PERKIN 1

Fluorination of sulfanyl amides using difluoroiodoarene reagents

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A range of sulfur-containing amides have been fluorinated with the hypervalent iodine difluoride reagents **1**, and two principal reaction pathways identified. Cephalosporin esters **2** having a heteroatom in the α-position to sulfur undergo fluorination in DCM with cleavage of the carbon–sulfur bond to form novel fluorinated β-lactams **4**. Sulfides with electron-withdrawing groups in the α-position undergo α-fluorination in a process analogous to the classical Pummerer reaction. This Fluoro-Pummerer reaction has been exemplified for a range of simple α-phenylsulfanylacetamides **14**–**19**. When β-hydrogens are present in the substrate a different route is followed, with deprotonation by basic fluoride taking place to yield vinyl sulfides **41**–**43**. When an excess of the fluorinating reagent is used these vinyl sulfides can undergo further reaction in a novel tandem Pummerer-Additive-Pummerer process to yield α,β-difluoro sulfides **45**–**47**.

Introduction

In the preceding paper we described the fluorination of a range of α-phenylsulfanylated esters with difluoroiodotoluene **1a** (Fig. 1).[1] Fluorination was observed to give the α-fluoro sulfides

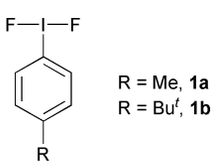


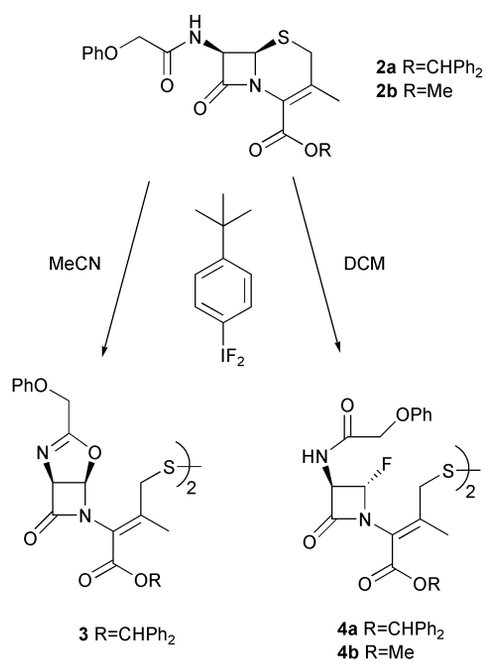
Fig. 1

through a Fluoro-Pummerer reaction, and we defined the mechanism as being of Type 2. The present paper presents, in full detail, our results from fluorinating two different classes of amido-sulfides with difluoroiodoarenes **1**.[2] The first study describes the reactions of some cephalosporin esters which exhibit Type 1 behaviour, where fluorination occurs through cleavage of the carbon–sulfur bond, whilst the second reports on the behaviour of α-phenylsulfanylated amides and lactams which follow a Type 2 pathway.

Results and discussion

The highly functionalised cephalosporin esters **2** were initially selected for study as an intriguing test bed for probing the reactivity of hypervalent iodoarene difluorides. In this particular instance, both Type 1 and Type 2 reactions are theoretically possible but the major directing influence for each pathway is attenuated by the overall connectivity within the molecular architecture. Thus, the carbonyl group of the β-lactam will, to some extent, diminish the nucleophilicity of the nitrogen atom and hence render direct participation by the Type 1 path more difficult than, for example, the case of dithioketals[3] or phenylthioglycosides.[4] In similar fashion, the electron withdrawing group which is required to enhance the acidity of the protons H_α for the Type 2 reaction resides in a vinylogous ester which also has enamide double bond character.

In the event, treatment of benzyhydryl ester **2a** with one equivalent of *p-tert*-butyliodobenzene difluoride **1b** in DCM afforded the chromatographically unstable fluoroazetidinone disulfide **4a** in up to 30% yield (Scheme 1).



Scheme 1

The stereochemistry of **4** was readily deduced from the proton and fluorine NMR spectra which indicated the absence of *cis*-vicinal coupling between the azetidinone ring protons.

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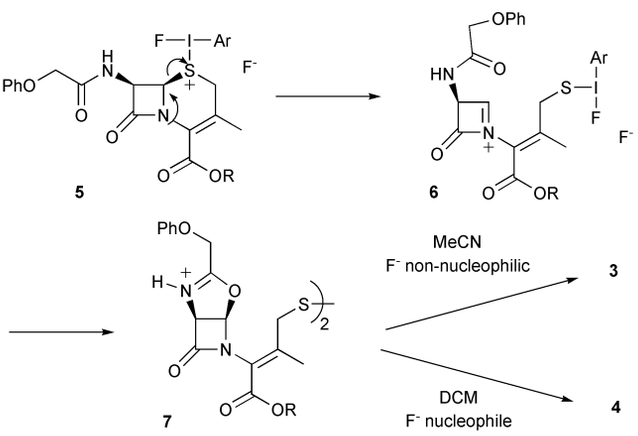
The methyl ester **2b** led to the analogous derivative **4b** in similar yield. By contrast, the reaction with acetonitrile as solvent led to the isolation of the oxazoline derivative **3** in 33% yield, most certainly as a result of the precedented participation of the side chain amide.[5]

The simplest mechanistic rationale for this solvent-dependant divergence of behaviour is that the iodine difluoride is first activating the sulfide leading to cleavage of the carbon–sulfur bond, with Type 1 anchimeric assistance from nitrogen (Scheme 2). The resultant acyl iminium ion is then trapped by



Scheme 2

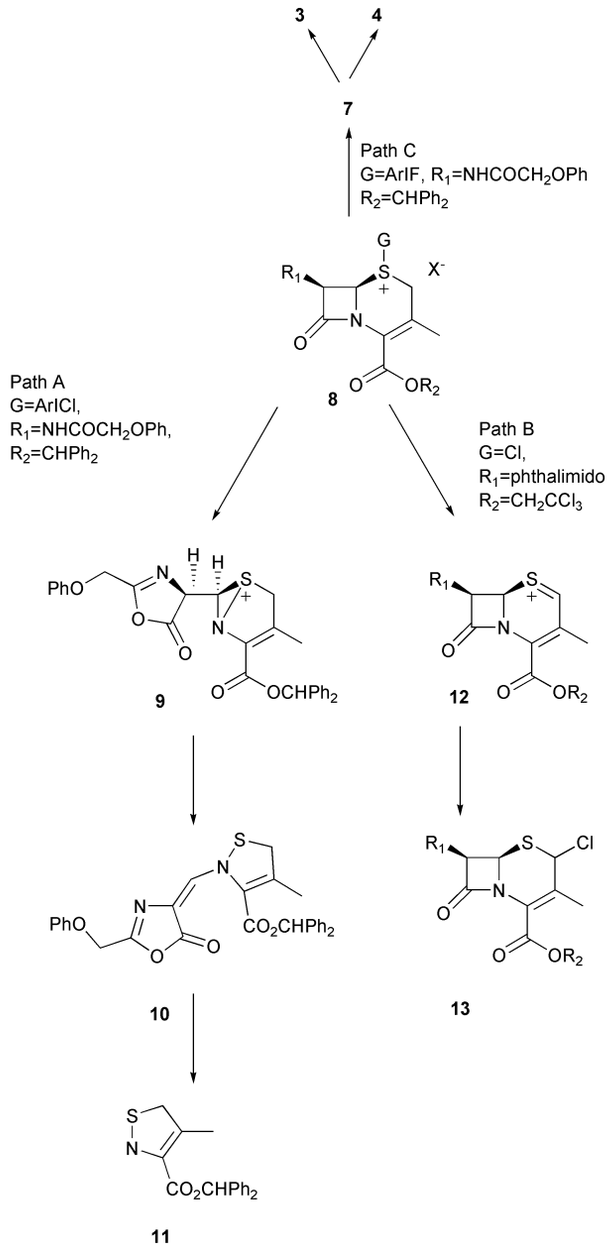
the amide carbonyl group to produce intermediate **7**. Use of dichloromethane as solvent then permits nucleophilic attack of fluoride on **7**, forming **4**, whereas the reduced nucleophilicity of fluoride in acetonitrile[6] precludes the fluorination of **7**, deprotonation giving the oxazoline **3**.

Cephalosporin(v) esters with non-nucleophilic amide side-chains have been reported to undergo the Pummerer reaction when treated with NCS, forming the 2-chloro cephems **13**, *via* **12**, in a Type 2 "Chloro-Pummerer" reaction.[7] In order to investigate whether a change of nucleophile could alter the course of our iodoarene mediated halogenation, we therefore treated **2a** with *p*-*tert*-butyliodobenzene dichloride under anhydrous conditions. The rearranged isothiazole **11** was isolated as the major product in 31% yield, (52% based on recovered starting material). Isothiazole formation has been observed for cephalosporins with nucleophilic amide side chains when treated with NCS.[7] An analogous mechanism, *via* **9** and **10** and involving initial oxazolone participation is presumably operating here (Scheme 3).

The striking differences in the behaviour of the iodoarene difluoride relative to the dichloride may be understood in terms of the relative leaving group ability of the initially formed halogeniodoarene sulfonium salt **8**. The chlorosulfonium salt (G = Cl), as evidenced by sulfoxide formation,[8] must be considered as a relatively long-lived entity. In the absence of water either isothiazole formation (path A) or Pummerer reaction (path B) is possible, depending on side-chain participation. The absence of these products in reactions of the iodoarene difluoride is indicative of a rapid cleavage of the C_6–S bond triggered by a superior leaving group (path C).

Although yields of fluorides were modest, we were encouraged by the compatibility of the fluorinating agent with a complex substrate as well as the mildness of the reaction conditions. We elected to synthesise a simpler set of substrates that might be used to examine the Type 2 behaviour of the difluoroiodoarenes, in analogy to our work on the Fluoro-Pummerer reaction of α-phenylsulfanyl esters.

Our investigations into the Type 2 reaction were initiated by preparing a simple range of α-phenylsulfanyl acetamides. The results of treating these amides with DFIT **1a** are shown in Table 1 which reveals that the outcome of the reaction is

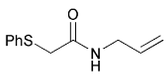
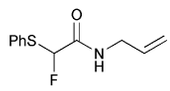
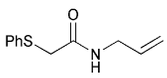
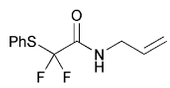
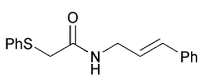
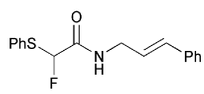
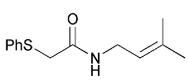
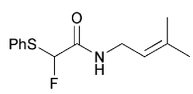
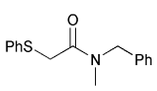
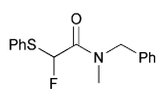
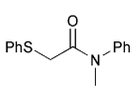
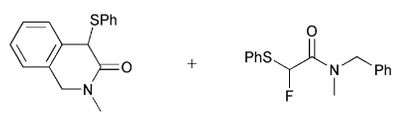
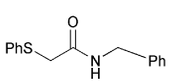
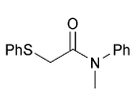
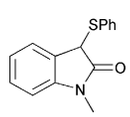
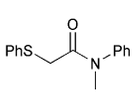
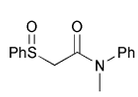
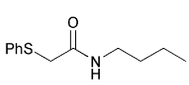
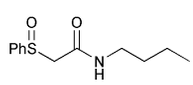
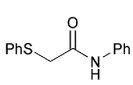
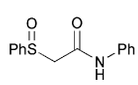


Scheme 3

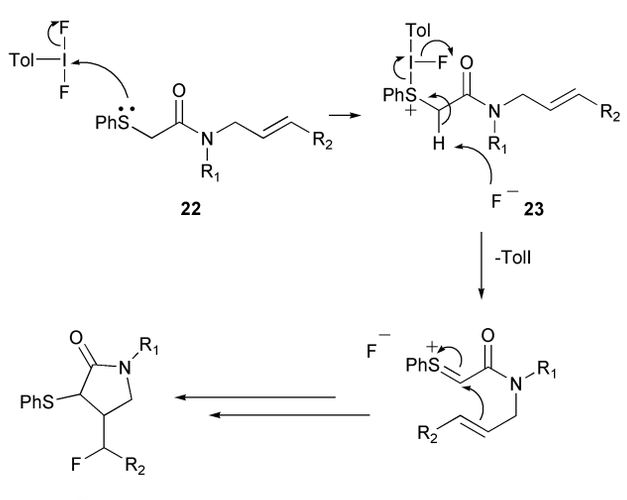
critically dependent on the nature of the substituents attached to the nitrogen atom of the amide and also on the reaction conditions employed. The series of allylic amides **14**, **15**, and **16** (Entries 1–4) were initially selected in order to investigate the possibility of intercepting the cationic acyl sulfonium intermediate **23** through intramolecular cyclisation to give fluorinated heterocycles **24** which retain the pattern of functionality required for further Fluoro-Pummerer chemistry (Scheme 4). In all cases however, no evidence for cyclisation was adduced, even when the potential carbocationic intermediate would have been either benzylic (Entry 3) or tertiary (Entry 4). The failure of substrates **14**–**16** to undergo cyclisation is in line with literature reports where secondary α-methylsulfinyl acetamides were found to be poor substrates for Pummerer cyclisations,[9] and it will therefore be of interest to prepare the tertiary amide analogues in order to examine the desired fluoro-cyclisation.

It was nevertheless pleasing to note that clean α-fluorination of these amides takes place in good overall yield. Moreover, and in contrast to Pummerer chemistry with sulfoxides using DAST, the use of a second equivalent of DFIT (Entry 2) leads to a very simple one-pot method for *α*, *α*-difluorination. Although no competing cyclisation reactions were observed at

Table 1 Treatment of α-phenylsulfanylacetamides with DFIT

Entry		Amide	Method[a]		Product	Yield (%)[b]
1	**14**		A	**25**[10]		71
2	**14**		C	**26**		61
3	**15**		A	**27**		55
4	**16**		A	**28**		25
5	**17**		B	**29**		68
6	**17**		A	**30** + **29**		**30**: 47, **29**: 25
7	**18**		A	**31** + **32**		**31**: 11, **32**: 35
8	**19**		A	**33**		59
9	**19**		B	**34**		86
10	**20**		C	**35**		86
11	**21**		B	**36**		78

[a] Method A: DFIT (1 eq.), DCM, reflux; B: DFIT (1 eq.), DCM, 0 °C; C: DFIT (2 eq.), DCM, 0 °C. [b] Isolated yields.



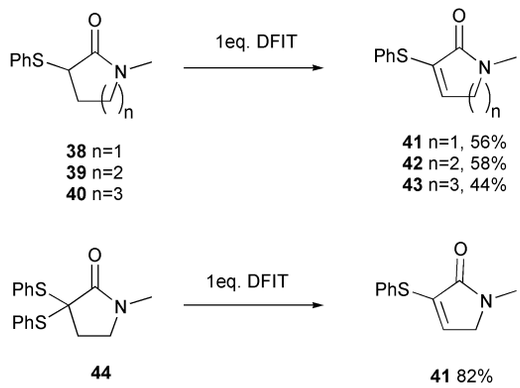
Scheme 4

0 °C presumably as a consequence of the preferred transoid conformation of the amide linkage, comparison of entries 5 and 6 for the benzylamine derivative **17** indicates that π-participation from the aromatic ring can intervene at higher temperatures. This phenomenon can also be seen in the case of the secondary benzylic amide **18** (Entry 7) and in the case of the amide **19** (Entry 8), where the exclusive formation of the benzo fused heterocycle **33** (Entry 8) can be considered to result from the faster rate of 5-*exo*-*trig* ring closure relative to the 6-*exo*-*trig* process required for substrates **17** and **18**.[11] The yields of heterocycles in Entries 6–8 are moderate, and poorer than those recorded by Tamura for similar cyclisations of α-phenylsulfanyl acetamides mediated by iodobenzene(bistrifluoroacetate).[12] In that system however, cyclisation is heavily favoured as the labile α-acetoxy sulfide Pummerer products are themselves substrates for cyclisation, whereas in our system the strength of the carbon–fluorine bond precludes displacement by intramolecular cyclisation of the olefin.

In stark contrast to the above examples, Entries 9, 10 and 11 indicate that DFIT can also function as a simple reagent for

oxidation of sulfide functionality to sulfoxide. Treatment of **20** with DFIT and caesium fluoride in acetonitrile in an attempt to increase the basicity of the medium led to the same sulfoxide, but with a reduced yield of 53%. Although these results clearly indicate that the hypervalent iodine reagent continues to function as a thiophilic oxidant, the subtle nature of the substituents around the nitrogen atom in controlling product evolution is far from clear at present, as for instance in comparison of Entries 2 and 10.

We extended the methodology to lactams **38**–**40** with a view to examining whether the presence of β hydrogens would lead to alternative products in the Fluoro-Pummerer reaction with DFIT. This proved to be the case, as treatment of the lactams with one equivalent of DFIT in DCM at 0 °C led to the novel unsaturated heterocycles **41**–**43** in moderate to high yield, by a β-elimination pathway (Scheme 5).



Scheme 5

The possibility of fluorination–dehydrofluorination was rejected on the basis that the α-fluoride of **38** has been prepared by electrochemical means in $Et_3N{\cdot}3HF$ and no elimination was reported to occur upon product isolation.[13] Fluoride is thus acting as a base, and not as a nucleophile in this reaction. The high yield of **41** starting from the bis-phenylsulfanylated compound **44** is presumably a consequence of the substantially easier generation of the sulfonium intermediate through thioketal cleavage with DFIT by the Type 1 mechanism.[3] Interestingly, we observed small amounts of fluorinated side-products in the above reactions, but were unable to characterise them at this stage. We were aware however, that vinyl sulfides can themselves be substrates for the so-called Additive-Pummerer reaction,[14] and that such a precursor could be the source of the fluorinated material. In order to test this theory, we therefore treated the starting lactams with an excess of DFIT. When treated with two equivalents of DFIT the pyrrolidinone **38** and piperidinone **39** were both fluorinated in the α and β positions to produce the diastereomeric difluorides **45** and **46** (Scheme 6).

The *syn* and *anti* diastereomers were separable by column chromatography and a single crystal could be grown for both *syn*-**45** and *anti*-**46**, thus unambiguously characterising the difluoride products by X-ray crystallography (Fig. 2).

Introduction of fluoride to the apparently unactivated β-position is readily understood by analogy with the Additive-

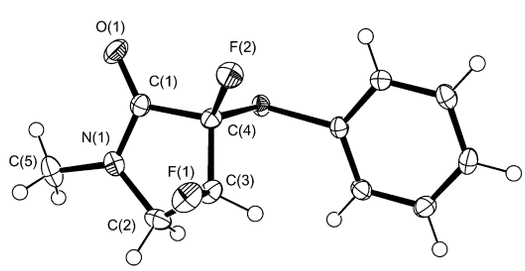
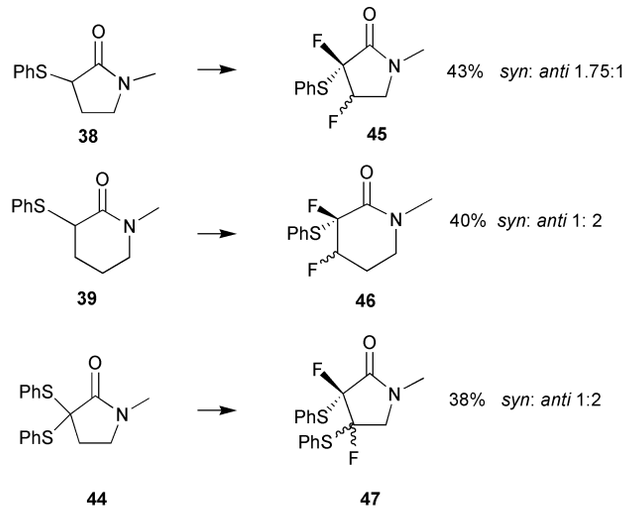
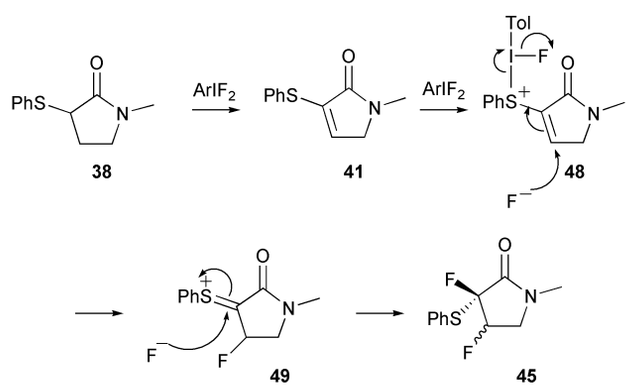


Fig. 2 ORTEP of *syn*-**45**.



Scheme 6

Pummerer reaction. This reaction involves sequential addition of two nucleophiles across the double bond of an α,β-unsaturated sulfoxide, generating the saturated α,β-difunctionalised sulfide, and as such is a powerful, though under-utilised synthetic method. The proposed mechanism for DFIT is shown in Scheme 7, whereby the first equivalent of fluorinating agent generates α,β-unsaturated sulfide **41** as previously discussed.



Scheme 7

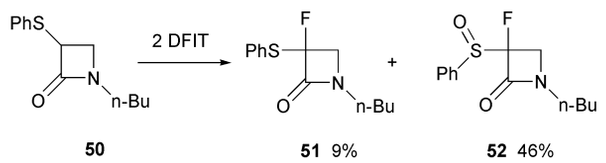
The second equivalent of reagent then activates the vinyl sulfide towards conjugate addition of fluoride at the β position forming the β-fluoro sulfonium species **49**, which can then capture a second fluoride nucleophile to provide the difluoride **45**. The success of this tandem process is due to the ability of the hypervalent iodine reagent to oxidise the sulfide *in situ*, allowing the two consecutive Pummerer processes to take place in one-pot. The modest stereoselectivity observed in these transformations presumably arises as a consequence of the small size of the initially introduced fluorine atom in the 4-position having little influence on the steric approach control of the second fluoride nucleophile.

Fluorination of the bis-phenylsulfanylated compound **44** with DFIT produced difluoride **47** as a diastereomeric mixture. In this instance, the strongly nucleophilic thiophenoxide anion generated upon thioketal cleavage of **44** with DFIT will add to the β-position of **41** upon DFIT activation in preference to fluoride. Basic fluoride then regenerates the α,β-unsaturation, presumably as a consequence of the now increased acidity of the β-proton, and an Additive-Pummerer reaction furnishes the observed difluoride. This mechanism dictates the consumption of three equivalents of DFIT, accordingly an improved yield of 46% was obtained with this stoichiometry.

We were surprised to find that treating the unsaturated sulfides **41** and **42** directly with one equivalent of DFIT led to

the difluorides being formed in comparable to lower yields than those obtained through the tandem process. The generation of two equivalents of HF in the first Pummerer reaction may be important in this regard, as it may have a catalytic effect on the second Additive process. However, attempts at promoting the direct fluorination of **41** and **42** with DFIT using py·9HF or $Et_3N·3HF$ as additives were not generally successful,[15] although in one case the yield of **45** from the sulfide **41** was improved to 59% through the addition of 25 mol% of $Et_3N·3HF$ to the reaction.

The reaction was extended to azetidinone **50**, as the four-membered ring would be expected to preclude α,β-unsaturated-sulfide formation and possibly lead to alternative products. Two equivalents of DFIT transformed **50** into the fluoro-sulfoxide **52** in 46% yield as a mixture of sulfoxide diastereomers, along with a small amount of the known[16] fluoro-sulfide **51** (Scheme 8).



50 **51** 9% **52** 46%

Scheme 8

Characterisation of **52** was secured by oxidation to the sulfone, whereby the two signals in the ^{19}F NMR of the starting material collapsed to one in the product. As expected, the Additive-Pummerer reaction is not observed in this case due to the prohibitively large ring-strain associated with formation of a double bond in the four-membered azetidinone ring.

Overview and conclusions

At this stage, it is also perhaps appropriate to provide a comparative overview of the essential difference in the reactivity of esters and lactones on one hand,[1] and amides and lactams on the other, as far as product evolution *via* Fluoro-Pummerer chemistry (the Type 2 mechanism) is concerned. In essence, the selection of an α-phenylsulfanyl ester or lactone can always be said to follow the "ideal" pathway and will always involve the intermediacy of an α-acylsulfonium cation which is apparently predisposed to capture fluoride anion as a nucleophile (Scheme 9). Thus, in our studies with ester and lactone functionality as the electron-withdrawing group, β-elimination was never observed as a competing process.

The contrasting behaviour of some amides, and especially lactams, therefore requires some explanation and it is interesting to speculate that this could possibly reside in a competing path leading to the formation of an intermediate such as **57** which is much more likely to form from an amide than an ester by virtue of the more nucleophilic nitrogen atom. Given the relatively electron rich nature of the carbon–carbon double bond in **57**, attack of fluoride anion as a nucleophile at the α carbon is disfavoured and the reaction then evolves *via* the β-elimination pathway with fluoride anion functioning as a base. The relative ease of formation of **56** will of course be a function of the substituents attached to the nitrogen atom of the amide and α-fluorination without amide participation is also possible.

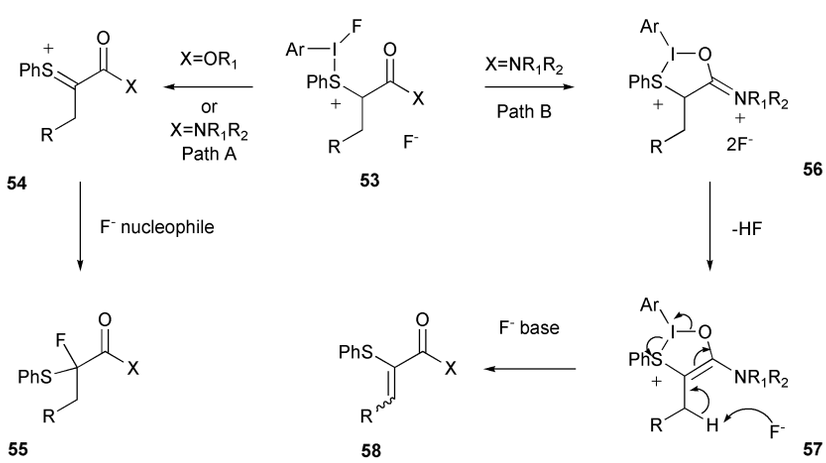
In conclusion, we have demonstrated in the present paper that hypervalent iodine difluorides are effective reagents for the fluorination of a variety of sulfur-containing amides, with most of the work being carried out on α-acyl sulfides. The α-fluoroacetamides synthesised through the Fluoro-Pummerer reaction are potentially versatile fluorinated synthons, and may be elaborated into more complex systems using the rich chemistry of sulfur. The most interesting chemistry from a mechanistic perspective is the tandem Pummerer-Additive-Pummerer fluorination reaction. The success of this reaction, which applies to those α-phenylsulfanyl acetamides having β-hydrogens, is due to the ability of the hypervalent iodine reagent to oxidise sulfur *in situ* thus allowing sequential Pummerer reactions to take place in one-pot. Furthermore, fluoride always acts first as a base, and second as a nucleophile, to form the novel α,β-difluorides. We are currently examining the scope and utility of this transformation in related systems.

Experimental

See reference 1 for general experimental procedures.

p-tert-Butyldifluoroiodobenzene 1b

p-tert-Butyliodobenzene dichloride[17] (4.02 g, 12 mmol) was dissolved in DCM (40 mL) in a polyethylene erlenmeyer flask. Yellow mercuric oxide (5.5 g, 25 mmol) and 48% aq. hydrofluoric acid (6 mL, 12 eq.) were then added. The slurry was vigorously shaken periodically over 10 min, after which time the almost colourless organic layer was decanted onto MgO, swirled briefly, then decanted into a polyethylene vessel. Argon was passed over the solution for 4 h to afford a white solid. Trituration with dry hexane yielded the title compound **1b** (2.6 g, 70%) which was collected and stored under argon in a



Scheme 9

polyethylene vessel at −20 °C; mp 40 °C (decomp.) (hexane); IR (KBr/cm^{-1}): ν_{max} 2962, 1522, 1392, 818, 788, 770, 750, 538, 466; ^{1}H NMR (90 MHz, $CDCl_3$): δ_H 1.38 (9H, s, $(CH_3)_3C$), 7.60 (2H, AA′BB d *J* 9 Hz, 3-H, 5-H), 7.90 (2H, AA′BB′ d *J* 9 Hz, 2-H, 6-H); ^{13}C NMR (23 MHz, $CDCl_3$): δ_C 31.1 (C-8), 34.9 (C-7), 128.1 (C-1), 128.5 (C-3), 130.1 (C-2) 155.4 (C-4); ^{19}F NMR (84 MHz, CD_3CN): δ_F −176.8; MS (EI): *m*/*z* 298 ($M^{\bullet+}$), 283 (M − Me), 260 (M − 2F); HRMS (EI) calcd. for $C_{10}H_{13}F_2I$: 298.0030. Found: 298.0038.

Bis(benzhydryl 2-{(1′*R*,5′*S*)-3′-phenoxymethyl-7′-oxo-4′-oxa-2′,6′- diazabicyclo[3.2.0]hept-2′-en-6′-yl}-3-methylbut-2-enoate)-4-disulfide 3

To a stirred solution of cephalosporin(v) benzhydryl ester **2a** (1.506 g, 2.93 mmol) in dry acetonitrile (45 mL) was added a solution of *p*-*tert*-butyliodobenzene difluoride (900 mg, 3.02 mmol) in dry acetonitrile (9 mL) *via* a polyethylene syringe dropwise over 10 min. After 4.5 h the orange reaction mixture was concentrated *in vacuo*, applied to a pad of silica and diluted initially with petrol to remove starting material (33 mg, 2%) and finally with ether to obtain the title compound **3** (400 mg, 27%). An analytical sample was prepared by dissolving in benzene and precipitating the required compound with petrol; mp 70 °C (benzene:PE 30–40); $[\alpha]_D^{25}$ +25.77° (*c*. 0.98, $CHCl_3$); IR (CH_2Cl_2/cm^{-1}): ν_{max} 3066, 2871, 1780 (β-lactam), 1719 (ester carbonyl), 1598 (N=C), 1493, 1370, 1217, 1040; ^{1}H NMR (250 MHz, $CDCl_3$): δ_H 2.18 (3H, s, 3-Me), 3.38 (1H, d *J* 13 Hz, 2-H), 3.50 (1H, d *J* 13 Hz, 2-H), 4.28 (1H, d *J* 12 Hz, 17-H), 4.40 (1H, d, *J* 12 Hz, 17-H), 5.16 (1-H, d *J* 4 Hz, 7-H), 5.82 (1H, d *J* 4 Hz, 6-H), 6.75–7.30 (15H, m, Ar–H); ^{13}C NMR (62.6 MHz, $CDCl_3$): δ_C 19.8 (C-9), 45.1 (C-2), 62.4 (C-17), 79.0 (C-11), 81.3 (C-7), 88.7 (C-6), 114.5 (C-20), 121.5 (C-3), 121.8 (C-21), 126.9, 127.1, 128.16, 128.21, 129.5 (Benzhy. and C-20), 139.1 and 139.4 (C-13 and C-13′), 151.6 (C-4), 157.6 (C-18), 162.0 (C-16), 165.5 (C-10), 166.5 (C-8); MS (FAB): *m*/*z* 407 $[M/2\text{-}PhOCH_2]^+$; Anal. calcd. for $C_{58}H_{50}N_4O_{10}S_2$: C, 67.82; H, 4.91; N, 5.46%. Found: C, 67.4; H, 4.9; N, 5.4%.

Bis[benzhydryl 2α-fluoro-4-oxo-3β-(2-phenoxyacetamido)-1-azetidine-3′-methylbut-2′-enoate]-4′-disulfide 4a

To a stirred solution of cephalosporin(v) benzhydryl ester **2a** (500 mg, 0.97 mmol) in DCM (25 mL) was added a solution of *p*-*tert*-butyliodobenzene difluoride (300 mg, 1.00 mmol) in DCM (9 mL) *via* a polyethylene syringe dropwise over 7 min. After 3 h the orange reaction mixture was concentrated *in vacuo*, and filtered through a short pad of silica to remove *p*-*tert*-butyliodobenzene, affording the fluoride **4a** as a solid; mp 79–80 °C; IR (CCl_4/cm^{-1}): ν_{max} 3426 (NH), 3065, 1793 (β-lactam), 1724 (ester carbonyl), 1695, 1599; ^{1}H NMR (270 MHz, $CDCl_3$): δ_H 2.25 (3H, s, 3-Me), 3.38 (1H, d *J* 14 Hz, 2-H), 3.80 (1H, d *J* 14 Hz, 2-H), 4.38 (1H, d *J* 14 Hz, 22-H), 4.47 (1H, d, *J* 14 Hz, 22-H), 4.90 (1H, dd *J* 7, 7 Hz, 7-H), 5.92 (1-H, d *J* 65 Hz, 6-H), 6.80–7.60 (15H, m, Ar–H); ^{13}C NMR (126 MHz, $CDCl_3$): δ_C 19.6 (C-9), 43.4 (C-2), 62.9 (d *J* 23 Hz, C-7), 67.1 (C-22), 78.8 (C-12), 98.7 (d *J* 242 Hz, C-6), 114.8 (C-25), 120.6 (C-3), 122.3 (C-27), 127–130 (C-26 + other Ar), 139.4 (C-13), 153.6 (C-4), 156.9 (C-24), 162.05 (C-21), 162.8 (d *J* 11 Hz, C-10), 169.5 (C-8); ^{19}F NMR (84.3 MHz, $CDCl_3$): δ_F −150.5 (dd *J* 65, 6 Hz); MS (FAB): *m*/*z* 501 $[M/2\text{-}S]^+$; Anal. calcd. for $C_{58}H_{52}N_4O_{10}S_2F_2$: C, 65.27; H, 4.91; N, 5.25%. Found: C, 65.90; H, 4.99; N, 5.22%.

Bis[methyl 2α-fluoro-4-oxo-3β-(2-phenoxyacetamido)-1-azetidine-3′-methylbuten-2′-oate]-4′-disulfide 4b

To a stirred solution of cephalosporin(v) methyl ester **2b** (500 mg, 1.40 mmol) in DCM (25 mL) was added a solution of *p*-*tert*-butyliodobenzene difluoride (425 mg, 1.43 mmol) in DCM (9 mL) *via* a polyethylene syringe dropwise over 7 min. After 3 h the orange reaction mixture was concentrated *in vacuo* to afford an oil which could be crystallised from benzene:petrol to give an orange solid. The solid was dissolved in DCM, shaken with decolourising charcoal, filtered then concentrated *in vacuo* to afford the title fluoride **4b** (220 mg, 21%) as a cream powder; mp 68–69 °C (benzene:petrol); IR (CCl_4/cm^{-1}): ν_{max} 3414 (NH), 2956, 1792 (β-lactam), 1725 (ester carbonyl), 1697, 1599; ^{1}H NMR (270 MHz, $CDCl_3$): δ_H 2.32 (3H, s, 3-Me), 3.45 (1H, d *J* 14 Hz, 2-H), 3.78 (3H, s, OMe), 3.80 (1H, d *J* 14 Hz, 2-H), 4.38 (1H, d *J* 14 Hz, 15-H), 4.47 (1H, d, *J* 14 Hz, 15-H), 5.00 (1H, dd *J* 7, 7 Hz, 7-H), 6.05 (1-H, d *J* 73 Hz, 6-H), 6.90–7.30 (5H, m, Ar–H); ^{13}C NMR (126 MHz, $CDCl_3$): δ_C 19.3 (C-9), 44.0 (C-2), 52.3 (C-12), 63.2 (d *J* 23 Hz, C-7), 67.5 (C-15), 98.4 (d *J* 242 Hz, C-6), 115.0 (C-18), 121.0 (C-3), 122.5 (C-20), 129.9 (C-14), 151.8 (C-4), 157.3 (C-17), 162.7 (d *J* 11 Hz, C-10), 163.6 (C-14), 169.4 (C-8); ^{19}F NMR (84.3 MHz, $CDCl_3$): δ_F −151.0 (dd *J* 73, 7 Hz); MS (EI): *m*/*z* 362 $[M/2\text{-}F]^{\bullet+}$, 349 $[M/2\text{-}S]^+$, 303 $[M/2\text{-}F - CO_2Me]^+$; Anal. calcd. for $C_{34}H_{36}N_4O_{10}S_2F_2$: C, 53.68; H, 4.50; N, 7.37%. Found: C, 53.22; H, 4.77; N, 7.11%.

Benzhydryl 4-methyl-2*H*,4*H*-isothiazole-3-carboxylate 11

To a stirred solution of cephalosporin(v) benzhydryl ester **2a** (1.0 g, 1.95 mmol) in acetonitrile (30 mL) was added a solution of *p*-*tert*-butyliodobenzene dichloride (660 mg, 2.00 mmol) in acetonitrile (7 mL) *via* a polyethylene syringe dropwise over 5 min. After 2 h silica was added and the orange reaction mixture was concentrated *in vacuo*. Flash chromatography (SiO_2, PE 30–40:ether 100:0 grading to 30:70) afforded the isothiazole **11** (190 mg, 31%), plus recovered starting material (400 mg, 40%). Recrystallisation from PE:ether afforded an analytical sample; mp 89–90 °C (PE:ether); IR (CH_2Cl_2/cm^{-1}): ν_{max} 3100–2900, 1725(ester carbonyl), 1410, 1340, 1235, 1150, 1080; ^{1}H NMR (90 MHz, $CDCl_3$): δ_H 2.51 (3H, d, *J* 0.8 Hz, 4-Me), 7.1–7.5 (11H, m, Ph_2CH), 8.28 (1H, d *J* 0.8 Hz, 5-H); ^{13}C NMR (68 MHz, $CDCl_3$): δ_C 14.3 (C-6), 78.0 (C-9), 128.6–127.3 (Ph), 138 (C-4), 147 (C-5), 160.5 (C-3), 189 (C-7); MS (EI): *m*/*z* 309 $M^{\bullet+}$, 183 (Ph_2CHO), 167 $(Ph_2CH)^+$, 126 (M − Ph_2CHO); Anal. calcd. for $C_{18}H_{15}NO_2S$: C, 69.88; H, 4.89; N, 4.53%. Found: C, 69.88; H, 4.84; N, 4.40%.

General procedure for the synthesis of α-phenylsulfanyl-acetamides

Triethylamine or pyridine (1 eq.) was added to a stirred solution of amine (1 eq.) in DCM (*ca*. 3 mL mmol^{-1}). The mixture was cooled in an ice–salt bath (<0 °C) and phenylsulfanylacetyl chloride was added dropwise. Consumption of starting amine was monitored by TLC and the reaction was quenched with water upon completion. The aqueous phase was extracted with DCM (×2), the combined extracts dried ($MgSO_4$) and concentrated *in vacuo*. Flash chromatography followed by Kugelröhr distillation or recrystallisation afforded pure products.

N-Allyl(phenylsulfanyl)acetamide 14

Colourless oil; R_f 0.22 (SiO_2, PE 30–40:ether 50:50); IR (thin film/cm^{-1}): ν_{max} 3289s (NH), 3075s, 2919s (CH), 1650 (amide I), 1537s (amide II), 1439s, 1311s, 1218s, 1154s, 1098m, 989m, 921m, 739s, 690s; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 3.61 (2H, s, SCH_2), 3.80–3.84 (2H, m, 1-H), 4.94–5.02 (2H, m, 3-H), 5.65–5.73 (1H, 2-H), 6.81 (1H, br, NH), 7.15–7.26 (5H, m, Ar–H); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 37.7 (SCH_2), 42.4 (1-C), 116.7 (3-C), 127.1, 128.4, 129.7, 134.0, 135.0 (C_{ipso}), 168.0 (C=O); MS (FAB): *m*/*z* 208 (MH^+, 100%); HRMS (FAB) calcd. for $C_{11}H_{14}NOS$ (MH^+): 208.0796. Found: 208.0793.

N-Cinnamyl(phenylsulfanyl)acetamide[18] 15

White solid; mp 101–102 °C (PE 30–40:ether); R_f 0.21 (SiO_2, PE 30–40:ether 50:50); IR (thin film/cm^{-1}): ν_{max} 3295m (NH), 3057w, 2915m, 1646s (C=O), 1578m, 1524m, 1483m, 1436m,

1320m, 1246w, 1022w, 968w, 737s, 689s; ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 3.62 (2H, s, SCH_2), 3.97 (2H, td *J* 6, 1 Hz, 1-H), 5.99 (1H, dt $^{trans}J_{AB}$ 16 Hz, $^3J_{2,1}$ 6 Hz, 2-H), 6.30 (1H, d $^{trans}J_{AB}$ 16 Hz, 3-H), 7.12–7.27 (10H, m, Ar–H); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 37.7, 42.0, 125.3, 126.7, 127.1, 128.1, 128.4, 128.9, 129.8, 132.4, 135.0 (C_{ipso}), 136.8 (C_{ipso}), 168.0 (C=O); MS (FAB): *m*/*z* 306 (MNa^+, 25%), 284 (MH^+, 100); Anal. calcd. for $C_{17}H_{17}NOS$: C, 72.05; H, 6.05; N, 4.96%. Found: C, 71.73; H, 5.89; N, 4.87%.

N-(3-Methylbut-2-enyl)(phenylsulfanyl)acetamide 16

White solid; mp 72–73 °C (ether); R_f 0.43 (SiO_2, ether); IR (thin film/cm^{-1}): ν_{max} 3286s (NH), 2967w (CH), 1649s (C=O), 1544w, 1480w, 735m, 693m; ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 1.75 (3H, s, CH_3), 1.83 (3H, s, CH_3), 3.78 (2H, s, SCH_2), 3.97 (2H, t *J* 6 Hz, 1-H), 5.23 (1H, t *J* 7 Hz, 2-H), 6.84 (1H, br, NH), 7.34–7.48 (5H, m, Ar–H); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 18.3, 26.0, 37.7, 38.3, 119.8, 127.0, 128.6, 129.7, 135.0, 137.5, 168.3; MS (FAB): *m*/*z* 258 (MNa^+, 20%), 236 (MH^+, 100); HRMS calcd. for $C_{13}H_{18}NOS$ (MH^+): 236.1109. Found: 236.1093.

N-Benzyl-*N*-methyl(phenylsulfanyl)acetamide 17

Colourless oil; R_f 0.51 (SiO_2, PE 30–40:ether 60:40); IR (thin film/cm^{-1}): ν_{max} 3058w, 3028w, 2924w, 1649s (C=O), 1582w, 1480, 1446m, 1400m, 1267w, 1092m, 738m, 696m; ^{1}H NMR (300 MHz, $CDCl_3$): (*E*/*Z*) δ_H 2.82 and 2.83 (2 × 3H, 2 × s, NCH_3), 3.66 and 3.69 (2 × 2H, 2 × s, SCH_2), 4.45 (2 × 2H, s, NCH_2), 7.04–7.43 (10H, m, Ar–H); ^{13}C NMR (75 MHz, $CDCl_3$): (*E*/*Z*) δ_C 34.7 and 35.8 (NCH_3), 37.3 and 37.5 (2-C), 51.6 and 54.3 (NCH_2), 126.4, 126.9 (2C), 127.4, 127.7, 128.0, 128.6, 128.9, 129.0, 130.2, 130.3, 135.4 (C_{ipso}), 135.5 (C_{ipso}), 136.5 (C_{ipso}), 137.3 (C_{ipso}), 169.0 and 169.3 (C=O); MS (FAB): *m*/*z* 272 (MH^+, 100%); HRMS (FAB) calcd. for $C_{16}H_{17}NOS$ (MH^+): 272.1109. Found: 272.1106.

N-Benzyl(phenylsulfanyl)acetamide 18

White solid; mp 52–54 °C (PE 30–40:ether); R_f 0.49 (SiO_2, PE 30–40:ethyl acetate 40:60); IR (thin film/cm^{-1}): ν_{max} 3287m (NH), 3063w, 2923w, 1651s (C=O), 1532m, 1476w, 1434w, 1315w, 1224w, 1155w, 1085w, 1022w, 742s, 686s; ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 3.84 (2H, s, SCH_2), 4.58 (2H, d *J* 6 Hz, NCH_2), 7.20–7.46 (10H, m, Ar–H); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 37.7 (SCH_2), 44.1 (NCH_2), 127.1, 127.9 (2C), 128.5, 129.7, 129.8, 134.9, 138.1, 168.1 (C=O); MS (FAB): *m*/*z* 280 (MNa^+, 15%), 258 (MH^+, 100); HRMS (FAB) calcd. for $C_{15}H_{16}NOS$ (MH^+): 258.0953. Found: 258.0958.

N-Phenyl-*N*-methyl(phenylsulfanyl)acetamide 19

Yellow crystals; mp 70 °C (DCM:PE 30–40); R_f 0.53 (SiO_2, PE 30–40:ether 60:40); IR (KBr disc/cm^{-1}): ν_{max} 2923w, 1651s (C=O), 1588s, 1383s, 1297s, 1233s, 1118m, 895w, 743s, 697s, 556s; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 3.29 (3H, s, CH_3), 3.52 (2H, s, SCH_2) 7.14–7.40 (10H, m, Ar–H); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 37.2 (SCH_2), 37.9 (NCH_3), 126.7, 127.4, 128.2, 128.9, 129.9, 130.2, 135.6 (SC_{ipso}), 143.4 (NC_{ipso}) 168.7 (C=O); MS (EI): *m*/*z* 257 ($M^{\bullet+}$, 50%); Anal. Calcd. for $C_{15}H_{15}NOS$: C, 70.00; H, 5.87; N, 5.44%. Found: C, 69.91; H, 5.91; N, 5.34%.

N-Butyl(phenylsulfanyl)acetamide 20

Colourless oil; R_f 0.46 (SiO_2, ether); IR (thin film/cm^{-1}): ν_{max} 3290s (NH) 2931m, 2869s (CH), 1653s (C=O), 1558s, 1442m, 1308m, 1152w, 1038s, 918w; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 0.85 (3H, t *J* 7 Hz, CH_3), 1.16–1.26 (2H, m, CH_2CH_3), 1.36–1.42 (2H, m, NCH_2CH_2), 3.24 (2H, m, NCH_2), 3.64 (2H, s, SCH_2), 6.81 (1H, br NH), 7.19–7.32 (5H, m, Ar–H); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 13.5 (CH_3), 19.8 (CH_2CH_3), 31.2 (NCH_2CH_2), 37.1 (SCH_2), 39.4 (NCH_2), 126.4, 127.8, 129.2, 134.6 (C_{ipso}), 167.4 (C=O); MS (FAB): *m*/*z* 224 (M^+, 100%), 123 (57); HRMS (FAB) calcd. for $C_{12}H_{17}NOS$: 224.1109. Found: 224.1120.

N-Phenyl(phenylsulfanyl)acetamide 21

Pink needles; mp 80–81 °C (DCM:hexane); R_f 0.68 (SiO_2, PE 30–40:ethyl acetate 40:60); IR (KBr disc/cm^{-1}): ν_{max} 3311s (NH), 3055w, 2924w, 1665s (C=O), 1599m, 1524s, 1439m, 1386m, 1317w, 1237m, 1152w, 1078w, 1025w, 888w, 749s, 688s, 485m; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 3.78 (2H, s, SCH_2), 7.11–7.50 (10H, m, Ar–H), 8.59 (1H, br, NH); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 38.8 (SCH_2), 120.3, 125.2, 127.5, 128.8, 129.5, 129.9, 134.5 (C_{ipso}), 137.6 (C_{ipso}), 166.4 (C=O); MS (EI): *m*/*z* 244 ($M^{\bullet+}$, 90%); Anal. Calcd. for $C_{14}H_{13}NOS$: C, 69.11; H, 5.38; N, 5.76; S, 13.18%. Found: C, 68.90; H, 5.33; N, 5.67; S, 12.85%.

General procedure for the fluorination of substrates using DFIT

Reactions conducted at 0 °C: a solution of DFIT[1] in DCM was prepared in a 25 mL polypropylene flask protected from light by aluminium foil. The solution was cooled to 0 °C in an ice–salt bath and a solution of the substrate in DCM was then added *via* cannula. The mixture was left to stir at this temperature. Upon completion (TLC) the reaction was quenched with water and extracted with DCM. The combined extracts were dried ($MgSO_4$) and concentrated *in vacuo*. Flash chromatography yielded pure materials.

Reactions conducted at reflux: a solution of DFIT in DCM was prepared in a 25 mL glass round-bottomed flask equipped with a water-cooled reflux condenser. A solution of the substrate in DCM was added *via* cannula and the mixture stirred at reflux. Upon completion (TLC) the reaction was cooled to room temperature and worked up as above.

N-Allyl(2-fluoro-2-phenylsulfanyl)acetamide 25 and *N*-allyl-(2,2-diphenylsulfanyl)acetamide 37

A solution of DFIT (91%, 294 mg, 1.1 mmol) and *N*-allyl-(phenylsulfanyl)acetamide **14** (200 mg, 0.97 mmol) in DCM (7 mL) refluxing for 2 h. Work-up according to the general procedure followed by flash chromatography (SiO_2, PE 30–40:ether 70:30) afforded the fluoride **25** (168 mg, 71%) as a colourless oil; R_f 0.22 (SiO_2, PE 30–40:ether 40:60); IR (thin film/cm^{-1}): ν_{max} 3296m (NH), 3077m, 2924w (CH), 1669s (C=O), 1534s (amide II), 1478m, 1437m, 1272m, 1202w, 1070w, 992m, 923m, 825w, 746s, 691s; ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 3.71 (2H, t *J* 6 Hz, 1′-H), 4.92–5.02 (2H, m, 3′-H), 5.46–5.59 (1H, m, 2′-H), 6.07 (1H, d $^2J_{HF}$ 53 Hz, 2-H), 6.22 (1H, br, NH), 7.27–7.55 (5H, m, Ar–H); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 41.6 (1′-C), 97.5 (d $^1J_{CF}$ 234 Hz, 2-C), 116.9 (3′-C), 129.1, 129.3, 132.8, 132.9 (C_{ipso}), 134.5, 164.7 (d $^2J_{CF}$ 24 Hz, C=O); ^{19}F NMR (282 MHz, $CDCl_3$): δ_F −156.5 (d $^2J_{FH}$ 53 Hz). Recrystallisation from DCM:PE 30–40 or MS analysis gave the amide **37**: ^{1}H NMR (500 MHz, $CDCl_3$): δ_H 3.77–3.80 (2H, m, 1-H), 4.89 (1H, s, PhS_2CH), 4.98–5.05 (2H, m, 3-H), 5.60–5.65 (1H, m, 2-H), 6.35 (1H, br, NH), 7.26–7.46 (10H, m, Ar–H); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 42.6 (1-C), 58.3 (PhS_2C), 117.2 (2-C), 128.9, 129.6, 132.6, 133.2, 133.6 (C_{ipso}), 167.4 (C=O); MS (FAB): *m*/*z* 316 (MH^+, 60%), 231 ($[(PhS)_2CH]^+$, 55), 206 ([M − PhS]$^+$, 90), 178 (90), 153 (45), 123 (100); Anal. Calcd. for $C_{17}H_{17}NOS_2$: C, 64.73; H, 5.43; N, 4.44%. Found: C, 64.44; H, 5.37; N, 4.46%.

N-Allyl(2,2-difluoro-2-phenylsulfanyl)acetamide 26

A solution of DFIT (494 mg, 1.9 mmol) and *N*-allyl-(phenylsulfanyl)acetamide **14** (200 mg, 0.97 mmol) in DCM (7 mL) refluxing for 16 h. The mixture was diluted with DCM and bound to SiO_2. Flash chromatography (SiO_2, PE 30–40:ether 70:30) afforded the difluoride **26** (129 mg, 61%) as a colourless oil; R_f 0.13 (SiO_2, PE 30–40:ether 50:50); IR (thin

film/cm^{-1}): ν_{max} 3312s (NH), 3090w (CH), 1678s (C=O), 1538s (amide II), 1436w, 1343w, 1265w, 1129w, 1084m, 1031w, 928m, 805w, 746m, 689m; ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 3.85 (2H, t J 6 Hz, 1′-H), 5.09–5.15 (2H, m, 3′-H), 5.63–5.76 (1H, m, 2′-H), 6.27 (1H, br, NH), 7.32–7.65 (5H, m, Ar–H); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 42.5 (1′-C), 118.1 (3′-C), 122.8 (t $^1J_{CF}$ 289 Hz, 2-C), 125.3 (C_{ipso}), 129.7, 131.0, 132.7, 137.2, 161.9 (t $^2J_{CF}$ 28 Hz, C=O); ^{19}F NMR (282 MHz, $CDCl_3$): δ_F −82.8; MS (FAB): m/z 244 (MH^+, 100%); HRMS (FAB) calcd. for $C_{11}H_{12}F_2NOS$ (MH^+): 244.0608. Found: 244.0613; plus *N*-allyl(2-fluoro-2-phenylsulfanyl)acetamide **25** (22 mg, 10%).

N-Cinnamyl(2-fluoro-2-phenylsulfanyl)acetamide 27

A solution of DFIT (270 mg, 0.97 mmol) and *N*-cinnamyl-(phenylsulfanyl)acetamide **15** (250 mg, 0.88 mmol) in DCM (5 mL) refluxing overnight. Work-up according to the general procedure followed by flash chromatography (SiO_2, PE 30–40:ether 50:50) afforded the fluoride **27** (146 mg, 55%) as a white solid; mp 74–78 °C (DCM:PE 30–40); R_f 0.52 (SiO_2, PE 30–40:ether 85:15); IR (thin film/cm^{-1}): ν_{max} 3391m (NH), 3025w, 2925w, 1666s (C=O), 1519s, 1441w, 1362w, 1303w, 1261w, 1011m, 980m, 800w, 746s, 689s; ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 3.74–3.92 (2H, m, 1-H), 5.77 (1H, dt $^{trans}J_{AB}$ 16 Hz, $^3J_{2,1}$ 6 Hz, 2-H), 6.05 (1H, d $^2J_{HF}$ 53 Hz, SCHF), 6.09 (1H, br, NH), 6.30 (1H, d $^{trans}J_{AB}$ 16 Hz, 3-H), 7.15–7.79 (10H, m, Ar–H); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 41.8 (1-C), 97.9 (d $^1J_{CF}$ 235 Hz, SCHF), 124.6, 126.8, 128.3, 129.0, 129.6, 130.0, 133.3, 135.26, 135.28, 136.6, 165.2 (d $^2J_{CF}$ 24 Hz, C=O); ^{19}F NMR (282 MHz, $CDCl_3$): δ_F −156.5 (d $^2J_{FH}$ 53 Hz); MS (FAB): m/z 302 (MH^+, 100%); HRMS (FAB) calcd. for $C_{17}H_{17}FNOS$ (MH^+): 302.1015. Found: 302.1017.

N-(2-Fluoro-2-phenylsulfanyl)acetyl-3-methylbut-2-enylamine 28

A solution of DFIT (90 mg, 0.35 mmol) and *N*-(3-methylbut-2-enyl)(phenylsulfanyl)acetamide **16** (75 mg, 0.32 mmol) in DCM (4 mL) refluxing overnight. The reaction mixture was diluted with DCM and bound to SiO_2. Flash chromatography (SiO_2, PE 30–40:ether 50:50) afforded the fluoride **28** (20 mg, 25%) as a colourless oil; R_f 0.33 (SiO_2, PE 30–40:ether 50:50); IR (thin film/cm^{-1}): ν_{max} 3299m (NH), 2923w, 1667s (C=O), 1531m, 1442w, 1274w, 978m, 746m, 691m; ^{1}H NMR (500 MHz, $CDCl_3$): δ_C 1.56 (CH_3), 1.65 (CH_3), 3.62–3.69 (2H, m, 1-H), 4.83–4.86 (1H, m, 2-H), 5.89 (1H, br, NH), 6.06 (1H, d $^2J_{HF}$ 53 Hz, SCHF), 7.31–7.56 (5H, m, Ar–H); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 18.2, 26.0, 37.7, 98.0 (d $^1J_{CF}$ 235 Hz), 119.3, 129.5, 129.8, 135.1 (2C), 137.6, 165.0 (d $^2J_{CF}$ 24 Hz, C=O); ^{19}F NMR (282 MHz, $CDCl_3$): δ_F −156.2 (d $^2J_{FH}$ 53 Hz); MS (FAB): m/z 254 (MH^+, 100%), 234 ([M − F]$^+$, 30); HRMS (FAB) calcd. for $C_{13}H_{17}FNOS$ (MH^+): 254.1015. Found: 254.1030.

N-Benzyl-*N*-methyl(2-fluoro-2-phenylsulfanyl)acetamide 29

A solution of DFIT (91%, 233 mg, 0.83 mmol) and *N*-benzyl-*N*-methyl(phenylsulfanyl)acetamide **17** (207 mg, 0.76 mmol) in DCM (6 mL) was stirred overnight. Work-up according to the general procedure followed by flash chromatography (SiO_2, PE 30–40:ether 70:30) gave the fluoride **29** (150 mg, 68%) as a colourless oil; R_f 0.49 (SiO_2, PE 30–40:ether 60:40); IR (thin film/cm^{-1}): ν_{max} 3061m, 2930m, 1666s (C=O), 1449s, 1265m, 1182m, 1115m, 1025s, 913m, 742s, 696s; ^{1}H NMR (300 MHz, $CDCl_3$): δ_H (*E*/*Z*) 2.85 and 2.96 (2 × 3H, s, CH_3), 4.27–4.74 (2 × 2H, m, NCH_2), 6.24 and 6.25 (2 × 1H, d $^2J_{HF}$ 55 Hz, 2-H), 7.12–7.51 (2 × 10H, m, Ar–H); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C (*E*/*Z*) 34.0 and 34.5 (CH_3), 51.5 and 53.1 (NCH_2), 96.8 and 97.8 (d $^2J_{CF}$ 232 Hz, 2-C) 127.4, 128.1, 128.4, 128.6, 129.2, 129.4, 129.5 (2C), 129.8, 131.8 (2 × C_{ipso}), 132.0, 133.4 (2C), 136.0 (C_{ipso}), 136.5 (C_{ipso}), 164.5 and 164.8 (d $^2J_{CF}$ 24 Hz, C=O); ^{19}F NMR (282 MHz, $CDCl_3$): δ_F −153.8 and 151.8 (d $^2J_{FH}$ 53 Hz); MS (FAB): m/z 290 (MH^+, 20%), 270 ([M − F]$^+$, 30); HRMS (FAB) calcd. for $C_{16}H_{17}FNOS$ (MH^+): 290.1015. Found: 290.1007.

2-Methyl-3-oxo-4-phenylsulfanyl-1,2,3,4-tetrahydroisoquinoline 30

A solution of DFIT (91%, 337 mg, 1.2 mmol) and *N*-benzyl-*N*-methyl(phenylsulfanyl)acetamide **17** (300 mg, 1.1 mmol) in DCM (6 mL) at reflux for 3 h. Work-up according to the general procedure followed by flash chromatography (SiO_2, PE 30–40:ether 70:30) gave the tetrahydroisoquinoline **30** (140 mg, 47%) as a yellow oil; R_f 0.32 (SiO_2, PE 30–40:ethyl acetate 40:60); IR (thin film/cm^{-1}): ν_{max} 3058m, 2926m, 1651s, 1439m, 1402m, 1139m, 1261m, 1087m, 747s, 695s; ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 2.90 (3H, s, CH_3), 3.71 (1H, d J_{AB} 13 Hz, 1-H), 3.87 (1H, d J_{AB} 16 Hz, 1-H), 4.63 (1H, s 3-H), 6.87–7.24 (9H, m, Ar–H); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 35.1 (CH_3), 51.6 (4-C), 52.4 (1-C), 124.6, 127.3, 127.6, 128.3, 128.5, 129.0, 130.9, 132.0, 133.0, 135.6, 167.2 (C=O); MS (FAB): m/z 292 (MNa^+, 15%), 270 (MH^+, 100); HRMS (FAB) calcd. for $C_{16}H_{15}NOS$ (MH^+): 270.0952. Found: 270.0958; and the fluoride **29** (94 mg, 25%) as a colourless oil.

3-Oxo-4-phenylsulfanyl-1,2,3,4-tetrahydroisoquinoline 31 and *N*-benzyl(2-fluoro-2-phenylsulfanyl)acetamide 32

A solution of DFIT (91%, 474 mg, 1.76 mmol) and *N*-benzyl-(phenylsulfanyl)acetamide **18** (400 mg, 1.55 mmol) in DCM (10 mL) at reflux for 1 h. Work-up according to the general procedure followed by flash chromatography (SiO_2, PE 30–40:ether 80:20) isolated the tetrahydroisoquinoline **31** (45 mg, 11%) as a colourless oil; R_f 0.21 (SiO_2, PE 30–40:ether 50:50); IR (thin film/cm^{-1}): ν_{max} 3248m (NH), 3082w (CH), 1644s (C=O), 1468w, 1420w, 1024w, 730m, 693m; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 4.33 (2H, d J 6 Hz, 1-H), 4.94 (1H, s, 4-H), 6.72 (1H, br, NH), 6.83–7.61 (9H, m, Ar–H); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 43.9 (1-C), 57.7 (4-C), 127.5, 127.7, 128.4, 128.6, 129.2, 129.7, 132.3, 132.7, 137.3, 167.1 (C=O); MS (FAB): m/z 256 (MH^+, 60%), 231 (55), 199 (40), 146 (100); HRMS (FAB) calcd. for $C_{15}H_{13}NOS$ (MH^+): 256.0800. Found: 256.0796; and the fluoride **32** (152 mg, 35%) as colourless crystals; mp 65 °C (DCM:PE 30–40); R_f 0.22 (SiO_2, PE 30–40:ether 50:50); IR (thin film/cm^{-1}): ν_{max} 3391s (NH), 1669s (C=O), 1516m (amide II), 1420w, 1300w, 1268w, 1065w, 1022w, 983m, 742m, 692m; ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 4.18–4.32 (2H, m, NCH_2), 6.02 (1H, d $^2J_{HF}$ 52 Hz, 2-H), 6.35 (1H, br, NH), 6.90–7.55 (10H, m, Ar–H); ^{19}F NMR (282 MHz, $CDCl_3$): δ_F −156.8 (dd J 53, 3 Hz); MS (FAB): m/z 298 (MNa^+, 20%), 276 (MH^+, 90); Anal calcd. for $C_{15}H_{14}FNOS$: C, 65.43; H, 5.12; N, 5.09; S, 11.65%. Found: C, 65.35; H, 5.00; N, 4.98; S, 11.89%.

1-Methyl-3-phenylsulfanylindol-2(3*H*)-one 33[19]

A solution of DFIT (91%, 237 mg, 0.86 mmol) and *N*-methyl-*N*-phenyl(phenylsulfanyl)acetamide **19** (200 mg, 0.78 mmol) in DCM (7 mL) at reflux for 4 h. Work-up according to the general procedure followed by flash chromatography (SiO_2, PE 30–40:ether 70:30) afforded the indolone **33** (117 mg, 59%) as a red solid; R_f 0.53 (SiO_2, PE 30–40:ether 80:30); IR (thin film/cm^{-1}): ν_{max} 3056m, 2932m (CH), 1715s (C=O), 1611s, 1470s, 1345s, 1308m, 1258m, 1162m, 1087s, 1021s, 922m, 865w, 746s, 691s; ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 2.95 (3H, s, CH_3), 4.49 (1H, s 3-H), 6.56 (1H, d J 8 Hz, 7-H), 6.90–7.31 (8H, m, Ar–H); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 26.7 (CH_3), 49.6 (3-C), 108.5 (7-C), 123.2, 125.6, 126.6, 129.0, 129.4, 131.3, 134.6, 144.3 (7a-C), 174.7 (C=O); MS (FAB): m/z 256 (MH^+, 40%), 159 (146, 100); HRMS (FAB) calcd. for $C_{15}H_{14}NOS$ (MH^+): 256.0796. Found: 256.0801.

N-Methyl-*N*-phenyl(phenylsulfinyl)acetamide 34

A solution of DFIT (219 mg, 0.85 mmol) and *N*-methyl-*N*-phenyl(phenylsulfanyl)acetamide **19** (200 mg, 0.78 mmol) in

DCM (5 mL) was stirred for 5 h. Work-up according to the general procedure followed by flash chromatography (SiO_2, PE 40–60:ether 50:50 grading to 10% MeOH) yielded the sulfoxide **34** (176 mg, 86%) as a white solid; mp 100–101.5 °C (DCM:PE 30–40); R_f 0.15 (SiO_2; ether); IR (thin film/cm^{-1}): ν_{max} 3058w, 2923w, 1650s (C=O), 1593m, 1496m, 1383m, 1297w, 1116m, 1085m, 1047s, 749m, 698s; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 3.14, (3H, s, CH_3), 3.42 (1H, AB d J_{AB} 14 Hz, SCH_2), 3.76 (1H, AB d J_{AB} 14 Hz, SCH_2), 6.84 (2H, d J 8 Hz, Ar–H), 7.24–7.54 (8H, m, Ar–H); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 37.3 (CH_3), 62.1 (SCH_2), 124.3, 127.2, 128.4, 129.1, 129.9, 131.4, 142.5, (C_{ipso}), 143.6 (C_{ipso}), 163.9 (C=O); MS (EI): m/z 273 ($M^{\bullet+}$, 80%), 225 (40), 148 (100); Anal. Calcd. for $C_{15}H_{15}NO_2S$: C, 65.91; H, 5.53; N, 5.12; S, 11.73%. Found: C, 65.94; H, 5.50; N, 5.12; S, 11.67%; plus 17 mg (9% recovery) of starting material.

N-Butyl(phenylsulfinyl)acetamide 35

A solution of DFIT (468 mg, 1.8 mmol) and *N*-butyl(phenylsulfanyl)acetamide **20** (186 mg, 0.83 mmol) in DCM (4 mL) was stirred for 1.5 h. Work-up according to the general procedure followed by flash chromatography (SiO_2, PE 40–60:ether 50:50 grading to 10% MeOH) yielded the sulfoxide **35** (170 mg, 86%) as a yellow oil, solidifying in the cold; R_f 0.08 (SiO_2, ether); IR (KBr disc/cm^{-1}): ν_{max} 3300s (NH) 3074m, 2957m, (CH), 1650s (C=O), 1544s, 1479m, 1222m, 1026w; ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 0.91 (3H, t J 7 Hz, CH_3), 1.30–1.46 (4H, m, CH_2CH_2), 3.19–3.23 (2H, m, NCH_2), 3.50 (1H, AB d J_{AB} 14 Hz, SCH_2), 3.71 (1H, AB d J_{AB} 14 Hz, SCH_2), 6.86 (1H, br NH), 7.53–7.62 (5H, m, Ar–H); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 13.6 (CH_3), 19.9 (CH_2CH_3), 31.3 (NCH_2CH_2), 39.4 (NCH_2), 58.6 (SCH_2), 123.8, 129.3 131.5, 141.4 (C_{ipso}), 163.4 (C=O); MS (FAB): m/z 262 (MNa^+ 80%), 240 (MH^+, 100); HRMS (FAB) calcd. for $C_{12}H_{17}NO_2S$: 239.0980; Found: 239.0971.

N-Phenyl(phenylsulfinyl)acetamide 36[20]

A solution of DFIT (231 mg, 0.9 mmol) and *N*-phenyl(phenylsulfanyl)acetamide **21** (200 mg, 0.82 mmol) in DCM (5 mL) was stirred for 5 h. Work-up according to the general procedure followed by flash chromatography (SiO_2, PE 30–40 grading to ether) yielded the sulfoxide **36** (165 mg, 78%) as a white solid; mp 165–166 °C (DCM:PE 30–40); R_f 0.19 (SiO_2, ether); IR (KBr disc/cm^{-1}): ν_{max} 3454s (NH) 1679s (C=O), 1599m, 1539s, 1443m, 1326m, 1016s (S=O), 745s, 689s; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 3.61 (1H, AB d J_{AB} 14 Hz, SCH_2), 3.94 (1H, AB d J_{AB} 14 Hz, SCH_2), 7.08–7.65 (10H, m, Ar–H), 9.07 (1H, br NH); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 58.9 (SCH_2), 120.3, 124.0, 124.7, 129.0, 129.6, 131.8, 137.4 (C_{ipso}), 140.9 (C_{ipso}), 161.7 (C=O); MS (EI): m/z 259 ($M^{\bullet+}$, 50%), 211 (20), 106 (100); Anal. Calcd. for $C_{14}H_{13}NO_2S$: C, 64.84; H, 5.05; N, 5.40; S, 12.36%. Found: C, 64.79; H, 5.03; N, 5.38; S, 12.08%; plus 41 mg (21% recovery) of starting material.

1-Methyl-2-oxo-3-phenylsulfanyl-3-pyrroline 41

1) From 1-methyl-3-phenylsulfanyl-2-pyrrolidinone **38**

A solution of DFIT (54%, 494 mg, 1.0 mmol) and 1-methyl-3-phenylsulfanyl-2-pyrrolidinone[21] **38** (200 mg, 0.96 mmol) in DCM (6 mL) was stirred for 18 h. Work-up according to the general procedure followed by flash chromatography (SiO_2, PE 30–40:ether 20:80) afforded the pyrroline **41** (110 mg, 56%) as a red solid, mp 75–76 °C (hexane:ethyl acetate); R_f 0.18 (SiO_2, ether); IR (thin film/cm^{-1}): ν_{max} 2920w, 1683s (C=O), 1597w, 1475m, 1443m, 1401m, 1291w, 1231w, 1036m, 933m, 801m, 761m, 690m; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 3.02 (3H, s, CH_3), 3.84 (2H, d $J_{5,4}$ 2 Hz, 5-H), 6.20 (1H, t $J_{4,5}$ 2 Hz, 4-H), 7.31–7.50 (5H, m, Ar–H); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 29.7 (CH_3), 53.6 (5-C), 128.8, 129.5, 130.7, 131.5, 133.7, 137.6, 168.2 (C=O); MS (FAB): m/z 206 (MH^+, 100%); Anal. Calcd. for $C_{11}H_{11}NOS$: C, 64.36; H, 5.40; N, 6.82; S, 15.66%. Found: C, 64.47; H, 5.32; N, 6.88; S, 15.78%; plus 3,(*syn*/*anti*)-4-difluoro-1-methyl-3-phenylsulfanyl-2-pyrrolidinone **46** (29 mg, 12%) as a side product.

2) From 1-methyl-3,3-diphenylsulfanyl-2-pyrrolidinone **44**

A solution of DFIT (325 mg, 1.27 mmol) and 1-methyl-3,3-diphenylsulfanyl-2-pyrrolidinone[21] **44** (380 mg, 1.21 mmol) in DCM (5 mL) was stirred for 18 h. The crude mixture was diluted with DCM and absorbed onto SiO_2. Flash chromatography (SiO_2, PE 30–40:ether 20:80) afforded the pyrroline **41** (202 mg, 82%) as a red solid, identical to material previously prepared.

1-Methyl-3-phenylsulfanyl-5,6-dihydro-2(1*H*)-pyridone 42

A solution of DFIT (54%, 463 mg, 0.98 mmol) and 1-methyl-3-phenylsulfanyl-2-piperidinone[21] **39** (200 mg, 0.90 mmol) in DCM (6 mL) was stirred for 24 h. Work-up according to the general procedure followed by flash chromatography (SiO_2, PE 30–40:ether 20:80) yielded the pyridone **42** (114 mg, 58%) as a white solid mp 95–96 °C (DCM:PE 30–40); R_f 0.32 (SiO_2, ethyl acetate); IR (thin film/cm^{-1}): ν_{max} 3053w, 2932m, 2851m, 1635s (C=O), 1602s, 1480s, 1434s, 1400s, 1347s, 1306m, 1266m, 1212s, 1078s, 1024s, 930w, 856m, 823m, 755m, 695s; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 2.27–2.33 (2H, m, 5-H), 3.00 (3H, s, NCH_3), 3.36 (2H, t J 7 Hz, 6-H), 5.76 (1H, t J 5 Hz, 4-H), 7.30–7.46 (5H, m, Ar–H); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 24.6 (5-C), 34.9 (CH_3), 47.6 (6-C), 128.5, 129.4, 130.8 (4-C), 132.0, 134.5, 136.8, 162.8 (C=O); MS (FAB): m/z 220 (MH^+, 100%); Anal. Calcd. for $C_{12}H_{13}NOS$: C, 65.72; H, 5.97; N, 6.39; S, 14.62%. Found: C, 65.69; H, 5.99; N, 6.35; S, 14.93%; plus 3,(*syn*/*anti*)-4-difluoro-1-methyl-3-phenylsulfanyl-2-piperidinone **47** (8 mg, 3%) as a side product.

1-Methyl-3-phenylsulfanyl-1,5,6,7-tetrahydroazepine-2-one 43

A solution of DFIT (240 mg, 0.94 mmol) and 1-methyl-3-phenylsulfanylcaprolactam **40**[21] (200 mg, 0.85 mmol) in DCM (6 mL) was stirred 48 h. Work-up according to the general procedure followed by flash chromatography (SiO_2, PE 30–40:ether 50:50) the tetrahydroazepin-2-one **43** (87 mg, 44%) as a yellow oil; R_f 0.24 (SiO_2, PE 30–40:ethyl acetate 40:60); IR (thin film/cm^{-1}): ν_{max} 3059m, 2950w, 2892m (CH), 1640s (C=O), 1476m, 1439m, 1396m, 1090m, 918w, 841w, 762m, 691m; ^{1}H NMR (500 MHz, $CDCl_3$): δ_C 1.94–2.00 (2H, m), 2.20–2.28 (2H, m), 3.06 (3H, s, CH_3), 3.38 (2H, t J 6 Hz, 7-H), 6.21 (1H, t J 7 Hz, 4-H), 7.26–7.50 (5H, m, Ar–H); ^{13}C NMR (126 MHz, $CDCl_3$): δ_C 24.8, 28.8, 35.2, 48.6, 128.1, 129.6, 132.9, 133.9, 134.1, 135.5, 168.2 (C=O); MS (FAB): m/z 234 (MH^+, 100%); HRMS (FAB) calcd. for $C_{13}H_{16}NOS$ (MH^+): 234.0953. Found: 234.0936.

3,(*antilsyn*)-4-Difluoro-1-methyl-3-phenylsulfanyl-2-pyrrolidinone 45

A solution of DFIT (82%, 640 mg, 2.1 mmol), $Et_3N{\cdot}3HF$ (0.03 mL, 0.19 mmol) and 1-methyl-3-phenylsulfanyl-2-pyrrolidinone **38** (200 mg, 0.97 mmol) in DCM (6 mL) was stirred for 16 h. Work-up according to the general procedure followed by flash chromatography (SiO_2, PE 30–40:ether 20:80) afforded 3,(*anti*/*syn*)-4-difluoro-1-methyl-3-phenylsulfanyl-2-pyrrolidinone **45** (139 mg, 59%) as a colourless oil; *syn*:*anti* 1.75:1, from which pure *syn*-**45** could be crystallised: mp 91.5–93 °C (DCM:PE); R_f 0.30 (SiO_2, ether); IR (thin film/cm^{-1}): ν_{max} 2927w (CH), 1717s (C=O), 1436m, 1307m, 1149m, 1053s, 756m, 694s; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 2.96 (3H, s, CH_3), 3.49 (1H, ddd $^3J_{HF}$ 22 Hz, $^2J_{HH}$ 12 Hz, $^3J_{HH}$ 1 Hz, 5-H), 3.80 (1H, ddd $^3J_{HF}$ 32 Hz, $^2J_{HH}$ 12 Hz, $^3J_{HH}$ 3 Hz, 5-H), 4.85 (1H, dd $^2J_{HF}$ 53 Hz, $^3J_{HH}$ 3 Hz, 4-H), 7.28–7.62 (5H, m, Ar–H); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 30.2 (CH_3), 51.9 (d $^2J_{CF}$ 24 Hz, 5-C), 87.3 (dd $^1J_{CF}$ 199 Hz, $^2J_{CF}$ 19 Hz, 4-C), 99.6 (dd $^1J_{CF}$ 238 Hz, $^2J_{CF}$ 17 Hz, 3-C), 127,2 (C_{ipso}), 129.5, 130.2, 135.3, 164.6 (d $^2J_{CF}$ 27 Hz, C=O); ^{19}F NMR (564 MHz, $CDCl_3$): δ_F −190.6–190.8 (m, 4-F), −155.9 (d J_{FF} 17

Hz, 3-F); MS (FAB): *m*/*z* 244 (MH^+, 100%); Anal. Calcd. for $C_{11}H_{11}F_2NOS$: C, 54.31; H, 4.56; N, 5.76; S, 13.18%. Found: C, 54.17; H, 4.30; N, 5.70; S, 13.37%; *anti*-**52**: R_f 0.35 (SiO_2, ether); ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 2.87 (3H, s, CH_3), 3.43–3.52 (1H, m, 5-H), 3.63–3.70 (1H, m, 5-H), 4.98–5.17 (1H, m, 4-H), 7.29–7.61 (5H, m, Ar–H); ^{19}F NMR (564 MHz, $CDCl_3$): δ_F −191.64–191.46 (m, 4-F), −136.79 (dd *J* 17, 12 Hz, 3-F); plus 1-methyl-2-oxo-3-phenylsulfanyl-3-pyrroline **41** (20 mg, 8%) as a side product.

3,(*anti*/*syn*)-4-Difluoro-1-methyl-3-phenylsulfanyl-2-piperidinone 46

A solution of DFIT (510 mg, 1.8 mmol) and 1-methyl-3-phenylsulfanyl-2-piperidinone **39** (200 mg, 0.9 mmol) in DCM (6 mL) was stirred for 4 h. Work-up according to the general procedure followed by flash chromatography (SiO_2, PE:ether 20:80) yielded 3,(*anti*/*syn*)-4-difluoro-1-methyl-3-phenylsulfanyl-2-piperidinone **46** (88 mg, 39%) as a clear oil; *anti*:*syn* 2:1; IR (thin film/cm^{-1}): ν_{max} 2946m (CH), 1666s (C=O), 1501m, 1441m, 1405m, 1349m, 1212m, 1051m, 1024m, 970m, 842m, 753m. Pure *anti*-**46** could be crystallised from the mixture: mp 83–84 °C (PE 30–40:ethyl acetate); R_f 0.29 (SiO_2, ether); ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 2.20–2.32 (2H, m, 5-H), 2.97 (3H, s, CH_3), 3.24–3.35 (1H, m, 6-H), 3.52–3.63 (1H, m, 6-H), 4.50 (1H, dm $^2J_{HF}$ 47 Hz, 4-H), 7.26–7.63 (5H, m, Ar–H); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 24.3 (d $^2J_{CF}$ 21 Hz, 5-C), 35.2 (CH_3), 44.6 (d $^3J_{CF}$ 7 Hz, 6-C), 86.6 (dd $^1J_{CF}$ 183 Hz, $^2J_{CF}$ 36 Hz, 4-C), 102.0 (dd $^1J_{CF}$ 224 Hz, $^2J_{CF}$ 25 Hz, 3-C), 127.8 (C_{ipso}), 129.0, 129.9, 136.9, 162.3 (d $^2J_{CF}$ 23 Hz, C=O); ^{19}F NMR (376 MHz, $CDCl_3$): δ_F −136.3–136.0 (m, 4-F), −72.0 (d, *J* 31 Hz, 3-F); MS (FAB): *m*/*z* 258 (MH^+, 100%), 210 (50); Anal. Calcd. for $C_{12}H_{13}F_2NOS$: C, 56.02; H, 5.09; N, 5.44; S, 12.46%. Found: C, 56.03; H, 4.93; N, 5.42; S, 12.27%; *syn*-**46** (160): R_f 0.33 (SiO_2, ether); ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 2.15–2.24 (1H, m, 5-H), 2.63–2.83 (1H, m, 5-H), 2.98 (3H, s, CH_3), 3.34 (1H, dd *J* 12, 7 Hz, 6-H), 3.59 (1H, td *J* 12, 5 Hz, 6-H), 4.76 (1H, dm $^2J_{HF}$ 51 Hz, 4-H), 7.26–7.63 (5H, m, Ar–H); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 25.8 (d $^2J_{CF}$ 23 Hz, 5-C), 35.0 (CH_3), 44.6 (6-C), 88.7 (dd $^1J_{CF}$ 185 Hz, $^2J_{CF}$ 22 Hz, 4-C), 97.6 (dd $^1J_{CF}$ 238 Hz, $^2J_{CF}$ 20 Hz, 3-C), 127.1 (C_{ipso}), 129.5, 130.3, 136.0, 163.3 (d $^2J_{CF}$ 25 Hz, C=O); ^{19}F NMR (376 MHz, $CDCl_3$): δ_F −145.3–145.0 (m, 4-F), −93.4 (d, *J* 18 Hz, 3-F).

3,(*syn*/*anti*)-4-Difluoro-1-methyl-3,(*syn*/*anti*)-4-diphenylsulfanyl-2-pyrrolidinone 47

A solution of DFIT (402 mg, 1.57 mmol) and 1-methyl-3,3-diphenylsulfanyl-2-pyrrolidinone **44** (150 mg, 0.47 mmol) in DCM (6 mL) was stirred for 1 h. The reaction was quenched with sat. aq. $NaHCO_3$ solution and worked up as normal. Flash chromatography (SiO_2, PE 30–40:ether 75:25) yielded 3,(*syn*/*anti*)-4-difluoro-1-methyl-3,(*syn*/*anti*)-4-diphenylsulfanyl-2-pyrrolidinone **47** (75 mg, 45%) as a clear oil; *anti*:*syn* 2:1. Pure *anti*-**47** could be crystallised from the mixture: mp 126–128 °C (DCM:PE 30–40); R_f 0.33 (SiO_2, PE 30–40:ether 60:40); IR (thin film/cm^{-1}): ν_{max} 1734s (C=O), 1475w, 1439w, 1404w, 1283w, 1209w, 1045m, 995w, 929w, 893w, 728m, 690m; ^{1}H NMR (300 MHz, $CDCl_3$): δ_C 2.81 (3H, s, CH_3), 3.27 (1H, dd $^2J_{HH}$ 11 Hz, $^3J_{HF}$ 2 Hz, 5-H), 3.57 (1H, t *J* 11 Hz, 5-H), 7.33–7.74 (10H, m, Ar–H); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 30.4 (NCH_3), 54.5 (d $^2J_{CF}$ 34 Hz, 5-C), 103.7 (dd $^1J_{CF}$ 242 Hz, $^2J_{CF}$ 19 Hz, 4-C) 106.8 (dd $^1J_{CF}$ 242 Hz, $^2J_{CF}$ 19 Hz, 3-C), 126.7 (C_{ipso}), 128.4 (C_{ipso}), 129.4, 129.9, 130.5, 130.6, 136.4, 136.9, 163.6 (dd $^2J_{CF}$ 30 Hz, $^3J_{CF}$ 4 Hz, 2-C); ^{19}F NMR (376 MHz, $CDCl_3$): δ_F −144.2 (d $^3J_{FF}$ 9 Hz 3-F), −132.9 (t, *J* 10 Hz, 4-F); MS (FAB): *m*/*z* 484 (MCs^+, 100%), 393 (33), 352 (MH^+, 35%); Anal. Calcd. for $C_{17}H_{15}F_2NOS_2$: C, 58.10; H, 4.30; N, 3.98; S, 18.25%. Found: C, 58.11; H, 4.11; N, 4.05; S, 18.40%; *syn*-**78**: ^{1}H NMR (300 MHz, $CDCl_3$): δ_C 2.81 (3H, s, CH_3), 3.34 (1H, dd $^3J_{HF}$ 14 Hz, $^2J_{HH}$ 11 Hz, 5-H), 3.75 (1H, dd $^2J_{HF}$ 25 Hz, $^3J_{HH}$ 11 Hz, 5-H), 7.33–7.74 (10H, m, Ar–H); ^{19}F NMR (376 MHz, $CDCl_3$): δ_F −154.0 (d $^3J_{FF}$ 17 Hz 3-F), −134.2 (m, 4-F).

(*syn*/*anti*)-1-*n*-Butyl-3-fluoro-3-phenylsulfinylazetidin-2-one 52 and 1-*n*-butyl-3-fluoro-3-phenylsulfanylazetidin-2-one 51

A solution of DFIT (304 mg, 1.2 mmol) and 1-*n*-butyl-3-phenylsulfanylazetidin-2-one[22] **50** (127 mg, 0.54 mmol) in DCM (4 mL) was stirred overnight. Work-up according to the general procedure followed by flash chromatography (SiO_2, hexane:ether 50:50) yielded the fluoro-sulfide **51** [16] (12 mg, 9%) as a colourless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 0.94 (3H, t *J* 7 Hz, CH_3), 1.31–1.57 (4H, m, CH_2CH_2), 3.22–3.32 (2H, m, NCH_2CH_2), 3.49 (1H, t, $^2J_{HH}$ 6 Hz, $^3J_{HF}$ 6 Hz, 4-H), 3.63 (1H, t $^2J_{HH}$ 6 Hz, $^3J_{HF}$ 6 Hz, 4-H), 7.26–7.67 (5H, m, Ar–H); ^{19}F NMR (376 MHz, $CDCl_3$): δ_F −137.9 (t, *J* 6 Hz); and the fluoro-sulfoxide **52** (66 mg, 45%) as a colourless oil; [*ca.* 3:1 ratio of diastereoisomers (unassigned)]; R_f 0.28 (SiO_2, PE 40–60:ether 50:50); IR (thin film/cm^{-1}): ν_{max} 2928s and 2874s (CH), 1770 (C=O), 1445m, 1404m, 1280m, 1182m, 1087s, 1055s, 876w, 750s, 689s; ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 0.80 (3H, t *J* 7 Hz, CH_3 minor diastereoisomer), 0.90 (3H, t *J* 7 Hz, CH_3 major), 1.06–1.60 (8H, m, 2 × CH_2CH_2), 2.99–3.35 (5H, m, 2 × NCH_2, 4-H major), 3.52 (1H, dd $^3J_{HF}$ 10 Hz, $^3J_{HH}$ 7 Hz, 4-H minor), 3.81 (1H, dd, $^2J_{HH}$ 7 Hz, $^3J_{HF}$ 7 Hz 4-H minor), 3.85 (1H, dd $^2J_{HH}$ 7 Hz, $^3J_{HF}$ 7 Hz, 4-H major), 7.26–7.75 (10H, m, Ar–H); ^{13}C NMR (151 MHz, $CDCl_3$): δ_C (major diastereoisomer only) 13.5 (CH_3), 19.9 (CH_2CH_3), 29.1 (NCH_2CH_2), 42.1 (NCH_2CH_2), 46.3 (d $^2J_{CF}$ 22 Hz, 4-C), 108.8 (d $^1J_{CF}$ 277 Hz, 3-C), 125.4, 129.1, 132.3, 137.6 (C_{ipso}), 159.7 (d $^2J_{CF}$ 22 Hz, 2-C); ^{19}F NMR (470 MHz, $CDCl_3$): δ_F −168.9 (t, J_{FH} 8 Hz, major), −165.6 (t J_{FH} 9 Hz, minor); MS (FAB): *m*/*z* 292 (MNa^+, 25%), 270 (MH^+, 100), 171 (95).

An analytical sample of fluorosulfoxide **52** (*ca.* 20 mg) was dissolved in DCM (1 mL) at 0 °C was treated with mCPBA (68%, 50 mg). After stirring for 1 h sat. aq. $NaHSO_3$ solution (1 mL) was added and the mixture stirred a further 3 h. The organic phase was separated, washed with sat. aq. $NaHSO_3$ solution, brine, then dried ($MgSO_4$) and concentrated *in vacuo* to afford the sulfone derivative contaminated with mCBA as a white solid; ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 0.98 (3H, t *J* 7 Hz, CH_3), 1.34–1.68 (4H, m, CH_2CH_2), 3.29–3.46 (2H, m, NCH_2), 3.66 (1H, dd $^3J_{HF}$ 10 Hz, $^3J_{HH}$ 7 Hz, 4-H), 4.18 (1H, dd $^2J_{HH}$ 7 Hz, $^3J_{HF}$ 7 Hz, 4-H), 7.28–8.12 (5H, m, Ar–H); ^{19}F NMR (470 MHz, $CDCl_3$): δ_F −165.8 (t, J_{FH} 8 Hz); MS (FAB): *m*/*z* 286 (MH^+, 70%); HRMS (FAB) calcd. for $C_{13}H_{17}FNO_3S$ (MH^+): 286.0913. Found: 286.0923.

Crystal data for *syn*-45

$C_{11}H_{11}F_2NOS$, *M* = 243.37, 0.50 × 0.50 × 0.40 mm^3, monoclinic, space group $P2_1/n$, *a* = 7.5687(4), *b* = 13.7172(7), *c* = 10.6303(5) Å, *V* = 1103.62(10)Å^3, *Z* = 4, D_c = 1.464 g cm^{-3}, F_{000} = 504, MoKα radiation, λ = 0.71070 Å, *T* = 100(2) K, $2\theta_{max}$ = 52.0°, 9585 reflections collected, 2163 unique (R_{int} = 0.0259). Final *GoF* = 1.050, *R1* = 0.0344, *wR2* = 0.0830, *R* indices based on 1882 reflections with $I > 2\sigma(I)$ (refinement on F^2), 146 parameters, 0 restraints. μ = 0.297 mm^{-1}.

Crystal data for *anti*-46

$C_{12}H_{13}F_2NOS$, *M* = 257.29, 0.40 × 0.30 × 0.25 mm^3, orthorhombic, space group *Pnma* (No. 62), *a* = 14.3816(12), *b* = 9.2890(9), *c* = 9.0729(4) Å, *V* = 1212.05(16) Å^3, *Z* = 4, D_c = 1.410 g cm^{-3}, F_{000} = 536, Nonius KappaCCD, MoKα radiation, λ = 0.71073 Å, *T* = 100(2) K, $2\theta_{max}$ = 55.0°, 2617 reflections collected, 1457 unique (R_{int} = 0.0517). Final *GoF* = 1.102, *R1* = 0.0514, *wR2* = 0.1049, *R* indices based on 1129 reflections with $I > 2\sigma(I)$ (refinement on F^2), 150 parameters, 0 restraints. Lp and absorption corrections applied, μ = 0.275 mm^{-1}. CCDC 197047. See http://www.rsc.org/suppdata/p1/b2/b209078c/ for crystallographic files in CIF or other electronic format.

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References

1 W. B. Motherwell, M. F. Greaney and D. A. Tocher, *J. Chem. Soc., Perkin Trans. 1*, preceding paper in this issue (DOI: 10.1039/b209079a).
2 For a preliminary account of this work, see: (*a*) M. F. Greaney and W. B. Motherwell, *Tetrahedron Lett.*, 2000, **41**, 4467; (*b*) M. F. Greaney, W. B. Motherwell and D. A. Tocher, *Tetrahedron Lett.*, 2001, **42**, 8523.
3 W. B. Motherwell and J. A. Wilkinson, *Synlett*, 1991, 191.
4 S. Caddick, L. Gazzard, W. B. Motherwell and J. A. Wilkinson, *Tetrahedron*, 1996, **52**, 149.
5 M. M. Campbell and G. Johnson, *J. Chem. Soc., Perkin Trans. 1*, 1975, 1077.
6 D. Landini, A. Maia and A. Rampoldi, *J. Org. Chem.*, 1989, **54**, 328 and references therein.
7 W. H. Koster, J. E. Dolfini, B. Toeplitz and J. Z. Gougoutas, *J. Org. Chem.*, 1978, **43**, 79.
8 (*a*) G. Barbieri, M. Cinquini, S. Colonna and F. Montanari, *J. Chem. Soc., C*, 1968, 659; (*b*) D. H. R. Barton, F. Comer, D. G. T. Greig, P. G. Sammes, C. M. Cooper, G. Hewitt and W. G. E. Underwood, *J. Chem. Soc., C*, 1971, 3540.
9 Y. Tamura, J.-I. Uenishi, H. Maeda, H.-D. Choi and H. Ishibashi, *Synthesis*, 1981, 534.
10 Characterisation of fluoride **25** was complicated by a facile transformation to *N*-allyl(2,2-diphenylsulfanyl)acetamide, a reaction which occurred during recrystallisation from DCM:PE mixtures. We are currently investigating this behaviour and will report our results in due course.
11 J. E. Baldwin, *Chem. Commun.*, 1976, 734.
12 Y. Tamura, T. Yakura, Y. Shirouchi and J.-I. Haruta, *Chem. Pharm. Bull.*, 1986, **34**, 1061.
13 A. Konno, W. Naito and T. Fuchigami, *Tetrahedron Lett.*, 1992, **33**, 7017.
14 For examples of the Additive-Pummerer reaction see: (*a*) H. Kosugi, H. Uda and S. Yamagiwa, *Chem. Commun.*, 1976, 71; (*b*) O. De Lucchi, U. Miotti and G. Modena, *Org. React.*, 1991, **40**, 157; (*c*) G. H. Posner, E. Asirvatham and S. F. Ali, *Chem. Commun.*, 1985, 542; (*d*) D. Craig, K. Daniels and A. Roderick-Mackenzie, *Tetrahedron*, 1993, **49**, 11263.
15 The effectiveness of amine-HF complexes in promoting hypervalent iodoarene difuoride fluorinations has been shown to be highly dependant on complex stoichiometry: (*a*) S. Hara, M. Sekiguchi, A. Ohmori, T. Fukuhara and N. Yoneda, *Chem. Comm.*, 1996, 1899; (*b*) S. Hara, J. Nakahigashi, K. Ishi-I, M. Sawaguchi, H. Sakai, T. Fukuhara and N. Yoneda, *Synlett*, 1998, 495.
16 S. Narizuka and T. Fuchigami, *J. Org. Chem.*, 1993, **58**, 4200.
17 S. Ranganathan, D. Ranganathan and S. K. Singh, *Tetrahedron Lett.*, 1985, **26**, 4955.
18 Cinnamylamine prepared according to A. M. Aronov and M. H. Gelb, *Tetrahedron Lett.*, 1998, **39**, 4947.
19 T. Wieland and D. Grimm, *Chem. Ber.*, 1965, **98**, 1727.
20 C. Fromont and S. Masson, *Tetrahedron*, 1999, **55**, 5405.
21 P. A. Zoretic, P. Soja and N. D. Sinha, *J. Org. Chem.*, 1978, **43**, 1379.
22 K. Hirai and Y. Iwano, *Tetrahedron Lett.*, 1979, **22**, 2031.