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Synthesis of fluorinated oxygen- and sulfur-containing heteroaromatics

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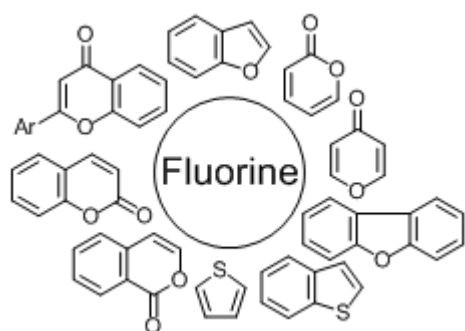
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ABSTRACT

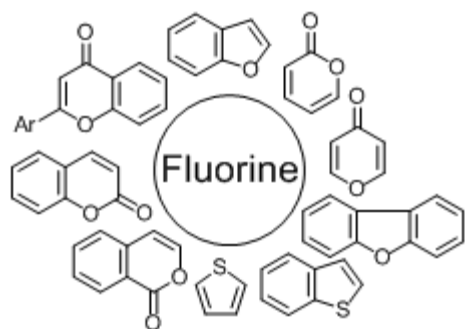
The incorporation of fluorine into a target molecule may have a considerable impact on its reactivity, selectivity, biological activity and physical properties. This is especially true in medicinal chemistry where fluorine is often employed as a bioisostere of hydrogen and where many important drug compounds also feature heteroaromatic rings. This work complements existing reviews on the synthesis of fluorinated, aromatic heterocycles, with a focus on less common oxygen-containing heteroaromatics as well as their sulfur-based analogues.

GRAPHICAL ABSTRACT - PICTOGRAM



GRAPHICAL ABSTRACT - SYNOPSIS

This review covers methods for the incorporation of fluorine into oxygen- and sulfur-containing heteroaromatic compounds.



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1 INTRODUCTION

Fluorine is seldom found in natural products, with the antibiotic 4-fluorothreonine and the toxin fluoroacetate representing two rare examples [1]. Despite this fact, fluorine is present in a significant number of drug compounds, agrochemical products and novel materials. As testament to the importance of fluorine in the pharmaceutical industry in particular, there are 128 fluorinated compounds with US tradenames according to the World Drug Index [2]. Furthermore, it is estimated that about 15-20% of pharmaceuticals licensed each year (new chemical entities) contain a fluorine atom [3, 4]. The presence of a fluorine serves to increase drug lipophilicity [5, 6] which is especially important when designing drugs that are intended to cross the blood-brain barrier [7]. Fluorination of drug compounds also affects physical properties [8], and can alter binding affinities with enzymes and receptors [9], rate of metabolism [10], clearance, absorption and transport [11].

Scaffolds containing one or more heteroaromatic rings are common in medicinal compounds [12]. A high percentage of drugs contain either aromatic or aliphatic heterocycles [13]. For example, the top ten small drug molecules all contain heterocyclic moieties [14]. Oxygen-containing heterocyclic drugs are of particular medical relevance, forming an important class of building blocks in organic synthesis [15, 16].

It is not surprising, therefore, that the development of new methods for the incorporation of fluorine into heteroaromatic ring systems is an area of active research in chemistry. Both Furin and Burger *et al.* have reviewed approaches to the synthesis of fluorinated, nitrogen containing, heterocyclic compounds [17-20]. More recently, Serduyk *et al.* have presented an overview of methods for the synthesis of fluorofurans and perfluoroalkylfurans [21]. More general reviews on the preparation of polyfluorinated heterocyclic and heteroaromatic compounds have been compiled by both Brooke and Yakobson [22, 23]. The aim of this

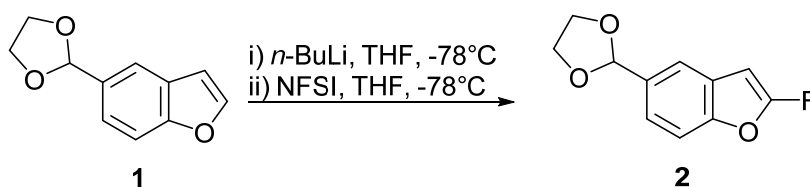
work is to complement these existing reviews and to address the remaining gaps. Our focus is directed towards the incorporation of fluorine into less common, oxygen-containing heteroaromatic rings, as well as the synthesis of fluorinated, sulfur-containing rings.

This review is split into two major sections : firstly, oxygen-containing heteroaromatics and secondly, sulfur-containing aromatic heterocycles. Each section is sub-divided by ring-type. Within each sub-division, the initial focus is on methods for direct fluorination of heteroaromatic rings, followed by methods where fluorine participates in formation of the product (e.g. S_NAr displacement of fluoride) and finally, routes where fluorine is present in the substrate prior to cyclization. Examples where fluorine is effectively a bystander in the formation of the fluorinated product have been omitted.

2 SYNTHESIS OF OXYGEN-CONTAINING HETEROAROMATICS

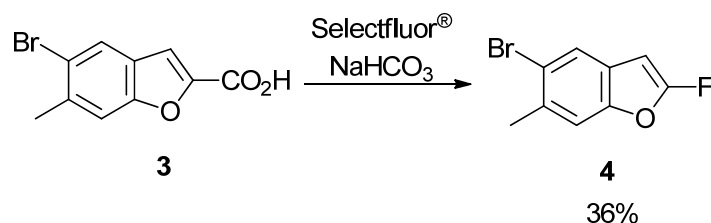
2.1 SYNTHESIS OF FLUORINATED BENZOFURANS

Both De Luca and Rueckle have developed a methodology for the direct incorporation of fluorine into 2-position of a benzofuran [24, 25]. Lithiation of **1** with *n*-BuLi, followed by addition of *N*-fluorobenzenesulfonimide (NFSI) at -78°C , afforded the target compound **2** (Scheme 1). Yields for this reaction were not reported as the product was used in the next step without any further purification.



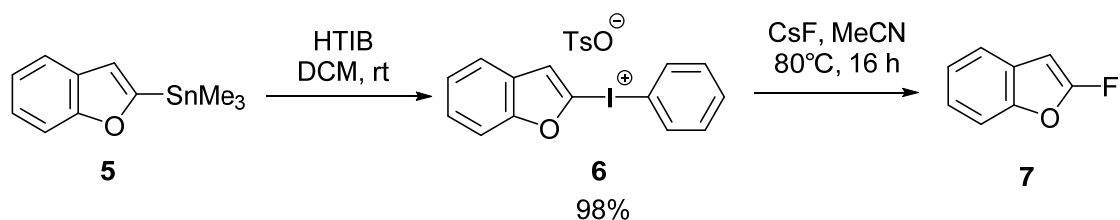
Scheme 1

Fluorodecarboxylation has been successfully used by a number of research groups to synthesise 2-fluorobenzofurans [26, 27]. In a typical example, Selectfluor[®] was added to a solution of **3** and sodium bicarbonate in water/ethyl acetate, from which fluorinated benzofuran **4** was isolated in 36% yield (Scheme 2).



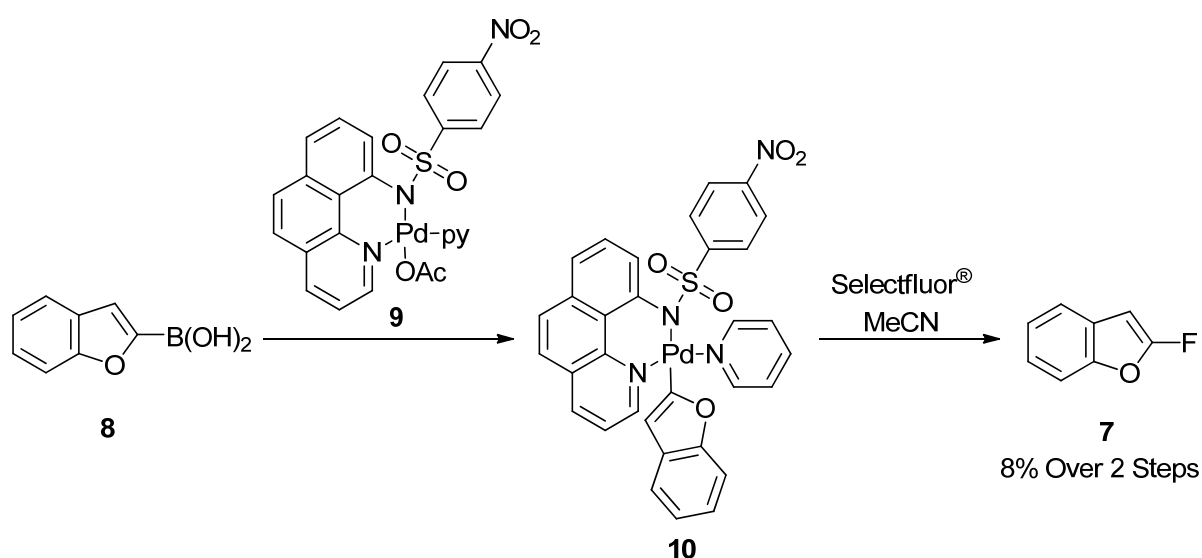
Scheme 2

Widdowson *et al.* have demonstrated the fluorination of arylheteroarylodonium salts, prepared from the corresponding aryltrialkylstannanes [28]. This methodology was applied to stannane **5**, which was converted to iodonium salt **6** with hydroxy(tosyloxy)iodobenzene (HTIB) in 98% yield, followed by subsequent fluorination with cesium fluoride to afford 2-fluorobenzofuran (**7**) (Scheme 3). Although actual yields are not quoted, the formation of **7** rather than fluorobenzene as the major product has been ascribed to a transition state where the 2-benzo[b]furyl group is equatorial, thus favouring fluorination of the heteroaryl ring.



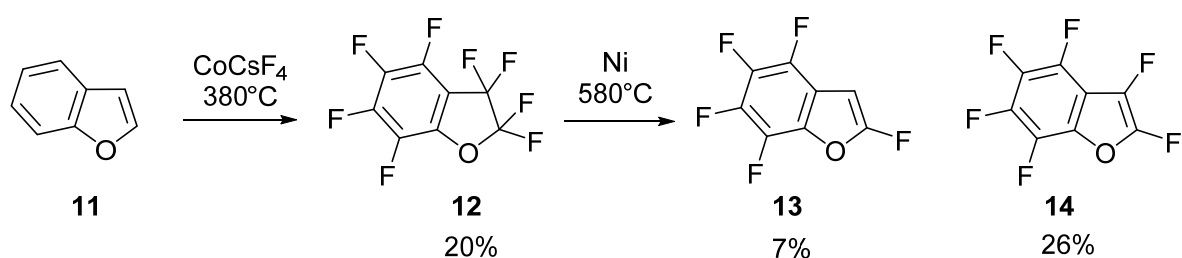
Scheme 3

Ritter *et al.* have designed a strategy for the fluorination of aryl and heteraryl boronic acids using novel palladium complexes [29, 30]. These palladium complexes incorporate nitrogenous, bidentate ligands which resist oxidation by electrophilic fluorination reagents, can support high-valence aryl palladium fluorides for subsequent carbon–fluorine reductive elimination and do not induce competing nitrogen–fluorine reductive elimination. Complex **10**, which was prepared from 2-benzofuranylboronic acid (**8**), was successfully fluorinated on treatment with Selectfluor[®] to furnish **7**, albeit in a modest overall yield of 8% (Scheme 4).



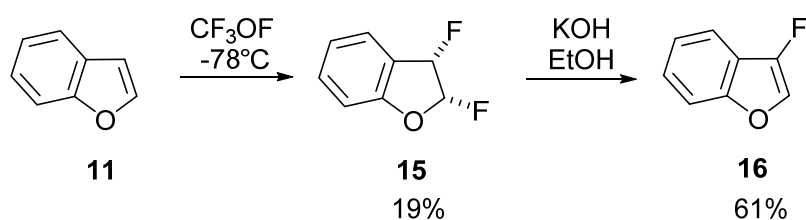
Scheme 4

In their search for a straightforward preparation of fluorinated benzofurans, Plevey and co-workers discovered that cesium tetrafluorocobaltate is a highly effective reagent for the perfluorination of unsubstituted benzofurans [31]. Fluorination of benzofuran (**11**) at 380°C afforded polyfluorinated intermediate **12** as the major product in 20% yield (Scheme 5). Subsequent pyrolysis of **12** over nickel gauze at 580°C gave 2-fluorobenzofuran **13** in 7% yield along with 2,3-difluorobenzofuran **14**.



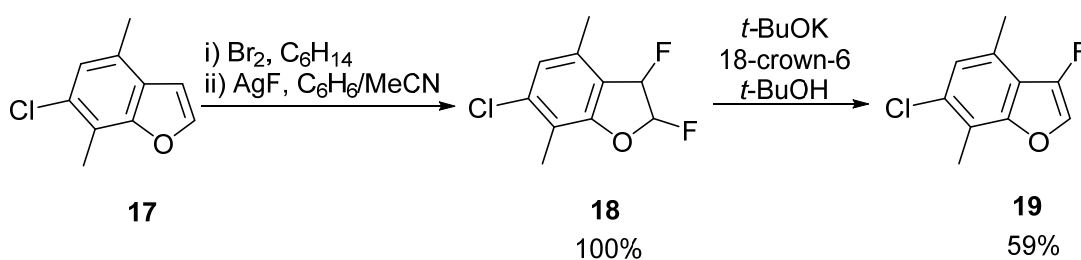
Scheme 5

Barton *et al.* have experimented with trifluorofluoro-oxymethane as a means of fluorinating benzofurans and indoles (Scheme 6). Accordingly, benzofuran (**11**) was converted to **15** in 19% yield on treatment with trifluorofluoro-oxymethane at -78°C [32]. Base-induced elimination with ethanolic potassium hydroxide afforded 3-fluorobenzofuran (**16**) in 61% yield.



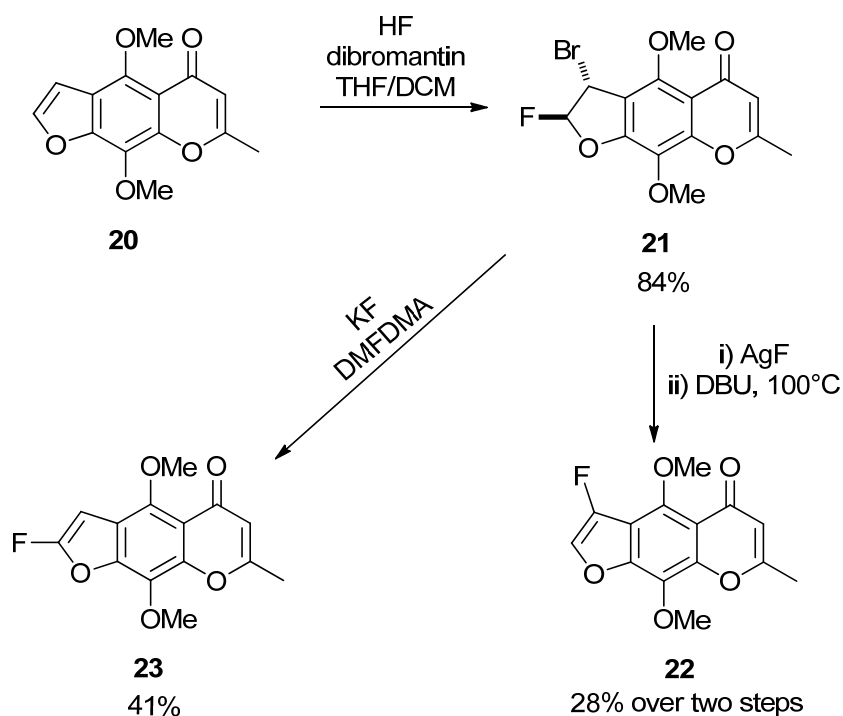
Scheme 6

Tagami *et al.* have described a route to 3-fluorobenzofurans in their work on the development of novel retinoic acid receptor agonists [33]. Bromination of **17**, followed by halogen exchange with silver fluoride, afforded **18** in quantitative yield (Scheme 7). Installation of the double bond was accomplished with potassium *tert*-butoxide and 18-crown-6 giving **19** in 59% yield.



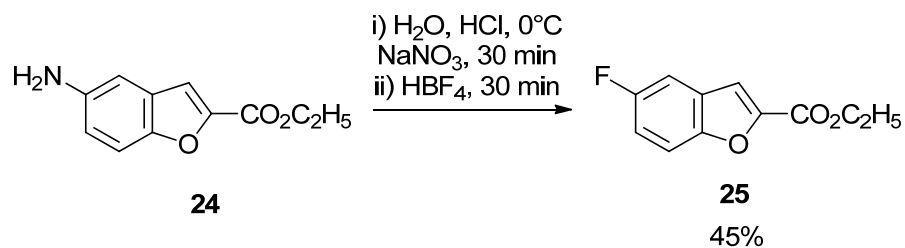
Scheme 7

Khellin (**20**), a benzofuran-containing natural product, has long been of interest due to its many interesting medicinal properties (Scheme 8) [34]. Gammill and Nash found that treatment of **20** with *in situ* generated BrF afforded *trans*-3-bromo-2-fluoro-2,3-dihydrokhellin (**21**) in 84% yield (Scheme 8) [35]. The difluorinated derivative could in turn be prepared from **21** on treatment with silver fluoride affording the *cis*- and *trans*- isomers in a ratio of 51:36 respectively. The *cis*-isomer underwent DBU-mediated elimination to furnish the 3-fluorobenzofuran adduct **22** in 55% yield. 2-Fluorobenzofuran **23** was accessed directly from **21** on addition of potassium fluoride in 41% yield. The use of *N,N*-dimethylformamide dimethyl acetal (DMFDMA) as solvent was found to dramatically accelerate this reaction.



Scheme 8

Methods for the incorporation of fluorine onto the benzene ring of benzofuran substrates have also been reported. Wang *et al.* used tetrafluoroboric acid to fluorinate benzofuran **24** via a Schiemann reaction (Scheme 9) [36, 37]. Over the course of the reaction, an aryldiazonium tetrafluoroborate forms and subsequently undergoes thermal decomposition to release boron trifluoride, producing the desired fluorinated benzofuran **25** in 45% yield.

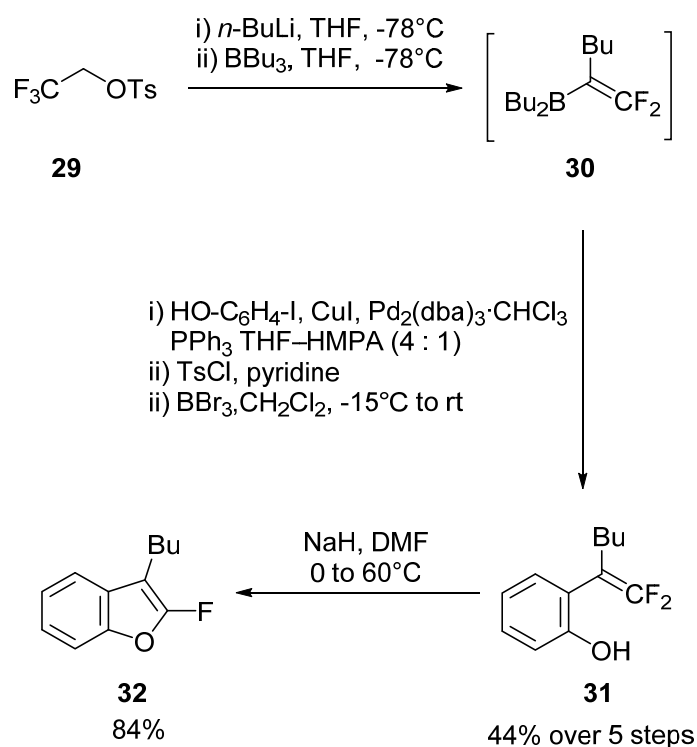


Scheme 9

Brooke *et al.* used intramolecular nucleophilic displacement of a fluorine atom by oxygen to prepare 4,5,6,7-tetrafluoro-benzofurans **28a-c** from the enolates **27a-c** of pentafluorobenzyl ketones **26a-c** (Scheme 10) [38]. Yields varied depending on the nature of the substituent. **28c** (R = Ph) was recovered in a yield of 76% due to the bulky phenyl group adopting a stable *trans*-configuration to the C₆F₅ group. Progressively lower yields of 33% and 13% were reported for **28b** (R = Me) and **28a** (R = H) respectively. Attempts to incorporate a fluorine atom into the 5-membered ring were unsuccessful; while it was possible to synthesise ethyl (2-ethoxycarbonyl-3,4,5,6-tetrafluorophenoxy)fluoroacetate from 2,3,4,5-tetrafluoro-6-hydroxybenzoate and ethyl chlorofluoroacetate, the subsequent cyclisation did not occur. The authors attribute this outcome to the unfavourable formation of a high energy carbanion.

Scheme 10

Ichikawa *et al.* have developed a novel synthesis of 2-fluorinated benzofurans from *gem*-difluorostyrenes [39]. Difluorovinylborane **30** was generated from 2,2,2-trifluoroethyl *p*-toluenesulfonate (**29**) in two steps (Scheme 11). Palladium-mediated coupling of **30** with *o*-iodoanisole and subsequent demethylation afforded *gem*-difluorostyrene **31** in 44% overall yield. 5-*Endo*-trigonal cyclisation of **31** was effected with sodium hydride in dimethylformamide resulting in an 84% yield of 2-fluorobenzofuran **32**. The highly polarised difluorovinylidene bond in **31** displays significant single bond character which facilitates ring formation.



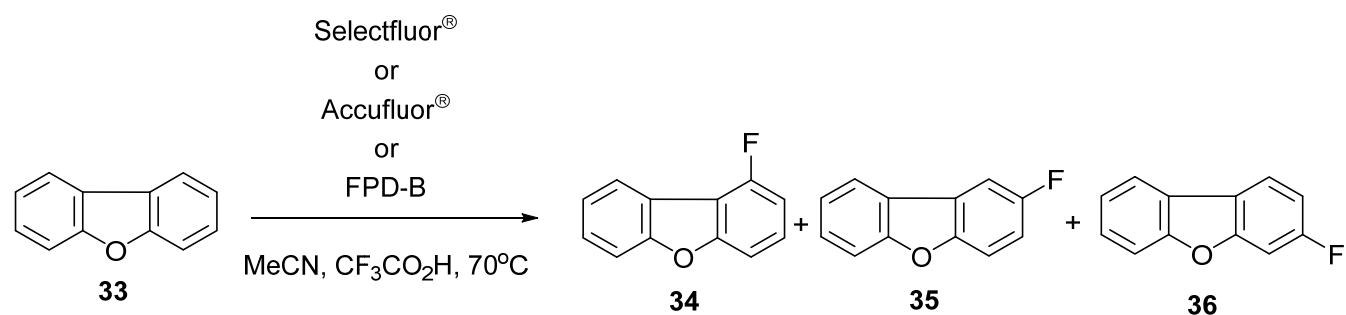
Scheme 11

2.2 SYNTHESIS OF FLUORINATED DIBENZOFURANS

Zupan *et al.* have studied the effects of a range of fluorinating agents on the regioselective fluorination of dibenzofuran (**33**) (Table 1) [40]. A representative sample of reagents was tested including Selectfluor[®], Accufluor[®], *N*-fluoro-2,6-dichloropyridinium tetrafluoroborate (FPD-B) and NFSI. Selectfluor[®] and Accufluor[®] are of similar chemical structure; both are 4-fluoro-1,4-diazabicyclo[2.2.2]octane derivatives. Selectfluor[®] contains a chloromethyl group at the 1-position, whereas Accufluor[®] bears a hydroxyl group at the same location. Regioselectivity was found to be reagent dependent (entry 1 vs. entries 8 & 9, Table 1). The choice of solvent also proved crucial to the reaction outcome as no reaction was observed in either methanol or methylene chloride, whereas a mixture of polar solvents (acetonitrile and trifluoroacetic acid) resulted in the highest overall yield of 39%. No reaction was observed when NFSI was used as the fluorinating agent.

Table 1

Effect of fluorinating reagent on product distribution



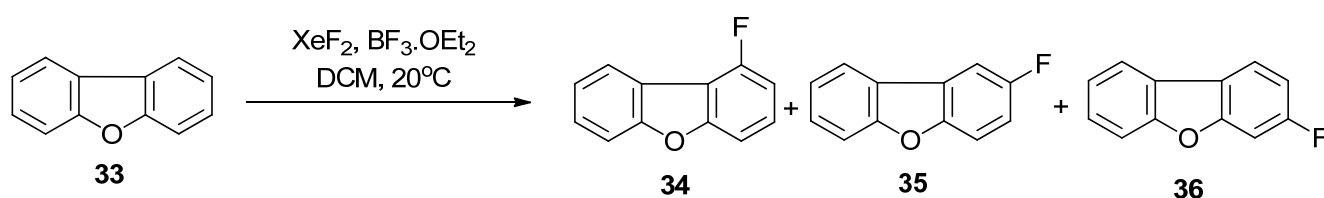
Entry	Reagent	Solvent	Combined Yield (%)	Product Distribution		
				34 (%)	35 (%)	36 (%)
1	Selectfluor [®]	MeCN	35	27	42	31
2	Selectfluor [®]	MeCN, PhNO ₂	34	28	41	31
3	Selectfluor [®]	MeCN, DCM	30	26	42	32
4	Selectfluor [®]	MeCN, MeOH	17	24	47	29
5	Selectfluor [®]	MeCN/CF ₃ CO ₂ H (9:1)	38	26	42	32
6	Selectfluor [®]	MeCN/CF ₃ CO ₂ H (1:1)	39	23	44	33
7	Selectfluor [®]	CF ₃ CO ₂ H	30	22	39	39
8	Accufluor [®]	MeCN	35	26	42	32
9	FPD-B	MeCN	38	18	53	29

Zupan has also investigated the use of xenon difluoride for the fluorination of dibenzofuran substrates [41]. Addition of xenon difluoride to **33** in dichloromethane at room temperature resulted in a mixture of regioisomeric, fluorinated products **34-36** in a low, combined yield of 17% (Table 2). An increase in yield to 30% was observed when boron trifluoride etherate was

employed as a catalyst. Interestingly, the use of boron trifluoride also affected regioselectivity, displaying a marked preference for fluorination at the 3-position.

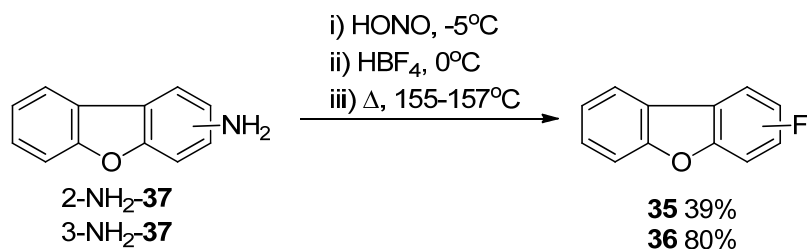
Table 2

Fluorination of dibenzofurans with XeF₂



Product Distribution			
Reagent	34 (%)	35 (%)	36 (%)
XeF ₂	25	31	44
XeF ₂ , BF ₃ .OEt ₂ , 0°C	23	23	54
XeF ₂ , BF ₃ .OEt ₂ , 20°C	26	21	53

Johnson *et al.* have indirectly prepared fluorinated dibenzofurans from the corresponding aminodibenzofurans *via* a Schiemann reaction [42]. Diazotisation of 2-aminodibenzofuran (2-NH₂-**37**) and 3-aminodibenzofuran (3-NH₂-**37**) with nitrous acid, followed by treatment with fluoroboric acid, afforded a diazonium fluoroborate intermediate which subsequently decomposed at elevated temperatures to afford 2-fluorodibenzofuran (**35**) or 3-fluorodibenzofuran (**36**) in yields of 39% and 80% respectively.



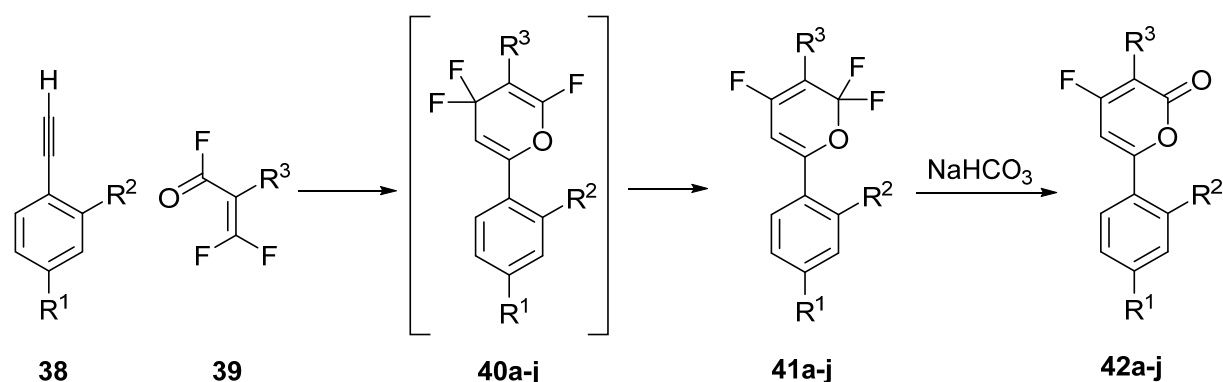
Scheme 12

2.3 SYNTHESIS OF FLUORINATED 2-PYRONES

To the best of our knowledge, methods for the direct fluorination of 2-pyrones have not been reported in the literature. Fluorinated 2-pyrones may, however, be indirectly prepared from fluorine-containing precursors. An early example is provided by England *et al.* [43]. A [4+2] cycloaddition reaction between perfluoroacryloyl fluoride **39** with an aromatic acetylene **38** affords cycloadducts **40a-j** (Table 3). This is followed by rearrangement to **41a-j** and subsequent hydrolysis to afford fluorinated 2-pyrones **42a-j**.

Table 3

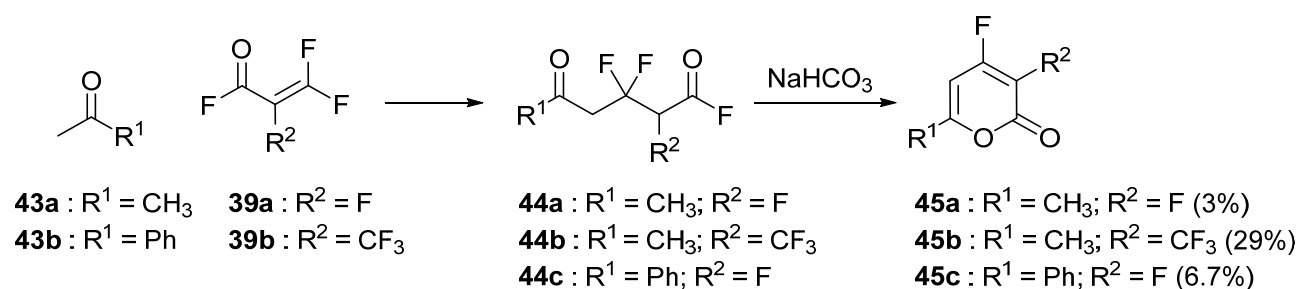
Preparation of fluorinated 2-pyrones



Product	R ¹	R ²	R ³	Overall Yield (%)
42a	H	H	F	2.5

42b	OMe	H	F	6
42c	H	H	CF ₃	15
42d	F	H	F	37
42e	Cl	H	F	5
42f	Br	H	F	5
42g	Me	H	F	10
42h	Me	Me	F	22
42i	Et	H	F	18
42j	<i>i</i> Pr	H	F	27

The authors also report a second route to fluorinated 2-pyrones **45a-c** in lower yields using a condensation reaction between either perfluoroacryloyl fluoride (**39a**) or perfluoromethacryloyl fluoride (**39b**) and either acetone (**43a**) or acetophenone (**43b**) (Scheme 13). The mechanism most likely involves conjugate addition of an α -carbon to the fluorinated double bond, followed by ring closure *via* the enol of **44a-c** and subsequent loss of HF.



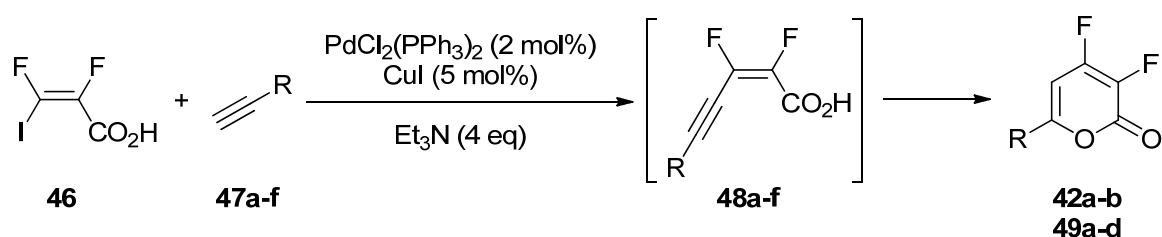
Scheme 13

Wang and Burton successfully synthesised a range of 3,4-difluoro-2-pyrones from (2*E*)-2,3-difluoro-3-iodoacrylic acid (**46**) and terminal acetylenes **47a-f** in the presence of palladium and copper co-catalysts (Table 4) [44]. Iodoacid **46** reacts with alkyne **47** under Pd(0)

catalysis to produce ynenic acid **48**. **48** is not isolated but is instead converted *in situ* to pyrones **42a-b** and **49a-d** by Pd(II) catalysis. Both aromatic and aliphatic acetylenes were well tolerated as were heterocyclic acetylenes. The presence of either electron withdrawing or donating groups on the aromatic ring was not found to impact upon yields.

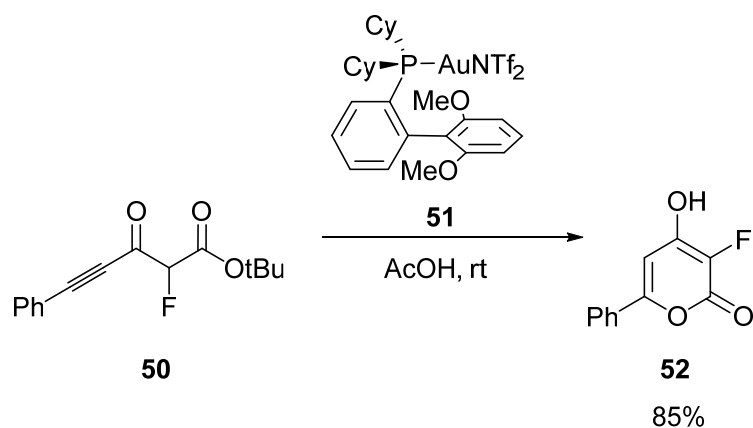
Table 4

Pd-Catalysed synthesis of 3,4-difluoro-2-pyrones



Product	R	Time (h)	Yield (%)
42a	C_6H_5	24	62
42b	4-MeOC ₆ H ₄	16	71
49a	<i>n</i> -C ₅ H ₁₁	24	59
49b	C ₆ H ₅ CH ₂ CH ₂	24	64
49c	4-CF ₃ C ₆ H ₄	12	69
49d	2-Pyridyl	24	43

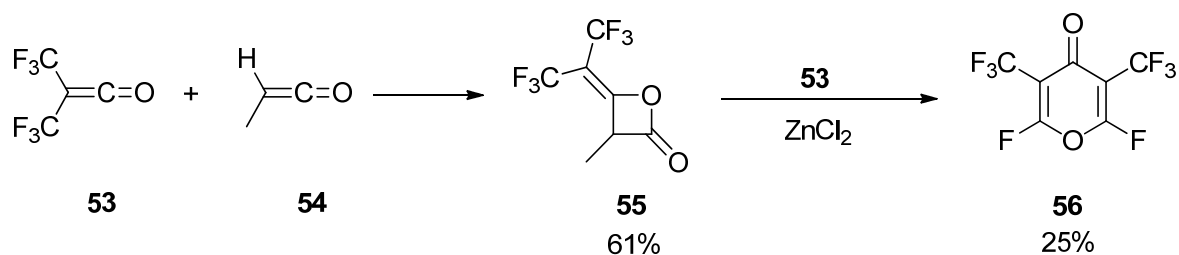
Fürstner *et al.* have developed a gold-containing catalyst which accelerates the cyclisation of widely available β -keto esters to furnish 4-hydroxy-2-pyrone [45]. Thus, β -keto ester **50** underwent cyclisation on exposure to catalyst **51** in acetic acid to afford 3-fluoropyrone **52** in 85% yield (Scheme 14).



Scheme 14

2.4 SYNTHESIS OF FLUORINATED 4-PYRONES

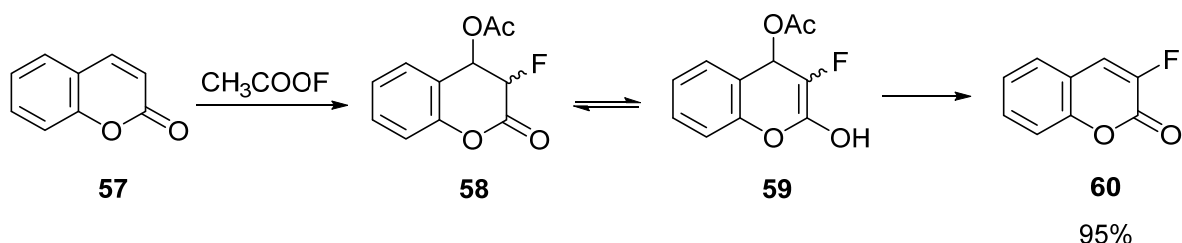
As with the 2-pyrones, methods for the direct fluorination of 4-pyrones have not been reported in the literature. An indirect method has been reported by England and Krespan by way of a fluorinated lactone intermediate [46]. Methylketene **54** underwent a cycloaddition reaction with *bis*(trifluoromethyl)ketene (**53**) to afford lactone **55** in 61% yield (Scheme 15). Treatment of **55** with zinc chloride initiated hydrogen fluoride elimination and difluorinated 4-pyrone **56** was recovered in 25% yield.



Scheme 15

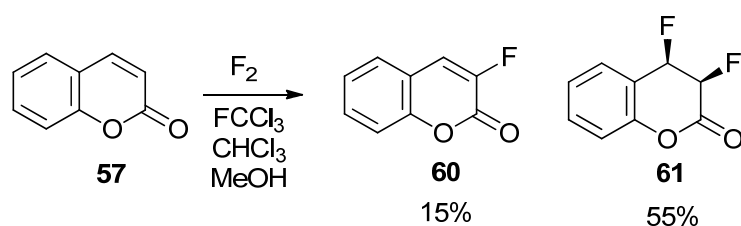
2.5 SYNTHESIS OF FLUORINATED COUMARINS

Rozen *et al.* employed acetyl hypofluorite as the fluorinating reagent in the electrophilic fluorination of coumarin (**57**) [47]. The product of electrophilic addition **58** tautomerises to its labile enol form **59**, which readily undergoes elimination of acetic acid to produce 3-fluorocoumarin (**60**) in 95% yield (Scheme 16).



Scheme 16

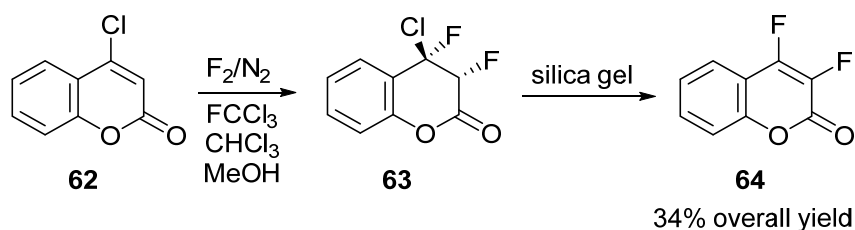
Rozen and Brand fluorinated coumarin using elemental fluorine, at a concentration of 1% in N_2 , in a mixture of fluorotrichloromethane, chloroform and ethanol (Scheme 17) [48]. Two products were isolated and identified as 3,4-dihydro-3,4-difluorocoumarin (**61**) (55% yield) and 3-fluorocoumarin (**60**) (15% yield) [48]. The authors noted that **61** could be quantitatively dehydrofluorinated to **60** by adsorbing it on a silica gel column for 24 hours. The easy elimination of HF is due to the *anti* configuration of the hydrogen and fluorine atoms resulting from *syn* addition of fluorine.



Scheme 17

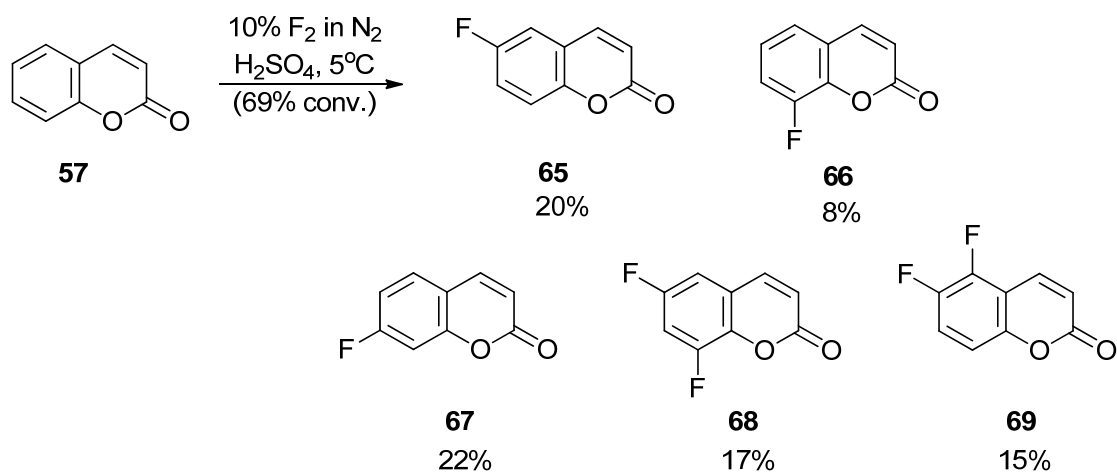
A similar approach has been utilised by Sato *et al.*, although they started with 4-chlorocoumarin (**62**) as their preferred substrate (Scheme 18) [49]. β -Chloro-enone **62** was firstly dissolved in the same solvent system employed previously by Rozen. On exposure to a stream of fluorine gas, **62** was then converted to difluorinated adduct **63**. Purification of **63** on silica gel was accompanied by spontaneous elimination of HCl, affording 3,4-

difluorocoumarin (**64**) in 34% overall yield, along with a significant amount of starting material **62** (55%).



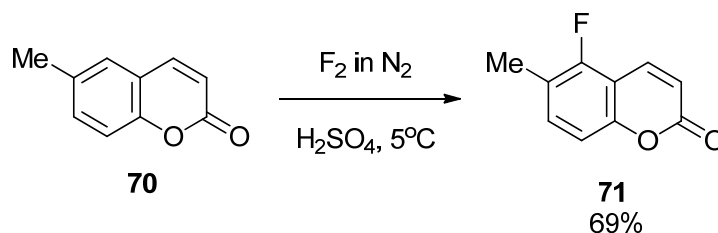
Scheme 18

In their investigation of the fluorination of coumarins in acidic solvents, Holling *et al.* found that fluorination of coumarin in sulfuric acid resulted in a mixture of products [50]. Fluorination of **57** gave five major products including 6-fluorocoumarin (**65**), 8-fluorocoumarin (**66**) and 7-fluorocoumarin (**67**) as well as smaller quantities of the difluorinated adducts **68** and **69** (Scheme 19). Only minute quantities of products arising from fluorination of the heterocyclic ring were observed, which would indicate that protonation of the oxygen atom by sulfuric acid deactivates the heterocyclic ring towards electrophilic fluorination.



Scheme 19

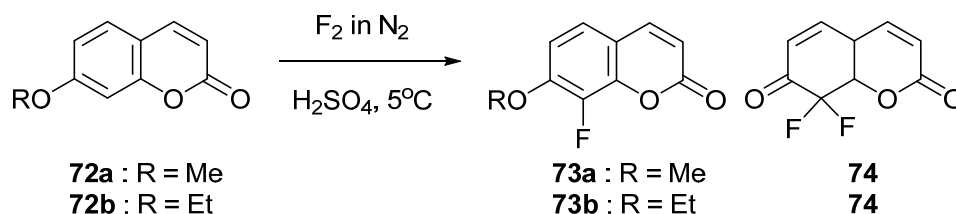
The same authors further reported that 6-methylcoumarin (**70**) may be selectively fluorinated *ortho* to the methyl group in synthetically useful yields (Scheme 20). By contrast, the fluorination of 7-methoxycoumarin (**72a**) is dependent on the amount of fluorine used (Table 5). The highest yields are obtained with 5 equivalents of fluorine, whereas 10 equivalents leads to an increase in the formation of the *gem*-difluoroketone side product **74**.



Scheme 20

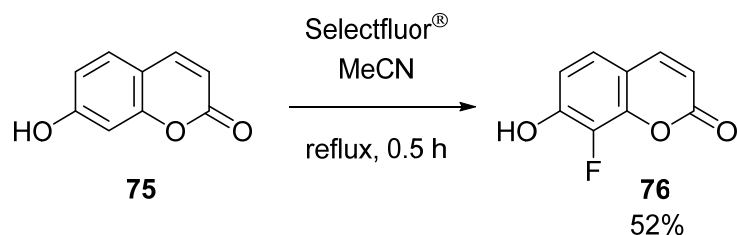
Table 5

Fluorination of coumarins in sulfuric acid



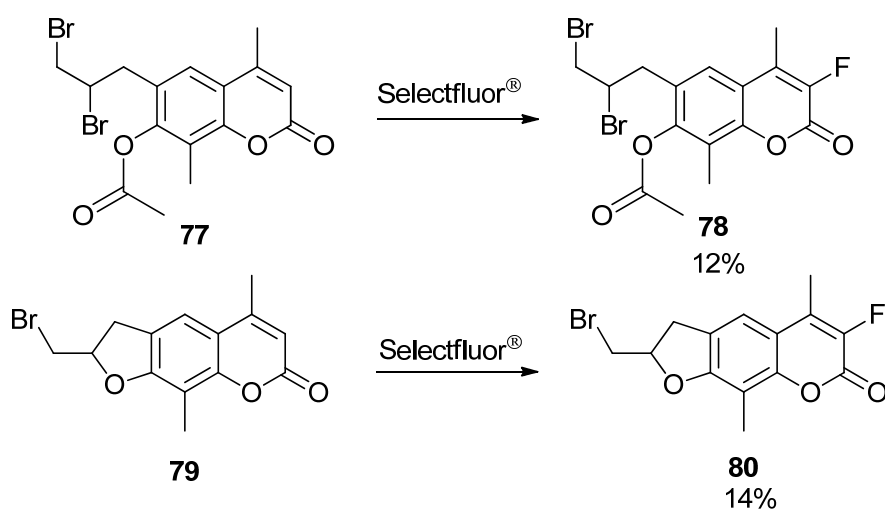
Entry	R	Equiv. of F ₂	Yield 73 (%)	Yield 74 (%)
1	Me	5	66	23
2	Me	10	trace	72
3	Et	5	55	26

In their search for novel anti-inflammatory compounds, Curini *et al.* attempted the direct fluorination of umbelliferone [51]. Treatment of **75** with Selectfluor[®] in refluxing acetonitrile for 30 minutes furnished **76** in 52% yield (Scheme 21).



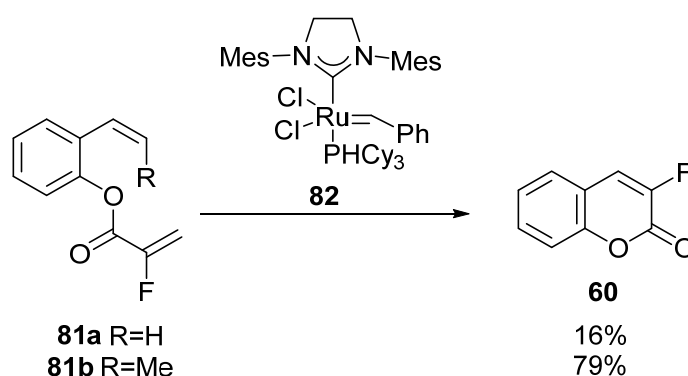
Scheme 21

Jabin *et al.* have successfully demonstrated the direct fluorination of selected coumarins and psoralens, albeit in low yields [52]. They examined the fluorination of **77** and **79** using three different N-F electrophilic fluorinating reagents, namely NFSI, *N*-fluoropyridinium triflate and Selectfluor[®] (Scheme 22). Monitoring of these reactions *via* GC-MS confirmed that fluorinated products had formed using all three of the reagents. However, the desired products were isolated only when Selectfluor[®] was employed as the fluorinating agent. Fluorocoumarin **78** and fluoropsoralen **80** were obtained in 12% and 14% yields respectively, with substantial amounts of starting material also recovered in both cases.



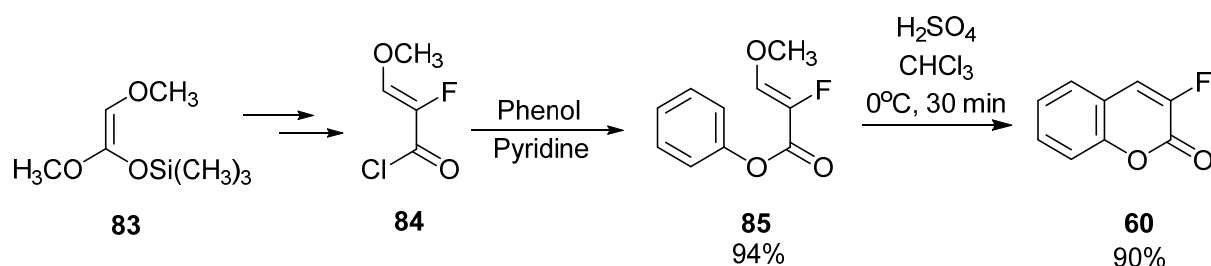
Scheme 22

Employing a ring-closing metathesis (RCM) reaction, Marhold *et al.* have prepared 3-fluorocoumarin (**60**) in 16% yield from 2-vinylphenyl- α -fluoroacrylate **81a** (R = H) and ruthenium-based catalyst **82** (Scheme 23) [53]. Additionally, 44% of a homodimer involving the non-fluorinated double bonds was isolated. High-dilution experiments over a range of concentrations from 0.5M to 0.05M did not show a significant change in the product ratio. On replacing hydrogen with a methyl group in the precursor, **81b** (R = Me) underwent RCM in a similar manner to afford **60** in a significantly increased yield of 79% [54, 55].



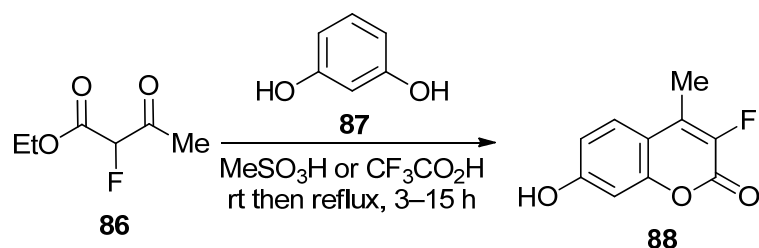
Scheme 23

Shi *et al.* have demonstrated that 2-fluoro-3-methoxyprop-2-enoyl chloride serves as a useful intermediate in the synthesis of fluorinated coumarins and other heteroaromatic ring systems (Scheme 24) [56]. In a typical example, acid chloride **84**, which may be readily prepared from 1,2-dimethoxy-1-trimethylsilyloxyethene (**83**) [57], reacted with phenol to form advanced ester adduct **85**. Exposure of **85** to sulfuric acid in chloroform afforded **60** in 90% yield.



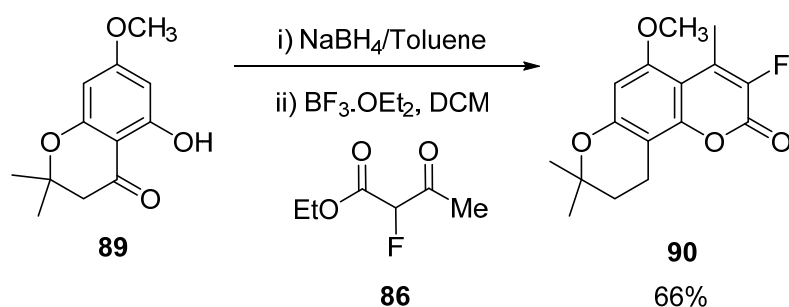
Scheme 24

The von Pechmann cyclisation is a popular route to the preparation of novel coumarins [58, 59]. For example, Harada *et al.* synthesised several substituted coumarins for use in the treatment of prostate cancer using this approach [60]. Reaction of resorcinol (**87**) and commercially available ethyl 2-fluoroacetoacetate (**86**) in the presence of methanesulfonic acid or trifluoroacetic acid afforded **88** in yields of 20-40% (Scheme 25). Other research groups have also reported synthesising fluorocoumarins in this manner [61, 62].



Scheme 25

In an investigation of novel anti-HIV drug candidates, Xie *et al.* synthesised **90** by firstly reducing ketone **89** with sodium borohydride to the corresponding methylene derivative (Scheme 26) [63]. Subsequent von Pechmann condensation with ethyl 2-fluoroacetoacetate (**86**), using boron trifluoride diethyl etherate as a catalyst, afforded dihydroseselin **90** in 66% overall yield.

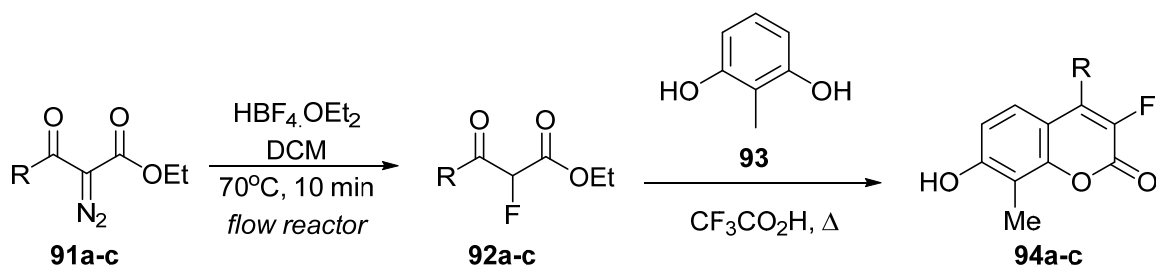


Scheme 26

α -Fluoro- β -ketoesters are highly versatile substrates and are particularly useful for the synthesis of fluorinated coumarins. Pasceri *et al.* have developed a novel methodology for the preparation of α -fluoro- β -ketoesters from α -diazo- β -ketoesters [64]. A series of α -diazo- β -ketoesters **91a-c** was treated with HBF_4 to furnish α -fluoro- β -ketoesters **92a-c** in yields of 51-82% (Table 6). The use of flow chemistry reduced the hazards normally associated with diazo compounds. Addition of α -fluoro- β -ketoesters **92a-c** to **93** in the presence of trifluoroacetic acid afforded fluorocoumarins **94a-c** in average to excellent yields.

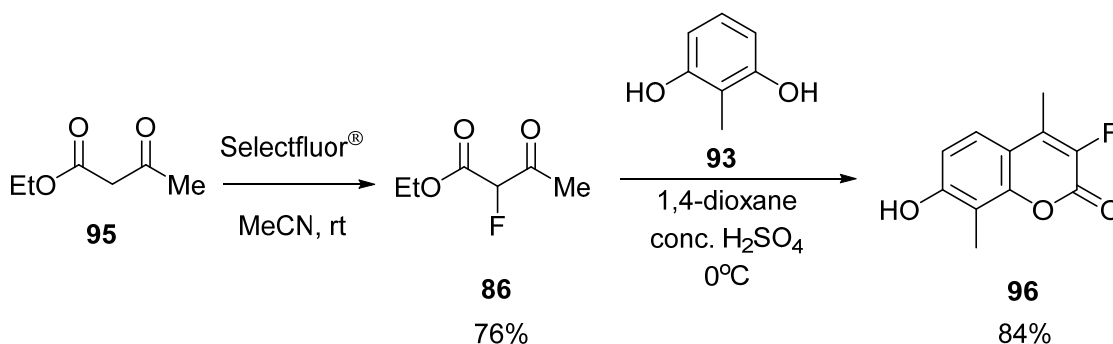
Table 6

Synthesis of 3-fluorocoumarins



α -Diazo- β -ketoester	R	Yield 92 (%)	Yield 94 (%)
91a	Ph	82	92
91b	2-thienyl	76	83
91c	$\text{CH}_2\text{CH}_2\text{Ph}$	51	51

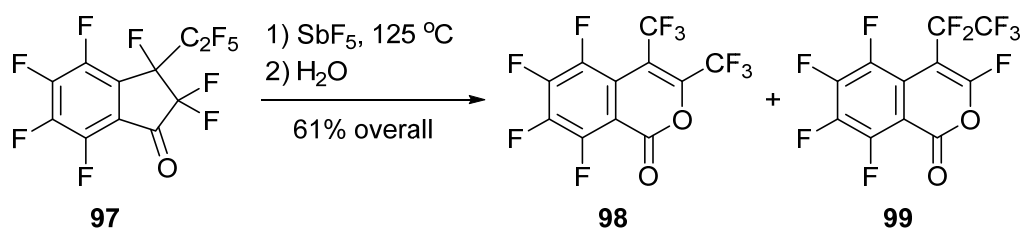
In a similar vein, Jabin *et al.* adapted the methodology developed by Banks [52] for the preparation of α -fluoro- β -ketoesters as precursors to fluorocoumarins [65]. Ethyl acetoacetate (**95**) was fluorinated with Selectfluor[®] in acetonitrile to afford **86** which then underwent von Pechmann condensation with **93** to produce **96** in 84% yield (Scheme 27).



Scheme 27

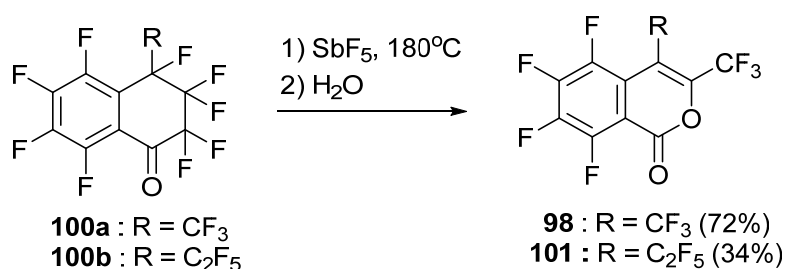
2.6 SYNTHESIS OF FLUORINATED ISOCOUMARINS

Zonov *et al.* have developed a procedure for the conversion of perfluoroindanones to fluorinated isocoumarins using antimony pentafluoride [66, 67]. Perfluoroindanone **97** was heated to 125°C in the presence of SbF₅ to produce a pair of isochromenyl salts which underwent hydrolysis to afford two isocoumarins, **98** and **99**, isolated in a combined yield of 61% in a ratio of 84:16 respectively (Scheme 28). The authors determined that the reaction is under kinetic control, as when the temperature was elevated to 130°C and the reaction time extended, isocoumarin **99** was not recovered.



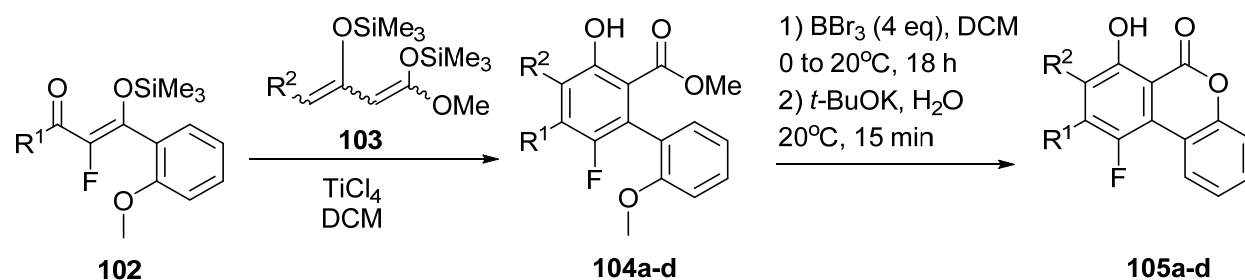
Scheme 28

This methodology has also been expanded to include tetralones [68]. Thus, when perfluorinated precursor **100a** ($R = CF_3$) was heated with SbF_5 at $180^\circ C$ and subsequently hydrolysed, isocoumarin **98** was formed in 72% yield (Scheme 29). Additionally, **100b** ($R = C_2F_5$) was also shown to form **101** in 34% yield under the same conditions.



Scheme 29

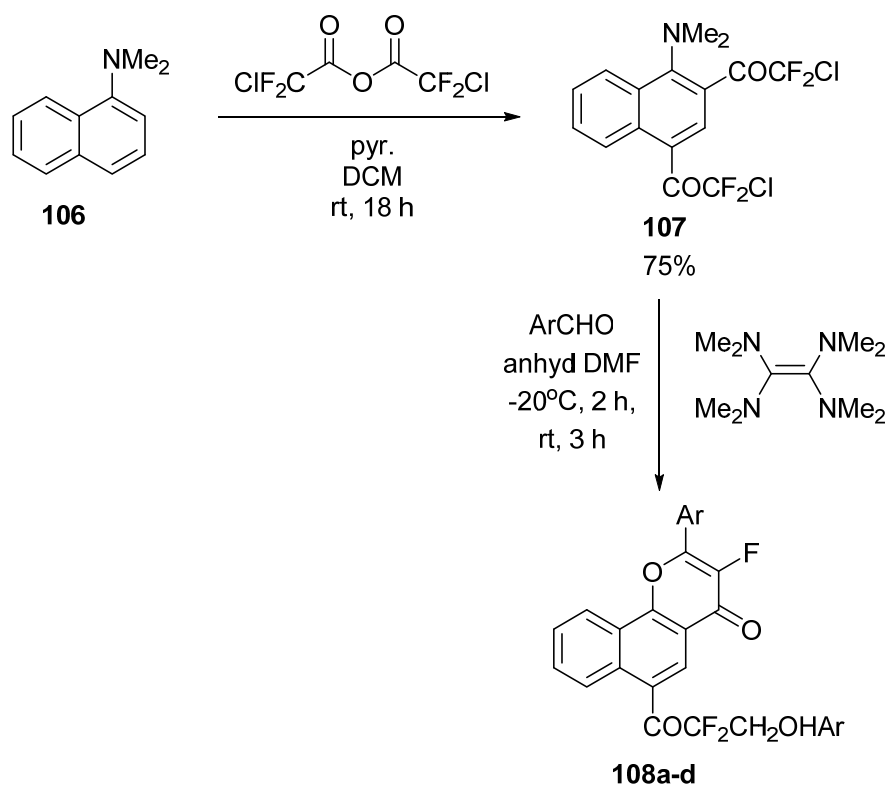
The $TiCl_4$ -mediated [3+3] cyclisation of 2-fluoro-1,3-diones **102** and 1,3-bis(silyl enol ethers) **103** offers a useful synthetic route to fluorinated isocoumarins (Table 7) [69, 70]. Reaction of **102** with **103** proceeds by an initial Mukaiyama-Michael reaction, followed by cyclisation *via* a Mukaiyama aldol reaction. Subsequent aromatisation by way of an elimination reaction affords fluorinated phenols **104a-d**. Demethylation of **104a-d** with boron tribromide and addition of a strong base effects lactonisation, furnishing fluorinated isocoumarins **105a-d**. This reaction was also successfully carried out with the ethyl ester derivative of **104**.

Table 7Synthesis of fluorinated isocoumarins **105a-d**

Product	R^1	R^2	Overall Yield (%)
105a	Me	H	91
105b	Me	Me	84
105c	<i>n</i> Pr	H	47
105d	<i>n</i> Pr	Me	55

2.7 SYNTHESIS OF FLUORINATED FLAVONES AND CHROMONES

As part of their ongoing efforts into the synthesis of novel heterocycles, Médebielle *et al.* have developed a one-pot aldolisation-intramolecular $\text{S}_{\text{N}}\text{Ar}$ process for the preparation of fluorinated flavones and quinolinones [71]. The first step involves bis-chlorodifluoroacetylation of *N,N*-dimethyl-1-naphthylamine (**106**) to afford key intermediate **107** in 75% yield (Scheme 30). Addition of TDAE (tetrakis(dimethylamino)ethylene) to **107** and eight equivalents of a suitable aromatic aldehyde results in the formation of fluorinated flavone products **108a-d** in yields ranging from 18% to 68% (Table 8).



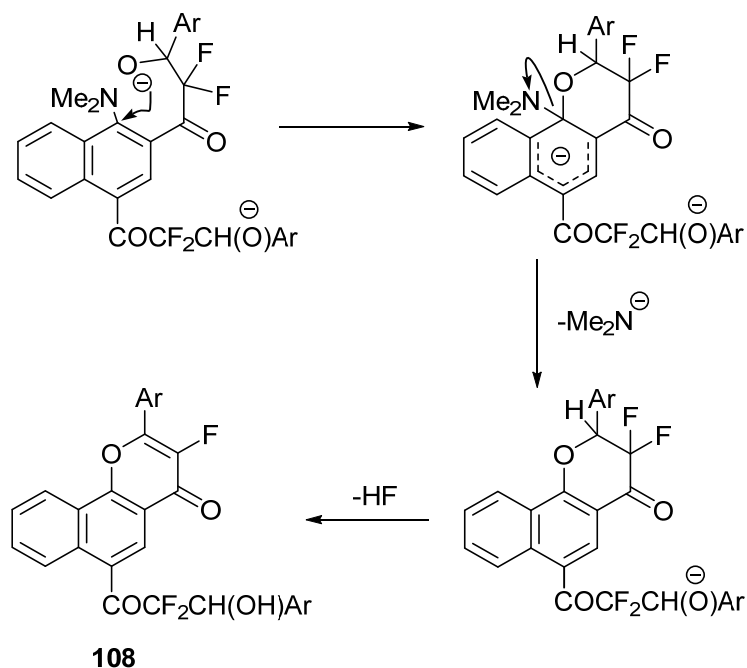
Scheme 30

Table 8

Preparation of fluorinated flavones from **107**

Product	Ar	Yield (%)
108a	Ph	65
108b	4-F-C ₆ H ₅	68
108c	3-pyridinyl	52
108d	3,4-dimethoxyphenyl	18

The authors propose that the reaction proceeds by reduction of **107** by TDAE to the bis-enolate, followed by reaction with the aldehyde to form a bis-alkoxide (Scheme 31). This is accompanied by an intramolecular nucleophilic aromatic substitution and elimination of a dimethylamide anion. The strongly basic dimethylamide induces elimination of HF to furnish the desired target **108**.



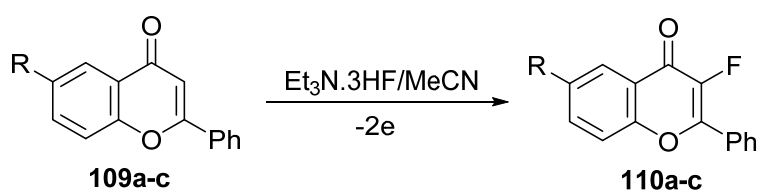
Scheme 31

Selective electrochemical fluorination is an efficient tool for the synthesis of fluorinated organic compounds. Hou *et al.* carried out a number of anodic fluorination experiments on several flavones [72]. Using a platinum electrode in anhydrous acetonitrile with $\text{Et}_3\text{N} \cdot 3\text{HF}$ as the supporting electrolyte, substrates **109a-c** were transformed to their fluorinated derivatives **110a-c** in yields ranging from 19% to 62% (Table 9). The reaction was found to be dependent on temperature, with higher yields recorded when the reaction temperature was increased from room temperature to 30°C. While $\text{Et}_3\text{N} \cdot 3\text{HF}$ led primarily to the desired 3-fluorinated product, use of $\text{Et}_3\text{N} \cdot 4\text{HF}$ as the supporting electrolyte resulted in the formation of 2,3-difluorinated products predominantly. In the paper, the authors note that **110a** could also be

prepared by the reaction of **109a** (R = H) with *N*-fluoropyridinium chloride in methylene chloride, albeit in a lower yield than their electrochemical fluorination methodology (21% vs. 43%).

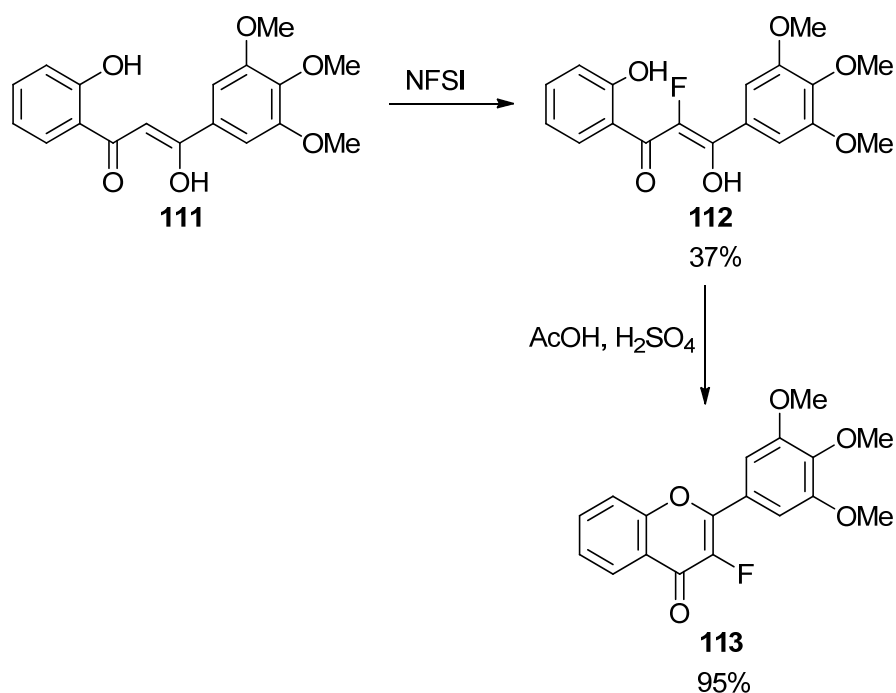
Table 9

Influence of substituents and temperature on the electrochemical fluorination of flavones.



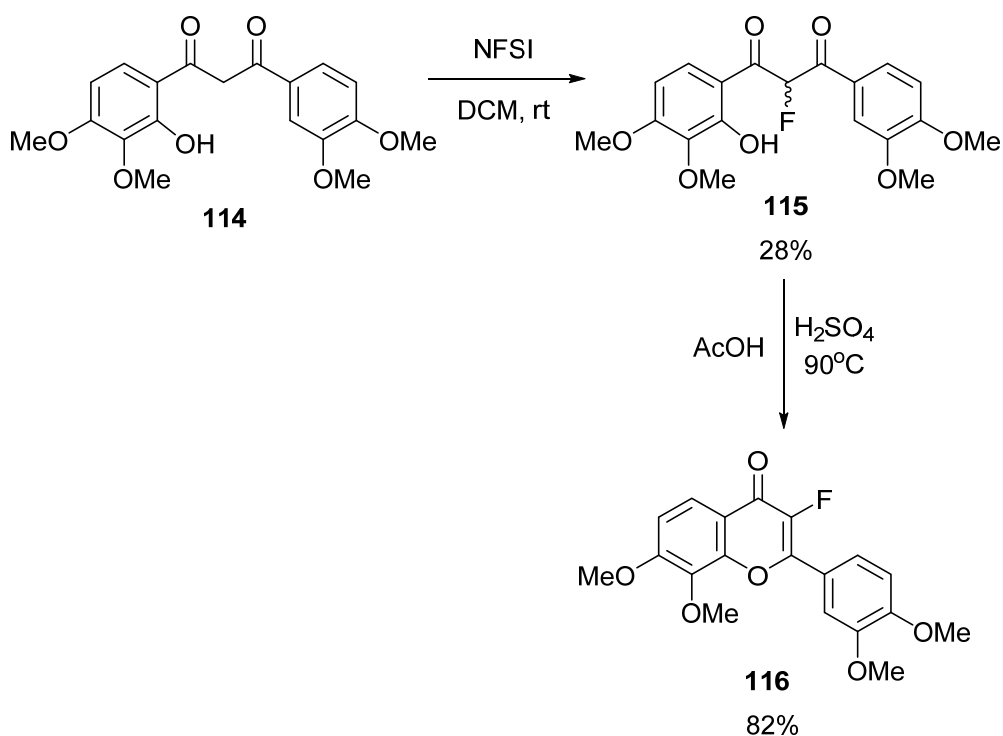
Product	R	Temperature (°C)	Yield (%)
110a	H	rt	43
110a	H	30	58
110b	CH ₃	rt	19
110b	CH ₃	30	20
110c	Cl	rt	41
110c	Cl	30	62

Britton *et al.* have prepared a range of flavone derivatives in order to evaluate their potential as anti-prostate cancer agents [73]. They successfully incorporated fluorine into **111** using NFSI, affording fluorinated adduct **112** in 37% yield (Scheme 32). Acidification of **112** led to spontaneous cyclisation and elimination of water to furnish fluoroflavone **113** in excellent yield.



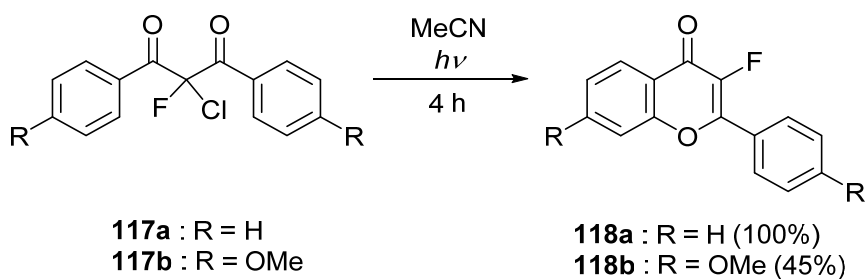
Scheme 32

Menichincheri *et al.* have adopted a similar approach for the preparation of novel telomerase inhibitors [74]. They report the synthesis of a fluorinated flavone analogue from the reaction of fluorinated propanedione **115** with sulfuric acid, resulting in an 82% yield of the fluorinated chromone **116** (Scheme 33). Fluorine was introduced in the step prior to cyclisation by reaction of diketone **114** with NFSI, resulting in a 28% yield of the fluorinated propanedione **115**.



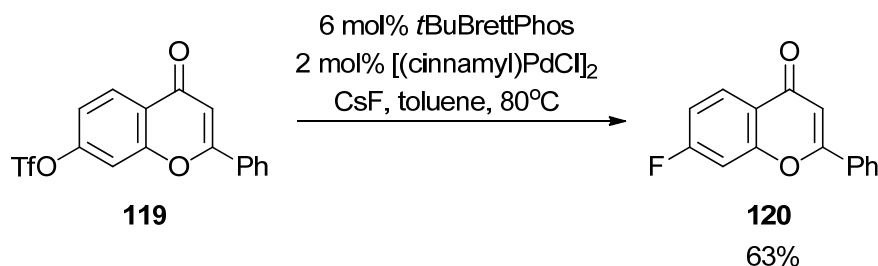
Scheme 33

The photocyclisation of 2-halo-1,3-diarylpropan-1,3-diones **117a-b** to 3-halo-3',4'-diarylflavones **118a-b** is outlined in a paper by Kosmrlj and Sket (Scheme 34) [75]. Irradiation at 352 nm effected photocyclisation of **117a** to form 3-fluoroflavone **118a** in 55% after two hours. Extending the reaction time to four hours resulted in a quantitative yield of **118a**. Photocyclisation of **117b** was similarly successful. None of the alternative 3-chloroflavone products was detected, indicating that cleavage of the C-F bond was not an issue under these reaction conditions.



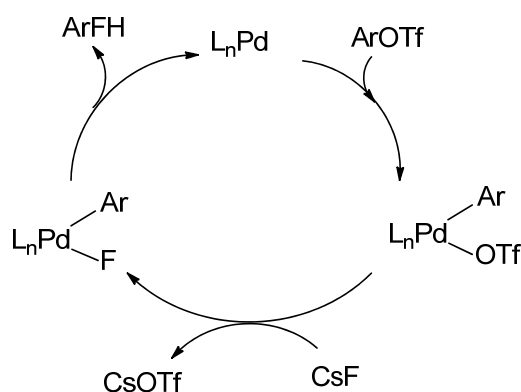
Scheme 34

Buchwald *et al.* have developed a general method for the conversion of aryl triflates to aryl fluorides using Pd-mediated catalysis [76]. In a typical example, triflate **119** reacted with caesium fluoride in the presence of [(cinnamyl)PdCl]₂ and the *t*BuBrettPhos ligand to furnish fluoroflavone **120** in 63% yield along with a small amount (2%) of the defluorinated by-product (Scheme 35).



Scheme 35

The proposed catalytic cycle is outlined in Scheme 36. A series of mechanistic studies by Grushin *et al.* had previously highlighted the challenges associated with formation of Ar-F bonds *via* reductive elimination [77-82]. The *t*BuBrettPhos ligand is crucial to the success of this methodology, as its large size both promotes reductive elimination of the Ar-F bond and also prevents the formation of unwanted dimeric [LPdAr(F)]₂ complexes.

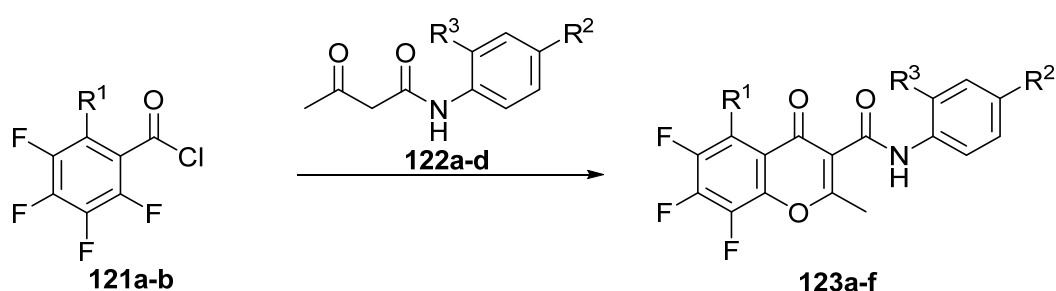


Scheme 36

Nosova *et al.* have pioneered the intramolecular nucleophilic substitution of aryl fluorides as a synthetic route to polyfluorinated chromones [83]. The reaction of acyl chlorides **121a-b** with acetoacetamides **122a-d** at room temperature for 3 hours furnished chromones **123a-f** in 63-76% yield (Table 10) [84]. Isothiocyanates may be used in place of acid chlorides affording the desired chromone target **123a** in slightly improved yields (73%) [83].

Table 10

Synthesis of polyfluorinated chromones

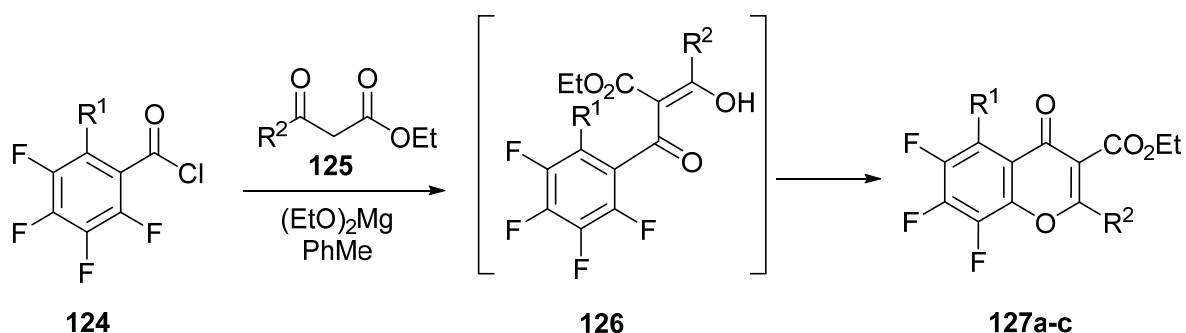


Product	R ¹	R ²	R ³	Yield (%)
123a	H	H	H	69
123b	H	CH ₃	H	64
123c	H	H	CH ₃	67
123d	H	OCH ₃	H	76
123e	F	CH ₃	H	63
123f	F	H	CH ₃	68

More recently, a similar approach has been described using β -ketoesters in place of acetoacetamides [85]. Shcherbakov *et al.* prepared tri- and tetrafluorochromenes *via* a one-pot synthesis involving the acylation of β -ketoesters **125** with tetra- and penta-fluorobenzoyl chlorides **124** in the presence of magnesium ethoxide (Table 11). The reaction proceeds *via* the *in situ* formation of polyfluorinated benzoyl acrylates **126a-c** which subsequently undergo

intramolecular nucleophilic aromatic substitution of the *ortho* fluorine with the hydroxyl group to give chromones **127a-c** [86]. Varying the substituents on the β -ketoester had little effect on the yield (Table 11).

Table 11

Preparation of polyfluorinated chromones from β -ketoesters

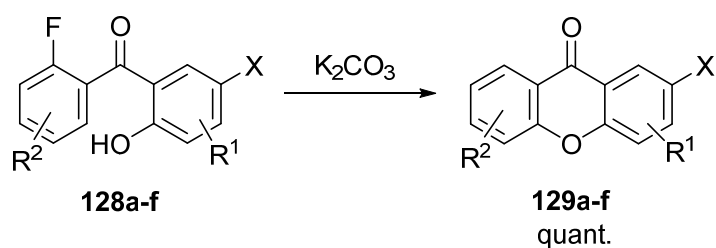
Product	R ¹	R ²	Yield (%)
127a	H	Ph	66
127b	F	Ph	70
127c	H	Me	68

2.8 SYNTHESIS OF FLUORINATED XANTHONES

In their search for novel mGlu1 receptor enhancers, Vieira *et al.* synthesised several fluorinated xanthenes using a synthetic methodology developed by Horne and Rodrigo [87, 88]. Friedel-Crafts acylation of *para*-substituted anisoles with 2-fluorobenzoic acid chlorides furnished 2-hydroxy-benzophenones **128a-f** (Table 12). Base-induced cyclisation *via* displacement of fluoride afforded a series of xanthenes **129a-f** in quantitative yields.

Table 12

Preparation of fluorinated xanthenes



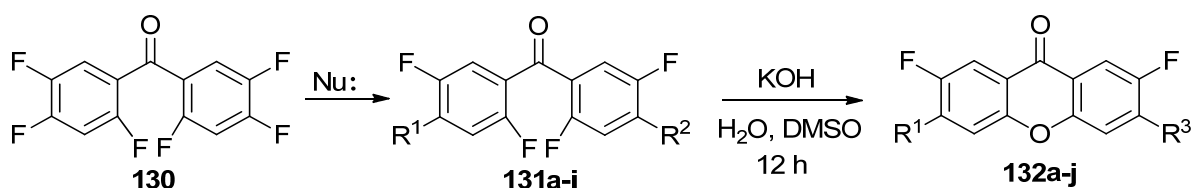
Product	X	R ¹	R ²
129a	F	H	H
129b	F	H	2-F
129c	Br	H	3-F
129d	Br	H	4-F
129e	Br	5-F	4-F
129f	Br	3-F	6-F

Woydziak *et al.* have outlined a synthetic route to fluorinated xanthenes starting from a common intermediate **130**, which can be prepared in 92% yield from reaction of 2,4,5-trifluorobenzaldehyde and the Grignard derivative of 1-bromo-2,4,5-trifluorobenzene, followed by TEMPO-mediated oxidation (Table 13) [89]. Nucleophilic aromatic substitution of **130** with a range of oxygen and nitrogen nucleophiles afforded a range of symmetrical and unsymmetrical products **131a-i**. A reduction in the reaction temperature (entry 3 vs. entry 4) or in the reaction time (entry 7 vs. entry 8) resulted in the formation of pentafluorinated, rather than tetrafluorinated, ketone intermediates (**131d** and **131h** respectively). Heating **131a-i** with aqueous sodium hydroxide in a sealed tube at 200°C effected displacement of fluoride which was followed by cyclisation to the target xanthenes **132a-j** in good to excellent yields. It is noteworthy that when R² was fluorine, it could be displaced by the hydroxide ion

through an addition elimination mechanism presumably facilitated by the *para*-ketone, whereas the two remaining fluorines remained intact [90, 91]. Synthesis of the related thioxanthenes was also reported in this paper.

Table 13

Synthesis of fluorinated xanthenes

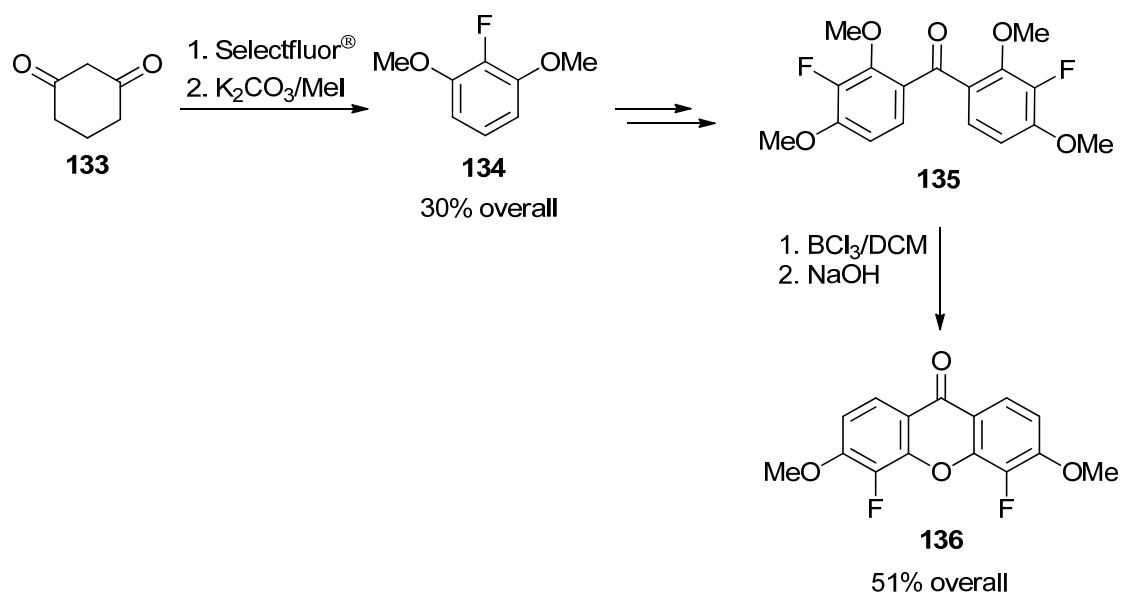


Entry	Nucleophile	Temp. (°C)	Ketone	R ¹	R ²	Yield (%)	Product	R ³	Yield (%)
1	NH ₄ OH	35	131a	NH ₂	F	75	132a	OH	80
2	HNMe ₂	60	131b	NMe ₂	NMe ₂	78	132b	NMe ₂	85
3	HNEt ₂	90	131c	NEt ₂	NEt ₂	85	132c	NEt ₂	85
4	HNEt ₂	26	131d	NEt ₂	F	70	132d	OH	95
5	<i>i</i> PrNH ₂	60	131e	<i>i</i> PrNH	<i>i</i> PrNH	92	132e	<i>i</i> PrNH	92
6	<i>t</i> BuNH ₂	46	131f	<i>t</i> BuNH	<i>t</i> BuNH	82	132f	<i>t</i> BuNH	90
7	Piperidine	26	131g	Piperidine	Piperidine	91	132g	Piperidine	92
8	Piperidine	26	131h	Piperidine	F	76	132h [^]	OH	95
9	Morpholine	26	131i	Morpholine	Morpholine	81	132i	Morpholine	83

[^]reaction time of 3h

Dodean *et al.* have demonstrated that difluorinated xanthenes display higher anti-malarial activity than their non-fluorinated analogues [92]. Treatment of **133** with Selectfluor[®] provided 2,2-difluoro-1,3-hexanedione which was converted to **134** in 30% overall yield (Scheme 37). Following elaboration of **134** to afford intermediate **135**, monodemethylation

with boron trichloride and subsequent base-induced cyclisation afforded xanthone **136** in a combined yield of 51%.

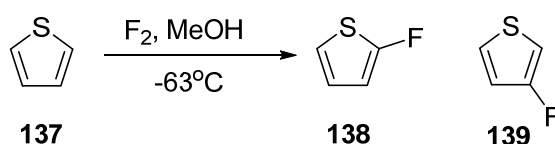


Scheme 37

3 SYNTHESIS OF SULFUR-CONTAINING HETEROAROMATICS

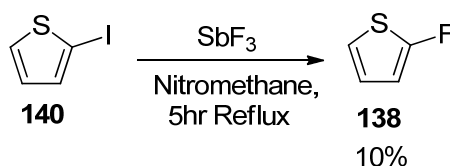
3.1 SYNTHESIS OF 2- AND 5-FLUOROTHIOPHENES

Direction fluorination of thiophene (**137**) using elemental fluorine produces a mixture of 2- and 3-fluorinated products. For example, Cerichelli *et al.* achieved an 86% conversion of thiophene (**137**) to a mixture of 2-fluorothiophene (**138**) and 3-fluorothiophene (**139**) in a ratio of 57:43 (Scheme 38) [93]. Similar reactions with furan and pyrrole proved unsuccessful.



Scheme 38

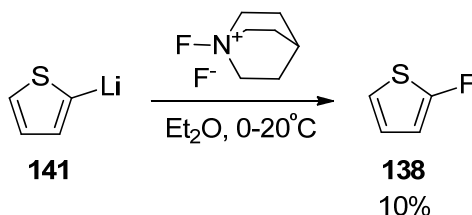
One of the earliest reported syntheses of 2-fluorothiophene involved the incorporation of fluorine by reaction of 2-iodothiophene (**140**) with antimony trifluoride in nitromethane (Scheme 39) [94]. This transformation could be accomplished using 2-iodothiophene, albeit in low yield, but was unsuccessful when using the corresponding chlorinated or brominated substrates.



Scheme 39

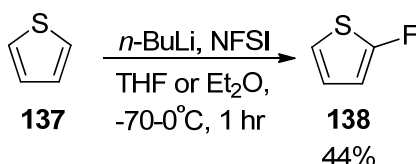
Preferential reaction of electrophiles at the 2-position of thiophene is well established. Regioselective fluorination of the 2-position is generally achieved by the use of electrophilic sources of fluorine [95]. Banks *et al.* demonstrated that it is possible to deliver electrophilic fluorine using *N*-fluoroquinuclidinium fluoride (NFQNF) [96]. NFQNF may be prepared in *ca.* 90% yield by direct, low-temperature, liquid-phase fluorination of quinuclidine using elemental fluorine. Lithium salt **141**, prepared from the reaction of thiophene with *n*-

butyllithium, was refluxed in the presence of NFQNF affording 2-fluorothiophene (**138**) in 10% yield (Scheme 40).



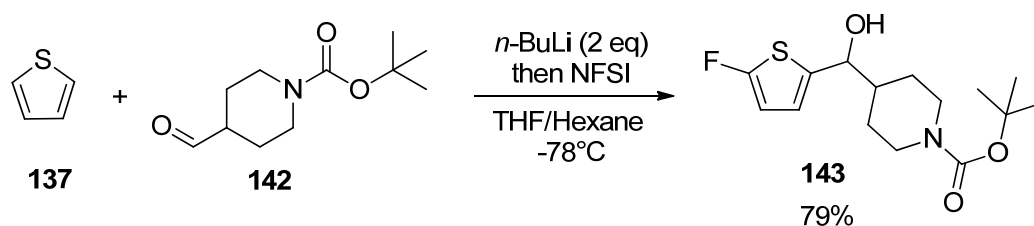
Scheme 40

Lundbeck reported increased yields for the electrophilic fluorination of thiophene (**137**) by replacing NFQNF with NFSI as the fluorine source (Scheme 41) [97]. 2-Fluorothiophene (**138**) was recovered in a 44% yield which represents a significant improvement on previous efforts.



Scheme 41

Gobbi *et al.* have developed a novel one-pot preparation of thiophene derivative **143** for potential use as a dual-inhibitor of 5-HT_{3A} and D₃ receptors (Scheme 42). Initial *in situ* fluorination of the dilithiated thiophene ring, followed by nucleophilic attack onto aldehyde **142**, afforded alcohol **143** in 79% overall yield [98].



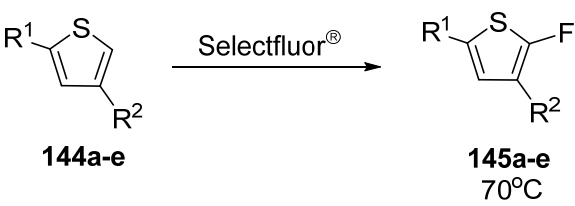
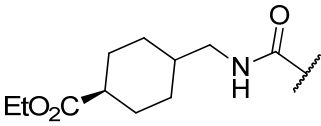
Scheme 42

The use of Selectfluor[®] is described in a patent on the development of a series thiophene-based matrix metalloproteinase 12 inhibitors **145a-e** as potential therapies for the treatment of Chronic Obstructive Pulmonary Disease (COPD) (Table 14) [99]. In related work, Badland *et*

al. used a similar approach to synthesise additional matrix metalloproteinase 12 inhibitors which have also been incorporated into Table 14 [100].

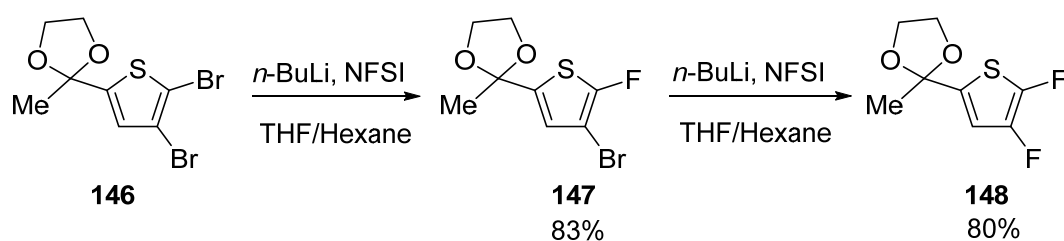
Table 14

Fluorination of disubstituted thiophene substrates using Selectfluor[®]

			
Compound	R ¹	R ²	Yield %
145a		<i>p</i> -CF ₃ OC ₆ H ₄	41
145b	CH ₃ OOC	<i>p</i> -BrC ₆ H ₄	40
145c	HC(O)	<i>p</i> -CF ₃ OC ₆ H ₄	30
145d	CH ₃ OOC	Br	*90
145e	HC(O)	Br	*30

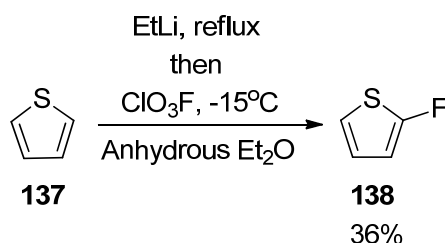
*Only % conversions (determined by HPLC) were reported by the authors for these compounds.

Synthesis of 2,3-difluorothiophene substrates has been achieved by way of selective, sequential halide exchange reactions [101]. Treating 2,3-dibromothiophene **146** with 1.3 equivalents of *n*-butyllithium and NFSI, afforded 2-fluorothiophene **147** in 83% yield (Scheme 43). This monofluorinated intermediate could be transformed into 2,3-difluorothiophene **148** in 80% yield under similar reaction conditions.



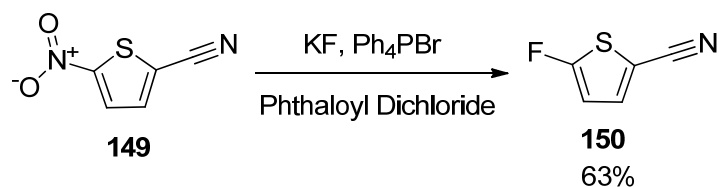
Scheme 43

Rodmar *et al.* have demonstrated selective monofluorination at the 2-position of thiophene using perchloryl fluoride, a source of electrophilic fluorine. Treatment of thiophene (**137**) with ethyllithium in anhydrous ether at gentle reflux, followed by addition of perchloryl fluoride at -15°C , provided the target compound (**138**) in approximately 36% yield (Scheme 44) [102].



Scheme 44

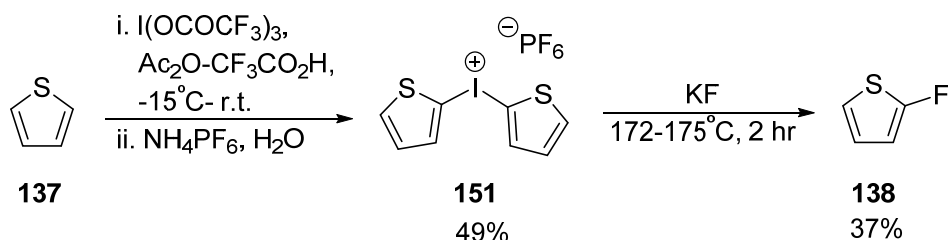
Nucleophilic fluorination has also been used in the preparation of 2-fluorothiophenes. Chambers and Marfat reported the displacement of a nitro group from 2-cyano-5-nitrothiophene (**149**) using potassium fluoride affording 2-cyano-5-fluorothiophene (**150**) in 63% yield (Scheme 45) [103]. Badland *et al.* also examined this route, but noted that the volatile nature of nitrile product **150** made scale-up difficult [100].



Scheme 45

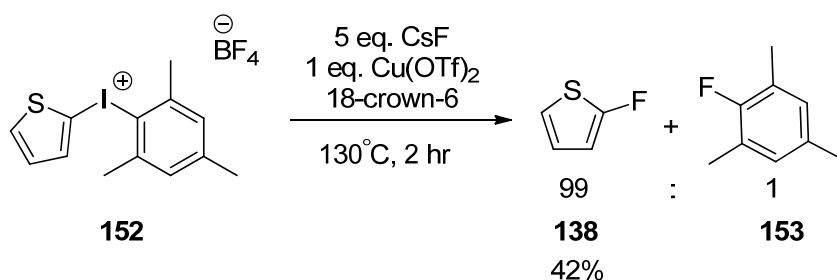
The synthesis of 2-fluorothiophenes from bis-aryl-iodonium salts has been pioneered by Onys'ko [104]. This methodology proceeds *via* a cascade iodination-fluorination where thiophene (**137**) is initially converted to the bis(2-thienyl)iodonium salt **151** using

tris(trifluoroacetoxy)- λ^3 -iodane, an electrophilic source of iodine (Scheme 46). Heating the salt in the presence of dry potassium fluoride furnishes the desired 2-fluorothiophene (**138**) in 37% yield. It was discovered that conversion to the hexafluorophosphate salt **151** is important as the trifluoroacetate salt leads to only trace amounts of the desired product, while the chloride salt results in formation of 2-chlorothiophene as the major product.



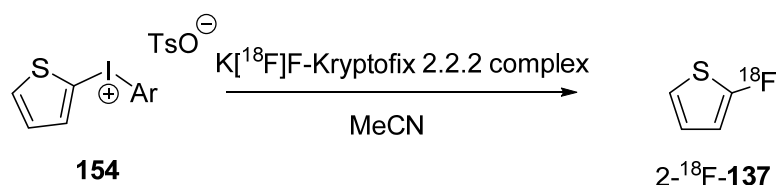
Scheme 46

Expanding on this work, Ichiishi *et al.* have employed copper catalysts to selectively fluorinate the smaller aromatic ligand in unsymmetrical diaryliodonium salts [105]. The reaction shows broad substrate scope, including electron rich aromatic rings. Accordingly, **152** was converted to 2-fluorothiophene in 42% yield in the presence of copper triflate (Scheme 47). In the absence of the copper catalyst, the selectivity was reversed and mesityl fluoride **153** formed the major product in a 2:98 ratio. The authors postulate that the mechanism proceeds *via* a Cu(I)/Cu(III) catalytic cycle based on preliminary DFT (Density Functional Theory) calculations.



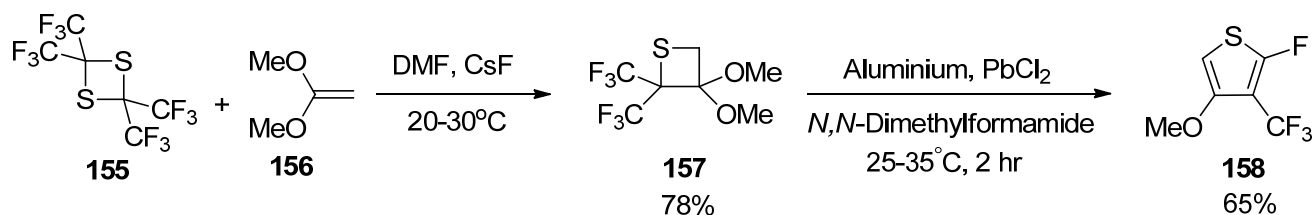
Scheme 47

Chun *et al.* have employed diaryliodonium salts as substrates for the incorporation of ^{18}F . While the focus of this work was the synthesis of radiolabelled benzene derivatives, 2- ^{18}F -thiophene (2- ^{18}F -**137**) was detected, albeit as a minor product in yields of less than 2% (Scheme 48) [106, 107].



Scheme 48

As direct fluorination of the thiophene ring is not always possible, methods have also been developed for the introduction of fluorine prior to formation of the aryl ring. Petrov and Marshall have demonstrated how thietane **157** can be converted to 2-fluorothiophene (**158**) in 65% yield on exposure to activated aluminium powder (Scheme 49) [108]. Thietane **157** was prepared from commercially available 2,2,4,4-tetrakis(trifluoromethyl)-1,3-dithietane (**155**) and 1,1-dimethoxyethylene (**156**) in the DMF in the presence of caesium fluoride catalyst. When the reaction was conducted in the absence of catalyst, the conversion took over three months to reach completion.

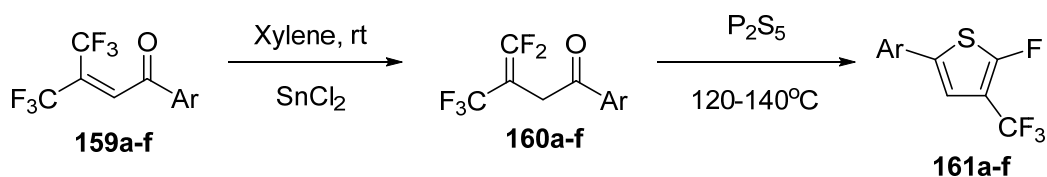


Scheme 49

Burger *et al.* reported the synthesis of a series of 2-fluorothiophenes by way of an apparent 1,5-electrocyclisation process induced by phosphorous pentasulfide [109, 110]. The yields and conditions for these reactions are reported in Table 15. It was observed that higher reaction temperatures and longer reaction times resulted in considerably reduced yields of the 2-fluorothiophene products **161a-f**.

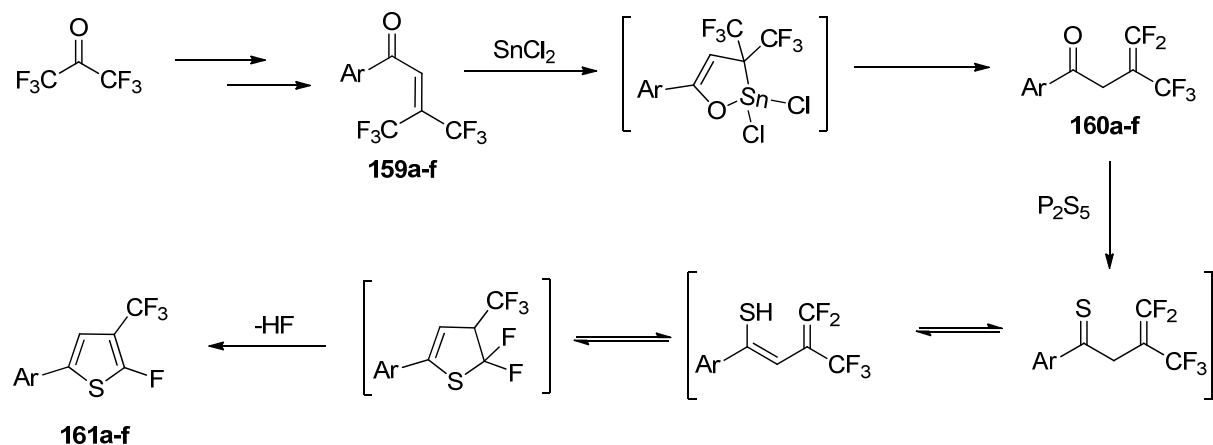
Table 15

1,5-Electrocyclic route to 2-fluorinated thiophenes.



Product	Ar	Yield (%)
161a	Phenyl	55
161b	4-Fluorophenyl	46
161c	2-Fluorophenyl	32
161d	4-Chlorophenyl	59
161e	4-Methoxyphenyl	27
161f	2,4,6-Trimethylphenyl	30

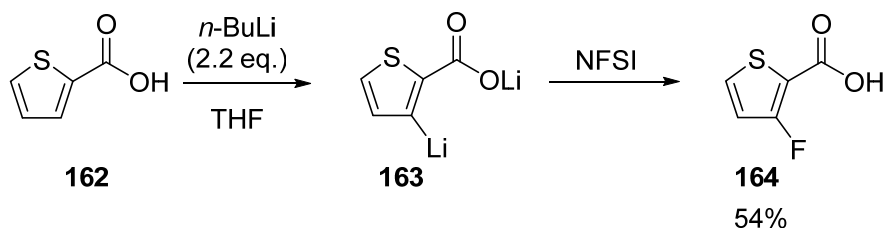
The mechanistic explanation for this reaction, as proposed by the authors, is shown in Scheme 50. Conversion of α,β -unsaturated ketones **159a-f** to β,γ -unsaturated ketone **160a-f** is achieved using tin (II) chloride. Complexation of enones **159a-f** with tin (II) chloride results in migration of the double bond and loss of fluoride to form the β,γ -unsaturated ketones **160a-f**. The ketone then cyclises in the presence of phosphorus pentasulfide *via* an enethiol intermediate to form **161a-f**.



Scheme 50

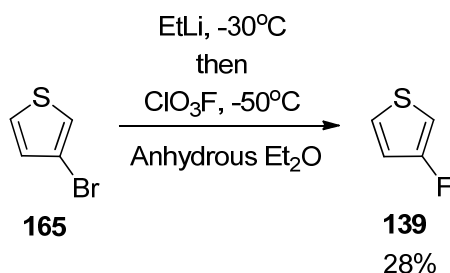
3.2 SYNTHESIS OF 3- AND 4-FLUOROTHIOPHENES

While several methods for selectively fluorinating the 2-position on thiophene have been described in the literature, selective fluorination of the 3-position is more challenging. The most frequently employed strategy involves 2-protected thiophenes, thereby blocking reaction at the 2-position. An early use of this strategy is reported by Taylor and Zhou who prepared 3-fluorothiophene **164** using 2-carboxythiophene (**162**) as a starting material (Scheme 51) [111]. A standard NFSI fluorination was carried out, which normally would be expected to yield the 2- or 5-fluorothiophene; however under the conditions reported 3-fluorothiophene **164** was generated in 54% yield. This regioselectivity is explained by the authors as being a direct result of intramolecular chelation control of the lithiation step by the carboxylic acid.



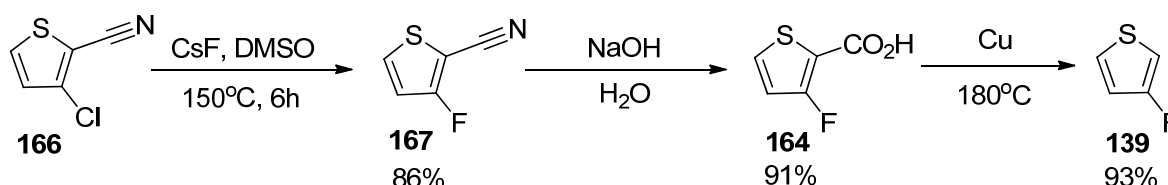
Scheme 51

Rodmar *et al.* achieved selective fluorination of thiophene at the 3-position by way of lithium-halide exchange [102]. Treatment of 3-bromothiophene (**165**) with ethyllithium, followed by reaction with perchloryl fluoride, furnished 3-fluorothiophene (**139**) in approximately 28% yield (Scheme 52).



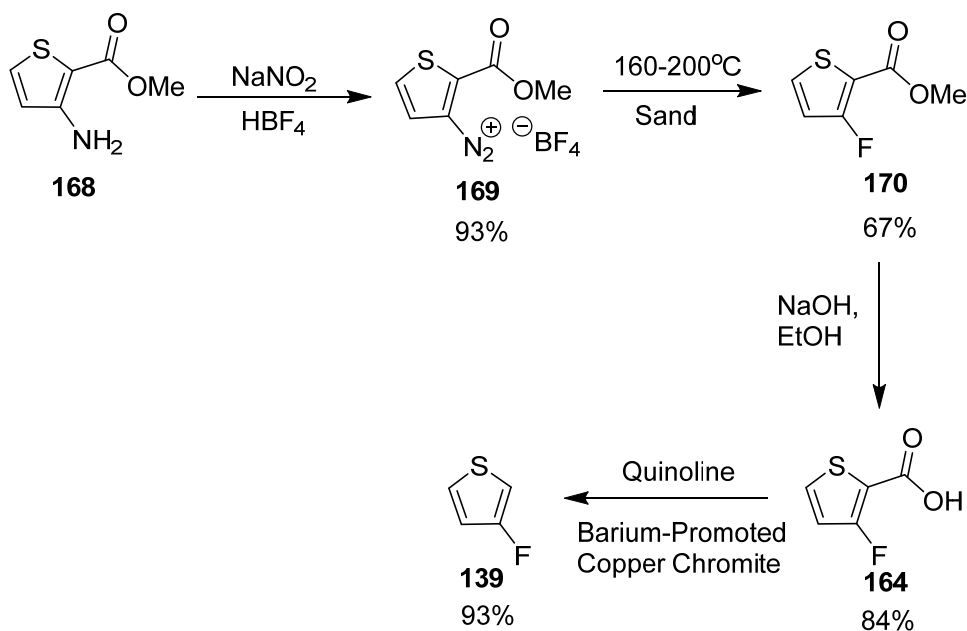
Scheme 52

An example of nucleophilic halide displacement as a way of incorporating fluorine can be seen in the work of El Kassmi *et al.* (Scheme 53) [112]. Chloride **166** is initially converted to fluoride **167** which then undergoes alkaline hydrolysis to furnish 2-carboxyl-3-fluorothiophene (**164**). Removal of the carboxylic acid group was achieved by heating **164** in the presence of copper dust, forming 3-fluorothiophene (**139**) in 93% yield.



Scheme 53

An adaptation of the Schiemann reaction was reported as a means of accessing 3-fluorothiophene (**139**) by Pomerantz and co-workers [113]. Firstly, the diazonium salt **169** was prepared from 3-aminothiophene **168** in 93% yield (Scheme 54). Diazonium salt **169** was then mixed with sand and heated to 160-200°C to form 3-fluorinated thiophene **170** in 84% yield. Basic hydrolysis of the ester, followed by decarboxylation, afforded 3-fluorothiophene (**139**) in 93% yield.



Scheme 54

Direct fluorination of the 3-position of thiophene is particularly challenging without chelation control or controlled halide-lithium exchange, as outlined above. Li *et al.* have overcome this obstacle by using *gem*-difluorohomopropargyl alcohol substrates, of which **171** below is an example (Scheme 55) [114]. Treatment of **171** with methanesulfonyl chloride and triethylamine to form the corresponding mesylate, followed by addition of sodium hydrosulfide, afforded 3-fluorothiophene **172** in 28% overall yield. This methodology has also been applied to the synthesis of 3-fluorofurans.

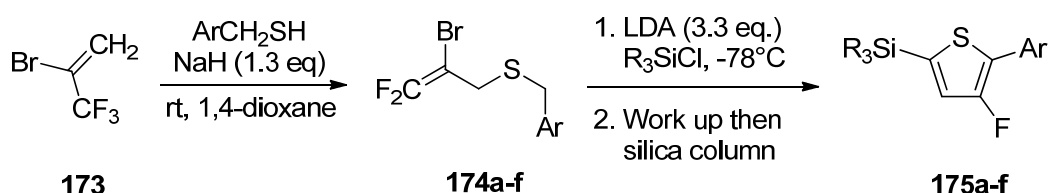


Scheme 55

In a similar vein, Hirotaki and Hanamoto have employed 2-bromo-3,3-difluoroallyl sulfides **174a-f** with great success in the synthesis of a range 3-fluorothiophenes **175a-f** (Table 16) [115]. These difluoroallyl sulfides may be readily synthesised from the S_N2 reaction of 2-bromo-3,3,3-trifluoropropene (**173**) with various thiols. The resulting difluoroallyls can be transformed into 2-aryl-3-fluoro-5-silylthiophenes in a one-pot synthesis. Yields were highest when chlorotriethylsilane was used as the silylating agent. It was also discovered that addition of triethylamine greatly accelerated cyclisation.

Table 16

One-pot synthesis of 2-aryl-3-fluoro-5-silylthiophenes



Entry	Difluoroallyl	Ar	Yield	Thiophene	R	Yield
-------	---------------	----	-------	-----------	---	-------

			(%)			(%)
1	174a	Ph	88	175a	Et	83
2	174b	Ph	88	175b	Me	79
3	174c	Ph	88	175c	PhMe ₂	70
4	174d	Ph	88	175d	Ph ₂ Me	45
5	174e	<i>p</i> -C ₆ H ₄ Me	78	175e	Et	81
6	174f	<i>p</i> -C ₆ H ₄ OH	73	175f	Et	89
7	174g	<i>p</i> -C ₆ H ₄ OMe	75	175g	Et	77
8	174h	<i>o</i> -C ₆ H ₄ Cl	79	175h	Et	77

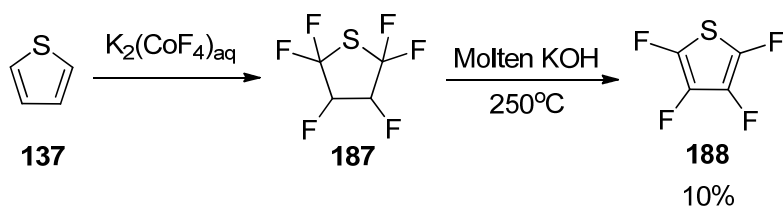
Sakamoto reported the synthesis of perfluorinated thiophene **181** using a series of Pd-mediated couplings (Scheme 56) [116]. 3,4-Dibromo-2,5-trimethylsilylthiophene (**176**) was converted to the difluoro compound **177** by initial formation of the lithium salt and subsequent fluorination with NFSI. **177** was then converted to the tributylstannane **183** via **182**, both of which were subsequently used in later Stille coupling reactions. Conversion of **177** to dibromothiophene **178** and subsequent reaction with two equivalents of *n*-butyllithium, followed by treatment with both NFSI and tributylstannane chloride, yielded **179**. **179** was coupled to **182** and then treated with *N*-bromosuccinimide in acetic acid to afford the 2-thienylthiophene **180**. Lastly, **180** underwent an additional coupling reaction with **183** to furnish the perfluorinated polythiophene **181**.

Table 17Synthesis of α -carboxy- γ -fluorothiophenes

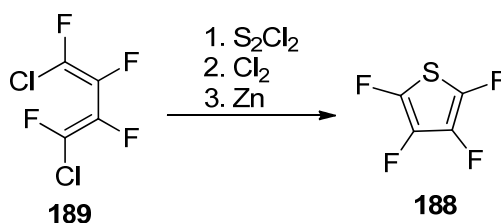
Product	R ¹	R ²	R ³	Yield (%)
186a	Me	H	Et	73%
186b	Me	Me	Et	54%
186c	Ph	Me	Et	85%
186d	H	Me	Et	41%
186e	H	<i>t</i> -Bu	Et	44%
186f	Me	H	Me	71%
186g	Ph	Me	Me	79%

3.3 SYNTHESIS OF PERFLUOROTHIOPHENES

Base-induced elimination of HF from fluorinated thiolane constitutes a short route to tetrafluorothiophenes. An early example is described by Burdon *et al* [118, 119]. Aqueous potassium hydroxide was not sufficiently reactive to effect aromatisation of hexafluorinated thiolane **187** – only on treatment with molten potassium hydroxide was **188** formed, albeit in a low yield of 10% (Scheme 57).

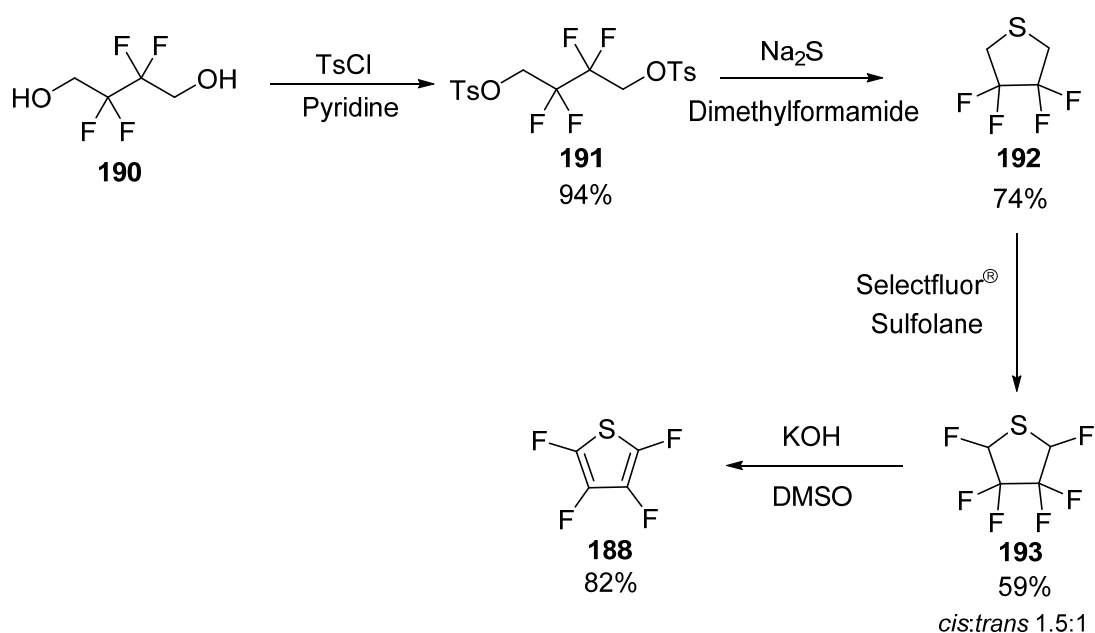
**Scheme 57**

In their search for novel fumigants, the Dow Chemical Company patented a method of synthesising tetrafluorothiophene **188** from polyhalogenated substrate **189**, as shown in Scheme 58 [120]. The yields and intermediates in this route are not elaborated upon in the patent.

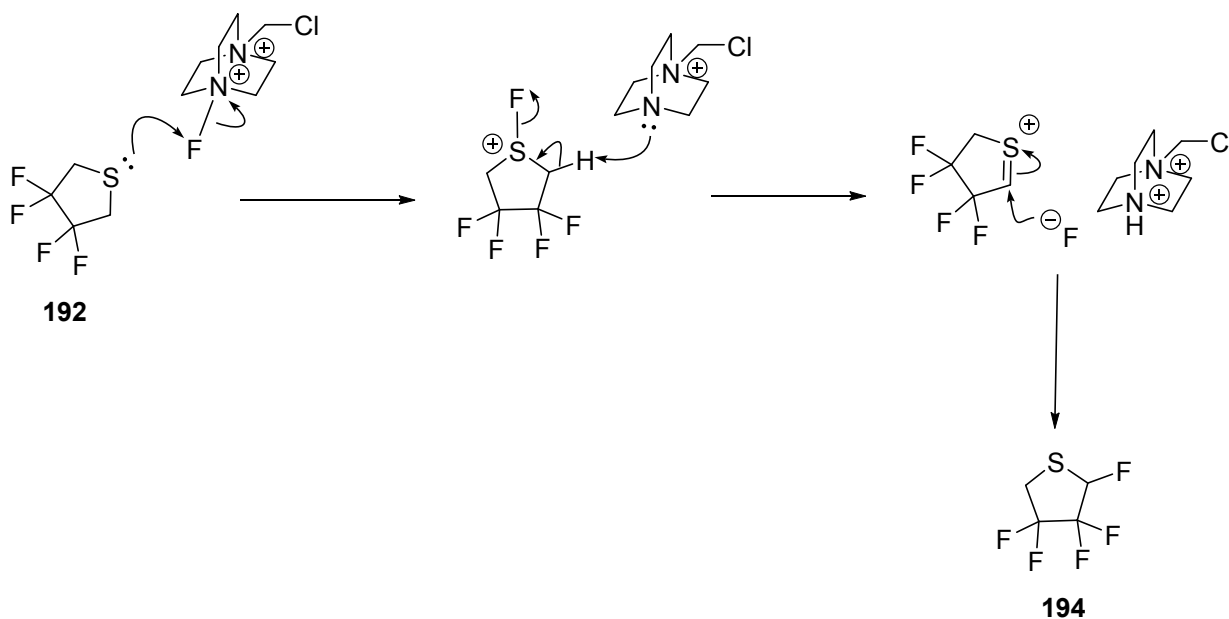


Scheme 58

An alternative route to **188** has been developed by Lemal *et al.* from a different starting point [121]. Reaction of commercially available diol **190** with tosyl chloride in pyridine afforded ditosylate **191** in 94% yield (Scheme 59). Subsequent cyclisation with sodium sulfide in dimethylformamide furnished 3,3,4,4-tetrafluorothiophane (**192**). Tetrafluorothiophane **192** then underwent tandem fluoro-Pummerer rearrangement on treatment with Selectfluor[®] in sulfolane to afford the hexafluorothiophane **193** as a mixture of *cis*- and *trans*-isomers. Sulfolane is sufficiently polar to dissolve Selectfluor[®], but is non-nucleophilic and consequently does not compete for the electrophilic intermediates generated during the fluoro-Pummerer rearrangement. The proposed mechanism for the monofluorination step is outlined in Scheme 60.

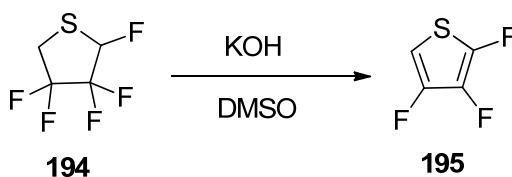


Scheme 59



Scheme 60

Interestingly, if only one equivalent of Selectfluor[®] is used in the penultimate step, pentafluorinated compound **194** is isolable and can be converted to 2,3,4-fluorothiophene (**195**) by reaction with potassium hydroxide in DMSO as shown in Scheme 61.

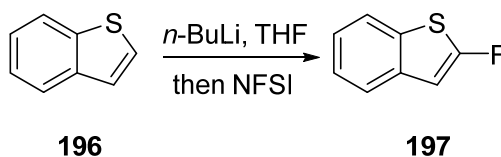


Scheme 61

3.4 SYNTHESIS OF FLUORINATED BENZOTHIOPHENES

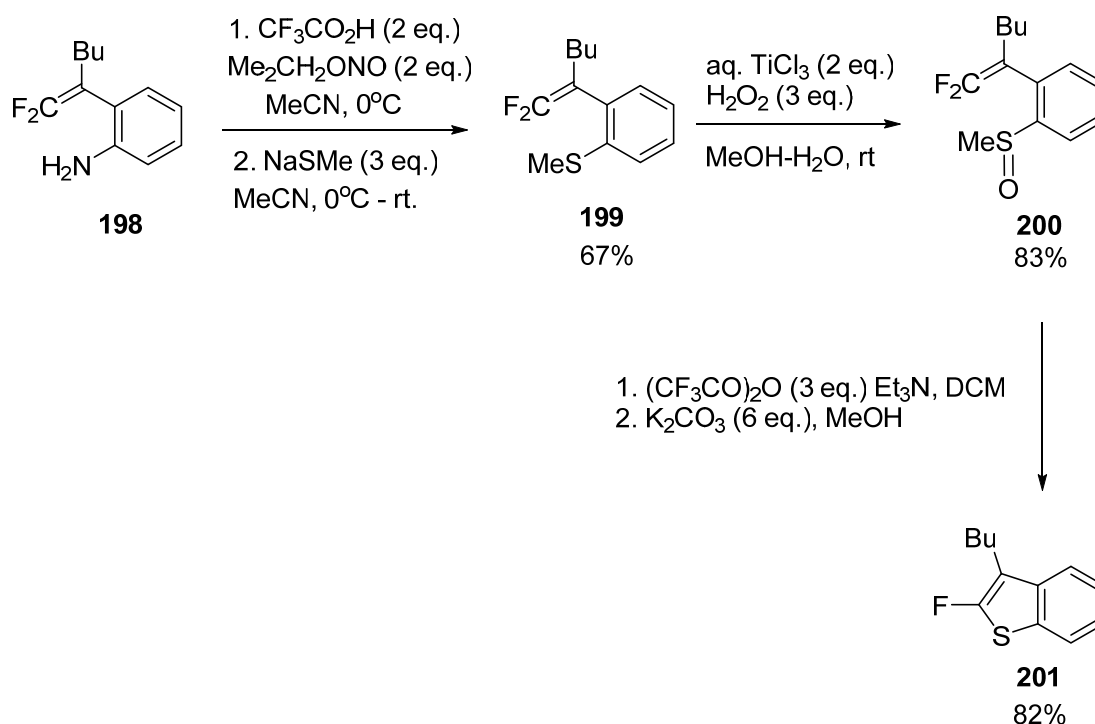
Few examples exist in the literature for the synthesis of fluorinated benzothiophenes to date. Fluorination of the 2-position of benzothiophene (**196**) is described in a 2007 patent on the development of substituted piperidines as potential renin inhibitors by Ehara *et al.*, using the

familiar combination of *n*-butyllithium and NFSI (Scheme 62). No yields are reported for this reaction [122].



Scheme 62

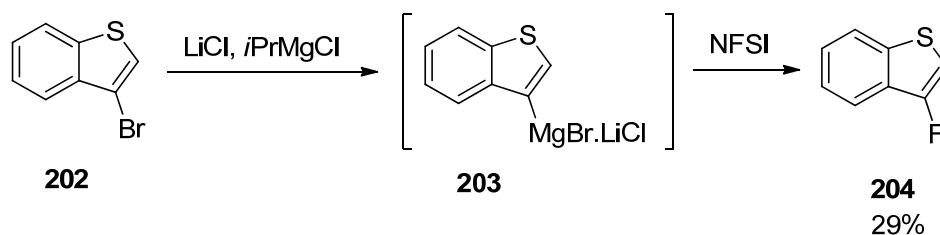
Ichikawa *et al.* synthesized 2-benzothiophene **201** by way of a 5-*endo*-trigonal cyclization, in an approach analogous to that reported earlier for benzofurans [39]. A methylsulfinyl group was introduced into aniline **198** via initial diazotization, followed by nucleophilic addition of sodium methylsulfide, affording **199** in 67% yield over two steps. Oxidation of **199** to sulfoxide **200** was carried out using hydrogen peroxide and titanium (III) chloride in 83% yield. Successive treatment of **200** with (i) trifluoroacetic anhydride and Et₃N and (ii) K₂CO₃ in MeOH provided 2-fluorobenzo[b]thiophene **201** in 82% yield (Scheme 63).



Scheme 63

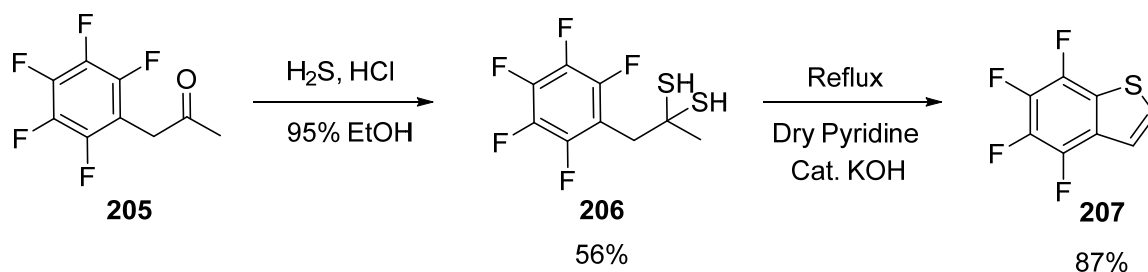
As part of an investigation by Gorelsky *et al.* into palladium-catalysed arylation reactions, 3-fluorobenzothiophene was prepared from 3-bromobenzothiophene (**202**) using a LiCl-mediated Grignard reaction [123]. The reaction proceeds by way of a modified Grignard intermediate **203**, followed by reaction with NFSI, to afford 3-fluorobenzothiophene (**204**) in

29% yield (Scheme 64). Addition of lithium chloride generally results in higher yields and greatly increased rates of formation of the Grignard intermediates [124].



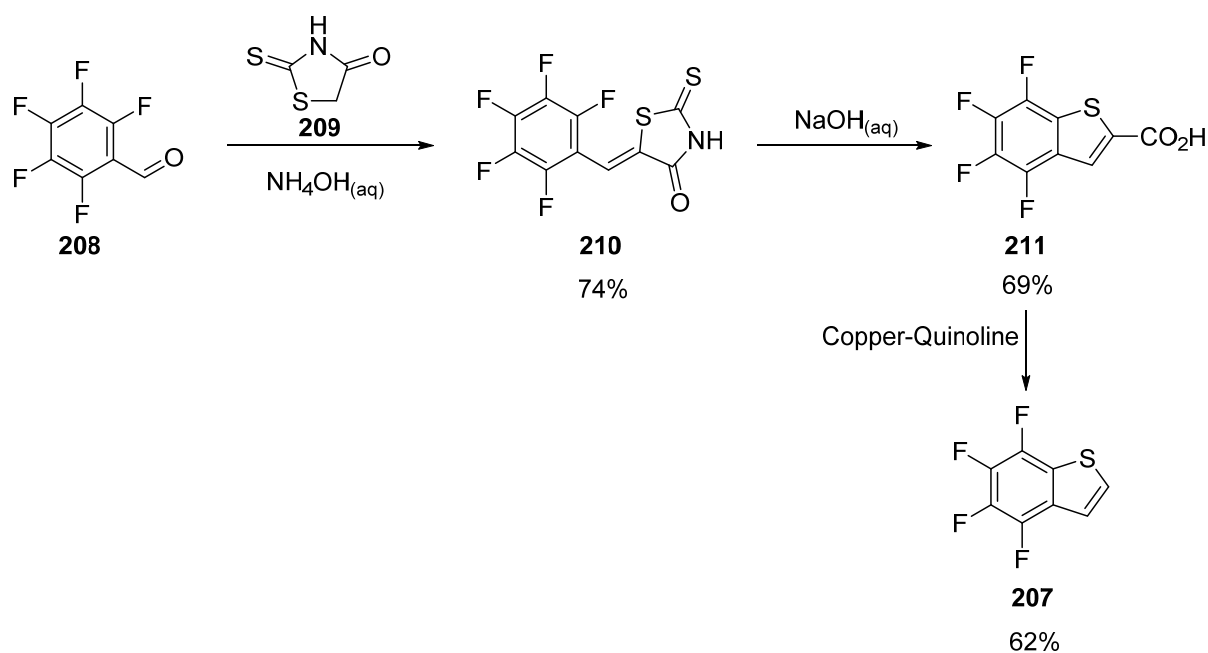
Scheme 64

Brooke has described the synthesis 4,5,6,7-tetrafluorobenzothiophene (**207**) by way of an intramolecular nucleophilic aromatic displacement of fluorine by sulfur as shown in Scheme 65 [125]. Initially, ketone **205** reacts with hydrogen sulphide and hydrogen chloride in 95% ethanol to yield *gem*-thiol **206** in 56% yield. Thiol **206** is subsequently refluxed in dry pyridine in the presence of a catalytic amount of potassium hydroxide affording target compound **207** in 87% yield. While unsure of the specific mechanism by which the potassium hydroxide catalyses the reaction, the authors report that in the absence of same a diminished yield of 47% is obtained.



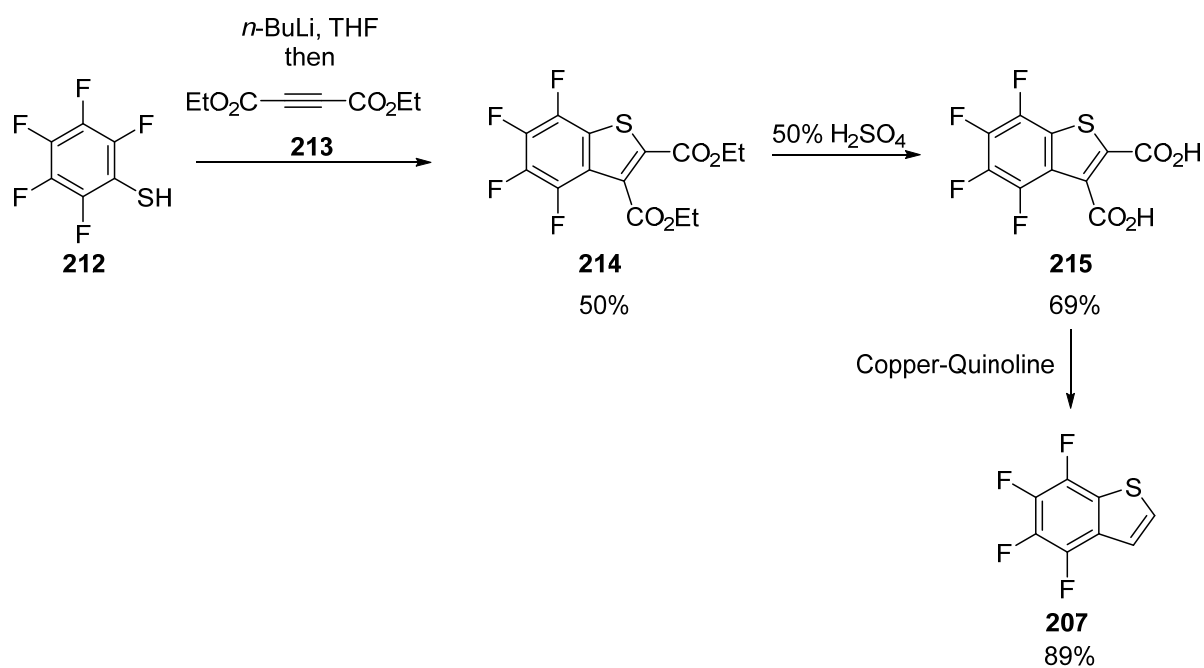
Scheme 65

Castle *et al.* reported the synthesis of benzothiophene **207** starting with rhodanine (**209**) and pentafluorobenzaldehyde (**208**) (Scheme 66) [126]. **208** and **209** were stirred in an aqueous solution of ammonium hydroxide to yield benzylidene **210** in 74% yield. Hydrolysis of **210** with sodium hydroxide generated the thiolate-carboxylate dianion intermediate, which subsequently underwent intramolecular cyclisation to form 4,5,6,7-tetrafluorobenzo[*b*]thiophen-2-carboxylic acid (**211**) in 69% yield. Finally, decarboxylation with copper-quinoline furnished **207** in 62% yield.



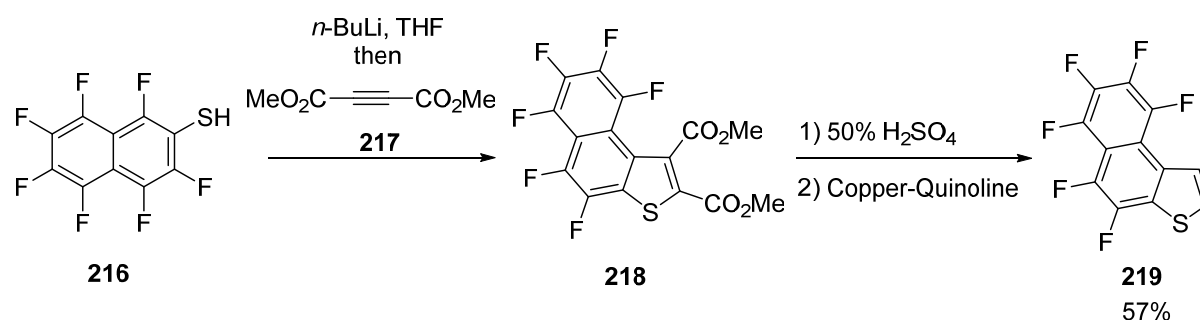
Scheme 66

Fluorinated benzothiophenes may also be accessed by intramolecular nucleophilic aromatic displacement of fluorine by a carbanion [127]. Initially, treatment of **212** with *n*-BuLi generates the thiolate anion which undergoes Michael addition with **213** to form diester **214** in 50% yield (Scheme 67). Acid-mediated ester hydrolysis, followed by decarboxylation over copper-quinoline, furnishes **207** in 89% yield.

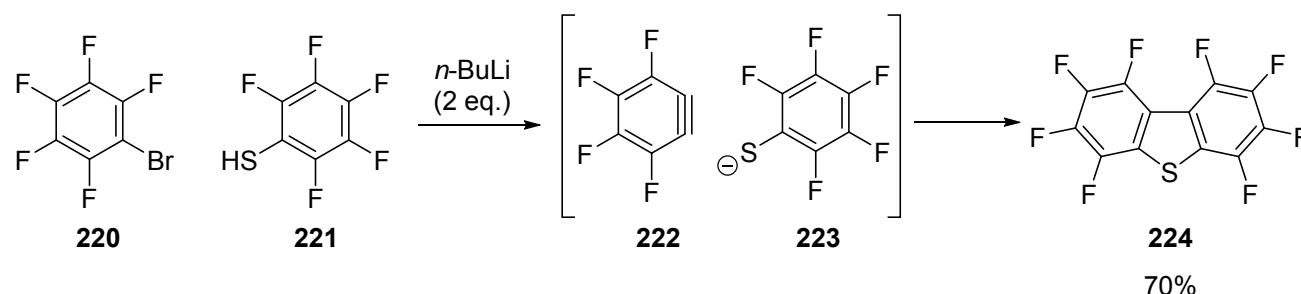


Scheme 67

An analogous approach was employed in the synthesis of naphthothiophene **219** (Scheme 68) [128]. Michael addition of the anion of **216** to **217** afforded diester **218** in quantitative yield as the major regioisomer (92:8). Subsequent hydrolysis and decarboxylation produced naphthothiophene **219** in 57% yield.



Related perfluorinated dibenzothiophenes have been synthesised by Chambers *et al.* (Scheme 69) [129]. Addition of two equivalents of *n*-BuLi to a mixture of **220** and **221** generated aryne **222** and thiolate **223** respectively. Nucleophilic addition of the thiolate to the aryne, followed by intramolecular cyclisation, resulted in a 70% yield of dibenzothiophene **224**.



4 CONCLUSIONS

As demonstrated in this review, several successful strategies have been employed to access fluorinated oxygen- and sulfur-containing heteroaromatics. Many selective methods have been developed for direct incorporation of fluorine into oxygen-containing heterocycles; however, it is also evident that some targets can only be accessed indirectly, using fluorinated substrates to access fluorinated heteroaromatic compounds.

Comparatively fewer procedures are present in the literature for the fluorination of sulfur-containing heterocycles in comparison to their oxygen analogues. This is, perhaps, a reflection of the greater level of interest in oxygen-based heteroaromatic targets.

In conclusion, a systematic review of the methods for accessing fluorinated oxygen and sulfur containing heterocycles has been presented which complements existing reviews in this area. The work presented here will be of broad interest to fluoroorganic chemists and those working in the field of heterocyclic synthesis.

ACKNOWLEDGMENTS

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REFERENCES

- [1] C.D. Murphy, D. O'Hagan, C. Schaffrath, *Angew. Chem. Int. Ed.* 40 (2001) 4479-4481.
- [2] A.M. Thayer, *Chem. Eng. News* 84 (2006) 15-21.
- [3] K.K.J. Chan, D. O'Hagan, *Methods Enzymol.* 516 (2012) 219-235.
- [4] J. Wang, M. Sanchez-Rosello, J.L. Acena, C. del Pozo, A.E. Sorochinsky, S. Fustero, V.A. Soloshonok, H. Liu, *Chem. Rev.* 114 (2014) 2432-2506.
- [5] R. Filler, R. Saha, *Future Med. Chem.* 1 (2009) 777-791.
- [6] J.C. Biffinger, H.W. Kim, S.G. DiMagno, *ChemBioChem* 5 (2004) 622-627.
- [7] M.D. Johnson, J. Chen, B.D. Anderson, *Drug Metab. Dispos.* 30 (2002) 191-198.
- [8] D. O'Hagan, *Chem. Soc. Rev.* 37 (2008) 308-319.
- [9] D.B. Berkowitz, M. Bose, *J. Fluorine Chem.* 112 (2001) 13-33.
- [10] B.K. Park, N.R. Kitteringham, P.M. O'Neill, *Annu. Rev. Pharmacol.* 41 (2001) 443-470.
- [11] J.-P. Bégué, D. Bonnet-Delpon, *J. Fluorine Chem.* 127 (2006) 992-1012.
- [12] T.J. Ritchie, S.J.F. Macdonald, R.J. Young, S.D. Pickett, *Drug Discov. Today* 14 (2009) 1011-1020.
- [13] A.W. Czarnik, *Acc. Chem. Res.* 29 (1996) 112-113.
- [14] A. Gomtsyan, *Chem. Heterocycl. Compd.* 48 (2012) 7-10.
- [15] N.R. Emmadi, K. Atmakur, G.K. Chityal, S. Pombala, J.B. Nanubolu, *Bioorg. Med. Chem. Lett.* 22 (2012) 7261-7264.
- [16] J.B. Sperry, D.L. Wright, *Curr. Opin. Drug Discov. Dev.* 8 (2005) 723-740.
- [17] G.G. Furin, *Adv. Heterocycl. Chem.* 86 (2003) 129-224.
- [18] G.G. Furin, *Adv. Heterocycl. Chem.* 87 (2004) 273-383.
- [19] G.G. Furin, *Adv. Heterocycl. Chem.* 88 (2005) 231-309.
- [20] K. Burger, L. Hennig, J. Spengler, F. Albericio, *Heterocycles* 69 (2006) 569-592.
- [21] O. Serdyuk, A. Butin, V. Abaev, *J. Fluorine Chem.* 131 (2010) 296-319.
- [22] G.M. Brooke, *J. Fluorine Chem.* 86 (1997) 115-223.
- [23] G.G. Yakobson, T.D. Petrova, L.S. Kobrina, *Fluorine Chemistry Reviews*, Marcel Dekker, New York, 1974.
- [24] G. De Luca, *US Pat. Appl.* US20050222225 A1 (2004).
- [25] T. Rueckle, X. Jiang, P. Gaillard, D. Church, T. Vallotton, *US Pat. Appl.* US20060122176 A1 (2006).
- [26] A.D. Borthwick, R.J. Hatley, D.M.B. Hickey, J. Liddle, D.G.H. Livermore, A.M. Mason, N.D. Miller, F. Nerozzi, S.L. Sollis, A.K. Szardengings, P.G. Wyatt, *US Pat. Appl.* US20050148572 A1 (2005).
- [27] E. Phillips, Y. Li, H.-F. Chang, *US Pat. Appl.* US20050176745 A1 (2005).
- [28] S. Martin-Santamaria, M.A. Carroll, C.M. Carroll, C.D. Carter, V.W. Pike, H.S. Rzepa, D.A. Widdowson, *Chem. Comm.* (2000) 649-650.
- [29] T. Ritter, T. Furuya, H.M. Kaiser, *US Pat. Appl.* US20110054175 A1 (2011).
- [30] T. Furuya, H.M. Kaiser, T. Ritter, *Angew. Chem.* 47 (2008) 5993-5996.
- [31] J. Bailey, R.G. Plevy, J.C. Tatlow, *Tetrahedron Lett.* 16 (1975) 869-870.
- [32] D.H.R. Barton, R.H. Hesse, G.P. Jackman, M.M. Pechet, *J. Chem. Soc. Perkin Trans. 1* (1977) 2604-2608.
- [33] S. Hibi, T. Hida, K. Kikuchi, K. Kobayashi, N. Kobayashi, M. Nagai, Y. Nagasaka, Y. Okamoto, M. Okita, T. Sato, K. Tagami, K. Tai, N. Tokuhara, H. Yoshimura, *US Pat. Grant* US6121309 A (2000).
- [34] A. Kandil, E.E. Galal, *J. Drug. Res. Egypt* 7 (1975) 109.
- [35] S.A. Nash, R.B. Gammill, *Tetrahedron Lett.* 28 (1987) 4003-4006.
- [36] Y. Wang, L. Li, W. Ye, Z. Tian, W. Jiang, H. Wang, S.C. Wright, J.W. Larrick, *J. Med. Chem.* 46 (2003) 634-637.
- [37] Y. Wang, H. Yuan, W. Ye, S.C. Wright, H. Wang, J.W. Larrick, *J. Med. Chem.* 43 (2000) 1541-1549.
- [38] G.M. Brooke, W.K.R. Musgrave, T.R. Thomas, *J. Chem. Soc. C* (1971) 3596-3599.
- [39] J. Ichikawa, Y. Wada, T. Okauchi, T. Minami, *Chem. Comm.* (1997) 1537-1538.
- [40] M. Zupan, J. Iskra, S. Stavber, *Tetrahedron* 52 (1996) 11341-11348.

- [41] M. Zupan, J. Iskra, S. Stavber, *J. Org. Chem.* 63 (1998) 878-880.
- [42] R.G. Johnson, H.B. Willis, G.A. Martin, W.H. Kirkpatrick, J. Swiss, H. Gilman, *J. Org. Chem.* 21 (1956) 457-460.
- [43] D.C. England, E.A. Donald, F.J. Weigert, *J. Org. Chem.* 46 (1981) 144-147.
- [44] Y. Wang, D.J. Burton, *J. Org. Chem.* 71 (2006) 3859-3862.
- [45] W. Chaladaj, M. Corbet, A. Fürstner, *Angew. Chem. Int. Ed.* 51 (2012) 6929-6933.
- [46] D.C. England, C.G. Krespan, *J. Org. Chem.* 35 (1970) 3322-3327.
- [47] S. Rozen, O. Lerman, M. Kol, D. Hebel, *J. Org. Chem.* 50 (1985) 4753-4758.
- [48] S. Rozen, M. Brand, *J. Org. Chem.* 51 (1986) 3607-3611.
- [49] M. Sato, T. Taniguchi, T. Hirokawa, C. Kaneko, *Tetrahedron Lett.* 36 (1995) 6705-6708.
- [50] D. Holling, G. Sandford, A.S. Batsanov, D.S. Yufit, J.A.K. Howard, *J. Fluorine Chem.* 126 (2005) 1377-1383.
- [51] M. Curini, F. Epifano, F. Maltese, M.C. Marcotullio, A. Tubaro, G. Altinier, S.P. Gonzales, J.C. Rodriguez, *Bioorg. Med. Chem. Lett.* 14 (2004) 2241-2243.
- [52] I. Jabin, N.D. Heindel, R.D. Rapp, J.D. Laskin, *J. Heterocycl. Chem.* 37 (2000) 31-39.
- [53] M. Marhold, A. Buer, H. Hiemstra, J.H. van Maarseveen, G. Haufe, *Tetrahedron Lett.* 45 (2004) 57-60.
- [54] M. Marhold, C. Stillig, R. Fröhlich, G. Haufe, *Eur. J. Org. Chem.* 2014 (2014) 5777-5785.
- [55] S. Fustero, A. Simón-Fuentes, P. Barrio, G. Haufe, *Chem. Rev.* 115 (2015) 871-930.
- [56] G.-Q. Shi, W. Qian, M. Schlosser, *Tetrahedron* 52 (1996) 4403-4410.
- [57] G.-Q. Shi, S. Takagishi, M. Schlosser, *Tetrahedron* 50 (1994) 1129-1134.
- [58] H. Von Pechmann, C. Duisberg, *Ber. Dtsch. Chem. Ges.* 16 (1883) 2119-2128.
- [59] H. Von Pechmann, *Ber. Dtsch. Chem. Ges.* 17 (1884) 929-936.
- [60] K. Harada, H. Kubo, Y. Tomigahara, K. Nishioka, J. Takahashi, M. Momose, S. Inoue, A. Kojima, *Bioorg. Med. Chem. Lett.* 20 (2010) 272-275.
- [61] J.M. Timonen, R.M. Nieminen, O. Sareila, A. Goulas, L.J. Moilanen, M. Haukka, P. Vainiotalo, E. Moilanen, P.H. Aulaskari, *Eur. J. Med. Chem.* 46 (2011) 3845-3850.
- [62] P. Reszka, R. Schulz, K. Methling, M. Lalk, P.J. Bednarski, *ChemMedChem* 5 (2010) 103-117.
- [63] L. Xie, C.-H. Zhao, T. Zhou, H.-F. Chen, B.-T. Fan, X.-H. Chen, J.-Z. Ma, J.-Y. Li, Z.-Y. Bao, Z. Lo, D. Yu, K.-H. Lee, *Bioorg. Med. Chem.* 13 (2005) 6435-6449.
- [64] R. Pasceri, H.E. Bartrum, C.J. Hayes, C.J. Moody, *Chem. Comm.* 48 (2012) 12077-12079.
- [65] R.E. Banks, N.J. Lawrence, A.L. Popplewell, *J. Chem. Soc. Chem. Comm.* (1994) 343-344.
- [66] Y.V. Zonov, V.M. Karpov, V.E. Platonov, *J. Fluorine Chem.* 128 (2007) 1065-1073.
- [67] Y.V. Zonov, V.M. Karpov, V.E. Platonov, *Russ. J. Org. Chem.* 46 (2010) 1517-1526.
- [68] Y.V. Zonov, V.M. Karpov, V.E. Platonov, *J. Fluorine Chem.* 135 (2012) 159-166.
- [69] I. Hussain, M.A. Yawer, M. Lau, T. Pundt, C. Fischer, H. Görls, P. Langer, *Eur. J. Org. Chem.* 2008 (2008) 503-518.
- [70] T. Pundt, M. Lau, I. Hussain, M.A. Yawer, H. Reinke, P. Langer, *Tetrahedron Lett.* 48 (2007) 2745-2747.
- [71] M. Médebielle, R. Keirouz, E. Okada, D. Shibata, W.R. Dolbier Jr, *Tetrahedron Lett.* 49 (2008) 589-593.
- [72] Y. Hou, S. Higashiya, T. Fuchigami, *J. Org. Chem.* 64 (1999) 3346-3349.
- [73] R.G. Britton, E. Horner-Glister, O.A. Pomenya, E.E. Smith, R. Denton, P.R. Jenkins, W.P. Steward, K. Brown, A. Gescher, S. Sale, *Eur. J. Med. Chem.* 54 (2012) 952-958.
- [74] M. Menichincheri, D. Ballinari, A. Bargiotti, L. Bonomini, W. Ceccarelli, R. D'Alessio, A. Fretta, J. Moll, P. Polucci, C. Soncini, M. Tibolla, J.-Y. Trosset, E. Vanotti, *J. Med. Chem.* 47 (2004) 6466-6475.
- [75] B. Košmrlj, B. Šket, *Org. Lett.* 9 (2007) 3993-3996.
- [76] D.A. Watson, M. Su, G. Teverovskiy, Y. Zhang, J. García-Fortanet, T. Kinzel, S.L. Buchwald, *Science* 325 (2009) 1661-1664.
- [77] G. Angelini, M. Speranza, A.P. Wolf, C.Y. Shiue, *J. Fluorine Chem.* 27 (1985) 177-191.
- [78] V.V. Grushin, *Chem. Eur. J.* 8 (2002) 1006-1014.

- [79] W.J. Marshall, V.V. Grushin, *Organometallics* 22 (2002) 555-562.
- [80] W.J. Marshall, V.V. Grushin, *Organometallics* 23 (2004) 3343-3347.
- [81] V.V. Grushin, W.J. Marshall, *J. Am. Chem. Soc.* 126 (2004) 3068-3069.
- [82] S.A. Macgregor, D.C. Roe, W.J. Marshall, K.M. Bloch, V.I. Bakhmutov, V.V. Grushin, *J. Am. Chem. Soc.* 127 (2005) 15304-15321.
- [83] E.V. Nosova, G.N. Lipunova, A.A. Laeva, V.N. Charushin, *Russ. J. Org. Chem.* 42 (2006) 1544-1550.
- [84] G.N. Lipunova, E.V. Nosova, M.I. Kodess, V.N. Charushin, *Russ. J. Org. Chem.* 40 (2004) 1162-1166.
- [85] K.V. Shcherbakov, Y.V. Burgart, V.I. Saloutin, *Russ. J. Org. Chem.* 49 (2013) 719-729.
- [86] S.P. Kisil', Y.V. Burgart, V.I. Saloutin, O.N. Chupakhin, *J. Fluorine Chem.* 108 (2001) 125-131.
- [87] E. Vieira, J. Huwyler, S. Jolidon, F. Knoflach, V. Mutel, J. Wichmann, *Bioorg. Med. Chem. Lett.* 19 (2009) 1666-1669.
- [88] S. Horne, R. Rodrigo, *J. Org. Chem.* 55 (1990) 4520-4522.
- [89] Z.R. Woydziak, L. Fu, B.R. Peterson, *J. Org. Chem.* 77 (2011) 473-481.
- [90] C.-A. Chen, R.-H. Yeh, D.S. Lawrence, *J. Am. Chem. Soc.* 124 (2002) 3840-3841.
- [91] L.F. Mottram, S. Boonyarattanakalin, R.E. Kovel, B.R. Peterson, *Org. Lett.* 8 (2006) 581-584.
- [92] R.A. Dodean, J.X. Kelly, D.H. Peyton, G.L. Gard, M.K. Riscoe, R.W. Winter, *Bioorg. Med. Chem.* 16 (2008) 1174-1183.
- [93] G. Cerichelli, M.E. Crestoni, S. Fornarini, *Gazz. Chim. Ital.* 120 (1990) 749-755.
- [94] R.T. VanVleck, *J. Am. Chem. Soc.* 71 (1949) 3256-3257.
- [95] R. Taylor, *Electrophilic Substitution of Thiophene and its Derivatives*, John Wiley & Sons, Hoboken, NJ, 2008.
- [96] R.E. Banks, R.A. Du Boisson, E. Tsiliopoulos, *J. Fluorine Chem.* 32 (1986) 461-466.
- [97] H. Lundbeck, *US Pat. Appl. WO2004/58739 A1* (2004).
- [98] L. Gobbi, G. Jaeschke, T. Luebbers, O. Roche, R.M. Rodriguez Sarmiento, L. Steward, *US Pat. Appl. US2007/197531 A1* (2007).
- [99] D. Compere, A.-C. Dublanchet, K. Courte, S. Blais, *US Pat. Appl. US20050014817 A1* (2005).
- [100] M. Badland, D. Compère, K. Courté, A.-C. Dublanchet, S. Blais, A. Manage, G. Peron, R. Wrigglesworth, *Bioorg. Med. Chem. Lett.* 21 (2011) 528-530.
- [101] G. Lai, T. Guo, *Synth. Commun.* 38 (2008) 72-76.
- [102] S. Rodmar, B. Rodmar, M.K. Sharma, S. Gronowitz, H. Christiansen, U. Rosen, *Acta Chem. Scand.* 22 (1968) 907-920.
- [103] A. Marfat, R.J. Chambers, *US Pat. Grant US6096901 A* (2000).
- [104] P.P. Onys'ko, T.V. Kim, O.I. Kiseleva, Y.V. Rassukana, A.A. Gakh, *J. Fluorine Chem.* 130 (2009) 501-504.
- [105] N. Ichiishi, A.J. Canty, B.F. Yates, M.S. Sanford, *Org. Lett.* 15 (2013) 5134-5137.
- [106] J.-H. Chun, S. Lu, V.W. Pike, *Eur. J. Org. Chem.* 2011 (2011) 4439-4447.
- [107] J.-H. Chun, V.W. Pike, *Org. Biomol. Chem.* 11 (2013) 6300-6306.
- [108] V.A. Petrov, W. Marshall, *J. Fluorine Chem.* 143 (2012) 220-225.
- [109] K. Burger, B. Helmreich, *J. Chem. Soc. Chem. Comm.* (1992) 348-349.
- [110] K. Burger, B. Helmreich, L. Hennig, J. Spengler, F. Albericio, A. Fuchs, *Monatsh. Chem.* 138 (2007) 227-236.
- [111] E.C. Taylor, P. Zhou, *Org. Prep. Proced. Int.* 29 (1997) 221-223.
- [112] A. El Kassmi, F. Fache, M. Lemaire, *Synth. Commun.* 24 (1994) 95-101.
- [113] M. Pomerantz, N. Turkman, *Synthesis* 2008 (2008) 2333-2336.
- [114] P. Li, Z. Chai, G. Zhao, S.-Z. Zhu, *Tetrahedron* 65 (2009) 1673-1678.
- [115] K. Hirota, T. Hanamoto, *Org. Lett.* 15 (2013) 1226-1229.
- [116] Y. Sakamoto, S. Komatsu, T. Suzuki, *J. Am. Chem. Soc.* 123 (2001) 4643-4644.
- [117] D.F. Andrès, E.G. Laurent, B.S. Marquet, *Tetrahedron Lett.* 38 (1997) 1049-1052.
- [118] J. Burdon, J.G. Campbell, I.W. Parsons, J.C. Tatlow, *J. Chem. Soc. Chem. Comm.* (1969) 27-28.

- [119] J. Burdon, J.G. Campbell, I.W. Parsons, J.C. Tatlow, J. Chem. Soc. C (1971) 352-355.
- [120] E.M. Ilgenfritz, R.P. Ruh, US Pat. Grant US2932651 A (1960).
- [121] D.M. Lemal, M. Akashi, Y. Lou, V. Kumar, J. Org. Chem. 78 (2013) 12330-12337.
- [122] T. Ehara, Y. Hitomi, K. Konishi, K. Masuya, US Pat. Appl. US20090137566 A1 (2009).
- [123] S.I. Gorelsky, D. Lapointe, K. Fagnou, J. Am. Chem. Soc. 130 (2008) 10848-10849.
- [124] A. Krasovskiy, P. Knochel, Angew. Chem. Int. Ed. 43 (2004) 3333-3336.
- [125] G.M. Brooke, Tetrahedron Lett. 37 (1968) 4049-4052.
- [126] M.D. Castle, R.G. Plevy, J.C. Tatlow, J. Chem. Soc. C (1968) 1225-1227.
- [127] G.M. Brooke, M. Abul Quasem, J. Chem. Soc. C (1967) 865-869.
- [128] G.M. Brooke, J. Fluorine Chem. 43 (1989) 393-403.
- [129] R.D. Chambers, D.J. Spring, Tetrahedron Lett. 29 (1969) 2481-2482.