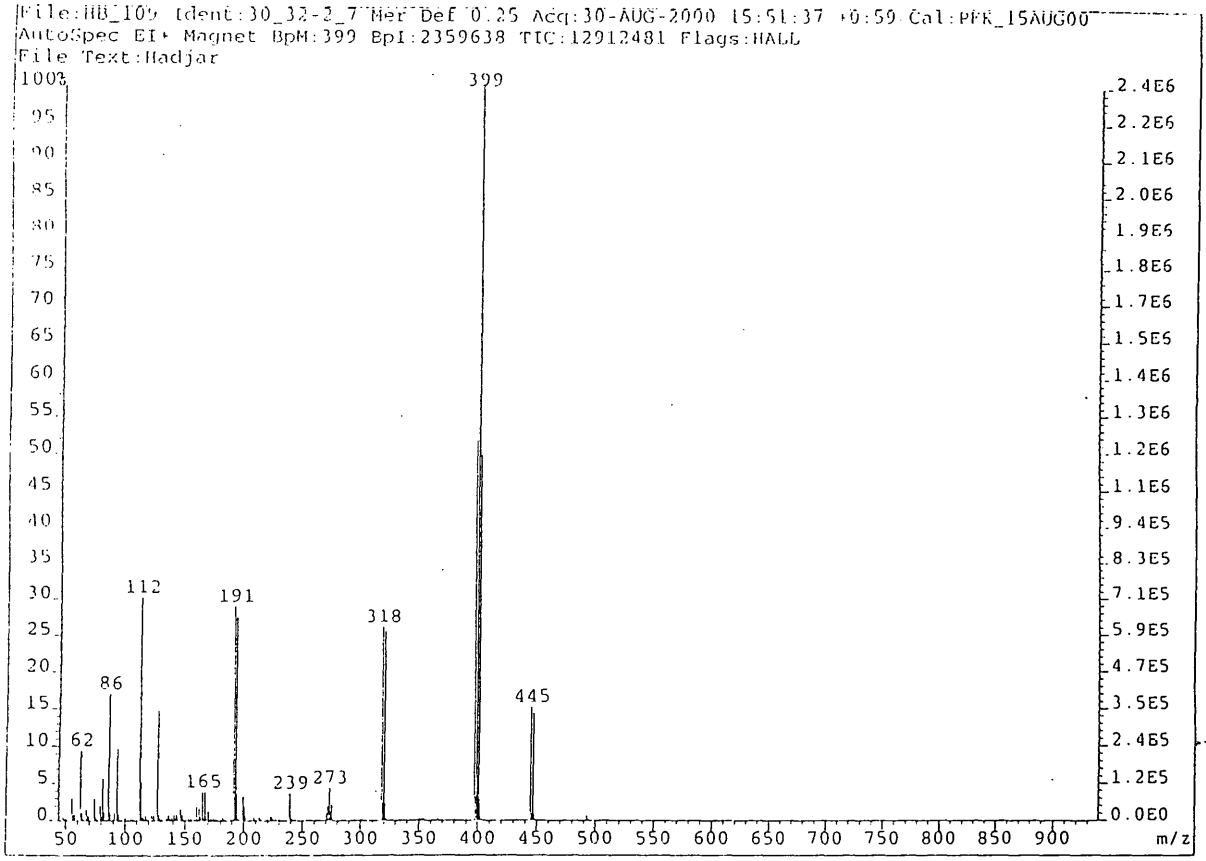


HB122 704 (11.734)

44646

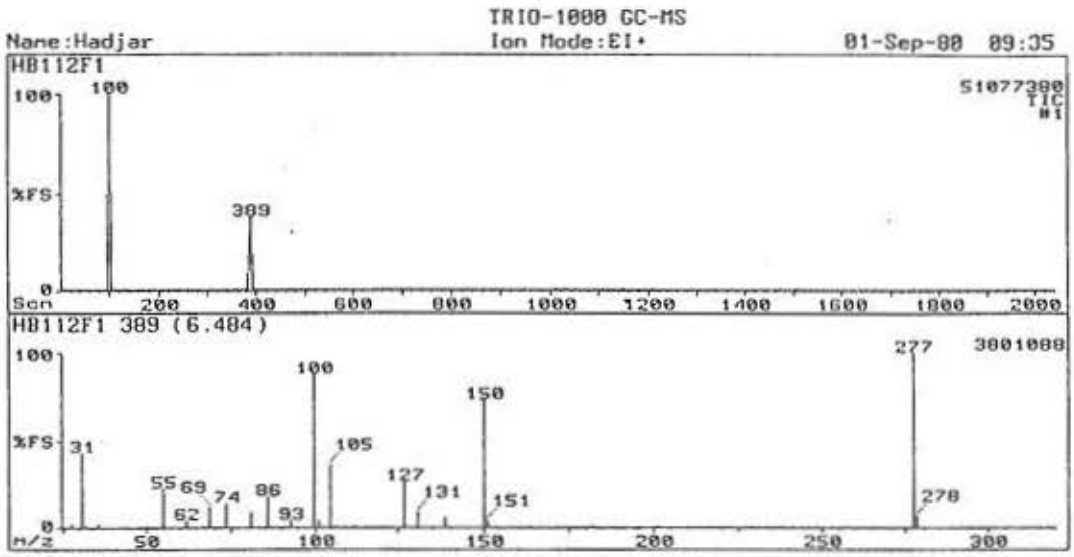
Mass	Rel Int	Mass	Rel Int	Mass	Rel Int	Mass	Rel Int
28	6.54	81	20.87	117	2.26	167	3.33
31	35.32	86	20.87	118	3.23	169	2.06
32	2.24	87	1.18	121	4.07	171	2.51
35	1.75	90	5.33	122	2.64	176	4.99
36	4.59	91	3.67	123	1.79	178	3.96
38	5.62	93	23.85	124	2.37	191	7.11
43	2.01	94	1.13	128	2.95	193	7.22
44	1.43	97	13.59	134	1.10	226	49.08
47	4.30	99	4.87	136	1.58	227	1.91
48	2.67	100	7.68	141	1.46	228	63.30
49	1.43	101	7.51	143	1.22	229	3.04
50	1.73	102	4.36	147	95.41	230	16.06
55	11.93	104	1.81	148	3.47	305	44.50
57	1.22	105	1.59	149	34.40	307	100.00
62	21.79	107	1.68	150	1.99	308	4.42
67	4.07	109	2.61	152	2.35	309	70.64
69	4.87	112	30.50	153	6.71	310	3.37
71	4.24	113	3.90	155	3.47	311	14.45
74	9.29	114	3.28	160	4.42		
78	5.91	115	1.15	162	4.42		
79	10.44	116	11.75	165	3.31		

3. 2 ,6-dibromo-3,5.-difluoro-4-iodopyridine (5)




```
! MS_USER:SPE_DEFAULT.LIS  30-AUG-2000  15:55
! Listing of raw data for -
!        data file HB_109
!        data identifier 30_32-2_7 Mer Def 0.25
! Axis display range        X_MASS (44.47, 939.11)
! Normalising intensity  2.35964E+06
! Data threshold 0.30% of normalising intensity
!
!       ABS      REL (%)       ABS      REL (%)       ABS      REL (%)       ABS      REL (%)
!       MASS      HEIGHT       MASS      HEIGHT       MASS      HEIGHT       MASS      HEIGHT
!
      48.0258        0.56     113.0531        5.19     166.9747        3.88     272.9184        4.34
      50.0291        0.32     114.0576        0.31     169.9666        1.38     273.9178        1.15
      55.0276        3.06     114.9667        0.55     171.9813        0.39     274.9170        2.16
      56.0637        0.68     116.9683        0.73     173.9793        0.36     317.9012       26.14
      57.0802        0.97     121.9712        0.85     181.9689        0.43     318.9069        2.28
      62.0335        9.48     123.9664        0.82     188.9713        0.31     319.8995       25.54
      63.0835        1.11     126.9618       14.88     190.9817       29.05     320.9052        2.30
      67.0313        1.62     127.9619        0.75     191.9864        3.09     350.8335        0.32
      69.0392        0.75     133.9654        0.52     192.9787       27.55     352.8340        0.32
      74.0352        2.98     136.0496        0.82     193.9817        3.53     396.8253       51.81
      75.0433        0.38     138.9605        0.52     198.4162        1.69     397.8282        1.15
      78.9624        2.11     140.9746        0.88     199.4143        3.34     398.8216      100.00
      79.9634        0.57     142.9745        0.90     200.3664        1.85     399.8256        5.88
      81.0123        5.83     145.9799        1.68     200.9654        0.45     400.8176       49.71
      82.0018        1.07     146.9984        0.62     207.9651        0.53     401.8208        2.83
      86.0358       17.14     147.9708        0.92     212.9704        0.54     444.8226       15.25
      87.0395        0.91     152.9738        0.44     222.2199        0.72     445.8275        0.94
      90.9681        1.07     154.9751        0.35     223.3726        0.49     446.8233       14.35
      93.0349        9.84     157.9619        0.35     226.9070        0.34     447.8262        0.89
      94.0465        0.87     159.9856        1.94     238.9764        3.67     492.8105        0.66
     100.0442        0.44     161.9765        1.75     269.9193        0.94
     105.0061        0.33     162.9694        0.49     270.9206        2.21
     112.0469       30.27     164.9758        3.88     271.9162        1.80
```

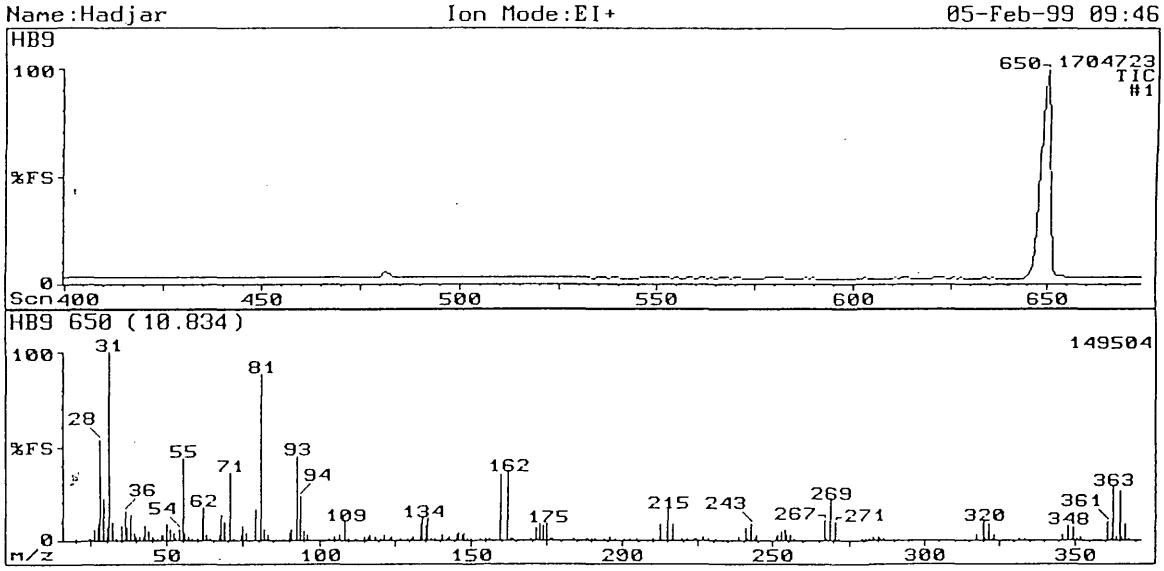
4. 2,3,5,6-tetrafluoro-4-iodopyridine (6)



HB112F1 389 (6.484)

Mass	Rel Int	Mass	Rel Int	Mass	Rel Int	Mass	Rel Int
28	2.10	67	1.36	101	4.15	150	72.84
31	42.67	69	11.64	105	35.78	151	4.18
32	1.04	74	13.58	106	1.45	182	1.14
36	1.72	81	8.41	112	1.09	201	1.22
50	1.01	86	17.35	127	25.86	258	1.25
55	22.52	93	3.80	131	8.30	277	100.00
62	3.93	100	87.50	138	5.71	278	7.00

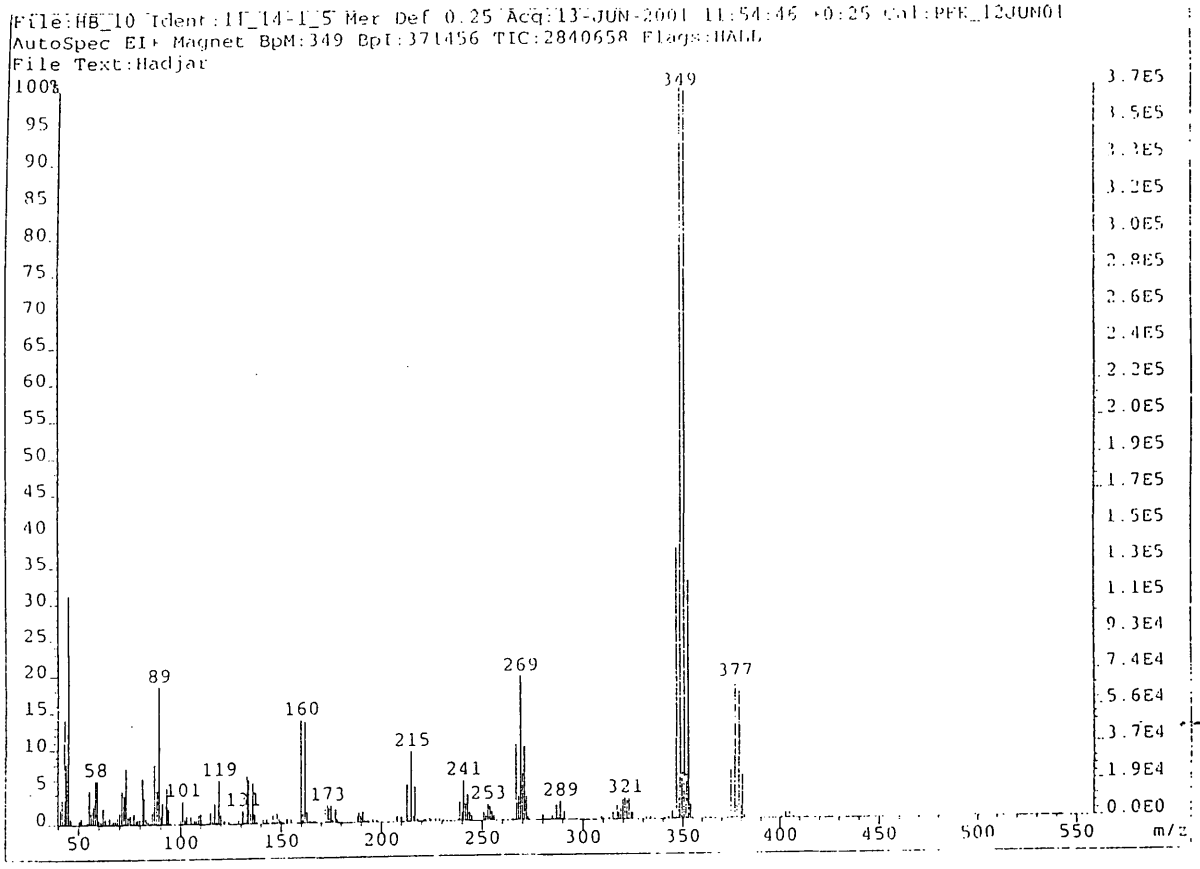
5. 2,4,6-tribromo-5-fluoro-3-methoxypyridine (7) and (58)



HB9 650 (10.834) 14950

Mass	Rel Int	Mass	Rel Int	Mass	Rel Int	Mass	Rel Int
20	0.59	74	3.34	149	1.20	251	2.34
24	1.17	75	7.96	150	0.77	252	2.78
25	1.17	76	3.68	153	0.57	253	5.09
26	6.04	79	16.61	155	0.89	254	5.65
27	9.20	81	88.36	156	0.28	255	3.25
28	53.42	82	5.39	160	35.10	256	3.00
29	21.92	83	3.34	162	35.96	257	0.61
30	6.64	90	3.42	163	1.21	267	10.74
31	100.00	91	5.69	164	0.47	268	0.51
32	9.85	93	44.52	170	0.22	269	21.40
33	0.48	94	22.95	172	6.93	270	1.36
35	7.53	95	4.79	173	9.08	271	10.19
36	15.75	96	2.83	174	7.96	272	0.74
37	6.93	103	0.39	175	9.12	280	0.38
38	13.70	105	2.25	176	1.26	281	0.29
39	4.32	107	3.04	177	0.22	282	0.88
40	2.42	109	9.89	184	0.36	283	1.78
41	1.94	110	0.78	188	0.86	284	0.90
42	1.99	112	0.38	189	0.36	285	2.13
43	7.88	115	2.13	190	0.68	286	0.28
44	4.79	116	2.05	191	0.45	287	0.90
45	1.82	117	3.13	194	0.34	318	3.34
46	0.76	119	2.03	196	1.52	320	9.38
47	0.49	121	1.05	198	1.03	321	0.45
48	2.51	122	2.64	201	0.48	322	8.99
49	2.95	123	0.93	203	0.67	323	0.44
50	8.90	124	1.66	205	0.72	324	2.95
51	5.86	127	0.16	210	0.29	332	0.22
52	3.72	129	1.01	213	8.86	334	0.30
53	1.03	130	1.39	215	16.95	346	2.58
54	5.95	131	1.83	217	8.60	348	7.36
55	43.84	133	8.35	220	0.45	349	0.48
56	4.32	134	11.99	222	0.61	350	6.93
57	2.22	135	8.22	224	0.29	351	0.47
58	0.29	136	11.64	225	0.54	352	2.17
60	0.34	137	0.80	227	1.66	361	9.80
62	17.12	138	0.35	229	1.10	362	0.70
63	2.62	141	2.58	231	0.39	363	27.74
64	1.28	142	1.35	239	2.13	364	1.70
67	2.95	143	1.77	241	7.19	365	26.20
68	13.70	145	2.66	242	0.72	366	1.55
69	9.72	146	3.60	243	8.26	367	8.48
71	36.13	147	3.38	244	0.40	368	0.55
72	0.53	148	4.20	245	2.95		

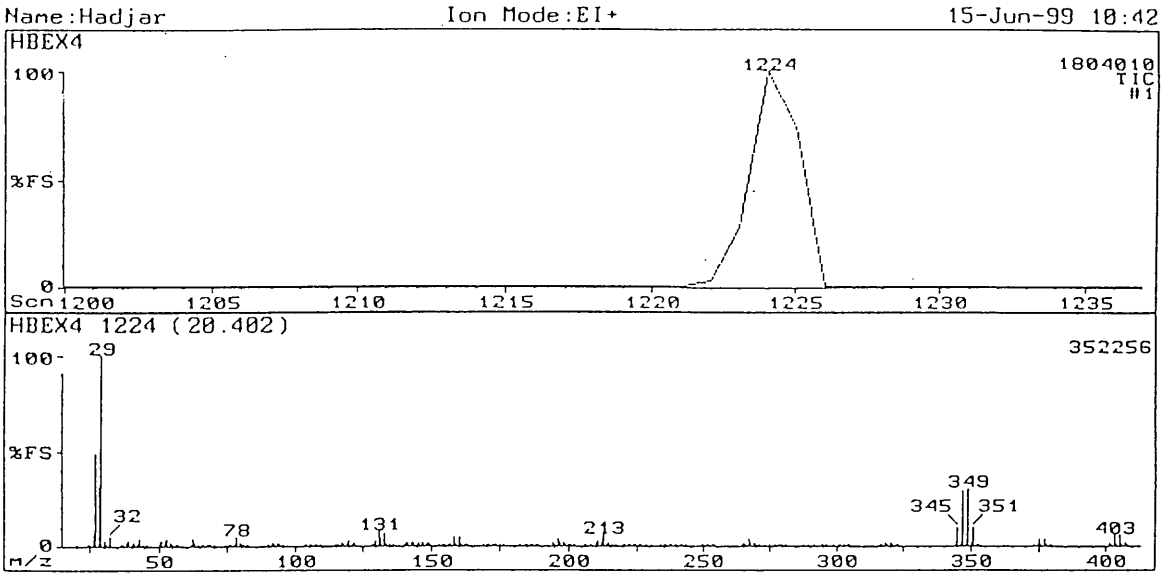
6. 2,4,6-tribromo-5-fluoro-3-ethoxypyridine (8)




```
MS_USER:SPE_DEFAULT.LIS  13-JUN-2001  11:56
Listing of raw data for -
        data file HB_10
        data identifier 11_14-1_5 Mer Def 0.25
Axis display range        X_MASS (40.00, 558.37)
Normalising intensity  3.71456E+05
Data threshold 0.30% of normalising intensity
```

ABS MASS	REL (%) HEIGHT	ABS MASS	REL (%) HEIGHT	ABS MASS	REL (%) HEIGHT	ABS MASS	REL (%) HEIGHT
41.0087	2.10	94.9652	0.31	171.8745	1.81	280.0241	0.66
42.0117	3.48	98.9967	0.36	172.8766	2.33	284.8004	0.59
42.9930	14.19	99.9864	0.63	173.8735	1.97	286.7910	2.01
43.9944	8.17	101.0113	3.22	174.8842	2.33	288.7898	2.54
45.0023	31.31	102.0173	0.93	175.8707	0.48	290.7895	1.14
46.0056	0.87	103.0254	1.18	177.0548	1.91	309.0729	0.53
49.9763	0.64	104.0048	0.31	177.9445	0.52	312.8373	0.35
50.9888	0.94	104.9772	1.13	187.8631	0.90	314.8281	1.03
51.9681	0.38	105.8959	0.34	188.8683	1.39	316.8994	1.97
54.9697	4.63	106.9267	0.69	189.8623	0.98	317.7277	1.03
55.9959	1.74	107.9491	0.68	190.8664	1.50	318.7560	1.52
56.9995	2.50	108.9677	1.36	191.8730	0.33	319.7223	2.67
58.0059	6.05	109.9665	1.41	195.7799	0.55	320.7247	2.92
59.0135	5.96	114.0176	0.35	197.7779	0.38	321.7192	2.57
59.9993	0.68	114.9565	1.65	207.8657	0.82	322.7224	2.84
60.9902	0.53	116.0067	0.53	209.8616	0.77	323.7207	1.02
61.9684	2.35	116.9732	2.85	212.7851	5.08	324.7197	1.04
62.9797	0.86	117.9738	0.52	214.7836	9.47	331.7109	0.47
63.9885	0.31	119.0095	5.89	215.8420	0.82	333.7142	0.45
65.0013	1.04	120.1136	1.25	216.7827	4.69	340.8856	0.33
66.9655	0.54	121.2407	0.34	217.8912	0.46	342.8593	0.48
67.9676	0.60	121.8692	0.63	221.0698	0.30	344.7376	1.14
68.9785	1.08	123.8686	0.47	221.7845	0.35	345.7560	0.32
70.0000	1.66	128.9254	0.58	223.9354	0.49	346.7248	37.32
70.9832	4.54	130.9619	1.85	226.7824	0.49	347.7287	2.82
72.0149	3.96	131.9752	0.59	228.7793	0.41	348.7220	100.00
72.9893	7.64	133.0204	6.46	237.9800	0.32	349.7272	6.39
73.9742	1.09	133.8790	5.94	238.7890	2.62	350.7242	99.56
74.9957	1.32	134.8797	1.49	239.7982	1.27	351.7280	6.04
76.9943	1.56	135.8663	5.49	240.7866	5.53	352.7199	32.64
77.9547	0.56	136.8681	1.38	241.7967	2.38	353.7253	2.05
78.8816	0.75	137.9554	0.37	242.7862	3.67	374.7567	6.69
79.8803	0.81	140.8686	0.66	243.7913	1.21	375.7564	0.90
80.9438	6.28	142.8696	0.70	244.7834	0.75	376.7596	18.56
81.9360	3.57	145.0184	0.31	250.7864	1.23	377.7611	1.90
82.9680	0.94	145.8664	1.18	251.7948	0.69	378.7569	17.26
83.9568	0.52	146.9086	0.44	252.7903	2.27	379.7573	1.77
85.0256	0.33	147.8647	1.44	253.8765	1.92	380.7554	5.95
85.9836	1.79	148.9477	0.69	254.7838	1.26	381.7593	0.60
86.9912	8.08	149.8686	0.38	255.7981	0.72	400.8040	0.34
87.9985	4.68	152.8676	0.71	266.7896	10.19	402.8020	0.85
89.0059	18.66	154.8634	0.64	267.7981	3.36	404.7957	0.85
90.0088	1.16	159.8672	13.88	268.7868	19.55	406.7916	0.35
90.9558	2.98	160.8807	1.45	269.7914	6.32	498.8098	0.33
92.0057	0.31	161.8671	13.67	270.7876	9.93	500.8168	0.35
92.9383	4.99	162.8732	1.49	271.7935	3.23		
93.9667	2.18	165.9673	0.33	272.7999	0.55		

7. 2,4,6-tribromo-3,5-diethoxypyridine (9)



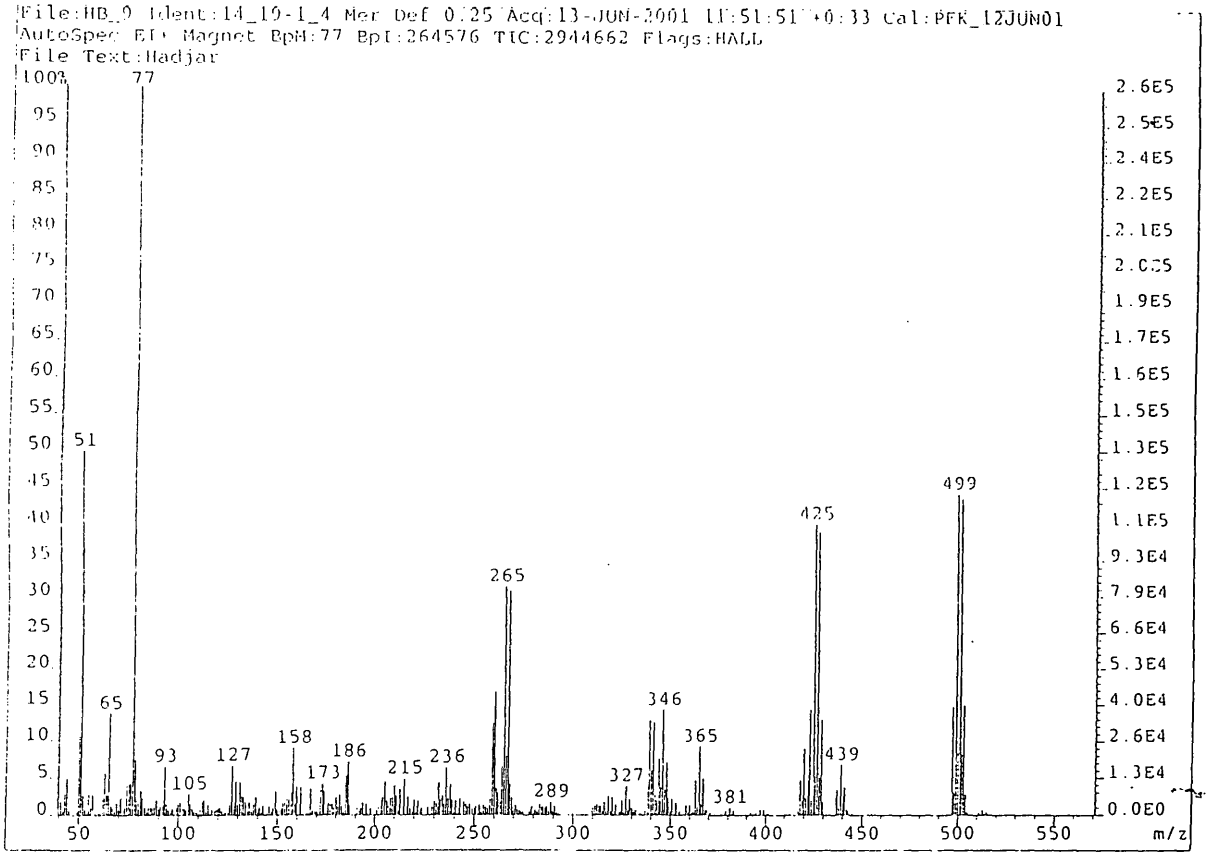
HBEX4 1224 (20.402)

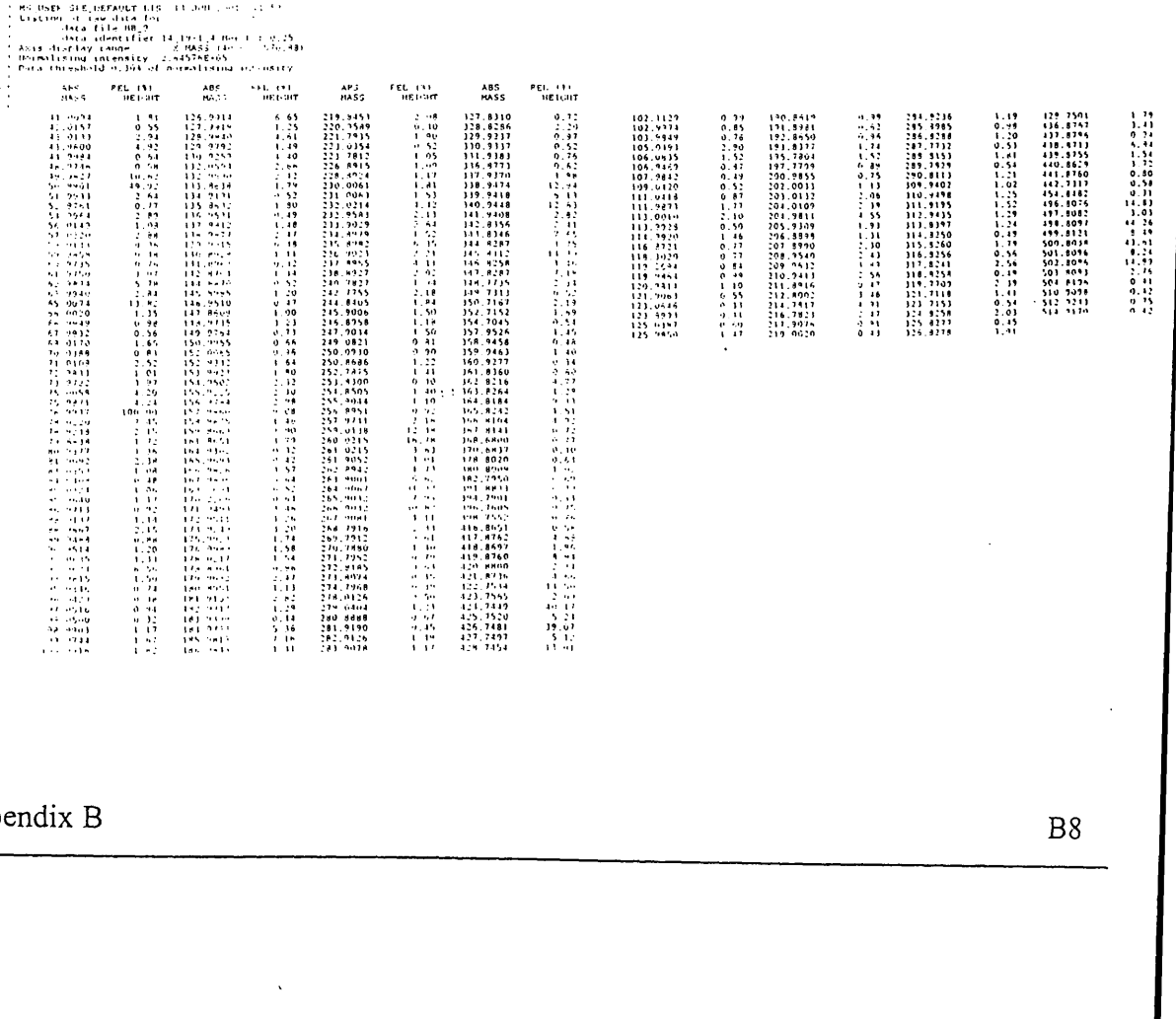
Mass	Rel Int	Mass	Rel Int	Mass	Rel Int	Mass	Rel Int
20	0.10	103	0.28	176	0.09	265	2.18
24	0.20	104	0.47	182	0.24	266	1.13
25	0.37	105	0.53	184	0.67	267	4.29
26	6.54	106	1.44	185	0.37	268	1.47
27	48.55	107	1.27	186	0.97	269	2.22
28	31.40	108	1.00	187	0.51	270	0.50
29	100.00	109	0.80	188	0.59	271	0.09
30	2.49	114	0.05	189	0.29	273	0.07
31	0.15	115	1.22	194	1.73	275	0.29
32	5.23	116	0.94	195	0.90	277	0.31
36	1.33	117	2.11	196	3.74	278	0.06
37	1.31	118	1.18	197	1.71	279	0.20
38	2.14	119	1.64	198	2.42	280	0.08
39	2.51	120	2.49	199	0.91	281	0.09
40	1.22	121	0.77	200	0.61	288	0.16
41	2.42	122	2.02	201	0.14	290	0.43
42	0.73	128	0.08	202	0.14	292	0.46
43	4.05	129	1.27	206	0.04	294	0.22
44	1.15	130	3.23	208	1.22	295	0.07
45	0.39	131	7.41	210	2.40	296	0.07
50	1.94	132	3.54	211	3.32	299	0.12
51	2.49	133	6.61	212	1.67	301	0.31
52	2.47	134	0.60	213	5.96	302	0.09
53	3.47	135	0.62	214	1.02	303	0.30
54	1.51	136	0.11	215	2.03	304	0.12
55	0.26	140	0.07	216	0.65	305	0.22
56	0.19	141	1.54	217	0.52	316	0.61
57	0.42	142	1.51	220	0.58	317	0.39
61	0.30	143	2.18	221	0.26	318	1.64
62	3.62	144	2.02	222	1.36	319	1.20
63	1.73	145	0.90	223	0.54	320	1.64
64	0.86	146	1.93	224	1.16	321	1.08
65	0.53	147	2.22	225	0.34	322	0.62
66	0.50	148	1.45	226	0.40	323	0.35
67	0.43	149	1.96	227	0.14	344	0.89
68	1.05	150	0.04	229	0.12	345	9.38
69	1.44	153	0.26	231	0.08	346	0.51
70	0.07	154	0.20	234	0.17	347	29.07
74	0.32	155	0.34	235	0.08	348	1.44
75	0.44	156	0.34	236	0.62	349	29.65
76	0.28	157	0.90	237	0.56	350	1.54
77	0.49	158	4.80	238	1.36	351	9.38
78	5.16	159	1.25	239	1.33	352	0.53
79	1.47	160	4.80	240	1.33	353	0.08
80	1.09	161	0.73	241	1.33	373	1.33
81	0.46	162	0.13	242	0.49	374	0.50
82	0.48	163	0.19	243	0.44	375	3.60
89	0.06	169	0.20	249	0.13	376	0.30
90	1.04	170	0.68	250	0.15	377	3.91
91	2.20	171	0.87	251	0.23	378	0.24
92	0.65	172	0.76	252	0.17	379	1.15
93	1.56	173	0.79	253	0.14	380	0.08
94	0.26	174	0.14	254	0.08	401	2.20
95	0.14	175	0.11	264	0.12	402	0.20

HBEX4 1224 (20.402)

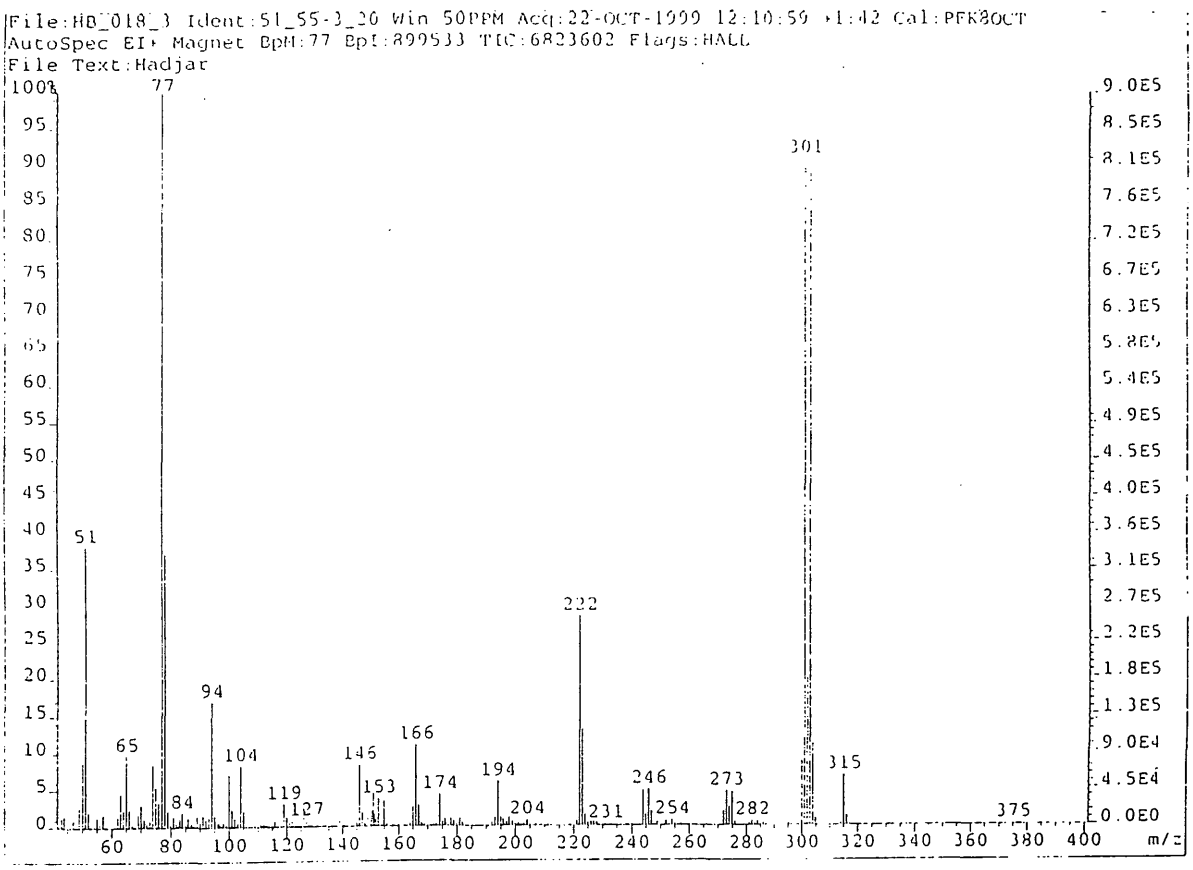
Mass	Rel Int	Mass	Rel Int	Mass	Rel In
403	5.10	405	5.67	407	1.8
404	0.60	406	0.60	408	0.2

8. 2,4,6-tribromo-3,5-diphenoxypyridine(13)





9. 4-bromo-3,5-difluoro-2,6-diphenoxypyridine (17)



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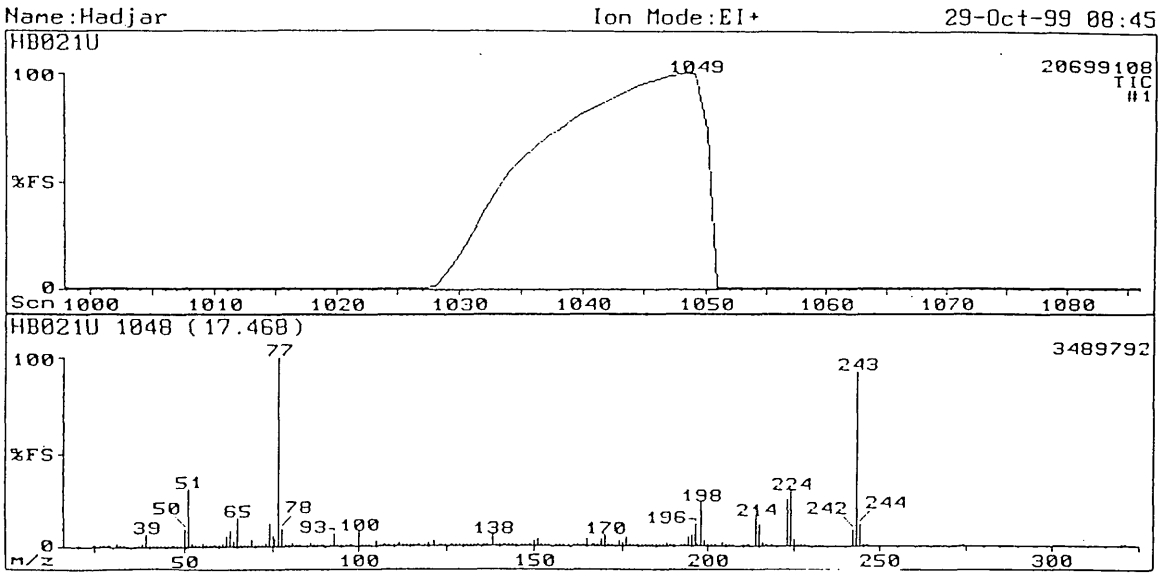
data identifier 51_55-3_20 Win 50PPM
Axis display range X MASS: 41.79, 401.07
Normalising intensity 8.99531E+05
Data threshold 0.10% of normalising intensity

ABS MASS	REL (%) HEIGHT	ABS MASS	REL (%) HEIGHT	ABS MASS	REL (%) HEIGHT	ABS MASS	REL (%) HEIGHT
42.0019	0.26	89.9727	0.78	138.9912	1.00	221.0062	0.73
42.9632	0.31	90.9847	1.70	139.9924	0.42	222.0158	28.52
43.0123	1.63	91.9836	1.06	143.9892	0.25	223.0228	13.17
43.9519	1.66	92.9899	1.38	144.9909	1.12	224.0238	1.67
45.9680	0.11	93.9983	17.04	145.9991	8.53	224.9199	0.1
45.9694	0.43	94.9989	1.65	147.0055	2.00	224.9261	0.57
46.9512	1.13	95.9938	0.63	147.8704	0.27	225.9384	0.70
47.9369	0.19	96.4738	0.69	148.0096	0.58	226.9205	0.70
47.9384	0.14	96.9733	0.37	148.9853	1.49	227.9392	0.56
48.9474	2.87	97.0578	0.16	149.8622	0.20	228.9318	0.21
49.9778	9.10	97.0601	0.22	149.9933	1.51	229.9267	0.15
50.9860	38.35	97.9684	0.82	150.4392	2.10	230.9416	0.37
51.9900	2.20	98.0670	0.11	150.9951	4.68	231.9246	0.11
52.9658	0.60	98.9714	0.51	151.4369	1.64	232.9277	0.21
53.9615	0.41	99.9669	7.30	151.4411	0.39	238.0217	0.36
54.9644	1.45	100.9681	2.47	151.9929	1.06	240.0615	0.34
55.9177	1.30	101.9607	1.26	152.8753	1.91	241.0877	0.13
57.9678	0.53	102.9954	0.66	153.8748	0.22	242.1370	0.15
58.0258	0.57	104.0062	8.47	154.0084	0.10	243.9419	4.81
58.9710	0.18	104.9958	2.26	154.0157	0.14	244.9470	1.58
57.0338	1.83	105.9873	0.19	154.8739	3.57	245.9421	4.99
57.9737	0.10	105.9903	0.13	155.9000	0.42	246.9437	2.00
58.0355	0.10	106.9885	0.10	157.9555	0.35	247.9364	0.39
58.9755	0.16	106.9926	0.16	159.8793	0.33	248.9311	0.57
59.9775	0.11	107.9933	0.32	161.8753	0.32	251.9333	0.73
60.9705	0.59	108.9608	0.30	162.0016	0.11	252.9409	0.24
61.9755	1.79	110.9749	0.61	162.9953	0.19	253.9347	0.82
62.9841	4.68	111.0897	0.17	163.9957	0.58	254.9444	0.31
63.0009	2.60	111.4780	0.20	165.0018	2.77	255.9500	0.36
64.9993	9.87	111.4812	0.13	166.0111	11.12	256.9833	0.26
66.0052	2.45	111.9679	0.29	167.0041	2.95	257.9480	0.17
67.0126	0.43	112.0820	0.45	167.9991	0.50	257.9574	0.13
67.9823	0.14	112.4346	0.17	168.9531	0.10	258.9519	0.19
67.9933	0.23	112.9681	0.17	168.9599	0.29	259.9371	0.11
68.9578	1.94	113.0876	0.21	169.8875	0.15	259.9440	0.18
69.0316	0.85	113.0913	0.14	171.0392	0.26	260.9391	0.19
69.9554	3.10	113.4362	0.18	172.0178	0.32	261.9414	0.15
69.9579	0.71	113.9789	0.20	172.9985	0.38	266.0482	0.18
70.0193	0.67	115.0046	0.26	173.9994	4.42	270.9430	0.16
70.9521	1.33	115.9559	0.92	175.0027	0.77	271.9488	2.15
71.0446	1.08	116.9680	0.22	175.8754	1.11	272.9569	4.76
71.9622	0.63	117.9717	0.34	176.0065	0.61	273.9530	2.62
72.4735	0.11	118.9878	3.24	177.0059	0.20	274.9570	4.59
72.9739	1.04	119.9928	1.44	177.8775	1.16	275.9610	0.62
73.4797	0.14	120.9901	0.63	178.8856	0.87	279.1593	0.39
73.9607	8.67	121.8655	0.11	179.8916	0.48	279.9319	0.11
74.9707	5.50	121.9967	0.94	180.8885	1.17	280.9574	0.49
75.4749	0.18	122.9902	0.15	181.8896	0.64	281.9554	0.76
75.9872	3.49	122.9934	0.11	182.8711	0.11	282.9483	0.19
76.9961	100.00	123.4330	0.16	182.8787	0.16	282.9560	0.37
76.0031	37.30	123.8669	0.11	183.8866	0.13	283.9582	0.65
78.8750	0.49	123.9731	0.13	185.0089	0.13	284.9618	0.15
79.0066	2.34	124.4311	0.12	190.0056	0.13	286.0635	0.46
79.8813	0.13	124.9764	0.24	191.9958	0.58	287.0703	0.12
79.8837	0.52	125.9898	2.66	193.0018	1.24	295.0686	0.40

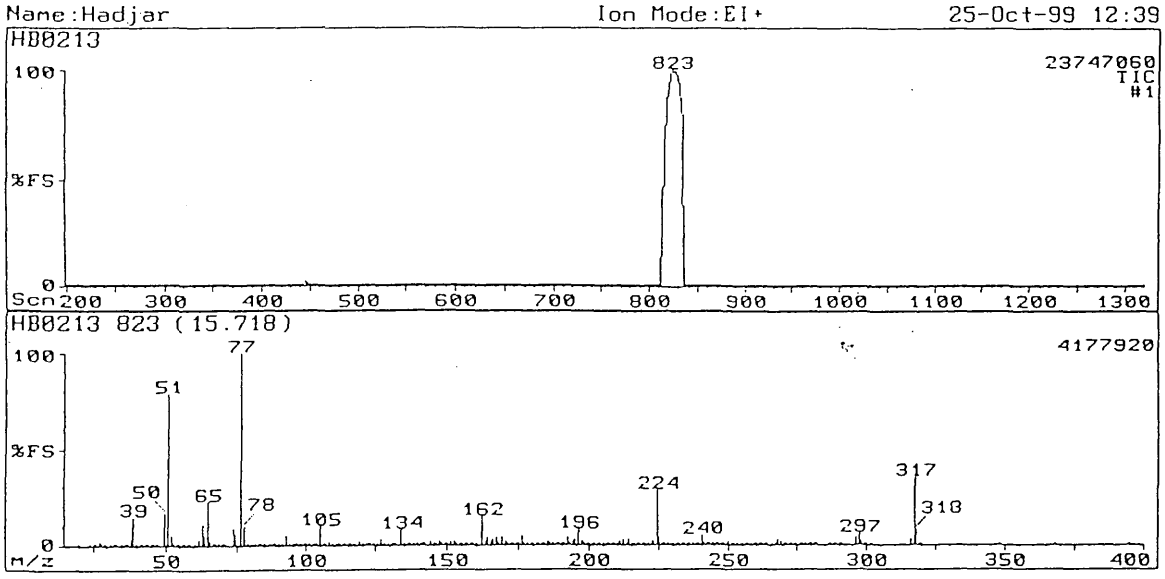
10. 2,3,5,6-tetrafluoro-4-phenoxypyridine (18)



HB021U 1048 (17.468)

Mass	Rel Int	Mass	Rel Int	Mass	Rel Int	Mass	Rel Int
20	0.01	75	6.25	128	0.09	181	0.05
24	0.01	76	4.25	129	0.14	182	0.06
25	0.04	77	100.00	130	0.19	183	0.17
26	0.42	78	10.09	131	0.65	184	0.10
27	1.22	79	0.45	132	0.31	185	0.05
28	0.20	80	0.23	133	0.03	186	0.04
29	0.06	81	1.47	134	0.41	187	0.44
31	2.26	82	0.74	136	0.08	188	2.41
32	0.06	83	0.84	137	0.09	189	0.32
33	0.02	85	0.48	138	6.16	190	0.03
37	0.75	86	1.81	139	0.68	192	0.62
38	2.41	87	0.44	140	0.03	193	0.48
39	6.98	88	1.45	141	0.04	194	5.02
40	0.30	89	0.18	142	0.05	195	5.99
41	0.11	90	0.29	143	0.51	196	11.85
42	0.05	92	0.67	144	0.51	197	1.29
43	0.08	93	6.75	145	0.74	198	23.00
44	0.05	94	0.81	146	0.89	199	2.52
45	0.04	95	0.14	147	0.23	200	0.19
46	0.07	96	0.72	148	0.36	201	0.11
47	0.13	97	0.30	149	0.27	202	0.05
48	0.04	98	0.64	150	3.23	204	2.26
49	0.60	100	8.22	151	3.46	205	0.50
50	9.51	101	0.50	152	0.44	206	0.07
51	30.99	102	0.14	153	0.06	207	0.02
52	1.80	103	0.10	154	0.21	210	0.15
53	0.78	105	3.35	156	0.19	211	0.03
54	0.12	106	0.51	157	0.34	212	0.18
55	1.88	107	0.76	158	0.20	214	15.26
56	0.26	108	0.84	160	0.01	215	11.74
57	0.62	109	0.16	161	0.15	216	1.54
58	0.08	110	0.02	162	0.17	217	0.29
59	0.04	111	0.69	164	0.74	218	0.03
60	0.41	112	1.55	165	3.84	223	24.77
61	1.56	113	0.14	166	0.46	224	29.46
62	5.87	114	0.16	167	0.40	225	3.46
63	8.92	115	0.13	168	0.94	226	0.30
64	3.23	116	0.27	169	3.61	227	0.03
65	15.14	117	0.14	170	5.69	228	0.10
66	1.28	118	0.10	171	0.54	242	8.45
67	0.21	119	1.06	172	0.06	243	92.49
68	0.92	120	1.85	174	2.70	244	12.09
69	4.02	122	2.90	175	1.94	245	0.92
70	0.24	123	0.32	176	4.67	246	0.09
71	0.83	124	0.22	177	0.81	274	0.02
72	0.11	125	0.14	178	0.23	320	0.10
73	1.78	126	0.69	179	0.18	321	0.02
74	12.21	127	0.22	180	0.05		

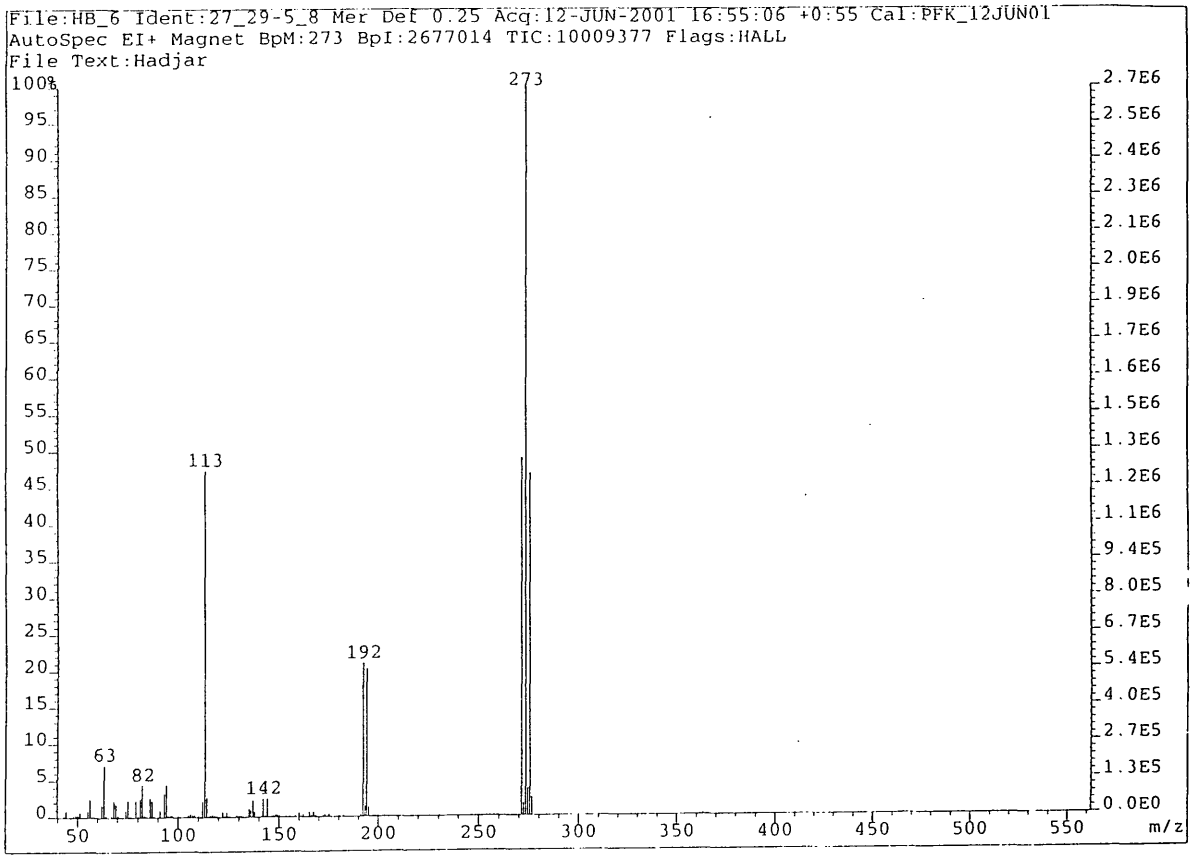
11. 3,5,6-trifluoro-2,4-diphenoxypyridine (19)



HB0213 823 (15.718) 4177920

Mass	Rel Int	Mass	Rel Int	Mass	Rel Int	Mass	Rel Int
20	0.02	87	0.95	146	1.08	201	0.28
24	0.01	88	0.51	147	1.57	202	0.23
25	0.03	89	0.24	148	0.54	203	0.10
26	0.30	90	0.22	149	0.60	204	0.41
27	2.03	92	0.93	150	0.61	205	0.42
28	0.56	93	5.15	151	2.01	206	0.10
29	0.09	94	1.25	152	1.79	207	0.16
31	0.49	95	0.47	153	0.85	208	0.11
32	0.07	96	0.56	154	0.61	209	0.08
33	0.02	97	0.07	155	0.10	210	0.56
35	0.02	98	0.08	156	0.22	211	1.81
36	0.15	99	0.75	157	0.47	212	2.99
37	0.63	100	1.09	158	1.25	213	0.81
38	3.16	101	0.34	159	0.27	214	2.45
39	14.80	102	0.25	160	0.02	215	0.38
40	0.71	103	0.19	162	14.22	216	0.14
41	0.19	104	0.82	163	1.67	217	0.04
42	0.09	105	9.31	164	3.63	218	0.13
43	0.10	106	0.85	165	2.28	219	0.45
44	0.38	107	1.23	166	2.60	220	1.05
45	0.04	108	1.74	167	3.70	221	1.22
46	0.07	109	0.17	168	0.56	222	1.57
47	0.23	110	0.07	169	3.55	223	1.96
50	16.27	112	0.15	170	1.89	224	28.63
51	78.43	112	0.11	171	0.19	225	4.07
52	4.51	113	0.14	172	0.07	226	0.40
53	1.02	114	0.23	173	0.36	227	0.10
54	0.21	115	0.48	174	0.58	228	0.07
55	0.65	116	0.23	175	0.27	229	0.09
56	0.19	117	0.13	176	4.98	230	0.80
57	0.67	119	2.28	177	0.75	231	0.15
58	0.12	120	1.16	178	0.32	232	0.08
59	0.10	121	0.45	179	0.13	233	0.09
61	0.67	122	0.31	180	0.14	234	0.16
62	2.84	123	0.21	181	0.20	235	0.08
63	10.49	124	0.21	182	0.33	236	0.07
64	4.78	125	0.28	183	1.30	237	0.05
65	22.06	127	2.62	184	1.45	238	1.05
66	2.21	128	0.39	185	1.81	239	0.61
67	0.17	129	0.06	186	0.38	240	5.02
68	0.29	130	0.30	187	0.33	241	1.19
69	0.74	131	0.27	188	0.11	242	0.79
70	0.38	132	0.50	189	0.04	243	0.36
71	0.33	134	7.75	190	0.33	244	0.08
74	9.12	135	1.23	191	0.13	245	0.03
75	5.34	136	0.66	192	4.04	246	0.04
77	100.00	137	0.14	193	0.69	247	0.02
78	9.80	138	1.16	194	2.08	248	0.22
79	0.44	139	0.51	195	2.52	249	0.99
81	1.07	141	0.23	196	8.14	250	1.59
82	0.29	141	0.22	197	1.55	251	0.41
83	0.27	142	0.07	198	0.26	252	0.42
84	0.06	144	1.48	199	0.06	253	0.16
85	0.16	145	0.85	200	0.19	254	0.10
255	0.03	258	3.14				
256	0.06	259	1.62				
257	0.03	270	0.75				
258	0.08	271	0.15				
259	0.03	272	0.06				
260	0.63	273	0.05				
261	0.12	274	0.02				
262	0.05	276	0.05				
263	0.20	277	0.39				
264	0.05	278	0.28				
266	0.08	279	0.05				
267	0.06	280	0.07				
231	0.02	300	0.24				
282	0.02	301	0.04				
286	0.01	302	0.02				
287	0.04	316	3.06				
288	0.75	317	34.51				
289	0.56	318	7.75				
290	0.10	319	0.89				
291	0.01	320	0.09				
296	3.60	348	0.01				
297	5.96	368	0.01				
298	1.69	394	0.03				
299	0.25	395	0.01				

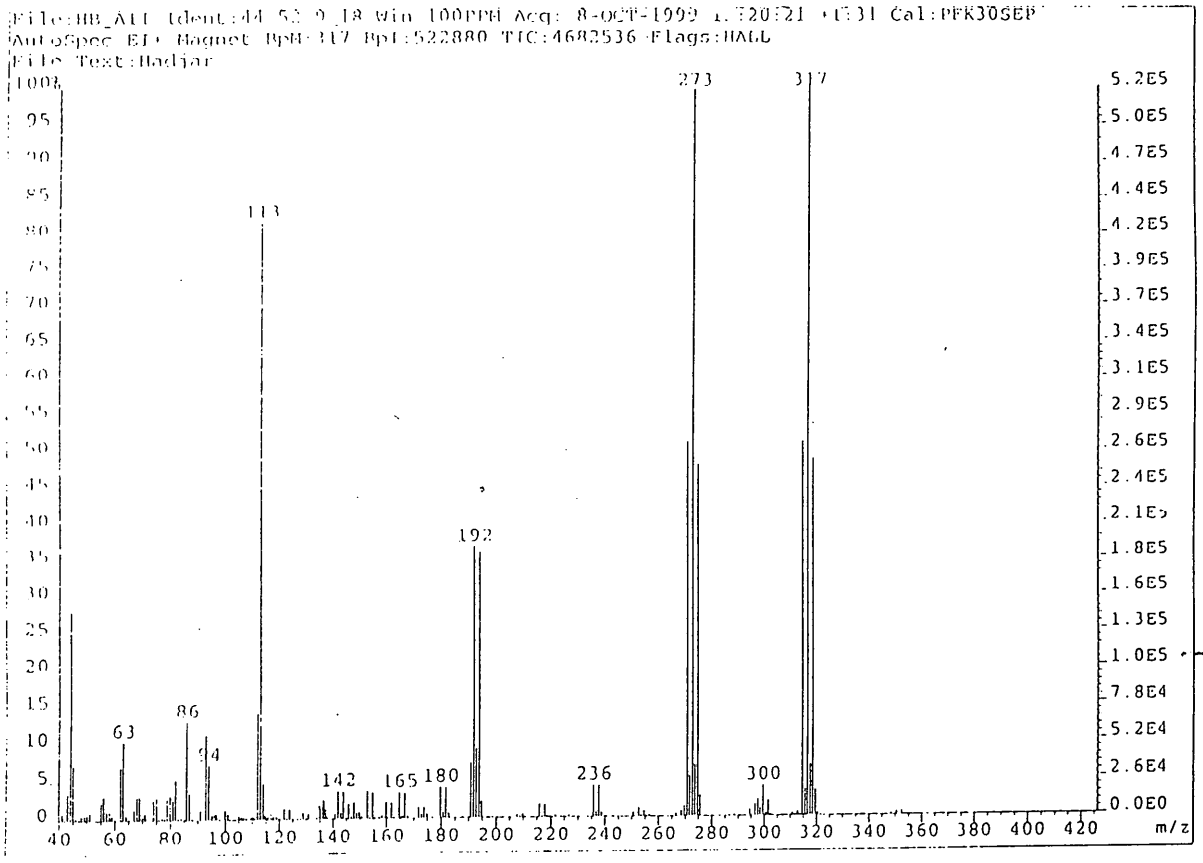
12. 2,6-dibromo-3,5-difluoropyridine (**21**)



MS_USER:SPE_DEFAULT.LIS 12-JUN-2001 16:56
Listing of raw data for -
data file HB_6
data identifier 27_29-5_8 Mer Def 0.25
Axis display range X_MASS (40.00, 561.95)
Normalising intensity 2.67701E+06
Data threshold 0.30% of normalising intensity

ABS MASS	REL (%) HEIGHT	ABS MASS	REL (%) HEIGHT	ABS MASS	REL (%) HEIGHT	ABS MASS	REL (%) HEIGHT
44.0596	0.86	81.0477	2.54	118.1252	0.33	173.1586	0.37
49.0677	0.40	82.1164	4.40	122.1052	0.74	175.1725	0.40
50.0681	0.32	86.1108	2.62	124.1090	0.72	192.2168	21.06
51.0731	0.68	87.1186	2.22	135.1382	1.17	193.2228	1.46
55.0701	0.85	91.0576	0.93	135.8370	0.90	194.2191	20.30
56.0777	2.51	93.1155	3.29	136.9145	2.29	195.2198	1.26
62.0871	1.65	94.1323	4.41	137.7790	0.71	271.3094	49.09
63.0898	7.20	105.0916	0.32	142.1520	2.51	272.3182	1.74
64.0926	0.36	106.0896	0.46	144.1542	2.53	273.3161	100.00
67.0928	0.43	108.0970	0.37	148.1717	0.39	274.3461	3.68
68.0984	2.28	112.1702	2.26	149.1896	0.30	275.3204	46.92
69.0986	1.83	113.1735	47.44	160.1274	0.55	276.3958	2.47
74.1042	0.95	114.1773	2.69	162.1619	0.36		
75.1102	2.30	116.1131	0.31	165.2019	0.72		
79.0370	2.33	117.1226	0.33	167.2091	0.71		

13. 2,6-dibromo-3,5-difluoroisonicotinic acid (22)

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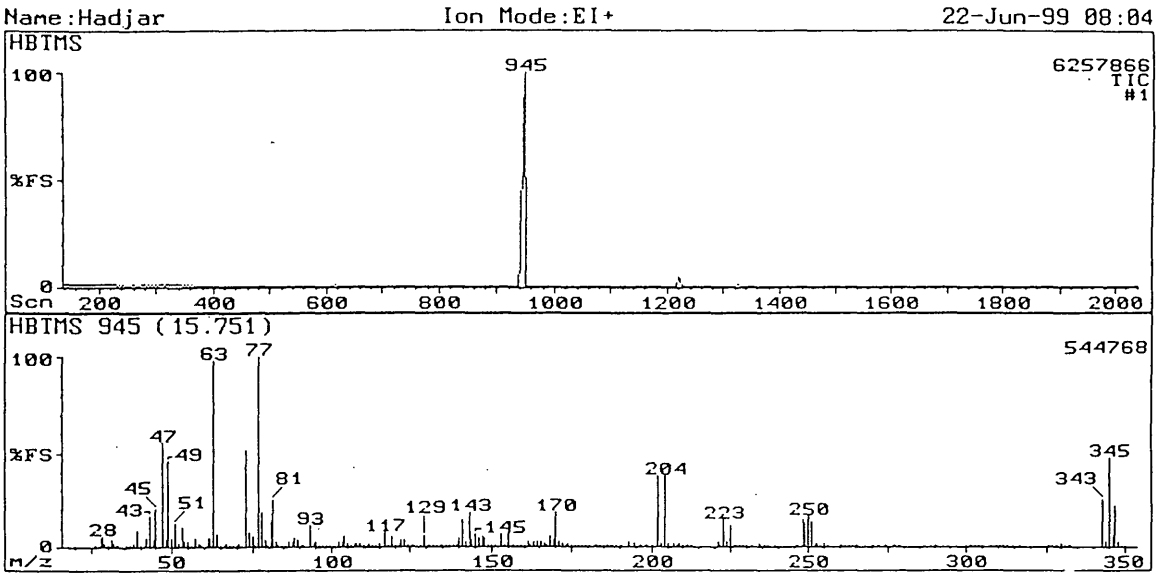
! MS_USER:SPE_DEFAULT.LIS   8-OCT-1999  12:24
! Listing of raw data for -
!       data file HB_ALL
!       data identifier 44_52-9_18 Win 100PPM
! Axis display range        X_MASS (40.00, 426.10)
! Normalising intensity  5.22880E+05
! Data threshold 0.20% of normalising intensity
!
```

ABS MASS	REL (%) HEIGHT	ABS MASS	REL (%) HEIGHT	ABS MASS	REL (%) HEIGHT	ABS MASS	REL (%) HEIGHT
40.9999	1.05	83.8854	0.32	136.2955	2.58	217.6994	1.68
42.9776	1.64	85.0251	0.27	136.7970	2.04	221.6307	0.30
43.0226	0.23	85.9214	13.16	137.2932	1.31	226.6223	0.30
43.9499	28.26	86.9282	3.56	137.7943	0.23	235.6889	4.27
44.9576	7.28	87.9323	0.26	140.7929	0.68	236.6901	0.71
45.9612	0.43	90.8389	1.34	141.8006	3.72	237.6841	4.18
46.9548	0.24	90.9733	0.45	142.7925	0.85	238.6835	0.66
47.9593	0.66	92.8215	0.64	143.7968	3.67	250.5953	0.64
48.9658	0.70	92.9203	11.40	145.7831	2.00	252.5914	1.21
49.9614	0.73	93.9261	7.28	146.7894	0.60	254.5997	0.76
50.9676	1.09	94.9253	0.50	147.7810	2.26	256.6532	0.25
54.9518	2.38	95.3746	0.82	148.7814	0.85	266.5759	0.39
55.0112	0.65	95.8776	0.74	148.8989	0.34	268.5690	0.42
55.9589	3.21	96.3730	0.86	149.7785	0.94	269.5740	1.41
56.0207	0.27	96.8760	0.71	150.7740	0.41	270.5796	51.20
56.9550	0.44	97.0140	0.39	152.7752	3.74	271.5778	9.40
57.0220	1.24	99.9113	1.35	154.7721	3.61	272.5758	99.70
57.9915	1.20	100.9248	0.87	157.2726	0.28	273.5744	6.86
58.9987	0.69	104.8283	0.37	158.2710	0.50	274.5724	48.18
59.9634	0.22	104.9704	0.64	159.2662	0.27	275.5749	2.81
61.9497	7.05	105.8360	0.40	159.7729	2.23	288.5494	0.23
62.9567	10.45	106.8251	0.35	161.7688	2.16	294.5356	0.85
63.9605	0.69	107.8377	0.31	162.7750	0.24	296.5309	1.59
66.9408	1.42	109.3586	0.43	164.7628	3.49	297.5376	2.25
67.9473	3.12	109.8213	0.29	165.7693	0.40	298.5275	0.95
68.9417	3.15	110.3553	0.43	166.7597	3.41	299.5323	4.08
69.0182	0.27	111.9003	14.24	167.7662	0.42	300.5376	0.39
69.9461	0.55	112.9073	81.82	171.7595	1.49	301.5272	2.04
70.0192	0.37	113.9099	4.80	172.7688	0.55	310.6519	0.39
70.9318	1.01	114.8156	0.56	173.7567	1.47	312.6496	0.55
71.0235	0.43	115.8227	0.44	174.7676	0.57	314.5245	51.19
73.9358	2.79	116.8142	0.86	179.7596	4.16	315.5271	3.58
74.9439	1.13	117.8205	0.49	180.7505	0.80	316.5197	100.00
75.9431	0.47	118.8147	0.38	181.7556	4.08	317.5172	6.85
76.9711	0.44	118.9776	0.27	182.7440	0.69	318.5127	48.86
77.9310	0.28	121.8073	1.44	190.7390	7.32	319.5142	3.42
78.8504	2.90	123.8034	1.39	191.7427	36.92	320.5168	0.40
79.8562	3.40	128.8016	0.86	192.7378	9.23	348.4016	0.22
80.8449	2.67	130.7974	0.82	193.7407	36.09	350.3943	0.48
80.9327	2.59	133.7951	0.59	194.7401	2.25	352.3922	0.43
81.8492	2.93	134.8006	1.92	207.7219	0.43		
81.9384	5.45	135.2977	1.18	209.7194	0.47		
83.0035	0.38	135.7930	1.70	215.7043	1.70		

14. 2,6-dibromo -3,5,4-trimethylsilylpyridine (23)



HBTMS 945 (15.751)

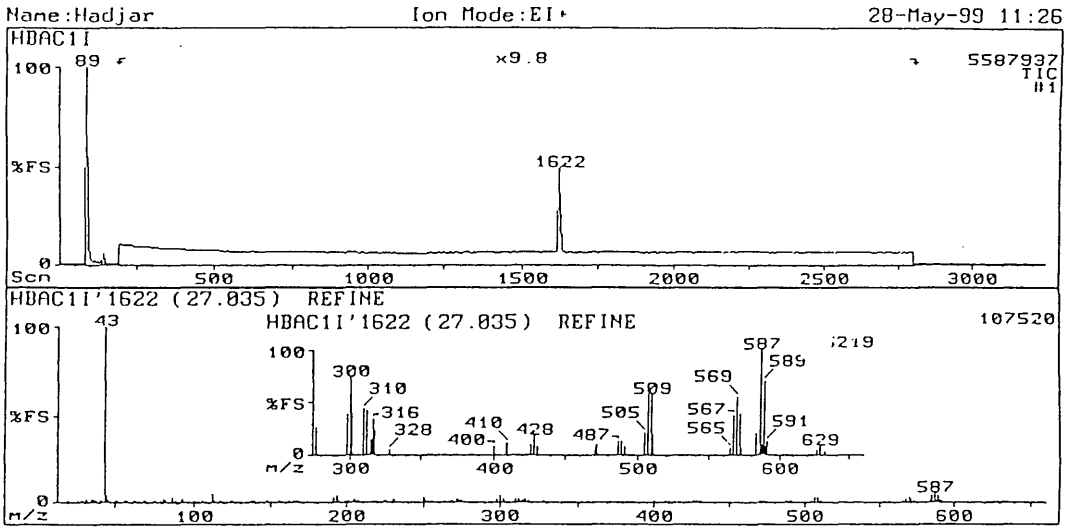
Mass	Rel Int	Mass	Rel Int	Mass	Rel Int	Mass	Rel Int
20	0.04	83	1.02	140	4.84	198	0.65
26	0.56	84	0.15	141	15.04	199	1.17
28	4.51	86	1.22	142	2.76	200	0.18
28	6.30	86	2.76	143	18.80	202	37.41
29	2.04	87	2.81	144	3.95	203	1.87
30	0.12	88	4.65	145	6.58	204	38.35
31	4.14	89	3.90	146	4.84	205	2.38
32	2.09	90	1.00	147	5.69	207	1.53
33	0.22	91	1.08	148	4.46	208	0.37
36	0.20	93	12.03	149	0.38	209	1.64
37	0.81	94	2.10	150	0.15	210	0.47
38	2.23	95	2.73	151	0.19	211	0.83
39	8.46	96	1.29	153	6.39	212	0.20
40	0.63	97	0.61	154	0.90	213	0.04
41	0.65	98	0.20	155	6.44	221	3.38
42	4.65	99	0.40	156	1.02	222	1.08
43	16.73	100	0.37	157	1.21	223	14.66
44	4.32	102	2.74	158	0.22	224	2.53
45	19.92	103	3.10	159	1.15	225	11.28
47	55.64	104	5.83	160	1.21	226	1.21
48	3.67	105	1.50	161	2.78	227	0.26
49	45.49	106	1.09	162	0.51	228	0.17
50	4.70	107	1.56	163	2.58	229	0.17
51	12.78	108	1.91	164	2.95	230	0.17
52	2.35	109	1.50	165	3.38	232	0.70
53	10.67	110	0.21	166	1.53	234	2.23
54	2.62	111	0.55	167	0.41	235	0.15
55	3.01	112	2.38	168	5.87	236	1.35
56	1.15	113	0.87	169	3.85	237	0.10
57	4.42	114	0.65	170	18.61	239	0.06
58	2.03	115	1.54	171	2.96	246	0.20
59	0.36	117	7.38	172	1.64	247	0.05
61	5.08	118	1.06	173	0.69	248	15.04
62	4.75	119	5.36	174	2.11	249	12.41
63	97.74	120	0.43	175	1.13	250	16.73
64	6.67	121	0.58	176	0.14	251	13.91
65	1.33	122	4.14	177	0.86	252	1.99
66	1.00	123	4.09	178	0.09	253	1.81
67	1.90	124	0.75	179	0.10	254	0.28
68	1.16	125	0.30	181	0.03	255	1.54
69	1.08	126	0.45	182	1.29	256	0.11
70	0.53	127	0.70	183	1.03	260	0.05
71	1.75	128	1.41	184	1.32	261	0.08
73	51.13	129	5.36	185	0.80	262	0.25
74	7.38	130	0.80	186	0.47	263	0.08
75	6.06	131	0.68	187	0.22	264	0.75
76	1.27	132	0.64	188	0.78	265	0.14
77	100.00	133	0.30	189	0.32	266	0.25
78	18.80	134	0.16	190	0.26	268	0.06
79	3.95	135	0.42	191	0.90	270	0.13
80	0.52	136	0.65	193	2.50	271	0.10
81	13.91	137	0.82	195	2.41	272	0.07
81	25.56	138	0.17	196	1.32	273	0.17
82	3.24	139	0.54	197	0.74	274	0.10

HBTMS 945 (15.751)

Mass	Rel Int	Mass	Rel Int
275	0.14	302	0.21
277	0.20	303	0.38
278	0.03	304	0.15
279	0.05	305	0.19
287	0.17	308	0.14
289	0.46	310	0.18
290	0.05	311	0.04
291	0.14	312	0.12
300	0.11	313	0.04
301	0.20	315	0.06

Mass	Rel Int	Mass	Rel Int
317	0.06	344	2.84
326	0.14	345	47.74
327	0.07	346	5.97
328	1.29	347	22.37
329	0.22	348	2.76
330	2.03	349	0.80
331	0.28	350	0.08
332	0.96		
333	0.13		
343	24.81		

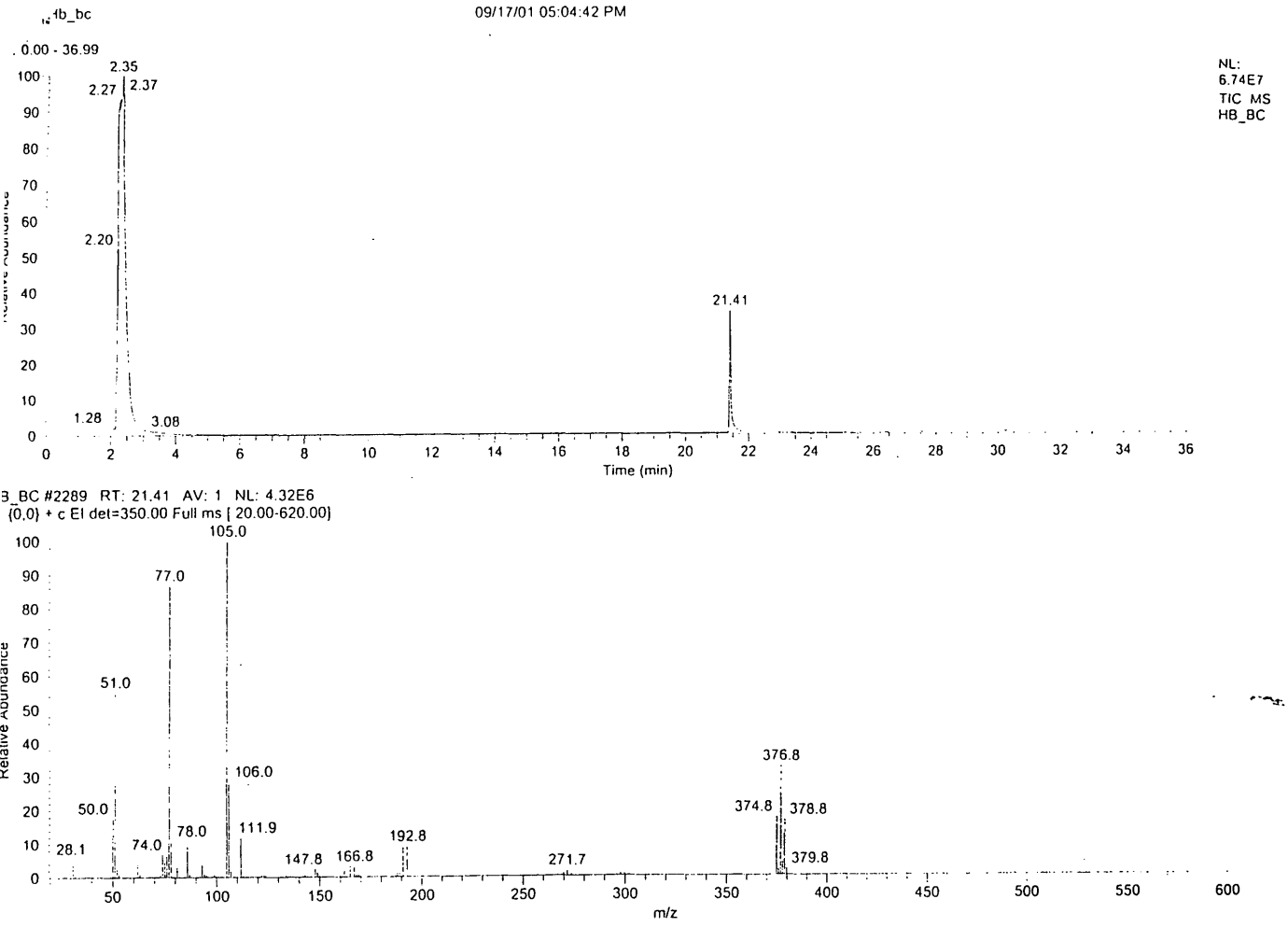
15. 1,1-di(2,6-dibromo-3,5-difluoro-4-pyridyl)ethyl acetate (27)



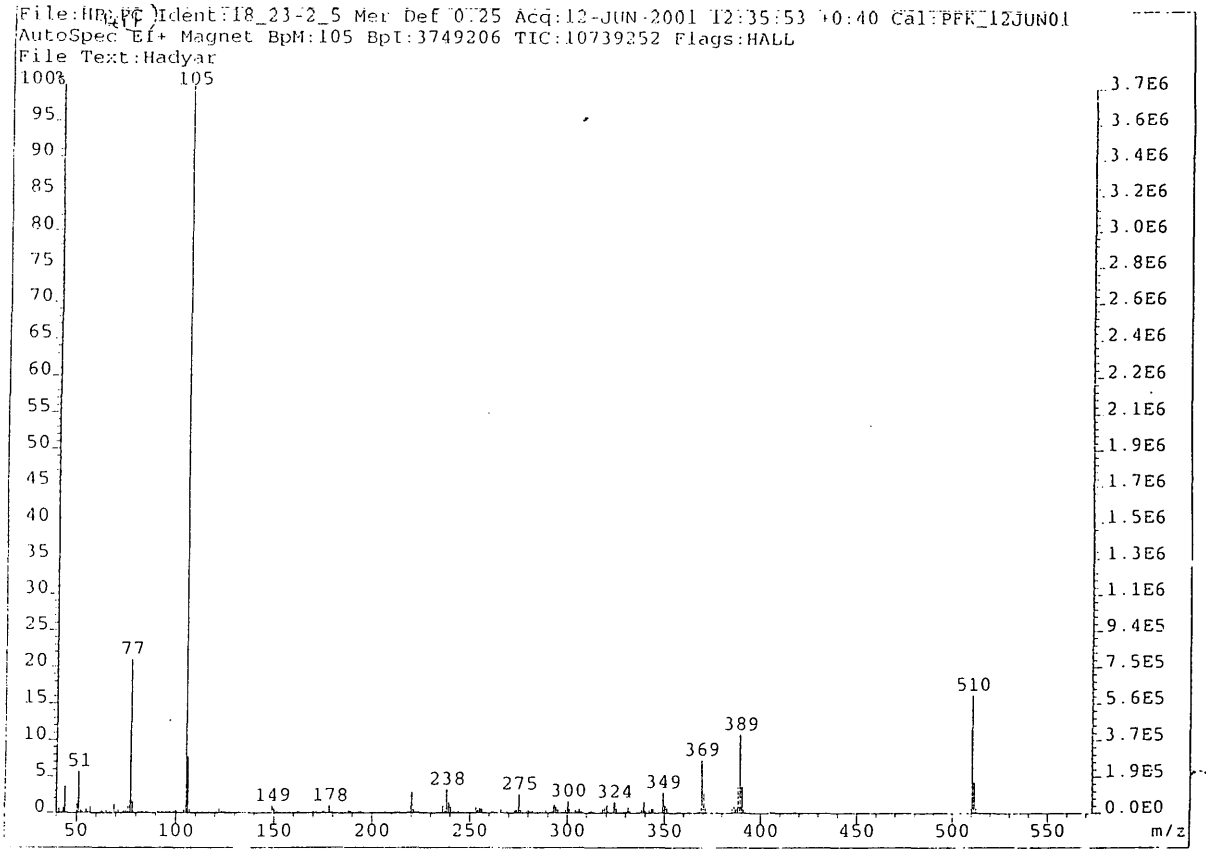
HBAC1I'1622 (27.035) REFINE 107520

Mass	Rel Int	Mass	Rel Int	Mass	Rel Int	Mass	Rel Int
20	0.13	81	1.92	207	0.58	426	0.47
26	0.34	82	0.70	217	0.75	428	0.90
28	0.86	86	2.71	219	0.85	430	0.38
29	0.77	88	1.43	224	1.01	470	0.31
31	2.05	93	1.86	225	0.60	472	0.44
35	1.52	100	0.67	230	0.83	487	0.65
36	2.29	106	0.47	231	2.29	489	0.61
37	0.57	112	4.52	250	3.05	491	0.39
38	0.90	113	1.41	251	0.65	505	1.04
40	0.14	118	0.35	269	0.56	507	2.78
41	0.57	124	0.54	272	1.96	509	2.81
43	100.00	125	0.52	273	0.76	511	0.94
44	3.57	137	0.63	274	1.24	565	0.35
45	0.83	138	0.54	275	0.15	567	1.86
50	0.48	139	0.94	298	1.93	569	2.71
51	0.42	148	0.47	300	3.56	571	1.95
56	0.35	155	0.65	302	1.95	573	0.33
57	0.61	162	0.38	310	2.14	583	1.01
61	0.33	165	0.92	312	2.08	585	3.59
62	1.22	167	0.88	314	0.75	587	5.24
63	0.59	191	3.08	315	0.74	588	0.52
68	0.62	193	3.66	316	1.70	589	3.41
69	1.07	194	0.72	318	1.09	590	0.36
74	0.40	199	0.47	328	0.25	591	0.67
75	0.87	201	0.20	400	0.38	627	0.25
76	0.60	204	0.42	408	0.56	629	0.39
79	1.28	205	1.76	410	0.58	632	0.19

16. 2,6-dibromo-3,5-difluoro-4-pyridyl-phenylmeyhanone (28)



17. *bis* (2,3,5,6-tetrafluoro(4-pyridyl))phenylmethyl benzoate (29)

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        data identifier 18_23-2_5 Mer Def 0.25
Axis display range        X_MASS (40.00, 572.67)
Normalising intensity  3.74921E-06
Data threshold 0.30% of normalising intensity
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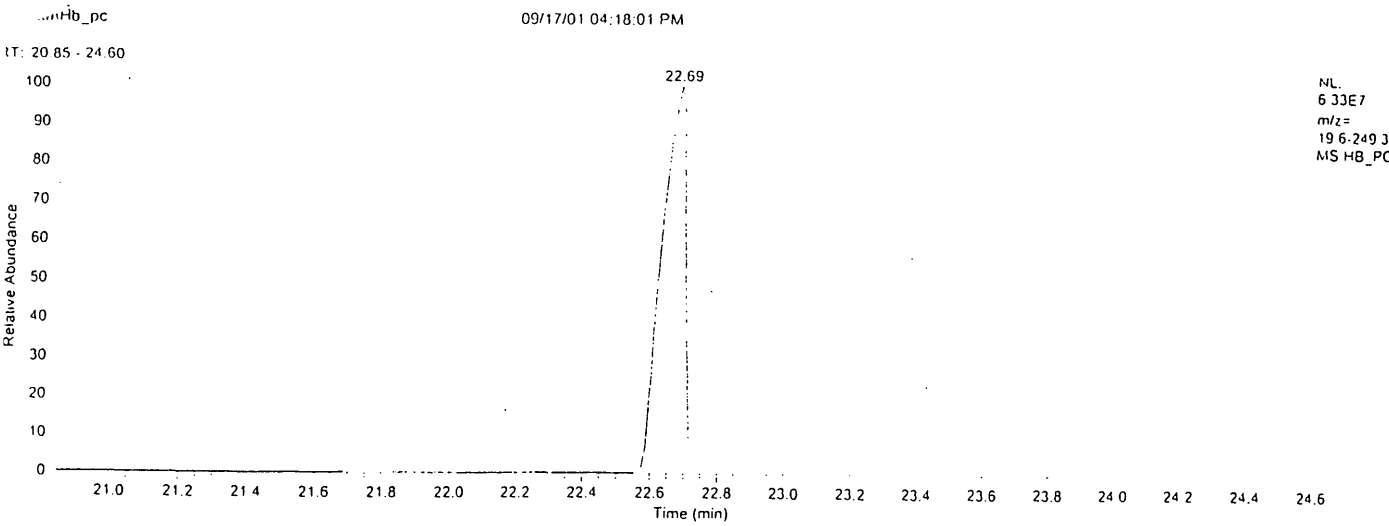
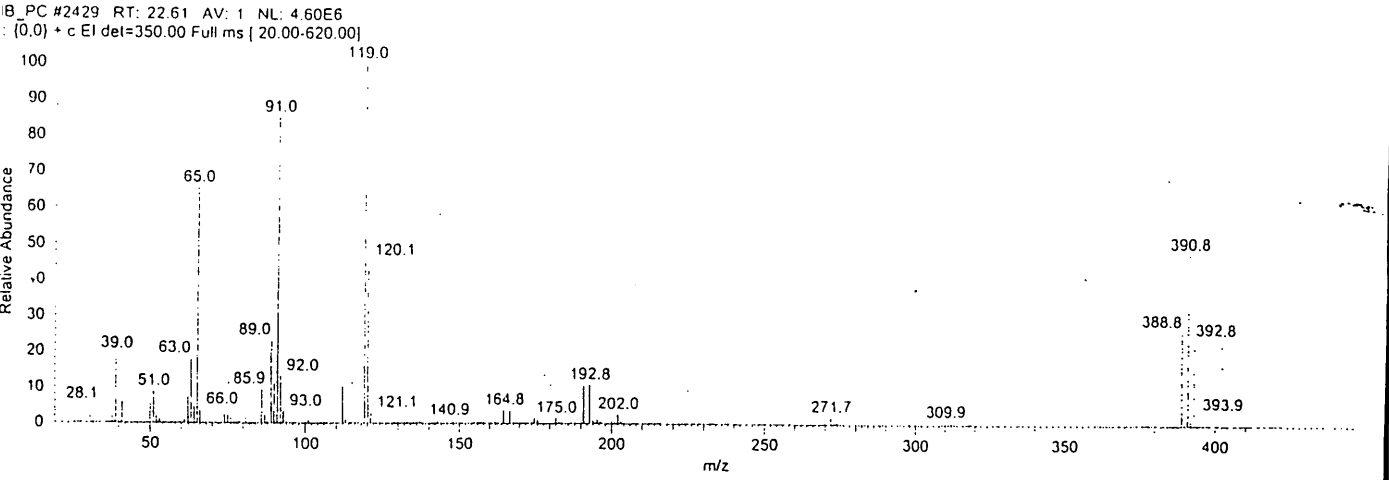
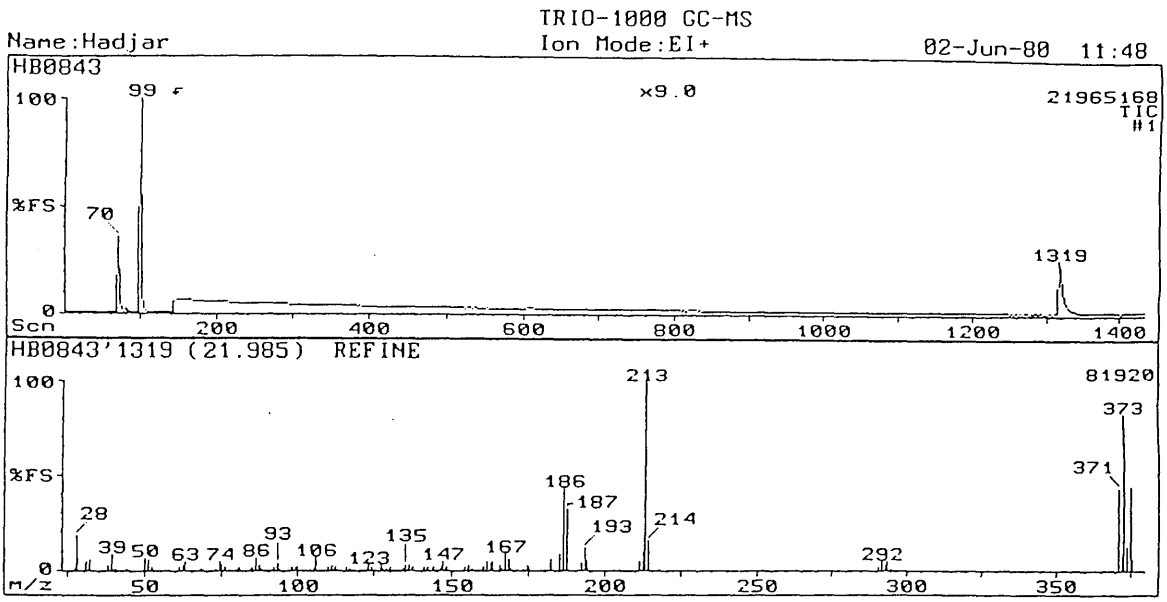
ABS MASS	REL (%) HEIGHT	ABS MASS	REL (%) HEIGHT	ABS MASS	REL (%) HEIGHT	ABS MASS	REL (%) HEIGHT
41.0505	0.71	106.0751	7.73	273.1257	0.39	338.1546	0.46
43.0618	0.74	107.0791	0.57	274.1284	0.56	339.1630	1.56
44.0032	3.68	122.0635	0.63	275.1466	2.64	340.1649	0.33
50.0308	1.26	149.0702	1.01	276.1430	0.51	342.1457	0.41
51.0387	5.74	150.0317	0.72	279.1325	0.37	343.1463	0.64
52.0437	0.38	151.0414	0.31	280.1367	0.40	344.1622	0.62
55.0721	0.59	174.9760	0.32	281.1337	0.30	349.1601	5.87
57.0851	0.91	178.0555	1.04	282.1418	0.37	350.1628	1.06
63.0445	0.32	188.0869	0.38	289.1476	0.41	351.1770	0.69
65.0615	0.38	189.1107	0.36	293.1331	1.22	368.1558	0.32
69.0396	1.25	218.1082	0.32	294.1428	0.88	369.1645	7.31
71.1071	0.44	220.1196	2.89	295.1906	0.49	370.1712	2.85
74.0187	0.38	221.1265	0.52	299.1361	0.48	371.1801	0.93
75.9903	0.48	236.1166	0.99	300.1434	1.66	385.1699	0.63
76.0518	0.91	238.1163	3.26	301.1494	0.56	386.1788	0.90
77.0604	21.05	239.1224	1.52	304.1372	0.44	387.1734	0.59
78.0641	1.59	240.1318	0.84	306.1516	0.60	388.1735	3.60
81.0764	0.31	244.1286	0.32	307.1543	0.34	389.1814	10.79
83.1047	0.34	253.1428	0.80	311.1405	0.32	390.1869	3.69
91.0762	0.40	254.1273	0.44	318.1467	0.58	391.1900	0.53
93.0504	0.30	255.1221	0.66	319.1500	0.77	510.2688	16.21
97.1296	0.30	256.0754	0.63	320.1616	1.09	511.2731	4.27
100.0312	0.40	262.1259	0.38	324.1483	1.57	512.2755	0.65
104.0630	0.46	266.1561	0.51	325.1512	0.68		
105.0708	100.00	269.1359	0.35	331.1520	0.84		

18. 2,6-dibromo-3,5-difluoro(4-pyridyl)-4-methylphenylketone (31)





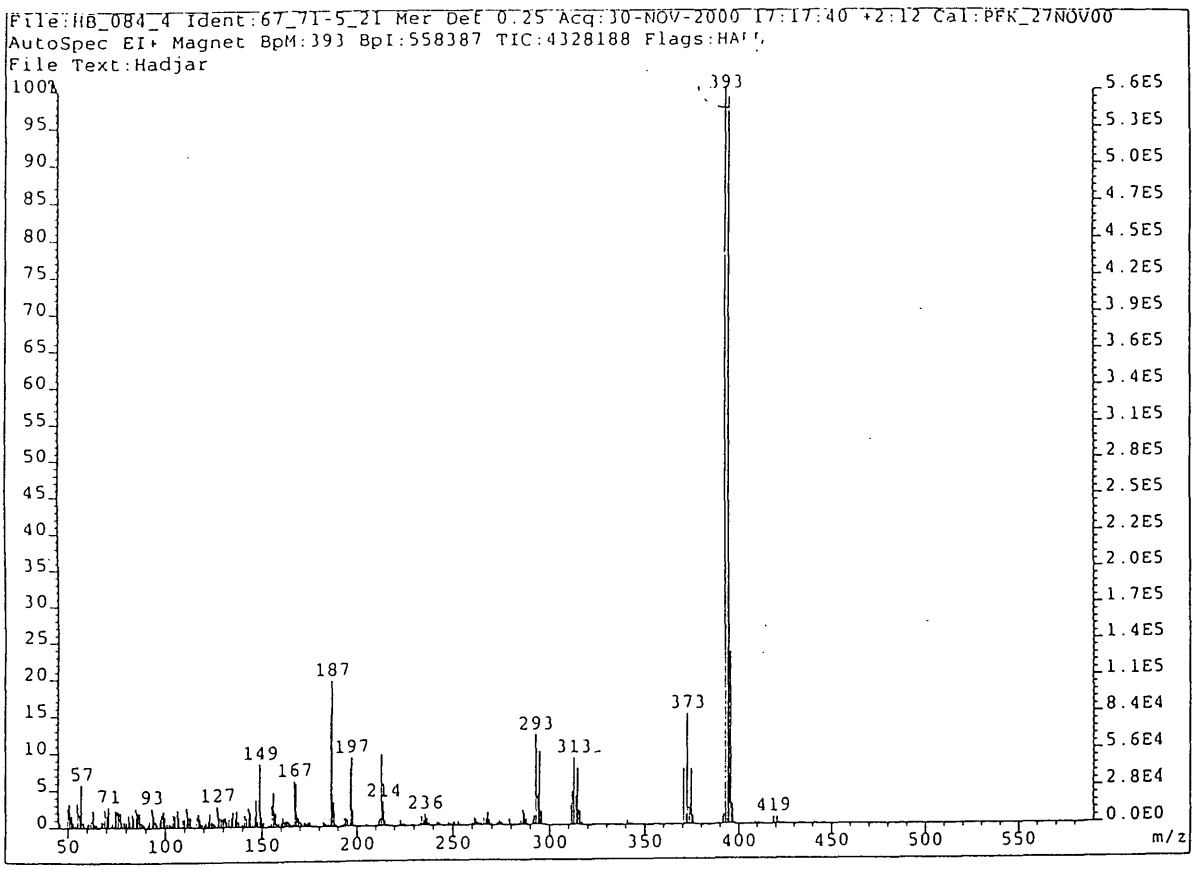
19. 4-dibromo-3,5-difluoro-6-(phenylacetenyl)pyridine (33)



HB0843'1319 (21.985) REFINE 81920

Mass	Rel Int	Mass	Rel Int	Mass	Rel Int	Mass	Rel Int
27	1.23	87	2.81	136	2.95	185	8.83
28	18.44	88	1.07	137	1.54	186	42.50
31	4.61	92	1.62	141	1.46	187	32.19
32	6.02	93	3.91	142	1.72	192	3.77
38	2.66	94	1.27	144	2.25	193	11.56
39	8.44	98	1.88	146	2.42	194	4.94
40	1.07	99	1.48	147	5.31	211	4.71
44	1.41	100	1.76	148	1.58	212	10.00
50	6.41	104	1.14	154	1.68	213	100.00
51	6.17	105	1.11	155	2.71	214	15.08
52	2.32	106	7.03	156	1.11	291	1.50
61	2.05	110	1.82	160	1.82	292	4.71
62	2.91	111	2.87	161	4.41	293	2.58
63	4.59	112	1.82	162	3.63	294	4.65
68	1.03	116	1.60	163	5.08	295	1.02
73	1.14	117	1.21	165	3.34	371	42.81
74	4.49	123	3.32	166	1.45	372	7.58
75	2.52	124	1.46	167	8.91	373	82.50
76	1.62	127	2.73	168	6.09	374	12.81
80	1.31	128	1.20	169	1.17	375	43.44
81	1.88	129	1.19	173	1.15	376	6.02
84	1.19	130	1.52	174	2.81		
85	2.36	134	1.19	175	2.05		
86	6.41	135	2.95	182	5.39		

20. 2,6-bis(2-phenylethynyl)-4-bromo-3, 5-difluoropyridine (34)

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        data identifier 67_71-5_21 Mer Def 0.25
Axis display range        X_MASS (45.16, 559.65)
Normalising intensity  5.58387E-05
Data threshold 0.30% of normalising intensity
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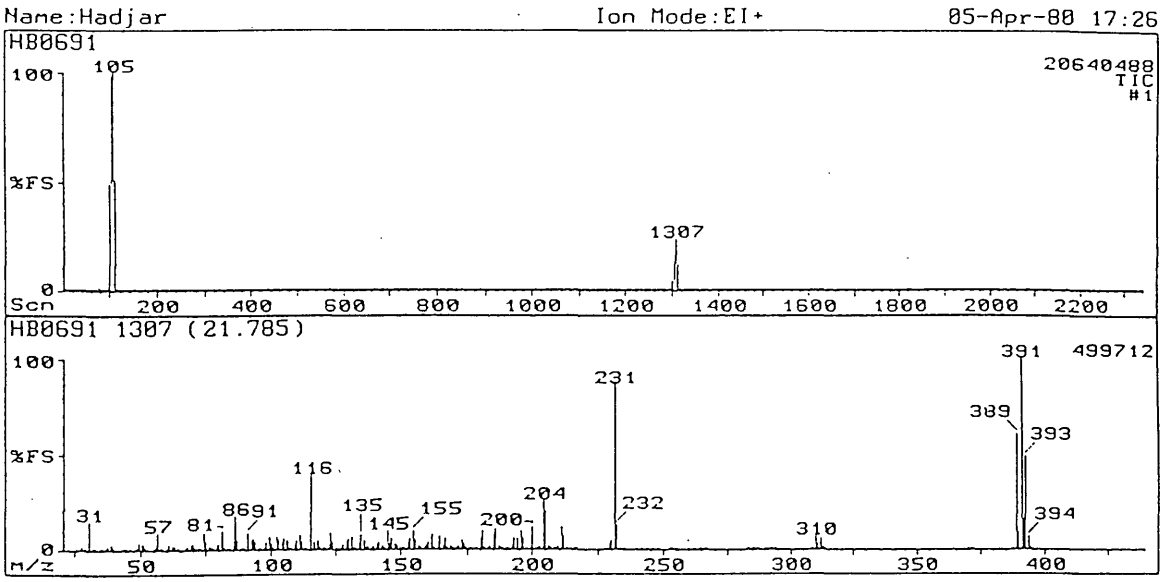
ABS MASS	REL (%) HEIGHT	ABS MASS	REL (%) HEIGHT	ABS MASS	REL (%) HEIGHT	ABS MASS	REL (%) HEIGHT
45.9747	0.77	102.9841	0.53	158.9527	0.72	250.9117	0.62
48.9756	0.31	103.9715	1.92	159.9560	0.62	252.8943	0.60
49.9864	2.78	104.9804	1.71	160.9559	1.37	259.9704	0.49
50.9932	3.34	106.3110	2.49	161.9704	0.80	260.9620	1.02
51.9982	1.79	107.0360	1.38	162.9843	0.93	261.9915	0.88
53.0043	0.86	108.0432	0.32	163.9856	0.69	262.9880	0.54
54.0150	0.48	109.0042	1.27	164.9688	0.46	263.9816	0.40
55.0236	3.43	109.9876	1.38	165.9648	0.39	265.9501	1.05
56.0310	1.94	110.9911	2.78	166.9685	6.20	266.9793	0.96
57.0386	5.91	112.0155	1.55	167.9734	5.84	267.9778	1.91
58.0351	0.87	113.0294	1.47	168.9835	1.28	269.0019	0.81
59.0155	0.35	115.0021	0.32	170.0824	0.72	272.9664	0.54
59.9882	0.72	115.9612	1.55	171.0403	0.50	273.9588	0.70
60.9758	0.83	117.0175	1.93	171.9846	0.72	274.9836	0.48
61.9794	1.10	118.0054	1.19	172.9557	0.59	279.0777	0.91
62.9875	2.46	119.0203	0.58	173.9827	0.69	283.9715	0.41
63.9968	0.64	120.0838	0.54	174.9750	0.73	284.9570	0.72
65.0026	0.64	121.0717	0.83	177.0034	0.31	285.9595	2.05
66.0067	0.31	121.9707	0.96	181.9867	0.77	286.9729	1.58
67.0205	1.01	123.0243	1.99	183.0387	0.58	287.9929	0.91
68.0497	0.84	124.0457	0.94	183.9715	0.42	290.9298	0.78
69.0258	2.60	125.0391	0.68	185.0786	1.37	291.9138	1.45
70.0418	1.73	125.0394	0.49	185.9776	15.20	292.8938	12.25
71.0469	2.85	126.9885	2.95	186.9776	19.79	293.9227	4.05
72.0319	0.42	127.9737	1.42	187.9628	3.32	294.8799	9.99
72.9875	0.80	129.0265	1.37	188.9753	0.43	295.9054	1.87
73.9779	2.43	130.0973	1.32	191.9798	0.43	310.9796	2.65
74.9797	2.58	131.0364	1.37	192.9638	1.20	311.9864	4.65
75.9872	2.28	131.9857	0.85	193.9767	1.25	312.9934	9.12
77.0016	2.12	133.1133	1.27	195.0258	0.96	313.9989	3.94
77.9947	0.83	134.0582	1.38	196.3812	7.87	314.9979	7.74
78.9946	0.99	134.9531	2.04	197.3055	9.34	316.0017	1.93
79.9965	0.99	136.0453	1.17	197.9831	2.17	317.0092	0.44
81.0836	1.85	136.9983	2.32	205.0149	0.37	340.8814	0.61
81.9902	0.99	137.9775	0.78	210.0009	0.33	348.9360	0.31
83.0857	1.94	139.0021	0.35	210.9656	0.84	370.6912	7.57
84.0293	1.41	139.9725	0.63	211.9566	1.14	371.7116	1.35
85.0085	2.70	140.9652	1.73	212.9666	9.71	372.7083	14.99
85.9664	2.07	142.0837	1.28	213.9742	3.35	373.7260	2.33
86.9747	2.06	143.1382	2.62	214.9829	0.71	374.7261	7.61
87.9779	0.87	144.0064	2.02	221.0123	0.84	375.7496	1.19
88.9962	0.59	145.0521	0.50	223.9832	0.41	390.9089	1.10
91.0054	0.60	146.2142	1.56	224.9889	0.34	391.9237	1.52
91.9784	1.03	147.0490	3.73	233.0126	0.43	392.9085	100.00
93.1217	2.75	147.9595	0.89	233.9078	1.34	393.9120	23.92
93.9865	1.75	148.9591	8.55	234.9225	0.79	394.9056	99.03
95.0361	1.09	149.9650	1.15	235.9197	1.61	395.9051	23.47
96.0765	0.60	150.9949	0.73	236.9482	1.09	396.9048	2.75
97.0573	1.13	153.0118	0.33	237.9728	0.42	408.8257	0.39
97.9835	1.90	153.9777	0.43	241.9742	0.58	410.8643	0.41
98.9937	2.28	155.0505	2.92	242.9753	0.51	418.7684	1.04
99.9790	1.56	156.1354	4.69	247.9806	0.52	420.7706	0.97
100.9805	0.70	157.1821	1.88	248.9650	0.37		
101.9909	0.56	157.9698	0.47	249.9867	0.52		

21. 2,4-dibromo-3,5-difluoro-6-[2-(4-fluorophenyl)ethynyl]pyridine (35)



HB0691 1307 (21.795) 499712.

Mass	Rel Int	Mass	Rel Int	Mass	Rel Int	Mass	Rel Int
26	0.64	90	0.21	146	2.89	201	0.72
27	0.71	91	9.12	147	5.84	202	0.35
28	2.15	92	4.87	148	3.20	203	1.59
29	0.05	93	6.25	149	1.78	204	25.41
31	14.14	94	3.59	150	1.33	205	19.88
32	0.92	95	1.26	151	0.37	206	2.39
33	1.42	96	0.37	152	0.79	207	0.33
35	0.15	97	1.02	153	3.79	208	0.08
36	0.61	98	4.30	154	6.20	209	0.40
37	0.83	99	6.71	155	9.43	210	2.39
38	1.68	100	3.02	156	4.71	211	11.78
39	2.77	101	0.78	157	2.33	212	7.07
40	0.18	102	6.92	158	0.69	213	0.92
43	0.08	103	4.66	159	2.04	215	0.29
44	0.70	104	4.10	160	2.84	216	0.11
45	0.85	105	6.30	161	3.69	217	0.14
46	0.44	106	4.92	162	7.79	228	0.09
48	0.08	107	1.45	163	1.23	229	3.18
49	0.50	108	0.58	164	0.50	230	4.87
50	4.35	109	3.07	165	6.66	231	86.07
51	2.47	110	4.76	166	2.32	232	12.45
52	0.27	111	7.43	167	5.89	233	0.91
55	1.19	112	4.15	168	0.74	235	0.06
56	2.02	113	0.53	169	2.16	240	0.11
57	8.40	116	38.52	170	0.35	242	0.13
58	0.54	117	3.74	171	1.29	244	0.39
60	0.10	118	4.46	172	1.51	246	0.72
61	2.55	119	1.40	173	5.33	248	0.37
62	2.37	120	0.54	174	3.02	252	0.08
63	2.13	121	0.60	175	0.41	253	0.11
64	0.34	122	2.68	176	0.80	254	0.10
67	0.77	123	8.91	177	0.33	255	0.11
68	2.04	124	3.69	178	1.19	260	0.12
69	2.60	125	1.19	179	0.77	262	0.10
70	2.96	126	0.27	180	5.84	264	0.07
71	0.25	127	1.14	181	9.48	265	0.16
72	0.17	128	3.38	182	1.43	266	0.08
73	0.93	129	5.12	183	0.32	267	0.14
74	8.50	130	5.94	184	2.31	283	0.37
75	3.64	131	6.76	185	7.84	284	0.56
76	2.00	132	1.45	186	10.76	285	0.40
77	0.62	133	1.02	187	2.36	286	0.52
78	0.40	134	3.43	188	0.44	287	0.06
79	3.19	135	7.33	189	0.18	290	0.41
80	2.74	136	4.41	190	0.31	291	0.73
81	9.48	137	1.09	191	0.79	292	0.51
82	1.31	138	1.50	192	1.64	293	0.68
83	0.49	139	0.31	193	5.53	294	0.11
84	0.59	140	1.82	194	5.79	309	1.40
85	4.46	141	2.59	195	9.43	310	6.35
86	17.83	142	3.64	196	5.58	311	2.57
87	4.41	143	1.63	198	0.49	312	6.25
88	1.45	144	0.19	199	0.51	313	1.14
89	0.60	145	9.73	200	11.53	314	0.13

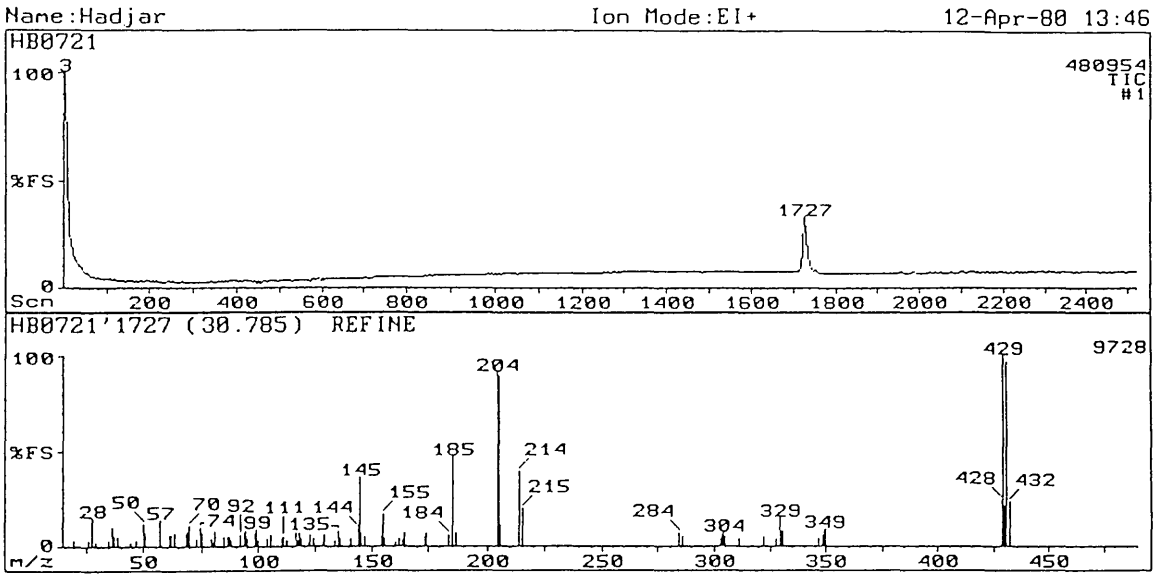
HB0691 1307 (21.735)

Mass	Rel Int	Mass	Rel Int
370	0.03	389	59.84
372	0.07	390	3.81
388	0.08	391	100.00

499712

Mass	Rel Int	Mass	Rel Int
392	15.16	395	0.53
393	48.35		
394	7.07		

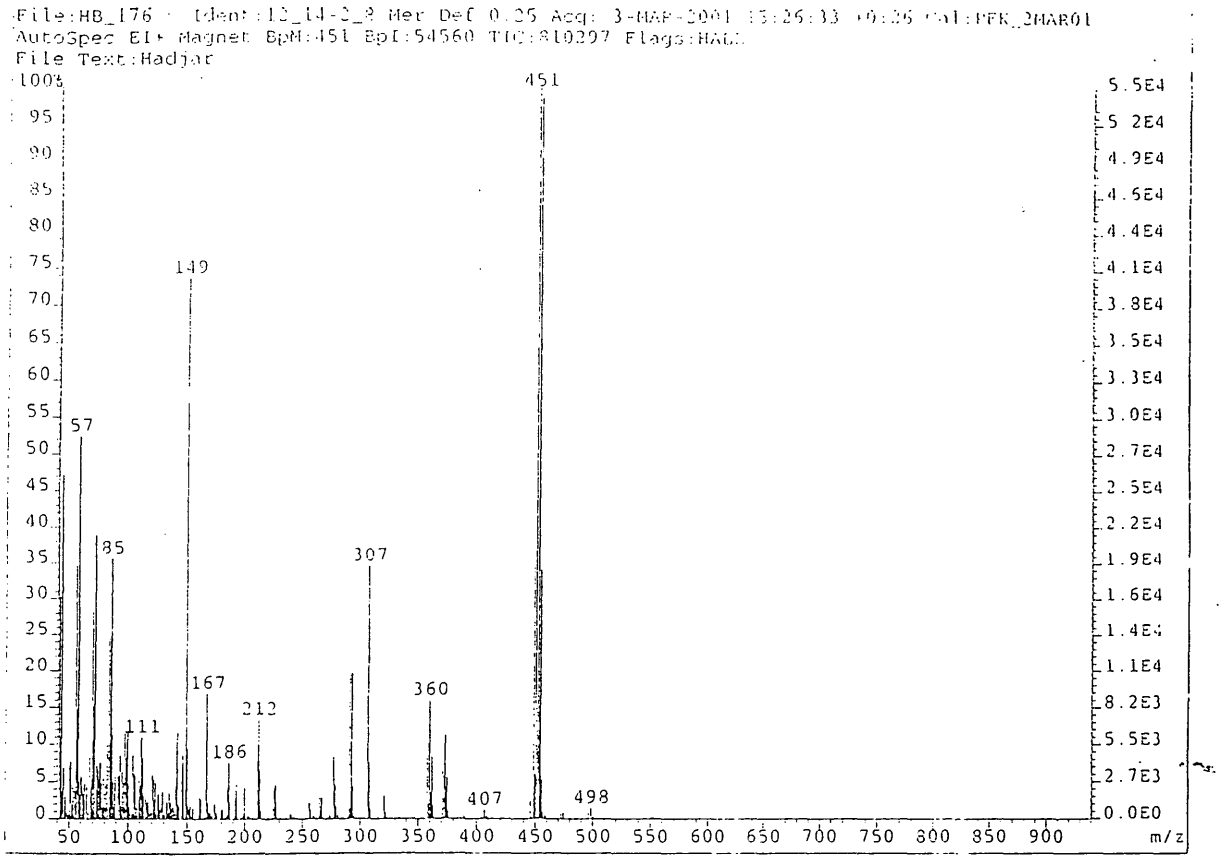
22. 4-bromo-3,5-difluoro-2-(4-fluorophenyl)-6-[2-(4-fluorophenyl)ethynyl]pyridine (36)

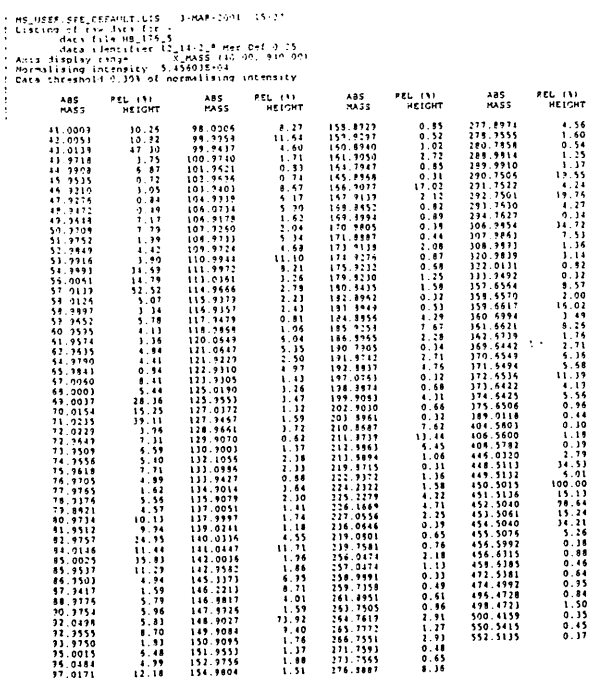


HB0721'1727 (30.785) REFINE 9728

Mass	Rel Int	Mass	Rel Int	Mass	Rel Int	Mass	Rel Int
20	3.21	81	7.65	128	1.78	206	10.44
26	3.04	85	5.06	129	5.35	214	39.31
28	14.47	86	4.98	134	3.04	215	19.08
29	1.73	87	5.02	135	7.57	284	6.66
35	2.84	88	2.84	136	3.54	286	4.69
36	9.95	92	5.47	141	3.50	302	4.28
37	4.77	93	6.91	144	8.88	303	5.35
39	5.02	94	7.94	145	36.18	304	6.95
44	1.97	95	3.74	146	6.70	305	4.40
47	3.17	98	7.20	147	4.77	311	4.07
50	11.68	99	8.26	154	4.65	322	4.56
51	6.33	100	3.13	155	16.45	328	3.45
57	13.32	104	3.41	156	3.62	329	14.64
61	6.21	105	6.00	161	2.08	330	7.44
62	5.55	110	3.70	162	3.62	331	7.94
63	6.33	111	5.14	164	2.58	347	4.36
68	6.33	112	3.33	165	6.70	348	5.59
69	7.69	116	6.50	173	4.89	349	8.63
70	10.69	117	3.25	174	6.62	350	8.31
73	3.99	118	6.99	184	5.35	428	24.18
74	9.54	119	3.95	185	46.71	429	100.00
75	6.74	122	1.54	187	6.41	430	21.55
79	4.07	123	5.43	204	91.45	431	97.37
80	2.03	124	3.78	205	89.47	432	23.36

23. Synthesis of 4-bromo-2,6-di[2-(4-bromophenyl)-1-ethynyl]-3,5-difluoropyridine (37)

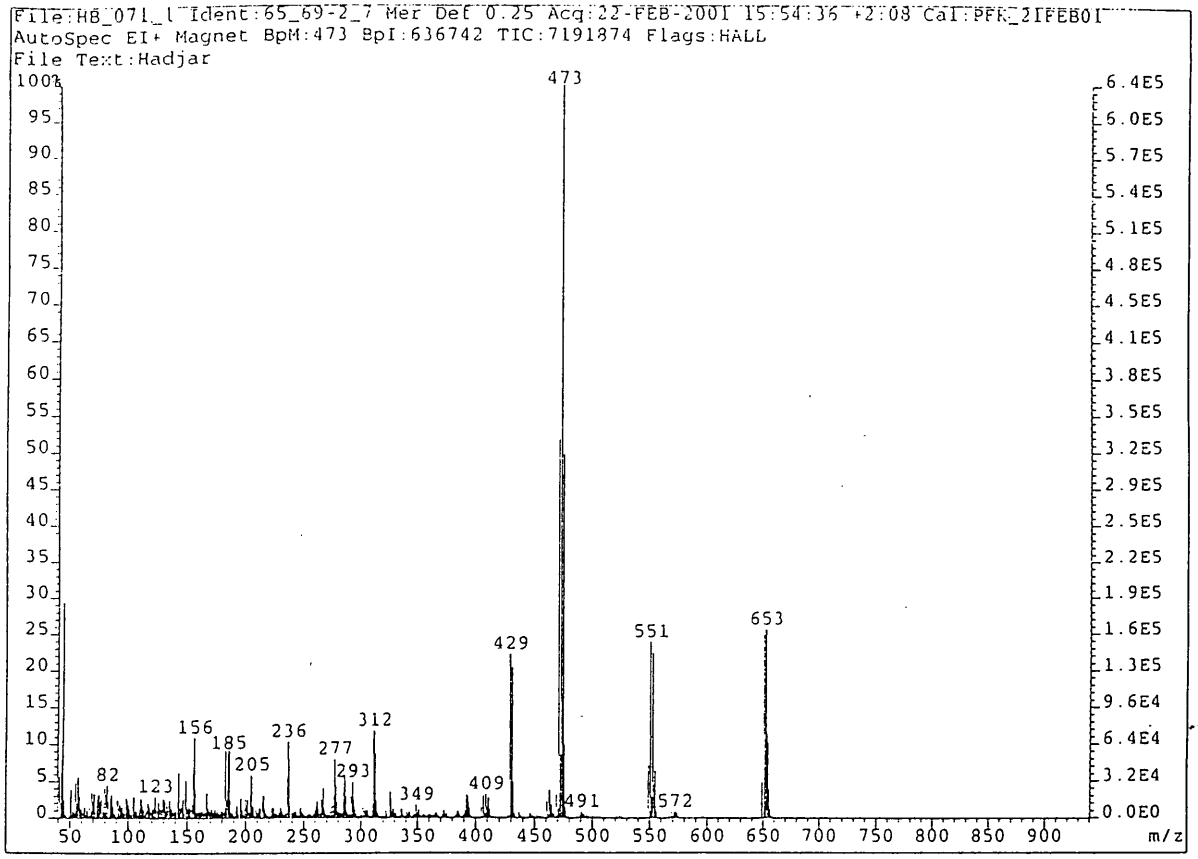


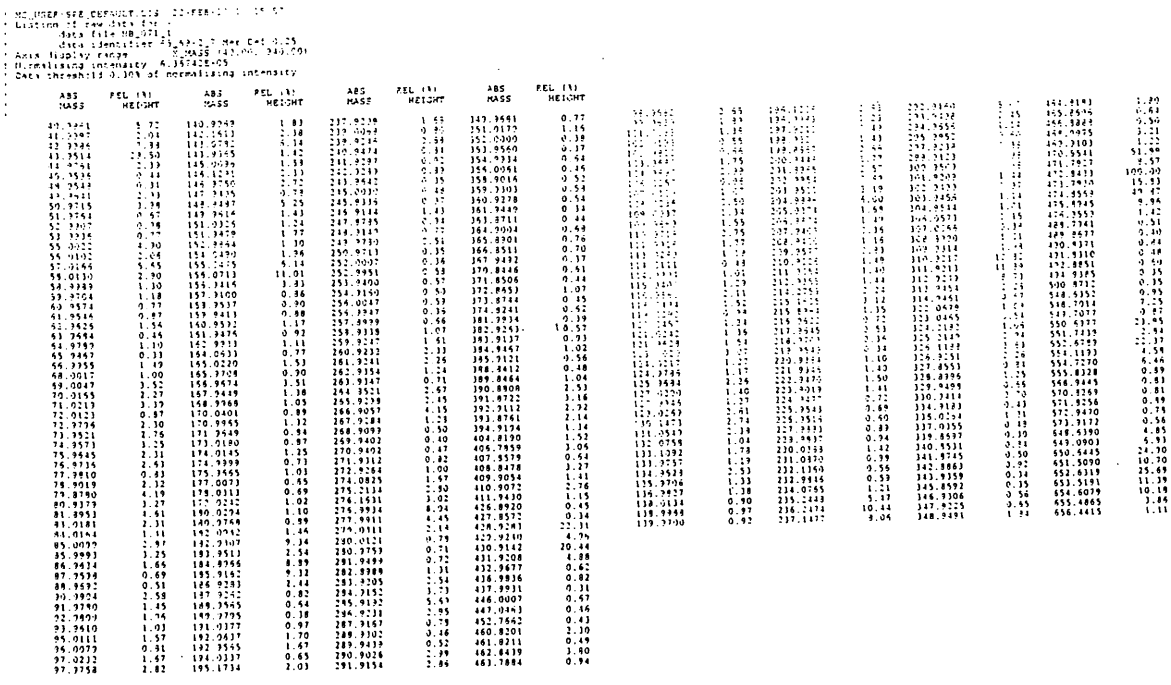


ABS MASS	REL (%) HEIGHT	ABS MASS	REL (%) HEIGHT	ABS MASS	REL (%) HEIGHT	ABS MASS	REL (%) HEIGHT
41.0003	30.26	98.0306	8.27	158.8729	0.85	277.8971	4.56
42.0053	10.32	99.9759	11.64	159.9297	0.52	278.7555	1.60
43.0139	47.30	99.9837	4.60	160.8940	1.02	280.7858	0.54
43.9718	3.75	100.9740	1.71	161.9050	2.72	288.9814	1.35
44.9908	6.87	101.9621	0.83	163.7967	0.85	289.9910	1.37
45.9535	0.72	103.9636	0.72	165.8948	0.31	290.7505	19.55
46.9210	3.05	104.9403	8.67	166.9077	17.02	291.7522	4.24
47.9276	0.84	104.9739	5.17	167.9139	2.12	292.7561	19.76
48.9372	0.49	106.0734	5.30	168.8952	0.82	293.7620	4.27
49.9414	7.17	109.9778	1.62	169.8994	0.89	294.7627	0.34
50.9708	7.79	107.9760	2.04	170.9805	0.39	306.9854	34.72
51.9752	1.39	108.9733	5.34	171.8887	0.44	307.9863	7.53
52.9849	4.42	109.9724	4.69	173.9139	2.08	308.9833	1.36
53.9946	3.89	110.9841	11.10	174.9276	0.87	320.9839	3.14
54.9993	31.59	111.9972	8.21	175.9232	0.68	322.0131	0.92
55.0061	14.79	113.0361	3.26	176.9230	1.25	333.3492	0.32
57.0133	52.52	114.9666	2.79	180.9435	1.58	357.6564	8.57
58.9125	5.07	115.9737	2.23	182.8962	0.32	358.6570	2.00
58.9897	3.34	116.9357	2.43	181.8949	0.53	359.6617	15.02
59.9452	5.78	117.9479	0.81	184.8955	4.29	360.6894	3.49
60.9539	4.13	118.9868	1.96	185.9251	7.67	361.6621	8.25
61.9574	3.38	120.0649	5.04	186.9965	2.28	362.6739	1.76
62.9635	4.84	121.0647	5.35	190.7305	0.34	369.6442	2.71
64.9790	4.41	121.9227	2.50	191.8742	2.71	370.6549	5.36
65.9841	0.84	122.9310	4.97	192.8837	4.76	371.5494	5.58
67.0060	8.41	123.9305	1.43	197.0763	0.32	372.6536	11.39
68.0003	5.44	125.0190	3.26	198.9874	0.68	373.6422	4.13
69.0037	28.36	125.9553	3.47	199.9083	4.31	374.6425	5.56
70.0154	15.25	127.0372	1.32	202.9030	0.66	375.6506	0.96
71.0235	39.11	127.9467	1.59	203.8961	0.32	389.0118	0.44
72.0229	3.96	128.9641	3.72	210.8987	7.62	404.5803	0.30
72.9447	7.31	129.9070	0.62	211.8739	13.44	406.5600	1.19
73.9509	6.59	130.9003	1.37	212.8863	5.45	404.5782	0.39
74.9556	5.40	132.1055	2.38	213.8894	1.06	445.0320	2.79
75.9618	7.71	133.0886	2.33	219.8715	0.31	448.5113	34.53
76.9705	4.89	133.9427	0.88	222.9372	1.36	449.5132	6.01
77.9765	1.62	134.9014	3.64	224.2322	1.58	450.5015	100.00
78.9376	5.56	135.9079	2.30	225.2279	4.22	451.5136	15.13
79.8421	4.57	137.0051	1.41	226.1669	4.71	452.5040	78.64
80.9734	10.13	137.9997	1.74	227.0536	2.25	453.5061	15.24
81.9532	9.74	139.0211	1.18	228.0646	0.39	454.5040	34.21
82.9757	24.55	140.0316	4.55	239.0501	0.65	455.5076	5.26
84.0126	11.44	141.0447	11.71	239.7581	0.76	456.5992	0.38
85.0025	35.83	142.0016	1.96	256.0474	2.18	456.6315	0.88
85.9537	11.29	142.9562	1.86	257.0474	1.13	458.6385	0.46
86.9503	4.94	145.0373	6.95	258.9991	0.33	472.5381	0.64
87.9417	1.59	146.2213	8.71	259.7358	0.49	474.4992	0.95
88.9776	5.79	146.9817	4.01	261.8951	0.61	496.4728	0.84
90.9754	5.96	147.9926	1.59	263.7505	0.86	498.4723	1.50
92.0496	5.83	148.9027	73.92	264.7617	2.91	500.4159	0.35
92.9555	8.70	149.9084	9.40	265.7772	1.27	550.9415	0.45
93.9750	1.93	150.9095	1.76	266.7551	2.93	552.5135	0.37
95.0015	6.48	151.9553	1.37	271.7593	0.48		
96.0484	4.99	152.9756	1.88	273.7565	0.65		
97.0171	12.18	154.9804	1.51	276.8887	8.36		

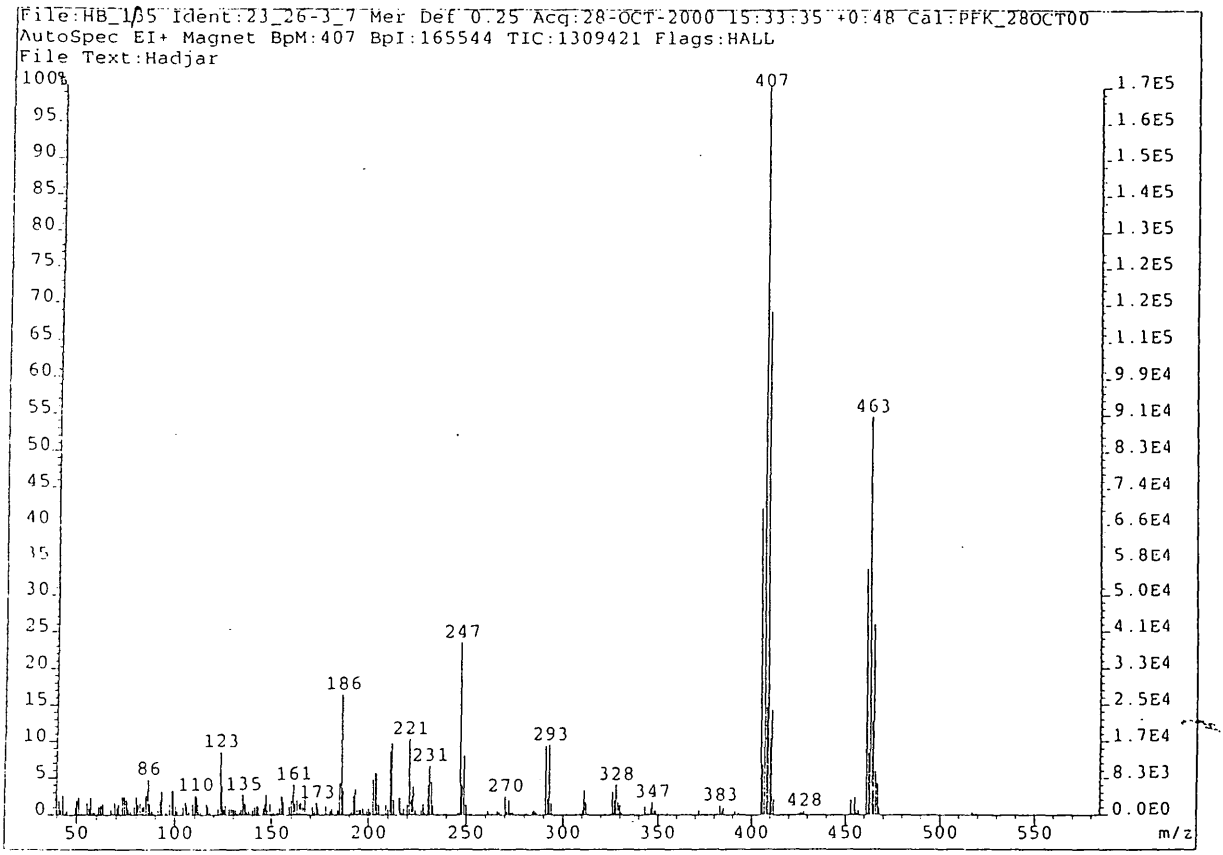
ABS MASS	REL (%) HEIGHT	ABS MASS	REL (%) HEIGHT	ABS MASS	REL (%) HEIGHT	ABS MASS	REL (%) HEIGHT
301.2041	0.63	354.7520	1.67	383.7364	3.27	390.8055	3.02
302.9253	0.59	369.7302	0.69	384.7339	0.81	391.8117	0.83
303.8133	0.50	370.9850	0.92	385.7276	0.48	401.8295	1.64
304.8433	1.00	371.8226	0.69	387.7318	0.37	402.8353	51.22
305.9733	0.54	372.7402	0.77	388.7359	0.52	403.8355	22.32
306.9152	1.41	373.7315	0.42	392.7333	0.33	404.8355	10.19
307.9545	2.51	374.7523	0.38	393.7276	0.64	405.8357	2.35
308.9240	1.21	375.7339	0.46	394.7365	1.09	406.8385	0.57
309.9509	1.56	376.9246	1.17	395.7323	0.56	485.8953	0.30
310.9234	2.21	377.8521	1.14	397.7182	0.57	500.9122	0.38
311.9240	1.14	378.9333	1.56	398.7393	1.65		
312.9239	1.32	379.8181	1.25	399.7290	0.68		

24. 3,5-difluoro-2,4,6-tris[2-(4-bromophenyl)ethynyl]pyridine (38)





25. 2,6-bis[2-(4-chlorophenyl)ethynyl]-4-bromo-3,5-difluoropyridine **(39)**

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MS_USER:SFE_DEFAULT.LIS  28-OCT-2000  15:35
Listing of raw data for :
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      data identifier 23_26-3_7 Mer Def 0.25
Axis display range        X_MASS (40.00, 584.29)
Normalising intensity  1.65544E+05
Data threshold 0.10% of normalising intensity
```
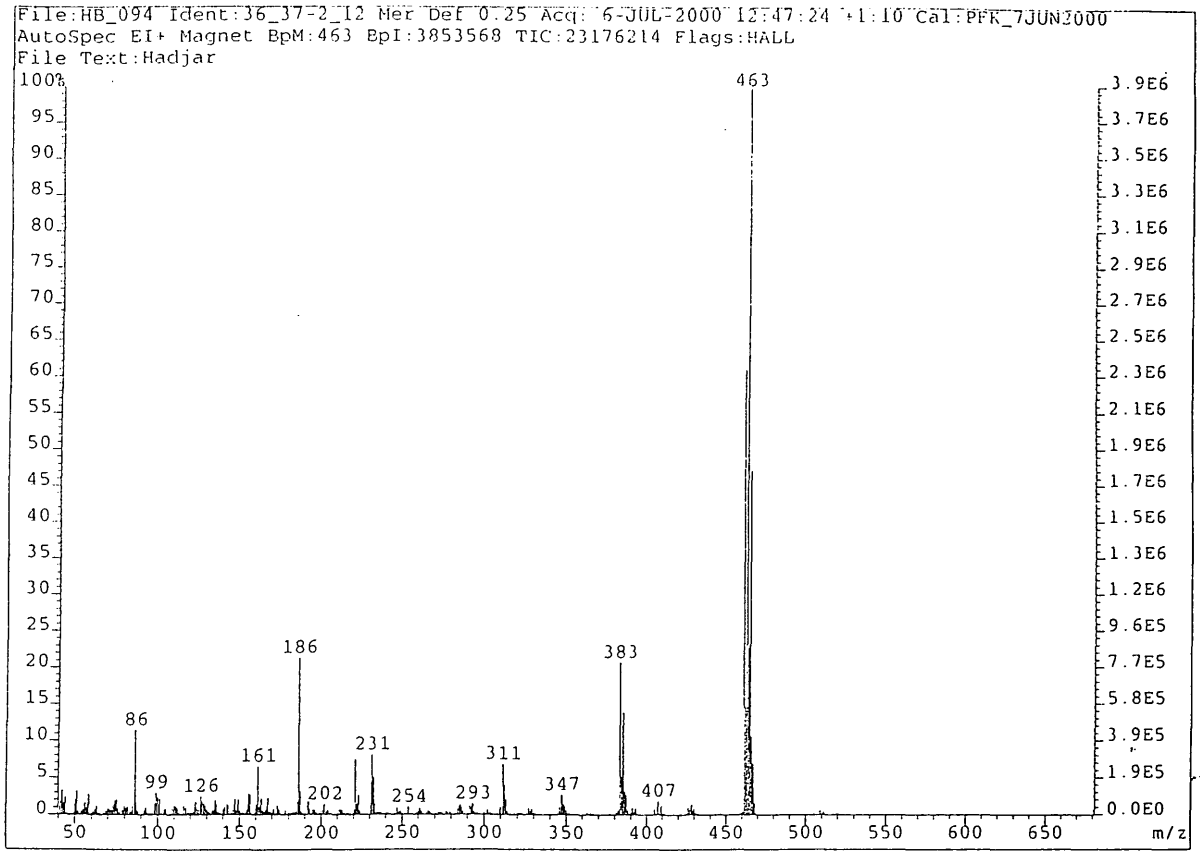

ABS MASS	REL (%) HEIGHT	ABS MASS	REL (%) HEIGHT	ABS MASS	REL (%) HEIGHT	ABS MASS	REL (%) HEIGHT	ABS MASS	REL (%) HEIGHT	ABS MASS	REL (%) HEIGHT	ABS MASS	REL (%) HEIGHT	ABS MASS	REL (%) HEIGHT
41.0373	1.93	117.0180	1.14	192.0426	2.57	309.0649	0.29	112.0186	1.43	186.0398	16.56	293.0026	9.58	517.1983	0.40
42.0420	0.77	118.0234	0.39	193.0427	3.57	310.1004	0.65	111.0215	0.55	187.0547	3.34	294.0044	1.60	519.1742	0.31
43.0464	2.68	121.0025	0.14	194.0453	0.70	311.1314	3.36	116.0110	1.48	190.9918	0.44	301.9954	0.22		
43.9879	0.24	122.0197	0.86	195.0423	0.76	312.1133	1.71								
45.0336	0.64	123.3756	8.68	196.0017	0.61	313.1227	0.25								
48.9842	1.06	124.2947	1.93	197.0106	1.00	324.9578	0.24								
50.0119	2.03	125.0140	0.34	198.0144	0.26	325.9749	3.14								
51.0192	2.40	126.0378	1.33	199.0229	0.58	326.9952	2.02								
52.0267	0.12	128.0134	0.84	200.0557	0.90	327.9772	4.16								
55.0515	1.64	129.0215	0.96	200.9989	0.47	328.9896	1.78								
56.0577	0.93	130.0201	0.87	202.2080	4.96	329.9756	1.39								
57.0686	2.47	131.9355	0.80	203.3677	5.77	330.9856	0.28								
58.0656	0.41	132.0093	0.17	204.2745	5.62	343.1780	1.16								
59.0486	0.34	133.0190	0.41	205.2200	1.48	344.1869	0.26								
61.0045	1.16	134.0167	0.78	209.0105	1.36	345.0628	0.24								
62.0119	1.33	135.0209	2.81	210.0114	0.82	346.0890	0.84								
63.0213	1.59	136.0189	1.61	211.0420	8.70	347.0904	1.75								
67.2127	0.70	137.0258	0.46	212.0490	9.86	348.0848	0.66								
68.0065	0.18	138.0187	0.58	213.0524	2.11	349.0851	0.60								
69.0535	1.64	140.0119	0.68	216.0186	2.35	355.1275	0.31								
70.0773	0.98	141.0229	1.21	217.0103	0.23	362.9743	0.13								
71.0858	1.48	142.0474	1.32	218.0145	0.88	371.9384	0.61								
73.0153	2.54	143.0311	1.26	220.0132	1.42	373.9334	0.19								
74.0108	2.51	145.4373	1.05	221.0202	10.38	381.0801	0.14								
75.0200	2.08	146.2654	1.48	222.0226	2.06	382.0492	0.13								
76.0224	0.78	147.0176	2.82	223.0196	3.82	383.0893	1.31								
77.0144	0.43	148.0252	0.71	224.0233	0.63	384.0847	0.50								
78.9905	1.13	149.0316	1.57	227.0091	0.67	385.0807	0.96								
79.9987	2.46	150.0129	0.28	228.0262	1.57	391.0561	0.49								
80.9504	1.39	150.9817	0.28	229.0154	0.36	393.0539	0.33								
81.9155	1.63	152.9988	0.36	230.4272	4.15	404.9231	42.35								
83.0870	1.02	154.0156	0.98	231.4120	6.72	405.9312	6.78								
83.9861	1.14	155.1045	2.53	232.3188	4.49	406.9202	100.00								
85.0361	2.68	155.9452	1.80	233.1834	1.26	407.9262	14.73								
86.9052	4.89	159.0202	1.19	239.9456	0.21	408.9176	69.02								
87.0183	1.56	160.0623	2.01	241.9561	0.13	409.9225	10.40								
88.0199	0.42	161.0176	4.19	246.0139	0.39	410.9137	14.38								
89.0044	0.16	162.0156	1.61	247.0317	23.54	411.9216	2.19								
91.0533	0.68	163.0140	2.05	248.0344	4.01	426.0360	0.42								
92.1557	1.91	164.0210	1.48	249.0240	8.13	427.0428	0.29								
93.0661	3.19	164.9621	1.74	250.0300	1.42	428.0402	0.57								
95.0875	0.11	165.0272	1.15	261.0677	0.60	429.1088	0.13								
97.0510	1.49	167.0242	2.25	266.0575	0.50	452.9206	2.01								
98.2915	3.32	168.0466	0.19	267.0766	0.42	453.9133	0.19								
99.1174	3.33	169.0422	0.24	270.0459	2.52	454.9294	2.43								
100.0163	1.46	171.0138	1.13	271.0425	0.52	455.9296	0.15								
101.0974	0.59	172.0245	0.57	272.0453	2.04	456.9163	0.71								
103.0508	0.13	173.2178	1.68	273.0667	0.35	461.0237	33.81								
104.0589	1.10	174.0447	0.88	274.0595	0.40	462.0139	8.40								
105.2129	1.79	178.0112	1.22	281.0519	0.21	463.0293	54.80								
106.0191	1.11	179.0310	0.13	284.0810	0.57	464.0314	12.88								
106.9573	0.56	180.0235	0.57	285.0830	0.75	465.0208	26.06								
108.9965	1.52	181.0317	0.89	286.0812	0.43	466.0306	5.96								
110.1691	2.72	184.9229	0.72	290.9998	9.45	467.0216	4.39								
111.0570	2.61	185.9296	4.38	292.0104	2.14	468.0348	1.05								

26. 2-(2-chlorophenyl)ethynyl]-4-bromo-3,5-difluoropyridine (40)

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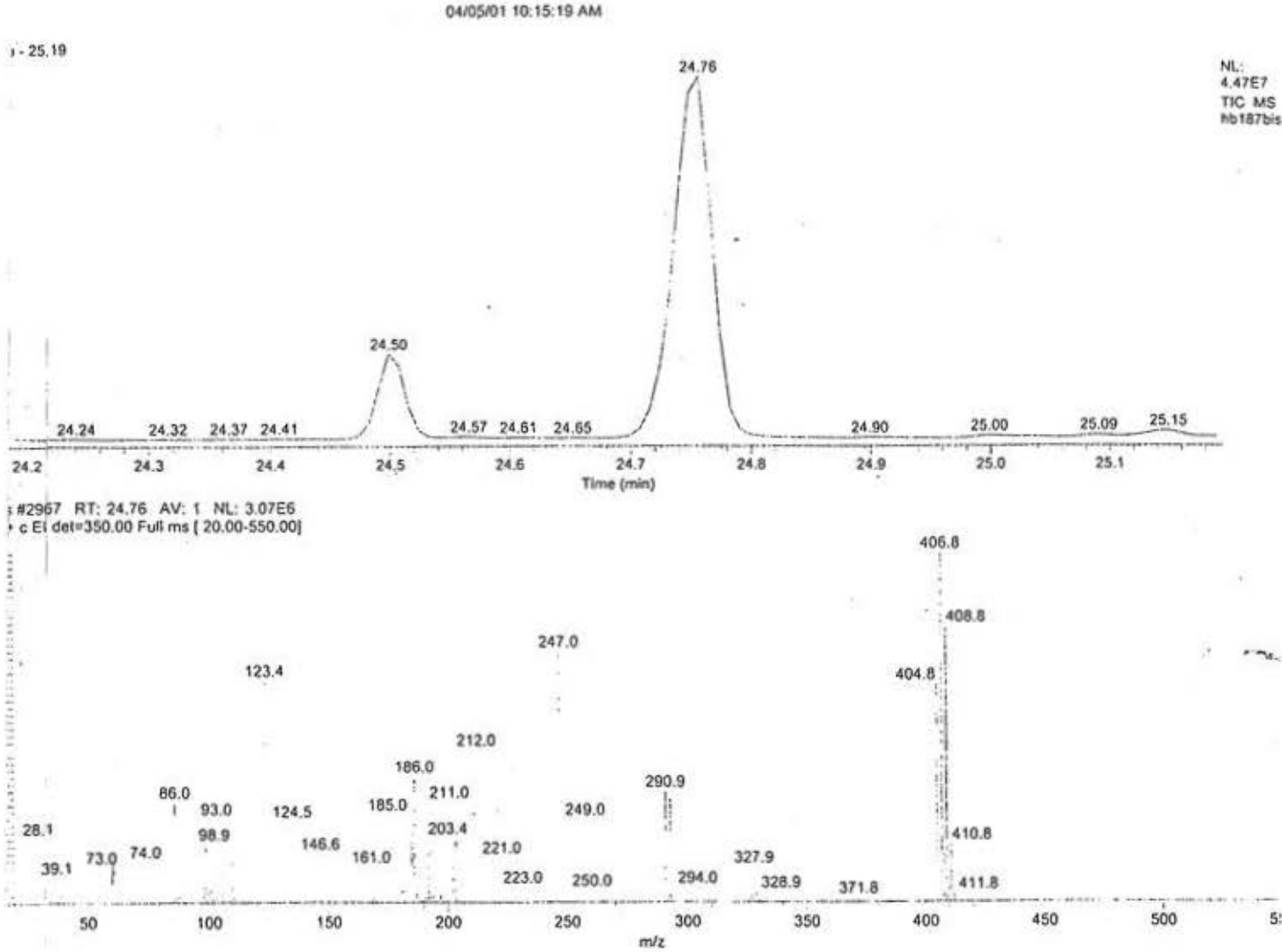
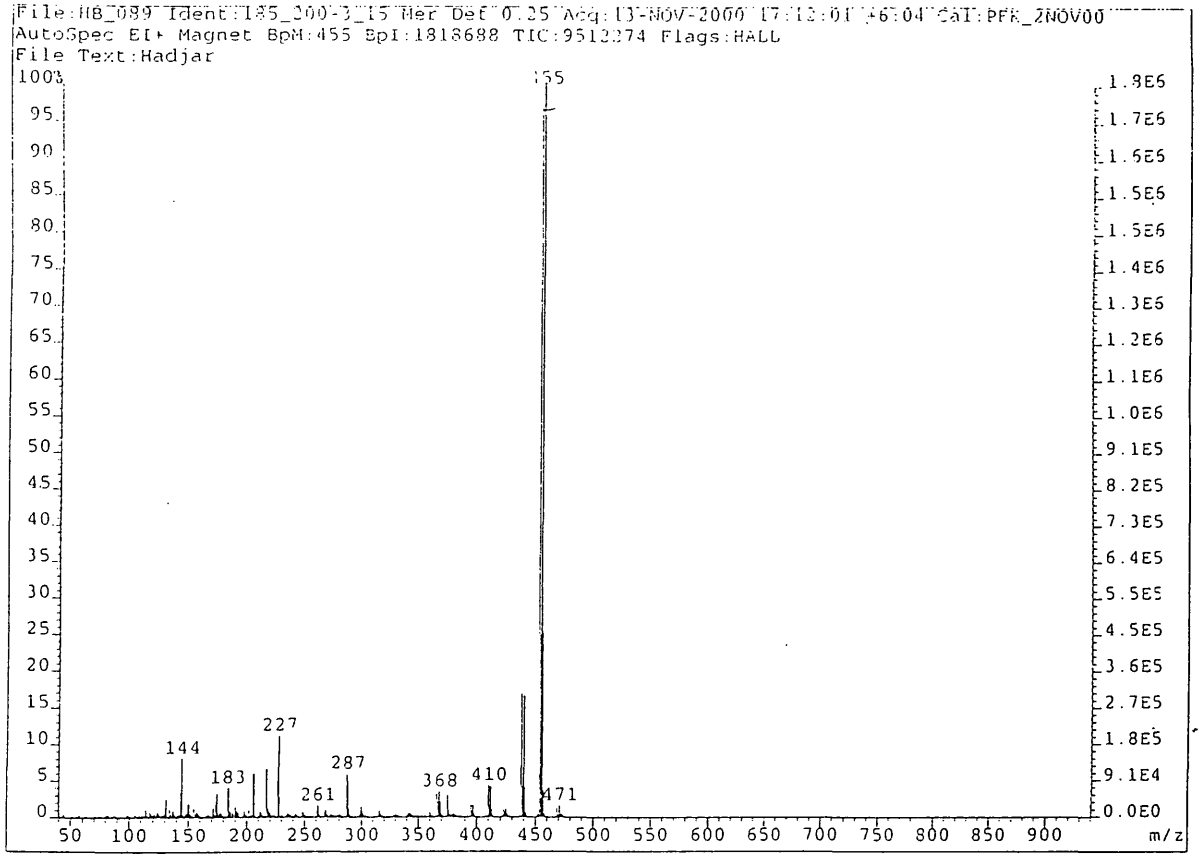
       data identifier 36_37-2_12 Mer Def 0.25
Axis display range       X_MASS (40.60, 680.81)
Normalising intensity  3.85357E+06
Data threshold 0.30% of normalising intensity
```

ABS MASS	REL (%) HEIGHT	ABS MASS	REL (%) HEIGHT	ABS MASS	REL (%) HEIGHT	ABS MASS	REL (%) HEIGHT
40.9703	1.82	118.0138	0.36	183.0297	0.43	294.0523	0.46
41.9744	3.35	118.9835	0.35	183.9702	0.35	299.9261	0.33
42.9797	1.61	120.0354	0.30	184.9768	1.83	301.9629	0.68
43.9631	2.40	120.9811	0.39	185.9827	21.38	309.0535	0.72
48.9318	0.36	121.9791	0.80	186.9884	3.15	310.0435	1.09
49.9575	2.02	123.0225	1.81	188.0266	0.41	311.0659	6.82
50.9653	3.22	124.0092	0.83	191.3779	1.92	312.0700	3.35
51.9701	0.46	124.9771	0.68	192.2614	1.73	313.0662	2.07
53.9824	0.51	125.9776	2.54	193.0875	0.75	314.0600	0.51
54.9947	0.81	126.8514	1.70	195.1036	0.70	327.0104	0.86
55.9995	1.61	127.9065	1.56	196.0787	0.61	328.0284	0.54
57.0102	0.99	129.0419	1.20	200.0880	0.58	329.0093	0.79
58.0205	2.84	130.1341	0.72	201.0269	0.58	345.0498	0.36
59.9451	0.33	131.0241	0.49	201.9738	1.42	346.0442	1.17
60.9494	0.61	132.1205	0.35	203.0908	0.41	347.0508	2.73
61.9626	0.80	133.0407	0.56	204.0254	0.63	348.0358	1.40
63.0189	1.23	133.9666	0.66	210.9973	0.67	349.0484	1.17
68.9856	0.58	134.9697	2.02	212.0387	0.69	350.0384	0.55
70.0252	0.84	135.9909	1.35	213.0528	0.61	362.9897	0.33
71.0302	0.73	137.0018	0.42	219.9638	0.77	381.0235	0.38
72.0141	0.62	138.0256	0.36	220.9680	7.49	382.0339	0.65
72.9526	1.25	139.9771	0.88	221.9747	1.47	383.0240	20.76
73.9631	1.94	141.0083	1.18	222.9638	2.67	384.0303	5.18
74.9683	2.08	142.1868	1.38	223.9736	0.51	385.0204	13.92
75.9708	0.86	143.0556	1.36	230.4147	4.34	386.0268	3.18
76.9811	0.35	145.1476	0.36	231.3624	8.09	387.0115	2.69
78.9172	0.70	146.0860	0.76	232.2557	5.02	388.0139	0.61
79.8970	1.22	146.9697	2.16	233.1464	1.40	390.0194	0.32
80.9264	0.95	148.0413	0.57	233.9941	0.33	391.0347	0.95
81.8938	1.11	148.9700	2.08	235.0038	0.41	392.0208	0.46
83.0365	0.35	150.0082	0.54	246.9980	0.94	393.0253	0.87
83.9720	0.53	151.0062	0.32	247.9992	0.42	404.9794	0.74
84.9713	1.18	154.1072	0.72	248.9965	0.45	407.0015	1.84
86.0539	11.52	155.1556	2.90	253.8814	1.06	408.9933	1.26
87.0068	1.39	156.0789	2.67	259.0153	0.38	426.0371	0.99
87.9624	0.52	157.0396	0.31	260.0158	0.50	427.0144	0.67
92.0166	0.64	158.9735	0.98	261.0177	0.90	428.0327	1.45
93.0016	0.97	160.0522	1.44	262.0154	0.53	429.0224	0.51
93.9923	0.31	160.9579	6.55	265.0081	0.36	430.0139	0.83
97.0022	0.75	161.9740	1.07	266.0281	0.64	459.9693	0.36
97.9854	1.56	162.9707	2.24	267.0352	0.47	460.9783	61.16
98.9680	2.97	164.0412	0.66	272.0182	0.42	461.9763	14.61
99.9965	2.37	164.9831	0.44	273.0374	0.33	462.9673	100.00
101.0750	2.11	165.9774	0.73	277.0533	0.44	463.9680	22.83
103.9804	0.70	166.9770	2.32	278.0577	0.33	464.9633	47.25
104.9938	0.85	167.9892	0.46	279.1230	0.39	465.9612	10.52
108.9661	0.91	169.0169	0.40	284.0379	0.87	466.9607	6.89
110.0088	1.31	170.9688	0.80	285.0447	1.32	467.9673	1.57
110.9930	1.15	172.0829	0.30	286.0361	1.01	509.0265	0.58
111.9919	0.91	173.1932	1.25	287.0288	0.45	511.0214	0.39
113.0375	0.35	174.1360	0.71	291.0513	1.21		
115.9673	1.28	177.9579	0.65	292.0448	0.91		
117.0021	0.96	182.1437	0.36	293.0521	1.48		

27. 4,6-dibromo-6-[2-(2-chlorophenyl)-1-ethynyl]-3,5-difluoropyridine (41)



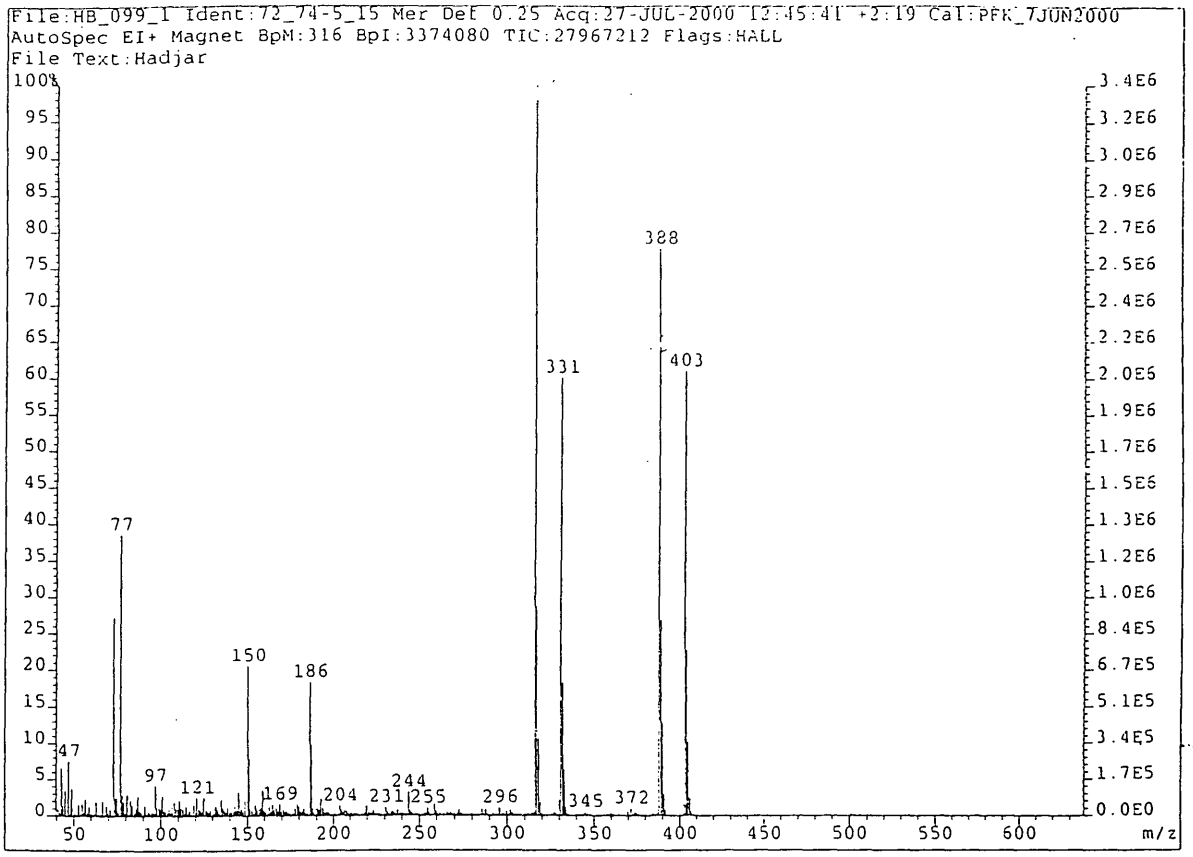
28. -{4-bromo-3, 5-difluoro-6- [2-(4- H methoxyphenyl) ethynyl](2-pyridyl)} ethynyl)-4-methoxybenzene (42)



MS_USER:SPE_DEFAULT.LIS 13-NOV-2000 17:21
Listing of raw data for -
data file HB_089
data identifier 185_200-3_15 Mer Def 0.25
Axis display range X_MASS 140.00, 940.00
Normalising intensity 1.813938E+06
Data threshold 0.30% of normalising intensity

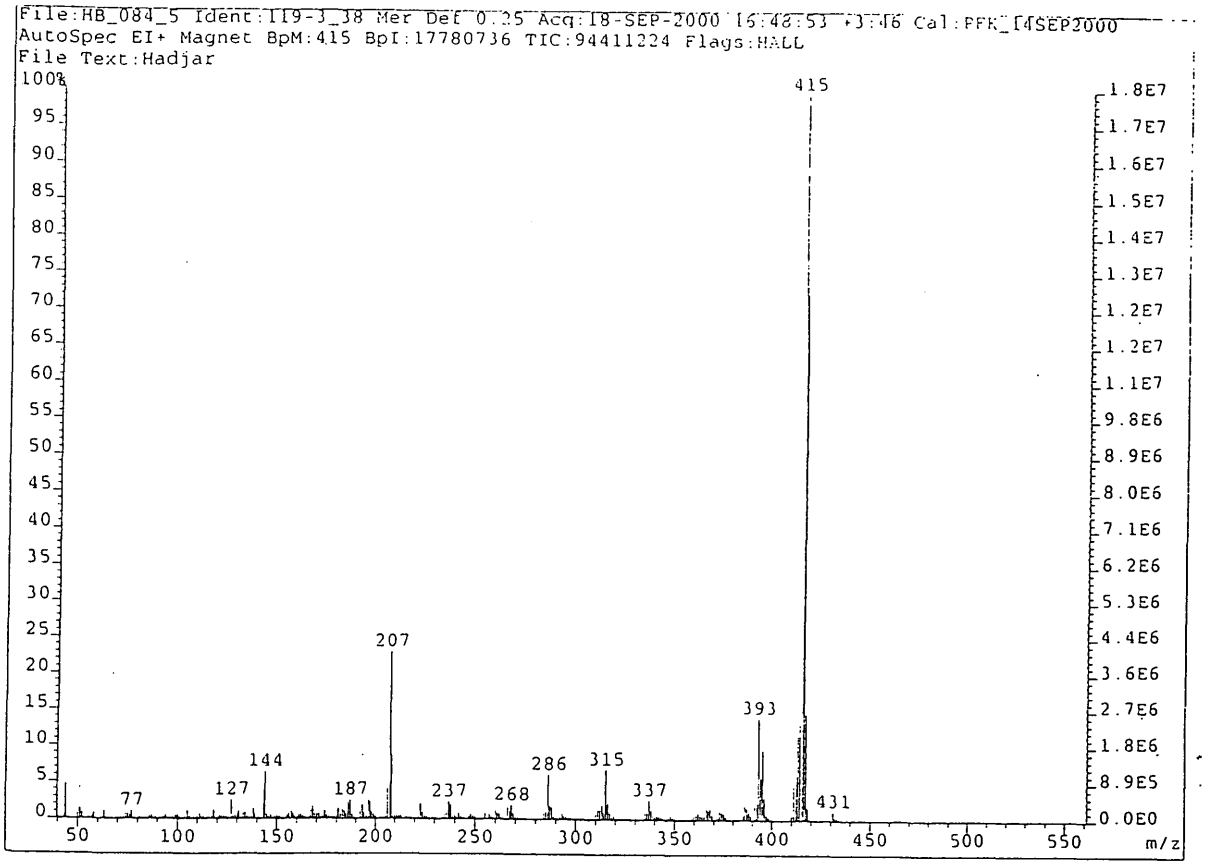
ABS MASS	REL (%) HEIGHT	ABS MASS	REL (%) HEIGHT	ABS MASS	REL (%) HEIGHT	ABS MASS	REL (%) HEIGHT
43.9905	0.49	154.8440	1.33	227.1631	11.27	366.7026	2.15
56.9424	0.41	155.9550	0.51	227.9362	2.63	367.6284	3.56
62.4055	0.31	156.9539	0.82	233.9458	0.42	368.7045	2.05
79.5303	0.36	158.0442	0.54	234.9130	0.67	369.7061	0.48
90.8442	0.35	165.1101	0.40	235.8426	0.47	373.8251	0.38
91.8040	0.38	165.9355	0.35	236.7926	0.33	374.8355	3.05
97.8683	0.33	166.8282	0.45	240.7878	0.32	375.8372	0.36
97.8915	0.54	170.1395	1.16	241.7950	0.51	376.9009	0.32
104.0003	0.32	171.1114	1.49	242.8029	0.41	377.7183	0.37
104.9574	0.45	171.8599	0.38	247.7865	0.78	378.7042	0.51
109.9619	0.31	172.8005	1.92	248.7934	0.72	379.7100	0.46
111.0259	0.35	173.8171	3.34	249.7957	0.30	380.7093	0.51
113.9025	1.08	174.8402	0.68	259.7852	0.82	393.7014	0.45
117.1039	0.88	176.0961	0.52	260.7844	4.68	394.7086	1.75
117.9791	0.49	177.0887	0.71	261.7927	1.43	395.7053	0.79
120.1621	0.31	177.9897	0.44	262.7927	0.37	396.7084	1.58
121.0202	0.57	183.0587	4.14	266.7883	0.69	397.7115	0.43
122.9992	0.70	184.0478	4.13	267.7964	0.96	409.7219	4.43
123.9497	0.74	184.9485	0.78	268.8050	0.99	410.7231	1.21
124.9969	0.30	185.8303	0.71	272.7930	0.42	411.7186	4.35
127.0371	0.41	187.0319	0.77	273.7898	0.36	412.7225	1.04
127.9804	0.38	187.9184	0.48	278.8205	0.37	421.7191	0.33
128.9191	0.59	189.1794	0.89	279.7933	0.39	422.6945	1.11
130.1402	1.37	190.0571	1.47	284.7984	0.35	423.7118	0.67
130.9244	2.53	190.9286	0.87	285.7859	1.56	424.6977	1.16
133.1511	0.31	191.8908	0.72	286.7947	6.06	425.7118	0.46
134.0052	1.21	192.8709	0.61	287.8027	5.02	437.7281	16.98
134.9110	0.47	196.9999	0.49	288.8047	1.13	438.7336	4.17
136.1769	0.70	197.8953	0.95	297.7856	0.55	439.7287	16.67
137.0322	0.96	198.8463	0.37	298.7904	0.87	440.7307	4.10
138.0255	0.37	201.7886	1.07	299.7948	1.50	441.7400	0.59
140.1576	0.47	204.8643	6.04	300.8044	0.70	451.7391	0.39
141.0167	0.41	205.8579	5.04	301.8027	0.30	452.7492	97.20
141.9793	0.49	210.0394	0.33	315.7907	0.94	453.7522	25.05
143.1436	1.32	211.0577	0.80	316.7797	0.40	454.7452	100.00
143.9252	8.20	211.9976	0.72	327.7437	0.42	455.7494	25.15
144.9414	0.32	212.8684	0.31	329.7165	0.45	456.7546	3.62
146.8185	0.64	216.8028	5.75	339.6996	0.38	457.7582	0.49
147.8661	0.76	217.8557	1.23	340.6980	0.59	468.7228	1.24
149.0677	1.84	218.9219	0.72	341.6915	0.50	469.7314	0.36
150.0263	1.99	219.8654	0.57	342.6942	0.59	470.7220	1.66
151.0136	0.51	222.7897	0.33	359.8022	0.70	471.7320	0.46
151.9761	0.31	226.2642	8.94	365.6952	3.22	472.7259	0.49

29. 4-[4,6-bis (3,3-dimethyl-3-silabut-1-ynyl)-3,5-difluoro (2-pyridyl)]-2,2-dimethyl-2-silabut-3-yne (43)



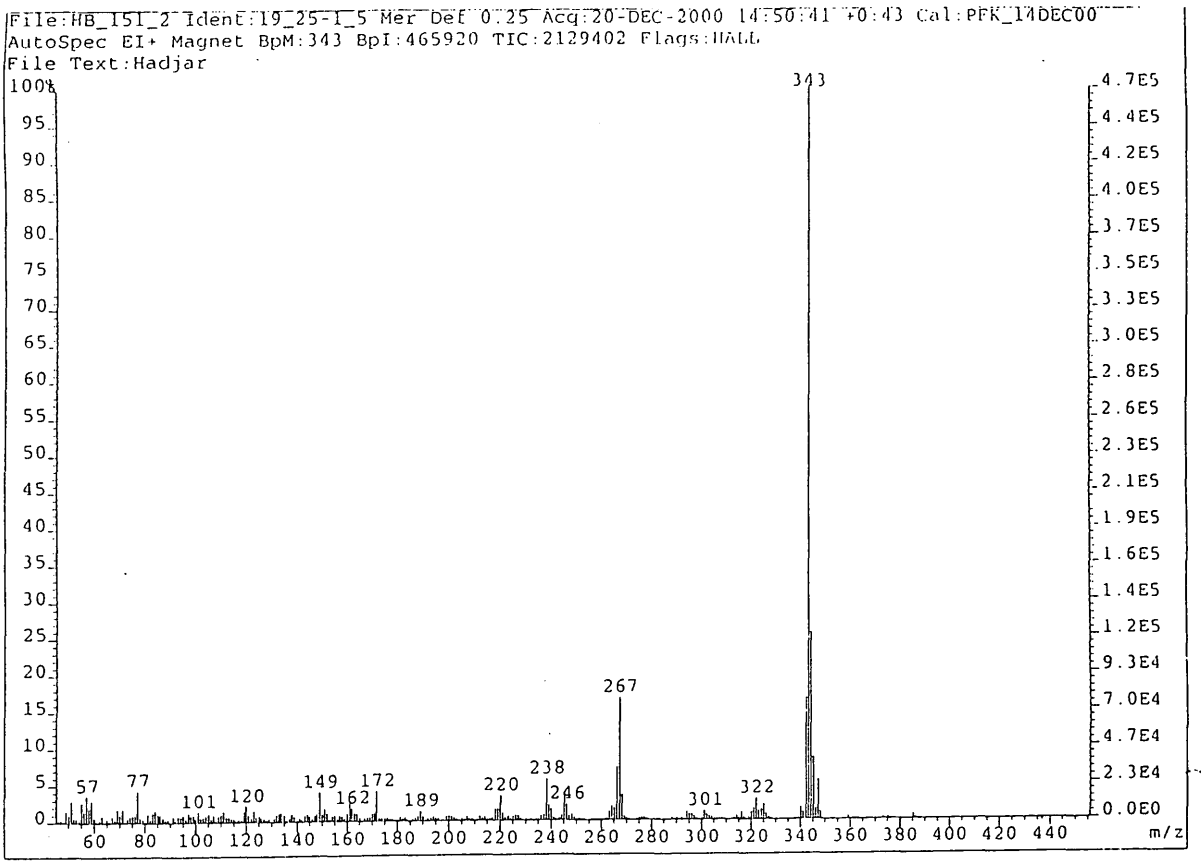
ABS MASS	REL (%) HEIGHT	ABS MASS	REL (%) HEIGHT	ABS MASS	REL (%) HEIGHT	ABS MASS	REL (%) HEIGHT
40.8929	1.04	113.8980	0.52	180.7563	0.65	261.7252	0.43
41.8778	0.54	114.8176	1.46	181.7595	0.61	265.7238	0.58
42.8655	6.67	115.8220	0.46	182.7556	1.06	267.7646	0.57
43.8489	1.49	116.8024	0.79	183.7602	0.40	268.7615	0.34
44.8650	3.63	117.8217	0.35	184.8288	0.37	269.7256	0.48
46.8243	7.65	119.0917	1.60	186.2535	18.46	271.7445	0.60
47.8229	0.43	119.9070	0.55	186.9081	9.78	272.7618	0.92
48.8378	3.77	120.8245	2.59	187.8224	1.15	273.7462	0.46
49.8526	0.43	121.8439	1.05	188.7483	0.38	279.7385	0.41
50.8675	0.57	122.8418	0.88	189.7455	1.11	280.7474	0.30
52.8410	1.69	123.8458	0.61	190.7515	1.14	283.7289	0.34
53.8484	0.50	124.7893	2.56	191.7552	0.93	285.7265	0.94
54.8777	1.83	125.8102	0.83	192.7779	2.42	286.7262	0.30
55.8900	0.63	126.8198	0.79	193.7676	1.18	287.7345	0.85
56.9053	2.43	127.9454	0.59	194.7428	0.60	291.7651	0.52
57.8721	0.64	128.7876	0.87	195.7469	0.49	293.7467	0.34
58.8687	1.34	129.8372	0.41	196.7374	0.69	295.7565	1.13
59.8606	0.42	130.7961	1.13	197.7293	0.47	296.7532	0.37
61.8419	0.52	131.7844	1.42	199.7502	0.35	297.7370	0.43
62.8477	2.02	132.7971	0.90	200.7693	0.41	299.7293	0.70
65.8243	0.40	133.8080	0.44	202.7495	0.39	300.7312	0.30
66.8346	2.13	134.9875	2.30	203.7414	1.44	301.7421	0.87
67.8538	0.48	135.8344	1.13	204.7419	0.89	302.7500	0.46
68.8688	1.51	136.8255	0.78	205.7479	0.60	309.7587	0.38
69.8860	0.62	137.8519	0.56	206.7542	0.92	311.7765	0.47
70.9154	1.08	138.7792	1.19	207.7436	0.76	312.8007	0.33
72.8700	27.40	139.8314	0.53	208.7452	0.45	313.7661	0.57
73.8666	2.58	140.8072	0.76	209.7476	0.42	314.7605	0.68
74.8514	2.55	141.9534	0.70	210.7421	0.55	315.7736	100.00
75.8493	0.58	142.9706	1.36	211.7362	0.49	316.7755	28.82
76.8402	38.66	143.8196	0.82	212.7461	0.38	317.7742	10.72
77.8404	2.88	144.7959	3.26	213.7448	0.52	318.7756	1.92
78.8310	1.99	145.7891	0.72	216.7367	0.46	319.7732	0.42
79.8129	0.56	146.7696	1.07	217.7469	0.72	325.7949	0.34
80.8234	2.92	147.7969	0.66	218.7525	0.57	326.8056	0.60
81.8707	0.52	148.7759	2.17	219.7567	1.37	327.7719	0.39
82.8614	2.18	150.2393	20.70	220.7494	0.51	329.7774	2.25
83.8482	1.41	150.8978	7.90	221.7375	0.44	330.7903	60.30
84.8757	1.12	151.8221	0.97	222.7426	0.38	331.7893	18.33
85.8380	1.15	152.7909	0.83	223.7310	0.84	332.7890	6.34
86.8210	2.80	153.7843	0.56	224.7521	0.40	333.7926	1.26
87.8223	0.81	154.7878	1.55	225.7359	0.34	344.8027	0.57
88.8347	0.56	155.8076	0.92	227.7453	0.32	357.7377	0.38
89.8524	0.32	156.8449	1.03	230.7420	1.18	359.7549	0.53
90.8297	1.47	157.8841	1.26	231.7431	0.65	369.6789	0.64
91.8192	0.41	158.7564	3.60	232.7470	0.39	371.7110	1.06
92.8179	0.74	159.7513	0.76	233.7584	0.64	372.7346	0.38
93.8319	0.44	160.7700	0.57	234.7574	0.71	373.7826	0.60
94.8547	0.75	161.7923	0.48	235.7326	0.47	374.7978	0.45
95.9040	0.53	162.7788	1.26	236.7316	0.32	384.7286	0.36
96.8434	4.25	163.8422	0.76	237.7427	0.85	385.7736	0.35
97.8237	1.18	164.8064	1.57	238.7517	0.53	386.7195	0.50
98.8295	1.24	165.7774	0.80	239.7458	0.43	387.8053	77.95
99.9585	1.05	166.7592	1.10	240.7568	0.38	388.8090	26.93
100.8121	2.81	167.7606	0.73	241.7382	0.36	389.8061	12.78

30. 3,5-difluoro-2,4,6-tris(2-phenylethynyl)pyridine (45)



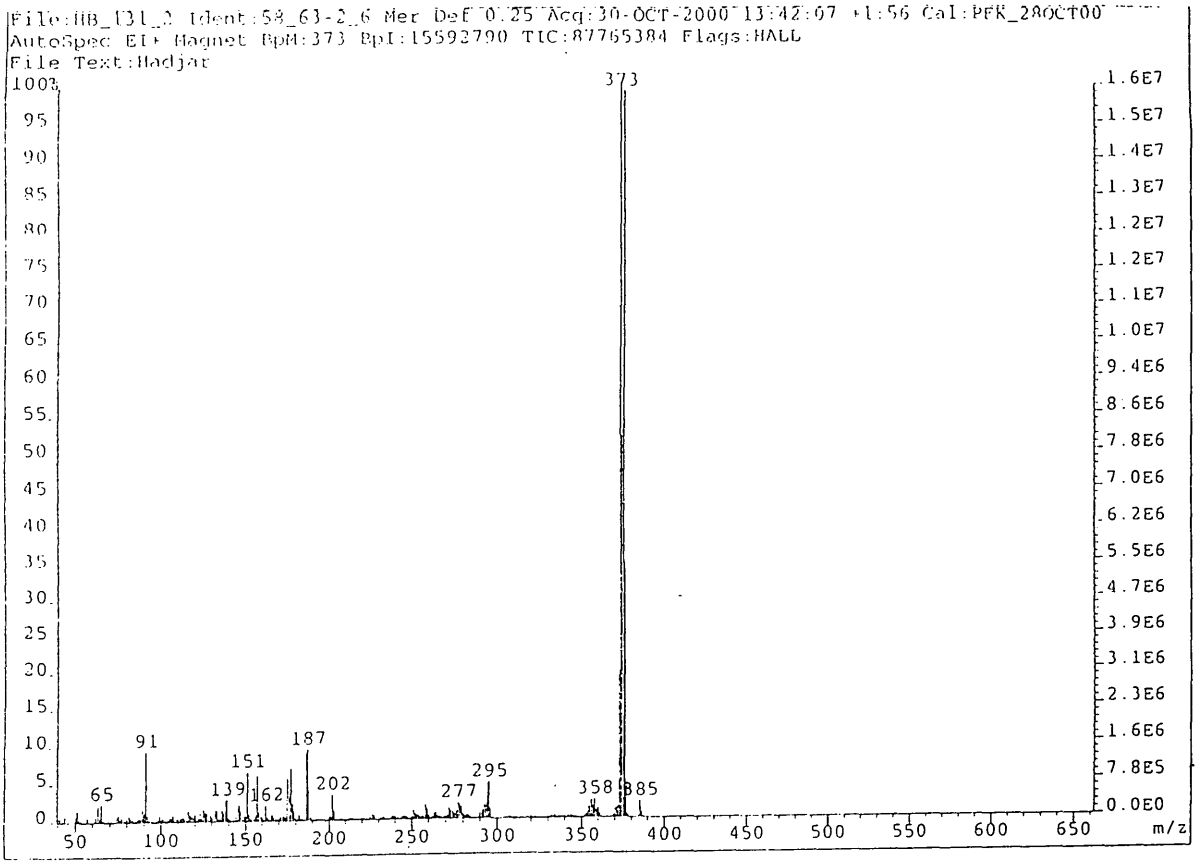
ABS MASS	REL (%) HEIGHT	ABS MASS	REL (%) HEIGHT	ABS MASS	REL (%) HEIGHT	ABS MASS	REL (%) HEIGHT
43.0212	0.52	149.0740	0.53	229.0110	0.46	336.0053	1.01
43.9740	1.69	150.0811	0.57	233.9917	0.33	337.0060	2.68
49.9972	0.90	151.0989	0.43	234.9992	0.68	338.0099	1.35
51.0059	1.43	154.1826	0.36	236.0024	1.23	339.0143	0.61
52.0149	0.88	155.1463	0.82	237.0279	2.44	340.0105	0.53
57.0179	0.51	156.1544	0.87	238.0137	1.99	341.0167	0.58
58.0425	0.85	157.2889	1.09	238.9950	0.43	342.0073	0.57
63.0078	1.09	158.0991	0.74	239.9955	0.58	343.0158	0.42
73.0504	0.32	159.1150	0.44	240.9965	0.42	344.0204	0.31
73.9950	0.83	160.1784	0.39	242.0122	0.84	346.0084	0.34
74.9989	0.83	161.1292	0.74	243.0210	0.39	347.0127	0.45
76.0087	0.65	162.0877	0.66	244.0199	0.30	348.0161	0.70
77.0166	1.15	163.1413	0.43	246.9955	0.59	349.0174	0.46
80.9997	0.40	164.1932	0.35	248.0135	0.76	350.0293	0.33
85.0196	0.34	166.1606	0.35	249.0087	0.53	351.0117	0.33
86.0246	0.62	167.1071	1.19	250.0125	0.41	359.0019	0.34
87.0013	0.61	168.0944	1.75	255.0061	0.84	360.0143	0.64
89.0201	0.35	169.1222	0.71	256.0101	0.31	361.0154	0.83
91.9956	0.41	170.1561	0.77	257.0474	0.73	362.0194	1.06
93.0532	0.34	171.1509	0.78	258.0028	0.41	363.0239	0.64
94.0082	0.64	172.1838	0.42	258.9978	0.35	364.0232	0.66
97.9896	0.59	173.2142	0.63	260.0049	1.18	365.0154	0.61
99.0075	0.69	174.1087	1.12	261.0240	0.86	366.0267	1.52
100.0094	0.61	175.0745	0.59	262.0271	0.81	367.0237	1.33
103.9901	0.32	176.1560	0.37	263.0045	0.30	368.0338	1.61
105.0223	1.14	177.1970	0.40	264.0273	0.31	369.0293	0.75
106.0549	0.42	178.1398	0.33	265.0045	0.31	370.0245	0.34
110.0119	0.40	179.1566	0.64	266.0064	1.77	371.0120	0.33
111.1183	0.72	180.1998	1.23	267.0114	1.26	372.0049	0.51
112.0439	0.37	181.1541	1.48	268.0225	2.01	373.0210	1.27
113.0343	0.40	182.1705	0.72	269.0168	0.86	374.0178	1.09
115.0250	0.34	183.1859	1.31	270.0378	0.32	375.0242	0.98
115.9998	0.40	184.1479	1.10	271.0187	0.33	376.0285	0.49
117.0738	0.52	185.1039	0.77	273.0138	0.35	384.0089	0.65
118.1021	1.29	186.0776	2.40	283.9936	0.91	385.0055	0.92
120.1470	0.34	187.0635	2.62	285.0008	1.05	386.0167	2.01
121.0320	0.62	188.0364	0.69	286.0065	6.19	387.0179	1.65
122.0061	0.46	192.1752	1.09	287.0068	1.88	388.0160	1.21
123.0652	0.65	193.1832	2.01	288.0190	1.73	389.0202	0.77
124.0880	0.42	194.1241	0.88	289.0199	0.48	390.0127	0.40
125.0550	0.30	195.3940	0.53	290.0057	0.33	391.0074	2.24
126.0533	0.32	196.3157	2.57	291.0023	0.41	392.0122	2.44
127.0261	2.62	197.2127	2.31	292.0104	0.57	392.9647	14.06
128.0681	0.57	198.0686	0.96	293.0095	0.85	393.9974	5.91
129.0961	0.69	199.1316	0.72	294.0135	0.51	394.9377	9.63
130.1178	0.92	200.0410	0.45	295.0233	0.44	395.9568	3.17
131.0696	1.16	205.2547	1.48	298.0245	0.30	397.0051	0.79
133.1301	0.83	206.2555	4.22	308.9935	0.34	398.0172	0.54
134.0649	1.00	207.4727	23.07	309.9984	0.83	408.9943	0.57
135.0532	0.53	208.0821	8.70	311.0013	1.37	410.0149	0.72
136.1361	0.36	209.0191	0.43	312.0097	1.38	411.0225	4.69
137.0647	0.45	210.0059	0.49	313.0190	2.05	412.0382	6.15
138.2605	1.43	211.0093	0.63	314.0196	1.16	413.0442	11.65
138.8447	0.68	212.0090	0.50	315.0263	6.90	414.0439	13.27
141.0832	0.41	213.0272	0.60	315.9811	2.21	415.1425	100.00

31. 3,5-difluoro (2,4,6-triphenyl)pyridine (46)



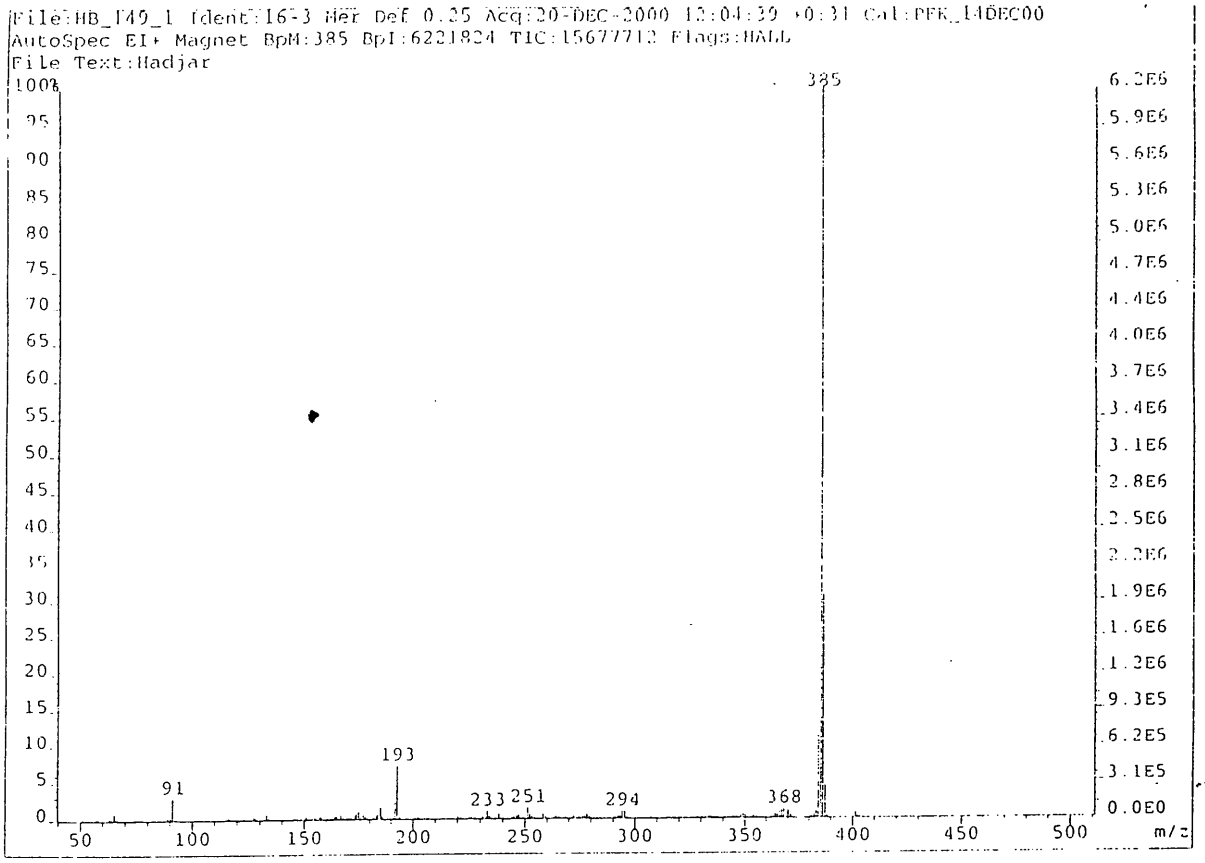
ABS MASS	REL. (%) HEIGHT	ABS MASS	REL. (%) HEIGHT	ABS MASS	REL. (%) HEIGHT	ABS MASS	REL. (%) HEIGHT
46.0126	0.37	110.0015	1.10	170.9740	1.23	248.1648	0.87
46.9815	0.38	111.0584	1.51	171.7509	4.12	249.1607	0.46
49.0012	1.64	112.1248	0.66	172.8265	0.47	250.1339	0.31
50.0330	1.10	113.0826	0.66	173.9161	0.44	251.1319	0.33
51.0380	2.98	114.0156	0.54	175.1081	0.44	262.1478	0.35
52.0489	0.66	115.1045	0.47	176.1228	0.43	263.1408	1.19
53.0597	0.60	117.0810	0.39	177.1513	0.36	264.1460	1.93
54.0676	0.38	118.0827	0.43	178.1437	0.36	265.1535	1.68
55.0787	2.74	119.0487	1.45	181.1107	0.55	266.1638	7.28
56.0870	1.62	120.0050	2.21	182.1194	0.31	267.1715	16.72
57.0955	3.65	120.9749	0.96	183.1325	0.44	268.1718	3.44
58.0844	2.01	122.0416	0.57	186.0927	0.36	269.1670	0.58
59.0780	3.02	122.9994	1.57	187.1082	0.54	270.1653	0.35
60.0532	0.71	123.9430	0.67	188.1094	0.71	275.1610	0.37
62.0453	0.43	125.0961	0.89	189.1214	1.36	276.1692	0.54
63.0544	0.91	125.9703	0.64	190.1176	0.65	277.1611	0.38
65.0710	0.50	127.1001	0.52	192.1047	0.40	283.1707	0.30
67.0892	0.91	128.0721	0.37	193.1024	0.53	288.1540	0.37
68.0956	0.49	129.0635	0.43	194.1193	0.66	290.1704	0.35
69.0988	1.81	131.0842	0.56	195.1247	0.39	292.1670	0.32
70.1074	1.05	131.9832	1.05	196.1506	0.36	294.1718	1.14
71.1229	1.84	132.9703	1.19	199.1157	0.70	295.1759	0.85
73.0749	0.66	133.8116	1.25	200.1211	0.71	296.1816	0.89
74.0562	0.84	135.0526	0.97	201.1273	0.65	297.1836	0.55
75.0609	0.96	137.1110	0.57	202.1401	0.48	301.1744	1.26
76.0693	1.08	137.9803	1.06	205.1365	0.41	302.1756	0.83
77.0799	4.35	138.9147	0.74	207.1277	0.70	303.1802	0.69
78.0843	0.68	140.9759	0.52	208.1349	0.33	304.1918	0.45
79.0956	0.54	141.9172	0.36	209.1429	0.35	314.1657	0.57
81.1024	1.23	143.0810	0.84	212.1165	0.63	315.1722	0.31
82.1215	0.59	144.0826	1.05	213.1174	0.41	316.1738	1.09
83.1293	1.37	144.9850	0.80	214.1298	0.58	317.1907	0.38
84.0442	1.70	146.0129	0.48	216.1291	0.36	319.1633	0.56
85.1441	1.17	147.0358	0.94	217.1221	0.44	320.1766	1.14
86.0367	1.07	147.9189	1.16	218.1279	1.67	321.1866	1.62
87.0718	0.69	149.0423	4.09	219.1360	1.67	322.1898	2.92
88.0581	0.40	150.0408	1.03	220.1430	3.43	323.1915	1.12
89.0878	0.48	150.9712	1.71	221.1373	1.03	324.2130	1.49
91.0996	0.89	151.8532	1.16	222.1455	0.47	325.2192	2.20
93.0846	0.88	153.9793	0.75	223.1680	0.61	326.2056	0.88
94.0453	0.83	155.0373	0.86	225.1361	0.61	327.1839	0.38
95.1010	1.07	156.0942	0.42	226.1348	0.78	339.1777	0.30
96.1366	0.51	157.0294	0.86	227.1416	0.74	340.1911	1.66
97.1231	1.30	157.9514	0.74	228.1560	0.35	341.1952	1.02
98.1170	0.89	158.9277	0.46	236.1222	0.68	342.2129	16.59
99.0975	0.97	160.0145	1.18	237.1273	0.78	343.2158	100.00
100.0075	0.49	160.9682	2.55	238.1363	5.66	344.2176	25.52
101.1001	1.47	161.8651	1.83	239.1417	2.12	345.1382	8.51
102.0974	0.62	163.0041	1.16	240.1472	1.61	346.1125	1.48
103.0902	0.74	163.9551	1.10	241.1506	0.41	347.0903	5.28
104.0829	0.90	165.1297	0.47	243.1279	0.42	348.0969	1.10
105.0970	1.21	167.1045	0.49	244.1361	0.78	359.1840	0.45
106.0697	0.52	168.1033	0.57	245.1430	3.37	373.1330	0.14
107.0296	0.96	169.1101	0.62	246.1485	2.24	375.1247	0.34
109.1196	0.91	170.0136	1.17	247.1472	0.71	385.2683	0.71

32. 2,6-bis(4-methylphenyl)-4-bromo-3,5-difluoropyridine (47)



ABS MASS	REL (%) HEIGHT	ABS MASS	REL (%) HEIGHT	ABS MASS	REL (%) HEIGHT	ABS MASS	REL (%) HEIGHT
41.0438	0.57	122.1191	0.51	178.1110	2.33	272.0708	1.49
43.9917	0.86	123.0503	1.18	178.9559	1.24	273.0777	1.15
50.0221	0.74	124.0535	1.00	179.9244	0.48	274.0945	1.08
51.0281	1.57	125.0690	1.72	182.0589	0.78	275.0732	0.74
52.0355	0.48	126.0462	1.31	183.0829	0.36	276.0514	1.16
53.0442	0.32	127.0301	1.22	184.1524	0.71	277.0583	2.17
57.0331	0.67	128.1928	0.45	185.3720	3.42	278.0600	1.98
62.0242	0.73	129.1900	0.90	186.2274	9.05	279.0518	1.67
63.0314	2.18	129.9042	0.58	187.0203	9.58	280.0292	0.71
64.0363	0.59	131.0970	1.13	187.8119	3.86	280.9743	0.48
65.0482	2.41	132.0814	1.58	188.9856	0.46	281.9791	0.60
74.0298	0.71	133.0473	1.50	200.0485	0.57	282.9827	0.50
75.0330	0.99	134.0531	0.48	201.0514	0.56	283.9871	0.35
76.0303	0.40	135.1767	0.66	202.0607	3.52	290.0542	0.76
77.0512	0.61	136.1169	1.62	203.0728	1.28	291.0609	1.18
78.0550	0.31	137.0732	1.11	213.0588	0.34	292.0693	1.89
79.9685	0.57	138.2960	2.80	225.0475	0.44	293.0813	1.87
81.0131	0.88	138.9714	2.94	226.0658	0.80	294.0940	4.76
81.9563	0.49	139.9092	0.46	227.0763	0.61	295.0786	4.96
83.0430	0.38	144.1313	0.67	231.0554	0.32	295.9951	1.31
86.0371	0.51	145.1636	1.81	232.0658	0.35	317.9531	0.31
87.0579	0.79	146.1448	2.22	233.0873	0.44	319.9531	0.35
88.0324	0.47	146.9978	1.32	238.0584	0.52	331.9530	0.35
89.0458	1.73	147.9930	0.37	239.0622	0.49	333.9633	0.39
90.0669	1.21	149.0041	0.74	240.0769	0.50	341.9287	0.35
91.0627	9.50	150.0368	0.78	244.0534	0.45	343.9295	0.44
92.0532	0.94	151.0492	6.69	245.0646	0.48	344.9361	0.30
93.0534	0.35	152.0987	0.96	246.0731	0.51	351.9518	0.41
98.0203	0.44	153.0780	0.46	247.0898	0.48	352.9498	0.62
99.0436	0.90	155.0261	0.47	250.0459	0.44	353.9640	1.49
100.0660	0.39	156.0338	0.86	251.0690	1.28	354.9317	1.56
101.0391	0.61	157.0587	6.23	252.0681	0.83	355.9471	2.43
102.0624	0.36	158.0522	1.23	253.0657	0.61	356.9193	1.65
104.0206	0.37	159.1027	0.61	254.0815	0.57	357.9334	2.50
105.0394	0.72	160.0456	0.50	255.0437	0.40	358.9240	1.04
106.0741	0.51	162.0188	2.15	256.0323	0.39	359.9351	1.31
107.0382	0.96	163.0512	0.50	257.0213	0.47	360.9232	0.54
109.0809	0.45	164.1193	0.37	258.0786	1.94	368.9275	0.45
110.0474	0.43	165.2598	0.72	259.0904	1.39	369.9358	1.32
111.0452	0.61	166.0816	0.86	260.0819	0.49	370.8795	1.43
112.1175	0.57	166.8364	0.47	262.0343	0.33	371.9627	19.94
113.1051	0.67	169.0851	0.31	263.0529	0.82	373.0451	100.00
113.9694	0.37	171.0991	0.55	264.0700	0.90	373.9689	52.30
115.1290	0.43	172.1279	0.67	265.0700	0.50	375.0489	99.56
116.0748	1.54	173.0411	0.70	266.0706	0.35	375.9660	34.93
117.0425	0.93	173.9694	0.58	267.0605	0.34	376.9231	4.74
118.0771	0.68	175.0461	5.80	269.0164	0.33	377.8961	0.41
119.1160	0.63	176.0677	3.20	270.0501	0.37	385.1917	2.26
120.0555	1.02	177.0863	7.12	271.0624	0.59	386.1473	0.76

33. 3,5-difluoro-2,4,6-tris (4-methylphenyl)pyridine (48)

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! MS_USER:SPE_DEFAULT.LIS  20-DEC-2000  12:06
! Listing of raw data for :
!       Data file HB_149_1
!       Data identifier 16-3 Mer Def 0.25
! Axis display range        X_MASS (40.00, 511.00)
! Normalising intensity  6.22182E+06
! Data threshold 0.30% of normalising intensity
```
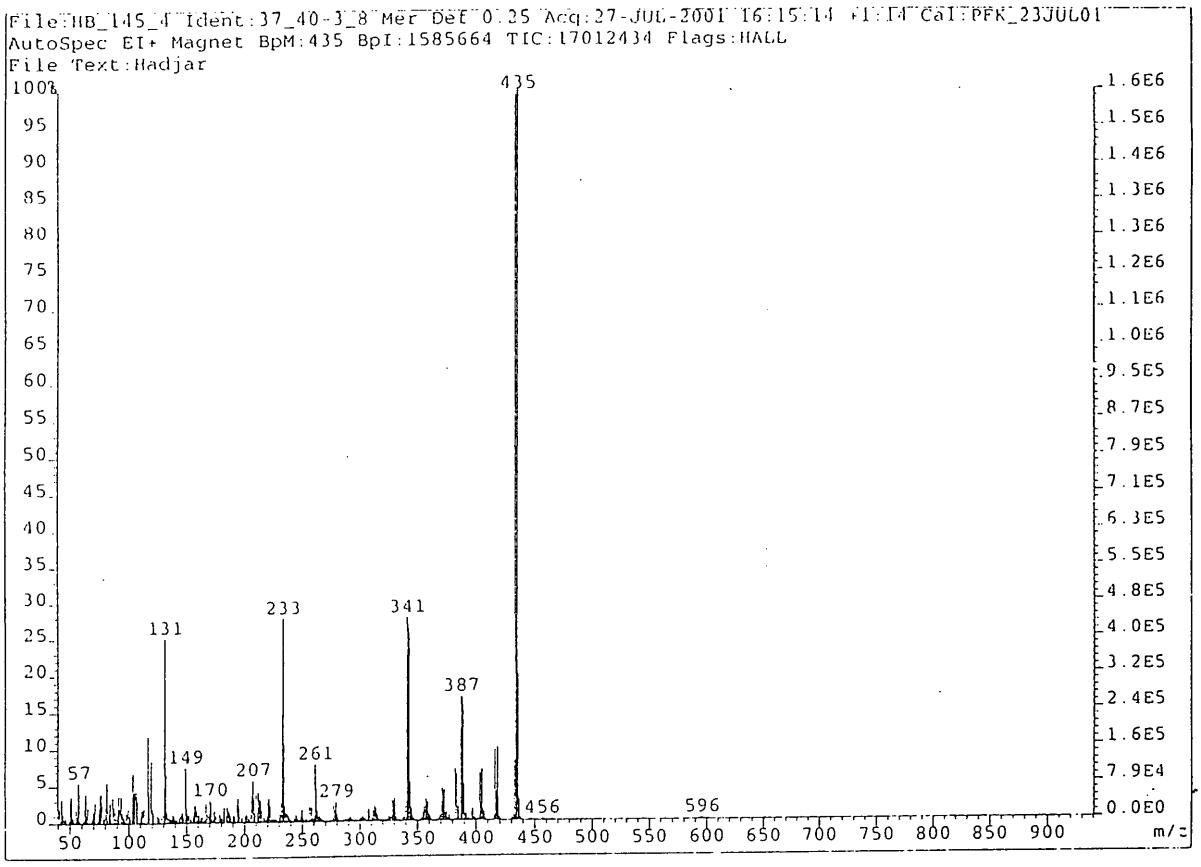
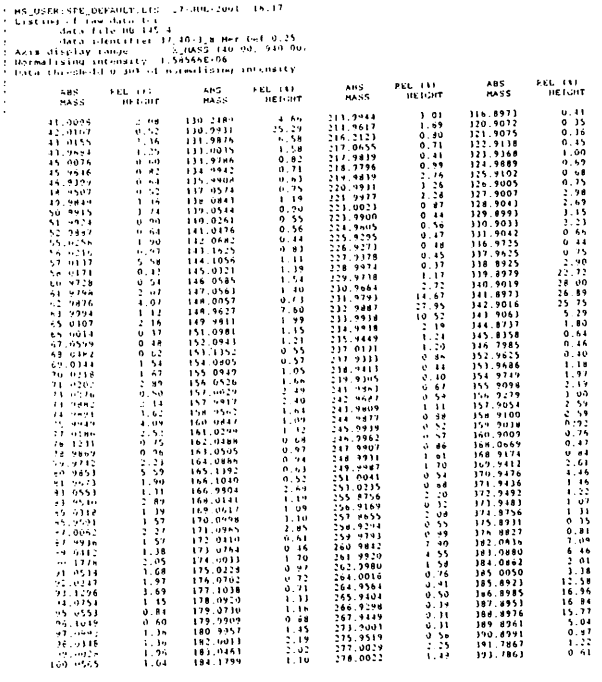
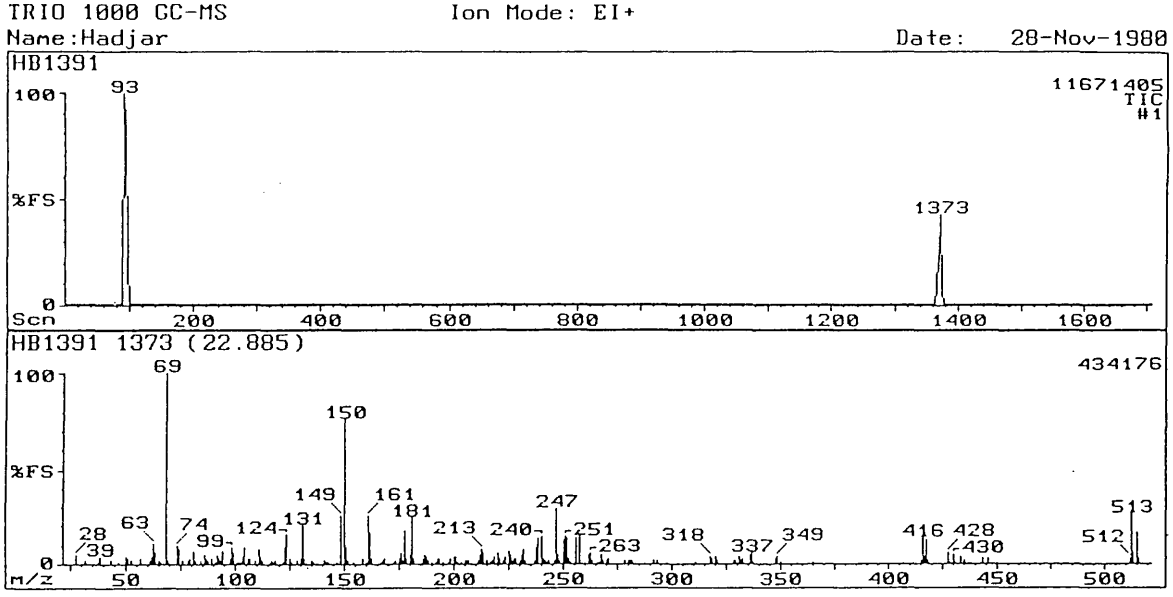

ABS MASS	REL (%) HEIGHT	ABS MASS	REL (%) HEIGHT	ABS MASS	REL (%) HEIGHT	ABS MASS	REL (%) HEIGHT
41.0565	0.30	169.2954	0.44	246.1986	0.54	344.2524	0.37
51.0572	0.33	170.8998	0.41	247.2013	0.62	346.3491	0.39
63.0723	0.35	171.8853	0.36	251.1752	1.59	347.2396	0.31
65.0895	0.97	173.0515	0.62	252.1807	0.70	348.2410	0.49
89.1052	0.46	173.8660	0.86	253.1871	0.40	349.3533	0.72
90.1128	0.39	174.9551	1.27	258.1782	0.80	350.2583	0.55
91.1222	3.09	175.9291	0.60	259.1867	0.47	354.2439	0.50
116.0758	0.33	176.9671	0.73	263.1750	0.35	363.2653	0.45
118.1124	0.30	177.9085	0.50	264.1807	0.45	364.2715	0.61
127.2617	0.53	181.9603	0.40	265.1887	0.41	365.2697	0.55
128.0210	0.42	182.9515	0.64	268.2056	0.31	366.2815	0.97
133.0862	0.86	183.8520	0.76	272.2027	0.50	367.2547	1.17
134.0543	0.33	184.9893	1.74	274.1978	0.35	368.2515	1.33
145.9053	0.33	185.7904	0.42	276.1830	0.48	369.2528	0.62
148.9786	0.31	191.8672	2.35	277.1884	0.59	370.2618	1.97
150.9923	0.56	192.7990	7.39	278.1921	0.72	371.2702	0.50
151.8344	0.32	193.8790	0.43	279.2005	0.40	381.2656	0.47
154.8350	0.40	202.1502	0.43	290.1994	0.31	382.2744	0.88
157.0523	0.54	207.1618	0.30	291.2028	0.31	383.2795	1.01
157.8675	0.43	220.1763	0.49	292.2113	0.53	384.2886	11.41
160.0158	0.33	225.1610	0.36	293.2157	0.51	385.2958	100.00
160.9119	0.42	226.1721	0.33	294.2246	1.07	386.2985	30.86
161.8577	0.36	231.1715	0.42	295.2378	1.01	387.3046	4.55
162.9376	0.36	233.1824	1.16	296.2247	0.33	388.3100	0.40
163.9462	0.65	234.1874	0.45	328.2329	0.32	401.2873	0.82
164.9006	0.59	238.1715	0.76	330.2365	0.33		
166.8455	0.80	244.1822	0.43	333.2237	0.32		
167.8502	0.57	245.1775	0.39	334.2319	0.37		

34. 4-bromo-5-fluoro-2,6-di(3-nitrophenyl)-3-pyridinol (49)





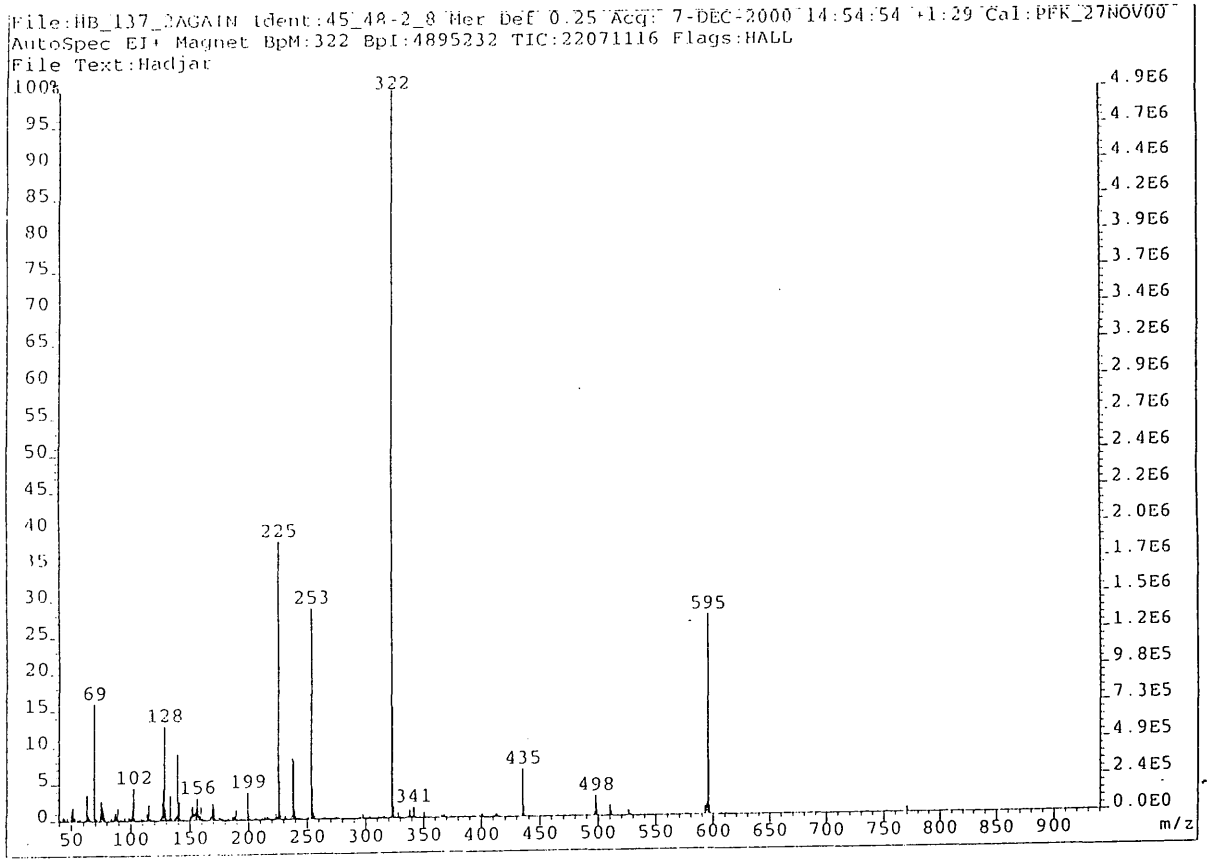
35. 4,6-bis(4-methylphenyl)-2-bromo-3,5-difluoropyridine (50)



HB1391 1373 (22.885) 43

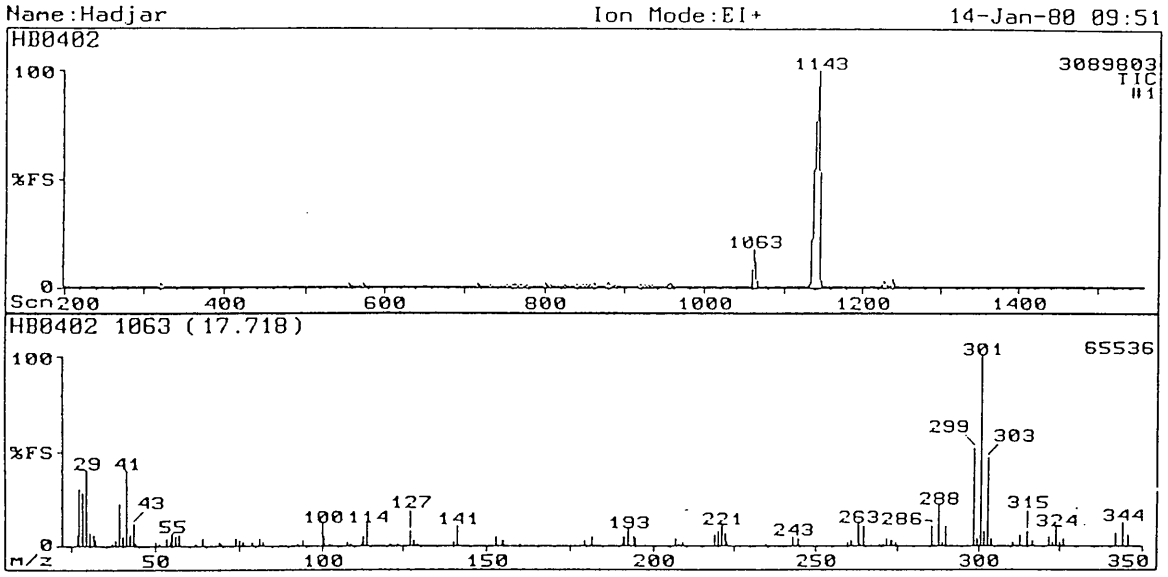
Mass	Rel Int	Mass	Rel Int	Mass	Rel Int	Mass	Rel Int
28	4.60	117	1.62	198	1.05	263	5.54
32	1.61	118	1.27	199	2.48	264	1.98
38	1.30	119	2.21	200	4.01	266	1.15
39	4.36	122	1.19	201	4.07	267	1.21
44	1.56	123	9.08	202	1.28	268	4.72
47	1.06	124	15.57	204	1.44	269	1.89
50	3.77	125	2.95	205	1.87	270	2.33
51	3.26	126	1.22	206	1.77	271	2.43
53	2.27	129	2.23	207	1.58	279	1.61
57	3.36	130	2.76	211	1.68	280	1.96
61	1.52	131	20.75	212	5.01	281	1.67
62	4.30	132	2.93	213	7.84	282	1.49
63	11.08	135	1.95	214	5.72	292	1.80
64	5.90	136	1.42	215	1.89	294	1.78
65	1.47	141	1.95	217	1.11	311	1.06
66	1.40	142	1.25	218	2.21	318	4.36
69	100.00	143	1.08	219	4.25	319	2.62
70	1.46	147	1.16	220	5.72	320	3.46
74	9.85	149	25.71	221	2.61	321	2.12
75	8.20	150	75.47	223	1.87	329	1.77
76	2.15	151	8.90	224	3.54	330	2.02
79	1.52	152	1.75	225	7.13	331	4.19
80	3.38	155	1.03	226	5.07	332	2.02
81	6.96	159	3.30	227	1.53	333	2.92
82	1.81	160	1.11	228	2.43	336	4.72
85	1.55	161	24.76	229	3.17	337	5.72
86	5.07	162	16.75	230	1.92	338	1.31
87	2.76	163	2.54	231	4.72	348	2.62
88	1.49	167	1.22	232	7.78	349	3.67
90	2.87	168	1.93	233	2.23	350	1.05
91	1.15	169	3.18	237	2.33	365	1.15
92	4.66	173	1.25	238	8.73	415	2.20
93	2.99	174	1.89	239	13.74	416	13.44
94	1.61	175	2.59	240	14.09	417	4.01
95	7.02	176	5.66	241	2.98	418	12.15
98	3.33	177	2.27	242	1.83	419	2.06
99	9.02	178	17.45	243	1.43	428	5.48
100	5.37	179	2.77	244	1.52	429	1.06
101	1.11	180	5.07	246	1.56	430	5.13
102	1.12	181	23.82	247	29.01	431	1.00
103	1.08	182	3.30	248	5.31	434	4.13
104	3.83	186	2.71	249	2.42	435	1.81
105	8.43	187	4.83	250	12.56	444	3.01
106	3.29	188	4.07	251	14.98	446	3.13
107	2.79	189	1.52	252	13.44	512	2.64
110	1.74	190	1.08	253	2.54	513	26.42
111	8.08	192	1.44	254	1.12	514	5.54
112	3.49	193	2.98	256	13.80	515	16.27
113	1.55	194	2.86	257	14.50	516	2.77
116	1.16	195	1.42	262	4.72		

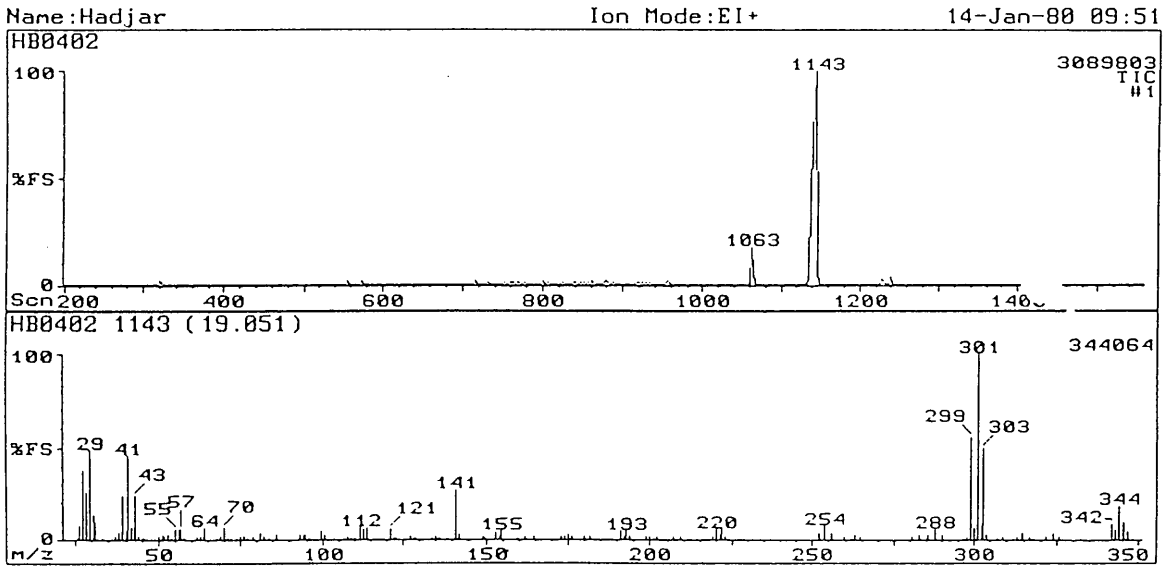
36. 3,5-difluoro-2,4,6-tri(trifluoromethoxyphenyl)pyridine **(51)**



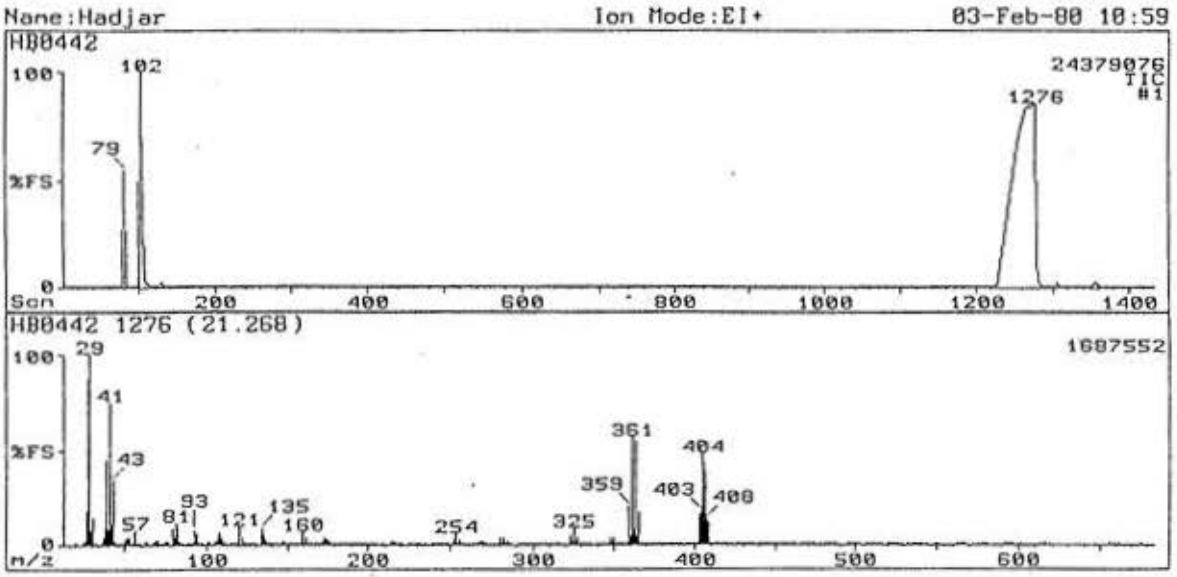
ABS MASS	REL (%) HEIGHT	ABS MASS	REL (%) HEIGHT	ABS MASS	REL (%) HEIGHT	ABS MASS	REL (%) HEIGHT				
40.9849	0.28	127.9544	12.94	320.9237	0.12	321.9037	100.00	106.9315	0.32	198.9905	3.82
42.9914	0.51	128.9508	1.58	321.9135	0.10	322.9079	15.26	108.9406	0.41	199.8955	0.63
43.9775	0.56	129.9338	0.58	322.8989	0.83	323.9090	1.59	109.9299	0.25	200.9046	0.16
44.9779	0.29	130.9241	0.29	323.9014	0.39	324.9092	0.21	110.9289	0.22	201.9069	0.13
46.9297	0.49	131.9256	0.31	324.9126	38.23	325.9133	0.15	111.9221	0.18	204.8847	0.29
47.9190	0.10	132.9336	1.52	325.9174	5.21	326.9297	0.14	112.9402	1.18	205.9506	0.17
48.9303	0.84	133.9337	0.38	326.9204	0.56	327.8767	0.82	113.9443	0.77	206.9142	0.18
49.9560	1.52	136.9200	0.42	327.9167	0.11	328.8847	0.17	114.9538	2.30	210.8905	0.20
50.9595	1.05	137.9287	0.78	330.8843	0.57	334.9206	0.11	115.9488	0.32	211.9031	0.21
51.9676	0.49	138.9355	9.09	331.9068	0.21	335.8971	0.15	116.9299	0.37	212.9089	0.18
52.9418	0.52	139.9437	2.43	332.9196	0.11	336.9076	0.38	118.2165	0.20	213.9124	0.45
54.9853	0.33	140.9483	2.60	334.8988	0.14	337.9121	1.17	119.9246	0.12	214.9281	0.18
56.0563	0.12	141.9506	0.35	335.9022	0.58	338.9166	0.30	119.9319	0.16	215.8890	0.45
57.0107	0.41	142.9155	0.11	336.9107	8.31	339.8918	0.12	122.9096	0.12	217.1231	0.24
58.9791	0.16	143.9161	0.13	337.9224	7.91	340.8621	1.52	124.9293	0.30	217.8854	0.15
60.9485	0.24	144.9171	0.14	338.9240	1.23	341.8670	1.32	125.9329	2.61	218.8985	0.14
61.9464	1.35	148.9079	0.27	339.9193	0.49	342.8721	0.18	126.9434	4.30	219.9163	0.12
62.9545	3.61	149.9209	0.56	340.9213	0.24	349.8468	0.74				
63.9587	0.80	150.9468	1.54	341.9028	0.12	350.8465	0.20				
64.9655	0.45	151.9365	2.10	342.8690	0.30	353.8012	0.12				
65.9317	0.18	152.9469	0.97	343.8976	0.14	365.7900	0.37				
68.9250	16.05	153.9557	1.31	348.9034	0.10	366.7900	0.11	297.3716	0.71	526.9210	0.23
69.9603	0.32	154.9277	1.63	349.9060	0.16	367.7846	0.45	297.9862	0.24	527.9353	0.20
70.9914	0.31	155.9331	3.07	350.9022	0.39	373.8559	0.17	298.8911	0.12	575.9641	0.12
72.9336	0.13	156.9275	1.45	351.9021	0.76	376.8606	0.13	299.9032	0.11	576.9550	0.14
73.9357	1.83	157.9109	0.61	352.9017	28.87	379.9068	0.12	300.9141	0.15	591.9442	1.09
74.9493	2.82	158.9405	1.95	353.9049	4.33	380.9225	0.11	301.9300	0.11	592.9674	1.16
75.9617	1.92	159.9416	0.26	354.9100	0.85	385.9189	0.11	302.9152	0.42	593.9432	1.62
76.9566	1.35	160.9221	0.24	355.9040	0.38	391.9355	0.11	303.9121	0.16	594.9480	27.40
77.9610	0.66	161.9011	0.13	356.9163	0.13	392.9445	0.13	305.9204	0.10	595.9631	7.25
78.9462	0.19	162.9191	0.10	359.8850	0.10	397.9312	0.32	308.9037	0.12	596.9874	1.12
80.9332	0.21	166.9262	0.54	361.9011	0.12	398.9246	0.14	310.8995	0.31	597.9851	0.13
82.9466	0.38	167.9195	1.48	362.9081	0.14	399.9232	0.51	311.9036	0.17	606.9579	0.15
83.9756	0.58	168.9378	2.36	363.9207	0.14	400.9313	0.41	312.9156	0.18	619.9408	0.16
84.9540	0.27	169.9306	1.72	364.9074	0.21	401.9216	0.12	313.9306	0.26	770.0161	0.67
85.9113	1.03	170.9156	0.61	365.8987	0.10	407.8865	0.12	314.9070	0.26	770.9698	0.17
86.9343	1.28	171.9367	0.13	367.9132	0.12	410.9197	0.19	315.9006	0.36	805.9680	0.13
87.9352	0.70	172.9029	0.10	368.9150	0.12	411.9259	0.33	320.8963	0.25		
88.9474	1.82	174.9120	0.46	369.9110	0.14	412.9349	0.48				
89.9499	0.24	175.9187	0.18	370.9059	0.13	413.9423	0.15				
90.9594	0.21	176.9215	0.27	372.8744	0.12	433.9100	0.39				
91.9327	0.31	177.9147	0.25	374.9038	0.32	434.9206	6.49				
92.9237	0.15	180.8991	0.15	375.9129	0.14	435.9255	1.40				
93.9284	0.10	182.9189	0.38	376.9237	0.15	436.9334	0.18				
94.9341	0.58	183.9102	0.13	379.9054	0.12	477.9200	0.11				
95.9343	0.12	184.9206	0.14	380.9107	0.12	495.9170	0.16				
96.9749	0.11	185.9081	0.63	381.9178	0.12	496.9125	0.56				
97.9192	0.50	186.9171	0.42	382.9272	0.15	497.9229	2.77				
98.9251	0.54	187.9121	0.50	383.9119	0.13	498.9256	0.75				
99.9330	0.40	188.8931	1.42	385.8765	0.13	499.9298	0.12				
100.9408	1.58	189.9064	0.19	387.9159	0.14	507.9319	0.17				
101.9503	4.52	192.9014	0.16	390.8911	0.11	509.9261	1.47				
102.9497	0.50	193.9147	0.26	391.9083	0.12	510.9177	0.56				
104.9293	0.16	194.9166	0.14	394.9283	0.17	511.9409	0.11				
105.9259	0.13	197.8920	0.12	395.9747	0.20	525.9216	0.77				

37. Mixture of N4-butyl-2,6-dibromo-3,5-difluoro-4-pyridinamine and N2-butyl-4,6-dibromo-3,5-difluoro-2-pyridinamine (53)





38. *N2*-butyl (2,4,6-tribromo-5-fluoro-3-pyridyl) amine (54)



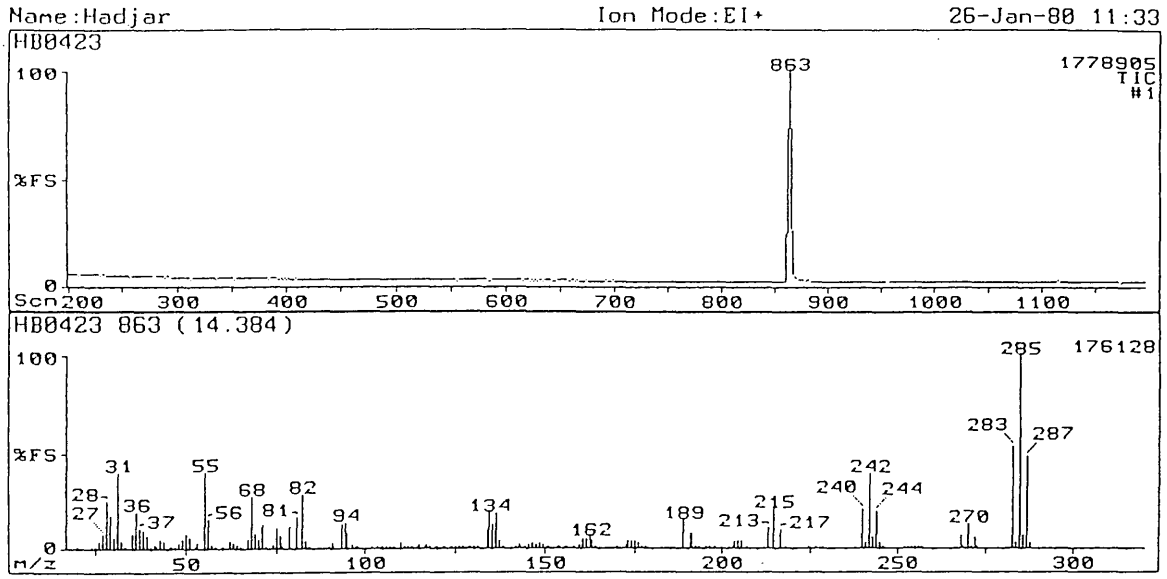
0442 1276 (21.268) 168755

as	Rel Int	Mass	Rel Int	Mass	Rel Int	Mass	Rel Int
58	0.05	323	4.61	377	0.69	434	0.06
59	0.02	324	2.18	378	0.18	435	0.20
61	0.08	325	8.62	379	0.32	436	0.05
63	0.09	326	2.12	380	0.05	437	0.08
65	0.11	327	4.19	381	0.10	439	0.02
66	0.59	328	0.61	382	0.04	440	0.03
67	1.11	329	0.18	383	0.06	441	0.05
68	1.70	330	0.20	384	0.03	442	0.06
69	1.81	331	0.07	385	0.09	443	0.08
70	1.88	332	0.33	386	0.03	444	0.07
71	1.00	333	0.28	387	0.10	445	0.18
72	0.93	334	0.60	388	0.06	446	0.05
73	0.35	335	0.30	389	0.24	447	0.17
75	0.05	336	0.29	390	0.04	448	0.04
77	0.10	337	0.17	391	0.16	449	0.07
79	1.18	338	0.05	392	0.05	450	0.04
80	0.64	339	0.03	393	0.03	451	0.03
81	3.73	340	0.02	394	0.02	452	0.07
82	1.26	341	0.04	395	0.02	453	0.03
83	4.31	342	0.03	396	0.02	454	0.05
84	0.80	343	0.05	397	0.03	455	0.06
85	1.64	344	0.06	398	0.02	456	0.08
86	0.14	345	0.35	399	0.06	457	0.07
87	0.03	346	1.35	400	0.04	458	0.06
92	0.08	347	1.35	401	0.42	459	0.07
93	0.59	348	3.88	402	15.78	460	0.05
94	0.77	349	1.84	403	17.48	461	0.06
95	1.30	350	3.84	404	47.57	462	0.03
96	1.18	351	1.38	405	41.26	463	0.03
97	0.66	352	1.38	406	42.96	466	0.02
98	0.62	353	0.45	407	37.86	467	0.02
99	0.24	354	0.23	408	13.65	468	0.02
100	0.03	355	0.06	409	11.29	469	0.02
101	0.07	356	0.11	410	1.12	470	0.02
102	0.01	357	0.50	411	0.14	471	0.02
103	0.03	358	0.71	413	0.06	472	0.01
104	0.02	359	20.39	414	0.04	473	0.02
105	0.12	360	5.10	415	0.07	474	0.01
106	0.07	361	55.83	416	0.04	475	0.01
107	0.72	362	7.40	417	0.08	479	0.01
108	0.31	363	54.37	418	0.06	481	0.03
109	0.97	364	4.79	419	0.03	482	0.02
110	0.30	365	17.21	420	0.05	483	0.06
111	0.53	366	1.76	421	0.03	484	0.04
112	0.10	367	0.22	422	0.03	485	0.07
113	0.10	368	0.17	424	0.02	486	0.04
114	0.03	369	0.05	426	0.02	487	0.06
115	0.02	370	0.04	427	0.03	488	0.03
116	0.02	371	0.04	428	0.02	489	0.02
117	0.02	372	0.07	429	0.05	495	0.02
118	0.27	373	0.24	430	0.02	496	0.03
120	0.80	374	0.33	431	0.13	497	0.02
121	0.60	375	0.64	432	0.05	498	0.05
122	1.26	376	0.33	433	0.22	499	0.04

HB0442 1276 (21.268)

Mass	Rel Int	Mass	Rel Int	Mass	Rel Int	Mass	Rel Int
20	0.31	80	4.31	141	0.64	195	0.11
21	0.03	81	11.71	142	0.50	196	0.08
24	0.96	82	8.74	143	0.60	198	0.21
25	2.20	83	2.34	144	0.34	199	0.75
26	17.72	84	0.27	146	1.02	200	0.17
27	86.41	85	0.06	146	1.32	200	0.97
28	46.84	86	0.06	148	1.85	201	1.18
29	100.00	88	0.35	148	1.56	202	1.02
30	7.71	88	0.29	149	1.08	203	0.97
31	14.32	89	0.78	150	0.38	204	0.30
32	0.48	90	0.88	151	0.14	205	0.11
33	0.53	91	1.37	152	0.24	207	0.05
35	0.68	93	7.28	153	0.60	209	0.03
36	2.25	94	5.95	154	0.50	210	0.03
37	4.13	95	5.46	155	0.57	213	1.63
38	8.31	96	1.26	156	0.41	214	0.38
39	44.17	97	0.57	157	0.07	214	1.73
40	8.56	98	0.08	158	0.07	215	1.96
41	74.76	100	0.63	160	6.43	216	0.32
42	10.86	101	1.46	161	0.51	217	1.96
43	34.22	102	0.34	162	4.31	218	0.12
44	2.09	103	0.51	162	3.43	219	0.02
45	0.53	105	2.23	163	0.94	219	0.03
46	0.92	106	1.77	164	0.46	220	0.04
47	0.11	107	5.04	165	0.17	222	0.05
48	0.56	108	6.55	166	0.03	225	0.26
49	0.90	109	5.22	167	0.03	226	0.04
50	2.50	110	3.14	168	0.07	226	0.37
51	3.82	111	0.81	169	0.15	227	0.42
52	3.69	112	0.18	170	0.19	228	0.10
53	4.07	113	0.30	171	0.86	229	0.82
54	0.51	115	0.95	172	1.99	230	0.21
55	7.22	116	0.93	173	3.50	231	0.29
56	3.79	117	1.17	174	3.35	232	0.06
57	7.28	118	0.73	175	2.73	234	0.04
58	0.57	119	0.85	176	1.59	236	0.08
59	0.09	121	10.07	177	0.34	239	0.14
60	0.14	122	3.72	178	0.08	240	0.37
62	2.09	123	2.31	179	0.06	241	0.31
63	1.56	124	0.77	180	0.12	242	0.72
64	0.50	125	0.18	181	0.13	243	0.32
65	0.38	126	0.55	182	0.10	244	0.79
66	0.27	127	0.67	183	0.08	245	0.62
67	0.84	129	0.79	184	0.07	246	0.47
68	1.79	129	0.69	185	0.16	247	0.34
69	1.65	130	1.02	186	0.44	248	0.04
70	3.34	131	0.75	187	0.99	249	0.02
71	0.69	132	1.33	188	1.27	251	0.58
72	0.44	134	5.28	189	1.11	252	2.94
74	1.11	135	8.31	190	0.95	253	1.41
75	2.11	136	5.22	191	0.37	254	5.58
76	2.29	137	2.91	192	0.09	255	1.08
77	1.35	139	0.03	193	0.09	256	2.84
79	8.98	140	0.04	194	0.04	257	0.30

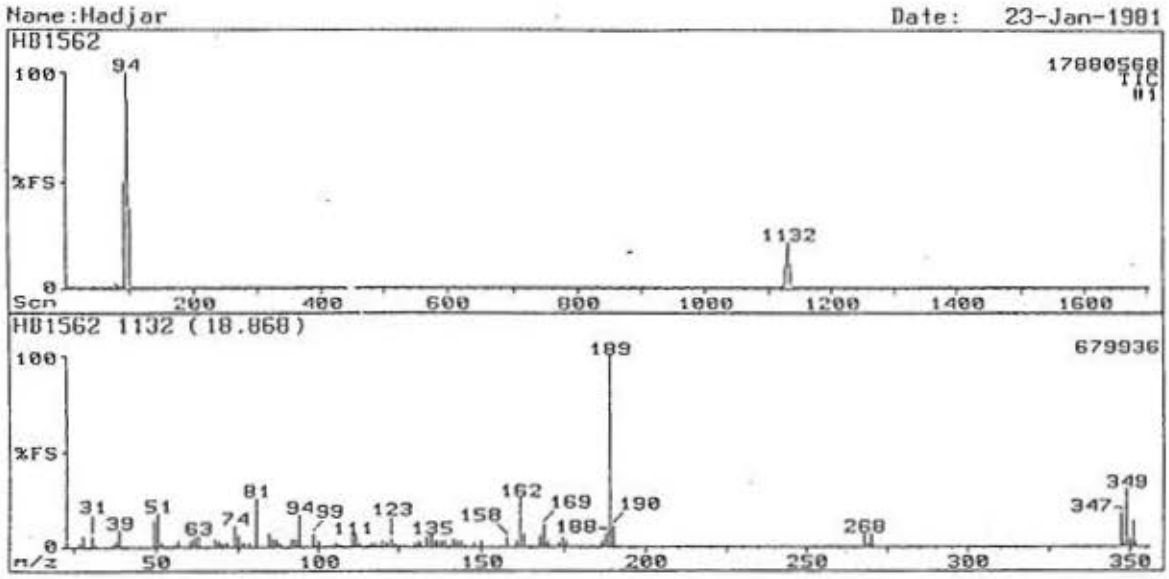
39. 2,6-dibromo-3-fluoro-5-methoxypyridine(55)



HB0423 863 (14.384) 176128

Mass	Rel Int	Mass	Rel Int	Mass	Rel Int	Mass	Rel Int
20	0.20	71	12.35	127	0.25	192	0.45
24	0.66	72	0.41	128	0.31	193	0.30
25	1.10	74	1.92	129	0.71	195	0.67
26	4.18	75	10.32	130	0.94	196	0.46
27	7.70	76	6.76	131	1.03	198	0.57
28	25.58	77	0.29	133	10.17	202	0.59
29	17.44	79	11.77	134	18.17	203	0.45
30	5.56	81	16.57	135	12.79	203	3.63
31	39.53	82	27.76	136	18.17	204	3.49
32	3.71	83	3.56	137	4.25	206	4.03
33	0.36	84	0.80	138	0.20	207	0.21
35	8.10	90	0.11	142	1.27	213	10.32
36	19.19	91	3.02	143	1.54	215	20.06
37	10.32	93	12.21	144	0.77	217	9.45
38	9.30	94	13.66	145	1.58	218	0.15
39	7.01	95	3.10	146	2.65	225	0.40
40	1.26	96	1.72	147	2.33	227	1.37
41	2.30	97	1.04	148	3.20	229	0.58
42	0.83	98	0.22	149	1.76	240	20.06
43	4.69	102	0.08	150	0.60	241	2.80
44	3.92	103	0.18	151	0.55	242	38.37
45	0.58	104	0.30	153	0.30	243	5.70
46	0.93	105	0.36	154	0.59	244	19.33
47	0.36	106	0.52	155	0.40	245	2.87
48	2.47	107	0.74	156	0.73	246	0.20
49	4.43	108	0.34	158	0.12	252	0.32
50	7.56	110	2.76	159	1.58	253	0.25
51	6.03	111	0.56	160	4.40	254	1.14
52	1.33	112	0.34	161	5.23	255	0.42
53	3.02	113	0.32	162	5.49	256	0.52
55	39.53	114	0.98	163	3.78	257	0.11
56	15.41	115	1.67	164	1.18	268	6.69
57	2.33	116	1.34	170	0.11	269	0.22
58	0.39	117	1.84	172	1.65	270	12.65
60	0.23	118	0.79	173	3.85	271	0.79
62	4.11	119	0.12	174	4.32	272	6.07
63	2.73	120	0.34	175	4.29	273	0.40
64	2.29	121	0.47	176	2.76	283	52.33
65	0.22	122	0.86	177	0.30	284	3.02
67	4.51	123	0.68	178	0.26	285	100.00
68	27.33	124	1.29	189	14.10	286	6.61
69	7.96	125	1.17	190	7.78	287	47.67
70	4.54	126	0.17	191	7.85	288	3.31

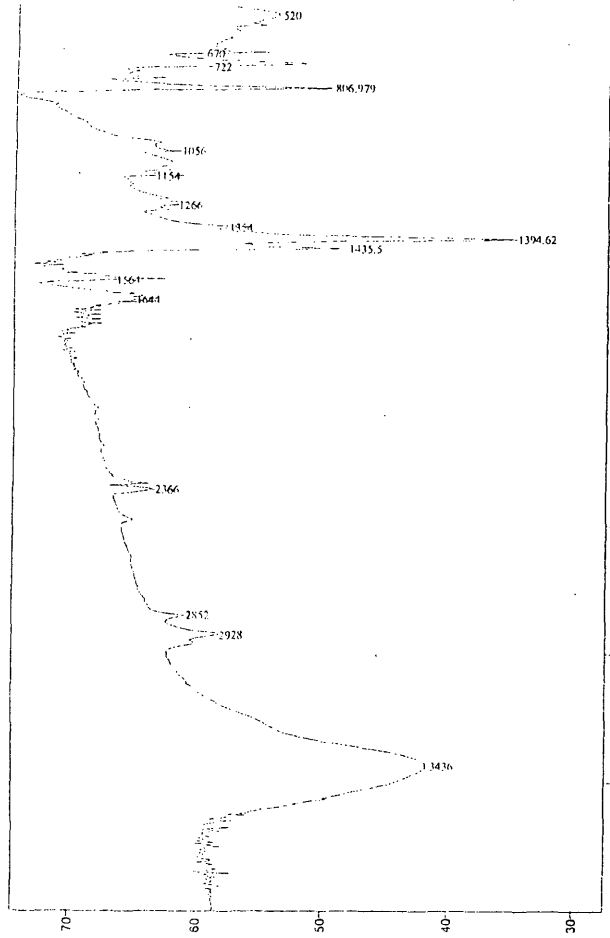
40. 2,6-dibromo-3,5-difluorophenylpyridine (60)



L562 1132 (18.868) 679936

ss	Rel Int	Mass	Rel Int	Mass	Rel Int	Mass	Rel Int
27	2.39	79	1.73	122	1.84	162	25.15
28	5.50	81	25.60	123	3.54	163	6.78
31	6.10	85	6.63	124	2.35	168	6.02
32	1.33	86	4.10	125	1.01	169	11.30
37	1.22	87	4.18	127	1.34	170	2.60
38	3.01	88	2.15	130	1.62	173	2.39
39	8.62	92	3.88	131	2.97	174	4.82
50	13.40	93	3.80	132	1.57	175	2.97
51	17.32	94	16.42	134	4.48	187	2.94
52	2.12	99	7.19	134	3.69	188	7.23
56	1.36	100	2.45	135	6.21	189	100.00
57	3.09	104	1.43	136	2.52	190	10.99
61	3.09	105	2.20	137	3.16	268	7.27
62	4.59	106	2.31	138	3.24	269	1.62
63	5.65	107	1.13	139	2.97	270	7.00
68	3.88	111	5.72	141	1.40	347	17.77
69	2.48	112	5.61	142	3.61	348	2.08
70	1.75	113	1.61	143	3.28	349	30.42
71	1.61	116	1.23	144	2.90	350	3.50
72	1.69	117	1.89	145	1.01	351	13.25
74	10.24	118	2.23	148	2.15	352	1.52
75	5.57	119	1.39	150	3.16		
76	2.07	120	2.90	158	5.23		
77	2.20	121	1.78	161	3.39		

APPENDIX C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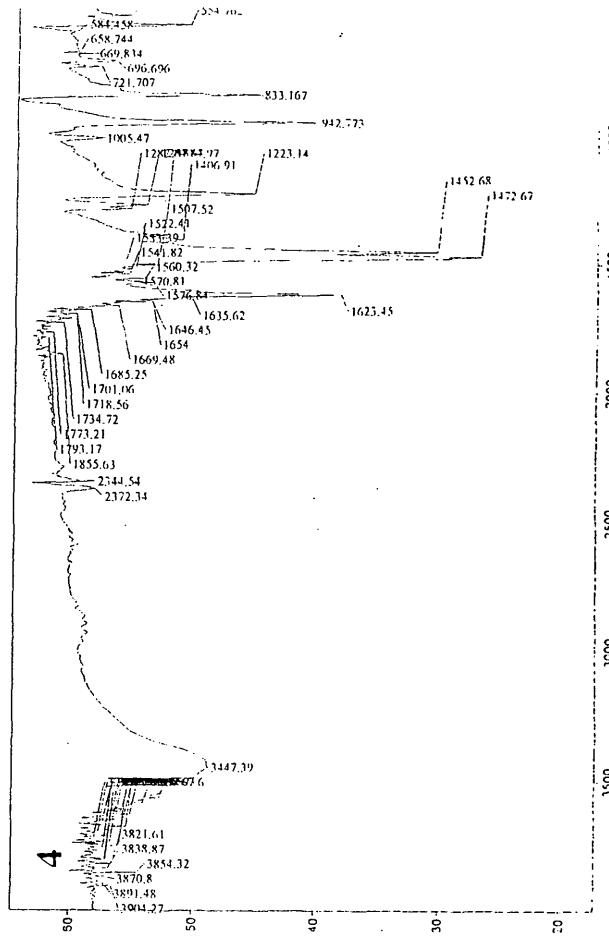
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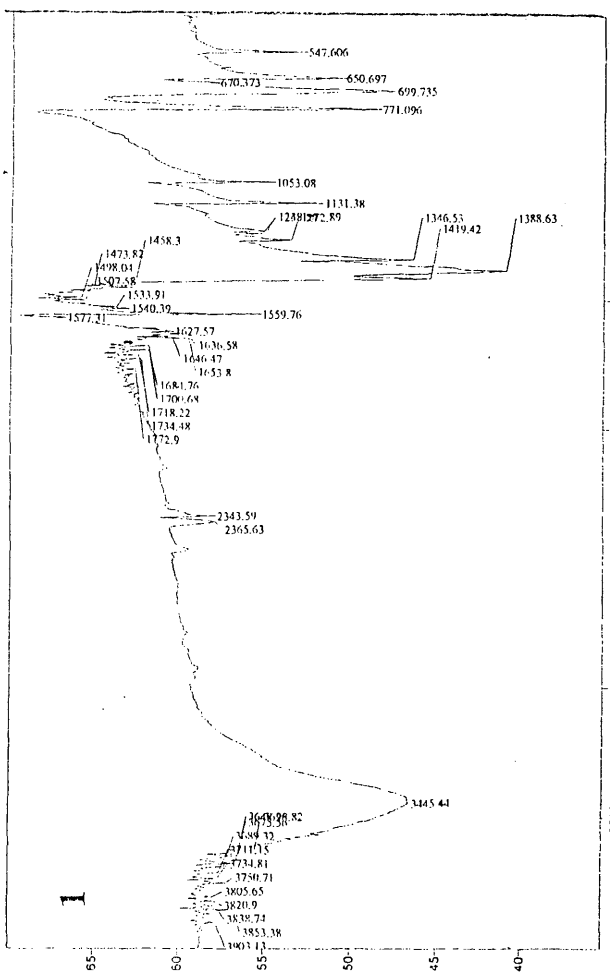
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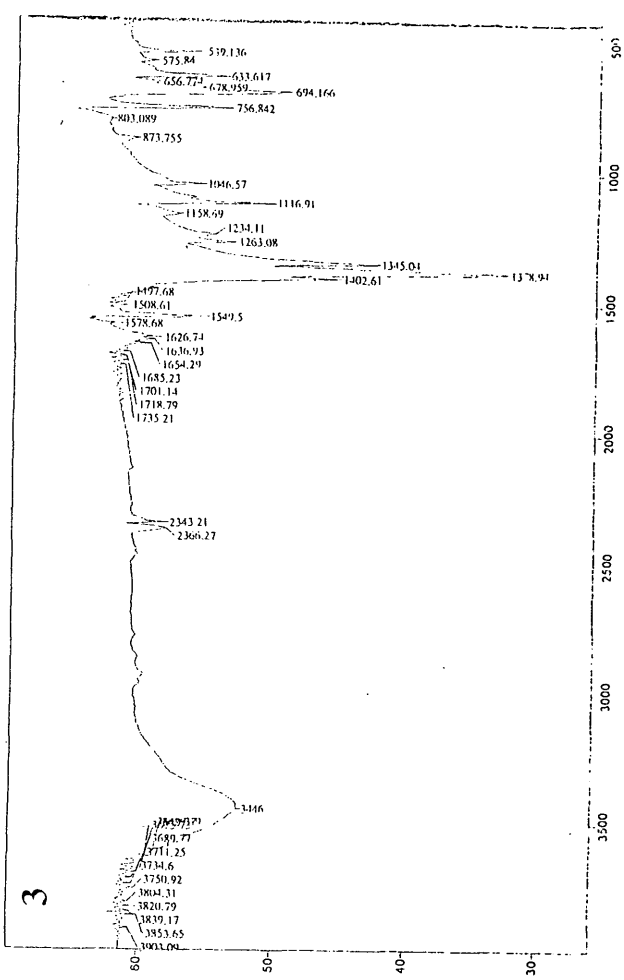
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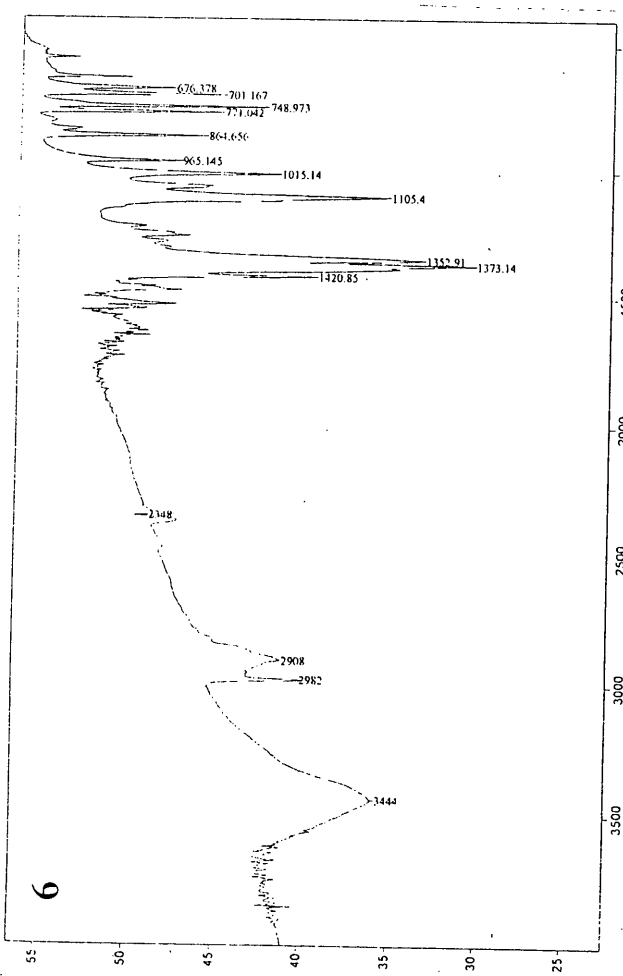
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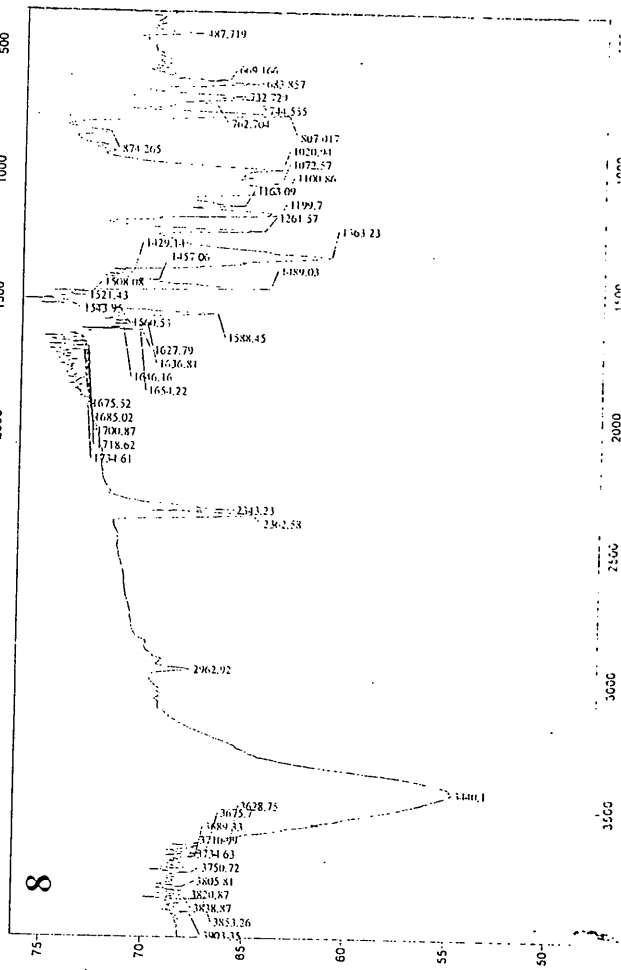
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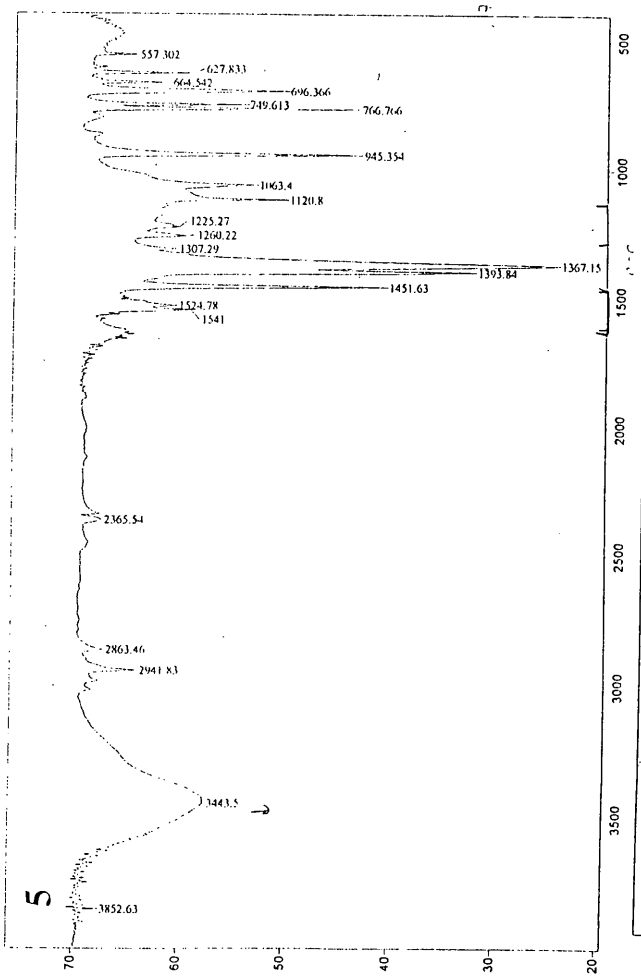
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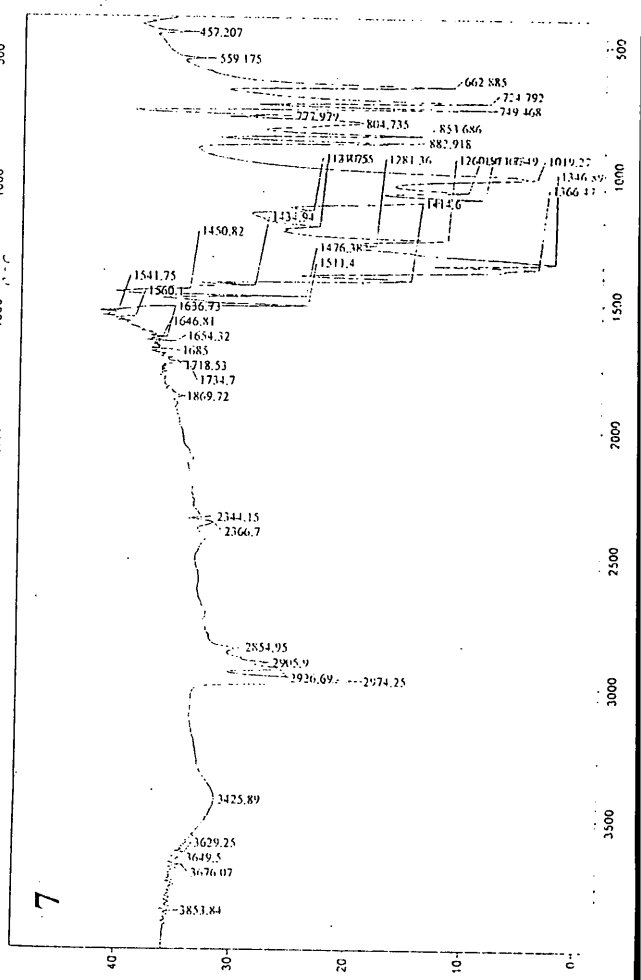
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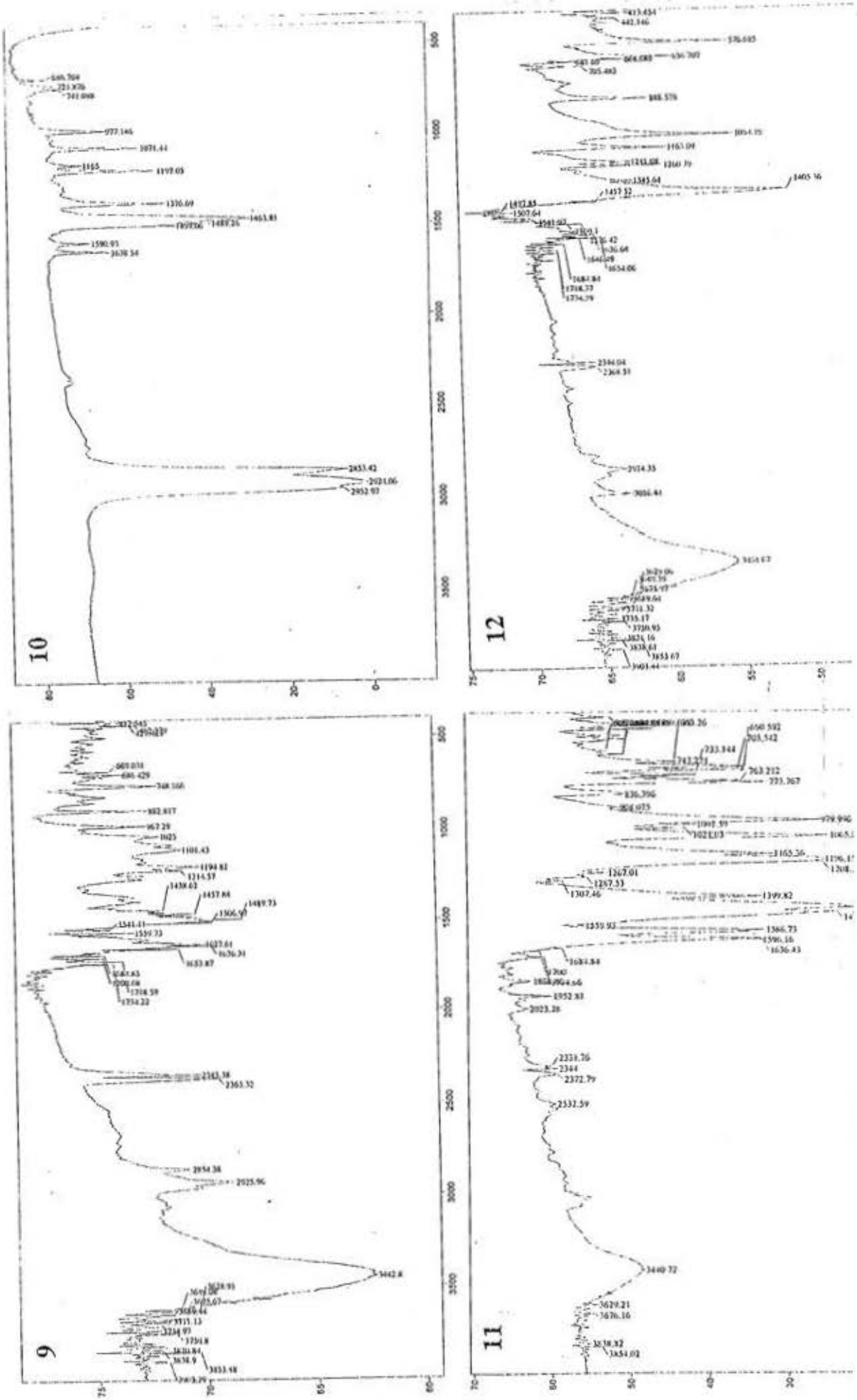
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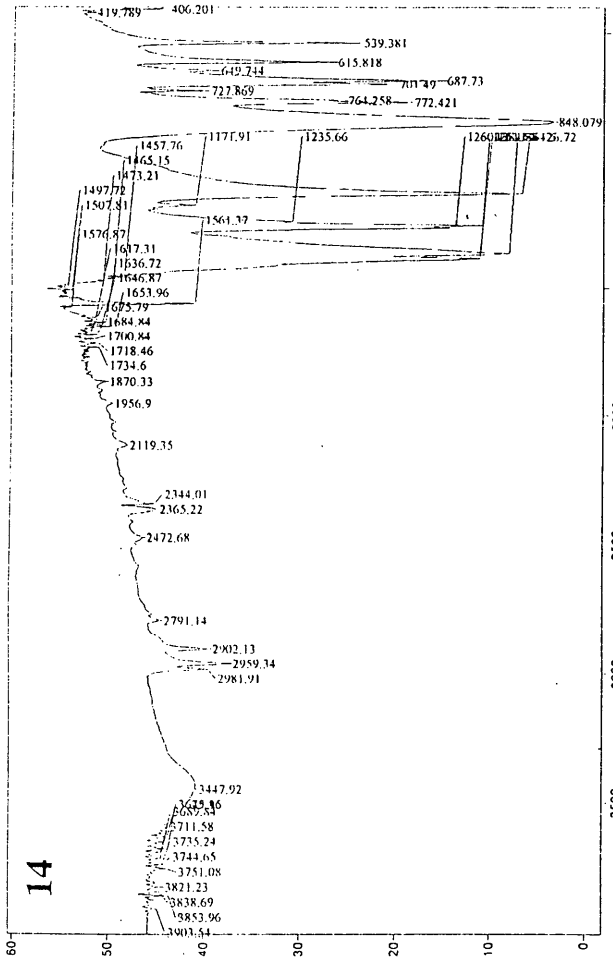
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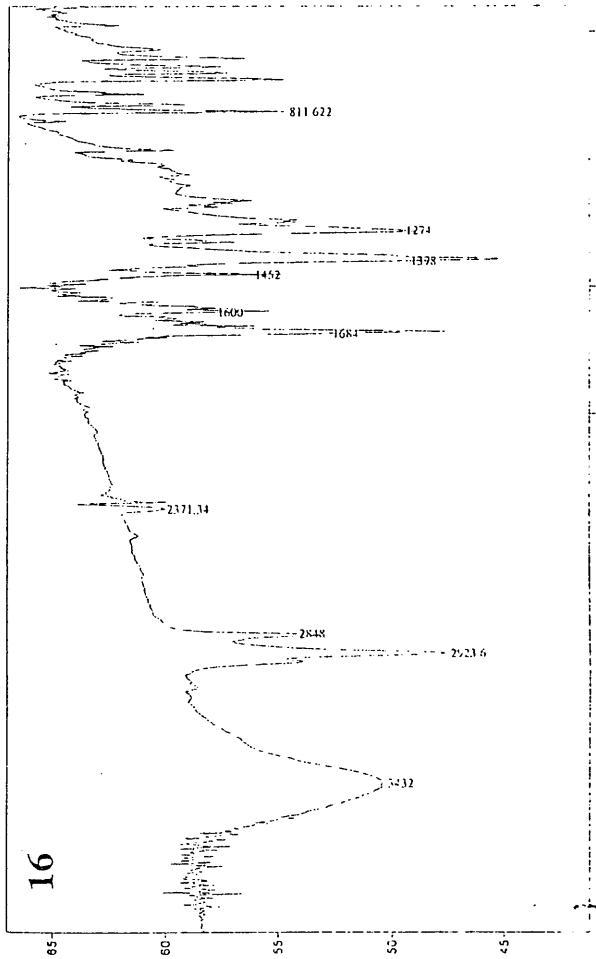
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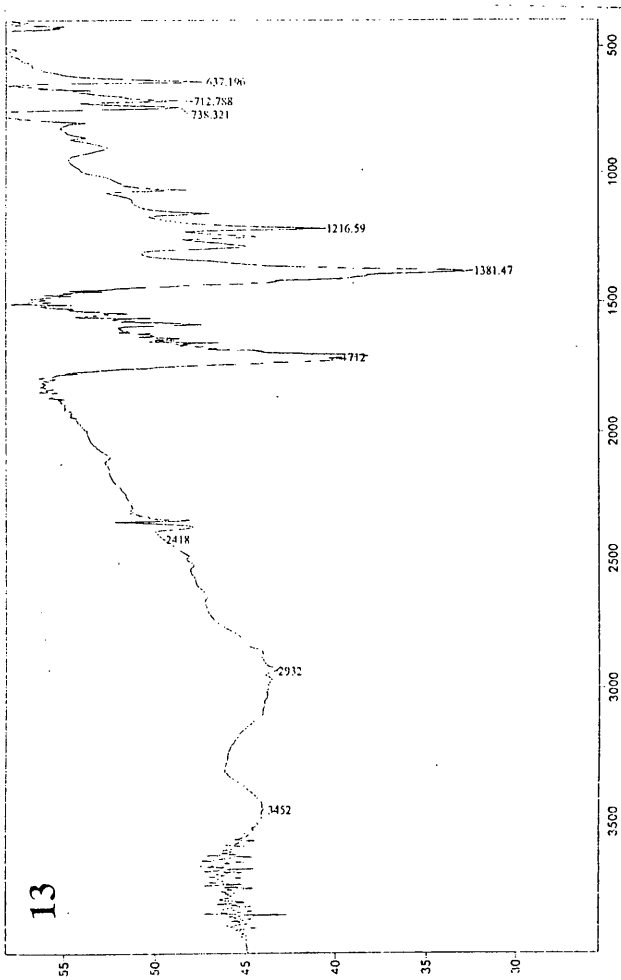
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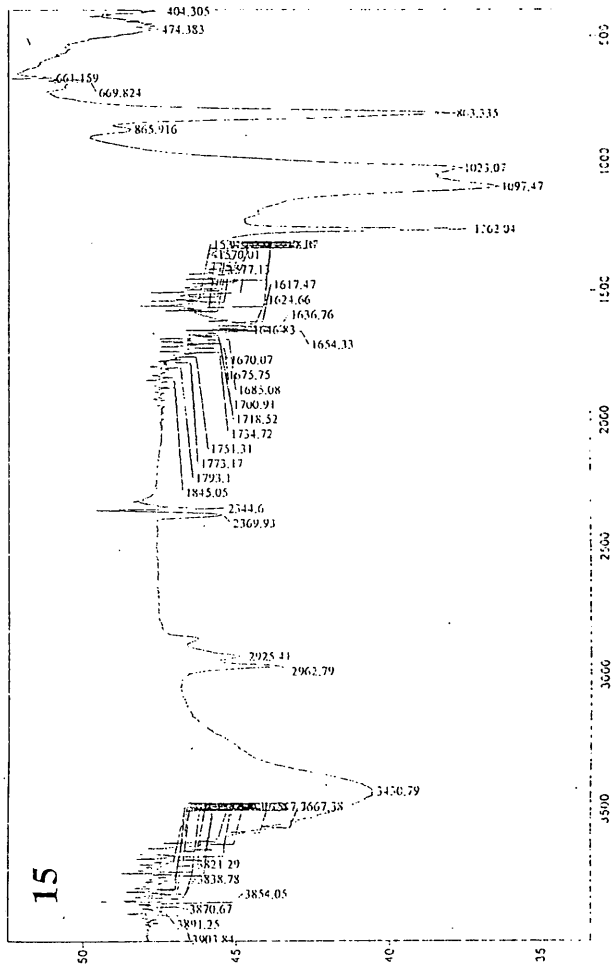
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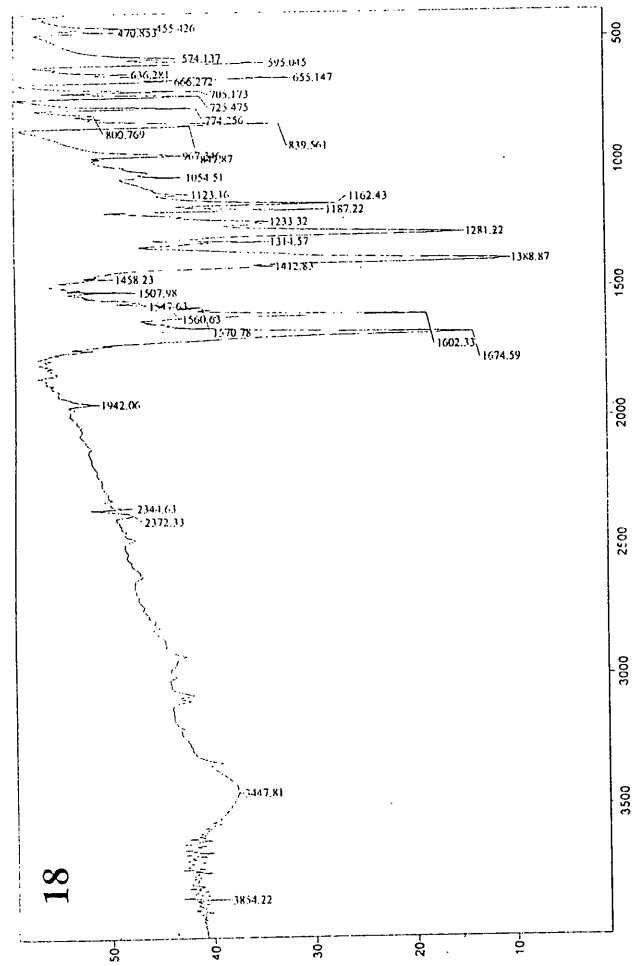
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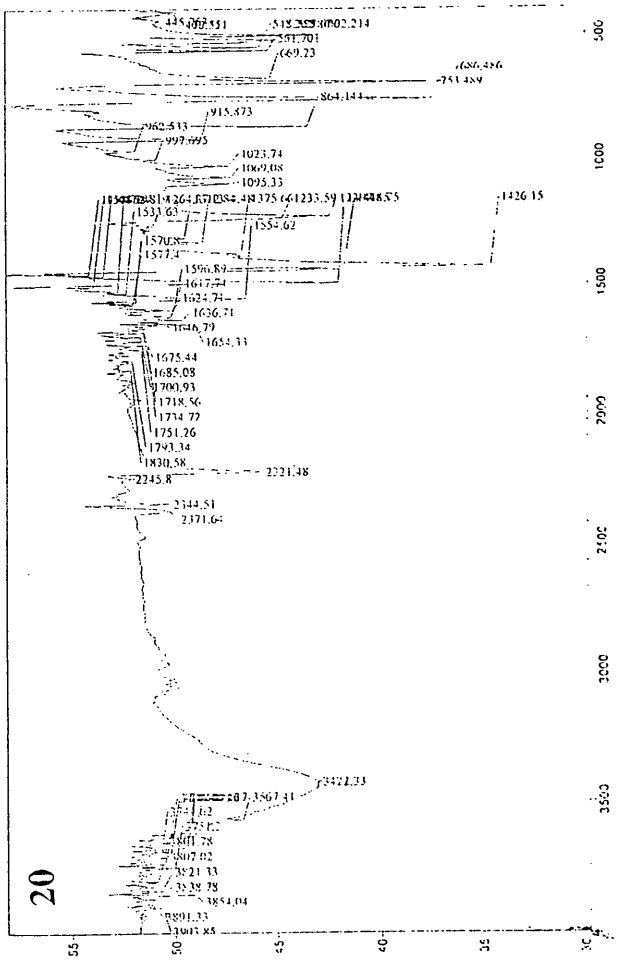
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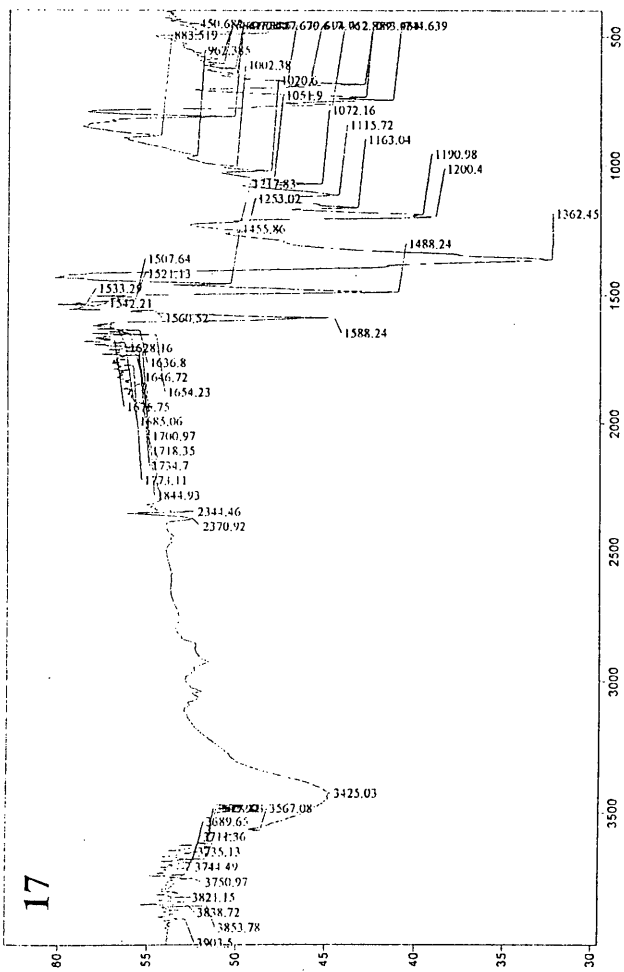
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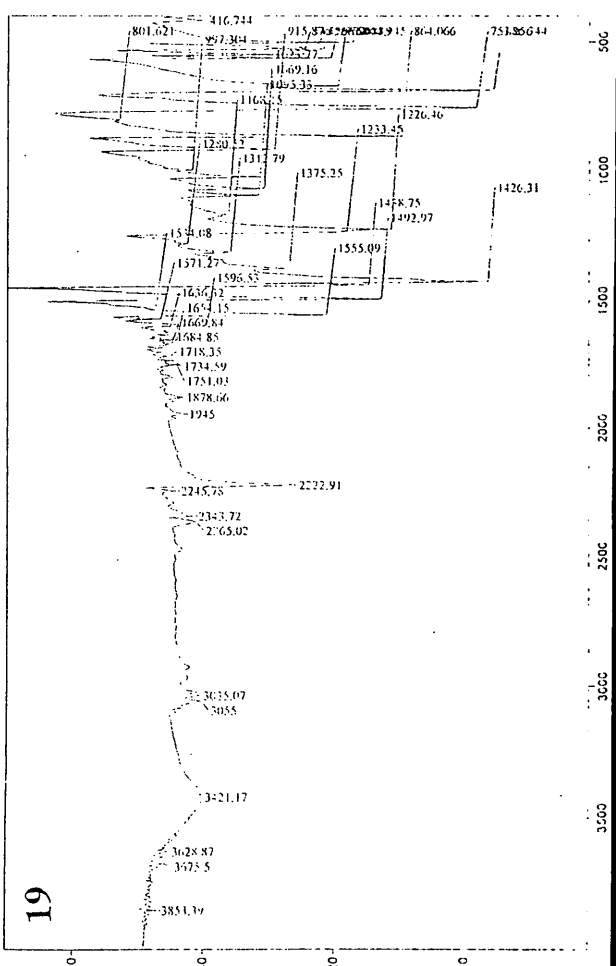
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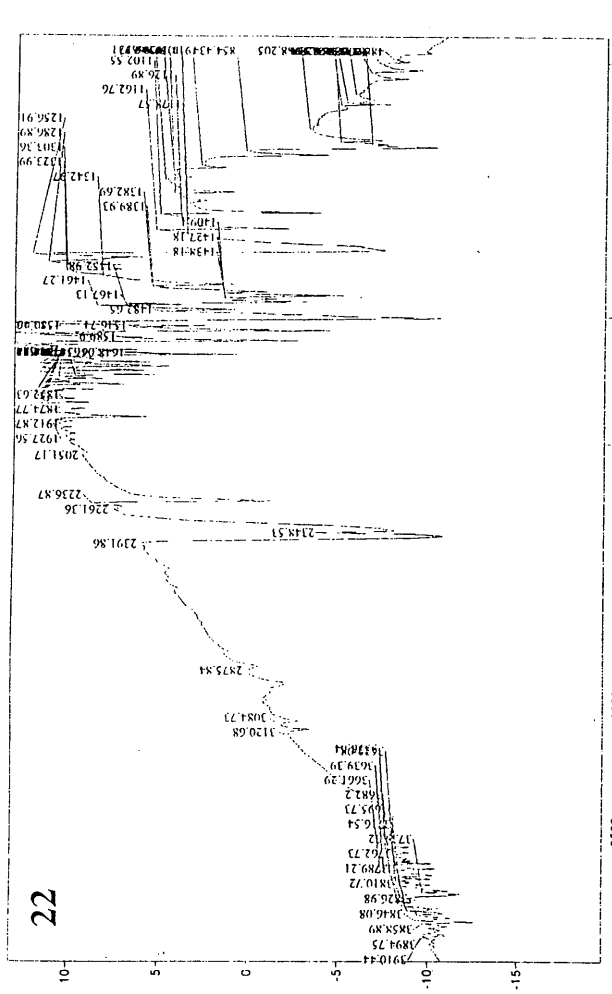
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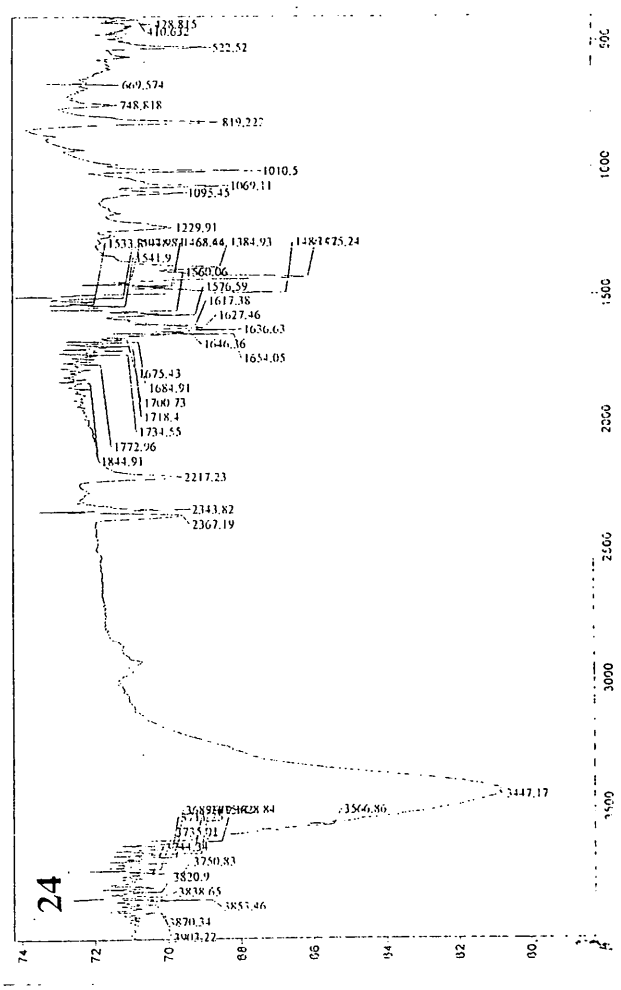
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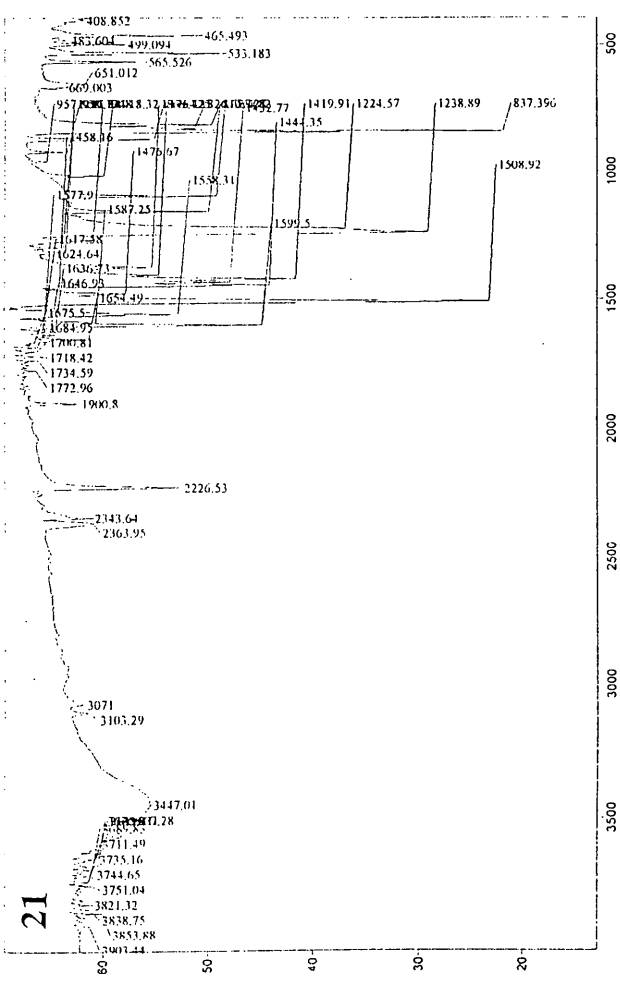
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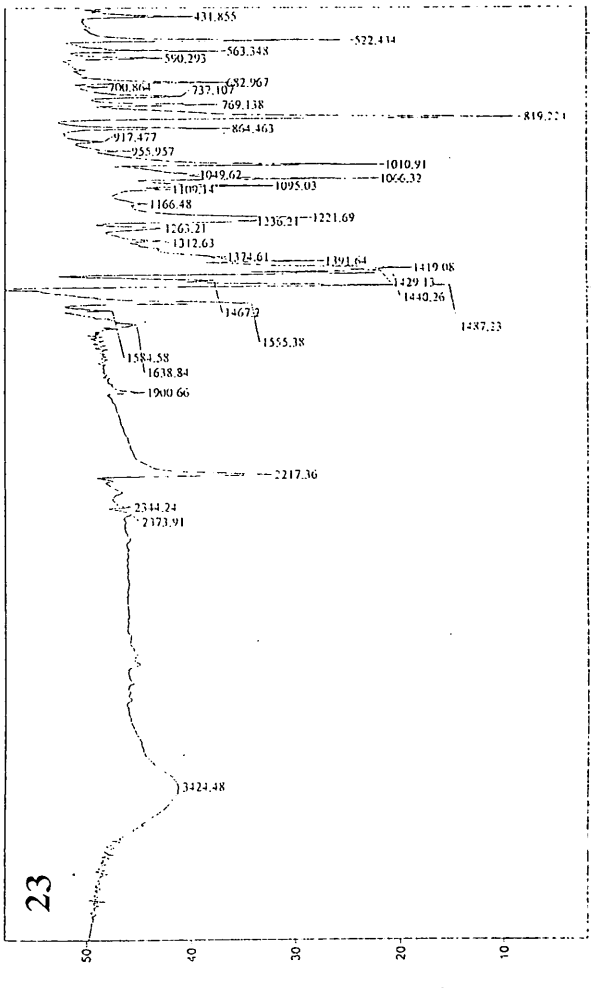
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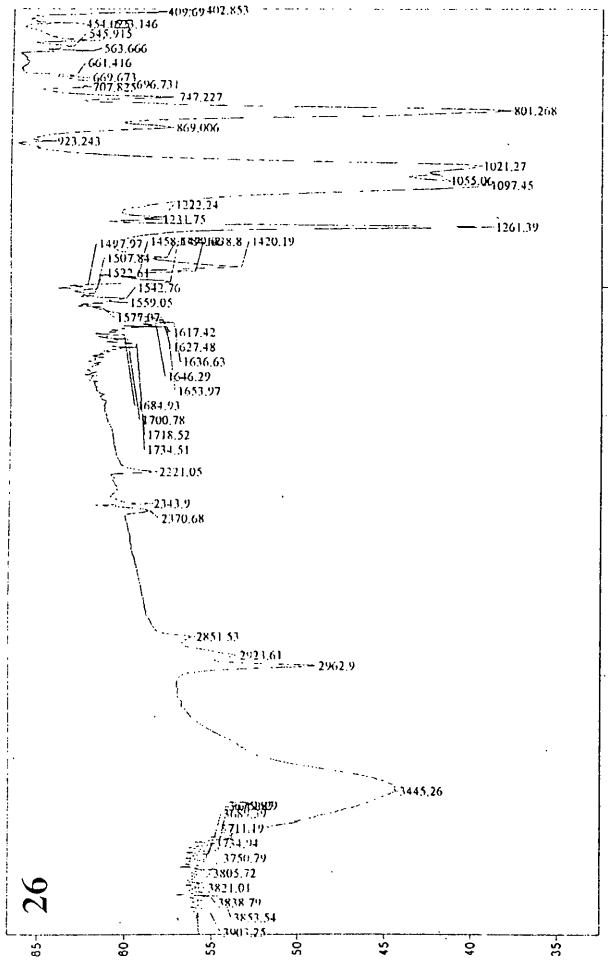
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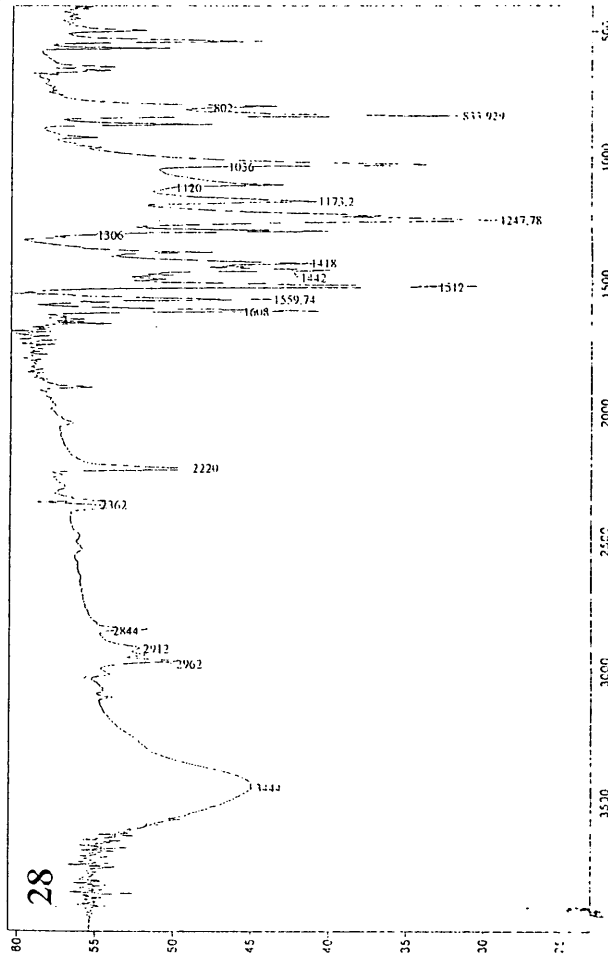
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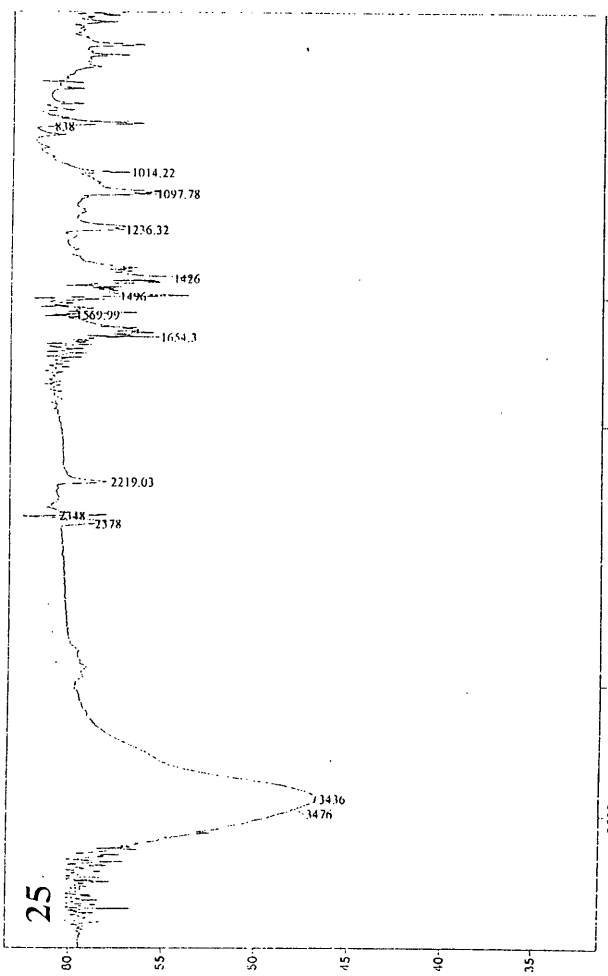
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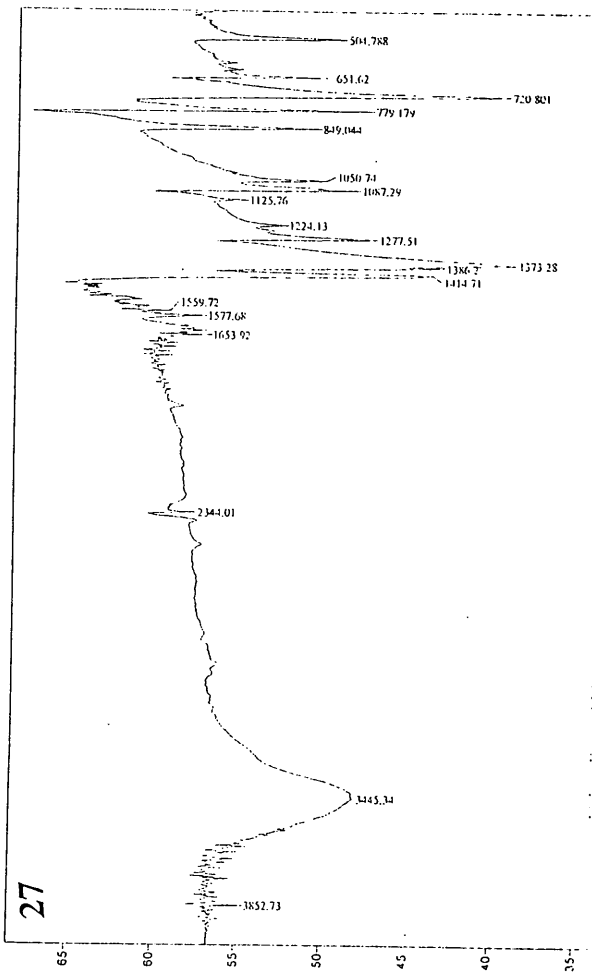
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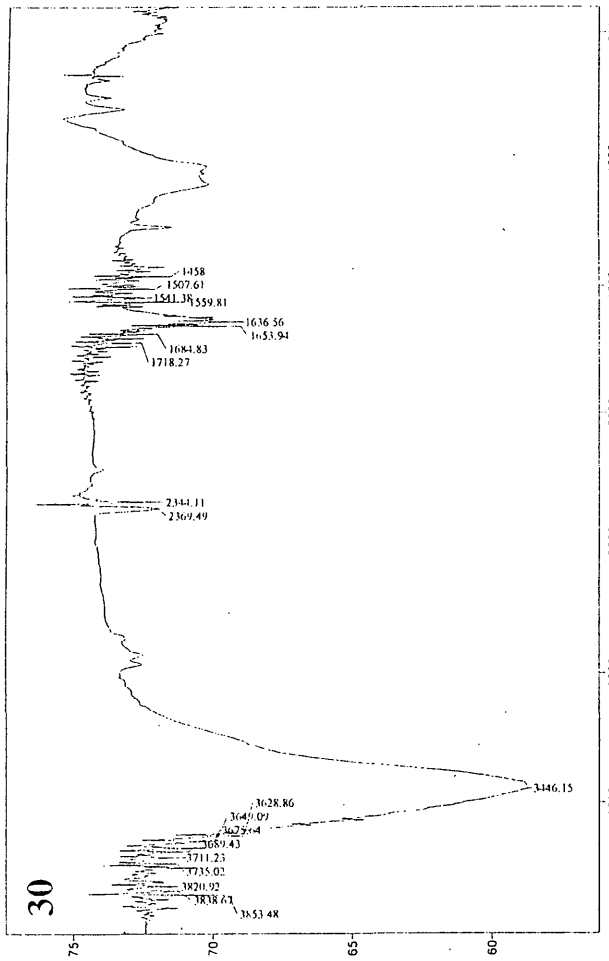
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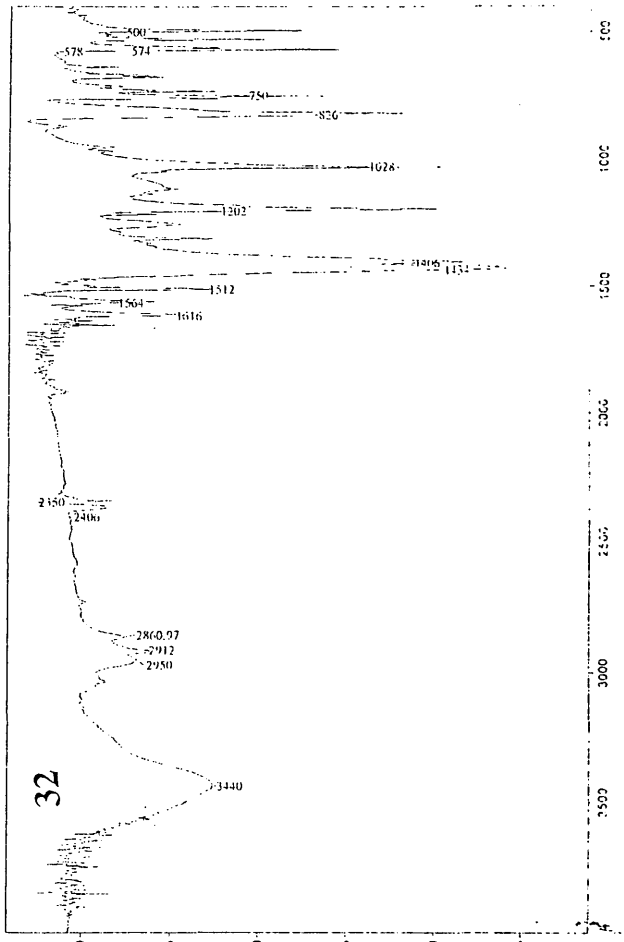
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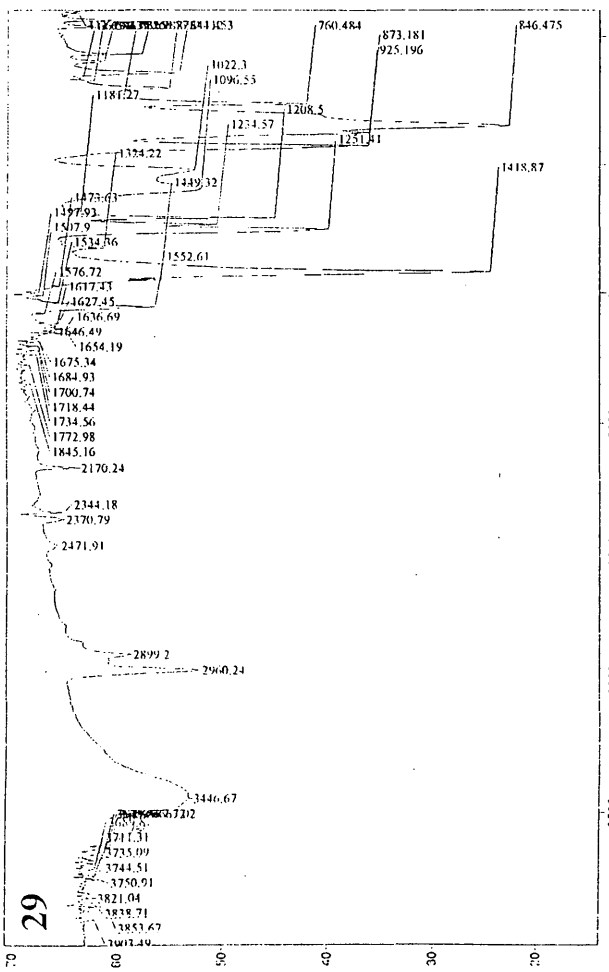
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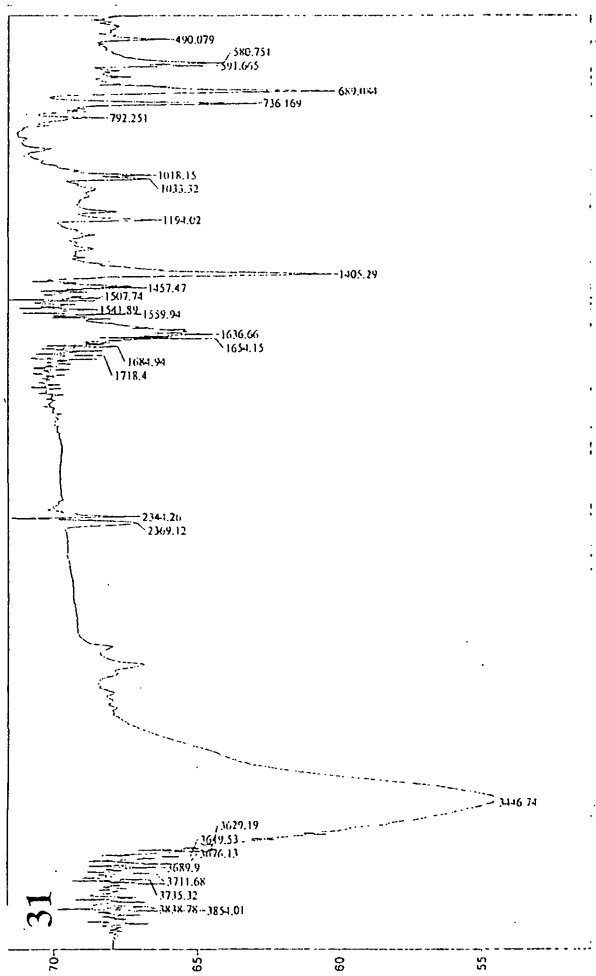
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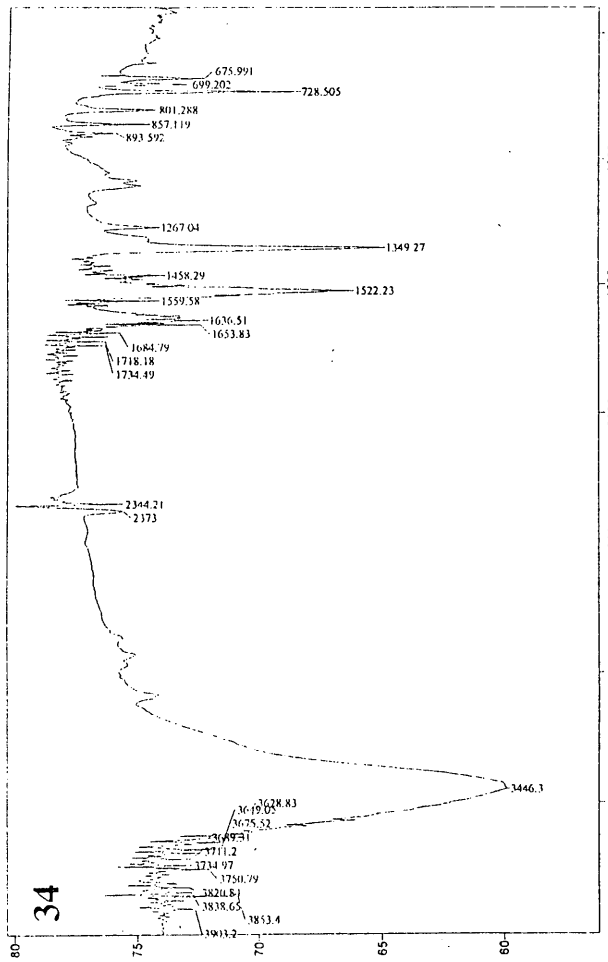
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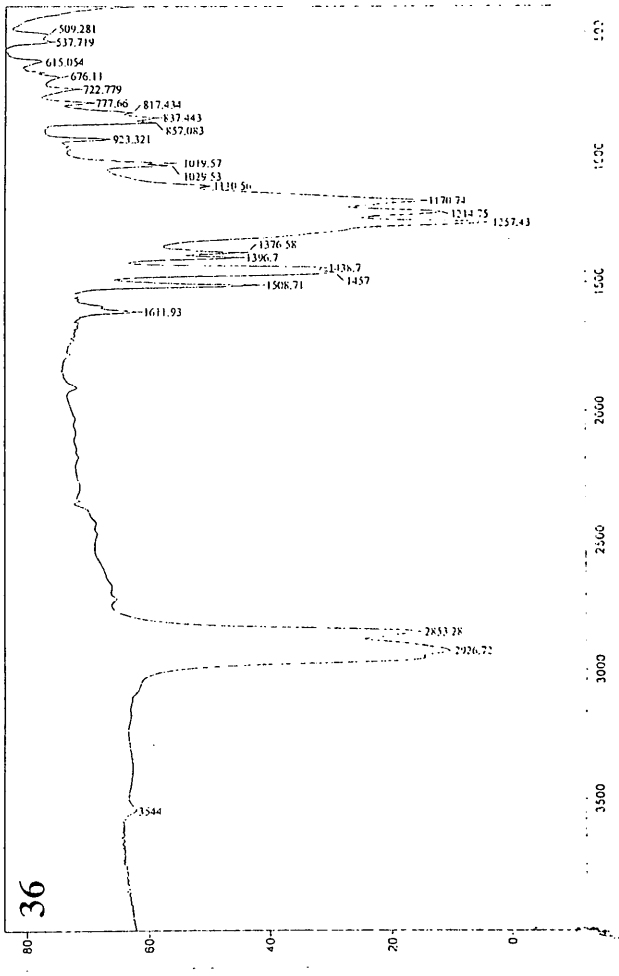
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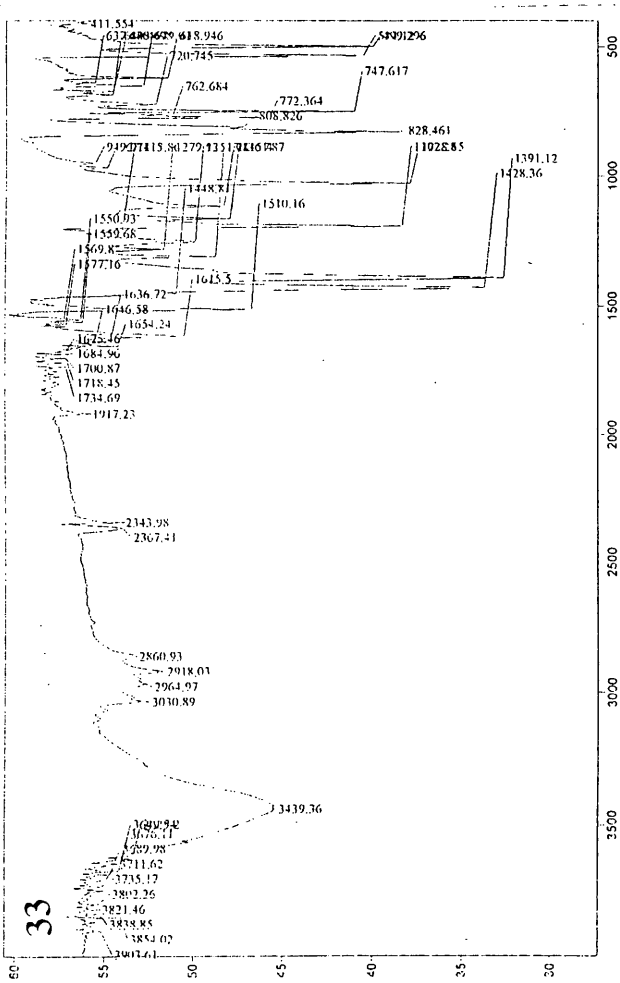
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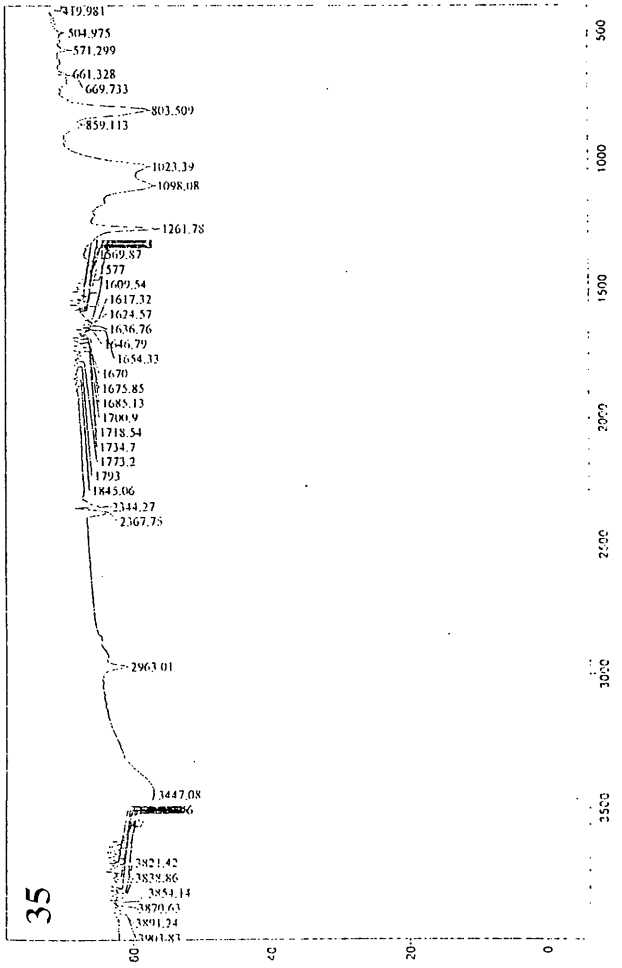
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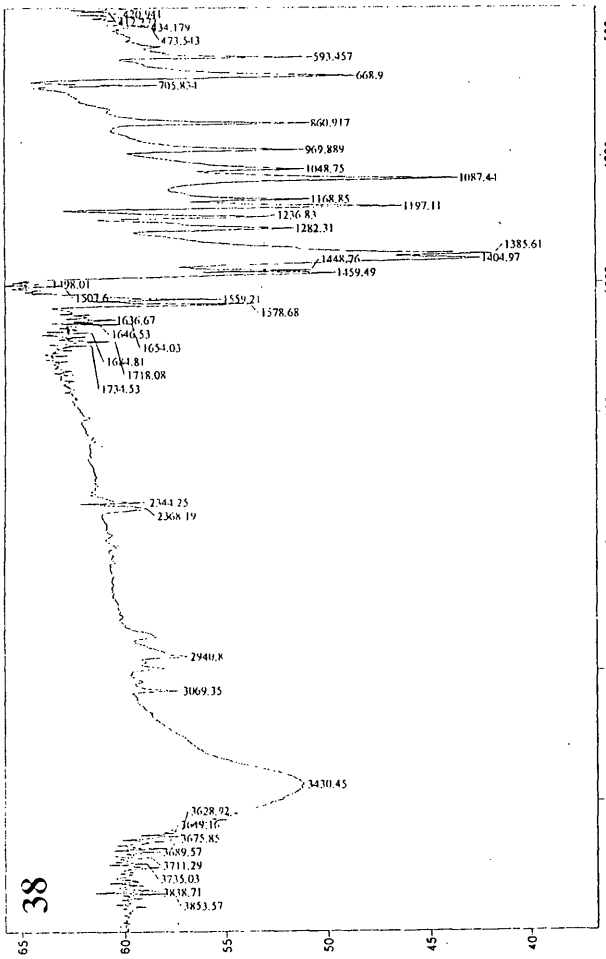
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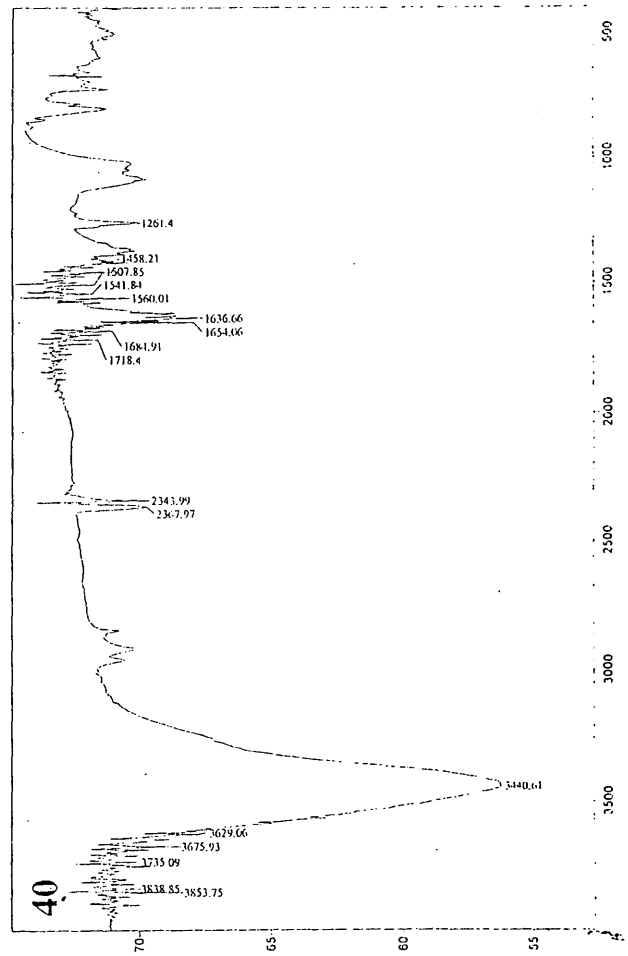
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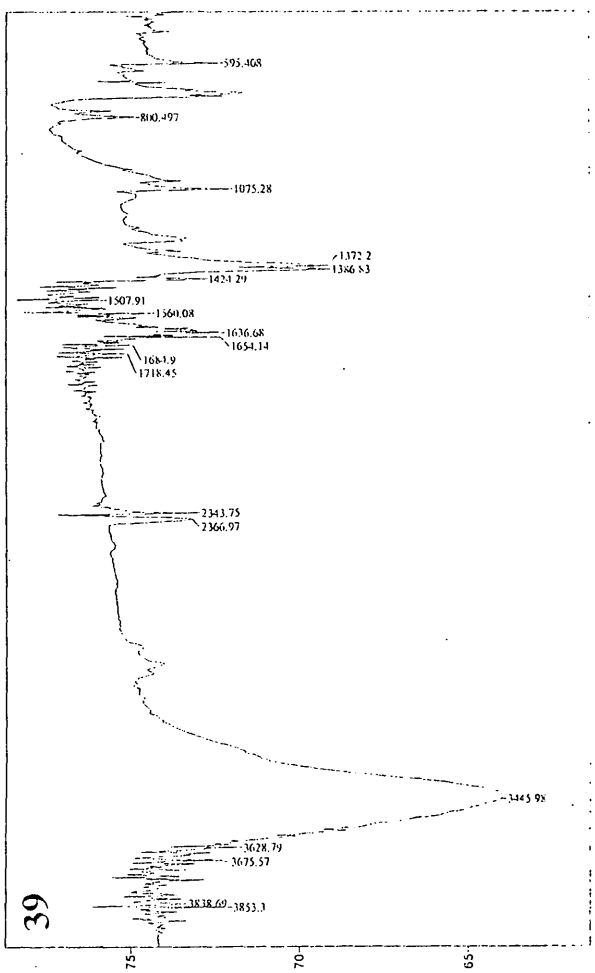
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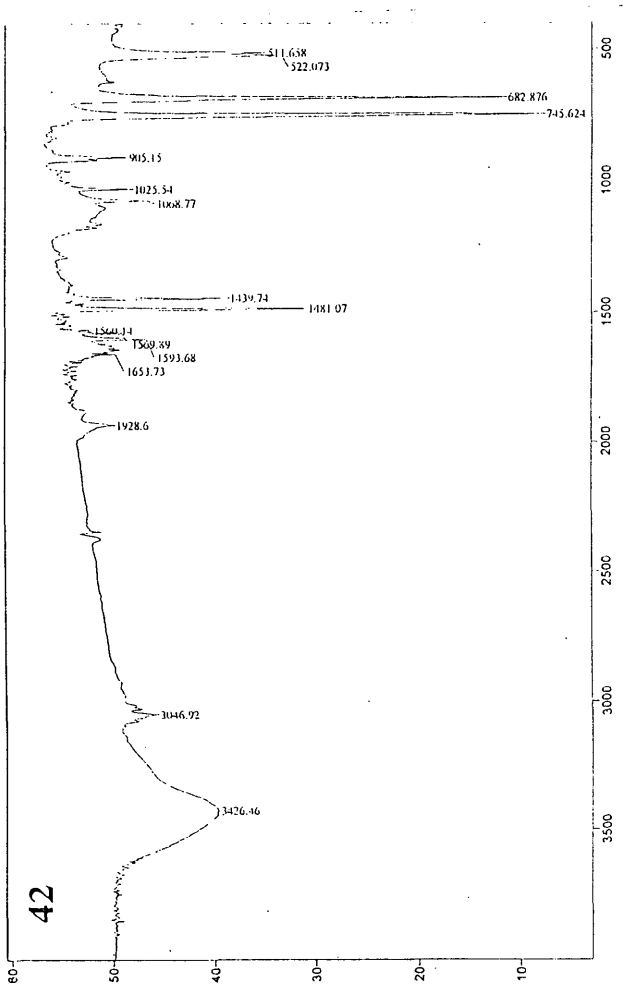
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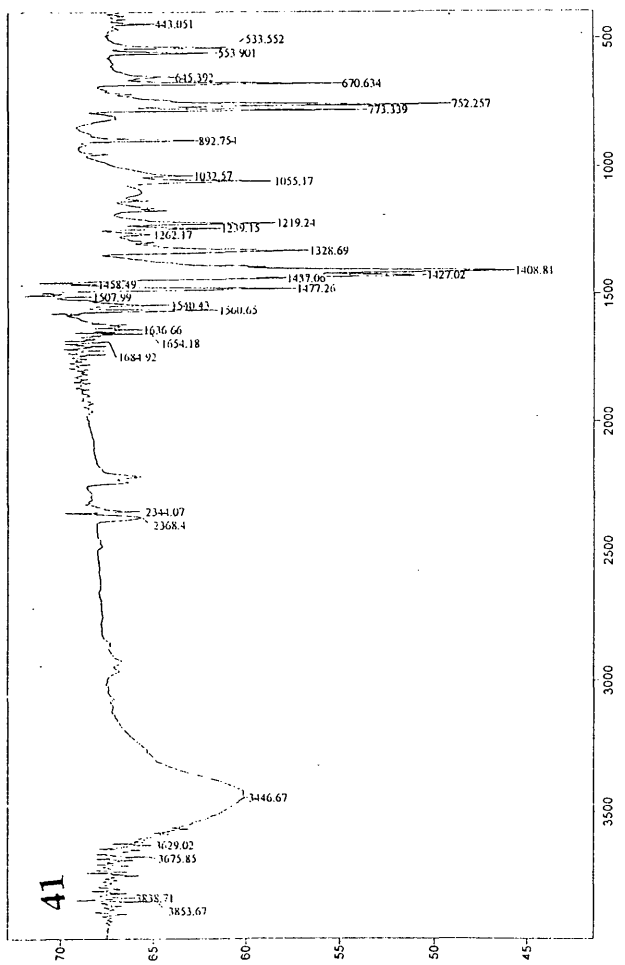
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APPENDIX D

1. 2,4,6-tribromo-3,5-difluoropyridine (**1**)

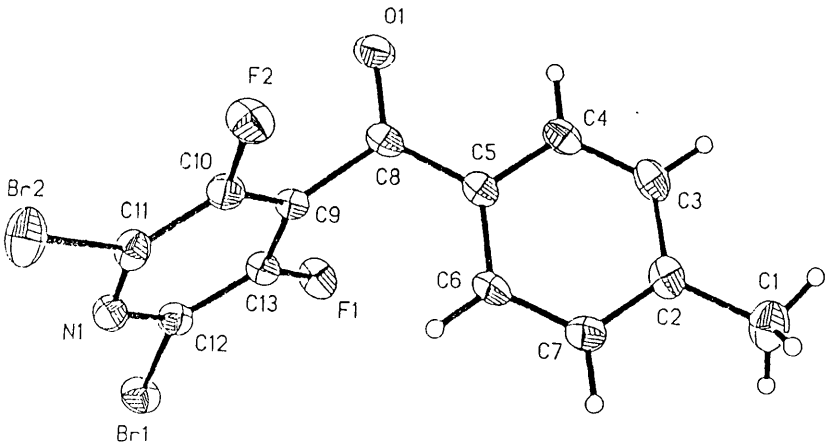

Table 1. Crystal data and structure refinement for Br2NF2OC13H7.

Identification code		
Empirical formula	C13 H7 Br2 F2 N O	
Formula weight	391.02	
Temperature	120(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)/c	
Unit cell dimensions	a = 7.4899(15) Å	α = 90°.
	b = 22.206(4) Å	β = 113.35(3)°.
	c = 8.6648(17) Å	γ = 90°.
Volume	1323.1(5) Å^3	
Z	4	
Density (calculated)	1.963 Mg/m^3	
Absorption coefficient	6.140 mm^{-1}	
F(000)	752	
Crystal size	0.44 x 0.20 x 0.20 mm^3	
Theta range for data collection	1.83 to 30.36°.	
Index ranges	-10<=h<=10, -31<=k<=31, -12<=l<=12	
Reflections collected	19375	
Independent reflections	3736 [R(int) = 0.0707]	
Completeness to theta = 30.36°	93.6 %	
Absorption correction	Guaussian (Tmin=0.151, Tmax=0.402)	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3736 / 0 / 172	
Goodness-of-fit on F^2	1.047	
Final R indices [I>2sigma(I)]	R1 = 0.0302, wR2 = 0.0714	
R indices (all data)	R1 = 0.0427, wR2 = 0.0758	
Largest diff. peak and hole	0.490 and -0.588 e.Å^{-3}	

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for Br2NF2OC13H7. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
Br(1)	2849(1)	5572(1)	8405(1)	31(1)
Br(2)	2410(1)	3781(1)	3894(1)	38(1)
F(2)	2058(2)	4843(1)	1588(2)	33(1)
F(1)	2296(2)	6379(1)	5393(2)	30(1)
C(9)	2144(3)	5634(1)	3416(3)	20(1)
N(1)	2545(3)	4771(1)	5873(2)	25(1)
C(12)	2534(3)	5353(1)	6212(3)	23(1)
O(1)	3523(3)	6148(1)	1791(2)	30(1)
C(11)	2390(3)	4609(1)	4356(3)	24(1)
C(6)	-1420(4)	6313(1)	1466(3)	23(1)
C(5)	306(3)	6464(1)	1301(3)	22(1)
C(4)	324(4)	6953(1)	290(3)	27(1)
C(8)	2081(4)	6103(1)	2107(3)	23(1)
C(7)	-3098(4)	6640(1)	607(3)	27(1)
C(13)	2318(3)	5794(1)	5016(3)	21(1)
C(10)	2201(3)	5025(1)	3105(3)	23(1)
C(2)	-3091(4)	7126(1)	-419(3)	26(1)
C(3)	-1344(4)	7283(1)	-540(3)	28(1)
C(1)	-4959(4)	7459(1)	-1391(4)	36(1)

Table 3. Bond lengths [Å] and angles [°] for Br2NF2OC13H7.

Br(1)-C(12)	1.884(2)	C(13)-C(12)-Br(1)	120.14(17)	C(7)-C(2)-C(1)	119.7(2)
Br(2)-C(11)	1.884(2)	N(1)-C(11)-C(10)	122.5(2)	C(4)-C(3)-C(2)	120.7(2)
F(2)-C(10)	1.338(2)	N(1)-C(11)-Br(2)	118.11(17)	C(4)-C(3)-H(3)	119.7
F(1)-C(13)	1.342(2)	C(10)-C(11)-Br(2)	119.36(17)	C(2)-C(3)-H(3)	119.7
C(9)-C(10)	1.384(3)	C(7)-C(6)-C(5)	119.9(2)	C(2)-C(1)-H(1A)	109.5
C(9)-C(13)	1.386(3)	C(7)-C(6)-H(6)	120.0	C(2)-C(1)-H(1B)	109.5
C(9)-C(8)	1.526(3)	C(5)-C(6)-H(6)	120.0	H(1A)-C(1)-H(1B)	109.5
N(1)-C(11)	1.323(3)	C(6)-C(5)-C(4)	119.3(2)	C(2)-C(1)-H(1C)	109.5
N(1)-C(12)	1.325(3)	C(6)-C(5)-C(8)	121.4(2)	H(1A)-C(1)-H(1C)	109.5
C(12)-C(13)	1.388(3)	C(4)-C(5)-C(8)	119.3(2)		
O(1)-C(8)	1.219(3)	C(3)-C(4)-C(5)	120.5(2)		
C(11)-C(10)	1.388(3)	C(3)-C(4)-H(4)	119.8		
C(6)-C(7)	1.385(4)	C(5)-C(4)-H(4)	119.8		
C(6)-C(5)	1.396(3)	O(1)-C(8)-C(5)	124.3(2)		
C(6)-H(6)	0.9500	O(1)-C(8)-C(9)	117.0(2)		
C(5)-C(4)	1.399(3)	C(5)-C(8)-C(9)	118.74(19)		
C(5)-C(8)	1.471(3)	C(6)-C(7)-C(2)	121.0(2)		
C(4)-C(3)	1.379(4)	C(6)-C(7)-H(7)	119.5		
C(4)-H(4)	0.9500	C(2)-C(7)-H(7)	119.5		
C(7)-C(2)	1.399(3)	F(1)-C(13)-C(9)	119.08(19)		
C(7)-H(7)	0.9500	F(1)-C(13)-C(12)	120.67(19)		
C(2)-C(3)	1.397(3)	C(9)-C(13)-C(12)	120.3(2)		
C(2)-C(1)	1.510(4)	F(2)-C(10)-C(9)	119.4(2)		
C(3)-H(3)	0.9500	F(2)-C(10)-C(11)	120.7(2)		
C(1)-H(1A)	0.9800	C(9)-C(10)-C(11)	120.0(2)		
C(1)-H(1B)	0.9800	C(3)-C(2)-C(7)	118.7(2)		
C(1)-H(1C)	0.9800	C(3)-C(2)-C(1)	121.6(2)		

2. 2,3,5,6-tetrafluoro-4-phenoxypyridine (18)

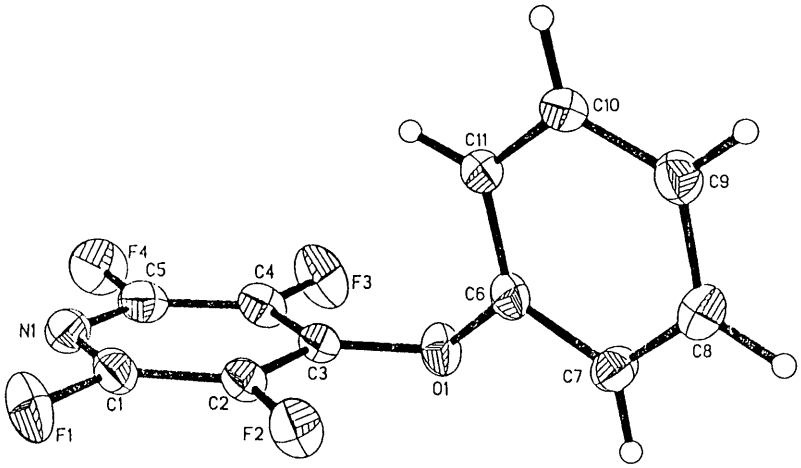

Table 1. Crystal data and structure refinement for s56ncs.

Identification code	s56ncs	
Empirical formula	C_{11} H$_5$ F4 N O	
Formula weight	243.16	
Temperature	120(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	P $2_12_12_1$	
Unit cell dimensions	a = 5.450(1) Å	α = 90°.
	b = 10.380(2) Å	β = 90°.
	c = 17.464(4) Å	γ = 90°.
Volume	987.9(3) Å^3	
Z	4	
Density (calculated)	1.635 Mg/m^3	
Absorption coefficient	0.157 mm^{-1}	
F(000)	488	
Crystal size	1.50 x 0.30 x 0.30 mm^3	
Theta range for data collection	2.28 to 29.99°.	
Index ranges	-7<=h<=7, -13<=k<=13, -23<=l<=23	
Reflections collected	11358	
Independent reflections	2664 [R(int) = 0.0379]	
Completeness to theta = 29.99°	94.7 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.9544 and 0.7986	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2664 / 0 / 175	
Goodness-of-fit on F^2	1.025	
Final R indices [I>2sigma(I)]	R1 = 0.0375, wR2 = 0.1001	
R indices (all data)	R1 = 0.0388, wR2 = 0.1016	
Absolute structure parameter	0.6(6)	
Largest diff. peak and hole	0.321 and -0.198 e.Å^{-3}	

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for s56ncs. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

Atom	x	y	z	U(eq)
F(1)	5445(2)	4694(1)	7737(1)	39(1)
F(2)	1442(2)	3781(1)	8475(1)	32(1)
F(3)	-460(3)	1415(1)	6231(1)	43(1)
F(4)	3638(3)	2453(1)	5588(1)	46(1)
O(1)	-1679(2)	2033(1)	7716(1)	28(1)
N(1)	4529(3)	3565(1)	6664(1)	30(1)
C(1)	3947(3)	3875(1)	7372(1)	27(1)
C(2)	1921(3)	3403(1)	7756(1)	23(1)
C(3)	378(3)	2534(1)	7389(1)	22(1)
C(4)	964(3)	2224(1)	6631(1)	28(1)
C(5)	3052(3)	2772(2)	6311(1)	30(1)
C(6)	-1430(3)	1515(1)	8464(1)	22(1)
C(7)	-3266(3)	1812(2)	8988(1)	26(1)
C(8)	-3155(3)	1247(2)	9712(1)	29(1)
C(9)	-1243(3)	413(1)	9904(1)	27(1)
C(10)	585(3)	138(1)	9367(1)	26(1)
C(11)	499(3)	694(1)	8637(1)	24(1)

Table 3. Bond lengths [Å] and angles [°] for s56ncs.

F(1)-C(1)	1.3400(18)	C(2)-C(3)	1.390(2)
F(2)-C(2)	1.3411(17)	C(3)-C(4)	1.400(2)
F(3)-C(4)	1.3388(19)	C(4)-C(5)	1.389(2)
F(4)-C(5)	1.3429(17)	C(6)-C(11)	1.387(2)
O(1)-C(3)	1.3610(17)	C(6)-C(7)	1.391(2)
O(1)-C(6)	1.4193(17)	C(7)-C(8)	1.395(2)
N(1)-C(5)	1.306(2)	C(8)-C(9)	1.395(2)
N(1)-C(1)	1.316(2)	C(9)-C(10)	1.397(2)
C(1)-C(2)	1.382(2)	C(10)-C(11)	1.400(2)

C(3)-O(1)-C(6)	116.86(11)	C(5)-C(4)-C(3)	118.21(14)
C(5)-N(1)-C(1)	116.66(14)	N(1)-C(5)-F(4)	116.86(15)
N(1)-C(1)-F(1)	117.09(14)	N(1)-C(5)-C(4)	125.01(14)
N(1)-C(1)-C(2)	124.19(15)	F(4)-C(5)-C(4)	118.12(16)
F(1)-C(1)-C(2)	118.71(14)	C(11)-C(6)-C(7)	122.53(13)
F(2)-C(2)-C(1)	120.44(13)	C(11)-C(6)-O(1)	120.40(13)
F(2)-C(2)-C(3)	120.24(13)	C(7)-C(6)-O(1)	116.97(13)
C(1)-C(2)-C(3)	119.32(13)	C(6)-C(7)-C(8)	118.20(14)
O(1)-C(3)-C(2)	123.57(13)	C(7)-C(8)-C(9)	120.67(14)
O(1)-C(3)-C(4)	119.79(14)	C(8)-C(9)-C(10)	119.92(14)
C(2)-C(3)-C(4)	116.57(14)	C(9)-C(10)-C(11)	120.18(14)
F(3)-C(4)-C(5)	121.45(14)	C(6)-C(11)-C(10)	118.50(13)
F(3)-C(4)-C(3)	120.33(15)		

3. 2,4-dibromo-3,5-difluoro-6-[2-(4-fluorophenyl)ethynyl]pyridine (35)

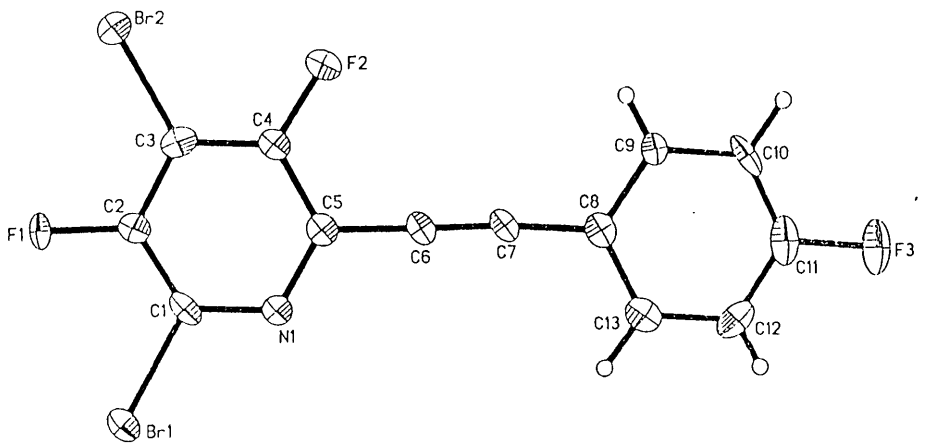

Table 1. Crystal data and structure refinement for 00srv356.

Identification code	sa356	
Empirical formula	C_{13} H$_4$ Br_2 F_3 N	
Formula weight	390.99	
Temperature	110.0(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	P bcm	
Unit cell dimensions	a = 7.7352(5) Å	α= 90°.
	b = 25.472(2) Å	β= 90°.
	c = 6.5491(5) Å	γ = 90°.
Volume	1290.4(4) Å^3	
Z	4	
Density (calculated)	2.013 Mg/m^3	
Absorption coefficient	6.301 mm^{-1}	
F(000)	744	
Crystal size	0.28 x 0.08 x 0.04 mm^3	
Theta range for data collection	1.60 to 27.50°.	
Index ranges	-9<=h<=10, -33<=k<=33, -8<=l<=8	
Reflections collected	10718	
Independent reflections	1617 [R(int) = 0.0937]	
Completeness to theta = 27.50°	99.9 %	
Absorption correction	Gaussian	
Max. and min. transmission	0.780 and 0.352	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	1617 / 0 / 127	
Goodness-of-fit on F^2	1.029	
Final R indices [I>2sigma(I)]	R1 = 0.0401, wR2 = 0.0832	
R indices (all data)	R1 = 0.0671, wR2 = 0.0913	
Largest diff. peak and hole	0.856 and -0.716 e.Å^{-3}	

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for 00srv356. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

Atom	x	y	z	U(eq)
Br(1)	1067(1)	11628(1)	2500	29(1)
Br(2)	-5365(1)	10541(1)	2500	23(1)
F(1)	-2847(4)	11468(1)	2500	22(1)
F(2)	-2789(4)	9624(1)	2500	28(1)
F(3)	5487(6)	7388(2)	2500	52(1)
N(1)	685(6)	10549(2)	2500	20(1)
C(1)	-226(8)	10993(2)	2500	22(1)
C(2)	-2094(7)	11006(2)	2500	18(1)
C(3)	-2948(8)	10546(2)	2500	23(1)
C(4)	-1995(8)	10087(2)	2500	22(1)
C(5)	-183(8)	10098(2)	2500	18(1)
C(6)	752(8)	9608(2)	2500	22(1)
C(7)	1505(8)	9190(2)	2500	18(1)
C(8)	2509(8)	8721(2)	2500	20(1)
C(9)	1746(9)	8224(2)	2500	24(1)
C(10)	2736(10)	7781(2)	2500	34(2)
C(11)	4487(10)	7831(3)	2500	36(2)
C(12)	5293(10)	8307(3)	2500	35(2)
C(13)	4306(9)	8756(3)	2500	29(2)

Table 3. Bond lengths [Å] and angles [°] for 00srv356.

Br(1)-C(1)	1.903(6)	C(1)-C(2)	1.376(8)	C(8)-C(13)	1.393(9)
Br(2)-C(3)	1.870(6)	C(2)-C(3)	1.381(8)	C(8)-C(9)	1.395(8)
F(1)-C(2)	1.345(6)	C(3)-C(4)	1.382(9)	C(9)-C(10)	1.365(9)
F(2)-C(4)	1.330(7)	C(4)-C(5)	1.402(9)	C(10)-C(11)	1.360(11)
F(3)-C(11)	1.367(7)	C(5)-C(6)	1.443(8)	C(11)-C(12)	1.363(11)
N(1)-C(1)	1.332(7)	C(6)-C(7)	1.213(8)	C(12)-C(13)	1.375(10)
N(1)-C(5)	1.332(7)	C(7)-C(8)	1.425(8)		

C(1)-N(1)-C(5)	117.8(5)	N(1)-C(5)-C(6)	119.7(5)
N(1)-C(1)-C(2)	123.4(5)	C(4)-C(5)-C(6)	119.0(5)
N(1)-C(1)-Br(1)	116.3(5)	C(7)-C(6)-C(5)	178.7(7)
C(2)-C(1)-Br(1)	120.3(5)	C(6)-C(7)-C(8)	175.7(7)
F(1)-C(2)-C(1)	120.4(5)	C(13)-C(8)-C(9)	118.7(6)
F(1)-C(2)-C(3)	119.1(5)	C(13)-C(8)-C(7)	119.3(6)
C(1)-C(2)-C(3)	120.5(6)	C(9)-C(8)-C(7)	122.0(6)
C(2)-C(3)-C(4)	115.9(5)	C(10)-C(9)-C(8)	120.9(7)
C(2)-C(3)-Br(2)	122.3(5)	C(11)-C(10)-C(9)	118.7(6)
C(4)-C(3)-Br(2)	121.9(5)	C(10)-C(11)-C(12)	122.6(7)
F(2)-C(4)-C(3)	120.3(5)	C(10)-C(11)-F(3)	119.0(7)
F(2)-C(4)-C(5)	118.6(5)	C(12)-C(11)-F(3)	118.3(7)
C(3)-C(4)-C(5)	121.1(6)	C(11)-C(12)-C(13)	119.1(7)
N(1)-C(5)-C(4)	121.4(6)	C(12)-C(13)-C(8)	120.0(6)

5. 4,6-dibromo-6-[2-(2-chlorophenyl)-1-ethynyl]-3,5-difluoropyridine (41)

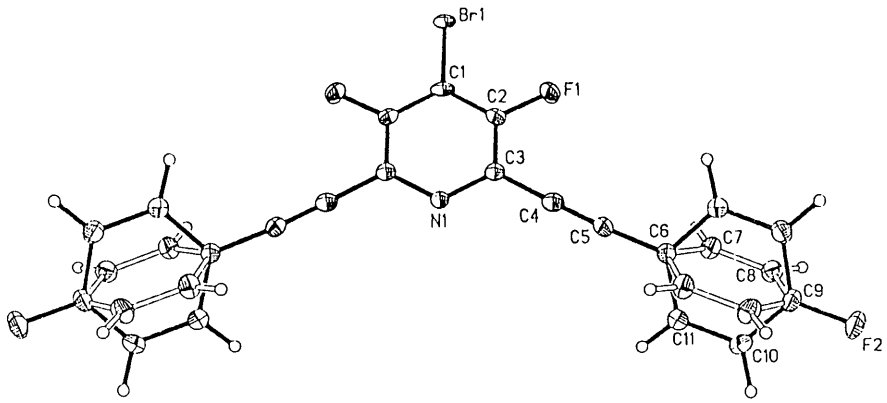

Table 1. Crystal data and structure refinement for 00srv362.

Identification code	s362sd	
Empirical formula	C_{21} H_8 Br F_4 N	
Formula weight	430.19	
Temperature	110.0(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	Cmcm	
Unit cell dimensions	a = 6.7571(5) Å	α= 90°.
	b = 7.5303(6) Å	β= 90°.
	c = 34.319(2) Å	γ = 90°.
Volume	1746.3(2) Å^3	
Z	4	
Density (calculated)	1.636 Mg/m^3	
Absorption coefficient	2.399 mm^{-1}	
F(000)	848	
Crystal size	0.40 x 0.40 x 0.40 mm^3	
Theta range for data collection	2.37 to 29.39°.	
Index ranges	-7<=h<=9, -10<=k<=9, -46<=l<=45	
Reflections collected	6575	
Independent reflections	1231 [R(int) = 0.0234]	
Completeness to theta = 29.39°	93.8 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.4471 and 0.4471	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	1231 / 0 / 110	
Goodness-of-fit on F^2	1.284	
Final R indices [I>2sigma(I)]	R1 = 0.0296, wR2 = 0.0675	
R indices (all data)	R1 = 0.0331, wR2 = 0.0684	
Extinction coefficient	0.0091(5)	
Largest diff. peak and hole	0.903 and -1.256 e.Å^{-3}	

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for 00srv362. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

Atom	x	y	z	U(eq)
Br(1)	0	2841(1)	2500	17(1)
F(1)	0	5453(2)	1813(1)	22(1)
F(2)	0	13004(3)	30(1)	31(1)
N(1)	0	9072(4)	2500	14(1)
C(1)	0	5336(5)	2500	17(1)
C(2)	0	6302(4)	2158(1)	16(1)
C(3)	0	8162(4)	2162(1)	15(1)
C(4)	0	9149(4)	1803(1)	19(1)
C(5)	0	9924(4)	1499(1)	18(1)
C(6)	0	10758(4)	1123(1)	18(1)
C(7)	1111(6)	9956(6)	820(1)	21(1)
C(8)	1138(6)	10712(6)	452(1)	22(1)
C(9)	0	12262(4)	393(1)	22(1)
C(10)	998(7)	13090(6)	682(1)	24(1)
C(11)	1000(7)	12334(6)	1053(1)	22(1)

Table 3. Bond lengths [Å] and angles [°] for 00srv362.

Br(1)-C(1)	1.879(4)	C(2)-C(3)	1.401(4)	C(6)-C(7)	1.417(4)
F(1)-C(2)	1.345(3)	C(3)-C(4)	1.439(4)	C(7)-C(8)	1.386(5)
F(2)-C(9)	1.364(3)	C(4)-C(5)	1.194(4)	C(8)-C(9)	1.412(5)
N(1)-C(3)	1.347(3)	C(5)-C(6)	1.437(4)	C(9)-C(10)	1.351(5)
C(1)-C(2)	1.382(3)	C(6)-C(11)	1.386(5)	C(10)-C(11)	1.396(5)

C(3)-N(1)-C(3)#1	118.9(3)	C(11)-C(6)-C(7)#2	119.7(3)
C(2)#1-C(1)-C(2)	116.5(4)	C(11)-C(6)-C(5)	122.0(3)
C(2)-C(1)-Br(1)	121.8(2)	C(7)-C(6)-C(5)	118.2(3)
F(1)-C(2)-C(1)	119.9(3)	C(8)-C(7)-C(6)	120.0(4)
F(1)-C(2)-C(3)	119.0(3)	C(7)-C(8)-C(9)	117.6(4)
C(1)-C(2)-C(3)	121.1(3)	C(10)-C(9)-F(2)	118.7(3)
N(1)-C(3)-C(2)	121.2(3)	C(10)-C(9)-C(8)#2	123.2(3)
N(1)-C(3)-C(4)	118.4(2)	F(2)-C(9)-C(8)	118.0(3)
C(2)-C(3)-C(4)	120.5(3)	C(9)-C(10)-C(11)	118.8(4)
C(5)-C(4)-C(3)	178.2(3)	C(6)-C(11)-C(10)	120.5(4)
C(4)-C(5)-C(6)	176.6(3)		

Symmetry transformations used to generate equivalent atoms:

#1 x,y,-z+1/2 #2 -x,y,z

5. 4,6-dibromo-6-[2-(2-chlorophenyl)-1-ethynyl]-3,5-difluoropyridine (41)

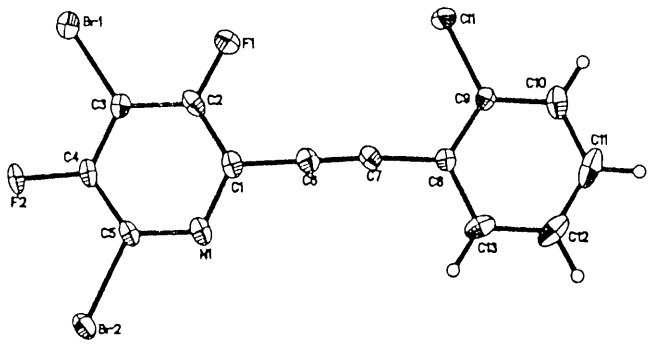

Table 1. Crystal data and structure refinement for 01srv089.

Identification code	s89a	
Empirical formula	$C_{13}H_4Br_2ClF_2N$	
Formula weight	407.44	
Temperature	110.0(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	P -1	
Unit cell dimensions	a = 7.3417(4) Å	α= 80.176(2)°.
	b = 8.0609(5) Å	β= 85.218(2)°.
	c = 12.1505(7) Å	γ = 64.941(2)°.
Volume	641.79(6) Å^3	
Z	2	
Density (calculated)	2.108 Mg/m^3	
Absorption coefficient	6.529 mm^{-1}	
F(000)	388	
Crystal size	0.22 x 0.08 x 0.02 mm^3	
Theta range for data collection	1.70 to 30.27°.	
Index ranges	-9<=h<=10, -10<=k<=11, -17<=l<=16	
Reflections collected	7269	
Independent reflections	3438 [R(int) = 0.0385]	
Completeness to theta = 30.27°	89.6 %	
Absorption correction	Gaussian	
Max. and min. transmission	0.88 and 0.36	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3438 / 0 / 172	
Goodness-of-fit on F^2	1.137	
Final R indices [I>2sigma(I)]	R1 = 0.0470, wR2 = 0.0966	
R indices (all data)	R1 = 0.0636, wR2 = 0.1010	
Largest diff. peak and hole	1.396 and -0.796 e.Å^{-3}	

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for 01srv089. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

Atom	x	y	z	U(eq)
Br(1)	3516(1)	3748(1)	2026(1)	29(1)
Br(2)	3131(1)	9334(1)	4419(1)	32(1)
Cl(1)	2039(2)	10639(2)	-2932(1)	29(1)
F(1)	2888(4)	6992(4)	119(2)	34(1)
F(2)	3545(4)	5575(4)	4016(2)	31(1)
N(1)	2831(5)	9788(5)	2137(3)	25(1)
C(1)	2747(6)	9239(6)	1154(4)	24(1)
C(2)	2952(6)	7460(7)	1101(3)	26(1)
C(3)	3245(6)	6157(6)	2063(4)	21(1)
C(4)	3303(6)	6749(6)	3057(3)	25(1)
C(5)	3100(6)	8529(6)	3055(3)	22(1)
C(6)	2432(6)	10570(6)	163(4)	27(1)
C(7)	2182(6)	11667(6)	-671(4)	24(1)
C(8)	1912(6)	13083(6)	-1620(3)	20(1)
C(9)	1840(6)	12766(6)	-2703(4)	22(1)
C(10)	1621(7)	14153(7)	-3617(4)	33(1)
C(11)	1449(7)	15845(7)	-3429(5)	41(1)
C(12)	1493(7)	16196(7)	-2351(5)	38(1)
C(13)	1744(6)	14812(6)	-1442(5)	30(1)

Table 3. Bond lengths [Å] and angles [°] for 01srv089.

Br(1)-C(3)	1.875(4)	C(1)-C(2)	1.389(7)	C(8)-C(9)	1.392(6)
Br(2)-C(5)	1.884(4)	C(1)-C(6)	1.432(6)	C(8)-C(13)	1.399(6)
Cl(1)-C(9)	1.727(4)	C(2)-C(3)	1.395(6)	C(9)-C(10)	1.401(6)
F(1)-C(2)	1.322(5)	C(3)-C(4)	1.383(6)	C(10)-C(11)	1.373(8)
F(2)-C(4)	1.341(4)	C(4)-C(5)	1.378(6)	C(11)-C(12)	1.392(8)
N(1)-C(5)	1.340(5)	C(6)-C(7)	1.196(6)	C(12)-C(13)	1.392(7)
N(1)-C(1)	1.357(6)	C(7)-C(8)	1.438(6)		

C(5)-N(1)-C(1)	116.4(4)	N(1)-C(5)-Br(2)	116.0(3)
N(1)-C(1)-C(2)	121.8(4)	C(4)-C(5)-Br(2)	119.6(3)
N(1)-C(1)-C(6)	117.4(4)	C(7)-C(6)-C(1)	179.3(5)
C(2)-C(1)-C(6)	120.7(4)	C(6)-C(7)-C(8)	175.2(5)
F(1)-C(2)-C(1)	119.3(4)	C(9)-C(8)-C(13)	119.5(4)
F(1)-C(2)-C(3)	119.5(4)	C(9)-C(8)-C(7)	121.7(4)
C(1)-C(2)-C(3)	121.2(4)	C(13)-C(8)-C(7)	118.7(4)
C(4)-C(3)-C(2)	116.1(4)	C(8)-C(9)-C(10)	120.7(4)
C(4)-C(3)-Br(1)	121.4(3)	C(8)-C(9)-Cl(1)	120.0(3)
C(2)-C(3)-Br(1)	122.5(3)	C(10)-C(9)-Cl(1)	119.3(4)
F(2)-C(4)-C(5)	120.9(4)	C(11)-C(10)-C(9)	119.0(5)
F(2)-C(4)-C(3)	119.2(4)	C(10)-C(11)-C(12)	121.2(5)
C(5)-C(4)-C(3)	119.9(4)	C(11)-C(12)-C(13)	120.0(5)
N(1)-C(5)-C(4)	124.5(4)	C(12)-C(13)-C(8)	119.5(5)

7. -{4-bromo-3, 5-difluoro-6- [2-(4- H methoxyphenyl) ethynyl](2-pyridyl)} ethynyl)-4-methoxybenzene (42)

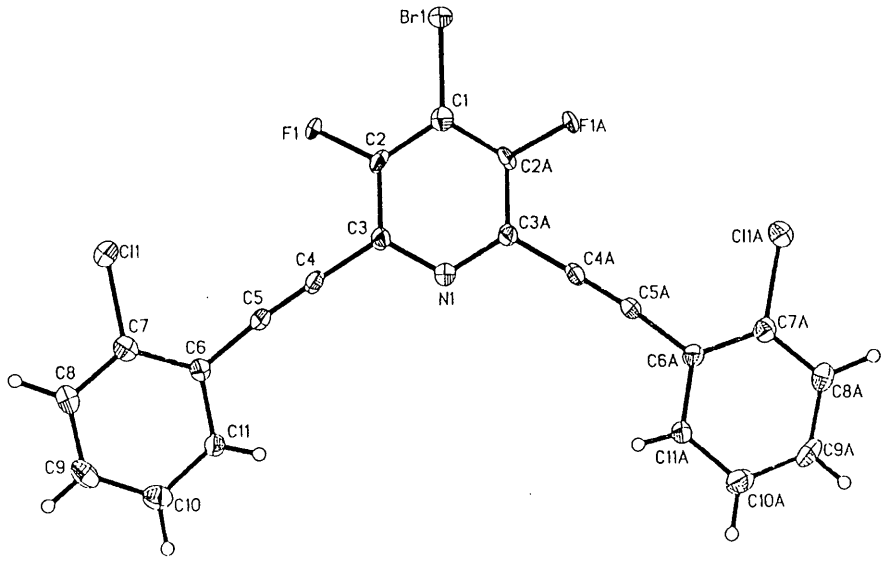

Table 1. Crystal data and structure refinement for 00srv357.

Identification code	s357s	
Empirical formula	$C_{21} H_8 Br Cl_2 F_2 N$	
Formula weight	463.09	
Temperature	110.0(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	C 2/c	
Unit cell dimensions	a = 30.759(3) Å	α= 90°.
	b = 8.0868(8) Å	β= 101.63(3)°.
	c = 7.3531(8) Å	γ = 90°.
Volume	1791.5(6) Å^3	
Z	4	
Density (calculated)	1.717 Mg/m^3	
Absorption coefficient	2.618 mm^{-1}	
F(000)	912	
Crystal size	0.30 x 0.08 x 0.02 mm^3	
Theta range for data collection	2.61 to 26.00°.	
Index ranges	-32<=h<=37, -9<=k<=7, -8<=l<=9	
Reflections collected	5151	
Independent reflections	1750 [R(int) = 0.0756]	
Completeness to theta = 26.00°	99.8 %	
Absorption correction	Multi-scan	
Max. and min. transmission	0.9495 and 0.5072	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	1750 / 0 / 140	
Goodness-of-fit on F^2	1.120	
Final R indices [I>2sigma(I)]	R1 = 0.0565, wR2 = 0.1182	
R indices (all data)	R1 = 0.0906, wR2 = 0.1322	
Largest diff. peak and hole	0.670 and -1.055 e.Å^{-3}	

Table 1. Crystal data and structure refinement for 01srv932.

Identification code	s32f	
Empirical formula	$C_{21} H_8 Br Cl_2 F_2 N$	
Formula weight	463.09	
Temperature	100.0(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	P 21212	
Unit cell dimensions	a = 31.194(1) Å	α= 90°
	b = 3.8128(2) Å	β= 90°
	c = 7.6002(4) Å	γ = 90°
Volume	903.94(8) Å^3	
Z	2	
Density (calculated)	1.701 Mg m^{-3}	
Absorption coefficient	2.594 mm^{-1}	
F(000)	456	
Crystal size	0.52 x 0.10 x 0.02 mm^3	
Theta range for data collection	2.61 to 24.58°.	
Index ranges	-35<=h<=35, -4<=k<=4, -8<=l<=8	
Reflections collected	5477	
Independent reflections	1412 [R(int) = 0.0698]	
Completeness to theta = 24.58°	95.7 %	
Absorption correction	Numerical	
Max. and min. transmission	0.963 and 0.508	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	1412 / 0 / 125	
Goodness-of-fit on F^2	1.105	
Final R indices [I>2sigma(I)]	R1 = 0.0369, wR2 = 0.0656	
R indices (all data)	R1 = 0.0515, wR2 = 0.0698	
Absolute structure parameter	0.003(17)	
Largest diff. peak and hole	0.509 and -0.324 e.Å^{-3}	

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for 00srv357. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

Atom	x	y	z	U(eq)
Br(1)	5000	4040(1)	2500	22(1)
Cl(1)	3148(1)	-1076(2)	-2683(2)	34(1)
F(1)	4284(1)	1584(4)	597(4)	22(1)
N(1)	5000	-1762(8)	2500	19(2)
C(1)	5000	1731(10)	2500	19(2)
C(2)	4643(2)	807(7)	1552(7)	17(1)
C(3)	4647(2)	-929(7)	1545(7)	15(1)
C(4)	4283(2)	-1843(7)	506(7)	17(1)
C(5)	3988(2)	-2628(6)	-405(8)	17(1)
C(6)	3653(2)	-3720(6)	-1362(8)	18(1)
C(7)	3245(2)	-3196(7)	-2405(7)	19(1)
C(8)	2921(2)	-4293(7)	-3224(8)	23(1)
C(9)	3008(2)	-5980(8)	-3015(8)	26(1)
C(10)	3410(2)	-6552(8)	-2014(8)	25(1)
C(11)	3729(2)	-5434(7)	-1180(8)	17(1)

Table 3. Bond lengths [Å] and angles [°] for 00srv357

Br(1)-C(1)	1.867(8)	C(1)-C(2)#1	1.392(7)	C(6)-C(11)	1.401(7)
Cl(1)-C(7)	1.745(6)	C(2)-C(3)	1.404(7)	C(7)-C(8)	1.379(9)
F(1)-C(2)	1.340(6)	C(3)-C(4)	1.429(8)	C(8)-C(9)	1.393(9)
N(1)-C(3)#1	1.348(6)	C(4)-C(5)	1.195(7)	C(9)-C(10)	1.383(9)
N(1)-C(3)	1.348(6)	C(5)-C(6)	1.431(8)	C(10)-C(11)	1.355(8)
C(1)-C(2)	1.392(7)	C(6)-C(7)	1.396(8)		

C(3)#1-N(1)-C(3)	120.0(7)	C(4)-C(5)-C(6)	177.6(6)
C(2)-C(1)-C(2)#1	115.1(7)	C(7)-C(6)-C(11)	117.8(5)
C(2)-C(1)-Br(1)	122.4(4)	C(7)-C(6)-C(5)	124.2(5)
C(2)#1-C(1)-Br(1)	122.4(4)	C(11)-C(6)-C(5)	118.0(5)
F(1)-C(2)-C(1)	119.6(5)	C(8)-C(7)-C(6)	122.3(5)
F(1)-C(2)-C(3)	118.3(5)	C(8)-C(7)-Cl(1)	119.3(5)
C(1)-C(2)-C(3)	122.1(5)	C(6)-C(7)-Cl(1)	118.4(4)
N(1)-C(3)-C(2)	120.3(5)	C(7)-C(8)-C(9)	118.4(6)
N(1)-C(3)-C(4)	118.9(5)	C(10)-C(9)-C(8)	121.3(6)
C(2)-C(3)-C(4)	120.9(5)	C(9)-C(10)-C(11)	119.7(6)
C(5)-C(4)-C(3)	177.5(6)	C(10)-C(11)-C(6)	120.7(6)

Symmetry transformations used to generate equivalent atoms

1,y,-z+1/2

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for 01srv032

U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

Atom	x	y	z	U(eq)
Br(1)	5000	5000	-687(1)	22(1)
Cl(1)	6823(1)	10088(6)	4407(2)	38(1)
F(1)	5683(1)	7634(7)	1917(4)	25(1)
N(1)	5000	5000	5493(7)	20(1)
C(1)	5334(1)	6351(11)	4583(6)	15(1)
C(2)	5337(1)	6290(11)	2757(7)	16(1)
C(3)	5000	5000	1732(8)	24(2)
C(4)	5683(2)	7853(12)	5543(7)	19(1)
C(5)	5978(2)	9222(11)	6304(6)	17(1)
C(6)	6318(1)	10802(11)	7287(6)	17(1)
C(7)	6724(2)	11334(13)	6574(7)	23(1)
C(8)	7054(2)	12825(14)	7540(8)	30(1)
C(9)	6975(2)	13842(12)	9266(8)	32(1)
C(10)	6577(2)	13402(14)	10004(7)	30(1)
C(11)	6247(2)	11886(12)	9024(7)	21(1)

Table 3. Bond lengths [Å] and angles [°] for 01srv032.

Br(1)-C(3)	1.839(6)	C(1)-C(4)	1.432(7)	C(6)-C(11)	1.401(7)
Cl(1)-C(7)	1.742(6)	C(2)-C(3)	1.399(6)	C(7)-C(8)	1.386(7)
F(1)-C(2)	1.354(5)	C(3)-C(2)#1	1.399(6)	C(8)-C(9)	1.390(8)
N(1)-C(1)#1	1.352(5)	C(4)-C(5)	1.204(6)	C(9)-C(10)	1.373(8)
N(1)-C(1)	1.352(5)	C(5)-C(6)	1.432(7)	C(10)-C(11)	1.396(7)
C(1)-C(2)	1.388(7)	C(6)-C(7)	1.392(7)		

C(1)#1-N(1)-C(1)	118.2(6)	C(4)-C(5)-C(6)	177.3(5)
N(1)-C(1)-C(2)	120.8(4)	C(7)-C(6)-C(11)	117.9(4)
N(1)-C(1)-C(4)	118.6(5)	C(7)-C(6)-C(5)	122.3(4)
C(2)-C(1)-C(4)	120.6(4)	C(11)-C(6)-C(5)	119.8(4)
F(1)-C(2)-C(1)	118.1(4)	C(8)-C(7)-C(6)	121.9(5)
F(1)-C(2)-C(3)	118.0(5)	C(8)-C(7)-Cl(1)	118.8(4)
C(1)-C(2)-C(3)	123.8(4)	C(6)-C(7)-Cl(1)	119.3(4)
C(2)-C(3)-C(2)#1	112.3(6)	C(7)-C(8)-C(9)	118.8(5)
C(2)-C(3)-Br(1)	123.8(3)	C(10)-C(9)-C(8)	120.8(5)
C(2)#1-C(3)-Br(1)	123.8(3)	C(9)-C(10)-C(11)	119.9(5)
C(5)-C(4)-C(1)	177.5(5)	C(10)-C(11)-C(6)	120.5(5)

Symmetry transformations used to generate equivalent atoms: #1 -x+1,-y+1,z

7. -{4-bromo-3, 5-difluoro-6- [2-(4- H methoxyphenyl) ethynyl](2-pyridyl)} ethynyl)-4-methoxybenzene (42)

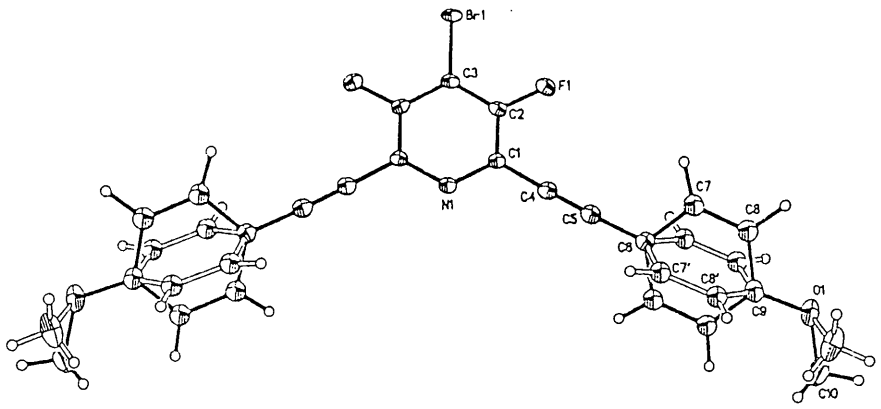

Table 1. Crystal data and structure refinement for 00srv335.

Identification code	s335	
Empirical formula	$C_{23} H_{14} Br F_2 N O_2$	
Formula weight	454.26	
Temperature	110.0(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	Fmm2	
Unit cell dimensions	a = 6.7680(2) Å	α= 90°.
	b = 39.553(1) Å	β= 90°.
	c = 7.4739(2) Å	γ = 90°.
Volume	2000.7(2) Å^3	
Z	4	
Density (calculated)	1.508 Mg/m^3	
Absorption coefficient	2.091 mm^{-1}	
F(000)	912	
Crystal size	0.42 x 0.38 x 0.02 mm^3	
Theta range for data collection	2.06 to 30.52°.	
Index ranges	-9<=h<=9, -54<=k<=54, -9<=l<=10	
Reflections collected	6179	
Independent reflections	1526 [R(int) = 0.0399]	
Completeness to theta = 30.52°	95.3 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.9594 and 0.4737	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	1526 / 1 / 108	
Goodness-of-fit on F^2	1.168	
Final R indices [I>2sigma(I)]	R1 = 0.0233, wR2 = 0.0565	
R indices (all data)	R1 = 0.0237, wR2 = 0.0569	
Absolute structure parameter	0.040(9)	
Largest diff. peak and hole	0.630 and -0.297 e.Å^{-3}	

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for 00srv335. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

Atom	x	y	z	U(eq)
Br(1)	5000	0	4717(1)	19(1)
F(1)	5000	598(1)	7340(2)	24(1)
O(1)	5000	2147(1)	15064(3)	32(1)
N(1)	5000	0	10975(4)	17(1)
C(1)	5000	293(1)	10077(3)	16(1)
C(2)	5000	299(1)	8201(3)	17(1)
C(3)	5000	0	7219(4)	17(1)
C(4)	5000	605(1)	11072(4)	21(1)
C(5)	5000	864(1)	11863(3)	22(1)
C(6)	5000	1188(1)	12756(3)	22(1)
C(7)	3770(6)	1455(1)	12068(5)	25(1)
C(8)	3834(6)	1770(1)	12867(5)	26(1)
C(7')	3926(6)	1244(1)	14272(4)	25(1)
C(8')	3846(5)	1564(1)	15079(4)	25(1)
C(9)	5000	1825(1)	14372(3)	24(1)
C(10)	6175(9)	2215(1)	16580(8)	43(1)

Table 3. Bond lengths [Å] and angles [°] for 00srv335.

Br(1)-C(3)	1.870(3)	C(1)-C(4)	1.439(3)	C(6)-C(7)	1.438(4)
F(1)-C(2)	1.346(3)	C(2)-C(3)	1.392(3)	C(7)-C(8)	1.382(5)
O(1)-C(9)	1.372(3)	C(4)-C(5)	1.186(4)	C(8)-C(9)	1.391(4)
O(1)-C(10)	1.411(5)	C(5)-C(6)	1.445(3)	C(7')-C(8')	1.403(5)
N(1)-C(1)	1.339(3)	C(6)-C(7')	1.364(4)	C(8')-C(9)	1.398(4)
C(1)-C(2)	1.402(3)				

C(9)-O(1)-C(10)	118.8(2)	C(4)-C(5)-C(6)	177.6(3)
C(1)#1-N(1)-C(1)	119.3(3)	C(7')#2-C(6)-C(7)	119.1(3)
N(1)-C(1)-C(2)	121.1(2)	C(7')-C(6)-C(5)	121.8(2)
N(1)-C(1)-C(4)	118.8(2)	C(7)-C(6)-C(5)	119.0(2)
C(2)-C(1)-C(4)	120.1(2)	C(8)-C(7)-C(6)	119.2(3)
F(1)-C(2)-C(3)	119.6(2)	C(7)-C(8)-C(9)	120.6(3)
F(1)-C(2)-C(1)	119.6(2)	C(6)-C(7')-C(8')	121.6(3)
C(3)-C(2)-C(1)	120.8(2)	C(9)-C(8')-C(7')	118.8(3)
C(2)-C(3)-C(2)#1	116.3(3)	O(1)-C(9)-C(8)	116.8(2)
C(2)-C(3)-Br(1)	121.8(2)	O(1)-C(9)-C(8')	122.7(2)
C(5)-C(4)-C(1)	178.8(3)	C(8)#2-C(9)-C(8')	120.4(3)

Symmetry transformations used to generate equivalent atoms:

#1 -x+1,-y,z #2 -x+1,y,z

8. 2,6-bis(4-methylphenyl)-4-bromo-3,5-difluoropyridine (47)

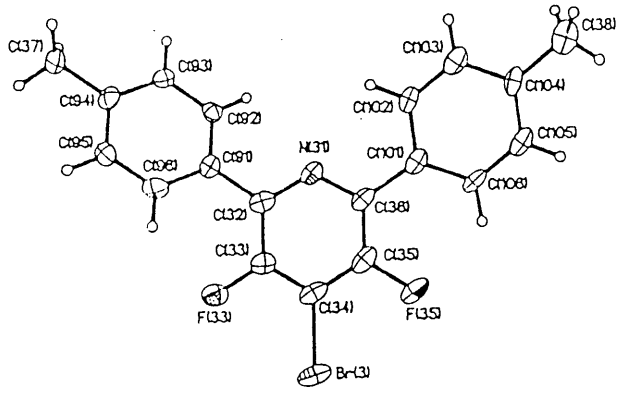

Table 1. Crystal data and structure refinement for 00srv347.

Identification code		
Empirical formula	C19 H14 Br F2 N	
Formula weight	374.22	
Temperature	110(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	P-1 (No. 2)	
Unit cell dimensions	a = 9.592(2) Å	α= 101.87(1)°
	b = 17.542(2) Å	β= 97.11(1)°
	c = 19.311(5) Å	γ = 97.88(1)°
Volume	3111(1) Å^3	
Z	8	
Density (calculated)	1.598 g/cm^3	
Absorption coefficient	2.662 mm^{-1}	
F(000)	1504	
Crystal size	0.50 × 0.13 × 0.04 mm^3	
θ range for data collection	1.09 to 24.99°.	
Index ranges	$-10 \le h \le 11$, $-19 \le k \le 20$, $-22 \le l \le 22$	
Reflections collected	18144	
Independent reflections	10921 [R(int) = 0.0524]	
Reflections with I>2σ(I)	5364	
Completeness to θ = 24.99°	99.7 %	
Absorption correction	Integration	
Max. and min. transmission	0.9081 and 0.6275	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	10921 / 0 / 816	
Largest final shift/e.s.d. ratio	0.001	
Goodness-of-fit on F^2	1.118	
Final R indices [I>2σ(I)]	R1 = 0.0613, wR2 = 0.1417	
R indices (all data)	R1 = 0.1238, wR2 = 0.1660	
Largest diff. peak and hole	0.629 and -0.666 e.Å^{-3}	

Benzene rings C(61—66) and C(81—86) are disordered by rotation around the C(61)...C(64) and C(81)...C(84) vectors. C(62), C(63), C(65), C(66), C(82), C(83), C(85), C(86) and their hydrogens are disordered with equal probability between positions A and B. Sublattice (a/2, b, c) is violated by different orientations of the benzene rings C(91—96) and C(121—126).

Table 2. Atomic coordinates ($\times 10^4$), and equivalent isotropic displacement parameters ($Å^2 \times 10^3$) for 00srv347. U(eq) is defined as one third of the trace of the orthogonalized U_{ij} tensor.

	x	y	z	U(eq)
Br(1)	-240.7(9)	3357.6(5)	6435.9(4)	28.6(2)
F(13)	1931(4)	4804(2)	5615(2)	27(1)
F(15)	-1236(5)	1701(3)	5553(2)	32(1)
N(11)	1215(6)	2117(4)	4358(3)	18(1)
C(12)	1797(8)	2874(5)	4653(4)	21(2)
C(13)	1377(7)	3249(4)	5283(4)	20(2)
C(14)	356(8)	2856(4)	5593(4)	20(2)
C(15)	-224(8)	2083(4)	5258(4)	20(2)
C(16)	219(8)	1707(4)	4630(4)	21(2)
C(17)	5507(8)	4224(5)	3015(4)	30(2)
C(18)	-1869(9)	1556(5)	3088(5)	31(2)
C(51)	2855(7)	3243(4)	4265(4)	20(2)
C(52)	3306(8)	2768(5)	3691(4)	23(2)
C(53)	4267(8)	3071(5)	3304(5)	26(2)
C(54)	4805(7)	3881(4)	3463(4)	21(2)
C(55)	4386(8)	4360(5)	4033(4)	27(2)
C(56)	3431(8)	4048(4)	4433(5)	28(2)
C(61)	-356(7)	876(5)	4241(4)	22(2)
C(62A)	-830(15)	313(9)	4614(9)	22(3)
C(63A)	-1332(15)	459(9)	4238(8)	21(3)
C(64)	-1353(8)	-705(4)	3484(4)	21(2)
C(65A)	-847(15)	-80(8)	3153(8)	19(3)
C(66A)	-348(16)	686(9)	3533(8)	23(3)
C(62B)	-1696(15)	462(8)	4262(8)	18(3)
C(63B)	-2162(16)	-321(9)	3905(8)	21(3)
C(65B)	-14(17)	-333(10)	3421(9)	28(4)
C(66B	483(16)	435(9)	3777(8)	21(3)
Br(2)	5068.2(9)	3475.0(5)	6389.7(5)	31.9(2)
F(23)	7144(5)	4091(3)	5514(2)	31(1)
F(25)	4040(5)	1795(3)	5549(2)	30(1)
N(22)	6399(6)	2167(4)	4299(3)	20(2)
C(22)	6992(7)	2933(5)	4582(4)	21(2)
C(23)	6394(7)	3330(4)	5209(4)	17(2)
C(24)	5609(8)	2952.5(5)	5536(4)	22(2)
C(25)	5619(8)	2164(5)	5223(4)	23(2)
C(26)	5417(7)	1778(4)	4593(4)	20(2)
C(27)	10989(8)	4226(5)	2585(4)	25(2)
C(28)	3137(9)	-1468(5)	3080(5)	35(2)
C(71)	8044(7)	3206(4)	4175(4)	23(2)
C(72)	8469(8)	2805(5)	3597(4)	21(2)
C(73)	9410(8)	3104(5)	3193(4)	25(2)
C(74)	9963(8)	3901(5)	3329(4)	23(2)
C(75)	9549(8)	4384(5)	3901(5)	24(2)
C(76)	8629(8)	4093(4)	4326(5)	28(2)
C(81)	4804(7)	953(4)	4221(4)	19(2)
C(82A)	4749(16)	745(9)	3496(8)	22(3)
C(83A)	4230(15)	-17(9)	3136(9)	27(3)
C(84)	3689(8)	-822(5)	3468(4)	24(2)
C(85A)	3859(15)	-357(9)	4229(8)	20(3)
C(86A)	4383(14)	388(8)	4603(8)	18(3)
C(82B)	5581(16)	462(9)	3776(8)	22(3)
C(83B)	6972(16)	-318(9)	3413(9)	24(3)
C(85B)	5808(16)	-177(9)	3875(8)	22(3)
C(86B)	5404(15)	586(8)	4233(8)	18(3)
Br(3)	43.7(10)	1613.3(5)	-1402.2(5)	32.8(3)
F(33)	309(5)	3277(3)	-554(2)	37(1)
F(35)	2237(5)	969(3)	-538(2)	42(1)
N(31)	2082(7)	2875(4)	691(4)	23(2)
C(32)	2152(8)	3278(5)	410(4)	25(2)
C(33)	1235(8)	2896(5)	-224(4)	27(2)
C(34)	1271(9)	2122(5)	-548(4)	23(2)
C(35)	2246(9)	1734(5)	-213(5)	29(2)
C(36)	3157(8)	2125(5)	413(4)	25(2)
C(37)	2313(9)	6545(5)	1906(5)	37(2)
C(38)	7332(9)	786(5)	2065(5)	41(2)
C(91)	2160(8)	4106(4)	806(4)	21(2)
C(92)	3400(8)	4541(4)	1222(4)	22(2)
C(93)	3444(8)	5325(5)	1583(4)	25(2)
C(94)	2243(8)	5691(5)	1527(4)	27(2)
C(95)	1003(8)	5237(5)	1106(4)	23(2)
C(96)	953(8)	4468(5)	755(4)	23(2)
C(101)	4225(8)	1753(4)	792(4)	26(2)
C(102)	5171(8)	2237(5)	1397(5)	28(2)
C(103)	6175(9)	1936(5)	1788(5)	33(2)
C(104)	6265(8)	1125(5)	1613(5)	27(2)
C(105)	5338(9)	654(5)	1032(5)	35(2)
C(106)	4340(9)	953(5)	628(5)	32(2)
Br(4)	-5055.9(10)	1558.5(5)	-1424.7(5)	40.6(3)
F(43)	-2779(5)	931(3)	-593(3)	38(1)
F(45)	-4810(5)	3219(3)	-559(3)	36(1)
N(41)	-1937(6)	2842(4)	646(3)	21(2)
C(42)	-1887(8)	2081(5)	361(5)	27(2)
C(43)	-2810(9)	1695(5)	-267(4)	28(2)
C(44)	-3786(9)	2076(5)	-590(4)	29(2)
C(45)	-3804(8)	2857(5)	-261(4)	25(2)
C(46)	-2863(8)	3238(5)	357(4)	24(2)
C(47)	2236(9)	760(5)	2042(5)	35(2)
C(48)	-2630(9)	6480(5)	1921(5)	30(2)
C(111)	811(5)	1709(5)	752(4)	25(2)
C(112)	147(8)	2205(4)	1333(4)	26(2)
C(113)	1157(8)	1899(5)	1726(5)	27(2)
C(114)	1225(9)	1094(5)	1586(5)	30(2)
C(115)	259(9)	616(5)	1020(5)	29(2)
C(116)	736(9)	901(5)	609(5)	31(2)
C(121)	2849(8)	4066(4)	745(4)	22(2)
C(122)	2432(7)	4282(4)	1185(4)	23(2)
C(123)	2263(7)	5053(4)	1368(4)	21(2)
C(124)	2727(8)	5641(4)	1516(4)	22(2)
C(125)	3155(7)	5415(4)	763(4)	21(2)
C(126)	3203(8)	4648(4)	390(4)	25(2)

Table 3. Bond lengths [Å] and angles [°] for 00srv347

Br(1)-C(14)	1.850(7)	C(22)-C(23)	1.393(10)
F(13)-C(13)	1.349(8)	C(22)-C(71)	1.501(10)
F(15)-C(15)	1.354(7)	C(23)-C(24)	1.370(9)
N(11)-C(16)	1.340(9)	C(24)-C(25)	1.398(11)
N(11)-C(12)	1.344(9)	C(25)-C(26)	1.386(10)
C(12)-C(13)	1.392(10)	C(26)-C(81)	1.482(10)
C(12)-C(51)	1.490(9)	C(27)-C(72)	1.510(10)
C(13)-C(14)	1.386(9)	C(28)-C(84)	1.508(11)
C(14)-C(15)	1.352(10)	C(71)-C(72)	1.397(11)
C(15)-C(16)	1.400(10)	C(71)-C(76)	1.399(10)
C(16)-C(61)	1.491(10)	C(72)-C(73)	1.380(10)
C(17)-C(54)	1.515(10)	C(73)-C(74)	1.385(11)
C(18)-C(64)	1.514(11)	C(74)-C(75)	1.383(11)
C(51)-C(52)	1.396(10)	C(75)-C(76)	1.393(10)
C(51)-C(56)	1.400(10)	C(81)-C(82A)	1.364(17)
C(52)-C(53)	1.376(10)	C(81)-C(86A)	1.399(15)
C(53)-C(54)	1.400(10)	C(81)-C(86B)	1.413(15)
C(54)-C(55)	1.385(11)	C(81)-C(82B)	1.417(17)
C(55)-C(56)	1.358(10)	C(82A)-C(83A)	1.37(2)
C(61)-C(66A)	1.340(17)	C(83A)-C(84)	1.420(16)
C(61)-C(62B)	1.397(15)	C(84)-C(83B)	1.299(16)
C(61)-C(62A)	1.398(16)	C(84)-C(85B)	1.426(16)
C(61)-C(66B)	1.453(16)	C(84)-C(85A)	1.429(17)
C(62A)-C(63A)	1.39(2)	C(85A)-C(86A)	1.35(2)
C(63A)-C(64)	1.429(17)	C(82B)-C(83B)	1.44(2)
C(64)-C(63B)	1.339(16)	C(85B)-C(86B)	1.38(2)
C(64)-C(65B)	1.390(16)	Br(3)-C(34)	1.879(8)
C(64)-C(65A)	1.437(16)	F(33)-C(33)	1.357(10)
C(65A)-C(66A)	1.38(2)	F(35)-C(35)	1.357(9)
C(62B)-C(63B)	1.39(2)	N(31)-C(36)	1.331(10)
C(65B)-C(66B)	1.37(2)	N(31)-C(32)	1.342(10)
Br(2)-C(24)	1.884(7)	C(32)-C(33)	1.399(11)
F(23)-C(23)	1.348(8)	C(32)-C(91)	1.493(11)
F(25)-C(25)	1.358(8)	C(33)-C(34)	1.380(11)
N(22)-C(26)	1.341(9)	C(34)-C(35)	1.399(12)
N(22)-C(22)	1.356(9)	C(35)-C(36)	1.392(12)

Table 3. Bond lengths [Å] and angles [°] for 00srv347

Br(1)-C(14)	1.850(7)	C(22)-C(23)	1.393(10)
F(13)-C(13)	1.349(8)	C(22)-C(71)	1.501(10)
F(15)-C(15)	1.354(7)	C(23)-C(24)	1.370(9)
N(11)-C(16)	1.340(9)	C(24)-C(25)	1.398(11)
N(11)-C(12)	1.344(9)	C(25)-C(26)	1.386(10)
C(12)-C(13)	1.392(10)	C(26)-C(81)	1.482(10)
C(12)-C(51)	1.490(9)	C(27)-C(72)	1.510(10)
C(13)-C(14)	1.386(9)	C(28)-C(84)	1.508(11)
C(14)-C(15)	1.352(10)	C(71)-C(72)	1.397(11)
C(15)-C(16)	1.400(10)	C(71)-C(76)	1.399(10)
C(16)-C(61)	1.491(10)	C(72)-C(73)	1.380(10)
C(17)-C(54)	1.515(10)	C(73)-C(74)	1.385(11)
C(18)-C(64)	1.514(11)	C(74)-C(75)	1.383(11)
C(51)-C(52)	1.396(10)	C(75)-C(76)	1.393(10)
C(51)-C(56)	1.400(10)	C(81)-C(82A)	1.364(17)
C(52)-C(53)	1.376(10)	C(81)-C(86A)	1.399(15)
C(53)-C(54)	1.400(10)	C(81)-C(86B)	1.413(15)
C(54)-C(55)	1.385(11)	C(81)-C(82B)	1.417(17)
C(55)-C(56)	1.358(10)	C(82A)-C(83A)	1.37(2)
C(61)-C(66A)	1.340(17)	C(83A)-C(84)	1.420(16)
C(61)-C(62B)	1.397(15)	C(84)-C(83B)	1.299(16)
C(61)-C(62A)	1.398(16)	C(84)-C(85B)	1.426(16)
C(61)-C(66B)	1.453(16)	C(84)-C(85A)	1.429(17)
C(62A)-C(63A)	1.39(2)	C(85A)-C(86A)	1.35(2)
C(63A)-C(64)	1.429(17)	C(82B)-C(83B)	1.44(2)
C(64)-C(63B)	1.339(16)	C(85B)-C(86B)	1.38(2)
C(64)-C(65B)	1.390(16)	Br(3)-C(34)	1.879(8)
C(64)-C(65A)	1.437(16)	F(33)-C(33)	1.357(10)
C(65A)-C(66A)	1.38(2)	F(35)-C(35)	1.357(9)
C(62B)-C(63B)	1.39(2)	N(31)-C(36)	1.331(10)
C(65B)-C(66B)	1.37(2)	N(31)-C(32)	1.342(10)
Br(2)-C(24)	1.884(7)	C(32)-C(33)	1.399(11)
F(23)-C(23)	1.348(8)	C(32)-C(91)	1.493(11)
F(25)-C(25)	1.358(8)	C(33)-C(34)	1.380(11)
N(22)-C(26)	1.341(9)	C(34)-C(35)	1.399(12)
N(22)-C(22)	1.356(9)	C(35)-C(36)	1.392(12)

C(36)-C(101)	1.434(12)	C(42)-C(43)	1.394(12)
C(37)-C(94)	1.516(12)	C(42)-C(111)	1.502(12)
C(38)-C(104)	1.524(13)	C(43)-C(44)	1.383(12)
C(91)-C(92)	1.381(10)	C(44)-C(45)	1.390(11)
C(91)-C(96)	1.394(11)	C(45)-C(46)	1.387(11)
C(92)-C(93)	1.399(11)	C(46)-C(121)	1.489(10)
C(93)-C(94)	1.397(11)	C(47)-C(114)	1.519(13)
C(94)-C(95)	1.394(11)	C(48)-C(124)	1.503(11)
C(95)-C(96)	1.371(11)	C(111)-C(116)	1.402(11)
C(101)-C(106)	1.395(11)	C(111)-C(112)	1.426(11)
C(101)-C(102)	1.424(11)	C(112)-C(113)	1.363(12)
C(102)-C(103)	1.379(12)	C(113)-C(114)	1.395(11)
C(103)-C(104)	1.410(11)	C(114)-C(115)	1.384(12)
C(104)-C(105)	1.379(12)	C(115)-C(116)	1.378(13)
C(105)-C(106)	1.356(13)	C(121)-C(122)	1.394(11)
Br(4)-C(44)	1.875(8)	C(121)-C(126)	1.397(11)
F(43)-C(43)	1.364(9)	C(122)-C(123)	1.389(10)
F(45)-C(45)	1.359(9)	C(123)-C(124)	1.407(11)
N(41)-C(46)	1.338(10)	C(124)-C(125)	1.418(10)
N(41)-C(42)	1.345(10)	C(125)-C(126)	1.382(10)

C(16)-N(11)-C(12)	123.3(6)	C(52)-C(51)-C(12)	118.9(6)
N(11)-C(12)-C(13)	118.8(6)	C(56)-C(51)-C(12)	124.2(7)
N(11)-C(12)-C(51)	115.9(6)	C(53)-C(52)-C(51)	122.0(7)
C(13)-C(12)-C(51)	125.2(7)	C(52)-C(53)-C(54)	120.7(7)
F(13)-C(13)-C(14)	117.2(6)	C(55)-C(54)-C(53)	118.1(7)
F(13)-C(13)-C(12)	122.6(6)	C(55)-C(54)-C(17)	121.1(7)
C(14)-C(13)-C(12)	120.2(7)	C(53)-C(54)-C(17)	120.9(7)
C(15)-C(14)-C(13)	117.9(6)	C(54)-C(55)-C(56)	120.9(7)
C(15)-C(14)-Br(1)	120.8(5)	C(55)-C(56)-C(51)	121.5(7)
C(13)-C(14)-Br(1)	121.2(5)	C(66A)-C(61)-C(62B)	99.2(10)
F(15)-C(15)-C(14)	118.3(6)	C(66A)-C(61)-C(62A)	121.8(11)
F(15)-C(15)-C(16)	121.9(7)	C(62B)-C(61)-C(62A)	46.5(8)
C(14)-C(15)-C(16)	120.9(6)	C(66A)-C(61)-C(66B)	44.7(8)
N(11)-C(16)-C(15)	118.4(7)	C(62B)-C(61)-C(66B)	114.4(10)
N(11)-C(16)-C(61)	117.7(6)	C(62A)-C(61)-C(66B)	100.7(10)
C(15)-C(16)-C(61)	123.9(6)	C(66A)-C(61)-C(16)	117.8(9)
C(52)-C(51)-C(56)	116.8(6)	C(62B)-C(61)-C(16)	125.4(9)

C(62A)-C(61)-C(16)	120.4(9)	C(56)-C(51)-C(52)	124.5(7)
C(66B)-C(61)-C(16)	120.1(8)	C(63)-C(62)-C(71)	121.6(7)
C(63A)-C(62A)-C(61)	118.9(13)	C(72)-C(73)-C(74)	122.2(7)
C(62A)-C(63A)-C(64)	122.4(13)	C(75)-C(74)-C(73)	116.3(7)
C(63B)-C(64)-C(65B)	120.3(11)	C(75)-C(74)-C(27)	121.6(7)
C(63B)-C(64)-C(63A)	44.3(8)	C(73)-C(74)-C(27)	122.0(7)
C(65B)-C(64)-C(63A)	100.5(10)	C(74)-C(75)-C(76)	122.5(7)
C(63B)-C(64)-C(65A)	98.7(10)	C(75)-C(76)-C(71)	120.8(7)
C(65B)-C(64)-C(65A)	45.4(8)	C(82A)-C(81)-C(86A)	120.7(10)
C(63A)-C(64)-C(65A)	114.1(10)	C(82A)-C(81)-C(26)	96.4(10)
C(63B)-C(64)-C(18)	120.4(9)	C(86A)-C(81)-C(26)	52.4(8)
C(65B)-C(64)-C(18)	119.3(9)	C(82A)-C(81)-C(82B)	47.2(6)
C(63A)-C(64)-C(18)	121.5(8)	C(86A)-C(81)-C(82B)	96.4(10)
C(65A)-C(64)-C(18)	124.5(9)	C(86B)-C(81)-C(82B)	114.6(10)
C(66A)-C(65A)-C(64)	123.0(13)	C(82A)-C(81)-C(26)	118.2(8)
C(61)-C(66A)-C(65A)	119.5(13)	C(86A)-C(81)-C(26)	121.6(9)
C(63B)-C(62B)-C(61)	123.1(13)	C(86B)-C(81)-C(26)	124.2(8)
C(64)-C(63B)-C(62B)	120.4(12)	C(82B)-C(81)-C(26)	121.1(8)
C(66B)-C(65B)-C(64)	120.6(14)	C(81)-C(82A)-C(83A)	119.7(13)
C(65B)-C(66B)-C(61)	121.2(12)	C(82A)-C(83A)-C(84)	123.9(14)
C(26)-N(22)-C(22)	122.3(6)	C(83B)-C(84)-C(83A)	47.1(9)
N(22)-C(22)-C(23)	119.3(6)	C(83B)-C(84)-C(85B)	121.3(11)
N(22)-C(22)-C(71)	115.5(7)	C(83A)-C(84)-C(85B)	96.6(10)
C(23)-C(22)-C(71)	124.9(7)	C(83B)-C(84)-C(85A)	95.3(10)
F(23)-C(23)-C(24)	117.7(6)	C(83A)-C(84)-C(85A)	112.1(10)
F(23)-C(23)-C(22)	121.5(6)	C(83B)-C(84)-C(85A)	52.4(9)
C(24)-C(23)-C(22)	120.4(7)	C(83B)-C(84)-C(28)	117.9(9)
C(23)-C(24)-C(25)	118.4(7)	C(83A)-C(84)-C(28)	124.4(9)
C(23)-C(24)-Br(2)	121.1(6)	C(85B)-C(84)-C(28)	120.2(8)
C(25)-C(24)-Br(2)	120.5(5)	C(85A)-C(84)-C(28)	123.2(9)
F(25)-C(25)-C(26)	121.5(7)	C(86A)-C(85A)-C(84)	123.4(13)
F(25)-C(25)-C(24)	117.9(6)	C(85A)-C(86A)-C(81)	118.0(13)
C(26)-C(25)-C(24)	120.6(7)	C(81)-C(82B)-C(83B)	120.5(12)
N(22)-C(26)-C(25)	119.0(7)	C(84)-C(83B)-C(82B)	121.2(14)
N(22)-C(26)-C(81)	117.4(6)	C(84)-C(83B)-C(84)	116.5(12)
C(25)-C(26)-C(81)	123.6(6)	C(84)-C(85B)-C(86B)	124.9(13)
C(72)-C(71)-C(76)	116.5(7)	C(32)-N(31)-C(32)	123.9(8)
C(72)-C(71)-C(22)	119.2(7)	N(31)-C(32)-C(33)	118.2(8)

9. 2,6-dibromo-4-[4-2,6-dibromo –3,5-difluoro-4-pyridyl)phenyl] 3,5-difluoropyridine (62)

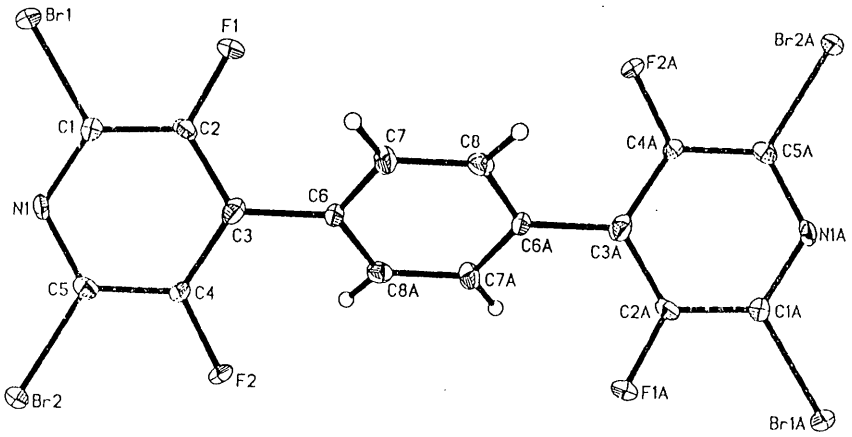

Table 1. Crystal data and structure refinement for 01srv023.

Identification code	s023a	
Empirical formula	$C_{10}H_4Br_4F_2N_2$	
Formula weight	619.85	
Temperature	100.0(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	$P 2_1/n$	
Unit cell dimensions	a = 3.9383(3) Å	α= 90°.
	b = 7.6032(5) Å	β= 90.004(3)°
	c = 28.916(2) Å	γ = 90°.
Volume	865.9(1) Å^3	
Z	2	
Density (calculated)	2.378 Mg/m^3	
Absorption coefficient	9.339 mm^{-1}	
F(000)	580	
Crystal size	0.40 x 0.06 x 0.02 mm^3	
Theta range for data collection	2.11 to 27.00°	
Index ranges	-4<=h<=5, -9<=k<=9, -36<=l<=36	
Reflections collected	7363	
Independent reflections	1864 [R(int) = 0.0703]	
Completeness to theta = 27.00°	99.9 %	
Absorption correction	Numerical	
Max. and min. transmission	0.8352 and 0.1179	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	1864 / 0 / 125	
Goodness-of-fit on F^2	1.160	
Final R indices [I>2sigma(I)]	R1 = 0.0394, wR2 = 0.0806	
R indices (all data)	R1 = 0.0478, wR2 = 0.0830	
Largest diff. peak and hole	0.946 and -1.893 e.Å^{-3}	

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for 01srv023. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

Atom	x	y	z	U(eq)
Br(1)	6947(2)	904(1)	1639(1)	15(1)
Br(2)	13152(2)	-5186(1)	2239(1)	14(1)
F(1)	7356(10)	-908(4)	708(1)	20(1)
F(2)	12867(10)	-6077(4)	1219(1)	17(1)
N(1)	10048(13)	-2263(6)	1845(2)	13(1)
C(1)	8822(14)	-1322(7)	1491(2)	9(1)
C(2)	8772(15)	-1924(7)	1041(2)	13(1)
C(3)	10061(16)	-3571(7)	929(2)	15(1)
C(4)	11410(16)	-4502(7)	1300(2)	12(1)
C(5)	11367(15)	-3839(7)	1750(2)	12(1)
C(6)	10035(16)	-4307(7)	446(2)	13(1)
C(7)	11134(16)	-3304(8)	74(2)	14(1)
C(8)	11129(15)	-3981(7)	-372(2)	14(1)

Table 3. Bond lengths [Å] and angles [°] for 01srv023.

Br(1)-C(1)	1.895(5)	N(1)-C(1)	1.337(7)	C(4)-C(5)	1.397(8)
Br(2)-C(5)	1.881(5)	C(1)-C(2)	1.382(7)	C(6)-C(7)	1.389(8)
F(1)-C(2)	1.353(6)	C(2)-C(3)	1.390(8)	C(6)-C(8)#1	1.397(8)
F(2)-C(4)	1.348(6)	C(3)-C(4)	1.391(8)	C(7)-C(8)	1.387(8)
N(1)-C(5)	1.334(7)	C(3)-C(6)	1.503(8)		

C(5)-N(1)-C(1)	117.7(5)	F(2)-C(4)-C(5)	119.2(5)
N(1)-C(1)-C(2)	123.3(5)	C(3)-C(4)-C(5)	122.1(5)
N(1)-C(1)-Br(1)	116.5(4)	N(1)-C(5)-C(4)	121.3(5)
C(2)-C(1)-Br(1)	120.2(4)	N(1)-C(5)-Br(2)	118.7(4)
F(1)-C(2)-C(1)	119.1(5)	C(4)-C(5)-Br(2)	119.9(4)
F(1)-C(2)-C(3)	120.0(5)	C(7)-C(6)-C(8)#1	119.6(5)
C(1)-C(2)-C(3)	120.8(5)	C(7)-C(6)-C(3)	120.9(5)
C(2)-C(3)-C(4)	114.8(5)	C(8)#1-C(6)-C(3)	119.5(5)
C(2)-C(3)-C(6)	123.3(5)	C(8)-C(7)-C(6)	121.1(5)
C(4)-C(3)-C(6)	122.0(5)	C(7)-C(8)-C(6)#1	119.3(5)
F(2)-C(4)-C(3)	118.8(5)		

Symmetry transformations used to generate equivalent atoms: #1 -x+2,-y-1,-z