Fluorinated liquid crystal systems

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A Thesis Entitled

FLUORINATED LIQUID CRYSTAL SYSTEMS

Submitted by

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2008

Acknowledgements

I would like to thank Dr. Graham Sandford and Dr. Gordon Love, my academic supervisors, for their invaluable help and support throughout this work. Thanks also go to all at SONY MSL, namely Pinar Kilickiran, Anthony Roberts, Akira Masutani, Akio Yasuda, Gabriele Nelles, Nadine Hollfelder, and to SONY and the EPSRC for funding.

To all members of the fluorine group, both past and present, I thank Professor Richard Chambers, Dr. Matthew Cartwright, Miss Emma Parks, Mr Ian Wilson, Mr Graham Patterson, Mr David Armstrong, Dr. Rachel Slater, Dr. Jelena Trmčić and Dr. Christopher Hargreaves.

This research would not have been possible without the help of the highly professional technical staff, namely: Dr. Alan Kenwright, Mr. Ian McKeag and Mrs Catherine Heffernan (NMR); Dr. Mike Jones and Miss Lara Turner (mass spectrometry); Mrs Jarika Dostal (elemental analysis); Dr. Dmitrii Yufit (X-ray crystallography), Mr Lenny Lauchlan (chromatography); Mr Malcolm Richardson and Mr Peter Coyne (glassblowing); Mr Dave Hunter (high pressure laboratory); Mr Tony Baxter and Mrs Elizabeth Wood (stores) and all the other people who worked and studied in the chemistry department and at SONY MSL who have not been mentioned.

I would also like to thank all my family and friends, especially Mum and Dad for their boundless support thoughout my years at Durham. And last but certainly not least, Louise for her patience and for cracking the whip, without which this tome might never have been finished…

Memorandum

The work described in this thesis was carried out at Durham University between August 2004 and September 2007. This thesis is the work of the author, except where acknowledged by reference and has not been submitted for any other degree.

This work has been presented, in part, at:

- Chemistry Department Final Year Postgraduate Symposium, Durham University
  May 2007
- SID International Symposium, Seminar and Exhibition, Long Beach, California
  May 2007
- 15th European Symposium on Fluorine Chemistry, Prague
  July 2007
- 7th Royal Society of Chemistry Fluorine Subject Group Meeting, Leicester
  September 2007

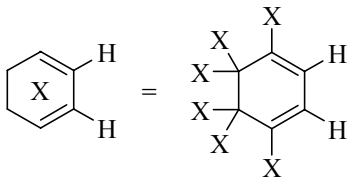
Statement of Copywright

Nomenclature and Abbreviations

Chemical

Ac	acetyl ($CH_3C=O$)
acac	acetylacetonate
Ar	aryl
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binapthyl
bipy	2,2'-bipyridyl
Bu	butyl
cod	cyclooctadiene
Cp	cyclopentadienyl
Cy	cyclohexyl
dba	dibenzylideneacetone
dme	1,2-dimethoxyethane
dmpe	1,2-bis(dimethylphosphanyl)ethane
dppe	1,2-bis(diphenylphosphino)ethane
dppf	1,1'-bis(diphenylphosphino)ferrocene
dppp	1,3-bis(diphenylphosphino)propane
Et	ethyl
LDA	lithium diisopropylamide
Me	methyl
Mes	mesityl (2,4,6-trimethylphenyl)
NIS	*N*-iodosuccinimide
NBS	*N*-bromosuccinimide
NMP	*N*-methyl-2-pyrrolidone
NPFB	nitropentafluorobenzene
Ph	phenyl
phen	1,10-phenanthroline
Pn	pentyl
Pr	propyl

Py	pyridine
RT	room temperature
S_NAr	nucleophilic aromatic substitution
THF	tetrahydrofuran
TMS	trimethylsilyl
Tol	*p*-tolyl
Ts	4-toluene sulphonyl,



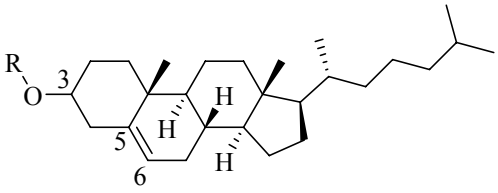
Liquid Crystal

AP	anti-parallel
CTAB	cetyltrimethylammonium bromide, where cetyl = hexadecyl
DFT	density functional theory
DSC	differential scanning calorimetry
E_{th}	threshold electric field
E_x	the applied electric field at *x* % light transmission
ITO	indium tin oxide
K_1, K_2, K_3	"splay, twist and bend" elastic constants
LC	liquid crystal
LCD	liquid crystal display
τ_{decay}	decay time
TN	twisted nematic
T_{NI}	nematic-isotropic transition temperature, or the "clearing temperature"
T_{off}	0% transmission
T_{on}	100% transmission

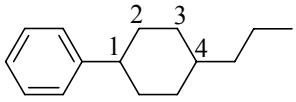
τ_{rise}	rise time
UV	ultraviolet
VA	vertically aligned
V_{th}	threshold voltage, or the “driving voltage”
V_x	the voltage at x % light transmission
γ	rotational viscosity
$\Delta\varepsilon$	dielectric anisotropy
Δn	birefringence

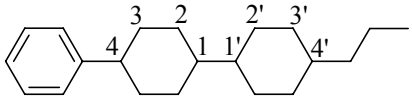
NMR Characterisation

HMBC	heteronuclear multiple bond correlation
HSQC	heteronuclear single quantum correlation
NMR	nuclear magnetic resonance
TOCSY	total correlation spectroscopy

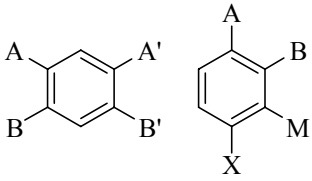


Numbering of carbons in cholesteric molecules





Numbering of carbons in cyclohexyl molecules



Generic labelling of atoms for second order NMR couplings

Instrumentation

Reagents, Materials and Solvents

All starting materials were obtained commercially (Acros, Aldrich, Lancaster, Fluorochem) and used as received. Solvents were dried by standard methods and stored over molecular sieves (4Å).

Gas Liquid Chromatography

Chromatographic analyses were obtained from a Shimadzu GC8A system fitted with a SE30 column.

Elemental Analysis

Carbon, hydrogen and nitrogen elemental analyses were obtained using an Exeter Analytical CE-440 elemental analyser.

NMR Spectroscopy

NMR spectra unless stated otherwise were run in deuteriochloroform and recorded using a Varian VXR 500S spectrometer operating at 500 MHz (^{1}H NMR), 376 MHz (^{19}F NMR) and 125 MHz (^{13}C NMR). Chemical shifts are measured in ppm from $CFCl_3$ (^{19}F) or residual $CHCl_3$ in $CDCl_3$ (^{1}H and ^{13}C) and coupling constants, J, are given in Hz.

Mass Spectroscopy

Mass spectra were obtained using a Fisons VG-Trio 1000 spectrometer linked to a Hewlett Packard 5890 Series II gas chromatograph fitted with a 25m HP1 (methylsilicone) column.

X-ray Analysis

All crystallographic data were collected at T = 120 K on a Bruker SMART-CCD 6000 diffractometer (Mo Kα, λ = 0.71073 Å, ω-scan, 0.3°/frame) equipped with an Oxford Cryostream cooling device. Structures were solved by direct method and refined by full-matrix least squares on F^2 for all data using SHELXTL software. All non-hydrogen

atoms were refined with anisotropic displacement parameters, H-atoms were located on the difference map and refined isotropically.

Melting Point Analysis

Melting points were recorded using a Gallenkamp apparatus at atmospheric pressure unless otherwise stated and are uncorrected.

Abstract

Chapter 1. An introduction to the principles of two different types of LC cell and the design of new fluorinated materials for modern LCD applications is presented here. Discussion includes reasons why fluorinated molecules have become the compounds of choice for display devices, and a history of organo-fluorine chemistry from early discovery of the element, through nucleophilic substitution and debromolithiation reactions of bromoperfluorobenzenes, to very recent developments in synthesis.

Chapter 2. This chapter presents a brief overview of some of our early ideas as to how new fluorinated LCs might be made synthetically, exploiting advances in the field of organo-fluorine chemistry, utilising perfluorobenzene and bromoperfluorobenzene "scaffolds."

Chapter 3. A discussion of how new "model" fluorinated LC materials were obtained via nucleophilic aromatic substitution in bromoperfluorobenzenes is presented in this chapter. The flexibility of the methodology is demonstrated through use of different substrate isomers to afford different aromatic fluorination patterns, and of different nucleophiles to create "families" of homologous materials.

Chapter 4. The versatility of bromoperfluorobenzenes as substrates is exemplified in this chapter, whereby a number of isomers of these "scaffold" molecules were built upon via debromolithiation followed by reaction with electrophiles. This methodology was also applied to functionalised bromofluorobenzenes from chapter 3, and a small library of related compounds was synthesised as in the previous chapter.

Chapter 5. Recent advances in metal C–F bond activation have assisted with our development of a new synthetic route to fluorobiphenyl moieties, based on Suzuki-Miyaura chemistry and presented in this chapter.

Chapter 6. Many of the novel fluorinated materials synthesised in chapters 3 to 4 were sent to SONY MSL, Stuttgart, and their properties determined by tests including electro-optical, DSC, and VHR analysis. The results are discussed and compared, and their potential for application in current LC display devices assessed.

Accompanying Compact Disc

X-ray crystal structure data are supplied on the CD.

1. Introduction

1.1 Liquid Crystalline Materials

There has been a recent rapid advance in active matrix liquid crystal display (AM-LCD) technology utilising materials forming calamitic mesophases.[1] Flat panel displays are becoming increasingly popular due to their high contrast, large viewing angle and rapid switching times, attributes lending to superior picture quality. As a result of these factors, combined with their flatness, low weight and low energy consumption, AM-LCD technology has found applications in many portable devices including mobile phones and laptops.

1.1.1 LC Applications in Display Technology

In AM-LCDs each picture element (or 'pixel') is controlled separately by a thin film transistor (TFT) integrated on the panel glass.[1] Each LCD consists of a glass substrate covered by an indium tin oxide (ITO) layer as transparent electrode material, polariser and birefringent compensator films, colour filters and finally a 5-6 μm thick film of a nematic liquid crystal.

1.1.1.1 Electronic Properties

If the dipole of a LC is aligned parallel to the orientational axis (the long molecular axis) the molecule is termed 'dielectrically positive', and if it is aligned perpendicular, 'dielectrically negative' (Figure 1). A dipole aligned perpendicularly to the long molecular axis may be achieved through lateral fluorination and a 'standard' twisted nematic (TN) cell contains such LCs having a positive dielectric anisotropy. In the 'off' state these are aligned parallel to the alignment layer of the cell, but with an applied voltage the molecules experience a torque towards an orientation perpendicular to the

applied electric field. A standard vertical alignment (VA) cell contains LCs with a negative dielectric anisotropy orientated homeotropically (perpendicularly) to the alignment layer in the 'off' state of the cell.

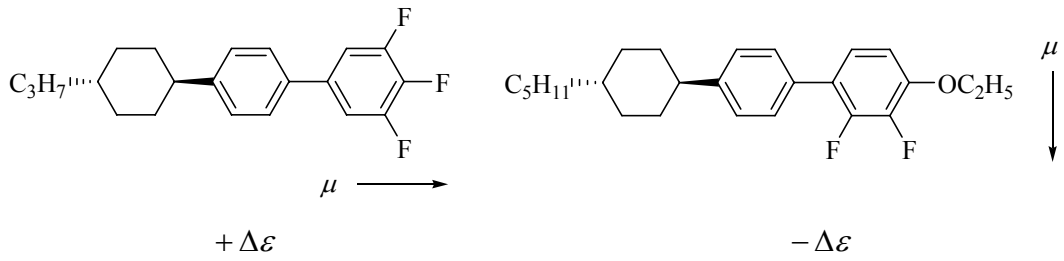


Figure 1. Dielectrically positive and dielectrically negative LCs

1.1.1.2 Twisted Nematic Cells

LC displays were introduced with the invention of the TN cell, invented by Schadt and Helfrich in 1971.[1] For this system, a nematic LC material, with positive dielectric anisotropy, is placed in an ITO lined glass cell and arranged in an homogeneously aligned layer (parallel to the glass) helically twisted by 90º between crossed polarisers (Figure 2). The orientation of the LC material is achieved with the inclusion of an alignment layer of directionally rubbed polyimide within the cell. A homogeneous 'handedness' of the helical structure is ensured with the addition of up to 0.1% of a chiral dopant to the LC material which also eliminates the formation of domains in the display. In the off state, incident light is polarised and the polarisation plane of the light passing through the LC layer is rotated by 90º and is therefore able to exit the second polariser. Under an applied electrical potential the LC helix is deformed and the incident light is unable to pass the crossed polarisers. The cell, illuminated from the back, therefore appears white in the off state and black in the on state. If the applied voltage is that between the threshold voltage and the saturation voltage a grey scale may be achieved.

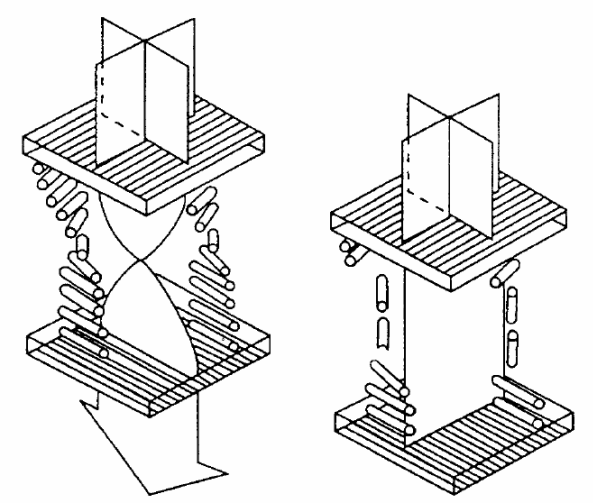


Figure 2.[1] Schematic representation of a TN cell

The time taken for a LC cell to alternate between its "on" and "off" state is known as the switching time. This characteristic has become increasingly important due to the demands of multimedia and video applications, and times of less than 20 – 25 ms (in the year 2000)[1] are particularly desirable.

1.1.1.3 Vertical Alignment Cells

Technological developments have brought about the introduction of other display modes such as vertically aligned (VA) cells. The operation of a VA cell is similar to that of a TN cell (Figure 2) but the polarisers lie parallel, and in the 'off' state with no field applied the long molecular axes of the LC molecules lie perpendicularly to the glass substrate. Incident light is polarised by the first polariser and passes through the second. The LC molecules rotate through 90° under an applied electrical field to lie parallel with the glass substrate. The slower switching time of these cells when compared with the TN cells is

offset by the superior contrast ratio i.e. the ratio of the luminance of the brightest colour (white) to that of the darkest colour (black).

1.1.2 Fluorinated LCs

Structures of early LCs that exhibited a nematic phase at room temperature and which were chemically and photochemically stable were based upon cyanobiphenyl and cyanophenylcyclohexane motifs. Cyano functional groups seemed ideal for use in LC materials as they impart a large dipole moment but limitations soon became apparent. The ability of these materials to 'hold' charge applied across the LC cell, a measurement referred to as the voltage holding ratio (VHR), was not satisfactory.[1] Whilst classes of materials such as tolanes have otherwise excellent properties they are also not generally used due to their relative photochemical instability. Impurities present in the LC blend lead to 'leakage' of current, or 'short-circuits' within the cell, problems highlighted by VHR measurements.

An alternative dipole source was sought and the introduction of robust superfluorinated materials (SFMs) in the early 1980s heralded an improvement in LC reliability. Fluorinated LC molecules were found to reduce rotational viscosities and so, furthermore, they are interesting mixture components for reduction of display switching times.

1.1.2.1 Synthesis

Pressure of the current market has led to a great deal of work on the development of effective methodology, namely short, high yielding, regioselective and flexible routes for the synthesis of new and improved liquid crystals (LC) materials. Typically LC molecules are of the form shown in the schematic representation shown below (Figure 3), based on "blocks" of different alkyl homologues of the same classes of materials. A and

B are commonly rigid cyclic units such as cyclohexane or benzene, a linking group X such as a carboxyl or another cyclic group may be present, Y may be a lipophilic non-polar tail such as a straight alkyl chain whilst Z is a polar group such as a fluorine atom.

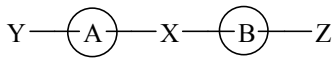
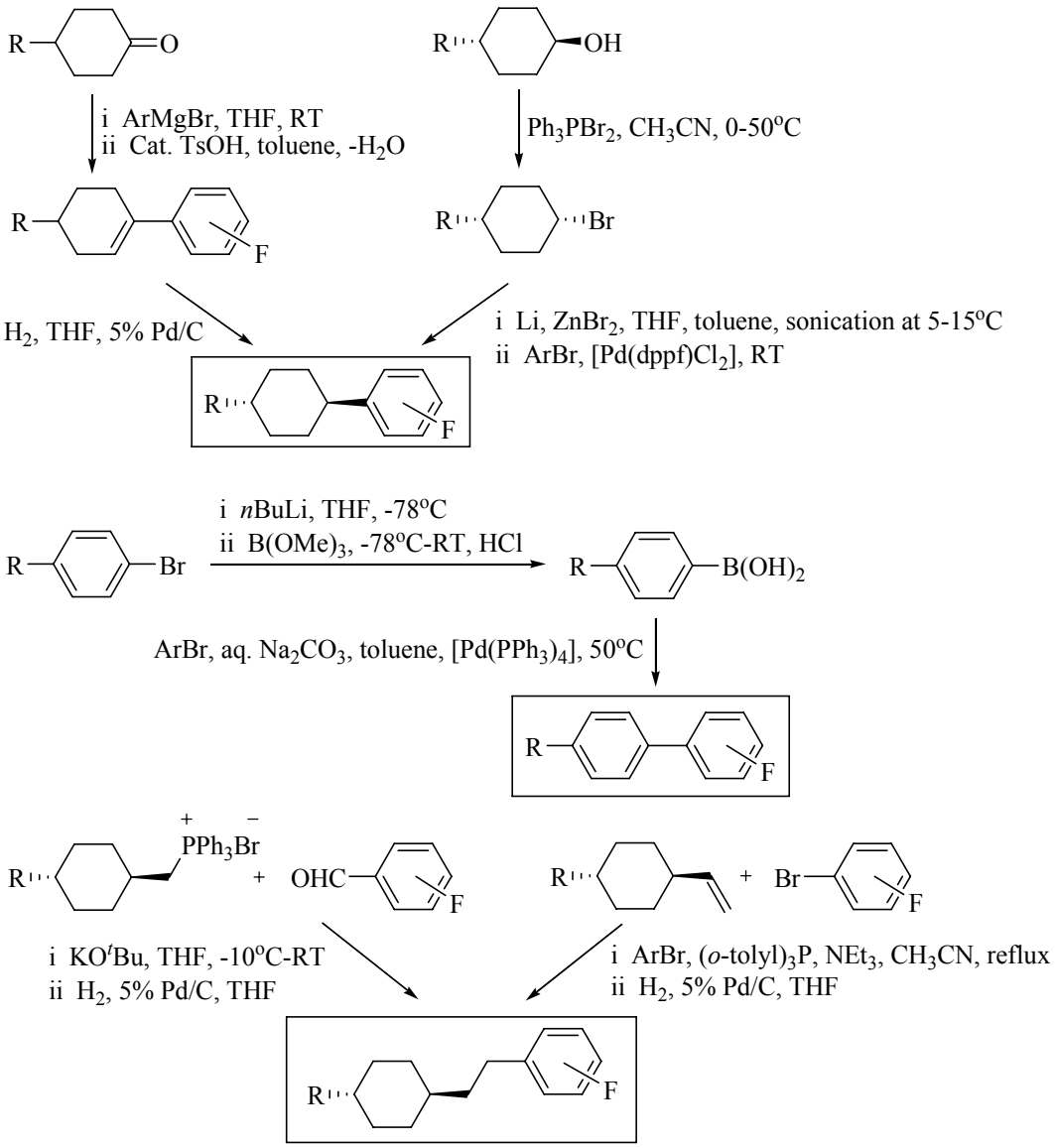


Figure 3. Representation of the rod-like structure of a LC

Syntheses of highly fluorinated LCs usually commence from commercially available aromatic building blocks already bearing the required fluorination pattern (Scheme 1).[1] *Ortho*-metallation of the building blocks generates intermediates which may then be subjected to a variety of organometallic C-C coupling reactions. The activated intermediates are typically coupled to carbonyl compounds, cycloalkyl bromides, aromatic halides, or boronic acids. The Wittig reaction and Heck couplings are synthetic methods commonly used.



Scheme 1.[1] Typical synthetic routes to nematic LCs.

1.2 Organofluorine Chemistry

Fluorine has only been found to occur naturally in twelve organic compounds[2, 3] and a vast new area of synthetic chemistry in which fluorocarbon skeletons replace the usual hydrocarbon skeletons is emerging. Fluorinated materials have been shown to have many

novel properties and effects due to the altered electronic environments present when compared to hydrocarbon systems. Indeed, fluorine-containing compounds are now found throughout the chemical and life-science industries.[4, 5]

Use of fluorinated LCs in modern LCD devices is now widespread due to favourable properties such as the 'robustness' and the strong dipole moments associated with these materials. Methods for synthesising new state-of-the-art materials with new fluorination patterns and novel properties are constantly being developed and so a discussion of major advances in fluorine chemistry is presented here, old and new, as an aid to the understanding of our work.

1.2.1 A Brief History of Fluorine

It is estimated that fluorine is the thirteenth most abundant element found in the earth's crust, the richest sources in the lithosphere being fluorspar (CaF_2) and cryolite (Na_3AlF_6). The development of organofluorine chemistry started relatively late in the 19th century due the hazards associated with and the difficult isolation and manipulation of fluorine. In 1764 a poorly characterised acid was discovered by A. Marggraf, following the reaction of sulfuric acid with fluorspar, which etched glass. This discovery of hydrofluoric acid was followed by the first synthesis of a fluorocarbon by Dumas and Péligot. They synthesised fluoromethane, prepared by heating a mixture of dimethyl sulphate and potassium fluoride. Elemental fluorine itself was only isolated in 1886 though the electrolysis of a HF-KF system by H. Moissan,[6] whilst the first synthesis of hexafluorobenzene was likely to have been obtained by the pyrolysis of tribromofluoromethane (Scheme 2).[7]

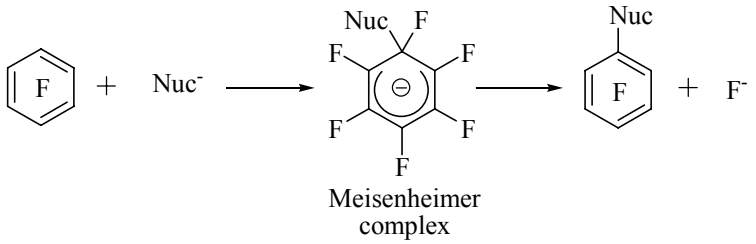
$$6CFBr_3 \xrightarrow[630\text{-}640^oC]{Pt} 9Br_2 + C_6F_6 \qquad 55\%\ \text{yield}$$

Scheme 2.[7] Synthesis of hexafluorobenzene

1.2.2 Properties and Electronic Effects of Fluorine in Organic Materials

The chemistry of fluorocarbons is mechanistically novel and often complimentary to reactions typically observed with hydrocarbons. The replacement of a hydrogen atom with a fluorine atom in a molecule does not greatly distort its geometry. The volatilities of fluorocarbons are surprisingly similar to those of analogous hydrocarbon systems despite their increased molecular weight and this is an indication of the weakened intermolecular bonding forces. Methods for handling these systems are, therefore, similar to those employed for hydrocarbons. They are renowned for their high thermal stability whilst elemental fluorine is so very reactive due to the fact that it forms such strong bonds with other elements including carbon. ^{19}F has a nuclear spin of ½ and this makes NMR spectroscopy a powerful structural probe for the characterisation of fluorocarbons.

Hexafluorobenzene has been shown to be largely unreactive to electrophiles,[8] the reagents that normally give rise to the substitution of hydrogen via cationic transition states in reactions involving benzenoid compounds because electrophilic substitution would require the elimination of "F^+", an energetically unfavourable species. It was quickly established that highly fluorinated heteroaromatic species are very susceptible to nucleophilic attack, from the reaction of methoxide ion with hexafluorobenzene[9] liberating fluoride ion. The reaction proceeds via a carbanionic transition state known as the Meisenheimer complex (Scheme 3), a characteristic intermediate found in nucleophilic substitution reactions of fluorinated heterocycles. A wide range of reagents have been used to form C_6F_5X derivatives from hexafluorobenzene via this mechanism[8] and an extensive chemistry has since emerged.



Scheme 3. Nucleophilic substitution in hexafluorobenzene

Ortho and *meta* fluorine atoms relative to a site of nucleophilic attack have been found to be significantly activating, whilst a *para* fluorine atom is slightly deactivating with respect to hydrogen at the same position. The origins of these effects of fluorine have been rationalised on the basis of the following principles. In a β-position to a carbanionic site (Figure 4, **A**) fluorine is strongly stabilising due to an inductive electron withdrawing effect, I_σ. Conversely, fluorine is slightly destabilising in an α-position to a carbanionic site (Figure 4, **B**) due the net result of two combined effects: stabilising inductive electron withdrawal, I_σ, is again present but electron pair repulsion, I_π, has a dominant destabilising effect. Repulsion occurs between the lone pairs of the carbanion and of the fluorine atom and is greater for sp^2 hybridised carbanions than for sp^3 carbanions due to the closer proximity of the electron pairs. The activating effect of *ortho* and *meta* fluorine atoms has been therefore attributed to ion-dipole interactions (Figure 4, **C**) making the carbon under attack more electron deficient in the initial state.[8] The explanation for the deactivating effect of *para* fluorine atoms is based on the assumption that the negative charge is greatest at the position *para* to the point of attack (Figure 4, **D**), and hence the carbanion is in an α-position to a fluorine atom. It has been suggested[10] that for other halogen atoms such a charge would be destabilised in the order: F > Cl > Br > I ≈ H.

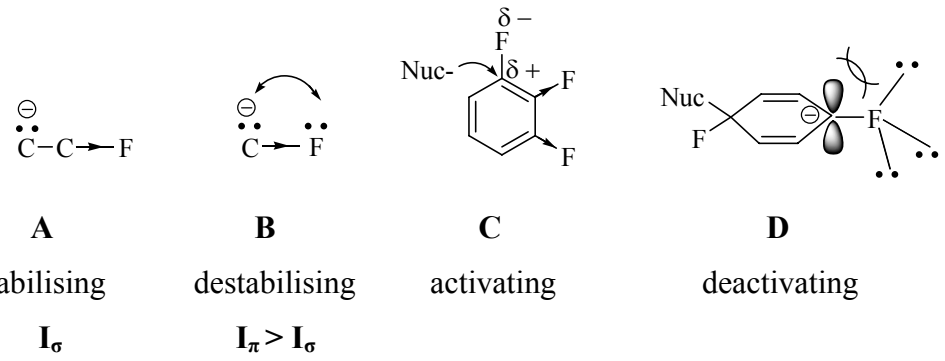
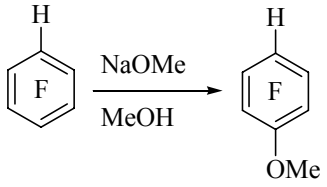


Figure 4. Electronic effects of fluorine atoms

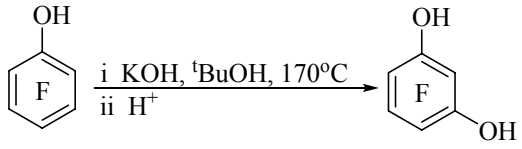
It follows that the orientations of substitution in polyfluorobenzenes are governed by the necessity to have the maximum number of activating fluorines (*ortho* and *meta*) and the minimum number of *para* fluorines. Three different possible sites are available for further attack on the aromatic ring of C_6F_5X systems following initial substitution. Substitution may be observed *ortho*, *meta* and *para* to the group X, and patterns for further substitution have been established. The fluorine atom preferentially displaced by a nucleophile on a polyfluorinated benzene ring, and the rate at which substitution occurs may be determined by several combined effects. The activating effects of the ring substituents, interactions between ring substituents and the incoming nucleophile, the solvent used and the position of fluorine atoms on the ring are all factors which may determine the position of substitution.

The *para* disubstituted product 1,4-C_6F_4XY is the isomer most commonly observed[8] resulting from the reaction between a C_6F_5X compound with a nucleophile Y (Scheme 4).[11]



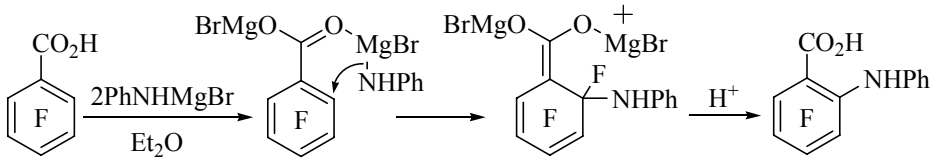
Scheme 4.[11] *para* substitution in pentafluorobenzene

Vigorous conditions are required for *meta* substitution which is the least common site of attack. C_6F_5OH (effectively $C_6F_5O^-$) with KOH gives exclusively meta orientation (Scheme 5).[12] If substitution was to occur at the *ortho* or *para* positions the result would be an unfavourable placement of negative charge on the carbon next to the OH group in the Meisenheimer intermediate.



Scheme 5.[12] *meta* substitution in pentafluorophenol

Ortho substitution may also occur preferentially and results from specific interaction between a ring substituent and the incoming nucleophile such as that between a carbonyl oxygen and the magnesium atom of a Grignard reagent (Scheme 6).[9]



Scheme 6.[9] *ortho* substitution in pentafluorobenzoic acid

The polarity of the solvent may profoundly influence the variation in the proportions of *ortho*, *meta* and *para* substitution of fluorine by nucleophiles in C_6F_5X compounds. The interactions between the substituent X in C_6F_5X and the incoming nucleophile may be greatly affected: predominantly *ortho* substitution arises due to a relatively strong bond in non-polar solvents which is weakened in polar solvents. With a nucleophile such as $C_6F_5O^-$ a large change in the *ortho*:*para* ratio for monosubstitution in $C_6F_5NO_2$ takes place on changing from a polar to a non-polar solvent despite the absence of hydrogen-

bonding effects. In acetonitrile the *ortho*:*para* ratio is 2:98 whereas it is 89:11 in dioxane.[13]

In conclusion, pentafluorobenzene derivatives C_6F_5X always undergo predominantly *para* substitution based on the effects of the fluorine alone. Strong electron donating groups will increase the proportion of *meta* substitution, provided steric effects do not prevent conjugation of the π-electrons on the substituent with the aromatic ring. Special interaction between the incoming nucleophile and the substituent X can be the only reason for enhanced *ortho* substitution.

Polychloro and polybromo derivatives have been studied to a lesser degree than polyfluoro systems. Fluorocarbon aromatic systems are more reactive than chlorocarbon systems which may be accounted for by taking into consideration the contribution to reactivity of ion-dipole effects imposed by structure. In reactions involving polybromofluoroheterocyclic systems, fluorine is preferentially substituted by "hard" nucleophiles such as MeO^- whereas bromine is substituted by "soft" nucleophiles such as PhS^-. Regioselective introduction of functional groups is therefore made possible with the use of polyfluorobromo starting materials.[14]

1.3 Preparation of Highly Fluorinated Aromatic Compounds

1.3.1 Bromoperfluorobenzene Systems

Bromoperfluorobenzenes pose as attractive synthetic scaffolds due to the lability of bromine atoms, upon which chemistry such as debromometallation or metal catalysed couplings may be performed, and also due to the highly electron deficient aromatic core of these molecules which presents the possibility of their functionalisation via S_NAr reactions. Selective replacement of fluorine atoms with bromine in hexafluorobenzene leads to a series of isomers (11 in total excluding hexafluorobenzene and hexabromobenzene) and provides a simple method in which many different halogenation

patterns on aromatic rings may be obtained which may be particularly useful in the synthesis of LC-type molecules. This body of work is based upon the use of bromoperfluorobenzene subtrates as synthetic 'scaffolds' and so an overview of relevant literature is included here.

1.3.1.1 Synthesis

There are many synthetic routes to bromoperfluorobenzenes which usually involve several steps. A summary is presented here (Table 1) of the more simple single step routes to these materials via direct bromination of the analogous fluorinated aromatic precursors.

Table 1. Synthesis of bromoperfluorobenzenes via bromination of analogous fluoroaromatic precursors

Product	Reagents	Yield /%	Ref.	Product	Reagents	Yield /%	Ref.
C_6BrF_5	NBS, $BF_3.H_2O$	96	15	1,2,4-$Br_3C_6F_3$	Br_2, Al	-	16
	BrF_3	27	17				
	SO_3/ H_2SO_4, $AlBr_3$, Br_2	81	18				
	SbF_5, BrF_3 (= BrF_2SbF_6)	57	19	1,3,5-$Br_3C_6F_3$	Br_2, *uv* light	impure, low yield	20
	BF_3, BrF_3 (= BrF_2BF_4)	47					
	i. KSH ii. Cl_2, Br_2	-	21				
1,2-	Br_2, SO_3/ H_2SO_4,	38	22	1,2-	Br_2, Al	-	23

Product	Reagents	Yield /%	Ref.	Product	Reagents	Yield /%	Ref.
$Br_2C_6F_4$	$AlBr_3$			$F_2C_6Br_4$			
1,3-$Br_2C_6F_4$	not reported	-	-	1,3-$F_2C_6Br_4$	Br_2, *uv* light	4	20
1,4-$Br_2C_6F_4$	Br_2, SO_3/ H_2SO_4, $AlBr_3$	78	24	1,4-$F_2C_6Br_4$	Br_2, *uv* light	3	20
1,2,3-$Br_3C_6F_3$	not reported	-	-	C_6Br_5F	H_2SO_4, Br_2, I_2, Fe	71	25
					Br_2, Al	-	26

1.3.1.2 S_NAr Reactions

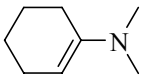
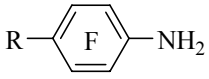
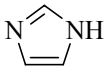
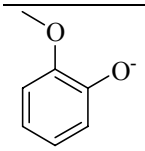
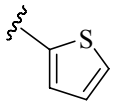
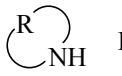
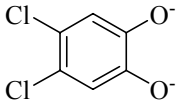
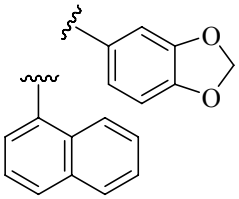
Nucleophilic aromatic substitution[8] provides a simple method for heteroatom (O, N, S) functionalisation of perfluoroaromatic compounds. Stabilisation of the charged Meisenheimer intermediate of these reactions may be achieved though replacement of fluorine with other halogens on the aromatic scaffold, of which the use of bromine is particularly interesting since it presents a labile 'handle' for further chemistry and functionalisation. A review of S_NAr reactions with $C_6F_nBr_m$ compounds (n + m = 6) is presented here.

1.3.1.2.1 Reactions of Bromopentafluorobenzene and Derivatives

Reactions of nucleophiles (such as O, C, N) with brominated perfluorobenzene systems described in the literature are mainly limited to C_6F_5Br (Table 2). Methoxide ion in methanol is used routinely to establish patterns of nucleophilic substitution in polyfluoroaromatic compounds and identifies sites for kinetically controlled reactions

because of the irreversibility of the reaction. Attack has been shown to occur predominantly in the *para* position relative to the bromine atom due to the greater stablisation attained by placing the negative charge build up in the Meisenheimer complex adjacent to a bromine atom rather than a fluorine (section 1.2.2). *Ortho* substitution may occur with some nucleophiles but only to a small extent, while meta substitution is rarely observed. Substitution of bromine has not been observed with 'hard' nucleophiles.

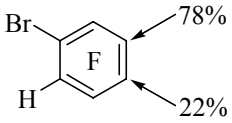
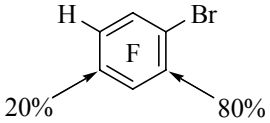
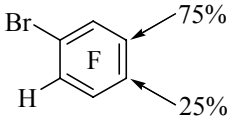
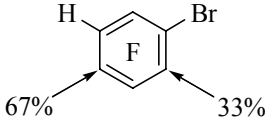
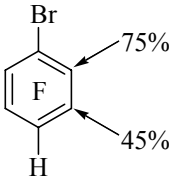
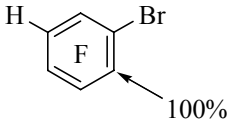
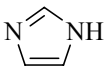
Table 2. S_NAr reactions (fluorine substitution) of C_6F_5Br. Substitution occurs predominantly *para* to the bromine in all cases.

Oxygen Nucleophile	Ref.	Carbon Nucleophile	Ref.	Nitrogen Nucleophile	Ref.
HO^-	11	C_6F_5Li	27	NH_3	28
MeO^-	11, 29	$PhC{\equiv}CLi$	30	$NHMe_2$	11
EtO^-	31	RCH_2CO_2Et R = CN, CO_2Et	32	N_2H_4	11
$^nPrO^-$	33		34*	 R = H, F	35
$C_6F_5O^-$	36	RCH_2CN $R = C_6F_5$	38		37
	39	Ph 3-Me-Ph 4-Me-Ph 3-OMe-Ph 4-OMe-Ph 3,4-$(OMe)_2$-Ph 		 R = $(CH_2)_{2\text{-}4}$	41
	42*		40		43
				$CH_3NH(CH_2)_2NHCH_3$	44*

*Initial substitution is followed by *ortho*-cyclisation

Examples of S_NAr reactions with the isomers C_6F_4BrH have also been reported (Table 3), illustrating the interesting effects of an additional functional group (in this case a hydrogen atom) on the regioselectivity of these reactions. Explanations for the selectivity of the resulting isomers are involved but mainly follow the rules outlined earlier in this chapter. The reaction of dimethylamine with 2-bromo-1,3,4,5-tetrafluorobenzene generates an unexpected isomer distribution, the nucleophile favouring a position *para* to the bromine rather than the hydrogen, and this regioselectivity has been explained through steric considerations.[45]

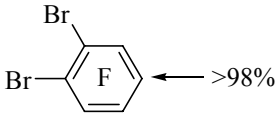
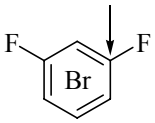
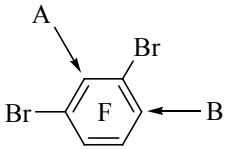
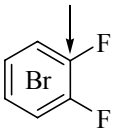
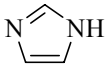
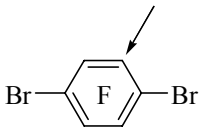
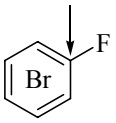
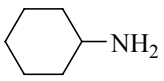
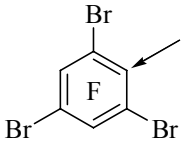
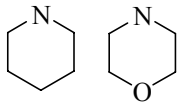
Table 3. S_NAr reactions (fluorine substitution) of bromopolyfluorobenzenes.

Substrate and site of nucleophile attack	Nucleophile	Ref.	Substrate and site of nucleophile attack	Nucleophile	Ref.
	MeO^-	45		MeO^-	45
	Me_2NH	45		Me_2NH	45
	MeO^-	29			37

1.3.1.2.2 Reactions of Dibromo and Polybrominated Perfluorobenzenes

Nucleophilic attack upon dibrominated and polybrominated perfluorobenzenes in S_NAr reactions has been studied less comprehensively. Literature precedent mainly concerns the action of methoxide ion upon these substrates (Table 4).

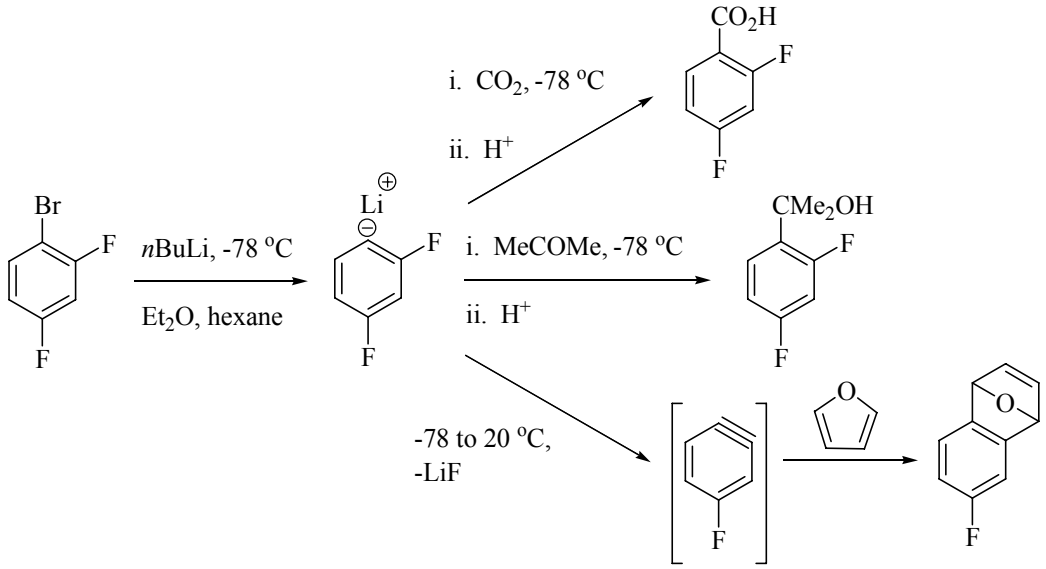
Table 4. S_NAr reactions (fluorine substitution) of polybromo-perfluorobenzenes, with product isomer distributions shown where possible.

Substrate	Nucleophile	Ref.	Substrate	Nucleophile	Ref.
	MeO^-	29		MeO^-	29
	MeO^- 3% A, 97% B	29		MeO^-	29
	 100% B	37			
	MeO^-	29		MeO^-, NH_2 	25
	$[(TMS)OCH_2CF_2]_2$	46			
	MeO^-	29		RO^- R = ^{i}Pr, $(CH_2)_{3\text{-}5}CH_3$	47
				H_2NMe, $HNMe_2$, 	48

1.3.1.3 Debromometallation

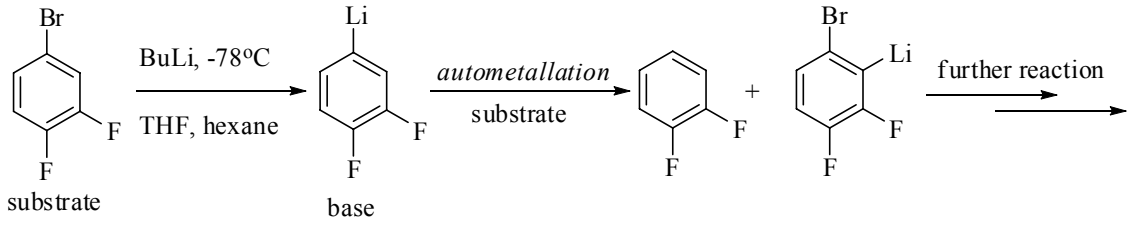
Halogen-metal exchange is a well-established technique for the regiospecific generation of aromatic anions.[49] Aromatic bromine-lithium exchange is very rapid and allows for lithiation to be carried out at positions in a molecule that would not normally be available due to the presence of kinetically or thermodynamically more acidic sites. Incorporation of bromine 'handle' atoms in bromoperfluorobenzenes facilitates the attachment of

functional groups via debromolithiation using strong bases such as butyllithium or lithium di*iso*propylamide. The intermediate lithiated anionic species may be reacted with electrophiles at -78 °C such as carbon dioxide to form carboxylic acids,[50] or with acetone to form fluorinated 2-arylpropan-2-ols[49] (Scheme 7). Alternatively, warming of the lithiated species to room temperature induces benzyne formation through *ortho* LiF elimination and these highly reactive species have been trapped with furan via Diels-Alder additions.[49]



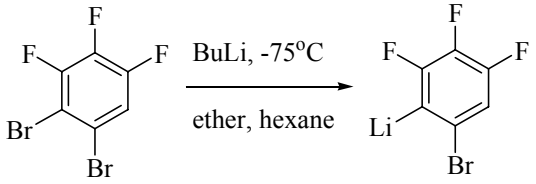
Scheme 7.[49, 50] Reactions of fluoroaryllithium species with electrophiles

In addition to temperature, solvent choice has also proven to be critical especially for non-perfluorinated bromobenzenes. Butyllithium in ether-hexane at -78 °C brings about clean bromine-lithium exchange, whilst in THF-hexane use of LDA results in hydrogen-lithium exchange.[49, 50] Other hydrocarbon solvents give more highly aggregated and less reactive organolithium species. Autometallation may also occur in THF (Scheme 8) in which the initially formed organolithium can act as a base toward unlithiated substrate leading to additional side products. The degree of autometallation is controlled mainly by the pK_a of the substrate bromide.



Scheme 8.[51] Autometallation in the lithiation of fluorinated benzenes

It is generally believed that bromine-lithium exchange is faster than acidic hydrogen-lithium exchange.[51] If butyllithium in ether-hexane is used, and both bromine and hydrogen atoms are available for lithium exchange on an aromatic substrate molecule, then the bromine atom is substituted preferentially (Scheme 9).[49, 51]



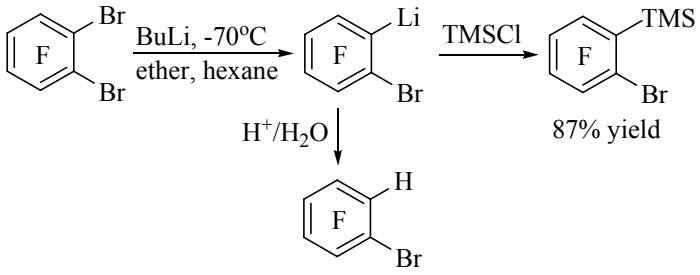
Scheme 9.[49, 52] Br-Li exchange occurring preferentially to H-Li exchange

1.3.1.3.1 Lithiation of Bromoperfluorobenzene Derivatives

Bromopentafluorobenzene is commonly used as a source of the pentafluorophenyl moiety, for example as described in recent work by Green and co-workers in the synthesis of $B(C_6F_5)_3$ from BCl_3.[53]

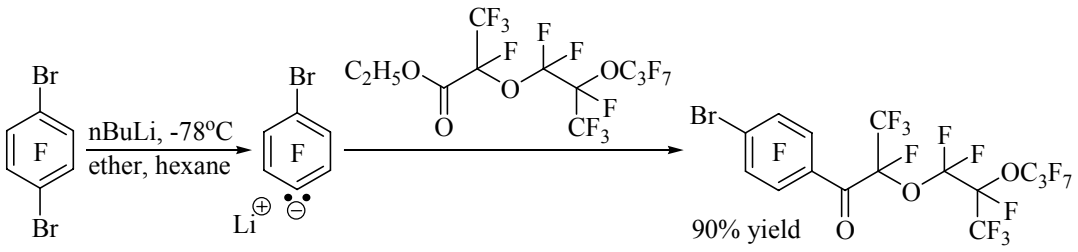
However, lithiation of bromoperfluorobenzenes bearing more than one bromine atom is less well described. One of the few reports of the lithiation of 1,2-dibromo-3,4,5,6-

tetrafluorobenzene describes the preparation of 2-bromotetrafluorophenyl derivatives (Scheme 10).[54]



Scheme 10.[54] Functionalisation of 1,2-dibromotetrafluorobenzene

In a similar manner, Chen and Tamborski reacted a perfluoroalkylether ester with the lithium derivative of 1,4-dibromotetrafluorobenzene (Scheme 11).[55] No other examples currently exist of debromometallation reactions of bromoperfluorobenzenes bearing more than two bromine atoms.

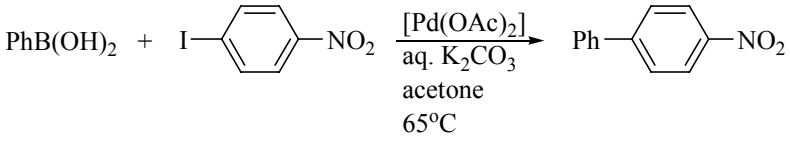


Scheme 11.[55] Functionalisation of 1,4-dibromotetrafluorobenzene

1.3.2 Cross-Coupling of Fluoroaromatic Systems via C−F Bond Activation at Metal Centres

Metal catalysed carbon-carbon cross-coupling reactions are commonly used as routes to biaryl 'backbones' of LC molecules, and so a short introduction to this chemistry is presented here.

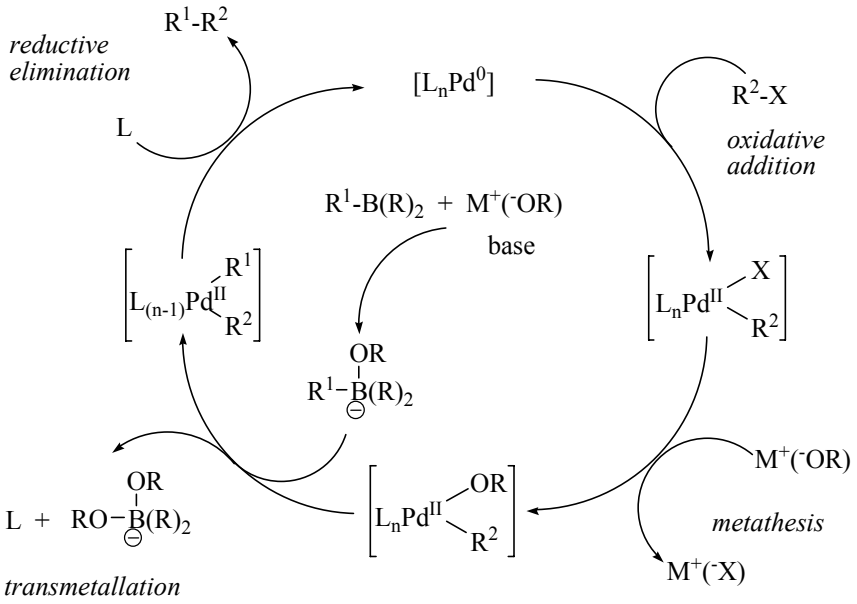
Millions of tons of chemicals are produced annually using homogeneous catalysis by transition metal complexes. Transition-metal catalysed chemistry has yielded many efficient, selective processes under mild, easily controllable conditions which are based on the activation of chemical bonds by transition metals, followed by transformations in the metal coordination sphere and subsequent liberation of the product. Synthesis of unsymmetrical biaryls by C−C bond formation, proceeding via metal-activation of carbon−halogen bonds (halogen = Cl, Br, I), is now well described (Scheme 12).[56]



Scheme 12.[56] Metal-catalysed biaryl synthesis

1.3.2.1.1 Suzuki-Miyaura Cross-Coupling Reactions

The Suzuki-Miyaura[57] C−C cross-coupling reaction is frequently used for forming the biphenyl backbone of many rod-like liquid crystals. Suzuki, and related palladium catalysed C−C couplings, usually require one of the alkyl or aryl moieties undergoing reaction to have a labile halogen, triflate or phosphonate ester 'handle' at the site of the coupling (Scheme 13).



R = alkyl, OH, O-alkyl; R^1 = alkyl, allyl, alkenyl, aryl;

R^2 = alkenyl, aryl, alkyl; X = Cl, Br, I, OTf, $OPO(OR)_2$

Scheme 13.[57] Mechanism of Suzuki-Miyaura Cross-Coupling

1.3.2.1.2 Catalytic Activation of C−F Bonds

Despite extensive developments in the field of homogeneous metal catalysis, application to the activation of C−F bonds remains a fundamental research challenge. The difficulties associated with this chemistry, and the relative inertness of the C−F bond to activation through metal insertion, may be attributed to the strength of the C−F bond (485 kJ mol^{-1}) when compared to other C−halogen bonds (C−Br has a bond energy of 276 kJ mol^{-1}). Oxidative addition of the metal catalyst into the carbon−halogen bond is considered to be rate determining and so activation of these bonds gets progressively more difficult up the group, from iodine to fluorine.

Transition-metal catalysis may prove to be highly desirable for the functionalization of polyfluorinated organic compounds and, as a result, much research effort has been devoted to the activation of strong C−F bonds by transition metal complexes. Selective replacement of fluorine atoms in polyfluoroaromatic compounds by transition-metal catalysed processes for the synthesis of partially fluorinated molecules is still considered to be difficult, although much progress has been made in C−F bond activation of these substrates mainly at transition metal centres prompting the publication of a review in this field.[58]

Activation of C−F bonds is ultimately very important in organometallic chemistry and catalyst development because this reaction contributes to the fundamental understanding of the reactivity of very stable bonds. Only recently have successful C−C cross-couplings of fluoroaromatic compounds been reported that proceed via the catalytic activation of C−F bonds and a short review is included here as an introduction to our studies concerning palladium catalysed Suzuki-Miyaura reactions of perfluoraromatic systems that are described in this thesis.

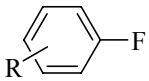
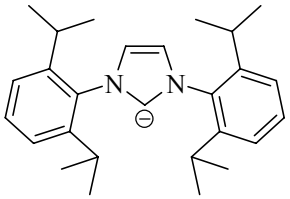
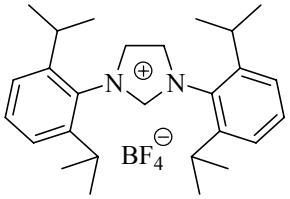
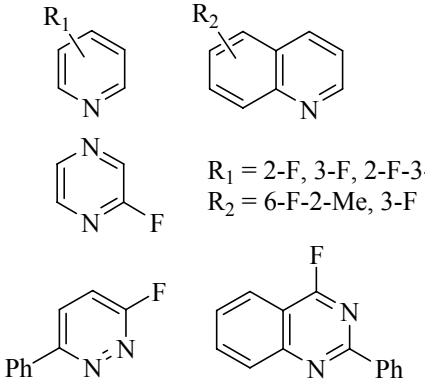
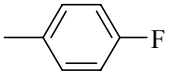
1.3.2.2 Monofluoroaromatic Compounds

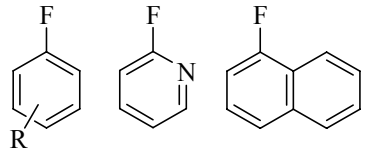
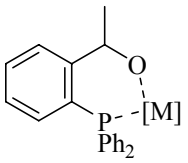
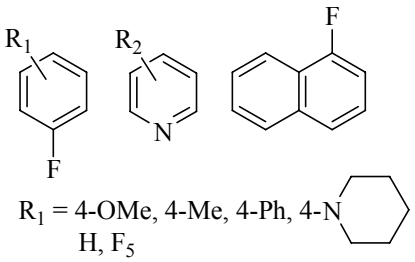
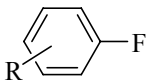
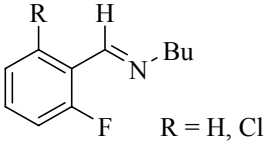
1.3.2.2.1 Kumada-Corriu Cross-Coupling Reactions

Most reported metal-catalysed C−C coupling reactions proceeding via C−F bond activation concern the conversion of monofluoroaryl systems into nonfluorinated derivatives. These reactions typically involve the reaction of these substrates with alkyl or aryl Grignard reagents at a metal centre, usually at nickel or palladium in Kumada-Corriu-type cross-coupling reactions.[57] One of the earliest examples of such a reaction describes the coupling of an aromatic-carbon to an sp^3-carbon, namely that of fluorobenzene to *iso*propylmagnesium chloride mediated by [Ni(dmpe)Cl_2].[59] More recently, the formation of Ar-C−Ar-C bonds has been achieved through C−F bond

activation and has now been studied extensively, the reactions of which are summarized in the following table (Table 5).

Table 5. Metal-catalysed cross-coupling reactions proceeding via C−F bond activation

Fluoroaryl Substrate	Ar group of Grignard ArMgX (X = Br or Cl)	[catalyst complex], ligand	Ref.
 R = 4-CF_3, 4-CH_3, 2-CH_3, 4-OCH_3, H	Ph 4-^{t}BuPh 2,4,6-Me_3Ph	$[Ni(cod)_2]$,  $[Ni(acac)_2]$, 	60
 R_1 = 2-F, 3-F, 2-F-3-Me R_2 = 6-F-2-Me, 3-F	Ph 4-MeOPh	$[NiCl_2(dppe)]$ $[Ni(acac)_2]$, dppe $[Ni(acac)_2]$, dppp $[Ni(acac)_2]$, dppf	61
	4-Mes	$[Ni_2(THF)_4Li_4(Me_8)]$	62

Fluoroaryl Substrate	Ar group of Grignard ArMgX (X = Br or Cl)	[catalyst complex], ligand	Ref.
 R = 4-Me, 4-OMe, 4-NMe_2, 2-Me, 2-OMe	Ph 4-MePh 4-MeOPh 2-MePh Me	$[Ni(acac)_2]$, 	63
$1,2\text{-}PhF_2$ $1,2,3\text{-}PhF_3$ $1,3\text{-}PhF_2$ $1,3,5\text{-}PhF_3$ $1,4\text{-}PhF_2$	4-MePh	$[Ni(dppp)Cl_2]$ $[Ni(dppf)Cl_2]$ $[PdCl_2(PPh_3)_2]$	64
 R_1 = 4-OMe, 4-Me, 4-Ph, 4-N H, F_5 R_2 = 2-F, 3-F	Ph 4-MeOPh 4-Mes	$[Ni(acac)_2]$, ^{t}BuPHO	65
 R = 2-Me, 2-Ph, 2-OMe, 4-Me, 4-MeO	Ph, 3,4-Me_2Ph 4-EtPh 2,4,6-Me_3Ph	$[Pd(acac)_2]$ $[Pd(dba)_2]$ $[Pd(dba)_2]$, $PhPCy_2$ $[Ni(acac)_2]$, P(OPh-2, 4-^{t}Bu_2)$_3$ $[Ni(acac)_2]$, P(Ph-4-NMe_2)$_3$ and a screen of many others	66
 R = H, Cl	Bu C_6H_5	$[MnCl_2]$	67

The use of an *o*-(1-hydroxylethyl)triphenylphosphine ligand in these Kumada-Corriu-type reactions has facilitated highly efficient cross-coupling reactions of aryl fluorides to aryl Grignard reagents in a [$Ni(acac)_2$] catalysed system and is postulated to draw the nickel and magnesium ions close together in the transition state (Figure 5).[63]

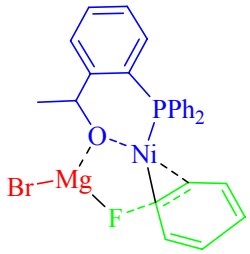
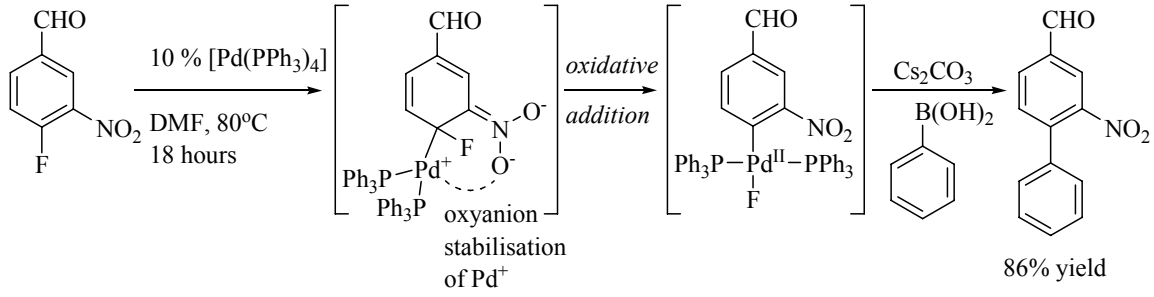


Figure 5.[63] Bimetallic cooperation in the stabilisation of a fluoroarene transition state

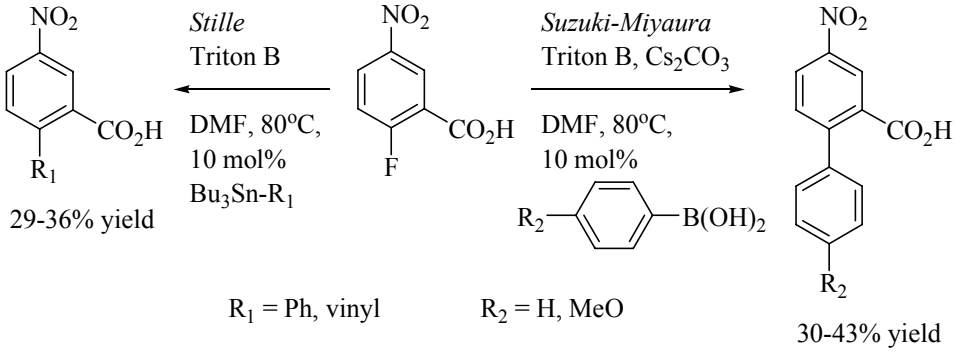
1.3.2.2.2 Other Metal-Catalysed Cross-Coupling Reactions

Functionalisation of *ortho*-fluoronitrobenzenes through a series of amination, Stille and Suzuki-Miyaura-type coupling reactions in the synthesis of biaryl amines and biaryls respectively has been reported in recent work by Kim and Yu.[68] Notably, phenylboronic acid was coupled to 4-fluoro-3-nitrobenzaldehyde using [$Pd(PPh_3)_4$] catalyst furnishing the biaryl product in excellent yield (Scheme 14). These are the first examples of Ar-C−Ar-C bond forming reactions following C−F bond metal activation under 'standard' palladium-catalysis conditions. The proposed mechanism initially involves nucleophilic attack of [$Pd^0(PPh_3)_2$] on an electron deficient carbon atom adjacent to a fluorine atom with subsequent electron delocalisation onto the nitro group. The positively charged palladium of the transition state is stabilised by a lone pair of the fluorine atom and also by an oxyanion of the *ortho* nitro group, facilitating oxidative C−F bond palladium insertion. An electron withdrawing aldehyde group *para* to the fluorine atom also stabilizes the negative charge build up of the transition state, lowering the energy barrier for reaction. Indeed, in many respects, these reactions have similar attributes to S_NAr processes.



Scheme 14.[68] Suzuki-Miyaura-type C−C coupling through C−F bond activation.

Soon after the discovery of this stabilization effect, Widdowson and Wilhelm also reported the coupling of a series of *ortho*-nitrofluoroaryls to a range of boronic acids using $[Pd_2(dba)_3]$ catalyst with PMe_3 ligand and Cs_2CO_3 in DME,[69] whilst Mikami et al. coupled Sanger's Reagent (2,4-dinitrofluorobenzene) to phenylboronic acid at $[((\pm)\text{-BINAP})Pd(MeCN)_2](SbF_6)_2$ in excellent yield (91%) during their studies of asymmetric couplings.[70] This general methodology has been extended to the coupling of 2-fluoro-5-nitrobenzoic acid to arylboronic acids in Suzuki-Miyaura-type cross-coupling reactions and to organotin reagents in Stille-type couplings (Scheme 15).[71] The coupled products were obtained in low to moderate yields. No other palladium-catalysed Suzuki-Miyaura reactions of perfluoroaromatic derivatives using 'standard' conditions have been reported to date.



Scheme 15.[71] Stille and Suzuki-Miyaura couplings of 2-fluoro-5-nitrobenzoic acid

The coupling of phenylboronic acid to fluorobenzene has been described by Ruiz et al. using a Mg/Al layered double hydroxide (LDH) heterogenous catalyst support (Figure 6).[72] Structurally, LDHs are very similar to brucite [$Mg(OH)_2$] but with some Mg^{2+} ions in the lattice replaced with Al^{3+} cations. The resulting positively charged structure is rendered electrically neutral through sorption of an equivalent number of carbonate ions. 86% conversion to the biphenyl is achieved using a [$Pd(AcO)_2(Py)_2$] complex impregnated into the LDH support.

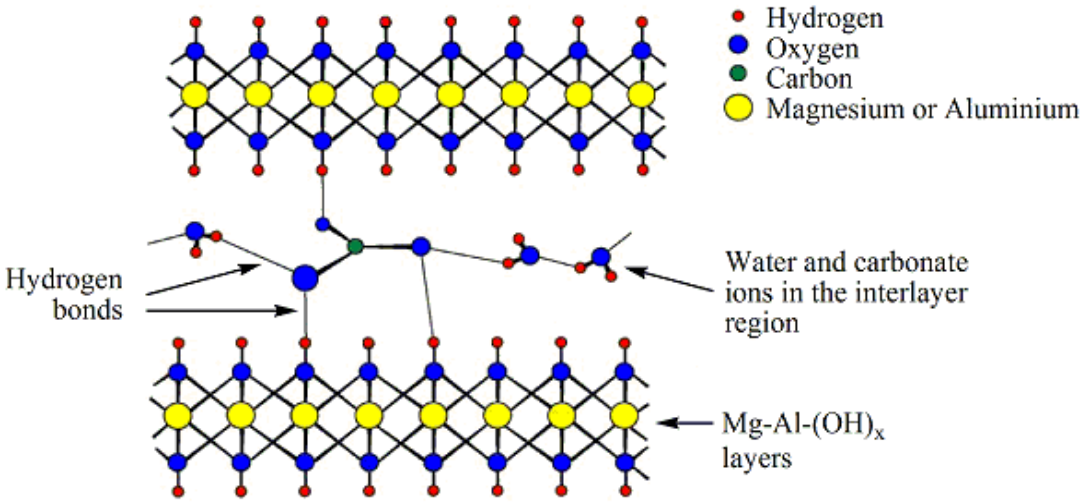


Figure 6.[72] Structure of Mg/Al layered double hydroxide (LDH)

1.3.2.3 Perfluoroaromatic Compounds

1.3.2.3.1 Non-Catalysed Derivatisations – [$MF(Ar)(PR_3)_2$] Complexes

Metal C−F bond activation of numerous perfluoroaromatic compounds has been achieved by reacting these substrates with [$M(cod)_2$] complexes (M = Ni, Pd, Pt or Rh) in the presence of trialkylphosphine ligands (PR_3) forming complexes typically of the form [$MF(Ar)(PR_3)_2$]. C−F bonds of perfluorobenzene, perfluoronaphthalene[73] and C−F bonds

at the 2-positions of pentafluoropyridine,[74] 2,3,5,6-tetrafluoropyridine and 2,3,4,5-tetrafluoropyridine[75] have been activated with nickel in this manner. Perfluorobenzene forms complexes with rhodium,[76] whilst platinum has been observed to activate C−F bonds of fluorobenzonitriles[77] and together with palladium, but in contrast with nickel, reacts at the 4-position of pentafluoropyridine.[75] The alternative chemo- and regioselective attack observed with nickel may be explained by assuming that the reaction proceeds via a concerted oxidative addition mechanism with a three-centred transition state combining the carbon, the fluorine and the metal centre (Figure 7).[73] An alternative electron transfer reaction pathway via a tight ion pair or a S_NAr type nucleophilic mechanism via a Meisenheimer intermediate would give rise to the expected substitution patterns at the 4-position in the products.

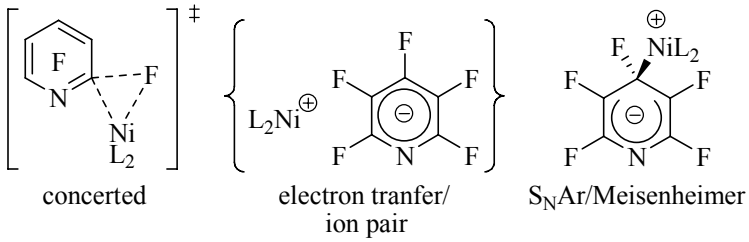
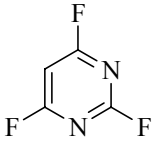
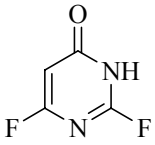
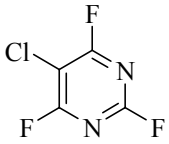
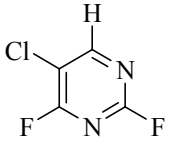
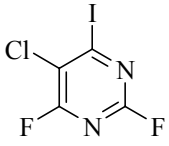
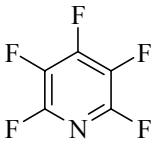
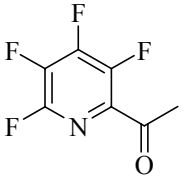
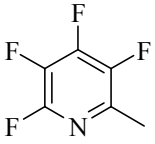


Figure 7.[73] Possible intermediates and transition state for the C–F activation of pentafluoropyridine at nickel

There are several examples of aryl−metal bond cleavage in $[MF(Ar)(PR)_2]$ complexes which upon stoichiometric reaction with a number of reagents furnish functionalized polyfluoroaromatics (Table 6).

Table 6. Reagents added to intermediate $[MF(Ar)(PR_3)_2]$ complexes to cleave C−M bonds

Fluoroaryl Substrate	M in complex	Reagent added to $[MF(Ar)(PR_3)_2]$ complex	Fluoroaryl Product	Ref.
	Ni	i. CsOH ii. HCl		78
	Ni	HCl		79
		I_2		
	Ni	i. $ZnMe_2$ ii. CO		80
		i. $ZnMe_2$ ii. air		

1.3.2.3.2 Metal-Catalysed Derivatisations

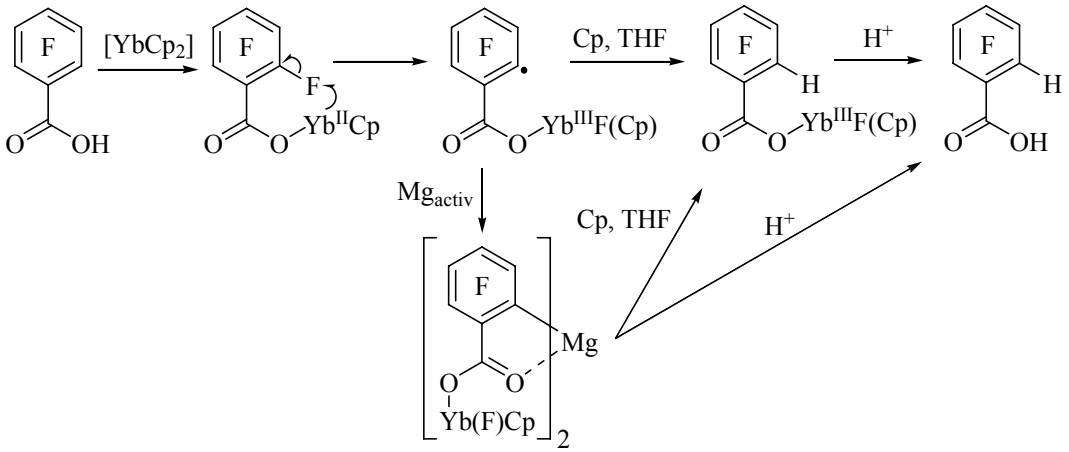
1.3.2.3.2.1 Catalytic Defluorination Reactions

Homogeneous catalytic transformations of perfluoroaromatic compounds reported to date are largely limited to single defluorination reactions such as those of hexafluorobenzene. Reaction of this substrate with $[Rh^{I}(PMe_3)_3SiR]$ (R = Me_2Ph, Ph_3) yields $[Rh(PMe_3)_3C_6F_5]$, which upon reaction with triphenylsilane[81] or hydrogen[76] in an

oxidative addition step subsequently reductively eliminates pentafluorobenzene. Similarly, Adonin and Starichenko observed in their studies of perfluoroaromatic compounds that the respective defluorinated materials may be obtained using a nucleophilic hydride source formed *in situ* that is believed to be of the form $[Ni^{II}HXL_n]$ (X = OH, OC_2H_5 or NH_2, L = bipy or phen, n = 1,2).[82]

$[Yb^{II}Cp_2]$ may be used in the defluorination of perfluorobenzoic acid[83] by a mechanism (Scheme 16) involving initial acidolysis giving $[C_6F_5CO_2Yb^{II}Cp]$, which then undergoes intermolecular electron transfer and fluoride abstraction in a favourable cyclic six membered transition state. The resulting radical can abstract an hydrogen atom from cyclopentadiene or THF and, following hydrolytic work up, 2,3,4,5-tetrafluorobenzoic acid is obtained. An alternative route involves the formation of an intermediate carbanionic organometallic complex with the activated magnesium coreductant.

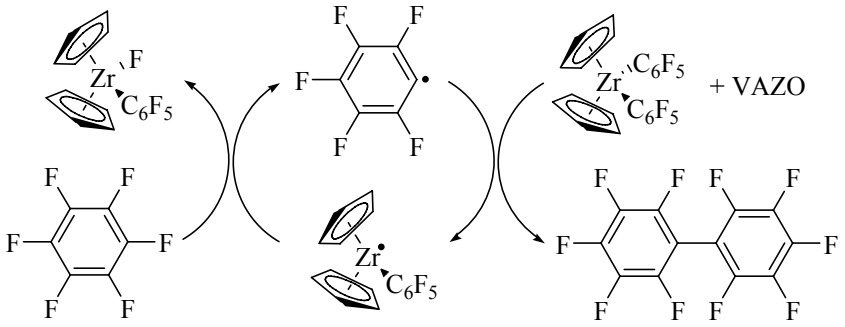
Fluoroacetophenones and (fluorophenyl)oxazolines furnish the respective *ortho*-(TMS)fluorobenzenes with $(TMS)_2$ in the presence of a catalytic amount of $[Rh(cod)_2]BF_4$.[84]



Scheme 16.[83] Selective defluorination of perfluorobenzoic acid

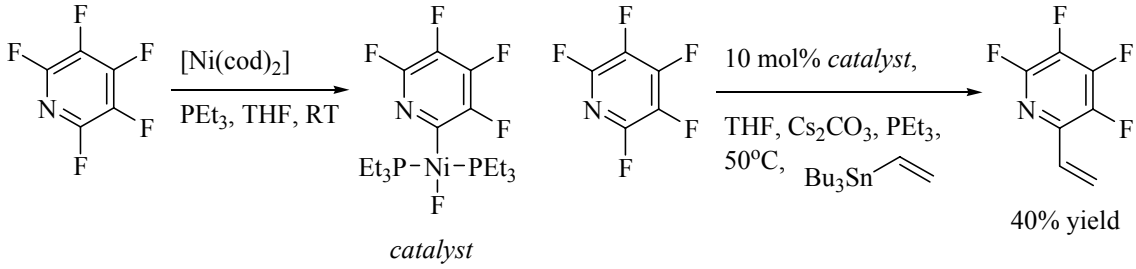
1.3.2.3.2.2 Catalytic C−C Bond Forming Reactions

One of the first C−C bond formations between perfluoroaromatic compounds was achieved in the synthesis of perfluorobiphenyl and higher-molecular weight linear oligomers via the zirconium-activated radical homocoupling of perfluorobenzene (Scheme 17).[85] Heating $[Cp_2Zr(C_6F_5)_2]$ in the presence of hexafluorobenzene and the radical initiator 1,1'-azobis(cyclohexanecarbonitrile) (VAZO) gave mixtures of the linear oligomers.



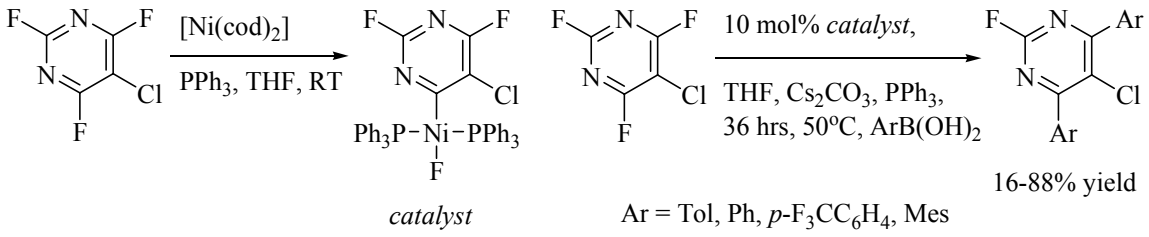
Scheme 17.[85] Zirconium-activated homocoupling of perfluorobenzene

More recently Braun and Perutz reported the nickel-mediated cross-coupling of pentafluoropyridine to vinyl tin[86] in a Stille-type[57] reaction furnishing the corresponding vinyl aromatics in moderate yield (Scheme 18). The reaction is not strictly a 'catalytic' process as the substrate itself is initially required to form the catalyst.



Scheme 18.[86] Coupling of a fluoropyridine to vinyl tin via C−F bond activation

Further to this the coupling of perfluoroaromatic compounds to arylboronic acids using similar metal-catalysed C−F bond activation methodology in Suzuki-Miyaura-type cross-couplings has been achieved. Braun and co-workers described the synthesis of a highly reactive nickel-fluorine complex which catalyses the coupling of 5-chloro-2,4,6-trifluoropyrimidine to boronic acids (Scheme 19). Activation of 5-chloro-2,4,6-trifluoropyrimidine initially at a $[Ni(PCy_3)_2]$ complex in an oxidative addition reaction gives the catalyst, *trans*-$[NiF(4\text{-}C_4N_2ClF_2)(PCy_3)_2]$.[87] The C−F bond is cleaved preferentially in the presence of a thermodynamically weaker C−Cl bond. A 10% loading of the catalyst facilitates the reaction of the substrate furnishing the coupled biphenyls in moderate to good yields.

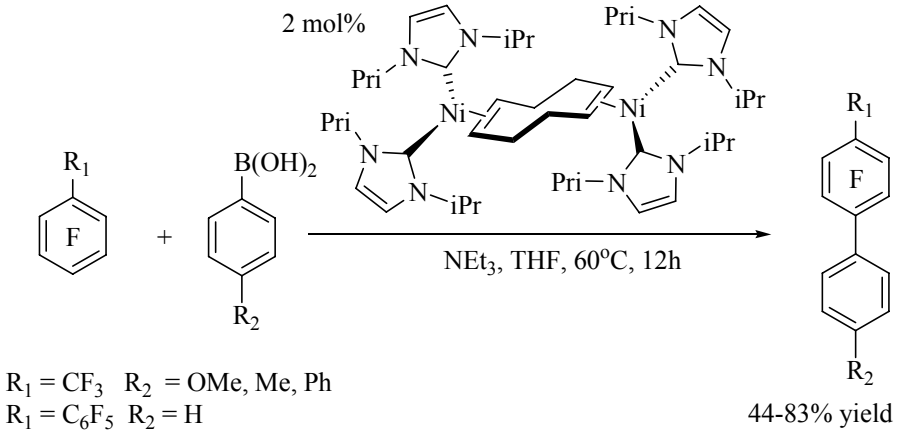


Scheme 19.[87] Coupling of a fluoropyrimidine to arylboronic acids via C−F bond activation

Coupling of fluoroarenetricarbonylchromium^0 complexes to functionalized aryl boronic acids and to vinyl-tin in Suzuki-Miyaura[88] and Stille[89] reactions respectively has been described, using a catalytic amount of $[Pd_2(dba)_3]$ in the presence of base and PMe_3 ligand in DME. The electron withdrawing η^6-$Cr^0(CO)_3$ group activates the C−F bond of the fluoroarene bond to the oxidative addition of the electron rich palladium^0.

Examples of catalytic processes proceeding initially through C−F bond activation of perfluoroaromatic substrates in which derivative fluoroaromatic compounds are eliminated from the intermediate metal complexes in the final stage of the cycle are rare. However, Radius and co-workers very recently described the use of the N-heterocyclic

carbene-stabilised nickel complex [Ni_2(1,3-di(^{i}Pr)imidazol-2-ylidene)$_4$(cod)] to couple perfluorotoluene to range of aryl boronic acids in moderate to good yield (Scheme 20).[90]



Scheme 20.[90] A cross-coupling reaction using a C-F bond activating N-heterocyclic carbene-stabilized nickel complex

1.4 Conclusions

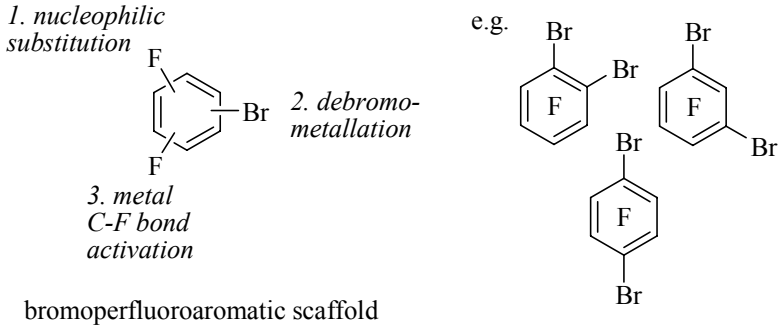
Replacement of hydrogen with fluorine in organic materials alters their electronic properties, notably their dipole moment, which has resulted in their widespread use in modern LCD display materials. Rapid technological progress in the current electronics industry has placed demands for the development of new, highly selective and high-yielding routes to novel fluorinated materials with improved properties, such as stronger dipole moments. Molecules based on the biaryl moiety often feature in LC mixtures and may be synthesised by methods including nucleophilic aromatic substitution or metal-catalysed C−C cross-coupling reactions via C−F bond activation, hitherto unseen chemistries in routes to these materials. New fluorination patterns in the molecules and hence new properties may be achieved as a result.

2 General Approach to the Design and Synthesis of Fluorinated Model LCs

Novel fluorinated molecules are required to gain a better understanding of structure-property relationships of materials in LC blends, and so the development of new and flexible synthetic methodology providing routes to families of related fluorinated 'model' compounds became the focus of this body of work.

Biphenyl or cyclohexyl-phenyl units are a common structural feature of modern state of the art LCs[1] as they are sterically ideal for forming the backbone of these rod-like materials. These 'scaffolds' may be synthesised by connecting two or more cyclic ring structures together; an electron withdrawing halogenated 'head' group may be attached to a non-polar lipophilic 'tail' group and the contrasting electronic properties of head and tail-groups lends to the overall dipole moment of the molecule. Importantly, for LC blends used in LCD applications, the resulting material need not necessarily display any liquid crystalline phase as LC mixtures are made up of many components selected individually for their favourable properties.

As discussed in chapter 1.1, fluorine induces a strong dipole in molecules which is required for a response to an electric field in LCD devices. Perhalogenated aromatic scaffolds, ideal for the introduction of several fluorine atoms into the materials, were selected as versatile molecules from which to begin the syntheses of model LC systems. Three different synthetic concepts may be applied to a bromoperfluoroaromatic system (Scheme 21). Nucleophilic substitution (section 1.3.1.2) and debromometallation (section 1.3.1.3) are now well established methods for the functionalisation of electron deficient aromatic compounds whilst work on metal-catalysed C-F bond activation has only been reported very recently. The principle 'scaffolds' selected upon which these chemistries were to be performed were the three isomers of dibromotetrafluorobenzene, and the three isomers of tribromotrifluorobenzene. Use of perfluorobenzene isomers could ultimately offer different fluorination patterns on the head-groups of the product molecules leading to variations in properties such as the strength and orientation of their dipole moments.



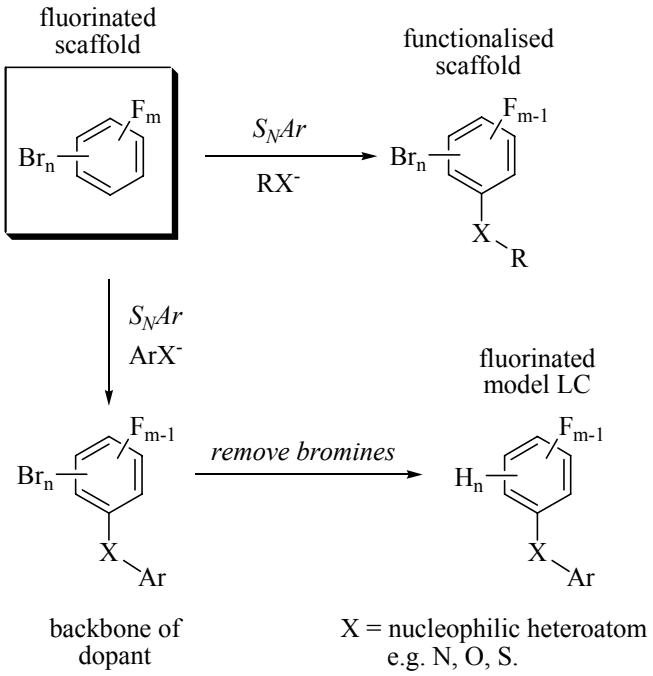
Scheme 21. Methodologies employed for the synthesis of fluorinated materials

2.1 Methodologies Employed for the Synthesis of Model LCs from Perfluoroaromatics

Outlines of each of the methodologies for LC synthesis adopted in this thesis, starting from bromoperfluoroaromatic scaffolds, are presented here.

2.1.1 S_NAr Reactions of Fluorine

Nucleophilic substitution of fluorine in electron deficient aromatic systems is now well described,[8] and in principle this methodology could provide synthetic routes to diverse ranges of rod-like biphenyl structures with bridging heteroatoms as outlined in Scheme 22. A fluorinated scaffold may be further functionalised in this manner using small nucleophiles such as alkoxides, whilst the use of larger nucleophiles such as aryloxides might lead to the desired product structure.



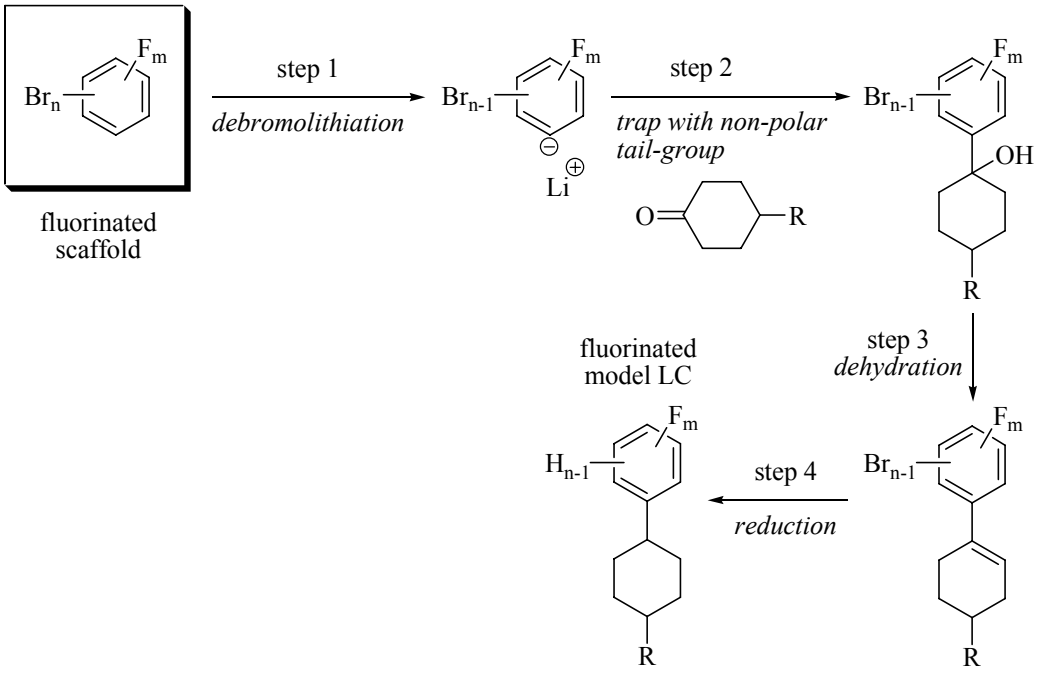
Scheme 22. Synthetic route to heteroatom bridged fluorinated biphenyl structures via nucleophilic aromatic substitution

The approach shown in Scheme 22 would, potentially, provide access to a wide range of functionalised fluoroaryl 'head-groups' that are very difficult to synthesise by other methods. Consequently, by development of this strategy, we hoped to be able to synthesise new model LC molecules by simple, economic, regioselective procedures.

2.1.2 Debromometallation

Debromometallation of perfluorobenzenes bearing more than one bromine atom has not been well established in the literature. The methodology proposed in this thesis (Scheme 23) involves use of bromoperfluoroaromatic head-group, such as a dibromotetrafluorobenzene or a tribromotrifluorobenzene, which may have been previously functionalised via an S_NAr type reaction (section 2.1.1). One bromine atom on

the head-group is then removed with *n*-butyllithium to generate a carbanion (step 1), which is then 'trapped' with an electrophile such as an alkylketone (step 2), the non-polar tail-group, forming a C−C bond generating an alcohol precursor. Subsequent acid-catalysed dehydration (step 3) and palladium-catalysed reduction (step 4) of the resulting alkene could, potentially, yield the desired cyclohexane-aryl backbone of the molecule. Any remaining bromine atom may be displaced during the reduction step.

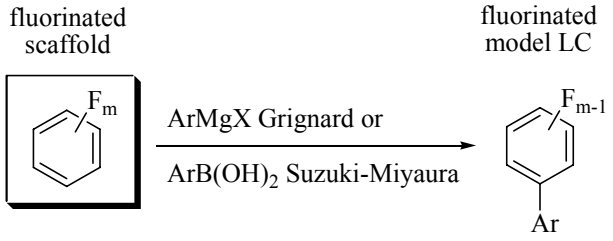


Scheme 23. Synthetic route to fluorinated cyclohexylphenyl structures via debromolithiation

A combination of replacement of fluorine and/or bromine should, therefore, lead to several families of LC-type materials with a variety of fluorinated aromatic head-groups.

2.1.3 C-F Bond Activation at Metal Centres

There have been many major developments in the catalytic activation of carbon-halogen bonds in the formation of Ar-C−Ar-C bonds (section 1.3.2) although little literature precedent exists concerning cross coupling through C−F bond activation of perfluoroaromatic substrates. Our work includes investigations into the action of aryl Grignard reagents and Suzuki-Miyaura-type cross couplings in the formation of fluorinated biphenyl structures (Scheme 24).

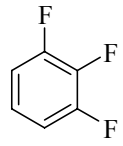
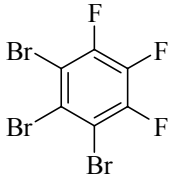
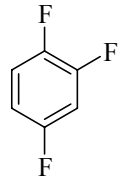
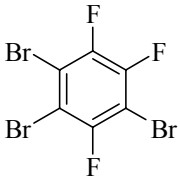
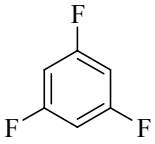
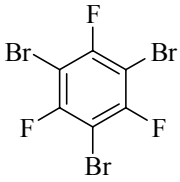


Scheme 24. Synthetic route to fluorinated biphenyl structures via C−F bond activation

2.2 Availability of Perfluorinated Substrates

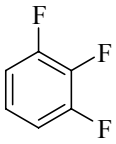
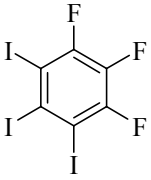
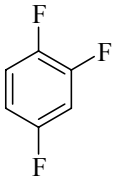
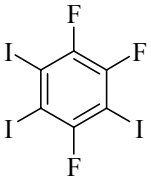
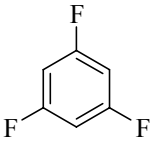
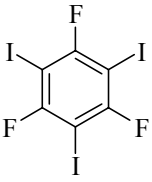
The three dibromotetrafluorobenzene systems (section 2.1) are commercial products but the three isomers of tribromotrifluorobenzene are not supplied. However, materials can be derived from the three isomers of trifluorobenzene, available commercially, and we found that bromination with NBS in triflic acid at room temperature (Table 7) furnishes the corresponding tribromotrifluorobenzenes **1-3** with complete conversion of starting material, by adapting the iodination method of Olah.[91] The lower yields than expected (9-33%) can be attributed to the repeated crystallisations and sublimation required to afford the analytically pure samples.

Table 7. Tribromotrifluorobenzenes synthesised via bromination of trifluorobenzenes

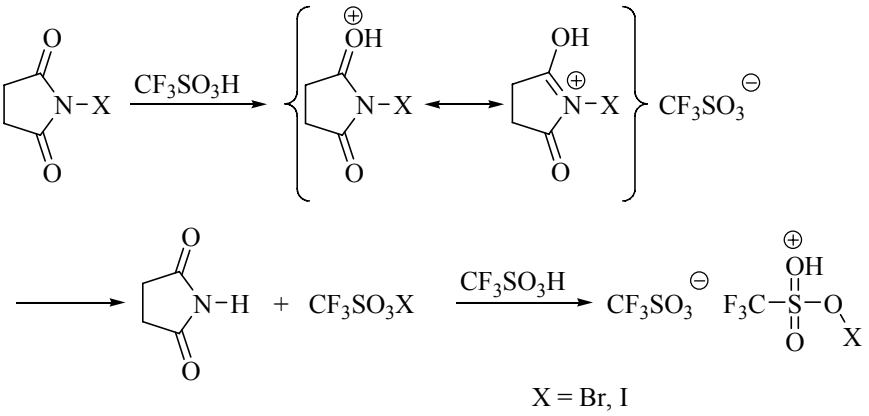
Starting material	Product		Conversion /%	Isolated Yield /%
		**1**	100	9
		**2**	100	33
		**3**	100	16

The halogenation methodology applied to the trifluorobenzenes may also be extended to iodinations using NIS in place of NBS (Table 8). Complete conversion was again achieved whilst the reported yields are higher than for the corresponding tribromotrifluorobenzenes as those given are the calculated yields following recrystallisation rather than the yields of analytically pure product obtained following sublimation.

Table 8. Trifluorotriiodobenzenes synthesised via iodination of trifluorobenzenes

Starting material	Product		Conversion /%	Isolated Yield /%
		**4**	100	88
		**5**	100	70
		**6**	100	92

The proposed active species involved in the halogenation of the trifluorobenzenes was proposed to be formed *in situ* by displacement of the proton of triflic acid with the respective halogen (from NBS or NIS) which then reacts with another equivalent of the acid to yield the halogenating salt (Scheme 25). The halogenations of the trifluorobenzenes then proceed via the usual electrophilic aromatic substitution mechanism.



Scheme 25.[91] Proposed mechanism for generation of active species in the halogenation of fluorobenzenes

2.3 Conclusion

Polybromoperfluorinated aromatic compounds may be versatile 'scaffolds' from which to begin the synthesis of fluorinated model LC molecules, and several established methodologies including nucleophilic substitution and debromometallation may be used to create related families of materials with novel fluorination patterns. Use of these fluorinated substrates may also lead to new developments in new emerging areas of chemistry such as cross coupling reactions through metal catalysed C−F bond activation.

2.4 Experimental

2.4.1 Preparation of Tribromotrifluorobenzenes

Triflic acid (3.1 equiv.) was added slowly to a stirred mixture of the trifluorobenzene (1.0 equiv.) and NBS (3.1 eq.) at 0 °C. The solution was allowed to warm to room temperature, left to stir for 72 hours and then poured onto ice water. The product was

extracted with DCM (3 × 30 ml), the combined extracts were washed with water (100 ml) and then dried ($MgSO_4$). The solvent was removed *in vacuo*, and the product purified by recrystallisation in ethanol/water followed by sublimation. Reported yields are those of the analytically pure product obtained following sublimation.

1,2,3-Tribromo-4,5,6-trifluoro-benzene 1. 1,2,3-Trifluorobenzene (1.32 g, 10 mmol) afforded the perhalogenated benzene (0.33 g, 9%) as a white solid, mp 70.5-72.0 °C (Found: C, 19.33. $C_6Br_3F_3$ requires C, 19.54%); δ_C 109.98 (d, $^2J_{CF}$ 24.5, 1-*C*), 123.11 (m, 2-*C*), 139.65 (dt, $^1J_{CF}$ 258.7, $^2J_{CF}$ 17.3, 5-*C*), 148.55 (ddd, $^1J_{CF}$ 251.9, $^2J_{CF}$ 11.8, $^3J_{CF}$ 4.3, 4-*C*); δ_F -117.70 (2F, d, $^3J_{FF}$ 21.3, 4-C*F*), -153.65 (1F, t, $^3J_{FF}$ 21.1, 5-C*F*); *m/z* (EI^+) 372 (M^+, 20%), 370 (M^+, 56), 368 (M^+, 56), 366 (M^+, 19), 210 (44), 208 (42), 129 (71), 110 (30), 98 (29), 79 (100).

1,2,4-Tribromo-3,5,6-trifluoro-benzene 2. 1,2,4-Trifluorobenzene (2.64 g, 20 mmol) afforded the perhalogenated benzene (2.41 g, 33%) as a clear oil (Found: C, 19.55. $C_6Br_3F_3$ requires C, 19.54%); δ_C 99.18 (dd, $^2J_{CF}$ 27.9, $^2J_{CF}$ 22.0, 4-*C*), 108.76 (dd, $^2J_{CF}$ 25.6, $^3J_{CF}$ 4.9, 2-*C*), 113.73 (ddd, $^2J_{CF}$ 20.7, $^3J_{CF}$ 1.6, $^3J_{CF}$ 1.1, 1-*C*), 145.76 (A or B of ABMX, $^1J_{CF}$ 235.5, 5- or 6-*C*), 147.99 (A or B of ABMX, $^1J_{CF}$ 251.6, 5- or 6-*C*), 153.21 (ddd, $^1J_{CF}$ 246.8, $^3J_{CF}$ 4.2, $^4J_{CF}$ 3.1, 3-*C*); δ_F -95.48 (X of ABMX, $^5J_{FF}$ 9.9, $^4J_{FF}$ 6.9, 3-C*F*), -124.54 (A of ABMX, $^3J_{FF}$ 22.9, $^5J_{FF}$ 10.0, 6-C*F*), -124.97 (B of ABMX, $^3J_{FF}$ 22.1, $^4J_{FF}$ 6.1, 5-C*F*); *m/z* (EI^+) 372 (M^+, 52%), 370 (M^+, 90), 368 (M^+, 100), 366 (M^+, 78), 289 (73), 210 (88), 208 (83), 129 (88), 110 (76), 79 (100).

1,3,5-Tribromo-2,4,6-trifluoro-benzene 3. 1,3,5-Trifluorobenzene (2.64 g, 20 mmol) afforded the perhalogenated benzene (1.18 g, 16%) as a white solid, mp 98.0-99.0 °C (Found: C, 19.54. $C_6Br_3F_3$ requires C, 19.54%); δ_C 94.82 (td, $^2J_{CF}$ 27.1, $^4J_{CF}$ 5.1, 1-*C*), 156.27 (dt, $^1J_{CF}$ 248.5, $^3J_{CF}$ 5.8, 2-*C*); δ_F -95.79 (s); *m/z* (EI^+) 372 (M^+, 13%), 370 (M^+, 38), 368 (M^+, 38), 366 (M^+, 12), 210 (26), 208 (27), 129 (44), 110 (30), 98 (22), 81 (22), 79 (100).

2.4.2 Preparation of Trifluorotriiodobenzenes

The preparation was carried out as for tribromotriiodobenzenes using NIS in place of NBS. Reported yields are those obtained following recrystallisation rather than yields of analytically pure product obtained following sublimation.

1,2,3-Trifluoro-4,5,6-triiodo-benzene 4. 1,2,3-Trifluorobenzene (1.32 g, 10 mmol) afforded the perhalogenated benzene (4.49 g, 88%) as a pale yellow solid, mp 90.5-91.5 °C (Found: C 14.15. $C_6F_3I_3$ requires C, 14.14%); δ_C 91.06 (m, 5-*C*), 115.20 (d, $^2J_{CF}$ 4.7, 4-*C*), 137.57 (dt, $^1J_{CF}$ 261.6, $^2J_{CF}$ 18.7, 2-*C*), 151.23 (ddd, $^1J_{CF}$ 250.2, $^2J_{CF}$ 11.1, $^3J_{CF}$ 3.8, 1-*C*); δ_F -95.52 (2F, d, $^3J_{FF}$ 22.1, 1-C*F*), -151.89 (1F, t, $^3J_{FF}$ 22.3, 2-C*F*); *m/z* (EI^+) 510 (M^+, 100%), 383 (37), 256 (82), 254 (51), 129 (85), 127 (86), 110 (30), 98 (30), 79 (79), 31 (16).

1,2,4-Trifluoro-3,5,6-triiodo-benzene 5. 1,2,4-Trifluorobenzene (1.32 g, 10 mmol) afforded the perhalogenated benzene (3.59 g, 70%) as a white solid, mp 66.0-67.0 °C (Found: C 14.12. $C_6F_3I_3$ requires C, 14.14%); δ_C 71.48 (dd, $^2J_{CF}$ 35.7, $^2J_{CF}$ 26.3, 3-*C*), 89.87 (ddd, $^2J_{CF}$ 32.9, $^3J_{CF}$ 4.6, $^3J_{CF}$ 1.5, 6-*C*), 98.17 (d, $^2J_{CF}$ 24.9, 5-*C*), 146.82 (ddd, $^1J_{CF}$ 248.8, $^2J_{CF}$ 16.1, $^4J_{CF}$ 4.2, 1-*C*), 150.40 (ddd, $^1J_{CF}$ 252.2, $^2J_{CF}$ 17.6, $^3J_{CF}$ 6.2, 2-*C*), 157.44 (ddd, $^1J_{CF}$ 242.0, $^3J_{CF}$ 3.8, $^4J_{CF}$ 3.8, 4-*C*); δ_F -63.45 (d, $^5J_{FF}$ 10.7, 4-C*F*), -105.13 (dd, $^3J_{FF}$ 24.3, $^5J_{FF}$ 10.7, 1-C*F*), -110.91 (d, $^3J_{FF}$ 23.8, 2-C*F*); *m/z* (EI^+) 510 (M^+, 22%), 256 (44), 254 (26), 129 (61), 127 (100), 110 (29), 98 (22), 79 (88), 55 (8), 31 (11).

1,3,5-Trifluoro-2,4,6-triiodo-benzene 6. 1,3,5-Trifluorobenzene (1.32 g, 10 mmol) afforded the perhalogenated benzene (4.70 g, 92%) as a white solid, mp 151.0-152.5 °C (Found: C 14.05. $C_6F_3I_3$ requires C, 14.14%); δ_C 63.98 (td, $^2J_{CF}$ 33.7, $^4J_{CF}$ 4.2, 2-*C*), 162.33 (dt, $^1J_{CF}$ 243.8, $^3J_{CF}$ 7.7, 1-*C*); δ_F -69.35 (s); *m/z* (EI^+) 510 (M^+, 41%), 383 (18), 256 (51), 129 (63), 127 (100), 110 (30), 98 (18), 79 (83), 74 (7), 31 (10).

3 Synthetic Routes to LCs via Nucleophilic Aromatic Substitution of Fluorine

3.1 S_NAr Reactions of Perhalogenated Benzenes

3.1.1 Oxygen Nucleophiles

Investigations into S_NAr reactions of 1,2-dibromotetrafluorobenzene, 1,3-dibromotetrafluorobenzene, 1,4-dibromotetrafluorobenzene, and 1-bromo-2,3,5,6-tetrafluoro-4-(trifluoromethyl)-benzene have so far been limited to reactions with methoxide ion to afford the respective bromo-perfluoro-methoxybenzenes **7**, **15**, **23**[29] and **27**[92] (Figure 8), and a discussion of this chemistry is presented in section 1.3.1.2. The products are suitable candidates as intermediates for LC head-groups due to the high polarity that may remain in these aromatic rings even after several synthetic steps.

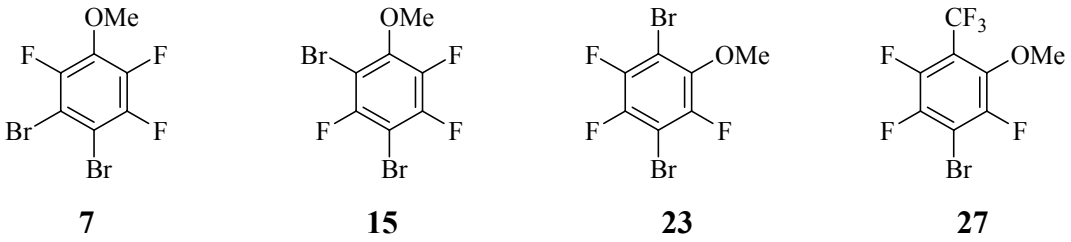


Figure 8. Potential LC head-group scaffolds

Synthesis of the materials above (Figure 8) was initially repeated (see sections 3.1.1.1 to 3.1.1.4) as described in the literature,[29, 92] in order to obtain comprehensive characterisation of the products and the use of these materials as model LC head-groups was also demonstrated subsequently (section 4.2).

The methodology employed above may be easily modified to allow for the incorporation of any alkyl alcohol in the synthesis to form the "tail-group" of a model LC, whilst leading to an easily accessible oxygen bridge between the head and the tail. There is a requirement for robust LCs for electronic applications, and the performance of molecules

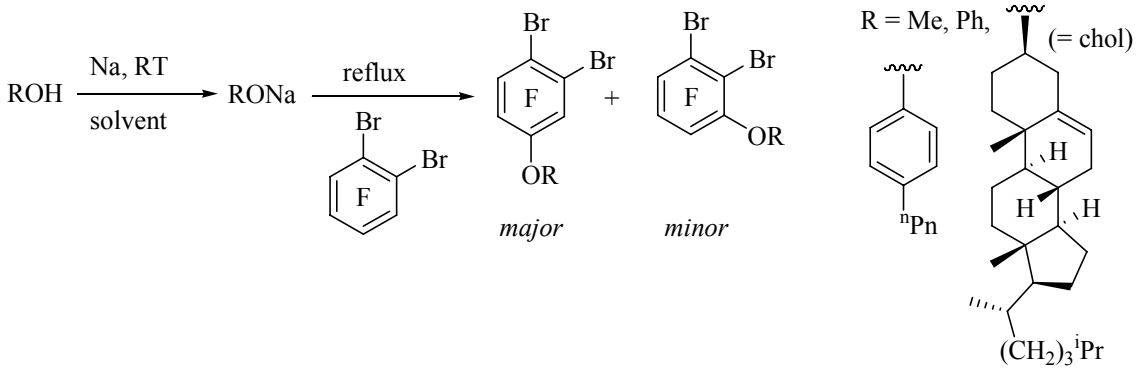
with solubility and polarity enhancing bridges such as difluorooxymethylene bridges[93] between the tail and head-groups has been investigated is currently of interest.

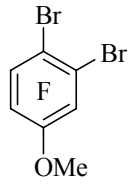
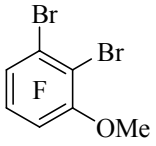
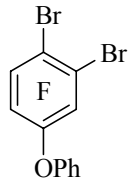
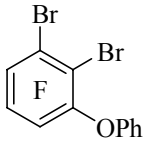
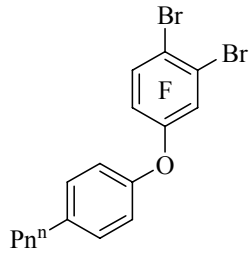
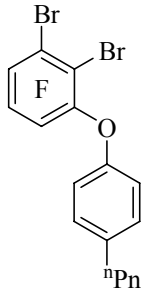
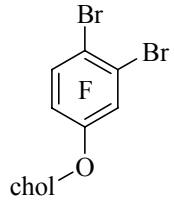
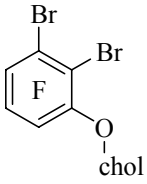
The action of two aryl oxides and one other alkoxide upon the three dibromotetrafluorobenzene isomers and 1-bromo-2,3,5,6-tetrafluoro-4-(trifluoromethyl)benzene was investigated here. Reactions were performed with phenoxide ion, a 'softer' nucleophile than methoxide, and 4-pentylphenoxide, to afford more 'rod-like' materials resembling LC-type molecules. Steroidal chiral dopants are often included in LC mixtures to impart a helical 'twist' in the otherwise homeotropic alignment of molecules.[1] The reaction of octafluorotoluene with cholesterol (3β-hydroxy-5-cholestene) as its sodium salt via an S_NAr mechanism has been described,[94] and reactions were carried out in a similar manner using the isomers of dibromotetrafluorobenzene as substrate.

3.1.1.1 Reactions of 1,2-Dibromotetrafluorobenzene

Reactions of oxygen nucleophiles with 1,2-dibromotetrafluorobenzene are shown in Table 9.

Table 9. S_NAr reactions of 1,2-dibromotetrafluorobenzene.



Isomers in Crude Product Mixture		Isomer Ratio	Conversion to Products /%	Isolated Yield of Major Isomer /%
major	*minor*			
 **7**	 **8**	97:3	100	76
 **9**	 **10**	95:5	84	24
 **11**	 **12**	94:6	88	*
 **13**	 **14**	92:8	88	*

*carried through to next synthetic step (section 3.2.1) without purification to maximise yield

The major isomer **7** was afforded as a mixture with its respective minor isomer **8** (97:3), the distribution of which was found to be consistent with reported results (98:2).[29] Reactions with the other nucleophiles were slightly less selective, whilst conversion of the substrate was lower in reactions involving the larger nucleophiles (84-88%, affording materials **9**, **11** and **13**) than with methoxide ion (100%, affording **7**). Theoretically, reactions with the more basic methoxide ion would be expected to proceed under a

greater amount of thermodynamic control and therefore proceed with greater selectivity. Using a more 'bulky' nucleophile may also be expected to increase selectivity due to steric considerations, as substitution of fluorine would be less likely to occur in a position *ortho* to a large bromine atom.

Only materials **7** and **9** were purified, isolated as pure isomers and characterised. The reactions were fairly clean and so material **11**, impure, was characterised by GC-MS only and carried through to the next synthetic step (section 3.2.1) without purification in order to maximise product yields. The impure material **13** was passed through a short silica plug and attempts to characterise this intermediate by GC-MS and LC-MS were unsuccessful as the molecular ions were not observed. Information from ^{19}F NMR was relied upon, comparing peaks shifts against those for the other synthesised 1,2-dibromotrifluoroarylethers. The material was then carried through to the next synthetic step. Despite high conversion from 1,2-dibromotetrafluorobenzene, isolated yields of **7** and **9** were low (76 and 24%) as purification was required by column chromatography and for **9**, crystallisation also in order to remove the minor isomer.

Isomer ratios were assigned for each of the crude product mixtures through consideration of ^{19}F NMR spectra in the following manner. 1,2-Dibromo-3,4,6-trifluoro-5-methoxybenzene **7**, (Table 9) obtained in the product mixture with its isomer 1,2-dibromo-3,4,5-trifluoro-6-methoxybenzene **8**, was determined to be the major product in the reaction of methoxide ion with 1,2-dibromotetrafluorobenzene. The fluorine spectrum shows one signal of the three minor peaks at 155.37 ppm that closely resembles a triplet indicating that this atom has two neighbouring fluorine atoms. This may be assigned to the 4-C fluorine atom of **8** (as **7** will show three doublet of doublets for each of its three fluorines) and enabled labelling of all the peaks in the spectrum and consequently calculation of isomeric ratios from peak integrals.

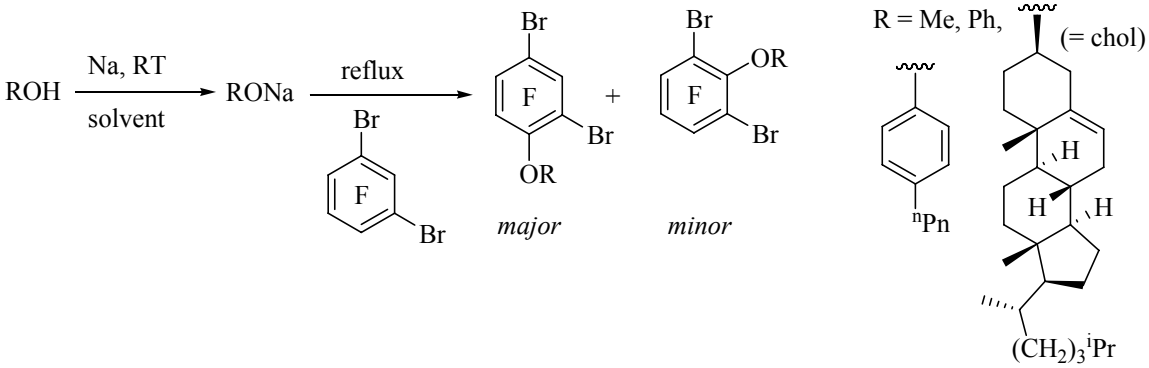
The isomers formed from alkoxydefluorination result from nucleophilic attack which preferentially occurs at the site with the maximum number of activating *ortho* fluorine atoms (an initial state effect), and the minimum number of deactivating *para* fluorine

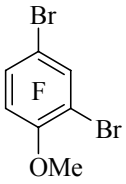
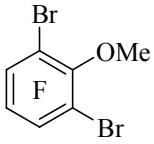
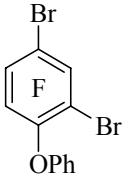
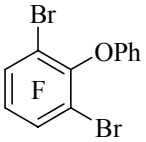
atoms (a transition state effect). For 1,2-dibromo-3,4,5,6-tetrafluorobenzene, substitution is observed to occur predominantly at the 4-*C* position.

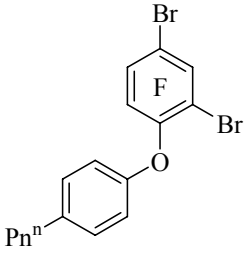
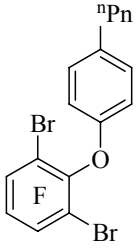
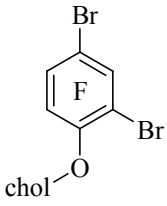
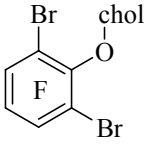
3.1.1.2 Reactions of 1,3-Dibromotetrafluorobenzene

Reactions of oxygen nucleophiles with 1,3-dibromotetrafluorobenzene are shown in Table 10.

Table 10. S_NAr reactions of 1,3-dibromotetrafluorobenzene.



Isomers in Crude Product Mixture		Isomer Ratio	Conversion to Products /%	Isolated Yield of Major Isomer /%
major	*minor*			
 **15**	 **16**	98:2	98	70
 **17**	 **18**	98:2	89	60

Isomers in Crude Product Mixture		Isomer Ratio	Conversion to Products /%	Isolated Yield of Major Isomer /%
major	*minor*			
 **19**	 **20**	92:8	86	*
 **21**	 **22**	100:0	100	*

*carried through to next synthetic step (section 3.2.1) without purification to maximise yield

The major isomer **15** was afforded as a mixture with its respective minor isomer **16** (98:2), the distribution of which was found to be consistent with reported results (97:3).[29] Reactions with the other nucleophiles offered similar selectivities. Formation of the minor isomer **22** was not observed probably due to the steric bulk of the steroid and its inability to attack between the two bromine atoms. Conversion of the substrate was lower in reactions involving the phenoxy nucleophiles (89 and 86%, affording materials **17** and **19**) than with methoxide ion (98%, affording **15**) as found previously (section 3.1.1.1). Quantitative conversion was surprisingly obtained from the reaction of 1,3-dibromotetrafluorobenzene with the sodium derivative of cholesterol, affording material **21**.

Only materials **15** and **17** were purified, isolated as pure isomers and characterised. As previously (section 3.1.1.1) the reactions were fairly clean and so material **19**, impure, was characterised by GC-MS only and carried through to the next synthetic step (section

3.2.1) without purification in order to maximise product yields. The impure material **21** was passed through a short silica plug and, following confirmation of its identity by ^{19}F NMR, carried through to the next synthetic step.

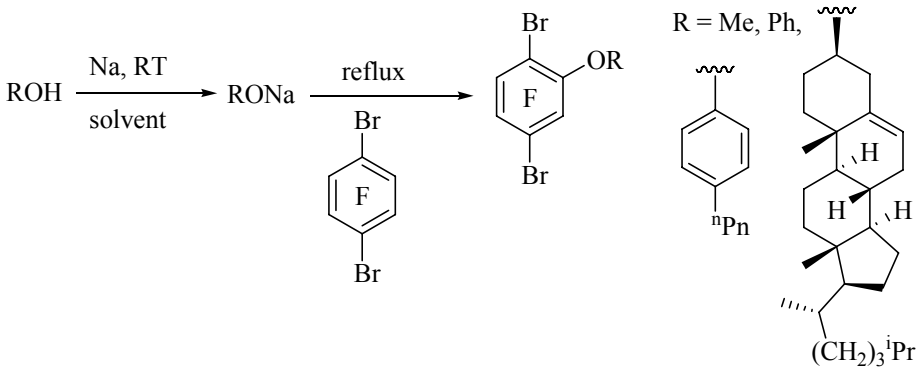
Isomer ratios were assigned for each of the crude product mixtures through consideration of ^{19}F NMR spectra in the following manner. The spectrum of 1,3-dibromo-2,4,5-trifluoro-6-methoxybenzene **15**, (Table 10) the expected major isomer from the reaction of methoxide ion with 1,3-dibromotetrafluorobenzene, shows three signals for the three fluorine environments. The two other possible product isomers have only two fluorine environments. The minor isomer obtained, 1,3-dibromo-4,5,6-trifluoro-2-methoxybenzene **16**, is in agreement with the literature.[29] A doublet at -124.96 ppm with a 22 Hz coupling, characteristic of a $^{3}J_{FF}$ coupling,[95] and a triplet at -159.25 ppm also with a 22 Hz coupling confirm its identity. The alternative isomer 1,3-dibromo-2,4,6-trifluoro-5-methoxybenzene would, however, be the expected minor product as two fluorine atoms, activating to nucleophilic substitution, lie *ortho* to 5-*C* in the substrate whereas none lie *ortho* to 2-*C* where substitution actually occurs. The site of the 2-*C* carbon in the substrate is also more sterically hindered by the two adjacent bromine atoms.

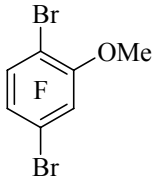
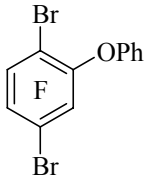
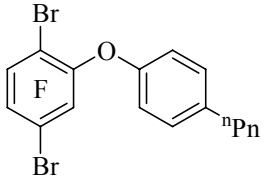
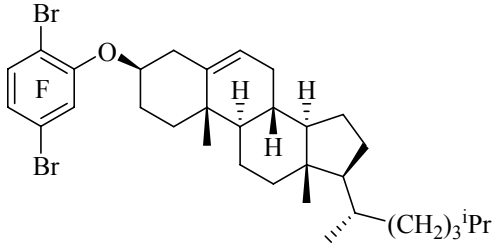
Nucleophilic attack on 1,3-dibromotetrafluorobenzene suggests that a *para* fluorine atom imparts a predominant deactivating influence over one extra activating *ortho* fluorine atom. Attack occurs predominantly at the 4 position (1 *ortho* fluorine atom, no *para* fluorine atoms) rather than at the 5 position (2 *ortho* fluorine atoms, 1 *para* fluorine atom).

3.1.1.3 Reactions of 1,4-Dibromotetrafluorobenzene

Reactions of oxygen nucleophiles with 1,4-dibromotetrafluorobenzene are shown in Table 11.

Table 11. S_NAr reactions of 1,4-dibromotetrafluorobenzene.



Products		Conversion to Product /%	Isolated Yield /%
	**23**	88	52
	**24**	74	22
	**25**	53	*
	**26**	69	*

*carried through to next synthetic step (section 3.2.1) without purification to maximise yield

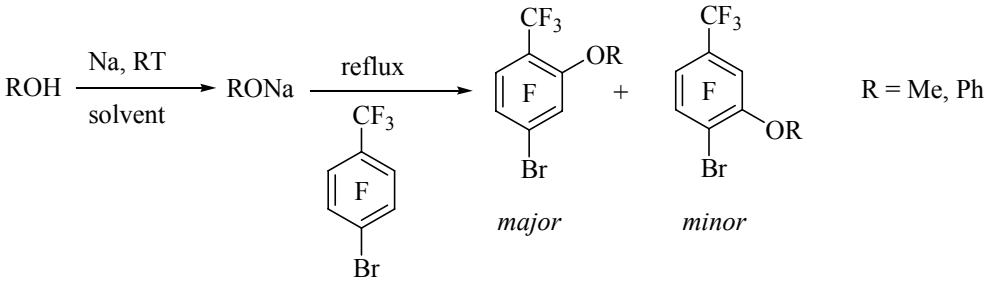
Only one isomer is possible from the action of nucleophiles upon 1,4-dibromotetrafluorobenzene, and ^{19}F NMR spectroscopy shows the three expected signals of the single products. Conversions are generally lower than for reactions with 1,2- and 1,3-dibromotetrafluorobenzenes due to the fact that attack must occur at a site *para* to a deactivating and destabilising fluorine atom. Conversion of the substrate was also lower in reactions involving the larger nucleophiles (53-74%, affording materials **24**, **25** and **26**) than with methoxide ion (88%, affording **23**) as found previously (section 3.1.1.1).

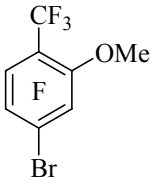
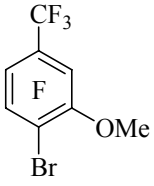
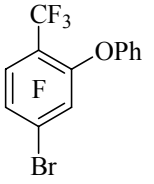
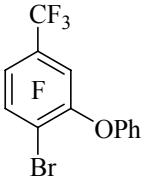
Only materials **23** and **24** were purified, isolated as pure isomers and characterised. The reactions were fairly clean and so material **25**, impure, was characterised by GC-MS only and carried through to the next synthetic step (section 3.2.1) without purification in order to maximise product yields. The impure material **26** was passed through a short silica plug and, following confirmation of its identity by ^{19}F NMR, carried through to the next synthetic step. Despite good conversion from 1,4-dibromotetrafluorobenzene, isolated yields of **23** and **24** were low (52 and 22%) as purification was required by column chromatography and for **24**, crystallisation also.

3.1.1.4 Reactions of 1-bromo-2,3,5,6-tetrafluoro-4-(trifluoromethyl)-benzene

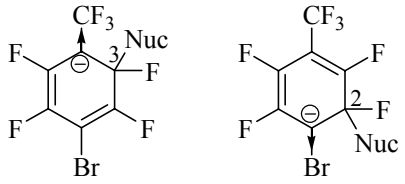
Reactions of oxygen nucleophiles with 1-bromo-2,3,5,6-tetrafluoro-4-(trifluoromethyl)-benzene are shown below (Table 12).

Table 12. S_NAr reactions of 1-bromo-2,3,5,6-tetrafluoro-4-(trifluoromethyl)-benzene.



Isomers in Crude Product Mixture		Isomer Ratio	Conversion to Products /%	Isolated Yield of Major Isomer /%
major	*minor*			
 **27**	 **28**	92:8	100	70
 **29**	 **30**	92:8	88	53

Nucleophilic attack of methoxide ion on 1-bromo-2,3,5,6-tetrafluoro-4-(trifluoromethyl)benzene results in the formation of two isomers, 1-bromo-2,3,6-trifluoro-4-(trifluoromethyl)-5-methoxybenzene **27** and 1-bromo-2,3,5-trifluoro-4-(trifluoro-methyl)-6-methoxybenzene **28**. The selectivity observed is likely to be governed by two factors. We may postulate that the trifluoromethyl group is likely to incur a greater inductive activation in the initial state for nucleophilic attack at the 3-C position than the bromine exerts at the 2-C positions (Figure 9), whilst also contributing a greater inductive stabilisation upon the carbanionic Meisenheimer intermediate than the bromine atom. Bromine lone pair repulsion is also a factor disfavouring substitution at the 2-*C* position.



94% 6%

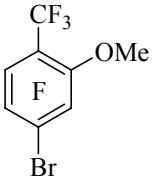
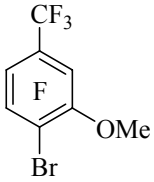
Figure 9. Meisenheimer intermediates following nucleophilic attack on 1-bromo-2,3,5,6-tetrafluoro-4-(trifluoromethyl)benzene at positions 3 and 2 respectively.

Regioselectivity in the reaction of methoxide with 1-bromo-2,3,5,6-tetrafluoro-4-(trifluoromethyl)-benzene may be elucidated by analysis of the ^{13}C NMR spectrum of the product mixture. The major isomer **27** (Table 12) shows a signal at 104.72 ppm for 1-*C* adjacent to the bromine which resembles a triplet owing to two $^{2}J_{CF}$ couplings, while a similar signal is observed at 108.91 ppm for 4-*C* adjacent to the trifluoromethyl group in the minor isomer **28**.

3.1.1.4.1 Solvent Effects in Nucleophilic Aromatic Substitution Reactions

In order to determine whether solvent has any effect on the resulting isomeric distribution of the products, the action of methoxide ion on 1-bromo-2,3,5,6-tetrafluoro-4-trifluoromethylbenzene was investigated using THF as the reaction solvent instead of methanol. The resulting isomeric distribution was only slightly different to that found when methanol was used (Table 13) whilst the conversion to products was also lower despite the longer reaction time (7 hours versus 4 hours). The phenomena might be explained though consideration of a proposed energy pathway (Figure 10). Transition state 1 may be less stable in methanol than THF giving rise to the slightly greater selectivity observed in the former solvent (greater thermodynamic control) whilst transition state 2 may be more stable in methanol resulting in a higher overall conversion to product (greater kinetic control). Polar solvents stabilise charged intermediate Meisenheimer complexes and therefore this species will be lower in energy when methanol is used. The observed selectivity could of course be attributed simply to experimental error in the measurements of the ^{19}F NMR integrals for each isomer.

Table 13. Solvent effect on isomeric distributions following nucleophilic substitution.

Solvent			Reaction time /hours	Conversion /%
MeOH	92	8	4	100
THF	88	12	7	83

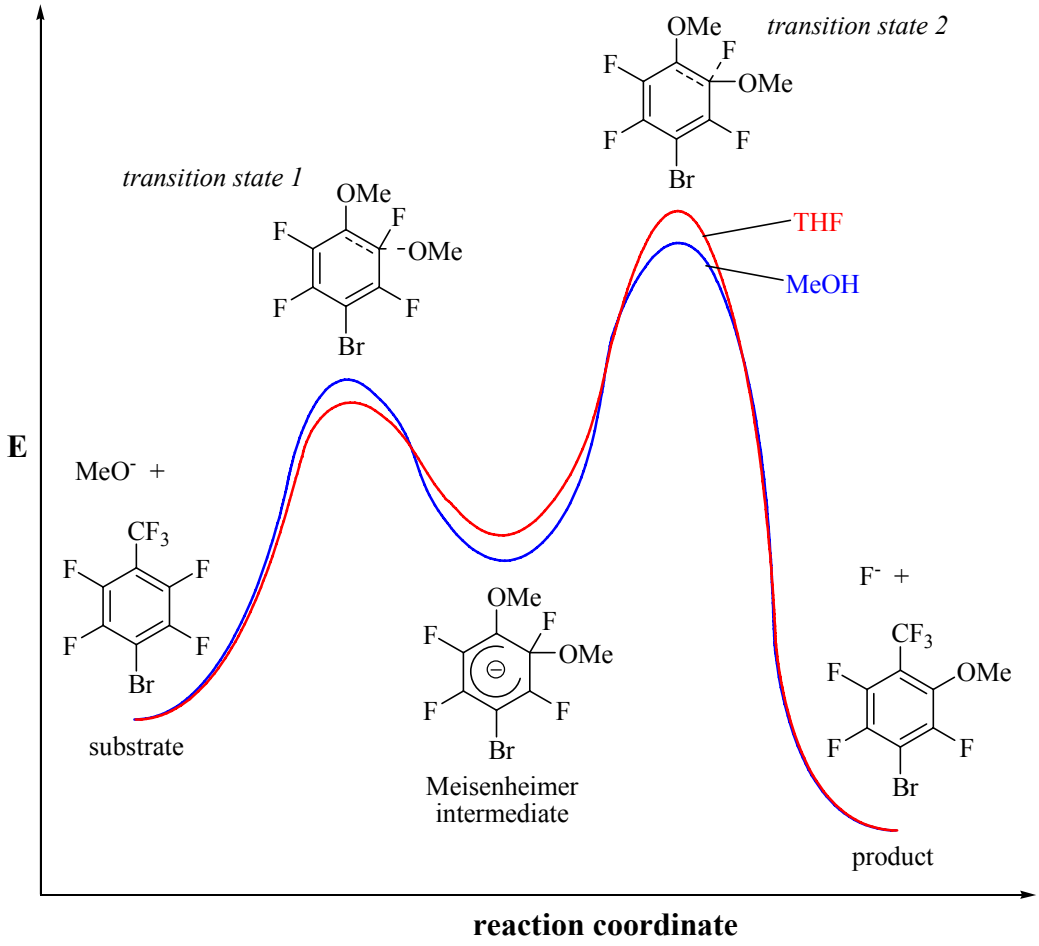


Figure 10. Solvent effects in the reaction of an alkoxide with a fluoroaryl

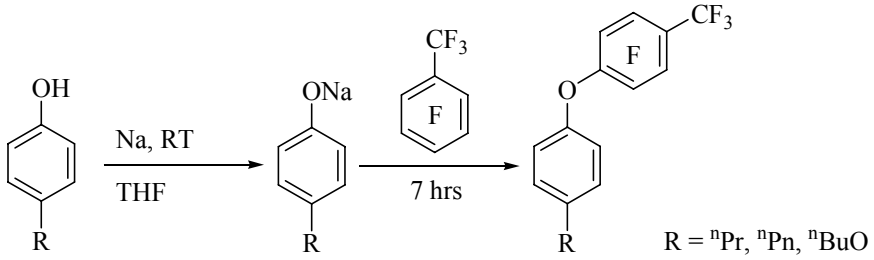
3.1.1.5 Reaction of Difluorobenzenes with Pentylphenoxide

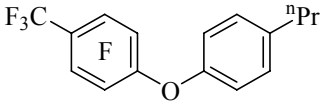
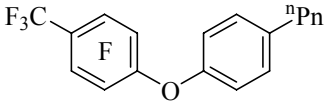
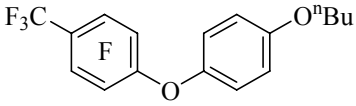
An attempt was made to react sodium 4-pentylphenoxide with 1,2,3,4-tetrafluorobenzene, 1,2,3,5-tetrafluorobenzene and 1,2,4,5-tetrafluorobenzene as in reactions using dibromotetrafluorobenzene substrates previously. No appreciable conversion was observed after 20 hours reflux in THF, indicating that the two bromine atoms of the dibromotetrafluorobenzenes used previously are required to provide inductive activation and stabilisation effects that facilitate S_NAr reactions in these systems.

3.1.1.6 Reaction of Perfluorotoluene with a Series of Aryl Tail-Groups

Three biphenyl ethers were synthesised through the reaction of propyl, pentyl and butoxy phenoxides with perfluorotoluene via S_NAr reactions replacing the fluorine atom *para* to the trifluoromethyl group (Table 14). The 1,2,4,5-tetrafluoro-3-(phenoxy)-6-trifluoromethylbenzenes **31**, **32** and **33** were obtained with quantitative conversion in excellent yields (74-86%) following 7 hours reflux in THF. These dielectrically positive model LCs are likely to have strong dipole moments due to the presence of a trifluoromethylgroup.

Table 14. S_NAr reactions of perfluorotoluene with oxygen nucleophiles.



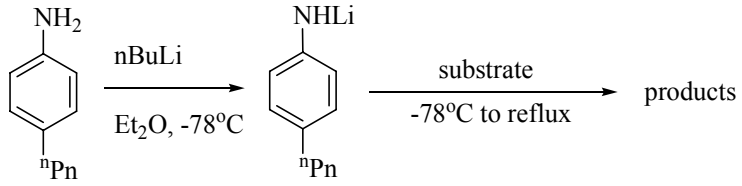
Product		Conversion /%	Pure Isolated Yield /%
	**31**	100	86
	**32**	100	74
	**33**	100	76

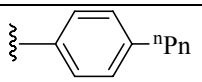
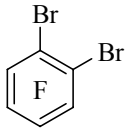
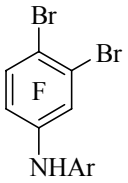
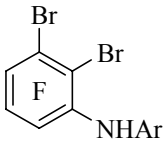
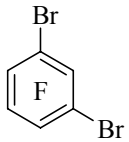
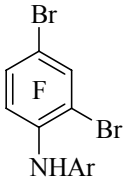
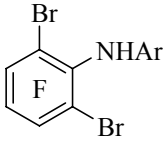
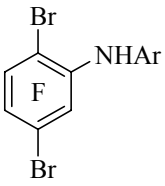
3.1.2 Nitrogen Nucleophiles

The methodology employed for oxygen nucleophiles (section 3.1.1) may be easily modified for the incorporation of any phenylamide in the synthesis to form the tail-group of a model LC, whilst leading to an easily accessible nitrogen bridge between the head and the tail.

Reactions of relatively 'hard' nitrogen nucleophiles, as 4-pentylphenylamide, in S_NAr reactions of fluorine with the three isomers of dibromotetrafluorobenzene were investigated (Table 15). Substitution occurred at the same sites as observed for oxygen nucleophiles and is governed by the same selection rules. However, the low selectivity observed in the reaction of 4-pentylphenylamide with 1,3-dibromotetrafluorobenzene to afford the isomers **36** (68%) and **37** (32%) may be attributed to the greater nucleophilicity of the nitrogen nucleophile with respect to the oxygen nucleophile leading to a reaction with greater kinetic control. This maybe contrasted to the reaction of 4-pentylphenoxide with 1,3-dibromotetrafluorobenzene to afford the isomers **19** (92%) and **20** (8%) (Table 10) showing greater thermodynamic control. The biphenylamine products were carried through to the next synthetic step (section 3.2.2) without purification.

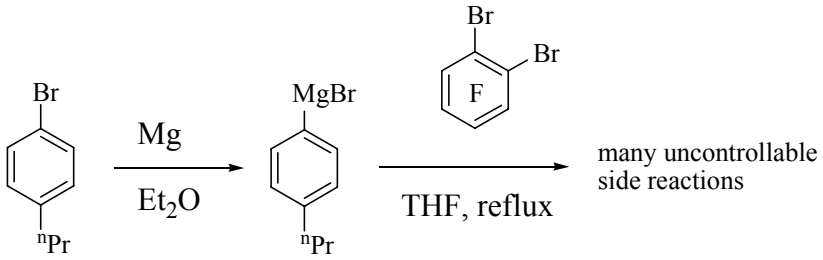
Table 15. S_NAr reactions of dibromotetrafluorobenzenes with nitrogen nucleophiles.



Substrate	Products Ar = 		Isomeric ratio (%) in crude product mixture	Conversion /%
	major	*minor*		
	 **34**	 **35**	96:4	54
	 **36**	 **37**	68:32	57
	 **38**		-	71

3.1.3 Carbon Nucleophiles

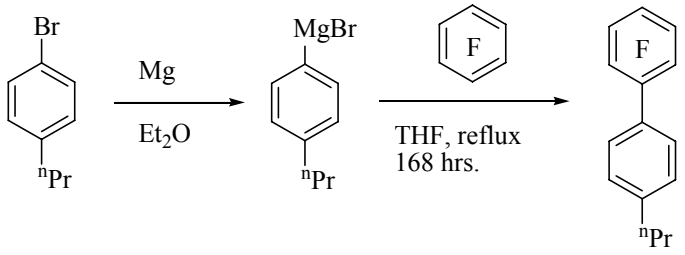
'Soft' carbon nucleophiles attack bromine rather than displacing fluorine atoms in S_NAr reactions of bromofluoroaromatics, leading to many undesirable by-products. The application of the methodology developed so far to the dibromotetrafluoroaromatic template in C-C coupling reactions, in the formation of the fluorobiphenyl moiety, is therefore not possible (Scheme 26).

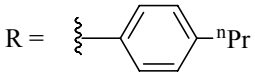
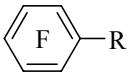
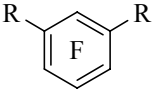
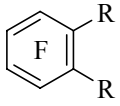


Scheme 26. Grignard reactions do not give the desired biphenyls with dibromotetrafluorobenzene substrates.

Grignard reagents do undergo the desired reaction with perfluorinated aromatics and for that reason the reaction of 4-n-propylphenylmagnesiumbromide with hexafluorobenzene was investigated. 2,3,4,5,6-Pentafluoro-4'-propyl-biphenyl was afforded slowly in moderate yield (58%) and three isomers of a biaddition product were also obtained (Table 16). The slow conversion to product reflects the destabilisation of the intermediate Meisenheimer complex by the electron lone pairs on the fluorine *para* to the site of attack.

Table 16. S_NAr reaction of perfluorobenzene with a carbon nucleophile.



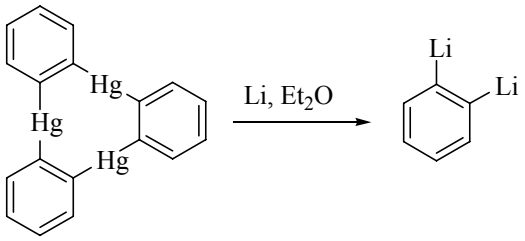
Substrate	Products R = 		Conversion /%	Isolated yield /%
		**39**	77	58
		**40**		1*
		**41**		
		**42**		

*obtained as a pure mixture of the isomers shown

3.2 Debromo-Lithiation of Substituted Dibromotrifluoroaryls

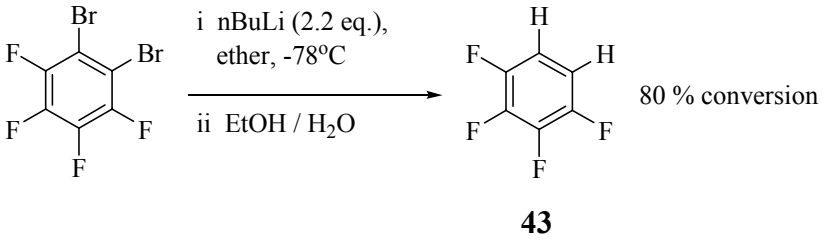
The bromine atoms on the headgroups of the materials synthesised so far served to activate these aromatic systems to S_NAr reactions. Despite adding to the polarity of the molecules these fairly labile atoms are susceptible to proto-debromination under elevated levels of heat or light and hence are unsuitable for electronic LCD devices due to their stringent purity demands.

Wittig and Bickelhaupt[96] described the preparation of *o*-phenylenedilithium via lithium metal cleavage of *o*-phenylene-mercury (Scheme 27). Gilman and Zuech[97] suggested its use was preferable over *o*-bromophenyllithium, obtained via lithiation of *o*-dibromobenzene, as a practical route for the synthesis of o-phenylene derivatives.[98]



Scheme 27.[96] Synthesis of *o*-phenylenedilithium

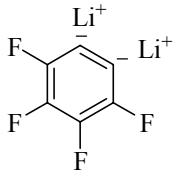
The possibility of removing both bromine atoms from 1,2-dibromo-3,4,5,6-tetrafluorobenzene in one step was explored, as a route to *o*-phenylenedilithium and derivatives. Adding a slight excess of nBuLi (2.2 equivalents) with subsequent protonation affords 1,2,3,4-tetrafluorobenzene **43** (Scheme 28).



43

Scheme 28. Removal of two bromine atoms from 1,2-dibromotetrafluorobenzene in a one step procedure

Only eighty percent conversion was obtained with the remainder consisting of 1-bromo-2,3,4,5-tetrafluorobenzene but crucially the reaction proceeded with little undesirable by-product formation indicating that benzyne formation had not occurred. Reaction must proceed via the dilithiated species **44** (Figure 11) with the two carbanions stabilised by the electron withdrawing fluorine atoms.



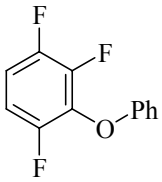
44

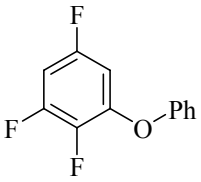
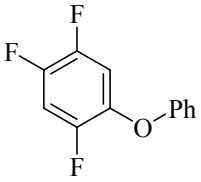
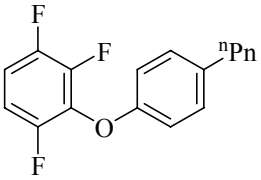
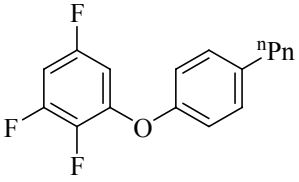
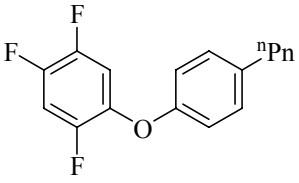
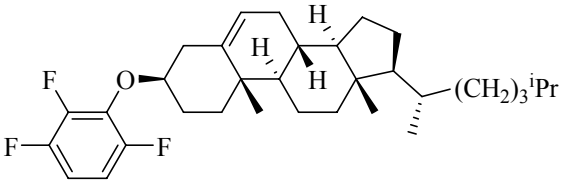
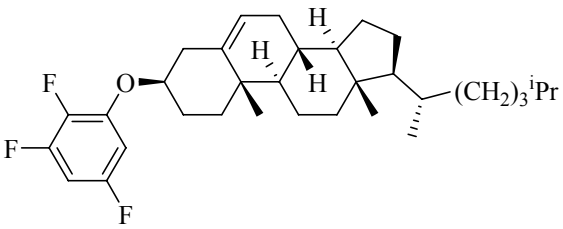
Figure 11. Dilithiated intermediate formed following removal of bromine atoms from 1,2-dibromotetrafluorobenzene

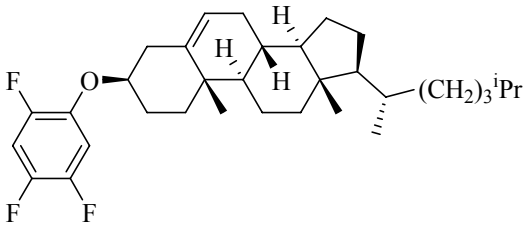
3.2.1 Dibromotrifluorophenylethers

The dibromotrifluorophenoxybenzenes **9**, **17** and **24** (section 3.1.1), dibromo-trifluoro(pentylphenoxy)benzenes **11**, **19** and **25** and the dibromotrifluorophenoxycyclopentaphenanthrenes **13**, **21** and **26** synthesised previously were debrominated with 2.2 equivalents of butyllithium, as shown in Scheme 28, and the resulting carbanions protonated in a one step procedure to yield their protodebrominated analogues (Table 17). Conversion was generally quantitative, although by-products were often formed leading to poor product recovery (5-40%). This was especially true in the synthesis of trifluorophenoxybenzenes for which many attempts had to be made in an attempt to synthesise them. Isolation of 1,2,5-trifluoro-3-phenoxybenzene was not achieved. Further development is required for this work.

Table 17. Trifluorophenyl-ethers synthesised via debromolithiation

Substrate	Product	Conversion /%	Pure Isolated Yield /%
9	 **45**	100	24

Substrate	Product		Conversion /%	Pure Isolated Yield /%
17		**46**	100	not isolated pure
24		**47**	100	7
11		**48**	100	40
19		**49**	100	32
25		**50**	100	5
13		**51**	100	33
21		**52**	100	11

Substrate	Product	Conversion /%	Pure Isolated Yield /%
26	 **53**	87	20

Proton and carbon NMR spectra of the 3β-(trifluoro-phenoxy)-5-cholestenes were assigned by comparison with data for cholesterol from the literature.[99] Crystals of 2,3,5-trifluorophenoxycyclopentaphenanthrene **52** were grown of a quality suitable for X-ray analysis (Figure 12) to confirm the structure, however, the other two isomers of the compound, **51** and **53**, could not be crystallised. GC-MS or LC-MS data could again not be obtained for these steroidal based materials as the molecular ions were not observed using these techniques. Elemental analysis showed incorrect compositions possibly due to the materials failing to combust, a phenomenon common to fluorinated compounds.

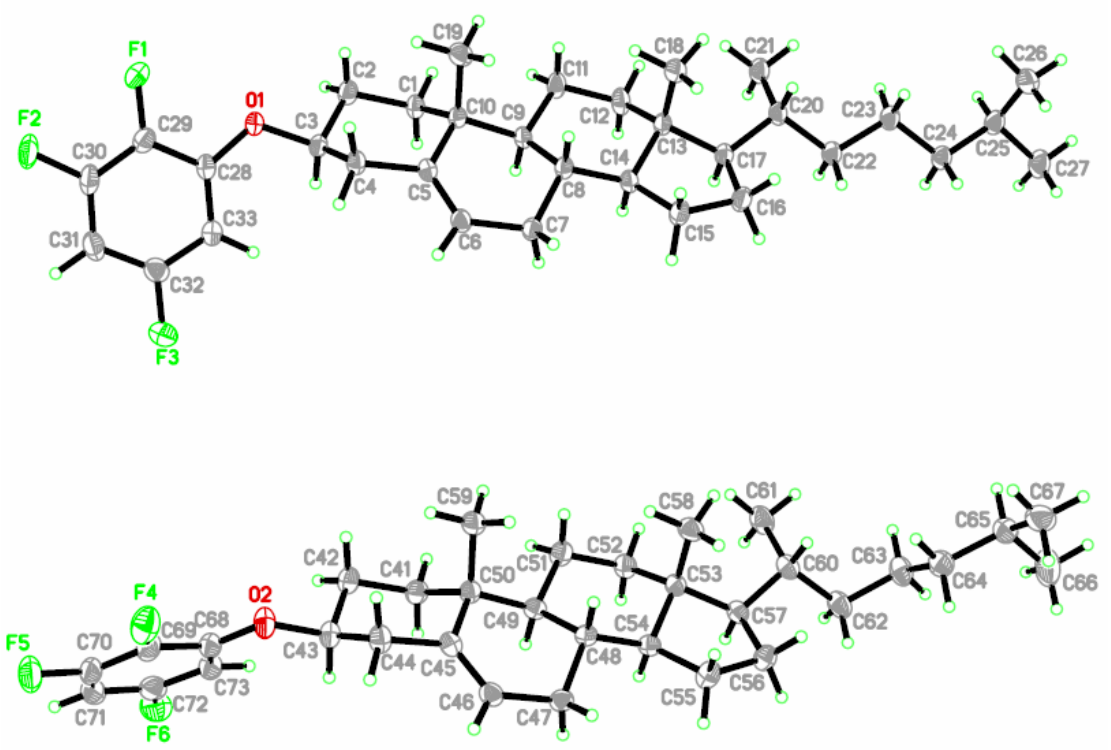
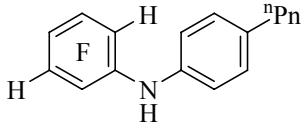


Figure 12. X-ray crystal structure of 3β-(trifluoro-phenoxy)-5-cholestene **52**.

3.2.2 Dibromotrifluorobiphenylamines

The dibromotrifluorophenyl(pentylphenyl)amine **38** (3.1.2) was debrominated with 2.2 equivalents of butyllithium in the same manner as for the dibromotrifluorobiphenylethers in a one step procedure to afford (4-pentyl-phenyl)-(2,4,5-trifluoro-phenyl)-amine **54** (Table 18) in poor yield (3%). The product was prone to decomposition and could not be isolated pure following both column chromatography and distillation, and therefore the material was not fully characterised. Consequently, the syntheses of (4-pentyl-phenyl)-(2,3,6-trifluoro-phenyl)-amine and (4-pentyl-phenyl)-(2,3,5-trifluoro-phenyl)-amine were not carried out to complete this family of nitrogen bridged biphenyls and these materials would not be suitable for display applications.

Table 18. (4-Pentyl-phenyl)-(2,4,5-trifluoro-phenyl)-amine, synthesised via debromolithiation

Substrate	Product	Conversion /%	Crude Isolated Yield /%
38	 **54**	100	3

3.3 Conclusion

Nucleophilic aromatic substitution in a number of perfluoro- and bromoperfluoro-aryl substrates has been proven to be a successful method for the synthesis of oxygen-bridged functionalised LC scaffolds and also model LC families with fluorination patterns that would be very difficult to achieve using other techniques. The intermediates are afforded selectively in good yield, and remaining bromine atoms may be removed in a one step debromolithiation and protonation procedure. This flexible methodology allows the attachment of many different tail-groups forming families of model LC molecules.

Synthesis of nitrogen-bridged biphenyl compounds may also be achieved in a similar manner, however, these materials are unstable and consequently are not viable LC materials. Carbon nucleophiles may only be reacted with non-brominated aromatic substrates.

3.4 Experimental

3.4.1 S_NAr Reactions of Perhalogenated Benzenes

3.4.1.1 Preparation of Bromofluorophenylethers

3.4.1.1.1 Reactions with Methoxide

Sodium methoxide was freshly prepared for each bromofluorobenzene by adding sodium metal (0.25 g, 11 mmol) to methanol (33 ml) under an atmosphere of dry argon. The bromofluorobenzene (10 mmol) was added and the mixture heated with stirring under reflux for 4 h. The mixture was left to cool, poured onto water (60 ml) and the product extracted with diethyl ether (3 × 40 ml). The combined ether extracts were washed with water (100 ml) and dried ($MgSO_4$). The solvent was removed *in vacuo*. Flash chromatography on silica gel with hexane as the eluent afforded the product.

1,2-Dibromo-3,4,6-trifluoro-5-methoxybenzene 7. 1,2-Dibromotetrafluorobenzene (3.08 g) afforded the anisole (2.44 g, 76%) as a clear oil (Found: C, 26.31; H, 0.92; F, 17.72. $C_7H_3OF_3Br_2$ requires C, 26.28; H, 0.95; F, 17.82%); δ_H 4.06 (3H, m, C*H*$_3$); δ_C 62.28 (m, *C*H$_3$), 106.72 (d, $^2J_{CF}$ 21.3, 2-*C*), 108.34 (dd, $^2J_{CF}$ 22.6, $^3J_{CF}$ 4.7, 1-*C*), 137.64 (ddd, $^2J_{CF}$ 16.3, $^2J_{CF}$ 11.5, $^3J_{CF}$ 2.4, 5-*C*), 144.02 (ddd, $^1J_{CF}$ 253.6, $^2J_{CF}$ 15.9, $^3J_{CF}$ 5.7, 4-*C*), 146.10 (ddd, $^1J_{CF}$ 247.7, $^2J_{CF}$ 13.5, $^4J_{CF}$ 4.3, 3-*C*), 149.66 (ddd, $^1J_{CF}$ 246.9, $^3J_{CF}$ 4.1, $^4J_{CF}$ 4.1, 6-*C*); δ_F -119.62 (d, $^5J_{FF}$ 6.8, 6-C*F*), -126.95 (dd, $^3J_{FF}$ 21.8, $^5J_{FF}$ 7.9, 3-C*F*), -149.64 (dd, $^3J_{FF}$ 21.5, $^4J_{FF}$ 5.3, 4-C*F*); *m/z* (EI$^+$) 322 (M$^+$, 49%), 320 (M$^+$, 99), 318 (M$^+$, 52), 305 (44), 277 (46), 117 (100), 98 (29), 79 (34).

1,3-Dibromo-2,4,5-trifluoro-6-methoxybenzene 15. 1,3-Dibromotetrafluorobenzene (3.08 g) afforded the anisole (2.24 g, 70%) as a clear oil (Found: C, 26.15; H, 0.94; F, 17.57. $C_7H_3OF_3Br_2$ requires C, 26.28; H, 0.95; F, 17.82%); δ_H 4.04 (3H, m, C*H*$_3$); δ_C 61.97 (m, *C*H$_3$), 93.26 (dd, $^2J_{CF}$ 28.0, $^2J_{CF}$ 22.2, 3-*C*), 100.23 (ddd, $^2J_{CF}$ 24.4, $^3J_{CF}$ 4.3, $^4J_{CF}$ 1.9, 1-*C*), 141.8 (ddd, $^1J_{CF}$ 251.6, $^2J_{CF}$ 15.2, $^4J_{CF}$ 4.6, 5-*C*), 146.17 (ddd, $^2J_{CF}$ 10.1, $^3J_{CF}$ 3.5, $^3J_{CF}$ 3.5, 6-*C*), 148.50 (ddd, $^1J_{CF}$ 249.8, $^2J_{CF}$ 13.9, $^3J_{CF}$ 5.7, 4-*C*), 152.64 (ddd, $^1J_{CF}$ 243.5, $^3J_{CF}$ 4.3, $^4J_{CF}$ 4.3, 2-*C*); δ_F -102.40 (d, $^5J_{FF}$ 7.5, 2-C*F*), -127.66 (d, $^3J_{FF}$ 22.1, 4

or 5-C*F*), -154.85 (m, 4 or 5-C*F*); *m/z* (EI^+) 322 (M^+, 70%), 320 (M^+, 89), 318 (M^+, 74), 305 (74), 277 (75), 130 (62), 117 (100), 98 (68), 79 (81).

1,4-Dibromo-2,3,5-trifluoro-6-methoxybenzene 23. 1,4-Dibromotetrafluorobenzene afforded the anisole (1.65 g, 52%) as a clear oil (Found: C, 26.51; H, 0.96; F, 17.63. $C_7H_3OF_3Br_2$ requires C, 26.28; H, 0.95; F, 17.82%); δ_H 3.96 (3H, m, C*H*$_3$); δ_C 62.09 (m, *C*H$_3$), 99.04 (ddd, $^2J_{CF}$ 24.4, $^2J_{CF}$ 22.1, $^3J_{CF}$ 2.1, 4-*C*), 105.72 (ddd, $^2J_{CF}$ 19.5, $^3J_{CF}$ 3.4, $^3J_{CF}$ 1.5, 1-*C*), 142.60 (ddd, $^2J_{CF}$ 14.9, $^3J_{CF}$ 4.2, $^4J_{CF}$ 1.6, 6-*C*), 144.94 (ddd, $^1J_{CF}$ 248.8, $^2J_{CF}$ 16.3, $^4J_{CF}$ 4.0, 2-*C*), 145.26 (ddd, $^1J_{CF}$ 248.3, $^2J_{CF}$ 15.5, $^3J_{CF}$ 4.4, 3-*C*), 149.73 (ddd, $^1J_{CF}$ 248.5, $^3J_{CF}$ 3.8, $^4J_{CF}$ 3.1, 5-*C*); δ_F -125.74 (d, $^5J_{FF}$ 7.2, 5-C*F*), -131.00 (dd, $^3J_{FF}$ 23.3, $^5J_{FF}$ 9.0, 2-C*F*), -132.61 (dd, $^3J_{FF}$ 23.7, $^4J_{FF}$ 3.8, 3-C*F*); *m/z* (EI^+) 322 (M^+, 13%), 320 (M^+, 27), 318 (M^+, 14), 277 (19), 132 (16), 130 (30), 129 (20), 117 (100), 98 (34), 79 (49), 31 (34).

Preparation of 1-bromo-2,3,6-trifluoro-4-(trifluoromethyl)-5-methoxybenzene 27 in methanol. 1-Bromo-2,3,5,6-tetrafluoro-4-(trifluoromethyl)benzene (2.97 g) afforded the anisole (1.50 g, 49%) as a clear oil; δ_H 3.99 (3H, m, C*H*$_3$); δ_C 63.02 (m, *C*H$_3$), 104.72 (dd, $^2J_{CF}$ 23.3, $^2J_{CF}$ 23.3, 1-*C*), 113.39 (qdd, $^2J_{CF}$ 32.6, $^2J_{CF}$ 8.8, $^3J_{CF}$ 2.5, 4-*C*), 121.78 (qdd, $^1J_{CF}$ 274.8, $^3J_{CF}$ 5.4, $^4J_{CF}$ 3.4, *C*F$_3$), 142.99 (dm, $^2J_{CF}$ 15.3, 5-*C*), 144.78 (ddq, $^1J_{CF}$ 261.4, $^2J_{CF}$ 16.2, $^3J_{CF}$ 1.5, 3-*C*), 145.25 (ddd, $^1J_{CF}$ 248.0, $^2J_{CF}$ 16.2, $^3J_{CF}$ 3.5, 2-*C*), 150.14 (ddd, $^1J_{CF}$ 248.0, $^3J_{CF}$ 3.7, $^4J_{CF}$ 2.5, 6-*C*); δ_F -57.06 (3F, m, C*F*$_3$), -124.66 (1F, d, $^5J_{FF}$ 11.3, 6-C*F*), -132.23 (1F, dd, $^3J_{FF}$ 22.2, $^4J_{FF}$ 2.3, 2-C*F*), -140.18 (1F, dqd, $^3J_{FF}$ 27.8, $^4J_{FF}$ 22.6, $^5J_{FF}$ 11.7, 3-C*F*); *m/z* (EI^+) 310 (M^+, 88%), 308 (M^+, 92%), 295 (47), 293 (49), 267 (58), 265 (59), 186 (100), 117 (99), 93 (42), 69 (42).

Preparation of 1-bromo-2,3,6-trifluoro-4-(trifluoromethyl)-5-methoxybenzene 27 in THF. Sodium methoxide was freshly prepared by adding sodium metal (0.25 g, 11 mmol) to methanol (0.45 ml, 11 mmol) in THF (33 ml) under an atmosphere of dry argon. 1-Bromo-2,3,5,6-tetrafluoro-4-(trifluoromethyl)benzene (2.97 g, 10 mmol) was added and the mixture heated with stirring under reflux for 7 h. The mixture was left to cool, poured onto water (60 ml) and the product extracted with diethyl ether (3 × 40 ml). The combined extracts were washed with water (100 ml) and dried ($MgSO_4$). The solvent was removed *in vacuo*. Chromatography on silica gel with hexane as the eluent afforded

the anisole **27** (1.25 g, 40%) (characterised above). The isomer *1-bromo-2,3,5-trifluoro-4-(trifluoromethyl)-6-methoxybenzene* **28** (0.27 g, 9%) was also obtained as a clear oil; δ_H 3.99 (m, C*H*$_3$); δ_C 62.26 (m, *C*H$_3$), 108.91 (qdd, $^2J_{CF}$ 34.3, $^2J_{CF}$ 14.3, $^2J_{CF}$ 12.2, 4-*C*), 111.64 (d, $^2J_{CF}$ 18.0, 1-*C*), 121.24 (qm, $^1J_{CF}$ 274.0, *C*F$_3$), 143.26 (ddm, $^2J_{CF}$ 13.8, $^3J_{CF}$ 3.9, 6-*C*), 144.21 (ddd, $^1J_{CF}$ 261.1, $^2J_{CF}$ 16.9, $^4J_{CF}$ 1.7, 2-*C*), 145.61 (ddd, $^1J_{CF}$ 248.3, $^2J_{CF}$ 14.9, $^3J_{CF}$ 4.4, 3-*C*), 149.22 (dm, $^1J_{CF}$ 259.6, 5-*C*); δ_F -56.79 (3F, m, C*F*$_3$), -130.33 (1F, dd, $^3J_{FF}$ 22.6, $^5J_{FF}$ 11.3, 2-C*F*), -133.14 (1F, qdd, $^4J_{FF}$ 22.0, $^5J_{FF}$ 11.1, $^4J_{FF}$ 5.7, 5-C*F*), -140.55 (1F, dqd, $^3J_{FF}$ 22.7, $^4J_{FF}$ 22.7, $^4J_{FF}$ 5.6, 3-C*F*); *m/z* (EI$^+$) 310 (M$^+$, 84%), 308 (M$^+$, 87%), 295 (54), 293 (56), 267 (22), 265 (23), 199 (19), 186 (100), 117 (58), 69 (21), 28 (32).

3.4.1.1.2 Reactions with Phenoxide

Sodium phenoxide was freshly prepared for each bromofluorobenzene by adding sodium metal (0.30 g, 13 mmol) to phenol (0.99 g, 11 mmol) in THF (33 ml) under an atmosphere of dry argon. The bromofluorobenzene (10 mmol) was added and the mixture heated with stirring under reflux for 7 h. The mixture was left to cool, poured onto water (60 ml) and the product extracted with ethyl acetate (3 × 40 ml). The combined extracts were washed with water (100 ml) and dried ($MgSO_4$). The solvent was removed *in vacuo*. Chromatography on silica gel with hexane as the eluent afforded the solid product. Recrystallisation in ethanol/water removed any trace isomer present.

1,2-Dibromo-3,4,6-trifluoro-5-phenoxybenzene 9. 1,2-Dibromotetrafluorobenzene (3.08 g) afforded the phenoxybenzene (0.91 g, 24%) as a white solid, mp 108-109 °C (Found: C, 37.63; H, 1.29; F, 14.67. $C_{12}H_5OF_3Br_2$ requires C, 37.73; H, 1.32; F, 14.92%); δ_H 7.24 (2H, m, 3′-C*H*), 7.03 (1H, m, 4′-C*H*), 6.86 (2H, m, 2′-C*H*); δ_C 108.90 (dd, $^2J_{CF}$ 22.4, $^3J_{CF}$ 4.8, 2-*C*), 109.89 (d, $^2J_{CF}$ 21.1, 1-*C*), 115.66 (s, 2′-*C*), 124.02 (s, 4′-*C*), 130.00 (s, 3′-*C*), 132.88 (ddd, $^2J_{CF}$ 17.4, $^2J_{CF}$ 13.0, $^3J_{CF}$ 2.4, 5-*C*), 144.72 (ddd, $^1J_{CF}$ 257.3, $^2J_{CF}$ 16.1, $^3J_{CF}$ 4.6, 4-*C*), 146.33 (ddd, $^1J_{CF}$ 249.1, $^2J_{CF}$ 12.9, $^4J_{CF}$ 4.5, 3-*C*), 150.40 (ddd, $^1J_{CF}$

250.5, $^{3}J_{CF}$ 3.8, $^{4}J_{CF}$ 3.8, 6-*C*), 157.09 (s, 1′-*C*); δ_F -116.85 (d, $^{5}J_{FF}$ 9.0, 6-C*F*), -125.61 (dd, $^{3}J_{FF}$ 22.2, $^{5}J_{FF}$ 9.0, 3-C*F*), -146.23 (d, $^{3}J_{FF}$ 22.2, 4-C*F*); *m/z* (EI^+) 384 (M^+, 2%), 382 (M^+, 5), 380 (M^+, 3), 354 (2), 275 (3), 222 (8), 193 (5), 129 (5), 117 (14), 77 (100), 51 (63), 39 (22).

1,3-Dibromo-2,4,5-trifluoro-6-phenoxybenzene 17. 1,3-Dibromotetrafluorobenzene (3.08 g) afforded the phenoxybenzene (2.30 g, 60%) as a white solid, mp 76-77 °C (Found: C, 37.72; H, 1.30; F, 14.64. $C_{12}H_5OF_3Br_2$ requires C, 37.73; H, 1.32; F, 14.92%); δ_H 7.25 (2H, m, 3′-C*H*), 7.04 (1H, m, 4′-C*H*), 6.84 (2H, m, 2′-C*H*); δ_C 96.12 (dd, $^{2}J_{CF}$ 27.7, $^{2}J_{CF}$ 22.2, 3-*C*), 102.10 (dd, $^{2}J_{CF}$ 25.1, $^{3}J_{CF}$ 4.8, 1-*C*), 115.50 (s, 2′-*C*), 123.81 (s, 4′-*C*), 130.02 (s, 3′-*C*), 141.72 (ddd, $^{2}J_{CF}$ 12.1, $^{3}J_{CF}$ 3.5, $^{3}J_{CF}$ 3.5, 6-*C*), 142.32 (ddd, $^{1}J_{CF}$ 255.8, $^{2}J_{CF}$ 15.2, $^{4}J_{CF}$ 4.9, 5-*C*), 148.58 (ddd, $^{1}J_{CF}$ 251.1, $^{2}J_{CF}$ 13.5, $^{3}J_{CF}$ 5.4, 4-*C*), 153.08 (ddd, $^{1}J_{CF}$ 245.0, $^{3}J_{CF}$ 4.2, $^{4}J_{CF}$ 4.2, 2-*C*), 156.62 (s, 1′-*C*); δ_F -101.55 (d, $^{5}J_{FF}$ 9.4, 2-C*F*), -126.43 (d, $^{3}J_{FF}$ 21.5, 4-C*F*), -150.11 (dd, $^{3}J_{FF}$ 21.3, $^{5}J_{FF}$ 8.5, 5-C*F*); *m/z* (EI^+) 384 (M^+, 15%), 382 (M^+, 32), 380 (M^+, 16), 223 (29), 222 (100), 193 (27), 117 (21), 77 (97), 65 (18), 51 (78), 50 (25), 39 (23).

1,4-Dibromo-2,3,5-trifluoro-6-phenoxybenzene 24. 1,4-Dibromotetrafluorobenzene (3.08 g) afforded the phenoxybenzene (0.83 g, 22%) as a white solid, mp 113-114 °C (Found: C, 37.74; H, 1.31; F, 15.06. $C_{12}H_5OF_3Br_2$ requires C, 37.73; H, 1.32; F, 14.92%); δ_H 7.23 (2H, m, 3′-C*H*), 7.01 (1H, m, 4′-C*H*), 6.79 (2H, m, 2′-C*H*); δ_C 99.48 (dd, $^{2}J_{CF}$ 23.0, $^{2}J_{CF}$ 23.0, 4-*C*), 107.13 (d, $^{2}J_{CF}$ 20.3, 1-*C*), 115.36 (s, 2′-*C*), 123.66 (s, 4′-*C*), 130.00 (s, 3′-*C*), 137.87 (dd, $^{2}J_{CF}$ 15.2, $^{3}J_{CF}$ 5.2, 6-*C*), 145.72 (ddd, $^{1}J_{CF}$ 248.8, $^{2}J_{CF}$ 14.9, $^{3}J_{CF}$ 4.6, 3-*C*), 146.21 (ddd, $^{1}J_{CF}$ 249.8, $^{2}J_{CF}$ 15.0, $^{4}J_{CF}$ 3.6, 2-*C*), 150.16 (ddd, $^{1}J_{CF}$ 251.3, $^{3}J_{CF}$ 3.5, $^{4}J_{CF}$ 3.5, 5-*C*), 156.88 (s, 1′-*C*); δ_F -122.00 (dd, $^{5}J_{FF}$ 9.0, $^{4}J_{FF}$ 2.3, 5-C*F*), -129.75 (dd, $^{3}J_{FF}$ 23.3, $^{4}J_{FF}$ 2.6, 3-C*F*), -130.39 (dd, $^{3}J_{FF}$ 22.8, $^{5}J_{FF}$ 9.2, 2-C*F*); *m/z* (EI^+) 384 (M^+, 1%), 382 (M^+, 3), 380 (M^+, 2), 277 (4), 222 (36), 193 (8), 129 (7), 117 (16), 77 (100), 65 (14), 51 (64), 39 (29).

1-Bromo-2,3,6-trifluoro-4-(trifluoromethyl)-5-phenoxybenzene 29. 1-Bromo-2,3,5,6-tetrafluoro-4-(trifluoromethyl)benzene (2.97 g) afforded the phenoxybenzene (1.95 g, 53%) as a white solid, mp 96-96.5 °C (Found: C, 42.12; H, 1.32; F, 30.57. $C_{13}H_5OF_6Br$ requires C, 42.08; H, 1.36; F, 30.72%); δ_H 7.26 (2H, m, 3′-C*H*), 7.04 (1H, m, 4′-C*H*), 6.85 (2H, m, 2′-C*H*); δ_C 105.04 (dd, $^{2}J_{CF}$ 22.6, $^{2}J_{CF}$ 22.6, 1-*C*), 114.40 (qd, $^{2}J_{CF}$ 33.6, $^{2}J_{CF}$ 9.5,

4-*C*), 115.27 (s, 2′-*C*), 121.31 (q, $^{1}J_{CF}$ 275.0, *C*F$_3$), 123.73 (s, 4′-*C*), 129.87 (s, 3′-*C*), 137.34 (d, $^{2}J_{CF}$ 16.1, 5-*C*), 145.00 (dd, $^{1}J_{CF}$ 263.8, $^{2}J_{CF}$ 15.0, 3-*C*), 146.27 (ddd, $^{1}J_{CF}$ 250.3, $^{2}J_{CF}$ 15.7, $^{3}J_{CF}$ 3.1, 2-*C*), 149.89 (d, $^{1}J_{CF}$ 252.6, 6-*C*), 157.48 (s, 1′-*C*); δ_F -56.92 (3F, m, C*F*$_3$), -120.31 (1F, d, $^{5}J_{FF}$ 11.7, 6-C*F*), -129.29 (1F, d, $^{3}J_{FF}$ 21.8, 2-C*F*), -139.04 (1F, dqd, $^{3}J_{FF}$ 25.5, $^{4}J_{FF}$ 22.6, $^{5}J_{FF}$ 11.6, 3-C*F*); *m/z* (EI$^+$) 372 (M$^+$, 3%), 370 (M$^+$, 4), 271 (2), 222 (8), 186 (5), 148 (3), 117 (8), 77 (100), 65 (13), 51 (40), 39 (15).

3.4.1.1.3 Reactions with Pentylphenoxide

Sodium 4-*n*-propylphenoxide was freshly prepared for each dibromotetrafluorobenzene by adding sodium metal (0.30 g, 13 mmol) to 4-*n*-propylphenol (1.80 ml, 10.5 mmol) in THF (33 ml) under an atmosphere of dry argon. The dibromotetrafluorobenzene (3.08 g, 10 mmol) was added and the mixture heated with stirring under reflux for 20 h. The mixture was left to cool, poured onto water (60 ml) and the product extracted with DCM (3 × 30 ml). The combined extracts were washed with water (100 ml) and dried ($MgSO_4$). The solvent was removed *in vacuo*. The products were carried through to the next stage without purification.

1,2-Dibromo-3,4,6-trifluoro-5-(4-pentyl-phenoxy)-benzene 11. 1,2-Dibromotetrafluorobenzene yielded a mixture of isomers (4.21g crude material). Major isomer **11**; *m/z* (EI$^+$) 454 (M$^+$, 17%), 452 (M$^+$, 35), 450 (M$^+$, 19), 397 (49), 396 (18), 395 (100), 393 (55), 235 (28), 90 (32), 89 (30). Minor isomer *1,2-Dibromo-3,4,5-trifluoro-6-(4-pentyl-phenoxy)-benzene* **12**; *m/z* (EI$^+$) 454 (M$^+$, 43%), 452 (M$^+$, 76), 450 (M$^+$, 50), 397 (96), 395 (100), 393 (84), 91 (36), 90 (51), 89 (55), 77 (44).

1,3-Dibromo-2,4,5-trifluoro-6-(4-pentyl-phenoxy)-benzene 19. 1,3-Dibromotetrafluorobenzene yielded a mixture of isomers (4.21g crude material). Major isomer **19**; *m/z* (EI$^+$) 454 (M$^+$, 14%), 452 (M$^+$, 28), 450 (M$^+$, 15), 397 (50), 395 (100), 393 (55), 90 (21), 89 (26), 77 (17), 41 (30), 29 (24). Assumed minor isomer *1,3-dibromo-*

4,5,6-trifluoro-2-(4-pentyl-phenoxy)-benzene **20**; *m/z* (EI^+) 454 (M^+, 31%), 452 (M^+, 65), 450 (M^+, 34), 397 (66), 395 (100), 393 (80), 315 (32), 313 (35), 90 (35), 89 (43), 77 (32).

1,4-Dibromo-2,3,5-trifluoro-6-(4-pentyl-phenoxy)-benzene 25. 1,4-Dibromotetrafluorobenzene yielded the phenoxy benzene (4.31g crude material); *m/z* (EI^+) 454 (M^+, 15%), 452 (M^+, 31), 450 (M^+, 15), 397 (49), 395 (100), 393 (55), 90 (30), 89 (33), 78 (23), 77 (25), 41 (25).

3.4.1.1.4 Preparation of 3β-(Dibromo-trifluoro-phenoxy)-5-cholestenes

The alkoxide of 3β-hydroxy-5-cholestene was freshly prepared for each dibromotetrafluorobenzene by adding sodium metal (2.3 equiv.) to 3β-hydroxy-5-cholestene (2 equiv.) in THF (60 ml) under an atmosphere of dry argon. The dibromotetrafluorobenzene (1 equiv.) was added and the mixture heated with stirring under reflux for 7 days. The mixture was left to cool, poured onto water (100 ml) and the product extracted with DCM (3 × 30 ml). The combined extracts were washed with water (100 ml) and dried ($MgSO_4$). The solvent was removed *in vacuo*, and the resulting material passed through a silica gel plug with hexane as the eluent to afford the crude product. The materials were not characterised.

(3S,8S,9S,10R,13R,14S,17R)-3-(3,4-Dibromo-2,5,6-trifluoro-phenoxy)-17-((R)-1,5-dimethyl-hexyl)-10,13-dimethyl-2,3,4,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1*H*-cyclopenta[*a*]phenanthrene 13. 1,2-Dibromotetrafluorobenzene (0.51 g, 1.65 mmol) afforded the crude product (0.20 g).

(3S,8S,9S,10R,13R,14S,17R)-3-(2,4-Dibromo-3,5,6-trifluoro-phenoxy)-17-((R)-1,5-dimethyl-hexyl)-10,13-dimethyl-2,3,4,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1*H*-cyclopenta[*a*]phenanthrene 21. 1,3-Dibromotetrafluorobenzene (3.08 g, 10.00 mmol) afforded the crude product (1.08 g).

(3S,8S,9S,10R,13R,14S,17R)-3-(2,5-Dibromo-3,4,6-trifluoro-phenoxy)-17-((R)-1,5-dimethyl-hexyl)-10,13-dimethyl-2,3,4,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-

1*H*-cyclopenta[*a*]phenanthrene 26. 1,4-Dibromotetrafluorobenzene (0.51 g, 1.65 mmol) afforded the crude product (0.16 g).

3.4.1.2 Preparation of 1,2,4,5-Tetrafluoro-3-(4-aryloxy)-6-trifluoromethyl-benzenes

Each aryloxide was freshly prepared by adding sodium metal (1.3 equiv.) to the aryl alcohol (1 equiv.) in THF (33 ml) under an atmosphere of dry argon. 1,2,3,4,5-Pentafluoro-6-(trifluoromethyl)benzene (1 equiv.) was added and the mixture heated with stirring under reflux for 7 h. The mixture was left to cool, poured onto water (60 ml) and the product extracted with DCM (3 × 40 ml). The combined extracts were washed with water (100 ml) and dried ($MgSO_4$). The solvent was removed *in vacuo*. Chromatography on silica gel with hexane/DCM as the eluent afforded the product.

1,2,4,5-Tetrafluoro-3-(4-propyl-phenoxy)-6-trifluoromethyl-benzene 31.
4-*n*-Propylphenol (0.57 g, 4.19 mmol) afforded the product (1.27 g, 86%) as a clear oil (Found: C, 54.41; H, 3.13. $C_{16}H_{11}F_7O$ requires C, 54.56; H, 3.15%); δ_H 0.98 (3H, t, $^3J_{HH}$ 7.3, C*H*$_3$), 1.67 (2H, qt, $^3J_{HH}$ 7.6, $^3J_{HH}$ 7.4, C*H*$_2$CH$_3$), 2.61 (2H, t, $^3J_{HH}$ 7.4, C*H*$_2$CH$_2$CH$_3$), 6.95 (2H, dm, $^3J_{HH}$ 8.6, 3'-C*H*), 7.19 (2H, dm, $^3J_{HH}$ 8.8, 2'-C*H*); δ_C 13.78 (s, *C*H$_3$), 24.78 (s, *C*H$_2$CH$_3$), 37.37 (s, *C*H$_2$CH$_2$CH$_3$), 105.63 (qt, $^2J_{CF}$ 34.8, $^2J_{CF}$ 12.9, 6-*C*), 115.98 (s, 3'-*C*), 121.13 (q, $^1J_{CF}$ 274.1, *C*F$_3$), 129.96 (s, 2'-*C*), 138.00 (tt, $^2J_{CF}$ 12.6, $^3J_{CF}$ 3.4, 3-*C*), 139.26 (s, 4'-*C*), 141.96 (A or A' of AA'BB', $^1J_{CF}$ 253.2, 2-*C*), 145.18 (ddm, $^1J_{CF}$ 259.9, $^2J_{CF}$ 13.8, 1-*C*), 154.94 (s, 1'-*C*); δ_F -56.41 (3F, t, $^4J_{FF}$ 22.3, C*F*$_3$), -141.16 (2F, A or A' of AA'BB', 1-C*F*), -152.67 (2F, B or B' of AA'BB', 2-C*F*); *m/z* (EI$^+$) 352 (M$^+$, 67%), 324 (33), 323 (100), 117 (12), 115 (10), 91 (20), 90 (48), 89 (39), 78 (16), 77 (18).
1,2,4,5-Tetrafluoro-3-(4-pentyl-phenoxy)-6-trifluoromethyl-benzene 32. 4-*n*-Pentylphenol (3.28 g, 20 mmol) afforded the product (5.66 g, 74%) as a clear oil (Found: C, 56.95; H, 4.01. $C_{18}H_{15}F_7O$ requires C, 56.85; H, 3.98%); δ_H 0.96 (3H, t, $^3J_{HH}$ 6.9, *C*H$_3$), 1.40 (4H, m, 2 × *C*H$_2$), 1.67 (2H, tt, $^3J_{HH}$ 7.4, $^3J_{HH}$ 7.5, *C*H$_2$), 2.65 (2H, t, $^3J_{HH}$ 7.7, *C*H$_2$(CH$_2$)$_3$CH$_3$), 6.97 (2H, dm, $^3J_{HH}$ 8.6, 3'-*C*), 7.21 (2H, dm, $^3J_{HH}$ 8.8, 2'-*C*); δ_C 14.07 (s,

*C*H$_3$), 22.74 (s, *C*H$_2$CH$_3$), 31.45 (s, *C*H$_2$CH$_2$CH$_3$), 31.66 (s, *C*H$_2$(CH$_2$)$_2$CH$_3$), 35.33 (s, *C*H$_2$(CH$_2$)$_3$CH$_3$), 105.66 (qt, $^2J_{CF}$ 35.1, $^2J_{CF}$ 12.7, 6-*C*), 116.01 (s, 3'-*C*), 121.17 (q, $^1J_{CF}$ 275.4, *C*F$_3$), 129.90 (s, 2'-*C*), 138.06 (tt, $^2J_{CF}$ 12.2, $^3J_{CF}$ 3.4, 3-*C*), 139.55 (s, 4'-*C*), 142.00 (A and A' of AA'BB', 2-*C*), 145.22 (ddm, $^1J_{CF}$ 259.9, $^2J_{CF}$ 13.8, 1-*C*), 154.96 (s, 1'-*C*); δ_F -56.34 (3F, t, $^4J_{FF}$ 23.1, C*F*$_3$), -141.11 (2F, A and A' of AA'BB', 1-C*F*), -152.61 (2F, B and B' of AA'BB', 2-C*F*); *m/z* (EI$^+$) 380 (M$^+$, 67%), 324 (38), 323 (100), 104 (14), 91 (35), 90 (61), 89 (39), 78 (18), 77 (23), 41 (12).

1-(4-Butoxy-phenoxy)-2,3,5,6-tetrafluoro-4-trifluoromethyl-benzene 33. 4-*n*-Butoxyphenol (0.70 g, 4.19 mmol) afforded the product (1.21 g, 76%) as a clear oil (Found: C, 53.47; H, 3.46. $C_{17}H_{13}F_7O_2$ requires C, 53.41; H, 3.43%); δ_H 1.00 (3H, t, $^3J_{HH}$ 7.3, C*H*$_3$), 1.52 (2H, qt, $^3J_{HH}$ 7.6, $^3J_{HH}$ 7.5, C*H*$_2$CH$_3$), 1.78 (2H, m, C*H*$_2$CH$_2$CH$_3$), 3.95 (2H, t, $^3J_{HH}$ 6.6, OC*H*$_2$), 6.88 (2H, dm, $^3J_{HH}$ 9.3, 3'-C*H*), 6.98 (2H, dm, $^3J_{HH}$ 9.3, 2'-C*H*); δ_C 13.89 (s, *C*H$_3$), 19.38 (s, *C*H$_2$CH$_3$), 31.48 (s, *C*H$_2$CH$_2$CH$_3$), 68.34 (s, O*C*H$_2$), 105.31 (qt, $^2J_{CF}$ 34.8, $^2J_{CF}$ 13.1, 4-*C*), 115.53 (s, 3'-*C*), 117.56 (s, 2'-*C*), 121.13 (q, $^1J_{CF}$ 274.5, *C*F$_3$), 138.55 (tt, $^2J_{CF}$ 12.3, $^3J_{CF}$ 3.4, 1-*C*), 141.82 (A and A' of AA'BB', $^1J_{CF}$ 252.1, 2-*C*), 145.16 (ddm, $^1J_{CF}$ 259.7, $^2J_{CF}$ 13.9, 3-*C*), 150.61 (s, 4'-*C*), 156.29 (s, 1'-*C*); δ_F -56.32 (3F, t, $^4J_{FF}$ 21.3, C*F*$_3$), -141.20 (2F, m, 3-C*F*), -153.02 (2F, ddd, $^3J_{FF}$ 25.1, $^5J_{FF}$ 12.9, $^4J_{FF}$ 6.1, 2-C*F*); *m/z* (EI$^+$) 382 (M$^+$, 51%), 327 (22), 326 (100), 200 (12), 109 (55), 93 (14), 81 (12), 65 (27), 57 (25), 41 (24), 29 (23).

3.4.1.3 Preparation of (Dibromo-trifluoro-phenyl)-(4-pentyl-phenyl)-amines

4-Pentylaniline (2.0 ml, 11 mmol) was added slowly to a solution of *n*-butyllithium (4.0 ml, 2.5 M in hexanes) in dry diethyl ether (33 ml) at -78 °C under an atmosphere of dry argon, and the solution stirred for 1 hr. The dibromotetrafluorobenzene (3.08 g, 10 mmol) was then added to the reaction mixture over 0.5 hr and the solution stirred for a further 1 hr at -78 °C. The mixture was left to warm to room temperature and then refluxed under an atmosphere of dry argon until NMR showed appreciable conversion. The solution was allowed to cool to room temperature and quenched slowly with ethanol (5 ml) followed

by water (5 ml). The mixture was stirred for 0.5 hr, poured onto water (60 ml) and the product extracted with ether (3 × 30 ml). The combined extracts were washed with water (100 ml) and dried ($MgSO_4$). The solvent was removed *in vacuo*. The products were carried through to the next stage without purification.

(3,4-Dibromo-2,5,6-trifluoro-phenyl)-(4-pentyl-phenyl)-amine 34. Following reflux for 24 hrs, 1,2-dibromotetrafluorobenzene yielded a mixture of isomers (4.08g crude material). Major isomer **34**; *m/z* (EI^+) 453 (M^+, 17%), 451 (M^+, 34), 449 (M^+, 17), 396 (63), 395 (21), 394 (100), 393 (14), 392 (66), 235 (10), 234 (66). Minor isomer *(2,3-dibromo-4,5,6-trifluoro-phenyl)-(4-pentyl-phenyl)-amine* **35**; *m/z* (EI^+) 453 (M^+, 21%), 451 (M^+, 41), 449 (M^+, 22), 396 (79), 394 (100), 392 (86), 314 (21), 312 (21), 234 (34), 233 (29), 43 (27).

(2,4-Dibromo-3,5,6-trifluoro-phenyl)-(4-pentyl-phenyl)-amine 37. Following reflux for 120 hrs, 1,3-dibromotetrafluorobenzene yielded the amine (5.19g crude material); *m/z* (EI^+) 453 (M^+, 29%), 451 (M^+, 58), 449 (M^+, 30), 396 (81), 394 (100), 392 (82), 314 (18), 312 (17), 233 (26), 43 (17).

(2,5-Dibromo-3,4,6-trifluoro-phenyl)-(4-pentyl-phenyl)-amine 38. Following reflux for 264 hrs, 1,4-dibromotetrafluorobenzene yielded the amine (6.41g crude material); *m/z* (EI^+) 453 (M^+, 15%), 451 (M^+, 30), 449 (M^+, 15), 396 (51), 395 (16), 394 (100), 392 (53), 314 (14), 312 (11), 233 (11).

3.4.1.4 Preparation of 2,3,4,5,6-Pentafluoro-4'-propyl-biphenyl.

4-*n*-Propylphenylmagnesiumbromide, 0.5 M in THF (30 ml, 15 mmol) was added to a stirred solution of hexafluorobenzene (1.86 g, 10 mmol) in dry THF (30 ml) under argon. Following reflux for 168 hrs, the mixture was left to cool, poured onto water (60 ml) and the product extracted with DCM (3 × 30 ml). The combined ether extracts were washed with water (100 ml) and dried ($MgSO_4$). The solvent was removed *in vacuo*. Flash chromatography on silica gel with hexane as the eluent afforded the biphenyl **39 (**1.65g,

58%) as a white solid, mp 54.5-56.0 °C (Found: C, 62.99; H, 3.84. $C_{15}H_{11}F_5$ requires C, 62.94; H, 3.87%); δ_H 1.01 (3H, t, $^3J_{HH}$ 7.2, C*H*$_3$), 1.72 (2H, tq, $^3J_{HH}$ 7.6, $^3J_{HH}$ 7.6, C*H*$_2$CH$_3$), 2.68 (2H, t, $^3J_{HH}$ 7.6, C*H*$_2$CH$_2$CH$_3$), 7.34 (4H, m, 2' and 3'-C*H*); δ_C 13.98 (s, *C*H$_3$), 24.53 (s, *C*H$_2$CH$_3$), 38.01 (s, *C*H$_2$CH$_2$CH$_3$), 116.14 (tt, $^2J_{CF}$ 17.1, $^3J_{CF}$ 3.9, 1-*C*), 123.75 (s, 4'-*C*), 128.97 (s, 2' or 3'-*C*), 130.12 (s, 2' or 3'-*C*), 137.99 (dddd, $^1J_{CF}$ 252.4, $^2J_{CF}$ 17.1, $^2J_{CF}$ 12.1, $^3J_{CF}$ 2.3, 3-*C*), 140.32 (dtt, $^1J_{CF}$ 253.4, $^2J_{CF}$ 13.1, $^3J_{CF}$ 5.0, 4-*C*), 144.28 (s, 1'-*C*), 144.32 (dddd, $^1J_{CF}$ 246.4, $^2J_{CF}$ 15.1, $^3J_{CF}$ 7.1, $^3J_{CF}$ 4.2, 2-*C*); δ_F -143.85 (2F, dd, $^3J_{FF}$ 23.0, $^5J_{FF}$ 8.3, 2-C*F*), -156.71 (1F, t, $^3J_{FF}$ 20.7, 4-C*F*), -162.99 (2F, ddd, $^3J_{FF}$ 21.5, $^3J_{FF}$ 21.5, $^5J_{FF}$ 7.2, 3-C*F*); *m/z* (EI$^+$) 286 (M$^+$, 68%), 258 (27), 257 (100), 238 (9), 237 (59), 206 (13), 188 (13), 39 (9). The bi-addition product was obtained as a white solid (0.03g, 1%) as mixture of three isomers (Found: C, 74.73; H, 6.01. $C_{24}H_{22}F_4$ requires C, 74.60; H, 5.74%); The major isomer was determined to be *2',3',5',6'-tetrafluoro-4,4''-dipropyl-[1,1'; 4',1'']terphenyl* **40**; δ_H 1.01 (3H, t, $^3J_{HH}$ 7.2, C*H*$_3$), 1.72 (2H, q, $^3J_{HH}$ 7.6, C*H*$_2$CH$_3$), 2.68 (2H, t, $^3J_{HH}$ 7.6, C*H*$_2$CH$_2$CH$_3$), 7.33 (2H, d, $^3J_{HH}$ 8.0, 2 or 3-C*H*), 7.45 (2H, d, $^3J_{HH}$ 8.0, 2 or 3-C*H*); δ_C 14.05 (s, *C*H$_3$), 20.14 (s, *C*H$_2$CH$_3$), 38.05 (s, *C*H$_2$CH$_2$CH$_3$), 119. 47 (m, 1'-*C*), 124.96 (s, 4-*C*), 128.86 (s, 2 or 3-*C*), 130.16 (s, 2 or 3-*C*), 144.01 (s, 1-*C*), 144.28 (dddd, $^1J_{CF}$ 255.5, $^2J_{CF}$ 21.1, $^3J_{CF}$ 16.1, $^4J_{CF}$ 5.0, 2'-*C*); δ_F -145.19 (s); *m/z* (EI$^+$) 386 (M$^+$, 84%), 358 (41), 357 (100), 329 (9), 328 (53), 306 (10), 293 (9), 164 (36), 29 (11). *3',4',5',6'-Tetrafluoro-4,4''-dipropyl-[1,1'; 2',1'']terphenyl* **41** was identified as one of the minor isomers; δ_F -138.41 (d, $^3J_{FF}$ 23.0, 3'-C*F*), -143.54 (m, 4'-C*F*). *2',4',5',6'-Tetrafluoro-4,4''-dipropyl-[1,1'; 3',1'']terphenyl* **42** was also obtained; δ_F -123.02 (1F, d, $^5J_{FF}$ 10.5, 2'-C*F*), -139.33 (2F, m, 4'-C*F*), -165.35 (1F, td, $^3J_{FF}$ 22.6, $^5J_{FF}$ 11.6, 5'-C*F*); *m/z* (EI$^+$) 386 (M$^+$, 77%), 385 (7), 358 (22), 357 (100), 356 (7), 329 (7), 328 (32), 29 (18), 28 (7).

3.4.2 General Method for Debromolithiation of Dibromotrifluoroaryls

Each dibromotrifluoroaryl was added dropwise over 0.5 hr to a solution of *n*-butyllithium (2.2 equiv., 1.6 M in hexanes) in dry diethyl ether (33 ml) at -78 °C under an atmosphere

of dry argon. The solution was stirred for 2 hrs, and then quenched slowly with ethanol (5 ml) followed by water (5 ml) maintaining a temperature of -78 °C. The mixture was stirred for 0.5 hr, allowed to warm to room temperature, poured onto water (60 ml) and the product extracted with DCM (3 × 30 ml). The combined extracts were washed with water (100 ml) and dried ($MgSO_4$). The solvent was removed *in vacuo*, and chromatography on silica gel with hexane or hexane/DCM as the eluent afforded the products.

3.4.2.1 Preparation of Trifluoro-phenoxy-benzenes

1,2,4-Trifluoro-3-phenoxy-benzene 45. 1,2-Dibromo-3,4,6-trifluoro-5-phenoxybenzene **9** (7.75 g, 20.29 mmol) afforded the phenoxybenzene (1.09 g, 24%) as a clear oil (Found: C, 64.30; H, 3.11. $C_{12}H_7F_3O$ requires C, 64.29; H, 3.15%); δ_H 6.97 (1H, m, 5 or 6-C*H*), 7.02 (2H, dm, $^3J_{HH}$ 8.2, 2'-C*H*), 7.05 (1H, m, 5 or 6-C*H*), 7.14 (1H, tm, $^3J_{HH}$ 7.3, 4'-C*H*), 7.36 (2H, ddm, $^3J_{HH}$ 8.8, $^3J_{HH}$ 7.3, 3'-C*H*); δ_C 110.97 (ddd, $^2J_{CF}$ 21.1, $^3J_{CF}$ 7.7, $^3J_{CF}$ 4.3, 6-*C*), 112.35 (dd, $^2J_{CF}$ 19.5, $^3J_{CF}$ 8.5, 5-*C*), 115.42 (s, 3'-*C*), 123.44 (s, 4'-*C*), 129.84 (s, 2'-*C*), 132.95 (ddd, $^2J_{CF}$ 16.8, $^2J_{CF}$ 12.3, $^3J_{CF}$ 2.7, 3-*C*), 145.23 (ddd, $^1J_{CF}$ 252.3, $^2J_{CF}$ 15.0, $^3J_{CF}$ 4.6, 2-*C*), 147.94 (ddd, $^1J_{CF}$ 245.7, $^2J_{CF}$ 11.1, $^4J_{CF}$ 3.5, 1-*C*), 152.29 (ddd, $^1J_{CF}$ 247.4, $^3J_{CF}$ 3.5, $^4J_{CF}$ 2.7, 4-*C*), 157.55 (s, 1'-*C*); δ_F -131.38 (m, 4-C*F*), -140.32 (dddd, $^3J_{FF}$ 20.5, $^5J_{FF}$ 13.7, $^3J_{HF}$ 9.1, $^4J_{HF}$ 4.5, 1-C*F*), -148.66 (dd, $^3J_{FF}$ 20.21, $^4J_{FF}$ 7.23, 2-C*F*); *m/z* (EI^+) 224 (M^+, 95%), 204 (16), 196 (67), 195 (46), 177 (16), 119 (19), 81 (16), 77 (100), 51 (56), 50 (16).

1,2,4-Trifluoro-5-phenoxy-benzene 47. 1,4-Dibromo-2,3,5-trifluoro-6-phenoxybenzene **24** (8.04 g, 21.05 mmol) afforded the phenoxybenzene (0.33 g, 7%) as a clear oil (Found: C, 64.19; H, 3.22. $C_{12}H_7F_3O$ requires C, 64.29; H, 3.15%); δ_H 6.95 (1H, ddd, $^3J_{HF}$ 10.6, $^4J_{HF}$ 7.6, $^4J_{HF}$ 7.6, 6-C*H*), 7.03 (2H, dm, $^3J_{HH}$ 7.6, 2'-C*H*), 7.09 (1H, ddd, $^3J_{HF}$ 10.0, $^3J_{HF}$ 10.0, $^4J_{HF}$ 7.3, 3-C*H*), 7.18 (1H, tm, $^3J_{HH}$ 7.5, 4'-C*H*), 7.40 (2H, ddm, $^3J_{HH}$ 8.5, $^3J_{HH}$ 7.4, 3'-C*H*); δ_C 106.57 (ddd, $^2J_{CF}$ 23.8, $^2J_{CF}$ 21.8, $^3J_{CF}$ 1.6, 3-*C*), 110.35 (ddd, $^2J_{CF}$ 21.1, $^3J_{CF}$ 2.0, $^3J_{CF}$ 1.1, 6-*C*), 117.48 (s, 3'-*C*), 123.94 (s, 4'-*C*), 130.04 (s, 2'-*C*), 139.98 (ddd, $^2J_{CF}$

13.0, $^{3}J_{CF}$ 8.1, $^{4}J_{CF}$ 3.8, 5-*C*), 146.09 (ddd, $^{1}J_{CF}$ 250.9, $^{2}J_{CF}$ 18.1, $^{3}J_{CF}$ 9.3, 2-*C*), 146.43 (A of ABMX, $^{1}J_{CF}$ 238.0, 1-*C*), 149.65 (ddd, $^{1}J_{CF}$ 248.1, $^{3}J_{CF}$ 9.2, $^{4}J_{CF}$ 3.5, 4-*C*), 156.89 (s, 1'-*C*); δ_F -132.60 (ddd, $^{5}J_{FF}$ 13.7, $^{3}J_{HF}$ 10.0, $^{4}J_{FF}$ 7.6, 4-C*F*), -139.99 (B of ABMX, $^{3}J_{FF}$ 22.1, $^{3}J_{HF}$ 9.8, $^{4}J_{FF}$ 7.6, 2-C*F*), -140.31 (A of ABMX, $^{3}J_{FF}$ 21.4, $^{5}J_{FF}$ 13.7, $^{3}J_{HF}$ 10.6, $^{4}J_{HF}$ 7.5, 1-C*F*); *m/z* (EI^+) 224 (M^+, 95%), 204 (22), 196 (80), 195 (73), 177 (22), 119 (31), 81 (23), 77 (100), 51 (64), 50 (22).

3.4.2.2 Preparation of Trifluoro(4-pentyl-phenoxy)-benzenes

Yields have been calculated for the total synthesis of each molecule over two steps, from the corresponding dibromotetrafluorobenzene substrate.

1,2,4-Trifluoro-3-(4-pentyl-phenoxy)-benzene 48. 1,2-Dibromo-3,4,6-trifluoro-5-(4-pentyl-phenoxy)-benzene **11** (4.21 g crude material) afforded the product (1.18 g, 40%) as a clear oil (Found: C, 69.43; H, 5.83. $C_{17}H_{17}F_3O$ requires C, 69.38; H, 5.82%); δ_H 0.94 (3H, t, $^{3}J_{HH}$ 7.12, C*H*$_3$), 1.37 (4H, m, C*H*$_2$CH$_3$ and CH$_2$C*H*$_2$CH$_3$), 1.64 (2H, tt, $^{3}J_{HH}$ 7.5, $^{3}J_{HH}$ 7.5, C*H*$_2$(CH$_2$)$_2$CH$_3$), 2.61 (2H, t, $^{3}J_{HH}$ 7.6, C*H*$_2$(CH$_2$)$_3$CH$_3$), 6.91 (2H, d, $^{3}J_{HH}$ 8.5, 2' or 3'-C*H*), 6.98 (2H, m, 5 and 6-C*H*), 7.15 (2H, d, $^{3}J_{HH}$ 8.7, 2' or 3'-C*H*); δ_C 14.14 (s, *C*H$_3$), 22.69 (s, *C*H$_2$CH$_3$), 31.44 (s, *C*H$_2$CH$_2$CH$_3$), 31.61 (s, *C*H$_2$(CH$_2$)$_2$CH$_3$), 35.23 (s, *C*H$_2$(CH$_2$)$_3$CH$_3$), 110.90 (ddd, $^{2}J_{CF}$ 21.0, $^{3}J_{CF}$ 7.7, $^{3}J_{CF}$ 4.2, 6-*C*), 112.14 (dd, $^{2}J_{CF}$ 19.1, $^{3}J_{CF}$ 8.4, 5-*C*), 115.29 (s, 3'-*C*), 129. 62 (s, 2'-*C*), 133.37 (ddd, $^{2}J_{CF}$ 16.4, $^{2}J_{CF}$ 11.9, $^{3}J_{CF}$ 2.3, 3-*C*), 138.07 (s, 4'-*C*), 145.31 (ddd, $^{1}J_{CF}$ 253.1, $^{2}J_{CF}$ 15.0, $^{3}J_{CF}$ 5.1, 2-*C*), 147.97 (ddd, $^{1}J_{CF}$ 245.9, $^{2}J_{CF}$ 11.1, $^{4}J_{CF}$ 3.5, 1-*C*), 152.39 (ddd, $^{1}J_{CF}$ 247.5, $^{3}J_{CF}$ 3.1, $^{4}J_{CF}$ 2.7, 4-*C*), 155.71 (s, 1'-*C*); δ_F -131.44 (dddd, $^{5}J_{FF}$ 15.9, $^{3}J_{HF}$ 9.2, $^{4}J_{FF}$ 4.6, $^{4}J_{HF}$ 2.3, 4-C*F*), -140.48 (dddd, $^{3}J_{FF}$ 25.1, $^{5}J_{FF}$ 13.7, $^{3}J_{HF}$ 9.1, $^{4}J_{HF}$ 4.64, 1-C*F*), -148.69 (dd, $^{3}J_{FF}$ 20.6, $^{4}J_{FF}$ 7.6, 2-C*F*); *m/z* (EI^+) 294 (M^+, 12%), 237 (100), 90 (66), 89 (58), 78 (32), 77 (49), 41 (74), 39 (41), 29 (63), 27 (48).

1,2,5-Trifluoro-3-(4-pentyl-phenoxy)-benzene 49. 1,3-Dibromo-2,4,5-trifluoro-6-(4-pentyl-phenoxy)-benzene **19** (4.21 g crude material) afforded the product (0.95 g, 32%) as a clear oil (Found: C, 69.30; H, 5.71. $C_{17}H_{17}F_3O$ requires C, 69.38; H, 5.82%); δ_H 0.92

(3H, t, $^3J_{HH}$ 6.9, CH_3), 1.36 (4H, m, CH_2CH$_3$ and CH_2CH$_2$CH$_3$), 1.63 (2H, tt, $^3J_{HH}$ 7.5, $^3J_{HH}$ 7.5, CH_2(CH$_2$)$_2$CH$_3$), 2.62 (2H, t, $^3J_{HH}$ 7.6, CH_2(CH$_2$)$_3$CH$_3$), 6.44 (1H, m, 6-C*H*), 6.65 (1H, dddd, $^4J_{HH}$ 13.8, $^3J_{HF}$ 8.3, $^4J_{HF}$ 5.6, $^5J_{HF}$ 3.1, 4-C*H*), 6.97 (2H, d, $^3J_{HH}$ 8.6, 2' or 3'-C*H*), 7.20 (2H, d, $^3J_{HH}$ 8.8, 2' or 3'-C*H*); δ_C 14.17 (s, *C*H$_3$), 22.70 (s, *C*H$_2$CH$_3$), 31.40 (s, *C*H$_2$CH$_2$CH$_3$), 31.62 (s, *C*H$_2$(CH$_2$)$_2$CH$_3$), 35.38 (s, *C*H$_2$(CH$_2$)$_3$CH$_3$), 99.46 (dd, $^2J_{CF}$ 27.6, $^2J_{CF}$ 21.4, 6-*C*), 102.34 (dd, $^2J_{CF}$ 26.9, $^3J_{CF}$ 3.5, 4-*C*), 119.05 (s, 3'-*C*), 130.04 (s, 2'-*C*), 139.54 (ddd, $^1J_{CF}$ 245.6, $^2J_{CF}$ 14.5, $^4J_{CF}$ 5.0, 2-*C*), 139.77 (s, 4'-*C*), 147.52 (ddd, $^2J_{CF}$ 12.7, $^3J_{CF}$ 9.6, $^3J_{CF}$ 4.6, 3-*C*), 151.50 (ddd, $^1J_{CF}$ 248.9, $^2J_{CF}$ 15.0, $^3J_{CF}$ 11.9, 1-*C*), 153.44 (s, 1'-*C*), 157.47 (ddd, $^1J_{CF}$ 244.7, $^3J_{CF}$ 13.1, $^4J_{CF}$ 3.8, 5-*C*); δ_F -114.96 (ddd, $^5J_{FF}$ 17.5, $^3J_{HF}$ 11.4, $^4J_{FF}$ 2.3, 5-C*F*), -133.67 (dd, $^3J_{FF}$ 20.6, $^3J_{HF}$ 9.9, 3-C*F*), -162.47 (dddd, $^3J_{FF}$ 19.7, $^5J_{FF}$ 11.5, $^4J_{HF}$ 6.1, $^4J_{HF}$ 5.4, 2-C*F*); *m/z* (EI$^+$) 294 (M$^+$, 55%), 237 (90), 189 (31), 188 (44), 103 (30), 90 (100), 78 (31), 77 (45), 41 (38), 29 (36).

1,2,4-Trifluoro-5-(4-pentyl-phenoxy)-benzene 50. 1,4-Dibromo-2,3,5-trifluoro-6-(4-pentyl-phenoxy)-benzene **25** (4.31 g crude material) afforded the product (0.14 g, 5%) as a clear oil (Found: C, 69.40; H, 5.80. $C_{17}H_{17}F_3O$ requires C, 69.38; H, 5.82%); δ_H 0.93 (3H, t, $^3J_{HH}$ 6.5, CH_3), 1.36 (4H, m, CH_2CH$_3$ and CH_2CH$_2$CH$_3$), 1.63 (2H, t, $^3J_{HH}$ 7.2, CH_2(CH$_2$)$_2$CH$_3$), 2.61 (2H, t, $^3J_{HH}$ 7.7, CH_2(CH$_2$)$_3$CH$_3$), 6.88 (1H, ddd, $^3J_{HF}$ 10.5, $^4J_{HF}$ 7.5, $^4J_{HF}$ 7.5, 6-C*H*), 6.92 (2H, d, $^3J_{HH}$ 8.5, 2' or 3'-C*H*), 7.06 (1H, ddd, $^3J_{HF}$ 9.5, $^3J_{HF}$ 9.5, $^4J_{HF}$ 8.5, 3-C*H*), 7.17 (2H, d, $^3J_{HH}$ 8.0, 2' or 3'-C*H*); δ_C 14.15 (s, *C*H$_3$), 22.70 (s, *C*H$_2$CH$_3$), 31.42 (s, *C*H$_2$CH$_2$CH$_3$), 31.63 (s, *C*H$_2$(CH$_2$)$_2$CH$_3$), 35.31 (s, *C*H$_2$(CH$_2$)$_3$CH$_3$), 106.51 (ddd, $^2J_{CF}$ 23.8, $^2J_{CF}$ 22.1, $^3J_{CF}$ 1.4, 3-*C*), 109.81 (d, $^2J_{CF}$ 21.5, 6-*C*), 117.73 (s, 2' or 3'-*C*), 129.89 (s, 2' or 3'-*C*), 138.87 (s, 4'-*C*), 140.69 (ddd, $^2J_{CF}$ 12.8, $^3J_{CF}$ 8.3, $^4J_{CF}$ 3.9, 5-*C*), 145.76 (dd, $^1J_{CF}$ 232.6, $^2J_{CF}$ 10.1, 1-*C*), 146.40 (ddd, $^1J_{CF}$ 249.3, $^2J_{CF}$ 16.7, $^3J_{CF}$ 3.8, 2-*C*), 149.42 (ddd, $^1J_{CF}$ 247.8, $^3J_{CF}$ 9.1, $^4J_{CF}$ 3.3, 4-*C*), 154.63 (s, 1'-*C*); δ_F -133.39 (1F, ddd, $^5J_{FF}$ 13.1, $^3J_{HF}$ 9.7, $^4J_{FF}$ 7.8, 4-C*F*), -140.58 (1F, dddd, $^3J_{FF}$ 21.8, $^5J_{FF}$ 20.7, $^3J_{HF}$ 10.5, $^4J_{HF}$ 7.5, 1-C*F*), -140.83 (1F, ddd, $^3J_{FF}$ 22.0, $^3J_{HF}$ 9.9, $^4J_{FF}$ 7.8, 2-C*F*); *m/z* (EI$^+$) 294 (M$^+$, 66%), 238 (40), 237 (100), 188 (15), 91 (14), 90 (25), 89 (29), 78 (11), 77 (18), 41 (14).

3.4.2.3 Preparation of 3β-(Trifluoro-phenoxy)-5-cholestenes

Yields have been calculated for the total synthesis of each molecule over two steps, from the corresponding dibromotetrafluorobenzene substrate.

(3S,8S,9S,10R,13R,14S,17R)-17-((R)-1,5-Dimethyl-hexyl)-10,13-dimethyl-3-(2,3,6-trifluoro-phenoxy)-2,3,4,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1*H*-cyclopenta[*a*]phenanthrene 51. Dibromotrifluorophenoxycholestene **13** (0.20 g crude material), following recrystallisation from isopropyl alcohol, afforded the product (0.13 g, 33%) as a white solid. δ_H 0.68 (3H, s, CH_3), 0.86 (6H, dm, $^3J_{HH}$ 6.6, CH(CH_3)$_2$), 0.91 (3H, d, $^3J_{HH}$ 6.6, CH_3), 1.06 (3H, s, CH_3), 0.94-2.56 (28H, m), 4.02 (1H, tt, $^3J_{HH}$ 11.2, $^3J_{HH}$ 5.4, 3-C*H*), 5.37 (1H, d, $^3J_{HH}$ 5.2, 6-C*H*), 6.82 (2H, Ar 4- and 5-C*H*); δ_C 12.00 (s), 18.86 (s), 19.53 (s), 21.23 (s), 22.72 (s), 22. 98 (s), 23.97 (s), 24.43 (s), 28.28 (m), 28.68 (s), 32.03 (m), 35.94 (s), 36.33 (s), 36.79 (s), 37.13 (s), 39.18 (s), 39.66 (s), 39.88 (s), 42.46 (s), 50.21 (s), 56.28 (s), 56.86 (s), 84.17 (s, 3-*C*), 110.11 (dd, $^2J_{CF}$ 19.0, $^3J_{CF}$ 8.3, Ar 5-*C*), 110.29 (ddd, $^2J_{CF}$ 21.7, $^3J_{CF}$ 8.1, $^3J_{CF}$ 3.8, Ar 4-*C*), 122.84 (s, 6-*C*), 135.91 (ddd, $^2J_{CF}$ 16.1, $^2J_{CF}$ 11.1, $^3J_{CF}$ 2.7, Ar 1-*C*), 139.95 (s, 5-*C*), 145.50 (ddd, $^1J_{CF}$ 249.7, $^2J_{CF}$ 14.1, $^3J_{CF}$ 5.8, Ar 2-*C*), 147.86 (ddd, $^1J_{CF}$ 244.7, $^2J_{CF}$ 11.5, $^4J_{CF}$ 3.5, Ar 3-*C*), 152.71 (ddd, $^1J_{CF}$ 243.8, $^3J_{CF}$ 3.1, $^4J_{CF}$ 3.1, Ar 6-*C*); δ_F -132.50 (m, 6-C*F*), -141.57 (ddd, $^3J_{FF}$ 20.2, $^5J_{FF}$ 8.2, $^3J_{HF}$ 5.3, 3-C*F*), -150.08 (ddd, $^3J_{FF}$ 20.2, $^4J_{FF}$ 5.3, $^4J_{HF}$ 4.5, 2-C*F*).

(3S,8S,9S,10R,13R,14S,17R)-17-((R)-1,5-Dimethyl-hexyl)-10,13-dimethyl-3-(2,3,5-trifluoro-phenoxy)-2,3,4,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1*H*-cyclopenta[*a*]phenanthrene 52. Dibromotrifluorophenoxycholestene **21** (1.08 g crude material), following recrystallisation from DCM and acetonitrile, afforded the product (0.25 g, 11%) as a clear colourless crystalline solid. δ_H 0.70 (3H, s, CH_3), 0.88 (6H, dm, $^3J_{HH}$ 6.6, CH(CH_3)$_2$), 0.93 (3H, d, $^3J_{HH}$ 6.6, CH_3), 1.07 (3H, s, CH_3), 0.95-2.08 (26H, m), 2.47 (2H, m), 4.08 (1H, m, 3-C*H*), 5.41 (1H, d, $^3J_{HH}$ 4.7, 6-C*H*), 6.49 (2H, m, Ar 4- and 6-C*H*); δ_C 11.98 (s), 18.86 (s), 19.50 (s), 21.23 (s), 22.72 (s), 22. 97 (s), 24.02 (s), 24.44 (s), 28.18 (s), 28.40 (s), 31.99 (s), 32.07 (s), 35.97 (s), 36.36 (s), 36.87 (s), 37.16 (s), 38.56 (s), 39.69 (s), 39.89 (s), 42.46 (s), 50.28 (s), 56.32 (s), 56.86 (s), 79.82 (s, 3-*C*), 97.14 (dd, $^2J_{CF}$ 27.6, $^2J_{CF}$ 21.9, Ar 4-*C*), 99.71 (dd, $^2J_{CF}$ 26.8, $^3J_{CF}$ 3.0, Ar 6-*C*), 123.14 (s, 6-*C*), 139.12 (ddd, $^1J_{CF}$ 261.2, $^2J_{CF}$ 13.9, $^4J_{CF}$ 5.1, Ar 2-*C*), 139.65 (s, 5-*C*), 147.80 (ddd,

$^{2}J_{CF}$ 17.3, $^{3}J_{CF}$ 8.8, $^{3}J_{CF}$ 4.3, Ar 1-*C*), 151.31 (ddd, $^{1}J_{CF}$ 247.6, $^{2}J_{CF}$ 15.7, $^{3}J_{CF}$ 11.9, Ar 3-*C*), 157.68 (ddd, $^{1}J_{CF}$ 264.0, $^{3}J_{CF}$ 13.4, $^{4}J_{CF}$ 3.5, Ar 5-*C*); δ_F -116.20 (ddm, $^{5}J_{FF}$ 10.7, $^{4}J_{FF}$ 8.4, 5-C*F*), -134.62 (ddm, $^{3}J_{FF}$ 19.8, $^{4}J_{FF}$ 10.7, 3-C*F*), -164.08 (ddm, $^{3}J_{FF}$ 20.6, $^{5}J_{FF}$ 10.5, 2-C*F*).

(3S,8S,9S,10R,13R,14S,17R)-17-((R)-1,5-Dimethyl-hexyl)-10,13-dimethyl-3-(2,4,5-trifluoro-phenoxy)-2,3,4,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1H-cyclopenta[a]phenanthrene 53. Dibromotrifluorophenoxycholestene **26** (0.16 g crude material), following recrystallisation from isopropyl alcohol, afforded the product (0.08 g, 20%) as a white solid. δ_H 0.69 (3H, s, CH_3), 0.87 (6H, dm, $^{3}J_{HH}$ 6.8, CH(CH_3)$_2$), 0.92 (3H, d, $^{3}J_{HH}$ 6.8, CH_3), 1.05 (3H, s, CH_3), 0.93-2.48 (28H, m), 3.98 (1H, m, 3-C*H*), 5.39 (1H, d, $^{3}J_{HH}$ 4.9, 6-C*H*), 6.83 (1H, ddd, $^{3}J_{HF}$ 11.4, $^{4}J_{HF}$ 7.7, $^{4}J_{HF}$ 7.7, Ar 6-C*H*), 6.95 (1H, ddd, $^{3}J_{HF}$ 10.3, $^{3}J_{HF}$ 10.3, $^{4}J_{HF}$ 7.5, Ar 3-C*H*); δ_C 12.00 (s), 18.86 (s), 19.53 (s), 21.22 (s), 22.72 (s), 22. 98 (s), 23.97 (s), 24.43 (s), 28.21 (m), 28.38 (s), 32.03 (m), 35.94 (s), 36.33 (s), 36.89 (s), 37.16 (s), 38.68 (s), 39.66 (s), 39.87 (s), 42.46 (s), 50.26 (s), 56.28 (s), 56.86 (s), 80.59 (s, 3-*C*), 106.07 (ddd, $^{2}J_{CF}$ 24.5, $^{2}J_{CF}$ 21.8, $^{3}J_{CF}$ 1.6, Ar 3-*C*), 107.14 (dd, $^{2}J_{CF}$ 21.0, $^{3}J_{CF}$ 2.4, Ar 6-*C*), 123.00 (s, 6-*C*), 139.83 (s, 5-*C*), 141.82 (ddd, $^{2}J_{CF}$ 12.7, $^{3}J_{CF}$ 8.1, $^{4}J_{CF}$ 3.5, Ar 1-*C*), 143.97 (ddd, $^{1}J_{CF}$ 243.7, $^{2}J_{CF}$ 14.1, $^{3}J_{CF}$ 10.7, Ar 4-*C*), 146.21 (ddd, $^{1}J_{CF}$ 244.1, $^{2}J_{CF}$ 13.3, $^{4}J_{CF}$ 3.8, Ar 5-*C*), 149.02 (ddd, $^{1}J_{CF}$ 244.7, $^{3}J_{CF}$ 8.9, $^{4}J_{CF}$ 3.1, Ar 2-*C*); δ_F -135.10 (ddd, $^{5}J_{FF}$ 13.0, $^{3}J_{HF}$ 10.7, $^{4}J_{FF}$ 7.6, 2-C*F*), -141.80 (dddm, $^{3}J_{FF}$ 22.0, $^{5}J_{FF}$ 11.5, $^{3}J_{HF}$ 7.5, 5-C*F*), -144.46 (ddd, $^{3}J_{FF}$ 22.1, $^{3}J_{HF}$ 9.9, $^{4}J_{FF}$ 7.5, 4-C*F*).

3.4.2.4 Preparation of 4-Pentyl-phenyl(trifluoro-phenyl)-amines

(4-Pentyl-phenyl)-(2,4,5-trifluoro-phenyl)-amine 54. (2,5-Dibromo-3,4,6-trifluoro-phenyl)-(4-pentyl-phenyl)-amine **38** (6.41g crude material), following chromatography and further purification by distillation under reduced pressure afforded the product (0.08g, 3%, calculated for the total synthesis of the molecule over two steps, from the corresponding dibromotetrafluorobenzene substrate) as a clear oil; δ_H 0.92 (3H, t, $^{3}J_{HH}$ 6.8, CH_3), 1.36 (4H, m, CH_2CH$_3$ and CH_2CH$_2$CH$_3$), 1.63 (2H, m, CH_2(CH$_2$)$_2$CH$_3$), 2.59

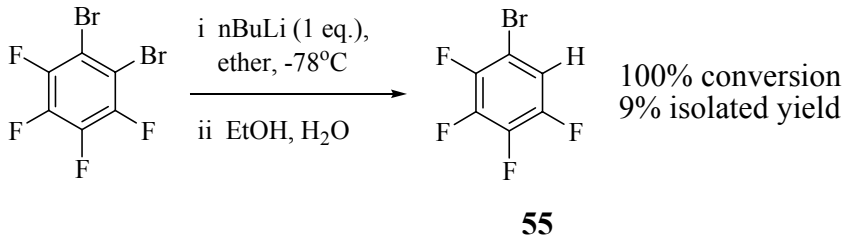
(2H, t, $^{3}J_{HH}$ 7.6, CH_2(CH_2)$_3$CH_3), 5.61 (1H, s, N*H*), 6.96 (1H, ddd, $^{3}J_{HF}$ 10.8, $^{3}J_{HF}$ 10.0, $^{4}J_{HF}$ 7.2, 3-C*H*), 7.03 (1H, dddd, $^{3}J_{HF}$ 12.0, $^{4}J_{HF}$ 8.0, $^{4}J_{HF}$ 8.0, $^{5}J_{HH}$ 3.4, 6-C*H*), 7.03 (2H, dd, $^{3}J_{HH}$ 6.4, $^{4}J_{HH}$ 2.1, 2' or 3'-C*H*), 7.16 (2H, dm, $^{3}J_{HH}$ 8.4, 2' or 3'-C*H*); δ_C 14.18 (s, *C*H$_3$), 22.72 (s, *C*H$_2$), 31.44 (s, *C*H$_2$), 31.64 (s, *C*H$_2$), 35.41 (s, *C*H$_2$), 104.24 (dd, $^{2}J_{CF}$ 23.1, $^{3}J_{CF}$ 3.5, 6-*C*), 105.37 (ddd, $^{2}J_{CF}$ 25.1, $^{2}J_{CF}$ 22.1, $^{3}J_{CF}$ 1.5, 3-*C*), 120.19 (s, 3'-*C*), 129.53 (m, 1-*C*), 129.65 (s, 2'-*C*), 138.08 (s, 1' or 4'-*C*), 138.60 (s, 1' or 4'-*C*), 142.52 (ddd, $^{1}J_{CF}$ 242.4, $^{2}J_{CF}$ 14.1, $^{3}J_{CF}$ 11.6, 4-*C*), 146.81 (ddd, $^{1}J_{CF}$ 241.4, $^{2}J_{CF}$ 13.1, $^{4}J_{CF}$ 3.4, 5-*C*), 147.18 (ddd, $^{1}J_{CF}$ 238.4, $^{3}J_{CF}$ 9.3, $^{4}J_{CF}$ 2.7, 2-*C*); δ_F -136.39 (m, 2-C*F*), -142.30 (dddd, $^{3}J_{FF}$ 22.2, $^{5}J_{FF}$ 13.2, $^{3}J_{HF}$ 13.2, $^{4}J_{HF}$ 7.9, 4-C*F*), -147.36 (ddd, $^{3}J_{FF}$ 22.2, $^{3}J_{HF}$ 9.0, $^{4}J_{FF}$ 9.0, 5-C*F*); *m/z* (EI$^+$) 293 (M$^+$, 59%), 237 (38), 236 (100), 234 (7), 216 (7), 89 (10), 78 (7), 77 (18), 41 (8), 29 (7).

4 Synthetic Routes to LCs via Debromolithiation

4.1 Studies of Debromolithiation

One strategy employed in the synthesis of model LC molecules was to remove the bromine atom of a bromoperfluoroaryl head-group with butyllithium and to trap the resulting carbanion with an electrophilic tail-group (Scheme 23, page 52).

In initial model studies, 1,2-dibromo-3,4,5,6-tetrafluorobenzene was selected as a simple system to ascertain whether 1-bromo-2,3,4,5-tetrafluorobenzene could be synthesized cleanly via a single debromolithiation of the substrate followed by protonation (Scheme 29). Fluorine NMR analysis of the product mixture showed that complete conversion had been achieved from a clean reaction to afford the bromofluorobenzene **55** only. Despite this the desired product was afforded in low yield (9%) due to poor recovery of the volatile compound during column chromatography. Repeating the reaction and extracting the crude organic material using diethyl ether in place of ethyl acetate and purifying the crude material by distillation did not improve the isolated yield of the product (7%).

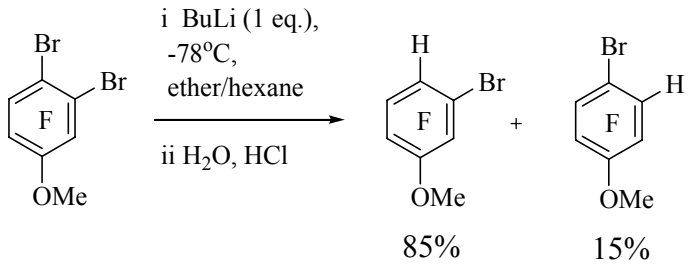


55

Scheme 29. Protodebromination of 1,2-dibromotetrafluorobenzene

This study was extended to the removal of a single bromine atom from 1,2-dibromo-3,4,6-trifluoro-5-methoxybenzene **7**, 1,3-dibromo-2,4,5-trifluoro-6-methoxybenzene **15** and 1,4-dibromo-2,3,5-trifluoro-6-methoxybenzene **23** (synthesised previously, section 3.1.1) to establish the regioselectivity of debromolithiation in these systems. Reaction of

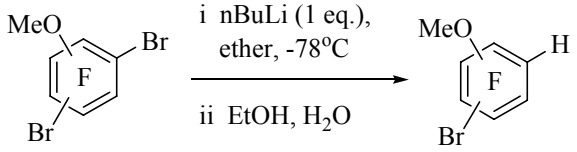
1,2-dibromo-3,4,6-trifluoro-5-methoxybenzene, a non-symmetrical anisole, with BuLi has been described in the literature[100] and displays some selectivity in favour of lithiation at the 2-*C* position (Scheme 30).

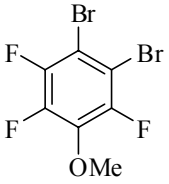
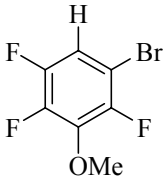
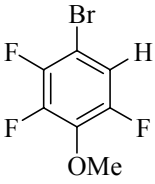
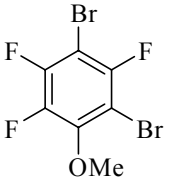
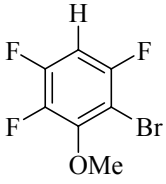
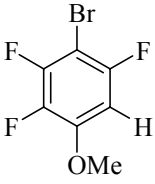
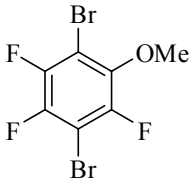
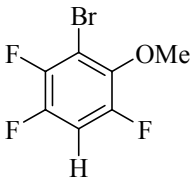
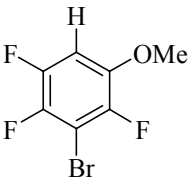


Scheme 30. Selective bromine-lithium exchange

Reacting anisoles **7**, **15** and **23** with one equivalent of n-BuLi followed by quenching of the reaction by adding ethanol/water yielded mixtures of isomers in all cases (Table 19). 1,2-Dibromo-3,4,6-trifluoro-5-methoxybenzene **7** afforded two isomers, 1-bromo-2,4,5-trifluoro-3-methoxybenzene **56** and 1-bromo-2,3,5-trifluoro-4-methoxybenzene **57**. 1,3-Dibromo-2,4,5-trifluoro-6-methoxybenzene **15** gave bromo-1,4,5-trifluoro-3-methoxybenzene **58** and 2-bromo-1,3,4-trifluoro-5-methoxy-benzene **59**, while 1,4-dibromo-2,3,5-trifluoro-6-methoxybenzene **23** yielded 3-bromo-1,2,5-trifluoro-4-methoxybenzene **60** and 3-bromo-1,2,4-trifluoro-5-methoxy-benzene **61**. The isomers from the reaction of **7** could not be separated by column chromatography and were characterized as a mixture of the two products. Anisoles **58** and **60** were characterised as pure isomers. Elemental analysis for these anisoles repeatedly gave inaccurate values due to the volatile nature of these materials. Isomer ratios of crude product mixtures were calculated from peak integrals in fluorine NMR spectra.

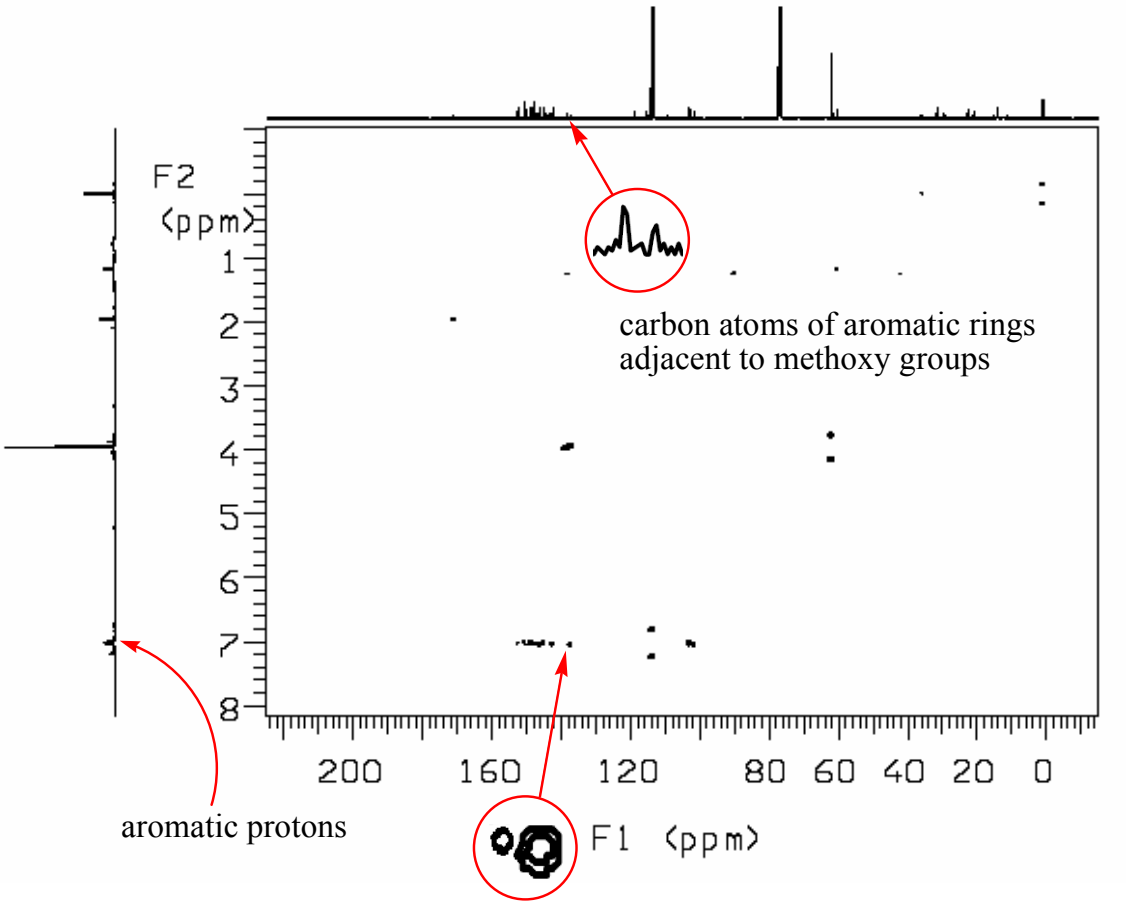
Table 19. Isomeric distributions and isolated yields of bromotrifluoromethoxybenzenes, following debromolithiation and protonation of dibromotrifluoromethoxybenzenes.



Starting Material	*Major* Isomer	*Minor* Isomer	Isomer Ratio of Crude Product Mixture	Isolated Yield /%
 **7**	 **56**	 **57**	87 : 13	*major and minor* 88
 **15**	 **58**	 **59**	95 : 5	*major* 22
 **23**	 **60**	 **61**	94 : 6	*major* 69

HMBC NMR spectroscopy enabled the resulting isomer ratio from the debromolithiation of **7** to be assigned. Isomer **56** was established as the major product as stated in the literature.[100] The J_{CH} coupling between the ring carbon adjacent to the methoxy group and the aromatic protons for each isomer should be larger for **57** than for **56**, having $^{3}J_{CH}$ and $^{4}J_{CH}$ couplings respectively. This was indeed seen to be the case (Figure 13).

Figure 13. HMBC NMR spectrum of the product mixture of bromofluoromethoxybenzenes **56** and **57**.



signals showing $^{4}J_{CH}$ (left) and $^{3}J_{CH}$ (right) couplings of anisoles **56** and **57** respectively

Confirmation of the identity of isomers **58** and **59** was realised through consideration of the proton NMR spectra. Anisole **59** has one $^{3}J_{HF}$ coupling ($^{3}J_{HF} \approx 10$ Hz)[95] one $^{4}J_{HF}$ coupling and one small $^{5}J_{HF}$ coupling whereas the couplings observed for the major product correlate to the two $^{3}J_{HF}$ and one $^{4}J_{HF}$ couplings which would be expected for the isomer **58**. Similarly anisole **61** has one $^{3}J_{HF}$ and two $^{4}J_{HF}$ couplings. On the other hand its isomer **60** has two $^{3}J_{HF}$ and one $^{4}J_{HF}$ couplings, which correspond to those observed for the major product.

The isomers that are predominantly formed for each fluorinated anisole are those which arise from removal of the bromine atom having the greatest number of inductively activating proximal fluorines. These atoms impart an activation effect on bromines by increasing their electrophilicity whilst also stabilising intermediate carbanions formed on the aromatic ring of the substrate. Fluorines in *ortho* positions exert a predominant influence over those situated in positions *meta* to the bromine atom. 1-Bromo-2,4,5-trifluoro-3-methoxybenzene **7**, for example, has two possible initial activated states (Figure 14) and two intermediate carbanionic states, each having one activating and stabilising *ortho* fluorine atom next to the site of interest. However, 2-*C* has two *meta* fluorine atoms whereas 1-*C* has only one, therefore, attack occurs preferentially at the former site. As a result of these effects the anisoles **56**, **58** and **60** form as the predominant isomers.

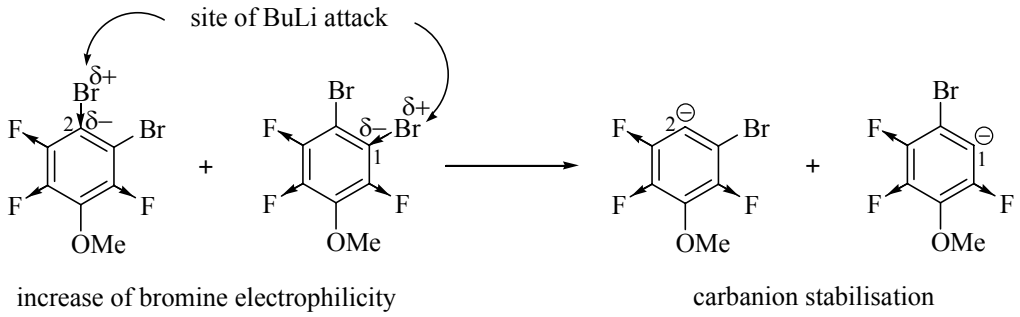


Figure 14. Starting material showing the activating and stabilisation effects of fluorine for the formation of isomers **56** and **57**

Differing reaction conditions were applied to debromolithiation of anisole **7** to determine if selectivity of the reaction could be improved. Slow addition of the base with stirring of the reaction mixture for six hours previously (Table 19) produced an isomeric ratio of 87% and 13% respectively consistent with that reported in the literature.[100] Rapid addition of butyllithium with stirring of the reaction mixture for one hour produced the anisoles **56** and **57** in the ratio 65% and 35% respectively, in 34% isolated yield. The difference in the isomer ratios may be attributed to the higher concentration of the base in

solution in the case of rapid butyllithium addition to the reaction mixture leading to lower selectivity.

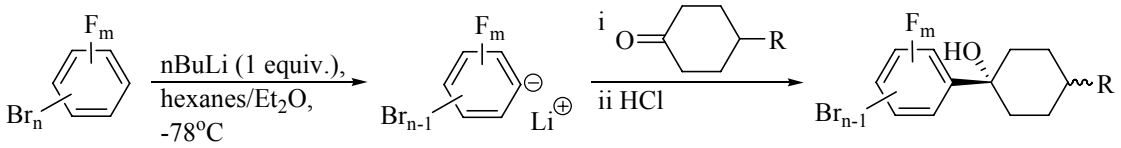
4.2 Synthesis of Cyclohexylpolyfluorobenzene Model LC Molecules

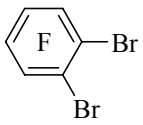
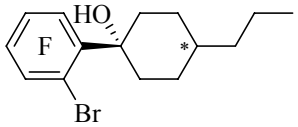
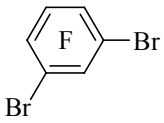
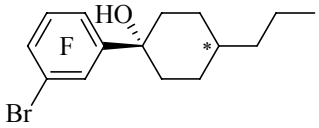
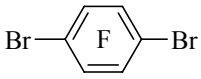
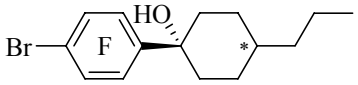
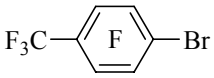
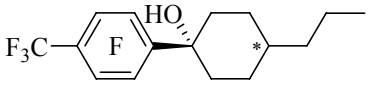
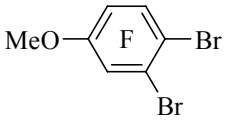
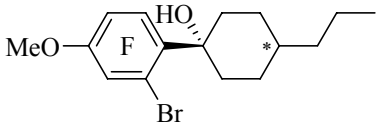
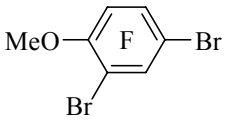
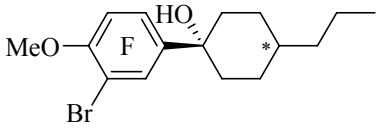
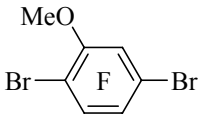
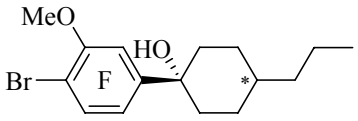
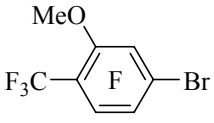
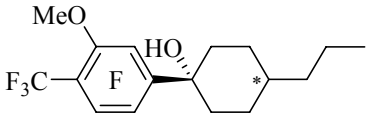
4.2.1 Synthesis of Cyclohexanol Precursors

Following debromolithiation studies of the bromoperfluoroaryl derivatives which established the site of debromolithiation the next step was the full synthesis of model LC molecules. The three isomers of dibromotetrafluorobenzene, 1-bromo-2,3,5,6-tetrafluoro-4-(trifluoromethyl)-benzene, and the dibromotrifluoro-methoxybenzenes **7**, **15**, **23** and **27** synthesised previously (section 3.1.1), were all suitable candidates as headgroups for new model LC materials. They were each reacted with one equivalent of *n*-butyllithium and the resulting carbanion trapped with 4-*n*-propylcyclohexanone. Tribromotrifluorobenzenes **1-3** synthesised previously (section 2.2) were reacted in a similar manner with 4-(trans-4'-n-propylcyclohexyl)cyclohexanone. Acidic work-up yielded alcohols **62-72** (Table 20), precursors to the desired model LC molecules.

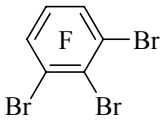
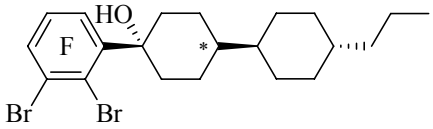
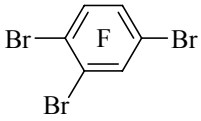
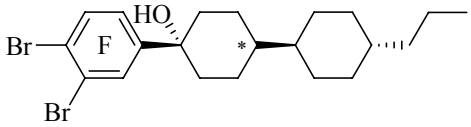
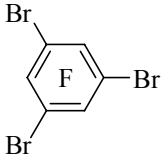
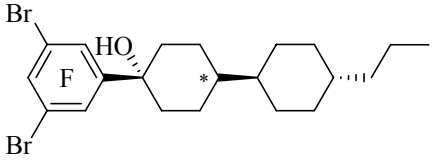
Altering the number and arrangement of fluorine atoms on the aromatic headgroup in the resulting model LC materials through the use of the isomers of dibromotetrafluorobenzene and tribromotrifluorobenzene substrates affording alcohols **62-64** and **70-72** respectively will change the strength and net direction of the dipole moment. The introduction of a trifluoromethyl group, in alcohols **65** and **69**, will generate large dipole moments in the molecules, a favourable property for the fast switching of LC mixtures in LCD devices. Adding alkoxy groups to the headgroups of LC molecules has been shown to alter properties such as their phase transition temperatures.[101] The use of bromoperfluoromethoxybenzenes **7**, **15**, **23** and **27** as starting materials provides a simple method for the introduction of methoxy groups onto the headgroup of a model LC molecule to afford alcohols **66-69**.

Table 20. Synthesis of alcohol precursor molecules via debromolithiation



Substrate	Alcohol product		Stereochemistry of R at * *axial*:*equatorial*	Conversion[i] /%
		**62**	1 : 8.4	59
		**63**	1 : 6.7	100
		**64**	1 : 2.5	99
		**65**	1 : 1.7	100
		**66**	mainly *equatorial* isomer	61
		**67**	1 : 3.3	100
		**68**	1 : 2.4	100
		**69**	1 : 3.6	100

[i] Carried through to next synthetic step without purification so yield not recorded

Substrate	Alcohol product		Stereochemistry of R at * *axial*:*equatorial*	Conversion[i] /%
		**70**	1 : 3.6	93
		**71**	1 : 3.1	97
		**72**	1 : 3.1	99

Purification of the alcohols **62** and **63** by column chromatography was attempted but failed to remove a trace amount (less than 5%) of protodebrominated product alcohol present in the product mixture. The remaining bromine atoms were to be removed in the last stage of the syntheses of the model LC molecules so this 'impurity' was, therefore, not perceived to be a problem. The remaining alcohols were carried through to the next synthetic step without purification to prevent loss of material, and, for that reason, all the alcohols were characterized by GC-MS only.

Two retention times are observed in GC-MS spectra of alcohols **62**-**72** indicating the presence of two possible isomeric configurations for each, and in agreement with this observation, fluorine NMR spectra of these materials clearly show twice the expected number of peaks. The two configurations are those with the propyl tail attached to the equatorial and axial positions on the cyclohexane ring, with the OH group lying axial in both cases (Figure 15). A discussion for the assignment of this configuration may be found in section 4.2.3.1.

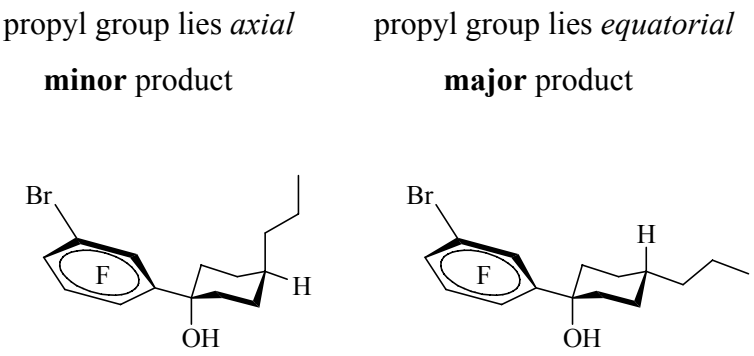


Figure 15. Two possible configurational isomers of **63**

Configurational isomer ratios (Table 20) were calculated by comparison of fluorine NMR integrals of equivalent atoms on the aromatic head-groups of each isomer.

Following debromolithiation of the three isomers of dibromotetrafluorobenzene or the dibromotrifluoromethoxybenzenes **7**, **15** and **23** we would expect the resulting aromatic anion from each substrate to attack the less sterically hindered face of *n*-propylcyclohexanone (Figure 16). Also, the bromofluoroaromatic group of each product would occupy the equatorial position as it is larger than the hydroxy group. For systems where a bromine atom is situated *ortho* to the carbanionic site, this is found to be more selective affording the *trans* configurational isomer and is readily explained due to steric hindrance provided by the large bromine atom. This is the case in all examples e.g. with the bromine atom in positions *para* to *meta* to *ortho*, affording alcohols **64**, **63** and **62** (*axial* : *equatorial* isomer ratios 1 : 2.5, 1 : 6.7 and 1 : 8.4), or **68**, **67** and **66** respectively (1 : 2.4, 1 : 3.3 and mainly *equatorial*).

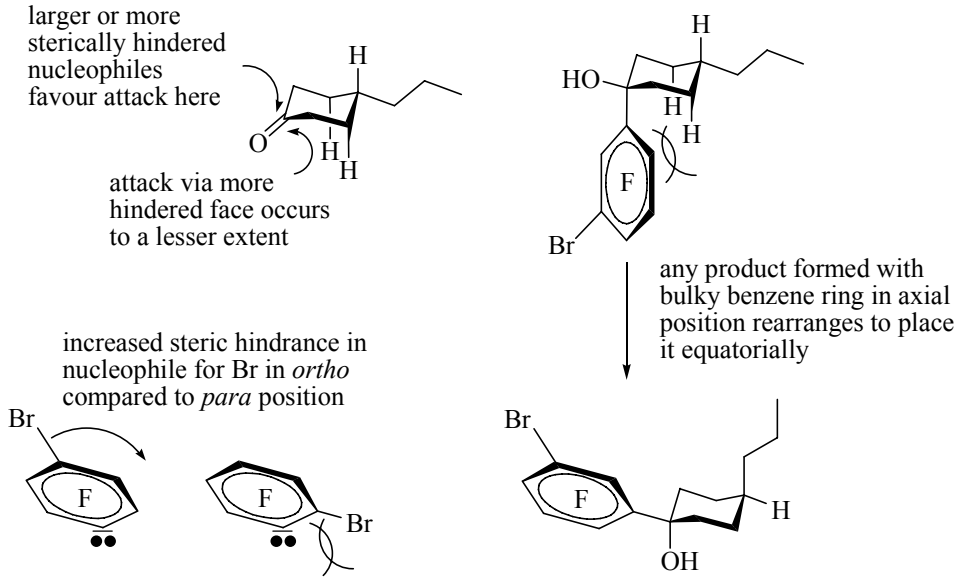


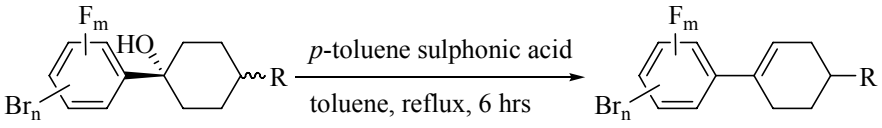
Figure 16. Explanation for the formation of the configurational isomers of **62-64**

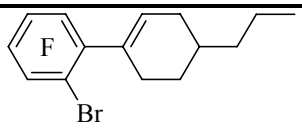
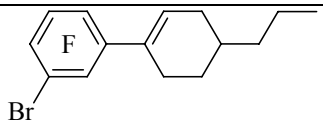
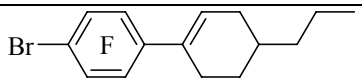
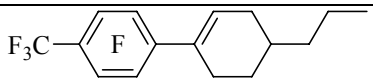
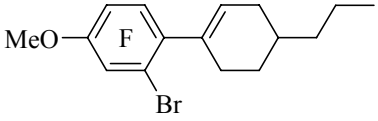
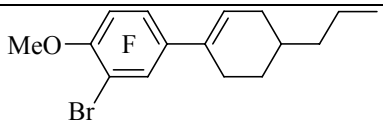
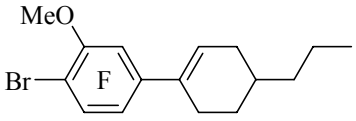
4.2.2 Synthesis of Cyclohexene Precursors

Alcohols **62-72** were dehydrated by reflux for six hours in toluene with *p*-toluenesulphonic acid monohydrate with azeotropic removal of water, to generate the alkenes **73-83** (Table 21) with excellent conversion (74-100%). Introduction of a double bond into the 1′-2′ position of the six-membered ring of the tail eliminates the possibility of having two isomeric configurations of the molecule found in the alcohols synthesised previously. This is illustrated in the fluorine NMR spectra which only show one set of signals corresponding to only one configuration for each alkene, and GC-MS only shows one product peak for each alkene. Attempts to separate any proto-debrominated 'impurity' from the alkenes **73-75** by column chromatography were unsuccessful. Alkenes **77-83** were carried through to the next synthetic step without purification to prevent loss of material. For that reason, the products were only characterised by NMR and GC-MS. It is interesting to note that neither alcohols **65** or **69**, both bearing

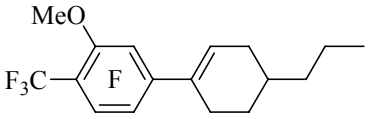
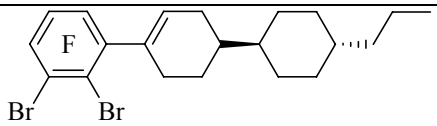
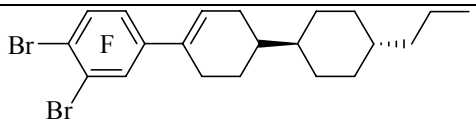
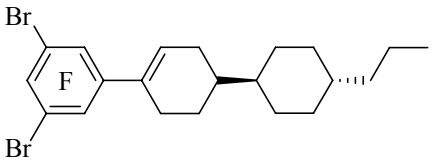
trifluoromethyl groups on the aromatic ring, underwent complete conversion following dehydration.

Table 21. Synthesis of alkene precursor molecules via dehydration



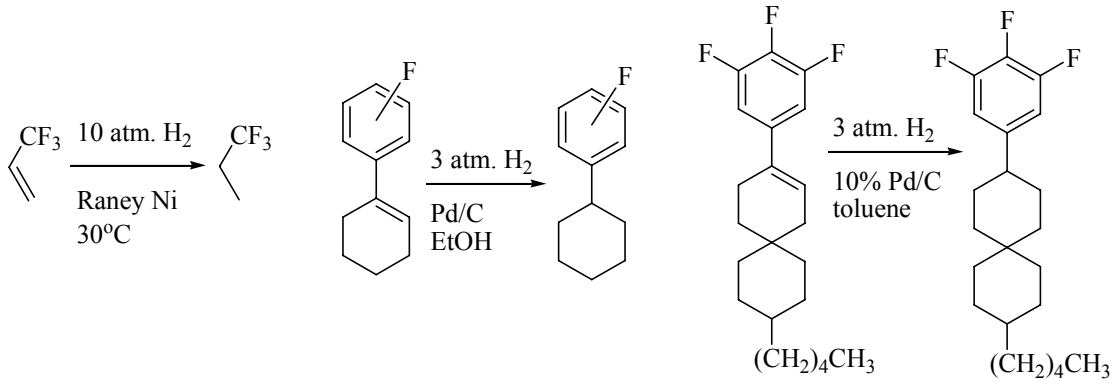
Substrate	Alkene product		Conversion[ii] /%
62		**73**	98
63		**74**	100
64		**75**	100
65		**76**	91
66		**77**	99
67		**78**	100
68		**79**	100

[ii] Carried through to next synthetic step without purification so yield not recorded

Substrate	Alkene product		Conversion[ii] /%
69		**80**	74
70		**81**	100
71		**82**	89
72		**83**	100

4.2.3 Synthesis of Cycloalkane Model LC Molecules

Fluorinated cycloalkene derivatives frequently appear as intermediates in synthetic routes to LC molecules (section 1.1.2.1)[1] but are rarely used themselves in LCD blends. These bonds are typically reduced with hydrogen in the presence of a transition metal catalyst to form saturated non-polar cyclohexane "tail" groups, examples of which are shown below (Scheme 31).[102-104]



Scheme 31.[102-104] Reductions of unsaturated fluorinated compounds.

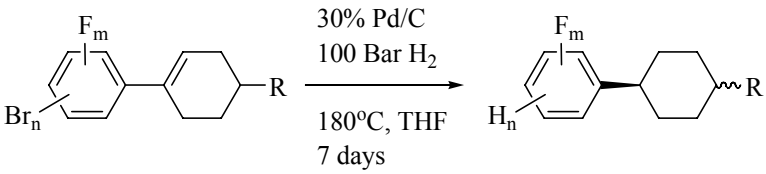
Methodology decribed in the literature[104] for similar fluorinated cyclohexene based systems was initially followed for reduction of the cyclohexene double bonds of **73** to **83**. Reduction of alkene **73** was attempted with 5% palladium on carbon in THF at ambient temperature using a Parr hydrogenation apparatus with a hydrogen pressure of 4 Bar. GC-MS analysis showed that the bromine atom was removed but very little product alkane had been afforded even after several days. The presence of several fluorine atoms on the aromatic ring may render the adjacent double bond less electron rich and sufficiently deactivate it to palladium catalysed reduction so that with these substrates more forcing conditions are required.

Reduction of alkene **73** was attempted under increasingly forcing conditions until complete conversion was obtained. The use of an alternative solvent, ethanol, was investigated and also a different catalyst, 20% palladium hydroxide on carbon, both having no beneficial effect. Reductions of alkenes **73-83** were eventually performed in an autoclave (Figure 17) for seven days using a 30% w/w palladium catalyst on carbon, in THF at 180 °C under a hydrogen pressure of 100 Bar.

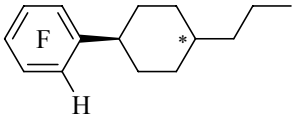
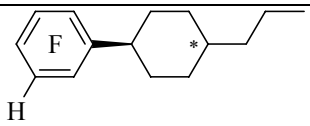
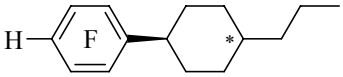
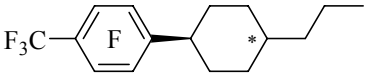
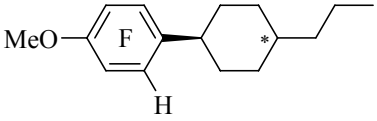
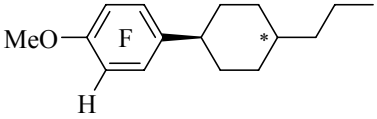
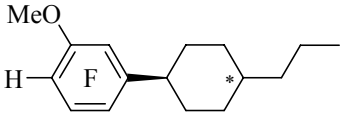
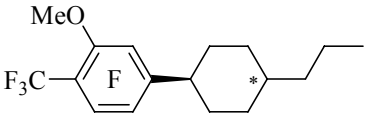
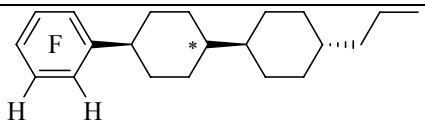
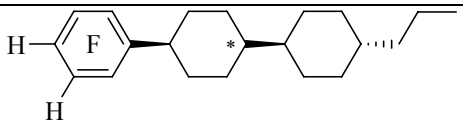
Figure 17. Autoclave vessel (25cm^3) used for high pressure reductions of alkenes

Complete conversion of the starting materials is required as the product alkane cannot be separated from the alkene starting material. The alkanes **84** – **94** (Table 22) were generally afforded in low yields [iii] (2-86%) as mixtures of configurational isomers. Materials **84-90** could not be separated from their minor isomers by column chromatography or crystallisation whilst the major isomers of alkanes **92-94** were isolated pure from the crude product mixtures through crystallisation in THF and hexanes.

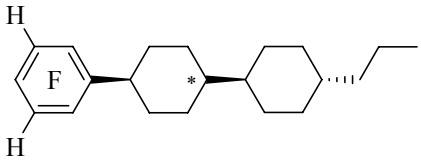
Table 22. Synthesis of alkane model LC molecules via reduction



[iii] Yields have been calculated for the total synthesis of the molecule over two steps, from the corresponding perhalogenated benzene starting material

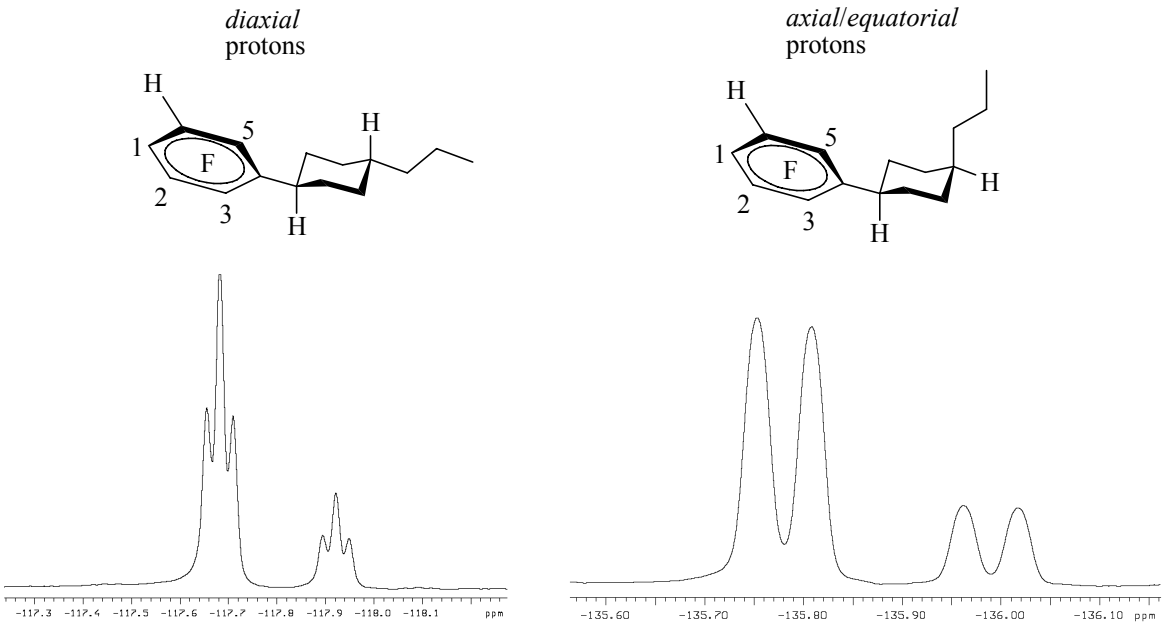
Substrate	Alkane product		Stereochemistry of R at * *axial*:*equatorial*	Pure isolated yield[iv] /%
73		**84**	1 : 2.2	5
74		**85**	1 : 4.1	2
75		**86**	1 : 2.5	22
76		**87**	1: 2.1	86
77		**88**	1 : 1.3	40
78		**89**	1 : 2.2	16
79		**90**	1 : 1.9	3
80		**91**	1 : 3.2	negligible
81		**92**	1 : 1.8	45
82		**93**	1 : 18.0	16

[iv] All materials characterised by elemental analysis, NMR, GC-MS, and melting points where applicable

Substrate	Alkane product	Stereochemistry of R at * *axial*:*equatorial*	Pure isolated yield[iv] /%
83	 **94**	1 : 3.5	21

4.2.3.1 Assignment of Stereochemistry

Two configurational isomers of each of the alkanes **84-94** were obtained (Table 22), as for their alcohol precursors **62-72** previously (4.2.1), resulting from non-stereoselective reduction of the respective alkenes **73-83**. For example, the energetically favourable configuration of alkane **85** has 1'-*C* and 4'-*C* protons lying diaxially with the large aromatic head-group and propyl tail-group lying equatorially, and this configuration forms predominantly as found for the previously synthesised alcohols. The fluorine NMR spectrum of **85** (Figure 18) shows two sets of signals for both the aromatic 5-*C* fluorine atom (-117.7 and -118.0 ppm) and the 3-*C* fluorine atom (-135.78 and -135.99 ppm) and the integrals provide the relative ratios for the two isomers. Only one set of signals were observed for the fluorine atoms at the 1-*C* and 2-*C* positions. This may be due to the fact that they are situated further away from the cyclohexane ring and therefore their electronic environments are unaffected by the isomeric configurations of the rest of the molecule.



5-C*F* NMR peaks of major and minor isomers

3-C*F* NMR peaks of major and minor isomers

Figure 18. The configurational isomers of **85** which arise following the reduction of alkene **74** and the additional fluorine NMR signals observed

Stereochemistry of the major and minor configurational isomers of alkenes **84-94** has been assigned through consideration of NMR spectra of **86** (see appendix 7.1). The carbon spectrum of the product isomer mixture was firstly fully assigned using HSQC and HMBC 2D NMR techniques. The HSQC spectrum was then used to assign clean (non-overlapping) splitting patterns in the proton NMR spectra through correlation with individual carbon atom environments. TOCSY 1D NMR also facilitated the correct assignment of signals in the proton NMR spectra to the major and minor isomers.

The Karplus relationship[105] states that a coupling of approximately 12 Hz is observed for two vicinal axial protons on sp^3 hybridised carbon atoms with a dihedral angle of 180°. For alkane **86** (Figure 19) a triplet with a 12Hz $^3J_{HH}$ coupling is observed for the proton in the 1'-*C* position found in both major (3.00 ppm) and minor (3.04 ppm) isomers

suggesting that the benzene ring lies equatorially in both isomers. Different splitting patterns are, however, observed for the protons found in the 3'-C position of the major and minor isomers. Three 12Hz couplings (a quartet at 1.04 ppm) are observed for the major isomer suggesting that the propyl tail-group lies equatorially, but only two (a triplet at 1.60 ppm) are observed for the minor isomer suggesting that the propyl group lies axially.

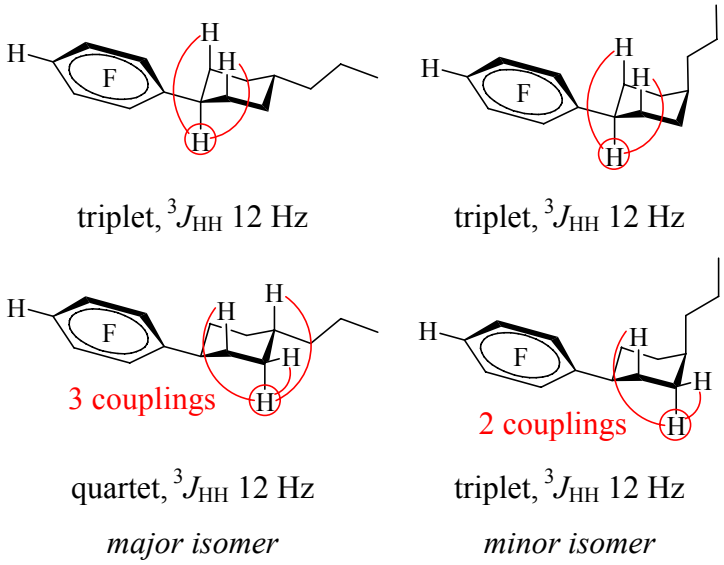


Figure 19. Couplings between protons in major and minor isomers of **86**

For the testing of fluorinated model LC materials in the investigation of their electronic properties for LC technology, ideally, pure configurational isomers are required. The true properties of many of the alkanes synthesised cannot be characterised using mixtures of isomers. The methodology for the synthesis of these molecules may still, however, be applicable to the synthesis of larger LC molecules for which separation of the isomers may be possible.

In this context, we were able to separate a pure isomer of the phenylbicyclohexyl model LC molecule **94** and an X-ray crystal structure was obtained to confirm that the isomer

isolated was in fact that with all the tertiary hydrogens of the two cyclohexyl rings lying axially (Figure 20) i.e. the molecule having the most 'rod-like' configuration.

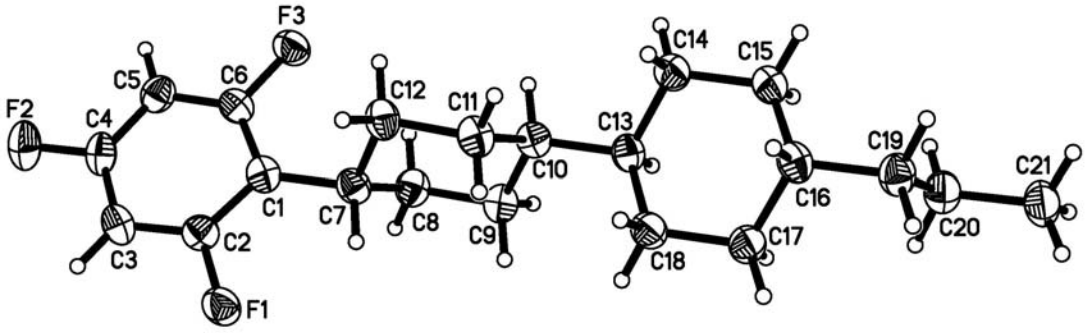


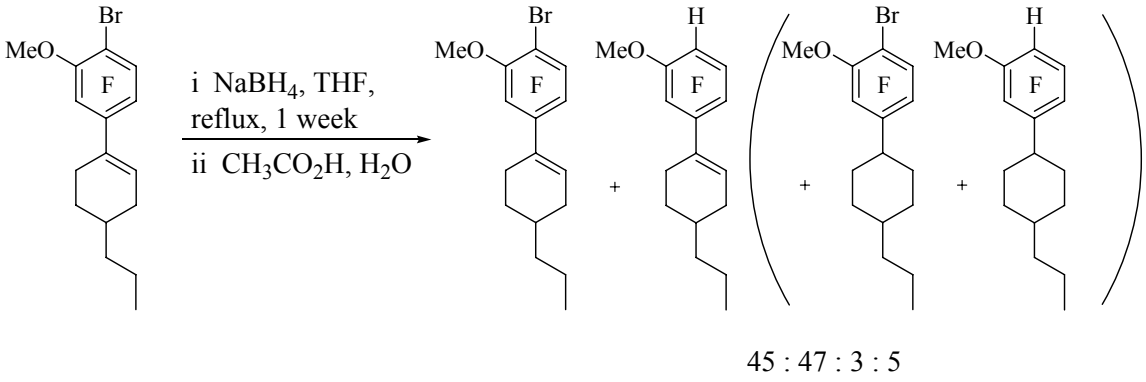
Figure 20. X-Ray crystal structure of bicyclohexylaryl **94**

4.2.3.2 Alternative Reduction Methods

The forcing and prolonged conditions required for the reduction of alkenes **73**-**83** synthesised so far were clearly not ideal and it is perhaps surprising that such conditions are required considering that other similar fluorinated alkenes reduce under much milder conditions.[102-104] Consequently, alternative methodology was sought for the final reduction step.

4.2.3.2.1 Borohydride Reducing Agents – "H^-" Reductions

Sodium borohydride, a common reducing agent used in the reduction of alkenes,[106] was used in an attempt to reduce alkene **79**. Following reaction with the alkene, and quenching of the intermediate with mild acid before work-up, GC-MS confirmed that the more labile bromine atoms were substituted, but only minor reduction of the alkene occurred after reflux for one week (Scheme 32).

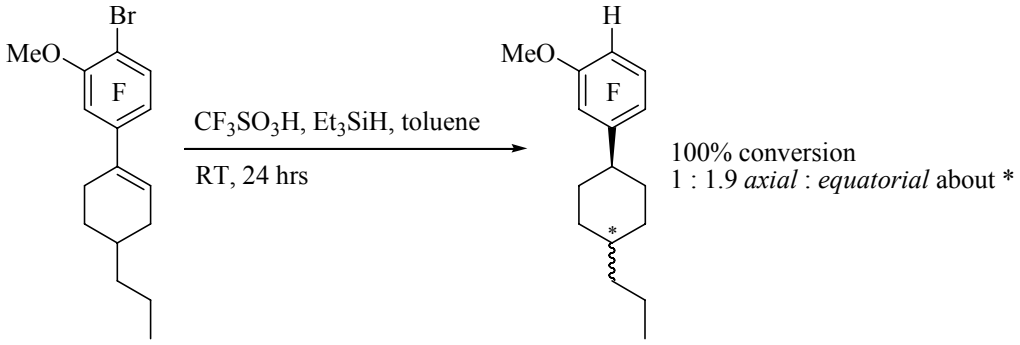


Scheme 32. Attempted reduction of alkene **79** using sodium borohydride.

Reduction of alkene **79** was subsequently attempted with 9-borabicyclo[3.3.1]nonane and also sodium triethylborohydride, a powerful "super hydride," but both reagents offered no improvement in conversion to the alkane.

4.2.3.2.2 Strong Organic Acid with Triethylsilane – "H^+" Reductions

It is possible that the aryl fluorine atoms deactivate the alkenes **73-83** to reaction with hydride ion. Reductions of phenylcycloalkenes have been carried out[107] in the presence of trifluoroacetic acid, combined with triethyl silane, a source of "H^-" ion. No conversion from the alkene **79** was observed with trifluoroacetic acid but triflic acid offered complete conversion (Scheme 33). Unfortunately, sufficient purification of the product for characterisation was not achieved following column chromatography despite the fact that GC-MS showed that the product mixture contained few impurities. No improvement in stereoselective control was observed, resulting in an *axial*:*equatorial* configurational isomer ratio of 1 : 1.9 as before.

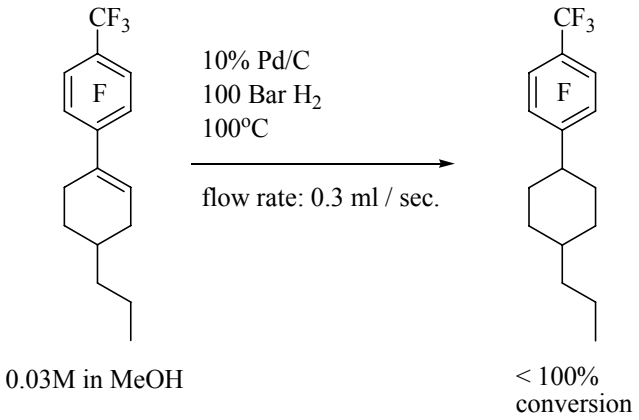


Scheme 33. Reduction of alkene **79** with triflic acid and triethylsilane.

4.2.3.2.3 Continuous-Flow Reactor Versus Batch Reactor – H_2 Reductions

Reductions of the fluorinated alkenes **73-83** synthesised so far have been successfully performed in high pressure batch reactors (4.2.3). Complete conversion is required as the product alkane is inseparable from the starting material. Surprisingly forcing conditions are required for this deactivated alkene, and they are at the limit of what is experimentally feasible. Problems include the danger of using hydrogen gas at high pressures, frequent leaks in the reactor gasket and a high loading of a relatively expensive catalyst is also required.

Continuous flow reductions, as may be performed in a continuous flow apparatus such as the H-Cube™ (Scheme 34), present obvious advantages over the more traditional batch process and include improved safety, reduced time for reductions, the catalyst may be re-used and does not need to be filtered from the reaction mixture as it is housed within a removable cartridge, and the resulting product-containing reaction mixture is much cleaner. Reduction of alkene **76** was attempted using this reactor, but complete conversion to the alkane was not achieved despite the facile adaptation of the reaction conditions when using this equipment. Improvements included reducing the flow rate to increase the contact time of the alkene with the catalyst, further dilution of the alkene and increasing the temperature and the pressure (to the maximum possible).

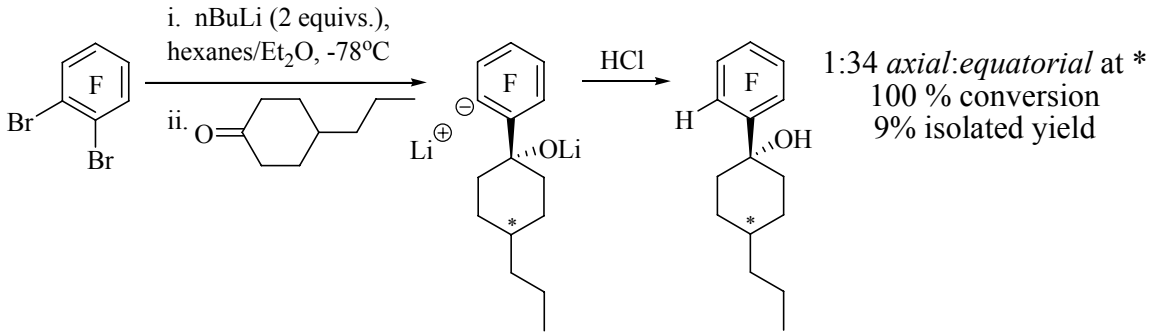


Scheme 34. Attempted reduction of fluorinated alkene **76** in an 'H-Cube'.

4.2.4 An Alternative Synthetic Strategy

An alternative synthetic strategy was considered in an attempt to improve the stereocontrol in the synthesis of the model LC molecules from dibromoaromatic substrates. Rather than removing any remaining bromine atoms of the aromatic headgroup in the final reduction step in the synthesis of the molecule (step 4, Scheme 23) this displacement step could be included in the initial debromolithiation step (step 1, Scheme 23).

1,2-Dibromo-3,4,5,6-tetrafluorobenzene was reacted with two equivalents of *n*-butyllithium to remove both the bromine atoms (Scheme 35). Trapping one carbanionic site with 4-*n*-propylcyclohexanone and quenching the resulting lithiated species with acid afforded the alcohol **95** with none of the brominated alcohol **62** present. This approach could also be applied successfully to the synthesis of other molecules using dibromotetrafluorobenzene substrates.



95

Scheme 35. Alternative alcohol synthesis using two equivalents of butyllithium

It is interesting to note that one configurational isomer is formed almost exclusively and it is again likely to be that with the benzene head-group and the propyl tail-group both lying equatorially. Again, a discussion for the assignment of this configuration may be found in section 4.2.3.1. This result may be contrasted with the synthesis of alcohol **62** which forms as an isomeric mixture in the ratio 1:8.4 (propyl group lying *axial*:*equatorial*). Repulsion between the approaching nucleophile and the axial hydrogens of 4-n-propylcyclohexanone, similar to that observed in the formation of alcohols formed previously from dibromotetrafluorobenzenes (Figure 16), may be greater for a substrate bearing a carbanion in place of a bromine atom leading to greater selectivity. This stereocontrol could be synthetically valuable, however, recovery of the product alcohol **95** was low (9%) following purification by column chromatography even though the reaction was fairly clean, probably due to a loss of material in the column.

Selectivity in the removal of single bromine atoms from the dibromotrifluoroanisoles **7**, **15** and **23** with one equivalent of *n*-butyllithium has been determined (section 4.1). Following on from this study, the polyhalogenated anisoles **7** and **15** were reacted following the methodology outlined above for 1,2-dibromotetrafluorobenzene (Scheme 35). Both bromine atoms were removed with two equivalents of *n*-butyllithium, one carbanion was trapped with *n*-propylcyclohexanone and the other was trapped with a

proton during acidic workup. The desired products were obtained but were inseparable from the many by-products produced. These substrates, in comparison to 1,2-dibromo-3,4,5,6-tetrafluorobenzene reacted previously, have an electron donating methoxy group in place of an electron withdrawing fluorine on the aromatic ring. The intermediate dilithiated species, generated following the removal of the two bromine atoms, experiences less stabilisation as a result. Benzyne formation may occur leading to undesirable side reactions of this reactive species. This methodology can therefore not be applied to synthesis of model LC molecules using dibromotrifluoroanisole substrates.

4.3 Conclusion

The strategy adopted in this chapter, simplified, is outlined as follows: selective debromolithation of a bromo or polybromoperfluoroaryl scaffold is followed by reaction of the carbanion with a cyclohexanone derivative, dehydration of the resulting alcohol and reduction of the alkene, affording materials with novel fluorination patterns on cyclohexylphenyl units. Whilst the products are often isolated as mixtures of isomers, these can be separated in the case of larger systems, as for phenylbicyclohexanes **92-94**.

A range of LC model systems was made by the above methodology and its application to LC materials would be possible. Indeed, synthesis of the trifluorotricycle **92** has been described by an alternative method,[108] and the material is reported to have low viscosity, a high clearing temperature (116.8 ºC), and a broad nematic phase range (79.4 ºC), ideal for use in LCD applications.

4.4 Experimental

4.4.1 Debromolithiation Studies of Bromofluorobenzenes

1-Bromo-2,3,4,5-tetrafluorobenzene 55. A solution of *n*-butyllithium (4.0 ml, 2.5 M in hexanes) in dry diethyl ether (20 ml) was added via a dropping funnel over 0.5 hr to a solution of 1,2-dibromo-3,4,5,6-tetrafluorobenzene (3.08 g, 10 mmol) in dry diethyl ether (40 ml) at -78 °C under an atmosphere of dry argon. The solution was stirred for 2 hrs, and then quenched slowly with ethanol (10.0 ml) followed by water (10.0 ml) maintaining a temperature of -78 °C. The mixture was stirred for 0.5 hr, allowed to warm to room temperature, poured onto water (60 ml) and the product extracted with ethyl acetate (3 × 40 ml). The combined extracts were washed with water (100 ml) and dried ($MgSO_4$). The solvent was removed *in vacuo*. Chromatography on silica gel with hexane and ethyl acetate (4:1) as the eluent afforded the product (0.20 g, 9%) as a yellow oil (characterised below).

Second preparation of 1-bromo-2,3,4,5-tetrafluorobenzene 55. The above procedure was repeated, but the product was extracted with diethyl ether. The crude material purified by distillation (35 mBar) affording the halogenated benzene (0.16 g, 7%) as a clear oil (Found: C, 31.23; H, 0.38. C_6HBrF_4 requires C, 31.47; H, 0.44%); δ_H 7.15 (dddd, $^3J_{HF}$ 9.2, $^4J_{HF}$ 7.6, $^4J_{HF}$ 6.0, $^5J_{HF}$ 2.8); δ_C 103.55 (ddd, $^2J_{CF}$ 20.0, $^3J_{CF}$ 9.5, $^3J_{CF}$ 4.9, 1-*C*), 115.00 (dd, $^2J_{CF}$ 21.87, $^3J_{CF}$ 3.87, 6-*C*), 140.26 (ddd, $^1J_{CF}$ 254.8, $^2J_{CF}$ 12.7, $^2J_{CF}$ 2.4, 3 or 4-*C*), 141.49 (ddd, $^1J_{CF}$ 256.9, $^2J_{CF}$ 13.0, $^2J_{CF}$ 4.2, 3 or 4-*C*), 145.78 (ddd, $^1J_{CF}$ 247.3, $^2J_{CF}$ 4.5, $^3J_{CF}$ 1.6, 2 or 5-*C*), 147.35 (ddd, $^1J_{CF}$ 251.14, $^2J_{CF}$ 4.3, $^3J_{CF}$ 2.6, 2 or 5-*C*); δ_F -130.98 (m), -138.38 (m), -152.85 (m), -155.64 (m); *m/z* (EI^+) 230 (M^+, 48%), 228 (M^+, 67), 149 (99), 130 (48), 115 (31), 114 (31), 99 (100), 79 (75), 75 (36), 61 (31), 31 (32).

1-Bromo-2,4,5-trifluoro-3-methoxybenzene 56 and **1-bromo-2,3,5-trifluoro-4-methoxybenzene 57.** *n*-butyllithium (1.0 ml, 2.5 M in hexanes) was added to a mixture of the anisole **7** (0.78 g, 2.44 mmol) in dry diethyl ether (25 ml) at -78 °C under an atmosphere of dry argon. The solution was stirred for 1 hr, and then quenched slowly with ethanol (7.5 ml) followed by water (7.5 ml) maintaining a temperature of -78 °C. The mixture was stirred for 0.5 hr, allowed to warm to room temperature, poured onto

water (30 ml) and the product extracted with ethyl acetate (3 × 30 ml). The combined extracts were washed with water (100 ml) and dried ($MgSO_4$). The solvent was removed *in vacuo*. Chromatography on silica gel with hexane and ethyl acetate (4:1) as the eluent afforded the product (0.20 g, 34%) as a mixture of the isomers **56** (65%) and **57** (35%) as a pale yellow oil. *Found for* **56**: δ_H 4.05 (3H, m, OC*H*$_3$), 7.10 (1H, m, 6-C*H*); δ_C 62.13 (m, O*C*H$_3$), 103.19 (ddd, $^2J_{CF}$ 21.4, $^3J_{CF}$ 10.0, $^4J_{CF}$ 4.6, 1-*C*), 113.67 (d, $^2J_{CF}$ 21.8, 6-*C*), 138.74 (ddd, $^2J_{CF}$ 15.7, $^2J_{CF}$ 11.5, $^3J_{CF}$ 2.6, 3-*C*), 143.87 (ddd, $^1J_{CF}$ 251.1, $^2J_{CF}$ 14.6, $^3J_{CF}$ 4.2, 4-*C*), 147.63 (ddd, $^1J_{CF}$ 248.9, $^2J_{CF}$ 12.0, $^4J_{CF}$ 3.9, 5-*C*), 149.40 (ddd, $^1J_{CF}$ 244.9, $^3J_{CF}$ 3.5, $^4J_{CF}$ 3.5, 2-*C*); δ_F -126.10 (dm, $^5J_{FF}$ 11.4, 2-C*F*), -140.09 (ddd, $^3J_{FF}$ 19.8, $^5J_{FF}$ 10.7, $^3J_{HF}$ 9.9, 5-C*F*), -151.77 (ddd, $^3J_{FF}$ 20.6, $^4J_{FF}$ 6.6, $^4J_{HF}$ 6.6, 4-C*F*). *Found for* **57**: δ_H 4.03 (3H, m, OC*H*$_3$), 7.10 (1H, m, 6-C*H*); δ_C 62.27 (m, O*C*H$_3$), 101.77 (ddd, $^2J_{CF}$ 20.0, $^3J_{CF}$ 11.2, $^3J_{CF}$ 1.5, 1-*C*), 114.65 (dd, $^2J_{CF}$ 23.7, $^3J_{CF}$ 3.4, 6-*C*), 137.46 (ddd, $^2J_{CF}$ 15.1, $^2J_{CF}$ 12.1, $^3J_{CF}$ 2.0, 4-*C*), 145.11 (ddd, $^1J_{CF}$ 253.3, $^2J_{CF}$ 15.4, $^3J_{CF}$ 6.5, 3-*C*), 145.89 (ddd, $^1J_{CF}$ 245.3, $^2J_{CF}$ 13.8, $^4J_{CF}$ 3.8, 2-*C*), 151.41 (ddd, $^1J_{CF}$ 260.8, $^3J_{CF}$ 4.2, $^4J_{CF}$ 4.2, 5-*C*); δ_F -133.02 (ddd, $^5J_{FF}$ 10.1, $^3J_{HF}$ 4.1, $^4J_{FF}$ 4.1, 5-C*F*), -133.39 (ddd, $^3J_{FF}$ 20.2, $^5J_{FF}$ 10.4, $^4J_{HF}$ 6.1, 2-C*F*), -148.78 (d, $^3J_{FF}$ 20.3, 3-C*F*); *m/z* (EI$^+$) 242 (M$^+$, 97%), 240 (M$^+$, 100), 227 (60), 225 (62), 199 (86), 197 (88), 130 (43), 118 (60), 99 (88), 80 (38), 68 (34).

Second preparation of 1-bromo-2,4,5-trifluoro-3-methoxybenzene 56 and **1-bromo-2,3,5-trifluoro-4-methoxybenzene 57.** A solution of *n*-butyllithium (0.9 ml, 2.5 M in hexanes) in dry diethyl ether (5 ml) was added via a dropping funnel over 0.5 hr to solution of the anisole **7** (0.71 g, 2.22 mmol) in dry diethyl ether (10 ml) at -78 °C under an atmosphere of dry argon. The solution was stirred for 6 hrs, and then quenched slowly with ethanol (7.5 ml) followed by water (7.5 ml) maintaining a temperature of -78 °C. The mixture was stirred for 0.5 hr, allowed to warm to room temperature, poured onto water (30 ml) and the product extracted with diethyl ether (3 × 30 ml). The combined extracts were washed with water (100 ml) and dried ($MgSO_4$). Removal of the solvent *in vacuo* afforded the product (0.47 g, 88%) as a mixture of the isomers **56** (87%) and **57** (13%) as a yellow oil (characterised above).

2-Bromo-1,4,5-trifluoro-3-methoxybenzene 58. A solution of *n*-butyllithium (2.0 ml, 2.5 M in hexanes) in dry diethyl ether (5 ml) was added via a dropping funnel over 0.5 hr

to solution of the anisole **15** (1.54 g, 4.81 mmol) in dry diethyl ether (20 ml) at -78 °C under an atmosphere of dry argon. The solution was stirred for 0.5 hr, and then quenched slowly with ethanol (7.5 ml) followed by water (7.5 ml) maintaining a temperature of -78 °C. The mixture was stirred for 0.5 hr, allowed to warm to room temperature, poured onto water (30 ml) and the product extracted with diethyl ether (3 × 30 ml). The combined extracts were washed with water (100 ml) and dried ($MgSO_4$). The solvent was removed *in vacuo*. Chromatography on silica gel with diethyl ether as the eluent afforded the product **58** (0.26 g, 22%) as a clear oil. δ_H 4.02 (3H, m, OC*H*$_3$), 6.77 (ddd, $^3J_{HF}$ 10.0, $^3J_{HF}$ 8.2, $^4J_{HF}$ 6.5, 6-C*H*); δ_C 61.77 (m, O*C*H$_3$), 99.79 (ddd, $^2J_{CF}$ 23.2, $^3J_{CF}$ 4.6, $^4J_{CF}$ 1.4, 2-*C*), 100.24 (dd, $^2J_{CF}$ 28.6, $^2J_{CF}$ 22.4, 6-*C*), 141.65 (ddd, $^1J_{CF}$ 248.1, $^3J_{CF}$ 14.3, $^4J_{CF}$ 4.9, 1-*C*), 147.32 (ddd, $^2J_{CF}$ 10.3, $^3J_{CF}$ 4.8, $^3J_{CF}$ 3.6, 3-*C*), 150.38 (ddd, $^1J_{CF}$ 250.3, $^2J_{CF}$ 14.2, $^3J_{CF}$ 13.1, 5-*C*), 154.82 (ddd, $^1J_{CF}$ 242.7, $^2J_{CF}$ 15.3, $^4J_{CF}$ 3.5, 4-*C*); δ_F -108.74 (m, 1-C*F*), -134.52 (ddd, $^3J_{FF}$ 20.7, *J* 9.8, *J* 1.5, 4 or 5-C*F*), -157.54 (m, 4 or 5-C*F*); *m/z* (EI$^+$) 242 (M$^+$, 100%), 240 (M$^+$, 95), 227 (70), 225 (67), 199 (90), 197 (82), 130 (79), 118 (68), 99 (89), 81 (64).

3-Bromo-1,2,5-trifluoro-4-methoxybenzene 60. A solution of *n*-butyllithium (2.3 ml, 2.5 M in hexanes) in dry diethyl ether (10 ml) was added via a dropping funnel over 1 hr to solution of the anisole **23** (1.80 g, 5.63 mmol) in dry diethyl ether (40 ml) at -78 °C under an atmosphere of dry argon. The solution was stirred for 0.5 hr, and then quenched slowly with ethanol (7.5 ml) followed by water (7.5 ml) maintaining a temperature of -78 °C. The mixture was stirred for 0.5 hr, allowed to warm to room temperature, poured onto water (30 ml) and the product extracted with diethyl ether (3 × 30 ml). The combined extracts were washed with water (100 ml) and dried ($MgSO_4$). The solvent was removed *in vacuo*. Chromatography on silica gel with diethyl ether as the eluent afforded the product **60** (0.93 g, 69%) as a clear oil. δ_H 3.93 (3H, m, OC*H*$_3$), 6.97 (1H, ddd, $^3J_{HF}$ 10.9, $^3J_{HF}$ 10.9, $^4J_{HF}$ 7.5, 6-C*H*); δ_C 61.84 (m, O*C*H$_3$), 105.16 (dd, $^2J_{CF}$ 25.2, $^2J_{CF}$ 22.3, 6-*C*), 107.05 (ddd, $^2J_{CF}$ 18.9, $^3J_{CF}$ 4.6, $^3J_{CF}$ 2.4, 3-*C*), 142.43 (dd, $^2J_{CF}$ 14.4, $^3J_{CF}$ 3.8, 4-*C*), 145.03 (ddd, $^1J_{CF}$ 246.0, $^2J_{CF}$ 14.9, $^4J_{CF}$ 4.3, 2-*C*), 146.19 (ddd, $^1J_{CF}$ 249.4, $^2J_{CF}$ 15.2, $^3J_{CF}$ 12.1, 1-*C*), 151.15 (ddd, $^1J_{CF}$ 248.7, $^3J_{CF}$ 10.2, $^4J_{CF}$ 3.5, 5-*C*); δ_F -138.66 (dd, $^3J_{FF}$ 23.0, $^5J_{FF}$ 9.9, 2-C*F*), -132.82 (ddd, $^3J_{FF}$ 22.8, $^3J_{HF}$ 11.1, $^4J_{FF}$ 7.3, 1-C*F*), -130.93 (ddd, $^5J_{FF}$

10.6, $^{3}J_{HF}$ 10.6, $^{4}J_{FF}$ 1.41, 5-C*F*); *m/z* (EI^{+}) 242 (M^{+}, 100%), 240 (M^{+}, 93), 227 (74), 225 (70), 199 (75), 197 (71), 130 (40), 118 (47), 99 (63), 81 (37).

4.4.1.1 Synthesis of Fluorinated Model LC Molecules

4.4.1.1.1 Preparation of Alcohol Precursors

A solution of *n*-butyllithium (1 equiv., 2.5 M in hexanes) in dry diethyl ether (10 ml) was added via a dropping funnel over 0.5 hr to solution of each bromofluorobenzene (1 equiv.) in dry diethyl ether (40 ml) at -78 °C under an atmosphere of dry argon. The solution was stirred for 0.5 hr and then *n*-propylcyclohexanone (1.05 equiv.) added dropwise over 0.5 hr maintaining a temperature of -78 °C. The mixture was stirred for 2 hrs and then quenched slowly with water (10 ml) maintaining a temperature of -78 °C. The mixture was stirred for a further 0.25 hrs, allowed to warm to room temperature, poured onto dilute HCl (30 ml) and the product extracted with diethyl ether (3 × 30 ml). The combined extracts were washed with water (100 ml) and dried ($MgSO_4$). The solvent was removed *in vacuo* to leave the crude product. Attempts to purify and remove any proto-debrominated alcohol from the products **62** and **63** by column chromatography proved unsuccessful. Alcohols **64-72** were carried through to the next synthetic step without purification.

1-(2-Bromo-3,4,5,6-tetrafluorophenyl)-4-propylcyclohexanol 62. 1,2-Dibromotetrafluorobenzene (6.16 g, 20 mmol), following purification by column chromatography with hexane:DCM (1:1) as the eluent and another column with hexane:ethyl acetate (4:1) as the eluent afforded the alcohol (3.57 g, 48%) as a clear oil; *m/z* (EI^{+}) 370 (M^{+}, 2%), 368 (M^{+}, 2), 285 (34), 283 (34), 204 (48), 177 (38), 98 (53), 96 (38), 85 (48), 55 (51), 43 (100), 41 (47).

1-(3-Bromo-2,4,5,6-tetrafluorophenyl)-4-propylcyclohexanol 63. 1,3-Dibromotetrafluorobenzene (6.16 g, 20 mmol), following purification by column chromatography with hexane:ethyl acetate (4:1) as the eluent afforded the alcohol (1.77

g, 24%) as a clear oil; *m/z* (EI^+) 370 (M^+, 6%), 368 (M^+, 6), 285 (82), 283 (85), 272 (59), 270 (58), 257 (55), 255 (55), 98 (90), 96 (77), 85 (69), 55 (79), 43 (100), 41 (68).

1-(4-Bromo-2,3,5,6-tetrafluorophenyl)-4-propylcyclohexanol 64. 1,4-Dibromotetrafluorobenzene (3.08 g, 10 mmol) afforded the alcohol (3.48 g of crude material); *m/z* (EI^+) 370 (M^+, 4%), 368 (M^+, 5), 285 (37), 283 (36), 99 (30), 98 (47), 96 (36), 85 (36), 55 (52), 43 (100), 41 (44), 28 (53).

1-(2,3,5,6-Tetrafluoro-4-(trifluoromethyl)phenyl)-4-propylcyclohexanol 65. 1-Bromo-2,3,5,6-tetrafluoro-4-(trifluoromethyl)benzene (3.08 g, 10 mmol) afforded the alcohol (2.24 g of crude material); *m/z* (EI^+) 358 (M^+, 1%), 245 (24), 199 (30), 98 (63), 96 (27), 85 (85), 70 (29), 69 (36), 57 (33), 55 (67), 43 (100), 41 (47).

1-(2-Bromo-3,5,6-trifluoro-4-methoxyphenyl)-4-propylcyclohexanol 66. 1,2-Dibromo-3,4,6-trifluoro-5-methoxybenzene **7** (1.05 g, 3.28 mmol) afforded the alcohol (1.50 g of crude material); *m/z* (EI^+) 382 (M^+, 23%), 380 (M^+, 23), 297 (89), 295 (95), 284 (82), 282 (84), 269 (47), 267 (45), 217 (33), 216 (100), 189 (49), 55 (83), 43 (69), 41 (64).

1-(3-Bromo-2,5,6-trifluoro-4-methoxyphenyl)-4-propylcyclohexanol 67. 1,3-Dibromo-2,4,5-trifluoro-6-methoxybenzene **15** (0.89 g, 2.78 mmol) afforded the alcohol (0.80 g of crude material); *m/z* (EI^+) 382 (M^+, 54%), 380 (M^+, 58), 297 (73), 295 (100), 284 (73), 282 (83), 269 (64), 267 (88), 255 (51), 253 (55), 55 (78), 43 (58), 41 (64).

1-(4-Bromo-2,3,6-trifluoro-5-methoxyphenyl)-4-propylcyclohexanol 68. 1,4-Dibromo-2,3,5-trifluoro-6-methoxybenzene **23** (1.70 g, 5.31 mmol) afforded the alcohol (2.51 g of crude material); *m/z* (EI^+) 382 (M^+, 58%), 380 (M^+, 62), 297 (82), 295 (100), 284 (84), 282 (99), 269 (64), 267 (66), 98 (61), 96 (69), 81 (64), 55 (92), 43 (75), 41 (76).

1-(2,3,6-Trifluoro-4-(trifluoromethyl)-5-methoxyphenyl)-4-propylcyclohexanol 69. 1-Bromo-2,3,6-trifluoro-4-(trifluoromethyl)-5-methoxybenzene **27** (0.97 g, 3.14 mmol) afforded the alcohol (1.95 g of crude material); *m/z* (EI^+) 370 (M^+, 42%), 285 (100), 272 (64), 257 (51), 98 (49), 96 (56), 85 (62), 81 (45), 70 (42), 57 (45), 55 (60), 43 (81), 41 (53).

4-(2,3-Dibromo-4,5,6-trifluoro-phenyl)-4'-propyl-bicyclohexyl-4-ol 70. 1,2,3-Tribromo-4,5,6-trifluoro-benzene (1.37 g, 3.72 mmol) afforded the alcohol (1.66 g of

crude material); *m/z* (EI^+) 514 (M^+, 1%), 512 (M^+, 1%), 510 (M^+, 1%), 83 (35), 81 (42), 69 (84), 67 (50), 55 (100), 43 (43), 41 (88).

4-(3,4-Dibromo-2,5,6-trifluoro-phenyl)-4'-propyl-bicyclohexyl-4-ol 71. 1,2,4-Tribromo-3,5,6-trifluoro-benzene (2.41 g, 6.54 mmol) afforded the alcohol (2.96 g of crude material); *m/z* (EI^+) 514 (M^+, 2%), 512 (M^+, 4%), 510 (M^+, 2%), 178 (60), 81 (59), 69 (94), 67 (61), 55 (100), 43 (53), 41 (66).

4-(3,5-Dibromo-2,4,6-trifluoro-phenyl)-4'-propyl-bicyclohexyl-4-ol 72. 1,3,5-Tribromo-2,4,6-trifluoro-benzene (1.18 g, 3.20 mmol) afforded the alcohol (1.20 g of crude material); *m/z* (EI^+) 514 (M^+, 1%), 512 (M^+, 2%), 510 (M^+, 1%), 178 (87), 97 (80), 83 (87), 81 (71), 69 (100), 55 (94), 41 (73).

1-(2,3,4,5-Tetrafluorophenyl)-4-propylcyclohexanol 95. The procedure was followed as above except that 2 equiv. *n*-butyllithium and only 1 equiv. *n*-propylcyclohexanone were used. Column chromatography on silica gel with DCM and hexane (1:1) as the eluent afforded the alcohol (0.25 g, 9%) as a clear oil which converted to a white solid upon standing (Found: C, 61.76; H, 6.23. $C_{15}H_{18}F_4O$ requires C, 62.06; H, 6.25%); δ_H 0.98 (3H, t, $^3J_{HH}$ 7.2, C*H*$_3$), 1.26 (2H, m), 1.37 (5H, m), 1.70 (4H, m), 2.02 (1H, m), 2.06 (2H, m), 7.29 (1H, m, 6-C*H*); δ_C 14.44 (s, *C*H$_3$), 20.07 (s, *C*H$_2$CH$_3$), 28.30 (s, 3′-*C*), 36.29 (s, 4′-*C* or *C*H$_2$CH$_2$CH$_3$), 36.61 (m, 2′-*C*), 39.44 (s, 4′-*C* or *C*H$_2$CH$_2$CH$_3$), 72.74 (d, $^3J_{CF}$ 3.0, 1′-*C*), 108.33 (ddd, $^2J_{CF}$ 20.9, $^3J_{CF}$ 3.3, $^3J_{CF}$ 3.3, 6-*C*H), 132.82 (m, 1-*C*), 139.14 (dddd, $^1J_{CF}$ 252.3, $^2J_{CF}$ 12.5, $^2J_{CF}$ 17.2, $^3J_{CF}$ 2.8, 3- or 4-*C*F), 141.06 (dddd, $^1J_{CF}$ 251.8, $^2J_{CF}$ 18.4, $^3J_{CF}$ 12.3, $^4J_{CF}$ 4.1, 2- or 5-*C*F), 144.76 (ddd, $^1J_{CF}$ 245.3, $^2J_{CF}$ 11.3, $^3J_{CF}$ 3.4, 2- or 5-*C*F), 146.69 (ddm, $^1J_{CF}$ 244.44, $^2J_{CF}$ 9.4, 3- or 4-*C*F); δ_F -139.92 (m, 2- or 5-C*F*), -140.45 (m, 2- or 5-C*F*), -156.30 (dd, $^3J_{FF}$ 20.3, $^3J_{FF}$ 20.3, 3- or 4-C*F*), -158.55 (ddd, $^3J_{FF}$ 19.6, $^3J_{FF}$ 19.6, $^4J_{FF}$ 3.0, 3- or 4-C*F*); *m/z* (EI^+) 290 (M^+, 25%), 206 (41), 205 (100), 192 (75), 177 (70), 163 (39), 85 (41), 57 (33), 55 (58), 43 (79), 41 (51).

4.4.1.1.2 Preparation of Alkene Precursors

To a solution of each previously synthesised alcohol (impure, approximately 1 equiv.) in toluene (30 ml) was added *p*-toluenesulphonic acid monohydrate (0.1 equiv.). Each mixture was refluxed for 6 hrs in a Dean and Stark vessel with azeotropic removal of water. The reaction mixture was allowed to cool and the solvent removed *in vacuo*. An attempt to purify alkenes **73-75** by column chromatography with hexane as the eluent afforded the alkenes containing a trace amount of proto-debrominated product. Alkenes **76-83** were carried through to the next synthetic step without purification.

1-Bromo-2,3,4,5-tetrafluoro-6-(4-propylcyclohex-1-enyl)benzene 73. The alcohol **62** (3.37 g, 9.13 mmol) afforded the alkene (2.04 g, 64%) as a clear oil; *m/z* (EI^+) 352 (M^+, 19%), 350 (M^+, 19), 243 (47), 241 (44), 201 (100), 187 (45), 151 (65), 96 (73), 81 (98), 68 (64), 67 (70), 55 (49), 41 (47).

1-Bromo-2,3,4,6-tetrafluoro-5-(4-propylcyclohex-1-enyl)benzene 74. The alcohol **63** (1.77 g, 4.79 mmol) afforded the alkene (0.97 g, 58%) as a clear oil; *m/z* (EI^+) 352 (M^+, 24%), 350 (M^+, 25), 295 (77), 293 (84), 243 (82), 241 (77), 201 (51), 96 (68), 81 (100), 68 (86), 55 (55), 41 (51).

1-Bromo-2,3,5,6-tetrafluoro-4-(4-propylcyclohex-1-enyl)benzene 75. The alcohol **64** (3.48 g crude material) afforded the alkene (2.55 g, 77%) as a clear oil; *m/z* (EI^+) 352 (M^+, 25%), 350 (M^+, 26), 295 (88), 293 (95), 243 (73), 241 (70), 201 (52), 151 (42), 96 (62), 81 (100), 68 (89), 55 (63), 41 (58).

1,2,4,5-Tetrafluoro-3-(trifluoromethyl)-6-(4-propylcyclohex-1-enyl)benzene 76. The alcohol **65** (2.24 g crude material) afforded the alkene (0.30 g crude material); *m/z* (EI^+) 340 (M^+, 47%), 297 (79), 283 (100), 250 (46), 231 (71), 201 (43), 96 (55), 81 (82), 68 (86), 55 (81), 41 (79).

1-Bromo-2,4,5-trifluoro-3-methoxy-6-(4-propylcyclohex-1-enyl)benzene 77. The alcohol **66** (1.50 g crude material) afforded the alkene (1.52 g crude material); *m/z* (EI^+) 364 (M^+, 21%), 362 (M^+, 23), 268 (64), 266 (64), 253 (33), 213 (36), 169 (38), 43 (58), 41 (100), 40 (41), 39 (35), 29 (74), 28 (47), 27 (51).

1-Bromo-2,4,5-trifluoro-6-methoxy-3-(4-propylcyclohex-1-enyl)benzene 78. The alcohol **67** (0.80 g crude material) afforded the alkene (0.96 g crude material); *m/z* (EI^+) 364 (M^+, 72%), 362 (M^+, 75), 307 (79), 305 (84), 294 (68), 292 (71), 268 (86), 266 (100), 255 (93), 253 (86), 55 (66), 41 (68).

1-Bromo-2,3,5-trifluoro-6-methoxy-4-(4-propylcyclohex-1-enyl)benzene 79. The alcohol **68** (2.51 g crude material) afforded the alkene (2.19 g crude material); *m/z* (EI^+) 364 (M^+, 59%), 362 (M^+, 61), 321 (78), 319 (79), 307 (88), 305 (92), 268 (95), 266 (100), 255 (73), 253 (75), 182 (55), 169 (44), 55 (60), 41 (64).

1,2,4-Trifluoro-6-(trifluoromethyl)-5-methoxy-3-(4-propylcyclohex-1-enyl)benzene 80. The alcohol **69** (1.95 g crude material) afforded the alkene (1.99 g crude material); *m/z* (EI^+) 352 (M^+, 8%) 295 (36), 243 (25), 169 (21), 81 (49), 68 (59), 67 (23), 55 (60), 43 (32), 41 (100), 39 (31), 29 (42), 27 (34).

4-(2,3-Dibromo-4,5,6-trifluoro-phenyl)-4'-propyl-bicyclohexyl-3-ene 81. The alcohol **70** (1.66 g crude material) afforded the alkene (1.82 g crude material); *m/z* (EI^+) 496 (M^+, 12%), 494 (M^+, 23%), 492 (M^+, 12%), 182 (44), 83 (46), 69 (100), 67 (58), 55 (91), 43 (41), 41 (88).

4-(3,4-Dibromo-2,5,6-trifluoro-phenyl)-4'-propyl-bicyclohexyl-3-ene 82. The alcohol **71** (2.96 g crude material) afforded the alkene (2.68 g crude material); *m/z* (EI^+) 496 (M^+, 20%), 494 (M^+, 39%), 492 (M^+, 20%), 123 (84), 81 (65), 69 (100), 67 (93), 55 (98), 43 (57), 41 (79).

4-(3,5-Dibromo-2,4,6-trifluoro-phenyl)-4'-propyl-bicyclohexyl-3-ene 83. The alcohol **72** (1.20 g crude material) afforded the alkene (1.34 g crude material); *m/z* (EI^+) 496 (M^+, 10%), 494 (M^+, 19%), 492 (M^+, 10%), 123 (48), 83 (42), 81 (50), 69 (100), 67 (71), 55 (90), 41 (80).

4.4.1.1.3 Preparation of Alkane Model LC Molecules

To a solution of each previously synthesised alkene in dry THF (5ml) was added palladium 30% wt. on carbon (0.1 equiv.). This was placed in an autoclave under 100 Bar

pressure of hydrogen at 180 °C for 1 week. The resulting cooled brown solution was filtered and the solvent removed *in vacuo*. Column chromatography on silica gel with hexane as the eluent afforded the saturated alkane. Alkanes **84-91** were characterised as mixtures of two configurational isomers. Yields have been calculated for the total synthesis of the molecule over two steps, from the corresponding perhalogenated benzene starting material.

1,2,3,4-Tetrafluoro-5-(4-propylcyclohexyl)benzene 84. The alkene **73** (2.04 g, 5.81 mmol) afforded the product (0.27 g, 5%) as a clear oil (Found: C, 65.79; H, 6.73. $C_{15}H_{18}F_4$ requires C, 65.68; H, 6.61%). *Found for major isomer:* δ_H 0.90 (3H, t, $^3J_{HH}$ 7.3, C*H*$_3$), 1.08 (m), 1.20 (m), 1.34 (m), 1.61 (m), 1.67 (m), 1.67 (m), 1.86 (m), 2.81 (1H, tt, $^3J_{HH}$ 12.1, $^3J_{HH}$ 2.8, 1′-C*H*), 6.82 (1H, m, 6-C*H*); δ_C 14.47(s, *C*H$_3$), 20.15 (s, *C*H$_2$CH$_3$), 30.06 (s, 1′-*C*), 32.90 (s, 2′-*C*), 33.29 (s, 3′-*C*), 37.03 (s, 4′-*C*), 39.68 (s, *C*H$_2$CH$_2$CH$_3$), 108.73 (ddd, $^2J_{CF}$ 19.1, $^3J_{CF}$ 4.9, $^3J_{CF}$ 3.5, 6-*C*), 130.92 (dddd, $^2J_{CF}$ 13.8, $^3J_{CF}$ 5.8, $^3J_{CF}$ 3.8, $^4J_{CF}$ 1.1, 5-*C*), 138.58 (dddd, $^1J_{CF}$ 250.4, $^2J_{CF}$ 17.1, $^2J_{CF}$ 13.1, $^3J_{CF}$ 3.4, 2 or 3-*C*F), 140.74 (dddd, $^1J_{CF}$ 251.4, $^2J_{CF}$ 18.1, $^2J_{CF}$ 12.1, $^3J_{CF}$ 4.2, 2 or 3-*C*F), 145.41 (dddd, $^1J_{CF}$ 243.4, $^2J_{CF}$ 10.0, $^3J_{CF}$ 3.4, $^4J_{CF}$ 1.6, 1 or 4-*C*F), 147.17 (dddd, $^1J_{CF}$ 245.4, $^2J_{CF}$ 9.9, $^3J_{CF}$ 3.8, $^4J_{CF}$ 2.3, 1 or 4-*C*F); δ_F -140.84 (m, 1 or 4-C*F*), -145.87 (ddd, $^3J_{FF}$ 20.7, $^5J_{FF}$ 12.4, $^4J_{FF}$ 5.6, 1 or 4-C*F*), -157.19 (dd, $^3J_{FF}$ 19.9, $^3J_{FF}$ 19.9, 2 or 3-C*F*), -160.68 (ddd, $^3J_{FF}$ 20.3, $^3J_{FF}$ 20.3, $^4J_{FF}$ 7.9, 2 or 3-C*F*). *Found for minor isomer:* δ_H 0.93 (3H, t, $^3J_{HH}$ 7.1, C*H*$_3$), 1.08 (m), 1.20 (m), 1.34 (m), 1.61 (m), 1.67 (m), 1.67 (m), 1.86 (m), 2.86 (1H, m, 1′-C*H*), 6.82 (1H, m, 6-C*H*); δ_C 14.44(s, *C*H$_3$), 21.05 (s, *C*H$_2$CH$_3$), 27.45 (s, 1′-*C*), 32.16 (s), 33.73 (s), 36.84 (s), 36.96 (s), 108.85 (ddd, $^2J_{CF}$ 19.1, $^3J_{CF}$ 4.6, $^3J_{CF}$ 3.4, 6-*C*), 131.01 (m, 5-*C*), 138.58 (dddd, $^1J_{CF}$ 250.4, $^2J_{CF}$ 17.1, $^2J_{CF}$ 13.1, $^3J_{CF}$ 3.4, 2 or 3-*C*F), 140.76 (dddd, $^1J_{CF}$ 251.4, $^2J_{CF}$ 18.0, $^2J_{CF}$ 12.2, $^3J_{CF}$ 4.1, 2 or 3-*C*F), 145.36 (dddd, $^1J_{CF}$ 243.4, $^2J_{CF}$ 10.0, $^3J_{CF}$ 3.8, $^4J_{CF}$ 2.2, 1 or 4-*C*F), 147.12 (dddd, $^1J_{CF}$ 245.4, $^2J_{CF}$ 10.0, $^3J_{CF}$ 3.8, $^4J_{CF}$ 2.3, 1 or 4-*C*F); δ_F -140.84 (m, 1 or 4-C*F*), -145.65 (ddd, $^3J_{FF}$ 20.7, $^5J_{FF}$ 12.4, $^4J_{FF}$ 6.0, 1 or 4-C*F*), -157.19 (dd, $^3J_{FF}$ 19.9, $^3J_{FF}$ 19.9, 2 or 3-C*F*), -160.68 (ddd, $^3J_{FF}$ 20.3, $^3J_{FF}$ 20.3, $^4J_{FF}$ 7.9, 2 or 3-C*F*); *m/z* (EI$^+$) 274 (M$^+$, 82%), 189 (75), 176 (100), 163 (93), 81 (56), 55 (100), 43 (63), 41 (68).

1,2,3,5-Tetrafluoro-4-(4-propylcyclohexyl)benzene 85. The alkene **74** (0.97 g, 2.76 mmol) afforded the product (0.10 g, 2%) as a clear oil (Found: C, 65.40; H, 6.54. $C_{15}H_{18}F_4$ requires C, 65.68; H, 6.61%). *Found for major isomer:* δ_H 0.90 (3H, t, $^3J_{HH}$ 7.3, C*H*$_3$), 1.04 (m), 1.21 (m), 1.26 (m), 1.33 (m), 1.46 (m), 1.75 (m), 1.84 (m), 1.94 (m), 2.89 (1H, tt, $^3J_{HH}$ 12.0, $^3J_{HH}$ 3.9, 1′-C*H*), 6.69 (1H, dddd, $^3J_{HF}$ 10.1, $^3J_{HF}$ 10.1, $^4J_{HF}$ 6.1, $^5J_{HF}$ 2.5, 6-C*H*); δ_C 14.52 (s, *C*H$_3$), 20.14 (s, *C*H$_2$CH$_3$), 29.91 (s, 2′-*C*), 30.97 (s, 1′-*C*), 33.58 (s, 3′-*C*), 36.82 (s, 4′-*C*), 39.80 (s, *C*H$_2$CH$_2$CH$_3$), 100.75 (ddd, $^2J_{CF}$ 30.1, $^2J_{CF}$ 20.9, $^3J_{CF}$ 3.8, 6-*C*), 119.83 (dddd, $^2J_{CF}$ 20.3, $^2J_{CF}$ 15.7, $^3J_{CF}$ 4.6, $^4J_{CF}$ 1.9, 4-*C*), 137.41 (dddd, $^1J_{CF}$ 246.9, $^2J_{CF}$ 17.2, $^2J_{CF}$ 15.1, $^4J_{CF}$ 5.2, 2-*C*), 148.76 (dddd, $^1J_{CF}$ 248.0, $^2J_{CF}$ 15.7, $^3J_{CF}$ 11.1, $^3J_{CF}$ 5.7, 1 or 3-*C*), 150.22 (dddd, $^1J_{CF}$ 248.0, $^2J_{CF}$ 12.3, $^3J_{CF}$ 10.8, $^3J_{CF}$ 5.4, 1 or 3-*C*), 155.49 (dddd, $^1J_{CF}$ 244.6, $^3J_{CF}$ 12.3, $^3J_{CF}$ 10.4, $^4J_{CF}$ 3.4, 5-*C*); δ_F -117.74 (dd, $^3J_{HF}$ 10.3, $^5J_{FF}$ 10.3, 5-C*F*), -135.78 (d, $^3J_{FF}$ 20.7, 3-C*F*), -137.25 (ddd, $^3J_{FF}$ 21.4, $^3J_{HF}$ 10.1, $^4J_{FF}$ 4.6, 1-C*F*), -166.23 (dddd, $^3J_{FF}$ 20.9, $^3J_{FF}$ 20.9, $^5J_{FF}$ 10.9, $^4J_{HF}$ 6.2, 2-C*F*). *Found for minor isomer:* δ_H 0.94 (3H, t, $^3J_{HH}$ 7.2, C*H*$_3$), 1.04 (m), 1.21 (m), 1.26 (m), 1.33 (m), 1.46 (m), 1.75 (m), 1.84 (m), 1.94 (m), 2.92 (1H, tt, $^3J_{HH}$ 12.9, $^3J_{HH}$ 3.7, 1′-C*H*), 6.69 (1H, m, 6-C*H*); δ_C 14.49 (s, *C*H$_3$), 21.12 (s, *C*H$_2$CH$_3$), 25.41 (s), 30.34 (s), 31.75 (s), 33.11 (s), 35.20 (s), 100.75 (ddd, $^2J_{CF}$ 30.1, $^2J_{CF}$ 20.9, $^3J_{CF}$ 3.8, 6-*C*), 119.83 (dddd, $^2J_{CF}$ 20.3, $^2J_{CF}$ 15.7, $^3J_{CF}$ 4.6, $^4J_{CF}$ 1.9, 4-*C*), 137.41 (dddd, $^1J_{CF}$ 246.9, $^2J_{CF}$ 17.2, $^2J_{CF}$ 15.1, $^4J_{CF}$ 5.2, 2-*C*), 148.76 (dddd, $^1J_{CF}$ 248.0, $^2J_{CF}$ 15.7, $^3J_{CF}$ 11.1, $^3J_{CF}$ 5.7, 1 or 3-*C*), 150.22 (dddd, $^1J_{CF}$ 248.0, $^2J_{CF}$ 12.3, $^3J_{CF}$ 10.8, $^3J_{CF}$ 5.4, 1 or 3-*C*), 155.49 (dddd, $^1J_{CF}$ 244.6, $^3J_{CF}$ 12.3, $^3J_{CF}$ 10.4, $^4J_{CF}$ 3.4, 5-*C*); δ_F -117.98 (dd, $^3J_{HF}$ 10.2, $^5J_{FF}$ 10.2, 5-C*F*), -135.99 (d, $^3J_{FF}$ 20.3, 3-C*F*), -137.25 (ddd, $^3J_{FF}$ 21.4, $^3J_{HF}$ 10.1, $^4J_{FF}$ 4.6, 1-C*F*), -166.23 (dddd, $^3J_{FF}$ 20.9, $^3J_{FF}$ 20.9, $^5J_{FF}$ 10.9, $^4J_{HF}$ 6.2, 2-C*F*); *m/z* (EI^+) 274 (M^+, 53%), 231 (16), 189 (38), 177 (14), 176 (73), 169 (14), 163 (100), 82 (14), 70 (16), 69 (14), 55 (61), 43 (23), 41 (33).

1,2,4,5-Tetrafluoro-3-(4-propylcyclohexyl)benzene 86. The alkene **75** (2.55 g, 7.26 mmol) afforded the product (0.60 g, 22%) as a clear oil (Found: C, 65.39; H, 6.64. $C_{15}H_{18}F_4$ requires C, 65.68; H, 6.61%). *Found for major isomer:* δ_H 0.91 (3H, t, $^3J_{HH}$ 7.3, C*H*$_3$), 1.04 (2H, dddd, $^2J_{HH}$ 13.0, $^3J_{HH}$ 13.0, $^3J_{HH}$ 12.0, $^4J_{HH}$ 3.1, 3'-C*H axials*), 1.21 (m), 1.34 (m), 1.46 (m), 1.79 (m), 1.86 (m), 3.00 (1H, tt, $^3J_{HH}$ 12.3, $^3J_{HH}$ 3.7, 1'-C*H*), 6.87 (1H, tt, $^3J_{HF}$ 9.5, $^4J_{HF}$ 7.0, 6-C*H*); δ_C 14.48 (s, *C*H$_3$), 20.13 (s, *C*H$_2$CH$_3$), 30.79 (m, 2'-*C*), 33.51 (s, 3'-*C*), 35.95 (s, 1'-*C*), 36.82 (s, 4'-*C*), 39.80 (s, *C*H$_2$CH$_2$CH$_3$), 103.29 (t, $^2J_{CF}$ 22.8, 6-

C), 125.86 (t, $^{2}J_{CF}$ 16.3, 3-*C*), 145.03 (dddd, $^{1}J_{CF}$ 244.6, $^{2}J_{CF}$ 13.4, $^{3}J_{CF}$ 7.2, $^{4}J_{CF}$ 3.8, 1 or 2-*C*), 146.18 (dddd, $^{1}J_{CF}$ 247.0, $^{2}J_{CF}$ 15.9, $^{3}J_{CF}$ 10.5, $^{4}J_{CF}$ 3.8, 1 or 2-*C*); δ_F -140.54 (ddd, $^{3}J_{FF}$ 21.8, $^{5}J_{FF}$ 12.4, $^{3}J_{HF}$ 9.8, 1-C*F*), -143.94 (m, 2-C*F*). *Found for minor isomer:* δ_H 0.94 (3H, t, $^{3}J_{HH}$ 7.2, CH_3), 1.21 (m), 1.34 (m), 1.46 (m), 1.60 (2H, dddd, $^{3}J_{HH}$ 13.4, $^{3}J_{HH}$ 13.4, $^{3}J_{HH}$ 3.9, $^{3}J_{HH}$ 3.9, 3'-C*H axial*), 1.79 (m), 1.86 (m), 2.01 (2H, ddd, $^{2}J_{HH}$ 12.9, $^{3}J_{HH}$ 12.9, $^{3}J_{HH}$ 12.9, 2'-C*H*), 3.03 (1H, tt, $^{3}J_{HH}$ 12.6, $^{3}J_{HH}$ 3.7, 1'-C*H*), 6.87 (1H, tt, $^{3}J_{HF}$ 9.5, $^{4}J_{HF}$ 7.0, 6-C*H*); δ_C 14.44 (s, *C*H_3), 21.12 (s, *C*H_2CH$_3$), 25.22 (m, 2'-*C*), 30.26 (s, 3'-*C*), 31.76 (m, 4'-*C*), 33.10 (s, *C*H_2CH$_2$CH$_3$), 35.92 (s, 1'-*C*), 103.29 (t, $^{2}J_{CF}$ 22.8, 6-*C*), 126.07 (t, $^{2}J_{CF}$ 16.3, 3-*C*), 145.03 (dddd, $^{1}J_{CF}$ 244.6, $^{2}J_{CF}$ 13.4, $^{3}J_{CF}$ 7.2, $^{4}J_{CF}$ 3.8, 1 or 2-*C*), 146.18 (dddd, $^{1}J_{CF}$ 247.0, $^{2}J_{CF}$ 15.9, $^{3}J_{CF}$ 10.5, $^{4}J_{CF}$ 3.8, 1 or 2-*C*); δ_F -140.54 (ddd, $^{3}J_{FF}$ 21.8, $^{5}J_{FF}$ 12.4, $^{3}J_{HF}$ 9.8, 1-C*F*), -144.14 (m, 2-C*F*); *m/z* (EI$^+$) 274 (M$^+$, 70%), 231 (49), 189 (73), 176 (72), 169 (42), 163 (70), 67 (31), 55 (100), 43 (28), 41 (58).

1,2,4,5-Tetrafluoro-3-(4-propylcyclohexyl)-6-trifluoromethyl-benzene 87. The alkene **76** (0.30 g crude material) afforded the product (0.26 g, 86%) as a white solid, mp 48.0-49.5 °C (Found: C, 56.22; H, 4.72. $C_{16}H_{17}F_7$ requires C, 56.14; H, 5.01%); *Found for major isomer:* δ_H 0.94 (3H, t, $^{3}J_{HH}$ 7.3, CH_3), 1.05 (2H, dddd, $^{2}J_{HH}$ 12.7, $^{3}J_{HH}$ 12.7, $^{3}J_{HH}$ 11.8, $^{4}J_{HH}$ 3.5, 3'-C*H*), 1.23 (m), 1.39 (m), 1.69 (m), 1.88 (m), 2.25 (m), 2.38 (m), 3.04 (1H, tt, $^{3}J_{HH}$ 12.1, $^{3}J_{HH}$ 3.6, 1'-C*H*); δ_C 14.41 (s, *C*H_3), 20.15(s, *C*H_2CH$_3$), 28.93(s), 32.45(s), 32.47(s), 33.30(s), 38.72(s), 107.65 (qt, $^{2}J_{CF}$ 34.3, $^{2}J_{CF}$ 12.7, 6-*C*), 121.17 (q, $^{1}J_{CF}$ 274.1, *C*F$_3$), 127.36 (t, $^{2}J_{CF}$ 18.17, 3-*C*), 144.34 (A and A' of AA'BB', 2-*C*F), 144.34 (B and B' of AA'BB', 1-*C*F); δ_F -56.73 (3F, t, $^{4}J_{FF}$ 21.34, CF_3), -141.14 (2F, A and A' of AA'BB', 1 or 2-C*F*), -142.09 (2F, B and B' of AA'BB', 1 or 2-C*F*); *Found for minor isomer:* δ_H 0.91 (3H, t, $^{3}J_{HH}$ 7.3, CH_3), 1.23 (m), 1.39 (m), 1.69 (m), 1.88 (m), 2.25 (m), 2.38 (m), 3.04 (1H, m, 1'-C*H*); δ_C 14.44(s, *C*H_3), 20.10(s, *C*H_2CH$_3$), 28.51(s), 30.51(s), 36.17(s), 36.74(s), 39.70(s), 107.55 (qt, $^{2}J_{CF}$ 34.5, $^{2}J_{CF}$ 14.4, 6-*C*), 121.17 (q, $^{1}J_{CF}$ 274.1, *C*F$_3$), 129.82 (t, $^{2}J_{CF}$ 16.12, 3-*C*), 145.40 (A and A' of AA'BB', 2-*C*F), 145.40 (B and B' of AA'BB', 1-*C*F); δ_F -56.78 (3F, t, $^{4}J_{FF}$ 21.21, CF_3), -141.51 (2F, A and A' of AA'BB', 1 or 2-C*F*), -142.06 (2F, B and B' of AA'BB', 1 or 2-C*F*); *m/z* (EI$^+$) 342 (M$^+$, 73%), 299 (72), 279 (71), 257 (99), 244 (77), 231 (77), 82 (66), 81 (70), 69 (71), 56 (64), 55 (99), 54 (79), 43 (67), 41 (100).

1,3,4-Trifluoro-2-methoxy-5-(4-propyl-cyclohexyl)-benzene 88. The alkene **77** (1.52 g, crude material) afforded the product (0.35 g, 40%) as a clear oil (Found: C, 67.26; H, 7.55. $C_{16}H_{21}F_3O$ requires C, 67.11; H, 7.39%). *Found for major isomer:* δ_H 0.90 (m), 1.08 (m), 1.27 (m), 1.59 (m), 1.85 (m), 2.78 (1H, tt, $^3J_{HH}$ 12.1, $^3J_{HH}$ 3.0, 1'-C*H*), 3.99 (3H, m, OCH_3), 6.73 (1H, m, 6-C*H*); δ_C 14.22 (s, CH_2CH_3), 20.15 (s, CH_2CH_3), 30.12 (s, 2'-*C*), 31.79 (s, 1'-*C*), 33.37 (s, 3'-*C*), 37.07 (s, 4'-*C*), 39.74 (s, $CH_2CH_2CH_3$), 61.98 (m, OCH_3), 108.35 (ddd, $^2J_{CF}$ 21.5, $^3J_{CF}$ 5.4, $^3J_{CF}$ 3.4, 5-*C*), 129.86 (dd, $^2J_{CF}$ 14.1, $^3J_{CF}$ 6.8, 6-*C*), 135.30 (ddd, $^2J_{CF}$ 15.7, $^2J_{CF}$ 11.5, $^3J_{CF}$ 2.3, 2-*C*), 144.59 (ddd, $^1J_{CF}$ 248.8, $^2J_{CF}$ 16.0, $^3J_{CF}$ 6.5, 3-*C*), 145.64 (ddd, $^1J_{CF}$ 242.8, $^2J_{CF}$ 11.1, $^4J_{CF}$ 3.5, 4-*C*), 151.45 (ddd, $^1J_{CF}$ 242.6, $^3J_{CF}$ 4.2, $^4J_{CF}$ 3.0, 1-*C*); δ_F -135.00 (ddd, $^5J_{FF}$ 12.2, $^3J_{HF}$ 12.2 $^4J_{FF}$ 3.8, 1-C*F*), -147.58 (ddd, $^3J_{FF}$ 19.9, $^5J_{FF}$ 13.1, $^5J_{HF}$ 6.3, 4-C*F*), -152.71 (dm, $^3J_{FF}$ 19.7, 3-C*F*). *Found for minor isomer:* δ_H 0.90 (m), 1.08 (m), 1.27 (m), 1.59 (m), 1.85 (m), 2.84 (1H, m, 1'-C*H*), 3.99 (3H, s, OCH_3), 6.73 (1H, m, 6-C*H*); δ_C 14.46 (s, CH_2CH_3), 21.05 (s, CH_2CH_3), 22.84 (s), 27.49 (s), 32.26 (s), 32.93 (s), 33.78 (s), 61.98 (m, OCH_3), 108.60 (ddd, $^2J_{CF}$ 21.4, $^3J_{CF}$ 5.4, $^3J_{CF}$ 3.4, 5-*C*), 129.95 (dd, $^2J_{CF}$ 13.7, $^3J_{CF}$ 6.9, 6-*C*), 135.30 (ddd, $^2J_{CF}$ 15.7, $^2J_{CF}$ 11.5, $^3J_{CF}$ 2.3, 2-*C*), 144.61 (ddd, $^1J_{CF}$ 248.8, $^2J_{CF}$ 16.0, $^3J_{CF}$ 6.5, 3-*C*), 145.66 (ddd, $^1J_{CF}$ 242.8, $^2J_{CF}$ 11.1, $^4J_{CF}$ 3.5, 4-*C*), 151.36 (ddd, $^1J_{CF}$ 242.6, $^3J_{CF}$ 4.2, $^4J_{CF}$ 3.0, 1-*C*); δ_F -135.06 (ddd, $^5J_{FF}$ 12.2, $^3J_{HF}$ 12.2, $^4J_{FF}$ 3.8, 1-C*F*), -147.34 (ddd, $^3J_{FF}$ 19.9, $^5J_{FF}$ 13.0, $^4J_{HF}$ 6.8, 4-C*F*), -152.71 (dm, $^3J_{FF}$ 19.7, 3-C*F*); *m/z* (EI^+) 286 (M^+, 76%), 201 (76), 188 (100), 175 (83), 173 (61), 145 (56), 55 (70), 43 (78), 41 (68), 29 (48).

1,3,4-Trifluoro-5-methoxy-2-(4-propyl-cyclohexyl)-benzene 89. The alkene **78** (0.80 g crude material) afforded the product (0.13 g, 16%) as a clear oil (Found: C, 67.39; H, 7.44. $C_{16}H_{21}F_3O$ requires C, 67.11; H, 7.39%). *Found for major isomer:* δ_H 0.90 (3H, t, $^3J_{HH}$ 7.3, CH_2CH_3), 1.02 (m), 1.19 (m), 1.33 (m), 1.44 (m), 1.57 (m), 1.74 (m), 1.83 (m), 1.94 (m), 2.86 (1H, tt, $^3J_{HH}$ 12.0, $^3J_{HH}$ 3.8, 1'-C*H*), 3.84 (3H, s, OCH_3), 6.45 (1H, ddd, $^3J_{HF}$ 11.6, $^4J_{HF}$ 6.8, $^5J_{HF}$ 2.2, 6-C*H*); δ_C 14.50 (s, CH_2CH_3), 20.14 (s, CH_2CH_3), 30.44 (s, 2'-*C*), 31.21 (m, 1'-*C*), 33.68 (3'-*C*), 36.86 (s, 4'-*C*), 39.84 (s, $CH_2CH_2CH_3$), 56.58 (s, OCH_3), 96.82 (dd, $^2J_{CF}$ 30.2, $^3J_{CF}$ 3.1, 6-*C*), 115.46 (ddd, $^2J_{CF}$ 20.6, $^2J_{CF}$ 16.3, $^3J_{CF}$ 2.3, 2-*C*), 138.42 (ddd, $^1J_{CF}$ 242.4, $^2J_{CF}$ 16.1, $^4J_{CF}$ 4.5, 4-*C*), 146.69 (ddd, $^2J_{CF}$ 13.1, $^3J_{CF}$ 9.2, $^3J_{CF}$ 5.3, 5-*C*), 150.05 (ddd, $^1J_{CF}$ 245.4, $^2J_{CF}$ 13.1, $^3J_{CF}$ 11.1, 3-*C*), 156.01 (ddd, $^1J_{CF}$ 241.4, $^3J_{CF}$ 11.1, $^4J_{CF}$ 3.8, 1-*C*); δ_F -119.02 (dd, $^3J_{HF}$ 10.9, $^5J_{FF}$ 10.9, 1-C*F*), -138.80 (d,

$^{3}J_{FF}$ 19.9, 3-C*F*), -165.73 (ddd, $^{3}J_{FF}$ 19.6, $^{5}J_{FF}$ 10.5, $^{4}J_{HF}$ 6.8, 4-C*F*). *Found for minor isomer:* δ_H 0.94 (3H, t, $^{3}J_{HH}$ 7.2, CH_2CH_3), 1.02 (m), 1.19 (m), 1.33 (m), 1.44 (m), 1.57 (m), 1.74 (m), 1.83 (m), 1.94 (m), 2.89 (1H, tt, $^{3}J_{HH}$ 12.8, $^{3}J_{HH}$ 3.8, 1'-C*H*), 3.85 (3H, s, OCH_3), 6.45 (1H, ddd, $^{3}J_{HF}$ 11.6, $^{4}J_{HF}$ 6.8, $^{5}J_{HF}$ 2.2, 6-C*H*); δ_C 14.47 (s, CH_2CH_3), 21.12 (s, CH_2CH_3), 25.65 (s), 31.83 (s), 33.13 (s), 34.98 (s), 34.99 (s), 56.58 (s, OCH_3), 96.82 (dd, $^{2}J_{CF}$ 30.2, $^{3}J_{CF}$ 3.1, 6-*C*), 115.75 (m, 2-*C*), 138.42 (ddd, $^{1}J_{CF}$ 242.4, $^{2}J_{CF}$ 16.1, $^{4}J_{CF}$ 4.5, 4-*C*), 146.69 (ddd, $^{2}J_{CF}$ 13.1, $^{3}J_{CF}$ 9.2, $^{3}J_{CF}$ 5.3, 5-*C*), 150.04 (ddd, $^{1}J_{CF}$ 245.4, $^{2}J_{CF}$ 13.1, $^{3}J_{CF}$ 11.1, 3-*C*), 155.97 (ddd, $^{1}J_{CF}$ 241.4, $^{3}J_{CF}$ 11.1, $^{4}J_{CF}$ 3.8, 1-*C*); δ_F -119.28 (dd, $^{3}J_{HF}$ 11.2, $^{5}J_{FF}$ 11.2, 1-C*F*), -138.99 (d, $^{3}J_{FF}$ 19.9, 3-C*F*), -165.73 (ddd, $^{3}J_{FF}$ 19.6, $^{5}J_{FF}$ 10.5, $^{4}J_{HF}$ 6.8, 4-C*F*); *m/z* (EI^+) 286 (M^+, 82%), 202 (49), 201 (90), 188 (100), 175 (87), 173 (31), 145 (36), 55 (50), 43 (50), 41 (44).

1,2,4-Trifluoro-5-methoxy-3-(4-propyl-cyclohexyl)-benzene 90. The alkene **79** (2.19 g crude material) afforded the product (0.04 g, 3%) as a waxy white solid (Found: C, 67.35; H, 7.55. $C_{16}H_{21}F_3O$ requires C, 67.11; H, 7.39%). *Found for major isomer:* δ_H 0.90 (3H, t, $^{3}J_{HH}$ 7.3, CH_2CH_3), 1.04 (m), 1.21 (m), 1.33 (m), 1.47 (m), 1.59 (m), 1.76 (m), 1.84 (m), 2.00 (m), 2.97 (1H, tt, $^{3}J_{HH}$ 12.5, $^{3}J_{HH}$ 3.7, 1'-C*H*), 3.82 (3H, s, OCH_3), 6.64 (1H, ddd, $^{3}J_{HF}$ 11.2, $^{4}J_{HF}$ 7.7, $^{4}J_{HF}$ 7.7, 6-C*H*); δ_C 14.50 (s, CH_2CH_3), 20.11 (s, CH_2CH_3), 30.30 (s, 2'-*C*), 30.82 (m, 1'-*C*), 33.57 (s, 3'-*C*), 36.82 (s, 4'-*C*), 39.83 (s, $CH_2CH_2CH_3$), 56.74 (s, OCH_3), 99.57 (dd, $^{2}J_{CF}$ 22.7, $^{3}J_{CF}$ 2.2, 6-*C*), 124.73 (dd, $^{2}J_{CF}$ 17.1, $^{2}J_{CF}$ 15.9, 3-*C*), 142.71 (ddd, $^{1}J_{CF}$ 236.7, $^{2}J_{CF}$ 13.8, $^{3}J_{CF}$ 8.1, 2-*C*), 143.85 (dd, $^{2}J_{CF}$ 16.8, $^{3}J_{CF}$ 8.4, 5-*C*), 146.27 (ddd, $^{1}J_{CF}$ 241.9, $^{2}J_{CF}$ 6.9, $^{4}J_{CF}$ 3.5, 1-*C*), 146.46 (ddd, $^{1}J_{CF}$ 242.3, $^{3}J_{CF}$ 3.8, 4-*C*); δ_F -141.68 (dd, $^{5}J_{FF}$ 12.5, $^{4}J_{FF}$ 8.0, 4-C*F*), -142.43 (ddd, $^{3}J_{FF}$ 22.1, $^{5}J_{FF}$ 12.9, 1-C*F*), -149.71 (dd, $^{3}J_{FF}$ 22.2, $^{4}J_{FF}$ 6.9, 2-C*F*). *Found for minor isomer:* δ_H 0.93 (3H, t, $^{3}J_{HH}$ 7.1, CH_2CH_3), 1.04 (m), 1.21 (m), 1.33 (m), 1.47 (m), 1.59 (m), 1.76 (m), 1.84 (m), 2.00 (m), 3.01 (1H, tt, $^{3}J_{HH}$ 12.5, $^{3}J_{HH}$ 3.7, 1'-C*H*), 3.82 (3H, s, OCH_3), 6.64 (1H, ddd, $^{3}J_{HF}$ 11.2, $^{4}J_{HF}$ 7.7, $^{4}J_{HF}$ 7.7, 6-C*H*); δ_C 14.46 (s, CH_2CH_3), 21.09 (s, CH_2CH_3), 25.20 (m), 31.81 (s), 33.06 (s), 35.68 (s), 35.76 (s), 56.76 (s, OCH_3), 99.57 (dd, $^{2}J_{CF}$ 22.7, $^{3}J_{CF}$ 2.2, 6-*C*), 124.73 (dd, $^{2}J_{CF}$ 17.1, $^{2}J_{CF}$ 15.9, 3-*C*), 142.68 (ddd, $^{1}J_{CF}$ 237.1, $^{2}J_{CF}$ 13.7, $^{3}J_{CF}$ 8.0, 2-*C*), 143.89 (dd, $^{2}J_{CF}$ 18.7, $^{3}J_{CF}$ 8.0, 5-*C*), 146.26 (ddd, $^{1}J_{CF}$ 241.5, $^{2}J_{CF}$ 6.9, $^{4}J_{CF}$ 3.1, 1-*C*), 146.61 (ddd, $^{1}J_{CF}$ 242.3, $^{3}J_{CF}$ 3.8, 4-*C*); δ_F -141.82 (dd, $^{5}J_{FF}$ 12.6, $^{4}J_{FF}$ 8.1, 4-C*F*), -142.43 (ddd, $^{3}J_{FF}$ 22.1, $^{5}J_{FF}$ 12.9, 1-C*F*), -149.93 (dd, $^{3}J_{FF}$ 22.2, $^{4}J_{FF}$ 6.9, 2-C*F*); *m/z* (EI^+) 286

(M^+, 77%), 188 (76), 175 (85), 173 (44), 170 (100), 145 (65), 67 (44), 55 (72), 43 (64), 41 (67), 29 (51).

1,2,4-Trifluoro-5-methoxy-3-(4-propyl-cyclohexyl)-6-trifluoromethyl-benzene 91. The alkene **80** (1.99 g crude material) afforded the product (negligible mass recovered); *m/z* (EI^+) 354 (M^+, 33%), 269 (13), 256 (22), 243 (18), 81 (12), 67 (18), 55 (100), 43 (31), 41 (46), 29 (21).

4'-Propyl-4-(2,3,4-trifluoro-phenyl)-bicyclohexyl 92. The alkene **81** (1.82 g crude material), following recrystallisation from THF/hexanes, afforded the product (0.57 g, 45%) as a white solid, mp 56.5-58.0 °C (Found: C, 74.57; H, 8.70. $C_{21}H_{29}F_3$ requires C, 74.52; H, 8.64%). δ_H 0.91 (3H, t, $^3J_{HH}$ 7.3, C*H*$_3$), 0.99-1.25 (10H, m), 1.35 (2H, m), 1.45 (2H, m), 1.79 (5H, m), 1.89 (4H, m), 2.79 (1H, tt, $^3J_{HH}$ 12.3, $^3J_{HH}$ 3.0, 4-C*H*), 6.90 (2H, m, Ar 5 and 6-C*H*); δ_C 14.56 (s, *C*H$_3$), 20.28 (s, *C*H$_2$CH$_3$), 30.28 (s), 30.34 (s), 33.31 (s), 33.78 (s), 37.33 (s), 37.88 (s), 40.06 (s), 43.05 (s), 43.56 (s), 111.62 (dd, $^2J_{CF}$ 16.7, $^3J_{CF}$ 3.8, Ar 5-*C*), 120.76 (ddd, $^3J_{CF}$ 7.6, $^3J_{CF}$ 5.7, $^4J_{CF}$ 4.3, Ar 6-*C*), 131.96 (ddd, $^2J_{CF}$ 12.2, $^3J_{CF}$ 3.6, $^4J_{CF}$ 1.4, Ar 1-*C*), 139.98 (ddd, $^1J_{CF}$ 249.9, $^2J_{CF}$ 16.4, $^2J_{CF}$ 15.2, Ar 3-*C*), 149.55 (ddm, $^1J_{CF}$ 247.0, $^2J_{CF}$ 9.6, Ar 2 and Ar 4-*C*); δ_F -139.29 (m, 4-C*F*), -140.97 (ddd, $^3J_{FF}$ 20.6, $^4J_{FF}$ 6.1, $^4J_{HF}$ 6.1, 2-C*F*), -161.85 (ddd, $^3J_{FF}$ 20.6, $^3J_{FF}$ 20.6, $^4J_{HF}$ 5.4, 3-C*F*); *m/z* (EI^+) 338 (M^+, 49%), 158 (65), 145 (65), 125 (41), 83 (100), 81 (56), 69 (76), 67 (46), 55 (68), 41 (54).

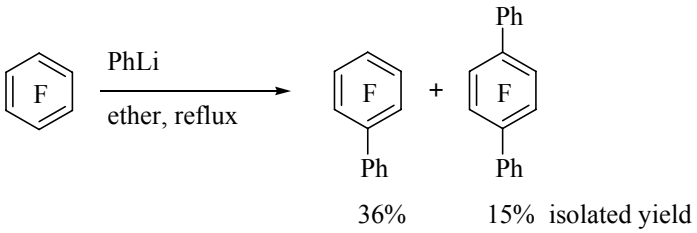
4'-Propyl-4-(2,3,6-trifluoro-phenyl)-bicyclohexyl 93. The alkene **82** (2.68 g, crude material), following recrystallisation from THF/hexanes, afforded the product (0.36 g, 16%) as a white solid, mp 86.5-88.0 °C (Found: C, 74.27; H, 8.63. $C_{21}H_{29}F_3$ requires C, 74.52; H, 8.64%). δ_H 0.89 (3H, t, $^3J_{HH}$ 7.3, C*H*$_3$), 0.98-1.36 (12H, m), 1.73-1.90 (11H, m), 2.95 (1H, tt, $^3J_{HH}$ 12.0, $^3J_{HH}$ 4.0, 4-C*H*), 6.74 (dddd, $^3J_{HF}$ 9.4, $^3J_{HH}$ 9.4, $^4J_{HF}$ 3.9, $^5J_{HF}$ 2.1, Ar 5-C*H*), 6.92 (ddd, $^3J_{HF}$ 9.0, $^3J_{HH}$ 9.0, $^4J_{HF}$ 4.9, Ar 4-C*H*); δ_C 14.57 (s, *C*H$_3$), 20.24 (s, *C*H$_2$CH$_3$), 30.20 (s), 30.44 (s), 31.14 (s), 33.76 (s), 33.64 (s), 37.82 (s), 40.01 (s), 42.75 (s), 43.58 (s), 110.65 (ddd, $^2J_{CF}$ 26.3, $^3J_{CF}$ 6.7, $^3J_{CF}$ 4.3, Ar 4-*C*), 113.91 (dd, $^2J_{CF}$ 19.6, $^3J_{CF}$ 10.4, Ar 5-*C*), 124.44 (dd, $^2J_{CF}$ 20.1, $^2J_{CF}$ 14.8, Ar 1-*C*), 147.56 (ddd, $^1J_{CF}$ 242.5, $^2J_{CF}$ 14.4, $^4J_{CF}$ 3.4, Ar 3-*C*), 149.25 (ddd, $^1J_{CF}$ 247.1, $^2J_{CF}$ 13.9, $^3J_{CF}$ 10.1, Ar 2-*C*), 156.77 (ddd, $^1J_{CF}$ 242.3, $^3J_{CF}$ 7.7, $^4J_{CF}$ 2.9, Ar 6-*C*); δ_F -119.32 (m, 6-C*F*), -137.92 (dd, $^3J_{FF}$ 20.5,

$^{4}J_{FF}$ 7.7, 2-C*F*), -143.36 (m, 3-C*F*); *m/z* (EI^{+}) 338 (M^{+}, 29%), 212 (20), 171 (21), 158 (39), 145 (41), 82 (100), 69 (54), 67 (33), 55 (47), 41 (36).

4'-Propyl-4-(2,4,6-trifluoro-phenyl)-bicyclohexyl 94. The alkene **83** (1.34 g crude material), following recrystallisation from THF/hexanes, afforded the product (0.23 g, 21%) as a white solid, mp 88.0-89.0 °C (Found: C, 74.28; H, 8.64. $C_{21}H_{29}F_3$ requires C, 74.52; H, 8.64%). δ_H 0.89 (3H, t, $^{3}J_{HH}$ 7.3, CH_3), 0.97-1.36 (12H, m), 1.73-1.84 (11H, m), 2.88 (1H, tt, $^{3}J_{HH}$ 11.7, $^{3}J_{HH}$ 3.8, 4-C*H*), 6.58 (2H, $^{3}J_{HF}$ 8.8, Ar 3-C*H*); δ_C 14.57 (s, *C*H_3), 20.24 (s, *C*H_2CH$_3$), 30.21 (s), 30.53 (s), 31.35 (s), 33.77 (s), 34.87 (s), 37.82 (s), 40.02 (s), 42.78 (s), 43.59 (s), 100.26 (m, Ar 3-*C*), 118.55 (td, $^{2}J_{CF}$ 18.6, $^{4}J_{CF}$ 4.8, Ar 1-*C*), 160.76 (dt, $^{1}J_{CF}$ 245.3, $^{3}J_{CF}$ 16.3, Ar 4-*C*), 161.66 (ddd, $^{1}J_{CF}$ 264.4, $^{3}J_{CF}$ 14.9, $^{3}J_{CF}$ 13.1, Ar 2-*C*); δ_F -111.03 (2F, m, 2-C*F*), -113.11 (1F, m, 4-C*F*); *m/z* (EI^{+}) 338 (M^{+}, 30%), 158 (93), 145 (97), 83 (63), 82 (53), 81 (59), 69 (100), 67 (43), 55 (82), 41 (63).

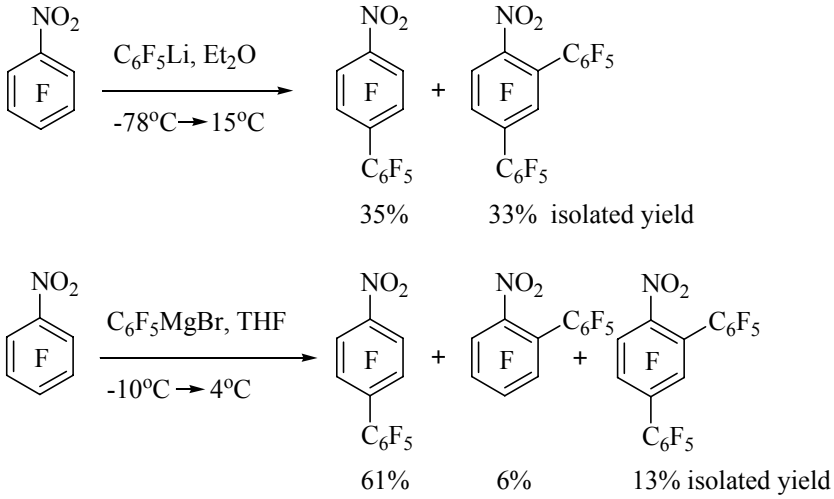
5 Cross-Coupling Reactions of Perfluorobenzenes

Fluorinated biaryl moieties are commonly found in LCs used for modern LCD devices.[1] The highly electron deficient core of hexafluorobenzene renders it susceptible to nucleophilic attack, and as such, may be functionalised via aromatic substitution to form a polyfluorobiphenyl unit in moderate yield as described by Chaudry and Stephens (Scheme 36).[109]



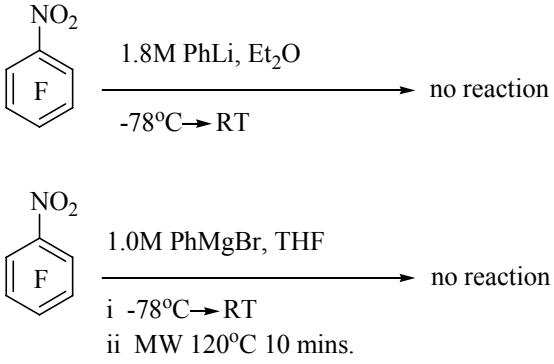
Scheme 36. Synthesis of a fluorobiphenyl via S_NAr of fluorine

In comparison to hexafluorobenzene, pentafluoronitrobenzene has a higher reactivity to nucleophilic attack and functionalisation is, therefore, relatively simple affording polyfluoronitrobiphenyls in higher yields. Coupling of the pentafluorophenyl moiety to pentafluoronitrobenzene using nucleophilic methodology was reported over forty years ago, and its reaction as a phenyl lithium salt[27] and also as a phenyl Grignard reagent[110] has been described (Scheme 37). Nucleophilic aromatic substitution occurs predominantly in the *para* position to the nitro group in both cases.



Scheme 37.[27, 110] Synthesis of fluorinated biphenyls via carbon nucleophiles

Success of these S_NAr reactions (Scheme 37) may be contrasted with our attempts to synthesise a fluorinated biphenyl LC "backbone" via reaction of pentafluoronitrobenzene with phenyllithium and phenylmagnesium bromide (Scheme 38). Analysis of the reaction mixtures by GC-MS showed no trace of the desired coupled products.



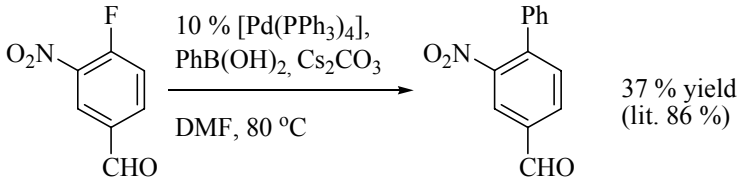
Scheme 38. Attempted synthesis of a fluorinated biphenyl

Due to the failure of phenyllithium and Grignard reagents to afford the required fluorinated biphenyl scaffolds for LC materials, alternative methodology was sought for

the formation of Ar-C−Ar-C bonds in cross-coupling reactions of perfluoroaryl groups. We turned our attention to recent developments in the field of palladium catalysed Suzuki-Miyaura chemistry, notably efficient aryl coupling reactions proceeding via C−F bond activation.

5.1 Extension of Suzuki-Miyaura Cross-Coupling Methodology to Perfluoronitrobenzene

Repeating the coupling of phenylboronic acid to 4-fluoro-3-nitrobenzaldehyde reported by Kim and Yu[68] (Scheme 39) using standard Suzuki-Miyaura conditions gave a slightly lower yield of the biaryl **96** (37%) than described (86%) as crystals were grown of a quality suitable for X-ray analysis (Figure 21). The two phenyl rings are twisted out of the same plane.



96

Scheme 39. Suzuki-Miyaura Cross coupling reaction through C−F bond activation

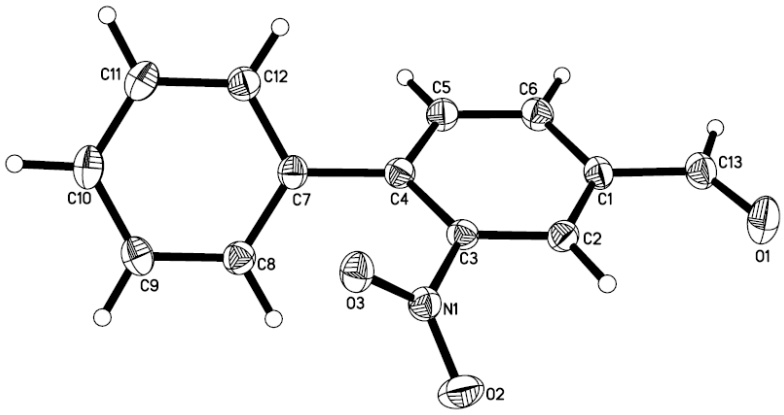


Figure 21. X-Ray crystal structure of nitrophenylbenzaldehyde **96**

It was envisaged that the methodology developed in this coupling of phenylboronic acid to an electron deficient fluoronitroaryl could be extended to the similarly electron deficient scaffold perfluoronitrobenzene under similar conditions. Following the proposed nucleophilic attack[68] of palladium on 4-fluoro-3-nitrobenzaldehyde, charge in the intermediate Meisenheimer complex is stabilised by the aldehyde group, and this group could potentially be substituted for four electron electron withdrawing fluorine atoms on the aromatic ring (Figure 22).

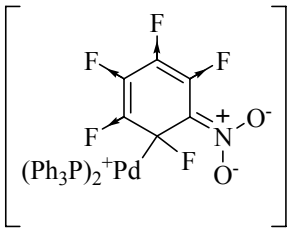
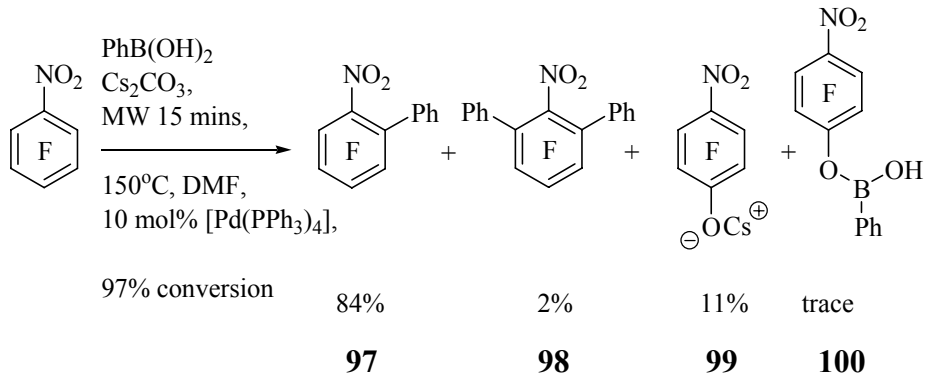


Figure 22. Intermediate Meisenheimer complex formed following attack of palladium on pentafluoronitrobenzene

Modern coupling studies are often performed with the use of microwave irradiation.[66] The reduced reaction times associated with the use of such technology enables the rapid optimisation of reaction conditions. Utilization of microwave screening allows for a rational high throughput screening (HTS) protocol thus minimising the number of experiments that need to be carried out. This synthetically efficient method of heating a reaction was adopted for the following studies of coupling reactions.

The coupling of phenylboronic acid to a fluoroaryl reported by Kim and Yu[68] was repeated using the same conditions used above but in a microwave using perfluoronitrobenzene in place of 4-fluoro-3-nitrobenzaldehyde. The reaction furnished 2,3,4,5-tetrafluoro-6-nitro-biphenyl with excellent conversion, in addition to several by-products (Scheme 40).

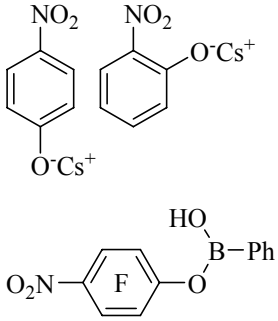
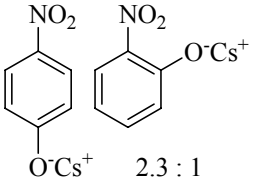


Scheme 40. Attempted coupling of a boronic acid to perfluoronitrobenzene

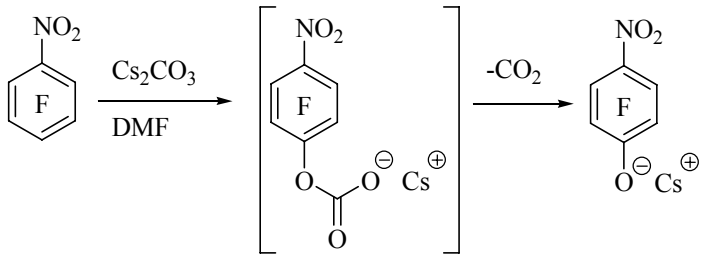
A number of undesirable side reactions occurred under these conditions due to the nucleophilic nature of the caesium carbonate base (yielding **99**), the boronic acid (yielding **100**) and the ligands of the catalyst $[Pd(PPh_3)_4]$. These reactions will not occur when 4-fluoro-3-nitrobenzaldehyde is used as the substrate as it is not as susceptible to S_NAr type reactions. Formation of homocoupled product from the boronic acid was not observed whilst the observation of the terphenyl **98** by ^{19}F NMR (a triplet at -155.2 ppm and a doublet at -133.4 ppm) and GC-MS (*m*/*z* (EI^+) 329) illustrates the reactivity of the

product to further Ar-C−Ar-C coupling. The source of each of these problematic side reactions was studied individually (Table 23).

Table 23. Investigation of cross-coupling side reactions, performed in a microwave for 15 minutes at 150 °C. Volumes/masses as per Kim and Yu[68] but scale ×0.08

Reactants	NPFB, DMF	NPFB, DMF, $PhB(OH)_2$	NPFB, DMF, $PhB(OH)_2$, Cs_2CO_3	NPFB, DMF, $[Pd(PPh_3)_4]$	NPFB, DMF, Cs_2CO_3
Products	none	none		many phosphine bound aryls	 2.3 : 1

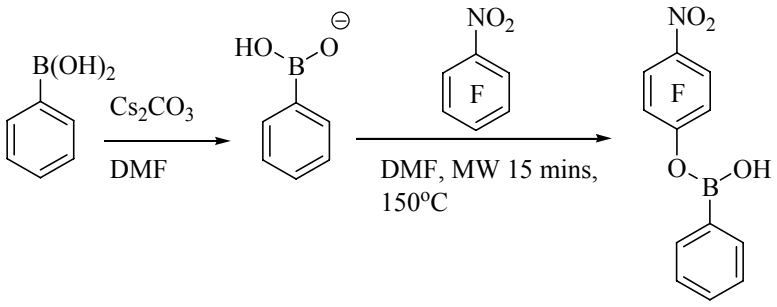
Despite the fact that almost complete conversion from perfluoronitrobenzene had been attained, one major by-product of the attempted coupling was most likely the caesium phenoxide salt **99** characterised by two signals in the fluorine NMR but not observable by GC-MS. This salt may be formed via direct nucleophilic attack of the carboxylate ion with subsequent loss of carbon dioxide (Scheme 41). The pure phenolate salt could not be isolated so acidification furnished a small amount of the phenol which could not be purified but was characterised by NMR and GC-MS and is consistent with structure **99**.



99

Scheme 41. Proposed mechanism leading to the formation of the phenoxide salt

One of the minor undesirable by-products, possibly the phenyl hydrogen phenylboronate **100**, may also have formed during the attempted coupling via a nucleophilic aromatic substitution reaction mechanism (Scheme 42). Deprotonation of the boronic acid with base followed by subsequent oxyanion nucleophilic attack leading to fluorine substitution in perfluoronitrobenzene yields the boronate by-product. Only a trace amount of the boronate was produced in the reaction and therefore no material could be isolated but was observed by GC-MS analysis of the crude reaction mixture (*m*/*z* (EI^+) 315).

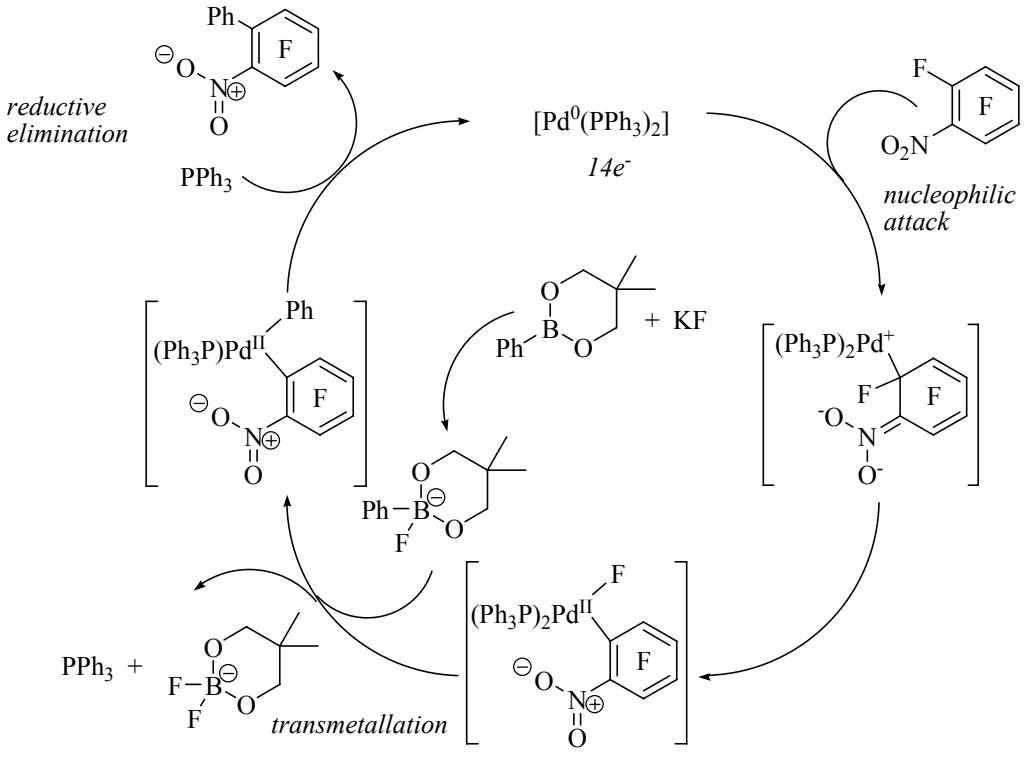


100

Scheme 42. Proposed mechanism leading to the formation of the phenylboronate

5.1.1 Optimisation of Suzuki-Miyaura Cross-Coupling Conditions

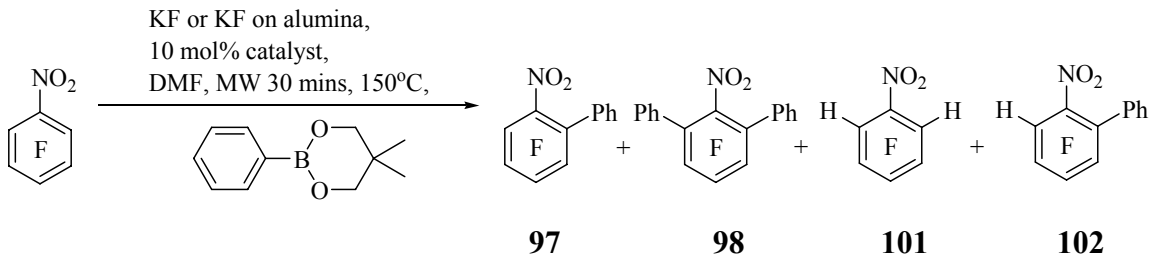
Alternative reagents were required to circumvent the side reactions encountered. An alternative base, potassium fluoride, was selected to prevent the formation of the caesium phenoxide salt **99**. Any nucleophilic attack from this base on perfluoronitrobenzene or its derivative intermediates formed during the reaction would ultimately have no effect on the resulting product. In order to prevent the formation of the boronate side product **100** (although only a trace amount) subsequent couplings were also carried out with 5,5-dimethyl-2-phenyl-[1,3,2]dioxaborinane. This alternative source of a nucleophilic phenyl group has no acidic protons which may be removed in the presence of base leaving any oxyanions which may become involved in nucleophilic attack of the substrate. The proposed catalytic cycle using these alternative reagents is shown below (Scheme 43).



Scheme 43. Mechanism of Suzuki-Miyaura type cross coupling via C−F bond activation

Success of Suzuki-Miyaura cross-coupling reactions via activation of aromatic C−F bonds and the choice of catalyst is dependant on the following factors.[60] *Kinetically* the catalyst must be able to selectively activate the C−F bond whilst allowing the completion of the catalytic cycle by reductive elimination and C−C bond formation. *Thermodynamically* the by-product must incorporate the fluorine atom and thus contribute significantly to the driving force of the reaction. It follows that a highly electron rich metal centre is required which may be obtained through the use of Lewis-basic ligands and low-valent metals. Further to this, the ligands attached to the metal must be sterically demanding to assist in the reductive elimination step of the catalytic cycle.

Different catalyst complexes traditionally used in metal catalysed C−C bond forming reactions vary greatly, different metals having varying sizes and charges, the ligands having different cone angles attributed to their steric bulk and different electron donating properties, factors which all contribute to the overall catalytic activity. Prediction of this activity for any one complex is therefore not simple and so the coupling reaction between perfluoronitrobenzene and phenyldioxaborinane using potassium fluoride as base (Scheme 44) was attempted using a series of common palladium$^{0/II}$ and also nickel^{II} complexes (Table 24) to establish which was the most effective and also whether the hypotheses outlined above were correct. Nickel^{0} catalysts were disregarded due to their instability in air.



Scheme 44. C−C coupling with perfluoronitrobenzene using alternative base and source of phenyl nucleophile

Table 24. Catalyst screen with a range of palladium and nickel catalysts using KF base, performed in a microwave for 15 minutes at 150 °C. Volumes/masses as per Kim and Yu[68] but scale ×0.08

Catalyst		Conversion from starting material /%	Total conversion to products /%	Conversion to product /%			
				97	**98**	**101**	**102**
Pd^0	Pd on alumina	41	1	1	0	0	0
	$[Pd(PPh_3)_4]$	100	95	11	4	22	58
	$[Pd(dba)_2]$, PCy_2Ph	97	95	22	6	25	42
	$[Pd(dba)_2]$, P^tBu_3	72	31	21	7	0	3
Pd^{II}	$[Pd(PPh_3)_2Cl_2]$	60	20	20	0	0	0
	$[Pd(dppf)Cl_2]$	76	56	43	9	0	4
	$[Pd(OAc)_2]$	80	24	20	4	0	0
Ni^{II}	$[Ni(PPh_3)_2Cl_2]$	7	7	7	0	0	0
	$[Ni(acac)_2]$, $(2,4\text{-}^tBu_2C_6H_3O)_3P$	67	27	27	0	0	0
	$[Ni(acac)_2]$, P^tBu_3	53	4	4	0	0	0
	$[Ni(dppp)Cl_2]$	22	0	0	0	0	0

The most effective catalysts for the C−C coupling reaction were found to be the electron rich palladium^0 complexes with bulky, electron rich ligands (Table 24), in agreement with the hypotheses outlined previously. Palladium^0 bearing triphenylphosphine and dibenzylideneacetone ligands offer excellent conversions to the coupled biaryl product **97** (Scheme 44).

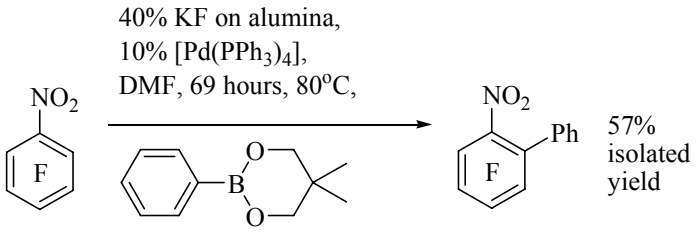
In the comparison of the activity of $[Pd^{II}(PPh_3)_2Cl_2]$ and $[Ni^{II}(PPh_3)_2Cl_2]$ complexes, it may be observed that the use of palladium is preferential to that of nickel (total conversion is 20% versus 7% respectively). Although no other direct comparisons of the

screened catalyst complexes can be made this trend generally holds for these metals used in these C−C coupling reactions.

The fact that by-products **98**, **101** and **102** were also obtained illustrates the reactivity of some of the catalysts and their ability to incur further fluorine substitutions in positions *ortho* to the nitro group; The origin of the protons is probably the solvent forming the latter two (usually minor) by-products. In order to regulate this activity of the palladium^0 catalysts, especially those bearing PPh_3 and dba ligands, potassium fluoride dispersed on alumina (40% by weight) was used alternatively as the base. Although use of this 'diluted' base increased reaction times the product yield of the desired biphenyl product **97** was also found to increase (Table 25). A 91% conversion to the product was achieved when $[Pd(PPh_3)_4]$ was used as catalyst. These reaction conditions were scaled up in a batch reaction to yield the biphenyl **103** in good yield (Scheme 45).

Table 25. Catalyst screen with a range of palladium and nickel catalysts using 40% KF on alumina, performed in a microwave for 15 minutes at 150 °C. Volumes/masses as per Kim and Yu[68] but scale ×0.08

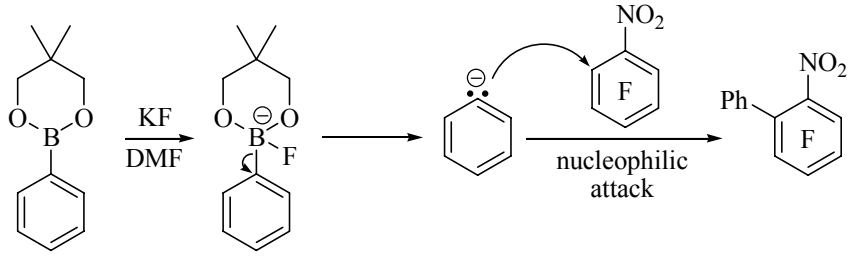
Catalyst		Conversion from starting material /%	Total conversion to products /%	Conversion to coupled product /%			
				97	98	101	102
Pd^0	$[Pd(PPh_3)_4]$	96	96	91	2	0	3
	$[Pd(dba)_2]$, $PhPCy_2$	78	78	72	4	0	2
	$[Pd(dba)_2]$, P^tBu_3	24	0	0	0	0	0
Pd^{II}	$[Pd(OAc)_2]$	50	9	9	0	0	0
	$[Pd(dppf)Cl_2]$	8	4	4	0	0	0
Ni^{II}	$[Ni(acac)_2]$, P^tBu_3	38	2	2	0	0	0



103

Scheme 45. Scale up of Suzuki-Miyaura cross coupling using optimised conditions.

To discount the possibility that the C−C coupling (Scheme 45) was proceeding via a non-catalytic path (Scheme 46) the reaction was repeated without any catalyst. GC-MS and NMR analysis confirmed that none of the biphenyl coupled product had been obtained.



Scheme 46. Possible route to the cross coupled biphenyl product via a non-catalytic mechanism

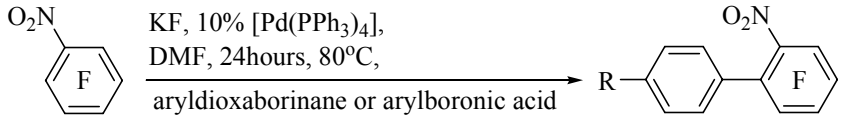
5.1.2 Alternative Functionalised Boronic Esters and Acids

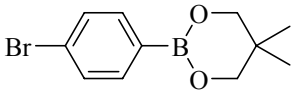
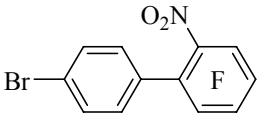
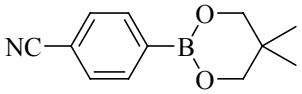
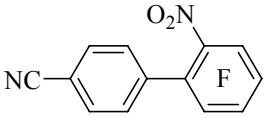
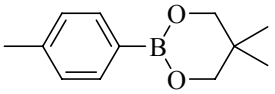
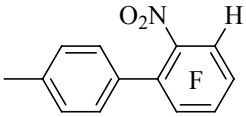
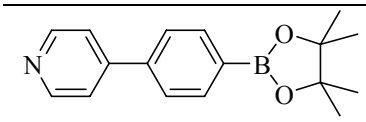
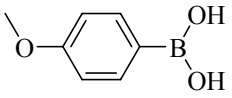
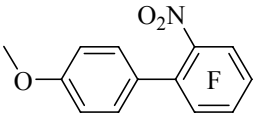
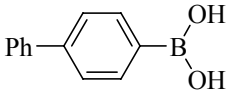
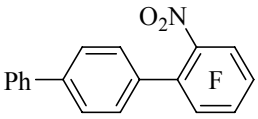
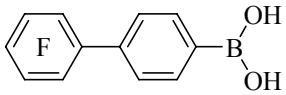
The scaled up cross coupling reaction with optimised conditions (Scheme 45) was repeated for seven commercially available functionalised arylboron compounds

Table 26), as four boronic esters and three boronic acids (not available as protected esters), in order to introduce further functionality into the bi-aryl scaffolds. Four boronic acids were included as the undesired formation of the minor phenylboronate by-product **100** seen earlier (Scheme 42) was not perceived to be a major problem. The inclusion of methyl and methoxy electron donating groups, an electron withdrawing cyano group and a bromine 'handle' potentially allowing further palladium catalysed chemistry would illustrate the flexibility of the synthetic methodology employed. Unsupported potassium fluoride was also used as it was observed that with this reagent the reactions proceeded cleanly enough for purification when not performed using microwave heating whilst benefiting from the faster reaction times (24 hours versus 69 hours).

Most of the coupled bi-aryls were obtained in moderate to good yield. The synthesis of 4'-bromo-2,3,4,5-tetrafluoro-6-nitro-biphenyl **104** resulted in many side reactions and much polymeric material due to the preference of the catalyst for activation of the more labile C−Br bond. Consequently only a small amount of this material was isolated and could not be purifed. 2,3,4-Trifluoro-4'-methyl-6-nitro-biphenyl **106** was isolated instead of the expected 2,3,4,5-tetrafluoro-4'-methyl-6-nitro-biphenyl, illustrating the reactivity of the 5-C*F* atom to further reaction and substitution by a hydrogen, probably from the solvent, in the absence of any other nucleophile source. 2,3,4,5-Tetrafluoro-4'-methoxy-6-nitro-biphenyl **107** was characterised by X-ray analysis (Figure 23). Reactions of 4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-pyridine and perfluorophenylboronic acid with perfluoronitrobenzene furnished none of desired coupled bi-aryls, a result of the poor nucleophilicity of these electron deficient aryl groups.

Table 26. Suzuki-Miyaura C−C couplings from dioxaborinanes and boronic acids



Aryldioxaborinane or arylboronic acid	Product		Conversion /%	Isolated Yield /%
		**104**	92	8
		**105**	62	57
		**106**	100	58
	n/a		0	0
		**107**	76	67
		**108**	99	83
	n/a		0	0

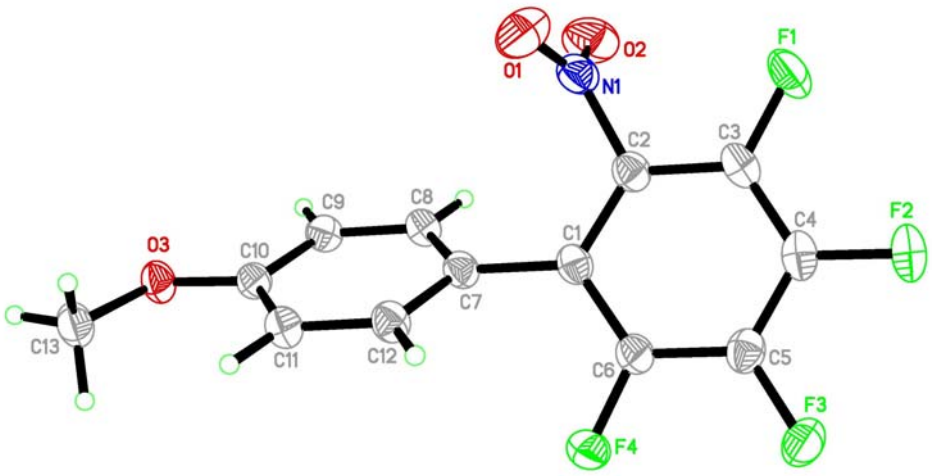


Figure 23. X-ray crystal structure of tetrafluoro-methoxy-nitro-biphenyl **107**

5.2 Other Perfluorinated Substrates

The flexibility of the developed synthetic approach (section 5.1.2) was explored by investigating whether the cross coupling methodology could be extended to different perfluorinated aryl scaffolds. It was envisaged that the oxyanion of pentafluorobenzoic acid could stabilise the positive charge on the intermediate palladium species in much the same way as a nitro group (Figure 24), as similar stabilisation affects have been reported by Bahmanyar and co-workers in their studies of 2-fluoro-5-nitrobenzoic acid.[71] Combined with the negative charge stabilisation effects of the electron withdrawing aromatic fluorine atoms and the stabilisation effect of the fluorine lone pair onto the adjacent positively charged palladium, it was believed that the addition of the palladium catalyst and coupling of 5,5-dimethyl-2-phenyl-[1,3,2]dioxaborinane to perfluorobenzoic acid might be possible. However, use of this substrate afforded none of the coupled biaryl product and reactions using a number of perfluorinated aryl analogs, including sodium perfluorobenzoate, perfluorobenzonitrile, perfluorotoluene, perfluorobenzene and

perfluoropyridine, also furnished none of the desired coupled materials, confirmed by analysis of the product mixtures by GC-MS and NMR.

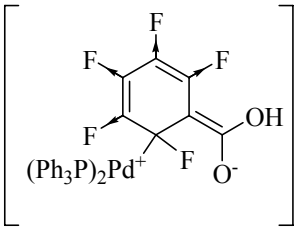
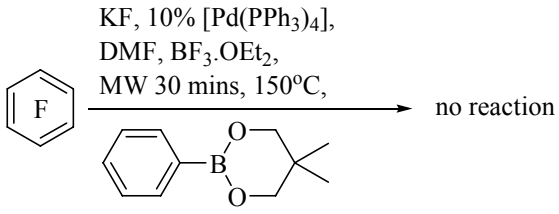


Figure 24. Proposed fluorine lone pair, oyxanion and fluorine electron withdrawing stabilisation effects following addition of palladium catalyst to perfluorobenzoic acid

The addition of a catalytic amount of the Lewis acid boron trifluoride diethyl etherate did not assist in the coupling reaction of hexafluorobenzene to 5,5-dimethyl-2-phenyl-[1,3,2]dioxaborinane (Scheme 47) using the conditions developed in section 5.1.1. Use of this Lewis acid may have assisted in breaking the C−F bond for palladium insertion due to the affinity of the boron atom for the electron lone pairs of fluorine.



Scheme 47. Attempted C-F bond palladium activation with a Lewis Acid

5.3 Conclusion

A new route to highly fluorinated nitrobiphenyls has been developed via Suzuki-Miyaura reactions of C–F bonds, using a “standard” tetrakistriphenylphosphinepalladium catalyst.

Use of potassium fluoride is required to prevent formation of phenol by-products which are formed with the use of conventional bases such as metal carbonates.

The fluorinated biphenyls afforded pose as potential scaffolds for LC development. Facile displacement of the nitro group may be achieved by reduction followed by either the Sandmeyer reaction,[111, 112] for adding functionality such as bromine, or the Schiemann reaction, for adding another fluorine.[113]

5.4 Experimental

Preparation of 2-nitro-biphenyl-4-carbaldehyde 96. The preparation was followed as in the literature.[68] The biphenyl was afforded (0.23 g, 37%) as a yellow solid, mp 109-110 °C (Found: C, 68.90; H, 4.20; N, 6.07. $C_{13}H_9NO_3$ requires C, 68.72; H, 3.99; N, 6.16%); δ_H 7.32-7.35 (2H, m, Ar'-C*H*), 7.43-7.45 (3H, m, Ar'-C*H*), 7.63 (1H, d, $^3J_{HH}$ 7.8, 6-C*H*), 8.11 (1H, dd, $^3J_{HH}$ 7.9, $^4J_{HH}$ 1.6, 5-C*H*), 8.31 (1H, d, $^4J_{HH}$ 1.5, 3-C*H*), 10.07 (1H, s, C*H*O); δ_C 125.03 (s), 127.72 (s, 2' or 3'-*C*), 128.96 (s, 2' or 3'-*C*), 129.14 (s), 132.38 (s), 132.99 (s), 135.91 (s), 136.14 (s), 141.54 (s), 149.72 (s, 2-C), 189.59 (s, *C*HO); *m/z* (EI^+) 227 (M^+, 10%), 210 (26), 199 (54), 170 (46), 152 (100), 151 (58), 150 (27), 142 (33), 139 (28), 115 (75).

Preparation of 2,3,5,6-tetrafluoro-4-nitro-phenol 99. Pentafluoronitrobenzene (2.13 g, 10 mmol), caesium carbonate (3.26 g, 10 mmol) and dry DMF (10 ml) were placed in a sealed vial and degassed three times at 50 mBar. The reaction mixture was heated in a microwave for 2 hours at 180ºC, poured onto water (60ml), the aqueous portion washed with ethyl acetate (3 × 30 ml) and acidified with dilute HCl. The organic product was extracted with DCM (3 × 30 ml) and the combined extracts were washed with water (100 ml) and dried ($MgSO_4$). The solvent was removed *in vacuo* and an attempt to purify the residual oil was made by distillation at reduced pressure. The phenol was isolated as a yellow oil (0.08 g, 4%); δ_H 5.85 (s, O*H*); δ_C 122.62 (m, 4-*C*), 137.72 (A and A' of AA'BB', $^1J_{CF}$ 245.0, 3-*C*), 140.58 (tt, $^2J_{CF}$ 13.8, $^3J_{CF}$ 3.8, 1-*C*), 141.95 (B and B' of

AA'BB', $^{1}J_{CF}$ 261.5, 2-*C*); δ_F -147.77 (A and A' of AA'BB', 3-C*F*), -160.86 (B and B' of AA'BB', 2-C*F*; *m/z* (EI^+) 211 (M^+, 62%), 181 (96), 137 (100), 133 (39), 117 (71), 105 (39), 98 (34), 71 (35), 69 (44), 30 (78).

5.4.1 General method for the preparation of 2,3,4,5-tetrafluoro-6-nitro-biphenyls

The boronic acid or boronic ester (1.0 equiv.), pentafluoronitrobenzene (1.5 equiv.), dry KF (1.4 equiv.), [$Pd(PPh_3)_4$] (0.1 equiv.) and DMF (25 ml) were charged to a round-bottomed flask. The contents were degassed three times by alternately connecting to house vacuum (~50 mmHg) and argon. The mixture was then heated with stirring to 80ºC for 24 hours under an atmosphere of dry argon, allowed to cool and then poured onto 150 ml ethyl acetate. The organic layer was washed with water (3 × 150 ml), dried ($MgSO_4$) and the solvent removed *in vacuo*. The residue was purified by column chromatography on silica gel using hexanes and DCM as the eluent. The product was further purified by recrystallisation from hexanes and THF to afford the analytically pure sample.

5.4.1.1 Synthesis of 2,3,4,5-tetrafluoro-6-nitro-biphenyls from boronic esters

2,3,4,5-Tetrafluoro-6-nitro-biphenyl 97. Using 40% KF on alumina in place of KF and heating the mixture for 69 hours, 5,5-dimethyl-2-phenyl-[1,3,2]dioxaborinane (0.51 g, 2.70 mmol) furnished the biphenyl (0.42 g, 57%) as a yellow solid, mp 92-93.5 °C (Found: C, 53.20; H, 1.82; N, 5.13. $C_{12}H_5F_4NO_2$ requires C, 53.15; H, 1.86; N, 5.17%); δ_H 7.36 (2H, m, Ar'-C*H*), 7.50 (3H, m, Ar'-C*H*); δ_C 120.97 (ddd, $^{2}J_{CF}$ 18.7, $^{3}J_{CF}$ 4.2, $^{3}J_{CF}$ 1.1, 1-*C*), 126.81 (s, 1'-*C*), 129.08 (s, 2' or 3'-*C*), 129.21 (s, 2' or 3'-*C*), 130.21 (s, 4'-*C*), 135.55 (dm, $^{2}J_{CF}$ 9.9, 6-*C*), 140.08 (dddd, $^{1}J_{CF}$ 253.70, $^{2}J_{CF}$ 14.9, $^{2}J_{CF}$ 13.3, $^{3}J_{CF}$ 3.5, 3 or 4-*C*), 140.87 (dddd, $^{1}J_{CF}$ 259.4, $^{2}J_{CF}$ 13.4, $^{3}J_{CF}$ 5.0, $^{4}J_{CF}$ 2.7, 2 or 5-*C*), 142.64 (dddd, $^{1}J_{CF}$ 260.9, $^{2}J_{CF}$ 17.7, $^{2}J_{CF}$ 12.2, $^{3}J_{CF}$ 3.1, 3 or 4-*C*), 144.70 (dddd, $^{1}J_{CF}$ 250.7, $^{2}J_{CF}$ 11.1, $^{3}J_{CF}$ 3.8, $^{4}J_{CF}$ 1.9, 2 or 5-*C*); δ_F -138.22 (ddd, $^{3}J_{FF}$ 22.0, $^{5}J_{FF}$ 10.7, $^{4}J_{FF}$ 3.8, 2 or 5-C*F*), -147.92

(ddd, $^{3}J_{FF}$ 21.3, $^{5}J_{FF}$ 10.6, $^{4}J_{FF}$ 5.3, 2 or 5-C*F*), -150.05 (ddd, $^{3}J_{FF}$ 22.0, $^{3}J_{FF}$ 19.7, $^{4}J_{FF}$ 5.3, 3 or 4-C*F*), -153.00 (ddd, $^{3}J_{FF}$ 20.7, $^{3}J_{FF}$ 20.7, $^{4}J_{FF}$ 3.7, 3 or 4-C*F*); *m/z* (EI^{+}) 271 (M^{+}, 41%), 243 (78), 242 (46), 226 (44), 224 (84), 215 (67), 213 (48), 206 (61), 204 (44), 193 (52), 187 (100).

4'-Bromo-2,3,4,5-tetrafluoro-6-nitro-biphenyl 104. 2-(4-Bromo-phenyl)-5,5-dimethyl-[1,3,2]dioxaborinane (0.50 g, 1.86 mmol) furnished the biphenyl (0.05 g, 8%) as an impure colourless oil; δ_H 7.20 (m, Ar'-C*H*), 7.63 (m, Ar'-C*H*); δ_C 119.83(dd, $^{2}J_{CF}$ 18.6, $^{3}J_{CF}$ 4.3, 1-*C*), 125.06 (s, 1'-*C*), 125.63 (s, 4'-*C*), 130.71 (s, 2' or 3'-*C*), 132.66 (s, 2' or 3'-*C*), 135.45 (m, 6-*C*), 140.36 (dddd, $^{1}J_{CF}$ 264.8, $^{2}J_{CF}$ 14.8, $^{2}J_{CF}$ 13.5, $^{3}J_{CF}$ 3.3, 3 or 4-*C*), 141.01(dddd, $^{1}J_{CF}$ 260.7, $^{2}J_{CF}$ 13.4, $^{3}J_{CF}$ 4.8, $^{4}J_{CF}$ 2.3, 2 or 5-*C*), 142.72(dddd, $^{1}J_{CF}$ 261.2, $^{2}J_{CF}$ 17.7, $^{2}J_{CF}$ 12.4, $^{3}J_{CF}$ 3.4, 3 or 4-*C*), 144.59 (ddm, $^{1}J_{CF}$ 251.8, $^{2}J_{CF}$ 11.5, 2 or 5-*C*); δ_F -137.79 (ddd, $^{3}J_{FF}$ 22.5, $^{5}J_{FF}$ 10.6, $^{4}J_{FF}$ 3.8, 2 or 5-C*F*), -147.10 (m, 2 or 5-C*F*), -149.23 (ddm, $^{3}J_{FF}$ 20.5, $^{3}J_{FF}$ 20.5, 3 or 4-C*F*), -151.79 (ddm, $^{3}J_{FF}$ 20.8, $^{3}J_{FF}$ 20.8, 3 or 4-C*F*); *m/z* (EI^{+}) 351 (M^{+}, 69%), 349 (M^{+}, 65%), 242 (84), 224 (100), 214 (88), 211 (73), 204 (82), 193 (83), 187 (82), 174 (93).

2',3',4',5'-Tetrafluoro-6'-nitro-biphenyl-4-carbonitrile 105. 4-(5,5-Dimethyl-[1,3,2]dioxaborinan-2-yl)-benzonitrile (0.50 g, 2.18 mmol) furnished the biphenyl (0.37 g, 57%) as a yellow solid, mp 91.5-93.0 °C (Found: C, 52.51; H, 1.31; N, 9.27. $C_{13}H_4F_4N_2O_2$ requires C, 52.72; H, 1.36; N, 9.46%); δ_H 7.39 (2H, m, Ar-C*H*), 7.71 (2H, m, Ar-C*H*); δ_C 114.43 (s, 1 or 4-*C*), 117.81 (s, 1 or 4-*C*), 119.08 (dd, $^{2}J_{CF}$ 18.2, $^{3}J_{CF}$ 4.3, 1'-*C*), 130.07 (s, 2 or 3-*C*), 131.49 (s, *C*N), 132.94 (s, 2 or 3-*C*), 135.16 (m, 6'-*C*), 140.79 (dddd, $^{1}J_{CF}$ 260.9, $^{2}J_{CF}$ 14.8, $^{2}J_{CF}$ 13.4, $^{3}J_{CF}$ 3.8, 3' or 4'-*C*), 141.26 (dddd, $^{1}J_{CF}$ 261.6, $^{2}J_{CF}$ 13.3, $^{3}J_{CF}$ 4.8, $^{4}J_{CF}$ 2.4, 2' or 5'-*C*), 142.84 (dddd, $^{1}J_{CF}$ 262.1, $^{2}J_{CF}$ 17.2, $^{2}J_{CF}$ 12.4, $^{3}J_{CF}$ 3.3, 3' or 4'-*C*), 144.53 (dddd, $^{1}J_{CF}$ 252.7, $^{2}J_{CF}$ 11.3, $^{3}J_{CF}$ 4.3, $^{4}J_{CF}$ 2.1, 2' or 5'-*C*); δ_F -137.39 (ddd, $^{3}J_{FF}$ 22.0, $^{5}J_{FF}$ 10.8, $^{4}J_{FF}$ 4.6, 2' or 5'-C*F*), -146.05 (ddd, $^{3}J_{FF}$ 21.3, $^{5}J_{FF}$ 10.6, $^{4}J_{FF}$ 6.1, 2' or 5'-C*F*), -148.19 (ddd, $^{3}J_{FF}$ 21.9, $^{3}J_{FF}$ 20.4, $^{4}J_{FF}$ 6.1, 3' or 4'-C*F*), -150.27 (ddd, $^{3}J_{FF}$ 21.5, $^{3}J_{FF}$ 20.4, $^{4}J_{FF}$ 4.7, 3' or 4'-C*F*); *m/z* (EI^{+}) 296 (M^{+}, 30%), 268 (52), 249 (57), 240 (52), 231 (37), 212 (38), 211 (51), 200 (61), 123 (35), 30 (100).

2,3,4-Trifluoro-4'-methyl-6-nitro-biphenyl 106. 5,5-Dimethyl-2-*p*-tolyl-[1,3,2]dioxaborinane (0.50 g, 2.45 mmol) furnished the biphenyl (0.38 g, 58%) as a yellow solid, mp 62.0-63.5 °C (Found: C, 58.48; H, 3.02; N, 5.24. $C_{13}H_8F_3NO_2$ requires

C, 58.43; H, 3.02; N, 5.24%); δ_H 2.43 (3H, s, C*H*$_3$), 7.18 (2H, m, Ar'-C*H*), 7.29 (2H, m, Ar'-C*H*), 7.65 (1H, ddd, $^3J_{HF}$ 9.2, $^4J_{HF}$ 6.6, $^5J_{HF}$ 2.2, 5-C*H*); δ_C 21.47 (s, *C*H$_3$), 109.32 (dd, $^2J_{CF}$ 21.9, $^3J_{CF}$ 3.8, 5-*C*), 123.74 (dd, $^2J_{CF}$ 17.7, $^3J_{CF}$ 4.3, 1-*C*), 125.55 (s, 4'-*C*), 128.78 (s, 3'-*C*), 129.76 (s, 2'-*C*), 139.64 (s, 1'-*C*), 142.99 (ddd, $^1J_{CF}$ 260.2, $^2J_{CF}$ 16.8, $^2J_{CF}$ 14.8, 3-*C*), 144.11 (m, 6-*C*), 149.13 (ddd, $^1J_{CF}$ 252.0, $^2J_{CF}$ 10.5, $^3J_{CF}$ 3.9, 2 or 4-*C*), 149.39 (ddd, $^1J_{CF}$ 254.0, $^2J_{CF}$ 11.1, $^3J_{CF}$ 3.8, 2 or 4-*C*); δ_F -130.80 (ddd, $^3J_{FF}$ 21.4, $^4J_{FF}$ 7.4, $^5J_{HF}$ 2.5, 2-C*F*), -131.97 (ddd, $^3J_{FF}$ 20.6, $^3J_{HF}$ 9.0, $^4J_{FF}$ 7.3, 4-C*F*), -150.90 (ddd, $^3J_{FF}$ 21.5, $^3J_{FF}$ 21.0, $^4J_{HF}$ 6.6, 3-C*F*); *m/z* (EI$^+$) 267 (M$^+$, 46%), 224 (49), 222 (100), 219 (65), 210 (52), 206 (65), 201 (54), 188 (40), 183 (39), 169 (72).

5.4.1.2 Synthesis of 2,3,4,5-tetrafluoro-6-nitro-biphenyls from boronic acids

2,3,4,5-Tetrafluoro-4'-methoxy-6-nitro-biphenyl 107. 4-Methoxyphenylboronic acid (0.50 g, 3.29 mmol) furnished the biphenyl (0.66 g, 67%) as a yellow solid, mp 91.5-93.0 °C (Found: C, 51.87; H, 2.32; N, 4.63. $C_{13}H_7F_4NO_3$ requires C, 51.84; H, 2.34; N, 4.65%); δ_H 3.85 (3H, s, C*H*$_3$), 7.00 (2H, m, Ar'-C*H*), 7.26 (2H, m, Ar'-C*H*); δ_C 55.41 (s, *C*H$_3$), 114.77 (s, 2' or 3'-*C*), 118.57 (s, 1'-*C*), 120.77 (dd, $^2J_{CF}$ 18.8, $^3J_{CF}$ 4.3, 1-*C*), 130.47 (s, 2' or 3'-*C*), 135.65 (dm, $^2J_{CF}$ 11.3, 6-*C*), 139.80 (dddd, $^1J_{CF}$ 257.7, $^2J_{CF}$ 14.8, $^2J_{CF}$ 13.4, $^3J_{CF}$ 3.4, 3 or 4-*C*), 140.80 (dddd, $^1J_{CF}$ 259.1, $^2J_{CF}$ 13.4, $^3J_{CF}$ 5.0, $^4J_{CF}$ 2.8, 2 or 5-*C*), 142.60 (dddd, $^1J_{CF}$ 260.2, $^2J_{CF}$ 17.7, $^2J_{CF}$ 12.2, $^3J_{CF}$ 3.4, 3 or 4-*C*), 144.70 (dddd, $^1J_{CF}$ 250.5, $^2J_{CF}$ 10.8, $^3J_{CF}$ 3.8, $^4J_{CF}$ 1.9, 2 or 5-*C*), 161.07 (s, 4'-*C*); δ_F -138.50 (dd, $^3J_{FF}$ 22.9, $^5J_{FF}$ 10.6, 2 or 5-C*F*), -148.27 (ddd, $^3J_{FF}$ 21.4, $^5J_{FF}$ 10.7, $^4J_{FF}$ 4.6, 2 or 5-C*F*), -150.35 (ddd, $^3J_{FF}$ 22.9, $^3J_{FF}$ 19.6, $^4J_{FF}$ 4.6, 3 or 4-C*F*), -153.66 (ddd, $^3J_{FF}$ 23.7, $^3J_{FF}$ 20.6, $^4J_{FF}$ 3.1, 3 or 4-C*F*); *m/z* (EI$^+$) 301 (M$^+$, 99%), 256 (24), 240 (38), 212 (61), 211 (100), 202 (27), 200 (50), 193 (89), 69 (43), 30 (52).

2,3,4,5-Tetrafluoro-6-nitro-[1,1';4',1'']terphenyl 108. Biphenyl-4-ylboronic acid (0.50 g, 2.52 mmol) furnished the biphenyl (0.73 g, 83%) as an off-white solid, mp 143-144.5 °C (Found: C, 62.34; H, 2.86; N, 3.80. $C_{18}H_9F_4NO_2$ requires C, 62.26; H, 2.61; N, 4.03%); δ_H 7.42 (3H, m, 2'' and 4''-C*H*), 7.49 (2H, m, 3''-C*H*), 7.64 (2H, AA' of AA'BB',

Ar'-C*H*), 7.72 (2H, BB' of AA'BB', Ar'-C*H*); δ_C 120.69 (dd, $^2J_{CF}$ 18.6, $^3J_{CF}$ 3.8, 1-*C*), 125.52 (s, 1''-*C*), 127.32 (s, *C*H), 127.97 (s, *C*H), 128.17 (s, 4''-*C*), 129.08 (s, *C*H), 129.56 (s, *C*H), 135.59 (dm, $^2J_{CF}$ 10.1, 6-*C*), 139.90 (s, 1' or 4'-*C*), 140.11 (dddd, $^1J_{CF}$ 257.9, $^2J_{CF}$ 17.0, $^2J_{CF}$ 13.8, $^3J_{CF}$ 3.7, 3 or 4-*C*), 140.93 (dddm, $^1J_{CF}$ 256.8, $^2J_{CF}$ 12.4, $^3J_{CF}$ 4.6, 2 or 5-*C*), 142.68 (dddd, $^1J_{CF}$ 260.6, $^2J_{CF}$ 17.6, $^2J_{CF}$ 11.9, $^3J_{CF}$ 2.9, 3 or 4-*C*), 143.19 (s, 1' or 4'-*C*), 144.76 (ddm, $^1J_{CF}$ 247.3, $^2J_{CF}$ 11.1, 2 or 5-*C*); δ_F -138.07 (ddd, $^3J_{FF}$ 22.3, $^5J_{FF}$ 10.7, $^4J_{FF}$ 3.3, 2 or 5-C*F*), -147.69 (ddd, $^3J_{FF}$ 21.5, $^5J_{FF}$ 10.7, $^4J_{FF}$ 5.0, 2 or 5-C*F*), -149.80 (ddd, $^3J_{FF}$ 20.6, $^3J_{FF}$ 20.6, $^4J_{FF}$ 5.0, 3 or 4-C*F*), -152.74 (ddd, $^3J_{FF}$ 23.9, $^3J_{FF}$ 21.4, $^4J_{FF}$ 3.5, 3 or 4-C*F*); *m/z* (EI^+) 347 (M^+, 100%), 302 (65), 300 (53), 290 (59), 280 (72), 269 (33), 251 (33), 115 (67), 102 (48), 77 (45).

6 Testing of Fluorinated Materials for LCD Devices

6.1 Introduction

Modern LCD technology places ever increasing demands on the LC materials found within them, and screens with high contrast ratios, that have wide viewing angles with no colour shifting or grey-scale inversion and show little 'blurring' with fast changing images are highly desirable. These qualities may be related to a number of physicochemical parameters of the LC materials that enable comparisons of their properties to be made. These specifications include, amongst others, the nematic phase range, nematic-isotropic transition temperature (T_{NI}), dielectric anisotropy ($\Delta\varepsilon$), rotational viscosity (γ), birefringence (Δn), and elastic constants (K_{11}, K_{22}, K_{33}).[1]

State-of-the-art LC materials used in display technologies still require development to achieve motion picture qualities that can compete with plasma or CRT displays.[114] Their switching times are slow in comparison and, therefore, there is a requirement for higher performance LC materials.

6.2 Physical and Material Property Requirements of LCs for Displays

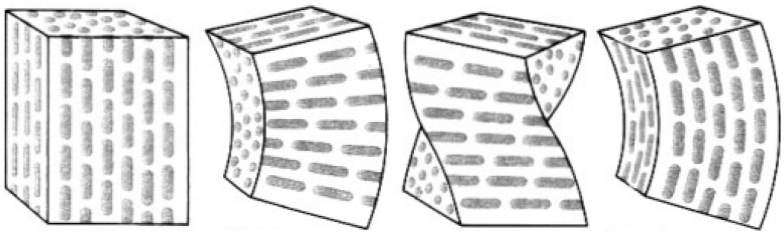
There are several physicochemical requirements that have to be met by LC materials for LCD applications. One of the most important is a broad nematic mesophase range, that is to say, the LC must maintain a stable nematic state in a wide temperature range. An LC must exhibit a dielectric anisotropy (the difference between the dielectric constants measured parallel and perpendicular to the director of the nematic phase) if it is to respond to an applied switching voltage. According to the Maier-Meier equation,[1] the dielectric anisotropy $\Delta\varepsilon$ may be correlated to the square of the dipole moment and to the angle between the dipole moment vector and the effective orientation axis of the

molecule, approximated as the 'long molecular axis' or defined as the rotation axis with the smallest moment of inertia.

The threshold voltage V_{th} (or the driving voltage) at which there is an electrooptical response in a dielectrically positive LC mixture in a TN display is dependent upon $\Delta\varepsilon$ and also K_{11}, K_{22}, K_{33} (Equation 1). These respectively describe the 'splay, twist and bend' elastic deformations (Figure 25) to the helical LC alignment under an applied electric or magnetic field, where K_{11} represents the most significant deformation for anti-parallel (AP) cells, K_{22} for twisted nematic (TN) cells and K_{33} for vertically aligned (VA) cells.

$$V_{th} = \pi\sqrt{\frac{K_{11} + \frac{(K_{33} - 2K_{22})}{4}}{\varepsilon_0 \Delta\varepsilon}} \cong \pi\sqrt{\frac{K_{11}}{\varepsilon_0 \Delta\varepsilon}}$$

Equation 1.[1]



equilibrium configuration | K_{11} (splay) | K_{22} (twist) | K_{33} (bend)

Figure 25.[6] Elastic deformations of calamitic, rod-like LCs in the nematic phase.

The contrast ratio, i.e. the ratio between the brightest and darkest states, of a normal TN mode display (90° twist, normally black mode with parallel polarisers) is dependent upon the birefringence, Δn, of the LC (the ordinary refractive index subtracted from the

extraordinary refractive index) and also the cell gap *d*. A good contrast ratio and the best viewing angle independence of the picture quality corresponds typically to a birefringence value of 0.0837 for a cell gap of 6 μm.[1]

One of the most crucial factors in determining whether an LC compound is selected for commercial use is based on the "reliability" of the material. This is a collective term for specifications of purity, long term chemical and photochemical stability and certain dielectric properties.

6.3 Improvement of Display Switching Times

The switching time of a LC cell may be improved by reducing both the rise time, τ_{rise}, and the decay time, τ_{decay}. Modern multimedia and video applications typically require a combined switching time τ ($\tau = \tau_{rise} + \tau_{decay}$) of less than 20-25ms (in 2000)[1]. τ_{decay} may be improved by decreasing γ or d (Equation 2).[115] Combining equations for τ_{rise} (Equation 3)[115] and the threshold electric field E_{th} (Equation 4)[116] yields a relationship showing that an increase in $\Delta\varepsilon$ or the applied field *E*, or a decrease in γ, will lead to an improvement in τ_{rise} (Equation 5).

$$\tau_{decay} = \frac{\gamma d^2}{K\pi^2}$$

Equation 2.[115] Decay time for LC cells

$$\tau_{rise} = \frac{\gamma}{\varepsilon_0 \Delta\varepsilon E^2 - \frac{\pi^2}{d^2} K}$$

Equation 3.[115] Rise time for LC cells

$$E_{th} = \frac{\pi}{d}\sqrt{\frac{K}{\varepsilon_o \Delta\varepsilon}}$$

Equation 4.[116] Threshold electric field

$$\tau_{rise} = \frac{\gamma}{\varepsilon_0 \Delta\varepsilon\left(E^2 - E_{th}^2\right)} \cong \frac{\gamma}{\Delta\varepsilon E^2}$$

Equation 5. Rise time for LC cells

The cells used for testing have the smallest cell gap that is practically feasible due to manufacturing limitations whilst, additionally, the applied field across the cell must be kept low to minimise power consumption of the device. Two variables which must therefore be considered in the design of LCs for fast switching displays are the rotational viscosity and dielectric anisotropy. Rotational viscosity is predominantly influenced by the length of the LC molecule and, therefore, tends to be smaller for shorter molecules with little or no branching, these materials having decreased Van der Waals interactions with neighbouring molecules. Heavy functionalisation of LC materials with highly polar groups such as fluorine introduces an inherent dipole moment and this increases the dielectric anisotropy.

6.4 A Doping Strategy for the Testing of New Fluorinated LCs

The complex property profile required for modern LC displays cannot be met by currently existing *single* nematic LC molecules. Most crucially a LC mixture that is nematic around room temperature must be produced and so, typically, 10-15 or more single substances are mixed in what has become a multidimensional optimization problem. New LC materials are commonly tested empirically by doping them into commercial LC blends and testing the mixtures in LC cells thereby establishing trends related to their structure. Alterations in chain length, fluorination patterns on the head-group and also substituting carbons for heteroatoms affect switching of the materials in the cells. Importantly, not every component of a LC mixture need exhibit a thermodynamically stable nematic phase and, therefore, advantageous properties of certain selected materials, such as those having a low rotational viscosity which might improve switching times, may be exploited through addition of the compound to a LC blend in low concentrations.

With this in mind we set about reducing the switching time of two commercially available LC mixtures, one dielectrically negative and one dielectrically positive,

following a ‘dopant strategy’ in which the fluorinated materials synthesised in the preceding chapters were added to the commercially sourced LC blends. The introduction of anisotropic dopant materials into the LC blend may, however, alter other important properties such as the T_{NI} of the blend, the birefringence or the alignment of the LCs, which consequently alters black levels (the percentage light transmission in the “black” state) and, therefore, the contrast of the cell. Providing these properties are not affected unfavourably, up to approximately 10% wt. dopant by weight may be added. A target has been set for material switching times of less than 1 ms to compete with displays that are likely be available on the market in just a few years time.

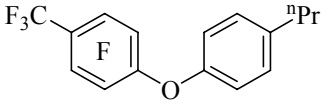
6.5 Relationships of Dopant Structure to the Switching Times of LC Blends

It is very difficult to predict the behaviour of new fluorinated LC materials within bulk LC blends. Computational chemistry is currently limited to calculating molecular geometries or other parameters such as dielectric and optical anisotropies of isolated molecules in the gas phase, whereas modelling of molecular ensembles requires substantial simplifications at the level of the individual molecule due to the enormous computational expense.[1] Simplistic predictions of the behaviour or properties of some LCs can be made through consideration of their structure. An increase in the dielectric anisotropy can be brought about by the introduction of stronger polar terminal substituents, or less obviously, the formation of smectic phases may be suppressed through lateral fluorination. Rotational viscosities, elastic constants or the nature and range of LC mesophases are related in an indistinct and unpredictable manner to molecular structures, and for that reason empirical methods are usually the only accurate way to establish structure-property relationships.

Geometry optimised structures of the trifluoro(4-pentyl-phenoxy)-benzenes **48**, **49** and **50** (Figure 26) are shown below (Figure 27) and are based on DFT calculations performed by P. Kilickiran at SONY MSL, Stuttgart, using Accelrys Materials Studio Modeling 4

software, DMol3 program.[114] Compound **48**, derived from the 1,2-dibromotetrafluorobenzene scaffold, has the smallest angle between the benzene rings with a C-O-C angle of 122.2° (Table 27). Materials **49** and **50** only have one fluorine atom *ortho* to the bridging oxygen and therefore have a larger C-O-C angle of 125.5°.

Figure 26. Materials synthesised in chapters 3-4, tested as dopants



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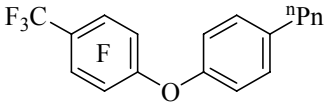

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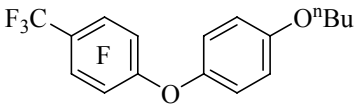

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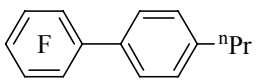

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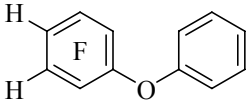

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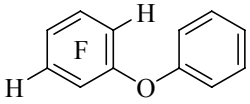

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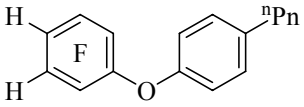

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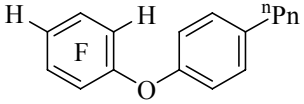

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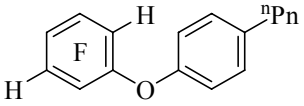

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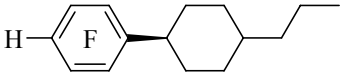

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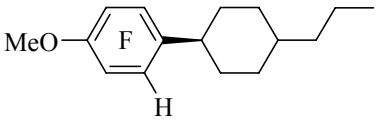

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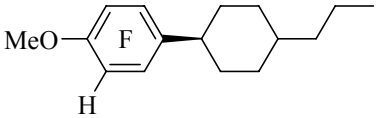

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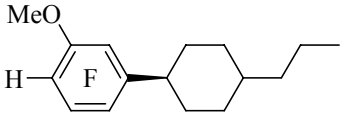

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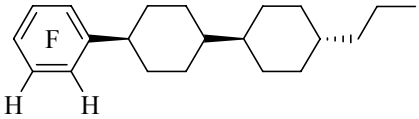

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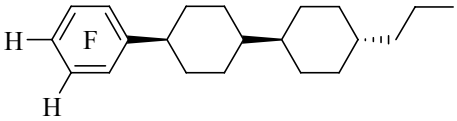

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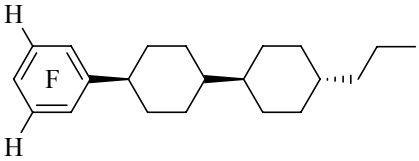

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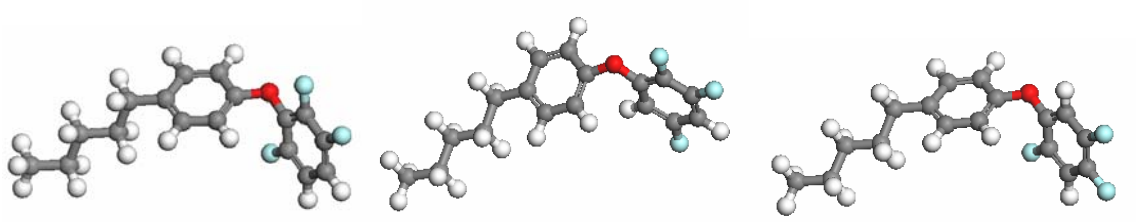


48 **49** **50**

Figure 27.[114] Molecular modelling of three trifluoro(4-pentyl-phenoxy)-benzenes

Table 27.[114] Dipole vector moments of trifluoro(4-pentyl-phenoxy)-benzenes showing the degree of planarity between the benzene rings

Fluorinated material	dipole moment vector /au			dipole magnitude /au	angle between phenyl rings /°
48	-3.09137	2.31190	0.01435	3.86027	122.2
49	-0.60715	0.93529	0.38090	1.17834	125.5
50	-1.97722	1.64396	0.03019	2.57156	125.5

Compounds based on the fluoro(phenoxy)-benzene scaffold are, therefore, non-planar and we propose that doping of these materials into the LC blend changes the bulk organisation by penetrating between the LC molecules, keeping individual molecules slightly apart without disturbing their orientation parallel to the longitudinal axes of the adjacent molecules (Figure 28). Increasing the distance between molecules in the blend decreases the Van der Waals interactions[1] and hence the viscosity of the LC mixtures, consequently improving switching times.

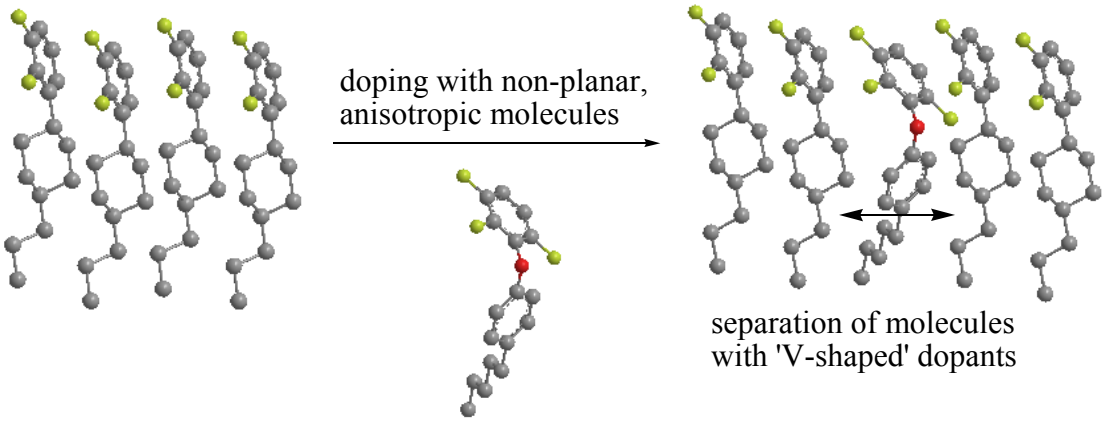


Figure 28.[114] Doping of commercial LC blends with trifluoro(phenoxy)-benzenes

Material **48** will separate adjacent molecules in the LC blend more so than the less 'V-shaped' materials **49** and **50** and when added to an LC blend we postulate that it would show a greater improvement in response times. Similarly, **45** would be expected to be faster than **47** having an analogous structure to **48**, but bearing no pentyl tail-group these two materials might improve switching times to a greater degree due to smaller inter-molecular interactions.

Compounds based on the 1,2,4,5-tetrafluoro-3-(4-alkyl-phenoxy)-6-trifluoromethyl-benzene moiety, namely **31**, **32** and **33**, which are also likely to have an angle close to 122.2º between the aromatic rings, also benefit from the large dipole of the trifluoromethyl group although this may be sterically hindering. Effects of different tail-groups on these materials upon the switching times were to be investigated, such as variation in length through the incorporation of propyl and pentyl groups (**31** and **32** respectively), and changes in 'flexibility' through the inclusion of a butoxy group (**33**). Reasoning for the use of fluorine as opposed to any other halogen on the phenoxybenzene scaffold was found in a comparison of 1-(4-fluorophenoxy)benzene against its chlorinated and brominated analogues[114] which showed that this material improved rise times more than the related materials, most likely due to the stronger dipole induced by the fluorine atom and also because this element is less sterically demanding.

Materials based on the 4'-propyl-4-(trifluoro-phenyl)-bicyclohexyl scaffold, namely **92**, **93** and **94**, have been reported as having low rotational viscosities.[108] Decreasing intermolecular interactions by shortening the length of these rod-like molecules and adding another fluorine atom on the headgroup to strengthen the dipole gives materials based upon the tetrafluoro-(4-propylcyclohexyl)benzene unit, such as **86**. Variations upon this compound include **39** whereupon the cyclohexyl unit is replaced with a second aromatic ring, and the trifluoro-methoxy-(4-propyl-cyclohexyl)-benzenes **88**, **89** and **90**, for which methoxy groups have been introduced into the head-group.

6.6 Testing of the Dopant Materials

6.6.1 Preparation of the Doped LC Blends

LC mixtures (200 mg) were made up for each of the fluorinated materials as a percentage by weight solution (typically 0, 1, 2, 4 and 6%) in a commercially available dielectrically positive or dielectrically negative LC blend. The blends were stirred for an hour at 60ºC and placed under vacuum for one hour to remove any air bubbles.

6.6.2 DSC – T_{NI} Analysis

DSC analysis of the fluorophenoxybenzene materials was performed to determine whether doping of these materials would have any detrimental affect on the clearing temperature of the commercially available LC blends. A large reduction of T_{NI}, measured as 79.8 °C for the standard dielectrically negative blend, could render the mixture useless for LCD applications as the backlights of displays warm LC materials well above ambient temperature.

DSC analysis for each fluorinated material was performed on a Netzsch DSC 204 calorimeter linked to a Task 414/4 controller, a CC200L controller and a CC200 liquid nitrogen supply system. The samples for analysis were weighed on a Netzsch TG209C balance. Netzsch Measurement and Netzsch Proteus-Thermal Analysis (Versions 4.2) software was used with three cycles from -100ºC to 150ºC performed for each sample at a rate of 10ºC min^{-1}.

Deviations for nematic LC molecules from a linear structure towards a bent arrangement qualitatively result in a decrease of the clearing temperatures[1] and as expected materials **45** and **47** both reduced the clearing temperature by 3.2 °C per percent of dopant added to the commercially sourced dielectrically negative LC blend (Table 28). Materials **32** and **31** reduce the clearing temperature by only 2.6 °C, as the inclusion of a trifluoromethyl group onto one phenyl ring and an alkyl group (a pentyl or a propyl group respectively) onto the other gives comparably larger and more rod-like molecules. These are likely to be more similar in terms of length to the compounds found in the pure LC blend and are therefore less likely to perturb phase transformations and the DSC profile of the LC mixture. An even smaller perturbation of the clearing temperature is observed for material **33** for which one carbon atom of the pentyl group has been substituted for oxygen. This functionality may provide the tail of the molecule with more rotational freedom which does not break up the order of the nematic system as much as the other materials.

Table 28. Alteration of clearing temperature with addition of dopant material to commercially sourced dielectrically negative LC blend

material	ΔT_{NI} per % dopant material added /ºC	appendix
31	-2.6	Graph 1
32	-2.6	Graph 2
33	-2.1	Graph 3
45	-3.2	Graph 4
47	-3.2	Graph 5

material	ΔT_{NI} per % dopant material added /ºC	appendix
48	-2.8	Graph 6
49	-2.7	Graph 7
50	-2.1	Graph 8

6.6.2.1 Conclusion

The addition of 'short' trifluorophenoxybenzene dopants to commercially sourced dielectrically negative LC blend decreases their clearing temperature by 3.2 ºC per percent of material added. 'Longer' dopants based on the fluorophenoxybenzene scaffold bearing alkyl chains on the tail-group have less of an impact, decreasing T_{NI} by 2.1 to 2.8 ºC.

6.6.3 Fabrication and Filling of the LC Cells

VA and TN cells were obtained from E.H.C. Co. Ltd. and were used for electro-optical measurements. The cells used were of 5μm or 10 μm cell-gap respectively and are lined with an indium tin oxide (ITO) electrode (10×10 mm). VA cells with a homeotropic cetyltrimethylammonium bromide (CTAB) alignment layer were used initially but were later substituted for cells coated with a polyimide alignment layer. The CTAB salt layer was prone to decomposition upon exposure to moisture, which is likely to have occurred during transport, and so, despite storage in an atmosphere of nitrogen, filling of the LC materials often resulted in poor alignment after and subsequent crystal formation. TN cells with a polyimide alignment layer were used throughout. Cells of a homogeneous thickness were selected by observation of the interference fringes under an Opus Metrology sodium monochromatic light source.

VA cells with a silicon dioxide alignment layer were fabricated to provide a replacement for the commercially available problematic CTAB lined VA cells. Glass slides (24×24 mm) lined with an ITO layer were firstly plasma cleaned using a Gala Instrumente Plasma Prep 5 instrument. This treatment has the added benefit of making the glass slides hydrophobic. A silicon dioxide alignment layer was then evaporated onto the ITO layer using an ULVAC ei-6 unit. The SiO_2 is coated onto the slides at a specified angle and thickness. The two glass slides for each cell were glued together with an epoxy resin containing 5.7 μm polystyrene spacers, the gap between the slides was adjusted by applying pressure to them whilst observing the interference fringes under a monochromatic light source and the glue cured under a UV lamp.

The cells were placed on a hotplate at 60ºC and filled with the LC materials by capillary action. The cells were annealed for two hours in an oven at 90ºC, ten degrees higher than the T_{NI} of the LC blend, and then left to cool slowly to room temperature. The cells were sealed with UHU Hart glue, and the cell gap was measured. This was necessary as the actual cell gap following filling can be smaller or bigger than the desired cell gap, caused by the pressure applied during assembly, curing of the sealing glue of the cells, capillary forces during the filling, dust particles, spacer concentration, etc. A Varian Cary 50 Scan UV-Visible Spectrophotometer was used for this measurement scanning from 500 to 400 nm. Positive LC mixtures in TN cells and SiO_2 cells required switching with 20V supplied from a TTi TGA 1242 40MHz Arbitrary Waveform Generator whilst the cell gap of each cell was measured, without which the light would not pass through the cell. Cell gaps were calculated from Equation 6,[117] where the integer x is the number of consecutive maxima between wavelengths λ_1 and λ_2 and n is the refractive index of the cell.

$$d = \frac{x\lambda_1\lambda_2}{10^3 n 2(\lambda_2 - \lambda_1)}$$

Equation 6.[117] Method for measuring the cell gap of an LC cell.

Two wires were glued onto the two sides of the cells with UHU Hart glue, and the tips painted onto the electrodes with silver paint for the commercial cells and soldered for the in-house fabricated cells, to ensure a good electrical contact (Figure 29).

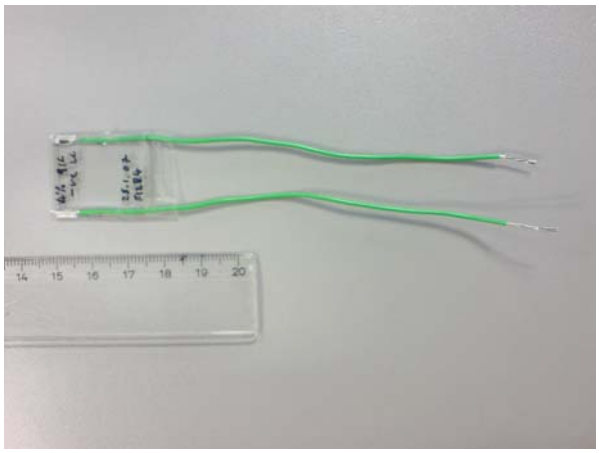


Figure 29. A fully assembled cell filled with fluorinated LC material

6.6.4 VHR – Purity and Reliability Analysis

The VHR (voltage holding ratio) of a cell is defined as the fraction of voltage remaining over a cell after a defined discharge time. A value of 100% is therefore desirable, but decreases when either the resistivity of the LC material or the capacitance of this layer changes. The measurement indicates the amount of charge 'leakage' through the cell which occurs due to the presence of impurities in the LC materials, especially ionic contaminants, and as such is a good method to determine the purity of a blend for LCD applications. VHRs for all cells were recorded at 35ºC using a Toyo Corp. LCM-1 LC Material Characteristics Measurement System.

Results from electro-optical testing of a cell showing a VHR of less than 95% were deemed unreliable, however most cells tested were found to be within acceptable limits.

6.6.5 Electro-optical Testing in VA and TN Cells – Switching Time Analysis

6.6.5.1 General Approach

Electro-optical tests were performed[v] on all the fluorinated LC dopants synthesised for which enough material was available in a study of their rise and decay times. Analysis of the materials was qualitative rather than quantitative, or more specifically their properties could only be compared against each other by performing a continuous series of tests within the shortest time possible (1-3 days), on a batch of cells each made up at the same time using cells of the same manufacturer's batch number with the materials selected for analysis. Property comparisons could not be drawn from different batches as this ensured that the number of potential variables was kept to a minimum.

One batch of cells was typically made up to compare either one material of several concentrations (typically 0, 1, 2, 4 and 6% solutions) against the pure undoped LC blend, or several materials of one or two concentrations (typically 2 or 4% solutions) against the pure undoped material. Three cells were made for every concentration of each solution as problems were often encountered with the cells such as crystallisation of material within them, trapped air bubbles and also with the reliability of comparisons as explained in the results section.

6.6.5.2 Experimental Apparatus and Testing Program

The liquid crystal cells were placed on a Linkam LTS 350 stage linked to a Linkam TMS 94 temperature controller and heated to 35ºC and the switching of the cells was powered by a Laboratory Power Supply PS-2403D. The transmission profiles of the cells were measured under a Leica DMRX confocal polarising microscope, between crossed

[v] All apparatus used and measurements made were performed in the SONY MSL laboratories in Stuttgart, Germany

polarisers for the VA cells and parallel polarisers for the TN cells (so the cells appear black in the off mode), and the switching controlled by in-house software.

To measure decay times of an LC material the software initially calculates values for V_{10} to V_{90}, the voltages for which 10 and 90% light transmission between T_{off} and T_{max} is detected through the cell. The program then measures decay times for the single LC material in the cell. To compare decay times of different solutions of fluorinated materials the applied voltage (nine values in equal increments from V_{10} to V_{90}, units V_{pg}) was plotted against the normalised decay time (units ms/μm^2).

When recording rise times of an LC material the program takes account of the cell gap and so applied field values E_{10} to E_{90} are calculated, where each value is equal to the respective voltage V_{10} to V_{90} divided by the cell gap d. The program then measures rise times for the single LC material in the cell. To compare rise times of different solutions of fluorinated materials the averaged field strength (nine calculated values in equal increments from E_{10} to $E_{90,}$ units V/μm) was plotted against the rise time (units ms).

6.6.5.3 Electro-Optical Response Time Measurement Results of Dopant Testing

The results of electro-optical testing presented here are qualitative rather than quantitative as explained previously and so the effects on decay and rise times in doping individual materials into negative and positive LC blends have been compared in this manner. Where comparisons have been made for several materials against the rise and decay times of pure negative and positive LC blends the compounds have been listed in order of decreasing speed, where '=' denotes a roughly similar speed and '<' may be translated as 'is faster than'.

Once the cells had been filled with material during fabrication, the resulting cell gaps were not the same for all cells. Only cells of a similar thickness (±1 μm where possible)

could be selected and compared because thicker cells give faster decay and rise times. Trend lines on plots of decay time with similar V_{10} to V_{90} values and plots of rise time with similar E_{10} and E_{90} values can also only be compared reliably against each other, and so for batches consisting of many fabricated cells many results were rejected in order that reliable material comparisons be made. It is important to note that a large number of variables exist when fabricating and testing cells containing the fluorinated materials; these have been controlled to the best of our ability but early attempts may have produced less reliable results. There is likely to be greater experimental error within these than in later experiments when methods were more robust, an example being the replacement of the CTAB alignment layer with polyimide in the VA cells.

6.6.5.3.1 Dopants in Dielectrically Negative Blends Tested in VA Cells

6.6.5.3.1.1 Decay Times

Doping of fluoro-phenoxy-benzenes in dielectrically negative LC blends in VA cells generally made decay times slower (Table 29), apart from trifluoromethylphenoxybenzene **32** added in low concentrations (1 or 2%).

Following the testing of each dopant the data in most cases suggested that doping results in an increase in normalised decay times from V_{10} to V_{90}, for example for material **50** in Figure 40, however, the V_{10} to V_{90} values are often lower than for the pure material potentially leading to unreliable comparisons.

Table 29. Effect of individual dopants on decay times in VA CTAB cells

dopant	effect on decay time compared to pure undoped blend	appendix
33	large increase	Figure 37
32	decrease in low concentration, increase in high concentration	Figure 38
31	increase	Figure 39
50	large increase at lower $V_{10\text{-}90}$	Figure 40
49	increase at lower $V_{10\text{-}90}$	Figure 41
48	large increase at lower $V_{10\text{-}90}$	Figure 42
45	large increase*	Figure 43
47	increase*	Figure 44

*could be unreliable results due to problems with CTAB alignment layer leading to crystal growth within the cell

Comparisons in performance of these and other materials against each other (Table 30) again show that doping with these compounds in dielectrically negative LC blends increases the decay time in almost all cases, although the trifluoro-methoxy-(4-propyl-cyclohexyl)-benzene **89** and the trifluorophenoxybenzene **47** appear to have little effect. The true effect of materials based on the fluoro-(4-propylcyclohexyl)benzene scaffold (**86**, **89**, **90**, **88**) cannot be reliably interpreted as they were tested as mixtures of configurational isomers (see section 4.2.3). Introduction of larger more bulky groups (R = H, Pr, BuO, Pn successively) onto the fluoro-phenoxy-benzene scaffold inhibits the switching of the LC blends probably due to increased Van der Waals interactions between neighbouring molecules, illustrated by the series of materials in Figure 46.

Table 30. Comparison of the effects of dopants on decay times in VA cells

dopants	alignment layer	decay time compared to pure undoped blend	appendix
39, **89**, **90**	CTAB	pure = **89** < **39** < **90**	Figure 45
31, **32**, **33**, 4-FPhOPh[vi]	CTAB	pure < 4-FPhOPh < **31** < **33** < **32**	Figure 46
45, **47**, **48**, **50**	CTAB	pure = **47** < **50** < **45** < **48**	Figure 47
86, **88**	polyimide	pure < **88** = **86**	Figure 48
92, **93**, **94**	polyimide	pure < **94** < **93** < **92**	Figure 49

Generally, addition of dopants to dielectrically negative blends in CTAB or polyimide VA cells had no beneficial effects on decay times, apart from for fluorophenoxybenzene **32** for which a decrease in decay time was observed when added in low concentration.

6.6.5.3.1.2 Rise Times

Doping the dielectrically negative blend with all materials based on the fluoro-biphenyl-ether scaffold showed improvements (Table 31) in the rise time (e.g. Figure 57), and may show that the LC blends respond to reduced applied field strengths (e.g. Figure 55), or both (e.g. Figure 51). As with graphs for electro-optical testing results of decay times this provides difficulties when comparing data for materials having different E_{10} to E_{90} values. There was a marked effect with compounds **48**, **49** and **50**, and an even greater improvement with the analogous materials **45** and **47**. Bearing no pentyl tail-group, these latter compounds may benefit from decreased Van der Waals interactions.

[vi] Obtained commercially

Table 31. Effect of individual dopants on rise times in VA CTAB cells

dopant	effect on rise time compared to pure undoped blend	appendix
33	decrease at lower $E_{10\text{-}90}$	Figure 50
32	decrease at lower $E_{10\text{-}90}$	Figure 51
31	little or no change/decrease	Figure 52
50	increase at lower $E_{10\text{-}90}$	Figure 53
49	increase at lower $E_{10\text{-}90}$	Figure 54
48	little or no change at lower $E_{10\text{-}90}$	Figure 55
45	large decrease*	Figure 56
47	large decrease*	Figure 57

*could be unreliable results due to problems with CTAB alignment layer leading to crystal formation within the cell

A comparison of the effects of the materials **39**, **89** and **90** on rise times in VA cells was inconclusive (Table 32) possibly due to a faulty batch of cells. Two 2% solutions of **90** in the dielectrically negative blend produced results which suggested that in one case doping with this material increased the switching time whilst in the other decreased it. Fluorinated biphenyl ether derivatives again showed an improvement in the switching time with the commercially available 1-(4-fluorophenoxy)benzene showing a greater improvement in the response time than materials **31**, **32** and **33**. Materials **45** and **47** increased the switching time more than **48** and **50**, which in turn both showed an improvement over the pure blend. The tetrafluoro-(4-propylcyclohexyl)benzene **86** and the trifluoro-methoxy-(4-propyl-cyclohexyl)-benzene **88** both improve the rise times, whilst the longer more rod-like 4'-propyl-4-(trifluoro-phenyl)-bicyclohexyl materials are all marginally inhibiting.

Table 32. Comparison of the effects of dopants on rise times in VA cells

dopants	alignment layer	rise time compared to pure undoped blend	appendix
39, **89**, **90**	CTAB	inconclusive	Figure 58
31, **32**, **33**, 4-FPhOPh	CTAB	4-FPhOPh < **32** = **33** = **31** < pure	Figure 59
45, **47**, **48**, **50**	CTAB	**45** < **47** = **48** = **50** < pure	Figure 60
86, **88**	polyimide	**86** = **88** < pure	Figure 61
92, **93**, **94**	polyimide	pure < **92** = **93** = **94**	Figure 62

To summarise, for doping of materials into dielectrically negative blends tested in CTAB and polyimide VA cells, appreciable reductions in rise times were observed with 4-fluorophenoxy benzene, but even more so with trifluorophenoxybenzenes **45** and **47**. Trifluorophenoxybenzene **48** greatly reduced the field required to switch the LC blend. These promising results[118] may be of value for the development of fast LC displays.

6.6.5.3.2 Dopants in Dielectrically Positive Blends Tested in TN Cells

6.6.5.3.2.1 Decay Times

Results of electro-optical testing in TN cells for materials doped into dielectrically positive blends were very similar to results for testing of dielectrically negative blends in VA cells. The trifluoro(4-pentyl-phenoxy)-benzenes **48** and **49** slowed down the decay time (Table 33), and interestingly **48** again had a greater effect.

Table 33. Effect of individual dopants on decay times in TN polyimide cells

dopant	effect on decay time compared to pure undoped blend	appendix
48	large increase at lower $V_{10\text{-}90}$	Figure 63
49	increase at lower $V_{10\text{-}90}$	Figure 64

All materials apart from **39** inhibited the switching time (Table 34) as found for testing in dielectrically negative blends. This dielectrically positive material improved the decay time of the cell when introduced into the LC blend as a 2% solution. The materials based on the 1,2,4,5-tetrafluoro-3-(4-alkyl-phenoxy)-6-trifluoromethyl-benzene scaffold in Figure 66 appear in the same order as when tested in dielectrically negative blends, whilst those based on trifluoro-phenoxy-benzene in Figure 67 all have roughly the same effect on the decay time. The dielectrically positive compound 4-FPhOPh does not inhibit the switching of the LC blend as much as the dielectrically negative compound 2-FPhOPh. The family of 4'-propyl-4-(trifluoro-phenyl)-bicyclohexyl materials had little effect on the decay times, and perhaps even show a slight improvement (Figure 69).

Table 34. Comparison of the effects of dopants on decay times in TN polyimide cells

dopants	decay time compared to pure undoped blend	appendix
86, **88**, **39**, **89**	**39** < pure < **86** = **88** = **89**	Figure 65
31, **32**, **33**	pure < **31** < **33** < **32**	Figure 66
45, **47**, **48**, **49**, **50**	pure < **45** = **50** = **49** < **47** < **48**	Figure 67
31, **32**, **33**, **45**, **47**, **48**, **49**, **50**, 2/4-FPhOPh[vii]	pure = 4-FPhOPh < **45** < **50** = **32** < 2-FPhOPh = **49** = **48** < **31** < **33** = **47**	Figure 68
93, **94**, **92**	pure = **93** = **94** = **92**	Figure 69

[vii] Obtained commercially

To conclude, as for dopants tested in dielectrically negative LC blends (6.6.5.3.1.1), addition of the materials to dielectrically positive LC blends in TN cells showed no beneficial effects apart from fluoro-4'-propylbiphenyl **39** which slightly reduced the decay time**.**

6.6.5.3.2.2 Rise Times

Table 35 and Table 36 show that all the fluorinated materials tested in TN cells improved the rise times when doped into dielectrically positive LC blends apart from the 4'-propyl-4-(trifluoro-phenyl)-bicyclohexyls **92**, **93** and **94** (Figure 76). The dielectrically positive fluoro-4'-propyl-biphenyl material **39** improved rise times more so than the fluoro-(4-propyl-cyclohexyl)-benzenes **86**, **88** and **89**. The series of related fluoro-phenoxy-benzenes again showed promise with materials **45** and **48** proving to be the fastest. It is interesting to note that these materials have the same fluorination pattern on the headgroup.

The performance of 2-FPhOPh and 4-FPhOPh is reversed in comparison to the decay time testing; here, 2-FPhOPh is observed to be faster. A fluorine atom placed in the *para* position, aligning the dipole of the carbon-fluorine bond closer to the long molecular axis of the rod-like molecule, will experience a greater torque under a perpendicularly applied field that one placed *ortho* to the bridging oxygen. 4-FPhOPh would therefore be expected to show a greater effect, be it detrimental or beneficial, to the switching of the dielectrically positive LC blend, assuming the long molecular axis is aligned parallel to all other molecules in the LC blend.

Table 35. Effect of individual dopants on rise times in TN polyimide cells

dopant	effect on rise time compared to pure undoped blend	appendix
48	little change at lower $E_{10\text{-}90}$	Figure 70
49	little change at lower $E_{10\text{-}90}$	Figure 71

Table 36. Comparison of the effects of dopants on rise times in TN polyimide cells

dopants	rise time compared to pure undoped blend	appendix
39, **86**, **88**, **89**	**39** < **88** < **86** < **89** < pure	Figure 72
31, **32**, **33**	**31** < **33** < **32** = pure	Figure 73
45, **47**, **48**, **50**, **49**	**48** < **45** = **49** < **47** = **50** < pure	Figure 74
31, **32**, **33**, **45**, **47**, **48**, **49**, **50**, 4/2-FPhOPh	**48** < **45** = **47** = **33** = **31** = 2-FPhOPh < **50** = **49** = **32** = 4-FPhOPh < pure	Figure 75
92, **93**, **94**	pure < **93** = **94** = **92**	Figure 76

In conclusion, most of the materials doped into dielectrically negative LC blends and tested in TN cells showed a slight reduction in the field required to switch the materials, apart from the larger trifluorobicyclohexylbenzenes **92**, **93**, **94**. The trifluorophenoxybenzene **48** was perhaps the best performing material, even outperforming materials **45** and **47** which showed very positive results when tested in dielectrically negative materials (6.6.5.3.1.2).

6.6.6 Measurement of Black Levels, Rotational Viscosity and Elastic Constants

Black levels following doping of phenoxybenzene derivatives into the LC blends have been studied[114, 116] and remain largely unaffected. Had this not been the case use of these

compounds in LC displays may have resulted in a loss of contrast (the difference in light levels when the LC cells are switched fully off and fully on).

6.7 Conclusion

Decay times for LC materials tested in VA cells were of the order of 10-30 ms whilst rise times were in the range of 200-1600 ms. Similarly, decay times measured in TN cells were approximately 30-80 ms whilst rise times were of the order of 200-900 ms. In mobile devices, for which you cannot apply a very high voltage, reduction of the rise time is clearly the most important factor in achieving the largest possible improvement in the overall switching time τ (where $\tau = \tau_{rise} + \tau_{decay}$). In larger devices, such as LCD TVs, you can apply high voltages and the rise times will be very fast accordingly. Decay times are independent of the the applied voltage and so for TV applications or in general for devices where we are not limited with the applied voltage, we need to reduce the decay time in order to get a very fast overall response.

Most of the fluorinated dopant materials tested reduced the rise times or reduced the voltage required to switch the dielectrically negative blends tested in VA cells, and the positive blends tested in TN cells. The combined improvements observed outweigh the negligible detrimental effects to decay times in both types of cell.

The most notable improvement in performance was achieved for rise times measured in VA and TN cells, doped with the fluorinated non-planar aromatic dopants **45**, **47** and **48**. The former two greatly improved response times and the latter decreased switching voltages, potentially lending to faster switching and lower power consumption of LCD devices. The success of materials **45** and **48** could be attributed to the strength of their dipole rather than due to their geometry, as out of the three trifluoro(4-pentyl-phenoxy)-benzene isomers material **48** not only has the smallest angle between the aromatic rings

but also the largest dipole (Table 27). The dependency of switching behaviour upon different fluorinated aromatic substitution patterns is currently being investigated.[114]

No significant changes to the off state transmittances were observed and, therefore, no alignment layer modification will be required. VHRs remain undisturbed also, whilst the undesirable reduction in the clearing temperatures of the commercial LC mixtures with the addition of these new fluorinated dopants remains an issue.

The improvement of results in switching time after addition of our fluorinated dopants to commercial LC blends has been patented[118] by SONY/Durham and initial results have been published at major LC display conferences.

7 Appendix

7.1 1D and 2D NMR Spectra of Material 86

Figure 30. ^{13}C NMR spectrum

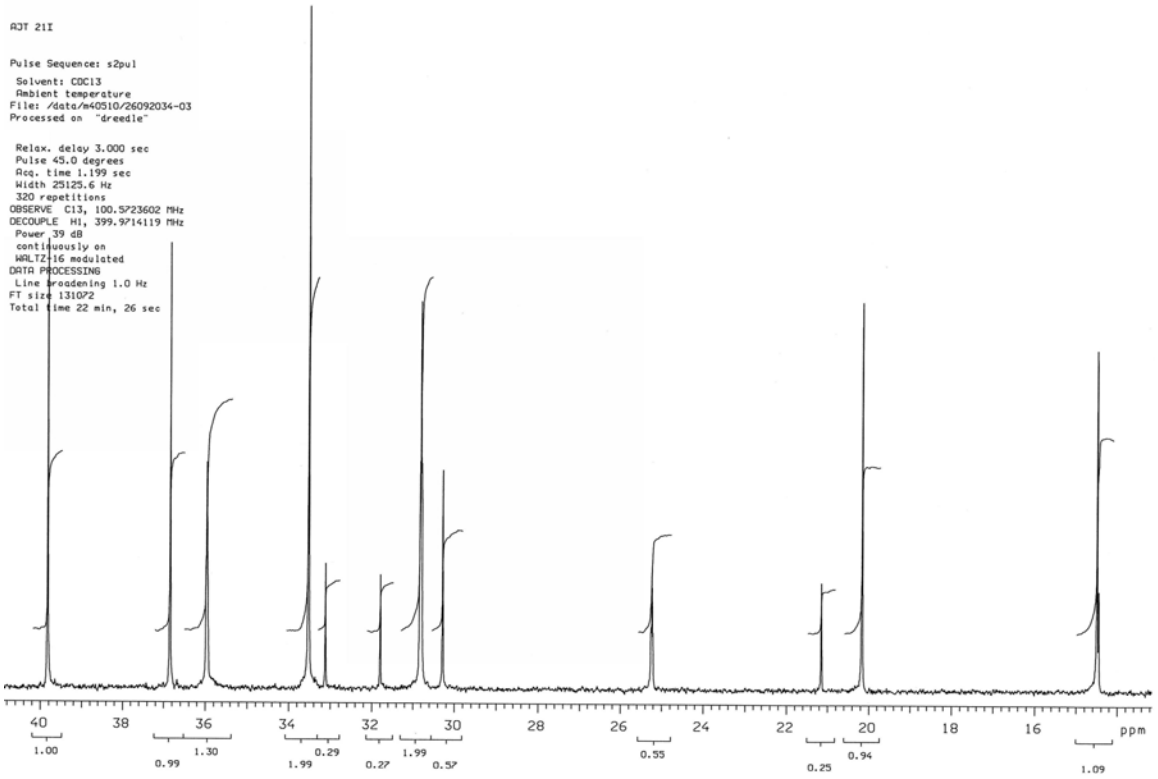


Figure 31. ^{1}H NMR spectrum

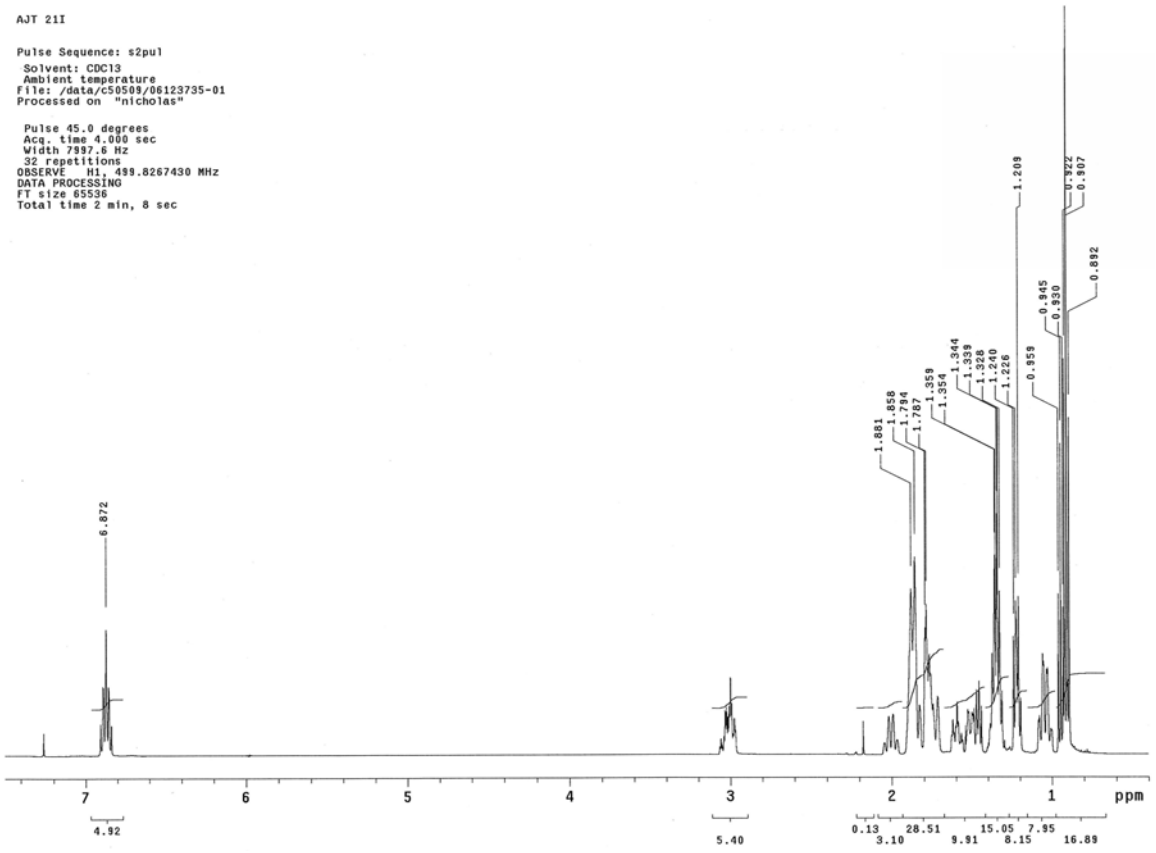


Figure 32. HMBC NMR spectrum

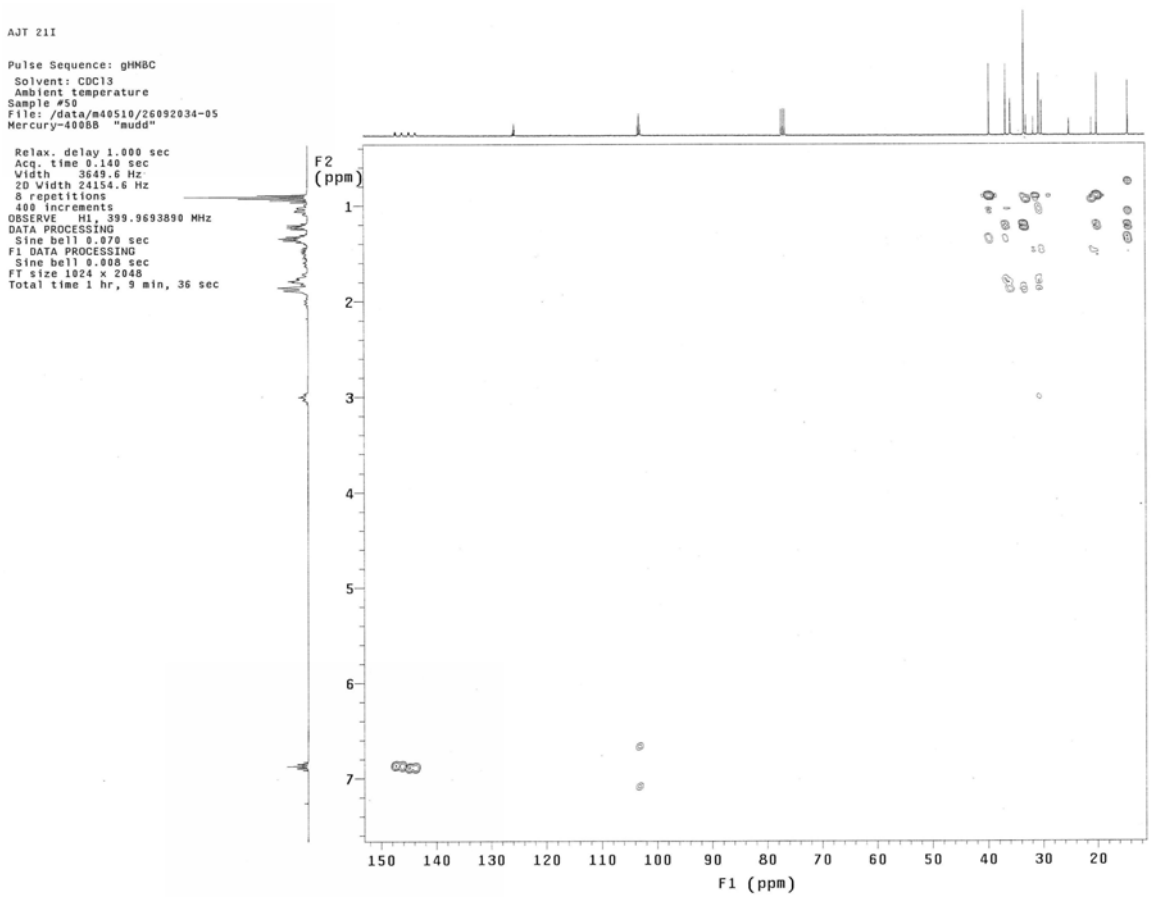


Figure 33. HSQC NMR spectrum

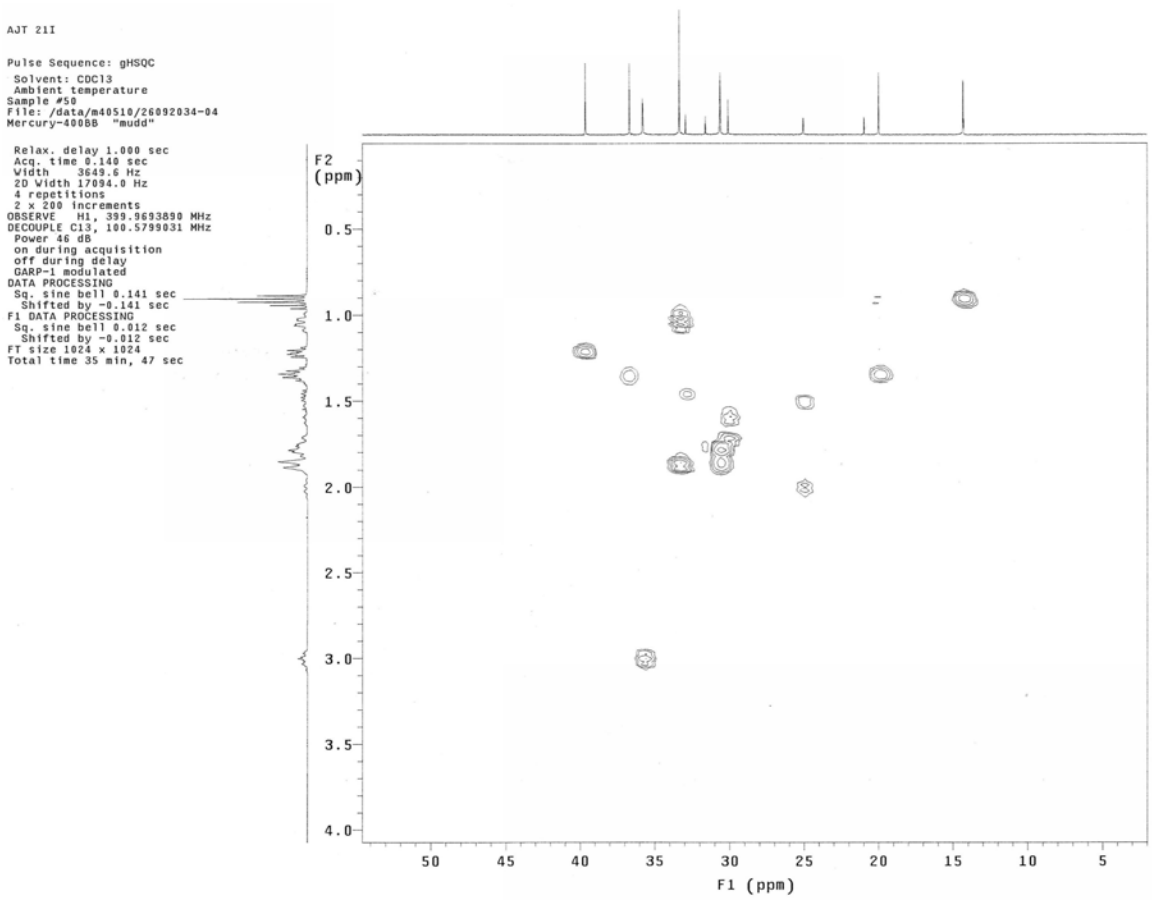


Figure 34. TOCSY NMR spectrum of *major* configurational isomer

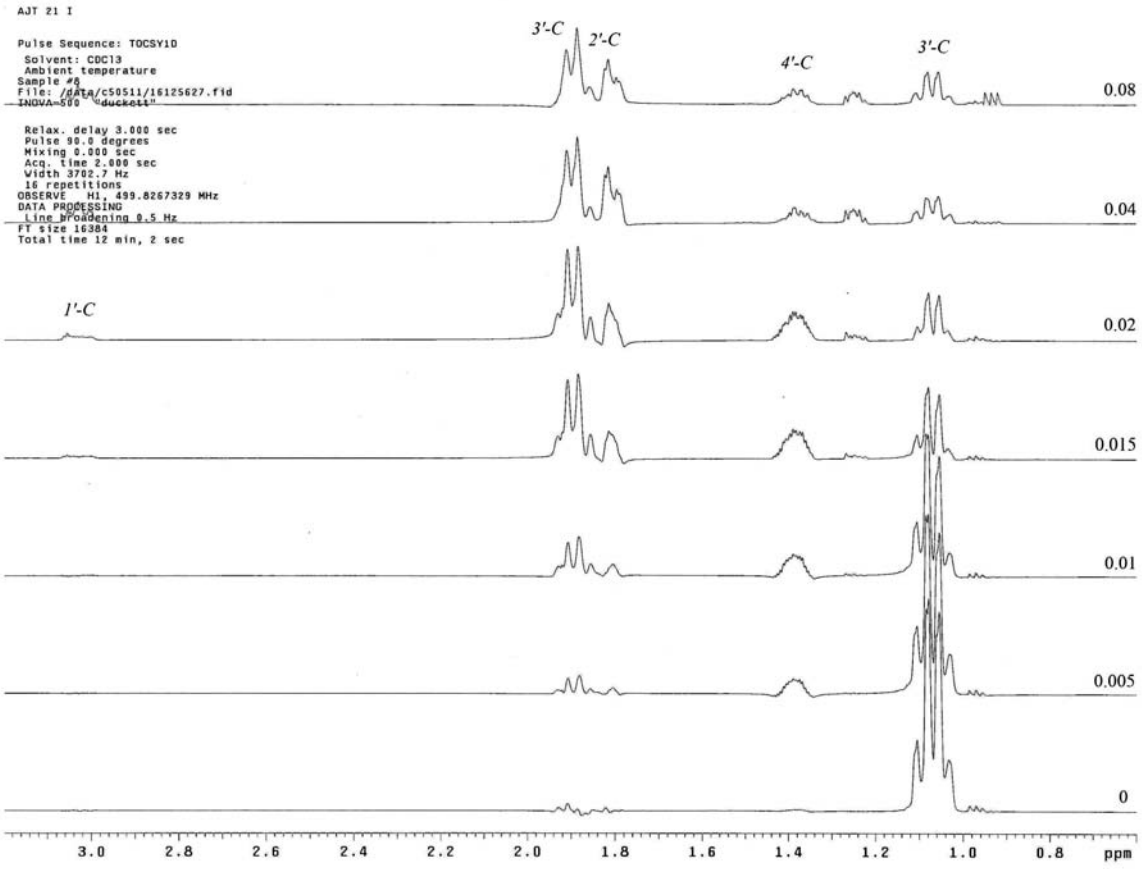


Figure 35. TOCSY NMR spectrum of *minor* configurational isomer

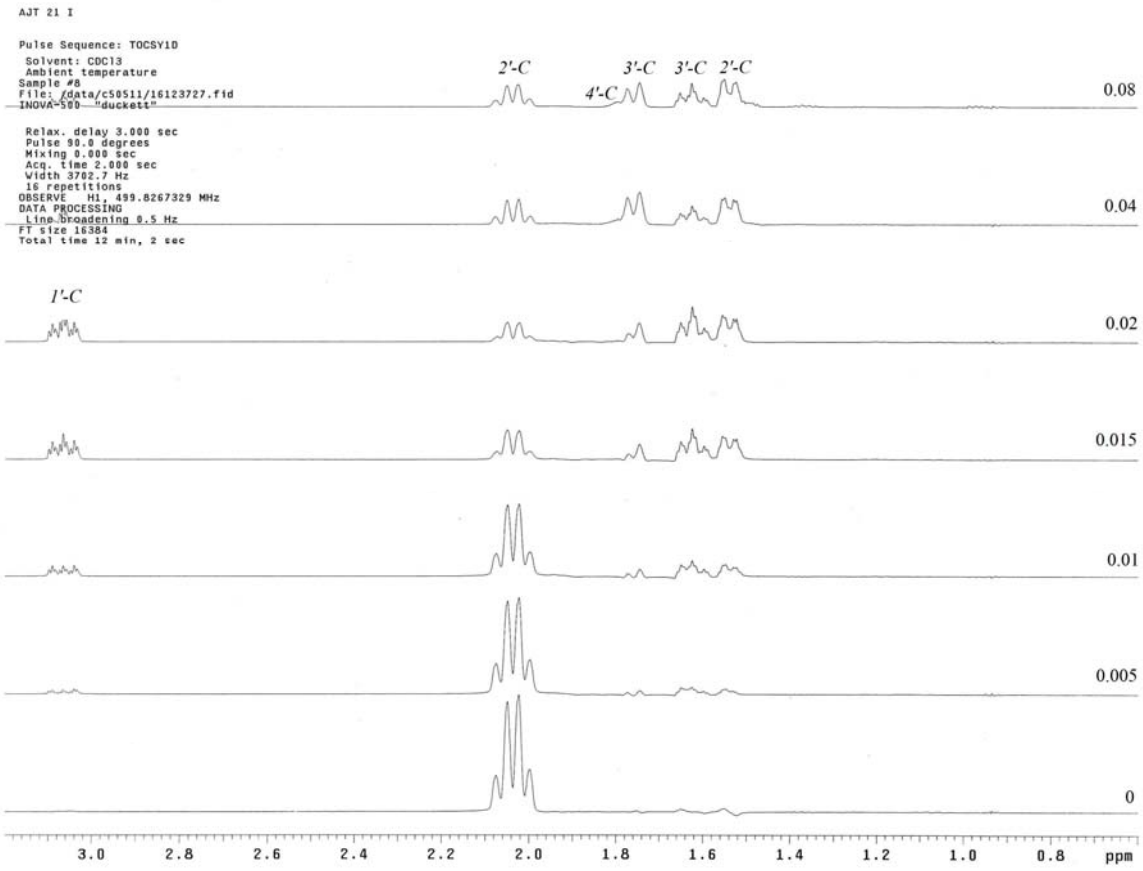
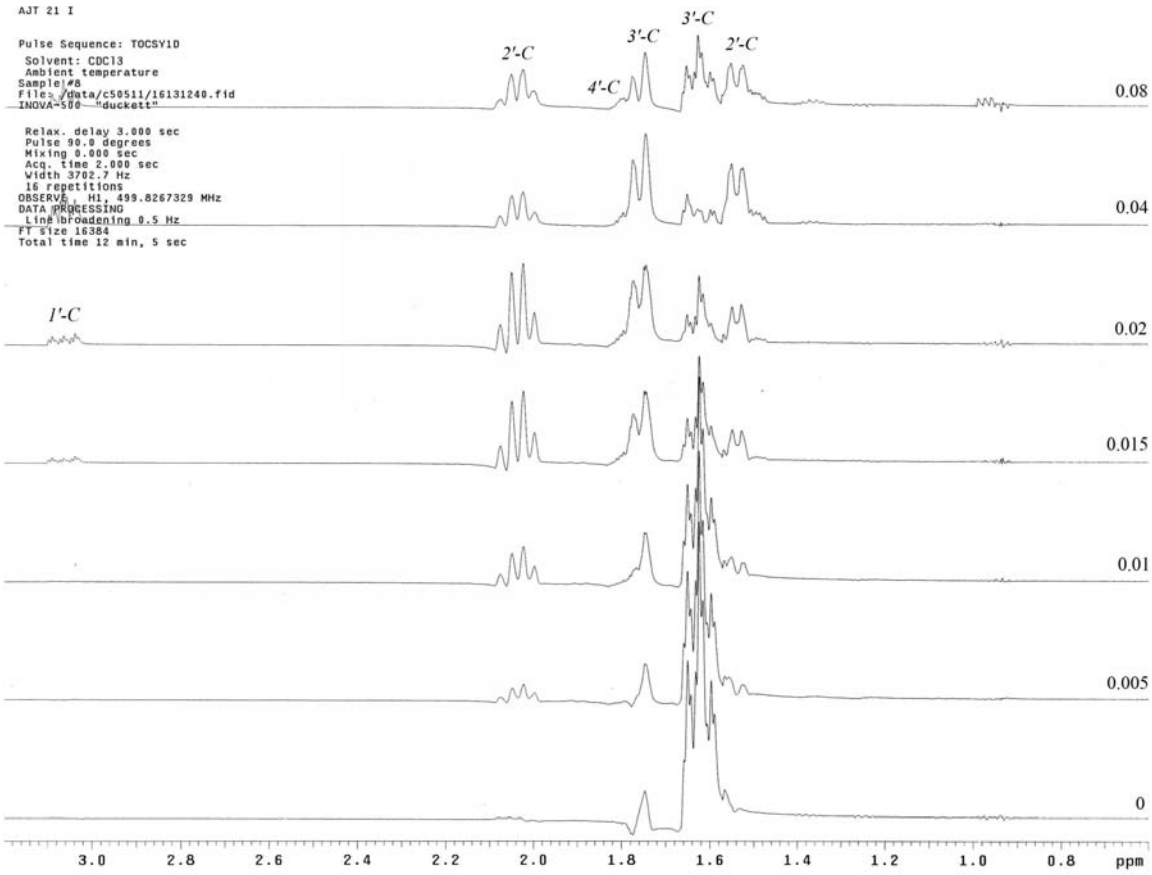
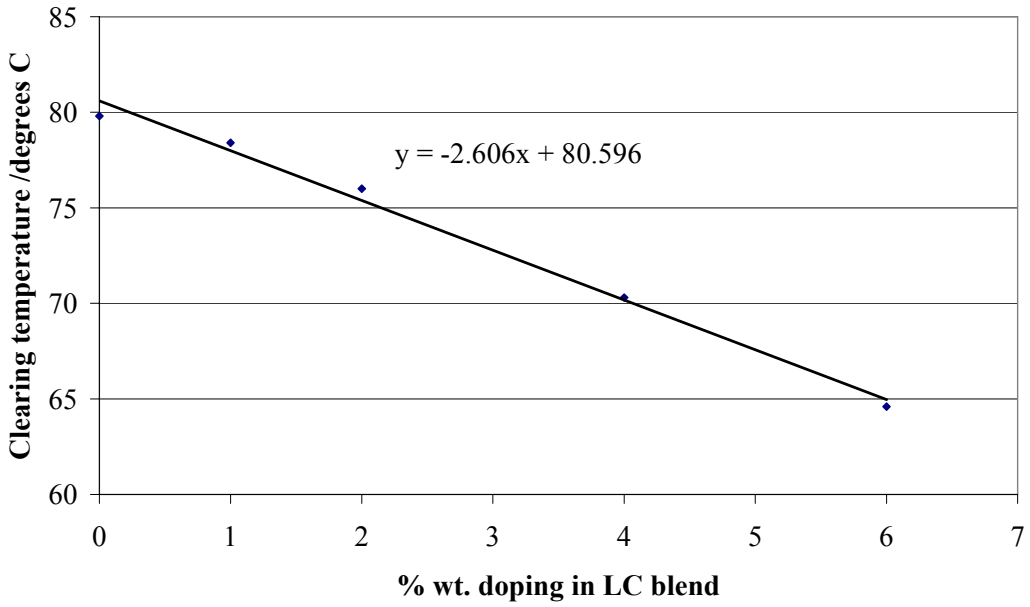


Figure 36. TOCSY NMR spectrum of *minor* configurational isomer

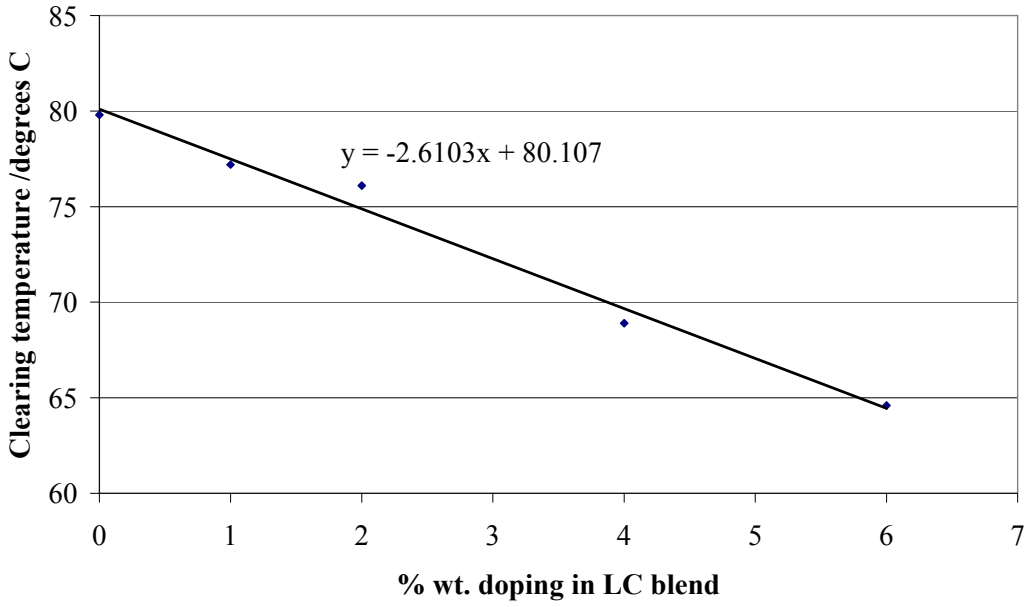


7.2 DSC Graphs

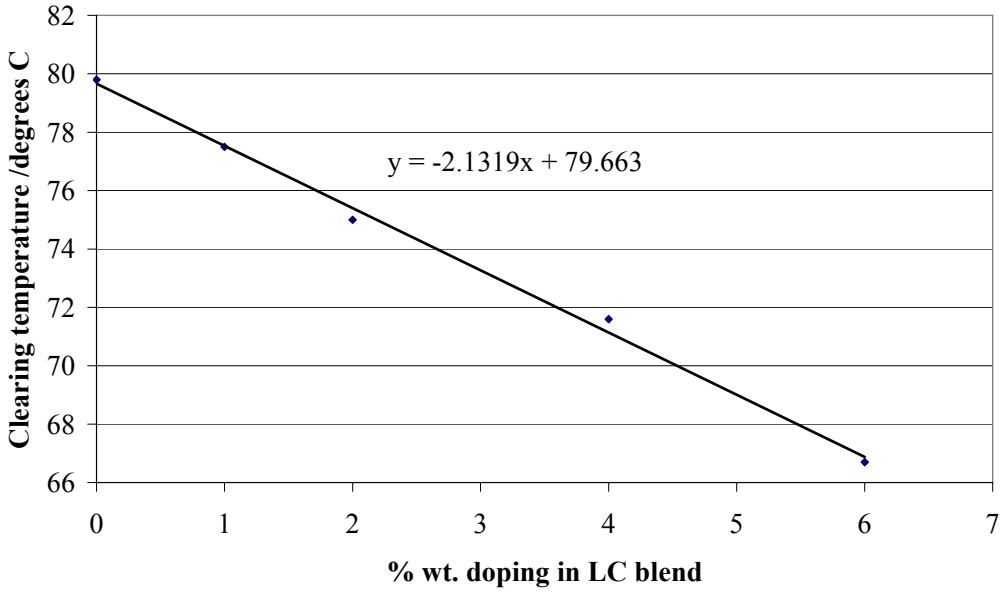
Graph 1. T_{NI} versus percentage doping of a dielectrically negative LC blend with **31**.



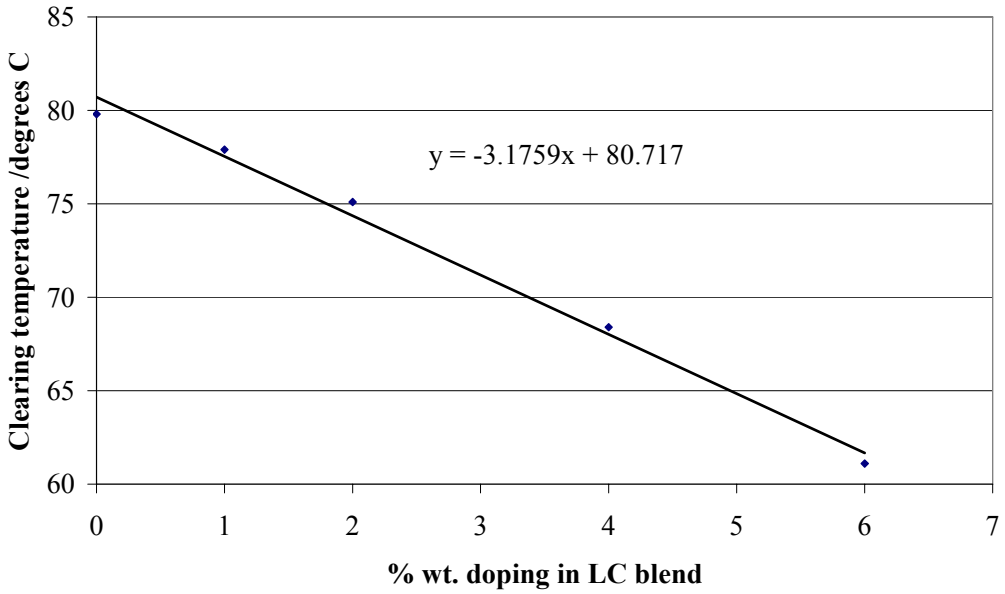
Graph 2. T_{NI} versus percentage doping of a dielectrically negative LC blend with **32**.



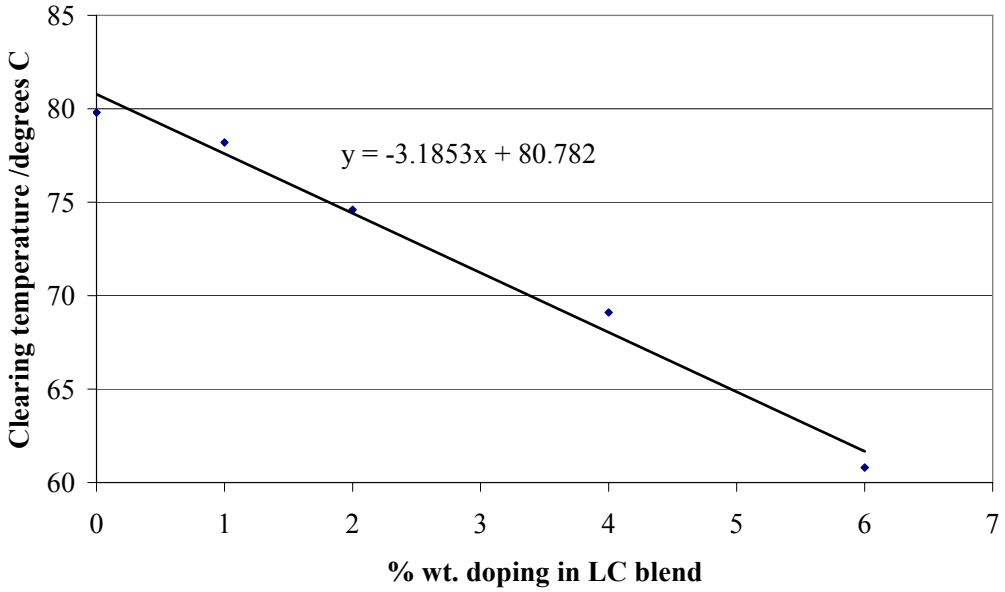
Graph 3. T_{NI} versus percentage doping of a dielectrically negative LC blend with **33**.



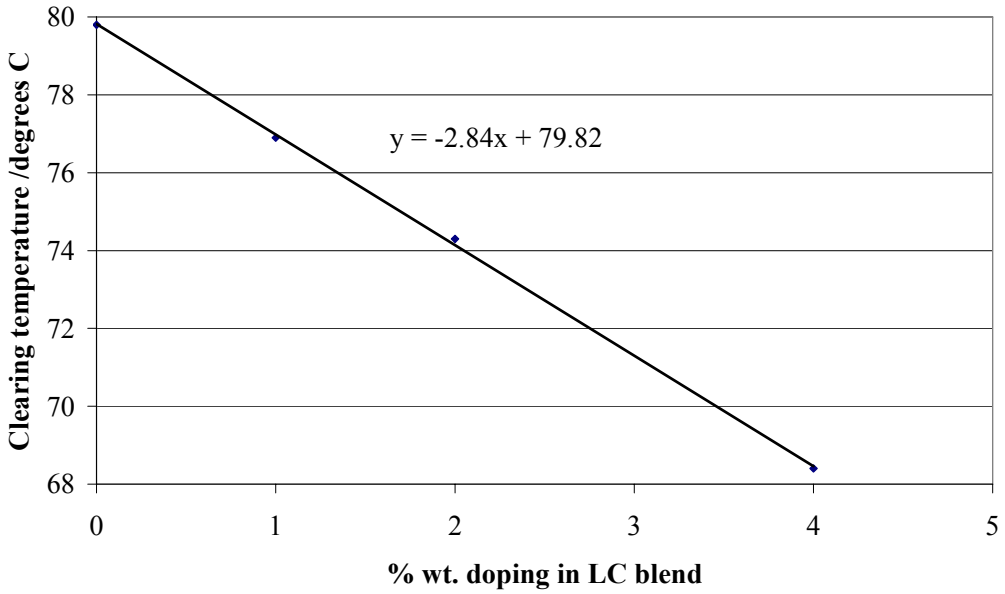
Graph 4. T_{NI} versus percentage doping of a dielectrically negative LC blend with **45**.



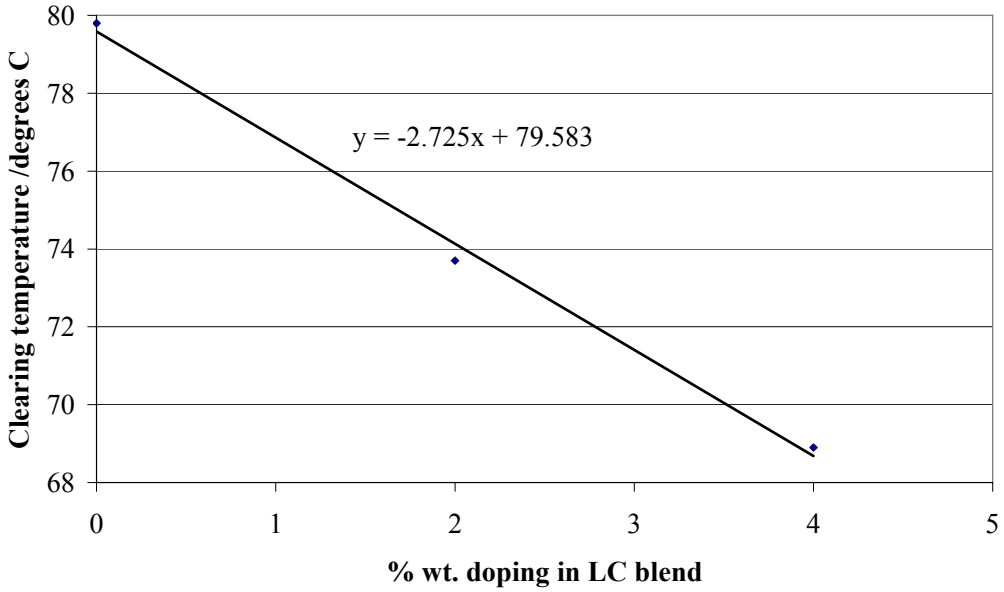
Graph 5. T_{NI} versus percentage doping of a dielectrically negative LC blend with **47**.



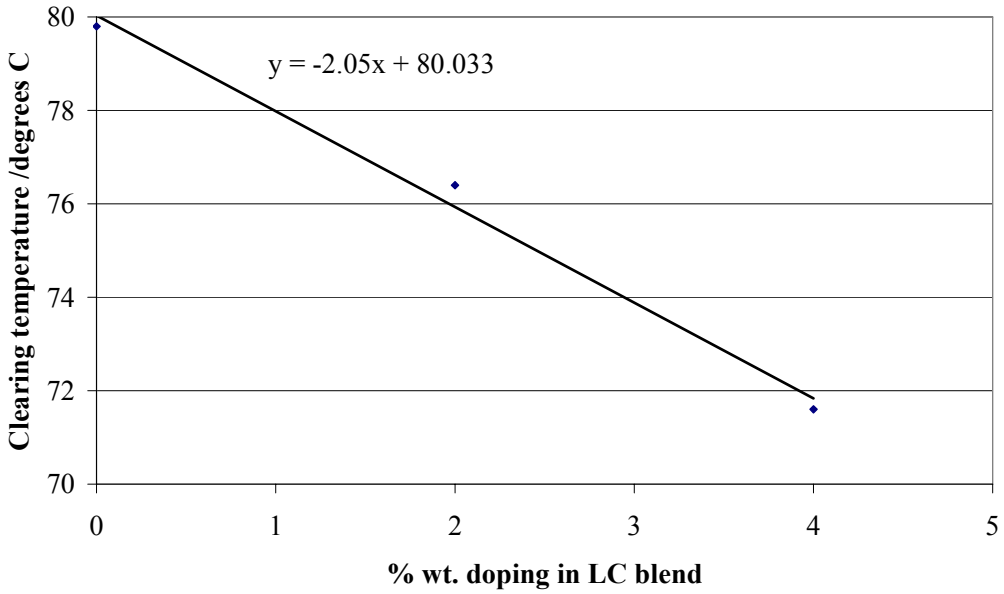
Graph 6. T_{NI} versus percentage doping of a dielectrically negative LC blend with **48**.



Graph 7. T_{NI} versus percentage doping of a dielectrically negative LC blend with **49**.



Graph 8. T_{NI} versus percentage doping of a dielectrically negative LC blend with **50**.



7.3 Electro-Optical Testing Graphs

7.3.1 Dopants in Dielectrically Negative Blends

7.3.1.1 Decay Times

The following experiments were performed using 5µm VA CTAB lined cells at 35 °C, with a 250Hz square wave.

Figure 37. Material **33**

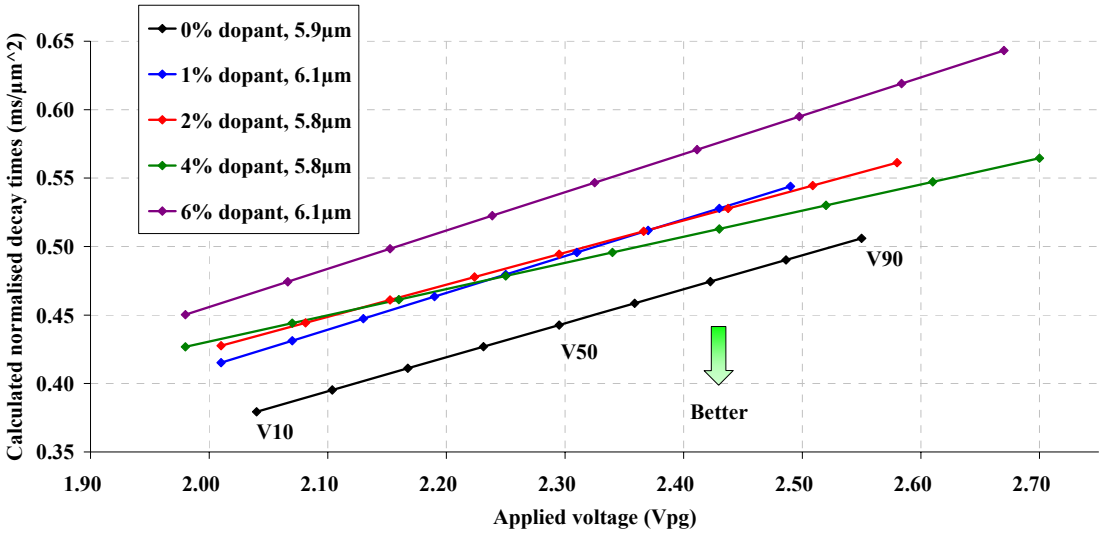


Figure 38. Material **32**

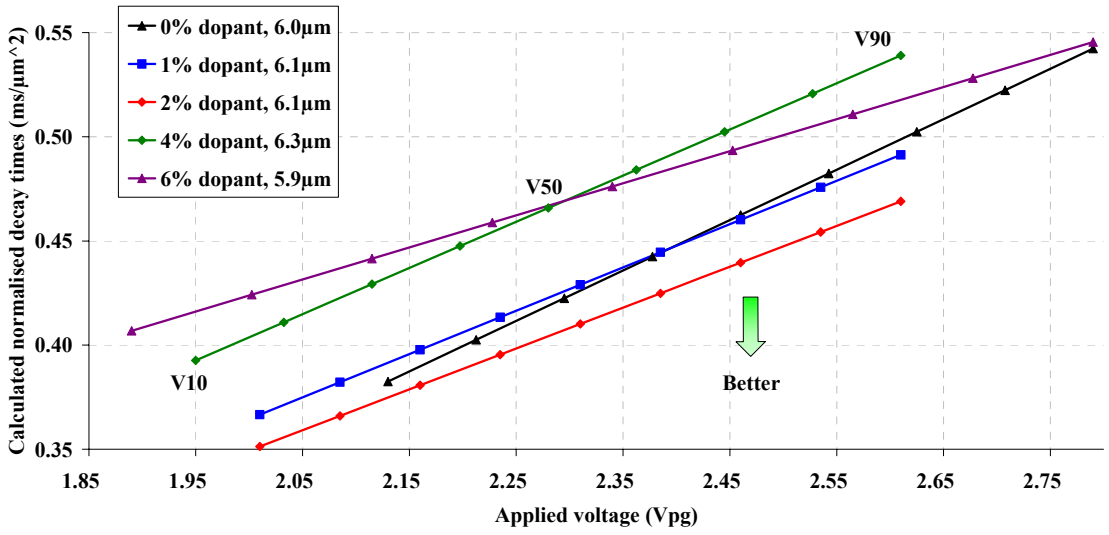


Figure 39. Material **31**

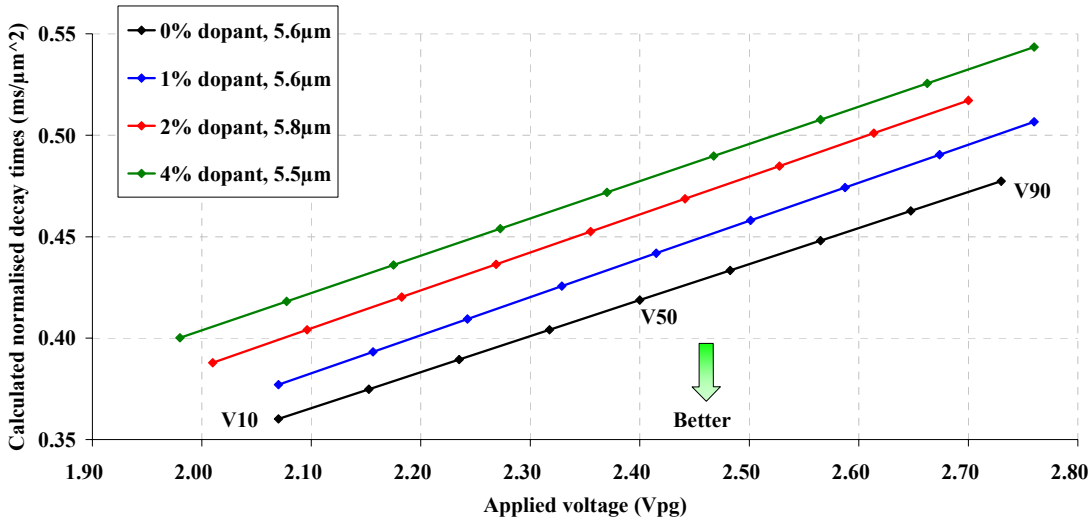


Figure 40. Material **50**

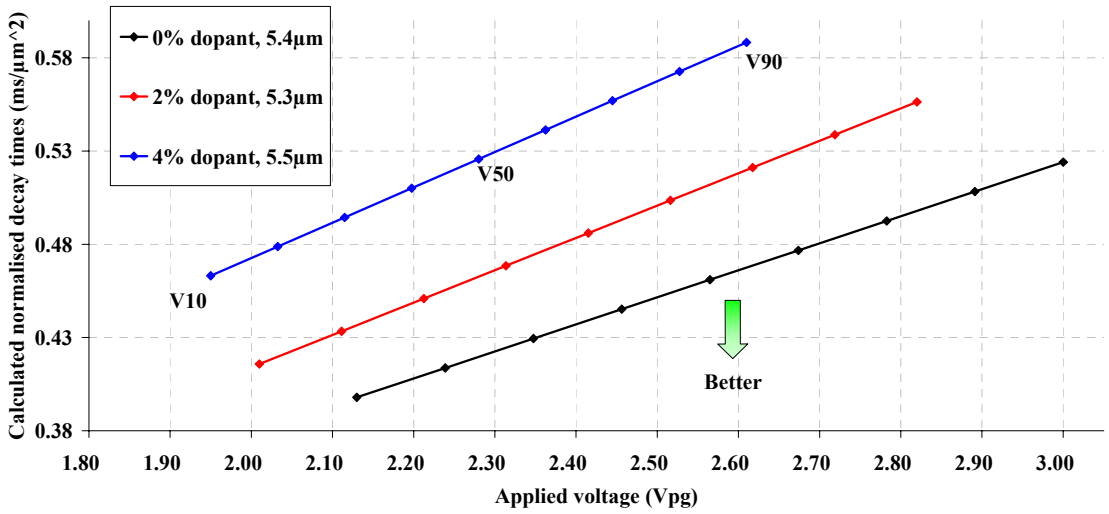


Figure 41. Material **49**

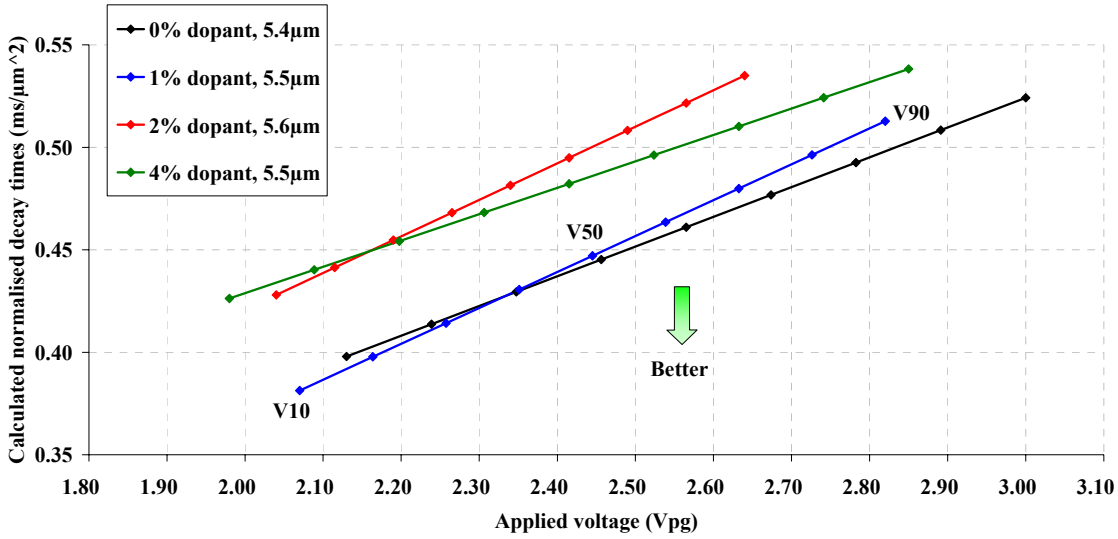


Figure 42. Material **48**

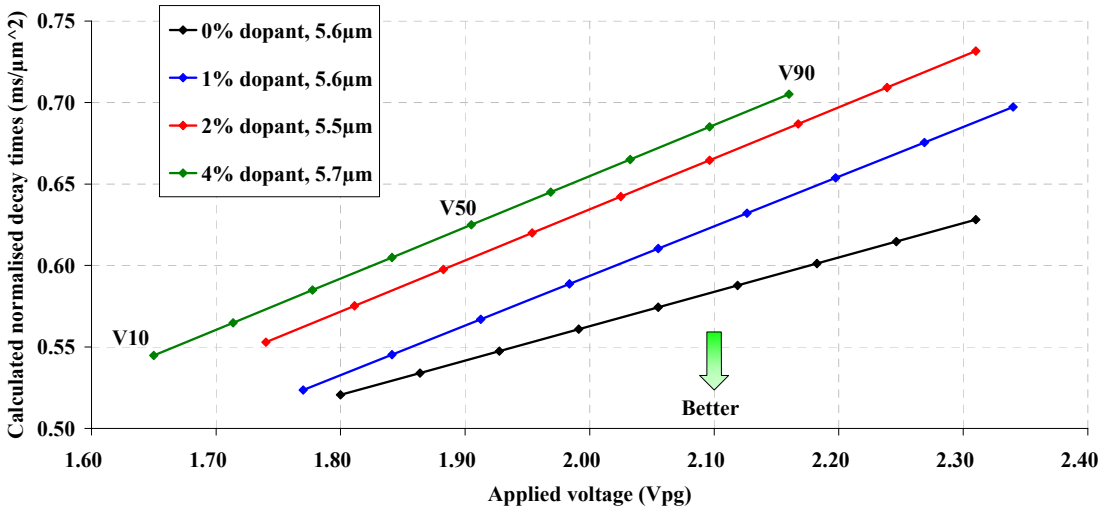


Figure 43. Material **45**

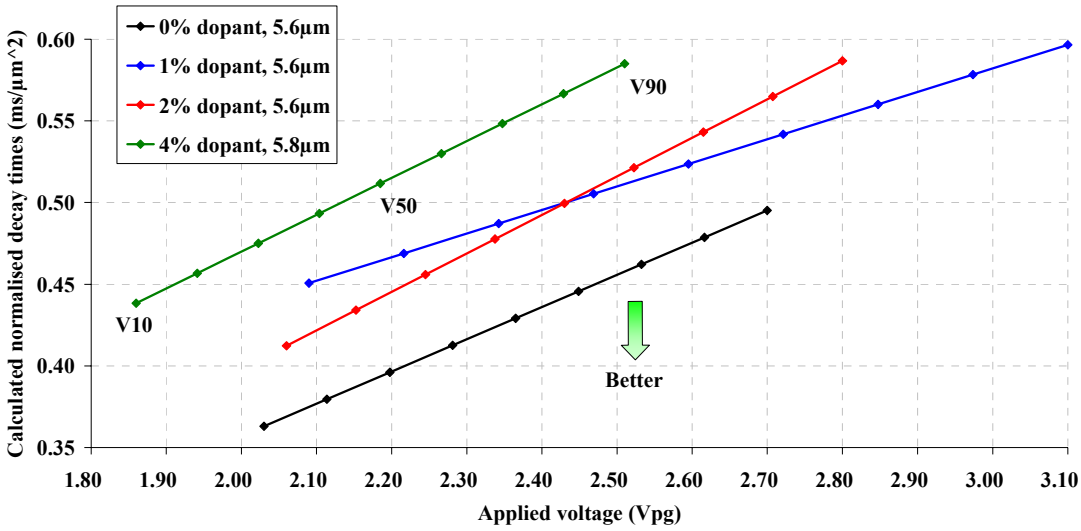


Figure 44. Material **47**

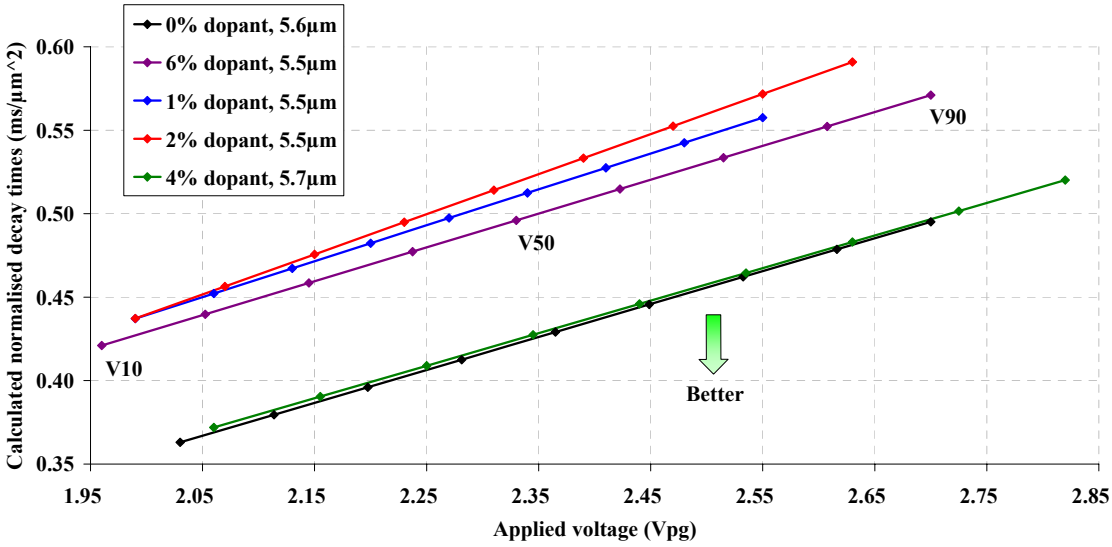


Figure 45. Comparison of materials **39** (38E), **89** (29D) and **90** (48G)

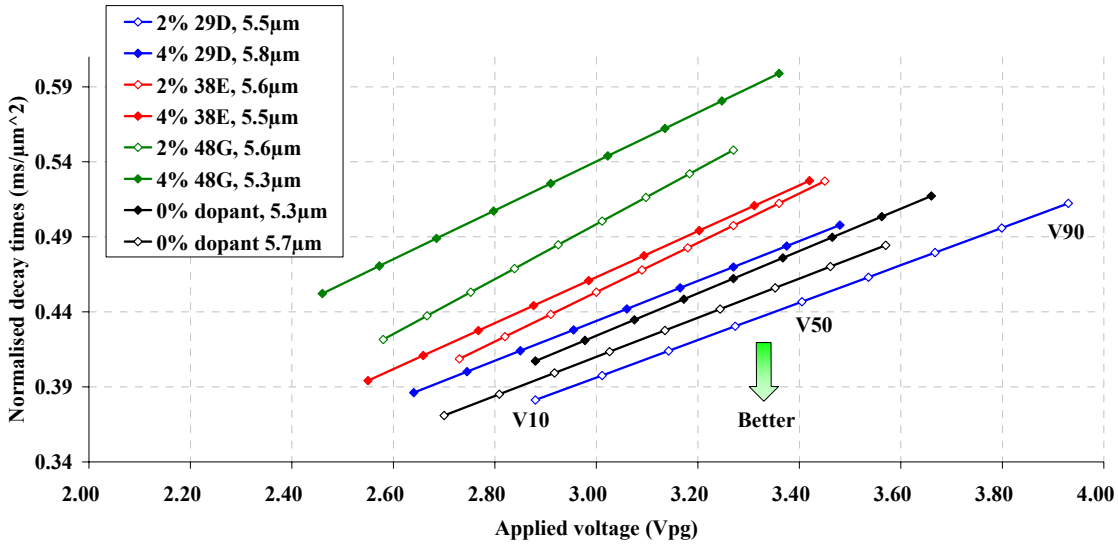


Figure 46. Comparison of materials **31** (93B), **32** (91C), **33** (92B) and **4-FPhOPh**

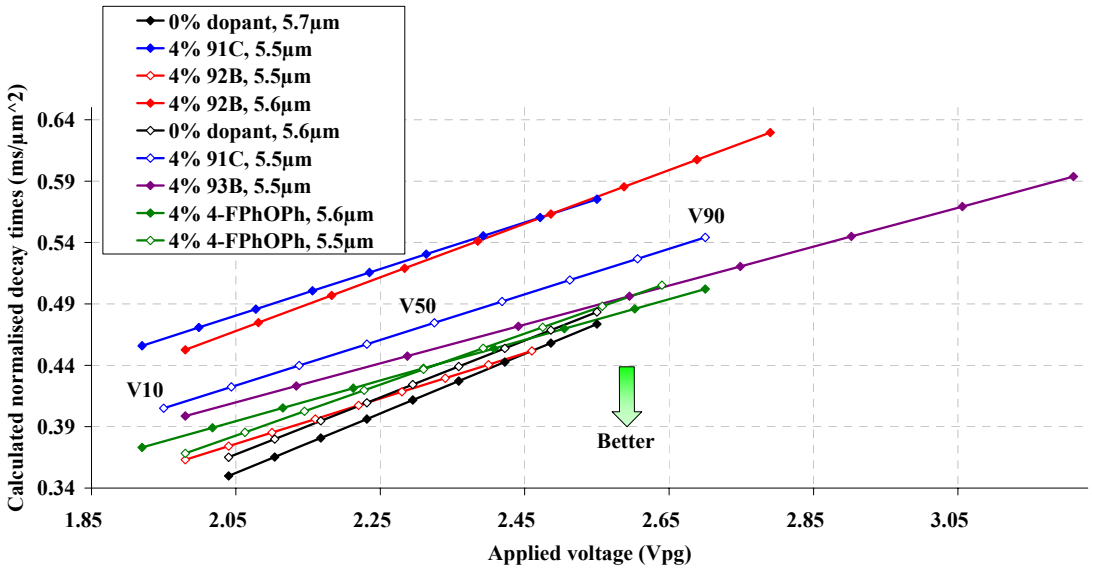
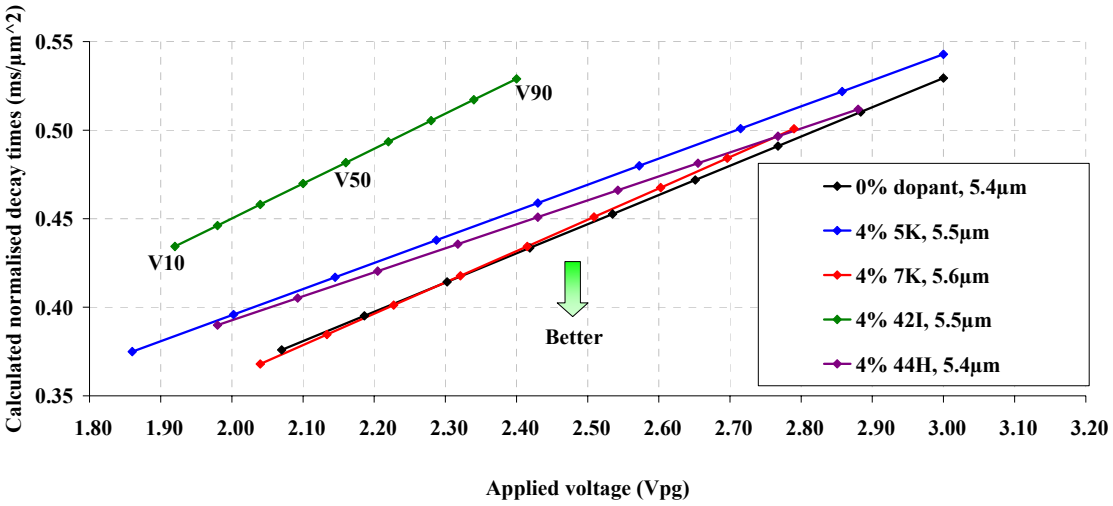


Figure 47. Comparison of materials **45** (5K), **47** (7K), **48** (42I) and **50** (44H)



The following experiments were performed using 5µm VA polyimide lined cells at 35 °C, with a 250Hz square wave.

Figure 48. Comparison of materials **86** (21I) and **88** (31H)

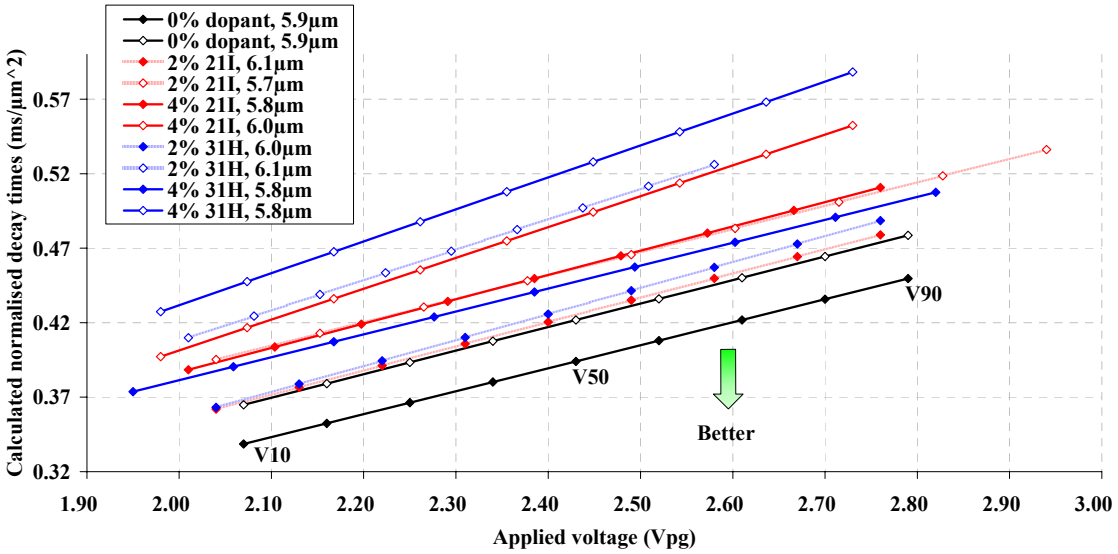
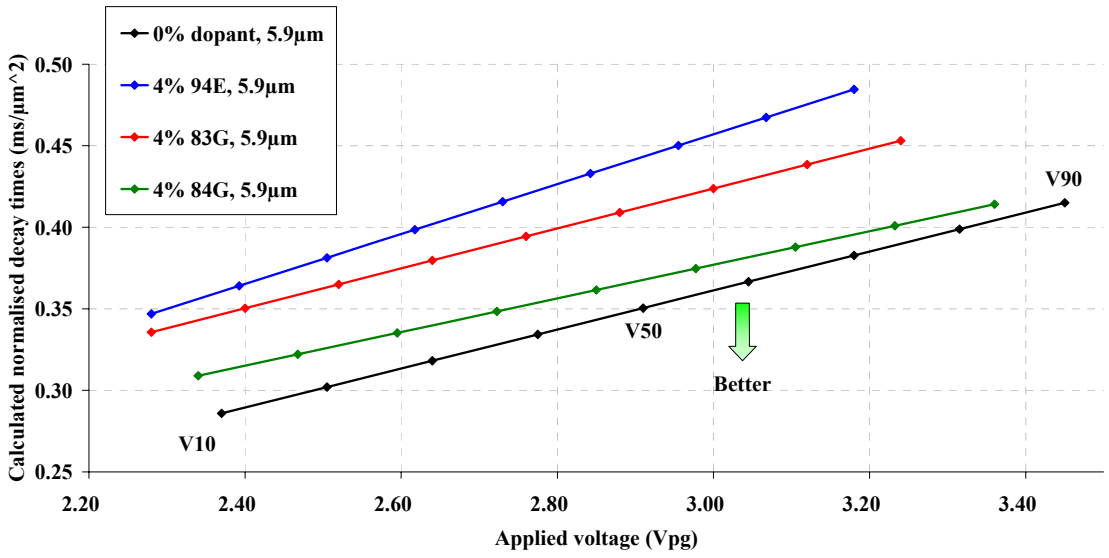


Figure 49. Comparison of materials **92** (94E), **93** (83G) and **94** (84G)



7.3.1.2 Rise Times

The following experiments were performed using 5µm VA CTAB lined cells at 35 °C, with a 250Hz square wave.

Figure 50. Material **33**

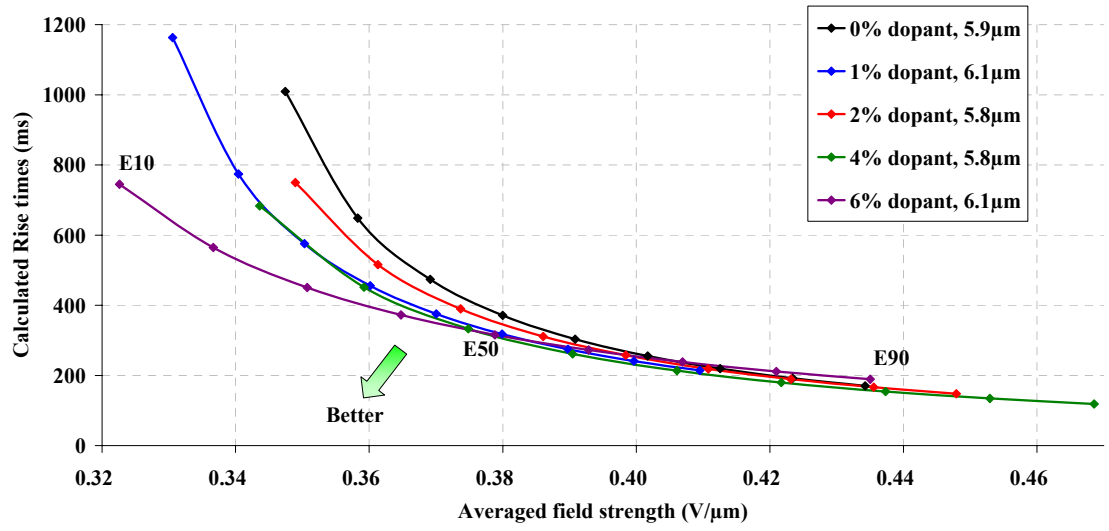


Figure 51. Material **32**

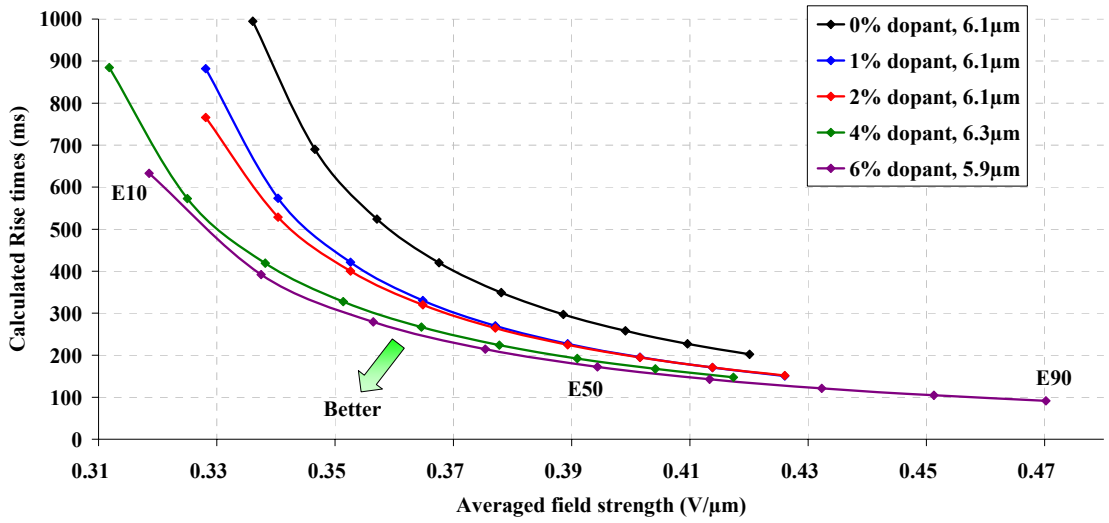


Figure 52. Material **31**

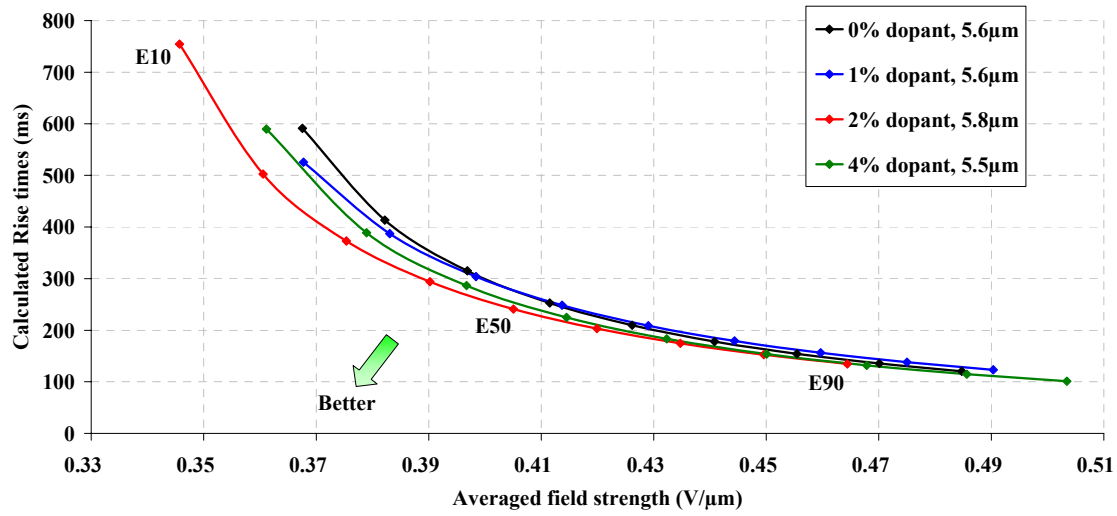


Figure 53. Material **50**

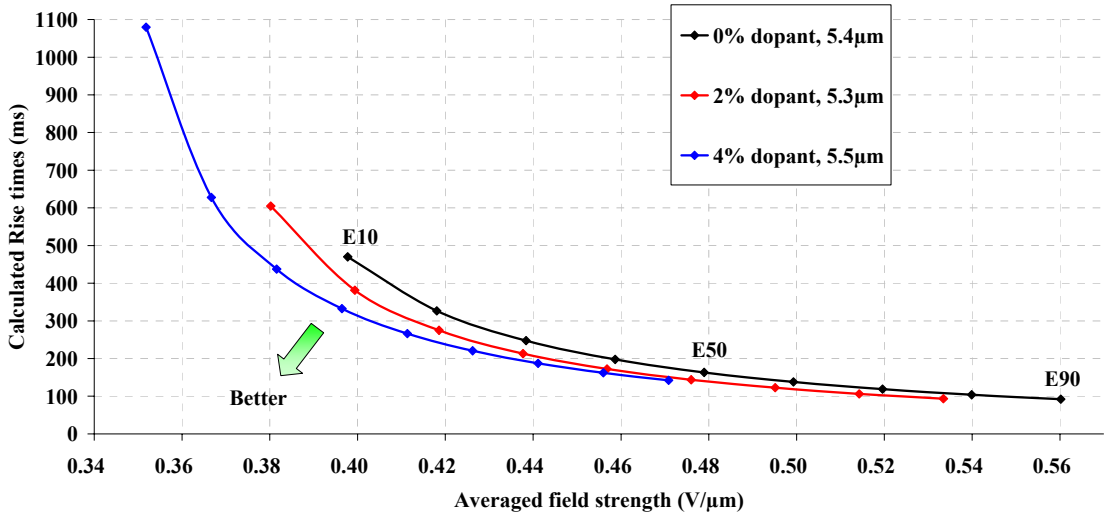


Figure 54. Material **49**

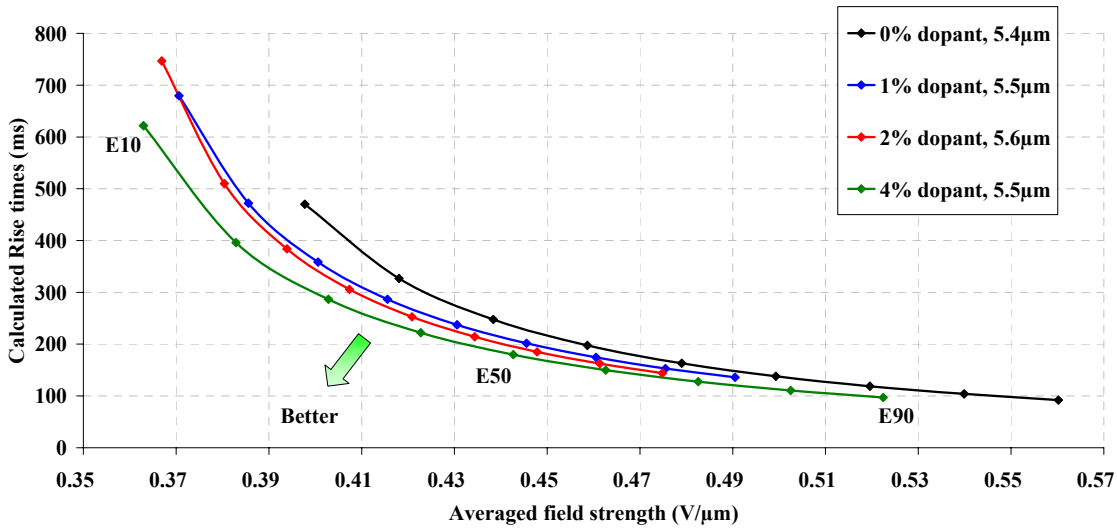


Figure 55. Material **48**

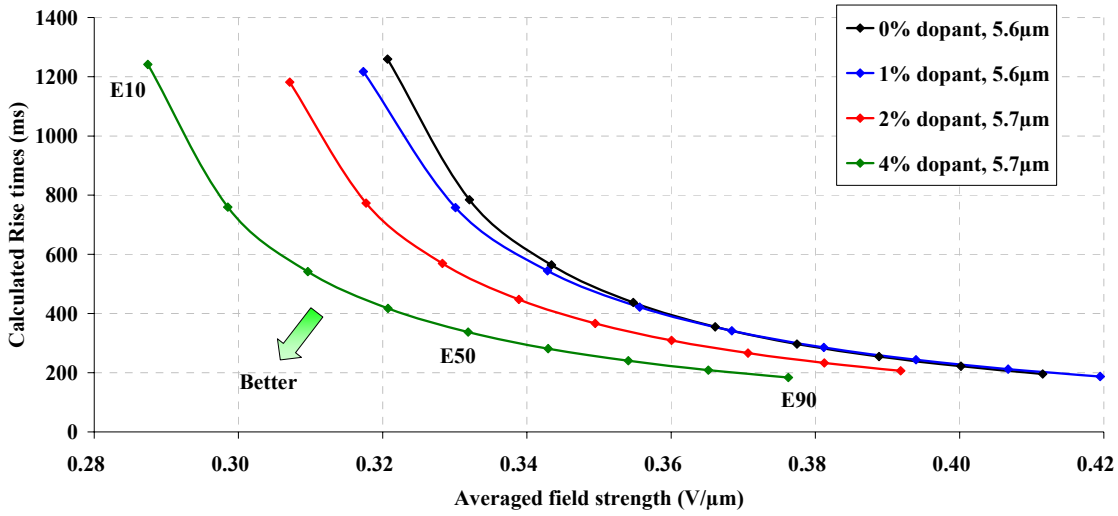


Figure 56. Material **45**

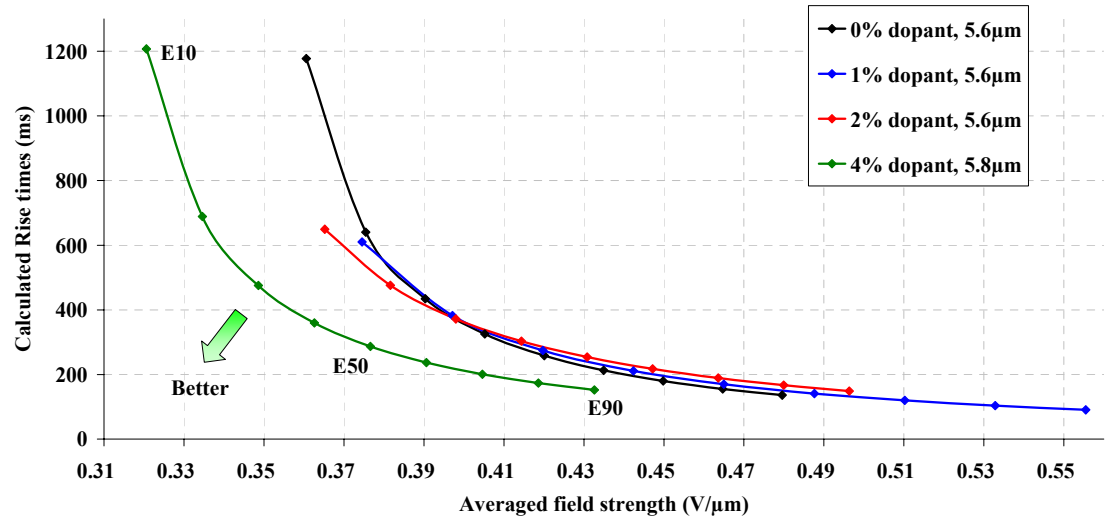


Figure 57. Material **47**

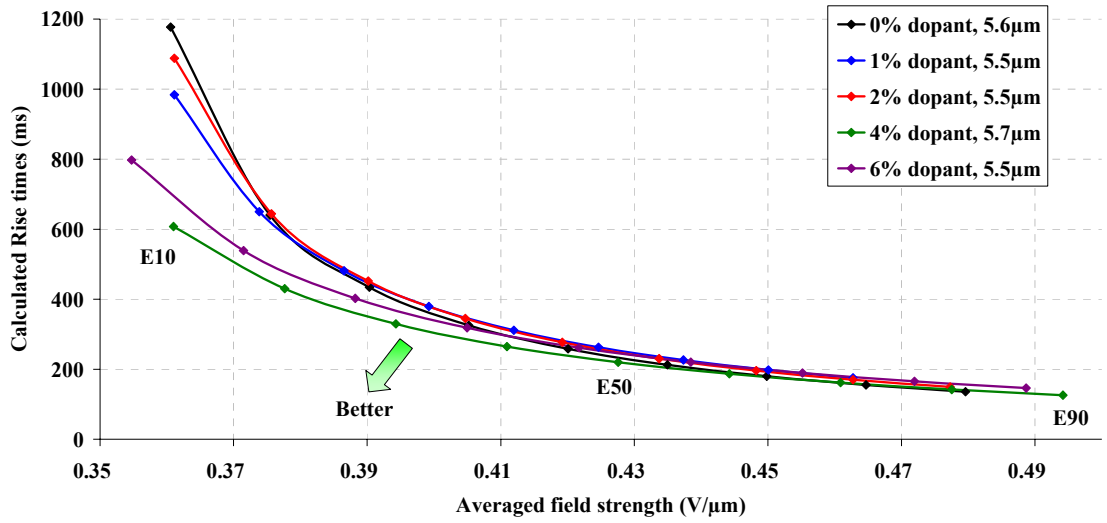


Figure 58. Comparison of materials **39** (38E), **89** (29D) and **90** (48G)

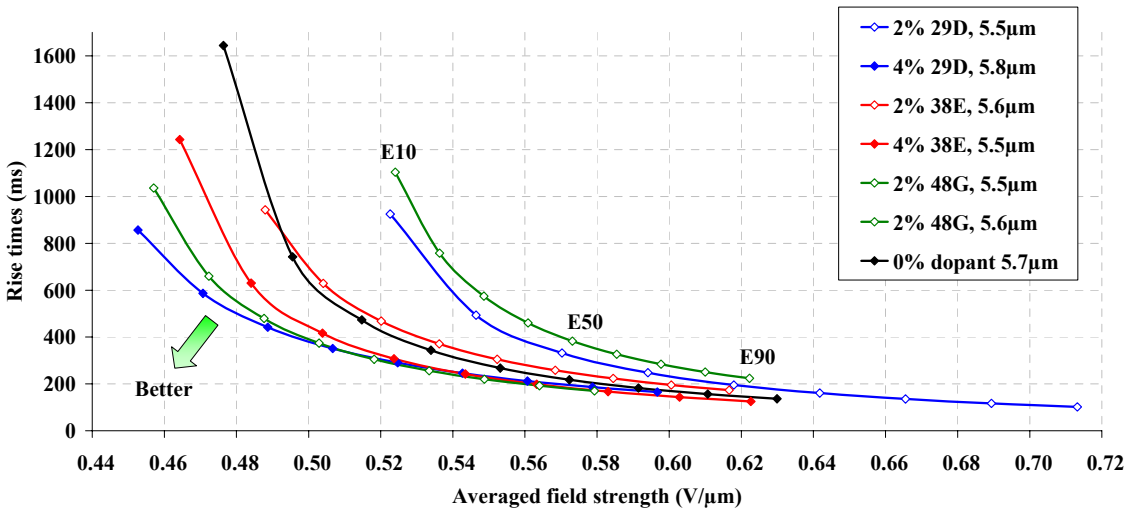


Figure 59. Comparison of materials **31** (93B), **32** (91C), **33** (92B) and 4-FPhOPh

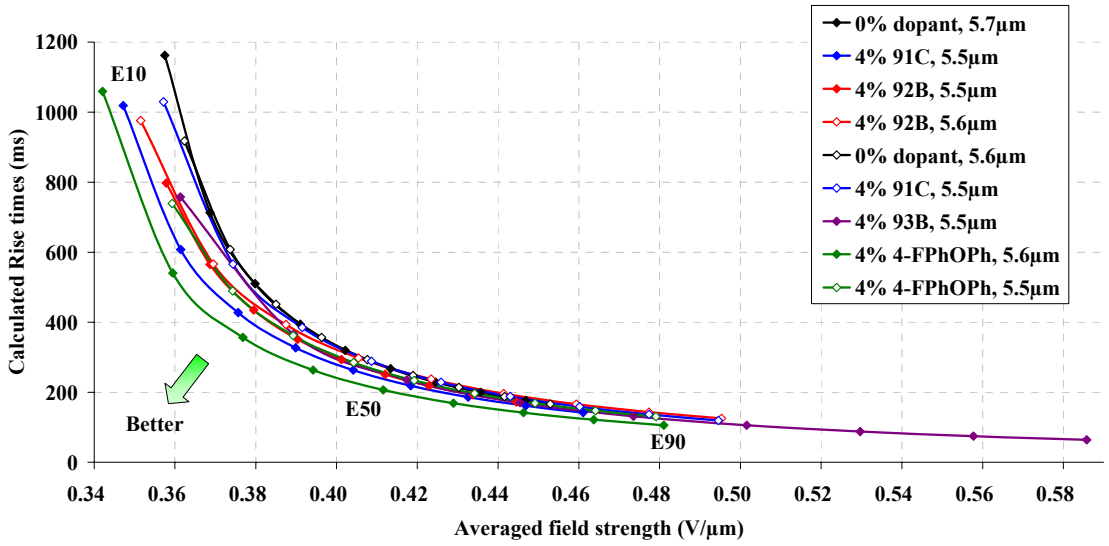
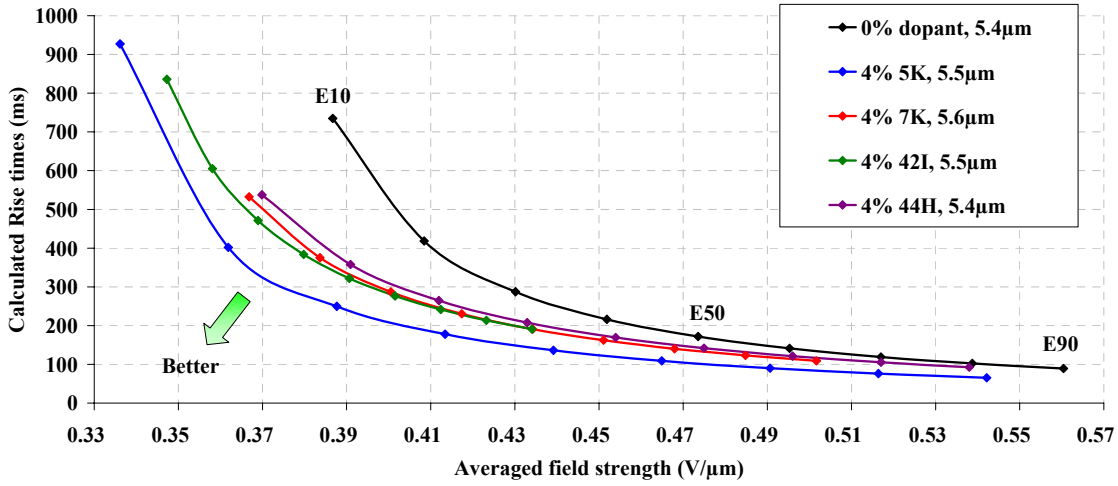


Figure 60. Comparison of materials **45** (5K), **47** (7K), **48** (42I) and **50** (44H)



The following experiments were performed using 5µm VA polyimide lined cells at 35 °C, with a 250Hz square wave.

Figure 61. Comparison of materials **86** (21I) and **88** (31H)

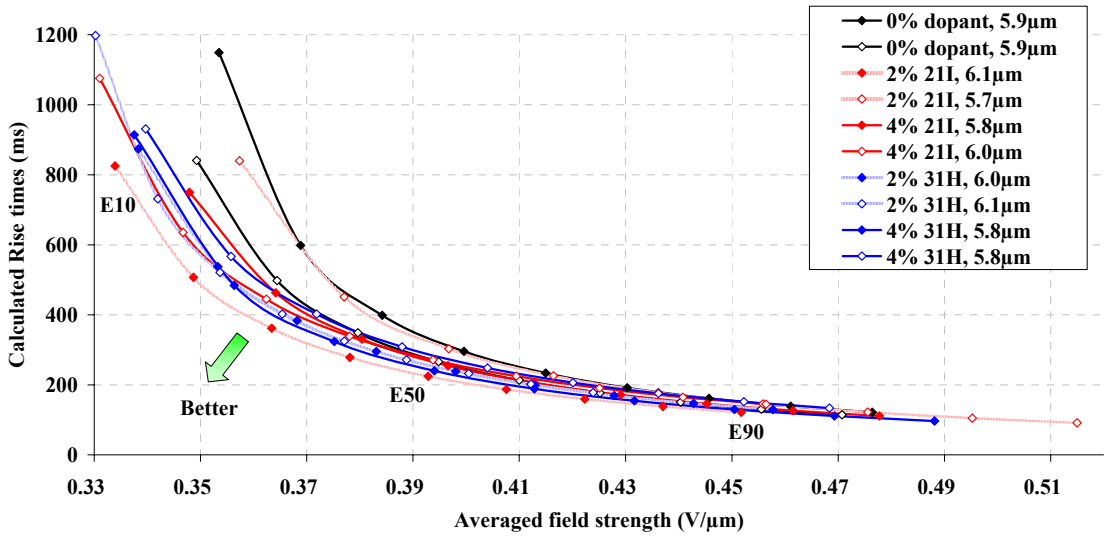
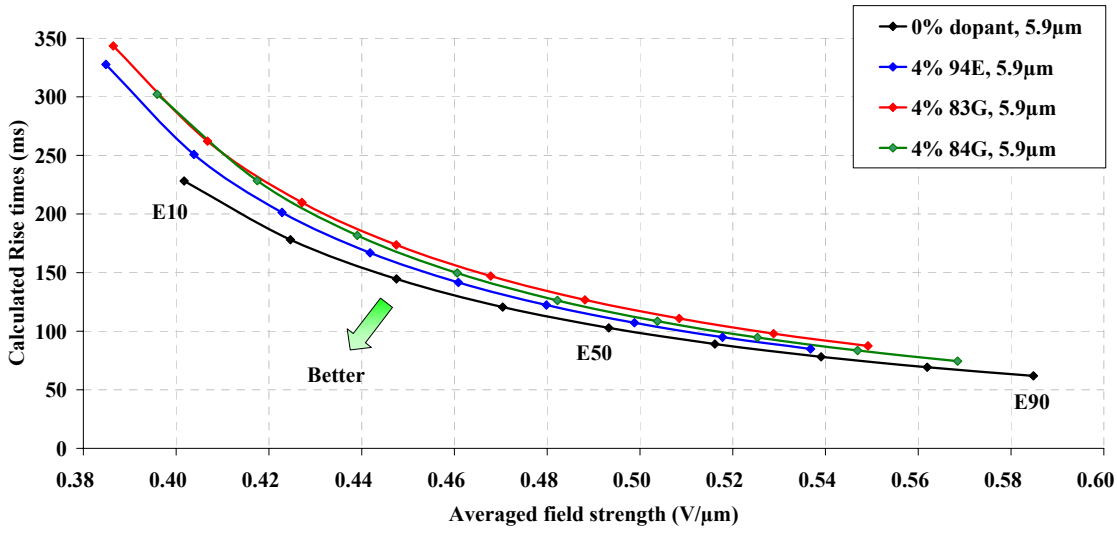


Figure 62. Comparison of materials **92** (94E), **93** (83G) and **94** (84G)



7.3.2 Dopants in Dielectrically Positive Blends

The following experiments were performed using 10µm TN polyimide lined cells at 35 °C, with a 250Hz square wave.

7.3.2.1 Decay Times

Figure 63. Material **48**

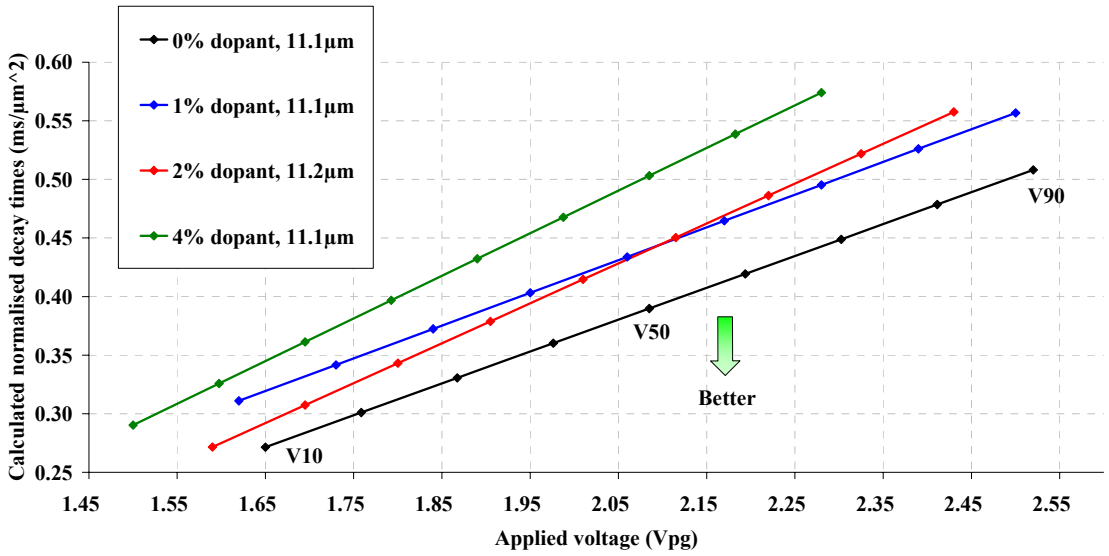


Figure 64. Material **49**

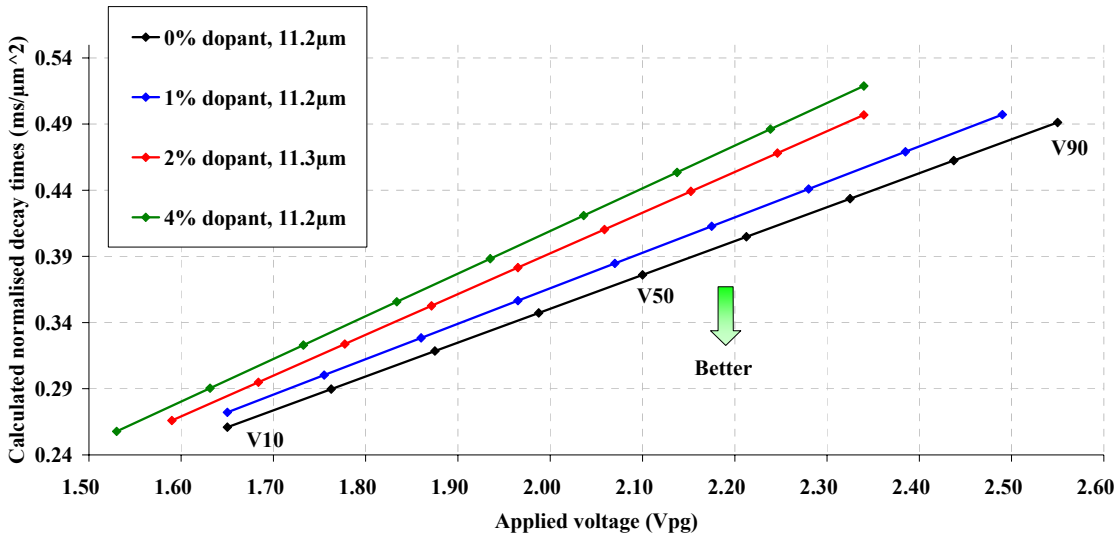


Figure 65. Comparison of materials **39** (38E), **86** (21I), **88** (31H) and **89** (29D)

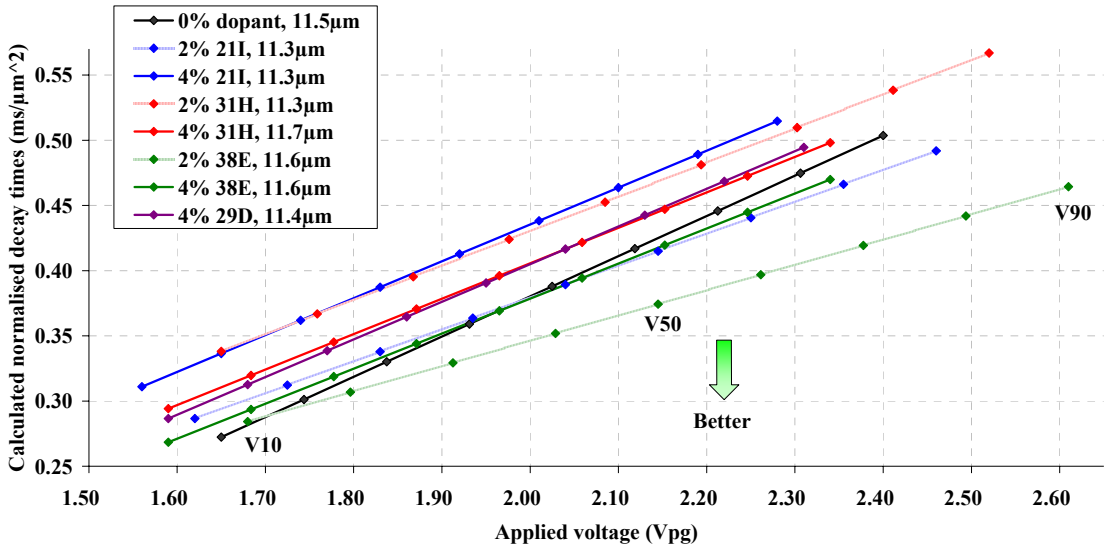


Figure 66. Comparison of materials **31** (93B), **32** (91C) and **33** (92B)

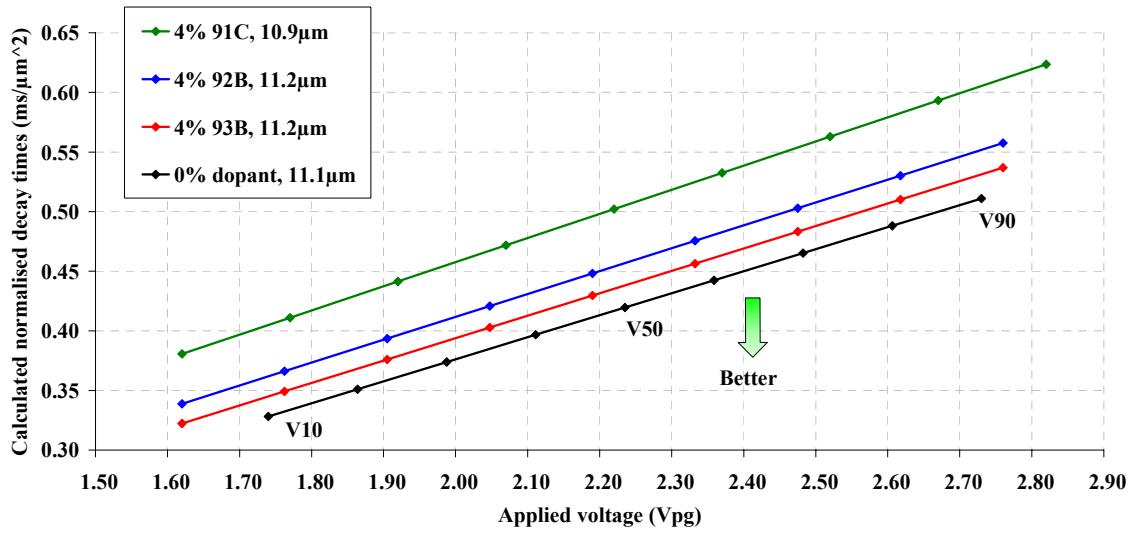


Figure 67. Comparison of materials **45** (5K), **47** (7K), **48** (42I), **49** (42G) and **50** (44H)

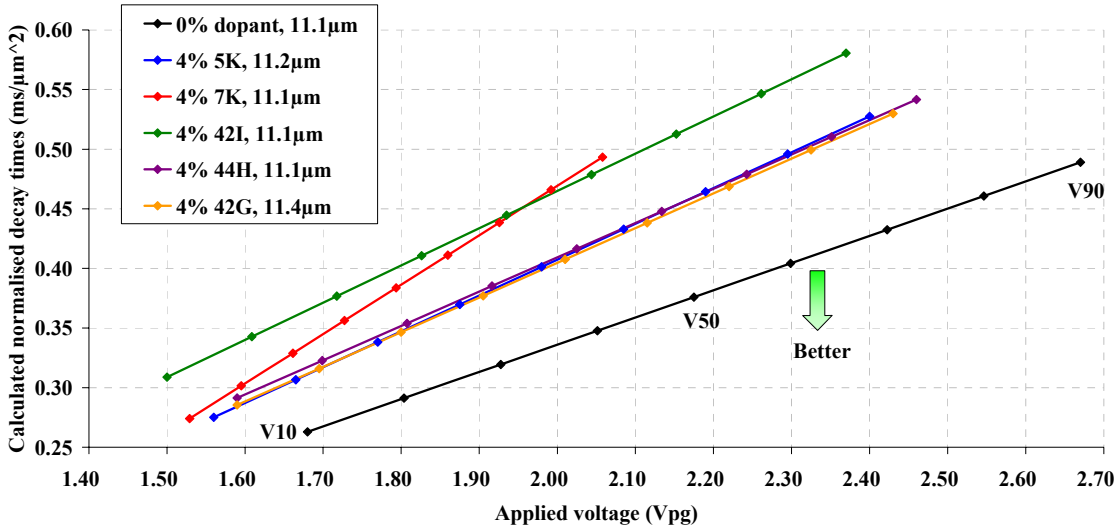


Figure 68. Comparison of materials **31** (93B), **32** (91C), **33** (92B), **45** (5K), **47** (7K), **48** (42I), **49** (42G), **50** (44H) and 2/4-FPhOPh

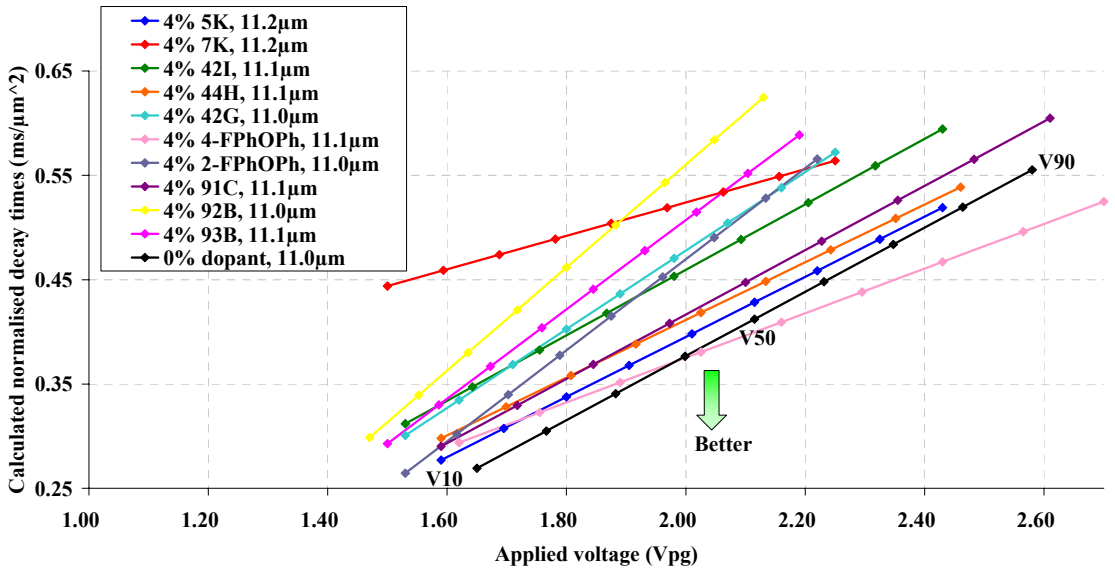
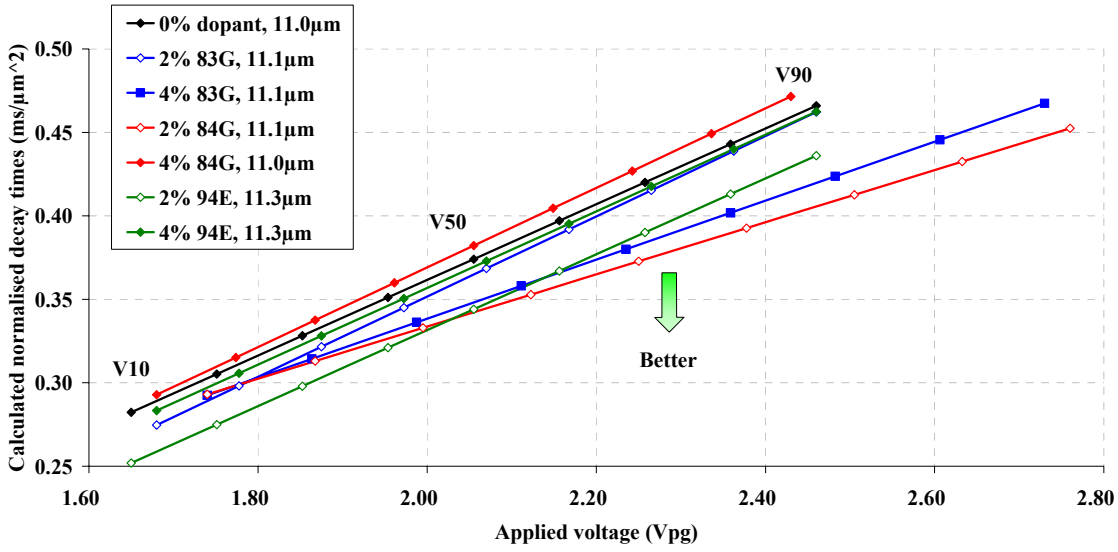


Figure 69. Comparison of materials **92** (94E), **93** (83G) and **94** (84G)



7.3.2.2 Rise Times

Figure 70. Material **48**

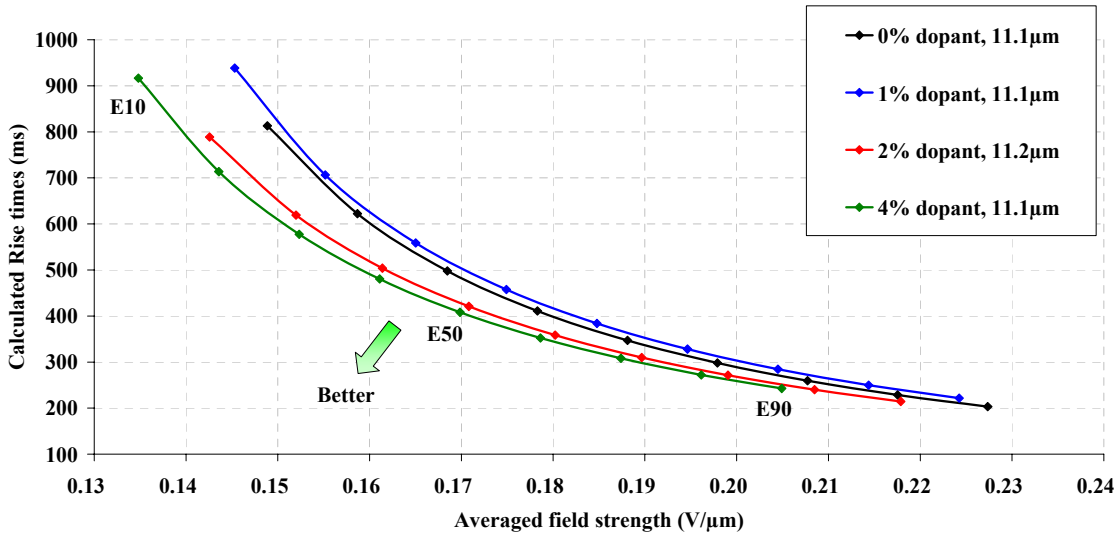


Figure 71. Material **49**

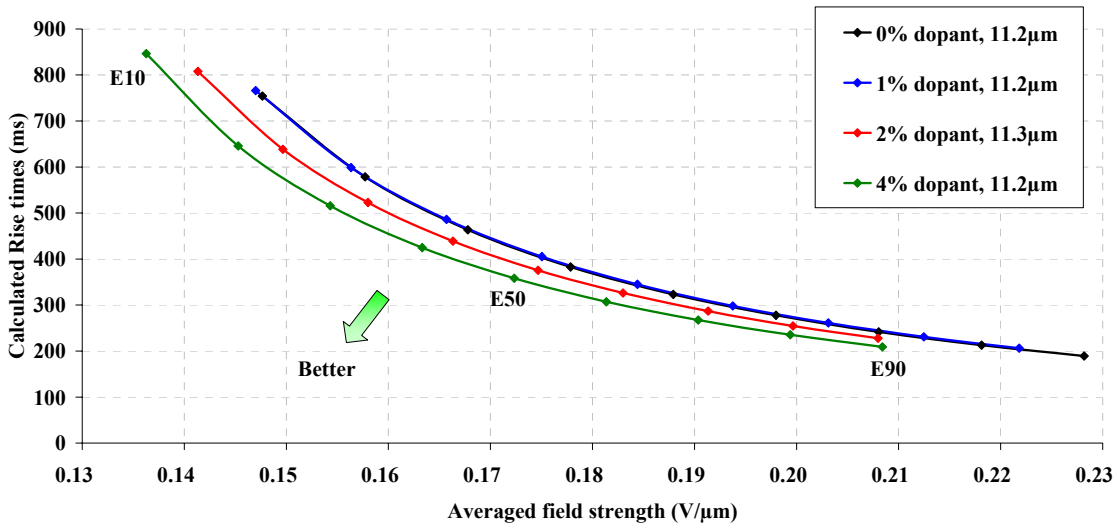


Figure 72. Comparison of materials **39** (38E), **86** (21I), **88** (31H) and **89** (29D)

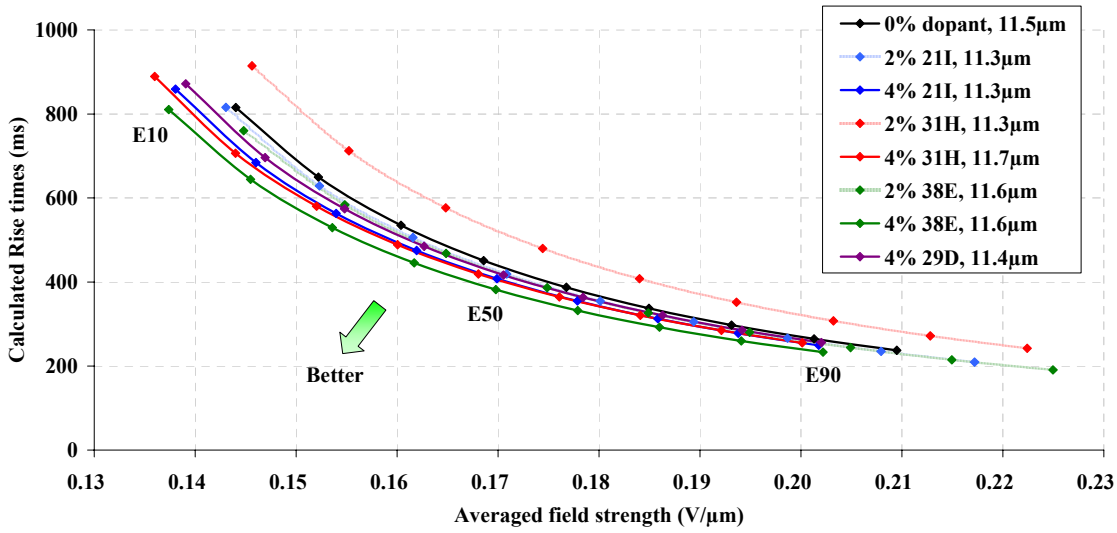


Figure 73. Comparison of materials **31** (93B), **32** (91C) and **33** (92B)

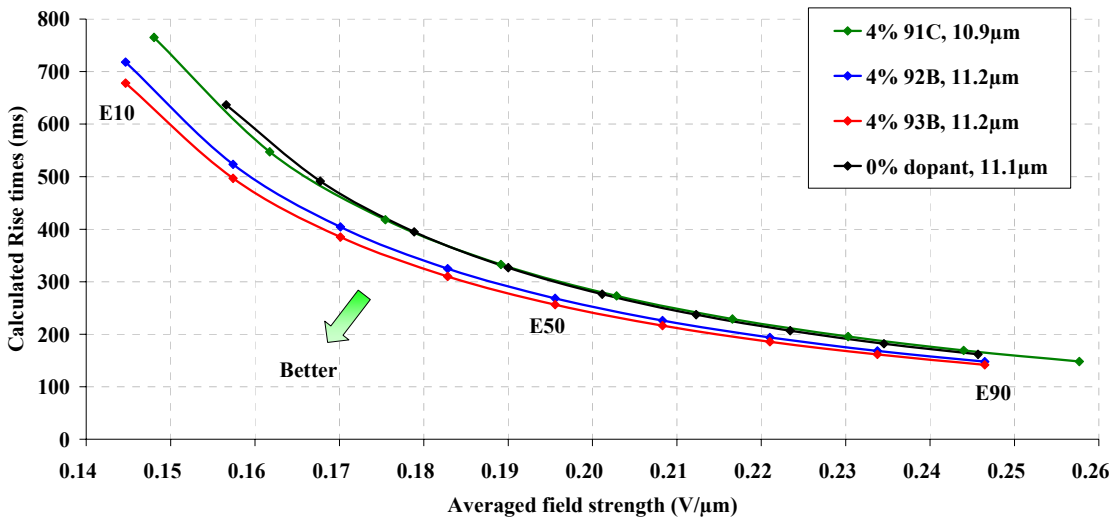


Figure 74. Comparison of materials **45** (5K), **47** (7K), **48** (42I), **49** (42G) and **50** (44H)

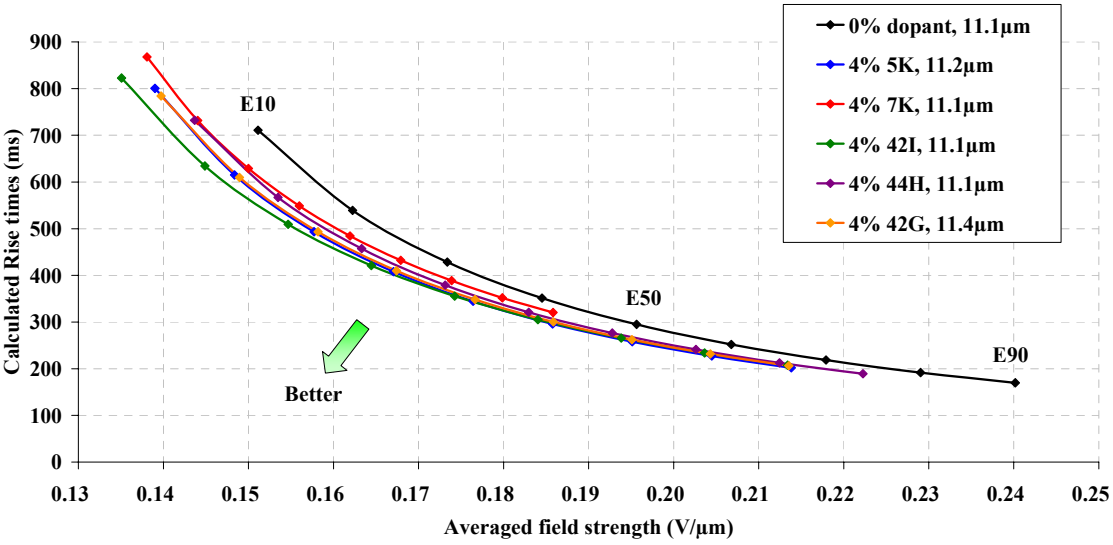


Figure 75. Comparison of materials **31** (93B), **32** (91C), **33** (92B), **45** (5K), **47** (7K), **48** (42I), **49** (42G), **50** (44H) and 2/4-FPhOPh

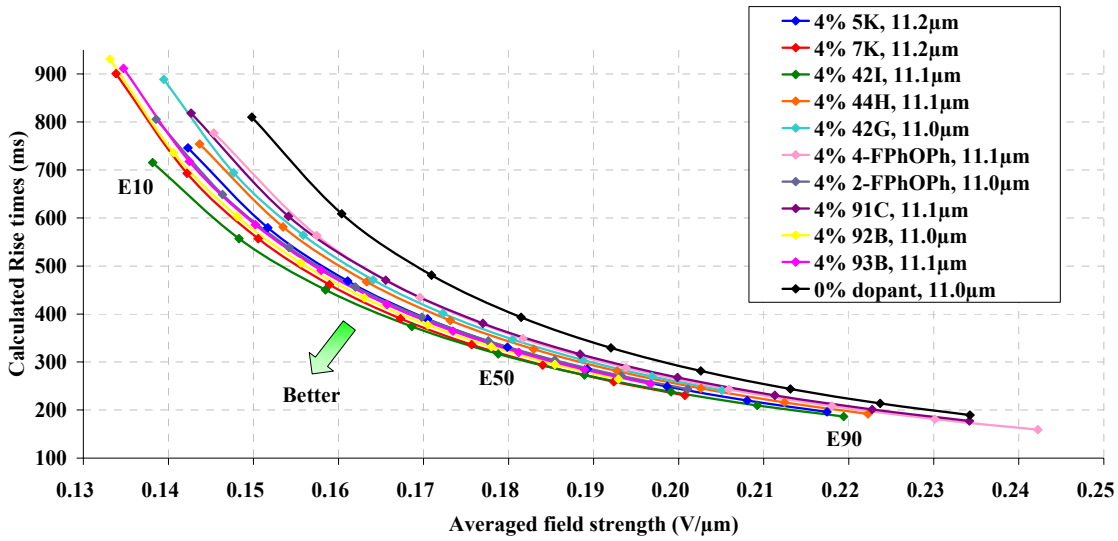
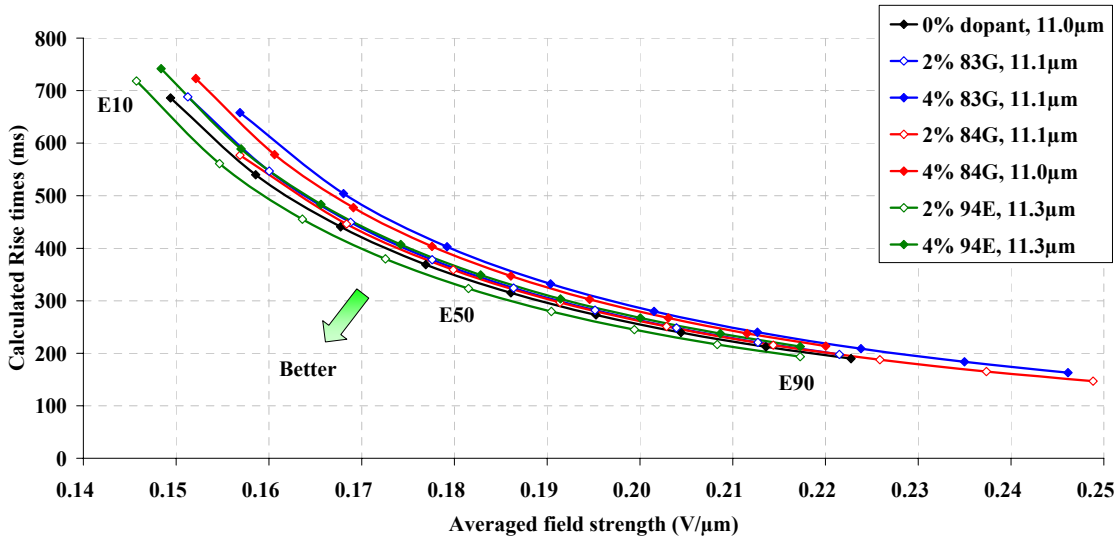


Figure 76. Comparison of materials **92** (94E), **93** (83G) and **94** (84G)



8 References

[1] P. Kirsch and M. Bremer, *Angew. Chem., Int. Ed. Engl.*, 2000, **39**, 4216.

[2] D. B. Harper and D. O'Hagan, *Nat. Prod. Rep.*, 1994, **11**, 123.

[3] D. O'Hagan and D. B. Harper, *J. Fluorine Chem.*, 1999, **100**, 127.

[4] G. Sandford, *Philos. Trans. R. Soc. London, A*, 2000, **358**, 455.

[5] W. R. Dolbier, *J. Fluorine Chem.*, 2005, **126**, 157.

[6] P. Kirsch, *Modern Fluoroorganic Chemistry: Synthesis, Reactivity, Applications*, Wiley-VCH., Weinheim, 2004.

[7] M. Hellmann, E. Peters, W. J. Pummer, and L.A. Wall, *J. Am. Chem. Soc.*, 1957, **79**, 5654.

[8] G. M. Brooke, *J. Fluorine Chem.*, 1997, **86**, 1.

[9] T. N. Gerasimova and N. A. Orlova, *J. Fluorine Chem.*, 1985, **28**, 361.

[10] J. A. Godsell, M. Stacey, and J. C. Tatlow, *Nature*, 1956, **178**, 199.

[11] J. Burdon, P. L. Coe, C. R. Marsh, and J. C. Tatlow, *Tetrahedron*, 1966, **22**, 1183.

[12] J. Burdon, W. B. Hollyhead, and J. C. Tatlow, *J. Chem. Soc.*, 1965, 5152.

[13] L. S. Kobrina, G. G. Furin, and G. G. Yakobson, *Zh. Obshch. Khim.*, 1968, **38**, 514.

[14] R. D. Chambers, C. W. Hall, J. Hutchinson, and R. W. Millar, *J. Chem. Soc., Perkin Trans. 1*, 1998, 1705.

[15] G. K. S. Prakash, T. Mathew, D. Hoole, P. M. Esteves, Q. Wang, G. Rasul, and G. A. Olah, *J. Am. Chem. Soc.*, 2004, **126**, 15770.

[16] G. G. Yakobson, V. E. Platonov, and Vorozhts.Nn, *J. Gen. Chem. USSR (Engl. Transl.)*, 1965, **35**, 1161.

[17] V. V. Bardin, G. G. Furin, and G. G. Yakobson, *Zh. Org. Khim.*, 1981, **17**, 999.

[18] E. Nield, R. Stephens, and J. C. Tatlow, *J. Chem. Soc.*, 1959, 166.

[19] V. V. Bardin, G. G. Furin, and G. G. Yakobson, *J. Fluorine Chem.*, 1983, **23**, 67.

[20] R. Bolton and E. S. E. Owen, *J. Fluorine Chem.*, 1990, **46**, 393.

[21] V. E. Platonov, A. M. Maksimov, K. V. Dvornikova, and P. V. Nikul'shin, *Russ. J. Org. Chem.*, 2005, **41**, 1647.

[22] E. Nield, R. Stephens, and J. C. Tatlow, *J. Chem. Soc.*, 1960, 3800.

[23] G. G. Yakobson, L. S. Kobrina, and Vorozhts.Nn, *J. Gen. Chem. USSR (Engl. Transl.)*, 1965, **35**, 136.

[24] M. Hellmann and A. J. Bilbo, *J. Am. Chem. Soc.*, 1953, **75**, 4590.

[25] I. Collins, S. M. Roberts, and H. Suschitzky, *J. Chem. Soc. (C)*, 1971, 167.

[26] N. Vorozhtsov, N. I. Krizhechkovskaya, and G. G. Yakobson, *J. Gen. Chem. USSR (Engl. Transl.)*, 1961, **31**, 1561.

[27] D. D. Callander, P. L. Coe, and J. C. Tatlow, *Tetrahedron*, 1966, **22**, 419.

[28] L.A. Wall, W. J. Pummer, J. E. Fearn, and J. M. Antonucci, *J. Res. Natl. Bur. Stand., Sect. A*, 1963, **67**, 481.

[29] R. Bolton and J. P. B. Sandall, *J. Chem. Soc., Perkin Trans. 2*, 1978, 137.

[30] J. Riera and R. Stephens, *Tetrahedron*, 1966, **22**, 2555.

[31] T. N. Vasilevskaya, T. N. Badachkeeva, V. A. Gerasimova, N. N. Barkhash, and N. N. Vorozhtsov, *Zh. Org. Khim.*, 1970, **6**, 126.

[32] V. M. Vlasov and O. V. Zakharova, *Zh. Org. Khim.*, 1975, **11**, 785.

[33] V. V. Bardin, L. S. Pressman, L. N. Rogoza, and G. G. Furin, *Zhurnal Obshchei Khimii*, 1992, **62**, 2342.

[34] J. C. Blazejewski and C. Wakselman, *J. Chem. Soc., Perkin Trans. 1*, 1980, 2845.

[35] G. Baum and C. Tamborski, *Chem. Ind.*, 1964, 1949.

[36] R. J. Depasquale and C. Tamborski, *J. Org. Chem.*, 1967, **32**, 3163.

[37] S. Fujii, Y. Maki, and H. Kimoto, *J. Fluorine Chem.*, 1989, **43**, 131.

[38] V. M. Vlasov and G. G. Yakobson, *Zh. Org. Khim.*, 1973, **9**, 1024.

[39] I. G. C. Coutts, M. R. Hamblin, and S. E. Welsby, *J. Chem. Soc., Perkin Trans. 1*, 1981, 493.

[40] H. M. Refat, A. A. Faddo, and E. Biehl, *J. Fluorine Chem.*, 1996, **76**, 99.

[41] M. Bellas, D. Price, and H. Suschitzky, *J. Chem. Soc. (C)*, 1967, 1249.

[42] V. V. Litvak, O. A. Korshunova, and E. G. Saikovich, *Chemosphere*, 2001, **43**, 493.

[43] V. V. Bardin, L. S. Pressman, L. N. Rogoza, and G. G. Furin, *J. Fluorine Chem.*, 1991, **53**, 213.

[44] G. Sandford, A. Tadeusiak, D. S. Yufit, and J. A. K. Howard, *J. Fluorine Chem.*, 2007, **128**, 1216.

[45] J. Burdon, D. R. King, and J. C. Tatlow, *Tetrahedron*, 1966, **22**, 2541.

[46] N. R. Patel, J. G. Chen, Y. F. Zhang, R. L. Kirchmeier, and J. M. Shreeve, *Inorg. Chem.*, 1994, **33**, 5463.

[47] V. N. Shishkin, K. K. Lapin, N. V. Olenina, and K. P. Butin, *Zh. Org. Khim.*, 1999, **35**, 1056.

[48] V. N. Shishkin, I. V. Esina, K. K. Lapin, and K. P. Butin, *Russ. J. Org. Chem.*, 2002, **38**, 374.

[49] P. L. Coe, A. J. Waring, and T. D. Yarwood, *J. Chem. Soc., Perkin Trans. 1*, 1995, 2729.

[50] A. J. Bridges, W. C. Patt, and T. M. Stickney, *J. Org. Chem.*, 1990, **55**, 773.

[51] M. Schlosser and C. Heiss, *Eur. J. Org. Chem.*, 2003, **3**, 447.

[52] C. Heiss and M. Schlosser, *Eur. J. Org. Chem.*, 2003, 447.

[53] A. N. Chernega, A. J. Graham, M. L. H. Green, J. Haggitt, J. Lloyd, C. P. Mehnert, N. Metzler, and J. Souter, *J. Chem. Soc., Dalton Trans.*, 1997, 2293.

[54] C. Tamborski and E. J. Soloski, *J. Organomet. Chem.*, 1967, **10**, 385.

[55] L. S. Chen and C. Tamborski, *J. Fluorine Chem.*, 1981, **19**, 43.

[56] N. Miyaura and A. Suzuki, *Chem. Rev.*, 1995, **95**, 2457.

[57] J. Hassan, M. Sevignon, C. Gozzi, E. Schulz, and M. Lemaire, *Chem. Rev.*, 2002, **102**, 1359.

[58] J. L. Kiplinger, T. G. Richmond, and C. E. Osterberg, *Chem. Rev.*, 1994, **94**, 373.

[59] Y. Kiso, K. Tamao, and M. Kumada, *J. Organomet. Chem.*, 1973, **50**, C12.

[60] V. P. W. Bohm, C. W. K. Gstottmayr, T. Weskamp, and W. A. Herrmann, *Angew. Chem., Int. Ed. Engl.*, 2001, **40**, 3387.

[61] F. Mongin, L. Mojovic, B. Guillamet, F. Trecourt, and G. Queguiner, *J. Org. Chem.*, 2002, **67**, 8991.

[62] K. Lamm, M. Stollenz, M. Meier, H. Gorls, and D. Walther, *J. Organomet. Chem.*, 2003, **681**, 24.

[63] N. Yoshikai, H. Mashima, and E. Nakamura, *J. Am. Chem. Soc.*, 2005, **127**, 17978.

[64] T. Saeki, Y. Takashima, and K. Tamao, *Synlett*, 2005, 1771.

[65] L. Ackermann, R. Born, J. H. Spatz, and D. Meyer, *Angew. Chem., Int. Ed. Engl.*, 2005, **44**, 7216.

[66] J. W. Dankwardt, *J. Organomet. Chem.*, 2005, **690**, 932.

[67] G. Cahiez, F. Lepifre, and P. Ramiandrasoa, *Synthesis (Stuttg)*, 1999, 2138.

[68] Y. M. Kim and S. Yu, *J. Am. Chem. Soc.*, 2003, **125**, 1696.

[69] D. A. Widdowson and R. Wilhelm, *Chem. Commun.*, 2003, 578.

[70] K. Mikami, T. Miyamoto, and M. Hatano, *Chem. Commun.*, 2004, 2082.

[71] S. Bahmanyar, B. C. Borer, Y. M. Kim, D. M. Kurtz, and S. Yu, *Org. Lett.*, 2005, **7**, 1011.

[72] J. R. Ruiz, U. Jimenez-Sanchidrian, and M. Mora, *J. Fluorine Chem.*, 2006, **127**, 443.

[73] T. Braun and R. N. Perutz, *Chem. Commun.*, 2002, 2749.

[74] L. Cronin, C. L. Higgitt, R. Karch, and R. N. Perutz, *Organometallics*, 1997, **16**, 4920.

[75] N. A. Jasim, R. N. Perutz, A. C. Whitwood, T. Braun, J. Izundu, B. Neumann, S. Rothfeld, and H. G. Stammler, *Organometallics*, 2004, **23**, 6140.

[76] M. Aizenberg and D. Milstein, *J. Am. Chem. Soc.*, 1995, **117**, 8674.

[77] S. Hintermann, P. S. Pregosin, H. Ruegger, and H. C. Clark, *J. Organomet. Chem.*, 1992, **435**, 225.

[78] T. Braun, S. P. Foxon, R. N. Perutz, and P. H. Walton, *Angew. Chem., Int. Ed. Engl.*, 1999, **38**, 3326.

[79] M. I. Sladek, T. Braun, B. Neumann, and H. G. Stammler, *J. Chem. Soc., Dalton Trans.*, 2002, 297.

[80] T. Braun, S. Parsons, R. N. Perutz, and M. Voith, *Organometallics*, 1999, **18**, 1710.

[81] M. Aizenberg and D. Milstein, *Science*, 1994, **265**, 359.

[82] N. Y. Adonin and V. F. Starichenko, *J. Fluorine Chem.*, 2000, **101**, 65.

[83] G. B. Deacon, C. M. Forsyth, and J. H. Sun, *Tetrahedron Lett.*, 1994, **35**, 1095.

[84] Y. Ishii, N. Chatani, S. Yorimitsu, and S. Murai, *Chem. Lett.*, 1998, 157.

[85] B. L. Edelbach, B. M. Kraft, and W. D. Jones, *J. Am. Chem. Soc.*, 1999, **121**, 10327.

[86] T. Braun, R. N. Perutz, and M. I. Sladek, *Chem. Commun.*, 2001, 2254.

[87] A. Steffen, M. I. Sladek, T. Braun, B. Neumann, and H. G. Stammler, *Organometallics*, 2005, **24**, 4057.

[88] D. A. Widdowson and R. E. Wilhelm, *Chem. Commun.*, 1999, 2211.

[89] R. Wilhelm and D. A. Widdowson, *J. Chem. Soc., Perkin Trans. 1*, 2000, 3808.

[90] T. Schaub, M. Backes, and U. Radius, *J. Am. Chem. Soc.*, 2006, **128**, 15964.

[91] G. A. Olah, Q. Wang, G. Sandford, and G. K. S. Prakash, *J. Org. Chem.*, 1993, **58**, 3194.

[92] R. K. Atwal and R. Bolton, *Aust. J. Chem.*, 1987, **40**, 241.

[93] P. Kirsch and T. Mergner, *J. Fluorine Chem.*, 2006, **127**, 146.

[94] M. Jarman and R. McCague, *J. Chem. Res. (M)*, 1985, **4**, 1301.

[95] S. Berger, S. Braun, and H. Kalinowski, *NMR Spectroscopy of the Non-Metallic Elements*, John Wiley & Sons 1997.

[96] G. Wittig and F. Bickelhaupt, *Angew. Chem.*, 1957, **69**, 93.

[97] H. Gilman and E. A. Zuech, *J. Am. Chem. Soc.*, 1960, **82**, 3605.

[98] H. Gilman and R. D. Gorsich, *J. Am. Chem. Soc.*, 1956, **78**, 2217.

[99] C. J. Pouchert and J. Behnke, *The Aldrich Library of 13C and 1H FT NMR Spectra*, Aldrich Chemical Company Inc. 1993 (1st Ed.), **3**, 568.

[100] J. Burdon, B. L. Kane, and J. C. Tatlow, *J. Fluorine Chem.*, 1971, **1**, 185.

[101] M. Klasen, M. Bremer, and K. Tarumi, *Jpn. J. Appl. Phys.*, 2000, **39**, 1180.

[102] R. N. Haszeldine, *J. Chem. Soc.*, 1952, 2504.

[103] J. Blackwell and W. J. Hickinbottom, *J. Chem. Soc.*, 1963, 518.

[104] Schmidt, Wolfgang, Voegtle, Poetsch, and Eike, *Liebigs Ann. Org. Bioorg. Chem.*, 1995, **7**, 1319.

[105] M. Karplus, *J. Am. Chem. Soc.*, 1963, **85**, 2870.

[106] H. C. Brown and K. J. Murray, *Tetrahedron*, 1986, **42**, 5497.

[107] G. H. Posner and C. Switzer, *J. Am. Chem. Soc.*, 1986, **108**, 1239.

[108] I. K. Huh and Y. B. Kim, *Liq. Cryst.*, 2002, **29**, 1265.

[109] M. T. Chaudhry and R. Stephens, *J. Chem. Soc.*, 1963, 4281.

[110] G. M. Brooke and W. K. Musgrave, *J. Chem. Soc.*, 1965, 1864.

[111] J. K. Kochi, *J. Am. Chem. Soc.*, 1957, **79**, 2942.

[112] H. H. Hodgson, *Chem. Rev.*, 1947, **40**, 251.

[113] C. G. Swain and R. J. Rogers, *J. Am. Chem. Soc.*, 1975, **97**, 799.

[114] P. Kilickiran, A. Masutani, N. Hollfelder, G. Nelles, A. Yasuda, A. Tadeusiak, and G. Sandford, *SID Symposium Digest*, 2007, **38**, 999.

[115] X. Nie, H. Xianyu, R. Lu, T. X. Wu, and S. T. Wu, *J. Displ. Tech.*, 2007, **3**, 280.

[116] P. Kilickiran, T. Roberts, N. Hollfelder, B. Schüller, A. Matsutani, G. Nelles, and A. Yasuda, *IDW*, 2006, LCT1-3.

[117] F. Bruyneel, H. De Smet, J. Vanfleteren, and A. Van Calster, *Opt. Eng.*, 2001, **40**, 259.

[118] P. Kilickiran, A. Masutani, A. Roberts, G. Nelles, A. Yasuda, A. Tadeusiak, and G. Sandford, *WO/2007/112985*, 2007.