Methodology for the Synthesis of 4 or 5-Substituted-3-Perfluoroalkyl Pyrazoles

Thesis Submitted for the degree of
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by

Laurence Oleksik
Department of Chemistry
University of Leicester

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ProQuest LLC
789 East Eisenhower Parkway
P.O. Box 1346
Ann Arbor, MI 48106-1346

Synopsis

The contents of this thesis describe four routes for the synthesis of various 4- and 5-substituted-3-perfluoroalkyl pyrazoles.

Initially the perfluoroacylation of a range of commercially available vinyl ethers and conversion of the resulting perfluoroacylated enol ethers to *1-H*-pyrazoles *via* reaction with hydrazine is reported.

The selective synthesis of a range of α-aryl vinyl ethers using Heck chemistry is then reported. Subsequent perfluoroacylations of the vinyl ethers followed by reaction of the resulting perfluoroacyl enol ethers with hydrazine affords a range of 5-aryl-3-perfluoroalkyl pyrazoles in good yields.

Alternative methodology for the synthesis of 5-aryl-3-perfluoroalkyl pyrazoles is then described in which resin bound esters are converted to vinyl ethers *via* a Tebbe reaction. Subsequent perfluoroacylations generate the expected resin bound perfluoroacyl enol ethers and cleavage with cyclisation with hydrazine liberates the desired pyrazoles in acceptable yields for this type of methodology.

Finally the microwave mediated Suzuki coupling of 4-iodo-1-methyl-3-trifluoromethyl-*1H*-pyrazole with various boronic acids is reported as a general way in which 4-substituted-3-perfluoroalkyl-pyrazoles can be synthesised rapidly in reasonable yields.

Acknowledgments

Firstly I would like to thank Professor Jonathan Percy for his help and advice throughout the course of my PhD. I would also like to thank Dr. David Davies at GlaxoSmithKline for his input into the project, especially during my time at Stevenage.

I would like to thank the EPSRC and GlaxoSmithKline for funding this research, and the Universities of Leicester and Birmingham for services and facilities.

I would also like to express my thanks to the support staff at both departments without whom this work could not have been completed.

I would like to thank the other members of the JMP group for their help, support and humour throughout the years.

However, mostly I would like to thank my family for their love, support and their belief in me. I am very lucky to have had this and it has been invaluable.

although you don't have a name yet I love you already

Abbreviations

ANP	FMOC-3-amino-3-(2-nitrophenyl)propionic Acid
m-CPBA	*meta*-Chloroperoxybenzoic Acid
DCC	Dicyclohexylcarbodiimide
DCM	Dichloromethane
DIC	Di*iso*propylcarbodiimide
DIPEA	Di*iso*propylethylamine
4-DMAP	4-Dimethylaminopyridine
DMF	Dimethylformamide
DPPP	1,3-bis-(diphenylphosphino)propane
DVB	Divinylbezene
Lit.	Literature Value
HMBA	4-Hydroxymethylbenzoic Acid
HMBC	Heteronuclear Multiple Bond Connectivity
MBTE	Methyl *tert*-butyl Ether
HOBt	1-Hydroxybenzotriazole
LDA	Lithium Di*iso*propylamide
NaHMDS	Sodium Hexamethyldisilazide
NMR	Nuclear Magnetic Resonance
ppm	Parts Per Million
PTC	Phase Transfer Conditions
rt	Room Temperature
TBAB	*Tetra-n*-butylammonium Bromide
TBAI	*Tetra-n*-butylammonium Iodide
TFA	Trifluroacetic Acid
TFAA	Trifluoroacetic Anhydride
THF	Tetrahydrofuran
TLC	Thin Layer Chromatography

Contents

1 Introduction

1.1 Some Useful Effects of Introducing Fluorine into Organic Molecules

The selective substitution of a hydrogen atom or a hydroxy group by fluorine in enzyme substrate analogues has been widely practised in various arenas of bioorganic and medicinal chemistry for the modification of physicochemical and physiological behaviour.

Fluorine is the most electronegative element (4.0 on the Pauling scale compared to 3.5 for oxygen and 2.1 for hydrogen). The introduction of fluorine into a molecule (for example the replacement of hydrogen with fluorine) can therefore have significant effects on the electron distribution within a molecule. This affects the dipole moment of the molecule and more importantly influences the chemistry of nearby functional groups. The introduction of fluorine close to an acidic group will increase its acidity and its introduction close to a basic group will have a base weakening effect. For example the pK_a of acetic acid is 4.76 and those of its α fluorinated analogues CH_2FCO_2H, CHF_2CO_2H and CF_3CO_2H are 2.59, 1.24 and 0.23 respectively.

Fluorine substituents are not particularly demanding sterically. The van der Waals radius of fluorine of the fluorine atom (1.47 Å) lies between that of oxygen (1.57 Å) and hydrogen (1.2 Å) and thus fluorine appears to have a closer steric relationship with oxygen while being larger than hydrogen. However, despite this difference fluorine emerges as being a reasonable hydrogen mimic in single atom substitutions. Enzyme substrate analogues that have such a substitution usually still have a high affinity for their target protein.

Replacement of a methylene for a difluoromethylene group (CH_2 for CF_2) can be much more dramatic than the single substitution [1] and it is widely accepted that the

CF_3 group bears little steric resemblance to the CH_3 group. Various lines of evidence place CF_3 significantly larger than methyl and a good upper estimate would equate it with the isopropyl group [1]. Seebach [2] has reasoned that when the van der Waals hemispheres of the CH_3 and CF_3 groups (16.8 $Å^3$ and 42.6 $Å^3$ respectively) are considered that the latter is two to three times larger than the former.

The replacement of C-H bonds with C-F bonds in a molecule is generally accepted to increase its lipophilicity. Lipophilicity is a key molecular parameter in medicinal chemistry and this strategy is one in the arsenal of the medicinal chemists used to accentuate the lipophilicity of lead molecules. However Böhm [3], based on ab initio quantum-chemical calculations, has found certain examples where fluorine substitutions made close to an oxygen increases the solvation energy of the molecule in water to a greater extent than in chloroform and cautions against blanket acceptance of the concept.

Once introduced the high carbon-fluorine bond strength renders the substituent relatively resistant to metabolic transformation [4].

Blockade of metabolically labile C-H bonds by selective replacement with C-F bonds is therefore practiced as a strategy within the pharmaceutical industry as a strategy for improving the metabolic stability of drug candidates.

Fluorinated compounds are now routinely synthesised by pharmaceutical and agrochemical companies. According to the world drug index, there are 128 fluorinated compounds with US trade names. Of the thirty one entities approved in 2002, nine compounds contained fluorine [3].

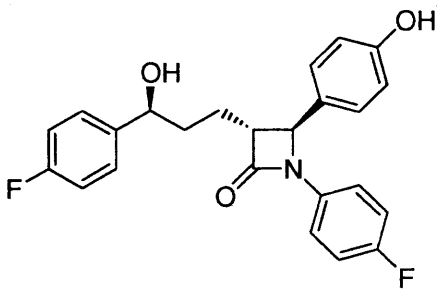
1.2 Fluorine in Medicinal Chemistry

While synthetic fluoro-organic chemistry has matured over recent decades, the specific use of fluorine in small-molecule drug-discovery research is more recent [3] The literature contains many examples of fluorine containing molecules with useful biological properties. Of these compounds the most commonly encountered are those which contain a fluorine substituent bonded directly to an aromatic ring.

1.2.1 Some Drug Molecules Containing Aryl-F Bonds

Ezetimib (SCH 85235) (1) [5,3]

Ezetimib (**1**) is an very effective chostererol-absorbtion inhibitor that was recently approved for use by the FDA. It consists of a 4 membered cyclic amide core, disposed around which are 4-fluorophenyl at N1, 4-hydroxylphenyl at C2 and 3-(4'-fluorophenyl)-3-hydroxypropyl with the stereochemistry as shown below at C3.



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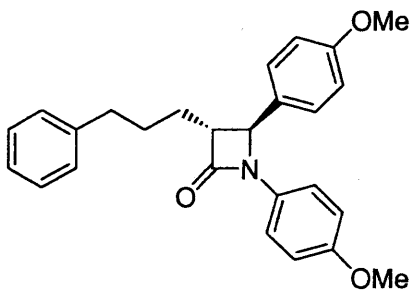
The fluorine atoms were introduced into the molecule to improve the metabolic stability of the lead SCH48461 (**2**) preventing the oxidation of the phenyl ring to phenol and dealkylation of the methoxy group.



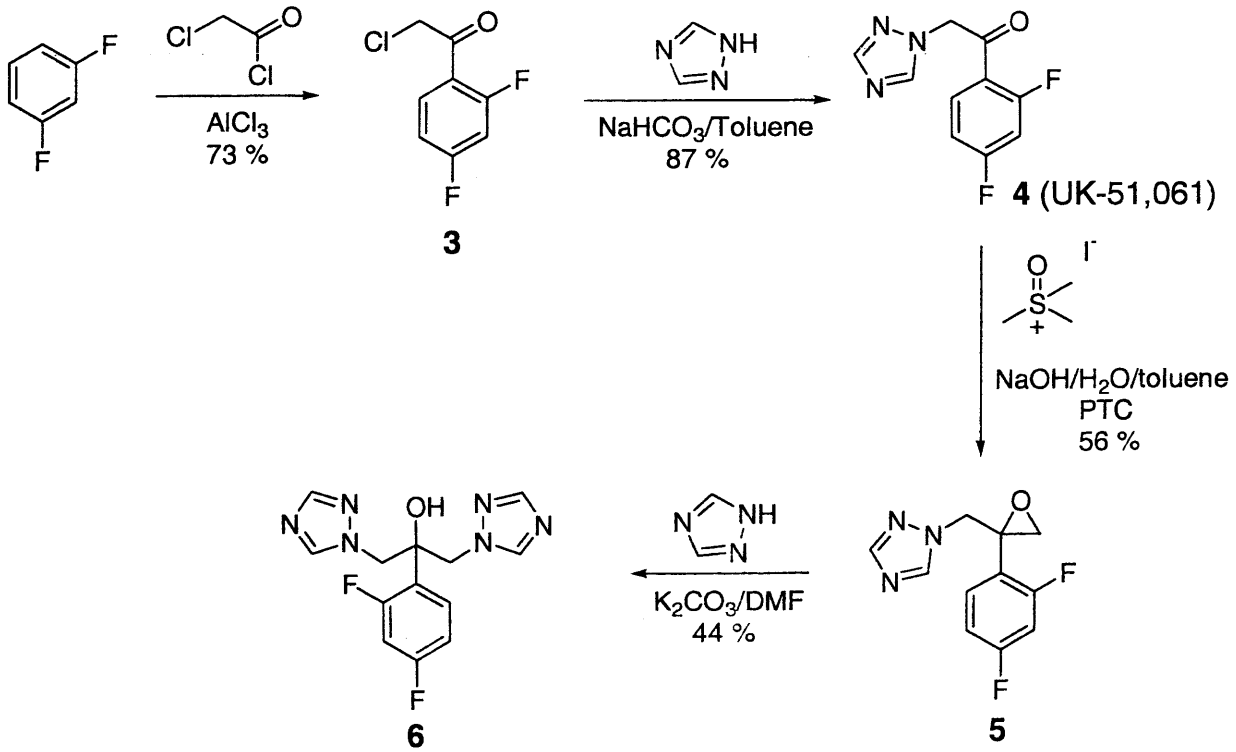
2

The ED_{50} (hamster) of the lead SCH 48461 (**2**) of 2.2 mg Kg^{-1} was improved in Ezetimib (**1**) to 0.04 mg Kg^{-1}.[5]

Fluconazole (6)

Fluconazole (**6**) is the worlds leading treatment for systemic fungal infections; it was developed by Pfizer and is sold under the product name of Diflucan. Annual sales of Diflucan in 1999 were $1 billion.

Fluconazole is synthesised from 1,3-difluorobenzene in a four step sequence (**Scheme 1**)

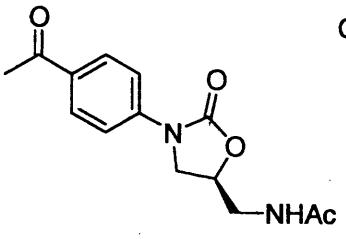


Scheme 1

The synthesis starts with the Friedel-Crafts acylation of 1,3-difluorobenzene with choroacetyl chloride to yield chloroacetophenone derivative **3** which is reacted with 1,2,4-triazole under basic conditions to form the intermediate UK-51,061 (**4**). Treatment of this intermediate with a sulfur ylid (generated by treatment of trimethylsulfoxonium iodide with aqueous sodium hydroxide under phase transfer conditions) yields epoxide **5**. Ring opening (regioselective) of the epoxide with a second molecule of 1,2,4 triazole affords fluconazole (**6**)

Further examples of where the presence of a fluorine attached to an aromatic ring has proved useful in enhancing the performance of a drug compound include Linezolid (PNU-100766) [6] (**7**) and Eperezolid (PNU-100592) [6] (**8**), Paroxetine [7] (**9**) and Astemizole (**10**) [8, 9].

Linezolid and Eperezoid were both discovered in a screening program in which the lead was DuP 721 (**11**). Early studies of DuP 721 revealed a number of attractive features, including activity against problematic resistant pathogens, a lack of cross resistance with existing microbial agents, oral activity in animal models of human infection, and a unique mechanism of action involving inhibition of a very early stage of protein synthesis [6]. Linezolid (**7**) and Eperezolid (**8**) exhibit useful levels of activity against staphylococci (including methicillin-resistant *Staphylococcus aureus* [MRSA] and methicillin-resistant *Staphylococcus epidermis* [MRSE]), entrococci (including vancomycin-resistant strains), and pneumococci (including penicillin-resistant strains) [6].



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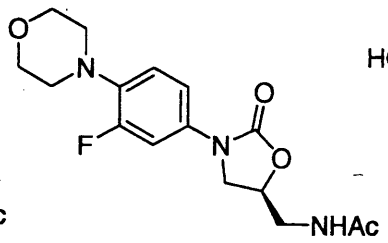

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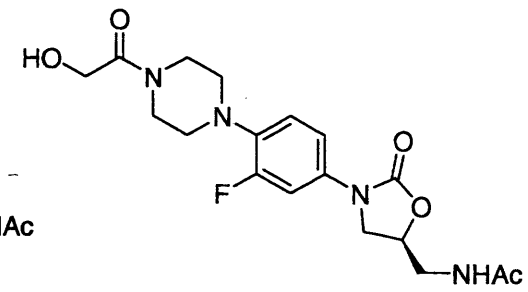
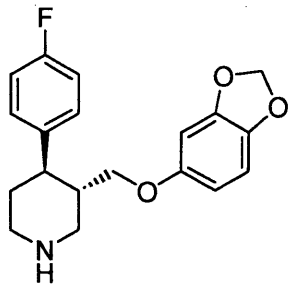


8

Linezolid is currently (at the time of the publication of the Tucker paper) undergoing phase III clinical trials.

Other examples of therapeutic agents that contain fluoro substituted aryl rings include Paroxetine (**9**) [7] which is a selective serotonin re-uptake inhibitor (SSRI) that is used in the treatment of depressive illnesses and Astemizole (**10**) [8,9] which is an antihistamine commonly used in the treatment of allergies.



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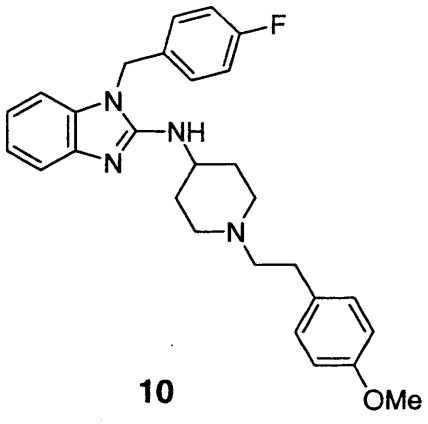

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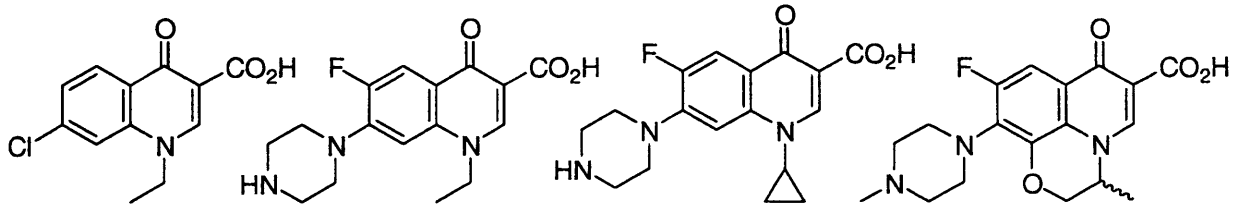
1.2.2 Some Drug Molecules Containing Fluorinated Heterocycles

Fluoroquinolones

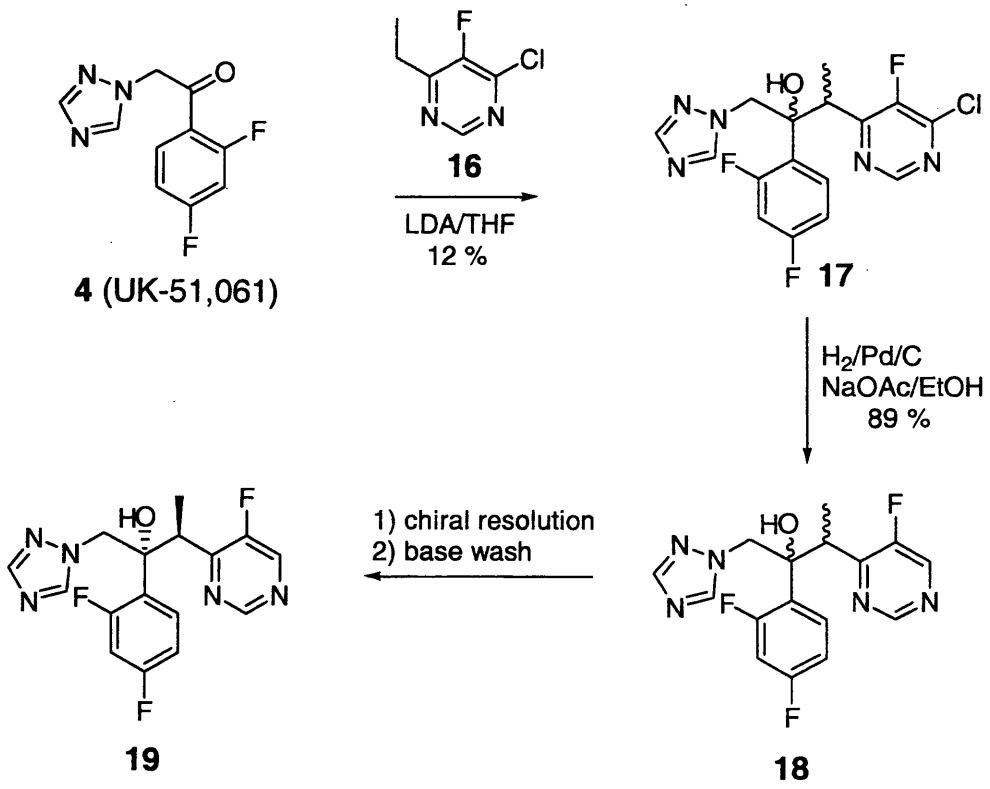
Fluoroquinolones are highly active and safe antibacterial agents that are widely used. The usage of a first generation of molecules, exemplified by nalidixic acid (**12**) was limited by a rather narrow antibacterial spectrum and a comparatively weak activity[3]. In order to improve the spectrum of activity and to combat increased levels of resistance a second generation of quinolones such as norfloxacin (**13**), ciprofloxacin (**14**), and ofloxacin (**15**) were synthesised each of which is now a widely used therapeutic agent. A key feature in the second generation compounds is the presence of the fluorine attached to C6 of the quinolone ring.



12 **13** **14** **15**

Voriconazole (19)

Fluconazole is effective against many species associated with systemic fungal infections; it is however, ineffective in patients infected by aspergillus species. Voriconazole was developed to meet this shortcoming. Not only is it effective against aspergillus infection but it also is potent against a broad spectrum of fungal pathogens. Voriconazole is structurally similar to Fluconazole and the intermediate UK-51,060 (**4**) is key in the synthesis of both these species (Scheme 2).



Scheme 2

The synthesis of Voriconazole begins with the LDA mediated coupling between intermediate **4** and ethylpyrimidine **16** which affords a mixture of diasteroisomers. The 2R,3S/2S,3R enantiomers (**17**) are isolated by chromatography or fractional crystalisation, the poor yield is due to competing enolisation of **4**. Hydrogenation of **17** affords **18** (2R,3S/2S,3R enantiomers) from which the 2R,3S enantiomer is resolved by recrystalisation as its 10-camphor-sulphonate salt; a base wash then liberates Voriconazole (**19**).

1.2.3 Trifluoromethyl Substituted Heterocycles (Medicinal and Agrochemical)

The synthesis of CF_3 substituted heterocycles has resulted in the discovery of many molecules with useful medicinal (or agrochemical) uses.

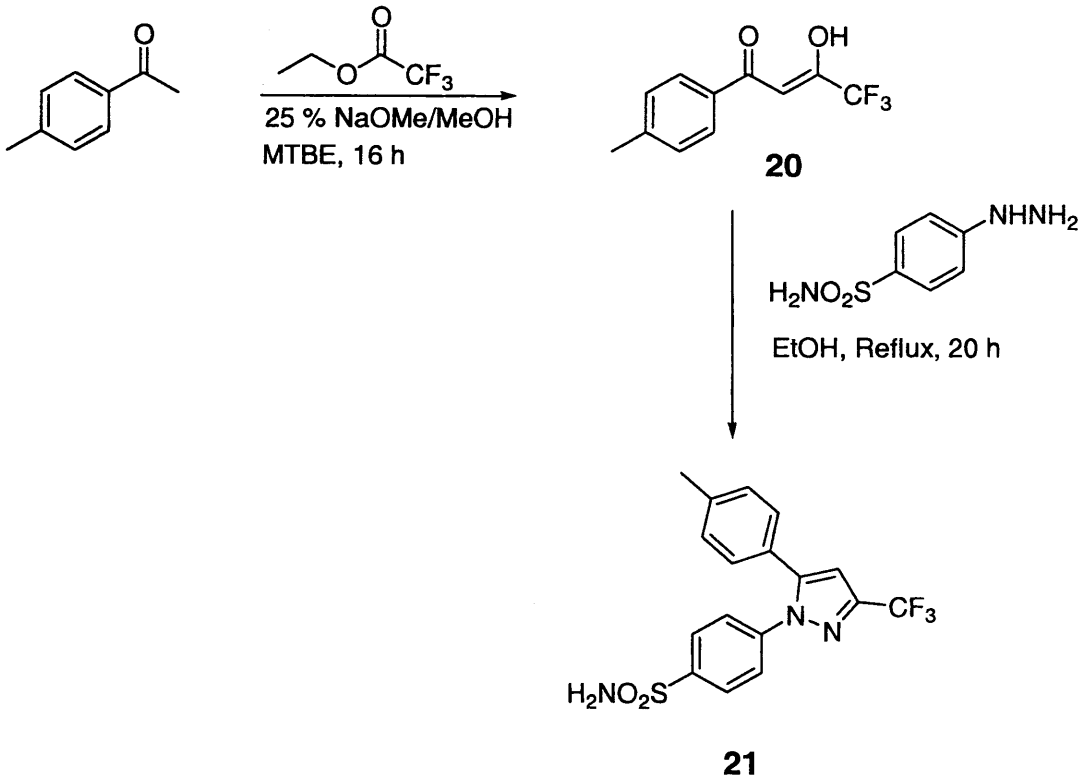
Trifluoromethyl imidazoles have found application in the medicinal and agrochemical fields [10], while fluoroalkylpyrazoles are compounds possessing high biological activities as herbicides, fungicides, insecticides, analgesics, antipyretics and antiinflammatories.[11]

Celecoxib (21)

Celecoxib (SC-58635) (**21**) is a nonsteroidial anti-inflammatory drug (NSAID) licensed for the treatment of osteoarthritis and rheumatoid arthritis under the trade name of Celebrex. It is a selective cyclooxygenase-2 (COX-2) enzyme inhibitor at therapeutic doses. NSAIDs work by blocking the formation of prostaglandins, which elicit a variety of beneficial and untoward biological responses. Among the undesirable properties of prostaglandins is their ability to induce pain, fever, and symptoms associated with the inflammatory response [12]. In the past it was thought that cyclooxygenase (COX) was a single enzyme that was present constitutively in most cells [12] and therefore it was believed that inhibition of COX would lead to beneficial and detrimental effects. However, recently a second form of COX (COX-2) was discovered that is expressed during inflammatory conditions along with a constitutive form (COX-1) that produces physiologically important prostaglandins and is present in tissues such as the gastrointestinal tract the kidneys. The discovery of the COX-2 enzyme led to the development of selective COX-2 inhibitors in the hope that treatments for inflammatory conditions with reduced side effects could be developed.

Celecoxib was the first selective COX-2 inhibitor.

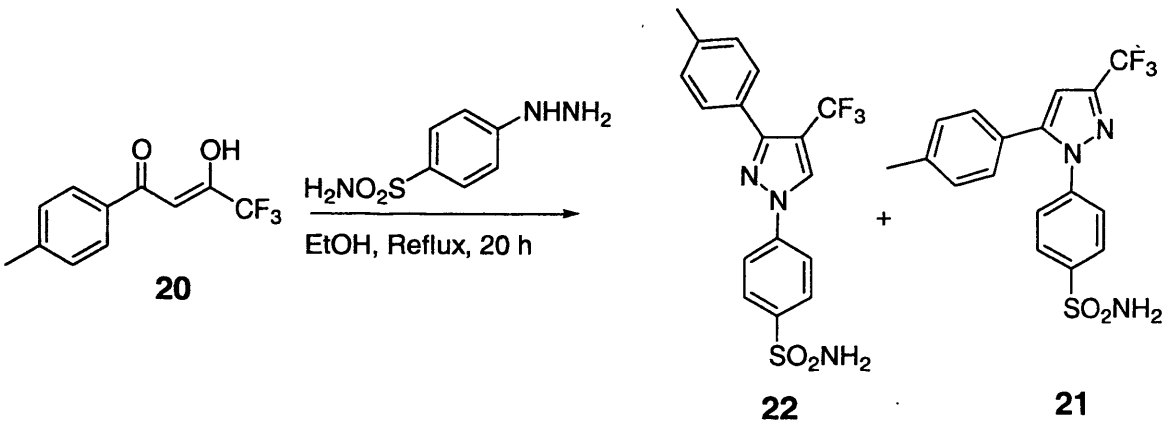
The Synthesis of Celecoxib (21)



Scheme 3

In the route of Penning [12] Claisen condensation between acetophenone and ethyl trifluoroacetate leads to the expected 1,3-dicarbonyl adduct (**20**) in a 94 % yield after the work up. Subsequent reaction of **20** (without further purification) with the hydrazine then leads to the almost exclusive formation of the 1,5 biaryl product (**21**) (as opposed to a mixture of the 1,3 and 1,5 biaryl species). After purification by recrystalisation from ethyl acetate and isooctane **21** was obtained in a 46 % yield.

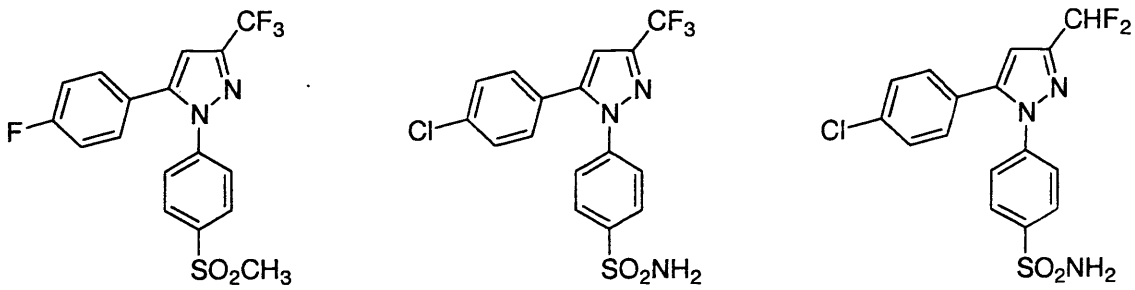
Penning also found that when Claisen adduct **20** was reacted with (4-sulfamoylphenyl)hydrazine (not the HCl salt) a mixture of 1,5- (**21**) and 1,3- (**22**) substituted pyrazoles were formed which were separable by chromatography (**Scheme 4**).



Scheme 4

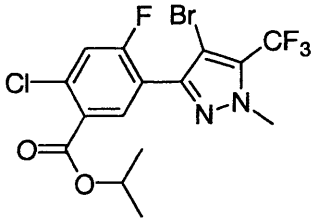
The 1,3-substituted product was found to be ineffective in inhibition of either COX-1 or COX-2.

During the development of Celecoxib the lead compund SC 58125 (**23**) showed good COX-2 inhibition but exhibited an unacceptably long plasma half life of 220 hours. Replacement of the fluorine by a metabolically labile methyl (and by changing the 4-(methylsulfonyl)phenyl moiety for 4-sulfamoylphenyl (**21**) reduces the plasma half life to 3.5 hours (the data for the 4-(methylsulfonyl)phenyl compound was not supplied by Penning). Similarly, by changing the CF_3 group of (**24**) to CHF_2 (**25**) the plasma half life of (**24**) was reduced from 117 hours to 4.5 hours (**25**) (note the data for **24** was generated by a 20 mg/Kg oral dose and the data for **25** was generated from a 10 mg/Kg intravenous dose (both administered to male rats)).



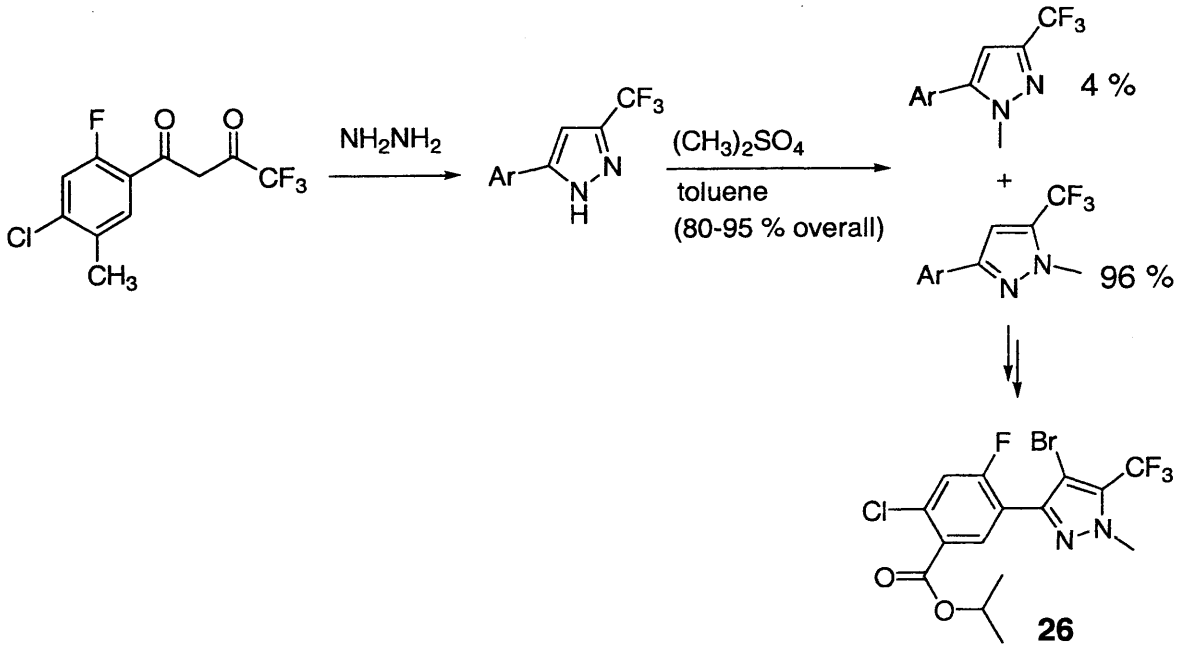
JV 485 (26)

3-Aryl-4-halo-5-(trifluoromethyl)-pyrazoles are highly active herbicides. JV 485 (**26**) (a potent herbicide) jointly developed by Monsanto Company and Bayer AG belongs to this class of compounds.



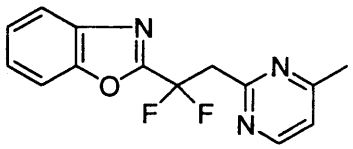
26

The synthesis of the pyrazole ring in **26** was approached using the same type of methodology used to construct the pyrazole ring in Celecoxib i.e. through the cyclocondensation of a hydrazine with a substituted 1,3-dicarbonyl compound (**Scheme 5**).



Scheme 5

Another example of a perfluoroalkylated heterocycle that compounds exhibits a useful biological activity is (**27**) which shows high levels of activity against HIV-1 [13]. Other results in the Burkholder study revealed that the presence of the difluoromethyl group was essential for high activity. When the CF_2 group of **28** was replaced with CH_2 (**29**) a ten fold decrease in activity against HIV-1 was observed.



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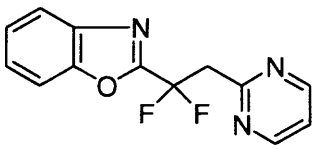

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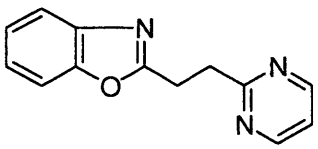

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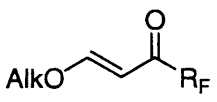
1.3 Pyrazole Formation from Perfluoroalkyl Enol Ethers

The synthetic access to pyrazoles is relatively well-explored using so-called [3+2] atom fragments [14, 15]. Usually β-diketones or derivatives thereof are used as 3-atom building blocks, and hydrazine is the two atom fragment [14]. This approach using masked 1,3-diketones such as enone **30** as the 3 atom fragment is well reported in the literature [14, 16].

Perfluoroalkyl enol ethers of type **30** were first synthesised by Hojo [17].



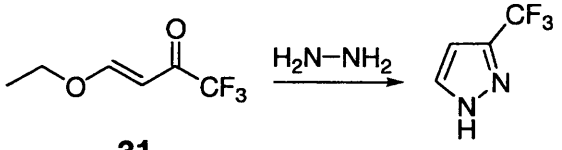
R_F = CF_3, C_2F_5, etc.
Alk =Alkyl

30

1.3.1 Literature 3+2 Atom Fragment Pyrazole Syntheses from Hojo Enones

1.3.1.1 Reactions with Hydrazine

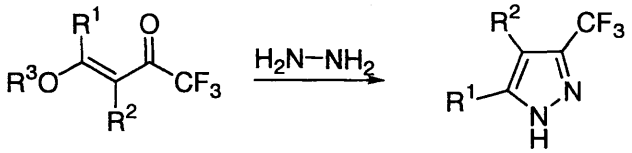
The reaction of 1,1,1-trifluoro-but-3-en-2-one (**31**) with hydrazine to afford 3-trifluoromethyl-*1H*-pyrazole (**32**) was first reported by Martins [14] and then by Gerus [16] (**Scheme 6**).



31 **34**

Scheme 6

Martins [14] also reported the cyclocondensations of enones **32** and **33** with hydrazine to afford pyrazoles **35** and **36** (**Scheme 7**).

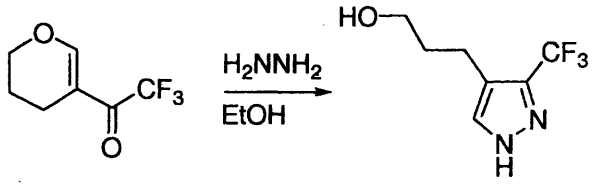


	R^1	R^2	R^3
32	Me	H	Me
33	H	Me	Et

	R^1	R^2
35	H	Me
36	Me	H

Scheme 7

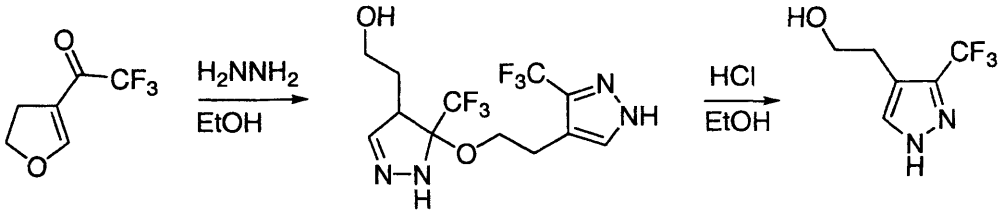
Threadgill [18] has utilised the same methodology to synthesise perfluoroalkyl pyrazole **38** from trifluoroacetylpyran **37** and hydrazine in near quantitative (99 %) yield (**Scheme 8**).



37 **38**

Scheme 8

Pyrazole **41** with one carbon less in the side chain was also synthesised starting from trifluoroacetylfuran **39**, however, the dimer **40** was initially formed (and isolated in 99 % yield). Threadgill found that the dimer could be readily and cleanly cracked by refluxing in mildly acidic ethanol to afford the monomer in 99 % yield (**Scheme 9**).

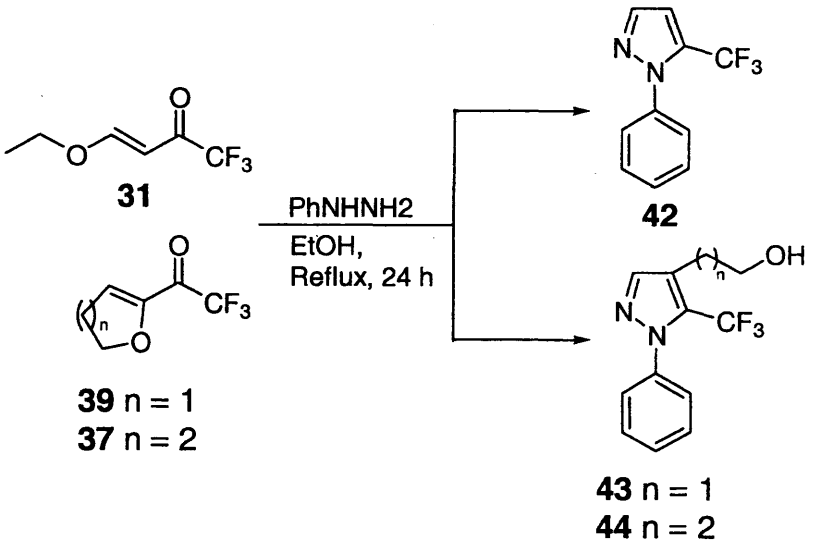


39 **40** **41**

Scheme 9

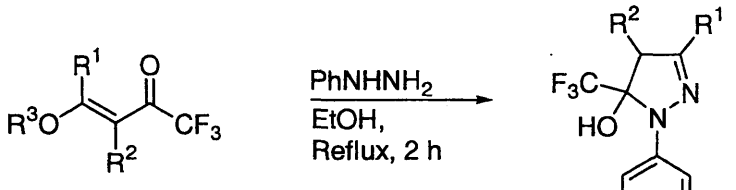
1.3.1.2 Reactions with Substituted Hydrazines

Song [19] has shown that enone **31** reacts with phenyl hydrazine (1:1 stoichiometry) in refluxing ethanol to afford pyrazole **42** in a 79 % yield. It was also found that when cyclic trifluoroacetyl enones **39** and **37** were reacted with phenyl hydrazine under the same conditions that pyrazoles **43** and **44** were formed respectively (**Scheme 10**).



Scheme 10

Under similar conditions (1.3 equivalents of phenylhydrazine and a two hour reaction time) Martins [14] found that trifluoroacetyl enones **31**, **32** and **33** yielded pyrazole hydrates **45**, **46** and **47** in yields of 73, 82 and 70 % respectively (**Scheme 11**).



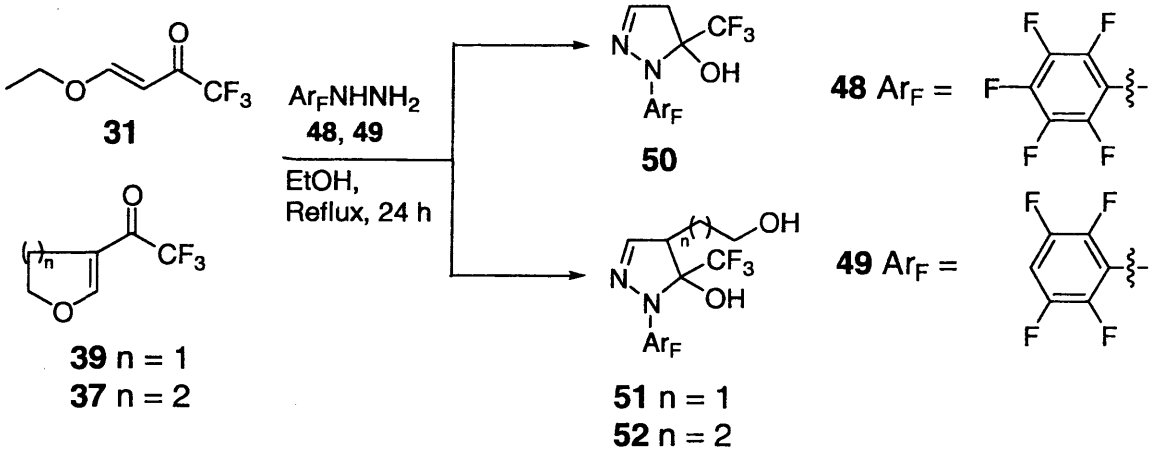
	R^1	R^2	R^3
31	H	H	Et
32	H	Me	Me
33	Me	H	Et

	R^1	R^2
45	H	H
46	H	Me
47	Me	H

Scheme 11

The authors attribute the stability of **45**, **46** and **47** to cross conjugation between phenyl and imine groups making the aromatisation of the systems difficult. It would seem that the longer reaction times of the Song methodology [19] are sufficient to force the aromatisation of these systems.

In the same paper Song also examines reactions of this type using fluorinated phenyl hydrazine derivatives **48** and **49** (**Scheme 12**).



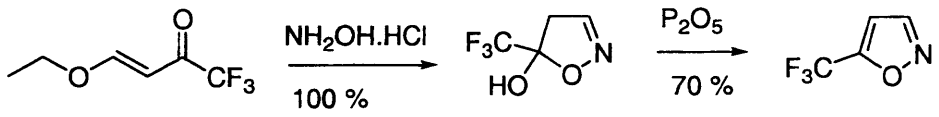
Scheme 12

In these reactions Song observed the formation of pyrazole hydrates **50**, **51**, and **52** instead of the expected pyrazoles. These observations are also explicable by invoking stabilisation of the hydrate forms due to cross conjugation between the very electron deficient aryl moieties and the imine groups. That Song did not observe the hydrates when the same reactions were performed with phenyl hydrazine bears testament to the powerful electron withdrawing properties of the fluorine atom (the p-orbital of the arylated nitrogen conjugates more strongy with the π-system making aromatisation less favourable). Dehydration of these molecules was subsequently achieved by treatment with P_2O_5 or PCl_3.

Not only does the literature contain examples of the generation of pyrazoles from perfluoroacetyl enol ethers it also contains examples of syntheses in which they are converted to other heterocyclic species.

1.4 Other Perfluoroalkyl Heterocycles Synthesised from Hojo Enones

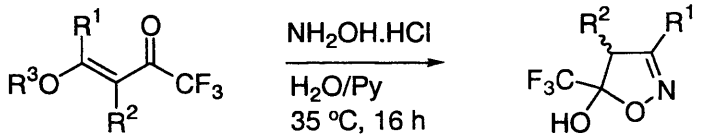
Gerus [16] has reported that the reaction of **31** with hydroxylamine hydrochloride leads to the formation of 3-trifluoromethylisoxazole hydrate (**53**) which dehydrates on treatment with phosphorus pentoxide to afford trifluoromethyl isoxazole **54** in good yield (**Scheme 13**).



31 **53** **54**

Scheme 13

Martins [20] has also reported this reaction as well as similar ones with perfluoroacyl enol ethers **32** and **33**. Martins, however, did not undertake the dehydration of the products and isoxazole hydrates **53**, **55** and **56** were isolated (**Scheme 14**).

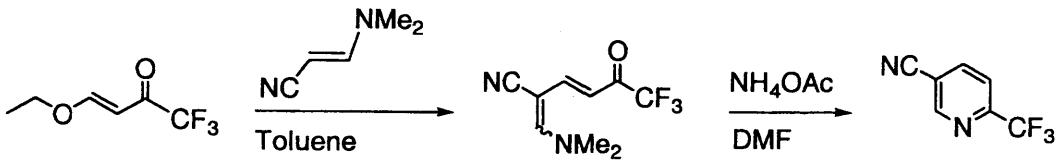


	R^1	R^2	R^3
31	H	H	Et
32	H	Me	Me
33	Me	H	Et

	R^1	R^2
53	H	H
55	H	Me
56	Me	H

Scheme 14

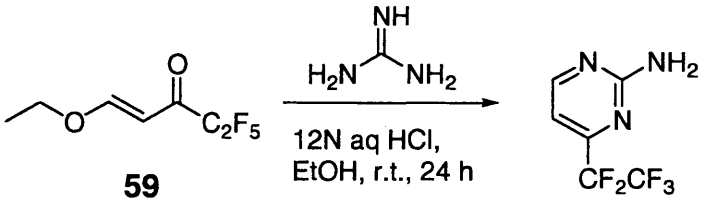
Recently Cooke [21] reacted **31** with 3-aminocrotononitrile to yield Michael adduct **57** in 73 % yield which cyclised in the presence of ammonium acetate in DMF to afford nicotinonitrile **58** in 82 % yield (**Scheme 15**).



31 **57** **58**

Scheme 15

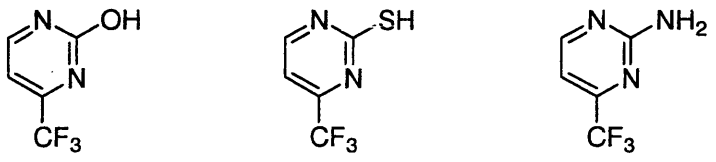
The aminopyrimidine **60** generated by the reaction of **59** with guanidine has been synthesised by Gerus [22] (**Scheme 16**).



59 **60**

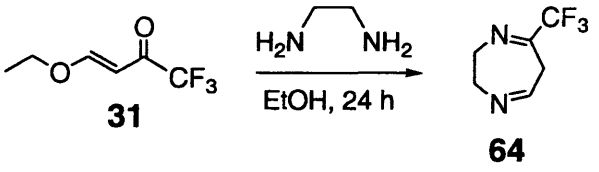
Scheme 16

Gerus [16] has reported the synthesis of the trifluoromethyl analogue of **60** (**63**) in an 80 % yield. Similarly derivatives **61** and **62** were also synthesised through reaction of **31** with thiourea and guanidine respectively, both were isolated in 70 % yields.



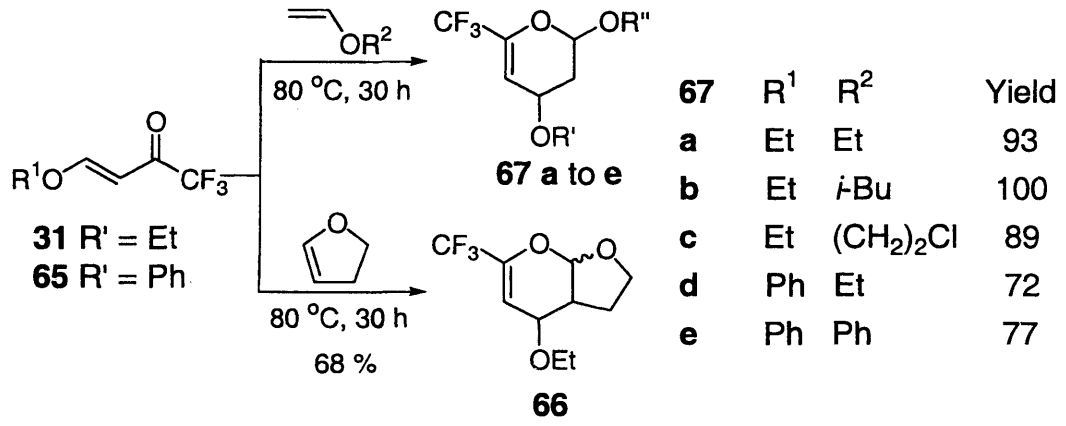
61 **62** **63**

Reaction of **31** with ethane-1,2-diamine leads to the formation of the trifluoromethylated diazepine derivative **64** in 92 % yield (**Scheme 17**) [23].



Scheme 17

Perfluoroacetyl enol ethers have been used successfully as a heterodienes in hetero-Diels-Alder reactions. For example Hojo[24] has synthesised trifluoromethyldihydropyrans **66** and **67 a** to **e** in solvent free sealed tube reactions from **31** and **65** respectively (**Scheme 18**)

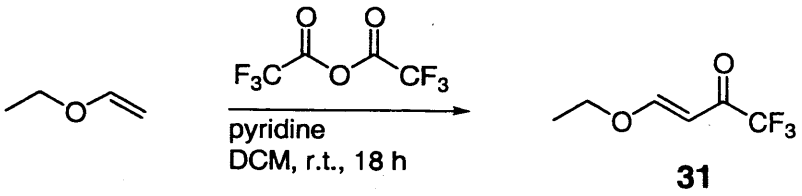


67	R^1	R^2	Yield
a	Et	Et	93
b	Et	*i*-Bu	100
c	Et	$(CH_2)_2Cl$	89
d	Ph	Et	72
e	Ph	Ph	77

Scheme 18

1.5 Generation of Perfluoroalkyl Enol Ethers *via* Hojo Methodology

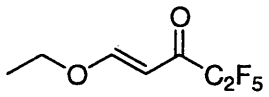
Hojo [17] demonstrated that ethyl vinyl ether underwent smooth trifluoroacetylation on reaction with trifluoroacetic anhydride in the presence of pyridine to afford vinylogous ester **31** in high yield (**Scheme 19**)



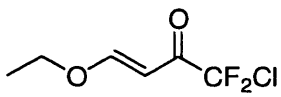
31

Scheme 19

This methodology is attractive as it allows for the facile variation of the perfluoroalkyl group of **31** by variation of the perfluoroalkyl anhydride in the reaction. For example Gerus [22] has reported the synthesis of **59** (Baraznenok [25] also reported the synthesis of **59** but presented no data for it) and **68** [26].

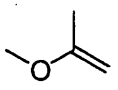


59

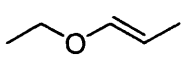


68

Although there are several reports of the perfluoroacetylation of enol ethers in the literature using this type of methodology they are commonly restricted to enol ethers in which the α and β carbons either bear no substituents as above or simple ones such **69** or **70**. Reactions in which more interesting substituents are present are rare.



69



70

Literature references for the perfluoroacetylations of **69** and **70** are provided in the results and discussion.

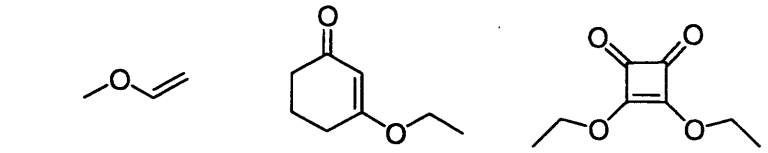
1.5.1 Limitations of Hojo's Methodology

The main problem associated with the synthesis of pyrazoles (or other heterocycles) from Hojo type vinylogous esters is the limited range of substituted vinyl ethers that are available commercially. This range controls the vinylic substitution in the perfluoroacyl enol ether and hence the substiuents in heterocycles synthesised from them.

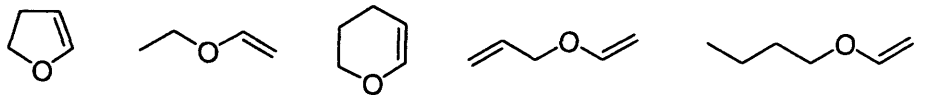
1.5.2 Survey of Commercially Available Vinyl Ethers.

Using the Lancaster synthesis online substructure search for the fragment **71** returned forty three hits (excluding one carbohydrate) of which 20 hits were either vinyl esters or vinyl lactones which do not perfluoroacylate under Hojo type conditions.

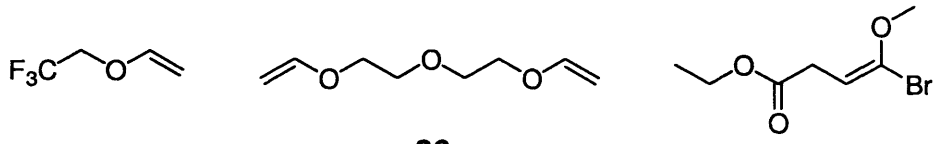
Twenty three other hits were returned which contained vinyl ether fragments. Seven of these vinyl ethers contained either carbonyl or ester functions on the β-carbon which are not applicable to perfluoroacetylation *via* Hojo methodology as they do not contain β–hydrogens. The above analysis does not take account for the presence of further functional groups within the molecules which might cause problems with the perfluoroacetylations such as hydroxyl groups which would react undergo perfluoroacylation themselves. Of the other eight hits (**74** to **81**) several have been shown to undergo perfluoroacylation (examples have been given previously in this section) and the others could be expected to undergo perfluoroacylation.



71 72 73



74 75 76 77 78

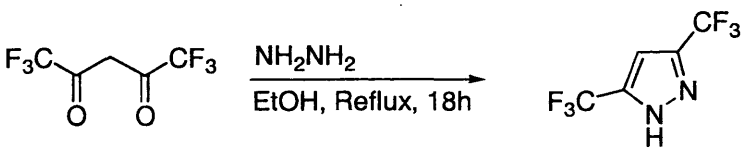


79 80 81

Although other commercial vinyl ethers are available from other companies for example 1-ethoxy-propene (**69**), 2-methoxy-propene (**70**) and β–methoxystyrene (**199**), this exercise has shown that the number of commercially available vinyl ethers that are suitable for Hojo type perfluoroacylation are very limited.

1.6 Synthetic Access to 3-Perfluoroalkyl Pyrazoles Not Involving Hojo Enones

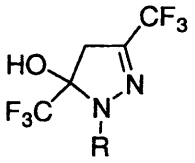
Classically pyrazoles are synthesised from 1,3-dicarbonyl compounds and hydrazines. These type of syntheses have been well represented in the literature. For example Threadgill [27] synthesised bis-trifluoromethyl pyrazole **82** from dione **83** and hydrazine (**scheme 20**).



83 **82**

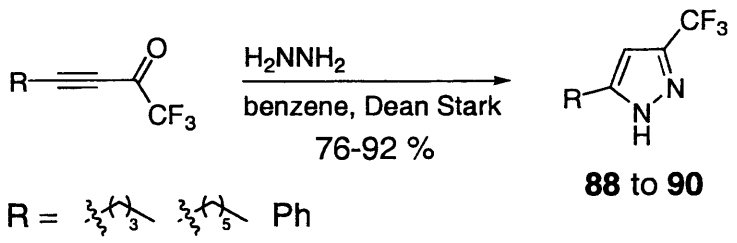
Scheme 20

Pyrazole **82** was synthesised as part of a small library in which variation was introduced through substituted hydrazines. However, in each case where a substituted hydrazine was used aromatisation did not occur and the hydrated pyrazoles **84** to **87** were isolated.



84 R = PhCO, **86** R = 4-$(NO_2)C_6H_4$
85 R = C_6H_5, **87** R = 2,4-$(NO_2)_2C_6H_3$

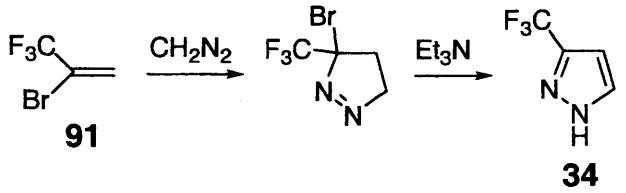
This type of methodology is synthetically equivalent to the previously discussed routes involving Hojo type enol ethers which are masked 1,3-dicarbonyl compounds. Pyrazole itself can be formed by the reaction of hydrazine with propargyl aldehyde and this synthetic approach has been exploited in the literature to give access to 3-trifluoromethyl pyrazoles in good to excellent yields. Linderman [28] reacted a variety of trifluoromethyl propargyl ketones with hydrazine in benzene under Dean Stark conditions to afford pyrazoles **88** to **90** (**Scheme 21**).



Scheme 21

A third way to access 3-trifluoromethyl pyrazoles is *via* 1,3-dipolar cycloadditions with diazo species and perfluoroalkyl alkenes or alkynes.

Xu [29] devised fast and efficient methodology to access **34** in quantitative yield starting from 2-bromotrifluoropropene (**91**) and diazomethane (**Scheme 22**).

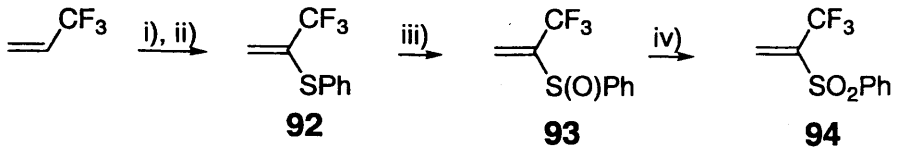


Scheme 22

Although the starting material is simple to prepare by dehydrobromination of the bromo adduct of trifluoropropene and the methodology is fast (0.5 hour reaction time) and efficient, the reaction has not been developed further to include variation of the perfluoroalkyl group or the introduction terminal vinylic substituents. The use of explosive diazomethane also limits the attraction of this reaction.

A very similar approach for accessing trifluoromethyl pyrazoles has also been investigated by Plancquaert [30]. Like Xu Plancquaert made use of α substituted 3,3,3-trifluoropropenes as the dipolarophile in 2+3 dipolar cycloadditions. However, unlike Xu Plancquaert used ethyl diazoacetate as the 1,3-dipolar species.

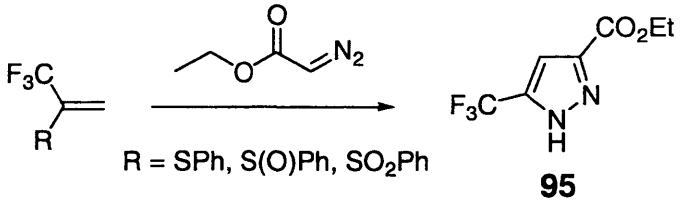
Starting from 3,3,3-trifluoropropene Plancquaert generated adducts **92** to **94** using the conditions below (**Scheme 23**).



i) PhSCl, DCM, 70 °C, 86 %; ii) KOH, MeOH, -40 to -10 °C, 30 min, 96 %; iii) *m*-CPBA, DCM, -40 to 20 °C, 3 h, 78 %; iv) as iii) 88 %

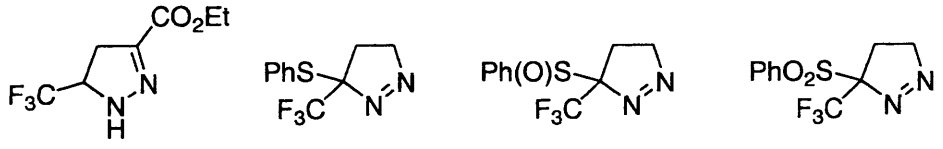
Scheme 23

Each of these adducts on reaction with ethyl diazoacetate under various conditions afforded pyrazole **95** (**Scheme 24**).



Scheme 24

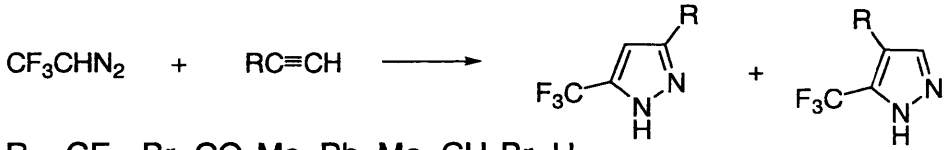
The reaction was also found to work well with 2-bromo-3,3,3-trifluoropropene (**91**). Plancuaret also reacted trifluoropropene with ethyl diazoacetate to afford dihydro pyrazole **96** which proved to be a stable molecule in its own right.



Plancuaret also reacted sulfur species **92** to **94** with diazomethane which lead to the isolation of adducts **97** to **99**. Of these **97** is very stable to thermolysis, **98** underwent

elimination of phenylsulfenate to afford 3-trifluoromethyl pyrazole (**34**) on heating at 80 °C and **99** decomposed when thermolysis was attempted.

Tomlinson [31] has also made use of 1,3-dipolar cycloadditions to access trifluoromethyl pyrazoles. However, unlike the approaches detailed above, the trifluoromethyl group was included in the dipolar species (trifluorodiazoethane) not the dipolarophile (**scheme 25**).

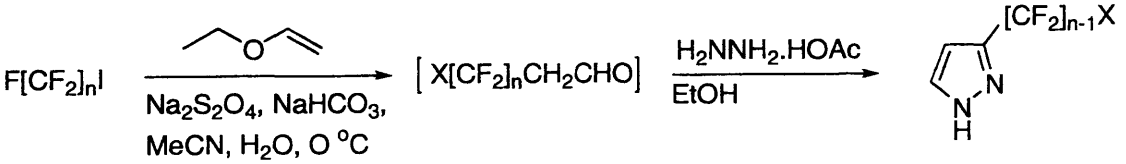


R = CF_3, Br, CO_2Me, Ph, Me, CH_2Br, H

Scheme 25

Although high yielding (quantitative (or near)) this methodology suffers from the fact that mixtures of products are formed, reactions are slow (from 12 hours to 8 weeks), the diazo species must be made and is explosive, and the range of commercially available alkynes is limited.

A third method developed for the synthesis of perfluoroalkyl pyrazoles from perfluoroalkyl aldehydes derived from ethyl vinyl ether and perfluoroalkyl iodides and hydrazinium acetate has been described by Hu [11] as a one pot procedure (**Scheme 26**).



n = 2, 4, 6, 8

Scheme 26

This methodology proved to be useful and reliable for the synthesis a variety of perfluoroalkyl pyrazoles in generally excellent yield. However the method has not been proved to be capable of withstanding the use of α or β substituted vinyl ethers and at present is only known to be capable delivering perfluoroalkyl pyrazoles without C-4 and C-5 substitution.

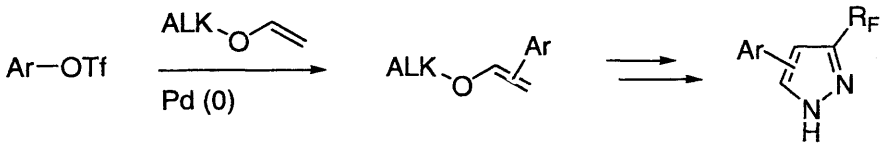
Despite the main problems associated with the use of Hojo type enol ethers as pyrazole precursors (the lack of commercially available substituted vinyl ethers), they remain interesting as three fold diversity can be built into them through variation of the perfluoroalkyl chain and their α and β substituents. This variation is then carried into subsequent pyrazole products.

The Hojo perfluoroacyl enol ethers also have the advantage that they can be used in the synthesis of other heterocycles.

In order to make full use of the perfluoroacyl enol ether to pyrazole transformation two methods for the generation of substituted vinyl ethers have been proposed.

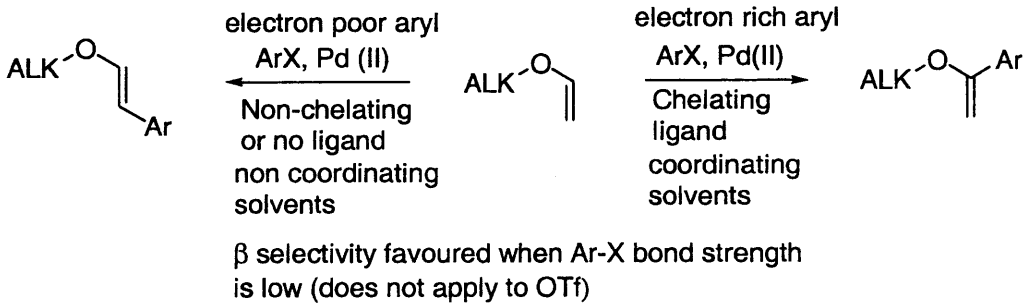
1.7 The Heck Reaction Route to Substituted Vinyl Ethers

One way to circumvent the problem of the lack of commercially available vinyl ethers would be to make use of the Heck reaction to construct substituted aryl vinyl ethers (and then proceed to process them to pyrazoles) (**Scheme 27**).



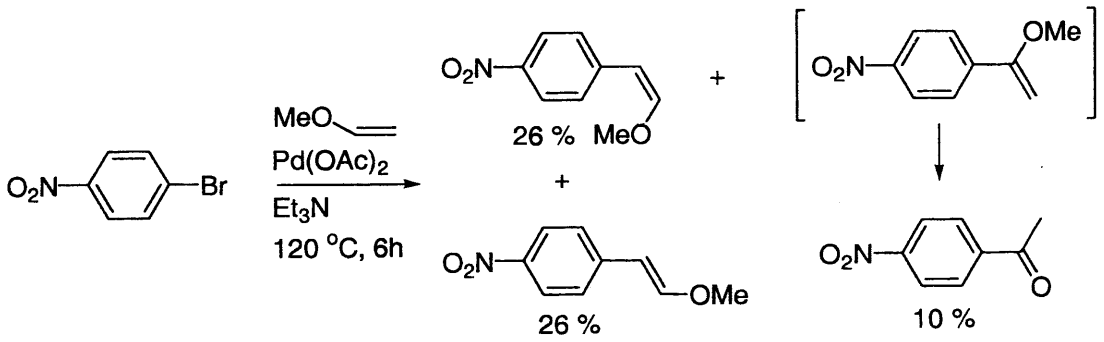
Scheme 27

This approach is very attractive and powerful as the literature reveals that both α and β substitutions can be made with the Heck reaction on vinylic ether systems. Studies show that the regiochemical outcome of palladium-mediated reactions of enol ethers is determined primarily by electronic factors in contrast to corresponding reactions with simple olefins where steric factors dominate, factors which direct α and β selectivity are summarised in **scheme 28** [32].



Scheme 28

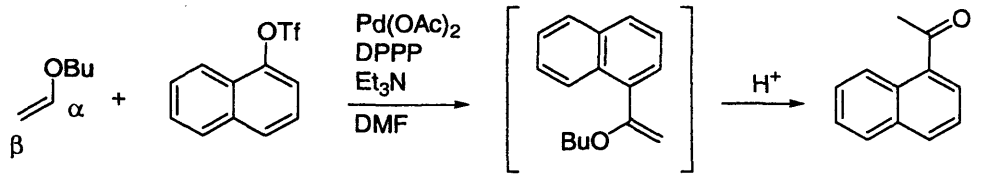
However, without careful control of the reaction conditions mixtures of products are produced (**Scheme 29** [33])



Scheme 29

However selective reactions have been developed. Cabri [34], has developed a robust and reliable method for the selective α arylation of butyl vinyl ether (**Scheme 30**).

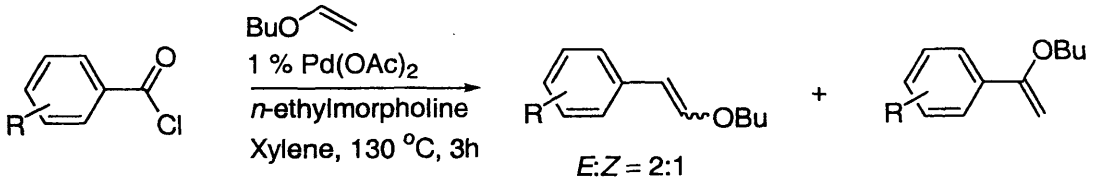
This reaction is discussed fully in the results and discussion section along with other methods for the selective α arylation of enol ethers.



Scheme 30

Hallberg has developed two separate methodologies for the β arylation of enol ethers.

The first of these methods [35] uses benzoyl chlorides as the acylating agents; however mixtures of α and β acylated products were produced (**Scheme 31**). **Table 1** outlines the preparative experiments carried out by Hallberg.



R = H, 4-NO_2, 4-Br, 4-Cl, 4-OAc,3-Cl, 3-NO_2, 2-OAc, 2-NO_2

Scheme 31

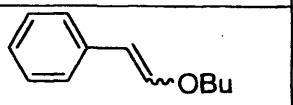
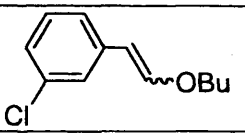
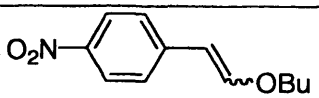
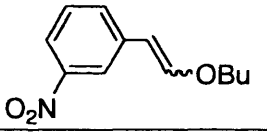
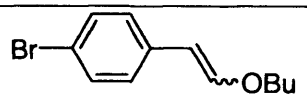
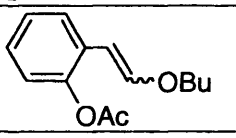
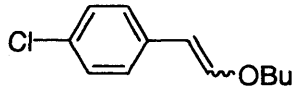
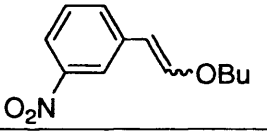
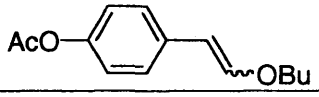
α–Product	Yield (%)	β to α ratio	Product	Yield (%)	β to α ratio
	53	3:1		43	3.7:1
	60	10:1		44	4.1:1
	55	2.5:1		trace	
	60	3:1		trace	
	40	2.7:1			

Table 1

Hallberg was able to separate the β–arylated product from the α product by first decomposing the α isomer to the corresponding methyl ketone by treatment of the reaction mixture with dilute acid followed by column chromatography.

Interestingly when similar reactions are carried out at 60 °C regiospecific β aroylation takes place [32]. This latter process is tolerant of significant diversity in the aroylating moiety and provides a direct route to monoprotected 1-aryl-1,3-dicarbonyl systems (**Table 2**).

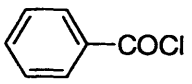
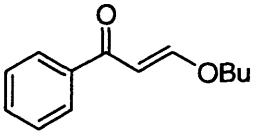
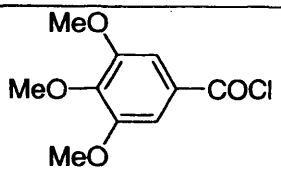
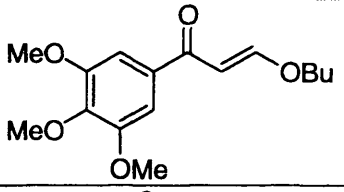
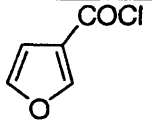
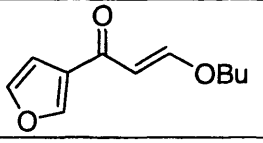
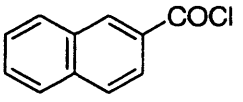
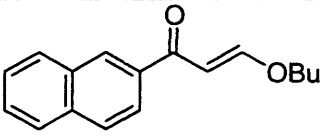
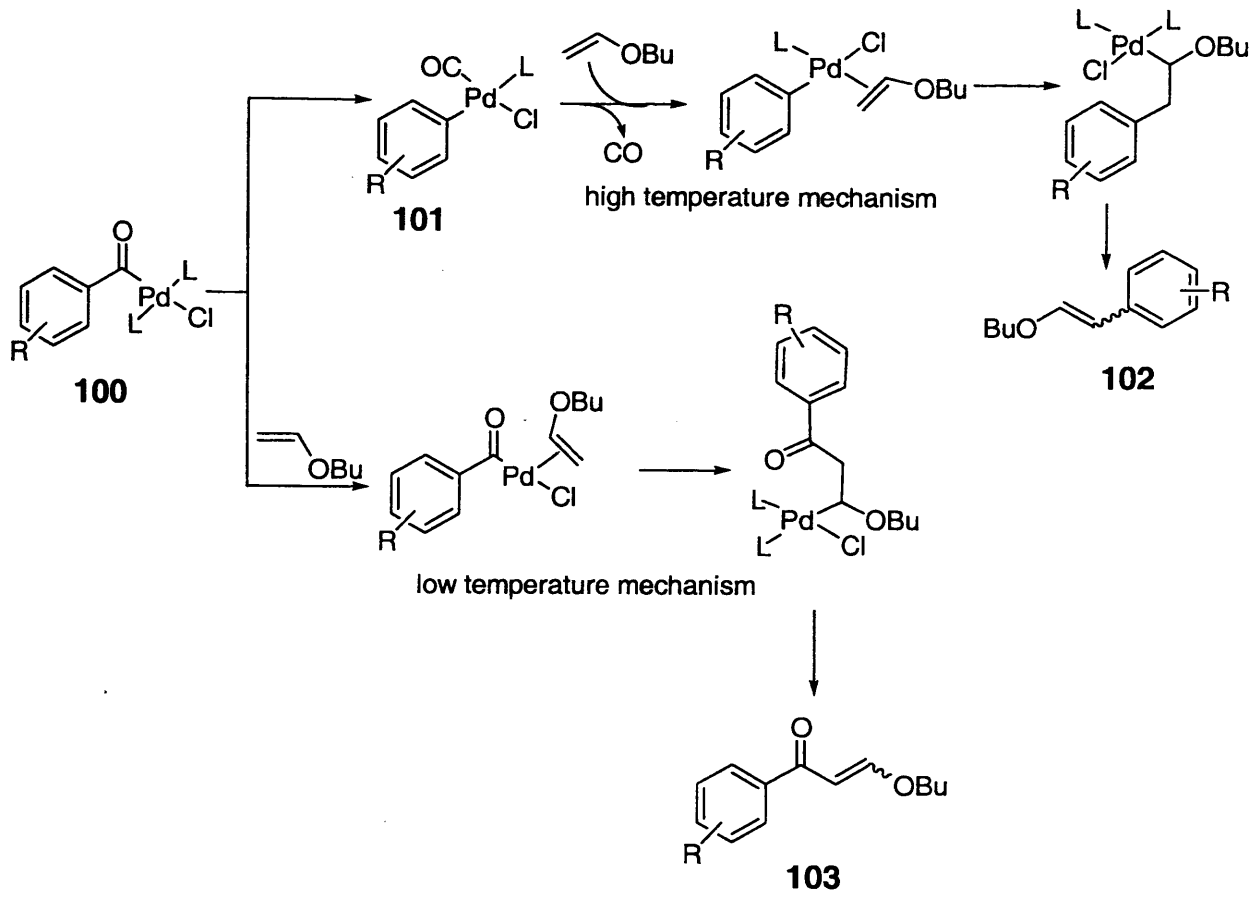
aoryl chloride	Product	yield (%)
		69
		57
		40
		55

Table 2

When the reaction is run at high temperature decarbonylation of aroyl moiety **100** after oxidative addition, leads to aryl palladium species **101**. Alkene coordination displaces the carbon monoxide ligand after which carbopalladation and β-hydride elimation extrudes the new alkene product (**102**). In the case when the reaction is run at low temperature, decarbonylation is avoided and after carbopalladation β-hydride elimination delivers the β–aroyl species (**103**) (**Scheme 32**).

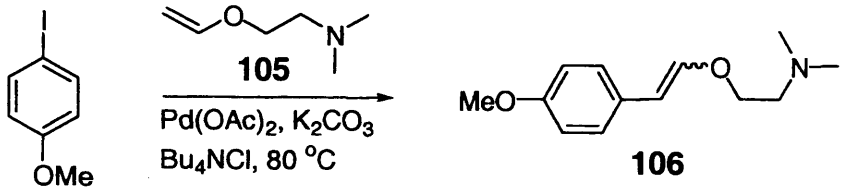


Scheme 32

Although Hallberg's results offered an improvement over the existing methodology for the selective β-arylation of enol ethers the regioselectivity was, especially in some cases, poor in terms of synthetic usefulness. The work was also hampered by low and variable yields 40 – 60 % which further limited the appeal of the methodology.

In response to these shortcomings Hallberg's research led him to investigate other ways in which selective β-arylation could be achieved.

In the literature Hallberg [37, 38] discovered a reaction (also reported by Badone and Guzzi [36] at a later date) in which [2-(dimethylamino)ethoxy]ethene (**105**) was arylated with 1-iodo-4-methoxy benzene (**104**) under phase transfer conditions to afford adduct **106** (**scheme 33**).



Scheme 33

Hallberg [37] showed that this reaction could be generalised and a range of β-arylated vinyloxyethylamines were prepared (**Table 3**). In all cases β to α ratios of 95:1 or better were observed and products were isolated as *E/Z* mixtures.

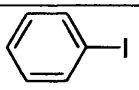
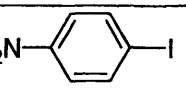
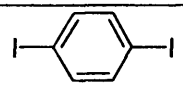
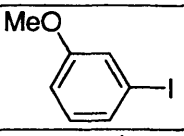
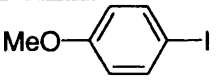
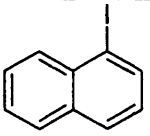
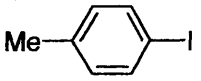
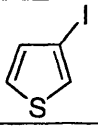
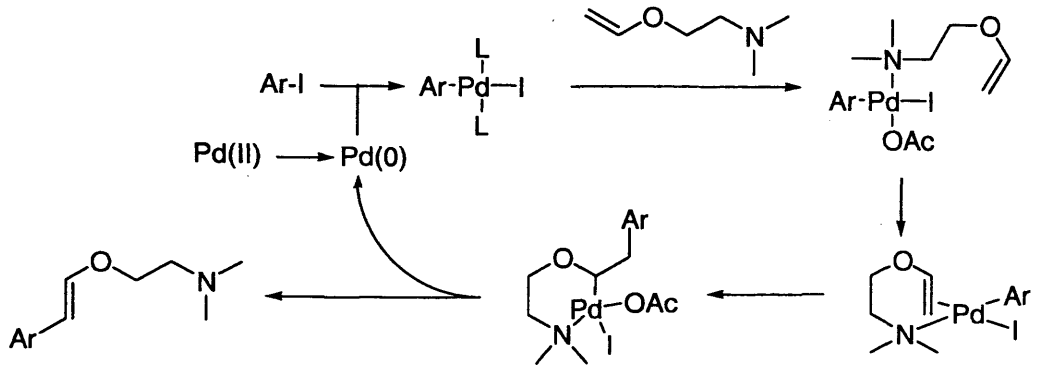
Aryl halide	Yield (%)	Aryl halide	Yield (%)
	80		45
	76		85
	83		76
	85		48

Table 3

The low yield for the reaction with 1-iodo-4-nitrobenzene was attributed to the formation of biaryl species, this phenomenon was also invoked to account for the low yield when the reaction was carried out with 3-iodothiophene.

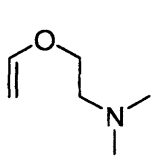
The following mechanism was proposed by Hallberg [38] to account for the selectivity displayed in these reactions (**Scheme 34**).



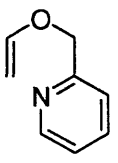
Scheme 34

After the initial reduction of Pd(II) followed by oxidative addition the arylpalladium iodide is trapped by the trialkylamine nitrogen and after a second ligand exchange a π-complex chelate is formed. Insertion of the olefin results in formation of a (presumably) relatively stable six membered σ-complex and after β-hydride elimination the substituted vinyl ether is extruded from the cycle. The collapse of the π-complex, governed by steric constraints, apparently favours the six-membered derivative over the more demanding seven membered alternative.

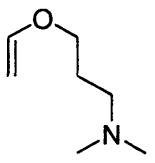
Hallberg [38] found that a two carbon tether between the oxygen and the nitrogen was essential for high β-selectivities as both enol ethers **107** and **108** were found to offer high selectivities whereas **109** to **110** offered either poor or no selectivities in arylations with iodobenzene and 1-iodonaphthalene under the conditions detailed above. In these experiments pyridine **108** was found to react slower than alkylamine **107** which was attributed to the formation of a more stable π-complex with the pyridinyl species.



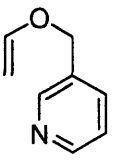
107



108



109



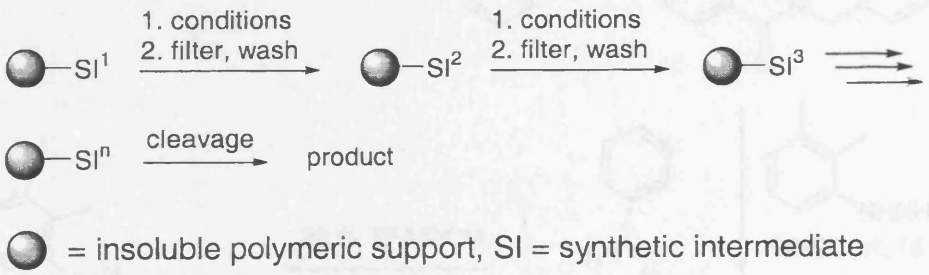
110

It was our intention to use the Cabri [34] methodology referred to above and expanded upon in the results and discussion for the synthesis of α-substituted vinyl ethers.

The second of our methods for the synthesis of substituted vinyl ethers relies on solid phase chemistry.

1.8 A Brief introduction to Solid Phase Syntheses

Solid-phase organic synthesis refers to syntheses in which the starting material and synthetic intermediates are linked to an insoluble material (support), which enables the facile mechanical separation of the intermediates from reactants and solvents [39]. Reactions are usually performed by shaking the solid supported intermediate suspended in a suitable solvent with the desired reagents for the desired amount of time. When required the solvent and excess reagents are removed from the supported intermediate, first by filtration then by repeated cycles of washing with suitable solvents and filtration. The final stage of the synthesis is the cleavage of the product from the support (**Scheme 35** outlines this approach)

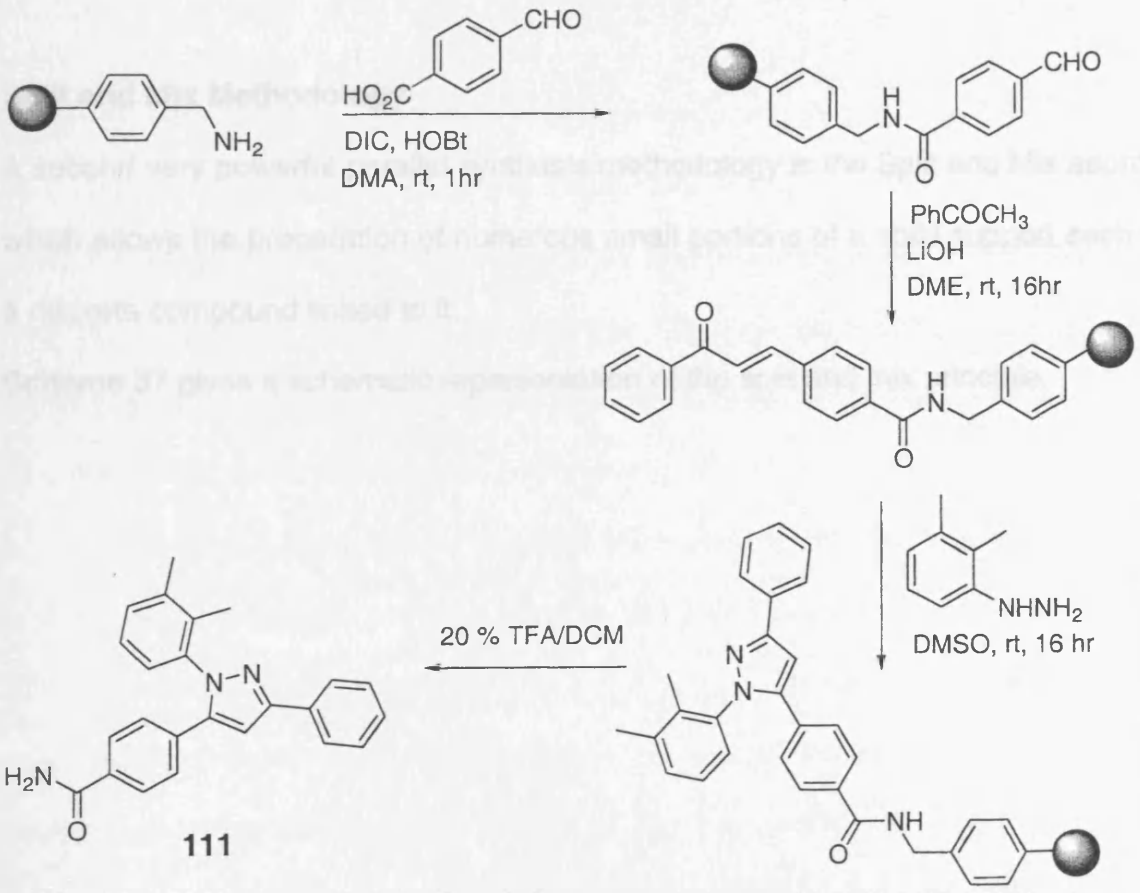


Scheme 35

1.8.1 Advantages of Solid Phase Chemistry

Purification Issues (Intermediates and final products)

One of the most alluring aspects of solid phase syntheses strategies is that intermediates are purified by simple resin washing procedures. Indeed, purification of the intermediates by any other method is not possible. However purifications may be needed at the end of the synthesis. This has the obvious advantage of having a considerable streamlining effect on a synthetic route when compared to a traditional solution phase route in which each intermediate has to be purified. For example the synthesis of pyrazole **111** was undertaken in four steps and involved only one purification (apart from the washing of resin bound intermediates) [40] (**Scheme 36**).



Scheme 36

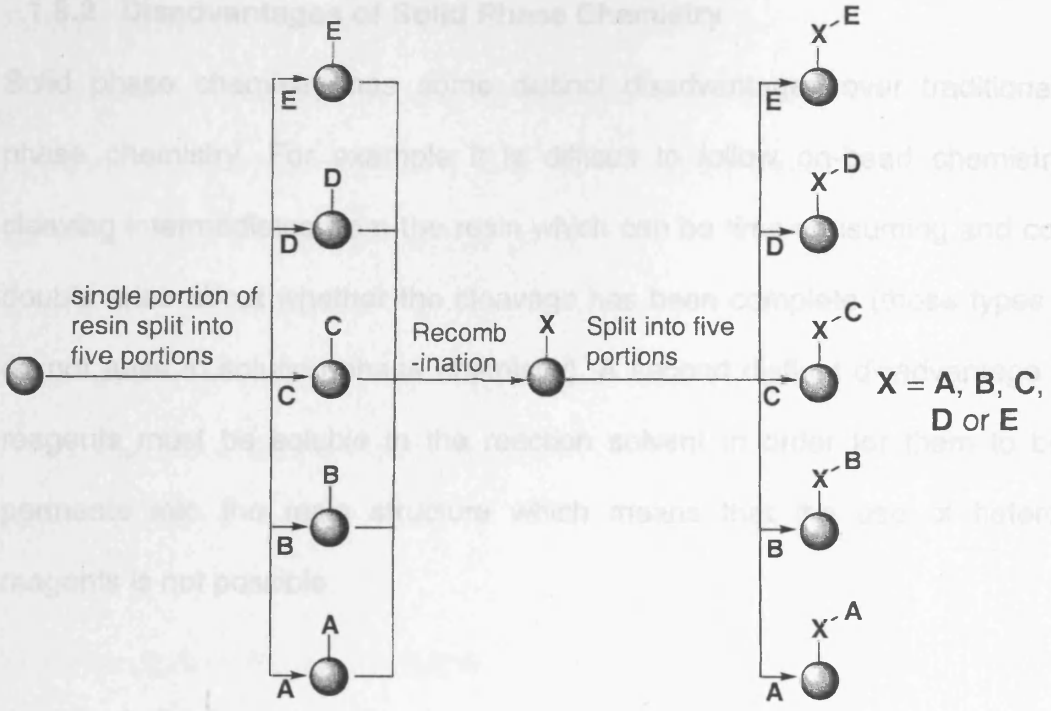
Solid Phase Parallel Syntheses

Solid phase chemistry is ideally suited to parallel synthesis. The simplest incarnation of this is simply running several reactions in separate reactors at the same time. Washing the resins separately, returning them to separate reactors and then performing the next stage of the synthesis. This type of approach relies on the fact that the purification of solid phase intermediates are facile but is limited by the researcher's ability to keep track of large numbers of similar reactions running together and the time spent in washing and setting up reactions. A development of this type of approach is to use an automated synthesiser which allows large numbers of discrete reactions to be run in parallel for the preparation of large libraries of compounds.

Split and Mix Methodology

A second very powerful parallel synthesis methodology is the Split and Mix approach which allows the preparation of numerous small portions of a solid support each with a discrete compound linked to it.

Scheme 37 gives a schematic representation of the split and mix principle.



Scheme 37

In the representation an amount of functionalised resin (e.g. Wang, Merrifield etc) is split into five portions and one of five monomers (**A** to **E**) is coupled to each portion. After the reactions are complete the washed and dried resins are recombined, mixed thoroughly and split again into five portions. Although each portion contains all five types of support particle, each particle is bound to only one of the reagents **A** to **E**. The five portions are now reacted each with a different monomer which generates 5 × 5 = 25 separate compounds. However each particle still only has one compound type bound to it. Iteration of the mixing, splitting and reaction of each portion with a different monomer would then lead to 5 × 5 × 5 = 125 compound and again each resin particle would only have a single compound bound to it. Split and mix syntheses are particularly well suited to the preparation of oligonucleotide and peptide libraries because even small amounts of these products enable screening and unambiguous structural elucidation [39].

1.8.2 Disadvantages of Solid Phase Chemistry

Solid phase chemistry has some distinct disadvantages over traditional solution phase chemistry. For example it is difficult to follow on-bead chemistry without cleaving intermediates from the resin which can be time consuming and confusing if doubts arise about whether the cleavage has been complete (these types of issues do not arise in solution phase chemistry). A second distinct disadvantage is that all reagents must be soluble in the reaction solvent in order for them to be able to permeate into the resin structure which means that the use of heterogeneous reagents is not possible.

1.8.3 Solid Supports

Physical Requirements

There are two main physical requirements that should be met by a solid support. Firstly they need to be mechanically stable under the reaction conditions that they will be exposed to. Break down of the support into smaller particles can lead to clogged filters and make handling the dry material problematic. Secondly the chosen polymeric support, if the intermediates are located within the support and not only on the surface, should be sufficiently porous and exhibit good swelling characteristics in the chosen solvent in order to allow diffusion of reagents into the polymer.

Merrifield realised early on that most (> 99%) of sites of attachment are inside the swollen beads. As the polymer swells, it now assumes the role that is traditionally associated with the solvent; that is, the swollen polymer *is* the solvent, with the important distinction of having a substantially greater viscosity[41].

Functionalised Polystyrene Resins

In the literature the vast majority of the solid phase syntheses are carried out with functionalised polystyrene resins, and, as we planned to use this type of support in our investigations focus here will be given to it.

Copolymers of styrene and divinylbenzene were initially developed for the production of ion exchange resins [39]. If the degree of cross linking in these polymers exceeds 0.2 % they become essentially insoluble but are able to swell to varying extents in organic solvents.

Bead formation, Functionalisation and Linkers

Formation

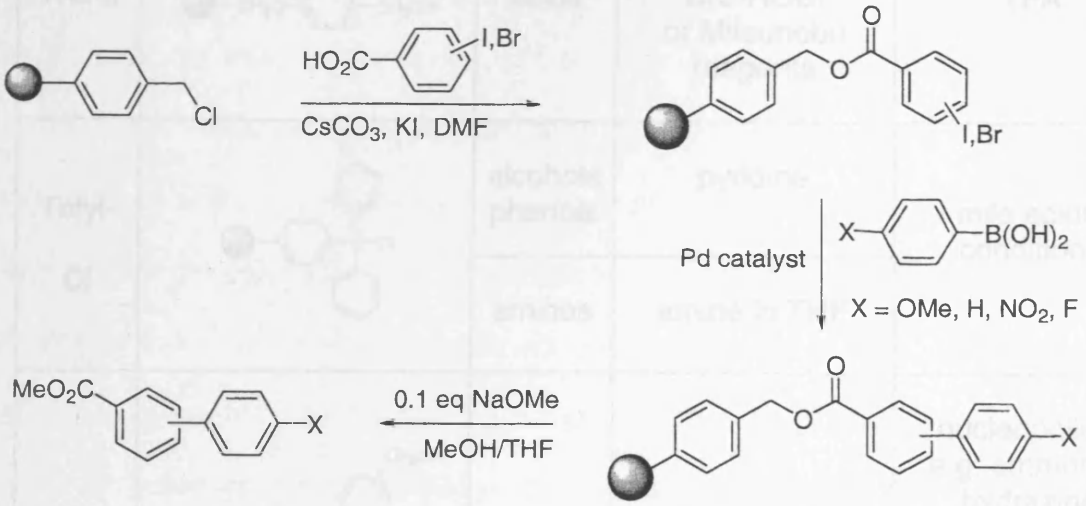
Cross linked polystyrene resins suitable for SPS are usually formed by radical polymerisation of styrene and divinylbenzene which is controlled in such a way as to produce beads that are usually between 0.04-0.15 mm in diameter.

Functionalised resins

Polystyrene does not enable the covalent, reversible attachment of synthetic intermediates, unless the support is derivatised with suitable functional groups [39]. Fuctionalised resins can be prepared either by functionalisation of the preformed beads or by copolymerisation of functionalised monomers.

Commercially there are a huge range of functionalised polystyrene resins available including those with halo, hydroxy, amino, thio, acetyl, acidic, etc substituents. Although these core resins (resins with functional groups e.g. hydroxymethyl, chloromethyl, etc bonded directly to the polymer) are commonly used in synthesis. For example Freisen [42] has carried out Suzuki couplings on bromo and iodo benzoic

acids bound to Merrifield (chloromethyl polystyrene) resin via ester linkages. (**scheme 38**).



Scheme 38

For a solid phase synthetic route to be successful easy loading of the first synthetic intermediate and easy cleavage of the product must be achievable. These parameters are often fulfilled by the use of linker molecules.

Linkers are molecules which are attached to functionalised core resins which allow easy attachment of specific synthetic intermediates as well as facile cleavage of products.

Although the number of resins with spacers that are available commercially is vast, certain linker types prevail. The following brief (and very limited and general) survey just represents some of the more useful or interesting ones (**Table 4**).

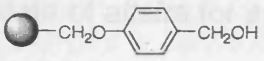
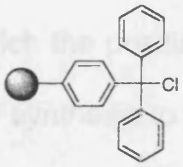
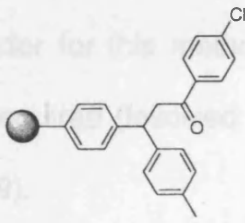
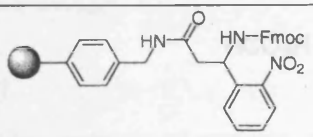
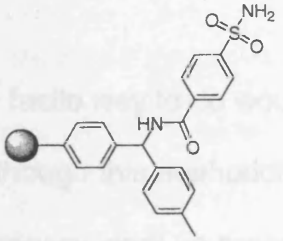
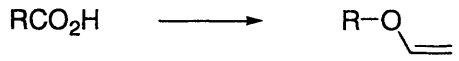
Linker Name	Structure	First residue	Attachment conditions	Cleavage
Wang		acids	DIC/HOBt or Mitsunobu reagents	TFA
Trityl-Cl		alcohols phenols	pyridine	mild acidic conditions
		amines	amine in THF	
HMBA		acids	DIC/HOBt or *via* acid chloride	nucleophiles. e.g. ammonia, hydrazine or sodium borohydride yield amides, hydrazines or alcohols
ANP		acids	1)piperidine/DCM 2) acid/DIC/HOBt	irradiate at 365 nm
Safety catch		acids	pentafluorophenyl ester of acid/ DMAP or acid/DIC/DIPEA /DMAP	1) diazomethane or bromoacetonitrile 2) hydroxide or amine to yield acid or amide

Table 4

1.9 Solid Phase Synthesis of Pyrazoles

A desirable state of affairs for any synthetic route is for it to be as simple and general as possible. In order to further extend the range of substituents available to us in the synthesis of 4-substituted-3-perfluoroalkyl pyrazoles it was decided to construct a synthesis in which the position 4 substituent was derived from a carboxylic acid. We also wished the synthesis to be amenable to the synthesis of libraries of compounds. At this juncture we were conversant with the conversion of Hojo perfluoroalkyl enol ethers to pyrazoles and we wished to use this reaction as the fianl step of the new route. In order for this methodology to be utilised conversion of the acid to a vinyl ether was required (followed by perfluoroacylation and then reaction with hydrazine) (**Scheme 39**).

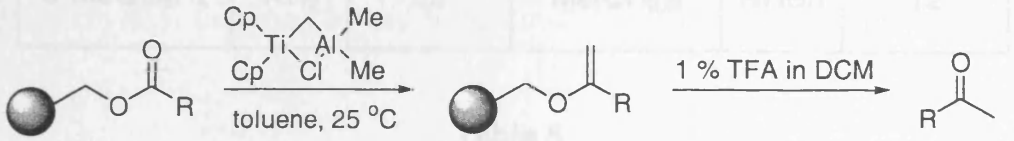


Scheme 39

A seemingly facile way to do would be to carry out a Tebbe olefination on the ester of the acid. Although this methodology is fine for the synthesis of single compounds the difficult and messy work up procedures due to aluminum and titanium residues make it unsuitable for library synthesis. However, as this approach was felt to be powerful in itelf a solution to this problem was sought. As solid phase work up procedures are facile, as previously discussed, the idea of a solid phase route involving the olefination of resin bound acids was considered. Perhaps surprisingly a precedent for successful solid phase Tebbe olefinations was found in the literature [43, 44]. As solid phase methodology is ideally suitable to parallel syntheses the use of this type of methodology would be helpful for library synthesis.

1.9.1 Tebbe Olefination Methodology

Barrett [43] developed methodology that allowed the Tebbe olefination of supported esters. Analysis of the reaction was undertaken by cleavage of the vinyl ethers to their methyl ketones under acidic conditions (**Scheme 40**).



R = $Me(CH_2)_6$, Ph, 4-BrC_6H_4, 4-$MeOC_6H_2CH_2$, 4-$PhC_6H_4$3-$MeOC_6H_4$, 2,4,6-$(MeO)_3C_6H_2$, 3-indoyl-CH_2CH_2 and 4-IC_6H_4

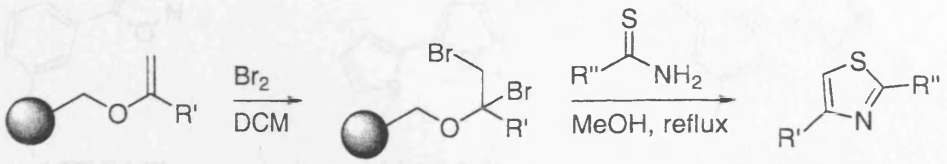
41-92 %

Scheme 40

The above results were generated from syntheses carried out on Wang resin. Barrett [43] also reports that the olefinations were successful when supported on Merrifield (chloromethyl polystyrene) resin.

Alternately cleavage of the vinyl ethers to their methyl ketones using 1 % H_2SO_4 in DMF and subsequent reductive aminations in the same pot afforded, after work up, a wide range of amines in yields from 13 to 89 %.

Barrett was able to convert the resin bound vinyl ethers to corresponding dibromo adducts *via* treatment with Br_2 in DCM. Subsequent treatment with of the bromides with thiourea and derivatives yielded a range of thiazoles in low yields but high purities. (**Scheme 41** and **Table 5**).

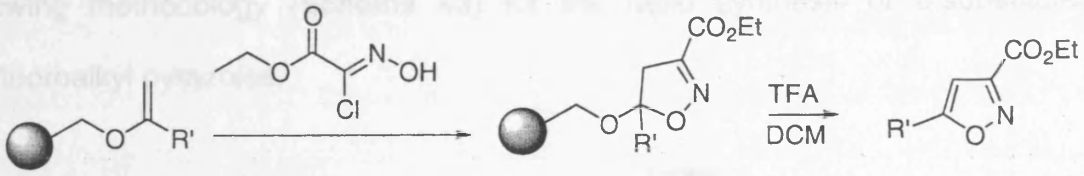


Scheme 41

R'	R''	Yield (%)	R'	R''	Yield (%)
Ph	NH_2	40	3-$MeOC_6H_4$	NHMe	15
Ph	NHMe	15	3-$MeOC_6H_4$	NHBn	13
Ph	NHBn	10	$Me(CH_2)_6$	NH_2	15
Ph	Me	14	$Me(CH_2)_6$	NHMe	10
3-$MeOC_6H_4$	NH_2	23	$Me(CH_2)_6$	NHBn	12

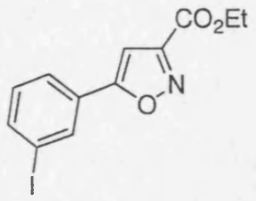
Table 5

In a second publication Barrett [44] made use of resin bound vinyl ethers as substrates for the synthesis of isoxazoles via 1,3-dipolar cycloadditions with chlorooximidoacetate (**Scheme 42**).

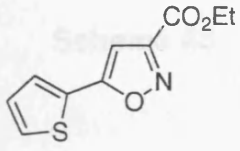


Scheme 42

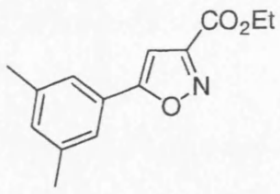
Barrett isolated a range of isoxazoles in yields from 36 to 72 %, some of which are shown below (**112** to **114**)



112 64 %

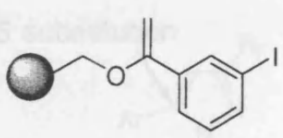


113 36 %

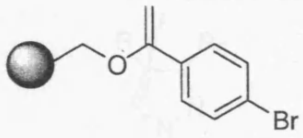


114 66 %

In order to increase the diversity of the isoxazoles vinyl ethers **115** and **116** were synthesised and were subjected to Suzuki couplings to produce a range of biaryl resin bound vinyl ethers. Cleavage of the coupling products under acidic conditions yielded the expected methyl ketones in yields between 60 and 79 %. Cyclisation of the resin bound biaryl vinyl ethers under the conditions previously discussed afforded isoxazoles in yields between 38 and 80 %.

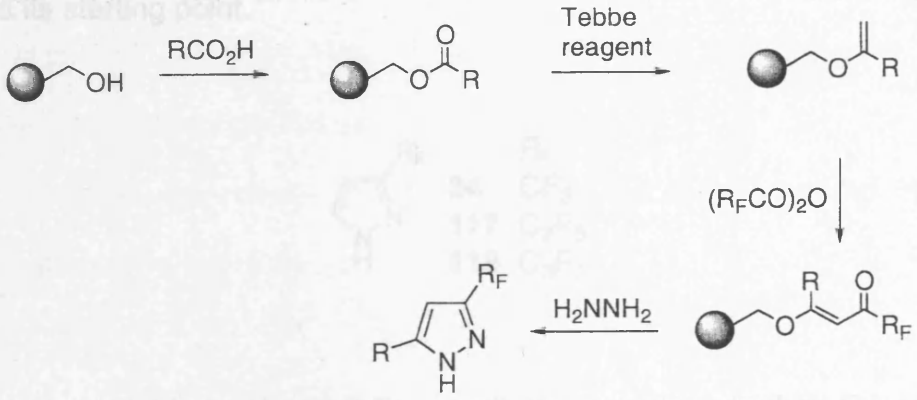


115



116

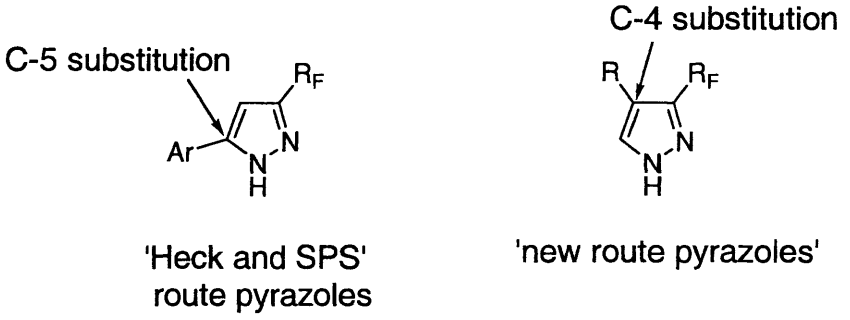
Utilising Barrett's resin bound Tebbe methodology we planned to develop the following methodology (**Scheme 43**) for the rapid synthesis of 5-substituted-3-perfluoroalkyl pyrazoles.



Scheme 43

1.10 Position-5 Substituted 3-Perfluoroalky Pyrazoles

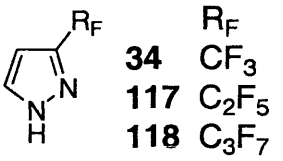
Having proposed methodologies (the 'Heck' and SPS routes previously described) which allowed the synthesis of a range of C-5 substituted 3-trifuoromethyl-*1H*-pyrazoles the development of methodologies that would afford derivatives with the alternate C-4 regiochemistry became an attractive synthetic proposition



'Heck and SPS' route pyrazoles

'new route pyrazoles'

As we were already competent in the synthesis of unsubstituted 3-perfluoroalkyl pyrazoles (**34**, **117** and **118**) we planned to develop a synthetic strategy using these species as its starting point.



	R_F
34	CF_3
117	C_2F_5
118	C_3F_7

As pyrazoles are liable to electrophilic substitution reactions in their C4 position we planned to utilise this reactivity in our synthetic plan.

Halogenation at this position would provide functionality that we hoped we would be able to exploit in transition metal catalysed cross coupling reactions.

1.10.1 The Stille and Suzuki Reactions

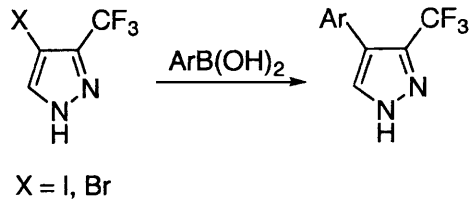
Of the palladium catalysed cross coupling reactions the most commonly used, robust and versatile versions are the Stille and Suzuki reactions.

The Stille reaction is the palladium catalysed coupling between unsaturated organic halides or triflates and aryl, vinyl, alkynyl, etc tin reagents and it provides a well know and reliable method to prepare a variety of cross coupled products.

Although the Stille reaction has received a lot of attention in the literature it has some synthetic disadvantages. The most obvious of these is its use of organostannanes which are toxic, smelly and problematic to remove by column chromatography. These disadvantages often prompt researchers to favour the Suzuki reaction over the Stille.

The Suzuki reaction provides the same types of disconnections as the Stille but has the advantage that it employs organoboron reagents instead of organostannanes. Organoboron reagents do not suffer from the same level of general toxicity as the tin reagents and tend not to streak during column chromatography (as the stannanes have a propensity to do). Also, more organoboron reagents are available commercially than organostannanes.

For these reasons we choose to develop a method based around the Suzuki (**Scheme 44**) reaction rather than the Stille.

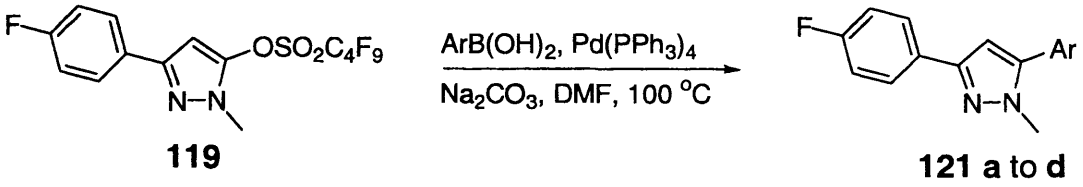


X = I, Br

Scheme 44

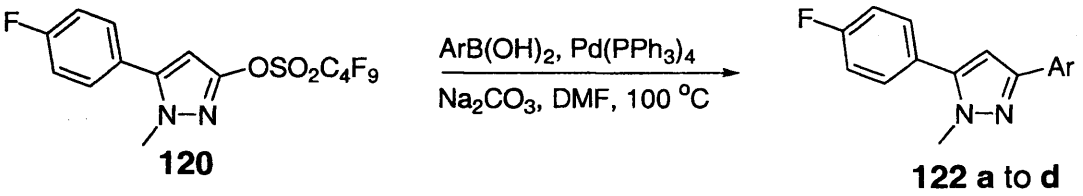
1.10.2 Literature Suzuki Couplings with Pyrazoles

Recently, Bourrain [45] has demonstrated that pyrazole nonafluorobutanesulfonates (nonaflates) undergo Suzuki cross coupling reactions. Nonaflates **119** and **120** were prepared smoothly from their parent hydroxypyrazoles by deprotonation with NaHMDS (sodium hexamethyldisilazide) then reaction with nonaflyl fluoride. The nonaflates were reacted with various aryl boronic acids (both electron rich and poor) (**Schemes 45** and **46**). **Table 6** summarises the results of these reactions.



119 **121 a** to **d**

Scheme 45



120 **122 a** to **d**

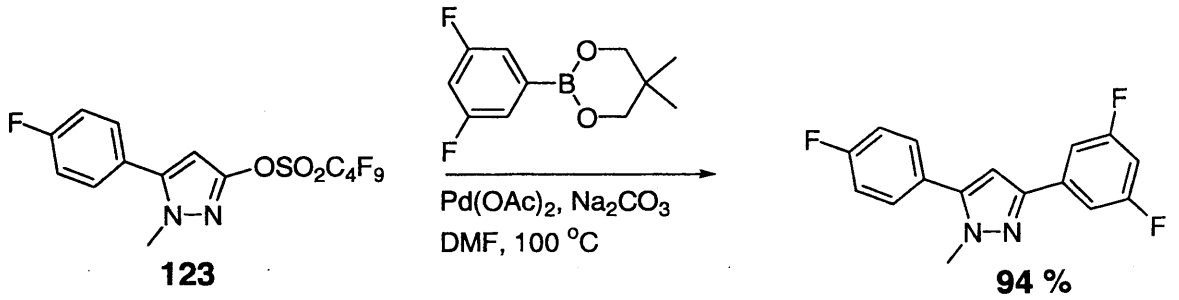
Scheme 46

Product	Ar	Yield (%)	Purity (%) (HPLC)	Product	Ar	Yield (%)	Purity (%) (HPLC)
121a	Ph	56	99.3	**122a**	Ph	34	97.1
121b	4-MeO-C_6H_4	64	98.7	**122b**	4-MeO-C_6H_4	32	94.4
121c	3-NO_2-C_6H_4	32	99.5	**122c**	3-NO_2-C_6H_4	10	96.6
121d	2-Me-C_6H_4	53	94.5	**122d**	2-Me-C_6H_4	37	94.0

Table 6

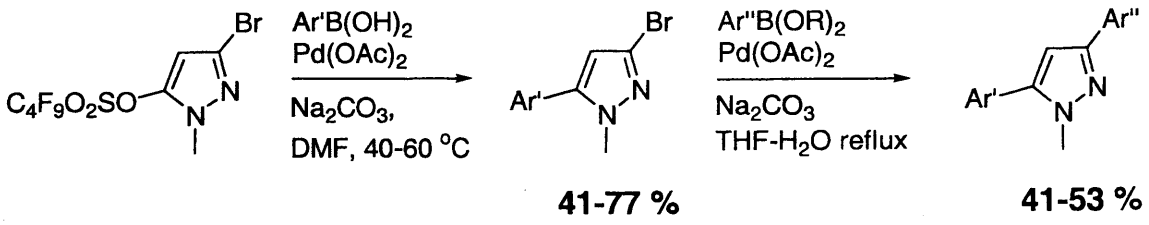
The products were isolated *via* automated normal-phase HPLC purification with UV-triggered fraction collection. The thing that stands out about these results (barring the poor yields) is that the yields for the 3-substituted pyrazoles (**122 a** to **d**) are significantly lower than those for their 5-substituted analogues. The authors tentatively attribute the increased reactivity of nonaflate **119** to 1,2-steric repulsions between the nonaflate group and the adjacent N-methyl group destabilising the system therefore increasing its reactivity relative to **120** where this interaction will be very much attenuated due to the space between the two groups.

Improvements in the yields of 5-nonaflyl pyrazoles was achieved by the use of boronate esters rather than boronic acid. An example of this is shown in **scheme 47**.



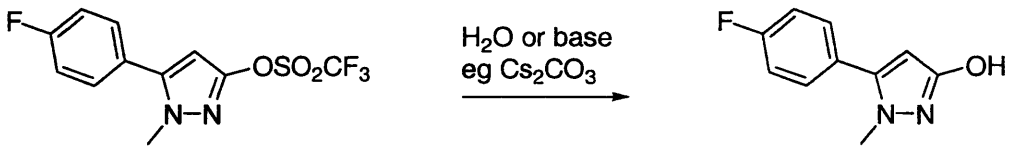
Scheme 47

Bourrain also proved that it was possible to carry out sequential chemoselective Suzuki reactions on 1-methyl-3-bromo-5-nonoflyl pyrazole using the conditions below (**Scheme 48**).



Scheme 48

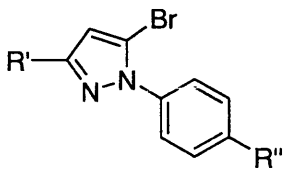
Reports of cross coupling reactions to pyrazole triflates are scarce [45]. Bourrain managed to synthesise pyrazole triflate **124**, however, it proved susceptible to hydrolysis to afford **125** under aqueous or strongly basic conditions (**Scheme 49**). Coupling was achieved with **124** under non aqueous conditions with a weak base, however the reactions were capricious with variable yields and degrees of cleavage to **125** were observed.



124 **125**

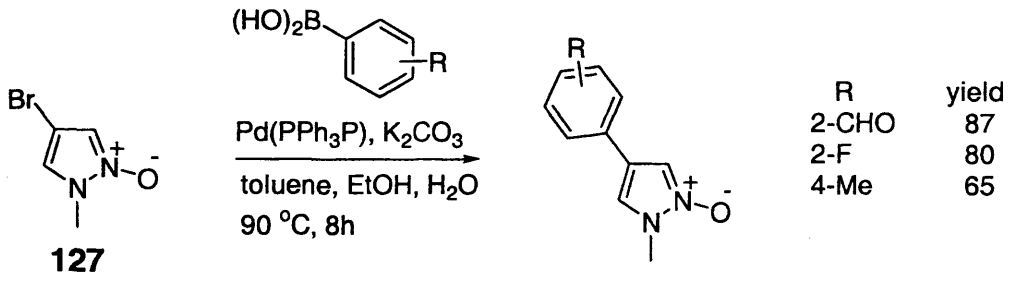
Scheme 49

Recently methods have become available for Pd catalysed cross-coupling reactions to *N*-alkyl and *N*-aryl-3-(5)-halopyrazoles [45]. For example Wang [46] has managed to successfully couple, under palladium catalysed conditions bromopyrazoles of the type **126** with alkynes, vinyltins and arylboronic acids in excellent yields.



126

Similarly Eskildsen [47] has reported Suzuki couplings carried out on N-oxybromopyrazole **127**, yielding coupled products in good to excellent yields (**Scheme 50**).



Scheme 50

However couplings to the 4-halo-3-trifluoromethyl pyrazoles or corresponding triflates are unreported.

After halogenation of the 4-position of pyrazole 34, we therefore proposed to develop methodology that would allow Suzuki couplings with this moiety.

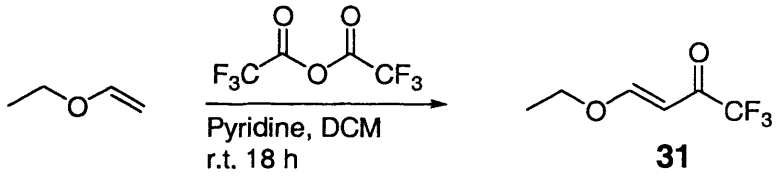
1.11 Study Goals

1) To learn how to perfluoroacylate vinyl ethers using the methodology of Hojo and to extend the range of compounds that have been reported in the literature.
2) Convert these perfluoroacyl enol ethers to pyrazoles using published routes (extending the range of compounds published in the literature).
3) Utilise the Cabri methodology for the synthesis of α-aryl vinyl ethers and then to apply the techniques above to the synthesis of pyrazoles from these products.
4) Develop methodology starting from Barrett's solid supported vinyl ethers that will allow the generation of pyrazoles by tailoring the perfluoroacylation and cyclisation chemistry used previously to solid phase conditions.
5) Using 3-trifluoromethyl-*1H*-pyrazole develop a method that will allow Suzuki couplings to be executed resulting in 4-substituted-3-perfluoroalkyl*1H*- pyrazoles

2 Results and Discussion

2.1 Perfluoroalkyl Vinylogous Esters from Vinyl Ethers

Hojo [16] reported that ethyl vinyl ether underwent smooth trifluoroacetylation when reacted with trifluoroacetic anhydride in the presence of pyridine in DCM to afford (*E*)-4-ethoxy-1,1,1-trifluoro-but-3-en-2-one (**31**) in 100 % yield (**Scheme 51**).



31

Scheme 51

Repeating his procedure yielded the expected product in high purity, but in a lower yield of 71 %. In the same paper, Hojo also reports the trifluoroacetylation of 1-(1-ethoxyvinyl)-4-nitro-benzene to afford (*E*)-4-ethoxy-1,1,1-trifluoro-(4-nitro-phenyl)-but-3-en-2-one in quantitative yield. This suggests that the acylation may tolerate a wide range of α–substituents allowing the generation of diversity. If a range of R_F groups are acceptable, the methodology could be used to generate arrays.

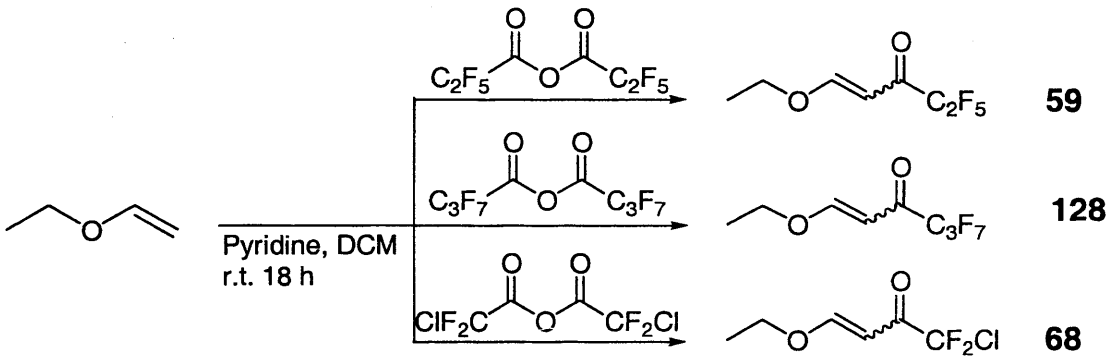
Other Trifluoroacetylations of Ethyl Vinyl Ether

Other comparable syntheses of **31** have been reported by Martins [20, 48] and Mellor [49]. Mellor synthesised **31** by adding ethyl vinyl ether to a solution of trifluoroacetic anhydride (1.1 equivalents) with catalytic amounts of 4-DMAP in DCM at -10 °C, then stirring at 0 °C for 19 hours to yield **31** in an 81 % yield after workup.

The procedure of Martins [48] involved the distillation of ethyl vinyl ether from $LiAlH_4$ directly into absolute pyridine (1.1 equivalents) then the addition of this mixture to trifluoroacetic anhydride (1.0 equivalents) cooled to ice/salt bath temperatures. The addition rate was such that the temperature of the reaction remained below 0 °C. After the addition the reaction was stirred at room temperature for 16 hours. At all stages of this reaction moisture was rigorously excluded and after the work up, which involved washing with dilute HCl, **31** was isolated in 79 % yield, with no need for further purification.

2.1.1 Perfluoroalkyl Enol Ether Syntheses

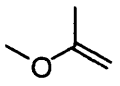
Under standard Hojo conditions ethyl vinyl ether reacted smoothly with pentafluoropropionic anhydride, heptafluorobutyric anhydride and chlorodifluoroacetic anhydride to afford vinylogous esters **59**, **128** and **68** in good yields (**Scheme 52**).



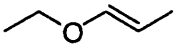
Scheme 52

Enones **59**, **128** and **68** are also known compounds; **59** and **128** were synthesised by Gerus [22] from ethyl vinyl ether and the respective acyl chlorides. Enone **68** was synthesised by Tietze [50] using Hojo methodology and by Gerus [26] using acetyl chloride as the acylating agent.

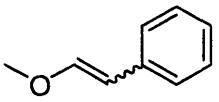
Variation of the perfluoroalkyl group in enones **31, 59, 128, and 68** proved to be facile and in order to introduce further diversity, the perfluoroacetylations of some commercially available substituted vinyl ethers were carried out. These were 2-methoxy-prop-1-ene (**69**), 1-ethoxy-prop-1-ene (**70**) and β-methoxystyrene (**199**).



69



70



199

Each of these vinyl ethers were reacted with various perfluoroalkanoic anhydrides; the results of these experiments (plus the results from the perfluoroacetylation of ethyl vinyl ether) are detailed in **Table 7**. The ease with which these reactions are set up and the products purified (by Kugelrohr distillation) made them suitable for carrying out in parallel. The 10 reactions were run simulateously in a Radleys Carousel reactor and the products were all worked up and isolated in one day after stirring overnight.

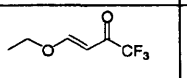
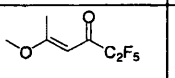
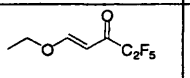
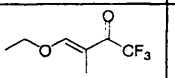
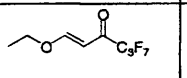
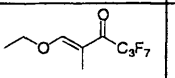
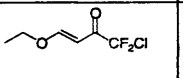
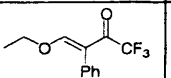
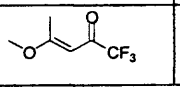
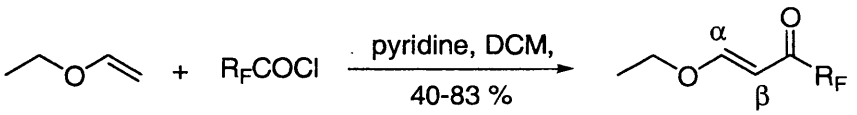
Structure	Comp'd	Yield %	ref.	Structure	Comp'd	Yield %	ref.
	**31**	71	17		**129**	76	
	**59**	49	22		**33**	82	20
	**128**	64	22		**130**	74	
	**68**	49	26, 50		**131**	54	51 52
	**32**	87	20				

Table 7

Of the compounds synthesised **129** and **130** are previously unreported. Some data, ^{13}C NMR, elemental analysis and boiling point is available for **33** [20] and all of the other compounds are known and leading references are as in **table 7**.

2.1.2 *E/Z* isomerism

Hojo [17] reported that the alkyenyl group in **31** is of *E*-configuration and Gerus [22] reported that compounds **200**, **59**, **128**, **201** and **202** as also have *trans* alkenyl groups. Enone **31** was synthesized in the manner described above whereas Gerus [22] made **200**, **59**, **128**, **201** and **202** by acylation of ethyl vinyl ether with the appropriate acyl chlorides (**Scheme 53**).



Comp'd	**200**	**59**	**128**	**201**	**202**
R_F	CHF_2	C_2F_5	C_3F_7	$CH(CF_3)_2$	CF_2SO_2F
$^3J_{H\alpha\text{-}H\beta}$	12.5	12.5	12.2	12.2	12.0

Scheme 53

The alkenyl geometry was assigned on the basis of the $^3J_{H\text{-}H}$ coupling constant. Though typical coupling constants for trans protons are *ca* 16 Hz, the presence of two strong –I groups in the vinylogous esters lowers *J* values so that a 12 Hz coupling constant is typical.

Analysis of compounds **31, 59, 128** and **68** revealed olefinic coupling constants of 12.5, 12.2, 12.1 and 12.5 respectively. This type of analysis is not possible where substituted enones are formed

2.1.3 Pyrazole Syntheses

Our initial attempt to synthesise pyrazole **34** from enone **31** following the procedure of Braibante [14] yielded the desired product but in a 35 % yield compared to the reported 98 %. The reaction was carried out in refluxing ethanol over four hours and the lower than expected yield could be due to loss of the volatile vinylogous ester (bp 51 °C/12mmHg[1]) from the reaction vessel. A mixture of **34** and 3-trifluoromethyl-3,4-dihydro-*2H*-pyrazol-3-ol was formed in the reaction and dehydration was undertaken by treatment with concentrated H_2SO_4 (Hojo [53] used this methodology to synthesise trifluoromethyl pyrazoles from trifluoromethyated β-diketones without the need for a dehydration step). When the reaction was repeated at room temperature and allowed to run overnight, an increase in yield was observed from 35 to 72 %. As expected, a mixture of **34** and 3-trifluoromethyl-3,4-dihydro-*2H*-pyrazol-3-ol was formed and the dehydration was undertaken by treatment with concentrated sulphuric acid as before. The dehydration was monitored by TLC and took less than 15 minutes.

The same methodology was then used to synthesise pyrazoles **35, 36, 117, 118** and **132** to **135**. **Table 8** shows the results of these syntheses.

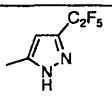
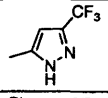
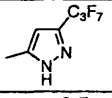
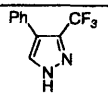
Pyrazole	Comp'd	Yield %	Ref.	Pyrazole	Comp'd	Yield %	Ref.
	**34**	72	14, 29		**133**	62	
	**35**	93	14		**118**	64	11
	**36**	86	14, 29		**134**	71	54
	**132**	84	55		**135**	81	
	**117**	79					

Table 8

Of these compounds **117**, **133**, and **135** are previously unreported; all of the other compounds are known and leading references are as in **table 8**.

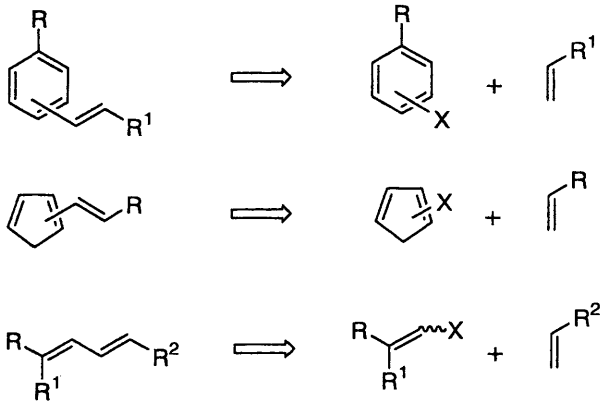
From Vinyl Ethers to Pyrazoles

Following these successful results modification of this methodology to allow the synthesis of perfluoroalkylated pyrazoles in which the C4 and C5 substitution did not rely on commercially available vinyl ethers became an attractive synthetic goal.

The following chapters describe our endeavours to this end.

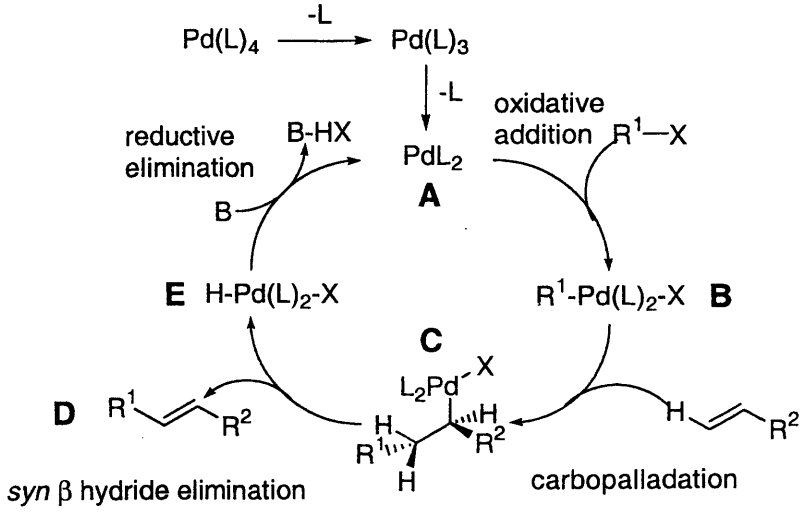
2.2 The Heck Reaction

The Heck reaction is the palladium catalyzed arylation, heteroarylation or vinylation of alkenes using aryl, heteroaryl or vinyl halides or triflates. Scheme **54** outlines the Heck disconnections.



Scheme 54

Mechanism of the Heck Reaction (Scheme 55)



Scheme 55

The catalytic cycle begins with oxidative addition of the coordinatively unsaturated 14e PdL_2 species into the C-X carbon bond to give the 16e complex B. Insertion of the vinyl fragment into the palladium-carbon bond then occurs. The sequence of events leading to this are thought to be dissociation of one of the neutral ligands from the palladium complex, followed by coordination of the vinyl moiety to the 14e complex, resulting in activation of the aryl palladium σ–bond to attack of the vinylic π bond. However, the initial dissociation is not necessarily required as the palladium at this point still has a free coordination site available. Carbopalladation then takes place resulting in intermediate **C**. With a β-hydrogen and the palladium in a common plane, β-hydride elimination then occurs extruding olefin (**D**). Palladium complex **E** then undergoes reductive elimination assisted by the presence of a base regenerating the active 14e catalytic species and allowing the cycle to continue.

Synthetic Utility of the Heck Reaction

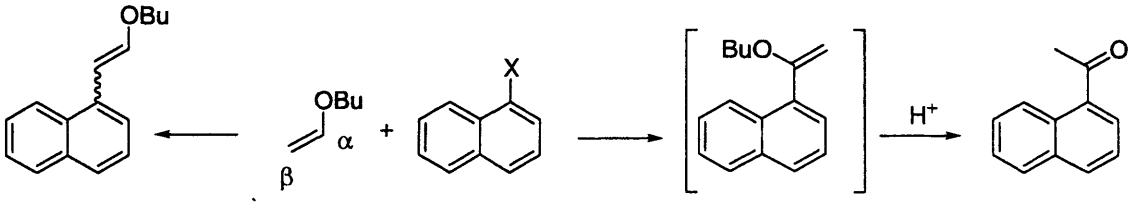
The Heck reaction is especially useful synthetically as it tolerates a wide range of functional groups on either the alkene or halide / triflate. Functionality tolerated on the halide includes CO_2R, CO_2H (requires extra base, *o*-CO_2H is not tolerated as it binds to palladium) CHO, CN, NO_2, OH, OR, NR_2, Cl and CF_2. The same functional groups are largely tolerated on the alkene; however –Cl and -OAc are sometimes lost *via* β-Cl or β-OAc elimination [56].

2.2.1 α–Selective Heck Reactions for Vinyl Ether Synthesis

Diphenylphosphinopropane (DPPP) and Triflates

By focusing attention on the relationship between ligand and leaving group and their effect on the reactivity of the catalytic system, Cabri [34] was able to develop a general

method for the α–selective Heck arylation of acyclic vinyl ethers. Cabri showed that the regioselectivity of the reaction between butyl vinyl ether and 1-naphthyl triflate could be influenced by ligand choice to give complete (>99/1) selectivity for the α-regioisomer. Scheme **56** [34] shows the regioisomeric possibilities of this reaction.



203 **140**

Scheme 56

For the reaction in **scheme 56** when the ligand was PPh_3, the selectivity of **140** versus **203** was 1.7:1. On changing the ligand to P(*p*-tolyl)$_3$ (which is more basic than PPh_3 but has the same cone angle of 145 °) the ratio decreased marginally to 1.6 : 1. Changing the catalyst to P(*o*-tolyl)$_3$ (with a cone angle of 194 °) had little effect on the regiochemical outcome with a ratio of 1.7 : 1 However, when the cone angle was decreased to 136 ° or 122 ° by using PCH_3Ph_2 and $P(CH_3)_2Ph$ respectively, the selectivity of the reaction increased to >99/1. These results suggested that higher selectivity towards **140** could also be achieved by using bidentate phosphine ligands as they have small cone angles.

Table 9 contains the results of the experiments using the bidentate ligands and those of the monodentate ligands detailed above. The most efficient ligands (based on catalyst loading) were 1,3-bis(diphenylphosphino)propane (DPPP) and 1,1'-bis(diphenylphosphino)ferrocene (DPPF), both of which only required 1.1 equivalents to the palladium to produce a stable catalyst. Of these two, the reaction with DPPP

offered the shortest reaction times i.e. 0.5 compared to 2 hours for DPPF versus 5 and 6 hours for the monodentate PCH_3Ph_2 and $P(CH_3)_2Ph$ ligands respectively. Further study of this system using aryl bromides and iodides resulted in decreased regioselectivity for the α position. Addition of either thallium or silver salts increased the regioselectivity of the reaction. These effects on the regioselectivity are discussed further on.

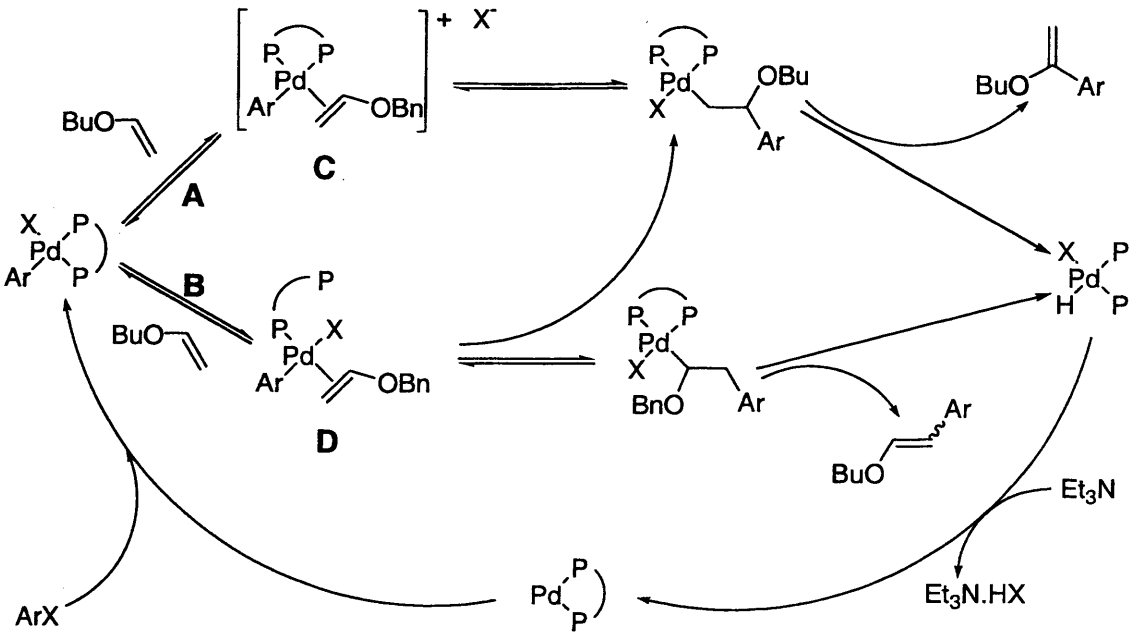
Ligand	L : Pd	cone angle (°)	T (°C)	T (h)	conv. (%)	3 :4	*E : Z*
None		145	100	24	8	55:45	71:29
PPh_3	2 : 1	145	100	1.5	100	63:37	80:20
P(*p*-tolyl)$_3$	2 : 1	194	100	5	100	61:39	72:28
P(*o*-tolyl)$_3$	2 : 1	136	100	5	100	63:37	76:24
PCH_3Ph_2	3 : 1	122	80	5	100	>99:1	
$P(CH_3)_2Ph$	3 : 1	121	80	6	100	>99:1	
DPPM	2 : 1	125	100	24	60	80:20	74:26
DPPE	2 : 1	125	80	24	95	>99:1	
DpTE	2 : 1	127	80	24	93	>99:1	
DPPP	1.1 : 1		80	0.5	100	>99:1	
DPPB	2 : 1		60	1.5	100	>99:1	
DPPF	1.1 : 1		60	2	100	>99:1	

DPPM = 1,1-bis(diphenylphospino)methane, DPPE = 1,2-bis(diphenylphospino)ethane, DpTE = 1,2-bis(di-*p*-tolylphospino)ethane, DPPB = 1,4-bis(dipenylphosphino)butane, c-DPPET = *c*-1,2-bis(diphenylphospino)ethylene

Table 9

2.2.2 Mechanism of α and β Selectivity

Scheme 57 details the mechanism suggested by Cabri [34] in which the oxidative addition step is governed by the relative binding affinities of ligand and counterion for palladium. The regioselectivity of the reaction is controlled by the oxidative addition step.



Scheme 57

Mechanistic Explanation

After the oxidative insertion of ArX, the reaction is able to follow one of two pathways depending on the relative affinities of the ligand and counterion for the palladium. In pathway **A,** a strongly binding ligand and weakly binding counterion lead to a cationic coordination complex between the vinyl fragment and the palladium (complex **C**). Due to the cationic nature of the palladium complex, the polarization of the vinyl π system is increased, and migration of the aryl moiety onto the α carbon becomes favoured.

In pathway **B,** a weakly binding ligand and a strongly binding counterion lead to neutral coordination complex **D**. In this complex the vinylic π system is much less polarised than that of the cationic comlpex **C**, thus the predilection for aryl migration onto the α–carbon is reduced, and either α- or β-migration can occur. The binding strength of monodentate phosphine ligands is inversely proportional to the cone angle as the extent of ligand dissociation is dominated by steric effects [57]. Therefore

ligands with smaller cone angles, including bidentate phosphine ligands would be expected to favour pathway **A**. Triflate counterions are also expected to favour pathway **A** as they are less strongly binding than halides.

2.2.3 Other Heck Routes to α Aryl Vinyl Ethers

Thallium and Silver Salt Additives

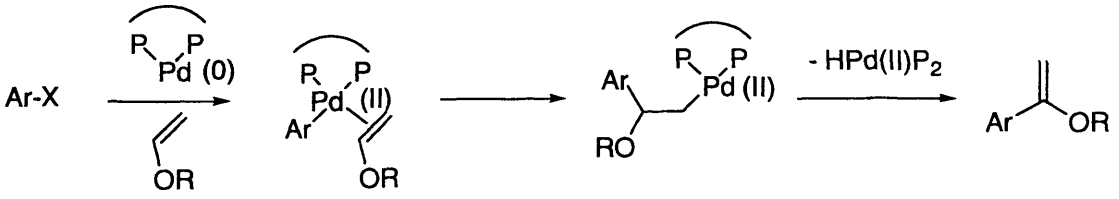
Although the $Pd(OAc)_2$ / DPPP internal arylation of butyl vinyl ether proved successful for a variety of aryl moieties regiochemical selectivity diminished when iodides and bromides were used. Cabri [34, 58] found the regioselectivities of a range of aryl bromides and iodides could be brought up to 100 % by the addition of thallium acetate. The addition of silver nitrate, although offering improvements in regioselectivity was not as effective as thallium acetate in terms of regioselectivity. The arylations with silver additives also proceeded at a slower rate than those doped with thallium.

Alternative Hallberg Conditions

As an alternative to methodologies involving thallium and silver additives, Hallberg [59] devised conditions which allowed selective α arylation of butyl vinyl ether using aqueous DMF, potassium carbonate and a palladium acetate DPPP ligand combination. The reactions were able to produce excellent selectivity for the internally arylated product (99:1) however high catalyst loadings were required (6.6 mol % palladium and 7.9 mol % DPPP). Even so longer reaction times were required to achieve good conversions, for example, under the fastest reaction conditions tried, a 98 : 2 α-regioselective reaction between butyl vinyl ether and 1-naphthyl bromide with a 92 % yield (of the methyl ketone after acidic treatment) took 16 hours. It was

found that increased water content in the reaction medium enhanced the reaction rates in general and with electron poor halides, larger amounts of water and / or higher reaction temperatures were crucial for high α selectivity [59].

Again the selectivity for α arylation is attributed by the author to the formation of a polar cationic palladium complex preceding oxidative insertion (**Scheme 58**).

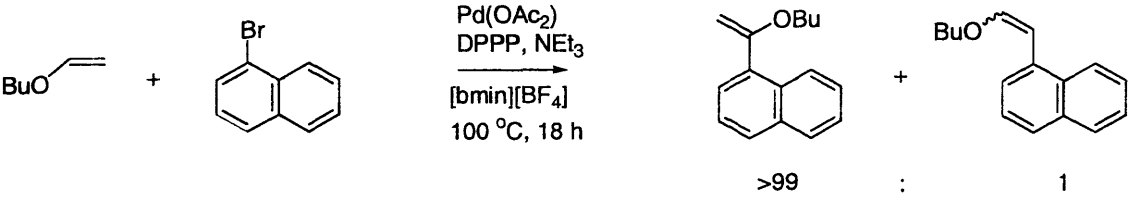


Scheme 58

The highly polar reaction system favours displacement of one of the phosphines by the halide and generation due to its stabilisting effects on the resulting cationic complex and its counterion. Again the polarised π system favours aryl migration onto the α carbon.

Reactions in Ionic Liquids ([bmin][BF_4]

Regioselective internal arylation of butyl vinyl ether has been carried out in ionic liquid ([bmin][BF_4]) using $Pd(OAc)_2$ / DPPP as the ligand / catalyst combination [60] (**Scheme 59**)



Scheme 59

Scheme 59 [60] shows the reaction of butyl vinyl ether and 1-naphthylbromide. Although the reaction offers excellent regioselectivity and uses a reasonable catalyst loading of 2.5 mol % and 2.75 mol % of DPPP it could only offer 50 % conversion of the halide over 18 hours.

Later it was found that when the equivalence of palladium was doubled and 2 equivalents of DPPP was used conversion for a variety of halides was increased to 100 % and regioselectivities of >99:1 were still observed. After acidic work up methyl ketones were obtained in good to excellent yields. However even under these conditions long reaction times (24 to 36 hours) were required for complete conversions.

2.2.4 Choice of Method

Each of the above methods for generating α-aryl vinyl ethers have inherent strengths and weaknesses making them more or less attractive synthetic options.

The ionic liquid methodology of Xaio [60] is attractive in that the reaction solvent can be recycled making it 'environmentally friendly'. The reaction also uses acceptable levels of palladium (2.5 mol %) but process is limited by prolonged reaction times (24 to 36 hours for complete conversions).

Halberg's [59] approach using palladium acetate and DPPP and potassium carbonate in aqueous DMF is limited by long reaction times as was the ionic liquid methodology. Reaction times of 16 to 86 hours were reported. The palladium loadings of 6.6 mol % are also high by today's standards.

Cabri's [34, 58] methodolology using aryl iodides and bromides with thallium salt additives proved capable of producing the desired regioisomeric results and isolated yields were generally high. However reaction times varied between 1 and 36 hours

for the arylation of butyl vinyl ether with 2-naphthyl bromide and 4-nitrobromo benzene respectively. However, the most obvious drawback of this methodology is the use of 1.1 equivalents of a toxic thallium salt which limits its appeal drastically.

Cabri's [34] aryl triflate methodology has the disadvantage that it requires the generation of an aryl triflate which adds an extra synthetic step to the route. However, triflation of phenols is facile and the fact that the aryl moieties used in this sequence are derived from phenols can also be seen as advantageous as a wide range of inexpensive phenols are available. The catalyst loading of 2.5 mol % is acceptable by modern standards and reaction times are uniformly short for a selection of electron withdrawing and donating aryl moieties (between 1 and 7 hours). The reaction also affords excellent regioselectivity and generally excellent chemical yields.

Due to the advantages that this method offers over the others we chose to investigate this method as a vehicle for preparing the aryl vinyl ethers we wished to synthesise.

2.2.5 α-Aryl vinyl Eher Syntheses and Product Isolation

Using the Cabri [34] procedure ($PdOAc_2$/DPPP/DMF) we were able to synthesise aryl vinyl ethers **136** to **140** from butyl vinyl ether and the appropriate aryl triflate (see **table 10**) efficiently with isolated chemical yields of 79 to 88 % and 100 % selectivity for the α-regioisomer.

The selectivity of the reaction was assessed by GCMS analysis of the crude reaction mixtures where, in each case, only one peak was found with the right mass for the expected aryl vinyl ether. This assessment proved to be reasonable based on the high chemical yields of the α arylated products subsequently obtained.

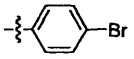
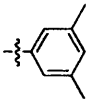
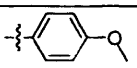
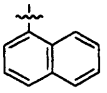
Ar OBu			
Compound	**Aryl moiety**	**α-selectivity (%)**	**Isolated yield (%)**
136		100	79
137		100	86
138		100	88
139		100	81
140		100	81

Table 10

All five reactions were performed simultaneously using a Radleys Carousel reactor. The reactions were allowed to run overnight and after 16 hours the aryl triflates were no longer present by TLC.

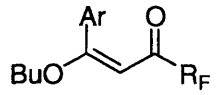
In the α-selective Heck arylations carried out by Cabri chromatographic purification of the aryl vinyl ethers was not attempted even on short columns, the products were hydrolyzed to the corresponding methyl ketones before isolation. This was presumably carried out because of the difficulty in isolating and handling the sensitive vinyl ethers.

Attempts to purify the vinyl ethers by column chromatography resulted in the expected decomposition to the methyl ketones. However, we found it possible to isolate the vinyl ethers by reduced pressure Kugelrohr distillation of the crude products after basic work up.

2.2.6 Perfluoroacylation of α Aryl vinyl Ethers

Using the methodology of Hojo [17], as previously described, we planned to perfluoroacylate the α aryl vinyl ethers synthesised *via* the Heck reaction to afford a range of perfluoroacetylated enones of type **204**.

The synthesis of these enones, which are masked 1,3-dicarbonyl compounds was undertaken to provide substrates that could then be reacted with hydrazine to yield a variety of substituted perfluoroalkyated pyrazoles.

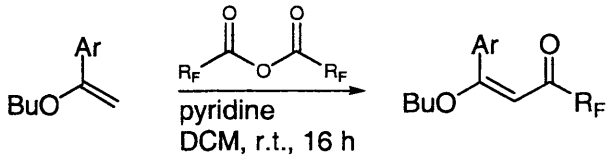


Ar = aryl
R_F = perfluoroalkyl

204

Enone Diversification

At this point in the synthetic route we planned to build in a further level diversity into our products by reacting each vinyl ether with a four member set of perfluoroalkanoic anhydrides (chlorodifluoroacetic, trifluoroacetic, pentafluoropropionic and heptafluorobutyric anhydrides) to yield 4 different perfluoroacyl enones from each vinyl ether. (**Scheme 60**).



R_F = CF_2Cl, CF_3, C_2F_5, C_3F_7
Ar = Aryl

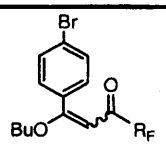
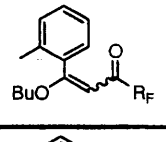
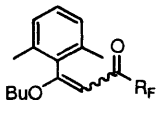
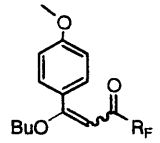
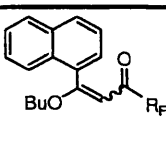
Scheme 60

Before beginning the sequence it was decided to purify only some of the vinyl ethers and to take the others on in their crude form to avoid the need for carrying out 20 (if all of the reactions were successful) similar purifications. This has the obvious

advantage of streamlining the synthesis but also cuts down the potential for the hydrolysis of the products while they are awaiting purification.

2.2.7 Synthetic Results

The application of this methodology to these new substrates yielded pleasing results i.e. generally clean crude products and respectable isolated yields (where purifications were undertaken). The purifications were carried out *via* reduced pressure Kugelrohr distillation. Table **11** summarises the results of these reactions.

Entry	Structure	R_F	Comp'd	*E*/*Z* Mix	Purified	Yield %
1		CF_3	**141**	No	Not req'd	76
2		C_2F_5	**142**	No	Not req'd	75
3		C_3F_7	**143**	No	Not req'd	81
4		CF_2Cl	**144**	No	Not req'd	77
5		CF_3	**145**	No	Yes	79
6		C_2F_5	**146**	No	Yes	73
7		C_3F_7	**147**	No	Yes	78
8		CF_2Cl	**148**	No	Yes	87
9		CF_3	**149**	Yes	No	N/A
10		C_2F_5	**150**	Yes	No	N/A
11		C_3F_7	**151**	No	Yes	80
12		CF_2Cl	**152**	No	Yes	78
13		CF_3	**153**	No	No*	N/A
14		C_2F_5	**154**	No	No*	N/A
15		C_3F_7	**155**	No	No*	N/A
16		CF_2Cl	**156**	No	No*	N/A
17		CF_3	**157**	No	Yes	71
18		C_2F_5	**158**	No	Yes	78
19		C_3F_7	**159**	No	Yes	68
20		CF_2Cl	**160**	No	No*	N/A

* taken on without analysis

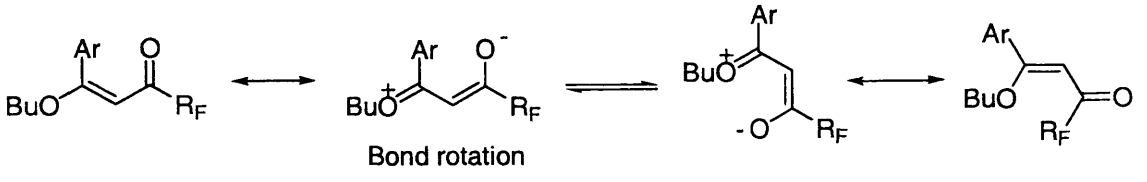
Table 11

2.2.8 *E/Z* Isomerism

It is unfortunate that it is not really possible to tell whether the products from the above reactions possess either *E* or *Z* stereochemistry. However, what is of note is that entries 9 and 10 show that **149** and **150** were formed as a mixture of *E* and *Z* steroisomers. This was ascertained from the ^{1}H and ^{19}F NMR spectra. These results are hard to explain as entries 11 and 12 show that both **151** and **152** were formed as single stereoisomers.

Interestingly, over time, it was observed that **149** and **150** (entries 9 and 10) were isomerising to a single stereoisomer. For **149**, after working up the reaction, two vinylic proton signals were observed at 5.94 and 5.49 ppm in a one to one ratio. After approximately one year of storage at -20 °C, the two signals were still present but in ratio of 7:3. Similarly for **150** after the work up two vinylic proton signals were observed at 6.04 and 5.58 ppm in a 1:1.2 ratio but after storage at -20 °C for one year, this ratio had altered to 7:3.

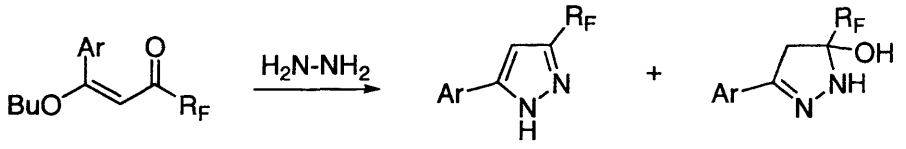
In both of these situations it seems reasonable to assume that the mixture is heading towards a thermodynamic product, i.e. the *Z* stereoisomer is converting to the *E* stereoisomer. This can be achieved by the mechanism detailed below (**Scheme 61**) which starts with the formation of the enolate, followed by rotation of the new C-C single bond and finishes with conversion back to the enone form. This transformation could also be catalysed by the presence of an acid or nucleophile.



Scheme 61

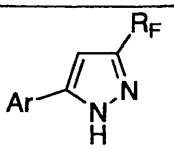
2.2.9 4-Aryl-3-Perfluroalky-*1H*-pyrazole Syntheses

When the perfluoroalkyl enones **141** to **160** were reacted with hydrazine, a mixture of the desired pyrazole and a pre-dehydration product were produced in each case (**Scheme 62**).



Scheme 62

Dehydration occurred smoothly when these mixtures were heated under microwave conditions in toluene to afford the pyrazole. After purification, yields of 61 to 89 % (ignoring entries 17 to 20 where the initial reaction was unsuccessful) were recorded. **Table 12** summarises these results.



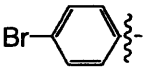
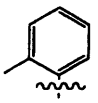
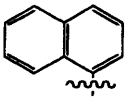
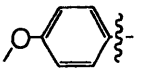
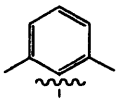
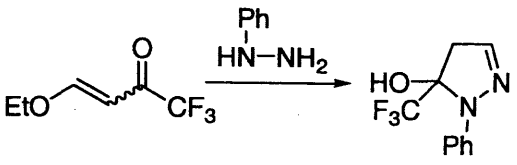
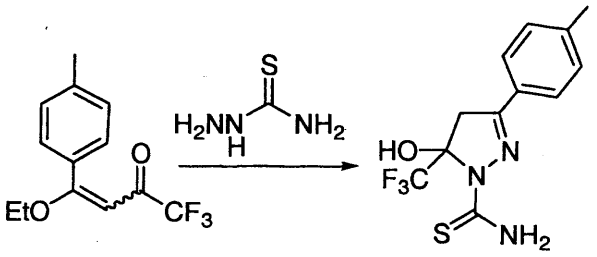
Entry	Compound	Aryl	R_F	Yield %
1	**161**		CF_3	62
2	**162**		C_2F_5	88
3	**163**		C_3F_7	75
4	**164**		CF_2Cl	89
5	**165**		CF_3	80
6	**166**		C_2F_5	85
7	**167**		C_3F_7	69
8	**168**		CF_2Cl	92
9	**169**		CF_3	85
10	**170**		C_2F_5	85
11	**171**		C_3F_7	80
12	**172**		CF_2Cl	61
13	**173**		CF_3	81
14	**174**		C_2F_5	73
15	**175**		C_3F_7	74
16	**176**		CF_2Cl	79
17	N/A		CF_3	no product
18	N/A		C_2F_5	no product
19	N/A		C_3F_7	no product
20	N/A		CF_2Cl	no product

Table 12

The formation of these hydrates was also observed during the synthesis of pyrazoles from commercial vinyl ethers, and in similar work Braibante [14], Bonacorso [61], Gerus [16] and Song [19] have reported the synthesis and isolation of these type hydroxydihydrated pyrazoles from perfluoroalkoxy enones. **Schemes 63** [14] and **64** [61] outline two of these syntheses.



Scheme 63



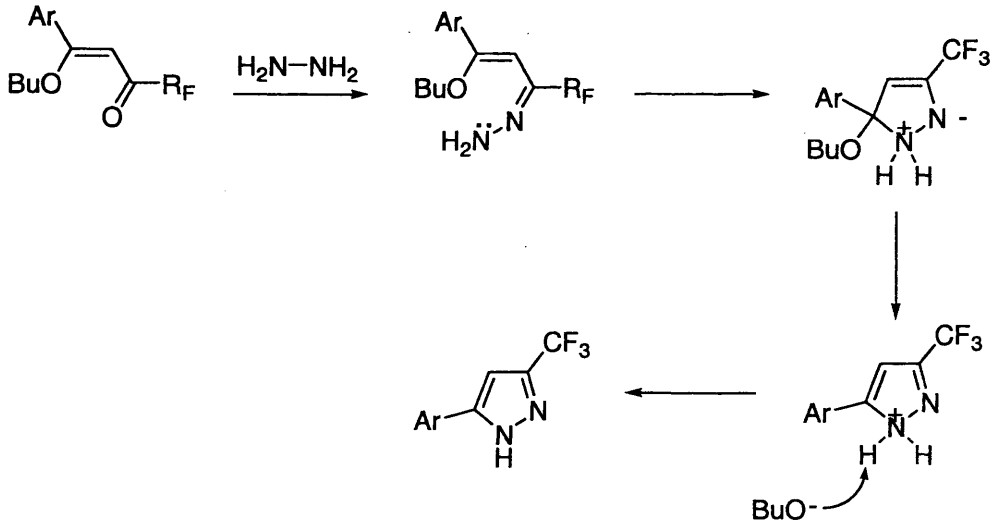
Scheme 64

It is important to note that in these two references, *N*-substituted pyrazoles were been synthesised rather than *1H*-pyrazoles.

Although no one has reported hydrated-*1H*-pyrazoles in the literature we were only able to dehydrate them under forcing conditions i.e. strong heating in toluene or by reaction with concentrated sulphuric acid or P_2O_5 and we found that they did not aromatise spontaneously on standing, even when the reactions were evaporated to dryness, suggesting that the hydrated pyrazoles are stable molecules in their own right.

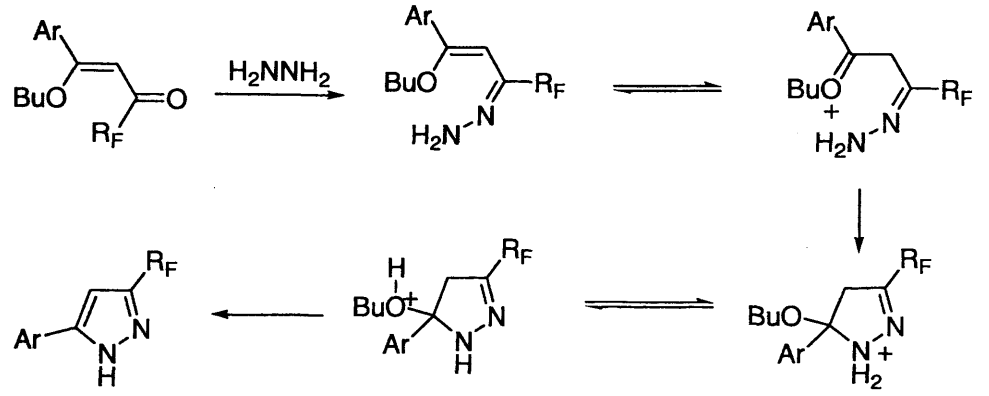
2.2.10 Cyclisation Mechanisms

There are two ways in which the cyclisation can initiate. These are *via* Michael addition, and by 1,2-addition of the hydrazine to the enone. **Pathway 4** examines the situation where the initial attack occurs in a Michael sense and **Pathways 1**, **2** and **3** examine mechanistic scenarios resulting from 1,2 addition.

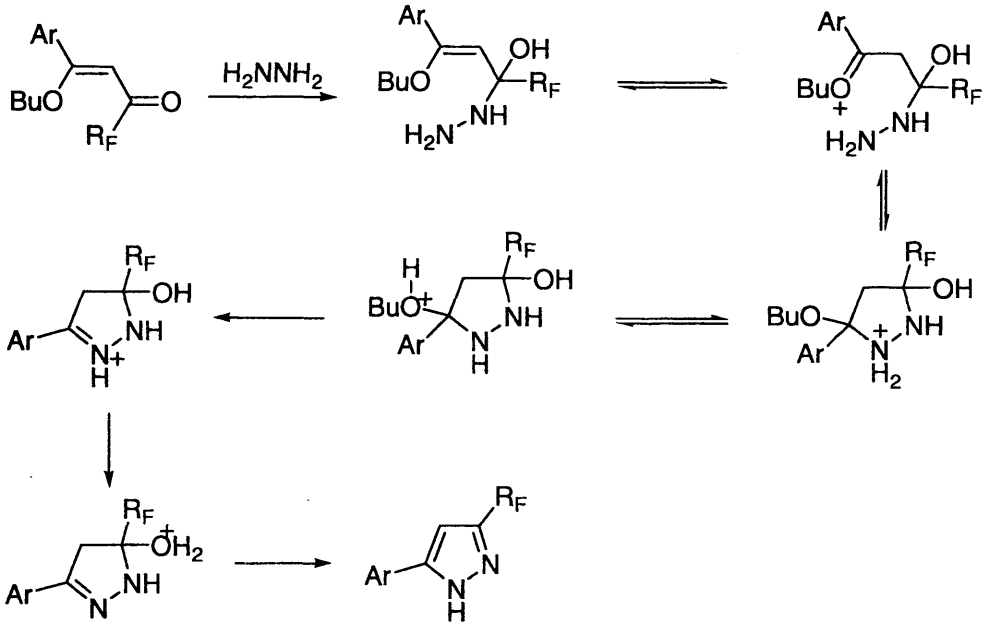


Pathway 01

Pathway 1 starts with the formation of a hydrazone between the hydrazine and enone carbonyl group. Formation of the pyrazole ring (in which butoxide is lost) then occurs through a Michael addition led by the NH_2 lone pair. Abstraction of an amino proton by the butoxide anion then generates the neutral species. **Pathway 2** differs from **pathway 1** in that after the formation of the hydrazone, protonation of the enol ether leads to a situation in which the favoured 5-*exo-trig* cyclisation can occur by attack of the nitrogen lone pair on the resultant oxcarbenium ion. **Pathway 3** differs from **pathway 2** in that the formation of the oxocarbenium ion occurs after the formation of the tetrahedral intermediate resulting from the attack of the hydrazine on the carbonyl group. In this situation a similar 5-*exo-trig* cyclisation as in **pathway 2** can occur. In **pathway 3** aromatisation could also occur through a second mechanism that involves the loss of water first then the elimination of butanol.

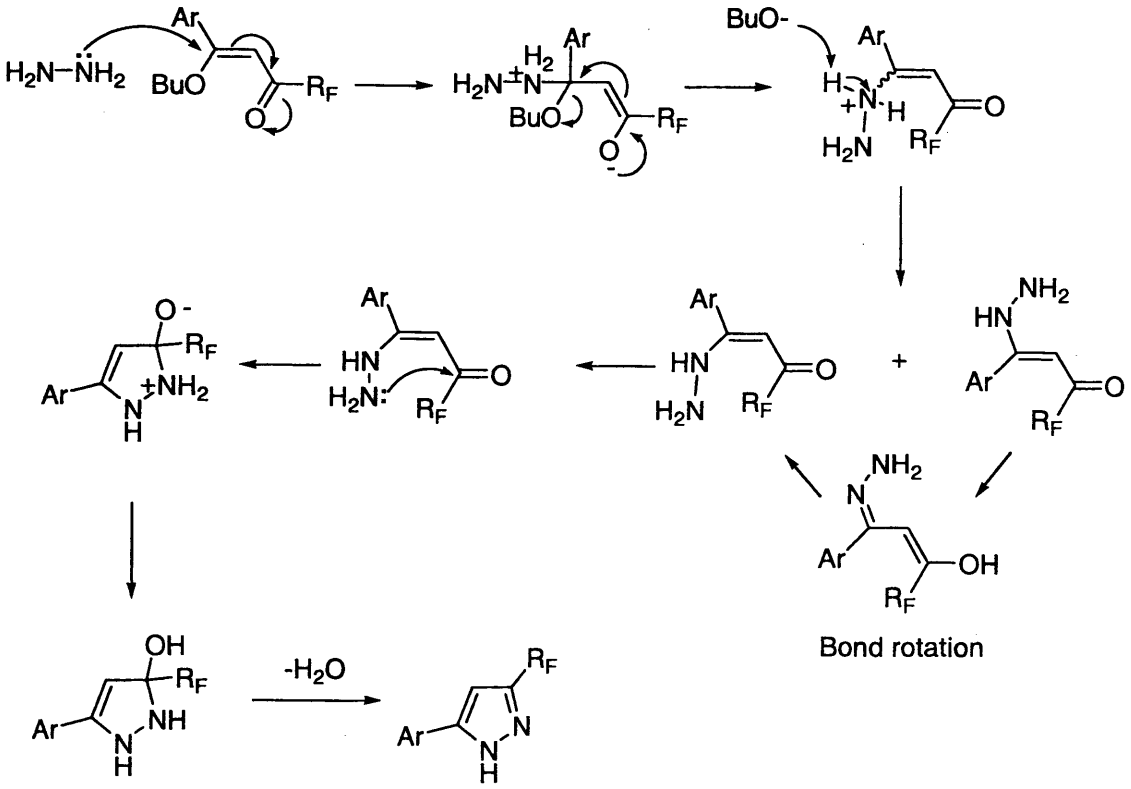


Pathway 2



Pathway 3

Pathway 4 begins with a Michael type reaction between the enone and hydrazine with the loss of butoxide. Direct addition of the amino nitrogen of the hydrazine to the enone carbonyl group then forms the ring system; loss of water from the ring subsequently provides the aromatic pyrazole.



Pathway 4

Of the proposed mechanisms **pathway 1** is unlikely to occur as it involves an anti-Balwin 5-*endo-trig* cyclisation. This pathway also does not account for the formation of the pyrazole hydrates which are observed under experimental conditions. **Pathway 2** involves the favoured 5-*exo-trig* cyclisation it, however, does not account for the formation of the pyrazole hydrates either. **Pathways 3** and **4** both invovle favoured 5-*exo-trig* cyclisations and the mechanisms can account for the formation of the pyrazole hydrates. Of these two mechanisms it is difficult to propose which would be more favourable.

Entries 17, 18, 19, and 20

The attempted syntheses of pyrazoles **157** to **160** were not successful under the conditions used (**Table 12**). This is probably due to steric hindrance arising from the disubstituted phenyl group preventing attack of the hydrazine at the α carbon.

2.2.11 Overview of the Heck Route

The arylations proceeded in very good yields ranging from 79-88 % based on the aryl triflate stoichiometry with an average yield over the five reactions carried out of 83 %. Purification of the sensitive vinyl ethers was found to be facile *via* reduced pressure Kugelrohr distillation.

Of the twently perfluoracylations carried out eighteen products were isolated as single steroisomers. Purification of the products was achieved by reduced pressure Kugelrohr distillation. Yields of 68-87 % were recorded with an average yield of 77% (In seven of the twenty reactions the vinylogous esters were taken on directly without purification and yields were not recorded for these compounds.). The efficiency of the perfluoroacylations was found to be independent of the R_F group been added.

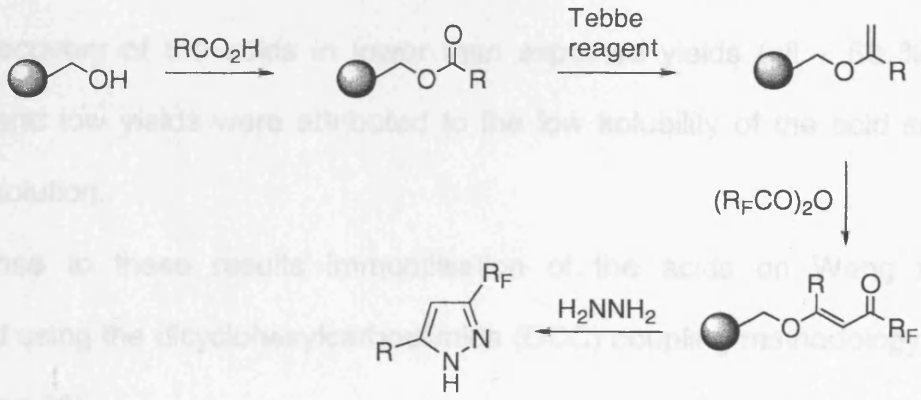
Cyclisations

Of the twenty cyclisations attempted sixteen were successful. The four that did not work were the four members of the group that contained the 2,5-dimethyl substituted phenyl ring. The failue of these reactions was attributed to steric hindrance arising from the 2,5-substitution pattern. Of the sixteen that worked yields of 62-92% were obseved with an average of 79 %.

Overall the route had an average efficiency (based on the average yields above) of 51 % and was able to provide products in analytically pure states.

2.3 Solid Phase Pyrazole Synthesis

The planned synthesis for the generation of C5 substituted 3-perfluoroalkyl pyrazoles *via* a solid phase route is shown in **scheme 65**.



Scheme 65

The first two steps of the scheme involve the loading of the acid onto the resin; followed by Tebbe olefination to generate a resin bound α-substituted vinyl ether. The two subsequent steps, the perfluoroacylation and cleavage of the pyrazole, are resin bound versions of chemistry used previously to generate pyrazoles in solution.

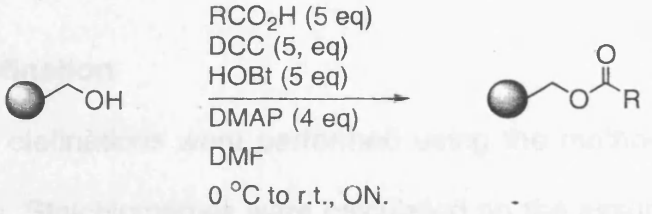
2.3.1 Acid Immobilisation: Choice of Resin

The formation of the resin bound carboxylic esters should be high yielding, reliable and preferably as simple as possible. Linkers, where applicable, should be chosen to be chemically inert to the reaction conditions used in steps subsequent to the loading.

Previously, Barrett had shown that carboxylic esters supported on Wang or Merrifield resin underwent smooth methylenation using the Tebbe reagent to produce supported vinyl ethers [43].

Initially Merrifield resin was loaded with carboxylate salts of octanoic acid, 4-iodo-benzoic acid, 4-methoxy-benzoic acid and 4-(methoxy-phenyl)-acetic acid generated with cesium carbonate. The salts were was added to the pre swelled resin in DMF as a suspension in DMF and shaken at room temperature for 24 hours. After washing small portions of the resin were cleaved with 10 % trifluoroacetic acid in DCM which lead to recovery of the acids in lower than expected yields (all < 50 %). These variable and low yields were attributed to the low solubility of the acid salts in the reaction solution.

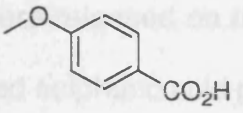
In response to these results immobilisation of the acids on Wang resin was attempted using the dicyclohexylcarbodiimide (DCC) coupling methodology of Barrett [44] (**Scheme 66**).



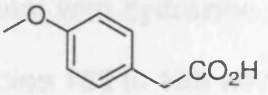
Scheme 66

However, when repeating Barrett's loading of 4-iodo-benzoic acid a fine white powder was formed in the reaction that proved impossible to wash away from the resin. This solid was assumed to be dicyclohexylurea resulting from the consumption of the DCC. This problem was circumvented by replacing the DCC with diisopropylcarbodiimide (DIC). DIC has the advantage that its urea by-product is more soluble than that of DCC and therefore easier to wash away and in practice this proved to be the case.

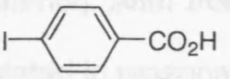
This methodology provided a simple and efficient way to immobilise acids on Wang resin. Acids **205** to **209** were loaded under these conditions on 5 mmol scales and cleavage of small portions of the resins indicated that loading efficiencies of greater than 90 % had been achieved in each case.



205

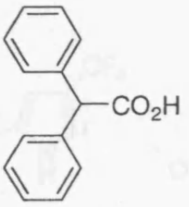


206



207

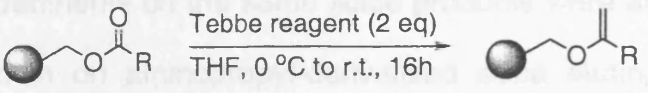
208



209

2.3.2 Tebbe Olefination

Initially four Tebbe olefinations were performed using the methodology of Barrett [44] on 0.3 mmol scales. Stoichiometries were calculated on the assumption that the acid loadings had proceeded quantitatively (**Scheme 67**).



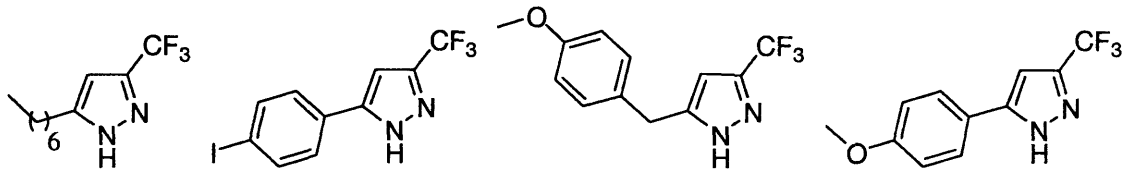
R derived from acids **205 to 209**

Scheme 67

When carrying out the reactions care was taken to repeat the procedures as described by Barrett [62] as closely as possible. On cleavage with 1 % trifluoroacetic acid in DCM the expected methyl ketones were formed by acid-catalysed hydrolysis

of the enol ether. The ketones were isolated by filtration and evaporation, purity was assessed by LCMS. Yields of 60 to 72 % were recorded, consistent with the results described by Barrett.

Subsequently the resin bound vinyl ethers were trifluoroacetylated (0.2 mmol scale) using the method described below, and the expected pyrazoles and pyrazole hydrates were released on treatment with hydrazine (0.2 mmol). After treatment with concentrated sulphuric acid pyrazoles **183** to **186** were isolated in reasonable yields.



183, 28 % **184**, 44 % **185**, 45 % **186**, 50 %

In the experiments described above the Tebbe reaction was carried out on a relatively small scale (0.3 mmol). Initially these products were isolated using mass-directed automated preparative HPLC, which is a preparative LCMS technique in which fraction collection is triggered by detection of the target mass. In subsequent repetition of the experiments on the same scale products were also isolated through solid phase extraction on aminopropyl-derivatised silica eluting sequentially with DCM, chloroform, diethyl ether, ethyl acetate and methanol with the pyrazole products isolated in the ethyl acetate wash. The yields above relate to isolation through the solid phase extraction.

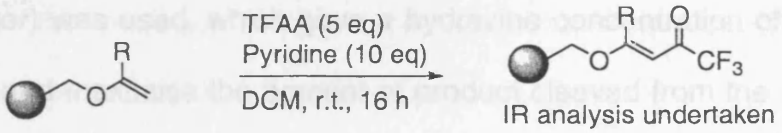
2.3.3 Tebbe Olefination Scale Up Issues

After the success of the reactions described above, the synthesis of pyrazole **183** was undertaken on a larger scale. In these experiments, the scale of the Tebbe reaction was increased to 2 mmol. At the end of the sequence it was found that the released pyrazole (1 mmol scale) was in a highly impure form (before and after dehydration with sulphuric acid). The proton NMR spectrum of the reaction product contained a very large complex envelope signal centred around 1.2 ppm. After dehydration the TLC showed a single spot that had eluted with the solvent front and a base line spot. Purifications were attempted *via* column chromatography and solid phase extraction on aminopropyl silica but isolation of the pyrazole was not possible. Cleavage of a portion of the resin-bound vinyl ether showed the presence of the same impurity in the proton NMR spectra. This impurity was not present when a portion of the acid was cleaved from the resin which demonstrated that the problem originated with the scaled up Tebbe reaction. This problem was overcome by slowing down the addition of the Tebbe reagent from over 5 minutes by hand to over 30 minutes by syringe pump and cooling the reaction to ≈ 3 °C during the addition and the rest of the reaction.

2.3.4 Perfluoroacetylation

The trifluoroacetylation of the resin-bound enones was carried out using a modified version of the solution phase perfluoroacetylation chemistry detailed previously, in which the number of equivalents of the trifluoroacetic anhydride and pyridine was increased to 5 and 10 equivalents from 1.2 and 0.33 equivalents respectively, in order to try to ensure complete conversion of the vinyl ether. The number of equivalents of pyridine was increased to twice that of the trifluoroacetic anhydride in

order to trap the trifluoroacetic acid made in the reaction efficiently, to minimise cleavage of the vinylogous ester from the resin. These conditions have not been optimised. The success of the reactions was ascertained by the appearance of the C=O stretch in the IR spectra of the resins. **Scheme 68** details the reaction conditions for the perfluoroacylation of the synthesis of the resin bound vinyl ethers.



IR analysis undertaken

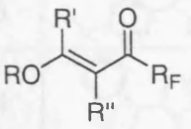
R derived from acids **203** to **207**

Scheme 68

As well as the trifluoroacylations one reaction was carried out using heptafluorobutyric anhydride and the resin bound vinylogous ester where R was derived from acid **204**.

2.3.5 Release of Pyrazole Products

In the literature solution phase pyrazole synthesis from vinylogous esters of type **207** with hydrazine tend to be carried out in methanolic or ethanolic solutions.



207

This presents a problem when transferring this type of chemistry to solid phase conditions as polystyrene resins do not swell well in either methanol or ethanol. In

fact, methanol is often employed in washing protocols to contract resins between washes with non-polar solvents with good swelling characteristics. This problem was circumvented by pre-swelling the resin in DCM for 30 minutes, draining off the excess solvent then adding the required amount of ethanol. This approach afforded reasonable swelling of the resin whist allowing the use of ethanolic conditions. In previous solution phase cyclisations, 1.2 equivalents of hydrazine (relative to the vinylogous ester) was used, which gave a hydrazine concentration of 2M. However, in order to try and maximise the amount of product cleaved from the resin, 10 times this amount (12 equivalents) was used for the resin bound cyclisations. These conditions are unoptimised.

Cleavage Results

Table 13 outlines the results of the cleavages. Pyrazoles **183** to **186** were synthesised on 0.3 mmol scales and purified using the SPE technique described above. Pyrazoles **187** and **188** were made on 1 mmol scales, **187** was purified by recrystallisation and **188** *via* flash chromatography.

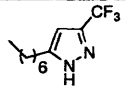
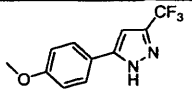
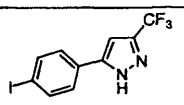
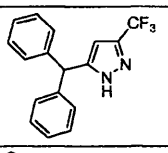
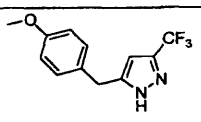
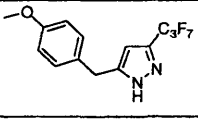
Pyrazole	Comp'd	Yield %	Pyrazole	Comp'd	Yield %
	**183**	28		**186**	50
	**184**	44		**187**	82
	**185**	53		**188**	45

Table 13

2.3.6 Overview of the Solid Phase Route

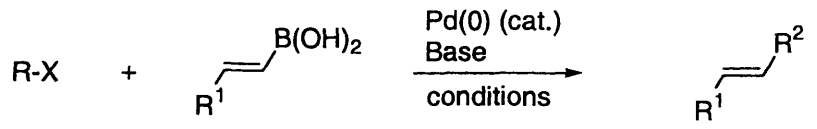
Six pyrazoles (**183** to **188**) were synthesised *via* the solid phase route described above in yields of 28 to 82 % based on the initial loading of the acids with an average of yield 49 %. The loading of the acids was accomplished easily *via* a standard DCC coupling procedure and cleavage of the acids revealed that loadings were in line with literature norms. After overcoming the scale associated problems of the Tebbe reactions the synthesis of resin bound α-substituted vinyl ethers became facile and a range of such compounds were generated. Cleavage of the vinyl ethers with a TFA/DCM mixture afforded methyl ketones in yields comparable with those reported by Barrett [44].

Perfluoroacylations of the resin bound vinyl ethers were carried out with a modified solution phase procedure and subsequent hydrazine induced cleavage released mixtures of the desired pyrazoles and pyrazole hydrates which afforded the desired compounds in reasonable (for SPS work) to excellent yields after dehydration.

After overcoming the scale associated problems of the solid phase Tebbe reactions the route provided a convenient way in which to synthesise a wide range of 4-substituted-3-perfluoroalkyl pyrazoles in reasonable purities.

2.4 The Suzuki Reaction

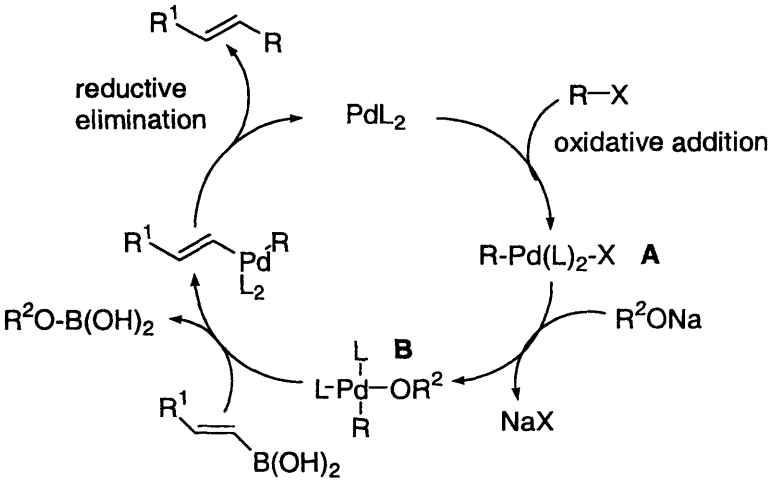
The Suzuki reaction is the cross coupling of alkenyl, aryl or allylic halides with an alkenylboron compound using a palladium (0) catalyst and a base such as sodium ethoxide or sodium hydroxide. (**Scheme 69**)



R = alkenyl, aryl or allylic
X = halogen

Scheme 69

The Suzuki Reaction Mechanism



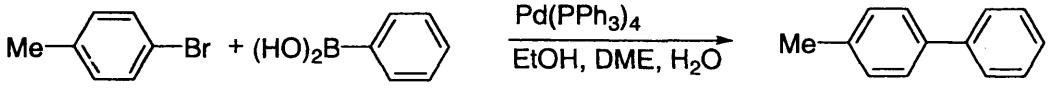
Scheme 70

The cycle begins with the oxidative addition of R-X to the 14e palladium (0) catalyst forming the 16e complex **A**. Displacement of the halide by the base then occurs to furnish the alkoxopalladium (II) complex **B**. Transmetalation then transfers the second organic fragment onto the palladium. Reductive elimination then expels the

cross coupling product from the cycle and regenerates the catalytic palladium(0) species.

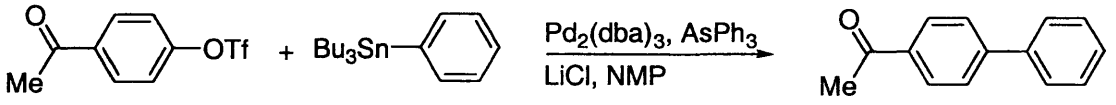
2.4.1 Microwave Mediated Suzuki Couplings

In 1988, Mills and co-workers first suggested that microwave irradiation could enhance Suzuki and Stille cross couplings [63] ; and subsequently much attention has been paid to this area. Schemes **71** and **72** [64] demonstrate the improvements in reaction rate that can be achieved by the use of microwave irradiation.



Microwave (55 W): 2.8 min
Conventional: 6 hrs

Scheme 71



Microwave (50 W): 2.8 min
Conventional: 70 hrs

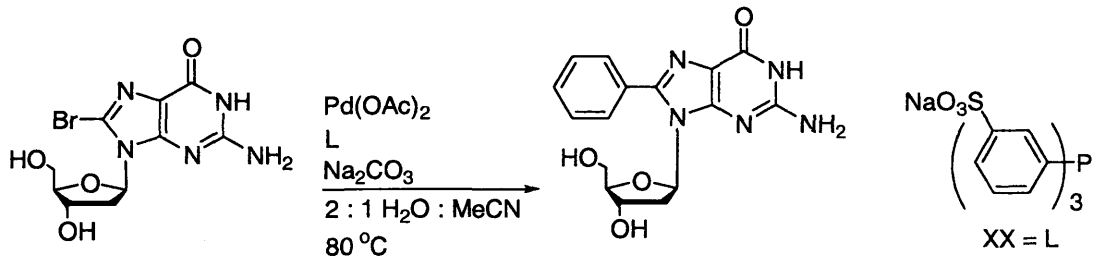
Scheme 72

A common theory as to why microwave mediated Suzuki (and other metal catalysed coupling) reactions are often quicker and higher yielding than the corresponding conventionally heated reactions cites the property of metals to strongly absorb microwave radiation. Due to this effect the catalytic metal species receive more energy than they would in a conventionally heated system at the same temperature and increases in the rate of catalyst turnover are seen, resulting in higher yields in shorter reaction times.

The Suzuki reaction is known to tolerate water and bases are often added as aqueous solutions. However an aqueous medium may not seem an obvious choice as a solvent for the Suzuki reaction due the low solubility of most organic reagents and 'traditional' phosphine ligands in water, and questions over the stability of the catalytic palladium species in such systems.

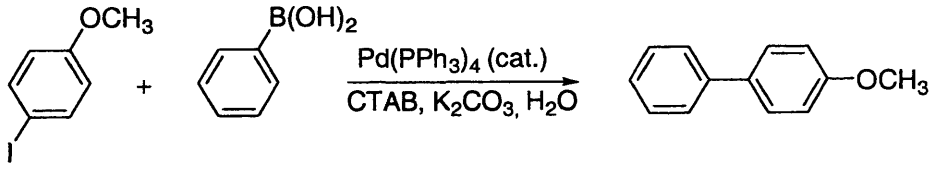
Despite these drawbacks the literature contains many examples of Suzuki reactions carried out in water or aqueous/organic mixtures under various conditions.

For example nucleoside **214** undergoes coupling with benzeneboronic acid using palladium acetate and a water soluble phosphine ligand in a 2:1 mixture of water and acetonitrile [65] (**scheme 73**).



Scheme 73

In cases where reagents are not readily soluble in water, phase transfer reagents or surfactants are often employed. **Scheme 74** [66] shows the use of CTAB, a surfactant, in this role.



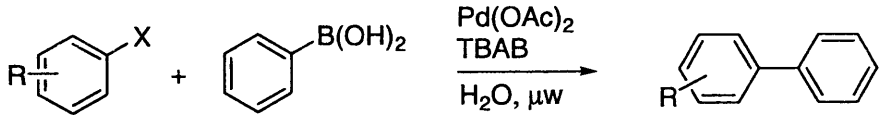
CTAB = Cetyltrimethylammonium bromide, $CH_3(CH_2)_{15}N(CH_3)_3^+Br^-$

Scheme 74

2.4.2 Synthetic plans

It was our plan to halogenate, at carbon-4, the unsubstituted 3-perfluoroalkyl pyrazoles that we had synthesised previously and then to use the products in Suzuki couplings reactions to provide us with 3-perfluoroalky pyrazoles with C4 substitution patterns complimentary to the C5 pattern which we were able access through the solid phase 'Tebbe' and solution phase 'Heck' routes.

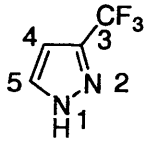
We planned to utilise the ligandless, aqueous microwave mediated Suzuki reaction protocol of Leadbeater [67, 68] (**Scheme 75**) to achieve this. Such methodology would be expected to have several synthetic advantages, including: 1) short reaction times; 2) high yields; 3) simplified workup procedures which would avoid the need for extraction of water soluble solvents e.g. DMF, and 4) a 'clean' crude proton NMR in which the aromatic region would not be crowded by signals from aromatic phosphine ligands.



Scheme 75

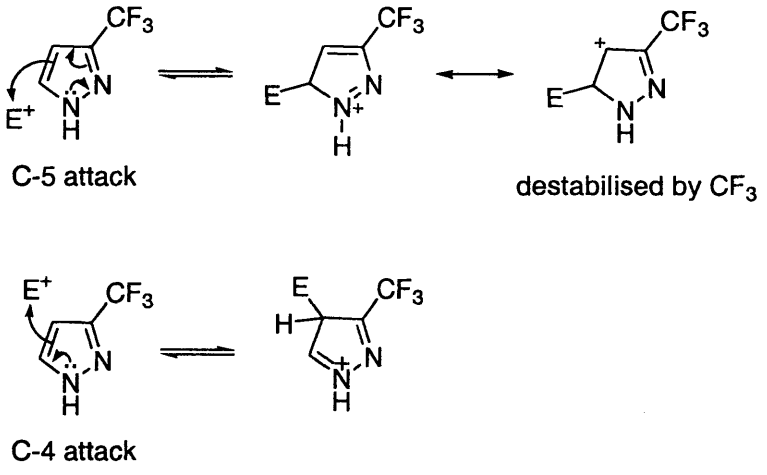
2.4.3 Reactivity and Regiochemistry of 3-Trifluoromethyl-*1H*-Pyrazole with Electrophiles

Pyrazole **34** only has two positions (4 and 5) available for attack by electrophiles due to the presence of the perfluoroalkyl group.



34

Electrophilic attack at position-5 is disfavoured as this places a positive charge on carbon-4 in the Wheland intermediates. This carbocation is destabilised by the proximity of the strongly electron withdrawing trifluoromethyl group. Substitution at position-4 is favoured as attack in this position does not generate the unfavourable carbocation intermediate. **Scheme 76** shows the Wheland intermediates for attack at these two positions.



Scheme 76

2.4.4 Iodine / Ceric Ammonium Nitrate iodinations

The first literature example of ceric ammonium nitrate mediated aromatic substitution iodinations were cited by Sugiyama [69] where he demonstrated that benzenoid aromatics can be iodinated using either iodine, or iodide salts and ceric ammonium nitrate as an *in situ* oxidant. In the presence of iodine, ceric ammonium nitrate

generates electrophilic iodo species [70] which are able to participate in electrophilic aromatic substitution reactions. The first examples of a ceric ammonium nitrate/iodine iodination of the pyrazole ring system were reported recently [71]. This system was shown to provide an efficient and mild way to iodinate pyrazoles to afford 4-iodopyrazoles even in the presence of electron withdrawing substituents. Unlike the original Sugiyama study, ceric ammonium nitrate was used in sub-stoichiometric amounts (0.5 equivalents in respect to the pyrazole).

We elected to use this methodology as the literature reports high yields and short reaction times and because CAN and iodine are relatively inexpensive.

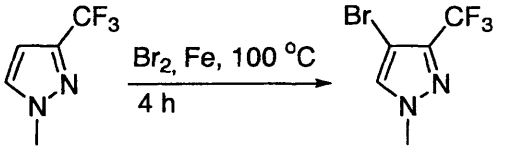
The initial attempt to iodinate 3-trifluoromethyl-1*H*-pyrazole (**34**) on a 0.5 mmol scale using 0.6 equivalents of iodine and 0.5 equivalents of ceric ammonium nitrate in anhydrous acetonitrile yielded a mixture of product and starting material in a 1:1 ratio by GCMS after 8 hours. Repeating the reaction at 80 °C in an Ace Tube™ yielded three iodo pyrazole products by GCMS after 16 hours. Two monoiodinated pyrazoles were detected along with a diiodinated pyrazole, in a ratio of approximately 1:7:2 respectively. Proton NMR confirmed that of the two monoiodo species, the major one was the C4 iodinated product. The major peak had a chemical shift of 7.78 ppm whereas the minor had one of 6.10 ppm. The assignment was made through comparison with the chemical shifts of the aromatic protons of 4-methyl-3-trifluoromethyl-*1H*-pyrazole (**35**) and 5-methyl-3-trifluoromethyl-*1H*-pyrazole (**36**) of 7.35 and 6.23 ppm respectively.

Reduction of the amount of iodine in the reaction from 0.6 to 0.5 equivalents coupled with a reduction of reaction temperature from 80 to 60 °C resulted in the formation of the 4-iodopyrazole exclusively (by GCMS) after 30 hours. At 16 hours, a mixture of starting material, C4 iodinated pyrazole and the diiodinated pyrazole was observed in

a ratio of 8:5:1 respectively. Failure to observe the C5 iodinated product at any point in the reaction indicated that the 5-iodo-pyrazole was consumed as rapidly as it was formed by a C4 iodination reaction. As none of the diiodinated product was seen after 30 hours it shows that it gradually decomposed to the C4 monoiodoinated pyrazole. By increasing the concentration of the reagents from 0.1 M to 0.2 M (in respect to the pyrazole) it was found that the selectivity of the reaction could be improved in favour of the C-4 product. The ratio of 4-iodopyrazole to starting material and other products was improved to 18:1:1 by lowering the reaction temperature to 60 °C. The pure **190** was obtained in 87 % yield after recrystalisation from hexane on a 15 mmol scale.

2.4.5 Bromination of 3-Trifluoromethyl-*1H*-Pyrazole

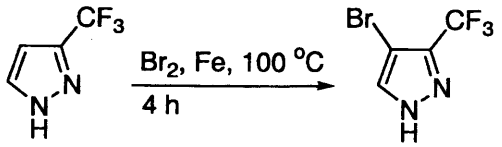
As a potential candidate for use in the Suzuki couplings the synthesis of 4-bromopyrazole **210** was undertaken. Using the procedure of Schlosser [72] who was able to selectively brominate 1-methyl-3-(trifluoromethyl)pyrazole (**211**) at the 4-position in 65 % yield using iron powder and neat bromine at 100 °C (Scheme **77**).



211

Scheme 77

This methodology when applied to pyrazole **34** afforded bromopyrazole **210** in 79 % yield after Kugelrohr distillation. (Scheme **78**).

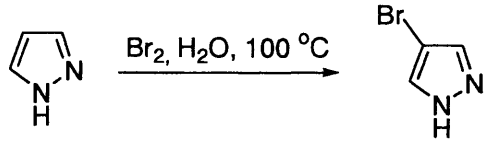


34 **210**

Scheme 78

The experimental data agreed with those reported by Fields [73] who was able to synthesise **210** from **34** using bromine in water in the presence of sodium acetate. Fields [67] methodology was not used as it was first found that the bromine and iron method provided a simple and efficient route to the target compound.

In the literature the bromination of pyrazole to afford 4-bromopyrazole using elemental bromine in boiling water has been reported by Ehlert [74] (**Scheme 79**).

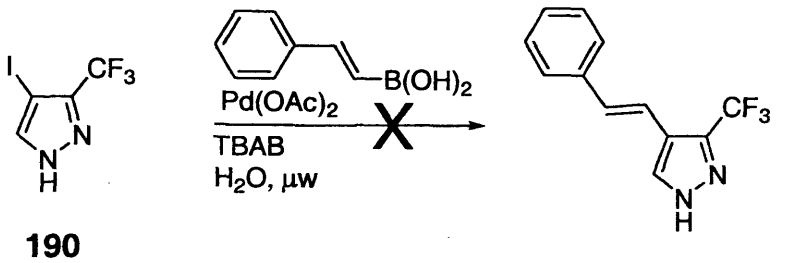


Scheme 79

The use of the harsher conditions reported by Schlosher and Fields to brominate the 3-trifluoromethyl pyrazoles **211** and **34** can be attributed to the presence of the powerful electron withdrawing trifluoromethyl group that deactivates the ring towards electrophilic attack.

2.4.6 Attempted Suzuki Couplings on Unprotected Pyrazoles 190 and 210

Utilising the conditions of Leadbeater [67, 68] we attempted to couple iodo pyrazole **190** with phenyl vinyl boronic acid to see if the coupling protocol would tolerate the unprotected pyrazole (**Scheme 80**)



190

Scheme 80

This reaction proved unsuccessful. The crude proton and fluorine NMR spectra showed a complex reaction mixture in which the product could not be detected. LRMS indicated the consumption of the starting material but provided no evidence of the product. The same reaction using bromide **210** was also carried out and similar results to those obtained for **190** were recorded.

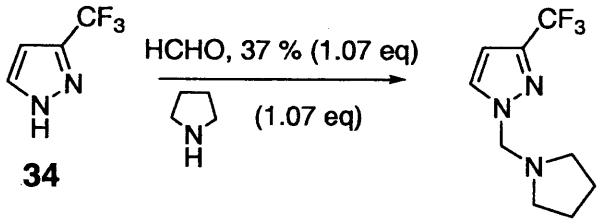
An assessment of the water/microwave stability of iodide **190** was carried out by running a blank reaction containing **190** and water. The experiment showed that no degradation of the substrate had occurred. This was expected as we had previously found it possible to aromatise hydrated pyrazoles by exposure to microwave irradiation without any degradation.

Protection of the pyrazole N-H bond was therefore attempted.

2.4.7 *N*-Protection of Halogenated Pyrazoles and Suzuki Couplings

An ideal protecting group is easy to install in the molecule, is stable to the ensuing reaction conditions and is easy to remove when required.

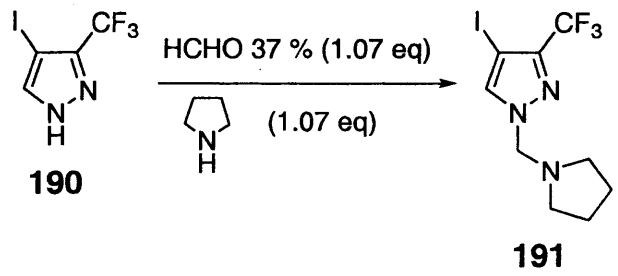
Our initial choice was the (pyrrolidino)methyl group which is facile to add to 3-trifluoromethyl-*1H*-pyrazole (**34**) using pyrrolidine and formaldehyde. The literature [29] quotes excellent yields for this reaction (94 %) after reduced pressure distillation of the crude product. (**Scheme 81**)



Scheme 81

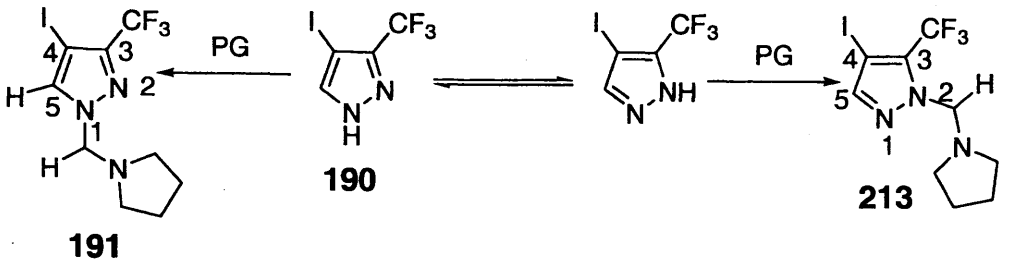
Repeating the reaction yielded **212** in a high yield (86 %) and the experimental data agreed with those published [29].

Under the same conditions the protection of the iodo pyrazole **190** proceeded smoothly. Distillation of the product was not attempted due to concerns over its volatility. However, it was found that the crude product crystallised well from the minimum amount of hot hexane to yield pure **191** (**Scheme 82**).



Scheme 82

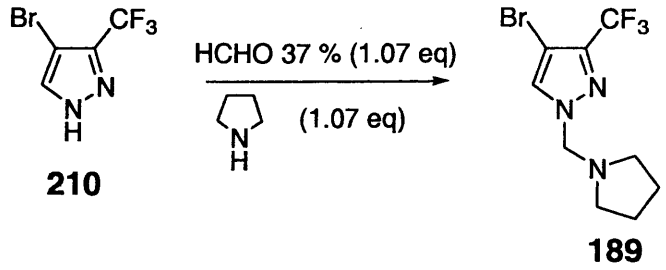
Due to the tautomeric equilibrium of 4-iodo-3(5)-trifluoromethyl-1*H*-pyrazole (**190**) (**Scheme 83**) it would be reasonable to expect that the reaction would produce a mixture of regioisomers **191** and **213**.



Scheme 83

This, however, was not the case and only one regioisomer was formed. The product was identified as **191** through 2D NMR (HMBC). Differentiation between **213** and **191** by HMBC was made possible by two features. Firstly, for isomer **213**, a $^{3}J_{C\text{-}H}$ coupling detectable *via* a cross peak between the methylene protons and the C3 quartet signal (split through $^{2}J_{C\text{-}F}$ coupling) would be expected whereas in isomer **191** the methylene protons and the $^{2}J_{C\text{-}F}$ split carbon signal are 4 bonds apart and should not show a cross peak. Secondly, in isomer **191** cross peaks between the methylene protons and C5 and between H5 and the methylene carbon (^{3}J) would be expected and these interactions would not be observable for **213**. Based on this reasoning the experimental data identified the product as **191**.

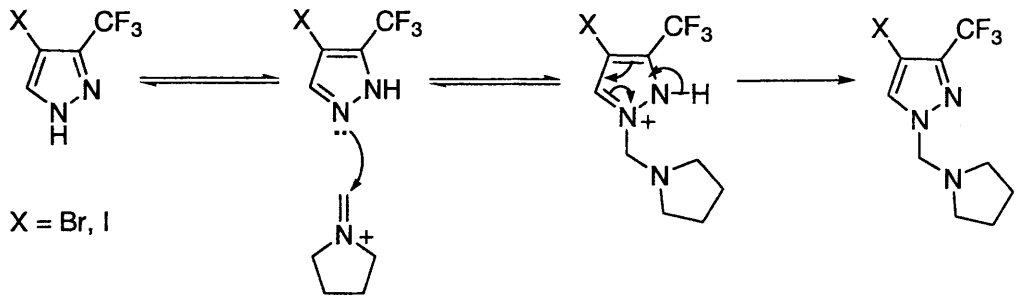
The protection of bromide **210** under the conditions used for the synthesis of **191** yielded **189** in high (89 %) yield after crystallisation from hexane (**Scheme 84**). Again only one regioisomer was produced and this was identified as **189** through 2D NMR (HMBC) using the same method as above.



Scheme 84

The reaction proceeds through the formation of an imminium ion between formaldehyde and pyrrolidine and subsequent nucleophillic attack on the imminium carbon by a nitrogen lone pair on the pyrazole. It is likely that the attack proceeds through an azomethine lone pair as this would preserve the pyrazole aromatic sextet. The experimental results indicate that the attack occurs from the nitrogen furthest from the CF_3 group. This is presumably because this position is less deactivated by the electron withdrawing effects of the CF_3 group than the adjacent position closer to the CF_3 group.

Substitution at N2 may also be impeded by steric interactions between the protecting group and the bulky CF_3 group that do not occur for substitution at N1. **Scheme 85** outlines this reaction mechanism. The CF_3 group is thought to be comparable in size to the *iso*propyl group (this was ascertained by the comparison of the molar volumes of a series of related compounds) [2].

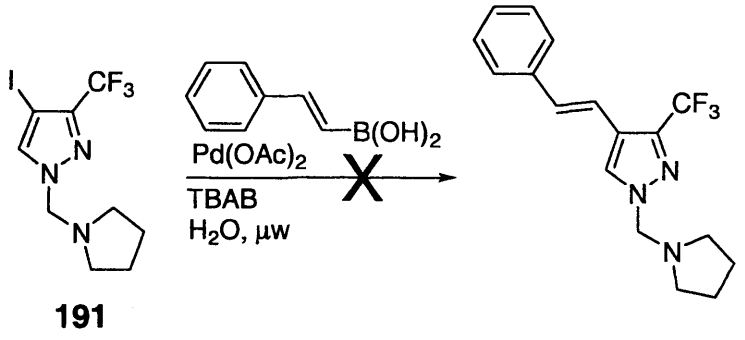


Scheme 85

The protecting group was facile to install and the final product required only a simple purification. Literature precedent suggests that deprotection should also be facile.

Attempted Suzuki Couplings for Protected Pyrazole 191

Using the same procedure as detailed above the Suzuki coupling of protected iodo pyrazole **191** and phenyl vinyl boronic acid was attempted (**Scheme 86**) .



191

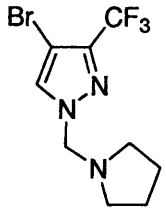
Scheme 86

The crude proton NMR spectrum showed a complex mixture of products and the fluorine NMR spectrum showed multiple fluorinated signals. The LRMS showed consumption of the substrate but no evidence for the formation of the product.

A second experiment in which the power input was reduced from 60 to 40 Watts was performed and similar results as described above were observed.

The stability of iodide **191** in water under the reaction conditions was then tested by running a blank reaction containing **191** and water alone. Under these conditions, iodide **191** proved to be stable. Due to these two results it was clear that factors other than the water and microwave irradiation were causing problems in the reaction. The same coupling using bromide **189** was also attempted which also proved unsuccessful. We therefore decided to investigate this reaction using an N-

substituted 4-iodo-3-trifluoromethyl pyrazole where the substituent was known to be tolerated in Suzuki couplings.

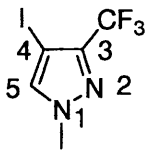


186

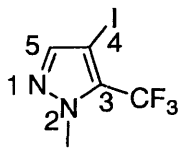
N-methyl of 190

While not a protecting group reaction, *N*-methylation of **190** would afford a product that would be useful in providing proof of concept for the Suzuki chemistry as the *N*-methyl group would be non labile and would not interfere with the Suzuki cycle.

Pyrazole **190** was reacted under phase transfer conditions with methyl iodide and TBAI in 50 % aqueous sodium hydroxide. TLC analysis showed complete consumption of **190** after 8 hours and two new spots were seen. The proton and fluorine NMR of the crude reaction showed that two regioisomers had been formed (**192** and **193**) in a 2 : 1 ratio. Further analysis was required to assign the product distribution



192



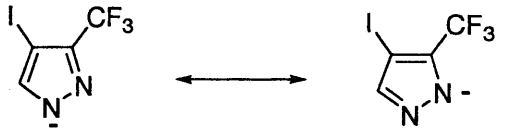
193

The two products were separated by flash chromatography and the regiochemistry of each isomer was elucidated using 2D NMR (HMBC). The less abundant isomer (top

running spot) (24 %) was identified as iodide **193**. The more abundant isomer (bottom running spot) (54 %) was found to be iodide **192**.

It was possible to differentiate between isomers **192** and **193** using HMBC as pyrazole **192** should show a cross peak between the methyl protons/carbon and C5/H5 respectively (^3J) whereas in **193** this cross peak would be absent as these nuclei would be 4 bonds away from each other. Isomer **193** should also shows cross peaks between the *N*-methyl protons and C3 that would not occur in **192**.

Once deprotonation of **190** has occurred then two resonance forms are possible (**Scheme 84**)



214 **215**

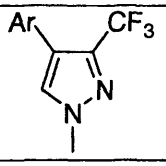
Scheme 87

The selectivity in favour of **192** suggests that resonance form **214** could be less stable than **215** and therefore more reactive. The main effect governing this is probably the additional inductive stabilisation that the negative charge receives when it is situated on the nitrogen closer to the trifluoromethyl group. The observed selectivity could also be influenced by negative steric interactions between the trifluoromethyl group and substitution at N2.

Using the same conditions as in previous attempts a coupling between **192** and phenyl vinyl boronic acid was attempted. However unlike in previous attempts, the crude NMR spectra were very clean (ignoring TBAB signals) and the desired product

was clearly present. However complete consumption of the starting material was not observed and a product to substrate (pyrazole) ratio of 4 : 1 was noted by NMR.

Pyrazole **194** was isolated by flash chromatography in 67 % yield based on the initial amount of starting material used. The reaction proved to be tolerant to a variety of different aryl boronic acids and **table 14** summarises the results of these experiments.



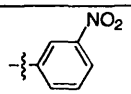
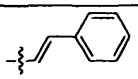
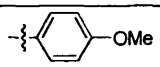
Comp'd	Aryl moiety	Yield (%)
194		67
195		55
196		67
197		80
198		74

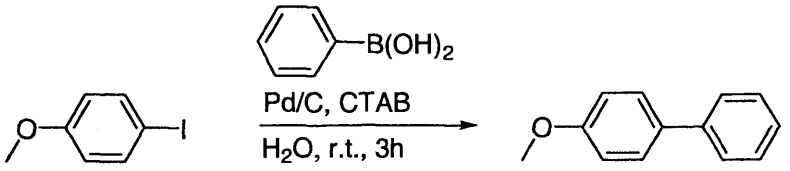
Table 14

These results were obtained using the unoptimised (for our system) conditions of Leadbeater and they show the suitability of the 4-iodo-3-trifluoromethyl moiety as a suitable candidate Suzuki coupling reactions under the chosen conditions.

Further work in this area would include identification of a true protecting group for the pyrazole moiety that was not detrimental to success of the reaction and optimisation of conditions for that system.

2.4.8 Ligand Free Suzuki Couplings

The catalytic species in the Suzuki reaction is zero valent palladium and zero valent palladium is not known to exist as a molecular species in solution in the absence of strong donor or acceptor ligands. These facts beg the question as to what is the catalytically active species in 'ligand free' systems. A probable answer to this that the active species is actually palladium metal precipitated from the reaction solution and that the reaction is occurring heterogeneously at the metal surface. Suzuki reactions carried out in the presence of metallic palladium (palladium black and palladium on charcoal) are known. For instance the coupling between 4-iodo-4-methoxy-benzene and phenylboronic acid in water/butanol with 2.5 mol % of palladium on charcaol afforded biaryl **216** after 3 hours reaction at room temperature in 98 % yield (**Scheme 88**) [75].



216

Scheme 88

The role of the ammonium salt is thought to be two fold in the reaction. Firstly it facilitates solvation of the organic substrates in the reaction medium. Secondly it is thought to enhance the rate of the coupling reaction by activating the boronic acid to reaction by formation $[ArB(OH)_3]^-[R_4N]^+$ [68] As the boron-carbon bond in the boronate species is weaker (more polarised) than in the neutral species the transmetalation proceeds at a faster rate.

3 Conclusions, Further Work and Comparisons

3.1 Overview of the Suzuki Route

The route starts from pyrazole **34** which we found simple to prepare in reasonably large scaled reactions (46 mmol scale) in high purity from the easily accessible vinylogous ester **31**. Iodination of **34** afforded a mixture of the 4- and 5-iodinated products **192** and **193** in 54 and 24 % yields respectively. Under ligand free, aqueous, microwave mediated conditions the coupling of **192** with a variety of aryl boronic acids afforded products in yields of 55 to 80 % with an average yield of 69 %. Overall the route exhibited an average efficiency of 26 % from starting pyrazole **34**. Of the five pyrazoles synthesised by this route two were isolated as solids one of which failed CHN analysis (but was clean by NMR and GC). The three oils that were isolated provided clean NMR spectra and gave GC purities of 100, 100 and 96 %.

Further work on this route would involve finding an easily removable protecting group that was compatible with the Suzuki reaction. Variation of the perfluoroalkyl group and testing to see if the route would tolerate the use 4-iodo-5-substituted pyrazoles allowing access to 4,5-substituted systems. A further strand of research would involve exposure of the iodo-pyrazole **193** to the Suzuki coupling conditions which would yield alternate methodology for the synthesis of 5-substituted-3-perfluoroalkyl pyrazoles.

3.2 Comparison of Routes to 5-Substituted-3-Perfluoroalky Pyrazoles

Position 5 Variation

In terms of the ultimate levels of variation that could be built into position 4 of the pyrazole ring the SPS route is at an advantage as it derives these from the ubiquitious acid pool whereas the Heck reaction based route relies on less common phenolic compounds. The SPS route has a second and distinct advantage in that the Heck based route could only ever include moieties which would undergo Heck reactions i.e. aryl, herteroaryl or vinylic groups. In our studies to date the solid phase route has proved tolerant of aryl, benzylic and heteroaryl moieties.

The speed in which compounds can be generated by both routes is about the same; each route is four steps long, including the triflate generation and acid loading. As expected the solid phase intermediates were much simpler to work up than the solution phase intermediates and if larger numbers of reactions were being carried out significant time savings would be offered by use of the solid phase methodology.

Compared to the solution phase methodology the solid phase methodology is significantly more expensive. The reason for this is is the costs of the solid support (£321 for 100g of 100-200 mesh 0.5-1.3 mmol/g resin (Novabiochem)) and the Tebbe reagent (£105 for 25 ml of a 0.5 M solution (Aldrich)).

A direct comparison of product purity *via* elemental analysis between the two routes is not possible as three of the six pyrazoles from the solid phase route were isolated as oils and were not submitted for elemental analysis and in the solution phase route all sixteen final compounds were isolated as solids and were all submitted for elemental analysis. However the oils isolated from the SPS route had very clean NMR spectra and GC purities of 94, 100 and 100 % were recorded. Of the other

three SPS compounds two were found to be elementally pure (however for the compound that failed CHN clean NMR spectra and a GC purity of 100 % were recorded). In the solution phase route all compounds were isolated as solids and of these sixteen twelve were elementally pure, this 75 % 'success rate' compares to 67 % for the solids isolated in the solid phase route.

The overall average yields for both of the routes are very similar at 49 % for the solid phase route and 51 % for the solution phase route. The 49 % average yield can be considered very good for a solid phase route.

Overall the solution phase route was able to supply 4-substituted 3-perfluoroalkyl pyrazoles in reasonable overall yield and with good purity profiles. The SPS route was able to supply the same type of compounds in the same types of yields but in a slightly lower purities.

The SPS route would prove useful for providing a large number of compounds quickly for a purpose in which elemental purity was not required whereas the solution phase route would prove more suitable for providing smaller numbers of compounds in highly pure forms.

4 Experimental

General Procedures

NMR spectra were recorded on a Bruker ARX 250 (^{1}H, 250.13 MHz; ^{13}C, 62.90 MHz; ^{19}F, 235.36 MHz) spectrometer, a Bruker DPX 300 (^{1}H, 300.13 MHz; ^{13}C, 75.47 MHz; ^{19}F, 282.40 MHz) spectrometer and a Bruker DRX 400 (^{1}H, 400.13 MHz; ^{13}C, 100.62 MHz; ^{19}F, 376.45 MHz) spectrometer. Chemical shifts for ^{1}H and ^{13}C NMR spectra were recorded using deuterated solvent as the lock and residual solvent as the internal standard. ^{19}F NMR spectra were referenced to fluorotrichloromethane as the external standard. They are reported consecutively as chemical shift (δ_H, δ_C, or δ_F), relative integral, multiplicity (s = singlet, d = doublet, dd = double doublet, dt = double triplet, t = triplet, q = quadruplet, m = multiplet, env. = envelope and br = broad), coupling constant (J / Hz) and assignment.

Electron Impact (EI) mass spectra were recorded on Kratos Concept 1H. Chemical Ionization (CI) mass spectra were recorded on a Kratos Concept 1H using ammonia as the reagent gas. Fast Atom Bombardment (FAB) mass spectra were recorded on a Kratos Concept 1H using xenon and *m*-nitrobenzyl alcohol as the matrix. Electrospray (ES) mass spectra were recorded on a Micromass Quattro LC spectrometer. High Resolution Mass Spectrometry (HRMS) was measured on a Kratos Concept 1H spectrometer using peak matching to stable reference peaks, depending on the technique used.

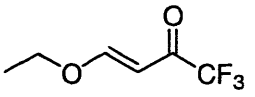
Flash column chromatography was performed using silica gel (Fluorochem, Silica gel 60, 40-63μ) or using a biotage flash chromatography system. Column fractions were collected and monitored by Thin Layer Chromatography (TLC) and carried out on precoated aluminium backed silica gel plates supplied by E. Merck, A.G. Darmstadt,

Germany (Silica gel 60 F_{254}, thickness 0.2 mm) or on precoated glass plates supplied by Merck (Silica gel 60 F_{254}). Solid phase extractions performed using 6 ml/1g DSC-NH_2 cartridges supplied by Supelco. The compounds were visualized using UV light, potassium permanganate, *p*-anisaldehyde, 2,4-dinitrophenylhydrazine (DNP) or phosphomolybdic acid (PMA).

Microwave experiments were carried on a CEM Discovery (variable power, max. 300W). Infra-red (IR) spectra were obtained on a Perkin Elmer 1600 series FTIR in the region 4000-500 cm^{-1}. Light petroleum refers to the fraction boiling between 40-60 ºC. Tetrahydrofuran (THF) was dried by refluxing with benzophenone over sodium wire under an atmosphere of nitrogen, and was distilled and collected by syringe as required. Dichloromethane, toluene and acetonitrile were dried by refluxing with calcium hydride. Dimethylformamide was distilled from barium oxide and was stored under an argon atmosphere. All chemicals (and other solvents) were used as received without any further purification. The Tebbe reagent was supplied by Aldrich Chemical Co. as a 0.5 M solution in toluene and the Wang resin (100-200 mesh, 2 % DVB, 0.81 mmol g^{-1}) was supplied by Novabiochem.

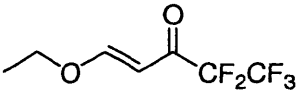
Aryl triflates were prepared by the method of Dolle [75] and acids were immobilised on Wang resin using the method of Barrett [62] substituting DCC for DIC.

4-Ethoxy-1,1,1-trifluoro-but-3-en-2-one (31)



Trifluoroacetic anhydride (9.93 ml, 70 mmol) was added to a solution of ethyl vinyl ether (4.80 ml, 50 mmol) and pyridine (1.27 ml, 16.5 mmol) in DCM (45 ml) under an atmosphere of nitrogen. The reaction was stirred overnight, washed with water (3 × 50 ml) dried ($MgSO_4$) and concentrated *in vacuo* leaving the crude product as a yellow oil which was purified by Kugelrohr distillation to afford **31** (5.98 g, 71 %) as a colourless oil; bp 55 °C/10 mmHg (Kugelrohr); GC 100%; ν_{max}(film)/cm^{-1} 2992, 1711 (C=O), 1588, 1317 (CF); δ_H (250 MHz, $CDCl_3$) 1.36 (3H, t, $^3J_{H-H}$ 7.0, CH_3), 4.02 (2H, t, $^3J_{H-H}$ 7.0, CH_2), 5.82 (1H, d, $^3J_{H-H}$ 12.5, CH=CO), 7.87 (1H, d, $^3J_{H-H}$ 12.5, OCH); δ_F (335 MHz, $CDCl_3$) -78.1 (s); *m/z* (CI) 186 ($[M+NH_4]^+$, 100 %) 99 (72), 52 (13), 44(14). The data were in agreement with those previously reported by Hojo [17]

4-Ethoxy-4,4,5,5,5-pentafluoro-pent-1-en-3-one (59)

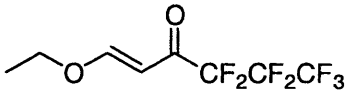


Pentafluoropropionic anhydride (5.24 ml, 26.9 mmol) was added to a solution of ethyl vinyl ether (1.84 ml, 19.2 ml) and pyridine (0.51 ml, 6.33 mmol) in DCM (9 ml) under an atmosphere of nitrogen. The reaction was stirred overnight, washed with water (3 × 15 ml) dried ($MgSO_4$) and concentrated *in vacuo* leaving the crude product as a yellow oil which was purified by Kugelrohr distillation to afford **59** (2.06 g, 49 %) as a colourless oil; bp 67 °C/6mmHg (Kugelrohr); ν_{max}(solid)/cm^{-1} 1703 (C=O), 1586, 1311, 1213; δ_H (250 MHz, $CDCl_3$) 8.09 (1H, d, $^3J_{H-H}$ 12.2, OCH), 6.13 (1H, d, $^3J_{H-H}$

12.2, CH), 4.26 (2H, q, $^3J_{H-H}$ 6.7, CH_2), 1.52 (3H, t, $^3J_{H-H}$ 6.74, CH_3); δ_F (335 MHz, $CDCl_3$) -83.7 (3F, s) -125.1 (2F, s) (s); *m/z* (EI) 219 ($[M+H]^+$, 6 %), 218 (M^+, 74), 101 (39), 69 (100).

The data were in agreement with those previously reported by Gerus [22]

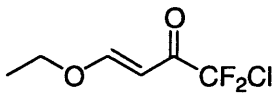
1-Ethoxy-4,4,5,5,6,6,6-heptafluoro-hex-1-en-3-one (128)



Heptafluorobutyric anhydride (3.52 ml, 14 .3 mmol) was added to a solution of ethyl vinyl ether (0.54 ml, 10 mmol) and pyridine (0.27 ml, 3.3 mmol) in DCM (5 ml) under an atmosphere of nitrogen. The reaction was stirred overnight, washed with water (3 × 5 ml) dried ($MgSO_4$) and concentrated *in vacuo* to leave **128** as a pale yellow oil (requiring no purification) (1.71 g, 64 %); ν_{max}(solid)/cm^{-1} 1704 (C=O), 1589, 1210; δ_H (250 MHz, $CDCl_3$) 7.80 (1H, d, $^3J_{H-H}$ 11.8, OCH), 5.83 (1H, d, $^3J_{H-H}$ 11.8, CHC=O), 3.98 (2H, q, $^3J_{H-H}$ 7.0, CH_2), 1.23 (3H, t, $^3J_{H-H}$ 7.0, CH_3); δ_F (335 MHz, $CDCl_3$) -81.8 (3F, s) -122.9 (2F, s), -127.8 (2F, s); *m/z* (EI) 269 ($[M+H]^+$, 6 %), 268 ($[M]^+$, 56), 69 (100).

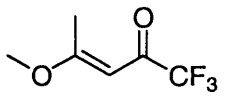
The data were in agreement with those previously reported by Tietze [50]

1-Chloro-4-ethoxy-1,1-difluoro-but-3-en-2-one (68)



Chlorodifluoroacetic anhydride (0.98 ml, 5.6 mmol) was added to a solution of ethyl vinyl ether (0.37 ml, 4.0 mmol) and pyridine (0.11 ml, 1.32 mmol) in DCM (2.5 ml) under an atmosphere of nitrogen. The reaction was stirred overnight, washed with water (3 × 5 ml) dried ($MgSO_4$) and concentrated *in vacuo* leaving the crude product as a pale yellow oil which was purified by Kugelrohr distillation to afford **129** as a clear oil (0.361 g, 49 %), bp 57 °C / 18 mmHg (Kugelrohr); ν_{max}(solid)/cm^{-1} 1678 (C=O), 1624, 1219, 1137; δ_H (250 MHz, $CDCl_3$) 7.86 (1H, d, $^3J_{H-H}$ 12.5, OCH), 5.84 (1H, d, $^3J_{H-H}$ 12.5, CH), 4.08 (2H, q, $^3J_{H-H}$ 7.0, CH_2), 1.37 (3H, t, $^3J_{H-H}$ 7.0, CH_3); δ_F (335 MHz, $CDCl_3$) -67.4 (s); *m/z* (EI) 186 ($[M+H]^+$, 11 %), 101 (48), 89 (56) 85 (100). The data were in agreement with those previously reported by Tietze [50] and Gerus [26]

1,1,1-Trifluoro-4-methoxy-pent-3-en-2-one (32)

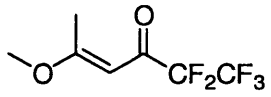


Trifluoroacetic anhydride (2.0 ml, 14 mmol) was added to a solution of 2-methoxy propene (0.96 ml, 10 mmol) and pyridine (0.27 ml, 3.3 mmol) in DCM (4.5 ml) under an atmosphere of nitrogen. The reaction was stirred overnight, washed with water (3 × 10 ml) dried ($MgSO_4$) and concentrated *in vacuo* leaving the crude product as a pale yellow oil which was purified by Kugelrohr distillation to yield **32** as a clear oil (1.46g, 87 %); bp 65 °C/18 mmHg (Kugelrohr); ν_{max}(film)/cm^{-1} 1703 (C=O), 1586,

1311, 1193; δ_H (250 MHz, $CDCl_3$) 5.64 (1H, s CH), 3.76 (3H, s, OCH_3), 2.36 (3H, s, CH_3); δ_F (335 MHz, $CDCl_3$) -78.6 (s); *m/z* (EI) 169 ($[M+H]^+$, 1 %), 168 ($[M]^+$, 7%), 99 (100).

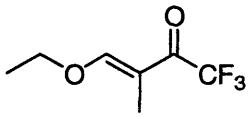
The data were in agreement with those previously reported by Colla [20] and Hojo [52]

1,1,1,2,2-Pentafluoro-5-methoxy-hex-4-en-3-one (129)



Pentafluoropropionic anhydride (5.24 ml, 26.9 mmol) was added to a solution of 2-methoxypropene (1.84 ml, 19.2 mmol) and pyridine (0.51 ml, 6.33 mmol) in DCM (12 ml) under an atmosphere of nitrogen. The reaction was stirred overnight, washed with water (3 x 20 ml), dried ($MgSO_4$) and concentrated *in vacuo* leaving the crude product as a pale yellow oil which was purified by Kugelrohr distillation to afford **129** as a clear oil (2.64 g, 63 %); bp 65 °C/6 mmHg (Kugelrohr); GC 100 %; ν_{max}(solid)/cm^{-1} 1703 (C=O), 1586, 1311, 1192, 996; δ_H (250 MHz, $CDCl_3$) 5.81 (1H, s, CH), 3.84 (3H, s, OCH_3), 2.42 (3H, s, CH_3); δ_C (63 MHz, $CDCl_3$) 191.5, 181.0 (t, $^2J_{C-F}$ 23.9), 126.0-103.5 (env, C_2F_5), 92.5, 56.7, 21.2; δ_F (335 MHz, $CDCl_3$) -83.1 (3F, s), -124.3 (2F, s); [HRMS (EI, M^+) Found 218.0366. Calc. for $C_7H_7F_5O_2$ 218.0366]; *m/z* (EI) 219 ($[M+H]^+$, 2 %), 218 ($[M]^+$, 14), 199 (48), 99 (78), 71 (100).

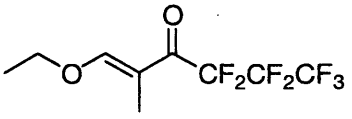
4-Ethoxy-1,1,1-trifluoro-3-methyl-but-3-en-2-one (33)



Trifluoroacetic anhydride (9.89 ml, 70 mmol) was added to a solution of 1-ethoxypropene(5.53 ml, 50 mmol) and pyridine (1.33 ml, 16.5 mmol) in DCM (22.5 ml) under an atmosphere of nitrogen. The reaction was stirred overnight, washed with water (3 × 50 ml) dried ($MgSO_4$) and concentrated *in vacuo* leaving the crude product as a pale yellow oil which was purified by Kugelrohr distillation to afford **33** as a clear oil; (7.47g 82 %); bp 75 °C/6mmHg (Kugelrohr); GC 100 %; ν_{max}(film)/cm^{-1} 1681 (C=O), 1624, 1214, 1133; δ_H (250 MHz, $CDCl_3$) 7.73 (1H, s, CH), 4.44 (2H, q, $^3J_{H-H}$ 7.1 OCH_2), 1.95 (3H, s, CH_3), 1.56 (3H, t, $^3J_{H-H}$ 7.12, CH_3); δ_C (63 MHz, $CDCl_3$) 180.9 (q, $^2J_{C-F}$ 33.6), 165.0 (q, $^3J_{C-F}$ 4.6), 121.9 (q, $^1J_{C-F}$ 290.9), 112.3, 72.0, 15.5, 8.3; δ_F (335 MHz, $CDCl_3$) -69.9 (s); [HRMS (EI, M) Found 182.0554. Calc. for $C_7H_9F_7O_2$ 182.0555]; *m/z* (EI) 183 ($[M+H]^+$, 3 %), 182 (M^+, 18), 113 (58), 85 (100).

The data were in agreement with those previously reported by Hojo [52]

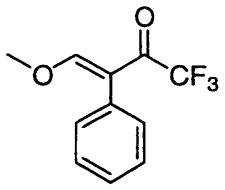
1-Ethoxy-4,4,5,5,6,6,6-heptafluoro-2-methyl-hex-1-en-3-one (130)



Heptafluorobutyric anhydride (0.70 ml, 2.8 mmol) was added to a solution of 1-ethoxypropene (0.22 ml, 2.0 mmol) and pyridine (0.05 ml, 0.66 mmol) in DCM under an atmosphere of nitrogen. The reaction was stirred overnight, washed with water (3 × 10 ml) dried ($MgSO_4$) and concentrated *in vacuo* leaving the crude product as a

pale yellow oil which which was purified by Kugelrohr distillation to afford **130** as a clear oil; (1.62 g, 74 %); bp 90 °C/7 mmHg (Kugelrohr) GC 100 %; ν_{max}(film)/cm^{-1}; 1683 (C=O), 1622, 1203, 1117; δ_H (250 MHz, $CDCl_3$) 7.66 (1H, s, CH), 4.23 (2H, q, $^3J_{H-H}$ 7.1 OCH_2), 1.82 (3H, s, CH_3), 1.40 (3H, t, $^3J_{H-H}$ 7.1, CH_3); δC (75 MHz, $CDCl_3$) 181.7 (t, $^2J_{C-F}$ 24.7), 165.3, 123.3-101.8 (env), 115.2, 71.6, 15.0, 8.24; δ_F (335 MHz, $CDCl_3$) -78.7 (3F, s), -120.1 (2F, s), -127.0 (2F, s); [HRMS (EI, M) Found 282.0490. Calc. for $C_9H_9F_7O_2$ 282.0491]; *m/z* (EI) 292 ([M+H]$^+$, 3 %), 282 (M$^+$, 8), 113 (63), 85 (100).

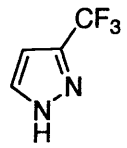
1,1,1-Trifluoro-4-methoxy-3-phenyl-but-3-en-2-one (131)



Trifluoroacetic anhydride (1.0 ml, 7 mmol) was added to a solution of β-methoxystyrene (0.670 g, 5.0 mmol) and pyridine (0.13 ml, 1.65 mmol) in DCM (2.5 ml) under an atmosphere of nitrogen. The reaction was stirred overnight, washed with water (3 x 10 ml) dried ($MgSO_4$) and concentrated *in vacuo* leaving the crude product as a pale yellow oil which was purified by Kugelrohr distillation to afford **131** as a clear oil (0.62 g, 54 %); bp 70 °C/8 mmHg (Kugelrohr); ν_{max}(film)/cm^{-1} 3061, 2950, 1683 (C=O), 1615, 1269, 1134; δ_H (250 MHz, $CDCl_3$) 7.75 (1H, s, CH), 7.36-7.18 (5H, m, ArH), 3.82 (3H, s, CH_3); δ_F (335 MHz, $CDCl_3$) -69.9 (s); *m/z* (EI) 231 ([M+H]$^+$, 8 %), 230 ([M]$^+$, 51%), 161 (63), 118 (100).

The data were in agreement with those previously reoprted by Schlosser[51]

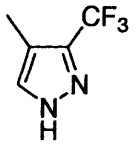
3(5)-Trifluoromethyl-*1H*- pyrazole (34)



Hydrazine monohydrate (2.7 ml, 55.2 mmol) was added to a stirred solution of **31** (7.73 g, 46 mmol) in ethanol (46 ml). The reaction was stirred for 18 hours at room temperature and then concentrated *in vacuo.* The residue was taken up in concentrated sulfuric acid (25 ml) and stirred for 15 minutes. The acidic mixture was carefully diluted with water (50 ml) then allowed to cool to room temperature and extracted with DCM (3 × 50 ml). The combined organic extracts were washed with brine (50 ml), then water (50 ml) and dried ($MgSO_4$). The solvent was removed *in vacuo* to leave a white solid which recrystallised from 40-60 petroleum to afford **34** (4.46 g, 71 %) as white needles; mp 47-48 °C, (lit.[29] 46-48 °C); GC 100 %; ν_{max}(solid)/cm^{-1} 2980, 1502, 1388, 1116, 1088; δ_H (250 MHz, $CDCl_3$) 7.58 (1H, s), 6.52 (1H s), δ_C (63 MHz, $CDCl_3$) 142.8 (q $^2J_{C-F}$ 38.1, 130.7, 122.0 (q $^1J_{C-F}$ 268.2), 104.3; δ_F (335 MHz, $CDCl_3$) -62.2 (s); *m/z* (CI) 137 ($[M+H]^+$, 8 %), 136 (100), 117 (75), 88 (30).

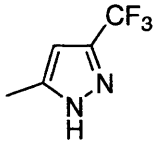
The data were in agreement with those previously reported by Xu [29]

5(3)-Methyl-3(5)-trifluoromethylpyrazole (35)



Pyrazole **35** was made in the same way as **34** from **33** (1.82 g, 10.0 mmol) and hydrazine monohydrate (0.60 ml, 12.0 mmol) in ethanol (10 ml). After stirring overnight the solvent was removed *in vacuo* and the residue taken up in concentrated sulfuric acid (5.0 ml) and stirred for 30 minutes. After the usual work up the crude product was recrystallised from light petroleum to afford **35** (1.14 g, 93 %) as white crystals; mp 46-47 °C (lit.[3] 48 °C); ν_{max}(solid)/cm^{-1} 3172, 2942, 1493, 1280, 1059; δ_H (250 MHz, $CDCl_3$) 7.38, (1H, s), 2.18 (3H, s); δ_C (63 MHz, $CDCl_3$) 140.5 (q, $^2J_{C\text{-}F}$ 36.0), 130.1, 122.6 (q, $^1J_{C\text{-}F}$ 268.8) 115.2, 8.24, 105.4; δ_F (335 MHz, $CDCl_3$) -60.8 (s) ; *m/z* (EI) 151 ([M+H]$^+$, 2 %), 150 (M$^+$, 48), 149 (100), 131 (24), 81 (45).
The data were in agreement with those reported by Braibante[3]

5-Methyl-3-trifluoromethyl pyrazole (36)

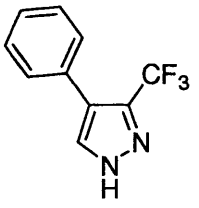


Pyrazole **36** was made in the same way as **34** from **32** (3.0 g, 17.7 mmol) and hydrazine monohydrate (1.04 ml, 21.25 mmol) in ethanol (18 ml). After stirring overnight the solvent was removed *in vacuo* and the residue taken up in concentrated sulfuric acid (9 ml) and stirred for 30 minutes. After working up the

crude product was recrystallised from light petroleum to afford **36** (2.28 g, 86 %) as a short white needles; mp 102-104°C, (lit. 102-104 °C); GC 100 %; δ_H (250 MHz, $CDCl_3$) 6.23 (1H, s), 2.26 (3H, s); δ_C (63 MHz, $CDCl_3$) 143.8, (q, $^2J_{C-F}$ 37.6) 141.8, 126.1 (q, $^1J_{C-F}$ 268.1), 103.3, 10.8, δ_F (335 MHz, $CDCl_3$) -62.2 (s); *m/z* (EI) 151 ($[M+H]^+$, 2 %) 150 ($[M]^+$, 48 %), 149 (100), 131 (23).

The data were in agrement with those previously reported by Braibante[3]

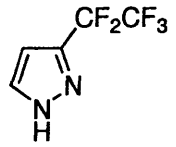
4-Phenyl-3(5)trifluoromethyl-*1H*-pyrazole (132)



Pyrazole **132** was made in the same way as **34** from **131** (3.0 g, 2.5 mmol) and hydrazine monohydrate (0.15 ml, 3 mmol) in ethanol (2.5 ml). After stirring overnight the solvent was removed *in vacuo* and the residue taken up in concentrated sulfuric acid (2.5 ml) and stirred for 30 minutes. After the usual work up the crude product was recrystallised from light petroleum to afford **132** (0.45 g, 84 %) as a white solid; mp 93-95°C (lit.[5] 93-94 °C); (Found: C, 55.8; H, 3.4; N, 13.0; $C_6H_3F_7N_2$ requires: C, 55.6; H, 3.3; N, 13.2 %); ν_{max}(solid)/cm^{-1} 3164, 2958, 1478, 1179, 1108; δ_H (250 MHz, $CDCl_3$) 7.79, (1H, s, H-5), 7.49-7.35, (5H, m, ArH); δ_F (335 MHz, $CDCl_3$) -59.1 (s); *m/z* (EI) 237 ($[M+H]^+$, 2 %) 236 ($[M]^+$, 17 %), 117 (100), 69 (25).

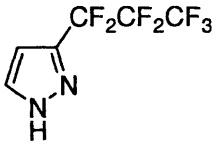
The data were in agreement with those reported by Hu[5]

3(5)-Pentafluoroethyl-*1H*-pyrazole (117)



Pyrazole **117** was made in the same way as **34** from **59** (1.09 g, 5.0 mmol) and hydrazine monohydrate (0.30 ml, 6.0 mmol) in ethanol (5 ml). After stirring overnight the solvent was removed *in vacuo* and the residue taken up in concentrated sulfuric acid (2.5 ml) and stirred for 30 minutes. After the usual work up, the crude product was recrystallised from light petroleum to afford **117** (0.73 g, 79 %) as white needles; mp 34-35 °C (Found: C, 32.15; H, 1.51; N, 14.87; $C_5H_3F_5N_2$ requires: C, 32.37; H, 1.62; N, 15.05 %); ν_{max}(solid)/cm^{-1} 3163, 2991, 2994, 1199, 1127; δ_H (250 MHz, $CDCl_3$) 7.73 (1H, s), 6.67 (1H, s); δ_C (63 MHz, $CDCl_3$) 141.1 (t, $^2J_{C\text{-}F}$ 27.9), 130.6, 121.8-107.6 (env C_2F_5), 105.4; δ_F (335 MHz, $CDCl_3$) -85.3 (3F, s) -113.7 (2F, s); *m/z* (EI) 187 ([M+H]$^+$, 3 %), 186 (M$^+$, 42), 117 (100).

3(5)-Heptafluorobutyl-*1H*- pyrazole (118)

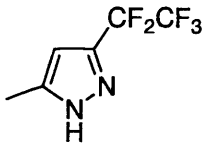


Pyrazole **118** was made in the same way as **34** from **128** (2.68 g, 10 mmol) and hydrazine monohydrate (0.60 ml, 12 mmol) in ethanol (10 ml). After stirring overnight the solvent was removed *in vacuo* and the residue taken up in concentrated sulfuric acid (5.0 ml) and stirred for 30 minutes. After the work up the crude product was

recrystallised from light petroleum to afford **118** (1.63 g, 69 %) as white crystals; mp 71-72 °C (lit. 71-73 °C); (Found: C, 30.3; H, 1.2; N, 11.7; $C_6H_3F_7N_2$ requires: C, 30.5; H, 1.3; N, 11.9 %); GC 100 %; ν_{max}(solid)/cm^{-1} 2942, 1349, 1179, 1111; δ_H (250 MHz, $CDCl_3$) 7.75 (1H, s), 6.70 (1H, s); δ_F (235 MHz, $CDCl_3$) -80.7 (3F, s), -111.3 (2F, s), -127.6 (2F, s); *m/z* (EI) 237 ([M+H]$^+$, 2 %), 236 ([M]$^+$, 19 %), 117 (100).

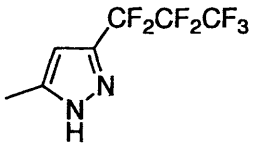
The data were in agreement with those reported by Hu [11]

5(3)-Methyl-3(5)-pentafluoroethyl-*1H*- pyrazole (129)



Pyrazole **136** was made in the same way as **34** from **131** (1.5 g, 6.9 mmol) and hydrazine monohydrate (0.40 ml, 8.25 mmol) in ethanol (7 ml). After stirring overnight the solvent was removed *in vacuo* and the residue taken up in concentrated sulfuric acid (3 ml) and stirred for 30 minutes. After the usual work up the crude product was recrystallised from light petroleum to afford **136** (0.86 g, 62 %) as a short white needles; mp 92-94 °C; (Found: C, 36.2; H, 2.5; N, 11.1; $C_6H_5F_5N_2$ requires: C, 36.0; H, 2.5; N, 14.1 %); ν_{max}(solid)/cm^{-1} 3111, 2812, 1339, 1194, 938; δ_H (250 MHz, $CDCl_3$) 6.21 (1H, s), 2.21 (3H, s), δ_C 141.7, 141.6 ($^2J_{C-F}$ 28.1), 122.1-107.0 (env, C_2F_5), 104.4, 10.6; δ_F (235 MHz, $CDCl_3$) -85.3, (3F, s), -1113.5, (2F, s); *m/z* (EI) 201 ([M+H]$^+$, 8 %), 200 ([M]$^+$, 70 %), 131 (100), 101 (28).

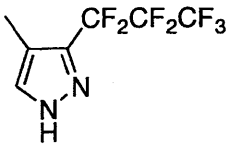
3(5)-heptafluorobutyl-5(3)-methyl-*1H*- pyrazole (134)



Pyrazole **137** was made in the same way as **34** from 5,5,6,6,7,7,7-heptafluoro-2-methoxy-hept-2-en-4-one (1.41 g, 5.0 mmol) and hydrazine monohydrate (0.29 ml, 6.0 mmol) in ethanol (5 ml). After stirring overnight the solvent was removed *in vacuo* and the residue taken up in concentrated sulfuric acid (2.5 ml) and stirred for 30 minutes. After the work up the crude product was recrystallised from light petroleum to afford **134** (0.89 g, 71 %) as white crystals; mp 72-74 °C; (Found: C, 33.6; H, 2.0; N, 11.1; $C_7H_5F_7N_2$ requires: C, 33.6; H, 2.0; N, 11.2 %); GC 100 %; ν_{max}(solid)/cm^{-1} 3106, 2990, 1201, 1178, 1114; δ_H (250 MHz, $CDCl_3$) 6.46, (1H, s), 2.46 (3H, s); δ_F (235 MHz, $CDCl_3$) -80.7, (3F, s), -111.3, (2F, s), -127.7, (2F, s); *m/z* (EI) 251 ([M+H]$^+$, 4 %), 250 ([M]$^+$, 45 %), 131 (100), 101 (20).

The data were in agreement with those previously reported by Cambon [54]

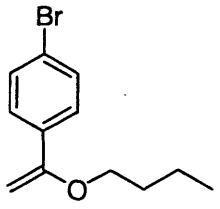
3-Heptafluorobutyl-4-methyl-*1H*- pyrazole (135)



Pyrazole **138** was made in the same way as **34** from **130** (2.82 g, 10.0 mmol) and hydrazine monohydrate (0.58 ml, 12.0 mmol) in ethanol (10 ml). After stirring overnight the solvent was removed *in vacuo* and the residue taken up in concentrated sulfuric acid (5 ml) and stirred for 30 minutes. After the work up the

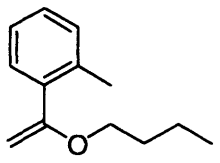
crude product was recrystallised from light petroleum to afford **138** (2.03 g, 81 %) as white needles; mp 47-48 °C; (Found: C, 33.6; H, 1.9; N, 11.1; $C_7H_5F_7N_2$ requires: C, 33.6; H, 2.0; N, 11.2 %); ν_{max}(solid)/cm^{-1} 3455, 3117, 1502, 1245, 1122; δ_H (250 MHz, $CDCl_3$) 7.45, (1H, s, H-5), 2.20 (3H, s, CH_3), δ_C (75 MHz, $CDCl_3$) 141.7, 141.3 ($^2J_{C\text{-}F}$ 23.8),124.3-105.1 (env, C_3F_7), 104.5, 10.1; δ_F (235 MHz, $CDCl_3$) -80.8, (3F, s), -111.1 (2F, s), -127.4 (2F, s); *m/z* (EI) 251 ($[M+H]^+$, 3 %), 250 (M^+, 43), 131 (100), 81 (22).

1-Butoxy-1-(4-bromophenyl)-ethene (136)



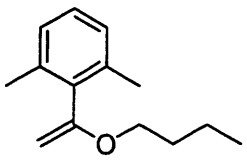
$Pd(OAc)_2$ (0.40 mmol, 0.181 g) in DMF (3 ml) was added to a solution of n-butyl vinyl ether (40.00 mmol, 5.15 g), 4-bromophenyl trifluoromethanesulfonate (8.00 mmol, 2.44 g), DPPP (0.44 mmol, 0.181 g) and Et_3N (9.60 mmol, 1.35 ml) in DMF (13 ml) at 60 °C under an atmosphere of argon. The reaction was stirred at this temperature for 16 hours, then poured into sodium hydroxide (20 ml of a 10 % aqueous solution) and extracted with EtOAc (3 x 20 ml). The combined extacts were washed sequentially with sodium hydroxide (3 x 20 ml of a 10 % aqueous solution), dried ($MgSO_4$) and concentrated *in vacuo* to yield a brown oil which was purified by Kugelrohr distillation to afford **136** as a light pink oil (1.62 g, 79 %); bp 95 °C/0.05 mmHg (Kugelrohr); GC 100 %; ν_{max}(film)/cm^{-1} 3106, 2945, 1601 (C=C), 1460, 1304, 1284; δ_H (300 MHz, $CDCl_3$) 7.46 (2H, d, $^3J_{H-H}$ 2.8, Ar*H*), 7.42 (2H, d, $^3J_{H-H}$ 2.8, Ar*H*), 4.60 (1H, d, $^3J_{H-H}$ 2.7, C=CH), 4.19 (1H, d, $^3J_{H-H}$ 2.7, C=CH), 3.82 (2H, t, $^3J_{H-H}$ 6.7, OCH_2), 1.81-1.71 (2H, m, OCH_2CH_2), 1.55-1.43 (2H, m, CH_2CH_3), 0.97 (3H, t, $^3J_{H-H}$ 7.4, CH_3); δ_c (75 MHz, $CDCl_3$) 158.9, 135.6, 131.1, 126.9, 122.3, 82.4, 67.5, 31.0, 19.4 13.9; [HRMS (EI, M^+) Found: 254.0306. Calc. for $C_{12}H_{15}BrO$ 254.0306], *m/z* (ES) 241 (M-CH_3, 62), 239 (M-CH_3, 62), 200 (50), 198 (50), 185 (98), 183 (100), 102 (52).

1-Butoxy-1-(2'-methylphenyl)-ethene (137)



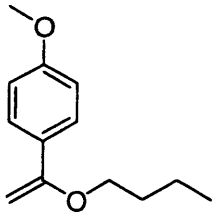
Vinyl ether **137** was synthesised in the same way as **136** using $Pd(OAc)_2$ (0.40 mmol, 0.181 g), butyl vinyl ether (40.00 mmol, 5.15 g), 2-methylphenyl trifluoromethanesulfonate (8.00 mmol, 1.92 g), DPPP (0.44 mmol, 0.181 g), Et_3N (9.60 mmol, 1.35 ml) in DMF (10 ml). After the work up the product was purified by distillation to afford **137** as a clear oil (1.31 g, 86 %); bp 70 °C/0.08 mmHg (Kugelrohr) GC 100 %; ν_{max}(film)/cm^{-1} 2959, 1600 (C=C), 1307, 1458; δ_H (300 MHz, $CDCl_3$) 7.32-7.10 (4H, m, Ar*H*), 4.28 (1H, d, $^2J_{H-H}$ 2.0, C=CH), 4.14 (1H, d, $^2J_{H-H}$ 2.0, C=CH), 3.80 (2H, t, $^3J_{H-H}$ 6.5, OCH_2), 2.35 (3H, s, $ArCH_3$), 1.76-1.67 (2H, m, OCH_2CH_2), 1.52-1.40 (2H, m, CH_2CH_3), 0.94 (3H, t, $^3J_{H-H}$ 7.3, CH_2CH_3); δ_c (75 MHz, $CDCl_3$) 162.4, 138.0, 136.2, 130.2, 129.0, 128.2, 125.4, 85.2, 67.5, 31.1, 20.0, 19.5, 13.8; [HRMS (EI, M) Found: 190.1358. Calc. for $C_{13}H_{18}O$ 190.1358]; *m/z* (ES) 190 (M^+, 4), 189 (8), 175 (55), 134 (52), 119 (100), 115 (56), 91 (61).

1-Butoxy-1-(2',6'-dimethylphenyl)-ethene (138)



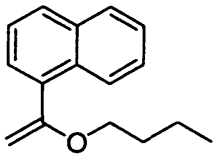
Vinyl ether **138** was synthesised in the same way as **136** from $Pd(OAc)_2$ (0.40 mmol, 0.181 g), n-butyl vinyl ether (40.00 mmol, 5.15 g), 2,6-dimethyl-phenyl trifluoromethanesulfonate (8.00 mmol, 2.03 g), DPPP (0.44 mmol, 0.181 g), and Et_3N (9.60 mmol, 1.35 ml) in DMF (13 ml). After the work up the product was purified by Kugelrohr distillation to afford **138** as a clear oil (1.63 g, 88 %); bp 72 °C/0.05 mmHg (Kugelrohr); ν_{max}(film)/cm^{-1} 2960, 1639 (C=C), 1464, 1288, 1214; δ_H (300 MHz, $CDCl_3$) 7.13-7.00 (3H, m, Ar*H*), 4.37 (1H, d, $^2J_{H\text{-}H}$ 2.1, =CH_aCH$_b$), 4.00 (1H, d, $^2J_{H\text{-}H}$ 2.1, =CH$_a$CH_b), 3.81 (2H, t, $^3J_{H\text{-}H}$ 6.3, OCH_2), 2.30 (6H, s, ArCH_3), 1.75-1.66 (2H, m, OCH$_2$CH_2), 1.50-1.38 (2H, m, CH_2CH$_3$), 0.93 (3H, t, $^3J_{H\text{-}H}$ 7.2, CH$_2$CH_3); δ_c (75 MHz, $CDCl_3$) 159.6, 137.9, 136.4, 127.8, 127.1, 85.5, 67.2, 31.1, 19.7, 19.5, 13.8; [HRMS (EI, M) Found: 205.1514. Calc. for $C_{14}H_{20}O$ 205.1514]; *m/z* (ES) 205 ([M+1]$^+$, 2 %), 204 (8), 189 (27), 133 (100), 105 (51).

1-Butoxy-1-(4'-methoxyphenyl)-ethene (139)



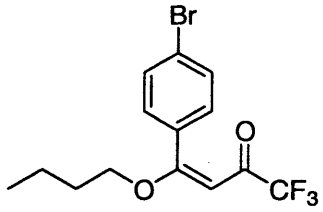
139 was synthesised in the same way as **136** using $Pd(OAc)_2$ (0.40 mmol, 0.181 g), butyl vinyl ether (40.00 mmol, 5.15 g), 4-methoxyphenyl trifluoromethanesulfonate (8.00 mmol, 2.05 g), DPPP (0.44 mmol, 0.181 g), and Et_3N (9.60 mmol, 1.35 ml) in DMF (13 ml). After the work up the product was purified by Kugelrohr distillation to afford **142** as a pale yellow oil (1.33 g, 81 %); bp 90 °C/0.05 mmHg (Kugelrohr); ν_{max}(film)/cm^{-1} 2958, 1610 (C=C), 1511, 1464, 1249; δ_H (300 MHz, $CDCl_3$) 7.56 (2H, d, $^3J_{H\text{-}H}$ 9.0, Ar*H*), 6.84 (2H, d, $^3J_{H\text{-}H}$ 9.0, Ar*H*), 4.51 (1H, d, $^2J_{H\text{-}H}$ 2.5, =CH_aCH_b), 4.10 (1H, d, $^2J_{H\text{-}H}$ 2.5, =CH_aCH_b vinylic), 3.83 (2H, t, $^3J_{H\text{-}H}$ 6.4, OCH_2), 3.79 (3H, s, OCH_3), 1.82-1.72 (2H, m, OCH_2CH_2), 1.57-1.45 (2H, m, CH_2CH_3), 0.98 (3H, t, $^3J_{H\text{-}H}$ 7.4, CH_2CH_3); δ_c (75 MHz, $CDCl_3$) 159.7, 130.5, 129.4, 126.6, 113.6, 80.4, 67.3, 55.2, 31.2, 19.4, 13.9; [HRMS, (EI, M^+) Found: 206.1308. Calc. for $C_{13}H_{18}F_3O_2$, 206.1307]; *m/z* (EI) 206 (M^+, 2), 191 (32), 150 (33), 135 (100).

1-Butoxy-1-(1'naphthyl)-ethene (140)



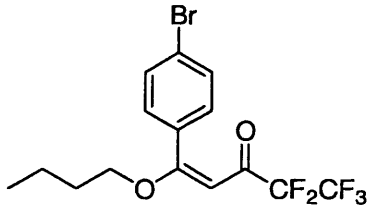
Vinyl ether **140** was synthesised in the same way as **136** using $Pd(OAc)_2$ (0.40 mmol, 0.181 g), butyl vinyl ether (40.00 mmol, 5.15 g), 1-naphthyl trifluoromethanesulfonate (8.00 mmol, 2.21 g), DPPP (0.44 mmol, 0.181 g), and Et_3N (9.60 mmol, 1.35 ml) in DMF (13 ml). After the work up the product was purified by Kugelrohr distillation to afford **140** as a yellow oil, (1.46 g, 81 %); bp 100 °C/0.03 mmHg (Kugelrohr); GC 100 %; ν_{max}(film)/cm^{-1} 2958, 1610 (C=C), 1511, 1464, 1249; δ_H (300 MHz, $CDCl_3$) 8.17-8.12 (1H, m, Ar*H*), 7.85-7.79 (2H, m, Ar*H*), 7.54-7.40 (4H, m, Ar*H*), 4.49 (1H, d, $^2J_{H\text{-}H}$ 2.0, =CH_aCH_b), 4.37 (1H, d, $^2J_{H\text{-}H}$ 2.0, =CH_aCH_b), 3.95 (2H, t, $^3J_{H\text{-}H}$ 6.4, OCH_2), 1.81-1.72 (2H, m, OCH$_2$CH_2), 1.55-1.43 (2H, m, CH_2CH$_3$), 0.96 (3H, t, $^3J_{H\text{-}H}$ 7.3 CH$_3$); δ_c (75 MHz, $CDCl_3$) 161.3, 136.3, 133.8, 131.5, 128.9, 128.3, 126.7, 126.1, 125.8, 125.2, 87.0, 67.9, 31.2, 19.6, 14.0; [HRMS (EI, M^+) Found: 226.1357. Calc. for $C_{16}H_{18}O$ 226.1358]; *m/z* (EI) 227 (8 %, $[M+1]^+$), 226 (46), 211 (46), 169 (100), 155 (95), 141 (98), 115 (49).

4-(4-Bromo-phenyl)-4-butoxy-1,1,1-trifluoro-but-3-en-2-one (141)



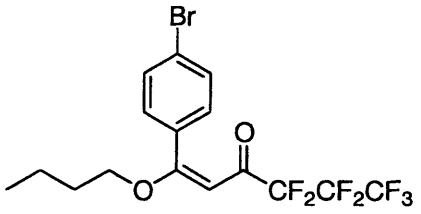
Trifluoroacetic anhydride (0.25 ml, 1.78 mmol) was added dropwise to a solution of **136** (0.32 ml, 1.25 ml) and pyridine (0.033 ml, 0.41 ml) in dichloromethane (0.60 ml) at 0 °C under an atmosphere of nitrogen over 10 minutes. The reaction was allowed to warm to room temperature and was stirred for 16 hours after which it was diluted with dichloromethane (10 ml) and extracted with water (5 × 10 ml). The organic layer was dried ($MgSO_4$) and concentrated *in vacuo* to leave **141** as light orange oil; (0.333 g, 76 %); GC 100 %; ν_{max}(film)/cm^{-1} 2962, 1705 (C=O), 1576, 1551, 1137, 1063; δ_H (300 MHz, $CDCl_3$) 7.54 (2H, d, $^3J_{H\text{-}H}$ 8.5, ArH), 7.36 (2H, d, $^3J_{H\text{-}H}$ 8.5, ArH), 5.81 (1H, s, C=CH), 4.09 (2H, t, $^3J_{H\text{-}H}$ 6.5, OCH_2), 1.86-1.77 (2H, m, OCH_2CH_2), 1.49 (2H, sextet, $^3J_{H\text{-}H}$ 7.5, CH_2CH_3), 0.98 (3H, t, $^3J_{H\text{-}H}$ 7.5, CH_3); δ_c (75.5 MHz, $CDCl_3$) 177.5 (q, $^2J_{C\text{-}F}$ 33.7), 176.4, 132.8, 131.3, 130.6, 126.8, 116.8 (q, $^1J_{C\text{-}F}$ 292.4), 92.4, 70.6, 30.9, 19.0, 13.7; δ_F (282 MHz, $CDCl_3$) -78.3 (s); [HRMS (EI, M) Found 350.0128. Calc. for $C_{14}H_{14}{}^{79}BrF_3O_2$ 350.0129]; *m/z* (ES+) 352 (^{81}BrM, 5 %), 350 (^{79}BrM, 5 %), 241 (30) 239 (30), 227 (82), 225 (80), 69 100, (ES-) 295 (^{81}Br-C_4H_9, 38), 293 (^{79}BrM-C_4H_9, 37), 225 (^{81}Br-C_4H_9-CF_3, 98), 223 (^{79}Br-C_4H_9-CF_3, 100).

4-(4-Bromo-phenyl)-4-butoxy-4,4,5,5,5-pentafluoro-pent-1-en-3-one (142)



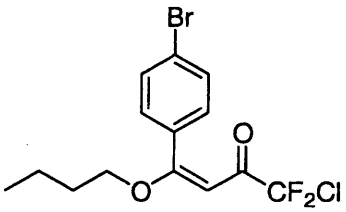
Enone **142** was synthesised in the same way as **141** from **136** (0.319 g, 1.25 mmol), pentafluoropropionic anhydride (0.35 ml, 1.78 mmol) and pyridine (0.033 ml, 0.41 mmol) in dichloromethane (0.60 ml) to yield **142** as a light orange oil; (0.378 g, 75 %); which required no purification after work up; GC 100 %; ν_{max}(film)/cm^{-1} 2963, 1700 (C=O), 1575, 1549, 1194, 1211, 1145; δ_H (300 MHz, $CDCl_3$) 7.54 (2H, d, $^3J_{H\text{-}H}$ 8.8, ArH), 7.35 (2H, d, $^3J_{H\text{-}H}$ 8.8, ArH), 5.90 (1H, s, C=CH), 4.09 (2H, t, $^3J_{H\text{-}H}$ 6.4, OCH_2), 1.87-1.76 (2H, m, OCH_2CH_2), 1.49 (2H, m, CH_2CH_3), 0.98 (3H, t, $^3J_{H\text{-}H}$ 7.4, CH_3); δ_c (75.5 MHz, $CDCl_3$) 179.8 (q, $^2J_{C\text{-}F}$ 24.2), 176.5, 132.7, 131.4, 130.5, 125.9, 123.1-104.5 (env), 93.1, 70.7, 30.5, 19.2, 13.7; δ_F (282 MHz, $CDCl_3$) -81.9 (3F, s), -112.9 (2F, s); [HRMS (EI, M) Found 400.0097 Calc. for $C_{15}H_{14}{}^{79}BrF_5O_2$ 400.0097]; *m/z* (EI+) 402 (^{81}Br, 5%), 400 (^{79}BrM, 5 %), 227 (90), 225 (91), 69 (100), (ES-) 345 (^{81}Br-C_4H_9, 30), 243 (^{79}BrM-C_4H_9, 29), 225 (^{81}Br-C_4H_9-C_2F_5, 98), 223 (^{79}Br-C_4H_9-C_2F_5, 100).

1-(4-Bromo-phenyl)-1-butoxy-4,4,5,5,6,6,6-heptafluoro-hex-1-en-3-one (143)



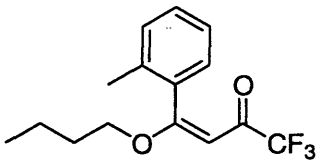
Enone **143** was synthesised in the same way as **141** from **136** (0.319 g, 1.25 mmol), heptafluorobutyric anhydride (0.44 ml, 1.78 mmol) and pyridine (0.033 ml, 0.41 mmol) in dichloromethane (0.60 ml) to yield **143** as a light orange oil; (0.459 g, 81 %); which was used without purification; GC 100 %; ν_{max}(film)/cm^{-1} 2964, 1702 (C=O), 1575, 1548, 1215, 1118; δ_H (300 MHz, $CDCl_3$) 7.54 (2H, d, $^3J_{H\text{-}H}$ 8.5, ArH), 7.35 (2H, d, $^3J_{H\text{-}H}$ 8.5, ArH), 5.88 (1H, s, C=CH), 4.09 (2H, t, $^3J_{H\text{-}H}$ 6.4, OCH_2), 1.86-1.76 (2H, m, OCH_2CH_2), 1.56-1.43 (2H, m, CH_2CH_3), 0.98 (3H, t, $^3J_{H\text{-}H}$ 7.4, CH_3); δ_c (75.5 MHz, $CDCl_3$) 175.1 (t, $^2J_{C\text{-}F}$ 23.9), 176.5, 132.8, 131.4, 130.6, 125.9, 120.0-105.5 (env), 93.6, 70.7, 30.5, 19.2, 13.7; δ_F (282 MHz, $CDCl_3$) -80.7 (3F, s), -121.2 (2F, s), -126.4 (2F, s); [HRMS (EI, M) Found 450.0065. Calc. for $C_{16}H_{14}{}^{79}BrF_7O_2$ 450.0065]; *m/z* (ES+) 452 (^{79}BrM, 3 %), 450 (^{81}BrM, 3 %) 277 (80), 227 (80), (ES-) 395 (^{81}BrM-C_4H_9, 39), 293 (^{79}BrM-C_4H_9, 39), 225 (^{81}Br-C_4H_9-C_3F_7, 82), 223 (^{79}Br-C_4H_9-C_3F_7, 82), 169 (C_3F_7, 100).

4-(4-Bromo-phenyl)-4-butoxy-1-chloro-1,1-difluoro-but-3-en-2-one (144)



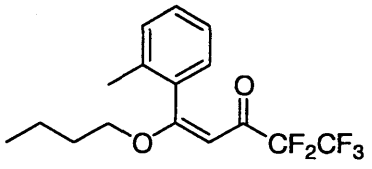
Enone **144** was synthesised in the same way as **141** from **136** (0.319 g, 1.25 mmol), chlorodifluoroacetic anhydride (0.31 ml, 1.78 mmol) and pyridine (0.033 ml, 0.41 mmol) in dichloromethane (0.60 ml) to yield **144** as a light orange oil; (0.355 g, 77 %) which required no further purification after work up; GC 100 %; ν_{max}(film)/cm^{-1} 2961, 1707 (C=O), 1576, 1551, 1285, 1113, 1064; δ_H (300 MHz, $CDCl_3$) 7.54 (2H, d, $^3J_{H\text{-}H}$ 8.8, ArH), 7.36 (2H, d, $^3J_{H\text{-}H}$ 8.8, ArH), 5.82 (1H, s, C=CH), 4.09 (2H, t, $^3J_{H\text{-}H}$ 6.3, OCH_2), 1.86-1.76 (2H, m, OCH_2CH_2), 1.57-1.43 (2H, m, CH_2CH_3), 0.98 (3H, t, $^3J_{H\text{-}H}$ 7.5, CH_3); δ_c (75.5 MHz, $CDCl_3$) 178.6 (t, $^2J_{C\text{-}F}$ 27.9), 176.2, 132.8, 131.3, 130.5, 125.9, 120.9 (t, $^1J_{C\text{-}F}$ 306.9), 91.6, 70.5, 30.5, 19.2, 13.7; δ_F (282 MHz, $CDCl_3$) -66.7 (s); [HRMS (EI, M) Found. 365.9834 Calc. for $C_{14}H_{14}{}^{79}BrClF_2O_2$ 365.9834]; *m/z* (ES+) 368 (^{81}BrM, 2%), 366 (^{79}BrM, 2 %), 227 (76), 225 (75), 69 (100), (ES-) 225 (^{81}BrM-C_4H_9, 82,), 223 (^{79}BrM-C_4H_9, 80), 81 (^{81}Br, 97), 79 (^{79}Br, 100).

4-*o*-Tolyl-4-butoxy-1,1,1-trifluoro-but-3-en-2-one (145)



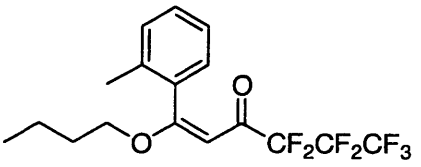
Trifluoroacetic anhydride (0.25 ml, 1.78 mmol) was added drop wise to a solution of **137** (0.239 g, 1.25 mmol) and pyridine (0.033 ml, 0.41 ml) in dichloromethane (0.60 ml) at 0 °C under an atmosphere of nitrogen over 10 minutes. The reaction was allowed to warm to room temperature and was stirred for 16 hours after which it was diluted with dichloromethane (10 ml) and washed with water (5 × 10 ml). The organic layer was dried ($MgSO_4$) and concentrated *in vacuo* to leave crude **145** as light brown oil which was purified by Kugelrohr distillation to afford **145** (0.284 g, 79 %) as a yellow oil; GC 100 %; bp 100 °C/0.04 mmHg (Kugelrohr); ν_{max}(film)/cm^{-1} 2962, 1708 (C=O), 1563, 1137, 1066; δ_H (300 MHz, $CDCl_3$) 7.36-7.11 (4H, m, ArH), 5.93 (1H, s, C=CH), 4.06 (2H, t, $^3J_{H-H}$ 6.4, OCH_2), 2.22 (3H, s, $ArCH_3$) 1.82-1.75 (2H, m, CH_2CH_2), 1.52-1.39 (2H, m, CH_2CH_3), 0.95 (3H, t, $^3J_{H-H}$ 7.3, CH_2CH_3); δ_c (75.5 MHz, $CDCl_3$) 178.1, 177.5 (q, $^2J_{C-F}$ 33.5), 135.5, 134.8, 130.2, 129.8, 127.8, 125.8, 116.7 (q, $^1J_{C-F}$ 391.2), 93.8, 70.3, 30.5, 19.2, 18.9, 13.6; δ_F (282 MHz, $CDCl_3$) -78.5 (s); [HRMS (EI, M) Found: 286.1181. Calc. for $C_{15}H_{17}F_3O_2$ 286.1181]; *m/z* (ES) 272 ($[M+1]^+$, 63), 254 (59), 242 (82), 231 (100).

1-Butoxy-4,4,5,5,5-pentafluoro-1-*o*-tolyl-pent-1-en-3-one (146)



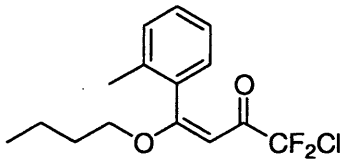
Enone **146** was synthesised in the same way as **141** from **137** (0.239 g, 1.25 mmol), pentafluoropropionic anhydride (0.35 ml, 1.78 mmol) and pyridine (0.033 ml, 0.41 mmol) in dichloromethane (0.60 ml). After work up the product was purified by Kugelrohr distillation to afford **146** (0.307 g, 73 %) as a pale yellow oil; GC 100 %; bp 100 °C/0.05 mmHg (Kugelrohr); ν_{max}(film)/cm^{-1} 2963, 1702 (C=O), 1560, 1192; δ_H (300 MHz, $CDCl_3$) 7.35-7.10 (4H, m, ArH), 6.03 (1H, s, C=CH), 4.06 (2H, t, $^3J_{H-H}$ 6.4, OCH_2), 2.21 (3H, s, $ArCH_3$) 1.82-1.73 (2H, m, OCH_2CH_2), 1.52-1.40 (2H, m, CH_2CH_3), 0.95 (3H, t, $^3J_{H-H}$ 7.3, CH_2CH_3); δ_c (75.5 MHz, $CDCl_3$) 179.4 (t, $^2J_{C-F}$ 24.5), 178.1, 135.5, 134.7, 130.3, 129.8, 127.7, 125.8, 120.6-104.3 (env, C_2F_5), 94.6, 70.4, 30.5, 19.2, 18.9, 13.6; δ_F (282 MHz, $CDCl_3$) -82.0 (s, 3F), -123.3 (s, 2F); [HRMS (EI, M) Found: 336.1149. Calc. for $C_{16}H_{17}F_5O_2$ 336.1149]; *m/z* (EI) 336 (M, 21 %), 321 (M-CH_3, 89) 265 (78), 217 (55), 161 (100).

1-Butoxy-4,4,5,5,6,6,6-heptafluoro-1-*o*-tolyl-pent-1-en-3-one (147)



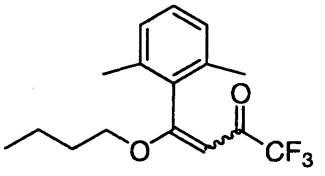
Enone **147** was synthesised in the same way as **141** from **137** (0.239 g, 1.25 mmol), heptafluorobutyric anhydride (0.44 ml, 1.78 mmol) and pyridine (0.033 ml, 0.41 mmol) in dichloromethane (0.60 ml). After work up the product was purified by Kugelrohr distillation to afford **147** (0.379 g, 78 %) as a pale yellow oil; GC 100 %; bp 100 °C/0.05 mmHg (Kugelrohr); ν_{max}(film)/cm^{-1} 2962, 1703 (C=O), 1560, 1206, 1118; δ_H (300 MHz, $CDCl_3$) 7.36-7.09 (4H, m, ArH), 6.01 (1H, s, C=CH), 4.06 (2H, t, $^3J_{H-H}$ 6.3, OCH_2), 2.21 (3H, s, $ArCH_3$) 1.83-1.73 (2H, m, OCH_2CH_2), 1.56-1.40 (2H, m, CH_2CH_3), 0.96 (3H, t, $^3J_{H-H}$ 7.3, CH_2CH_3); δ_c (75.5 MHz, $CDCl_3$) 179.0 (t, $^2J_{C-F}$ 23.9), 178.1, 135.5, 134.7, 130.2, 129.8, 127.7, 125.8, 119.5-99.6 (env, C_3F_7), 94.9, 70.3, 30.5, 19.1, 18.8, 13.6; δ_F (282 MHz, $CDCl_3$) -80.6 (s, 3F), -126.7 (s, 2F), -121.3 (s, 2F); [HRMS (EI, M) Found: 386.1116. Calc. for $C_{17}H_{17}F_7O_2$ 386.1117]; *m/z* (ES) 387 ([M+1]$^+$, 28 %), 372 (M+H-CH_3, 68), 331 (100), 313 (34).

4-*o*-Tolyl-4-butoxy-1-chloro-1,1-difluoro1,1-but-3-en-2-one (148)



Enone **148** was synthesised in the same way as **141** from **137** (0.239 g, 1.25 mmol), chlorodifluoroacetic anhydride (0.31 ml, 1.78 mmol) and pyridine (0.033 ml, 0.41 mmol) in dichloromethane (0.60 ml). After work up the product was purified by Kugelrohr distillation to afford **148** (0.330 g, 87 %) as a pale yellow oil; GC 100 %; bp 110 °C/0.05 mmHg (Kugelrohr); ν_{max}(film)/cm^{-1} 2961, 1710 (C=O), 1562, 1275, 1065; δ_H (300 MHz, $CDCl_3$) 7.35-7.12 (4H, m, ArH), 5.95 (1H, s, C=CH), 4.06 (2H, t, $^3J_{H-H}$ 6.4, OCH_2), 2.23 (3H, s, $ArCH_3$) 1.82-1.73 (2H, m, OCH_2CH_2), 1.52-1.40 (2H, m, CH_2CH_3), 0.95 (3H, t, $^3J_{H-H}$ 7.3, CH_2CH_3); δ_c (75.5 MHz, $CDCl_3$) 178.6 (t, $^2J_{C-F}$ 28.1), 178.0, 135.5, 134.8, 130.2, 129.7, 127.8, 125.8, 120.8 (t, $^1J_{C-F}$ 306.6), 93.0, 70.2, 30.5, 19.2, 18.9, 13.7; δ_F (282 MHz, $CDCl_3$) -66.7 (s); [HRMS (EI, M) Found: 302.0885. Calc. for $C_{17}H_{17}F_7O_2$ 302.0885]; *m/z* (ES) 303 ([M+1]$^+$, 12 %), 247 (100).

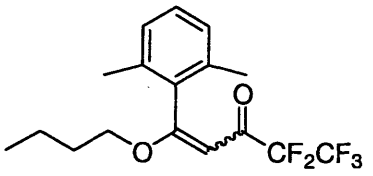
4-Butoxy-4-(2,6-dimethyl-phenyl)-1,1,1-trifluoro-but-3-en-2-one (149)



Enone **149** was synthesised in the same way as **141** from **148** (0.255 g, 1.25 mmol), chlorodifluoroacetic anhydride (0.31 ml, 1.78 mmol) and pyridine (0.033 ml, 0.41 mmol) in dichloromethane (0.60 ml). The reaction was worked up to afford **149** as an *E/Z* mixture (in a ratio of 1:1) (0.311 g, 78 %) as a pale yellow oil; GC 85 %; δ_H (300 MHz, $CDCl_3$) 7.19-6.78 (8H, m, ArH), 5.94 (1H, s, C=CH), 5.48 (1H, s, C=CH), 3.98 (2H, t, $^3J_{H\text{-}H}$ 6.4, OCH_2), 3.64 (2H, t, $^3J_{H\text{-}H}$ 6.4, OCH_2), 2.20 (6H, s, $ArCH_3$), 2.08 (6H, s, $ArCH_3$) 1.75-1.65 (2H, m, OCH_2CH_2), 1.64-1.57 (2H, m, OCH_2CH_2), 1.45-1.32 (4H, m, CH_2CH_3), 0.95 (3H, t, $^3J_{H\text{-}H}$ 7.3, CH_2CH_3) 0.86 (3H, t, $^3J_{H\text{-}H}$ 7.3, CH_2CH_3); δ_F (282 MHz, $CDCl_3$) -78.26 (s), -78.54 (s); [HRMS (EI, M) Found: 300.1337. Calc. for $C_{16}H_{19}F_3O_2$ 300.1337]; *m/z* (EI) 301 ($[M+1]^+$, 3 %), 300 (M, 14 %) 254 ($M+H-CF_3$, 24), 175 (34), 121 (100).

Purification and separation of the two isomers was not undertaken due to the expected difficulties in doing this and the mixture was taken on crude

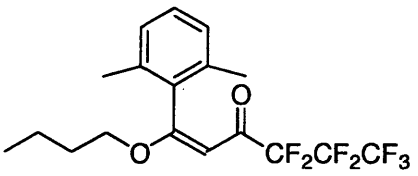
1-Butoxy-1-(2,6-dimehyl-phenyl)-4,4,5,5,5-pentafluoro-pent-1-en-3-one (150)



Enone **150** was synthesised in the same way as **141** from **138** (0.255 g, 1.25 mmol), pentafluoropropionic anhydride (0.35 ml, 1.78 mmol) and pyridine (0.033 ml, 0.41 mmol) in dichloromethane (0.60 ml). The reaction was worked up to afford **150** as an *E/Z* mixture (in a ratio of 1:1.2) as a pale yellow oil; GC 79 %; δ_H (300 MHz, $CDCl_3$) 7.20-6.97 (8H, m, ArH), 6.0 (1H, s, C=CH), 5.58 (1H, s, C=CH), 3.97 (2H, t, $^3J_{H\text{-}H}$ 6.4, OCH_2), 3.65 (2H, t, $^3J_{H\text{-}H}$ 6.4, OCH_2), 2.20 (7H, s, $ArCH_3$), 2.07 (6H, s, $ArCH_3$) 1.73-1.68 (2H, m, OCH_2CH_2), 1.64-1.55 (2.4H, m, OCH_2CH_2), 1.45-1.32 (4H, m, CH_2CH_3), 0.90-0.85 (7H, t, $^3J_{H\text{-}H}$ 7.31, CH_2CH_3); δ_F (282 MHz, $CDCl_3$) -82.08 (s, 3F), -82.15 (s, 3F) 1:1.2 ratio, -123.4 (s, 2F,) -123.5 (s, 2F) 1:1.2 ratio; [HRMS (EI, M) Found: 350.1305. Calc. for $C_{17}H_{19}F_5O_2$ 350.1305]; *m/z* (EI) 351 ($[M+1]^+$, 6 %), 350 (M, 23 %) 254 ([M+H-CF_3, 24), 175 (65), 121 (100).

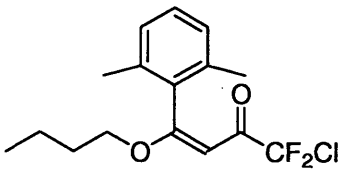
Purification and separation of the two isomers was not undertaken due to the expected difficulties in doing this and the mixture was taken on crude.

1-Butoxy-1-(2,6-dimethyl-phenyl)-4,4,5,5,5,6,6,6-heptafluoro-hex-1-en-3-one (151)



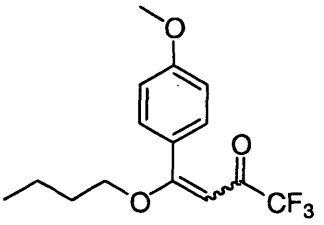
Enone **151** was synthesised in the same way as **141** from **138** (0.255 g, 1.25 mmol), heptafluorobutyric anhydride (0.44 ml, 1.78 mmol) and pyridine (0.033 ml, 0.41 mmol) in dichloromethane (0.60 ml). After the work up the product was purified by Kugelrohr distillation to afford **151** (0.400 g, 80 %) as a yellow oil; GC 96 %; bp 110 °C/0.06 mmHg (Kugelrohr); ν_{max}(film)/cm^{-1} 2959, 1721 (C=O), 1545, 1223, 1161, 1147; δ_H (300 MHz, $CDCl_3$) 7.15-6.97 (3H, m, ArH), 6.01 (1H, s, C=CH), 3.79 (2H, t, $^3J_{H\text{-}H}$ 6.3, OCH_2), 2.06 (6H, s, $ArCH_3$), 1.73-1.65 (2H, m, OCH_2CH_2), 1.41-1.32 (2H, m, CH_2CH_3), 0.87 (3H, t, $^3J_{H\text{-}H}$ 7.3, CH_2CH_3); δ_c (75.5 MHz, $CDCl_3$) 178.9 (t, $^2J_{C\text{-}F}$ 24.1), 179.9, 134.8, 129.5, 127.6, 120.8-105.7 (env, C_3F_7), 95.7, 70.2, 30.6, 19.2, 18.6, 13.6; δ_F (282 MHz, $CDCl_3$) -80.7 (s, 3F), -121.4 (s, 2F), -126.7 (s, 2F); [HRMS (EI, M) Found: 400.1274. Calc. for $C_{17}H_{17}F_7O_2$ 400.1273]; *m/z* (EI) 400 (M, 90 %), 385 (M-CH_3, 90) 344 (70), 329 (84), 321 M-C_3F_7, 83) 175 (100).

4-Butoxy-1-chloro-4-(2,6-dimethyl-phenyl)-1,1-difluoro-but-3-en-2-one (152)



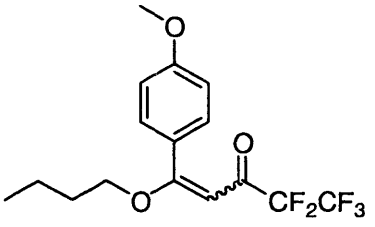
Enone **152** was synthesised in the same way as **141** from **138** (0.255 g, 1.25 mmol), chlorodifluoroacetic anhydride (0.31 ml, 1.78 mmol) and pyridine (0.033 ml, 0.41 mmol) in dichloromethane (0.60 ml). After work up the product was purified by Kugelrohr distillation to afford **152** (0.311 g, 78 %) as a pale yellow oil; GC 90 %; bp 110 °C/0.05 mmHg (Kugelrohr); (ν_{max}(film)/cm^{-1} 2958, 1723 (C=O), 1566, 1221, 1158; δ_H (300 MHz, $CDCl_3$) 7.25-7.05 (3H, m, ArH), 5.95 (1H, s, C=CH), 4.06 (2H, t, $^3J_{H-H}$ 6.4, OCH_2), 2.23 (3H, s, $ArCH_3$) 1.82-1.73 (2H, m, OCH_2CH_2), 1.52-1.40 (2H, m, CH_2CH_3), 0.95 (3H, t, $^3J_{H-H}$ 7.3, CH_2CH_3); δ_c (75.5 MHz, $CDCl_3$) 178.8 (t, $^2J_{C-F}$ 27.8) 177.6, 134.7, 129.1, 127.5, 120.8 (t, $^1J_{C-F}$ 306.5), 93.7, 70.0, 30.6, 19.0, 19.2, 13.6; δ_F (282 MHz, $CDCl_3$) -67.0 (s); [HRMS (EI, M) Found: 316.1043. Calc. for $C_{16}H_{19}ClF_2O_2$ 316.1042]; *m/z* (EI) 316 (M, 12 %), 254 (58) 231 (M-CF_2Cl, 38), 175 (62), 121 (100).

4-Butoxy-1,1,1-trifluoro-4-(4'-methoxy-phenyl)-but-3-en-2-one (153)



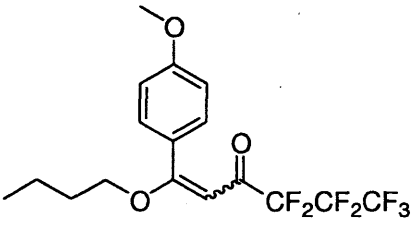
Enone **153** was synthesised in the same way as **141** from **139** (0.259 g, 1.25 mmol), trifluoroacetic anhydride (0.25 ml, 1.78 mmol) and pyridine (0.033 ml, 0.41 mmol) in dichloromethane (0.60 ml). After the work up the product was taken on without analysis.

1-Butoxy-4,4,5,5,5-pentafluoro-1-(4'-methoxy-phenyl)-pent-1-en-3-one (154)



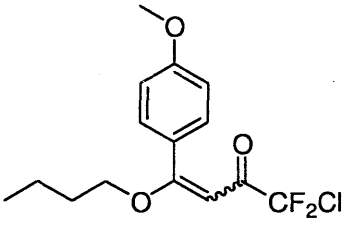
Enone **154** was synthesised in the same way as **141** from **139** (0.259 g, 1.25 mmol), pentafluoropropionic anhydride (0.35 ml, 1.78 mmol) and pyridine (0.033 ml, 0.41 mmol) in dichloromethane (0.60 ml). After the work up the product was taken on without analysis.

1-Butoxy-4,4,5,5,6,6,6-heptafluoro-1-(4'-methoxy-phenyl)-hex-1-en-3-one (155)



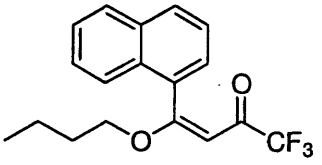
Enone **154** was synthesised in the same way as **141** from **139** (0.259 g, 1.25 mmol), heptafluorobutyric anhydride (0.42 ml, 1.78 mmol) and pyridine (0.033 ml, 0.41 mmol) in dichloromethane (0.60 ml). After the work up the product was taken on without analysis.

4-Butoxy-1-chloro,1,1-trifluoro-4-(4'-methoxy-phenyl)-but-3-en-2-one (156)



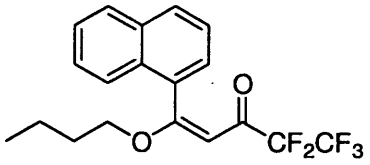
Enone **156** was synthesised in the same way as **141** from **139** (0.259 g, 1.25 mmol), chlorodifluoroacetic anhydride (0.31 ml, 1.78 mmol) and pyridine (0.033 ml, 0.41 mmol) in dichloromethane (0.60 ml). After the work up the product was taken on without analysis.

4-Butoxy-1,1,1-trifluoro-4-naphthalen-1yl-but-3-en-2-one (157)



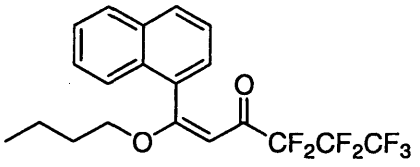
Enone **157** was synthesised in the same way as **141** from **140** (0.283 g, 1.25 mmol), trifluoroacetic anhydride (0.25 ml, 1.78 mmol) and pyridine (0.033 ml, 0.41 mmol) in dichloromethane (0.60 ml). After the work up the product was purified by Kugelrohr distillation to afford **157** (0.311 g, 71 %) as a pale yellow oil; GC 96 %; bp 125 °C, 0.05 mmHg (Kugelrohr); ν_{max}(film)/cm^{-1} 2961, 1707 (C=O), 1561, 1193, 1136; δ_H (300 MHz, $CDCl_3$) 7.94-7.85 (2H, m, ArH), 7.72-7.69 (1H, m, ArH), 7.51-7.46 (3H, m, ArH), 7.40-7.38 (1H, m, ArH) 6.14 (1H, s, C=CH), 4.15 (2H, t, $^3J_{H-H}$ 6.4, OCH_2), 1.81-1.72 (2H, m, OCH_2CH_2), 1.50-1.38 (2H, m, CH_2CH_3), 0.93 (3H, t, $^3J_{H-H}$ 7.3, CH_2CH_3); δ_c (75.5 MHz, $CDCl_3$) 178.8 (t, $^2J_{C-F}$ 33.9) 177.1, 133.5, 132.7, 130.3, 128.7, 127.0, 126.3, 125.1, 124.1, 116.7 (t, $^1J_{C-F}$ 292.5), 95.0, 70.5, 30.5, 19.1, 13.6; δ_F (282 MHz, $CDCl_3$) -78.5 (s); [HRMS (EI, M) Found 322.1180. Calc. for $C_{18}H_{17}O_2F_3$ 322.1181] ; *m/z* (EI+) 233 ([M+1]$^+$, 3 %), 322 (M, 19), 266 (M-CF_3, 22), 197 (100).

1-Butoxy-4,4,5,5,5-1-naphthalen-1yl-but-3-en-2-one (158)



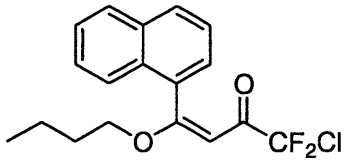
Enone **158** was synthesised in the same way as **141** from **140** (0.283 g, 1.25 mmol), pentafluoropropionic anhydride (0.35 ml, 1.78 mmol) and pyridine (0.033 ml, 0.41 mmol) in dichloromethane (0.60 ml). After the work up the product was purified by Kugelrohr distillation to afford **158** (0.339 g, 73 %) as a pale yellow oil; GC 100 %; bp 125 °C/0.05 mmHg (Kugelrohr); ν_{max}(film)/cm^{-1} 2962, 1702 (C=O), 1559, 1190; δ_H (300 MHz, $CDCl_3$) 7.94-7.86 (2H, m, ArH), 7.71-7.67 (1H, m, ArH), 7.52-7.46 (3H, m, ArH), 7.40-7.37 (1H, m, ArH) 6.23 (1H, s, C=CH), 4.16 (2H, t, $^3J_{H\text{-}H}$ 6.4, OCH_2), 1.81-1.72 (2H, m, OCH_2CH_2), 1.49-1.42 (2H, m, CH_2CH_3), 0.94 (3H, t, $^3J_{H\text{-}H}$ 7.3, CH_2CH_3); δ_c (75.5 MHz, $CDCl_3$) 179.3 (t, $^2J_{C\text{-}F}$ 24.6) 177.1, 133.5, 132.7, 130.4, 128.7, 127.0, 126.3, 125.2, 124.0 120.7-103.5 (env, C_2F_5), 95.8, 70.6, 30.6, 19.1, 13.6; δ_F (282 MHz, $CDCl_3$) -81.9 (3F, s), -123.2 (2F, s); HRMS [(EI, M) Found 372.1149. Calc. for $C_{19}H_{17}F_7O_2$ 372.1148]; *m/z* (EI+) 373 ([M+1]$^+$, 3 %), 372 (M, 14), 253 (M-C_2F_5, 22), 197 (100).

1-Butoxy-4,4,5,5,6,6,6-heptafluoro-1-napththalen-1yl-hex-1-en-3-one (159)



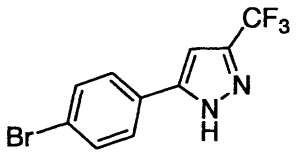
Enone **159** was synthesised in the same way as **141** from **140** (0.283 g, 1.25 mmol), heptafluorobutyric anhydride (0.44 ml, 1.78 mmol) and pyridine (0.033 ml, 0.41 mmol) in dichloromethane (0.60 ml). After the work up the product was purified by Kugelrohr distillation to afford **159** (0.359 g, 68 %) as a pale yellow oil; GC 100 %; bp 125 °C/0.05 mmHg (Kugelrohr); ν_{max}(film)/cm^{-1} 2963, 1703 (C=O), 1560, 1210, 1118; δ_H (300 MHz, $CDCl_3$) 7.94-7.86 (2H, m, ArH), 7.70-7.67 (1H, m, ArH), 7.52-7.45 (3H, m, ArH), 7.39-7.37 (1H, m, ArH) 6.22 (1H, s, C=CH), 4.15 (2H, t, $^3J_{H-H}$ 6.4, OCH_2), 1.80-1.73 (2H, m, OCH_2CH_2), 1.48-1.39 (2H, m, CH_2CH_3), 0.93 (3H, t, $^3J_{H-H}$ 7.5, CH_2CH_3); δ_C (75.5 MHz, $CDCl_3$) 179.0 (t, $^2J_{C-F}$ 24.2) 177.2, 133.5, 132.7, 130.4, 128.7, 126.9, 126.2, 125.1, 124.0, 120.0-105.7 (env C_3F_7), 96.1, 66.0, 30.6, 19.2, 13.6; δ_F (282 MHz, $CDCl_3$) -80.6 (3F, s), -121.3 (2F, s) -126.6 (2F, s); HRMS (EI, M) Found. 422.1117. Calc. for $C_{20}H_{17}O_2F_7$ 422.1117]; *m/z* (EI+) 423 ($[M+1]^+$, 4 %), 422 (M, 8), 253 (M-C_3F_7, 19), 197 (100).

4-Butoxy-1-chloro,1,1-trifluoro-4-naphthalen-1yl-but-3-en-2-one (160)



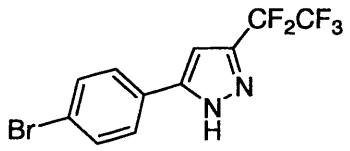
Enone **160** was synthesised in the same way as **141** from **140** (0.283 g, 1.25 mmol), chlorodifluoroacetic anhydride (0.31 ml, 1.78 mmol) and pyridine (0.033 ml, 0.41 mmol) in dichloromethane (0.60 ml). GCMS 100 %, ret. t. 22.26 min; *m/z* (EI) 339 (M+H, 3 %), 338 (M, 8), 253 (M-CF_2Cl, 40), 197 (100). After the work up the product was analysed by GCMS and taken on without further analysis.

5-(4-Bromo-phenyl)-3-trifluoromethyl-1*H*-pyrazole (161)



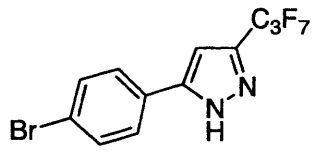
Hydrazine monohydrate (0.04 ml, 0.80 mmol) was added dropwise to a solution of **141** (0.140 g, 0.40 mmol) in ethanol (0.40 ml) over five minutes at room temperature. The solution was stirred overnight then concentrated *in vacuo*. The residue was taken up in toluene (3 ml) and tranfered into a microwave reaction vial. The sealed vial was heated in the cavity of a microwave reactor (100 W, 100 °C, air cooling) for ten minutes. After cooling, the reaction mixture was concentrated *in vacuo*, taken up in DCM (10 ml) and washed with water (3 × 10 ml). The combined aqueous layers were acidified (pH 5) with concentrated hydrochloric acid and extracted with DCM (2 × 10 ml). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo* to leave the crude product as a brown solid which was purified by flash chromatography to afford **161** (0.072 g, 62 %) as a white solid; mp 154-155 °C; R_F (35 % ethyl acetate in light petroleum) 0.42; (Found: C, 41.43; H, 1.96; N, 9.69; $C_{10}H_6BrF_3N_2$ requires: C, 41.26; H, 2.08; N, 9.62 %); ν_{max}(solid)/cm^{-1} 3234, 1482, 1270, 1246, 1113, 798; δ_H (250 MHz, $CDCl_3$) 7.57 (2H, d, $^3J_{H\text{-}H}$ 8.6, ArH), 7.42 (2H, d, $^3J_{H\text{-}H}$ 8.6, ArH), 6.73 (1H, s, H-4); δ_C (101 MHz, MeOD) 143.6, 132.0, 128.8, 127.5, 127.1, 122.6. 121.4 (q, $^1J_{C\text{-}F}$ 268.0), 100.7; δ_F (235 MHz, $CDCl_3$) -62.6 (s); *m/z* (EI) 292 ([^{81}BrM+H]$^+$, 98 %), 290 ([^{79}BrM+H]$^+$, 100 %), 273 (^{81}BrM-F, 8 %), 271 (^{79}BrM-F, 8%), 223 (^{81}BrM-CF_3, 13 %), 221 (^{79}BrM-CF_3, 13 %), 211 (M-Br, 5 %).

5-(4-Bromo-phenyl)-3-pentafluoroethyl-1*H*-pyrazole (162)



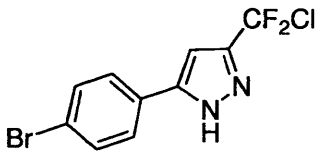
Pyrazole **162** was synthesised in the same way as **161** from **142** (0.160 g, 0.40 mmol) and hydrazine monohydrate (0.04 ml, 0.80 mmol) in ethanol (0.40 ml). After the work up the crude product was purified by flash chromatography to afford **162** (0.121 g, 88 %) as a white solid; mp 146-148 °C; R_F (35 % ethyl acetate in light petroleum) 0.34; (Found: C, 38.66; H, 1.74; N, 8.04; $C_{11}H_6BrF_5N_2$ requires: C, 38.74; H, 1.77; N, 8.21 %); ν_{max}(solid)/cm^{-1} 3152, 1488, 1222, 1115, 1030, 805; δ_H (250 MHz, $CDCl_3$) 7.58 (2H, d, $^3J_{H\text{-}H}$ 8.7, ArH), 7.44 (2H, d, $^3J_{H\text{-}H}$ 8.7, ArH), 6.78 (1H, s, H-4); δ_C (75 MHz, $CDCl_3$) 114.7, 141.9 (t, $^2J_{H\text{-}H}$ 28.0), 132.5, 129.2-110.2 (env, C_3F_7), 127.0, 126.7, 123.7, 102.6; δ_F (235 MHz, $CDCl_3$) -85.0 (3F, s, CF_3), -113.7 (2F, s, CF_2); *m/z* (EI) 343 ([^{81}BrM+H]$^+$, 8 %), 342 ([^{81}BrM]$^+$, 59 %), 341 ([^{79} BrM+H]$^+$, 8 %), 340 ([^{79}BrM+H]$^+$, 60%), 323 (^{81}BrM-F, 4), 321 (^{79}BrM-F, 4), 273 (^{81}BrM-CF_3, 68), 271 (^{79}BrM-CF_3, 70), 164 (100).

5-(4-Bromo-phenyl)-3-heptafluoroethyl-1*H*-pyrazole (163)



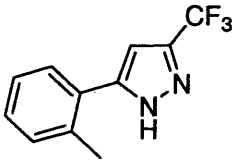
Pyrazole **163** was synthesised in the same way as **142** from **161** (0.160 g, 0.40 mmol) and hydrazine monohydrate (0.04 ml, 0.80 mmol) in ethanol (0.40 ml). After the work up the crude product was purified by flash chromatography to afford **163** (0.117 g, 75 %) as a white solid; mp 132-133 °C; R_F (25 % ethyl acetate in light petroleum) 0.21; (Found: C, 36.83; H, 1.68; N, 7.08; $C_{12}H_9BrF_7N_2$ requires: C, 36.85; H, 1.55; N, 7.16 %); ν_{max}(solid)/cm^{-1} 3143, 3017, 1348, 1226, 1108, 875; δ_H (250 MHz, $CDCl_3$) 7.55 (2H, d, $^3J_{H\text{-}H}$ 8.7, ArH), 7.42 (2H, d, $^3J_{H\text{-}H}$ 8.7, ArH), 6.75 (1H, s, H-4); δ_C (75 MHz, $CDCl_3$) 114.7, 141.9 (t, $^2J_{C\text{-}F}$ 28.0), 132.5, 129.2-110.2 (env, C_3F_7), 127.0, 126.7, 123.7, 102.6; δ_F (235 MHz, $CDCl_3$) -85.7 (3F, s), -111.3 (2F, s); 111.3 (2F, s); *m/z* (EI) 393 ([^{81}BrM+1]$^+$, 4 %), 392 (^{81}BrM$^+$, 32), 391 ([^{79}BrM+1]$^+$, 4 %), 390 ([^{79}BrM$^+$, 33), 273 (^{81}BrM-C_2F_5, 77), 271 (^{79}BrM-C_2F_5, 79), 164 (100).

5-(4-Bromo-phenyl)-3-trifluoromethyl-1*H*-pyrazole (164)



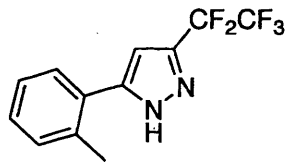
Pyrazole **164** was synthesised in the same way as **161** from **144** (0.147 g, 0.40 mmol) and hydrazine monohydrate (1.03 ml, 0.80 mmol) in ethanol (0.40 ml). After the work up the crude product was purified by flash chromatography to afford **144** (0.110 g, 89 %) as a white solid; mp 148-150 °C; R_F (25 % ethyl acetate in light petroleum) 0.25; (Found: C, 39.24; H, 1.87; N, 8.96; $C_{10}H_6BrClF_2N_2$ requires: C, 39.06; H, 1.97; N, 9.11 %); ν_{max}(solid)/cm^{-1} 3236, 1459, 1223, 1071, 1055; δ_H (250 MHz, $CDCl_3$) 7.55 (2H, d, $^3J_{H-H}$ 8.7, ArH), 7.44 (2H, d, $^3J_{H-H}$ 8.7, ArH), 6.70 (1H, s, H-4); δ_C (101 MHz, $CDCl_3$) 148.3 (t, $^2J_{C-F}$ 32.3), 144.4, 132.4, 127.1, 126.9, 132.6, 122.4 (t, $^1J_{C-F}$, 286), 100.9; δ_F (282 MHz, $CDCl_3$) -46.9 (s); *m/z* (EI) 292 ([^{81}BrM+H]$^+$, 98 %), 290 ([^{79}BrM+H]$^+$, 100 %), 273 (^{81}BrM-F, 8 %), 271 (^{79}BrM-F, 8%), 223 (^{81}BrM-CF_3, 13 %), 221 (^{79}BrM-CF_3, 13 %), 211 (M-Br, 5 %).

5-*o*-Tolyl-3-trifluoromethyl-1*H*-pyrazole (165)



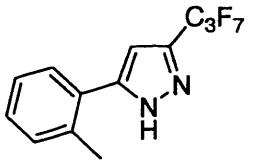
Pyrazole **165** was synthesised in the same way as **161** from **145** (0.100 g, 0.35 mmol), hydrazine monohydrate (0.034 ml, 0.70 mmol) in ethanol (0.35 ml). After the work up the crude product was purified by flash chromaography to afford **165** (0.063g, 80 %) as white solid; mp 85-86 °C; R_F (15 % ethyl acetate in light petroleum) 0.19; (Found: C, 58.65; H, 3.99; N, 12.14; $C_{11}H_9F_3N_5$ requires: C, 58.41; H, 4.01; N, 12.38 %); GC 100 %; ν_{max}(solid)/cm^{-1} 3101, 2964, 1250, 1125, 983, 759; δ_H (300 MHz, $CDCl_3$) 7.39-7.16 (4H, m, ArH), 6.66 (1H, s, H-4), 2.41 (3H, s, CH_3); δ_C (75 MHz, $CDCl_3$); 143.4, 142.6 (q, $^2J_{C\text{-}F}$ 37.7), 135.1, 130.1, 128.4, 127.9, 126.9, 125.3, 120.2 (q, $^1J_{C\text{-}F}$ 268.7), 102.8; δ_F (282 MHz, $CDCl_3$) -62.0 (s) 227 ($[M+H]^+$, 13), 226 (M^+, 100), 157 (M-CF_3, 100), 130 (81).

3-Pentafluoroethyl-5-*o*-tolyl-1*H*-pyrazole (166)



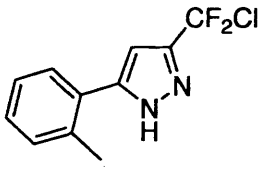
Pyrazole **166** was synthesised in the same way as **161** from **146** (0.117 g, 0.35 mmol), hydrazine monohydrate (0.034 ml, 0.70 mmol) in ethanol (0.35 ml). After the work up the crude product was purified by flash chromaography to afford **166** (0.082 g, 85 %) as white solid; mp 75-77 °C; R_F (20 % ethyl acetate in light petroleum) 0.24; (Found: C, 52.28; H, 3.14; N, 10.12; $C_{12}H_9F_3N_2$ requires: C, 52.18; H, 3.28; N, 10.14 %); ν_{max}(solid)/cm^{-1} 3097, 1198, 1126, 1029, 935, 760; δ_H (300 MHz, $CDCl_3$) 7.39-7.24 (4H, m, ArH), 6.67 (1H, s, H-4), 2.39, (3H, s, CH_3); δ_C (75 MHz, $CDCl_3$) 144.5, 141.8 (t, $^2J_{C-F}$ 28.7), 136.2, 131.2, 129.6, 128.9, 127.9, 126.4, 124.6-107.3 (env, C_2F_5), 105.2, 20.5; δ_F (282 MHz, $CDCl_3$) -84.4 (2F, s), -112.8 (3F, s); *m/z* (ES) 277 ([M+H]$^+$, 100), 149 (60).

3-Heptafluoropropyl-5-*o*-tolyl-1*H*-pyrazole (167)



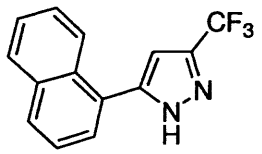
Pyrazole **167** was synthesised in the same way as **161** from **147** (0.135 g, 0.35 mmol), hydrazine monohydrate (0.034 ml, 0.70 mmol) in ethanol (0.35 ml). After the work up the crude product was purified by flash chromaography to afford **167** (0.079 g, 69 %) as white solid; mp 74-75 °C; R_F (35 % diethyl ether in light petroleum) 0.24; (Found: C, 47.86; H, 2.70; N, 8.69; $C_{13}H_9F_7N_2$ requires: C, 47.86; H, 2.78; N, 8.59 %); GC 100 %; ν_{max}(solid)/cm^{-1} 3136, 3004, 2865, 1739, 1207, 992, 912, 748; δ_H (300 MHz, $CDCl_3$) 7.40-7.26 (4H, m, ArH), 6.68 (1H, s, H-4), 2.40 (3H, s, CH_3); δ_C (100 MHz, $CDCl_3$) 144.3, 141.9 (t, $^2J_{C\text{-}F}$ 28.2), 136.1, 131.2, 119.7-106.2 (env, C_3F_7), 105.4, 20.4; δ_F (282 MHz, $CDCl_3$) -80.2 (3F, s), -110.9 (2F, s), -127.0 (2F, s); *m/z* (EI) 327 ([M+H]$^+$, 6 %), 326 (M$^+$, 38), 207 (M-CF_2CF_3, 100), 157 (M-C_3F_7, 33), 116 (M-CF_2CF_3, $ArCH_3$, 14).

3-(Chloro-difluoro-methyl)-5-*o*-tolyl-1*H*-pyrazole (168)



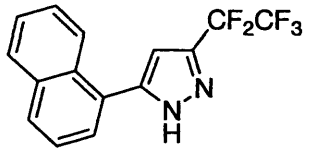
Pyrazole **168** was synthesised in the same way as **161** from **148** (0.106 g, 0.35 mmol), hydrazine monohydrate (0.034 ml, 0.70 mmol) in ethanol (0.35 ml). After the work up the crude product was purified by flash chromaography to afford **168** (0.078g, 92 %) as a white solid; mp 90-91 °C; R_F (20 % ethyl acetate in light petroleum) 0.26; (Found: C, 55.67; H, 3.82; N, 11.68; $C_{13}H_9F_7N_2$ requires: C, 55.45 ; H, 3.74; N, 11.68 %); ν_{max}(solid)/cm^{-1} 3016, 2955, 1221, 1113, 1090, 999; δ_H (300 MHz, $CDCl_3$) 7.39-7.26 (4H, m, ArH), 6.64 (1H, s, H-4), 2.41 (3H, s, CH_3); δ_C (75.5 MHz, $CDCl_3$); 147.0 (t, $^2J_{C\text{-}F}$ 31.7), 143.2, 135.1, 130.1, 128.4, 127.9, 126.9, 125.6, 121.9 (t, $^1J_{C\text{-}F}$ 284.5), 102.3 (t, $^3J_{C\text{-}F}$ 2.11), 19.5; δ_F (282 MHz, $CDCl_3$) -47.02 (s); *m/z* (EI) 243 ([M+H]$^+$, 6 %), 242 (M$^+$, 100), 227 (M-CH_3, 47), 199 (53), 151 (M-C_7H_7, 27).

5-Naphtalen-1-yl-3-trifluoromethyl-1H-pyrazole (169)



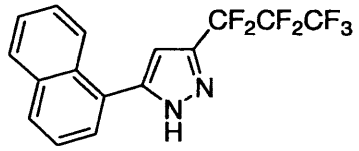
Pyrazole **169** was synthesised in the same way as **161** from **157** (0.097 g, 0.30 mmol) and hydrazine monohydrate (0.03 ml, 0.60 mmol) in ethanol (0.30 ml). After work up, the crude product was purified by flash chromatography to afford **169** (0.067 g, 85 %) as a white solid; mp 90-91 °C; R_F (20 % ethyl acetate in light petroleum) GC 100 %; ν_{max}(solid)/cm^{-1} 3214, 1490, 1388, 1173, 1111; δ_H (300 MHz, $CDCl_3$) 8.00-7.93 (3H, m, ArH), 7.62-7.54 (4H, m, ArH), 6.84 (1H, s, H-4); δ_C (75.5 MHz, $CDCl_3$) 143.5 (q, $^2J_{C\text{-}F}$ 38.5), 143.4, 133.7, 131.0, 130.1, 128.7, 127.5, 127.3, 126.1, 125.2, 124.5, 123.0, 121.2 (q, $^1J_{C\text{-}F}$ 269.6), 104.8; δ_F (282 MHz, $CDCl_3$) -61.9 (s); [HRMS (EI, M) Found: 262.0717. Calc. for $C_{14}H_9N_2F_3$ 262.0718]; *m/z* (EI) 263 ($[M+H]^+$, 17 %), 262 (M^+, 100 %), 241 (M-HF, 25 %), 193 (M-CF_3, 18 %).

5-Naphtalen-1-yl-3-pentafluoroethyl-1H-pyrazole (170)



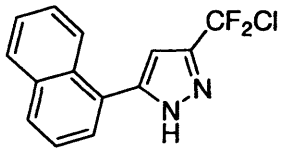
Pyrazole **170** was synthesised in the same way as **161** from **158** (0.107 g, 0.30 mmol) and hydrazine monohydrate (0.03 ml, 0.60 mmol) in ethanol (0.35 ml). After the work up the crude product was purified by flash chromatography to afford **170** (0.080 g, 85 %) as a white solid; mp 98-100 °C; R_F (25 % ethyl acetate in light petroleum) 0.43; ν_{max}(solid)/cm^{-1} 3151, 2980, 1197, 1132, 1097, 1027; δ_H (300 MHz, $CDCl_3$) 8.00-7.93 (3H, m, ArH), 7.62-7.53 (4H, m, ArH), 6.87 (1H, s, H-4); δ_C (75.5 MHz, $CDCl_3$) 143.7, 141.9 (t, $^2J_{C\text{-}F}$ 28.7), 133.8, 131.0, 130.2, 128.7, 127.5, 127.3, 126.6, 126.0, 125.2, 124.5, 124.8-107.2 (env, C_2F_5), 106.0; δ_F (282 MHz, $CDCl_3$) -84.4 (3F, s, CF_3), -113.3 (2F, s, CF_2); [HRMS (EI, M) Found: 312.0687: Calc. for $C_{15}H_9N_2F_5$ 312.0686]; *m/z* (EI+) 313 ($[M+H]^+$, 18 %), 312 (M^+, 100 %), 243 (M-CF_3, 20 %), 193 (M-C_2F_5, 25 %).

3-Heptafluoropropyl-5-naphthalen-1-yl-1*H*-pyrazole (171)



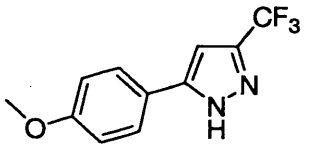
Pyrazole **171** was synthesised in the same way as **161** from **159** (0.127 g, 0.30 mmol) and hydrazine monohydrate (0.03 ml, 0.60 mmol) in ethanol (0.30 ml). After work up the crude product was purified by flash chromatography to afford **171** (0.087 g, 80 %) as a pale yellow oil; R_F (30 % ethyl acetate in light petroleum) 0.37; GC 100 %; ν_{max}(film)/cm^{-1} 3148, 1710, 1226, 1210, 1314, 922; δ_H (300 MHz, $CDCl_3$) 7.98-7.90 (3H, m, ArH), 7.56-7.47 (4H, m, ArH), 6.83 (1H, s, H-4); δ_C (75.5 MHz, $CDCl_3$) 143.7, 141.8 (t, $^2J_{C\text{-}F}$ 28.7), 133.8, 131.0, 130.1, 128.7, 127.5, 127.3, 126.5, 126.0, 125.1, 124.4, 123.9-104.7 (env, C_3F_7), 106.3; δ_F (282 MHz, $CDCl_3$) -80.1 (3F, s, CF_3), -126.9 (2F, s, CCF_2), -110.7 (2F, s, CF_2CF_3); [HRMS (EI, M) Found: 362.0654. Calc. for $C_{16}H_9F_7N_2$ 362.0654] *m/z* (EI) 363 ([M+H]$^+$, 22 %), 362 (M$^+$, 100), 243 (M-C_2F_5, 72), 193 (M-C_3F_7, 30).

3-(Chloro-difluoro-methyl)-5-napthalen-1-yl-*1H*-pyrazole (172)



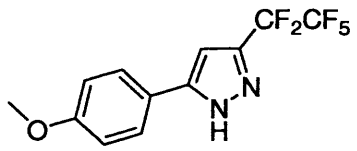
Pyrazole **172** was synthesised in the same way as **161** from **160** (0.097 g, 0.30 mmol) and hydrazine monohydrate (0.03 ml, 0.60 mmol) in ethanol (0.30 ml). After work up the crude product was purified by flash chromatography to afford **172** (0.051 g, 61 %) as a white solid; mp 119-120 °C; R_F (20 % ethyl acetate in light petroleum) 0.36; (Found: C, 60.68; H, 3.02; N, 9.68; $C_{14}H_9ClF_2N_2$ requires: C, 60.34; H, 3.26; N, 10.05 %); ν_{max}(solid)/cm^{-1} 3150, 1197, 1028m; δ_H (300 MHz, $CDCl_3$) 8.02-7.91 (3H, m, ArH), 7.60-7.50 (4H, m, ArH), 6.81 (1H, s, CF_3CH); δ_C (101 MHz, $CDCl_3$) 148.3 (t, $^3J_{C\text{-}F}$ 32.2) 143.4, 133.8, 131.1, 130.1, 128.7, 127.5, 127.4, 126.6, 125.2, 124.6, 122.9 (t, $^2J_{C\text{-}F}$ 287.4), 104.3 ; δ_F (282 MHz, $CDCl_3$) -46.6 (s); *m/z* (EI) 280 ([M+H]$^+$, 28 %), 278 (M-H, 87 %), 243 (M-Cl+F, 100 %), 193 (M-CF_2Cl, 12 %).

5-(4-Methoxy-phenyl)-3-trifluoromethyl-1*H*-pyrazole (173)



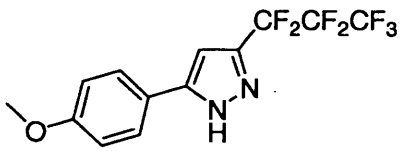
Pyrazole **173** was synthesised in the same way as **161** from **153** (0.365 g, 1.25 mmol) and hydrazine monohydrate (0.12 ml, 2.5 mmol) in ethanol (1.25 ml). After the work up the crude product was purified by flash chromatography to afford **173** (0.247 g, 81 %) as a white solid; mp 115-117 °C; R_F (dichloromethane) 0.16; (Found: C, 54.24; H, 3.54; N, 11.36; $C_{11}H_9F_3N_2O$ requires: C, 54.55; H, 3.75; N, 11.57 %); ν_{max}(solid)/cm^{-1} 3185, 3138, 1616, 1513, 1253, 887; δ_H (300 MHz, $CDCl_3$) 7.66 (2H, d, $^3J_{H\text{-}H}$ 9.1, ArH), 7.03 (2H, d, $^3J_{H\text{-}H}$ 9.1, ArH), 6.86 (1H, s, H-4), 3.85 (3H, s, CH_3); δ_C (101 MHz, MeOD) 162.8, 147.1, 145.4 (q, $^2J_{C\text{-}F}$ 37.2), 129.2, 124.0 (q, $^1J_{C\text{-}F}$ 274.8), 123.1, 116.5, 101.8, 56.8; δ_F (282 MHz, MeOD) -48.3 (s); *m/z* (EI) 243 ([M+H]$^+$, 13 %), 242 (M$^+$, 100 %), 227 (M-CH_3, 54 %), 199 (61), 151 (47).

5-(4-Methoxy-phenyl)-3-pentafluoroethyl-1*H*-pyrazole (174)



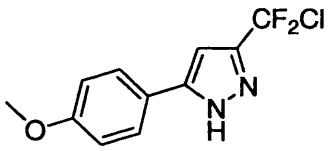
Pyrazole **174** was synthesised in the same way as **161** from **154** (0.458 g, 1.25 mmol) and hydrazine monohydrate (0.12 ml, 2.5 mmol) in ethanol (0.40 ml). After the work up the crude product was purified by flash chromatography to afford **174** (0.266 g, 73 %) as a white solid; mp 130-131 °C; R_F (30 % ethyl acetate in light petroleum) 0.35; (Found: C, 49.22; H, 3.12; N, 9.47; $C_{12}H_9F_5N_2O$ requires: C, 49.32; H, 3.10; N, 9.59 %); ν_{max}(solid)/cm^{-1} 3141, 1512, 1258, 1185, 1029, 930; δ_H (300 MHz, $CDCl_3$) 7.50 (2H, d, $^3J_{H\text{-}H}$ 8.8, ArH), 6.98 (2H, d, $^3J_{H\text{-}H}$ 8.8, ArH), 6.71 (1H, s, H-4), 3.86 (3H, s, CH_3); δ_C (101 MHz, MeOD) 160.5, 145.0, 141.6 (t, $^2J_{C\text{-}F}$ 28.4), 130.4-108.4 (env, C_3F_7), 126.9, 120.8, 114.2, 100.7, 54.4; δ_F (282 MHz, $CDCl_3$) -84.3 (3F, s), -113.1 (2F, s); *m/z* (ES) 293 ([M+H]$^+$, 100 %), 149 (22).

3-Heptafluoropropyl-5-(4-methoxy-phenyl-1*H*-pyrazole (175)



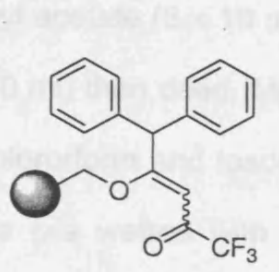
Pyrazole **175** was synthesised in the same way as **161** from **155** (0.503 g, 1.25 mmol) and hydrazine monohydrate (0.12 ml, 2.5 mmol) in ethanol (1.25 ml). After the work up the crude product was purified by flash chromatography to afford **175** (0.319 g, 74 %) as a white solid; mp 117-119 °C; R_F (dichloromethane) 0.24; GC 100 %; ν_{max}(solid)/cm^{-1} 3141, 1512, 1258, 1185, 1029, 930; δ_H (300 MHz, $CDCl_3$) 7.60 (2H, d, $^3J_{H\text{-}H}$ 9.1, ArH), 6.99 (2H, d, $^3J_{H\text{-}H}$ 9.1, ArH), 6.72 (1H, s, H-4), 3.85 (3H, s, CH_3); δ_C (101 MHz, MeOD) 160.4, 145.2, 141.7 (t, $^2J_{C\text{-}F}$ 28.5), 127.2, 126.9-106.2 (env, C_3F_7), 120.9, 114.6, 101.7, 54.4; δ_F (282 MHz, $CDCl_3$) -80.6 (3F, s, CF_3), -111.2 (2F, s, CF_3CF_2), -122.4 (2F, s, CCF_2); [HRMS (EI, M) Found: 342.0603. Calc. for $C_{13}H_9F_7N_2O_1$ 342.0603]; *m/z* (EI) 343 ([M+H]$^+$, 14 %), 342 (M$^+$, 100 %), 327 (M-CH_3, 29 %), 299 (47), 223 (77).

3-Chloro-difluoro-methyl-5-(4-Methoxy-phenyl)-1*H*-pyrazole (176)

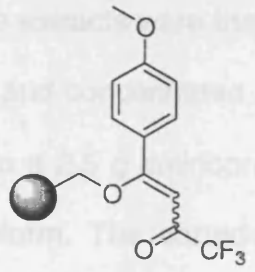


Pyrazole **176** was synthesised in the same way as **161** from **156** (0.398 g, 1.25 mmol) and hydrazine monohydrate (0.12 ml, 2.5 mmol) in ethanol (1.25 ml). After the work up the crude product was purified by flash chromatography to afford **176** (0.257 g, 79 %) as a white solid; mp 140-142 °C; R_F (25 % ethyl acetate in light petroleum) 0.32; (Found: C, 51.24; H, 3.35; N, 10.51; $C_{13}H_7F_7N_2O$ requires: C, 51.08; H, 3.51; N, 10.83 %); ν_{max}(solid)/cm^{-1} 3228, 1615, 1458, 1125, 1110; δ_H (300 MHz, $CDCl_3$) 7.49 (2H, d, $^3J_{H\text{-}H}$ 8.8, ArH), 6.97 (2H, d, $^3J_{H\text{-}H}$ 8.8, ArH), 6.67 (1H, s, H-4), 3.85 (3H, s, CH_3); δ_F (282 MHz, MeOD) -62.2 (s); *m/z* (EI) 260 ([M+1]$^+$, 24 %), 259 (M$^+$ 100).

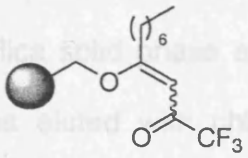
Resin bound Vinylogous Esters Synthesised



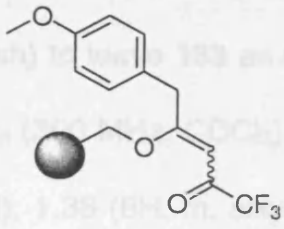
177



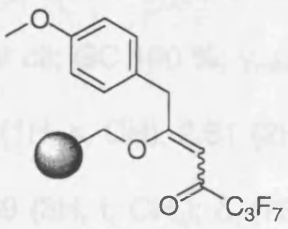
178



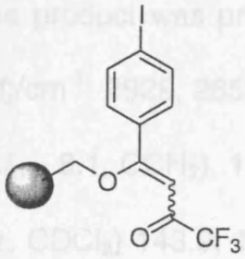
179



180

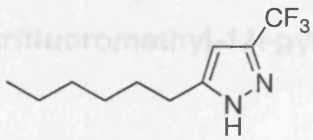


181



182

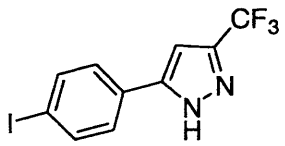
5-Heptyl-3-trifluoromethyl-1*H*-pyrazole (183)



Resin bound vinylogous ester **179** (0.316g, 0.3 mmol) was pre swollen in DCM (3 ml) for 10 minutes. Ethanol (3 ml) was then added and the suspension was shaken for 30 minutes. Hydrazine monohydrate (0.174 ml, 3.6 mmol) was added in one portion and the reaction was shaken at room temperature for 18 hours. The reaction solution was filtered off and the resin was washed with twice alternately with DCM (10 ml) and MeOH (10 ml). The filtrate and the washing were combined and concentrated *in*

vacuo. The resulting clear oil was taken up in concentrated sulfuric acid (5 ml) and stirred for 30 minutes. The acidic solution was diluted with water (20 ml) and extraced with ethyl acetate (3 × 10 ml). The extracts were then washed with water (10 ml) and brine (10 ml) then dried ($MgSO_4$) and concentrated *in vacuo*. The residue was taken up in chlororform and loaded onto a 2.5 g aminopropyl silica solid phase extraction cartridge pre wetted with chloroform. The cartridige was eluted with chloroform, DCM, diethyl ether, EtOAc and MeOH (15 ml of each solvent). The EtOAc wash was concentrated *in vacuo* (TLC analysis had revealed that the product was present in this wash) to leave **183** as a clear oil; GC 100 %; ν_{max}(solid)/cm^{-1} 2929, 2859, 1244, 1129; δ_H (300 MHz, $CDCl_3$) 6.19 (1H, s, CH), 2.51 (2H, t, $^3J_{H-H}$ 8.1, CCH_2), 1.61 (2H, m, alkyl), 1.38 (8H, m, alkyl), 0.89 (3H, t, CH_3); δ_c (75 MHz, $CDCl_3$) 143.9, 140.1 (q, $^2J_{C-F}$ 37.7), 119.0 (q, $^1J_{C-F}$ 268.5), 99.2, 29.1, 26.5, 26.3, 22.6, 20.0, 11.4; δ_F (282 MHz, $CDCl_3$) -61.8 (s); [HRMS (EI, M) Found: 242.1344: Calc. for $C_{11}H_{17}N_2F_3$ 234.1344]; *m/z* (EI) 235 (M+H, 1 %), 234 (M, 9 %), 215 (M-F, 10 %), 164 (M-CF_3, 17 %), 163 (62), 150 (100), 130 (36).

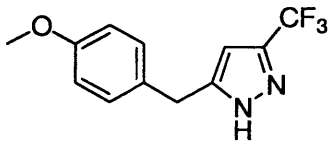
5-(4-Iodo-phenyl)-3-trifluoromethyl-1*H*-pyrazole (184)



Pyrazole **184** was synthesised in the same way as **183** from resin bound vinylogous ester **182** (0.34 g, 0.3 mmol) and hydrazine monohydrate (0.17 ml, 3.6 mmol). After dehydration the crude product was purified using the same SPE technique as used to purify **183** to leave **184** as a white solid; mp 138-140 °C; (Found: C, 35.6; H, 1.9; N,

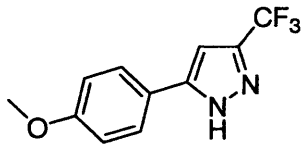
8.3; $C_{10}H_6F_3IN_2$ requires: C, 35.5; H, 1.8; N, 8.3 %); GC 100 %; ν_{max}(solid)/cm^{-1} 3231, 2148, 1246, 1129; δ_H (250 MHz, MeOD) 7.72 (2H, d, $^3J_{H-H}$ 8.5, ArH), 7.38 (2H, d, $^3J_{H-H}$ 8.2, ArH), 6.86 (1H, s, CF_3CCH); δ_C (75 MHz, $CDCl_3$) 145.1, 144.8 ($^2J_{C-F}$ 28.7), 139.5, 129.1, 128.4, 122.9 ($^1J_{C-F}$ 268.0), 102.1, 95.6; δ_F (282 MHz, $CDCl_3$) -63.6 (s); *m/z* (EI) 339 (M+1, 12 %), 338 (M, 100 %), 211 (M-I, 13 %), 191 (68), 142 (M-CF_3I, 37 %).

5-(4-Methoxy-benzyl)-3-trifluoromethyl-1*H*-pyrazole (185)



Pyrazole **185** was synthesised in the same way as **183** from resin bound vinylogous ester **178** (0.31 g, 0.3 mmol) and hydrazine monohydrate (0.17 ml, 3.6 mmol). After dehydration the crude product was purified using the same SPE technique as used to purify **183** to leave **185** as a pale yellow oil; GC 100 %; ν_{max}(solid)/cm^{-1} 2959, 1513, 1244, 1126; δ_H (250 MHz, MeOD) 7.09 (2H, d, $^3J_{C-F}$ 8.9, ArH), 6.81 ($^3J_{C-F}$ 8.9, ArH), 6.38 (1H, s, CF_3CCH), 3.65 (3H, s, CH_3); δ_C (250 MHz, MeOD) 160.0, 143.8 ($^2J_{C-F}$ 37.7), 131.0, 130.9, 130.2, 123.0 ($^1J_{C-F}$ 267.8), 115.2, 103.4, 55.7, 30.1; δ_F (250 MHz, MeOD) -63.0 (s); [HRMS (EI, M) Found: 256.0825: Calc. for $C_{12}H_{11}F_3N_2O$ 256.0824]; *m/z* (EI) 257 (M+1, 23 %), 256 (M, 100), 241 (48), 187 (M-CF_3, 32), 121 (47).

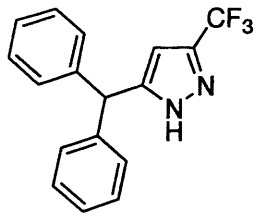
5-(4-Methoxy-phenyl)-3-trifluoromethyl-*1H*-pyrazole (186)



Pyrazole **186** was synthesised in the same way as **183** from resin bound vinylogous ester **178** (0.32 g, 0.3 mmol) and hydrazine monohydrate (0.17 ml, 3.6 mmol). After dehydration the crude product was purified using the same SPE technique as used to purify **183** to leave **186** as a white solid; mp 114-117 °C; GC 100 %; ν_{max}(solid)/cm^{-1} 3233, 1616, 1493, 1244, 1112; δ_H (300 MHz, $CDCl_3$) 7.66 (2H, d, $^3J_{H\text{-}H}$ 9.1, ArH), 7.03 (2H, d, $^3J_{H\text{-}H}$ 9.1, ArH), 6.86 (1H, s, $CHCCF_3$), 3.85 (3H, s, CH_3); δ_F (282 MHz, $CCCl_3$) -61.1 (s); HRMS (submitted); [HRMS (EI, M) Found: 242.0778: Calc. for $C_{11}H_9F_3N_2O$ 242.0667]; *m/z* (EI) 243 (M+1, 22 %), 242 (100), 227 (73), 199 (75), 151 (54).

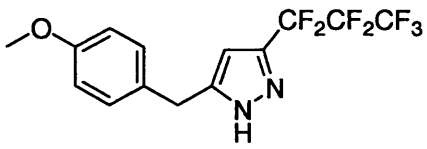
The data accords with those of the same compound synthesised by the solution phase route; page 159

5-Benzhydryl-3-trifluoromethyl-1*H*-pyrazole (187)



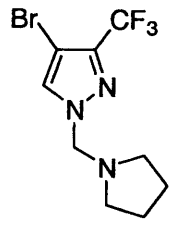
Resin bound vinylogous ester **177** (1.12 g, 1.0 mmol) was pre-swollen in DCM (5 ml) for ten minutes then ethanol (5 ml) was added and the suspension shaken for 30 minutes. Hydrazine monohydrate (0.58 ml, 12 mmol) was then added in one portion and the suspension shaken overnight at room temperature. The reaction solution was filtered off and the resin was washed three times with DCM (20 ml), then twice alternately with methanol (20 ml) and DCM (20 ml). The filtrate and the combined organic extracts were then condensed to a viscous clear yellow oil *in vacuo* which was taken up in concentrated sulphuric acid (25 ml) and stirred at room temperature for 1.5 hours. The acidic miture was carefully diluted with water (25 ml) then allowed to cool to room temperature and extraced three times with DCM (50 ml). The combined organic extracts were washed with brine (50 ml) and then water (50 ml) then dried over $MgSO_4$. The solvent was removed *in vacuo* to leave a white solid which recrystalised from light petroleum to afford **187** (0.248 g, 82 %) as a short white needles; mp 98-99 °C; (Found: C, 67.35; H, 4.19; N, 9.11; $C_{17}H_{13}F_3N_2$ requires: C, 67.54; H, 4.33; N, 9.27 %); GC 100 %; ν_{max}(solid)/cm^{-1} 3109, 3029, 1499, 1243, 1123; δ_H (250 MHz, $CDCl_3$) 7.36-7.13 (10H, m, ArH), 6.22 (1H, s, CF_3CCH), 5.50 (1H, s, $(Ar)_2CH$); δ_c (75 MHz, $CDCl_3$) 147.7, 142.8 (q, $^2J_{C\text{-}F}$ 38.5) 140.9, 128.9, 128.7, 127.4, 121.4 (q, $^1J_{C\text{-}F}$ 269.8), 104.2, 48.6; δ_F (282 MHz, $CDCl_3$) -62.1 (s); *m/z* (EI) 303 (M+1, 52 %), 302 (47), 301 (M-H, 100 %), 233 (M-CF_3, 62 %), 225 (M-C_6H_5, 91 %), 165 (98).

3-Heptafluoropropyl-5-(4-methoxy-benzyl)-1*H*-pyrazole (188)



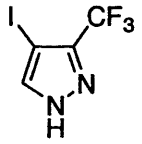
Pyrazole **188** was synthesised in the same way as **187** from resin bound vinylogous ester **181** (1.15g , 1.0 mmol) and hydrazine monohydrate (0.58 ml, 12 mmol). After dehydration the crude product was purified by flash chromatography to afford **188** as a pale yellow oil; R_F (25 % EtOAc in light petroleum) 0.34; GC 94 %; ν_{max}(solid)/cm^{-1} 2962, 2867, 1523, 1301, 1134; δ_H (300 MHz, $CDCl_3$) 7.12 (2H, d, $^3J_{H\text{-}H}$ 8.9, ArH), 8.88 (2H, d, $^3J_{H\text{-}H}$ 8.9), 6.34 (1H, s, CF_2CCH), 3.78 (3H, s, CH_3); δ_c (75 MHz, $CDCl_3$) 158.8, 145.1, 141.6 (t, $^2J_{C\text{-}F}$ 28.7, CF_2C), 129.7, 119.8-108.4 (env, C_3F_7), 114.4, 104.3, 55.2, 30.9; -79.9 (3F, s), -107.8 (2F, s), -126.9 (2F, s); [HRMS (EI, M) Found: 236.0760: Calc. for $C_{14}H_{11}F_7N_2O$ 356.0760]; *m/z* (EI), 357 (M+1, 19 %), 356 (100), 237 (M-C_2F_5, 32), 187 (M-C_3F_7, 41), 118 (43).

4-Bromo-1-pyrrolidin-1-yl-methyl-3-trifluoromethyl-1*H*-pyrazole (189)



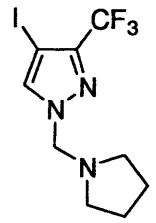
Formaldehyde (0.34 ml of a 37 % aqueous solution, 4.25 mmol) was added to a solution of 4-bromo-3-trifluoromethyl-*1H*-pyrazole (0.85g, 4.0 mmol), and pyrrolidine (0.35 ml, 4.25 mmol) in ethanol (1.3 ml). The reaction was stirred overnight at room temperature, concentrated *in vacuo*, taken up in DCM (30 ml) and washed with water (3 × 15 ml). The organic layer was dried ($MgSO_4$), and concentrated *in vacuo* to leave crude **189** as an off white solid which recrystalised from hexane to afford **189** (1.06 g, 89 %) as a white solid; mp 45-46 °C; (Found: C, 36.4; H, 3.65; N, 14.07; $C_9H_{11}BrF_3N_3$ requires: C, 36.26; H, 3.72; N, 14.10 %), ν_{max}(solid)/cm^{-1} 2951, 2833, 1494, 1210, 1168, 1118; δ_H (300 MHz, $CDCl_3$) 7.58 (1H, s, NCH) 5.05 (2H, s, NCH_2N), 2.71 (2H, t, $^3J_{H\text{-}H}$ 6.13, NCH_2CH_2), 1.78 (2H, t, $^3J_{H\text{-}H}$ 6.1, NCH_2CH_2); δ_C (75 MHz, $CDCl_3$) 140.1 ($^2J_{C\text{-}F}$ 37.0), 132.3, 120.7 ($^1J_{C\text{-}F}$ 270.2), 70.1, 50.4, 23.9; δ_F (282 MHz, $CDCl_3$) -61.9 (s); *m/z* (EI) 216 (^{81}BrM-$C_5H_{10}N$, 100), 214 (^{79}BrM-$C_5H_{10}N$, 98), 197 (11), 195 (12), 115 (35).

4-Iodo-3-trifluoromethyl-1*H*-pyrazole (190)



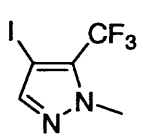
To a stirred solution of **34** (15 mmol, 2.04 g) and ceric ammonium nitrate (7.5 mmol, 3.51 g) in acetonitrile (7.5 ml) iodine (7.5 mmol, 0.95 g) was added and the reaction stirred at 60 °C overnight. After cooling the solvent was removed *in vacuo* and the residue taken up in ethyl acetate, wahed three times with water, dried ($MgSO_4$) and concentrated *in vacuo* to leave the crude product as an off white solid which recrystalised from the minimum amount of hot hexane to afford **190** (3.40 g, 87 %) as a white solid; mp 118-120 °C; (Found: C, 18.7; H, 0.6; N, 10.5; $C_4H_2IF_3N_2$ requires: C, 18.3; H, 0.8; N, 10.7 %), ν_{max}(solid)/cm^{-1} 3156, 2940, 1490, 1277, 1122; δ_H (300 MHz, $CDCl_3$) 7.77 (1H, s, NCH); *m/z* (EI-) 262 ([M+H], 6 %), 261 (M, 100).

4-Iodo-1-pyrrolidin-1-ylmethyl-3-trifluoromethyl-1*H*-pyrazole (191)

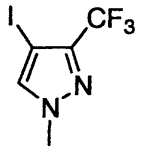


Formaldehyde (0.42 ml of a 37 % aqueous solution, 5.30 mmol) was added to a solution of **190** (1.31g, 5.0 mmol), and pyrrolidine (0.44 ml, 5.30 mmol) in ethanol (1.6 ml). The reaction was stirred overnight at room temperature, concentrated *in vacuo*, taken up in DCM (40 ml) and washed with water (3 x 15 ml). The organic layer was dried ($MgSO_4$), and concentrated *in vacuo* to leave crude **191** as an off white solid which recrystalised from hexane to afford **191** (1.45 g, 84 %) as a white solid; 49-50 °C; (Found: C, 31.52; H, 3.03; N, 12.28; $C_9H_{11}IF_3N_3$ requires: C, 31.32; H, 3.21; N, 12.18 %), ν_{max}(solid)/cm^{-1} 2978, 2846, 1479, 1165, 1121; δ_H (300 MHz, $CDCl_3$) 7.61 (1H, s, NCH) 5.07 (2H, s, NCH_2N), 2.73-2.68 (2H, m, NCH_2CH_2), 1.78 (2H, m, NCH_2CH_2); δ_C (75 MHz, $CDCl_3$) 140.4 ($^2J_{C-F}$ 36.5), 137.0, 120.9 ($^1J_{C-F}$ 36.1), 70.4, 50.1, 23.8; δ_F (282 MHz, $CDCl_3$) -61.6 (s); *m/z* (EI) 262 (M-$C_5H_{10}N$, 100), 243 (7), 207 (11).

4-Iodo-1-methyl-3-trifluoromethyl pyrazole (192) and 4-Iodo-1-methyl-5-trifluoromethyl pyrazole (193)



193



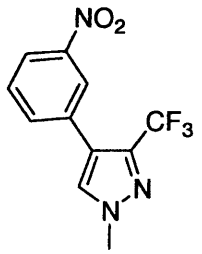
192

Methyl iodide (0.68 ml, 11 mmol) was added to a solution of **190** (2.62 g, 10 mmol) tetra-n-butylammonium bromide, (0.097 g, 0.3 mmol), tetra-n-butylammonium hydrogen sulfate (0.170 g, 0.5 mmol) and sodium hydroxide (2.8 g, 70 mmol) in water (2.8 ml). The reaction was stirred at room temperature for 8 hours then diluted with water (30 ml) and extracted with ethyl acetate (3 × 30 ml). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo* to leave a white solid which was purified by flash chromatography to afford **193** (0.663g, 24 %) R_F (20 % ethyl acetate in light petroleum) 0.76 as a white solid; mp 55-56 °C; GC 100 %; ν_{max}(solid)/cm^{-1} 1532, 1258, 1121, 1007; δ_H (300 MHz, $CDCl_3$) 7.52 (1H, s, NCH), 4.06 (3H, s, CH_3); δ_C (75 MHz, $CDCl_3$) 145.1, 132.2 (q, $^2J_{C\text{-}F}$ 37.0), 119.9 (q, $^3J_{C\text{-}F}$ 270.5), 58.5, 39.7; δ_F (282 MHz, $CDCl_3$) -57.9 (s); [HRMS (FAB, M+1) Found 276.9449. Calc. for $C_5H_5F_3IN_2$ 276.9450]; *m/z* (EI) 277 (M+1, 6 %), 276 (M, 100 %), 275 (4) and

192 (1.49 g, 54 %) as a white solid; mp 58-59 °C; R_F (20 % ethyl acetate in light petroleum) 0.34; (Found: C, 21.9; H, 1.2; N, 10.0; requires C, 21.8; H, 1.5; N, 10.2 %); ν_{max}(solid)/cm^{-1} 1489, 1470, 1210, 1114, 993, 812; δ_H (300 MHz, $CDCl_3$), 7.49 (1H, s, NCH), 3.96 (3H, s, CH_3); δ_C (75 MHz, $CDCl_3$) 143.6 ($^2J_{C\text{-}F}$ 37.22, C3), 137.2,

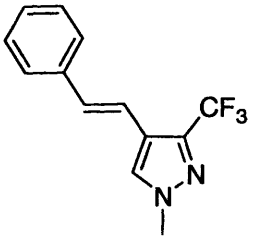
120.8 ($^1J_{C\text{-}F}$ 269.3), 53.8, 39.8; δ_F (282 MHz, $CDCl_3$) -61.6 (s); *m/z* (EI) 277 (M+1, 6 %), 276 (M, 100 %), 257 (8).

1-Methyl-4-(3-nitrophenyl)-3-trifluoromethyl-1*H*-pyrazole (194)



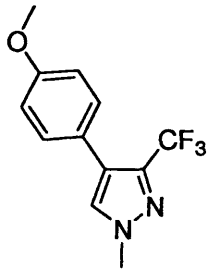
A mixture of pyrazole **192** (0.065 g, 0.23 mmol), 3-nitrophenylboronic acid (0.038g, 0.23 mmol), sodium carbonate (0.075g, 0.71 mmol), tetra-*n*-butylammonium bromide (0.076 g, 0.23 mmol) and palladium acetate (0.002g, 4 mol %) in degassed water (0.47 ml) in a sealed microwave vial flushed with argon was placed into a microwave reactor and heated to 100 °C for ten minutes using a maximum power setting of 60 W with air cooling throughout. After the vial had cooled the reaction solution was extracted with ethyl acetate (3 x 5 ml). The combined extracts were concentrated *in vacuo* to leave a brown solid which was purified by flash chromatography to afford **194** (0.042 g, 67 %) as a clear oil R_f (25 % ethyl acetate in light petroleum) 0.24; GC 100 %; δ_H (300 MHz, $CDCl_3$) 7.41 (1H, s, NCH), 7.31 (2H, d, $^3J_{H\text{-}H}$ 8.9, ArH), 6.92 (2H, d, $^3J_{H\text{-}H}$ 8.9, ArH), 3.82 (3H, s, NCH_3); δ_C (101 MHz, $CDCl_3$) 148.4, 134.7 (q, $^2J_{C\text{-}F}$ 36.4), 134.5, 132.2, 131.3, 129.6, 123.3, 122.5, 121.3 (q, $^1J_{C\text{-}F}$ 270.3), 120.1, 39.7; δ_F (282 MHz, $CDCl_3$) -59.3 (s); [HRMS (EI, M^+) Found: 256.0824. Calc. for $C_{12}H_{11}F_3N_2O$ 256.0832]; *m/z* (EI) 257 ($[M+1]^+$, 37 %), 256 (M^+, 100), 241 (M-CH_3, 93), 213 (72), 198 (M-CF_3), 163 (84)

1-Methyl-4-styryl-3-trifluoromethyl-1-*H*-pyrazole (195)



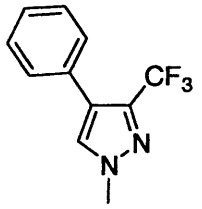
Pyrazole **195** was synthesised in the same way as **194** from **192** (0.097 g, 0.35 mmol), *trans*-2-phenylvinylboronic acid (0.052g, 0.35 mmol), sodium carbonate (0.111g, 1.05 mmol), tetra-*n*-butylammonium bromide (0.113 g, 0.35 mmol) and palladium acetate (0.003 g, 4 mol %) in degassed water (0.72 ml). After the work up the product was purified by flash chromatography to afford **195** (0.050 g, 55 %) mp 89-90 °C; as an off white solid; (Found: C, 60.76; H, 3.91; N, 11.84; $C_{12}H_9F_3N_2$ requires: C, 60.51; H, 3.81; N, 11.76 %), R_f (40 % ethyl acetate in light petroleum) 0.35; GC 100 %; δ_H (300 MHz, $CDCl_3$) 7.62 (1H, s, NCH), 7.45-7.42 (2H, m, ArH), 7.28-7.22 (1H, m, ArH), 6.97 (1H, d, $^3J_{H-H}$ 16.4, *H*C=CH), 6.82 (1H, d, $^3J_{H-H}$ 16.4, CH=C*H*), 3.93 (3H, s, NCH_3); δ_C (75 MHz, $CDCl_3$) 139.0 (q, $^2J_{C-F}$ 36.2), 136.8, 130.2, 128.7, 128.6, 127.8, 126.3, 121.7 (q, $^1J_{C-F}$ 269.5) 119.5, 115.9, 39.6; δ_F (282 MHz, $CDCl_3$) -60.3 (s); [HRMS (EI, M^+) Found: 252.0874. Calc. for $C_{13}H_{11}F_3N_2$ 252.0874]; *m/z* (EI) 253 ($[M+1]^+$, 18), 252 (M^+, 100), 237 (M-CH_3, 8), 231 (20), 183 (M-CF_3, 32), 168 (M-CF_3CH_3, 30), 115 (40).

4-(4-Methoxy-phenyl)-1-Methyl-3-trifluoromethyl-1*H*-pyrazole (196)



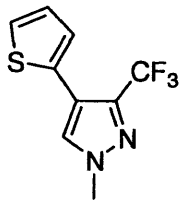
Pyrazole **196** was synthesised in the same way as **194** from **192** (0.097 g, 0.35 mmol), 4-methoxy-benzeneboronic acid (0.054g, 0.35 mmol), sodium carbonate (0.111g, 1.05 mmol), tetra-*n*-butylammonium bromide (0.113 g, 0.35 mmol) and palladium acetate (0.003 g, 4 mol %) in degassed water (0.72 ml). After work up, the product was purified by flash chromatography to afford **196** (0.057 g, 64 %) as a clear oil R_f (25 % ethyl acetate in 40 – 60 petrol) 0.24; GC 100 %; ν_{max}(film)/cm^{-1} 1510, 1248, 1165, 1104; δ_H (300 MHz, $CDCl_3$) 7.41 (1H, s, NCH), 7.31 (2H, d, $^3J_{H\text{-}H}$ 8.9, ArH), 6.92 (2H, d, $^3J_{H\text{-}H}$ 8.9, ArH), 3.95 (3H, s, NCH_3) 3.82 (3H, s, OCH_3); δ_C (75 MHz, $CDCl_3$) 159.2, 138.4 (q, $^2J_{C\text{-}F}$ 36.2), 130.6, 129.7, 122.9, 122.2, 121.7 (q, $^1J_{C\text{-}F}$ 269.4), 113.9, 55.2, 39.5; δ_F (282 MHz, $CDCl_3$) -59.3 (s); [HRMS (EI, M) Found: 256.0824. Calc. for $C_{12}H_{11}F_3N_2O$ 256.0832]; *m/z* (EI) 257 ([M+1]$^+$, 37), 256 (M, 100), 241 (M-CH_3, 93), 213 (72), 198 (M-CF_3, 8), 163 (84).

1-Methyl-4-phenyl-3-trifluoromethyl-1*H*-pyrazole (197)



Pyrazole **197** was synthesised in the same way as **194** from **192** (0.097 g, 0.35 mmol), benzeneboronic acid / anhydride (0.043g, 0.35 mmol), sodium carbonate (0.111g, 1.05 mmol), tetra-*n*-butylammonium bromide (0.113 g, 0.35 mmol) and palladium acetate (0.003 g, 4 mol %) in degassed water (0.72 ml). After the work up the product was purified by flash chromatography to afford **197** (0.065 g, 80 %) as a clear oil (R_f 40 % ethyl acetate in 40 – 60 petrol); GC 100 %; ν_{max}(film)/cm^{-1} 1482, 1290, 1167, 1106 761, 697; δ_H (300 MHz, $CDCl_3$) 7.46 (1H, s, NCH), 7.39-7.31 (5H, m, ArH), 3.97 (3H, s, NCH_3); δ_C (75 MHz, $CDCl_3$) 138.5 (q, $^2J_{C-F}$ 36.2), 130.9, 130.6, 128.6, 128.5, 127.7, 121.6 (q, $^1J_{C-F}$ 269.5), 39.5; δ_F (282 MHz, $CDCl_3$) -59.2 (s); [HRMS (EI, M^+) Found: 226.0718. Calc. for $C_{11}H_9F_3N_2$ 226.0718]; *m/z* (EI) 227 (M+1, 33), 226 (M, 100), 157 (M-CF_3, 42), 142 (M-CF_3CH_3), 116 (36), 89 (47).

1-Methyl-4-thiophen-2-yl-3-trifluoromethyl-1*H*-pyrazole (198)



A mixture of pyrazole **192** (0.097 g, 0.35 mmol) thiophene-2-boronic acid (0.044g, 0.35 mmol), sodium carbonate (0.114g, 1.05 mmol), tetra-*n*-butylammonium bromide (0.113 g, 0.35 mmol), palladium acetate (0.014 g, 4 mol %) and degassed water (0.72 ml) were sealed in a microwave vial under argon. The vial was heated in the cavity of a microwave reactor (100 °C , 60 W, air cooling). After cooling, the reaction solution was extracted with ethyl acetate (3 x 5 ml). The combined organic extracts were concentrated *in vacuo* to leave a brown solid which was purified by flash chromatography to afford **198** (0.060 g, 74 %) as a clear oil R_f (10 % diethyl ether in light petroleum) 0.17; GC 96 %; ν_{max}(film)/cm^{-1} 1489, 1277, 1163, 1118, 1099; δ_H (300 MHz, $CDCl_3$) 7.53 (1H, s, NCH), 7.27 (1H, d, $^3J_{H\text{-}H}$ 5.1, SCH), 7.14 (1H, d, $^3J_{H\text{-}H}$ 3.5, SCCH), 7.05 (1H, dd $^3J_{H\text{-}H}$ 5.1, $^3J_{H\text{-}H}$ 3.5 SCHC*H*) 3.95 (3H, s, NCH_3); δ_C (75 MHz, $CDCl_3$) 138.2, (q, $^2J_{C\text{-}F}$ 40.0), 130.1, 130.9, 127.8, 126.4, 125.1, 123.9 (q, $^1J_{C\text{-}F}$, 269.4) 115.2, 39.5; δ_F (282 MHz, $CDCl_3$) -60.3 (s); [HRMS (EI, M) Found: 232.0282. Calc. for $C_9H_7F_3N_2S$ 232.0282]; *m/z* (EI) 233 ([M+1]$^+$, 24), 232 (M, 100), 217 (M-CH_3, 7), 163 (M-CF_3, 52), 148 (M-CF_3CH_3, 13).

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