NEW AROMATIC FLUORINATIONS

A Thesis Presented by

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To Mum and Dad

Abstract

This thesis is divided into four parts. The first two Chapters offer a review of the field of aromatic fluorination from 1980 until June 1991. The reactions studied are divided into two groups, those based on nucleophilic fluorination (Chapter one, Fluoride ion-based methodology) and those using electrophilic reactions (Chapter two, Molecular fluorine and reagents derived from this). Mention is made throughout of methods used in radiolabelling studies with the unstable isotope, fluorine-18.

In the third Chapter, the development of a method for producing regioselective fluoroaromatics based on the fluorodemetallation process is discussed. The reagent used in this study was the electrophilic, fluorinating agent, caesium fluoroxysulphate, which was readily prepared in multigram quantities from molecular fluorine. The variation of the metalloid leaving group from the initial choice of silicon through to boron is discussed and the investigation of the role of the ligands surrounding the metal is rationalised.

An hypothesis is presented to explain the different results seen in various solvents. This proposes the formation *in situ* of new fluorinating agents by reaction of caesium fluoroxysulphate with solvent molecules. Of the solvents investigated, methanol was found to give the most rapid reaction with a number of tricoordinate arylboron compounds. This was attributed to the formation of methyl hypofluorite whose reactivity was mediated by adduct formation with the substrate. The final section of this Chapter describes a study into the regiospecific fluorination of a derivative of the female hormone, estrone. The speed of this process was found to be suitably rapid to be applicable to fluorine-18 PETT applications.

The fourth Chapter describes experimental procedures used in this work.

CONTENTS

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Abbreviations

Ac	Acetyl
AcOF	Acetyl hypofluorite
Boc	*tert*-Butoxycarbonyl
Bu	Butyl
CFS	Caesium fluoroxysulphate
DCM	Dichloromethane
DMF	*N,N*-Dimethylformamide
DMSO	Dimethylsulphoxide
DMPU	1,3-Dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone
DNB	Dinitrobenzene
Et	Ethyl
GC	Gas chromatography
HMPA	Hexamethylphosphoramide
LDA	Lithium di*iso*propylamide
Me	Methyl
MS	Mass spectroscopy
NMDE	*N*-Methyldiethanolamine
NMR	Nuclear magnetic resonance
OEP	Octaethylporhyrin
PETT	Positron Emission Transaxial Tomography
Ph	Phenyl
PNB	*para*-Nitrobenzoate
PPTS	Pyridinium *para*-toluenesulphonate
PTSA	*para*-Toluenesulphonic acid
Py	Pyridine
RFS	Rubidium fluoroxysulphate
SET	Single electron transfer
TBAF	Tetrabutylammonium fluoride
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TIPS	Tri*iso*propylsilyl
TLC	Thin layer chromatography
TMEDA	*N,N,N',N'*-Tetramethylethylenediamine
TMS	Trimethylsilyl
Ts	4-Toluenesulphonyl

REVIEW

AROMATIC FLUORINATION SINCE 1980

General Introduction

The incorporation of fluorine into an aromatic ring has long been known to influence the chemical and physical properties of the molecule. Enhanced thermal stability and lipophilicity are just two of the benefits to be gained from fluorination. Commercially, fluorine is of great importance especially in the agrochemical industry where approximately 9% of all marketed compounds contain fluorine.

Biologically, fluorine is very important since it is essentially isosteric with hydrogen (Van der Waals radius 1.35 Å vs 1.20 Å). The substitution of F for H allows the blocking of sites of possible metabolic oxidation since the aromatic C-F bond is largely inert to chemical attack. This does not block the recognition of the enzyme or receptor and thus can lead to an increase in potency.

The lack of background biological fluorine leads to its application as a suitable marker for ^{19}F NMR[1] or energy loss spectroscopic[2] studies. As a diagnostic tool however, it is most prominent in the field of Positron Emission Transaxial Tomography (PETT)[3] using the unstable isotope ^{18}F which may be prepared as either fluoride ion[4,5,6] or molecular fluorine.[7,8] This is gaining in popularity due to its extended half-life (110 minutes) compared to other possible candidates *e.g.* ^{11}C ($t_{1/2}$ 20 minutes), ^{15}O ($t_{1/2}$ 2 minutes).

Aromatic fluorination is much less well developed than in the alkyl series where the substitution of a large number of groups by fluoride anion is an established part of synthetic methodology and continuous improvements in fluoride sources (*e.g.* diethylaminosulphur trifluoride, DAST) are rapidly commercialised.

In this review, the field of aromatic fluorination from 1980 to the end of June 1991 has been surveyed and is presented by reagent type. The emphasis has been placed on procedures which are suitable for synthetic purposes rather than those which only proceed smoothly at low conversions.

CHAPTER 1

FLUORIDE ION-BASED METHODOLOGY

1.0 Introduction

The use of fluoride ion (or complex fluoride ion) to introduce fluorine into an aromatic ring is the oldest and most established technique for this transformation.[9,10] The classical Balz-Schiemann reaction involves the thermolysis of aryldiazonium tetrafluoroborate salts. Although many modifications to the decomposition of the salt (dilution with solvent,[11] photochemical,[12] sonochemical[13]) have appeared, polymeric tars are frequently the major product.

1.1 Aryldiazonium Tetrafluoroborate Salts

The use of aryldiazonium tetrafluoroborate salts appears to be slowly diminishing. This is mainly as a result of the side reactions to which the probable aryl cation intermediate is prone. These side reactions can lead to low yields of the fluoroaromatic and isolation problems.

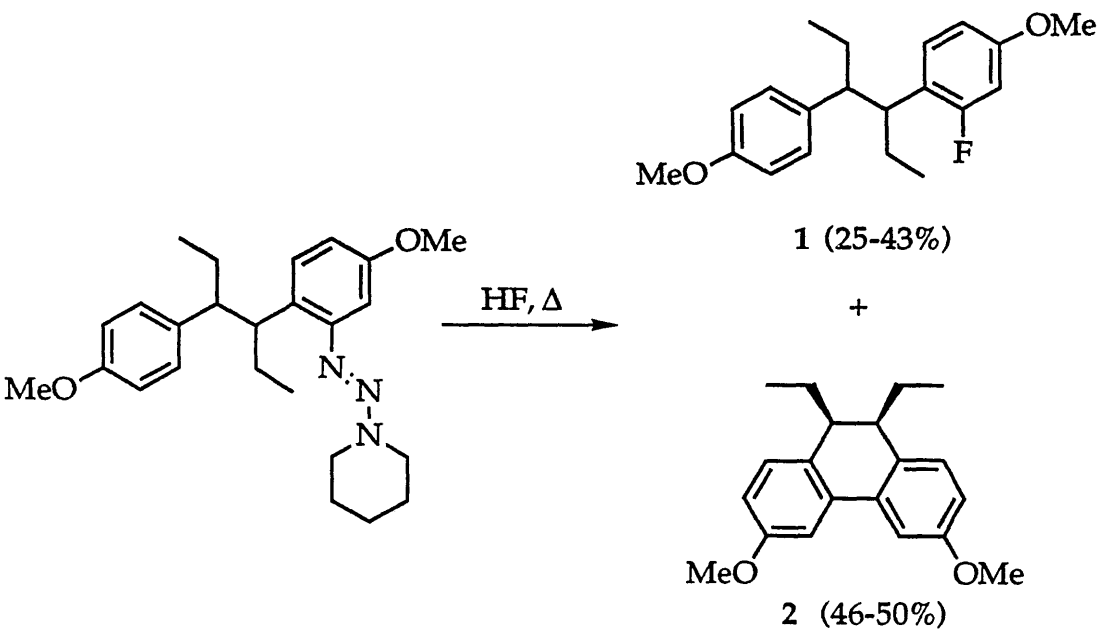
The use of *tert*-butyl nitrite in the presence of tetrafluoroboric acid as the diazotisation medium has been used to give an improved yield of 4-fluoroveratrole[14] (40-50% overall) compared to the conventional procedure using $NaNO_2$/HCl followed by tetrafluoroboric acid. 4-Fluoroveratrole was subsequently carried through to 6-fluoro-L-DOPA.

1.2 Reactions using Hydrogen Fluoride

The Balz-Schiemann reaction requires isolation and careful drying of the intermediate diazonium tetrafluoroborate salt if side reactions with external nucleophiles (*e.g.* Cl, H_2O from the preparation medium) are to be avoided. Furthermore, generation of $[^{18}F]$-BF_4^- for use in the generation of labelled substrates is very wasteful, leading to a maximum radiochemical yield of only 25% and thus low specific activity. To overcome these drawbacks, attempts have been made to use diazonium fluorides and decompose them *in situ*.

1.2.1 Aryl Triazenes as precursors

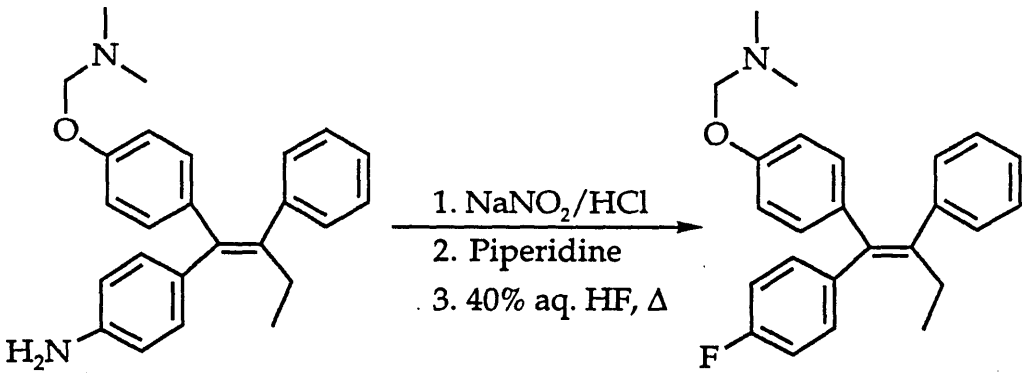
The acid-catalysed decomposition of aryl triazenes was the first reported method for aromatic fluorination.[15] The triazenes are stable, easily purified intermediates and are prepared from diazonium salts by trapping with a secondary amine. Following preliminary reports on the suitability for radiofluorination,[16,17] the method was applied to some suitable estrogen systems. In the case of *meso*-hexestrol, however, the major product was the cyclised dihydrophenanthrene **2** and not the required fluoride **1** (Scheme 1).[18]



Scheme 1

A similar approach led to the formation of fluorotamoxifen **3** (Scheme 2),[19] which is another possible estrogen receptor imaging agent.

In both of these cases, the yields were comparable when using either 40% aqueous hydrogen fluoride or pyridine/hydrogen fluoride (1:9) as the source of fluoride ion.



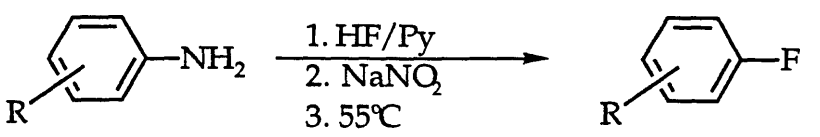
3 (25%)

Scheme 2

1.2.2 *In situ* decomposition of Aryldiazonium Fluorides

Although the triazene route is an improvement on the standard Balz-Schiemann procedure, it still involves the isolation of an intermediate followed by decomposition. The obvious step is to develop a 'one pot' procedure based on aryl diazonium fluorides.

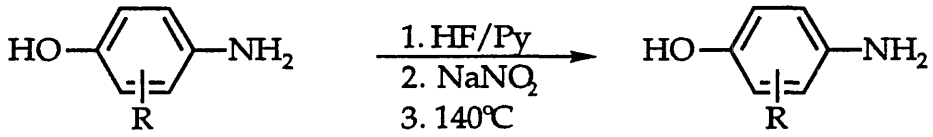
Yoneda has demonstrated that organic base-hydrogen fluoride adducts may be successfully used to carry out fluorodeamination in one pot.[20] It was necessary to ensure complete protonation of the anilines 4 before diazotisation to minimise side reactions. Fluoroarenes 5 were formed in high yields (65-99%, Scheme 3) except where *ortho*-substituents bearing chemically active electron pairs were present (OMe, NH_2, NO_2, yields of 0-17%). In the absence of the organic base (generally pyridine), yields were substantially lower. This was also the case if the decomposition of the salt was carried out at temperatures at which free HF was present.



4 5

Scheme 3

The same system has also been used to prepare a series of substituted 4-fluorophenols 6 from the corresponding aminophenols 7 (Scheme 4)[21] which had previously proven problematic to prepare by diazonium salt methodology.[22]

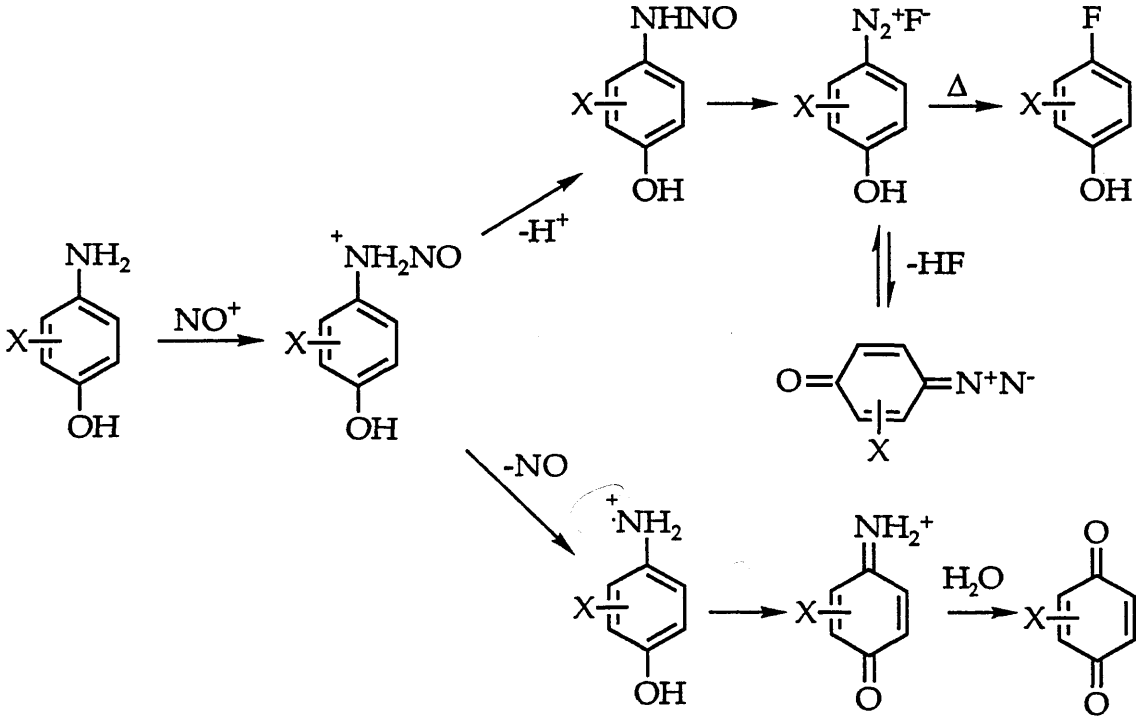


7 6 (0-85%)

R=H, 2-Me, 3-Me, 2-CO_2H, 3-CO_2H, 2-NO_2, 3-NO_2

Scheme 4

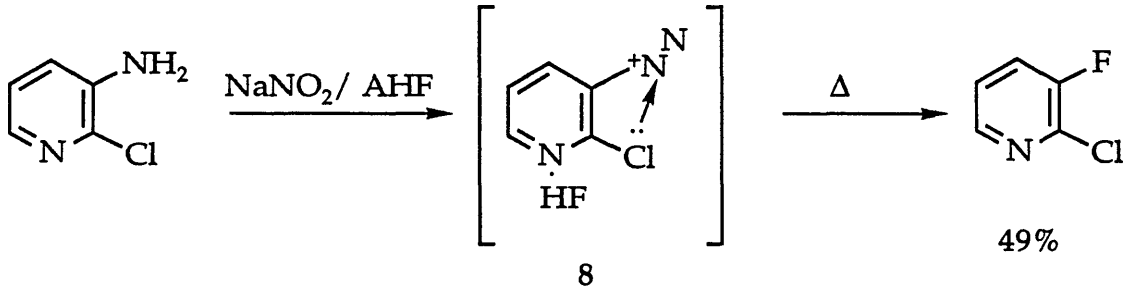
The system tolerated electron-withdrawing groups *ortho* to the hydroxyl group but, in common with other routes,[23] not to the amino group. This is attributed to intramolecular competition for the diazonium salt. A rationale was presented for the small amounts of quinones found (Scheme 5).



Scheme 5

The above procedure has been applied to some heterocycles. The highly labile 4-fluoropyridine was isolated as its hydrogen chloride salt in an overall yield of 54%[24] while previous efforts had led to the 4-pyridyl pyridinium salt.

It was also reported that *ortho*-chlorine atoms were tolerated as in the diazotisation of 2-chloro-3-aminopyridine. Gentle thermolysis of the diazonium intermediate 8 gave 2-chloro-3-fluoropyridine in 49% yield (Scheme 6).

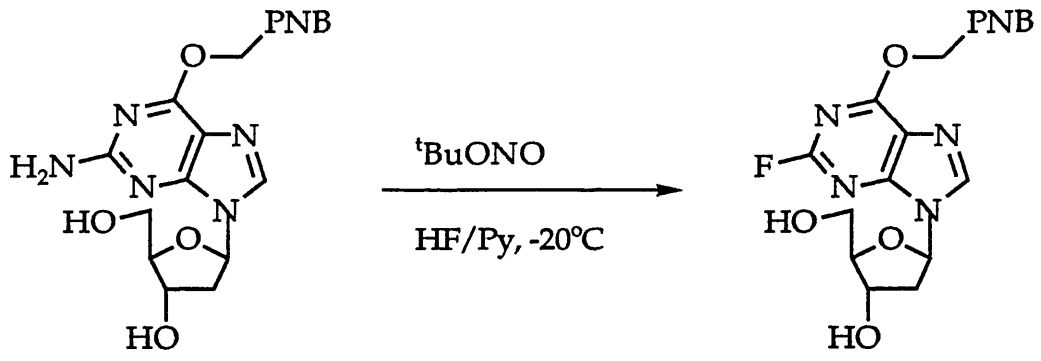


8

Scheme 6

This is in contrast to the carbocyclic case where fluorodeamination of 2-chloro-4-fluoroaniline, for example, gave a very low yield of 1-chloro-2,4-difluorobenzene (~6%).[25] The better yield for 8 was attributed to the highly electron-deficient nature of the pyridinium ring in 8, minimising the interaction of the chlorine lone pairs with the diazonium moiety. This could not happen in the benzenoid case.

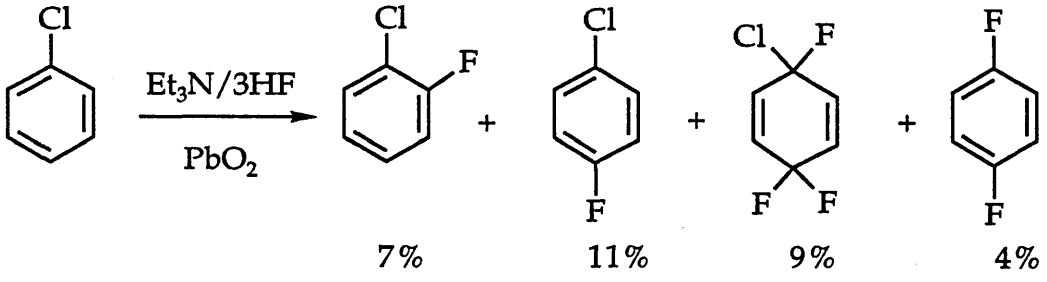
A number of purine nucleosides have also been fluorinated at C-2 of the pyrimidine ring in moderate to good yields.[26,27] All occurred under very mild conditions. In both reports, diazotisation was carried out using *tert*-butyl nitrite in the presence of pyridine-hydrogen fluoride and decomposition of the intermediate occurred *in situ* at -20°C (Scheme 7).[27] The case of 9 below is notable since there was no need to protect the two hydroxyl groups.



Scheme 7

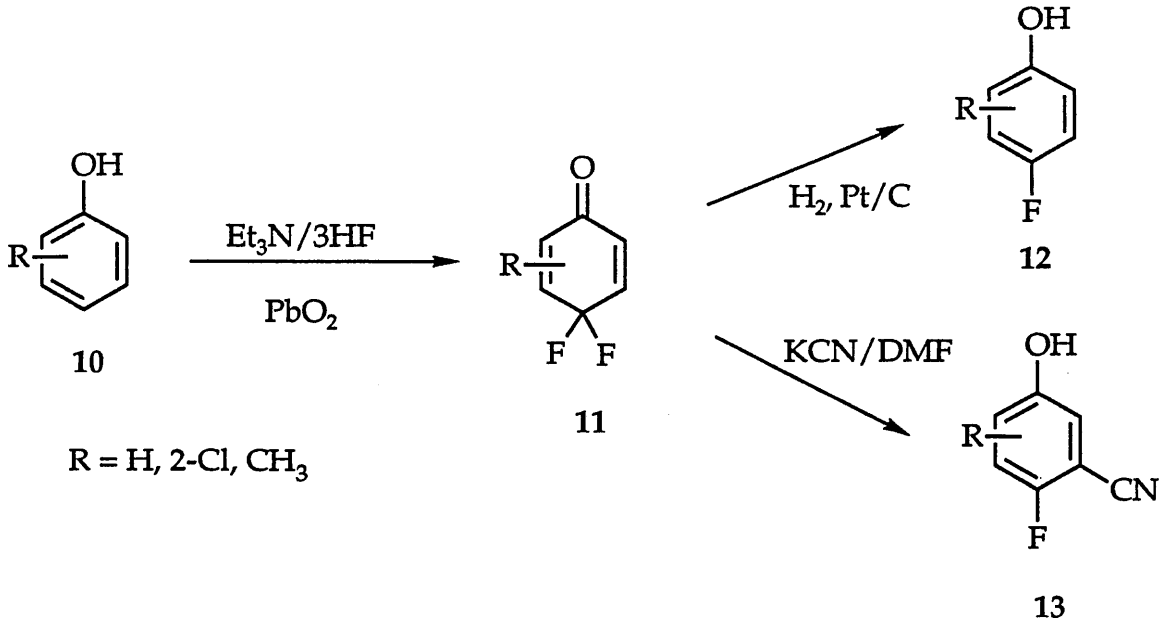
1.2.3 Oxidative Fluorination

Electrochemical fluorination using HF is a well established technique.[28] Similar processes have been described using stoichiometric quantities of Pb^{IV} salts as the oxidant.[29] Mixtures of fluorinated aromatics and dienes resulted from simple aromatics; chlorobenzene gave the mixture shown in Scheme 8 with a conversion of 76%.



Scheme 8

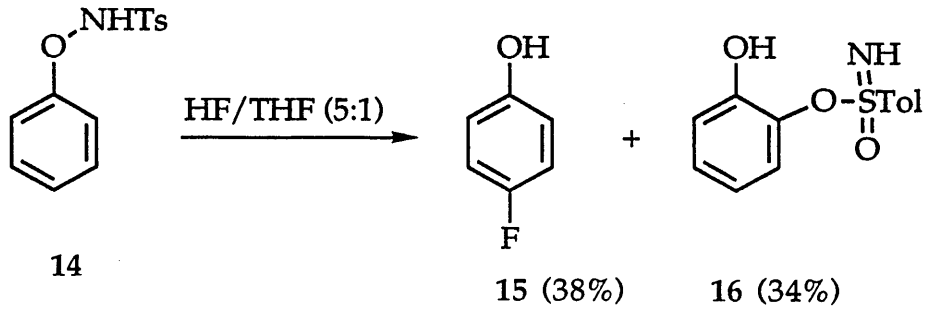
It was necessary to have a base present otherwise only polymers were formed and the optimum reagent was found to be triethylamine-tris-(hydrogen fluoride). Phenols 10 were converted to 4,4-difluorinated-2,5-dienones 11 which were readily converted to various 4-fluorophenols 12, 13 (Scheme 9). Alkyl-substituted benzenes underwent reaction at the benzylic site.



Scheme 9

1.2.4 Miscellaneous fluorinations with HF

The nucleophilic THF-HF adduct has been used in the solvolysis of *N*-tosyl-*O*-phenylhydroxylamine 14 to give 4-fluorophenol 15 in 38% yield together with a rearranged product 16 (Scheme 10).[30] The optimum ratio of THF:HF was 5:1.



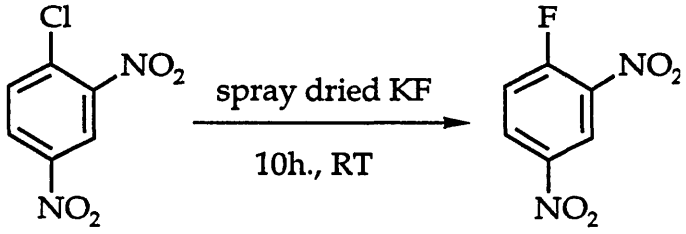
Scheme 10

Anhydrous HF was too weak a nucleophile for the transformation whereas HF/pyridine was insufficiently acidic.

1.3. Reactions based on Fluoride ion

1.3.1 Alkali Metal Fluorides

The use of certain metal fluorides generating 'naked' fluoride is gaining popularity despite the fact that they are are not easy to handle due to their hygroscopic nature.[31-33] It has been reported that spray-dried potassium fluoride is much less hygroscopic than the standard calcined reagent, although the water content is approximately the same.[34] On heating with 1-chloro-2,4-dinitrobenzene 17 in acetonitrile, the fluorinated dinitrobenzene 18 was obtained in 58% yield after 10 hours (Scheme 11).

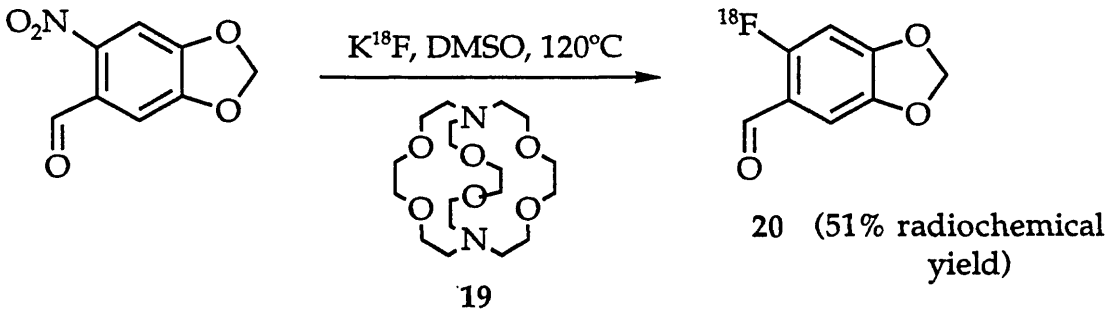


17 18 (58%)

Scheme 11

The solubilisation of 'naked' fluoride by crown ethers has been studied using 17 as the substrate.[35] The relative effect of the crown ethers investigated was found to be dibenzo-24-crown-8 (DB-24-C-8) < dicyclohexyl-18-crown-6 < 18-crown-6 (18-C-6) for all of the cations used (Cs, Rb, K). The larger cations would be expected to fit best with the cavity of DB-24-C-8 (~4.5 Å), their preference for 18-C-6 may be attributed to the inclusion of a caesium cation between two molecules of the smaller crown ether as a sandwich.[36]

This approach has been taken to the extreme with a number of radio-fluorinations where the additive Kryptofix 222 19 is used to encapsulate a potassium ion inside a cage. It has been demonstrated that electron-rich aromatics may be fluorinated if suitable activating groups are present (Scheme 12).[37,38]

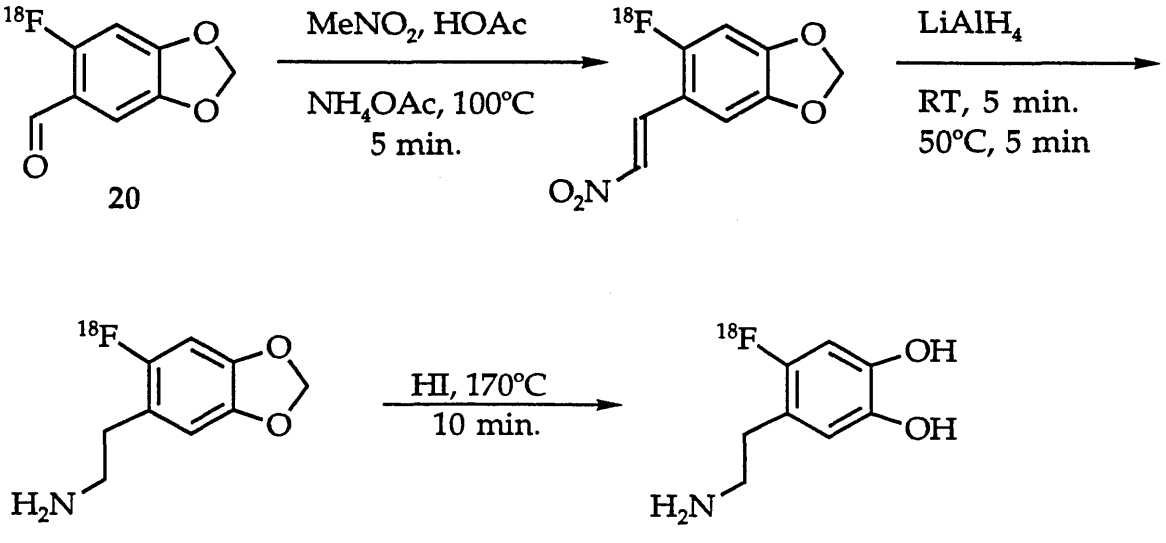


19

20 (51% radiochemical yield)

Scheme 12

In the initial report, a number of protecting groups for the catechol residue were investigated and, of these, the methylenedioxy group was found to be the most effective.[37] This was attributed to steric crowding in the dioxolane ring which forces the oxygen lone pairs out of the plane of the aromatic ring and therefore lowers electron density at the *para*-position. This twisting effect was much less marked in the case of the corresponding 1,3-dioxan and 1,3-dioxepane and these gave much lower yields of the aryl fluoride. The protected [^{18}F]-4-fluoroveratrole **20** is a useful intermediate and may be taken on to either radiolabelled 6-fluorodopamine **21** (Scheme 13)[38] or 6-fluoro-L-DOPA.[37]



21 (20% radiochemical yield)

Scheme 13

As Scheme 12 shows, other groups besides halogen may be used as leaving groups in nucleophilic fluorinations under suitable conditions. NO_2^- is a very good leaving group if steric effects cause it to be twisted from co-planarity with the aromatic π-system.

Aryltrimethylammonium salts have been used as substrates in various radiochemical studies.[39,40] Initial reports showed their greater stability to the reaction conditions than the corresponding aryldimethylsulphonium salts (see Section 1.3.2).

Treatment of a number of aryltrimethylammonium salts **22** bearing various electron-withdrawing groups, with anhydrous caesium fluoride in hot DMSO gave the relevant fluoroaromatics in moderate to excellent radiochemical yield (Scheme 14).

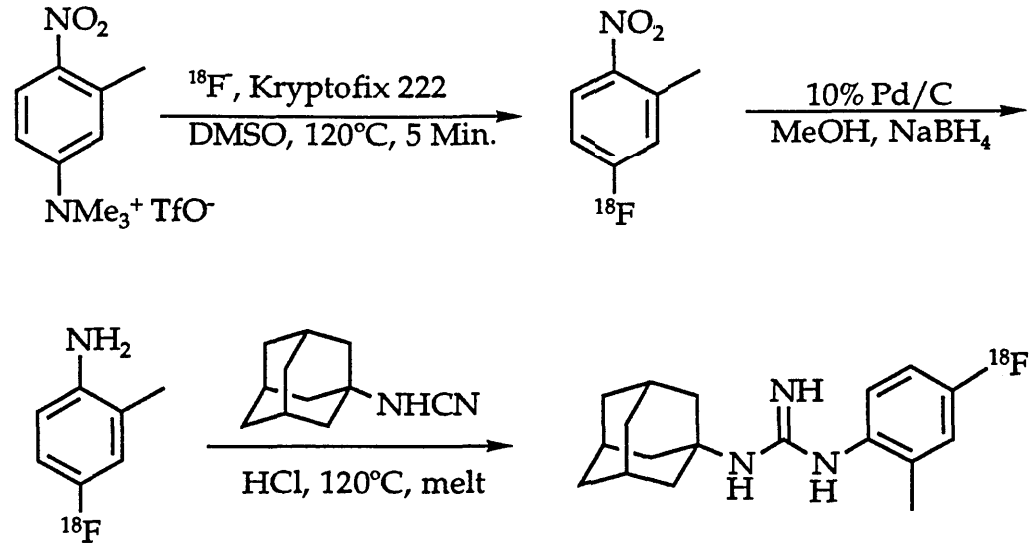
22 35-91%

R = 4-NO_2, 4-CN, 4-Ac, 3-NO_2

Scheme 14

It should be noted that both fluorodenitration and demethylation (*via* fluoride attack at a methyl group) are negligible processes during this transformation.

The same approach as for **22** has been used in the synthesis of radiolabelled fluoroguanidines **23** for PETT studies (Scheme 15).[40] In this study, the solubilising additive, Kryptofix 222, was employed to hasten the reaction time to only 5 minutes.

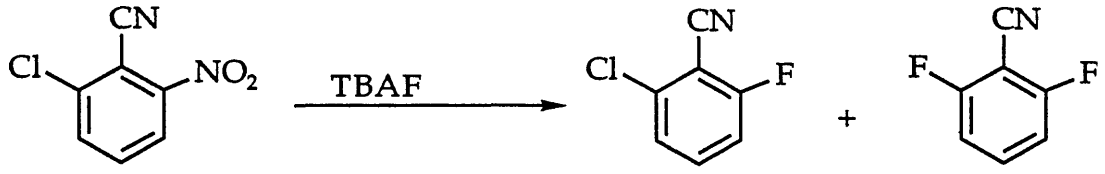


23 (7-12% radiochemical yield)

Scheme 15

1.3.2 Group V Fluorides

Clark has shown that 'anhydrous' TBAF is an excellent source of fluoride for fluorodenitration at room temperature when the nitro group is activated.[41] 2-Chloro-6-nitrobenzonitrile 24 gave a mixture of the the two fluorinated arenes 25, 26 (Scheme 16) whilst none of the fluorinated nitrobenzonitrile was detected, thus indicating that fluorodenitration is significantly faster than halogen exchange.



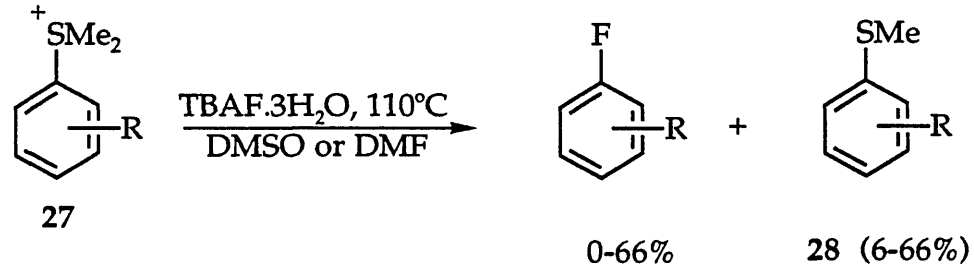
24 25 (75%) 26 (25%)

Scheme 16

This is in contrast to the reaction of 24 with rubidium fluoride in hot DMSO

where a mixture of denitration and halogen exchange occurs with no difluorination products.[42]

Radiolabelled TBAF has also been used to fluorinate aryl dimethylsulphonium salts 27 with a variety of counteranions (Scheme 17).[43,44] The most useful salts had the methylsulphate counteranion and were more stable than the perchlorate salts. A substantial side-reaction was found to be demethylation, induced by fluoride ion, giving the thioanisoles 28 along with fluoromethane.



27

0-66%

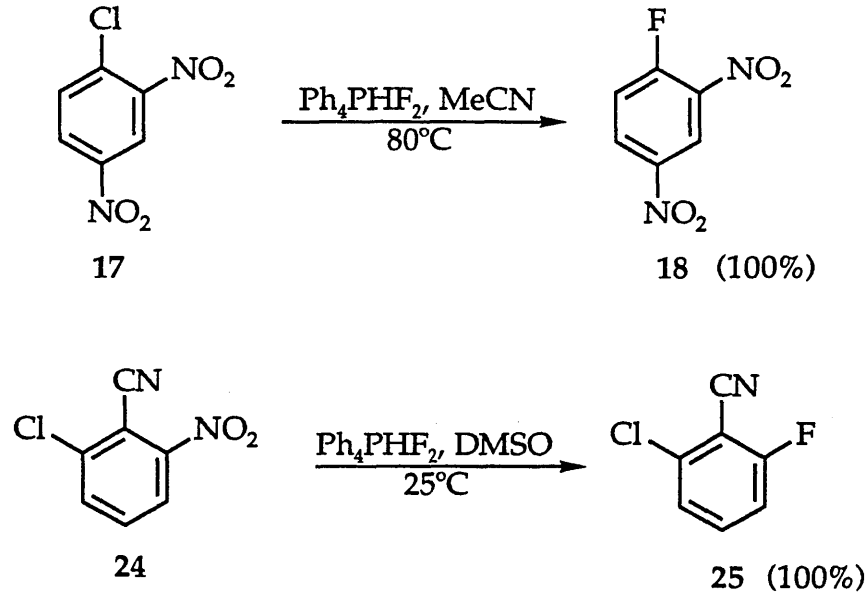
28 (6-66%)

R = 2-NO_2, 4-NO_2, 4-CN, 4-Ac, 4-Me

Scheme 17

Demethylation could also be brought about in the absence of fluoride ion by heating to the reaction temperature in the nucleophilic solvents employed. These side-reactions could be minimised and the highest yields for the fluorination procedure obtained with the strongest electron-withdrawing groups (NO_2, CN). Weakly electron-withdrawing or donating groups (Ac, Me) completely suppressed the fluorination reaction and gave only demethylation.

Although TBAF is an excellent source of fluoride ion, it is thermally sensitive (above 50°C) and therefore of limited use on less activated substrates. It has been demonstrated that tetraphenylphosphonium hydrogendifluoride is a versatile source of fluoride ion which can promote Michael additions, alkylation (by acting as a base), fluorocarbon oligomerisation and halogen exchange (by nucleophilic attack) (Scheme 18).[45]

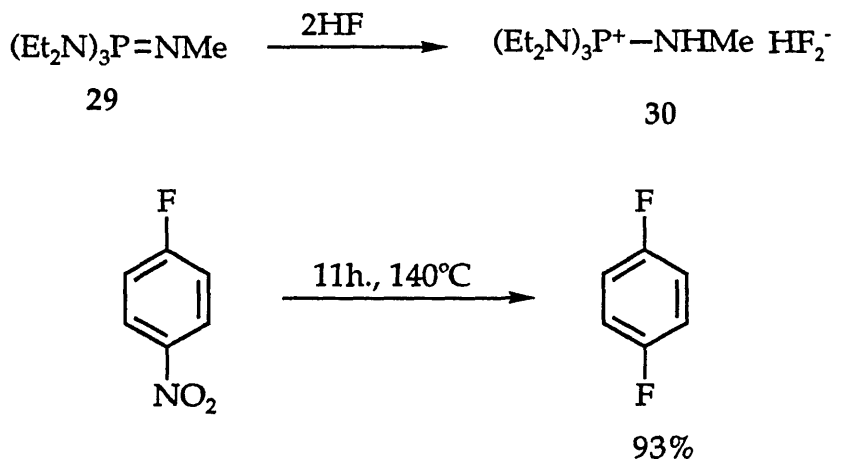


Scheme 18

It was also possible to carry out fluorodenitration in quantitative yield under mild conditions,[46] as in the previously mentioned case 24 where it occurred as the sole reaction pathway giving only 25 (Scheme 18).

A report has been published on the use of tetraphenylphosphonium bromide as a phase transfer catalyst for KF in halogen exchange reactions although no absolute yields were reported.[47] The increase noted in rate was found to be most profound in less polar solvents and an order of ranking was established: DME > acetonitrile > NMP > sulpholane > DMSO. This order was the opposite to that with KF alone and was partly attributed to stabilisation of the intermediate Meisenheimer complex by the large cation. This stabilisation would be most effective when the solvent is poor at this function.[48]

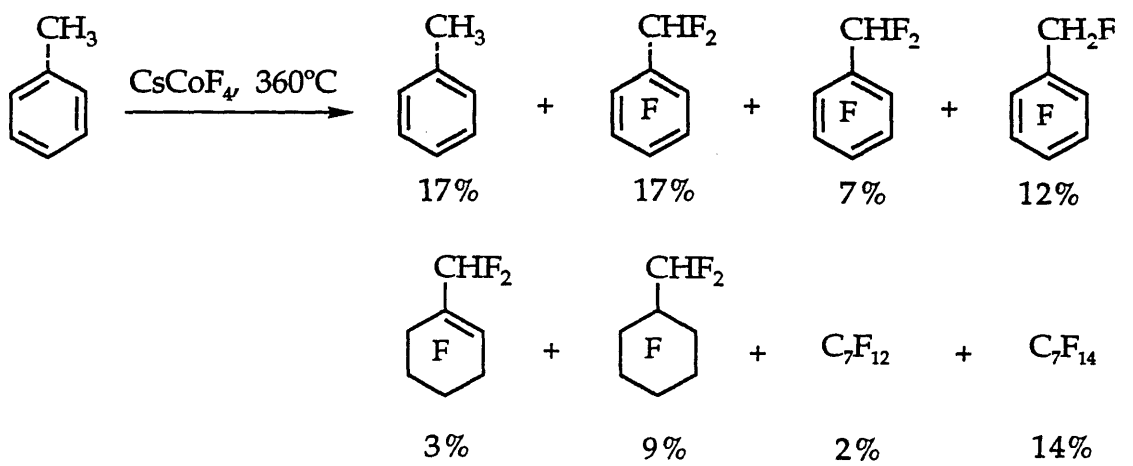
Most recently, a Russian report has described a fluoride source based on a derivative of HMPA.[49] The highly basic phosphinimine 29 was treated with two equivalents of hydrogen fluoride to give tris(diethylamino)(methylamino)phosphonium hydrogendifluoride 30. A single example of aromatic fluorodenitration using this reagent was noted giving 1,4-difluorobenzene in good yield (Scheme 19).



Scheme 19

1.4 High Valent Metal Fluorides

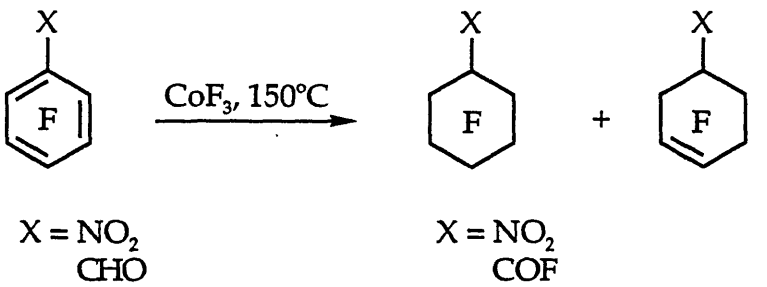
High valent metal fluorides (*e.g.* CoF_3) are very powerful fluorinating agents which have been known for some time.[50,51] The reactions with aromatic systems are generally carried out under extreme temperature conditions and a wide range of products usually results (see Scheme 20, for example).[52]



Scheme 20

It is very difficult to achieve any selectivity in these reactions, although a

report on electron-deficient benzene derivatives indicates the formation of just two products (Scheme 21).[53]



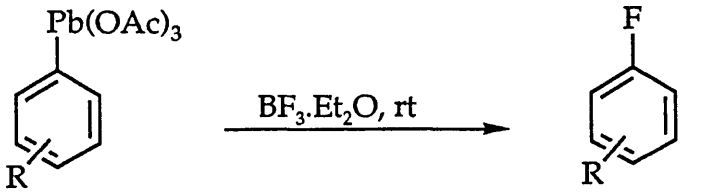
Scheme 21

This, however, does not extend to the electron-deficient heterocyclic case since pyridine reacts with $CsCoF_4$ (300-400°C) to give five products in low yield,[54] and with $KCoF_4$ (220°C) to give nineteen products.[55] In both cases, substantial ring cleavage was noted. A rationale invoking 1,2-fluorine migration has been proposed to account for the product distribution in the reactions of the less reactive CoF_4^- species.[56]

Although the high valent reagents above are not of any synthetic significance, the related silver reagent, AgF_2, has slightly more promise although it has been little used. In a study on benzene, Zweig showed that it was possible to obtain fluorobenzene in yields of up to 61% together with lesser amounts of difluorobenzenes and fluorinated 1,3-cyclohexadienes.[57]

1.5 Miscellaneous reactions of fluoride ion

It has been demonstrated that $BF_3.Et_2O$ may be used as a fluoride source in fluorodemetallation reactions with aryllead triacetates **31**.[58] These may be either preformed or generated *in situ* from the corresponding aryl-trimethylsilane or, better still, triarylboroxine with lead tetraacetate. Reactions were performed overnight at room temperature (Scheme 22).

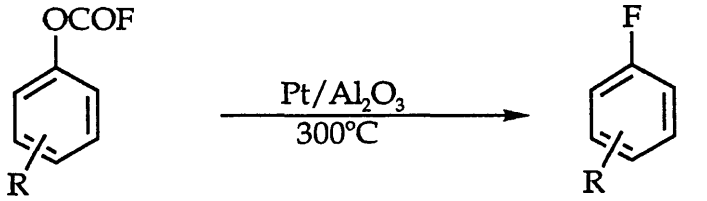


31 49-82%

R = 4MeO, 4-Me, H,
4-F, 4-CF_3, 2,3-$(CH)_4$,
3,4-$(CH)_4$

Scheme 22

An early report on aryl fluoroformates 32 stated that they were stable to 800°C after which they decomposed to the aryl fluoride.[59] An industrial team has shown that this decomposition can be catalysed by passing them over supported transition metals, with a contact time of 0.1s (Scheme 23).[60]



32 11-61%

R = H, 2,4,6-Me_3, 4-Cl

Scheme 23

CHAPTER 2

MOLECULAR FLUORINE AND DERIVED REAGENTS

2.0 Introduction

In the preceding chapter, all fluorinations were carried out *via* attack of some form of fluoride ion (F^-) on an electron-deficient aromatic substrate. A simplistic alternative to this could involve electrophilic fluorination with an electron-rich substrate and fluoronium ion (F^+).

Since F^+ is a highly energetic species (ΔH_f 1760 $kJmol^{-1}$) it is likely to be too reactive for synthetic purposes. Indeed, it could only be generated electrochemically due to the the electronegativity of fluorine. There is no need, however, for a formal positive charge to be associated with the fluorine atom and a number of reagents which act as fluorine electrophiles have been developed.

The structural requirement for these reagents is simply that a highly electronegative group be weakly bonded to fluorine (invariably through a heteroatom). This results in a molecule with minimal dipole moment (*e.g.* F_2, $FClO_3$). As an electron-rich centre approaches, the part of the reagent with the greatest electron affinity will be attracted to it causing a concerted ejection of the good leaving group. At no time is there a need for any fraction of positive charge to be located on fluorine.

In the following chapter, reactions of molecular fluorine are described along with a number of derivatives which follow the guidelines laid out above for reagent structure.

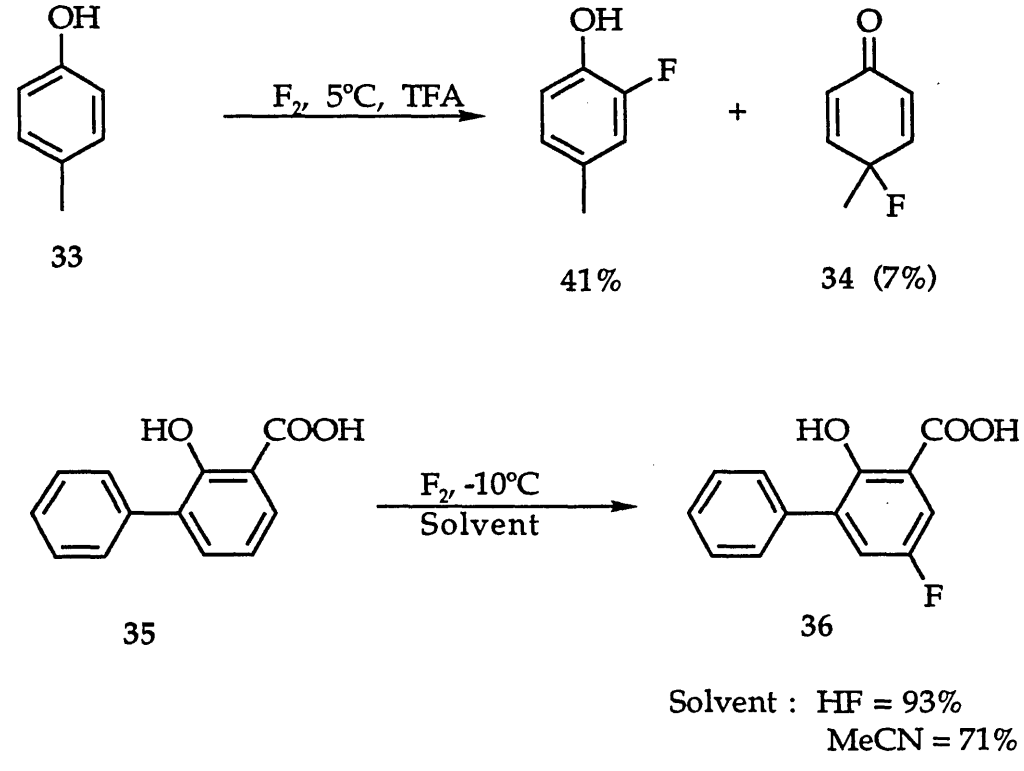
2.1 Molecular Fluorine

Since its discovery in 1886 by Moissan,[61] fluorine has held a unique place amongst all the elements. The reactivity, which results from the low F-F bond strength (157 $kJmol^{-1}$) and high electronegativity, has given molecular fluorine an aura of being difficult to handle under standard laboratory conditions without highly specialised apparatus and totally unselective in its reactions with organic substrates.

Over the last three decades however, the acceptance of fluorine as a synthetic

tool has been gaining momentum as organic chemists have come to realise that, under carefully controlled conditions, fluorine can be used to carry out specific transformations.[62] In general, these reactions are found to proceed much more smoothly in more polar media, thus minimising homolytic reactions which create the highly reactive and destructive fluorine radical ($F^{\cdot}$).

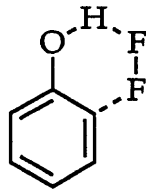
Misaki has shown that cresols can be directly fluorinated to give mixtures of *ortho*-and *para*-substituted cresols in either tetraglyme or trifluoroacetic acid.[63] In the case of *para*-cresol 33, (Scheme 24), the minor product was the dienone 34 although the proportion of this product increased to give a 1:1 mixture in tetraglyme. It was also found that the *ortho*: *para* ratio rose as the solvent polarity increased. The yields increased in the case of phenyl-substituted phenols where carboxylic acid 35 gave a single product 36 in excellent yield (Scheme 24).[64]



Scheme 24

Purrington has shown that the addition of a Lewis acid to the reaction

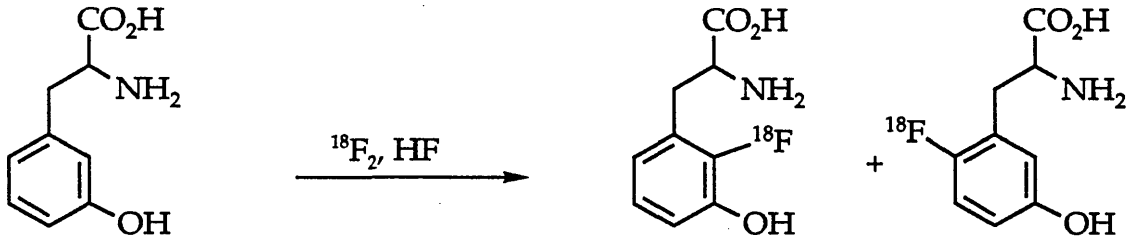
results in a drop in the *ortho*: *para* ratio.[65] This can be rationalised by Misaki's suggestion that a cyclic transition state 37 may explain the preference for *ortho*-fluorination of phenols.[66]



37

The complexation of the phenolic oxygen by a Lewis acid would therefore lower the availability of this pathway. On other aromatic systems, it was found that BCl_3 gave improved yields of fluoroaromatics in all cases. This was attributed to polarisation of the fluorine molecule brought about by the Lewis acid.

The use of direct fluorination in the generation of radiolabelled PETT substrates is a highly desirable process and is typified by the reaction of *m*-tyrosine 38 (Scheme 25).[67]



38

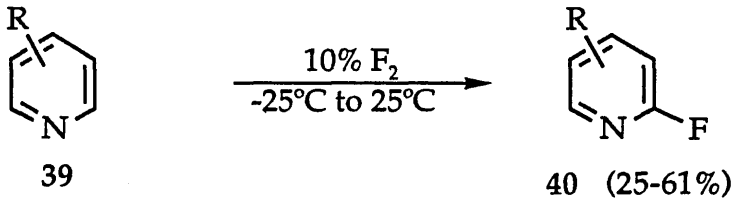
7 : 12

43% radiochemical yield

Scheme 25

It is also possible for heterocycles to be fluorinated with molecular fluorine as has been shown by Van Der Puy who showed that various pyridines 39 undergo reaction at C-2 40 (Scheme 26).[68] Although yields were moderate

(26-61%), functional group tolerance was quite good. In the case of 3-substituted pyridines, mixtures of 2-fluoro- and 5-fluoropyridines were formed.



39 40 (25-61%)

R = 4-alkyl, 3-Me, 3,5-Me_2, 3,5-Cl_2, 4-Ac, 3-COOMe, 4-COOMe

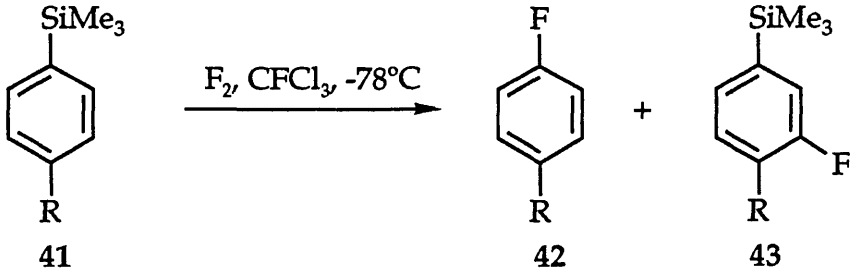
Scheme 26

It is probable that pyridine difluorides (Py.F_2) are intermediates as shown by Meinert's observation that isolated pyridine difluoride undergoes violent decomposition at 0°C to give 2-fluoropyridine.[69]

Although it has been shown that fluorine can be used in electrophilic substitution reactions, a problem occurs in the absence of suitable blocking groups (*e.g.* see 36 above). Typical electrophilic substitution patterns result with mixtures of regioisomers. To overcome this, fluorodemetallation has been introduced.

In 1981, Adam showed that exposure of phenyltributyltin or tetraphenyltin to fluorine at -78°C gave fluorobenzene in 70% and 15% yields respectively.[70] Radiolabelling studies showed similar efficiencies. Later it was demonstrated that this substitution phenomenon was not limited to tin and that lead, germanium, silicon and mercury also underwent the transformation, although not as successfully.[71]

A radiofluorination study on aryltrimethylsilanes 41 showed that, in activated systems, conventional electrophilic substitution (→42) could compete with fluorodesilylation (→43) and was a minor side-reaction in other cases (Scheme 27).[72]



41 42 43

	42	43
R=H:	25%	4%
=Me	28%	3%
=OMe	21%	19%
=Cl	22%	3%
=TMS	22%	trace

Scheme 27

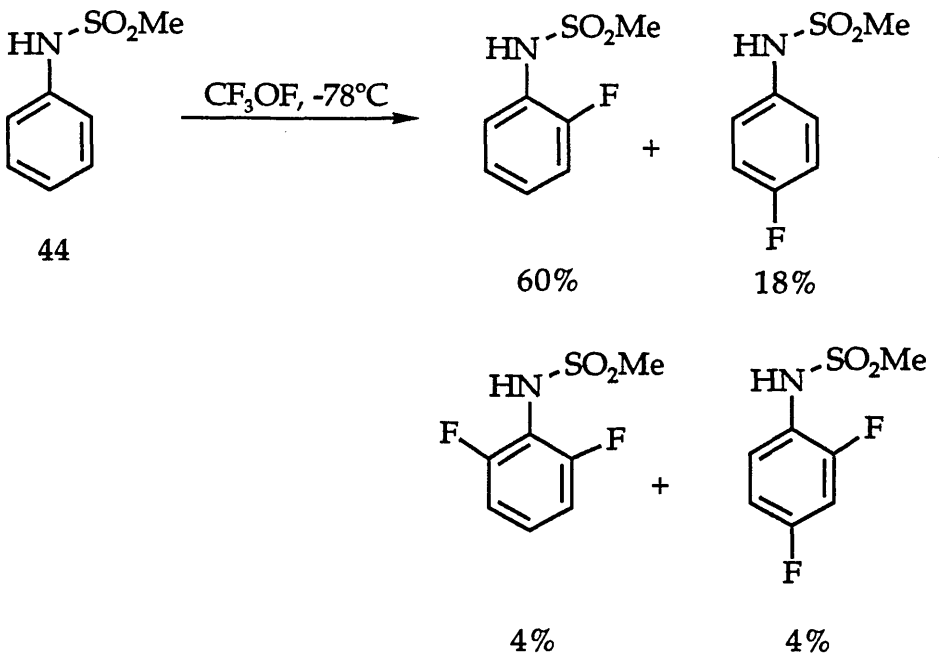
An interesting point in this study was that the presence of a second trimethylsilyl group did not result in the formation of any 1,4-difluorobenzene and only a trace of fluorodeprotonation was noted.

A separate investigation extended these studies and showed that trimethyltin was an even better leaving group than tributyltin and substantially more so than either trimethylsilyl or trimethylgermyl.[73] Even if an electron-withdrawing group such as *para*-CF_3 was present, the yield was still of the order of 35%.

2.2 Trifluoromethyl Hypofluorite

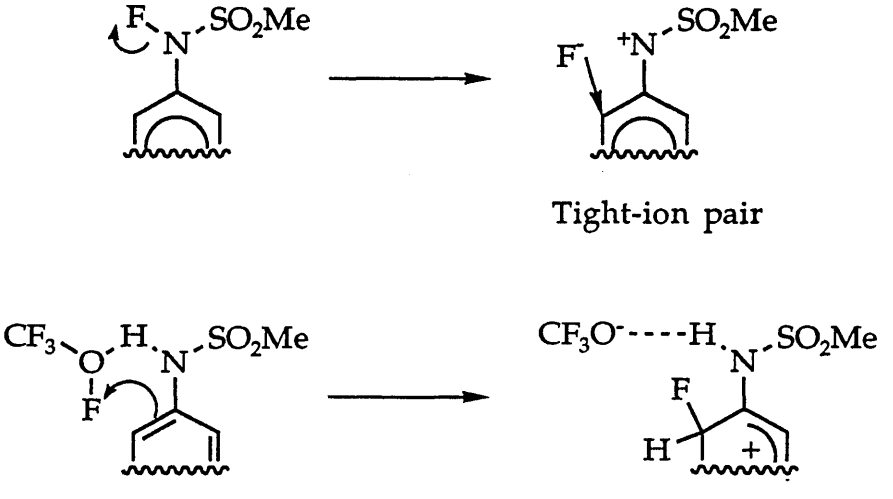
Trifluoromethyl hypofluorite is one of the earliest known fluorine-derived reagents and may be prepared from a mixture of fluorine and carbon monoxide by passing over a bed of hot, activated CsF.[74]

It was shown by Fifolt that *N*-substituted anilines 44 underwent predominantly *ortho*-substitution with the optimum substituent being the methanesulphonyl group (Scheme 28).[75]



Scheme 28

Two possible mechanisms were proposed. The first involved formation of an N-F bond followed by dissociation to a tight ion-pair (Scheme 29) similar to that in the Orton rearrangement of *N*-haloanilines. The second proposed hydrogen-bonding between the amino proton and the reagent oxygen (Scheme 29).



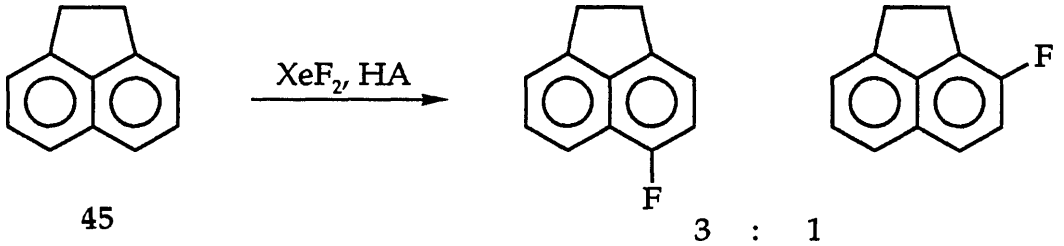
Scheme 29

Fluorodemetallation with CF_3OF was found to follow a different order to that with molecular fluorine in that mercury was a more effective leaving metal than tin.[76] For example, reaction with diphenylmercury gave fluorobenzene in 83% yield as opposed to 50% with phenyltrimethyltin or only 22% with tetraphenyltin.

2.3 Xenon Difluoride

Xenon difluoride has been known for 20 years[77,78] and is an easily handled, crystalline solid. It is readily prepared from the respective elements under photolytic conditions.[79] It is also available commercially but is prohibitively expensive.[80]

Zupan has shown, in reactions of acenaphthene 45, that the nature of the catalyst added to the reaction mixture has no influence on the regioselectivity observed but does affect the overall chemical yield (Scheme 30).[81]



45

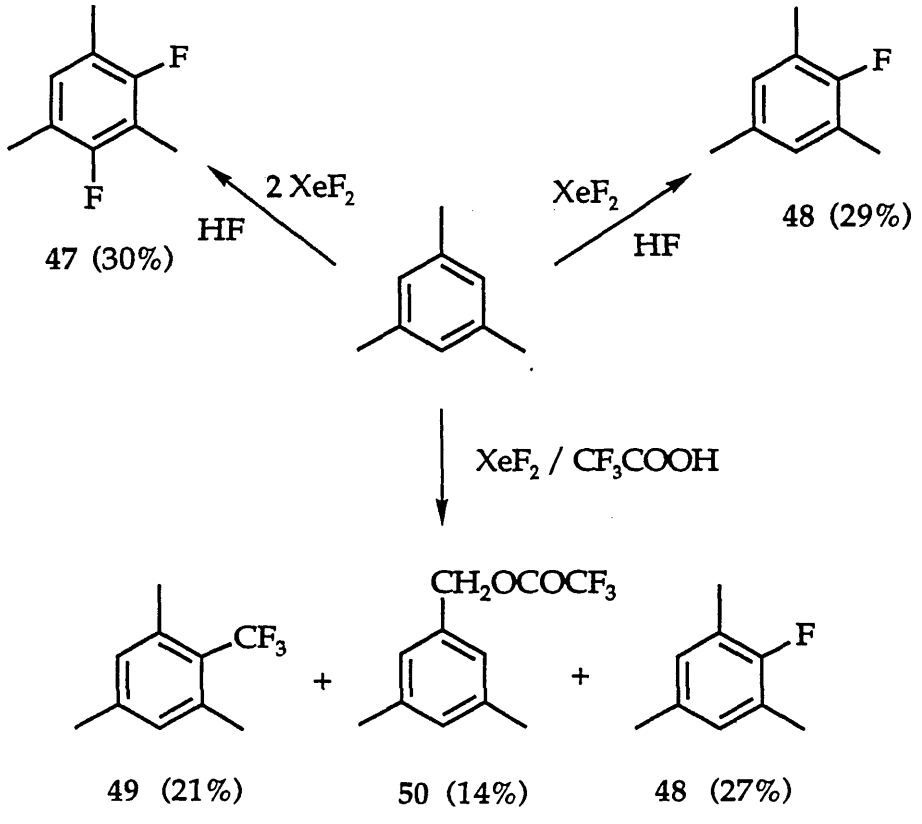
3 : 1

		Yield
HA:	HF	50%
	BF_3	20%
	C_6F_5SH	45%

Scheme 30

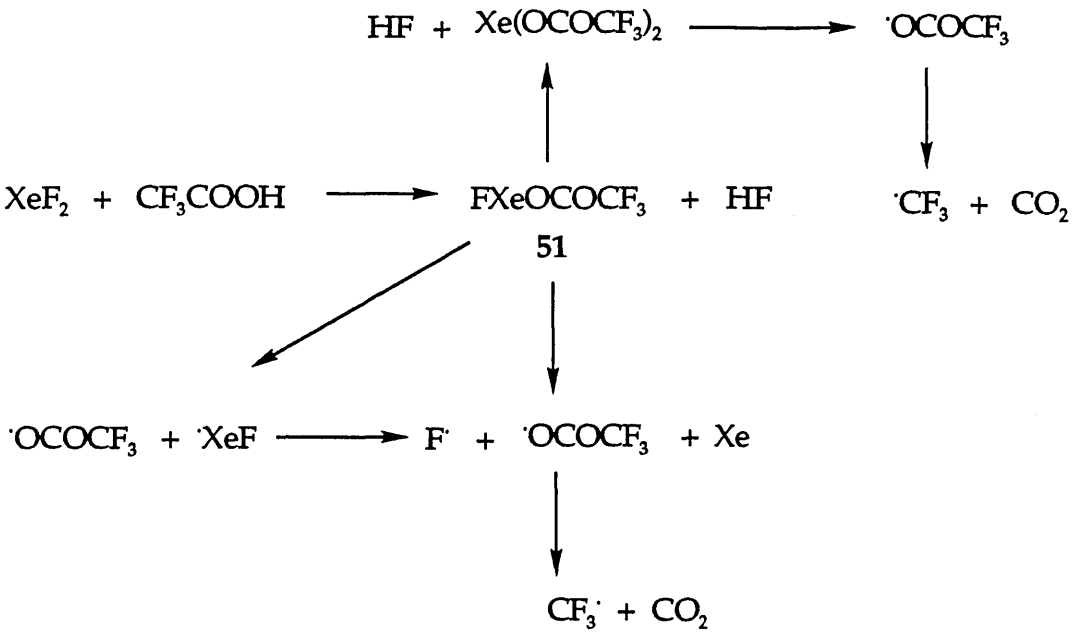
In a related study it was demonstrated that, in reactions of methyl-substituted benzenes, the catalyst affected the product type.[82] Thus, using HF as catalyst, 1,3,5-trimethylbenzene 46 gave either 47 or 48 depending on the

actual amount of XeF_2 introduced (Scheme 31). Using TFA as catalyst, however, a mixture of fluorine-containing products 48, 49 and 50 was obtained suggesting a number of competitive pathways (Scheme 31).



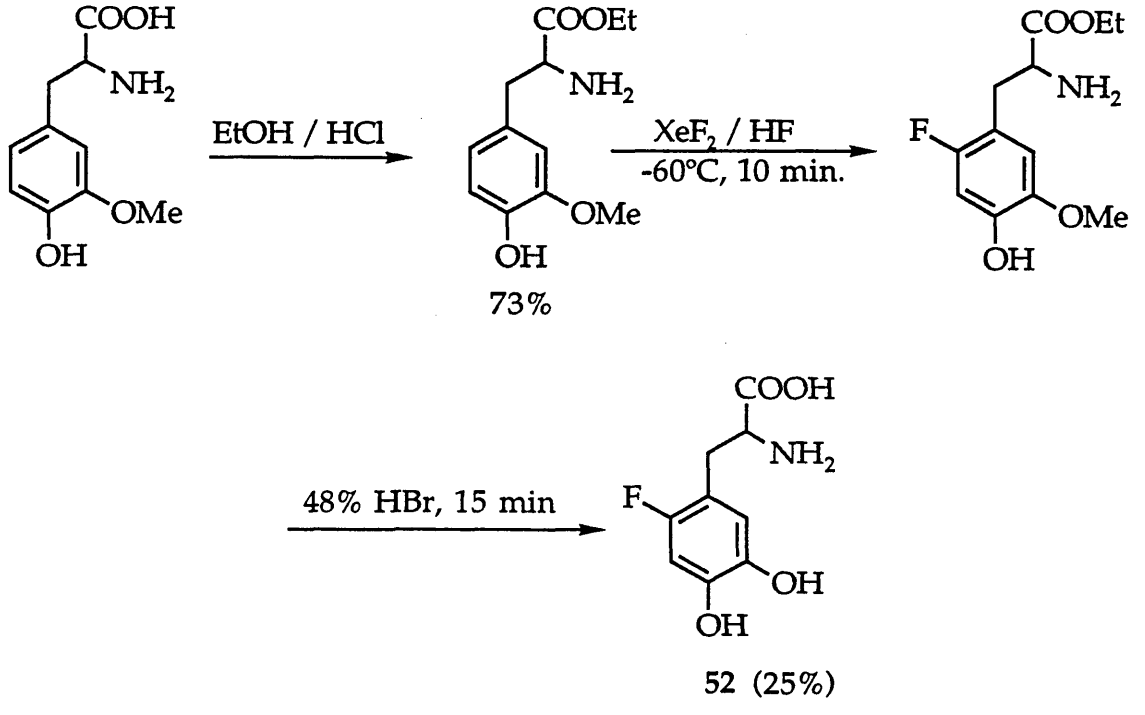
Scheme 31

These formation of the fluorinated species 48, 49, 50 in the TFA-catalysed reactions is attributed to the generation of the fluoroxenon carboxylate ester 51. It has previously been demonstrated that esters of this type can undergo homolytic decomposition by a variety of pathways giving rise to a number of product-forming radicals (Scheme 32).[83-85] These various radicals could then either add to the aromatic system accounting for 49 and 51 or abstract a hydrogen atom from one of the benzylic positions which would ultimately give rise to 50.



Scheme 32

It is well known that XeF_2 reacts with electron-rich oxygenated aromatics in the absence of a catalyst. This approach has been applied to a synthesis of 6-fluoro-L-DOPA 52 (Scheme 33).[86]



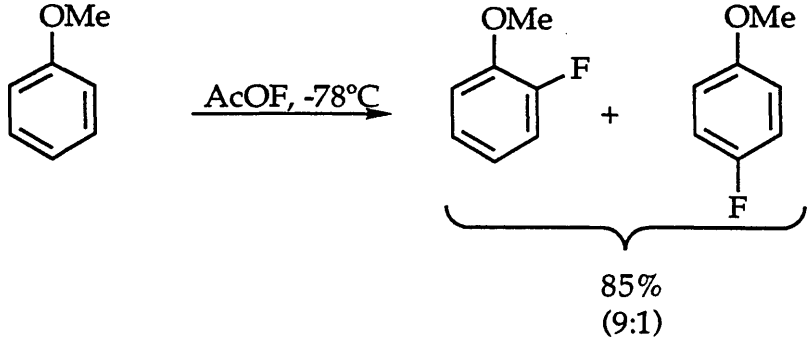
Scheme 33

Unsurprisingly, it was not possible to carry out direct fluorination with this reagent of L-DOPA due to oxidation of the catechol ring to give the corresponding quinone. The overall speed and excellent regiocontrol of the synthesis should readily lend itself to radiochemical applications using $Xe^{18}F_2$.

2.4 Acetyl Hypofluorite

Since its introduction by Rozen in 1981[87] as a modification of the highly reactive trifluoro- derivative (CF_3COOF),[88] acetyl hypofluorite has become one of the most widely used electrophilic fluorinating reagents. Its preparation requires the passage of dilute fluorine either through solid KOAc.2HOAc,[89] or through a suspension of NaOAc in Freon at -78°C.[87] In each case, the acetyl hypofluorite is generally transferred to the reaction vessel in a stream of dry nitrogen. It is notable that the chemistry of the reagent was explored in some detail before its structure was confirmed by Appelman in 1985![89]

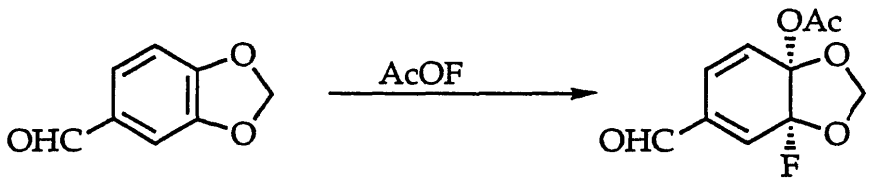
In his initial report, Rozen showed that electron-rich aromatic systems underwent fluorination to give mixtures of *ortho*- and *para*-fluorinated products which were substantially enriched in the *ortho*-isomer (Scheme 34).[87]



Scheme 34

It was later found that the product distribution could be explained by an

addition-elimination mechanism and indeed, in the case of piperonal 53 it was possible to isolate the adduct 54 (Scheme 35).[90]

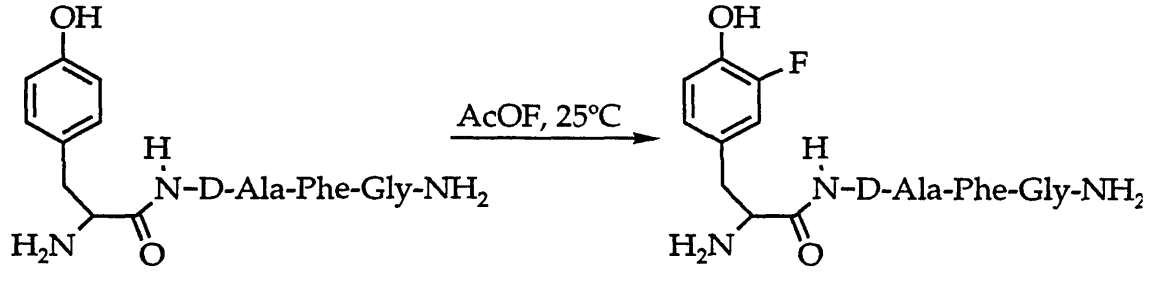


53 54 (55%)

Scheme 35

In many cases, however, the intermediate cyclohexadienes underwent side-reactions generating *ortho*-quinones or undergoing further fluorination. An interesting observation was that 6-methoxyquinoline underwent clean reaction to give 5-fluoro-6-methoxyquinoline in 75% yield with no apparent attack *via* the lone pair of the nitrogen.

A recent report has demonstrated the direct fluorination of a tyrosine residue in an unprotected tetrapeptide 55 gave a single fluorinated arene in 50% yield with a conversion of 75% (Scheme 36).[91] At higher conversions, phenolic oxidation became a competing reaction although this could be totally suppressed by protection of the hydroxyl as the benzyl ether. In each case, fluorination was restricted to the position *ortho* to the hydroxyl with no substitution of other aromatic protons.

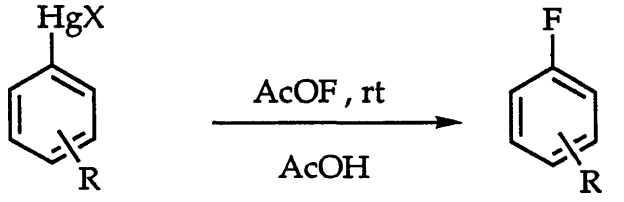


55 50%

Scheme 36

Although in this example 55, regiospecific fluorination was achieved, reactions with acetyl hypofluorite have generally given product mixtures. To overcome this, the trend with acetyl hypofluorite reactions seems to be moving towards fluorodemetallation.

As early as 1984, Visser showed that arylmercurials 56 gave better yields compared to the parent arenes (except in the case of highly activated aromatics) and total regiocontrol *via ipso* fluorination (Scheme 37).[92]



56 45-65%

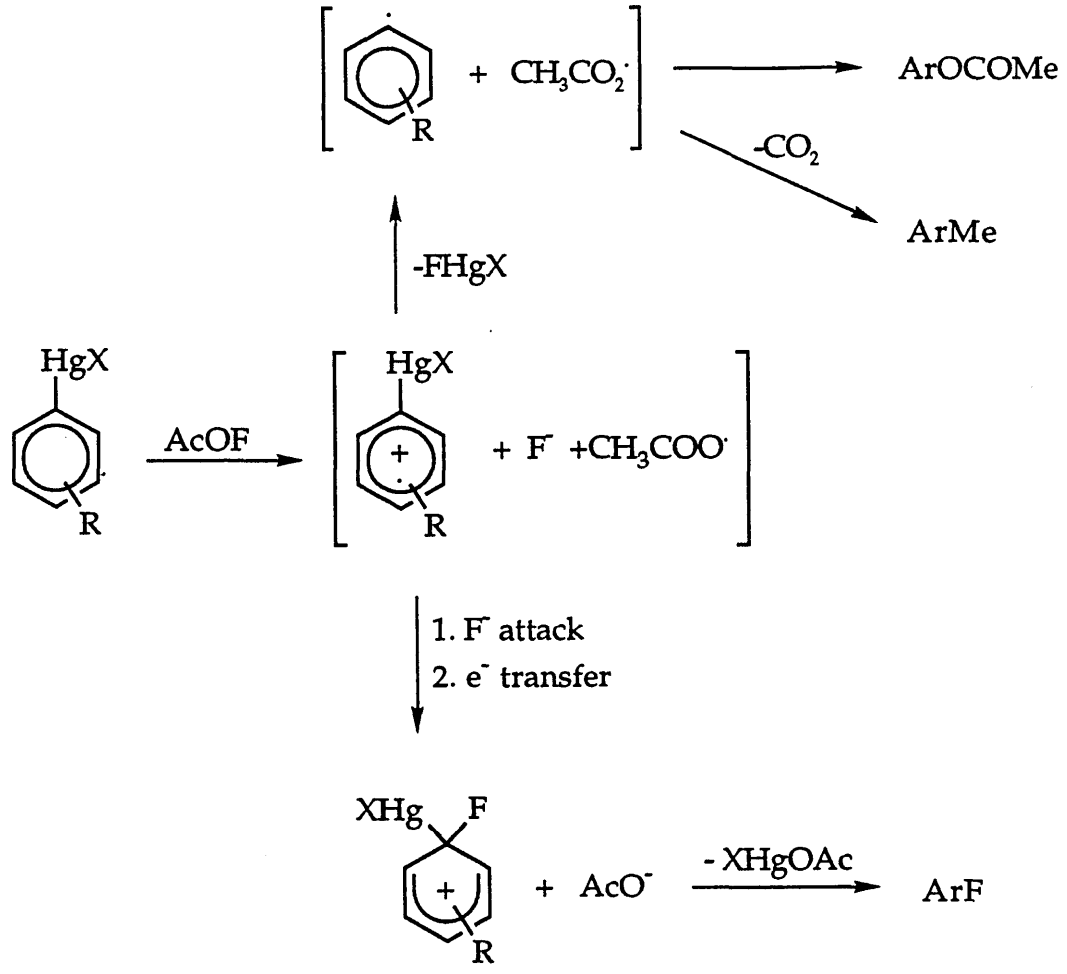
X = Cl, OAc
R = 4-MeO, 2 and 4-OH,
Me, H, 4-MeCONH

Scheme 37

A later study from the same group extended this work and a single electron transfer mechanism was proposed to explain the various side-products formed in the reaction (Scheme 38).[93] These were regiospecific acetoxy- and methyl-substituted aromatics formed at *ipso* position.

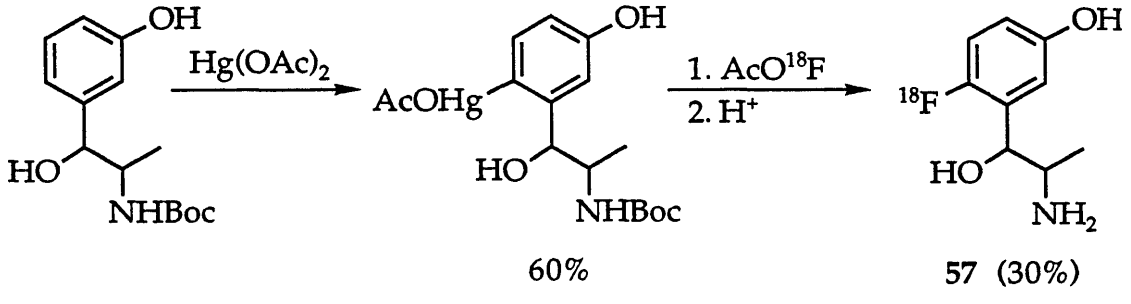
Solvent-dependance was noted in several cases with the excellent hydrogen-atom donor THF resulting in poor to negligible yields of fluoroarenes while the poor hydrogen atom-donor acetic acid proved to be the optimum solvent.

Other reports have concentrated on Group IV aryltrimethylmetals and have shown that, except for tin, these are not as effective as arylmercurials.[72,73] In the case of silicon, fluorodeprotonation was a competitive reaction and yields of the *ipso* product were in the range 6-16%.[72] Acetyl hypofluorite was found to be as efficient as molecular fluorine for reactions of aryltrimethyltins.[73]



Scheme 38

Radiolabelled [^{18}F]-AcOF is readily prepared[92] and has been used in the preparation of a number of radiopharmaceuticals. Wieland has synthesised 6-[^{18}F]-fluorometaraminol 57 (Scheme 39)[94] and demonstrated its use in neuronal mapping of the canine heart.[95] A notable point here is that there was no need to protect the secondary benzylic alcohol.



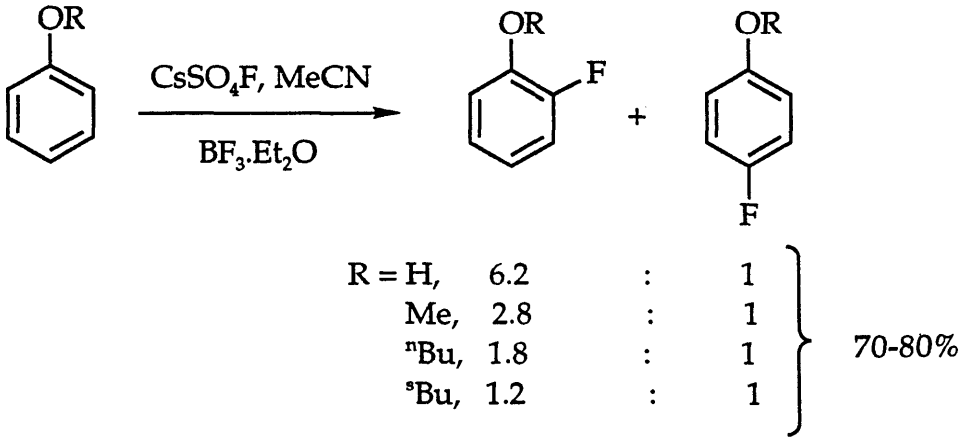
Scheme 39

2.5 Caesium Fluoroxysulphate

Caesium fluoroxysulphate was first characterised by Appelman in 1979 and is a readily handled, crystalline solid prepared from cold, aqueous caesium sulphate and dilute fluorine.[96] It was initially reported that aqueous solutions fluorinated toluene to give a wide range of products including oxygenated products. It was later found that acetonitrile was a more suitable solvent for these reactions,[97] partly due to greater reagent stability in the organic solvent. An electrophilic mechanism was proposed although side-reactions involving single electron transfer were noted with some less activated substrates *e.g.* toluene underwent fluorination predominantly at the benzylic position with no oxygenation.[97]

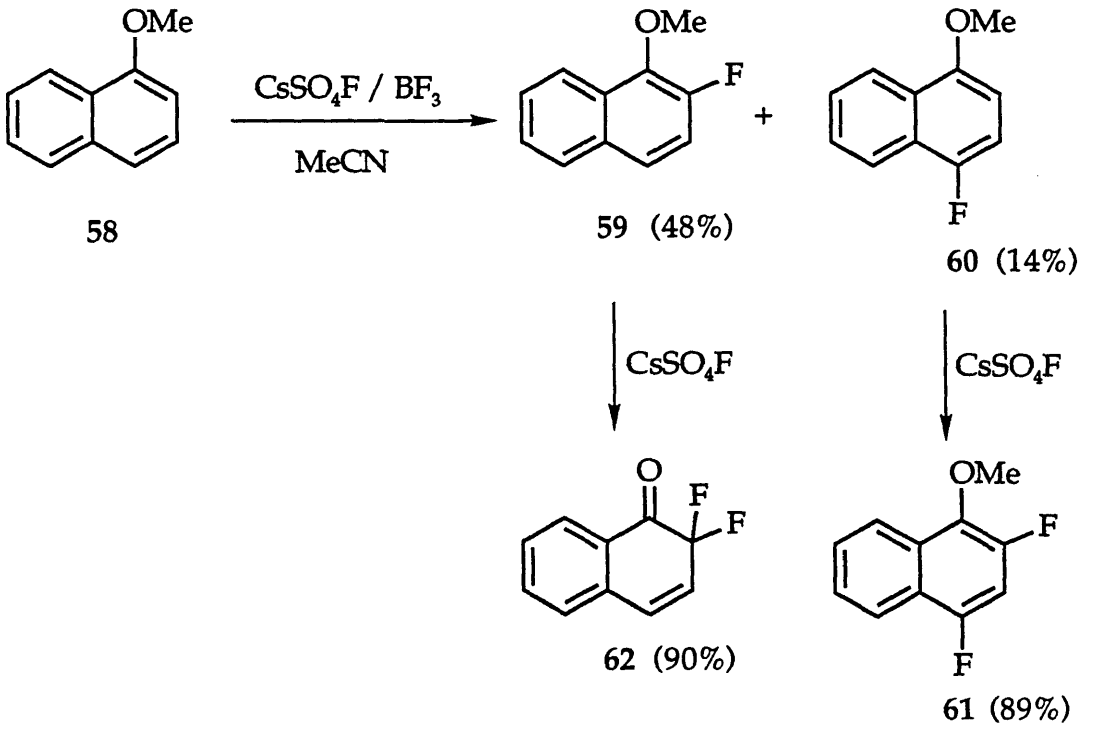
Subsequently, boron trifluoride (among other acids) was shown to be a useful catalyst giving significantly better yields.[98,99] In the case of toluene, side-chain fluorination was completely suppressed and only *ortho-* and *para*-fluorotoluenes were observed. An early report from Zupan showed that benzene could be transformed to fluorobenzene in 35% yield in the presence of BF_3 compared to 12% otherwise.[99]

In reactions of phenol and acetanilide, a high degree of *ortho*-substitution was noted,[100,101] as in reactions of AcOF,[87,90] although this was much less pronounced in the case of *O*-alkylated phenols (Scheme 40).



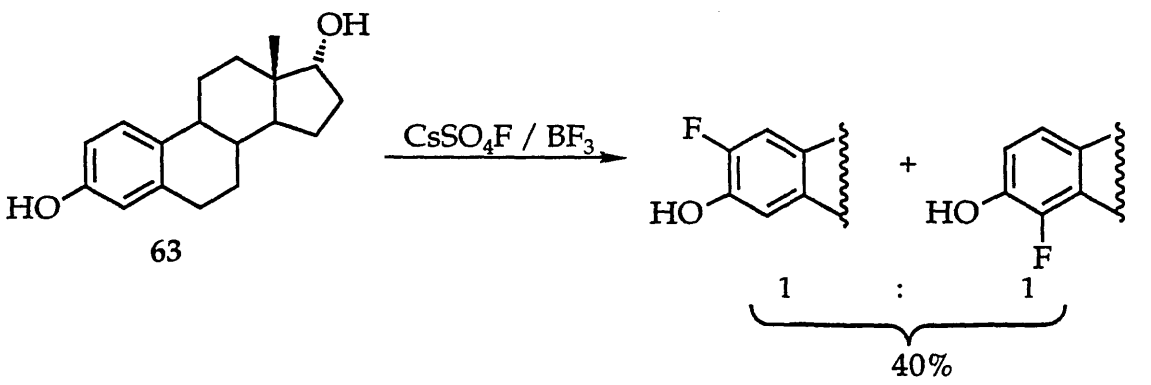
Scheme 40

As the alkyl group became more sterically demanding, *para*-substitution became more important. Oxygen-substituted naphthalenes 58 gave mixtures of fluoronaphthalenes 59, 60, 61 and fluorinated enones 62 (Scheme 41).



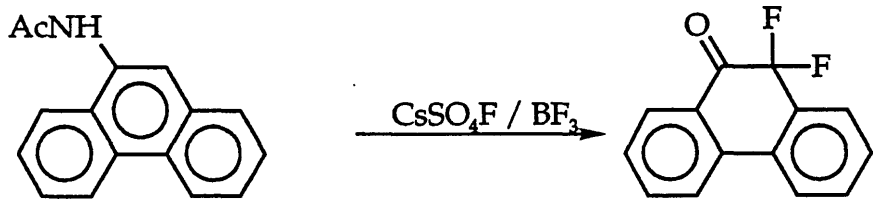
Scheme 41

In a study of activated systems, Patrick has shown that 17-β-estradiol 63 underwent clean fluorination with $CsSO_4F/BF_3$ to give a 1:1 mixture of 2-fluoro and 4-fluoro-17-β-estradiol (Scheme 42).[102]



Scheme 42

Various benzo-fused acetanilide derivatives were also reacted to give mixtures of *ortho*-fluorinated products and α,α-difluoro ketones (Scheme 43).

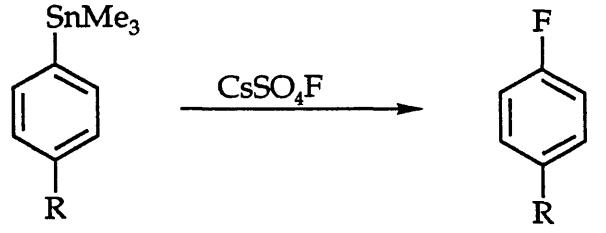


75%

Scheme 43

Zupan has also shown that pyridines may be fluorinated at C-2 although, in the presence of external nucleophiles, 2-substituents other than fluorine were incorporated.[103] The fluorination was most effective in non-polar solvents (*e.g.* CCl_4, cyclohexane) although no absolute yields were given.

As with other reagents, a range of regioisomers is obtained on reaction of $CsSO_4F$ with aromatics unless blocking groups are employed. To this end, Chambers showed that it is possible to carry out fluorodestannylation in a regioselective manner (Scheme 44).[104,105] The efficiency of the leaving groups were found to be Me_3Sn > Bu_3Sn >> *c*-Hex_3Sn. This was attributed to reduced solubility with the larger groups, even in mixed solvent systems, and increased hindrance of the approaching electrophile.



69-86%

R = H, Me, OMe, Cl

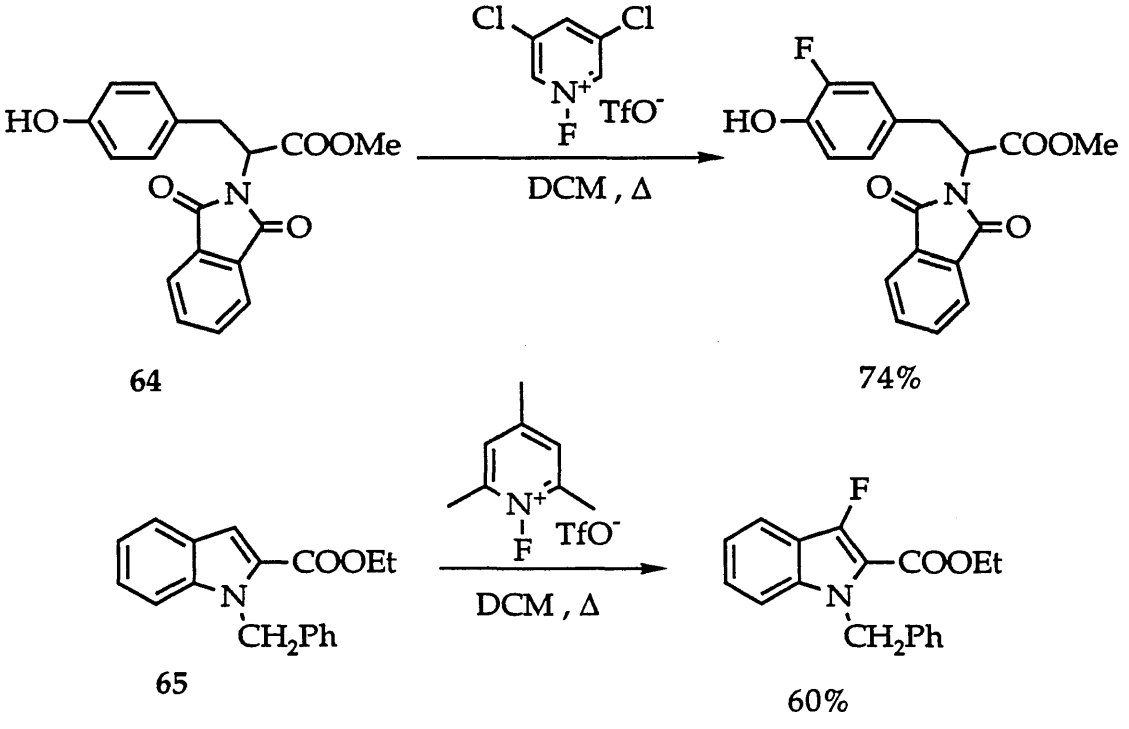
Scheme 44

2.6 *N*-Fluoropyridinium Salts

N-Fluoropyridinium salts were introduced in 1986 by Umemoto who generated pyridine difluoride as described by Meinert[69] but subsequently carried out an anion exchange to the non-nucleophilic triflate ion.[106] It was later found that a range of these reagents bearing a range of functional groups could be prepared.[107] The resulting highly stable, crystalline solids were able to fluorinate various nucleophiles including aromatics.

Benzene gave fluorobenzene in 56% yield (based on *N*-fluoropyridinium salt). Phenol gave a mixture of 2-fluoro, 4-fluoro- and 2,4-difluorophenols; the product distribution could be tuned to give *ortho*: *para* ratios of 3.5:1 to 1.25:1 by varying the substituents on the pyridine ring.

A more recent, comprehensive report has described the fluorination of a wide range of substrates including carbanions, β-diketones, silyl or alkyl enol ethers, vinyl acetates ketene silyl acetals and alkenes.[108] A variety of aromatics were fluorinated including the tyrosine derivative 64 and the indole 65 (Scheme 45).

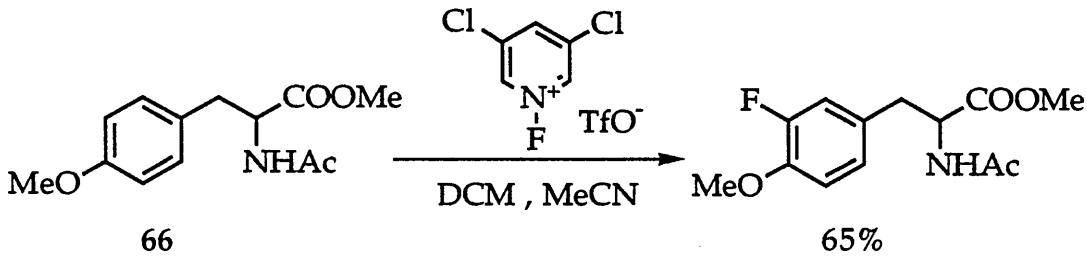


Scheme 45

A number of heterocycles (furan, pyrrole, thiophene) and derivatives, however, could not be fluorinated. It was also possible to fluorinate phenylmagnesium bromide, but not phenyllithium, at 0°C in THF to give fluorobenzene in 58% yield. The proposed mechanism for all these reactions invoked single electron transfers to explain the observed by-products.

More recently, it has been claimed by Differding in a study of various electrophilic fluorinating agents that fluorination of ketone enolates occurs by a conventional S_N2 displacement at fluorine.[109,110] By-products may be formed by single electron transfer to generate radical intermediates which undergo other reactions. The fluorine-containing products are *not* derived from radical intermediates. Although the study did not include *N*-fluoro-pyridinium salts, it did include XeF_2 which was previously thought to fluorinate *via* single electron transfer.

A number of potentially useful biological tracers have been fluorinated using *N*-fluoro-3,5-dichloropyridinium triflate[111]. Tyrosine 66 (Scheme 46), dopamine and L-DOPA derivatives were regiospecifically fluorinated in the predicted positions in yields of 20-65%. 17-β-estradiol gave a 1:1 mixture of the 2-fluoro and 4-fluoro-17-β-estradiol.



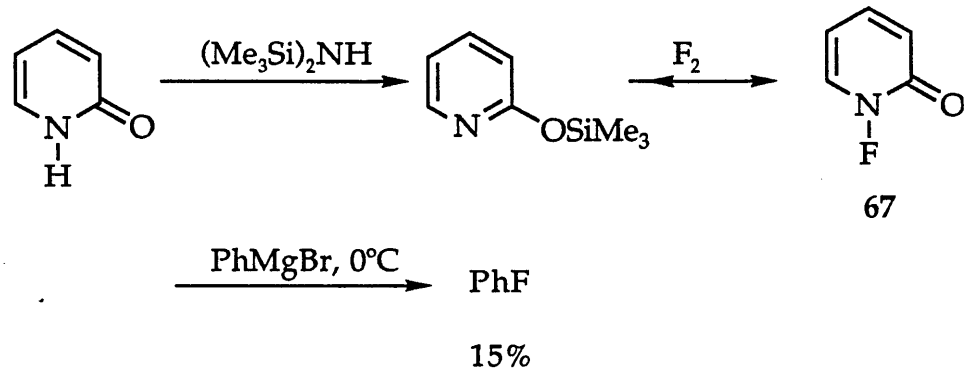
66 65%

Scheme 46

2.7 Related *N*-Fluoro Compounds

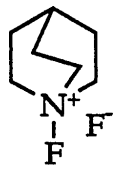
Purrington demonstrated that 2-pyridone could be selectively fluorinated on nitrogen in two steps to give 1-fluoro-2-pyridone 67.[112] This reacted with phenylmagnesium bromide to give fluorobenzene in 15% yield (Scheme

47).[113] The use of this reagent in fluorination does not appear to have been pursued further.



Scheme 47

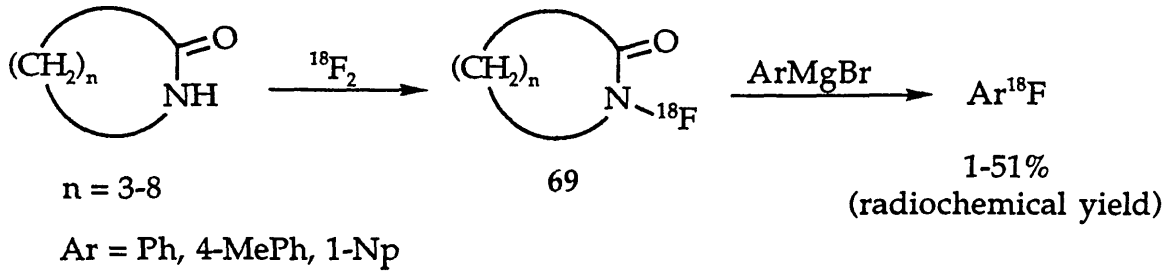
The Banks reagent, *N*-fluoroquinuclidinium fluoride 68, prepared from quinuclidine and fluorine, has been used to prepare fluorobenzene from phenylmagnesium bromide in 26%.[114]



68

A major problem, however, is the hygroscopicity of this reagent, especially in the fluorination of carbanions. Although not powerful enough to fluorinate benzene, phenyltrichlorosilane may be converted to fluorobenzene in 22% yield at ambient temperature.

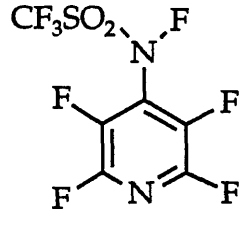
A process which was directed towards radiofluorination was described by Satyamurthy based on *N*-fluorolactams 69 prepared from the corresponding lactams.[115] The reaction with aryl Grignard reagents provided fluoroaromatics in poor to moderate yield (Scheme 48). Reaction with aryllithiums failed to provide any fluorinated products, probably as a result of elimination of HF.



Scheme 48

The introduction of *N*-alkyl-*N*-fluorosulphonamides by Barnette was one of the earliest efforts to obtain stable, fluorinating agents.[116] A variety were prepared (yields of 11-71%) and the best had tertiary groups on nitrogen to avoid the possibility of elimination of HF on reaction with carbanions. Reactions with aromatics were limited to three examples (an aryllithium, a Grignard reagent and a phenoxide) although yields of fluoroaromatics for these substrates were in the range 50-60%.

A more powerful version based on a perfluorinated skeleton 70 was introduced by Banks.[117] This reacted with a variety of nucleophiles and it was possible to fluorinate benzene in 88% yield at 60°C.



70

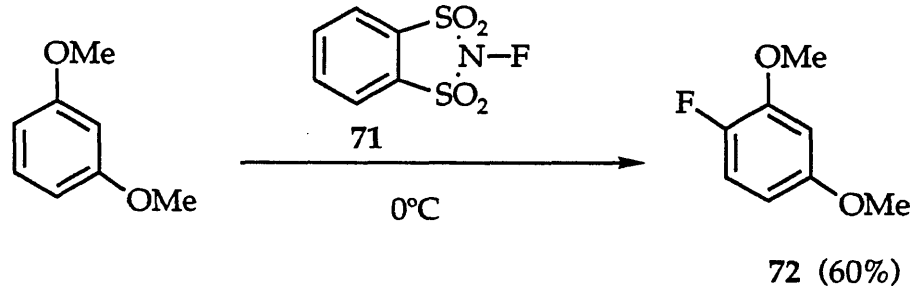
A major drawback of this reagent is that its preparation requires six steps from trifluoromethane sulphonyl chloride.

The major recent advance in electrophilic fluorination has probably been the extension of the above approach to the *N*-fluorosulphonimides which were originally introduced by DesMarteau.[118] A number were synthesised with the most effective being $(CF_3SO_2)_2NF$. A range of aromatics could be

fluorinated at 22°C with this reagent (as judged by ^{19}F NMR) although no absolute yields were given; aromatics bearing electron-deficient groups did not react. A major problem of this reagent is that the original preparation required 11 steps including a reaction with liquid fluorine, however a very recent publication shows this has been reduced to a still fairly lengthy five steps.[119]

Two related compounds have recently been reported based on aryl-sulphonimides.[120,121] They have the added bonus of ease of purification (either by recrystallisation or chromatography). The first from Davis is *N*-fluoro-*o*-benzenedisulphonimide 71, readily prepared in 90% yield from the sulphonimide.[120]

Although 71 was introduced primarily as a reagent for enolate fluorination, phenylmagnesium bromide underwent rapid (5 minutes) reaction to give fluorobenzene in 80% yield. The activated aromatic, 1,3-dimethoxybenzene, also underwent reaction at 0°C to give a regioselective product 72 (Scheme 49).

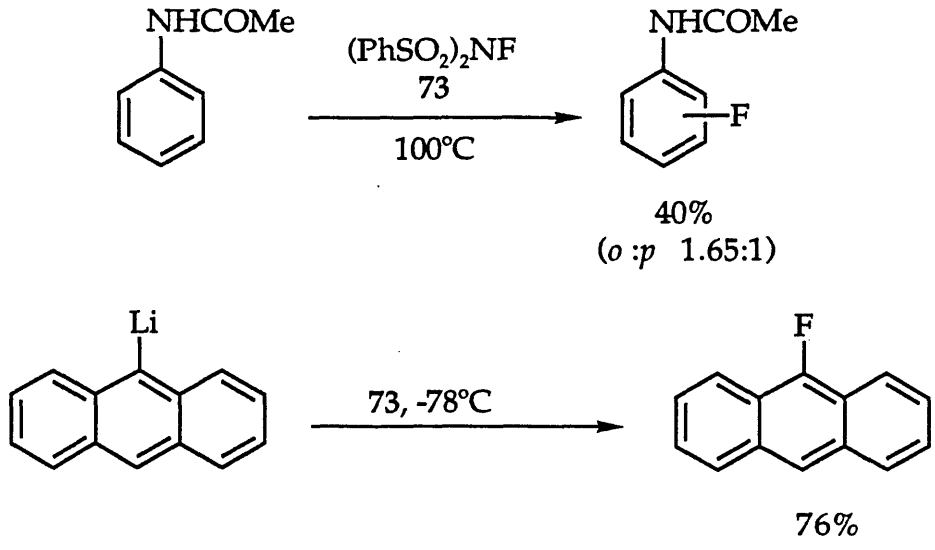


Scheme 49

A more versatile reagent was introduced by Differding based on the commercially available benzenesulphonimide.[121,122] This reagent 73 is soluble in a range of organic solvents and can be used to fluorinate a number of aromatics by heating at reflux using excess substrate as solvent (Scheme 50).

Of added interest is the observation that aryl (and vinyl) lithiums also underwent reaction at -105°C to -78°C to give the corresponding fluorides in

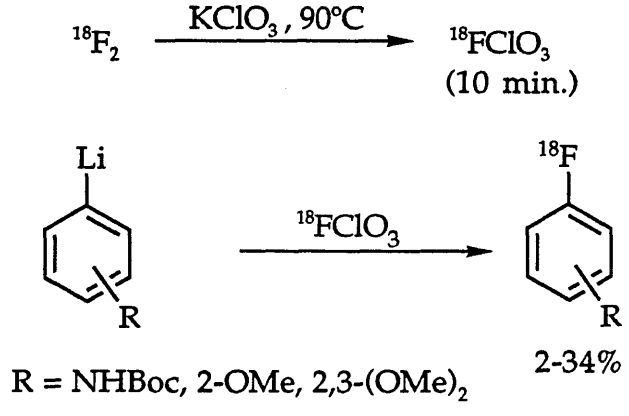
good yield (40-76%).



Scheme 50

2.8 Perchloryl Fluoride

[^{18}F]-ClO_3F has been used in the generation of a number of simple labelled fluoroaromatics, in modest yields, from the aryllithiums (Scheme 51).[123]



Scheme 51

2.9 Chlorine Pentafluoride

It has been shown that chlorine pentafluoride will fluorinate benzene in 54% yield.[124] A smaller proportion of chlorination was also noted from subsequent generation of chlorine monofluoride.

Conclusion

In the last decade, several major advances have occurred in the regiospecific synthesis of fluoroaromatics. Fluorine chemists now realise that it is not enough just to introduce fluorine onto an aromatic ring, their methods must also produce the required regioisomer if they are to gain general acceptance by mainstream organic chemists.

The scope of the fluorodeamination process has been improved by the modification of the hydrogen fluoride methodology to include hydrogen fluoride-base complexes as illustrated by the work of Yoneda.[20,21,24] The wide background of knowledge which has been built up around related systems will most probably extend the lifetime of these reactions even further. The initial requirement of regiospecific amination of the aromatic ring remains a drawback since this must be either carried through from starting materials (probably needing protection) or introduced *via* nitration which then suffers from problems of regioselectivity in its own right. Furthermore, the intermediacy of the highly reactive aryl cation is a major drawback in that side-reactions are frequently unavoidable and sometimes override the fluorination pathway.

Direct displacement using fluoride ion has gained in popularity due to the discovery that other groups (*e.g.* NO_2, $^+NMe_3$) besides halogen may be displaced.[37-40] These reactions frequently occur under milder conditions than in the halogen cases and give comparable or better yields. This increase in the range of suitable substrates has been paralleled by the considerable advances in nucleophilic fluoride sources which have appeared in the past decade.

The introduction of fluorides based on more organic-soluble ammonium

and phosphonium salts has aided the development of milder and quicker reactions which have greater applicability in the generation of radiolabelled fluoroaromatics than conventional metal fluorides. These reagents will probably continue to be the method of choice on electron-deficient aromatics in the future.

The use of high valent metal fluorides has never been of any synthetic significance and appears to have essentially died out. It has become clear that the use of such systems on even the most elementary aromatics is incompatible with single product formation and the approach is of no more than academic interest.

Without a doubt, the greatest advances in aromatic fluorination during the past decade has been the establishment of electrophilic fluorination as a viable, controllable technology. Initial reports of regioselective reactions with molecular fluorine have largely been superceded by the development of a range of 'F^+' reagents which temper the reactivity of fluorine by the use of a carrier molecule.

A large number of these are now available commercially (*inter alia* XeF_2, CF_3OF, $CsSO_4F$, *N*-fluoropyridinium salts, *N*-fluorosulphonamides).[80] Product mixtures have, in most cases, largely been alleviated by the use of these reagents in regioselective *ipso*-fluorodemetallation which has allowed their application to a large number of complex molecules. This includes a range of radiolabelled-fluoroaromatics due to the rapidity of many of the reactions.

The future of aromatic fluorination probably lies largely in the area of electrophilic fluorination *via* fluorodemetallation. This is due to the variety of metals which the various reagents can replace and the large body of knowledge available on regioselective metallation. The wide range of reagents available means that the reactivity can be tailored to meet the requirements of the substrate. It is unlikely that any one of the currently available reagents will fill all of the requirements as yet although the *N*-fluorosulphonimides of Differding and Davies look the most promising at the moment[120, 121].

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CHAPTER 3

RESULTS AND DISCUSSION

3.0 Introduction

The introduction of a fluorine atom onto an aromatic system is a process that, historically, is prone to low yields and tarry by-products (see Review). The legendary reactivity of molecular fluorine has led to most syntheses of fluoroaromatics starting with the fluorine already present. This is feasible since the aromatic C-F bond is generally inert to most chemical processes. Important exceptions to this are the displacement of fluoride ion by nucleophiles in the presence of *ortho/para* activating groups[1] and the oxidative addition to complexes of certain metals *e.g.* platinum (II).[2]

As the content of the Review demonstrates, there is still a great deal of work directed towards aromatic fluorination at a later stage in a synthetic scheme. A major impetus for this has been the development of PETT scanning as a common non-invasive diagnostic tool.[3,4]

This technique involves the preparation of a substrate containing fluorine-18 and subsequent injection into the patient. As the isotope decays, positrons are emitted and these interact with body tissue to produce two γ-ray photons in opposite directions. These may be detected by the PETT camera and, by combining the results obtained from a number of 'slices' through the target organ, a picture of the receptor density may be obtained.

The unstable nucleus ^{18}F may be prepared in either of the forms F^- or F_2 by the use of the following or similar reactions (Equations 1, 2):

$$^{20}Ne\ (p, n)\ ^{18}F \qquad (1)$$

$$^{16}O\ (^{3}He, p)\ ^{18}F \qquad (2)$$

The half-life of the fluorine-18 isotope is only 110.9 minutes and therefore the restraining factor on any synthesis is that the total time allowed from generation of the isotope to introduction into the patient, which is of the order of two half-lives (this includes all purification procedures). Despite this limitation, the use of fluorine is gaining in popularity due to the much shorter half-lives of other possible isotopes *e.g.* ^{11}C, ^{15}O.

The importance of PETT scanning and the desirability of introducing fluorine into an advanced intermediate have given an impetus to the field of aromatic fluorination. As a possible general approach to this, electrophilic fluorinating agents have been introduced (see Chapter 2 of the Review). In the majority of these reagents, there is good tolerance to atmospheric moisture as opposed to the fluoride-based reagents where their reactivity is related to the water content of the reaction.

The reagent chosen for the following study was the inorganic salt, caesium fluoroxysulphate ($CsSO_4F$, CFS). It was considered to have greater selectivity than molecular fluorine, while possessing sufficient reactivity to carry out aromatic fluorinations at ambient temperatures unlike the various *N*-fluorinated compounds described earlier.

3.1 Caesium Fluoroxysulphate

3.1.1 General background

CFS was first prepared and characterised by Appelman in 1979 by the action of dilute fluorine on cold, aqueous caesium sulphate.[5] The reagent was isolated by filtration and stored at 0°C under nitrogen.

The general characteristics of the reagent itself are listed below:

- Purity may be assessed by iodometric titration and it is therefore possible to add precise portions of reagent to reaction mixture
- Readily stored, microcrystalline solid
- Mild reaction conditions
- Soluble in acetonitrile (0.07M) and nitromethane (0.07M)
- Easily prepared on fairly large scale (10-20 g)

Potential drawbacks of the reagent are as a consequence of the weak O-F bond. This results in a highly oxidising species (ΔE +2.52 V) which is not

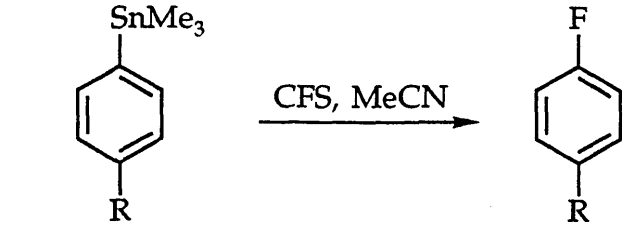
compatible with certain functional groups *e.g.* S (II) and P (III). This also leads to intolerance of certain nucleophilic solvents, *e.g.* DMSO, DMF, DMPU, probably *via* S_N2 attack on fluorine. It should also be noted that the thermodynamic instability of CFS may lead to decomposition or even detonation if placed under stress. This, however, is avoidable if suitable precautions are taken (see Experimental section).

3.1.2 Previous work

The ease of preparation of this reagent (and its rubidium analogue $RbSO_4F$, RFS) has led to its use in a range of fluorinations with varying degrees of success. Substrates have included alkanes,[6] alkenes (both addition[7-10] and substitution[8,11]) alkynes,[12] silyl enol ethers/ enol acetates,[13,14] β-diketones,[10] alcohols[15] and porphyrins.[16,17] These reactions are summarised in Scheme 1.

The earliest reports of CFS demonstrated its use in aromatic fluorination in aqueous solution although a wide range of products were identified in the reaction with toluene.[5] Subsequently it was shown that acetonitrile was a suitable solvent[18] and yields were increased by Lewis acid catalysis, of which BF_3 was the most effective.[19,20] Significant effects were noted, even in the case of the otherwise unreactive nitrobenzene.[20] Electron-rich aromatics were found to be excellent substrates with yields in the range 60-80%.[21-23]

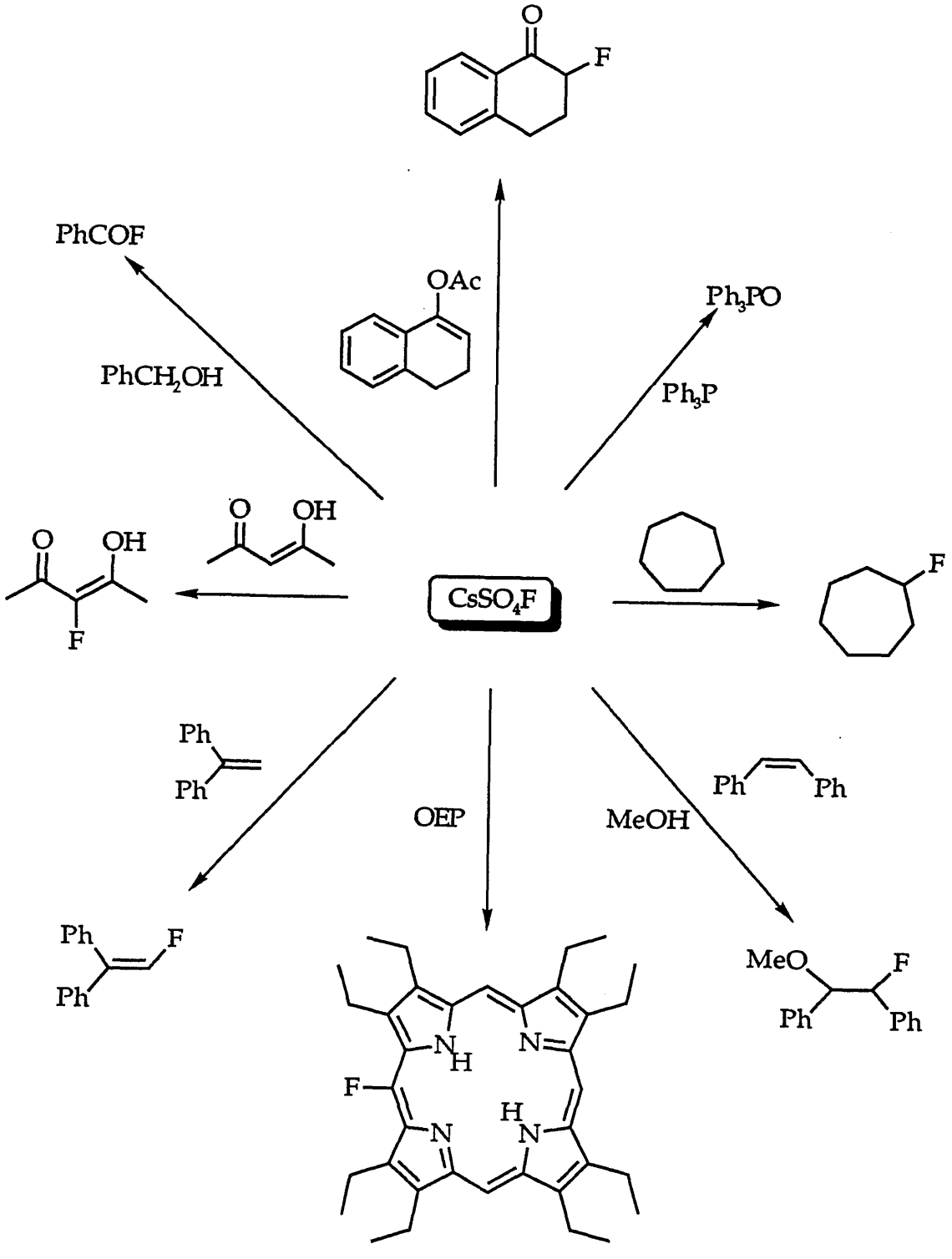
The production of regioisomers was still a major problem as in conventional electrophilic substitution. Except in the presence of blocking groups, this problem was not overcome until 1986, when Chambers showed that aryltrimethyltin compounds were suitable substrates giving *ipso*-fluorination products in good yields (Scheme 2).[24]



R=H, Me, OMe, Cl 69-87%

Scheme 2

Some previous Reactions of CFS



Scheme 1

Other tin groups (tributyl, tricyclohexyl) were less effective or unreactive and this was attributed to their lower solubility and increased steric hindrance.

The introduction of tin into an aromatic nucleus may be achieved in a number of ways to give regiospecific products in good yield. These include making use of aromatic lithiation,[25] the $S_{RN}1$ reaction[26] and palladium catalysed stannylation.[27] This versatility gave the initial impression of being an ideal solution and was potentially ripe for further exploitation.

Although more preferable to fluorodeprotonation in terms of product purity, this approach possessed a number of drawbacks:

- The relatively high cost of the organotin precursors
- The difficulty in removing residual tin-containing species from crude products
- Mammalian toxicity of organotrimethyltin compounds.

These reasons and the obvious advantage of the metal-based approach in terms of regiospecificity led to a more detailed study of the aromatic fluorodemetallation process using CFS.

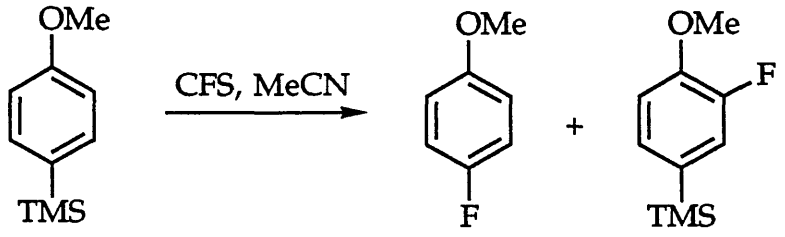
3.2 Silicon Approach

3.2.1 Preliminary reactions with arylsilanes

The obvious choice for replacement of tin in an electrophilic process is silicon due to its ready introduction and similar chemistry. The synthesis of aryltrimethylsilanes has been reviewed and many approaches are available.[28] The C-Si bond is also relatively inert to a number of reagents and may thus be carried through various transformations.

Substitution of aryltrimethylsilanes in an *ipso* fashion is an established process[29] and fluorination of these compounds has previously been achieved by molecular fluorine and acetyl hypofluorite.[30,31]

The initial studies were based on the activated system, 4-methoxyphenyltrimethylsilane 1, prepared from 4-bromoanisole *via* metal-halogen exchange in 73% yield (Scheme 3). The reaction of 1 with CFS in acetonitrile led to the formation of two fluorinated products in a ratio of 1:2.5 (GC, ^{19}F NMR). These were assigned the structures 2 and 3 on the basis of chemical shifts and retention times.

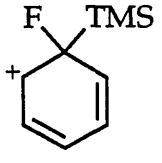


1 2 (10%) 3 (25%)

Scheme 3

The product mixture is analogous to that found in the previous fluorination studies.[30,31] It was therefore obvious that conventional electrophilic substitution was occurring at a greater rate than the desired *ipso* process. This was found to be the case for a range of temperatures from -10°C to room temperature.

The mechanism of the electrophilic substitution of arylsilanes is believed to occur by the same pathway as the conventional process involving an intermediate of the type 4. In the case of most electrophiles, the initial addition to the arene is a reversible process and the ability of silicon to stabilise a β-cation leads to regioselectivity.[32]



4

Although there are competing reactions involving hydrogen substitution,

these lead to less thermodynamically favoured intermediates and, therefore, are less likely to lead to products. In the case of fluorination with CFS, any intermediate formed of the type 4 is highly unlikely to lose the high energy species F^+ to rearomatise and, therefore, the formation of 4 is not a reversible process. Thus, the degree of regiocontrol is likely to be less than for more polarisable electrophiles since there can be no equilibration between Wheland intermediates formed *via* addition to sites other than the *ipso* position.

A further complication by the presence of the methoxy group which is a powerful *ortho/para* directing group. Indeed, the products formed in Scheme 3 are obviously derived from electrophilic substitution at positions dictated by the methoxy group. The product ratio and yields are found to be the same as in the fluorination of anisole[18] and indicate that at least with CFS, silicon and hydrogen are replaced at comparable rates.

This situation has been noted with other electrophiles and, among the halogens, bromine,[33] iodine[33] and iodine monochloride[34] replace silicon faster than hydrogen whereas chlorine (in the presence of iron powder) shows comparable reactivity.[35] The trend therefore is for the harder halogens to be less prone to *ipso*-substitution of aryl Si-C bonds.

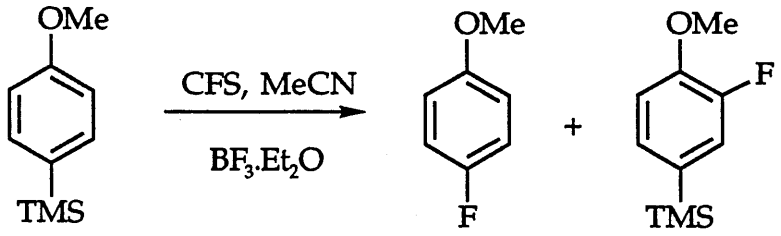
3.2.2 The possibility of Lewis acid catalysis

In a previous fluorination study on arylsilanes, it was observed that the proportion of *ipso*-fluorination rose as the aromatic became less electron-rich.[30] To counteract the effect of the methoxy group on 1, a Lewis acid was added to the system with the possibility that it might coordinate the phenolic oxygen and thereby minimise its directing ability. $BF_3.Et_2O$ was chosen as the Lewis acid since it is known to be stable to the fluorination process (Scheme 4).

The result of this was to increase the total yield of fluorination, unfortunately the product ratio was essentially the same as in the basic reaction (and also mirrored the Lewis acid catalysed reaction of anisole).[21]

The yields in Scheme 4 were independant of whether the substrate or the

reagent was premixed with $BF_3.Et_2O$ or if the Lewis acid was added after. It was also immaterial whether the substrate was added to the reagent or *vice versa*.

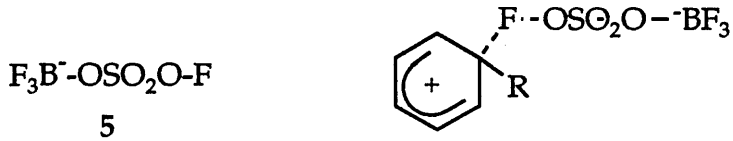


1 2 (18%) 3 (48%)

Scheme 4

3.2.3 Influence of the Lewis acid

It was apparent that the role of the Lewis acid was to modify the fluorinating agent through some form of adduct formation rather than interaction with the substrate. It is not known conclusively whether this adduct formation occurred on contact with the reagent (to give 5) or solely in the Wheland intermediate giving 6, although the latter is probably the more favoured option.



5 6

Some evidence for the latter pathway is evident from the observation that mixing the silane 1, CFS and $BF_3.Et_2O$ gives a homogeneous solution whereas CFS and any other component does not. The use of solvents other than acetonitrile (EtOAc, Et_2O, THF, DCM) did not lead to homogeneous solutions and no fluorinated products were detected by ^{19}F NMR analysis of

the crude reaction mixtures with these solvents.

Attempts to investigate the formation of a discrete intermediate 5 based on the assumed changes in chemical shifts of BF_3 on adduct formation were investigated by ^{11}B and ^{19}F NMR. This led only to signals derived from the two individual components thus providing further proof for the idea of stabilising the transition state.

3.2.4 Possibility of fluoride catalysis *via* attack at silicon

The high affinity of fluorine for silicon is a result of the extremely strong Si-F bond (ΔH_f 810 kJmol^{-1}) which is one of the strongest single bonds known. This can be utilised in the formation of 'ate' complexes which increase the nucleophilicity of the ligand. Although mainly of use in the more reactive silanes (allyl,[36] benzyl[37]), this nucleophilic catalysis has been used in the aryl series.[38]

Since fluoroxysulphate is stable to fluoride ion, the reaction of **1** with CFS was conducted in the presence of various fluoride sources (Table 1).

Table 1: Effect of fluoride salts on fluorination of 4-methoxyphenyl-trimethylsilane

Entry	*Fluoride Source*	*Yield of Fluoroaromatic (%)*
1	KF/18-C-6	0
2	CsF	6
3	TBAF.3H_2O	0
4	HF/Py	6

In the case of the alkali metal fluorides, there is no appreciable effect with CsF (entry 2) compared to the parent reaction (Scheme 3) whereas the use of KF/18-C-6 (entry 1) causes suppression of the fluorination reaction implying

that the crown ether is not compatible with CFS (see section 3.7.2.2). In each case, the fluoride salt was dried carefully so as to minimise the water content in the reaction.

The tetrabutylammonium salt (entry 3) was supplied as the trihydrate (Aldrich Chemicals) and it is possible that residual water caused decomposition of the reagent. A further possibility is that the tetrabutylammonium cation is susceptible to oxidation under the reaction conditions (see section 3.7.2.1).

In an early paper describing acid catalysis of CFS reactions on aromatics, HF was found to be effective in increasing yields during F/H exchange.[20] The Py/HF reagent (entry 4), however, was found to result in slightly lower yields possibly as a result of reaction of CFS with the pyridine ring although no effort was made to confirm this.

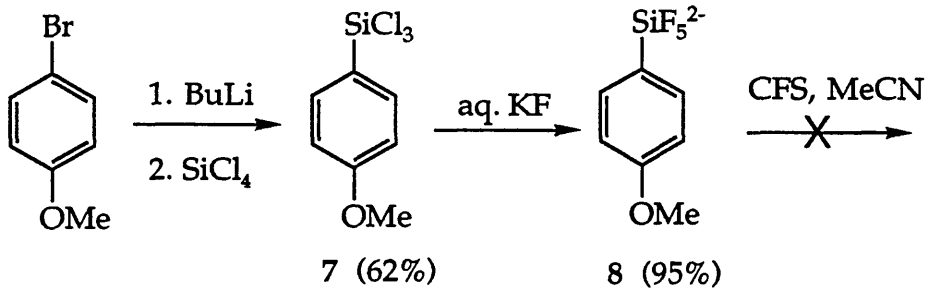
3.2.5 The use of more reactive silyl groups

A report from Banks on reactions of *N*-fluoroquinuclidinium fluoride (see Review) stated that although benzene did not react, phenyltrichlorosilane was sufficiently reactive enough to give fluorobenzene in 22% yield.[38] The trichlorosilyl group would not be of any use with CFS since Zupan has reported that the reaction of CFS with TMS-Cl gave TMS-F[10] and, with an aryltrichlorosilane, the resulting trifluorosilyl group may be too electron-withdrawing to react. The use of the more nucleophilic pentafluorosilicate group was considered to be more feasible.

4-Methoxyphenyltrichlorosilane 7 was prepared by slow, inverse addition of 4-lithioanisole to $SiCl_4$ giving a highly moisture-sensitive oil in 62% yield. No attempt was made to fluorinate this material which was taken through to the pentafluorosilicate 8 in 95% yield by inverse addition to an aqueous solution of KF (Scheme 5) .[39] This compound was highly insoluble in suitable reaction solvents and a suspension of 8 in a solution of CFS in acetonitrile did not lead to the formation of any 4-fluoroanisole (GC, ^{19}F NMR) even in the presence of 10 eq. of CFS.

A similar result was found in the reaction of dipotassium phenyl-

pentafluorosilicate prepared in 96% yield from the commercially available phenyltrichlorosilane.



Scheme 5

3.2.6 The use of less reactive substrates

In an attempt to determine whether a substrate bearing no powerful activating groups would exhibit any bias towards *ipso*-fluorination, 4-biphenyltrimethylsilane was prepared from the bromide in 25% yield.[40] Treatment of this silane with CFS in acetonitrile gave a mixture of fluorinated biphenyls in low yield (~6%) with the major product being 4-fluorobiphenyl (~3%). It was again found that $BF_3.Et_2O$ catalysis increased the total product yield (to 16%) but the product ratio remained essentially constant and similar to that in the Lewis acid-catalysed reaction of biphenyl itself.

3.3 Other metals

Since it was now apparent that silicon was not a suitable metalloid for the *ipso*-fluorination process, it was decided to search for more suitable metals which could still be readily introduced under mild conditions and would provide stable substrates.

3.3.1 Aryllead (IV) triacetates

The use of arylleads in fluorination has been mainly restricted to aryltriorganolead species in reaction with molecular fluorine and yields were low.[41] By analogy with the tin series, it was likely that the aryltrimethyllead compounds would be the substrates of choice. These were undesirable from our point of view due to the high toxicity of organolead compounds and also because of the photosensitive nature of the C-Pb bond. More recently, the fluorination of aryllead triacetates by $BF_3.OEt_2$ has been reported by Pinhey (see Review).[42]

For our studies, the lead triacetates were chosen as possible substrates as the simple derivatives were known compounds.[43] 2-Methoxyphenyllead triacetate was prepared from the tributylstannane *via* mercury (II) catalysed reaction with lead tetraacetate in 50% yield.[43] Treatment of this aryllead species with CFS gave no fluorinated products in either acetonitrile or DCM (by ^{19}F NMR of the crude reaction mixture). This was partly attributed to extreme insolubility in these solvents although, as a rule, these particular substrates function as carbon electrophiles *e.g.* in the arylation of β-diketones.[44]

3.3.2 Arylmercury chlorides

The mercuration of aromatics is a readily achieved process under mild conditions and the products are versatile synthetic intermediates.[45] Previously, fluorination has been achieved with molecular fluorine[41] and acetyl hypofluorite[46-48] in good yields.

1-(Benzenesulphonyl)indole was treated with mercury (II) acetate in acetic acid followed by aqueous sodium chloride to give the 3-chloromercury derivative in 97% yield.[49] This compound was relatively insoluble in the fluorination solvents studied (acetonitrile, DCM) and treatment with CFS failed to provide any 3-fluoroindoles. The solubility problem could be solved by the addition of mercury (II) acetate but this still gave no identifiable products.

Later, it was demonstrated that 1-(benzenesulphonyl)indole, itself, was not a

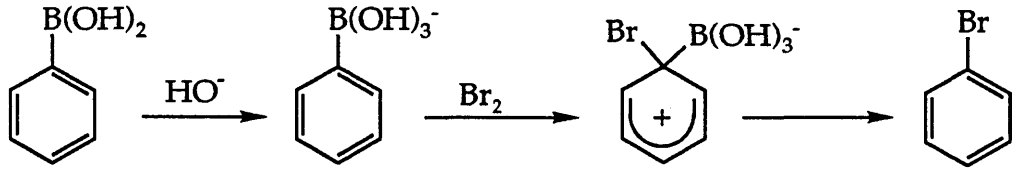
good substrate for CFS and that complicated reaction mixtures were formed.[50] Further investigation of other arylmercury substrates was not carried out due to the toxicity of these types of compounds.

3.4 Arylboronic acids as fluorination substrates

3.4.1 Introduction

The use of arylboronic acids in synthesis is gaining in popularity due mainly to the work of Suzuki who discovered that they were suitable partners for aryl halides in palladium-catalysed coupling reactions.[51] In these reactions, there is a formal electrophilic substitution of palladium (II) for boron prior to the coupling step.

The halogenation of arylboronic acids is an established process for all of the halogens apart from fluorine and is considered to follow a conventional electrophilic aromatic substitution pathway.[52] Catalysis by base and inhibition by acid are general characteristics and this is explained by formation of an 'ate' complex 9, thus creating a better leaving group (Scheme 6).[53]

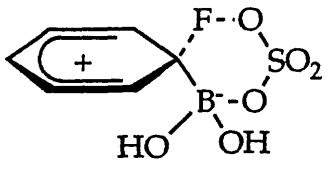


9

Scheme 6

On this basis, arylboronic acids appeared to be suitable substrates for CFS reactions. A further possible benefit arises from the vacant coordination site on tricoordinate boron which could result in adduct formation with CFS to give a complex, the structure of which suggests a transition state 10 which

should then result in delivery of 'F^+' to the *ipso* site.

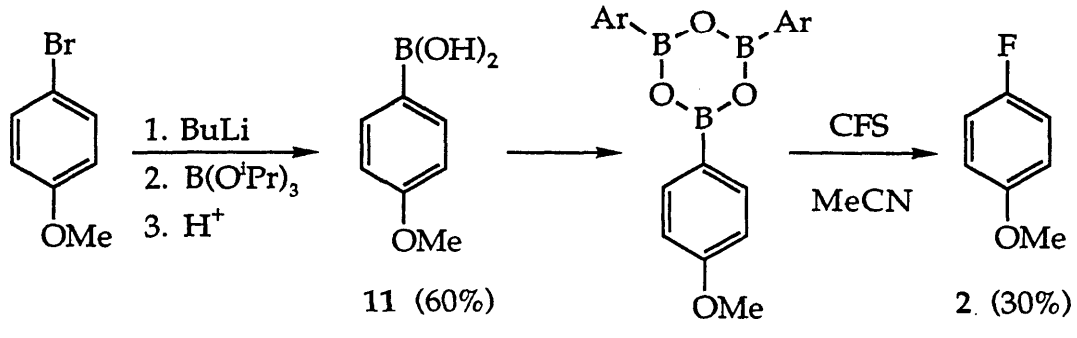


10

If the nucleophilicity of the anionic oxygen in CFS was insufficient to allow adduct formation then the possibility of coordinating the caesium atom with the dihydroxyboryl group remained.

3.4.2 Preliminary reactions with boronic acids

The formation of arylboronic acids is generally achieved by transmetallation from the corresponding aryllithium or Grignard reagent. In this way, 4-methoxyphenylboronic acid **11** was prepared from 4-bromoanisole in 60% yield as a white solid which dehydrated over a period of time to give the trimeric boroxine **12**. This was treated with CFS in acetonitrile to give 4-fluoroanisole **2** as the the only fluoroarene species (by ^{19}F NMR) in 30% yield (Scheme 7).



11 (60%)

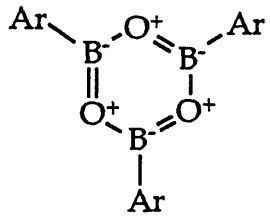
12

2 (30%)

Scheme 7

This regiospecificity of this fluorination was surprising but, nonetheless, a

great encouragement. The formation of the boroxine involves the generation of a hetero-aromatic system 13 which should greatly reduce the Lewis acidity of the boron atom[54] and, thus, its ability to interact with the fluorinating agent.



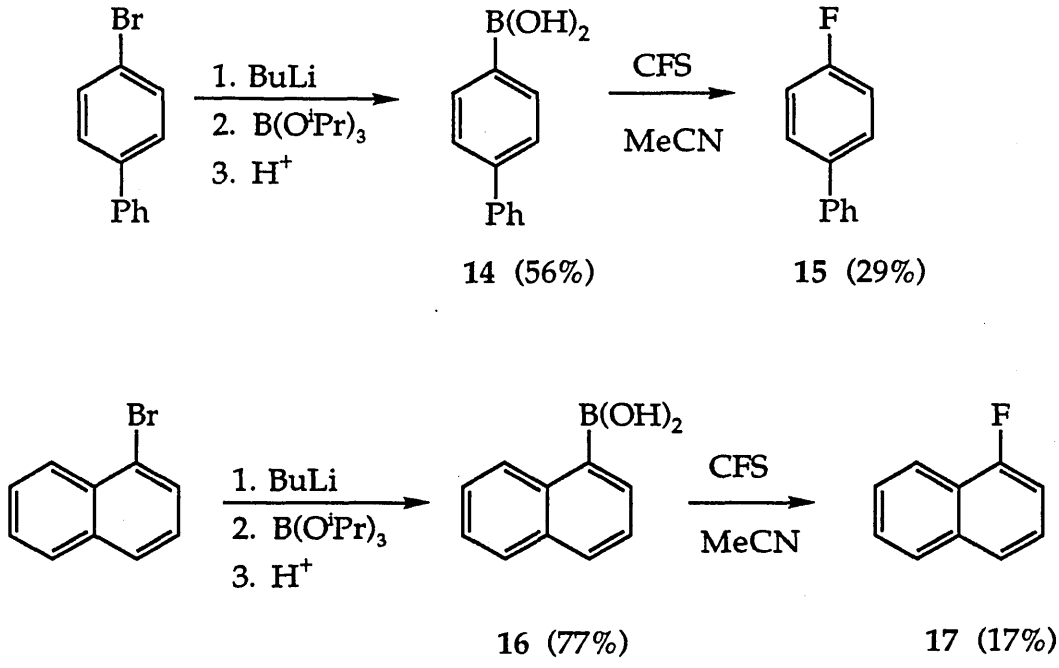
13

This property of boroxine generation is a characteristic of all boronic acids, although generally the dehydration must be carried out *in vacuo* with some drying agent (*e.g.* over concentrated sulphuric acid) to achieve complete conversion. For this reason of partial boroxine formation, it was not always possible to obtain elemental analyses for all of the boronic acids prepared at later stages of this work.

In an effort to increase the yield, it was decided to investigate the effect of Lewis acids on the fluorodeboronation process. Using $BF_3.Et_2O$, no increase in yield could be achieved for either the boronic acid 11 or the boroxine 12 in acetonitrile solution. With DCM as solvent, no fluorine-containing products were observed. In the case of the boroxine 12, the reaction in acetonitrile was carried out in both 'wet' and dried, redistilled solvent in order to assess the role, if any, of traces of water in carrying out *in situ* regeneration of the boronic acid 11. No significant change in yield was noted.

It was also possible to carry out fluorodeboronation on less activated boronic acids such as 4-biphenylboronic acid 14 (giving 4-fluorobiphenyl 15 in 29% yield) and 1-naphthylboronic acid 16 (giving 1-fluoronaphthalene 17 in 17% yield, Scheme 8).

At this stage, it appeared that boronic acids were a possible candidate for the fluorination process although the yields were still low. A great effort was now put into boosting the reaction yields.



Scheme 8

3.5 Initial development of the fluorodeboronation reaction

A number of parameters were suitable for investigation in this process and these are listed below:

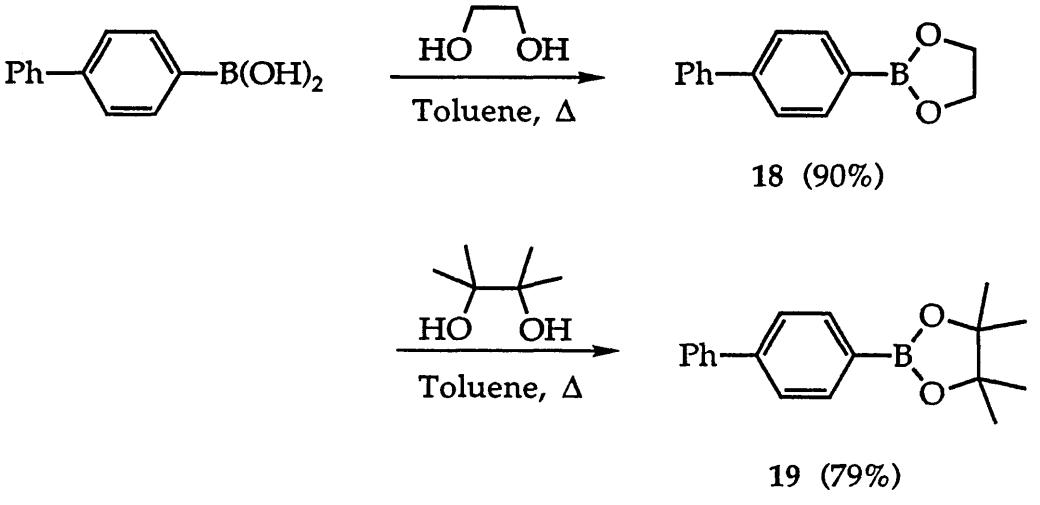
- Nucleophilicity of the aryl ligand bonded to boron
- Solubility of the boron reagent in reaction solvents
- Ligands bound to the arylboron moiety
- Solubility of the fluorinating agent
- *In situ* structure of the fluorinating agent
- Reaction solvent

These properties may be conveniently split into two groups, those affecting the substrate and those affecting the reagent. In a systematic investigation, each of these groups was investigated under a range of conditions using 4-

biphenylboronic acid as the parent substrate due to the ready isolation of 4-fluorobiphenyl. Thus, a reliable monitor for the success of reaction conditions was available - the *isolated* yield of 4-fluorobiphenyl.

3.5.1 Synthesis of some tricoordinate 4-biphenylboronic acid derivatives

The preparation of esters of boronic acids is readily achieved from a number of organoboron precursors.[55] In this case, the boronic acid was used as starting material and the ethylene glycol 18 and pinacol esters 19 (Scheme 9) were prepared as examples of cyclic esters in yields of 90% and 79% respectively by simply mixing the acid and diol in toluene and removing the liberated water by azeotropic distillation.



Scheme 9

The lower yield for the pinacol ester was due to the chromatographic purification employed (using silica as column packing) which caused some of the retro reaction to occur (as could be demonstrated by 2D TLC). This separation was not attempted in the case of the more water-sensitive ethylene glycol ester 18. No simple acyclic esters were prepared due to their even greater sensitivity to atmospheric moisture.

3.5.2 The effect of additives on fluorination of 4-biphenylboronic acid and esters

It had been demonstrated in the palladium-catalysed coupling reactions with aryl halides that the boronate ester derivatives did not react under the standard conditions for boronic acids.[56] Transmetallation *in situ* to the organothallium derivative was required for ethylene glycol or catechol esters and even this was not applicable to the pinacol series, probably as a result of greater steric hindrance.

It had also been reported that chlorine, bromine or iodine did not undergo reaction with lower alkyl esters of phenylboronic acid indicating the much lower reactivity of the esters compared to the boronic acids.[57] This was also found to be the case with the two ester derivatives 18 and 19 in the reaction with CFS in acetonitrile. It was considered, however, that the presence of the ester gave increased scope for ligand modification and was therefore worth pursuing.

It was disclosed in the first report of CFS that, in water, the initial half-life of CFS was approximately 30 minutes and that aqueous base caused instantaneous decomposition and a complex product composition.[5] Since it was known previously that electrophilic reactions of boronic acids were subject, in most cases, to general base catalysis this approach was investigated in a non-aqueous system.

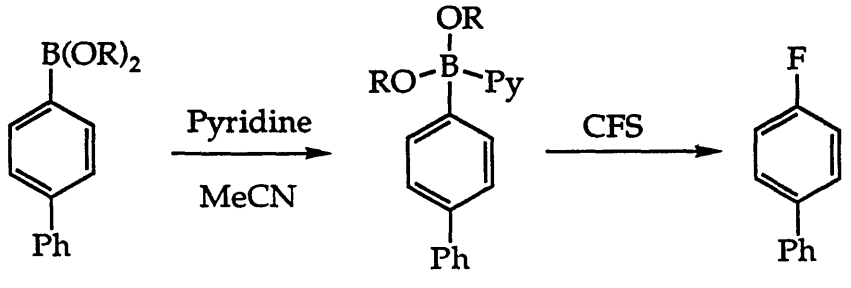
3.5.2.1 Sodium methoxide catalysis

In order to maintain a non-aqueous medium, acetonitrile was chosen as the reaction solvent due to the solubility of CFS and an ethanolic solution of NaOEt was used as the base. With the boronic acid as substrate, no product was noted and, at the time, this was attributed to the presence of ethanol resulting in side reactions. Using solid NaOMe as base, the formation of the more nucleophilic 'ate' complex should occur readily but, under ambient conditions, no fluoroarenes were observed. Similar results were noted for the two esters 18 and 19 and this was explained by attack of MeO^- on CFS (however, see section 3.7.4).

3.5.2.2 Amine catalysis

Since amine adducts are long established derivatives of tricoordinate boron,[58] the possibility of forming these *in situ* as alternatives to an 'ate' complex was considered. The addition of triethylamine to the substrate in acetonitrile prior to the addition of CFS gave none of the required product in the case of the two esters, and only a low yield (~5%) with the acid. The low yields may be a consequence of reaction of CFS with the amine.

A switch from triethylamine to pyridine caused apparent adduct formation **20** with the esters (substrate dissolved completely within 2 minutes) but not with the acid. Treatment with CFS led to a slow reaction and low yields of product (Scheme 10, Table 2).



20

Scheme 10

Table 2: Effect of pyridine on fluorination of 4-biphenylboronic acid and derivatives

Entry	*R*	*Yield(%)*
1	H	15
2	$-CH_2-$	5
3	$-CMe_2-$	2

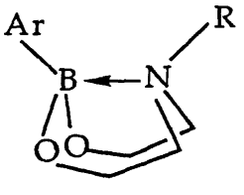
It was apparent that the prior addition of an amine to the boronate ester reactions could potentially result in an increase in yields (albeit slight in the above case, Table 2). One possible reason for the low yields in these cases (despite adduct formation) is the possibility of dissociation to give free pyridine.

The reaction of pyridine with CFS in a range of solvents was previously known to give 2-substituted pyridines although reaction in acetonitrile was not reported.[59] This side reaction could also explain the lower yields in the case of the boronic acid itself. It seemed obvious that the obvious next stage was to minimise the ability of the adduct to dissociate by using intermolecular coordination since the above result indicated that the fluorination yields might then increase.

3.6 (*N-B*)-Perhydro-2-aryl-1,3-dioxa-6-aza-2-boracine esters 21

3.6.1 Background

The use of (*N-B*)-perhydro-2-aryl-1,3-dioxa-6-aza-2-boracine esters **21** is the classic method for the characterisation of boronic acids since the derivatives have sharp melting points (unlike many of the acids which may undergo initial decomposition to the boroxine).[60] They are also crystalline solids which are generally formed in very high yields.



21

A notable point in these compounds is the presence of a transannular B-N bond which can be readily deduced from the ^{1}H NMR where the ring protons are shown to be part of an ABCD spin system. Such dative B-N

bonding may also be recognised from inspection of the ^{11}B NMR where the chemical shift moves to higher field (*i.e.* greater electron density on boron).[61] The stability of these cycloadducts depends strongly on the presence of the B-N bond and steric requirements at boron and nitrogen. Except in a few cases, protonation/alkylation at nitrogen causes decomposition .[62]

The presence of the B-N bond has a number of effects on the properties of the substrate as shown below:

- Increased solubility in most organic solvents
- Less prone to aerial oxidation on standing for long periods
- No probability of boroxine formation
- Sharp melting point.

As an extra bonus, it was expected that the greater electron density on boron would increase the nucleophilicity of the aromatic system (since the dihydroxyboryl group is a Lewis acid and therefore an electron-withdrawing group).

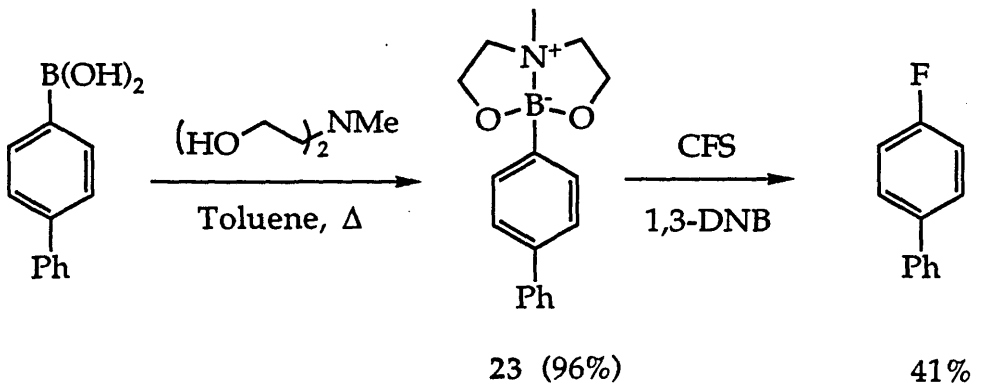
3.6.2 Synthesis and fluorination of (*N-B*)-perhydro-2-aryl-1,3-dioxa-6-aza-2-boracine esters of 4-biphenylboronic acid

The synthesis of these derivatives generally involves mixing the boronic acid and diethanolamine as a suspension in toluene and azeotropically distilling off the liberated water to drive the equilibrium to completion. On cooling the reaction mixture, the product **21** frequently precipitates as analytically pure crystals.

In this manner, (*N-B*)-perhydro-2-(4-biphenyl)-1,3-dioxa-6-aza-2-boracine **22** was prepared in 90% yield. On treatment with CFS in acetonitrile in which it had only limited solubility, **22** gave 4-fluorobiphenyl in a disappointing yield of 10%.

It was considered that the free N-H bond was a possible source of problems from side reactions and so an *N*-alkylated derivative **23** was prepared from *N*-methyldiethanolamine (NMDE) in 96% yield. When **23** was subjected to the fluorination reaction (together with 10 mol% 1,3-DNB to suppress any

SET or radical reactions), 4-fluorobiphenyl was obtained in 41% yield (Scheme 11) thus confirming the earlier concern about the presence of free N-H bonds.



Scheme 11

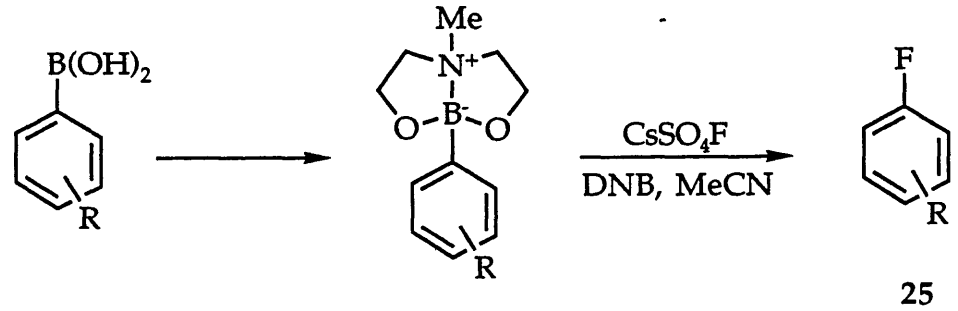
From NMR studies it was possible to show that, under the conditions for the fluorination reaction in acetonitrile, the NMDE ester was not degraded to the boronic acid or other derivative even in the presence of added water (up to 3 eq.). This reactivity towards electrophilic fluorination with CFS is in contrast to the palladium-catalysed coupling reactions with aryl or vinyl halides where these tetracoordinated boronic acid derivatives do not give any reaction.[63]

3.6.3 Extension of the reaction to other carbocyclic arylboronic acids

Since it was now apparent that the NMDE esters were much more reactive than the parent hydrocarbons towards reaction with CFS, a range of substrates 24 bearing this leaving group were prepared and subjected to the fluorination reaction (Scheme 12, Table 3).[64]

In the reactions where R=4-OMe, 4-Ph (entries 1, 2), small amounts (<1%) of difluorinated products were detected (by MS) but this was not so in the other entries. Similarly, no products were detected from simple electrophilic substitution of hydrogen indicating that the replacement of boron is a faster

process. Furthermore, where R=4-OMe (entry 1), it was pleasing to observe only a trace of fluorination at the activated position *ortho* to the methoxy group.



24 25

Scheme 12

Table 3: Synthesis of Fluoroaromatics from NMDE esters in acetonitrile

Entry	*Substrate* (R)	*Ester* 24 (% yield)	*Fluoroaromatic* 25 (% yield)
1	4-MeO	92	52
2	4-Ph	96	41
3	2-Ph	98	0
4	2,3-$(CH)_4$	94	35
5	3,4-$(CH)_4$	97	30
6	4-Br	98	15
7	3-Cl-4-F	97	30
8	2,4-Cl_2	98	40
9	3-NO_2	91	15

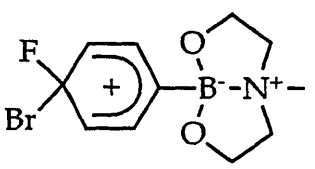
The contrast of R=2-Ph (entry 3) with R=4-Ph (entry 2) is interesting but no explanation can be offered except for the increased steric hindrance at C-2 as opposed to C-4 of the biphenyl system. It was not possible to overcome this protolysis, even in the presence of added base ($NaHCO_3$).

For the case where R=3-NO_2 (entry 9), it was interesting to see that, under the standard conditions, the only reaction observed was protolysis of the C-B bond to give nitrobenzene as the sole product. It was found that this could be alleviated if $NaHCO_3$ was added to neutralise any extraneous acid present. Under these conditions, fluorination occurred as before to give 3-fluoro-1-nitrobenzene in 15% yield.

A surprising result was found in the reaction involving a bromine substituent (R=4-Br, entry 6) which seems to be anomalous. The low yield which was observed appears to be completely at odds to the results found for other halogen-substituted substrates (entries 7, 8).

Initially, two possibilities were considered, both of which involved attack at bromine. The bromine may be initially oxidised to give an arylbromine difluoride which may undergo further reactions. This has some precedent in reactions of CFS, where Zupan has shown that iodoethane undergoes reaction to give ethyliodine difluoride in 40% yield.[10]

A second possibility was that attack of 'F^+' occurred at C-4 to give the intermediate 26 which could then lose Br^+ to give a 4-fluorophenylboronic acid derivative.



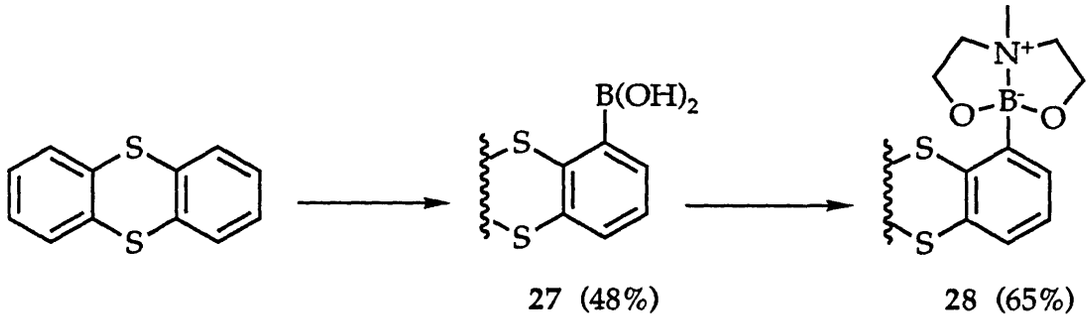
26

A more detailed look at the reaction mixture by GC-MS showed the presence of an isomer of dibromobenzene thus implying the presence of a bromine electrophile. This was taken to be indicative of the second pathway (*i.e.* *ipso*-substitution of bromine) as a competitive process. Bromine, therefore,

appears to be an incompatible functional group during CFS reactions. The irony is that, considering the above results and the earlier silicon-based studies, trimethylsilyl may, be a suitable synthon for bromine in these reactions.

Similar side reactions were not observed in the other halogen-substituted substrates (entries 7, 8), probably due to the lower stability of the corresponding halonium ions.

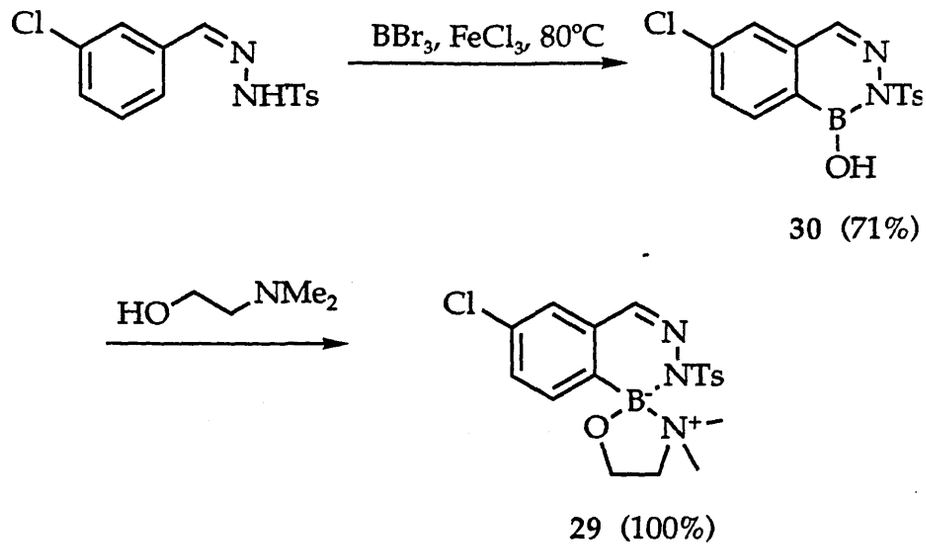
A number of carbocyclic arylboronic acids could not be fluorinated using the above procedure. 1-Thianthreneboronic acid 27 was prepared from thianthrene in 48% yield and subsequently converted to the NMDE ester 28 in a 65% yield (Scheme 13). Attempted fluorination of 28 gave a complex reaction mixture and no fluorine-containing products could be observed by (^{19}F NMR), probably due to preferential oxidation of the diarylsulphide groups.



27 (48%) 28 (65%)

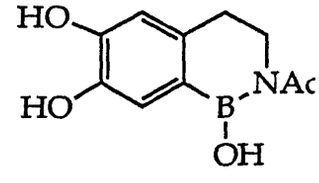
Scheme 13

A potentially interesting substrate 29 was available from 3-chloro-benzaldehyde.[65] Preparation of the tosylhydrazone followed by Friedel-Crafts type boronation (using $BBr_3/FeCl_3$) gave the 2,3,1-benzodiazaborine derivative 30. This was not converted to the NMDE ester but to the related *N,N*-dimethylethanolamine derivative 29 in a similar manner (Scheme 14). 29 Resisted all attempts to undergo fluorination even in the presence of 5 eq. of CFS (possibly as a result of extreme electron-withdrawal by the tosylhydrazone group).



Scheme 14

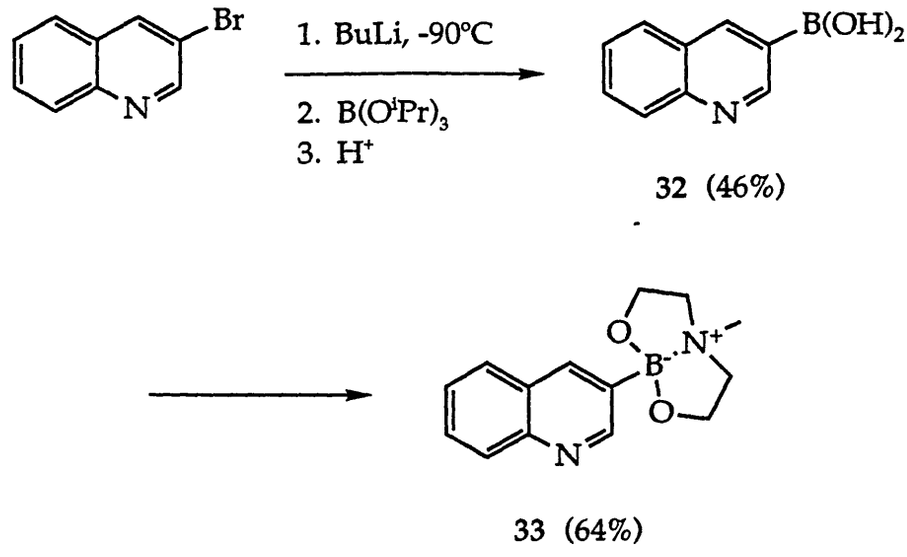
The interest in compound **29** is due to the possibility of extending this approach to the biologically important *N*-acetyldopamine and related phenethylamines (*via* intermediates of the type **31**).



31

3.6.4 Heteroarylboronic acids

The previously unknown 3-quinolineboronic acid **32** was prepared from 3-bromoquinoline in 46% yield *via* low temperature metal-halogen exchange and transmetallation (Scheme 15). This was converted to the NMDE ester **33** in 64% yield but, on carrying out the fluorination procedure, no fluorine-containing products were detected (by ^{19}F NMR); TLC analysis of the reaction mixture showed a complex product distribution under a wide range of reaction conditions.



Scheme 15

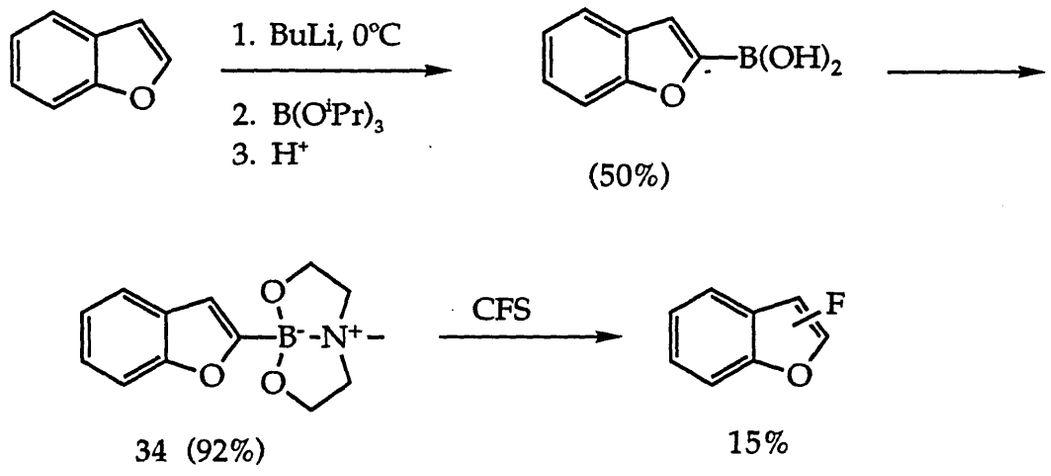
3-Bromothiophene-2-boronic acid was readily available from 3-bromothiophene in 75% yield *via* directed metallation with LDA. This compound was converted to the NMDE ester in 86% yield but could not be successfully fluorinated. In retrospect, this substrate was not likely to succeed since it contained a thiophene ring (Zupan had shown this to be oxidised earlier)[10] and a bromine atom (*vide supra* section 3.6.3).

2,4-Di-(*tert*-butyloxy)pyrimidyl-5-boronic acid was derived from the corresponding bromo-compound[66] and converted to the NMDE ester in 84% yield. Again, this compound resisted all attempts to fluorinate.

The failure to fluorinate this compound and the quinoline derivative 33 may possibly be explained by initial reaction at the aromatic nitrogen giving an *N*-fluoro species followed by side reactions. It was subsequently shown that, under the standard conditions for the boron-based CFS reactions, commercially available *N*-fluoropyridinium salts did not result in fluorodeboronation, instead a complex reaction mixture was formed which resulted from decomposition of the starting material.

The only heterocyclic example for which any degree of success can be claimed is with the benzofuran-based substrate 34 which could be easily prepared from benzofuran in 46% overall yield. In the fluorination reaction

two products were formed which were isomers of fluorobenzofurans in a total of 15% yield in a ratio of 14:1 (Scheme 16).



Scheme 16

The major product had a chemical shift of δ_F -112 which is not indicative of fluorine in an *ortho* position to an oxygen substituent (*i.e.* not a fluorine at C-7 of benzofuran). This suggests 2-fluorobenzofuran as the major product since substitution would be preferred at the 2-position. Confirmation, however, could not be obtained due to the problem of isolating small quantities of volatile products.

3.7 Further development of the fluorodeboronation reaction

3.7.1 Possible structure of the fluorinating species in acetonitrile

The report that some solvents underwent violent reaction with CFS[18] does not appear to have caused any speculation on the nature of the possible reaction occurring. The solvents reported to give vigorous reactions were DMSO and DMF, both of which possess nucleophilic heteroatoms (*c.f.* the intermediates generated during the Swern oxidation or Vilsmeier formylation). Although not mentioned in the earlier reports, it is probable

that there is transfer of fluorine from CFS to the solvent molecule generating a new reactive species.

It seemed possibile that the nucleophilicity of acetonitrile might be sufficient to allow the *in situ* formation of a new fluorinating agent based on acetonitrile. The ability of acetonitrile to act as a Lewis base is apparent from its role as a labile ligand in stable transition metal complexes such as bis(acetonitrile)palladium dichloride. Of more relevance, however, was the report that an acetonitrile-iodine complex **35** had been isolated at low temperature.[67] This seemed to imply that the actual fluorinating agent in acetonitrile solution might be an acetonitrile/F^+ complex, the structure of which was proposd to be **36**.

$MeCN^+$-I AsF_6^- **35**

$MeCN^+$-F $CsSO_4^-$ **36**

Attempts to characterise this reagent were based on NMR studies. It had been reported by Appelman that δ_F for CFS in acetonitrile solution was +132 ppm and this was claimed to confirm the presence of the O-F bond as opposed to an S-F bond.[5] It occurred to us that this chemical shift might also be explained by structure **36** and was not necessarily direct proof for the presence of the O-F bond.

A more obvious approach was thought to be the use of ^{15}N NMR since this would demonstrate any perturbation in the electronic environment of the solvent nitrogen (*i.e.* adduct formation with 'F^+'); unfortunately, due to the prohibitively high cost of [^{15}N]-enriched acetonitrile, this technique was not feasible.

As a result, it was decided to use ^{13}C NMR and monitor any shifting of the ^{13}C signal of the nitrile carbon of acetonitrile using RFS as the source of fluoroxysulphate due to its greater solubility (0.12M) in acetonitrile. Results were inconclusive, however, due to the swamping of any signals due to **36** by solvent resonances.

3.7.2 Attempted increase in solubility of fluorinating agent

As a consequence of the failure to confirm or deny the structure of the proposed *in situ* fluorinating agent 36 plus the requirement to utilise other solvents, this provided an impetus to increase the solubility of the fluorinating agent. Initially, the effect of some phase transfer catalysts on the reactions was investigated in reactions of substrates bearing 4-biphenyl residues.

3.7.2.1 Tetrabutylammonium salts

As a more soluble alternative to CFS, it was decided to prepare the tetrabutylammonium derivative, Bu_4NSO_4F. Initially, this was attempted using the same method as for CFS starting from aqueous $(Bu_4N)_2SO_4$ which was prepared from the hydrogen sulphate by neutralisation with a solution of the hydroxide. On treatment with dilute fluorine at-5°C, a deep yellow solution was formed and no oxidising solids could be isolated. A similar situation occurred on treatment of the hydrogen sulphate with dilute fluorine. In both cases, reaction at -20°C was also unsuccessful.

As an alternative to this, cation exchange between CFS and a number of tetrabutylammonium salts was attempted in DCM in which CFS is not appreciably soluble. Iodometric titration of the yellow, filtered solutions showed only a slight increase in the concentration of oxidising species (0.0021 mol·dm^{-3}) when compared to CFS/DCM with no added salts (0.0015 mol·dm^{-3}). This was found to be the case for the fluoride, hydrogen sulphate and triflate salts.

The use of DCM as solvent was also found not to be suitable for the fluorination procedure and no fluorinated biphenyls could be isolated with any of the substrates in DCM with added tetrabutylammonium salts, even with the highly soluble NMDE ester.

3.7.2.2 Crown ethers

The success of crown ethers for solubilising alkali metal fluorides in

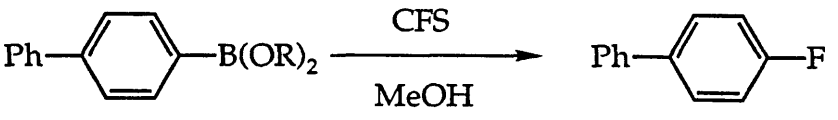
displacement reactions was discussed in the Review. It was considered that they could also be used to our benefit in solubilising CFS in the fluoro-deboronation reaction. Reactions using 18-C-6 were carried out in acetonitrile and DCM but results were disappointing. Even in the presence of 1,3-DNB in an effort to minimise SET reactions with the crown ether α-hydrogens, it was not possible to obtain yields of greater than 10% (with the NMDE ester in acetonitrile).

From the above results, the attempt to further solubilise CFS in acetonitrile was abandoned since it was thought that the possibility of side reactions may be increased in the presence of additives.

3.7.3 The use of other solvents

It was apparent that during the work so far, that the solubility of the reactive boron substrates was not very high. The solubility seemed to be a suitable factor to increase and therefore possibly affect product yields. The use of DCM alone as a solvent was found to be useless in terms of product yield. Acetonitrile or acetonitrile/DCM mixtures resulted in long reaction times (up to 48h.).

The solubility of various boronic acid derivatives in some other solvents was briefly investigated. Of these, the optimum solvent found was methanol which readily dissolved all of the derivatives. The fluorination of all of the biphenyl derivatives 37 was carried out in methanol (Scheme 17) and a large difference in reactivity was noted between the substrates (Table 4).



37

Scheme 17

Table 4: Effect of boron ligands on the fluorination of 4-biphenylboronic acid derivatives in methanol

Entry	*Substrate 37* (R)	*Fluoroaromatic* (% yield)
1	H	56
2	$-(CH_2)_2-$	40
3	$-(CMe_2)_2-$	2
4	$-(CH_2CH_2)_2NMe$	5

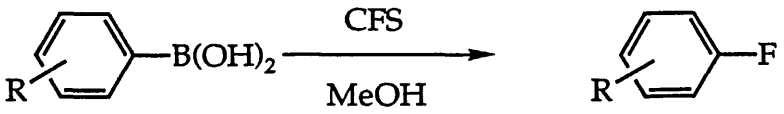
From these results in Table 4, it can be seen that the boronic acid was the most reactive compound although *in situ* it is converted to the dimethyl ester. The fluorination reaction for the boronic acid was essentially complete within 5h. and represented a great increase in reaction rate.

The methanolysis reaction does not occur with the glycol esters and this explains the difference in reactivity found. The ethylene glycol ester is as unhindered as the dimethyl ester and is fairly reactive towards fluorination. The pinacol ester on the other hand is much more hindered and so is less reactive.

The case of the NMDE ester is interesting as the yield is very low in comparison to the acetonitrile reactions. This cannot be explained but an NMR study of the NMDE ester showed that, under the reaction conditions, a 9:1 mixture of the NMDE ester and the dimethyl ester is present. It is therefore probable that the active species in the reaction in this case is also the dimethyl ester.

The generation of the dimethyl ester from the acid should increase the Lewis acidity of the boron and therefore aid in the generation of an intermediate of the type 10 which was proposed above (see section 3.4.1).

This reaction was applied to some other substrates as a test of the reaction conditions and these are presented below (Scheme 18, Table 5).



38 39

Scheme 18

Table 5: Fluorination of phenylboronic acids in methanol

Entry	*Substrate* 38 (R)	*Temperature* (°C)	*Fluoroaromatic* 39 (% yield)
1	4-MeO	0	35 (+ 45% 2-fluoro)
2	3-MeO	rt	-
3	3-MeO	0	10 (+ 40% 2-fluoro, 4-fluoro)
4	3-MeO	-30	10 (+ 20% 2-fluoro, 4-fluoro)
5	4-Ph	rt	56
6	4-Ph	0	45
7	4-Ph	-40	21
8	2-Ph	0	28
9	3,4-$(CH)_4$	rt	0
10	3,4-$(CH)_4$	0	0
11	4-Br	0	20
12	2,4-Cl_2	-10	28
13	3-NO_2	0	14

The reactivities observed in these cases are clearly different to those found using acetonitrile as the solvent. A number of substrates give different products to the reactions of the NMDE esters in acetonitrile (Table 3).

Of these, 2-naphthaleneboronic acid (entry 9) failed to give any fluoronaphthalenes at either 0°C or room temperature although an intense yellow colour was observed in the reaction mixture (SET reaction?). This is in contrast to the reaction of CFS with either the boronic acid or NMDE ester in acetonitrile where yields of 17-30% were obtained. In the case of 4-methoxyphenylboronic acid (entry 1), the change of solvent resulted in the loss of all regiocontrol since the major product was now as a result of fluorination *ortho* to the methoxy group with *ipso*-fluorination as a slightly lower yielding pathway.

3-Methoxyphenylboronic acid (entries 2,3,4) was used to test the degree of regiocontrol and selectivity that could be exerted on an activated substrate. It was required to selectively introduce fluorine into a position that was not activated by the methoxy substituent. The results show that this was carried out to some extent but, even at -30°C, a greater amount of fluorination directed by the methoxy group was observed.

This inability to overcome directional effects appears to be a characteristic of reactions involving strongly activated substrates. Literature examples of the fluorodemetallation reaction invariably have the metal at an activated position (see Review). Possibly the only way to circumvent this problem is to use a more electronegative substituent on aryl oxygens to lower the electron donation into the ring.

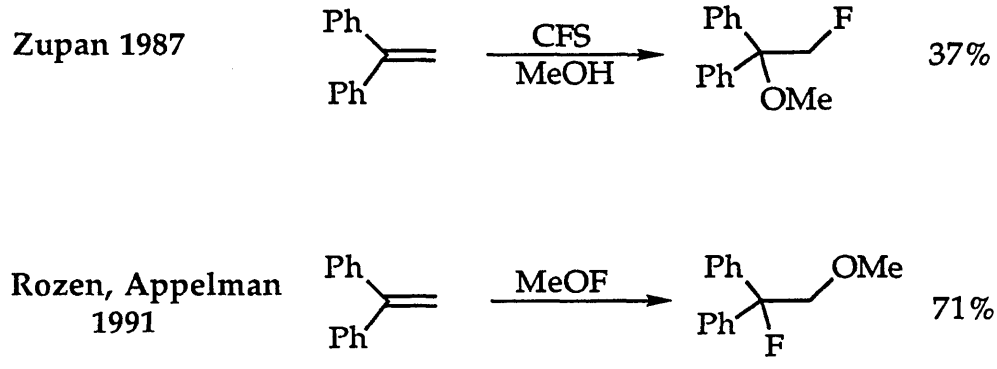
The variable temperature reactions on 4-biphenylboronic acid (entries 5, 6, 7) illustrate that, even at -40°C, a poorly activated system can undergo reaction to give moderate yields of fluoroarenes. It is interesting that, in methanol, 2-biphenylboronic acid (entry 8) underwent fluorination to give 2-fluorobiphenyl whereas in acetonitrile, with the NMDE ester, only protolysis was seen to occur (Table 3, entry 3), even in the presence of added base. For the remaining entries, the product yields were similar to the earlier reactions (Table 3).

3.7.4 Generation of a new reagent *in situ*?

This difference in reactivity for some substrates indicates that a change in

reaction pathway is occurring. An intriguing possibility is that a new reagent is being formed *in situ*, this seemed likely since, in the absence of substrate, a highly exothermic reaction occurs between solvent molecules and CFS to give an oxidising solution. If this reaction generates a new 'F^+' species, the rational reaction of CFS with solvent molecules would be to generate methyl hypofluorite, MeOF. This idea seemed probable and became more favoured after a recent report from Appelman and Rozen detailing the synthesis and isolation of methyl hypofluorite.[68]

Previous work with CFS on additions to alkenes in the presence of nucleophilic solvents had shown that the elements of MeO-F could be added across double bonds. In these reactions, the products formed were found to be derived from Markownikov-type addition of an 'F^+' reagent (Scheme 19).[8] This correlates directly to our own observations on the fluorodeboronation reaction with CFS in methanol involving an 'F^+' species.



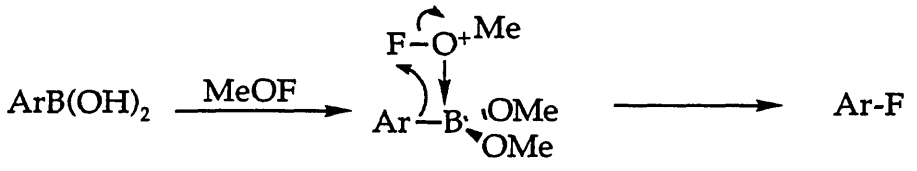
Scheme 19

This poses an interesting problem since, based on electronegativities and the results of Appelman and Rozen, MeOF should behave as an MeO^+ reagent, in the presence of HF (Scheme 19).[68] Although reactions on aromatic substrates were not reported, it is unlikely that changing from an alkene to an aromatic substrate would alter the electrophilic centre of the reagent.

The fact that fluorination was the dominant process in the arylboronic acid systems studied in our work might point towards no reaction between CFS and methanol *i.e.* the active 'F^+' species in the reaction is CFS. The

vigorous reaction observed in the absence of the substrate, however, is not consistent with this hypothesis. Assuming the initial formation of MeOF, this indicates some interaction with the metalloid altering the nature of the reagent from an MeO^+ source to an F^+ source.

The most straightforward interaction which can be considered likely is coordination of the hypofluorite oxygen with the Lewis acid centre of the substrate aided by an α-effect from the fluorine atom (Scheme 20).



40

Scheme 20

Such O→B coordination would also serve to polarise the O-F bond by generation of a positive charge on oxygen and thus incline the reagent towards fluorination. The adduct 40 could then collapse *via* S_Ni attack to give the fluoroaromatic product.

Adduct formation would then explain the minimal reactivity found for the NMDE esters in methanol. Since these esters have no vacant coordination site, adduct formation could not occur except *via* initial methanolysis to the dimethyl ester.

If this is indeed the case, the reaction in methanol involves an aryl σ-bond process rather than the more conventional π-bond reaction of electrophilic, aromatic substitution. If no reagent modification is occurring with either acetonitrile or methanol, it is possible that the presence of the O-F group in CFS might also allow a similar adduct-forming pathway to occur in reaction of CFS with arylboronic acids.

Such a pathway would not be available to the NMDE esters due to the lack of a vacant coordination site and these would therefore be more likely to follow the standard π-bond pathway. This is one possible explaination of the

differences in reactivities found in the two sets of reactions in methanol and acetonitrile.

In the reactions of MeOF reported by Appelman and Rozen, the reaction mixtures contained an equivalent of HF as a by-product which should also be expected to interact with the reagent. In this case, however, the formation of a hydrogen bond (such as in **41**) to the fluorine atom (similar to those present in liquid HF) would polarise the O-F bond in the opposite sense *i.e.* the reagent would act as an MeO^+ electrophile.

$$\overset{\delta-\ \delta+}{F\text{-}H\text{---}F\text{-}OMe}$$

41

The different positions of adduct formation with Lewis acid and protic acid might result from the greater ability of oxygen, aided by an α-effect from the fluorine, to act as a bridging centre (and thus, form the adduct **40**) in the presence of a Lewis acid containing substrate. This situation should favour electrophilic fluorination.

In comparison, the stronger hydrogen bond-accepting properties of the fluorine atom should predominate under protic acid conditions, since this is expected to be the more electron-rich centre of the two heteroatoms due to its greater electronegativity. The net result should then be electrophilic oxygenation.

If the situation proposed above is actually occurring, this indicates that any potential Lewis acids in the reaction medium would be expected to dictate the chemistry of methyl hypofluorite as a result of the position favoured for adduct formation.

In the reactions of 4-biphenylboronic acid with CFS in MeOH, it was found that additives could affect the reaction. The weak Lewis acid $B(OMe)_3$ caused only a slight drop in yield (to 51%) while the more powerful $BF_3.OEt_2$ or BF_3.MeOH caused a significant drop (to 38%). The presence of added Lewis acid may be considered to involve competitive complexation with the

oxygen of MeOF thus aiding decomposition since the product-forming intermediate would not be formed. The greater suppression of fluorination seen for BF_3 over $B(OMe)_3$ would then result from the greater Lewis acidity of BF_3 and, therefore, greater competitive adduct formation.

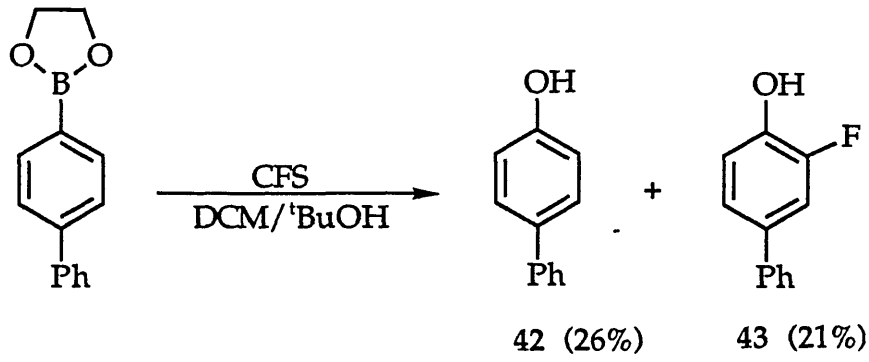
The most significant effect was seen in the reaction with NaOMe which completely inhibited the fluorination reaction. The suppression with NaOMe might appear to be anomalous to formation of MeOF but its basicity should be sufficient for the loss of the elements of HF from MeOF with the subsequent generation of formaldehyde. Alternatively, the generation of an 'ate' complex from the substrate would block the formation of the intermediate adduct 40.

3.7.5 Miscellaneous work

The addition of methanol to a DCM solution of the ethylene glycol ester of 4-biphenylboronic acid (or suspension of the acid) resulted in 4-fluoro-biphenyl in 57% yield (over 20h.). This was the first example of an arylboronic acid derivative undergoing fluorination in DCM and again supports the idea of reagent modification.

Considering the likely pathways for decomposition of MeOF (mainly loss of HF), it was thought that *tert*-BuOF would be a more stable analogue. Addition of *tert*-BuOH to an acetonitrile suspension of 4-biphenylboronic acid followed by CFS gave 4-fluorobiphenyl in 47% yield.

In contrast to the reaction in DCM/MeOH however, it was found that reaction of the ethylene glycol ester 18 with CFS in DCM/*tert*-BuOH at ambient temperature did not occur. Due to an extremely slow conversion, it was necessary to heat the reaction to 40°C in order to obtain significant reaction. Under these conditions, *ipso*-fluorination was found not to occur to any extent. Instead, the major product was 4-hydroxybiphenyl 42 in 26% yield with a slightly lesser amount of 3-fluoro-4-hydroxybiphenyl 43 (21%, Scheme 20). Obviously, oxidation of the C-B bond is occurring as the initial process.



42 (26%) 43 (21%)

Scheme 20a

The use of *tert*-BuOH in these reactions was therefore less desirable than the use of methanol as a solvent. If the proposed mechanism for the methanol-based reactions is correct, then the much greater steric demands required by *tert*-BuOF would oppose the generation of the intermediate adduct (*c.f.* 40) making *tert*-BuOH useless as a substitute solvent. Also the formation of *tert*-BuOF should be much less facile than for MeOF.

As an attempt to speed up the reaction time, a totally homogeneous reaction was carried out using aqueous methanol as solvent. It was found that 4-biphenylboronic acid could be converted to 4-fluorobiphenyl in a yield of 26% in only 15 minutes. The reaction time achieved is sufficient to carry out radiofluorinations, therefore the fluorodeboronation process was applied to a more, biologically interesting molecule.

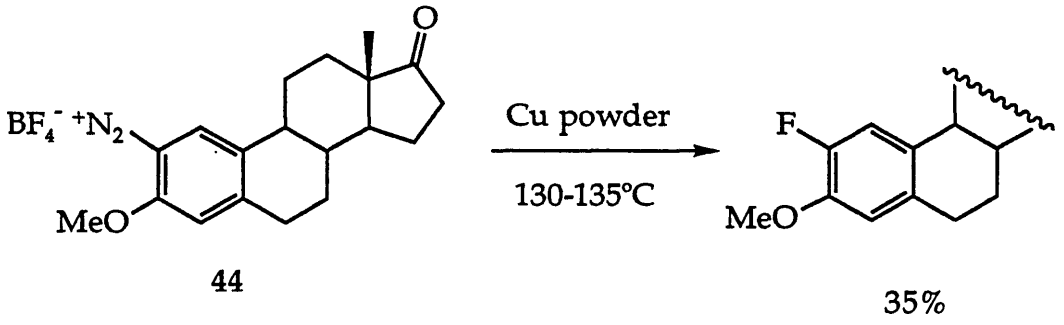
3.8 The rapid, regioselective fluorination of 3-*O*-methylestrone - a suitable method for ^{18}F PETT scanning applications

3.8.1 Background

The synthesis of ring A fluorinated estrones has been the subject of much investigation over the last 30 years,[69] originally because these fluorinated estrones were used as chemotherapy reagents, but more recently for their

use as a diagnostic tool in ^{18}F PETT scanning techniques. A number of different approaches have been used to introduce fluorine into the aromatic A-ring with varying degrees of success.

The earliest methods for the preparation of A-ring fluorinated estrones were based on fluorodeamination for example, the approach of Utne who used diazonium salt 44 prepared from estrone (along with the 4-substituted isomer *via* nitration and reduction) in four steps.[70] Thermal decomposition of these salts over copper powder (Scheme 21) gave the 2-fluoro- or 4-fluoro-compounds in 35% yield in either case.

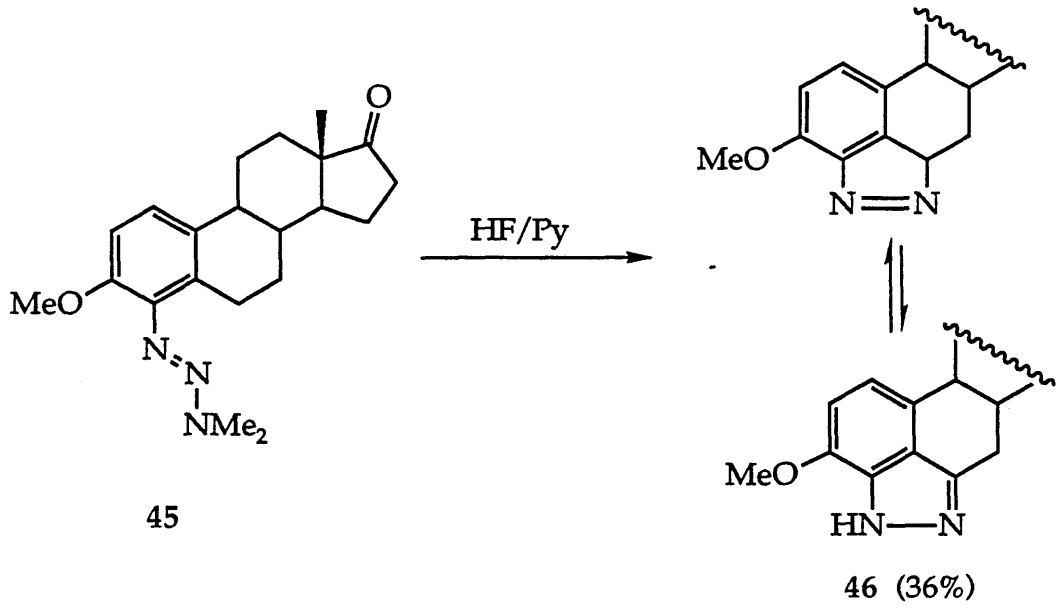


44 35%

Scheme 21

This illustrates the major drawback of most of the approaches to these compounds since the initial, electrophilic substitution of the A-ring (in this case, nitration) gives essentially 1:1 mixtures of 2- and 4-substituted estrones, thus requiring separation of isomers.

Triazene routes to the fluoroestrones have been attempted by a number of groups although the results have been contradictory. The *N,N*-dimethyl-triazene 45 was initially reported to give 4-fluoro-3-*O*-methylestrone in 85% yield with Py/HF in acetic acid,[71] but another group later obtained the benzpyrazole 46 as the major product in 36% yield under the same conditions (Scheme 22).[72] This latter result appears to follow the general trend of *ortho*-oxygen substituents inhibiting the fluorination pathway (see Review).

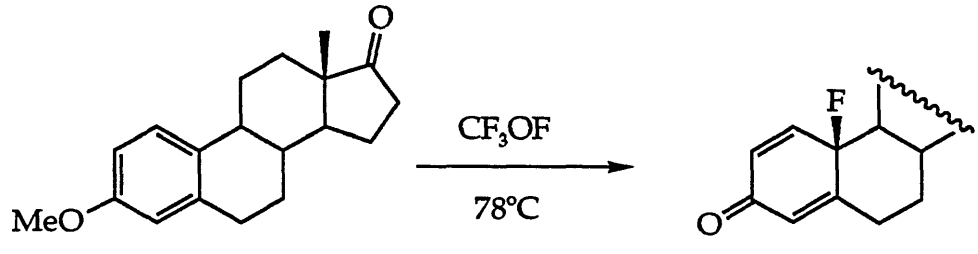


45

46 (36%)

Scheme 22

Later reports appear to have concentrated on electrophilic reagents to carry out the fluorination. Barton and Hesse showed that reaction of the 3-*O*-methyl ether 47 with CF_3OF gave predominantly the fluorinated dienone 48 in 65% (Scheme 23).[73]



47

48 (65%)

Scheme 23

The milder *N*-fluoro reagents have also been investigated; *i.e.* estrone gave a 1:1 mixture of 2-fluoro and 4-fluoroestrone in 52% yield with the reactive *N*-fluoro-3,5-dichloropyridinium triflate.[74] The same fluorinating agent agent was used with the related estradiol to give a 1:1 mixture of 2-fluoro- and 4-fluoroestradiol in 60% yield.[75] These results appear at odds

with a report that preferential fluorination of estrone can be achieved at C-2 over C-4 by use of the very mild *N*-fluoropyridinium triflate. In this case, the resulting isomers could only be separated by chromatography after conversion to the 3-acetoxy derivatives.[76]

CFS has also been used to fluorinate estradiol to give a 1:1 mixture of 2-fluoro- and 4-fluoro- isomers in a total yield of 40%.[77]

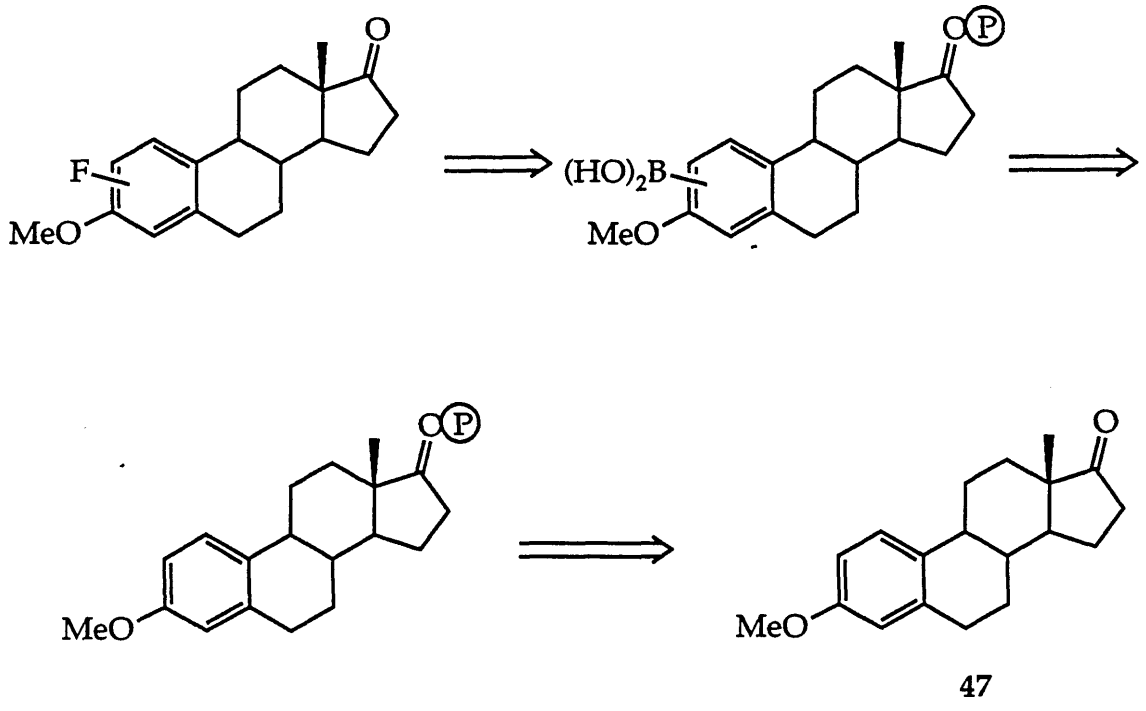
As can be seen, regioisomeric product mixtures are unavoidable with these substrates which is undesirable in a PETT application. The challenge facing us was to develop a route to a specific, fluorinated estrone in a rapid, synthetic sequence. The fluorodeboronation reaction in methanol appeared to be ideal for the intended synthesis as it is rapid, even on unactivated substrates, and was, therefore, investigated further using 3-*O*-methylestrone 47 as the substrate.

3.8.2 Strategy

The directed metallation reaction has been applied to the synthesis of a number of arylboronic acids for use in the palladium-catalysed coupling reaction with aryl halides.[78,79] It was considered that the methoxy group might be used as a directing group for *ortho*-metallation.[25] Protection of the C-17 ketone should allow this to occur with no side reactions due to the lack of other functionality in the molecule. Subsequent boronation and fluorination should occur regiospecifically assuming only a single metallated derivative was formed (Scheme 24).

3.8.3 Synthesis of fluorinated 3-*O*-methylestrone

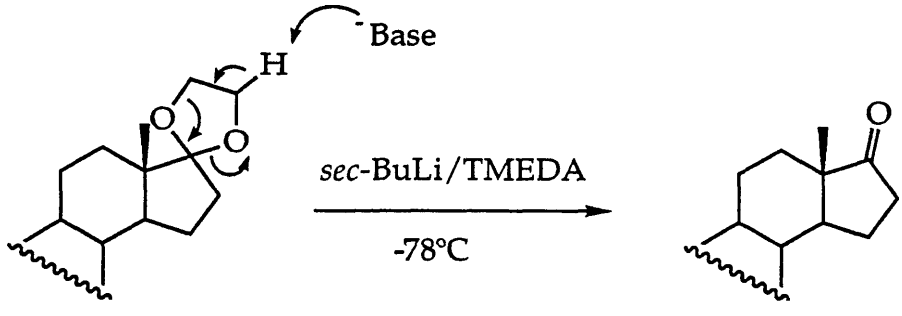
The C-17 ketone was readily protected as the ketal 49 under standard conditions (toluene, cat. PTSA, Dean-Stark) in 97% yield. Metallation of 49 was attempted with a number of organolithium bases. However, reaction with n-BuLi, n-BuLi/TMEDA or *sec*-BuLi and subsequent trapping with TMSCl, either *in situ* during the lithiation or added after, was unsuccessful. In each case starting material was reclaimed in greater than 95% yield.



47

Scheme 24

The standard conditions used by Snieckus for *ortho*-metallation in arylboronic acid synthesis are *sec*-BuLi/TMEDA/-78°C/THF.[78,79] Treatment of 49 under these conditions followed by TMSCl regenerated 3-*O*-methyl-estrone in 82% yield. Comparable yields could be obtained by quenching *in situ* with TMSCl or without a quench. The likely mechanism involves attack at the ketal α-hydrogens followed by ring opening (Scheme 25) in a similar manner to the well known reaction of THF with strong bases.



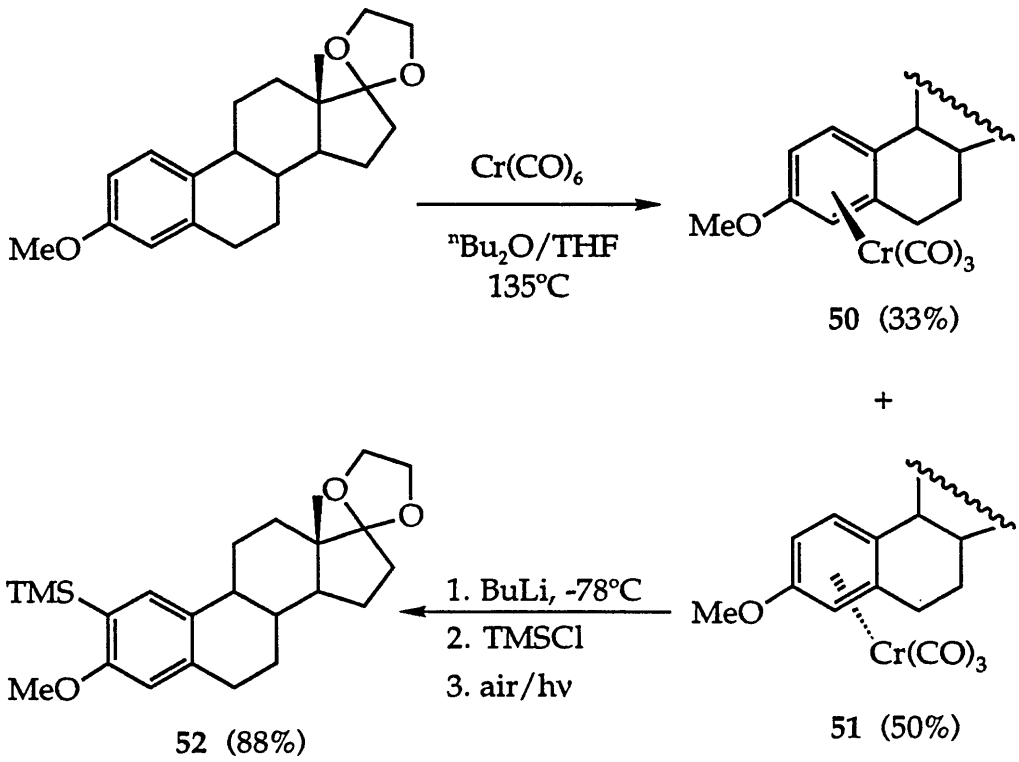
49 82%

Scheme 25

In order to overcome this, it was decided to increase the acidities of the A-ring protons by formation of the chromium tricarbonyl complex. This should also lead to an increase in the directing ability of the methoxy group.[80]

Formation of the complex was achieved by treatment with $Cr(CO)_6$ at 135°C in Bu_2O/THF under strictly anaerobic conditions. This gave an 83% yield of the bright yellow, air-stable complex as a 1:1.6 mixture of diastereomers 50, 51 (Scheme 26) in favour of the α-diastereomer 51. The stereochemistry was assigned by comparison to published 500 MHz NMR data for the related estradiol complexes whose structure had been determined by X-ray analysis.[81]

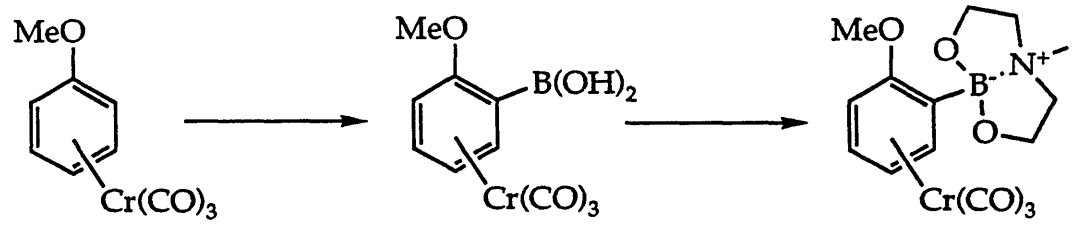
The favoured position of metallation for 51 was established by generating the aryllithium (with n-BuLi at -78°C) and trapping with TMSCl followed by decomplexation of the crude reaction mixture. This gave 2-trimethylsilyl-3-methoxy-17-ethylenedioxyestrane 52 in 88% yield (Scheme 26).



Scheme 26

The 4-silylylated derivative was not observed (by 270 MHz NMR of the crude reaction mixture) and it was therefore pleasing to see that the metallation was totally regiospecific.

Since the stability of arylboronic acid complexes was unknown and no data on stability could be found in the literature, a model system was studied based on tricarbonyl chromium(0) anisole 53. This could be metallated readily as for the steroid 51 and the use of $B(O^iPr)_3$ as quench gave the arylboronic acid complex 54 in 62% yield. As a point of interest, it was also found to be possible to prepare the NMDE ester of the complex 52 in 88% yield (Scheme 27) although this was much less air-stable.



53 54 (62%) 55 (88%)

Scheme 27

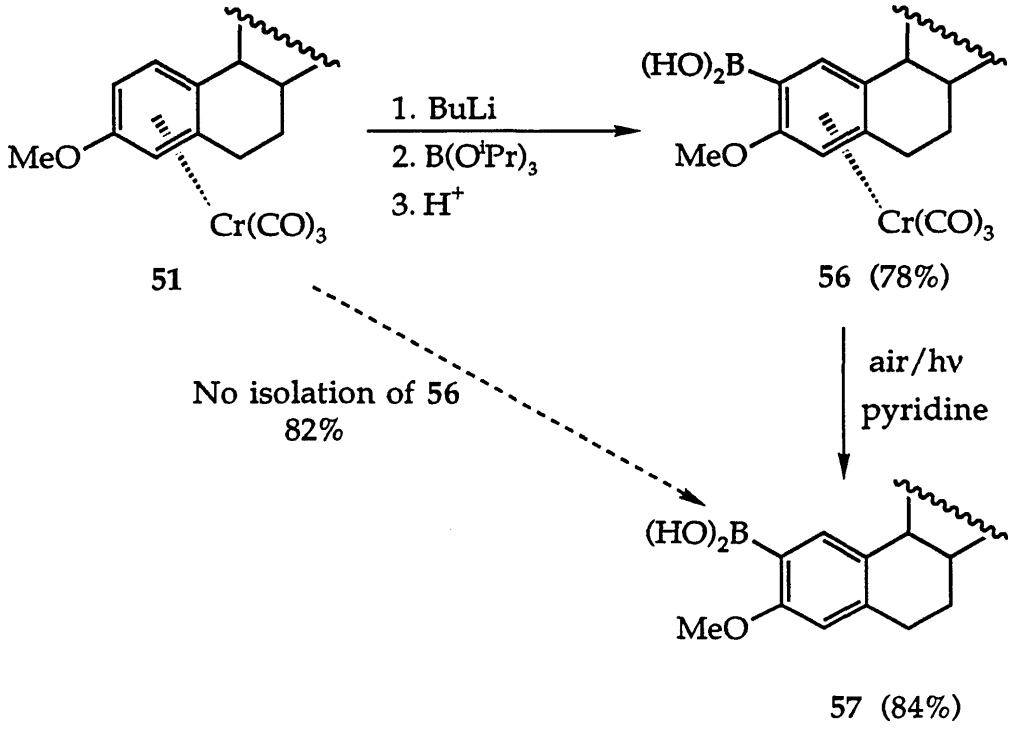
Following this, the boronic acid derived from 51 was formed *via* the aryllithium as a highly insoluble, air-stable complex 56 in 78% yield. The insolubility of 56 proved problematic but it was found that, in methanol, the addition of CFS induced rapid decomplexation and a homogeneous solution resulted. It was thought therefore that it should be possible to carry out the fluorination and decomplexation in a one pot process.

Although the presence of product could be detected (by TLC) during the reaction, decomposition occurred and the product, isolated in low yield, could not be identified although it did not appear to be aromatic (by inspection of the δ_H 6-8 region in the ^1H NMR). A possibility is that a dienone was being formed (*vide supra* the reaction of CF_3OF). A similar result was obtained if methanolic acetonitrile was used as reaction solvent. The addition of BF_3 or 1,3-DNB to the reaction mixture or lower

temperatures (0°C) also had no effect.

It was considered that the liberated Cr(III) species may be reacting with the product causing decomposition. The possibility of Cr(III) reacting with CFS was not considered since Appelman has demonstrated that Cr(II) is only oxidised up to Cr(III) during reaction with CFS.[82]

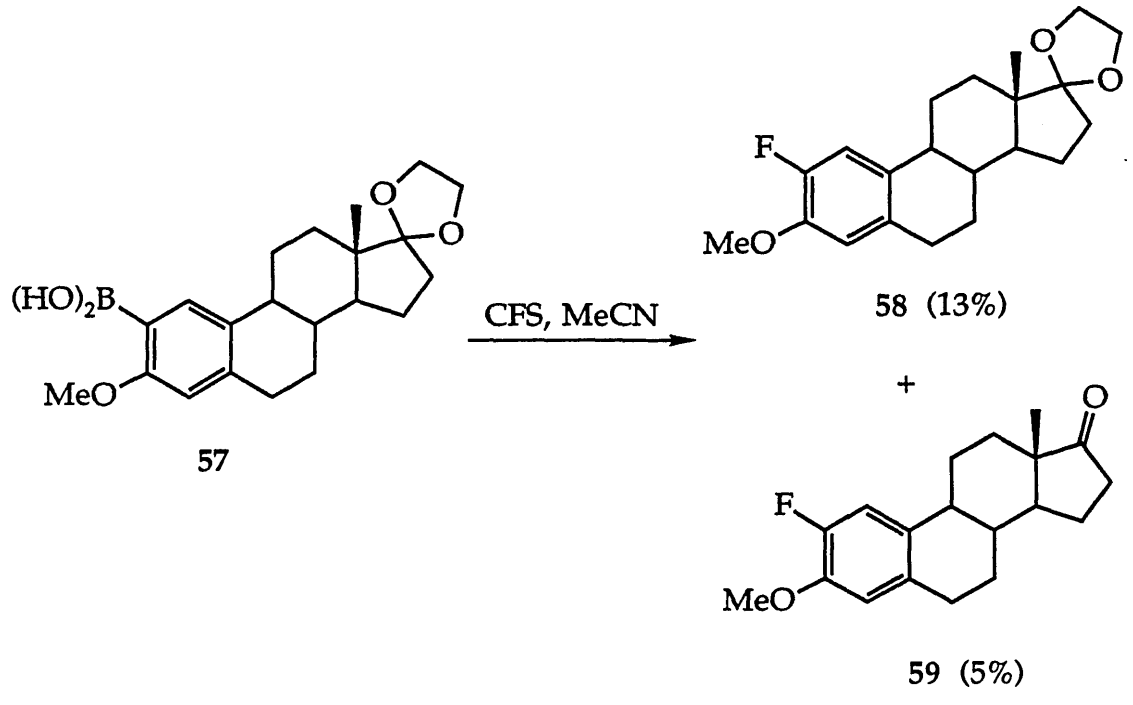
To overcome this possibility, decomplexation was attempted by exposing a suspension of 56 in DCM to air and sunlight. This proved unsuccessful but it was subsequently discovered that 56 would dissolve in pyridine and that exposure of this solution to air and sunlight readily gave the free ligand 57 in 84% yield. It was later found that 57 could be derived from the starting complex 51 in an overall yield of 82% by carrying through the synthesis without any isolation of the arylboronic acid complex 56 (Scheme 28).



Scheme 28

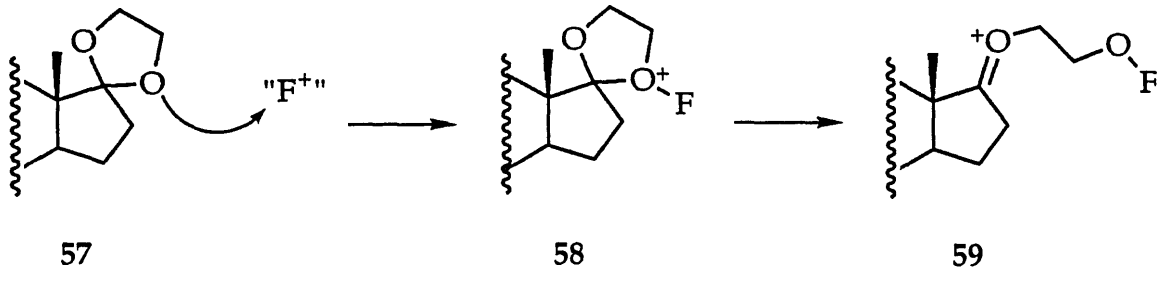
Treatment of 57 with CFS in methanol gave similar unidentified products, to the reaction of 56 with CFS, in low yield. However, a change in solvent to an acetonitrile/DCM mixture led to the isolation of the 2-fluorinated ketal

58 in 14% yield after 2h (Scheme 29). The deprotected 2-fluoro ketone 59 was also formed in 5% yield. It was noted that adding further CFS to the reaction mixture or leaving the reaction for longer periods of time caused product decomposition.



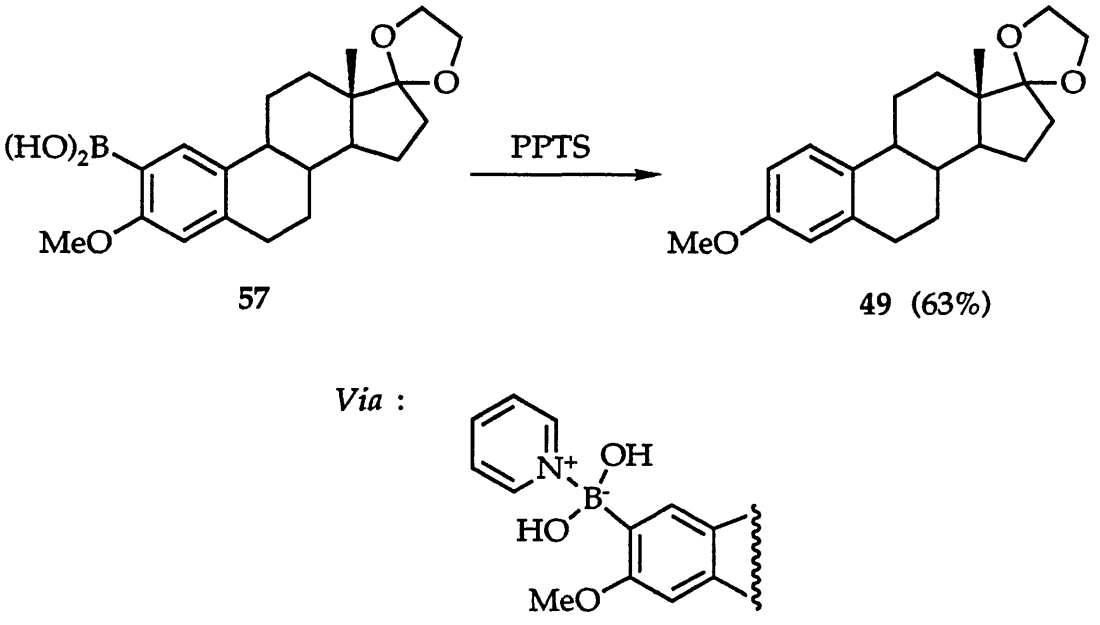
Scheme 29

A rationale for the deketalisation process involves attack of a ketal oxygen on CFS giving an *O*-fluorooxonium ion 60 (Scheme 30) which should undergo ring-opening. The fluoroxy reagent 61 thus generated could then follow a number of pathways (*e.g.* react as an F^+ source, lose HF). Such attack of an 'F^+' species on a ketal has been postulated in reactions of molecular fluorine[83] as well as for bromination of ketals.[84]



Scheme 30

The presence of the ketal was therefore undesirable and deprotection to the ketone was necessary. Treatment of 57 with the mild acid PPTS in acetone caused protolysis of the C-B bond to give the free arene 49 in 63% yield (Scheme 31). Most likely, the presence of the pyridine enhances the leaving group ability of the boron by tetracoordination (*c.f.* the increased reactivity of NMDE esters over boronic acids towards fluorination with CFS in acetonitrile).



57 49 (63%)

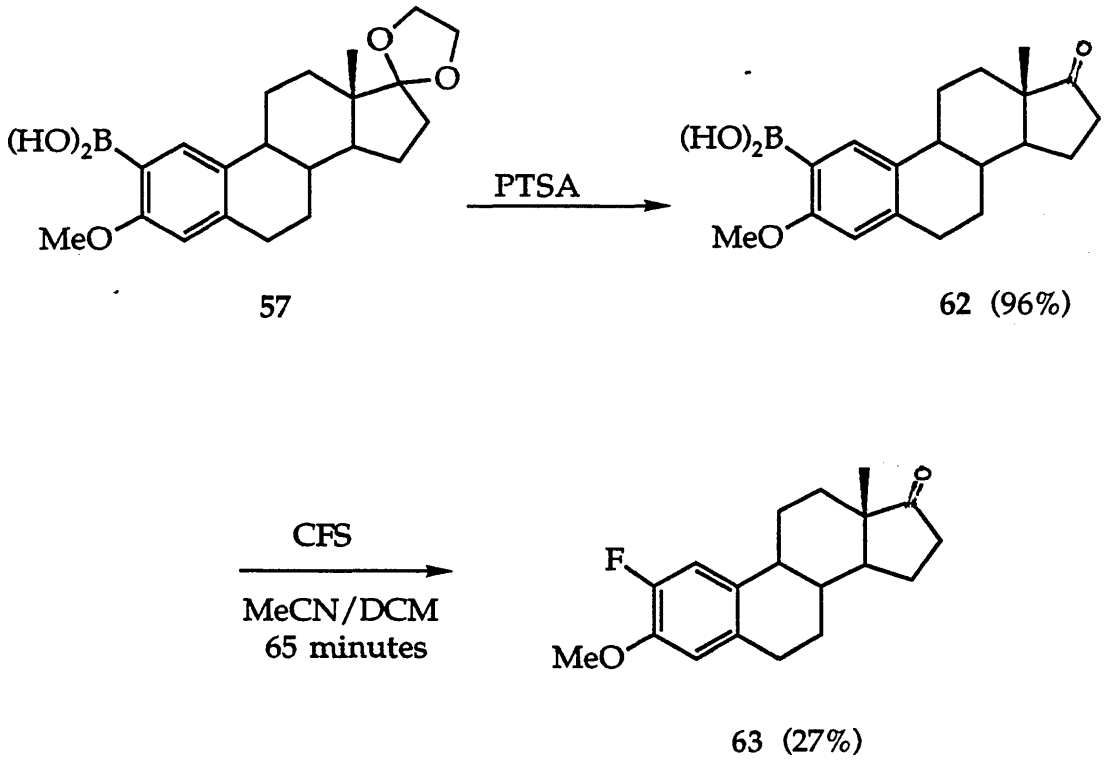
Via :

Scheme 31

A change to PTSA in acetone caused deketalisation to give 2-dihydroxyboryl-3-*O*-methylestrone 62 in a pleasing 96% yield. This underwent fluorination in acetonitrile/DCM to give the *ipso*-substitution product 63 in 27% yield after only 65 minutes (Scheme 32). The use of methanol-based solvent systems led to complicated product mixtures and was not pursued.

This compares directly to the BF_3-catalysed estradiol reaction of CFS (see 3.7.1) which required 24h. to give a yield of 20% of 2-fluoroestradiol together with an equal amount of the 4-fluoro- isomer.[77] It is thus apparent that the presence of the ring-bonded boron causes a significant increase in both the rate of reaction and the reactivity of C-2 relative to C-4. The speed of this

reaction makes it a suitable pathway to [^{18}F]-2-fluoro-3-*O*-methylestrone and should also be applicable to other A-ring fluorinated estrogens.



57

62 (96%)

63 (27%)

Scheme 32

Conclusion

The use of fluorodemetallation to improve the regiocontrol of aromatic fluorination with the ionic reagent, caesium fluoroxysulphate, has been investigated. It has been established that arylsilanes are not suitable alternatives to the reported arylstannanes and undergo H/F exchange at comparable rates to Si/F.

The use of arylboronic acids as fluorination substrates has been studied in great detail. Lewis acid catalysis was found to be detrimental to the product yield unlike the reactions of the parent aromatics or arylsilanes. This might be indicative of some Lewis acid interaction of the boron with the reagent and a possible intermediate was proposed.

The use of the readily available (*N-B*)-perhydro-2-aryl-6-methyl-1,3-dioxa-6-aza-2-boracines (NMDE esters) was found to give improved reaction over both the arylboronic acids and the parent arenes. A possible reagent modification *in situ* was postulated although it was not possible to detect this spectroscopically.

Subsequently it was found that many boronic acids underwent fluorination in methanol at a faster rate than in acetonitrile while others showed vastly different reactivity. This was tentatively attributed to the formation of an alternative fluorinating agent, methyl hypofluorite, although this should function as an electrophilic oxygen source. An intermediate adduct between the substrate and this new reagent was suggested to explain the electrophilic fluorine in these reactions.

The use of the fluorodeboronation reaction was demonstrated by application to 3-*O*-methylestrone to give the useful diagnostic tool 2-fluoro-3-*O*-methylestrone as a regiospecific product in 27% yield. The speed of this process (65 minutes) was found to be sufficiently short for PETT applications.

CHAPTER 4

EXPERIMENTAL

General:----Melting points were determined on a Kofler hot stage apparatus and are uncorrected; infrared spectra were recorded on a Perkin-Elmer model 1710 FT spectrometer; gas chromatographs were recorded on a Varian Vista 6000 chromatograph with a Chromosorb WHP 80-100 mesh column (OV 101) with a Varian Vista CDS 401 data system. .

^{1}H NMR spectra were recorded at 90 MHz on a JEOL FX90Q, at 250 MHz on a Bruker WH-250 , at 270 MHz on a JEOL GSX-270 and at 500 MHz on a Bruker AM-500. In each case, spectra were referenced to residual solvent. ^{19}F NMR spectra were recorded on a JEOL FX90Q at 84.27 MHz and referenced to $CFCl_3$. Quantitative ^{19}F NMR measurements were calibrated against a measured quantity of 2-bromobenzotrifluoride. Apparent coupling constants (J) are given in Hertz and apparent multiplicities are assigned br.-broad, s-singlet, d-doublet, t-triplet, q-quartet, m-multiplet.

Mass spectra and microanalyses were carried out at Imperial College; some accurate mass determinations were carried out at the SERC facility at Swansea.

Solvents were purified as follows: diethyl ether and THF were pre-dried over sodium wire and distilled from sodium benzophenone ketyl immediately before use; acetonitrile and DCM were distilled from calcium hydride immediately before use; methanol was distilled from magnesium methoxide and stored under nitrogen; toluene was dried by standing over sodium wire; petrol refers to that fraction boiling in the range 40-60°C. Other reagents were purified according to literature procedures.[85] Column chromatography was carried out on Rose Chemicals silica gel H.

All reactions involving organolithiums were carried out under an atmosphere of dry, oxygen-free nitrogen in oven- or flame-dried glassware. N-butyllithium was purchased from Aldrich Chemicals Ltd. as a 1.6M solution in hexanes, *sec*-butyllithium as a 1.3M solution in cyclohexane and *tert*-butyllithium as a 1.7M solution in pentane. In each case, the solutions were standardised by literature methods.[86]

Fluorine was purchased from Air Products Ltd. as a 5% mixture in helium and delivered *via* a Johnson Matthey SS 316 regulator.

PREPARATION OF FLUORINATING AGENT

Caesium fluoroxysulphate [5]

A teflon testtube (16 cm x 1.5 cm) was charged with a solution of caesium sulphate (10 g, 27.9 mmol) in distilled water (16 ml) and cooled to -5°C with an ice-salt bath. A dilute mixture of fluorine (5% in helium) was bubbled through the solution for a period of 40 minutes during which time a precipitate formed. This was collected by filtration on a fine porosity (grade 3) sinter, washed with ice-cold water (1 ml.) and dried on the sinter for 40 minutes while maintaining a flow of dry nitrogen through the sample. Half way through this preliminary drying, the solid was gently broken up with a teflon spatula. The solid was then transferred to a wide-necked, screw-capped, polypropylene bottle and dried overnight *in vacuo* over P_2O_5. Immediately after the filtration, the combined filtrates were transferred back to the testtube and the passage of fluorine through the solution was continued. This procedure of fluorination, filtration and drying was carried out a total of four times on each batch of caesium sulphate solution to give a combined yield of 4-5 g. (55-70%) of caesium fluoroxysulphate as a cream coloured, crystalline solid which was stored at 0°C under nitrogen in the polypropylene bottle.

CAUTION: This compound is potentially explosive and a powerful oxidising agent, It must not be subjected to mechanical pressure, direct heating, electrostatically charged equipment, tap water or metal surfaces. It may react vigorously with nucleophilic solvents (DMF, DMSO, DMPU, MeOH) and must be handled using teflon spatulas. It may be safely used in standard laboratory glassware.

Rubidium fluoroxysulphate

This was prepared in a similar manner to that described for the caesium salt except that a 1.3M aqueous solution was used. Rubidium fluoroxysulphate was isolated in 50% yield and stored as for the caesium salt. The same hazards are also applicable.

FORMATION AND FLUORINATION OF ARYLSILANES

4-Methoxyphenyltrimethylsilane (1)

4-Bromoanisole (1.87 g, 10 mmol) in dry ether (15 ml) was stirred at 0°C under a nitrogen atmosphere and *n*-butyllithium (7 ml of a 1.56M solution, 1.09 eq) was added over a period of 10 minutes *via* syringe. After stirring for 2h., neat chlorotrimethylsilane (4 ml, 3 eq.) was added *via* syringe and a white precipitate formed immediately. The reaction mixture was stirred overnight then aqueous 2M ammonium chloride (20 ml) was added and the layers separated. The aqueous layer was extracted with ether (3 x 40 ml) and the combined ether phases were washed with saturated, aqueous brine solution (2 x 20 ml), dried ($MgSO_4$) and evaporated under reduced pressure. Bulb to bulb distillation gave the title compound (1.189 g, 73%) as a colourless oil; b.p. 115°C/10 mmHg (lit.,[87] 220°C/740 mmHg); δ_H (90 MHz, $CDCl_3$) 7.5-6.85 (m, 4H, Ar-H), 3.80 (s, 3H, OMe), 0.25 (s, 9H, Si-CH_3)

Attempted fluorination of 4-methoxyphenyltrimethylsilane (1)

A suspension of caesium fluoroxysulphate (250 mg, 1.01 mmol) in acetonitrile (5 ml) was stirred for 5 minutes under a nitrogen atmosphere at room temperature and then a solution of 4-methoxyphenyltrimethylsilane (270 mg, 1.51 mmol) in acetonitrile (2 ml) was added in one portion followed by boron trifluoride etherate (3 drops). The reaction mixture was allowed to stir overnight after which GC and NMR analysis showed starting material (20%), **4-fluoroanisole** (20%, δ_F -125) and **3-fluoro-4-methoxyphenyltrimethylsilane** (48%, δ_F -137)

In the absence of boron trifluoride etherate, the corresponding yields were 60%, 10% and 25%.

4-Biphenyltrimethylsilane

To a stirred solution of 4-bromobiphenyl (9.32 g, 40 mmol) in ether (30 ml)

was added *n*-butyllithium (25.6 ml of 1.56M solution, 1 eq) *via* syringe at room temperature. After 45 minutes, neat chlorotrimethylsilane (5.5 ml, 1.1 eq.) was added *via* syringe and the reaction mixture was allowed to stir overnight. Dilute hydrochloric acid (2M, 15 ml) was added and the layers separated. The aqueous layer was extracted with ether (3 x 50 ml) and the combined organic phases were washed with saturated brine solution (2 x 40 ml), dried ($MgSO_4$) and evaporated under reduced pressure to yield a white solid. Fractional distillation of this material under reduced pressure gave the title compound as a white solid (2.409 g, 25%); m.p. 53°C (lit.,[40] 54°C); δ_H (90 MHz, $CDCl_3$) 7.3 (m, 9H, Ar-H), 0.28 (s, 9H, Si-Me)

FORMATION OF ARYL BORONIC ACIDS AND DERIVATIVES`

3-Methoxyphenyl boronic acid

A solution of 3-bromoanisole (3.74 g, 20 mmol, 2.53 ml) in dry ether (20 ml) was stirred at 0°C and *n*-butyllithium (15 ml of 1.47M solution in hexanes, 1.1 eq) was added *via* syringe over a period of 10 minutes. The reaction mixture was stirred at 0°C for 1.25h. and then transferred *via* cannula to a cold (-78°C) solution of tri*iso*propyl borate (6 ml, 25 mmol, 1.25 eq) in THF (30 ml) over 20 minutes. After stirring for 1h., the reaction mixture was allowed to reach room temperature over 3h. then poured onto dilute 2M HCl (30 ml) and the layers separated. The aqueous layer was extracted with ether (2 x 30 ml) and the combined organic phases were washed with brine (2 x 40 ml), dried ($MgSO_4$), and evaporated to yield a white solid which was washed with petrol (2 x 30 ml) to yield 3-methoxyphenyl boronic acid (2.158 g, 71%); m.p. 165-166°C; δ_H ($CDCl_3$, 270 MHz) 7.83 (dd, *J* 7.33, 0.98 Hz, 1H, H_6), 7.75 (d, *J* 2.69 Hz, 1H, H_2), 7.44 (t, *J* 7.69 Hz, 1H, H_5), 7.15 (ddd, *J* 8.30, 2.69, 0.98 Hz, 1H, H_4), 3.92 (s, 3H, OMe); ν_{max} (nujol) 2925, 1583, 1458, 1430, 1357, 1234, 730 cm^{-1}; *m/z* (EI) 402 (M^+ of trimer, 100%), 152 (M^+), 134, 108, 91, 78, 65; High resolution acc. mass, found 152.0645; $C_7H_9BO_3$ requires 152.0645

4-Methoxyphenyl boronic acid (11)

A solution of 4-bromoanisole (3.740 g, 20 mmol) in dry ether (20 ml) was cooled to 0°C under a nitrogen atmosphere and a solution of *n*-butyl-lithium (17 ml of 1.45 M solution, 1.25 eq) was added via syringe over a period of 5 minutes. After stirring for 1h. at 0°C, the pale yellow solution was transferred via cannula to a cold (-78°C) solution of tri*iso*propyl borate (9.2 ml, 40 mmol, 2 eq) in dry ether (10 ml) over a period of 0.5h. and stirring continued at this temperature for a further 1h. The reaction mixture was then allowed to reach room temperature over a period of 2h. during which time, a flocculent, white precipitate was formed. It was then transferred to a separating funnel and partitioned between 2M HCl (50 ml) and ether (100 ml). The aqueous layer was washed with ether (1 x 30 ml) and the combined organic phases were washed with water (1 x 50 ml), saturated aqueous brine (2 x 40 ml) then dried ($MgSO_4$). The crude solution was concentrated to approximately 30 ml under reduced pressure and petrol (30 ml) was added to deposit 4-methoxyphenyl boronic acid as white crystals (1.811 g, 60%); m.p. 209-210°C; δ_H (90 MHz, $CDCL_3$) 7.75 (d, *J* 7.8 Hz, 2H, H_2, H_6), 6.97 (d, *J* 7.7 Hz, 2H, H_3, H_5), 6.51 (s, 2H, B-OH), 3.87 (s, 3H, OMe); ν_{max} (nujol) 1585, 1460, 1410, 1355, 1230 cm^{-1}; *m/z* (EI) 402 (M^+ of trimer, 100%), 152 (M^+), 108, 65; Found C, 55.41;H, 5.92%; $C_7H_9BO_3$ requires C, 55.33; H, 5.97%

(N-B)-Perhydro-2-(4-methoxyphenyl)-6-methyl-1,3-dioxa-6-aza-2-boracine (24)

4-Methoxyphenyl boronic acid (455.7 mg, 3 mmol) and *N*-methyldiethanol-amine (358 mg, 3 mmol) were suspended in toluene (20 ml) and heated at reflux under a nitrogen atmosphere. A Soxhlet apparatus containing calcium hydride in the thimble was used to remove water by azeotropic distillation. After 12h., the cooled reaction mixture was concentrated to approximately 5 ml and triturated with petrol to yield a light brown solid which was collected by filtration and washed with cold ether to give the title compound (648.8 mg, 92%); m.p. 96-97°C; δ_H ($CDCl_3$, 250 MHz) 7.53 (d, *J* 8.08 Hz, 2H, H_2, H_6), 6.85 (d, *J* 8.05 Hz, H_3,H_5), 4.26-4.01 (m, 4H, OCH_2), 3.78 (s, 3H, OCH_3), 3.23-2.87 (m, 4H, NCH_2), 2.29 (s, NCH_3); ν_{max} (nujol) 1484, 1205, 1115,

1070, 997 cm^{-1}; *m/z* (EI) 235 (M^+), 149 , 128 (100%); High resolution acc. mass, found 235.1380; $C_{12}H_{18}BNO_3$ requires 235.1380

2-Biphenyl boronic acid

2-Bromobiphenyl (4.662 g, 20 mmol, 3.45 ml) in ether (50 ml) was cooled to 0°C and *n*-butyllithium (9.5 ml of 2.4M solution, 1.2 eq) was added *via* syringe over 15 minutes. after which the reaction mixture was warmed to room temperature and stirred for a further 40 minutes. The solution was transferred *via* cannula to a cold (-78°C) solution of tri*iso*propyl borate (7 ml, xs) in ether (30 ml) over 30 minutes. After stirring for a further 2h., the reaction mixture was allowed to reach room temperature over 1h. then partitioned between 10% aqueous HCl (30 ml) and ether (50 ml). The combined organic phases were washed with saturated brine solution (2 x 50 ml), dried ($MgSO_4$), and concentrated to approximately 30 ml. Hexane (50 ml) was added and concentration continued to give a precipitate which was collected by filtration and washed with hexane to give the title compound as a white solid (1.202 g, 30%); m.p. >300°C; δ_H (90 MHz, $CDCl_3$) 7.81-7.13 (m, 9H Ar-H), 5.42 (s, 2H, B-OH); ν_{max} (nujol) 3326, 1595, 1374, 1341, 1012, 742 cm^{-1}; *m/z* (EI) 198 (M^+), 180, 153; Found C, 72.59; H, 5.55%; $C_{12}H_{11}BO_2$ requires C, 72.70; H, 5.60%

(N-B)-Perhydro-2-(2-biphenyl)-6-methyl-1,3-dioxa-6-aza-2-boracine (24)

A mixture of 2-biphenylboronic acid (581.9 mg, 2.94 mmol) and *N*-methyl-diethanolamine (350.2 mg, 2.94 mmol, 337 µl) were suspended in toluene (20 ml) and heated in a distillation apparatus until the resulting solution was concentrated to approximately 7 ml. The hot reaction mixture was filtered rapidly and allowed to cool to room temperature at which point hexane (2 ml) was added. The resulting solid was collected by filtration and washed with cold ether to give the title compound as a white crystalline solid (810 mg, 98%); m.p. 154-155°C; δ_H (270 MHz, $CDCl_3$) 7.91 (m, 1H, Ar-H), 7.48-7.10 (m, 8H, Ar-H), 3.97 (m, 4H, OCH_2), 2.91-2.32 (m, 4H, NCH_2), 2.20 (s, 3H, NMe); ν_{max} (nujol) 3049, 3016, 1444, 1180, 1112, 1085, 995, 941. 849, 782, 754, 731, 698

cm^{-1}; *m/z* (EI) 281 (M^+), 280, 195, 180, 128 (100%) cm^{-1}; (CI, NH_3) 282 (MH^+, 100%); Found C, 72.34; H, 7.00; N, 4.91%; $C_{17}H_{20}BNO_2$ requires C, 72.62; H, 7.17; N, 4.98%

4-Biphenyl boronic acid (14)

A stirred solution of 4-bromobiphenyl (2.332 g, 10 mmol) in dry ether (25 ml) was cooled to 0°C under a nitrogen atmosphere and a solution of *n*-butyllithium (8.35 ml of 1.2M, 1.03 eq) was added *via* syringe. The reaction mixture was stirred at 0°C for 1.5h. after which time, the yellow solution was transferred *via* cannula to a cold (-78°C) solution of tri*iso*propyl borate (2.45 ml, 1.1 eq) in dry ether (50 ml) over a period of 20 minutes. After a further 40 minutes, the reaction mixture was allowed to warm to room temperature over a 3h. during which time a thick, white precipitate formed. The mixture was stirred at room temperature for 0.5h. and then poured into a separating funnel where it was partitioned between 2M HCl (40 ml) and ether (50 ml). The ether layer was washed with brine (2 x 30 ml), dried ($MgSO_4$) and evaporated to a white solid. This was recrystallised from toluene to yield 4-biphenyl boronic acid as white crystals (1.260 g, 64%); m.p. 246°C; δ_H (270 MHz, d_6-acetone) 8.08-7.36 (m, 9H , Ar-H), 3.31 (s, 2H, B-OH); *m/z* (EI) 198 (M^+), 180, 153; ν_{max} (nujol) 3407, 1398, 1335, 993, 764, 730, 690 cm^{-1}; Found C, 72.71; H, 5.54%; $C_{12}H_{11}BO_2$ requires C, 72.78; H, 5.60%

2-(4-Biphenyl)-1,3-dioxa-2-borolane (18)

A solution of 4-biphenyl boronic acid (597.6 mg, 3.01 mmol) and ethylene glycol (187.3 mg, 3.01 mmol) in toluene (20 ml) was concentrated under reduced pressure on a rotary evaporator to approximately 3 ml. Trituration of this solution with petrol (2 ml) yielded a white solid which was collected by filtration, washed with petrol (1 x 5 ml) and dried *in vacuo* to give the title compound (614.3 mg, 90%); m.p. 99-101°C; δ_H ($CDCl_3$, 90 MHz) 8.1-7.3 (m, 9H, Ar-H), 4.24 (s, 4H, OCH_2); ν_{max} (nujol) 1606, 1421, 1400, 1338, 1225, 1212 cm^{-1}; *m/z* (EI) 224 (M^+, 100%), 167, 152; Found C, 75.31; H, 5.83%; $C_{14}H_{13}BO_2$ requires C, 75.06; H, 5.85%

2-(4-Biphenyl)-4,4,5,5-tetramethyl-1,3-dioxa-2-borolane (19)

A mixture of 4-biphenyl boronic acid (1.409 g, 7.12 mmol) and pinacol (844.8 mg, 7.12 mmol) in toluene (35 ml) was heated in a distillation apparatus until approximately 5 ml of solvent remained. On cooling, the remainder of the solvent was removed under reduced pressure to yield an oil. This was purified by rapid (<5 minutes) flash chromatography (SiO_2; petrol-ether 9:1) to yield the title compound as a white solid (1.569 g, 79%); m.p. 103-104°C; δ_H ($CDCl_3$, 90 MHz) 8.05-7.30 (m, 9H, Ar-H), 1.01 (s, 6H, Me), 0.92 (s, 6H, Me); ν_{max} (nujol) 1610, 1398, 1324, 1142, 1094 cm^{-1}; *m/z* (EI) 280 (M^+), 265, 194, 180 (100%), 152; Found C, 77.34; H, 7.83%; $C_{18}H_{21}BO_2$ requires C, 77.17; H, 7.55%

(N-B)-Perhydro-2-(4-biphenyl)-1,3-dioxa-6-aza-2-boracine (22)

A mixture of 4-biphenyl boronic acid (191 mg, 0.969 mmol) and diethanolamine (104 mg, 0.99 mmol) in dry toluene (35 ml) were heated at reflux under Dean-Stark conditions for 6h. The hot reaction mixture was filtered and allowed to cool after which a white, crystalline solid was deposited. This was collected by filtration, washed with cold (0°C) toluene (1 x 5 ml) then dried *in vacuo* to give the title compound (206.4 mg, 80%); m.p. 243-244°C; δ_H (90 MHz, d_6-DMSO) 7.69-7.15 (m, 9H, Ar-H), 6.89 (br.s, 1H, NH), 4.01-3.73 (m, 4H, OCH_2), 3.48-3.08 (m, 4H, NCH_2); ν_{max} (nujol) 3093, 1272, 1232, 1097, 1071, 825 cm^{-1}; *m/z* (EI) 267 (M^+), 236, 180, 170, 154, 114, 74, 56 (100%); High resolution acc. mass, found 268.1509; $C_{16}H_{19}BNO_2$ requires 268.1509

(N-B)-Perhydro-2-(4-biphenyl)-6-methyl-1,3-dioxa-6-aza-2-boracine (23)

4-Biphenyl boronic acid (1.089 g, 5.5 mmol) and *N*-methyldiethanolamine (0.655 g, 5.5 mmol, 631 µl) suspended in toluene (50 ml) were heated under reflux with stirring in a distillation apparatus. As the temperature increased, the reactants dissolved and heating was continued until the volume of solvent left was approximately 10 ml. The hot solution was rapidly filtered and left to cool. A white, crystalline solid separated from the solution and this was collected by filtration, washed with cold (-10°C) toluene (2 x 5 ml)

then dried *in vacuo* to give the title compound (1.484 g, 96%); m.p. 150-151°C; δ_H ($CDCl_3$, 270 MHz) 7.80-7.31 (m, 9H, Ar-H), 4.30-4.15 (m, 4H, OCH_2), 3.31-2.97 (m, 4H, NCH_2), 2.41 (s, 3H, NMe); υ_{max} (nujol) 2923, 1096, 1075 cm^{-1}; *m/z* (EI) 281 (M^+), 195, 180, 128 (100%); Found C, 72.43; H, 7.21; N, 4.92%; $C_{17}H_{20}BNO_2$ requires C, 72.62; H, 7.17; N, 4.98%.

1-Naphthylboronic acid (16)

A solution of 1-bromonaphthalene (1.242 g, 6 mmol) in dry ether (20 ml) was added *via* cannula to a solution of *tert*-butyllithium (10 ml of 1.2M, 2 eq.) in ether (30 ml) at -78°C over a period of 30 minutes. After a further 30 minutes the resulting precipitate was dissolved by addition of THF (2 ml) and then transferred *via* cannula to a cold (-78°C) solution of tri*iso*propyl borate (2.33 ml, 10 mmol) in ether (10 ml) over a period of 45 minutes then stirred for a further 1h. at this temperature before allowing the solution to warm slowly to room temperature over 3h. The resulting suspension was partitioned between 2M aqueous HCl (40 ml) and ether (50 ml) and the ether phase was washed with saturated, aqueous brine (2 x 30 ml), dried ($MgSO_4$) and evaporated to yield a light brown solid. This was recrystallised from hot benzene then precipitated from an ethanol solution by trituration with water to yield a microcrystalline solid which was air-dried on the sinter then dried *in vacuo* to yield **1-naphthylboronic acid** (666 mg, 77%); m.p. 210-211°C (lit.,[88] 210-211°C); δ_H (90 MHz, $CDCl_3$) 7.94-7.38 (m, 7H, Ar-H), 5.44 (s, 2H, B-OH)

(N-B)-Perhydro-2-(1-naphthyl)-6-methyl-1,3-dioxa-6-aza-2-boracine (24)

A suspension of 1-naphthylboronic acid (172 mg, 1 mmol) and *N*-methyl-diethanolamine (119 mg, 1 mol) in toluene (30 ml) was heated at reflux in a distillation apparatus until the volume of solvent remaining was approximately 5 ml. The hot reaction mixture was filtered and the filtrate was allowed to cool to room temperature. A crystalline solid was deposited which was collected by filtration, washed with cold (0°C)toluene (1 x 5 ml), cold ether (2 x 5 ml) and allowed to air-dry to yield the title compound (240 mg, 94%); m.p. 138-140°C; δ_H ($CDCl_3$, 90 MHz) 7.94-7.11 (m, 7H, Ar-H), 4.41-

4.12 (m, 4H, OCH_2), 3.41-3.12 (m, 4H, NCH_2), 3.03 (s, 3H, NMe); ν_{max} (nujol) 1265, 1240, 1172 cm^{-1}; *m/z* (EI) 255 (M^+), 169, 154, 128 (100%); Found C, 70.43; H, 7.02; N, 5.61%; $C_{15}H_{18}BNO_2$ requires C, 70.55; H, 7.11; N, 5.49%

2-Naphthylboronic acid

A solution of 2-bromonaphthalene (2.063 g, 9.94 mmol) in dry ether (50 ml) was stirred at -78°C and a solution of *tert*-butyllithium (12.5 ml of 1.6M solution, 2 eq) was added via syringe over 5 minutes. The reaction mixture turned orange immediately and was stirred at this temperature for a further 50 minutes then transferred via cannula to a cold (-78°C) solution of tri*iso*propyl borate (4.6 ml, 2 eq) in dry ether (50 ml) over a period of 1h. The cloudy solution was allowed to reach room temperature over a period of 4h. The resulting suspension was transferred to a separating funnel and partitioned between 2M HCl (50 ml) and ether (100 ml). The aqueous layer was washed with ether (1 x 30 ml) and the combined organic phases were washed with water (1 x 50 ml), saturated, aqueous brine (2 x 40 ml) and dried ($MgSO_4$). The solution was concentrated to approximately 50 ml under reduced pressure and petrol (20 ml) was added. Further concentration yielded the product as white crystals (1.031 g, 60%); m.p. 225°C (dec.); δ_H (90 MHz, $CDCl_3$) 8.40 (s, 1H, H_1), 7.91-7.80 (m, 4H, H_5, H_6, H_7, H_8), 7.57-7.46 (m, 2H, H_3, H_4), 4.44 (s 2H, B-OH); *m/z* (EI) 172 (M^+, 100%), 154, 149, 128; ν_{max} (nujol) 3256, 1319, 1033, 828, 745 cm^{-1}; Found C, 69.53; H, 5.14%; $C_{10}H_9BO_2$ requires C, 69.74; H, 5.27%

(N-B)-Perhydro-2-(2-naphthyl)-6-methyl-1,3-dioxa-6-aza-2-boracine (24)

A suspension of 2-naphthaleneboronic acid (337 mg, 1.96 mmol) and *N*-methyldiethanolamine (234 mg, 1.96 mmol) in toluene (20 ml) was heated to reflux with stirring and the solvent was allowed to distill off. The solution was heated until the volume of solvent remaining was approximately 2 ml. The hot reaction mixture was filtered and the filtrate was allowed to reach room temperature during which time a white solid was deposited. This was collected by filtration and washed with cold (0°C)

toluene (1 x 5 ml) then dried *in vacuo* to give the title compound (486 mg, 97%); m.p. 140-142°C; δ_H ($CDCl_3$, 250 MHz) 8.13 (s, 1H, H_1), 7.90-7.70 (m, 4H, Ar-H), 7.45-7.38 (m, 2H, Ar-H), 4.31-4.17 (m, 4H, OCH_2), 3.26-3.15 (m, 4H, NCH_2), 2.29 (s, 3H, NMe); υ_{max} (nujol) 3040, 1270, 1240, 1172, 1125, 1090 cm^{-1}; *m/z* (EI) 255 (M^+), 169, 154, 128 (100%); Found C, 70.81; H, 7.22; N, 5.27%; $C_{15}H_{18}BNO_2$ requires C, 70.63; H, 7.11; N, 5.49%.

(N-B)-perhydro-2-(3-chloro-4-fluorophenyl)-6-methyl-1,3-dioxa-6-aza-2-boracine (24)

A mixture of 3-chloro-4-fluorophenylboronic acid (523.1 mg, 3 mmol) and *N*-methyldiethanolamine (357 mg, 3 mmol) in toluene (20 ml) was heated at reflux for 6h. with azeotropic removal of water using a Soxhlet apparatus with calcium hydride in the thimble. On cooling of the reaction mixture, an orange oil resulted which was dissolved in DCM and triturated with petrol to give the title compound as a cream-coloured powder (749 mg, 97%); δ_H (250 MHz, $CDCl_3$) 7.63 (dd, *J* 19.55, 3.91 Hz, 1H, H_2), 7.46 (ddd, *J* 20.33, 12.82, 3.36 Hz, 1H, H_6), 7.05 (dd, *J* 25.02, 20.33 Hz, 1H, H_5), 4.25-4.07 (m, 4H, OCH_2), 3.26-3.17 (m, 2H, NCH_2), 3.06-2.95 (m, 2H, NCH_2), 2.33 (s, 3H, NMe); δ_F (84.27 MHz, $CDCl_3$) -118.6; *m/z* (EI) 259, 257 (M^+), 171, 156, 128 (100%); ν_{max} (nujol) 1266, 1235, 1140, 860 cm^{-1}; Found C, 50.84; H, 6.16; N, 5.35%; $C_{11}H_{16}BClFNO_2$ requires C, 50.95; H, 6.22; N, 5.40%

(N-B)-perhydro-2-(4-bromophenyl)-6-methyl-1,3-dioxa-6-aza-2-boracine (24)

4-Bromophenyl boronic acid (1.020 g, 5.08 mmol) and *N*-methyldiethanolamine (630 mg, 5.29 mmol) in toluene (50 ml) were heated at reflux under a nitrogen atmosphere in a Soxhlet apparatus containing calcium hydride in the thimble. After 10h., the reaction mixture was allowed to cool and the solvent was removed under reduced pressure to give the title compound as a off-white solid (1.460 g, 98%); m.p. 142-143°C; δ_H (270 MHz, $CDCl_3$) 7.51-7.39 (m, 4H, Ar-H), 4.24-4.06 (m, 4H, OCH_2), 3.22-2.94 (m, 4H, NCH_2), 2.31 (s, 3H, NCH_3); υ_{max} (nujol) 1577, 1212, 1198, 1098, 993, 944, 813 cm^{-1}; *m/z* (EI) 285, 283 (M^+) 240, 199, 197, 184, 182, 128 (100%); Found C 46.55, H 5.07, N 4.82%; $C_{11}H_{15}BBrNO_2$ requires C, 46.53, H, 5.32, N, 4.93%

(N-B)-perhydro-2-(3-nitrophenyl)-6-methyl-1,3-dioxa-6-aza-2-boracine (24)

3-Nitrophenyl boronic acid (927.7 mg, 5.56 mmol) and *N*-methyldiethanolamine (663 mg, 5.56 mmol, 638 µl) in sodium-dry toluene (20 ml) were heated at reflux under Dean-Stark conditions for 20h. The reaction mixture was allowed to cool to room temperature which caused a brown oil to separate. Addition of cold (-5°C) hexane (5 ml) with vigorous swirling caused a pale yellow solid to precipitate which was collected by filtration, washed with cold (0°C) ether (1 x 5 ml) and dried *in vacuo* to give the title compound (1.264 g, 91%); m.p. 119-123°C; δ_H (270 MHz, $CDCl_3$) 8.39(dd, *J* 1.8, 1.6 Hz, 1H, H_2), 8.05 (ddd, *J* 7.1, 1.7, 1.6 Hz, 1H, H_4), 7.91 (d, *J* 7.1 Hz, 1H, H_6), 7.40 (t, *J* 6.9 Hz, 1H, H_5), 4.21-4.06 (m, 4H, OCH_2), 3.27-3.17(m, 2H, NCH_2), 3.09-2.94 (m, 2H, NCH_2), 2.29 (s, 3H, NCH_3); υ_{max} (nujol) 1519, 1352, 1199, 1100, 1072, 731, 710 cm^{-1}; *m/z* (CI, NH_3) 251 (MH^+, 100%), 221, 145, 128, 102; Found C, 52.89; H, 5.79; N, 11.11%; $C_{11}H_{15}BN_2O_4$ requires C, 52.84; H, 6.05; N, 11.20%

(N-B)-perhydro-2-(2,4-dichlorophenyl)-6-methyl-1,3-dioxa-6-aza-2-boracine (24)

A suspension of 2,4-dichlorophenyl boronic acid (482.7 mg, 2.53 mmol) and *N*-methyldiethanolamine (307.4 mg, 2.54 mmol) in toluene (20 ml) was heated at reflux under a nitrogen atmosphere with azeotropic removal of water (Soxhlet; calcium hydride) for 5h. The hot solution was filtered and the solvent removed The resulting solid was stirred in cold (0°C) ether (1 x 5 ml) and then collected by filtration to give the title compound as a white solid(678 mg, 98% yield); m.p. 99-101°C; δ_H (250 MHz, $CDCl_3$) 7.72 (d, *J* 8.1 Hz, 1H, H_6), 7.31 (d, *J* 1.5 Hz, 1H, H_3), 6.77 (dd, *J* 8.1, 1.5 Hz, 1H, H_5), 4.14 (m, 4H, OCH_2), 3.21 (m, 4H, NCH_2), 2.56 (s, 3H, NMe); υ_{max} (nujol) 1576, 1364, 1255, 1174, 1099, 943 cm^{-1}; *m/z* (EI) 273 (M^+), 195, 128 (100%); High resolution acc. mass, found 274.0573; $C_{11}H_{14}BCl_2NO_2$ requires 274.0573

1,2-Dihydro-6-chloro-1-(N-B)(2-(N,N-dimethylamino)ethoxy)-2-(4-tolyl-sulphonyl)-2,3,1-benzodiazaborine (30)

A suspension of 1,2-dihydro-6-chloro-1-hydroxy-2-(4-tolylsulphonyl)-2,3,1-benzodiazaborine (337 mg, 1.01 mmol) and *N,N*-dimethylethanolamine (89 mg, 1.01 mmol, 101 µl) in toluene (20 ml) was heated at 40°C as the solvent was removed under reduced pressure on a rotary evaporator to yield a colourless oil. This was dissolved in THF (10 ml) and evaporated at 30°C as before to give the title compound as a white foam (406 mg, 100%); m.p. 93-95°C; δ_H (250 MHz, $CDCl_3$) 8.10-7.13 (m, 9H, Ar-H), 3.70-3.62 (m, 2H, OCH_2), 2.73-2.64 (m, 2H, NCH_2), 2.45 (s, 3H, NMe), 2.42 (s, 3H, NMe), 2.35 (s, 3H, ArMe); ν_{max} (nujol) 1317, 1155, 1093, 1027, 1014, 733 cm^{-1}; *m/z* (EI) 405 (M^+), 270, 124, 91, 58 (100%); High resolution acc. mass, found, 405.1085; $C_{18}H_{21}BClN_3O_3S$ requires 405.1085

Tricarbonyl chromium(0) η^6-(2-methoxyphenyl boronic acid) (51)

Tricarbonyl chromium (0) η^6-anisole (781.1 mg, 3.20 mmol) in dry THF (20 ml) was degassed once then cooled to -78°C and *n*-butyllithium (2.6 ml of 1.5M solution, 1.2 eq) was added dropwise over 2 minutes *via* syringe. The reaction mixture became orange-brown immediately and then deep red in colour. After 1.2h., a cold (-78°C) solution of tri*iso*propyl borate (1.601 ml, 1.4 eq) in THF (4 ml) was added *via* cannula and stirring continued at -78°C for 1.5h. after which the reaction mixture was allowed to reach room temperature over 1h. TLC indicated no starting material remained and the mixture was partitioned between 2M aqueous HCl (30 ml) and ether (40 ml). The layers were separated and the aqueous layer was extracted with ether (1 x 20 ml). The combined organic phases were washed with saturated brine (2 x 30 ml), dried ($MgSO_4$) and evaporated under reduced pressure to yield a yellow-orange solid which was recrystallised from ether-petrol to yield the title compound as a yellow solid (574 mg, 62%); m.p. 119-120°C; δ_H ($CDCl_3$, 250 MHz) 5.95 (br.m,1H, H_6), 5.66 (br.m, 1H, H_4), 5.27 (br.s, 2H, B-OH), 4.96 (br.m, 1H, H_5), 4.85 (br.m., 1H, H_3), 3.76 (s, 3H, OMe); ν_{max} (nujol) 3350, 2955, 2926, 2854, 1959, 1863, 1423, 1348 cm^{-1}; *m/z* (EI) 288 (M^+), 244, 232, 204, 188, 171, 160, 108, 94, 78, 65, 52 (100%); High resolution *m/z*, found 287.9897;

$C_{10}H_9BCrO_6$ requires 287.9897

Tricarbonyl chromium (0) η^6-[(N-B)-perhydro-2-(2-methoxyphenyl)-6-methyl-1,3-dioxa-6-aza-2-boracine] (52)

A solution of tricarbonyl chromium(0) η_6-(2-methoxyphenyl boronic acid) (57.6 mg, 0.20 mmol) and *N*-methyldiethanolamine (23.70 mg, 23 µl, 0.2 mmol) in sodium-dried toluene (5 ml) was evaporated under reduced pressure on a rotary evaporator at 40°C. Two further portions of toluene were added and subsequently evaporated. The residue was dissolved in DCM (2 ml) and triturated with petrol (2 ml) to yield the title compound as a yellow, crystalline solid (65 mg, 88%); m.p. 178°C (dec.); δ_H (250 MHz, $CDCl_3$) 6.17 (dd, *J* 6.36, 1.40 Hz, 1H, H_3), 5.64 (dt, *J* 6.41, 1.45 Hz, 1H, H_5), 5.07 (d, *J* 7.16 Hz, 1H, H_6), 4.87 (t, *J* 6.24 Hz, 1H, H_4), 4.12-3.98 (m, 4H, OCH_2), 3.76 (s, 3H, OMe), 3.25-3.14 (m, 4H, NCH_2), 2.99 (s, 3H, NMe); ν_{max} (nujol) 1946, 1840, 1529, 1411 cm^{-1}; *m/z* (EI) 371 (M^+), 287 (100%), 272, 257, 128

FORMATION OF HETEROARYL BORONIC ACIDS AND DERIVATIVES

2-Benzofurylboronic acid

A solution of *n*-butyllithium (7 ml of 2.5M solution, 17.5 mmol) in dry THF (40 ml) was stirred at -20°C under nitrogen and a solution of benzofuran (2.038 g, 17.25 mmol) in THF (6 ml) was added dropwise *via* syringe over 5 minutes. The cooling bath was removed and the solution allowed to stir at room temperature for 1h. After this time, the solution was cooled to -50°C and transferred *via* cannula to a cold (-80°C) solution of tri*iso*propyl borate (4.90 ml, 1.25 eq) in THF (10 ml) over 20 minutes, stirred at this temperature for 1h. then allowed to reach room temperature over 2h. The cloudy reaction mixture was partitioned between 2M HCl (50 ml) and ether (100 ml). The organic phase was washed with saturated, aqueous brine (2 x 40 ml), dried ($MgSO_4$) and evaporated to give a brown oil. On standing for 3

days, crystals formed which were collected by filtration (805 mg, 29%). The mother liquor was dissolved in ether (1 ml) and triturated with hexane (2 ml) to yield a second crop (574 mg, 21%); m.p. 106-107°C; δ_H (270 MHz, $CDCl_3$) 7.63 (d, *J* 7.56 Hz, 1H, H_7), 7.54 (d, *J* 7.62 Hz, 1H, H_4), 7.42 (s, 1H, H_3), 7.33 (t, *J* 7.51 Hz, 1H, H_5), 7.22 (t, *J* 7.48 Hz, 1H, H_6), 6.84 (br.s, 1H, B-OH); ν_{max} (nujol) 3309, 3241, 1608, 1590, 1567, 1327, 1256, 1135, 1053, 988, 756 cm^{-1}; *m/z* (EI) 162 (M^+), 144, 118 (100%), 89, 63; Found C, 59.09; H, 4.31%; $C_8H_7BO_3$ requires C, 59.33; H, 4.36%

(N-B)-Perhydro-2-(2-benzofuryl)-6-methyl-1,3-dioxa-6-aza-2-boracine (34)

2-Benzofurylboronic acid (573 mg, 3.54 mmol) and *N*-methyldiethanolamine (422 mg, 3.54 mmol, 406 µl) were suspended in toluene (35 ml) and heated to reflux during which time the reactants dissolved. Approximately 30 ml of solvent was removed and the hot reaction mixture was filtered and then allowed to cool. A yellow-brown crystalline solid separated from the solution and was collected by filtration, washed with cold (0°C) toluene (1 x 5 ml) and dried *in vacuo* to give the title compound (798 mg, 92%); m.p. 155-156°C; δ_H ($CDCl_3$, 270 MHz) 7.55(dd, *J* 7.26, 1.13 Hz, 1H, H_7), 7.48 (d, *J* 7.35 Hz, 1H, H_4), 7.19 (dt, *J* 7.31, 1.11 Hz, 1H, H_5), 7.15 (dt, *J* 7.31, 1.11 Hz, 1H, H_6), 6.96 (s, 1H, H_3), 4.18 (t, *J* 6.17 Hz, 4H, OCH_2), 3.26 -3.04 (m, 4H, NCH_2), 2.56 (s, 3H, NMe); ν_{max} (nujol) 1552, 1252, 1248, 1174, 1124, 1082, 959, 815 cm^{-1}; *m/z* (EI) 245 (M^+), 144 (100%), 128; Found C, 63.51; H, 6.59; N, 5.60%; $C_{13}H_{16}BNO_3$ requires C, 63.71; H, 6.30; N, 5.71%

2-Thianthrene boronic acid (27)

A suspension of thianthrene (2.622 g, 12.12 mmol) in a mixture of dry ether/THF (45 ml, 1:2) was stirred at 0°C under a nitrogen atmosphere and a solution of *n*-butyllithium (5.8 ml of a 2.4M solution, 1.15 eq) was added dropwise *via* syringe over a period of 15 minutes. After the addition, the dirty-orange reaction mixture was stirred at room temperature for 5h. then transferred *via* cannula into a cold (-78°C) solution of tri*iso*propyl borate (4.6 ml, 1.9 eq) in dry ether (10 ml) over 15 minutes. This was then allowed

to reach room temperature over a period of 2h. then poured into a separating funnel and partitioned between 2M HCl (60 ml) and ether (100 ml). The ether phase was washed with water (1 x 30 ml), saturated, aqueous brine (2 x 30 ml) and dried ($MgSO_4$). The solution was concentrated to approximately 30 ml and triturated with hexane (25 ml) to give a white solid which was collected by filtration and washed with petrol to yield the title compound (1.519 g, 48%); m.p. 156-157°C; δ_H (270 MHz, $CDCl_3$) 7.89 (d, *J* 7.98 Hz, 1H, H_3), 7.62-7.19 (m, 6H, Ar-H), 6.48 (s, 2H, B-OH); ν_{max} (nujol) 1572, 1414, 1335, 1061, 779, 752, 727 cm^{-1}; *m/z* (CI, NH_3) 234 [$(M+NH_4)^+$], 216 (MH^+), 184, 141, 124, 32 (100%)

(N-B)-Perhydro-2-(1-thianthryl)-6-methyl-1,3-dioxa-6-aza-2-boracine (28)

A suspension of 1-thianthryl boronic acid (354 mg, 1.36 mmol) and *N*-methyldiethanolamine (162 mg, 1.36 mol, 156 µl) in toluene (20 ml) was heated to reflux giving a pale-yellow solution. Heating was continued until approximately 15 ml of solvent had been distilled off when the reaction mixture was filtered. On cooling the filtrate, a pale yellow solid separated and was collected by filtration, washed with cold ether and dried *in vacuo* to give the title compound (300 mg, 65%); m.p. 279-281°C; δ_H ($CDCl_3$, 270 MHz) 7.71 (dd, *J* 7.31, 0.81 Hz, 1H, H_4), 7.45 (m, 2H, H_6, H_9), 7.17 (m, 4H, H_2, H_3, H_7, H_8), 4.22 (m, 4H, OCH_2), 3.48-3.19 (m, 4H, NCH_2), 2.52 (s, 3H, NMe); ν_{max} (nujol) 1250, 1109, 1094, 1074 cm^{-1}; *m/z* (EI) 343 (M^+), 300, 242, 128 (100%); Found C, 59.37; H, 5.27; N, 4.15%; $C_{17}H_{18}BNO_2S_2$ requires C, 59.48; H, 5.29; N, 4.08%

3-Quinolylboronic acid (32)

A solution of *n*-butyllithium (10 ml of 1.5 ml, 1 eq) in dry ether (30 ml) was stirred under nitrogen at -78°C while a solution of 3-bromoquinoline (3.121 g, 15 mmol, 2.03 ml) in ether (5 ml) was added dropwise over 20 minutes *via* cannula. An orange-brown suspension formed and was stirred at -78°C for a further 40 minutes. To this was added a cold (-78°C) solution of tri*iso*propyl borate (5 ml, 21.46 mmol, 1.43 eq) in THF (5 ml) in one portion *via* cannula. The suspension slowly dissolved and, after stirring for 2h., the

reaction mixture was allowed to reach room temperature over 2h. The crude mixture was poured onto 2M NaOH (30 ml) and separated. The ether phase was extracted with 2M NaOH (1 x 20 ml) and the combined aqueous phases were neutralised by the careful addition of 2M HCl and the suspension was extracted with ethyl acetate (3 x 30 ml). The combined organic phases were washed with brine (2 x 30 ml), dried ($MgSO_4$) and evaporated to yield a pale yellow solid which was recrystallised from ethyl acetate to yield the title compound (1.069 g, 46%); m.p. 180°C (dec.); δ_H (250 MHz, $CDCl_3$) 9.29 (s, 1H, H_2), 8.69, s, 1H, H_4), 8.08 (d, *J* 7.64 Hz, H_5), 7.87 (d, *J* 7.51 Hz, H_8), 7.72 (t, *J* 7.55 Hz, H_7), 7.53 (t, *J* 7.49 Hz, H_6); ν_{max} (nujol) 3257, 1640, 1589, 1563, 1420, 1294, 1246, 1206 cm^{-1}; *m/z* (EI) 465 (M^+ for trimer), 155, 129 (100%), 102

(N-B)-Perhydro-2-(3-quinolyl)-6-methyl-1,3-dioxa-6-aza-2-boracine (33)

3-Quinolylboronic acid (178.9 mg, 385 µl) and *N*-methyldiethanolamine (137.5 mg, 386 µl, 132 µl) were suspended in toluene (25 ml) and heated to reflux in a distillation apparatus. The reactants dissolved and heating was continued until approximately 5 ml of solvent remained. The hot reaction mixture was filtered and allowed to cool. A brown oil separated from the solution which was isolated by evaporation. The residue was dissolved in DCM (~1 ml) and then triturated with petrol to give the title compound as a white, crystalline solid (187 mg, 64%); m.p. 176-178°C; δ_H (500 MHz, $CDCl_3$) 9.12 (d, *J* 1.74 Hz, 1H, H_2), 8.42 (s, 1H, H_4), 8.07 (dd, *J* 8.43, 1.21 Hz, 1H, H_8), 7.81 (dd, *J* 8.17, 1.29 Hz, 1H, H_5), 7.65 (ddd, *J* 8.43, 6.86, 1.47 Hz, 1H, H_7), 7.48 (ddd, *J* 8.11, 6.90, 1.16 Hz, 1H, H_6), 4.24 (m, 4H, OCH_2), 3.27 (m, 2H, NCH_2), 3.07 (m, OCH_2), 2.36 (s, 3H, NMe); υ_{max} (nujol) 1493, 1272, 1173, 1128, 1095, 1082, 863, 755 cm^{-1}; *m/z* (CI, NH_3) 257 (MH^+, 100%), 128; Found C, 65.52; H, 6.93; N, 10.94%; $C_{14}H_{19}BN_2O_2$ requires C, 65.63; H, 6.69; N, 10.94%

3-Bromo-2-thienyl boronic acid

A solution of *n*-butyllithium (10 ml of 1.5M) in dry ether (15 ml) was cooled to -5°C and neat di*iso*propylamine was added *via* syringe over 5 min. After a further 5 min., the temperature was dropped to -40°C and neat 3-

bromothiophene (4.90 g, 30 mmol, 2.90 ml) was added *via* syringe over 5 min. whilst maintaining the internal temperature below -25°C. The pale yellow solution was allowed to warm to 0°C then cooled to -78°C and transferred *via* cannula to a cold (-78°C) solution of tri*iso*propyl borate (8.15 g, 434 mmol 2.89 eq) in ether (20 ml) over 35 min. The reaction mixture was allowed to warm to room temperature over a period of 3h. then poured onto 2M HCl and the layers separated. The aqueous phase was extracted with ether (2 x 30 ml) and the combined organic phases were dried ($MgSO_4$) and evaporated under reduced pressure to yield a yellow oil which crystallised on standing. The crystals were washed with petrol (2 x 15 ml) to yield the title compound as white crystals (2.281 g, 75%); m.p. 169-170°C; δ_H (270 MHz, $CDCl_3$) 7.52 (d, *J* 6.41 Hz, 1H, H_5), 7.09 (d, *J* 6.43 Hz, 1H, H_4), 7.01 (s, 2H, B-OH); ν_{max} (nujol) 3216, 1415, 733, 605 cm^{-1}; *m/z* 566 (M^+ of trimer), 190, 164 (100%), 109, 83

(N-B)-Perhydro-2-(3-bromo-2-thienyl)-6-methyl-1,3-dioxa-6-aza-2-boracine

A suspension of 3-bromo-2-thienyl boronic acid (438.6 mg, 2.12 mmol) and *N*-methyldiethanolamine (252.6 mg, 2.12 mmol, 243 µl) in toluene (35 ml) was heated in a distillation apparatus. The starting materials dissolved and heating was continued until approximately 20 ml of solvent had been collected at which point the hot solution was filtered. On cooling the reaction mixture, a solid was deposited which was collected by filtration and washed with cold pentane to give the title compound as white crystals (474 mg, 77%). A second crop of crystals (52 mg, 9%) was obtained on cooling the filtrate and washings; δ_H ($CDCl_3$, 270 MHz) 7.31 (d, *J* 6.51 Hz, 1H, H_5), 7.03 (d, *J* 6.48 Hz, 1H, H_4), 4.18-4.12 (m, 4H, OCH_2), 3.22 (m, 4H, NCH_2), 2.58 (s, 3H, NMe); ν_{max} (nujol) 1161, 1134, 1080 cm^{-1}; *m/z* 289, 287 (M^+), 167 (100%), 128; Found C, 37.05; H, 4.40; N,4.82%; $C_9H_{13}BBrNO_2S$ requires C, 37.28; H, 4.52; N, 4.83%

(N-B)-Perhydro-2-[5-(2,4-di-tert-butyloxy)pyrimidyl]-6-methyl-1,3-dioxa-6-aza-2-boracine

5-(2,4-Di-*tert*-butyloxy)pyrimidyl boronic acid (709.2 mg, 2.65 mmol) and *N*-methyldiethanolamine (315.1 mg, 2.65 mmol, 303 µl) were suspended in toluene (35 ml) in a distillation apparatus and heated to dissolve the reagents. Heating was continued until approximately 10 ml of solvent remained in the reaction flask. The solution was filtered while hot and allowed to cool to room temperature during which time a solid was deposited. This was collected by filtration, washed with cold ether and dried *in vacuo* to give the title compound as a crystalline, white solid (776 mg, 84%); m.p. 157-159°C; δ_H (250 MHz, $CDCl_3$) 8.46 (s, 1H, H_6), 4.20-3.99 (m, 4H, OCH_2), 3.18-3.13 (m, 4H, NCH_2), 2.64 (s, 3H, NMe), 1.66 (s, 9H, O^{t}Bu), 1.62 (s, 9H, O^{t}Bu); υ_{max} (nujol) 2955, 2925, 1576, 1165 cm^{-1}; *m/z* (CI, NH_3) 352 (MH^+), 296, 240 (100%), 196; Found C, 58.09; H, 8.83; N, 12.05 %; $C_{17}H_{30}BN_3O_4$ requires C, 58.13; H, 8.61; N, 11.96 %

FLUORINATION OF ARYLBORONIC ACIDS IN ACETONITRILE

4-Methoxyphenyl boronic acid

A suspension of caesium fluoroxysulphate (130 mg, 0.52 mmol) in dry MeCN (2 ml) was stirred at room temperature for 5 minutes. 4-methoxyphenyl boronic acid (70 mg, 0.53 mmol) suspended in MeCN (2 ml) was added via pipette resulting in a yellow reaction mixture immediately. After 2.5h., DCM (10 ml) was added and the insoluble products were removed by filtration. The filtrate was washed with water (1 x 5 ml), dried (Na_2SO_4) and evaporated to yield an orange oil. Analysis of the reaction mixture by GC and ^{19}F NMR showed the presence of 4-fluoroanisole (30%) δ_F (84 MHz, $CDCl_3$) -124

4-Biphenyl boronic acid

A suspension of caesium fluoroxysulphate (146 mg, 0.59 mmol) and 4-biphenyl boronic acid (79 mg, 0.40 mmol) in dry MeCN (2 ml) was stirred at room temperature under a nitrogen atmosphere. After 20h., the reaction mixture was diluted with DCM (20 ml) and the insoluble products were removed by filtration. The filtrate was washed with water (1 x 5 ml), dried ($MgSO_4$) and evaporated. Chromatography of the residue (SiO_2; petrol) gave **4-fluorobiphenyl** a white solid (20.1 mg, 29%); m.p. 73-74°C (lit.,[89] 74-76°C); δ_F (84 MHz, $CDCl_3$) -116

1-Naphthalene boronic acid

A suspension of caesium fluoroxysulphate (169 mg, 0.68 mmol) in dry MeCN (1 ml) was stirred at room temperature for 5 minutes. 1-Naphthalene boronic acid (75.3 mg, 0.44 mmol) in MeCN (2.5 ml) was added via syringe in one portion and, after stirring overnight, the reaction mixture was poured onto water (10 ml). After extraction with ether (2 x 10 ml), the combined organic phases were dried (Na_2SO_4) and evaporated to yield an oil. This was subjected to flash chromatography (SiO_2; petrol) to give **1-fluoronaphthalene** as a colourless oil identical with an authentic sample (11 mg, 17%); δ_F (84 MHz, $CDCl_3$) -123

FLUORINATION OF (*N-B*)-PERHYDRO-2-(ARYL)-6-METHYL-1,3-DIOXA-6-AZA-2-BORACINES IN ACETONITRILE

General Procedure

A suspension of caesium fluoroxysulphate in dry acetonitrile was stirred at room temperature for 10 minutes and the ester and 1,3-dinitrobenzene (10 mol%) was added. Stirring was continued under a nitrogen atmosphere and product formation was followed by GC. Further portions of caesium fluoroxysulphate (0.5 eq.) were added after 6, 20, 28 and 38h. and after 48h.

the reaction mixture was analysed by either method A or B.

Method A (non-volatile products): The reaction mixture was diluted with DCM (20 ml) and filtered to remove inorganic products. The filtrate was washed with water (1 x 5 ml), dried ($MgSO_4$) and evaporated. Pure product was obtained by flash chromatography and compared to an authentic sample.

Method B (volatile products): The product was not isolated and so the reaction mixture was diluted with DCM (10 ml) and filtered. The resulting solution was analysed by GC against authentic samples and, subsequently, GC-MS. The solution was then evaporated in order to obtain the ^{19}F NMR spectrum.

Fluorination of (N-B)-perhydro-2-(4-biphenyl)-6-methyl-1,3-dioxa-6-aza-2-boracine

A suspension of caesium fluoroxysulphate (127.0 mg, 0.51 mmol) in acetonitrile (3 ml) was treated with (*N-B*)-perhydro-2-(4-biphenyl)-6-methyl-1,3-dioxa-6-aza-2-boracine (115.8 mg, 0.41 mmol) and 1,3-dinitrobenzene as described then worked up as for method A to give **4-fluorobiphenyl** (28.8 mg, 41%); m.p. 75-76°C (lit.,[89] 74-76°C); δ_F (84 MHz, $CDCl_3$) -116

Fluorination of (N-B)-perhydro-2-(1-naphthyl)-6-methyl-1,3-dioxa-6-aza-2-boracine

A suspension of caesium fluoroxysulphate (300 mg, 1.21 mmol) in acetonitrile (6 ml) was treated with (*N-B*)-perhydro-2-(1-naphthyl)-6-methyl-1,3-dioxa-6-aza-2-boracine (134 mg, 0.77 mmol) and 1,3-dinitrobenzene as above then worked up as for method A to show the presence of **1-fluoronapthalene** (35%); δ_F (84 MHz, $CDCl_3$) -123

Fluorination of (N-B)-perhydro-2-(2-naphthyl)-6-methyl-1,3-dioxa-6-aza-2-boracine

A suspension of caesium fluoroxysulphate (220 mg, 0.89 mmol) in acetonitrile (4 ml) was treated with (*N-B*)-perhydro-2-(2-naphthyl)-6-methyl-1,3-dioxa-6-aza-2-boracine (120 mg, 0.70 mmol) and 1,3-dinitrobenzene as above then worked up as for method A to show the presence of **2-fluoronapthalene** (30%); δ_F (84 MHz, $CDCl_3$) -115

Fluorination of (N-B)-perhydro-2-(4-methoxyphenyl)-6-methyl-1,3-dioxa-6-aza-2-boracine

A suspension of caesium fluoroxysulphate (16.1 mg, 64.5 μmol) in acetonitrile (0.8 ml) was treated with (*N-B*)-perhydro-2-(4-methoxyphenyl)-6-methyl-1,3-dioxa-6-aza-2-boracine (10.6 mg, 50 μmol) and 1,3-dinitrobenzene as above then worked up as for method B to show the presence of **4-fluoroanisole** (52%); δ_F (84 MHz, $CDCl_3$) -124; *m/z* (EI) 126 (M^+), 111, 95, 83 (100%), 75, 63, 57

Fluorination of (N-B)-perhydro-2-(3-nitrophenyl)-6-methyl-1,3-dioxa-6-aza-2-boracine

A suspension of caesium fluoroxysulphate (25.7 mg, 104 μmol) in acetonitrile (1 ml) was treated with (*N-B*)-perhydro-2-(3-nitrophenyl)-6-methyl-1,3-dioxa-6-aza-2-boracine (18.7 mg, 80 μmol), sodium hydrogen carbonate (5 mg, 75 μmol) and 1,3-dinitrobenzene as above then worked up as for method B to show the presence of 3-fluoro-1-nitrobenzene (15%); δ_F (84 MHz, $CDCl_3$) -110; *m/z* (EI) 141 (M^+), 111, 95 (100%), 83, 75

Fluorination of (N-B)-perhydro-2-(4-bromophenyl)-6-methyl-1,3-dioxa-6-aza-2-boracine

A suspension of caesium fluoroxysulphate (38 mg, 153 μmol) in acetonitrile (2 ml) was treated with (*N-B*)-perhydro-2-(4-bromophenyl)-6-methyl-1,3-

dioxa-6-aza-2-boracine (37 mg, 130 μmol) and 1,3-dinitrobenzene as above then worked up as for method B to show the presence of **1-bromo-4-fluorobenzene** (15%); δ_F (84 MHz, $CDCl_3$) -115; *m/z* (EI) 176 (M^+), 174, 95(100%), 75

Fluorination of (N-B)-perhydro-2-(2,4-dichlorophenyl)-6-methyl-1,3-dioxa-6-aza-2-boracine

A suspension of caesium fluoroxysulphate (17 mg, 68.5 μmol) in acetonitrile (0.8 ml) was treated with (*N-B*)-perhydro-2-(2,4-dichlorophenyl)-6-methyl-1,3-dioxa-6-aza-2-boracine (13.7 mg, 50 μmol) and 1,3-dinitrobenzene as above then worked up as for method B to show the presence of **1,3-dichloro-4-fluorobenzene** (40%); δ_F (84 MHz, $CDCl_3$) -119; *m/z* (EI) 166, 164 (M^+), 148, 146 (100%), 113, 111, 75

Fluorination of (N-B)-perhydro-2-(3-chloro-4-fluorophenyl)-6-methyl-1,3-dioxa-6-aza-2-boracine

A suspension of caesium fluoroxysulphate (22.3 mg, 90 μmol) in acetonitrile (1 ml) was treated with (*N-B*)-perhydro-2-(3-chloro-4-fluorophenyl)-6-methyl-1,3-dioxa-6-aza-2-boracine (18.2 mg, 70 μmol) and 1,3-dinitrobenzene as above then worked up as for method B to show the presence of **1-chloro-2,5-difluorobenzene** (30%); δ_F (84 MHz, $CDCl_3$) -116 (F_5), -122 (F_2); *m/z* (EI) 150, 148 (M^+), 129 (100%)

INVESTIGATION OF SOLVENT EFFECTS ON FLUORINATION OF 4-BIPHENYL BORONIC ACID AND DERIVATIVES

Acetonitrile

A suspension of caesium fluoroxysulphate (146 mg, 0.6 mmol) in acetonitrile (2 ml) was stirred at room temperature for 5 minutes then

powdered 4-biphenyl boronic acid (79 mg, 0.4 mmol) was added in one portion. The reaction mixture was allowed to react overnight then diluted with DCM (10 ml), filtered to remove inorganic products an evaporated. Flash chromatography (SiO_2; petrol) of the residue gave 4-fluorobiphenyl as a white solid (20.0 mg, 29%); m.p. 73-75°C (lit.,[89] 74-76°C); δ_F ($CDCl_3$, 84 MHz) -116

Methanol

1. Boronic acid

4-Biphenyl boronic acid (55 mg, 0.28 mmol) was dissolved in dry methanol (2 ml) under a nitrogen atmosphere and cooled to 0°C. Solid caesium fluoroxysulphate (116 mg, 0.47 mmol) was added in one portion and the cooling bath was removed after 10 minutes. Further portions of caesium fluoroxysulphate (~80 mg, 0.32 mmol) were added after 15, 30 and 60 minutes. After 5h. the reaction mixture was diluted with DCM (5 ml), filtered and evaporated under reduced pressure. The residue was subjected to flash chromatography (SiO_2; petrol) to give 4-fluorobiphenyl as a white solid (26.9 mg, 56%); m.p. 72-74°C (lit.,[89] 74-76°C); δ_F (84 MHz, $CDCl_3$) -116

2. 1,3-Dioxa-2-borolane

The borolane (51.2 mg, 0.23 mmol) was treated with caesium fluoroxysulphate (151 mg, 0.60 mmol) as for the acid. After 8h., the reaction mixture was worked up as before to give 4-fluorobiphenyl (15.7 mg, 40%) m.p.75°C (lit.,[89] 74-76°C); δ_F ($CDCl_3$, 84 MHz) -116

3. 4,4,5,5-Tetramethyl-1,3-dioxa-2-borolane

The borolane (80.5 mg, 0.29 mmol) was treated with caesium fluoroxysulphate (103 mg, 0.41 mmol) as for the acid. After 8h., the reaction mixture was worked up as before to give 4-fluorobiphenyl (2% vs. internal reference); δ_F ($CDCl_3$, 84 MHz) -116

4. (N-B)-Perhydro-2-(4-biphenyl)-6-methyl-1,3-dioxa-6-aza-2-boracine

The boracine (73.0 mg, 0.26 mmol) was treated with caesium fluoroxysulphate (105 mg, 0.42 mmol) as for the acid. After 8h., the reaction mixture was worked up as before to give 4-fluorobiphenyl (5% vs. internal reference); δ_F ($CDCl_3$, 84 MHz) -116

Aqueous methanol

4-Biphenyl boronic acid (87.4 mg, 0.44 mmol) was dissolved in dry methanol (10 ml) under a nitrogen atmosphere and a freshly prepared solution of caesium fluoroxysulphate (505 mg, 2.01 mmol, 4.6 eq) in distilled water (5 ml) was added *via* pipette. An exothermic reaction occurred and, after 15 minutes, the homogeneous reaction mixture was diluted with DCM (40 ml) and the layers separated. The aqueous layer was extracted with DCM (2 x 15 ml) and the combined organic phases were dried (Na_2SO_4), evaporated under reduced pressure and purified by chromatography (SiO_2; petrol) to give 4-fluorobiphenyl as a white solid (19.4 mg, 26%); m.p. 73-74°C (lit.,[89] 74-76°C); δ_F ($CDCl_3$, 84 MHz) -116

Methanol-dichloromethane

A solution of 2-(4-biphenyl)-1,3-dioxa-2-borolane (51.2 mg, 228 μmol) in DCM-MeOH (3 ml, 10:1) was stirred at room temperature and solid caesium fluoroxysulphate (151 mg, 0.61 mmol, 2.67 eq) was added. After 6h. stirring, a further portion of 146 mg was added and the reaction mixture was diluted with DCM (20 ml) after a total of 20h. The suspension was filtered to remove inorganic solids, evaporated under reduced pressure and purified by flash chromatography (SiO_2; petrol) to give 4-fluorobiphenyl as a white solid (23.2 mg, 57%); m.p. 73-74°C (lit.,[89] 74-76°C); δ_F ($CDCl_3$, 84 MHz) -116

Tert-butanol-dichloromethane

2-(4-Biphenyl)-1,3-dioxa-2-borolane (38.7 mg, 173 μmol) in DCM-^{t}BuOH (3 ml, 2:1) was stirred at room temperature and caesium fluoroxysulphate (150 mg, 605 μmol) was added. After 1h., no product formation was noted and the reaction mixture was heated under reflux. A further portion of caesium fluoroxysulphate (146 mg, 60 μmol) was added after 6h. and the reaction mixture was cooled after 20h. and diluted with DCM (15 ml). The suspension was filtered through celite, washed with water (1 x 5 ml) and evaporated under reduced pressure.to yield an oil. This was purified by chromatography (SiO_2; petrol-ether, 6:1) to give initially **3-fluoro-4-hydroxybiphenyl**[90] (8.5 mg, 26%); δ_F (84 MHz, $CDCl_3$) -140; *m/z* (EI) 188 (M^+), 169, 159, 139, 133

Further elution gave **4-hydroxybiphenyl** (6.2 mg, 21 %); m.p. 164-165°C (lit.[89] 165-167°C)

INVESTIGATION OF ADDITIVES ON FLUORINATION OF 4-BIPHENYL BORONIC ACID AND DERIVATIVES

Pyridine

1. Boronic acid

A suspension of 4-biphenyl boronic acid (94.3 mg, 0.55 mmol) in MeCN (3 ml) was stirred at room temperature and neat pyridine (43 mg, 44 μl, 1 eq) was added. There was no observable effect and on addition of caesium fluoroxysulphate (134 mg, 0.54 mmol) the reaction mixture became yellow in colour and an exothermic reaction was noted. After a further 3h. a further portion of caesium fluoroxysulphate (140 mg, 0.58 mmol) was added. After a total of 6h. the reaction mixture was diluted with DCM (10 ml) and filtered giving a yellow solution. This was evaporated and the residue subjected to flash chromatography to give **4-fluorobiphenyl** as a white solid (14 mg, 15%); m.p. 73-74°C (lit.,[89] 74-76°C); δ_F ($CDCl_3$, 84 MHz) -116

2. 1,3-Dioxa-2-borolane

A suspension of 2-(4-biphenyl)-1,3-dioxa-2-borolane (113.1 mg, 0.50 mmol) in MeCN (2 ml) was stirred at room temperature and neat pyridine (45 mg, 0.48 mmol) was added. The suspension dissolved giving a homogeneous solution. Caesium fluoroxysulphate (160 mg, 0.665 mmol) was added to the solution in one portion and the solution became a yellow suspension. After 30h., a further portion of caesium fluoroxysulphate (163 mg, 0.66 mmol) was added and stirring continued for a further 30h. after which DCM (10 ml) was added and the reaction mixture was filtered, washed with water (1 x 5 ml), dried and evaporated. ^{19}F NMR analysis of the crude product indicated the presence of **4-fluorobiphenyl** (5% vs. an internal standard); δ_F (84 MHz, $CDCl_3$) -116

3. 1,3-Dioxa-4,4,5,5-tetramethyl-2-borolane

A suspension of 1,3-dioxa-4,4,5,5-tetramethyl-2-borolane (161 mg, 0.575 mmol) in acetonitrile (2 ml) was stirred at room temperature and pyridine (52 mg, 0.55 mmol) was added. Over a period of 5 minutes, the suspension dissolved giving a homogeneous solution and solid caesium fluoroxysulphate (206 mg, 0.83 mmol) was added in one portion. After 48h., TLC indicated a trace of product and a further portion of caesium fluoroxysulphate was added. After 66h., the reaction mixture was diluted with DCM (15 ml), filtered to remove insoluble material and the resulting solution evaporated. ^{19}F NMR analysis of the resulting solid showed the presence of **4-fluorobiphenyl** (2% vs. internal standard); δ_F (84 MHz, $CDCl_3$) -116

Boron trifluoride

A solution of 4-biphenyl boronic acid (55 mg, 0.277 mmol) in dry methanol (1 ml) was stirred at 0°C and boron trifluoride-etherate (2 drops) was added *via* syringe. After 1 minute, solid caesium fluoroxysulphate (155 mg, 0.625) was added in two portions and, after 10 minutes, the cooling bath was removed. The reaction mixture was diluted with DCM (20 ml) after 4h. and filtered then evaporated. The resulting oil was purified by flash

chromatography (SiO_2; petrol) to yield 4-fluorobiphenyl as a white solid (17.3 mg, 38%); m.p. 72-73°C (lit.,[89] 74-76°C); δ_F (84 MHz, $CDCl_3$) -116

A similar result was obtained if boron trifluoride-methanol complex was used instead. A lower yield (~25%) was found if the reaction was run at -10°C with either source.

Trimethyl borate

A solution of 4-biphenyl boronic acid (48.5 mg, 196 μmol) in methanol (2 ml) was stirred at 0°C and neat trimethyl borate (~50 μl) was added *via* syringe followed by solid caesium fluoroxysulphate (125.1 mg, 500 μmol). After 5 minutes the cooling bath was removed and the reaction mixture was stirred at room temperature. After 2h., a further portion of caesium fluoroxysulphate (119 mg, 480 μmol) was added and the reaction mixture was diluted with DCM (15 ml) after 5h. and filtered. The resulting solution was washed with water (5 ml), dried ($MgSO_4$) and evaporated under reduced pressure to yield an orange oil. This was purified by flash chromatography (SiO_2; petrol) to give 4-fluorobiphenyl (17.2 mg, 51%); m.p. 74-75°C (lit.,[89] 74-76°C); δ_F (84 MHz, $CDCl_3$) -116

FLUORINATION OF ARYLBORONIC ACIDS IN METHANOL

General procedure

A solution of the boronic acid in dry methanol was stirred at 0°C and caesium fluoroxysulphate was added in one portion. The reaction mixture was monitored by TLC for disappearance of the dimethyl ester and further portions of CFS (0.5 eq) were added at 2-4h. intervals. If not complete within 10h., the reaction was worked up after 24h. Workup was carried out by either method A or B according to the volatility of the product.

Method A (non-volatile products): The reaction mixture was diluted with

DCM (20 ml) and filtered to remove inorganic products. The filtrate was washed with water (1 x 5 ml), dried ($MgSO_4$) and evaporated. Pure product was obtained by flash chromatography.

Method B (volatile products): The product was not isolated and so the reaction mixture was diluted with DCM (10 ml) and filtered. The resulting solution was analysed by GC against authentic samples. The solution was then evaporated in order to obtain the ^{19}F NMR spectrum.

3-Methoxyphenylboronic acid

The boronic acid (98.1 mg, 0.645 mmol) in methanol (3 ml) was treated with caesium fluoroxysulphate (191 mg, 0.770 mmol) as described. After 24h. at -30°C, the reaction mixture was worked up as for method B to show the presence of 3-fluoroanisole (10% vs. internal standard); δ_F (84 MHz, $CDCl_3$) -112. The presence of 2-fluoro- and 4-fluoroanisoles (20% vs. internal standard) was also observed.

A similar amount of 3-fluoroanisole was also formed if reaction was carried out at 0°C although the amount of byproducts increased to 40%.

4-Methoxyphenylboronic acid

The boronic acid (83.7 mg, 0.55 mmol) in methanol (1 ml) was treated with caesium fluoroxysulphate (159 mg, 0.64 mmol) as described. After 2h. at 0°C, the reagents were worked up as for method B to show the presence of 4-fluoroanisole (35% vs. internal standard) δ_F ($CDCl_3$, 84 MHz) -125. A larger amount of a 2-fluoroanisole isomer (45%, δ_F -137) was also observed.

2-Biphenylboronic acid

The boronic acid (165.9 mg, 0.83 mmol) in methanol (3 ml) was treated with caesium fluoroxysulphate (242 mg, 0.98 mmol) as described. After 10h. the

reaction mixture was worked up according to method A to give **2-fluoro-biphenyl** (40 mg, 28%); m.p. 73-74°C (lit.,[89] 74°C); δ_F ($CDCl_3$, 84 MHz) -118

4-Bromophenylboronic acid

The boronic acid (230.5 mg, 1.15 mmol) in methanol (3 ml) was treated with caesium fluoroxysulphate (340.1 mg, 1.37 mmol) as described. After 24h., the reaction mixture was worked up according to method B to show the presence of **1-bromo-4-fluorobenzene** (20% vs. internal standard) δ_F ($CDCl_3$, 84 MHz) -115

2,4-Dichlorophenylboronic acid

The boronic acid (111 mg, 0.58 mmol) in methanol (4 ml) was treated with caesium fluoroxysulphate (297 mg, 1.20 mmol) as described. After 24h. at -10°C, the reaction mixture was worked up according to method B to show the presence of **1,3-dichloro-4-fluorobenzene** (28% vs. internal standard) δ_F ($CDCl_3$, 84 MHz) -119

3-Nitrophenylboronic acid

The boronic acid (77.3 mg, 0.46 mmol) in methanol (3 ml) was treated with caesium fluoroxysulphate (269 mg, 1.08 mmol) as described. After 24h., the reaction mixture was worked up according to method B to show the presence of **1-fluoro-3-nitrobenzene** (14% vs. internal standard) δ_F ($CDCl_3$, 84 MHz) -110

SYNTHESIS OF 2-FLUORO-3-*O*-METHYLESTRONE

3-Methoxy-17-ethylenedioxyestrane (46)

A mixture of 3-*O*-methylestrone (2.700 g, 9.51 mmol), ethylene glycol (2 ml, xs) and *p*-toluene sulphonic acid hydrate (~100 mg) in toluene (50 ml) was heated at reflux for 20h. under a nitrogen atmosphere. Liberated water was removed using a Soxhlet apparatus with calcium hydride in the thimble. On cooling, the reaction mixture was poured into saturated, aqueous sodium bicarbonate solution (20 ml), diluted with water (20 ml) and extracted with ether (3 x 30 ml). The combined organic phases were washed with aqueous saturated brine (2 x 30 ml), dried ($MgSO_4$) and evaporated under reduced pressure. Flash chromatography of the residue (SiO_2; 10% ether in petrol) gave the title compound as a crystalline, white solid (3,027 g, 97%); m.p. 99-101°C; δ_H (500 MHz, $CDCl_3$) 7.21 (d, *J* 8.56 Hz, 1H, H_4), 6.71 (dd, *J* 8.53, 2.77 Hz, 1H, H_3), 6.63 (d, *J* 2.74 Hz, 1H, H_1), 3.98-3.89 (m, 4H, ketal OCH_2), 3.77 (s, 3H, OMe), 2.91-2.85 (m, 2H, $H_{6\alpha}$, $H_{6\beta}$), 2.39-1.31 (m, 13H, skeletal protons), 0.89 (s, 3H, C_{18}-Me); ν_{max} (nujol) 1280, 1255, 1180, 1159, 1105, 1047 cm^{-1}; *m / z* (EI) 328 (M^+), 283, 266, 99(100%); (CI, NH_3) 329 (MH^+, 100%); High resolution acc. mass, found 328.2038; $C_{21}H_{28}O_3$ requires 328.2038

Tricarbonyl chromium (0) -η^6-(3-methoxy-17-ethylenedioxyestrane) (47), (48)

A solution of 3-methoxy-17-ethylenedioxy-estrane (2.100 g, 6.37 mmol) and chromium hexacarbonyl (1.936 g, 8.8 mmol, 1.38 eq) in a mixture of di-*n*-butyl ether/THF (9:1, 60 ml) was degassed 12 times and then heated at 130-140°C under a purified nitrogen atmosphere using a modified Strohmeier apparatus. After 28h., the reaction mixture was allowed to cool to room temperature then filtered through a 2 cm silica pad which was flushed with ether to collect all of the complex. The solution was evaporated and the residue subjected to flash chromatography (SiO_2, 10% ether in petrol) to yield initially β-(tricarbonyl chromium (0))-η6-(3-methoxy-17-ethylenedioxy-estrane) as a light yellow solid (0.932 g, 33%); m.p. 162-164°C; δ_H (250 MHz,

$CDCl_3$) 5.78 (d, *J* 7.13 Hz, 1H, H_1), 5.11 (dd, *J* 7.04, 2.44 Hz, 1H, H_2), 4.97 (d, *J* 2.48 Hz, 1H, H_4), 3.95-3.84 (m, 4H, ketal OCH_2), 3.66 (s, 3H, OMe), 2.86-2.78 (m, 2H, $H_{6\alpha}$, $H_{6\beta}$), 2.14-1.25 (m, 13H, skeletal protons), 0.85 (s, 3H, C_{18}-Me); ν_{max} (nujol) 1955, 1882, 1866, 1836, 1547, 1280, 1257 cm^{-1}; *m/z* (CI, NH_3) 465 (MH^+, 100%), 329, 267, 99; High resolution *m/z*, found 465.1369; $C_{24}H_{29}CrO_6$ requires 465.1369; Found C, 62.32; H, 5.92%; $C_{24}H_{28}CrO_6$ requires C, 62.06; H, 6.08%

Further elution gave α-(tricarbonyl chromium (0))-η6-(3-methoxy-17-ethylenedioxyestrane) as a crystalline, bright yellow solid (1.475 g, 50%); m.p. 164-165°C; δ_H (250 MHz, $CDCl_3$) 5.65 (d, *J* 7.08 Hz, 1H, H_1), 4.99 (d, *J* 2.38 Hz, 1H, H_4), 4.92 (dd, *J* 7.04, 2.44 Hz, 1H, H_2), 3.96-3.86 (m, 4H, ketal OCH_2), 3.71 (s, 3H, OMe), 3.02 (m, 1H, $H_{6\beta}$), 2.71-2.64 (dd, *J* 16.37, 7.07 Hz, 1H, $H_{6\alpha}$), 2.08-1.18 (m, 13H, skeletal protons), 0.93 (s, 3H, C_{18}-Me); ν_{max} (nujol) 1956, 1881, 1861, 1839, 1546, 1281, 1251 cm^{-1}; *m/z* (CI, NH_3) 465 (MH^+, 100%), 397, 329, 267, 99; High resolution *m/z*, found 465.1369; $C_{24}H_{29}CrO_6$ requires 465.1369; Found C, 62.04; H, 6.10%; $C_{24}H_{28}CrO_6$ requires C, 62.06; H, 6.08%

2-Trimethylsilyl-3-methoxy-17-ethylenedioxyestrane (49)

A solution of α-(tricarbonyl chromium (0))-η6-(3-methoxy-17-ethylenedioxy-estrane) (140.5 mg, 0.30 mmol) in dry THF (5 ml) was degassed twice under a nitrogen atmosphere and cooled to -78°C. Butyllithium (0.35 ml of 1.5M solution, 0.525 mmol, 1.6 eq) was added dropwise *via* syringe over 2 minutes and the reaction mixture was stirred at -78°C for 1.5h. Neat trimethylsilyl chloride (0.2 ml, xs) was added to the solution and stirring continued for 4h. before allowing it to warm to room temperature. Aqueous 2M ammonium chloride (10 ml) was added and the layers separated. The aqueous layer was extracted with ether (2 x 20 ml) and the combined ether phases were washed with saturated, aqueous brine (1 x 10 ml), dried ($MgSO_4$) and evaporated under reduced pressure to yield a yellow oil. This was dissolved in DCM (5 ml) and exposed to air and sunlight for 24h. then filtered and evaporated. The residue was subjected to flash chromatography (SiO_2; petrol-ether, 4:1) to give the title compound as a crystalline, white solid (105.7 mg, 88%); m.p. 179-181°C; δ_H ($CDCl_3$, 270 MHz) 7.31 (s, 1H, H_1), 6.55 (s, 1H, H_4), 3.97-3.87 (m, 4H, ketal OCH_2), 3.77 (s, 3H, OMe), 2.89-2.82 (m,

1H, $H_{6\alpha}$), 2.41-2.19 (m, 1H, $H_{6\beta}$), 2.07-1.25 (m, 13H, skeletal protons), 0.87 (s, 3H, C_{18}-Me), 0.24 (s, 9H, Si-Me); ν_{max} (nujol) 1598, 1255, 1244, 1232, 1046, 950 cm^{-1}; *m/z* (CI, NH_3) 401 (MH^+, 100%), 357, 339, 329; High resolution acc. mass, found 400.2434; $C_{24}H_{26}O_3Si$ requires 400.2433

α-(Tricarbonyl chromium (0))-η⁶-(2-dihydroxyboryl-3-methoxy-17-ethylenedioxyestrane) (53)

α-(Tricarbonyl chromium (0))-η⁶-(3-methoxy-17-ethylenedioxyestrane) (544.4 mg, 1.17 mmol) in dry THF (20 ml) was degassed twice and cooled to -78°C under a nitrogen atmosphere. A solution of *n*-butyllithium (1.09 ml of 1.4M, 1.521 mmol, 1.3 eq) was added dropwise *via* syringe over a period of 12 minutes. After 2h., a cold (-78°C) solution of tri*iso*propyl borate (500 µl, 2.101 mmol, 1.8 eq) in THF (5 ml) was transferred to the orange-brown reaction mixture *via* cannula over a period of 2 minutes. The solution was stirred at -78°C for 1h. then allowed to warm to room temperature over 2h. and stirred for a further 1h. The mixture was then partitioned between 2M HCl (10 ml) and ether (50 ml) and the solid which separated was collected by filtration and washed repeatedly with ether (5 x 5 ml) to yield the title compound as a bright yellow solid (462 mg, 78%); m.p. >300°C; δ_H (500 MHz, d_6-DMSO) 7.64 (s, 2H, B-OH), 6.12 (s, 1H, H_1), 5.52 (s, 1H, H_4), 3.86-3.77 (m, 4H, ketal O-CH_2), 3.73 (s, 3H, OMe), 2.84-2.81 (br. d, 2H,), 2.15-2.07 (m, 2H,), 1.93-1.83 (m, 2H,), 1.73-1.60 (m, 3H,), 1.51-1.19 (m, 6H,), 0.79 (s, 3H, C_{18}-Me); ν_{max} (nujol) 3359, 2954, 2926, 1936, 1888, 1853 cm^{-1}; *m/z* (EI) 508 (M^+), 480, 464, 424, 408, 380, 336, 284, 111, 97, 83, 69, 55, 43(100%); High resolution acc. mass, found 508.4484; $C_{24}H_{29}BCrO_8$ requires 508.13605

2-Dihydroxyboryl-3-methoxy-17-ethylenedioxyestrane (54)

A solution of α-(tricarbonyl chromium (0))-η6-(2-dihydroxyboryl-3-methoxy-17-ethylenedioxyestrane) (119.2 mg, 234 mmol) in pyridine (2 ml) was exposed to direct sunlight and air for 4h. with occasional swirling. The solution was diluted with ether (20 ml) and partitioned between 2M HCl (20 ml) and ether (30 ml). The layers were separated and the organic phase was dried ($MgSO_4$) and evaporated to yield the title compound as a foam (73.5

mg, 84%); m.p. >300°C; δ_H ($CDCl_3$, 270 MHz) 7.74 (s,1H, H_1), 6.63 (s,1H, H_4), 5.64 (s, 2H, B-OH), 3.96-3.85 (m, 4H, ketal OCH_2), 3.87 (s, 3H, OMe), 2.90-2.86 (m, 2H, $H_{6\alpha}$, $H_{6\beta}$), 2.03-1.18 (m, 13H, skeletal H), 0.88 (s, 3H, C_{18}-Me); ν_{max} (nujol) 3392, 2922, 1559, 1457, 1378, 1255 cm^{-1}; *m/z* (EI) 398 (M^+), 354, 336, 328, 297, 284, 266, 227, 199, 160, 128, 115, 99 (100%);
Mass spectrometry showed an intermolecular reaction to give the 1,3-dioxa-2-borolane, High resolution acc. mass, found 398.2357; $C_{23}H_{31}BO_5$ requires 398.2264; This rearranged to the ketone 1,3-dioxa-2-borolane, high resolution acc. mass, found 354.19785; $C_{21}H_{27}BO_4$ requires 354.2002

Compound 54 could be prepared from α-(tricarbonyl chromium (0))-η6-(3-methoxy-17-ethylenedioxyestrane) in an improved yield of 82% for the two steps by not isolating the intermediate boronic acid chromium tricarbonyl species.

Fluorination of 2-dihydroxyboryl-3-methoxy-17-ethylenedioxyestrane (54)

A solution of 2-dihydroxyboryl-3-methoxy-17-ethylenedioxyestrane (26.2 mg, 70 μmol) in acetonitrile/DCM (1.5 ml, 2:1) was stirred at room temperature under a nitrogen atmosphere and solid caesium fluoroxysulphate (17.1 mg, 68.9 μmol) was added in one portion. After stirring for 2h., the reaction mixture was diluted with DCM (10 ml) and filtered to remove insoluble products. The filtrate was washed with water (1 x 5 ml), dried ($MgSO_4$) and evaporated under reduced pressure. The residue was subjected to flash chromatography (SiO_2; petrol-ether, 4:1) to give initially **2-fluoro-3-methoxy-17-ethylenedioxyestrane** as a white solid (3.4 mg, 14%); m.p. 102-103°C; δ_H ($CDCl_3$, 270 MHz) 6.98 (d, J_{H-F} 13.15 Hz, 1H, H_1), 6.64 (d, J_{H-F} 8.81 Hz, 1H, H_4), 3.98-3.88 (m, 4H, ketal OCH_2), 3.84 (s, 3H, OMe), 2.92-2.79 (m, 2H, $H_{6\alpha}$, $H_{6\beta}$), 2.26-1.08 (m, 13H, skeletal protons), 0.82 (s, 3H, C_{18}-Me); δ_F (84 MHz, $CDCl_3$) -139; ν_{max} (nujol) 1610, 1576, 1501, 1305, 1280, 1254, 1179, 1104 cm^{-1}; *m/z* (EI) 346 (M^+), 302, 287, 160, 115, 44(100%); High resolution acc. mass, found 346.1944; $C_{21}H_{27}FO_3$ requires 346.1944
Further elution gave **2-fluoro-3-*O*-methylestrone** as a white solid (1.1 mg, 5%); m.p. 126-127°C (lit.,[70] 125-128); δ_H (270 MHz, $CDCl_3$) 6.99 (d, J_{H-F} 13.19

Hz, 1H, H_1), 6.67 (d, $J_{H\text{-}F}$ 8.79 Hz, 1H, H_4), 3.85 (s, 3H, OMe), 2.88-2.84 (m, 2H, $H_{6\alpha}$, $H_{6\beta}$), 2.49-1.45 (m, 13H, skeletal protons), 0.91 (s, 3H, C_{18}-Me); δ_F (84 MHz, $CDCl_3$) -139; ν_{max} (nujol) 1738, 1608, 1504, 1316, 1246 cm^{-1}

2-Dihydroxyboryl-3-O-methylestrone (59)

A solution of 2-dihydroxyboryl-3-methoxy-17-ethylenedioxyestrane (450.6 mg, 1.21 mmol) and *p*-toluenesulphonic acid hydrate (48 mg, 20 mol%) in acetone (15 ml) was stirred under a nitrogen atmosphere for 20h. Saturated, aqueous sodium bicarbonate solution (2 ml) was added and the solution was diluted with water to approximately 50 ml. A white solid was deposited which was collected by filtration, washed with water (2 x 5 ml) and dried on the sinter to give the title compound which was recrystallised from DCM/petrol as a crystalline, white solid (381 mg, 96%); m.p. >300°C; δ_H ($CDCl_3$, 270 MHz) 7.76 (s, 1H, H_1), 6.64 (s, 1H, H_4), 5.76 (s, 2H, B-OH), 3.88 (s, 3H, OMe), 2.96-2.91 (m, 2H, $H_{6\alpha}$, $H_{6\beta}$), 2.56-1.45 (m, 13H, skeletal protons), 0.91 (s, 3h, C_{18}-Me); ν_{max} (nujol) 3390, 1727, 1496, 1413, 1338, 1247, 1050 cm^{-1}; *m/z* (EI) 328 (M^+), 284, 160, 144, 115, 97, 83, 69, 55, 44 (100%); Found C, 69.32; H, 7.76%; $C_{19}H_{25}BO_4$ requires C, 69.53; H, 7.68%

Fluorination of 2-dihydroxyboryl-3-O-methylestrone (59)

A solution of 2-dihydroxyboryl-3-*O*-methylestrone (92.0 mg, 280 μmol) in acetonitrile-DCM (3 ml, 2:1) was stirred at room temperature and solid caesium fluoroxysulphate (78.9 mg, 318 μmol) was added in one portion. After stirring the reaction mixture for 65 minutes, the reaction mixture was diluted with DCM (15 ml) and then filtered to remove insoluble products. The filtrate was washed with water (1 x 5 ml), dried ($MgSO_4$) and evaporated under reduced pressure. The residue was subjected to flash chromatography (SiO_2; petrol-ether, 4:1) to give 2-fluoro-3-*O*-methylestrone as a crystalline, white solid (22.6 mg, 27%); m.p. 127-128°C (lit.,[70] 125-128°C); δ_H (270 MHz, $CDCl_3$) 6.99 (d, $J_{H\text{-}F}$ 13.19 Hz, 1H, H_1), 6.67 (d, $J_{H\text{-}F}$ 8.79 Hz, 1H, H_4), 3.85 (s, 3H, OMe), 2.88-2.84 (m, 2H, $H_{6\alpha}$, $H_{6\beta}$), 2.49-1.45 (m, 13H, skeletal protons), 0.91 (s, 3H, C_{18}-Me); δ_F (84 MHz, $CDCl_3$) -139; ν_{max} (nujol) 1738, 1608, 1504, 1316, 1246 cm^{-1}; *m/z* (EI) 302 (M^+), 160, 115, 44 (100%); Found C, 75.21; H, 7.94%;

$C_{19}H_{23}FO_2$ requires C, 75.47;H, 7.67%

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