Metal-Catalysed Electrophilic Ring Closing Strategies to Organic Heterocycles

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Metal-Catalysed Electrophilic Ring Closing Strategies to Organic Heterocycles

Abstract

Oxygen and nitrogen heterocycles are well-known classes of compounds due to their excellent biological activity. Halogenated compounds are very useful synthetic intermediates and can function as suitable building blocks for pharmaceutical products. Thus, halocyclisation reactions to deliver fluorine and iodine into oxygen and nitrogen heterocycles have been investigated using electrophilic reagents *N*-fluorobenzensulfonimide and iodine with alkyne-containing tertiary alcohol substrates and alkyne-containing amides.

Chapter 2 describes the synthesis and characterisation of a series of alkyne-containing tertiary alcohol substrates that have been targeted as starting materials to allow an investigation of iodocyclisation/fluorocyclisation reactions in order to generate cyclised products. Complications caused by protocyclisation reactions to give undesired dihydroisobenzofuran products have been overcome by using the different reaction sequences. In **Chapter 3**, a new fluorocyclisation methodology for Ag-catalysed electrophilic fluorination of alkynes to give monofluorinated or difluorinated dihydroisobenzofuran products has been designed, including avenues for regiospecific control to expand both the utility and substrate scope of the reaction. **Chapter 4** shows divergent behaviour in the iodocyclisation reactions of the same alkyne substrates in different solvents where different regioselectivity for the *(E)*/*(Z)* 5-exo-dig product has been demonstrated. This regioselectivity depends on the functional groups present and the reaction conditions. Finally, **Chapter 5** describes the synthesis of terminal alkynes containing benzyl or aryl amides which have been prepared in excellent yields. The amide groups have been used as internal nucleophiles for iodocyclisation reactions using the methods outlined in Chapter 4. It was found that the aryl amide (**5.62e)** gave oxygen-heterocyclic product mixtures in both CH_2Cl_2 and MeCN solvents. However, the benzyl amides **(5.62a,b)** gave oxygen-heterocycles in MeCN and nitrogen-heterocycles in DCM. It is presumed that the relative nucleophilicities of the oxygen and nitrogen centres in these amides are influenced by both the electronic influence of the N-substituent and interactions with the solvent.

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This thesis is dedicated

to

my lovely family

Statement

This thesis is based on work conducted by the author in the Department of Chemistry at the University of Leicester, during the period between July 2015 and June 2018. The work not been submitted, and is not presently being submitted, for any other degree at this or any other university. All experimental work described in this thesis is original unless otherwise acknowledged in the text or by references.

Signed: date: / /

Rusul M. Alrubaay

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Abbreviations

OAc	Acetate
MeCN	acetonitrile
et al.	and others
Ar	aryl
ASAP	Atmospheric-Pressure Solid Analysis
Å	Angstroms
β	beta
BINAP	(2,2′-bis(diphenylphosphino)-1,1′-binaphthyl)
Bu	‘Normal’ butyl
^{n}Bu	n-Butyl
^{t}Bu	t-butyl
Bn	Benzyl
cat	catalyst
$CDCl_3$	chloroform
$COSY_{45}$	Correlation spectroscopy
Cp_2ZrCl_2	Bis(cyclopentadienyl)zirconium(IV) dichloride
CSA	Camphorsulfonic acid
^{o}C	degrees centigrade
δ	delta (NMR chemical shift)
DAST	diethylaminosulfur trifluoride
DCM	dichloromethane
d	doublet
dd	doublet of doublets
dt	doublet of triplets
DMA	*N*,*N*-Dimethylacetamide
DMAP	4-Dimethylaminopyridine
eq.	equivalents
eqn.	equation
E^+	electrophile

Et	Ethyl
Et_2O	diethyl ether
ES	electrophilic substitution
Et_3N	Triethylamine
EtOH	ethanol
EtOAc	Ethyl acetate
EtMgBr	Ethylmagnesium bromide
F-TEDA-BF_4	Selectfluor
g	gram
h	hour
HBF_4	Tetrafluoroboric acid solution
HMQC	Heteronuclear multiple-bond correlation spectroscopy
IPy_2BF_4	bis(pyridine)iodonium tetrafluoroborate
IR	Infra-red
m	multiplet
m/z	Mass/charge ratio
mg	milligrams
mL	millilitres
mol	mols
mp	Melting point
M	Metal
Me	Methyl
MeOH	Methanol
MS	molecular sieves
η	eta
NFSi	*N*-Fluorobenzenesulfonimide
NMP	*N*-Methyl-2-pyrrolidone
NMR	Nuclear magnetic resonance spectroscopy
NOESY	Nuclear Overhauser effect spectroscopy
Nu	nucleophile

OH	hydroxy
OMe	Methoxyl
$PdCl_2(PPh_3)_2$	Bis(triphenylphosphine)palladium(II) dichloride
PMP	p-anisidine
Ph	Phenyl
PPh_3	triphenylphosphine
py	pyridine
s	singlet
t	triplets
$TMSCF_3$	Trimethyl(trifluoromethyl)silane
TBAB	Tetra-n-butylammonium bromide
TBAF	$TMSCF_3$Trimethyl(trifluoromethyl)silane
THF	Tetrahydrofuran

Chapter1

Introduction

1.1 The Importance of Fluorine and Iodine in Organic Molecules

Non-halogenated heterocycles are commonly found in natural products, whilst halogenated heterocycles are often used as the building blocks for pharmaceutical compounds.[1,2] The introduction of fluorine and iodine atoms into molecules can greatly affect their acidity, their dipole moment and polarisability, their lipophilicity, and their bioavailability.[3]

This has meant that organohalogenated compounds have been found to be suitable for a wide range of applications in both the pharmaceutical and agrochemical industries.[4] For this reason, organofluorinated and organoiodinated compounds have been the object of a considerable amount of research, including halocyclisation in order to deliver halogenated heterocyclic products.

The development of fluorination chemistry began over 100 years ago with the introduction fluorine atoms into organic compounds. According to Fera *et al.*,[5] the presence of fluorine often leads to increased lipophilicity, greater activity and inhibition of the oxidative metabolism of drug molecules within the body. In fact, the C-F bond is the strongest single bond known in organic chemistry and a common reason for the incorporation of fluorine into drugs is to reduce the rate of oxidative metabolism of a constituent aromatic ring.[6]

1.2 Fluorine and Iodine in both the Pharmaceutical and Agrochemical Industries

In the second half of the 20th century, a wide variety of fluorinated drugs were synthesised successfully.[7] As a good illustration of this is the anti-cancer drug 5-fluoro-1H,3H-pyrimidine-2,4-dione (5-fluorouacil) **(1.1)**, and the anti-depressant drug Prozac **(1.2)** which acts by selectively inhibiting the reuptake of serotonin (**Figure 1.1**).

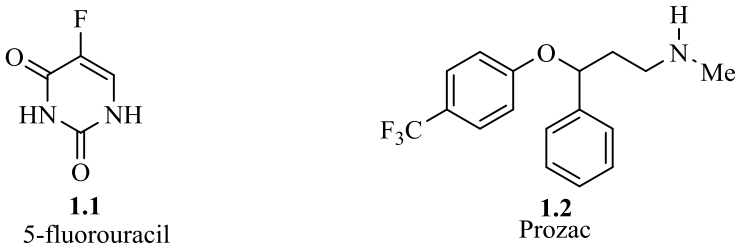


Figure 1.1: *5-Fluoro-1H,3H-pyrimidine-2,4-dione (5-fluorouracil)* ***(1.1)*** *and Prozac* ***(1.2)***

The inclusion of an aryl-CF_3 group in Prozac was found to increase its potency six-fold because the steric bulk of the CF_3 group allows the phenoxy group to adopt a conformation which favours binding to the serotonin transporter protein. Thus, in contemporary medicinal chemistry there is considerable interest in the ability to increase the range of synthetic fluorinated building blocks amenable to functional group manipulation.[8] Other examples of popular fluorinated drugs are shown in (**Figure 1.2)**; research carried out by Robertson *et al*. indicates that Tamoxifen **(1.3)** has gained some significant influence in the medical field because it has been successfully used for treatment of hormone-dependent breast cancer.[9] Among various organofluorine molecules, α-fluoroketones are of particular interest because of their potential applications in the synthesis of a wide variety of bioactive compounds, such as the IRAK4 inhibitor **(1.4)**.[10]

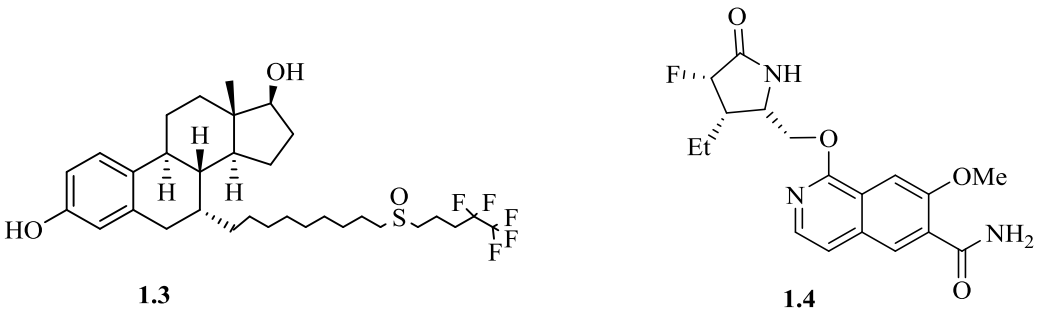


Figure 1.2*: Tamoxifen **(1.3)** and the IRAK4 inhibitor **(1.4)***

As Mabe and Fera[11] specifically mentioned, the antibiotic Erythromycin **(1.5)** plays a significant role in today's medicine; for instance, it is used to remedy an array of infections including bronchitis and Legionnaire's disease. Experimentally, the most important clinically relevant finding showed that Erythromycin can be used to help in the treatment of patients with penicillin allergies. The addition of a fluorine atom in the α-position on the ketone, as per (**Figure 1.3)**, resulted in a longer biological half-life, better bioavailability and higher tissue concentrations *in vivo*.

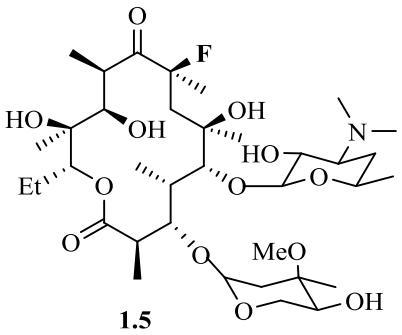
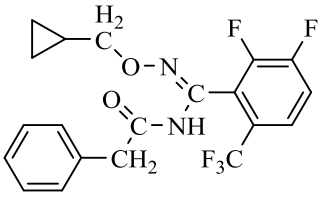
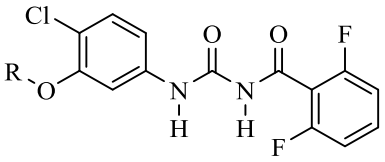


Figure 1.3: *Fluorithromycin drug molecule* ***(1.5)***

The use of fluorinated compounds in agriculture has seen a period of significant expansion to that of one of the largest uses of fluorine at the current time. Fluorinated compounds can be strategically used as agricultural pesticides; for instance, the use of species such as Cyflufenamid **(1.6)** {(Z)-*N*-(α-cyclopropylmethoxyimino-2,3-difluoro-6trifluoromethylbenzyl)-2-phenylacetamide} on primary crops such as wheat (cereals), apples and cucumbers has been studied in detail, as has the use of Fluazuron **(1.7)**[12] (**Figure 1.4)**.



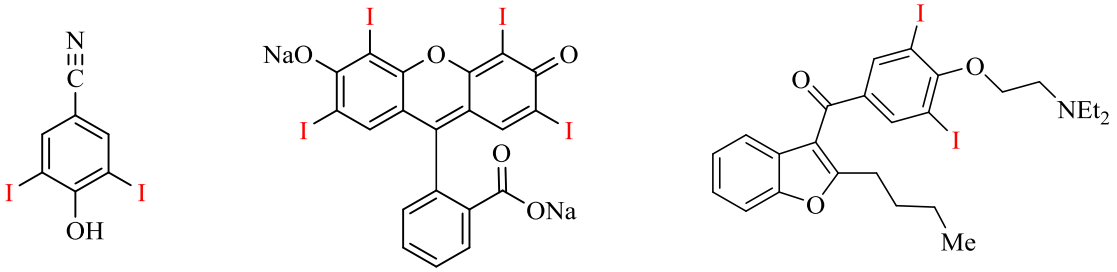
Cyflufenamid **1.6**



Fluazuron **1.7**

Figure 1.4: *Cyflufenamid* ***(1.6)*** *and Fluazuron* ***(1.7)***

In contrast, iodinated compounds are of concern as environmental contaminants owing to the very limited information that is available on their behaviour within the environment. However, the biological detoxification of these classes of contaminants has recently been reported. The first example is that of Ioxynil **(1.8)**[13] herbicides, which have been shown to undergo a variety of transformations in the environment, including reductive dehalogenation by anaerobic bacteria. A second example is Erythrosine **(1.9)**,[14] whose main medical application is in staining the aetiological agent of common oral diseases (dental plaque) and Amiodarone **(1.10)** [15] which is a commercial antiarrhythmic drug (**Figure 1.5)**.



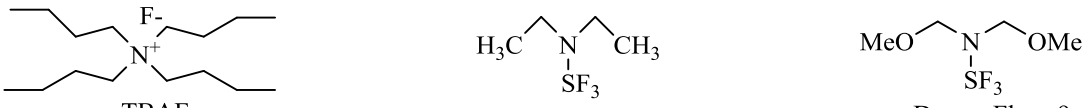
Ioxynil **1.8** Erythrosine **1.9** Amiodarone **1.10**

Figure 1.5: *Ioxynil **(1.8)**, Erythrosine **(1.9)** and Amiodarone **(1.10)***

1.3 Fluorinated Organic Molecules

1.3.1 Nucleophilic Fluorinating Reagents

Fluorine can be introduced into a molecule using a variety of fluorinating agents. These can be classified as sources of nucleophilic fluoride (F^-), fluorine radicals ($F^{\cdot}$) and electrophilic fluorine (F^+). However, the easiest method of introduction is to use a nucleophilic source of fluorine, since they are often cheap and readily available reagents. For example, TBAF (tetrabutylammonium fluoride) **(1.11)**, DAST (diethylaminosulfur trifluoride) **(1.12)** and Deoxo-Fluor 9 **(1.13)** are examples of nucleophilic fluorinating reagents[16-18] (**Figure 1.6**).



TBAF **1.11** DAST **1.12** Deoxo-Fluor 9 **1.13**

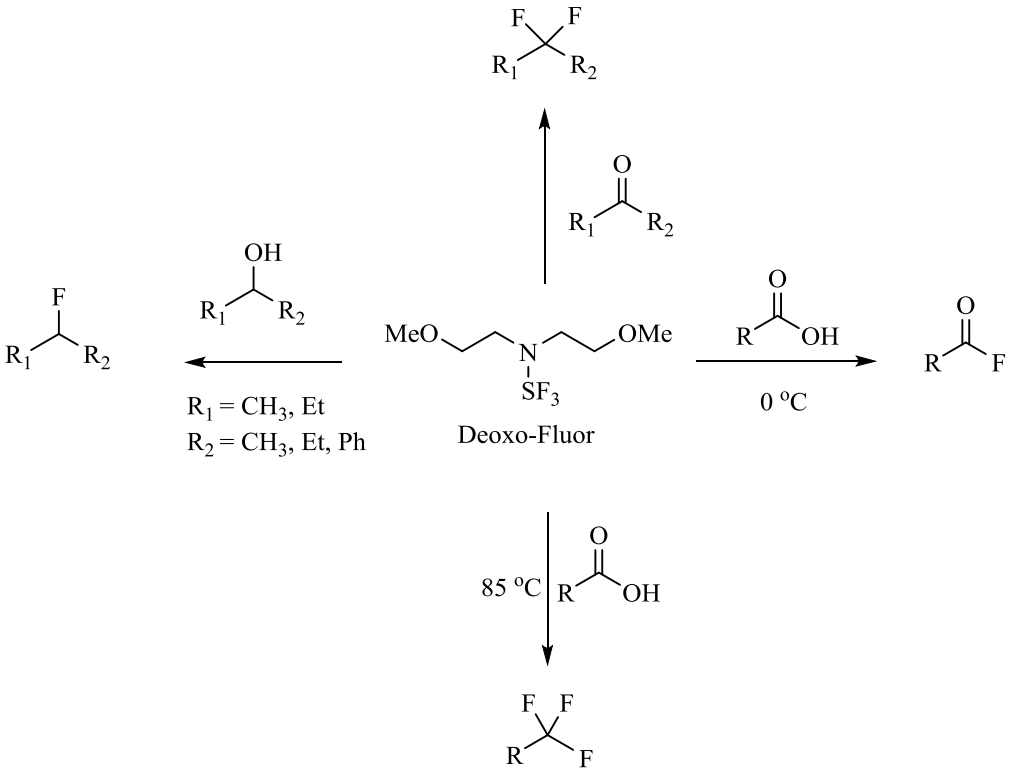
Figure 1.6: *TBAF (tetrabutylammonium fluoride) **(1.11)**, DAST (diethylaminosulfur trifluoride) **(1.12)** and Deoxo-Fluor 9 **(1.13)***

Another nucleophilic source of fluorine is anhydrous HF. However, HF has a low boiling point, high vapour pressure and is highly corrosive and toxic. Therefore, HF/base complexes, such as pyridinium poly(hydrogen fluoride) **(1.14)** and triethylamine tris(hydrogen fluoride) **(1.15)** have been developed as safer alternatives[19,20] (**Figure 1.7**).

1.14 **1.15**

Figure 1.7: *The fluorinating agents pyridinium poly(hydrogen fluoride)* ***(1.14)*** *and triethylamine tris(hydrogen fluoride)* ***(1.15)***

TBAF is an extremely convenient, safe and readily available reagent which is widely used in industry. DAST is also an especially useful source of nucleophilic fluoride, but its highly dangerous nature makes it unsuitable for industrial applications. Deoxo-Fluor 9 is a more thermally stable alternative to DAST which is used in such reactions as the fluorination of ketones, carboxylic acids and secondary alcohols[21] (**Scheme 1.1)**.



Scheme 1.1: *Reactions of Deoxo-Fluor 9*

It is known that aromatic substitution, either catalysed or non-catalysed, is one of the most direct methods of nucleophilic fluorination that allows for control over the regioselectivity. The insertion of the carbon-fluorine bond at a convenient stage using a fluorinating agent is the first such method. Carbon-fluorine bond activation, though less explored than carbon-fluorine bond formation, is invaluable, especially in the synthesis of partially fluorinated compounds which would be otherwise inaccessible or more difficult to prepare.[22,23]

1.3.2 Electrophilic Fluorinating Reagents

Nucleophilic sources of fluoride cannot be used to fluorinate electron-rich substrates, and for this an electrophilic source of fluorine is required. Fluoraza (NF) reagents such as *N*-fluorobis(phenyl)sulfonimide (NFSi) **(1.16)**,[24] *N*-fluoropyridinium salts **(1.17)**, [20] and 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo-2,2,2-octane bis(tetrafluoroborate) (Selectfluor) **(1.18)**[25] can formally behave as a sources of fluoronium cations (F^+) **(Figure 1.8)**. They are generally viewed as safer, more stable, easier to handle and more selective sources of electrophilic fluorine than elemental fluorine itself.

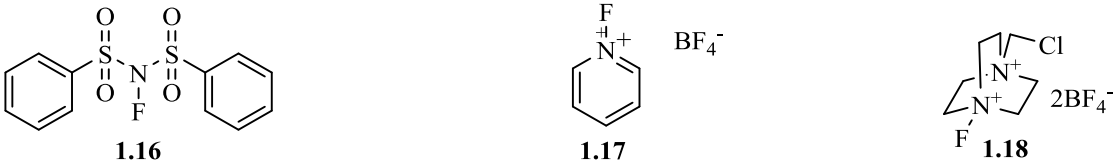
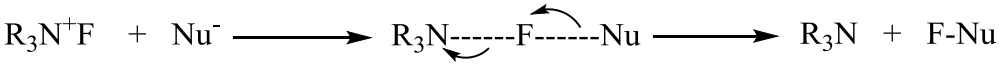


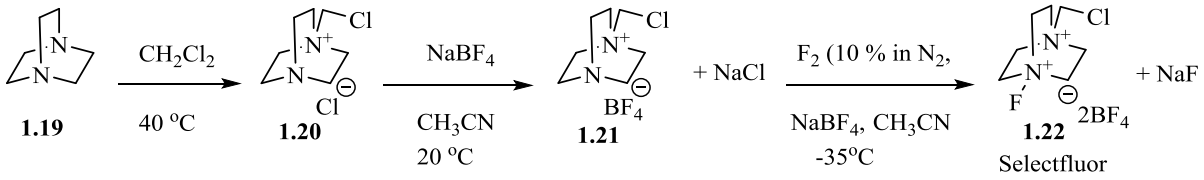
Figure 1.8: *NFSi, N-fluoropyridinium salt and Selectfluor electrophilic reagents*

Fluoraza (NF) electrophilic reagents are prepared from either secondary amines or tertiary amines to give R_2NF compounds or $R_3NF^+A^-$ salts respectively. In these reagents, the R_2N or R_3N^+ moieties are specifically chosen as they are good leaving groups in order to promote the transfer of fluorine to the nucleophile[26] (***Scheme 1.2).***



Scheme 1.2: *Fluoraza (NF) Electrophilic reagents*

Selectfluor is an example of a highly reliable, commercially available NF reagent. It is an exceptionally stable, virtually non-hygroscopic, crystalline white solid. It can be prepared through an efficient and flexible synthesis starting with the chloromethylation of triethylene diamine in dichloromethane. Anion metathesis incorporates BF_4^- with the precipitation of sodium chloride. Finally, low temperature fluorination in the presence of BF_4^- gives Selectfluor **(1.22)** in high yield and purity (**Scheme 1.3**).[27,28]



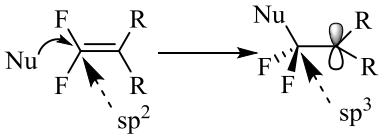
Scheme 1.3: *Synthesis of Selectfluor*

NFSi is among the most commonly used, and is an extremely popular, electrophilic reagents. It is a much milder electrophilic source of fluorine than Selectfluor. However, both reagents have several disadvantages. Firstly, they are expensive to prepare and contain a small amount of fluorine. In addition, the high polarity of Selectfluor means that it is only soluble in polar solvents such as acetonitrile and water. [28]

1.4 Approaches to Fluorination

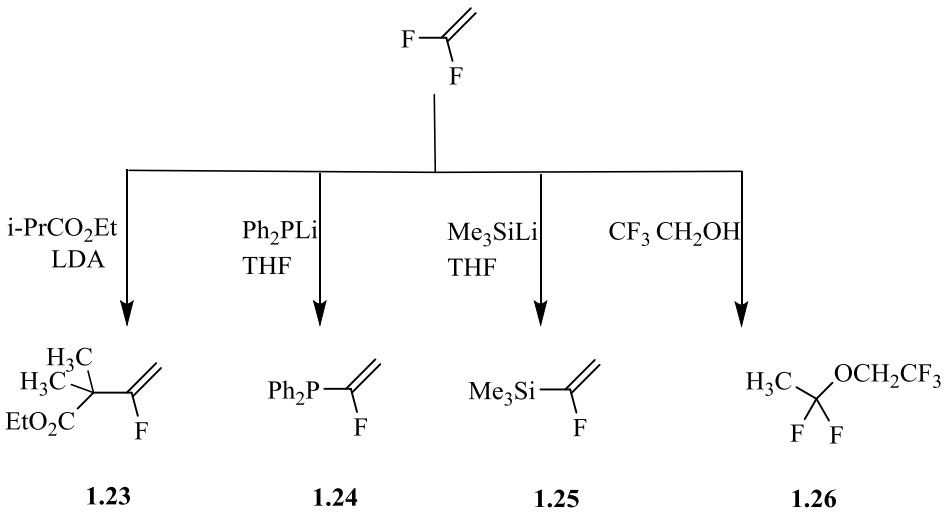
1.4.1 Building Block Approach

The "building block approach" is one of the most practical alternative ways of preparing fluorine compounds. For fluorinated compounds, it uses small amounts of readily available starting materials which already contain fluorine atoms.[29] Fluorocarbenes are the most common and useful building blocks in this field because of their ability to react with alkenes and enol ethers to give α-fluoro-*Z*-enals. Fluoroalkenes and *gem*-difluoroalkenes are highly reactive towards nucleophilic attack at the fluorinated sp^2 carbon due to highly electron deficient *gem*-difluoromethylene carbon, the thermodynamic instability and the formation of stable sp^3 hybridised *β*-fluorocarbanions (**Scheme 1.4**).



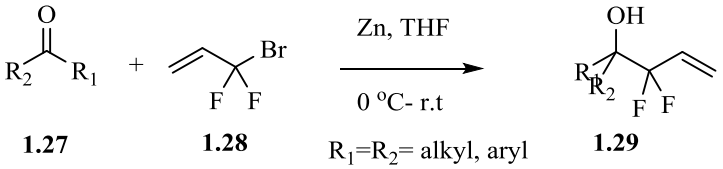
Scheme 1.4: *β-fluorocarbanions*

Therefore, 1,1-difluoroethene is an invaluable building block that can react with a variety of nucleophiles, giving the corresponding products in excellent yield (**Scheme 1.5**).[30]



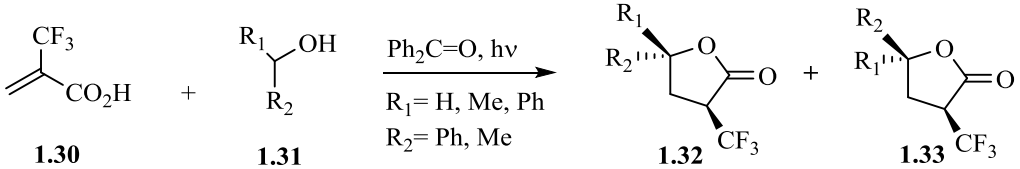
Scheme 1.5: *Building block approach*

In the previous studies, the direct allylation of aldehydes and ketones **(1.27)** via the *in situ* reaction of 3-bromo-3,3-difluoropropene **(1.28)** with acid, zinc and carbonyl substrates were used to give products **(1.29)** in good yield (**Scheme 1.6**). The advantage of this approach over previous reported work is that avoids the use of a thermally unstable intermediate, competitive reaction of the carbonyl subsrate and base and the prior preparation of allylation precursors.[31]



Scheme 1.6*: The direct allylation of aldehydes and ketones*

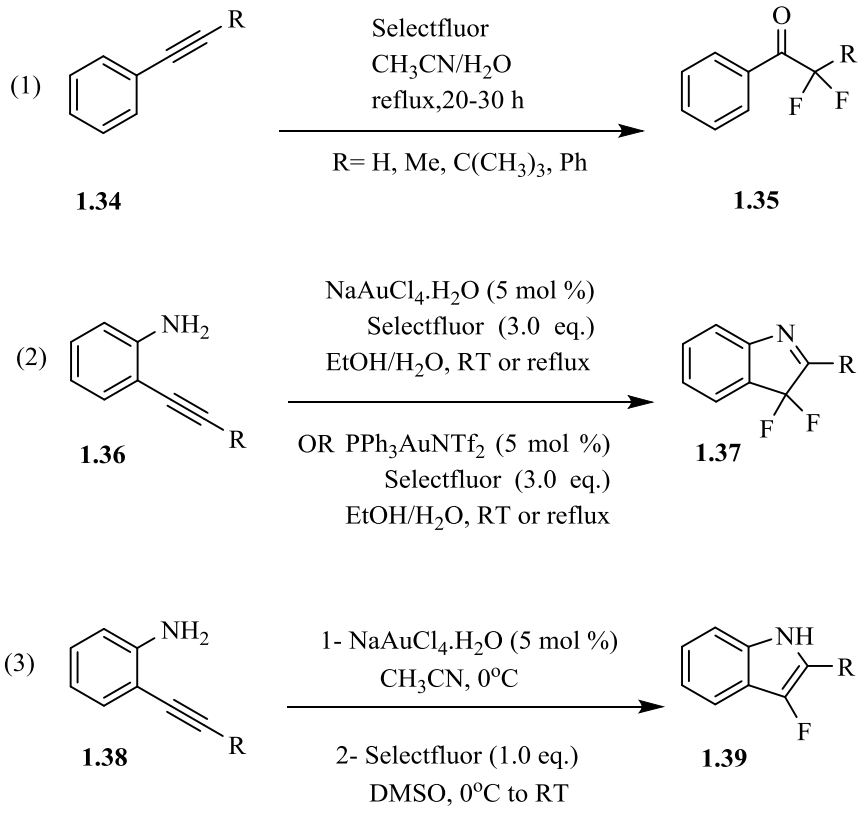
In their earlier work, the O'Hagan group used 2-(trifluoromethyl)acrylic acid **(1.30)** as a building block for the synthesis of 4-substituted 2-trifluoromethyl-γ-butyrolactones **(1.32)** and **(1.33)** (**Scheme 1.7**). The reaction was conducted by the addition of primary and secondary alcohols **(1.31)** to 2-(trifluoromethyl)acrylic acid **(1.30)** in the presence of benzophenone under UV light, with the corresponding products obtained as diastereoismers.[32,33]



Scheme 1.7: *The synthesis of 4-substituted 2-trifluoromethyl-γ-butyrolactones*

1.4.2 Strategies for Fluorination

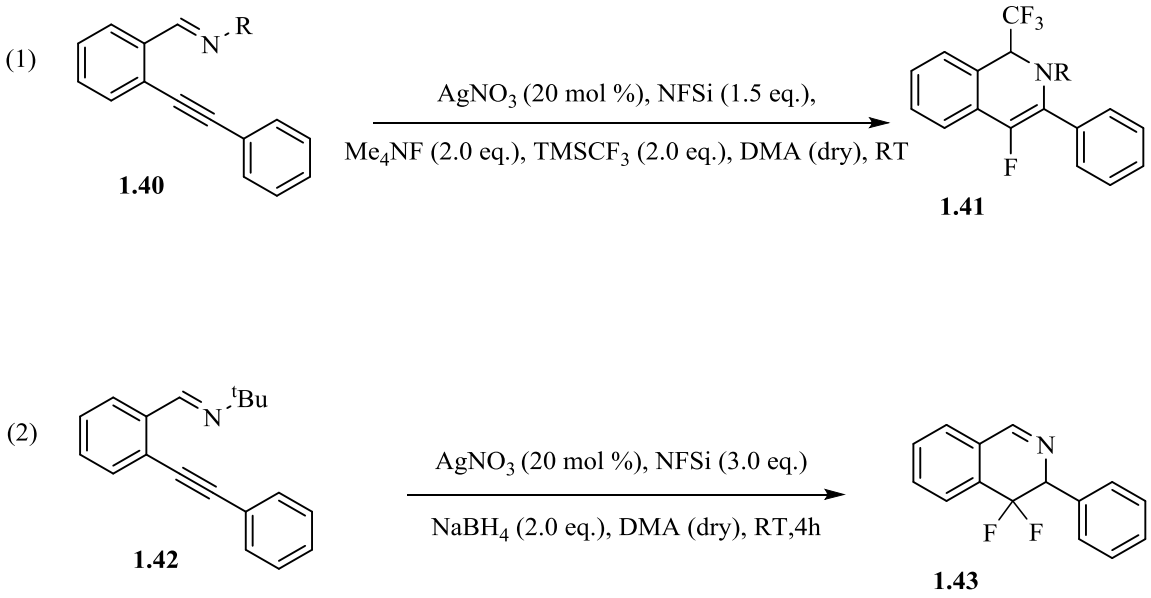
Nucleophilic and electrophilic reagents, as sources of fluorine, have been reported by various groups for the synthesis of fluorinated heterocycles.[34] It has been found that the products generated have different structures depending on the catalyst or reagent used. The scheme below gives some examples of the fluorination of organic molecules using Selectfluor or NFSi as the fluorinating reagents (**Scheme 1.8)**.



Scheme 1.8: *Cyclisation reactions*

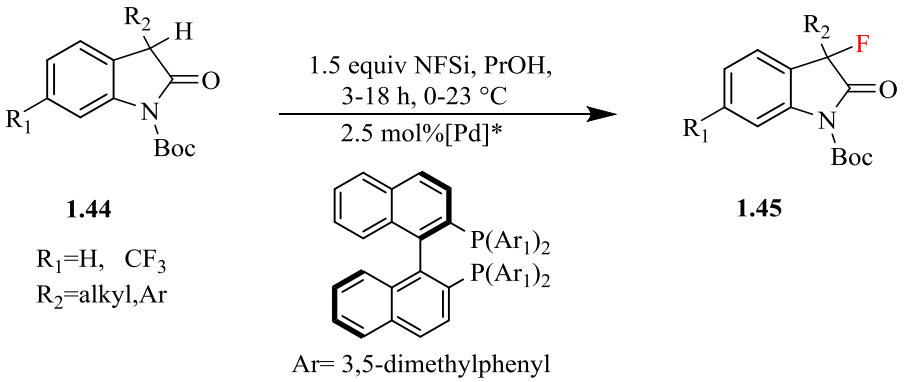
The Selectfluor reactions indicate that electrophilic fluorinating reagents have the ability to react with alkynes even though triple bonds are less reactive to electrophilic reagents than double bonds (sometimes by as much as a factor of ten). Of interest are the formation of difluorinated products (1) in a gold-catalysed reaction depending on the amount of Selectfluor. A similar reaction involving Selectfluor was examined using gold-catalysed to form difluorinated cyclised products (2) or monofluorinated cyclised products (3) depending on number of equivalents of Selectfluor.[35,36] On the other hand, (***Scheme 1.9)***, the reaction of the electrophilic fluorinating reagent NFSi with alkynes has been reported by Liu and co-workers in the synthesis of fluorinated heterocycles.[37,38] The reaction was carried out using a silver-catalyst (20 mol%), NFSi (1.5 eq.), Me_4NF (2.0 eq.), and

$TMSCF_3$ (2.0 eq.) in dry DMA as the solvent at room temperature for 3.5 h to give monofluorinated products **(1.41)**, while using different reaction conditions including $AgNO_3$ (20 mol %), NFSi (3.0 eq.), and $NaBH_4$ (2.0 eq.) in DMA at room temperature for 4 h gave difluorinated products **(1.43)**.



Scheme 1.9*: Cyclisation reactions*

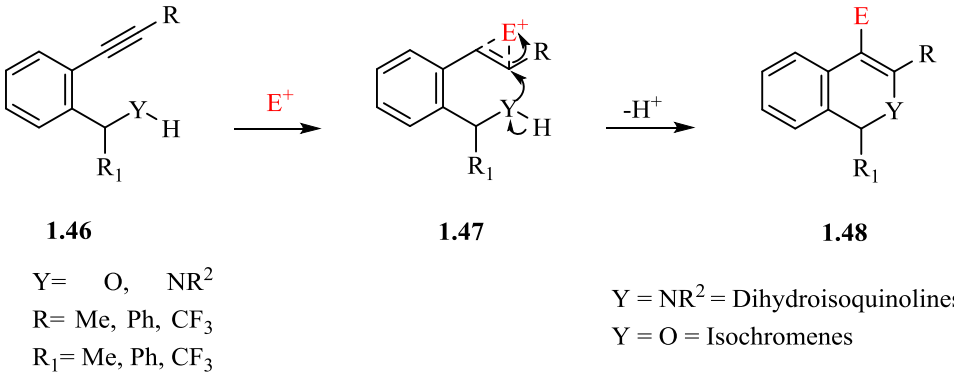
For the fluorination of arenes, a palladium catalyst was used with NFSi. This fluorination by electrophilic aromatic substitution (C-H to C-F) is difficult compared to other halogenations because the electronegativity of fluorine disfavours the rate-limiting formation of the halocyclohexadienyl cation. Sodeoka and co-workers[39] demonstrated that the halocyclohexadienyl cation can be applied to the synthesis of pharmaceutical products using NFSi as a fluorinating reagent to insert fluorine in the presence of a palladium catalyst and using a BINAP ligand to afford the desired fluorinated products **(1.45)** in very good yield (**Scheme 1.10)**.



Scheme 1.10: *Fluorination reaction using fluorinating reagent NFSi and palladium catalyst*

1.5 Approaches to Iodination

The synthesis and functionalisation of isochromenes and isoquinolines have been the major objectives of research for over one hundred years because they are commonly found in natural products, and they are often used as building blocks for pharmaceutical compounds. The synthesis of isochromenes and isoquinolines can be achieved through the electrophilic cyclisation of 2-alkynyl aromatics.

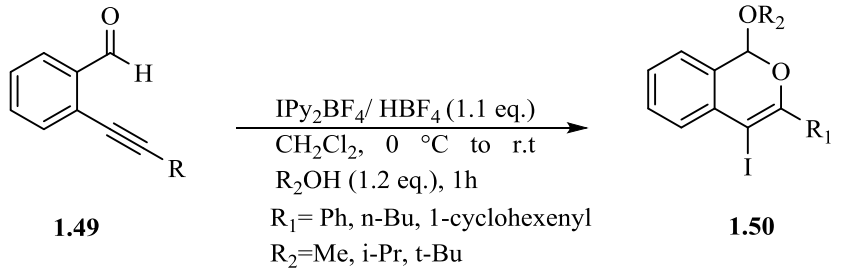


Scheme 1.11: *General synthetic procedure for electrophilic cyclisations*

The general mechanism of these reactions is shown in (**Scheme 1.11**), which starts through alkyne activation of the carbon-carbon triple bond by coordination to the electrophilic cation (E^+) generated from electrophilic reagents to form an intermediate species. This is followed by another functional group (nucleophile, Nu), either on the molecule itself or from an external source, which attacks the electron-deficient carbon of the alkyne.[40,41]

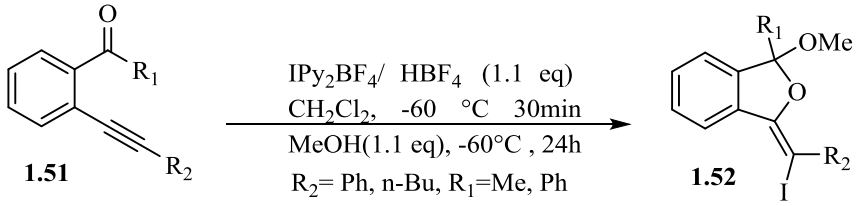
1.5.1 Electrophilic Cyclisation using the Iodonium compound, Bis(pyridine)iodonium Tetrafluoroborate (IPy_2BF_4)

One of the most common methodologies used in electrophilic cyclisations is iodocyclisation using electrophilic reagents. In 2003, Barluenga and co-workers[42] reported some examples of cyclisation reactions (**Scheme 1.12)** and **(Scheme 1.13)**.



Scheme 1.12*: Six-endo cyclisation products using bis(pyridine)iodonium tetrafluoroborate (IPy_2BF_4)*

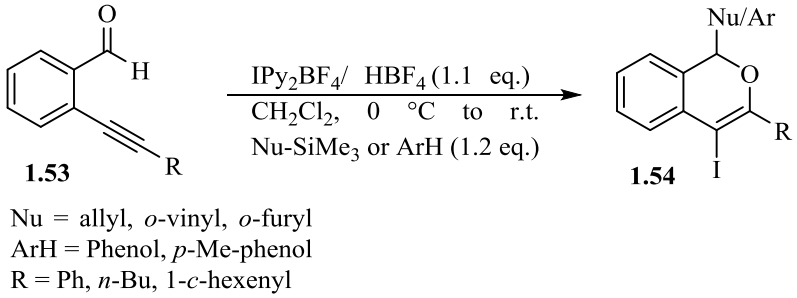
Essentially, the carbonyl functionalised alkynes react with bis(pyridine)iodonium tetrafluoroborate (IPy_2BF_4) to produce either 6-endo or 5-exo-dig cyclisation products. This high regioselectivity of the products depends on the groups present. The room temperature cyclisation of carbonyl groups with alkynes, as promoted by IPy_2BF_4 as the iodinating reagent and using external alcohols as the nucleophiles, gave six-membered heterocyclic products when acetylenic aldehydes were used as the starting materials (**Scheme 1.12)**. In contrast, employing alkynyl aryl ketones **(1.51)** as substrates gave five-membered heterocycles **(1.52) (Scheme 1.13)**.



Scheme 1.13*: Cyclisation reactions with IPy_2BF_4 gave five-membered heterocycles*

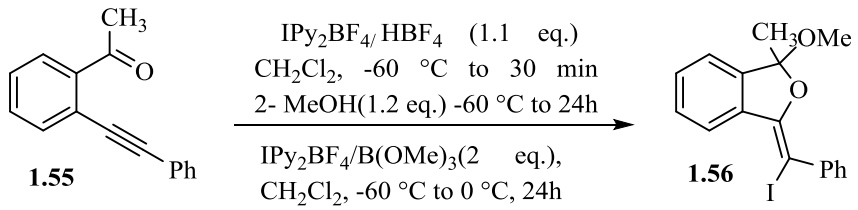
In both cases, the iodinating reagent is activated by the addition of HBF_4. Using this approach, the methoxy ketone was produced in moderate yield, most probably because of partial decomposition under acid media. In this case, the cyclisation follows the more common 5-exo-dig cyclisation mode, furnishing a five-membered ring, rather than the 6-endo cyclisation noticed for aldehydes. [43]

This cyclisation reaction, employing IPy_2BF_4, have generally proven to be quite successful. Barluenga *et al.*[42] suggested that the electrophilic addition reactions using a carbon-based nucleophile methodology, such as silyl-masked or electron-rich arenes as the nucleophilic source, gave highly substituted isochromenes **(1.54)** in moderate to good yields (**Scheme 1.14).**



Scheme 1.14: *The cyclisation reaction*

The iodonium ion allowed for a variant of the above process, as reported by Barluenga and co-workers[43] (**Scheme 1.15)**. They studied the cyclisation of acetylenic ketones **(1.55)** with a stoichiometric amount of IPy_2BF_4 and $B(OMe)_3$, which acted as the electrophilic source to obtain the products **(1.56)** in acceptable to good yields.

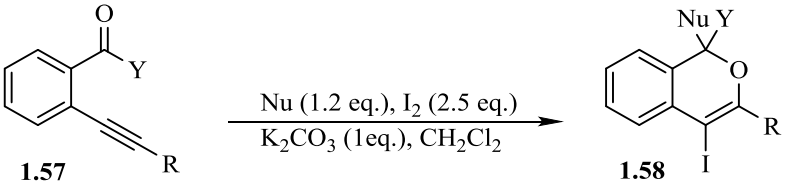


Scheme 1.15: *Cyclisation reaction using bis(pyridine) iodonium tetrafluoroborate (IPy_2BF_4)*

Barluenga *et al.* emphasised the fact that the electrophilic addition reactions using the iodinating reagent bis(pyridine)iodonium tetrafluoroborate (IPy_2BF_4) are one of the most efficient practical approaches for preparing cyclised products. They argued that the iodonium approach offers a number of advantages, such as a conceptually broad compatibility with the nucleophile. [43] It seems that this methodology offers a facile synthesis of cyclised derivatives from easily accessible starting materials, and which can be further elaborated by other chemistries such as palladium cross-coupling reactions and hypervalent iodine chemistry. However, the major drawback of Barluenga's approach is that it utilises a very expensive iodonium salt, IPy_2BF_4, plus the very strong, toxic acid HBF_4, which requires careful temperature control and provides variable yields.[44]

1.5.2 Electrophilic Cyclisation using Iodine

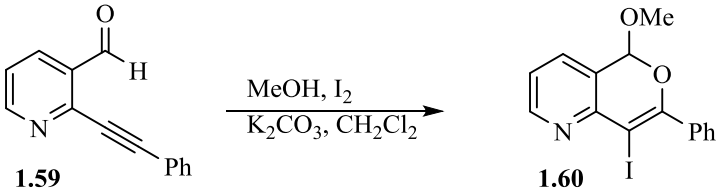
Among a variety of synthetic methodologies, an alternative approach described in the literature is the use of iodine with K_2CO_3 in DCM to promote the electrophilic cyclisation of various functional groups with alkynes **(1.57)** in excellent yields, as reported by Larock and co-workers[45] (**Scheme 1.16**).

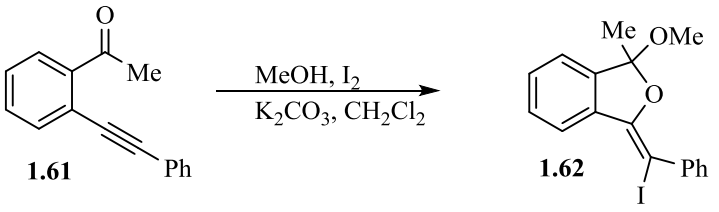


Y= H, Me
R= alkyl, vinylic, aryl
Nu= MeOH, EtOH, $PhNMe_2$, PhOH

Scheme 1.16: *Cyclisation reactions of aldehydes or ketones*

In a similar approach to that described by Barluenga, Larock *et al*. used either aldehydes **(1.59)** or ketones **(1.61)** in the presence of alcohols as external nucleophiles, but using iodine as the electrophilic reagent.

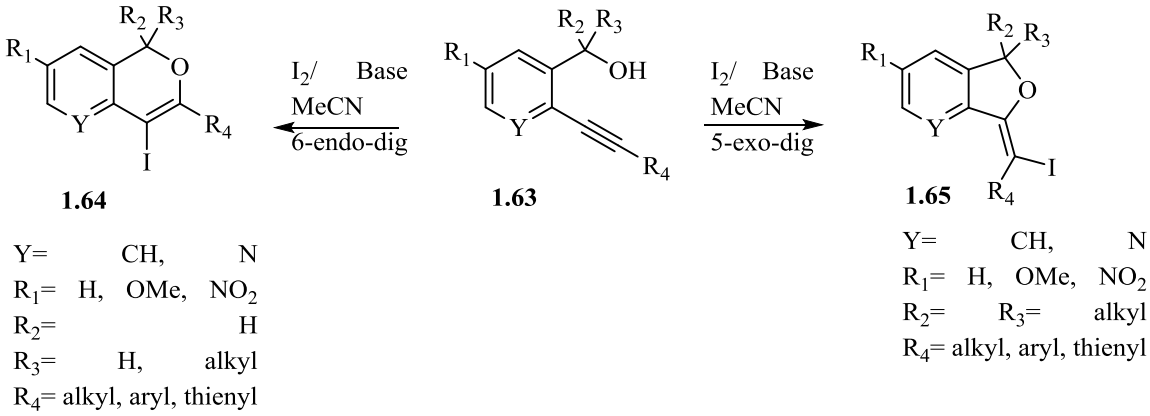




Scheme 1.17: *6-endo-dig or 5-exo-dig cyclisation products*

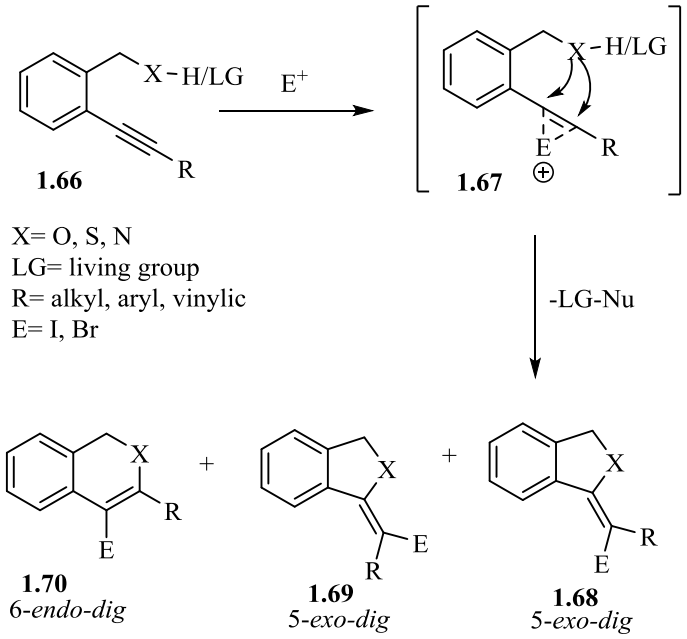
The results showed that a number of factors affect the cyclisation such as the nature of the electrophilic source, the polarisation of the carbon-carbon triple bond, as well as electronic and steric effects. This cyclisation could generate either 6-endo-dig **(1.60)** or 5-exo-dig cyclised **(1.62)** products depending on these factors (**Scheme 1.17**). [46,47]

On the other hand, using alcohols as internal nucleophiles both 6-endo-dig **(1.64)** and 5-exo-dig cyclised **(1.65)** products could be formed **Scheme 1.18.** The Larock group stated that the formation of the five- and six-membered cyclised products were dependent on the substituents on the starting materials **(1.63)**. They showed that tertiary alcohols would normally lead to five-membered ring cyclisation products, while primary and secondary alcohols would lead to six-membered ring cyclised products.[48]



Scheme 1.18: *Cyclisation reactions*

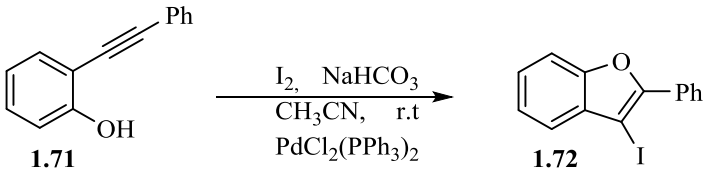
The mechanism for the synthesis of heterocycles using such electrophilic reagents is shown in **Scheme 1.19**.



Scheme 1.19: *General mechanism of electrophilic cyclisation*

In a general electrophilic cyclisation, the addition of the electrophilic source to the C(*sp*) bonds of the alkyne will give an intermediate **(1.67)** which activates the carbon-carbon

bond towards nucleophilic attack. A salt will be produced by nucleophilic anti-attack of the heteroatom on the intermediate, and then an S_N2 displacement by the Nu^- or base present in the reaction mixture will remove the group bound to the heteroatom to generate the heterocyclic products. Three different five- or six-membered products **(1.68)**, **(1.69)** and **(1.70)** can be formed. [49,50]

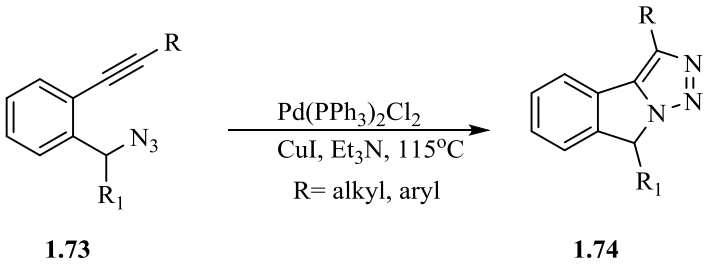


Scheme 1.20*: Synthesis of iodinated benzofurans under palladium catalysis*

Moro *et al.*[51] described the generation of five-membered heterocycles via the cyclisation of alkynes with nucleophiles tethered through an aromatic ring, which represents a powerful tool for the creation of indole and benzofuran rings (**Scheme 1.20)**; for example, one might consider the *o*-alkynyl phenols **(1.71)** after treatment with a $PdCl_2(PPh_3)_2$ catalyst, iodine and a base under mild conditions gave iodinated benzofuran products **(1.72)**.

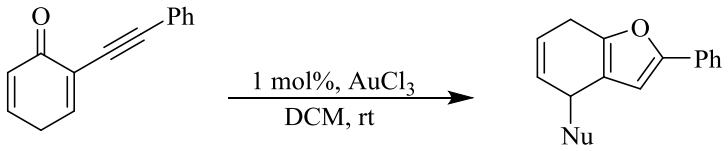
1.5.3 Electrophilic Cyclisation using Brønsted acids

In a closely related study of the use of a palladium-catalysed protocyclisation reaction, Yamamoto also described a new heterocycle with a triazole core **(1.74)**, (**Scheme 1.21),** generated by an azido-alkyne cyclisation mechanism using a Pd(II)- CuI catalyst in Et_3N as a base at high temperature. [52]



Scheme 1.21*: Palladium-catalysed protocyclisation*

The cyclization of 2-(1-alkynyl)-2-alken-1-ones **(1.75)** with nucleophiles in the presence of gold catalyzed condition gave substituted furans (**Scheme 1.22)**. The process seems to be very general and a number of nucleophiles such as primary and secondary alcohols, active methylene and electron rich arenes proved to be viable nucleophiles. [53]



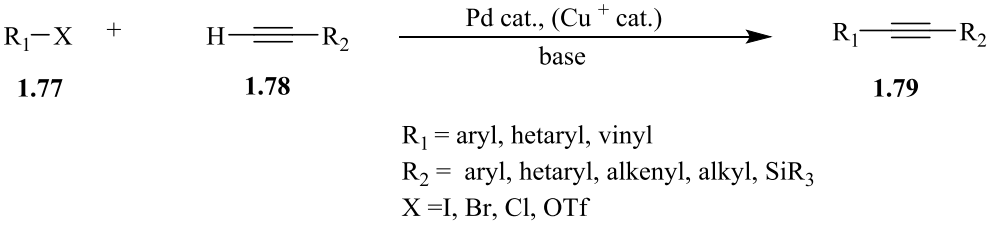
1.75 **1.76**

Scheme 1.22: *Gold-catalysed protocyclisation*

1.6 Aims and Objectives of the Project

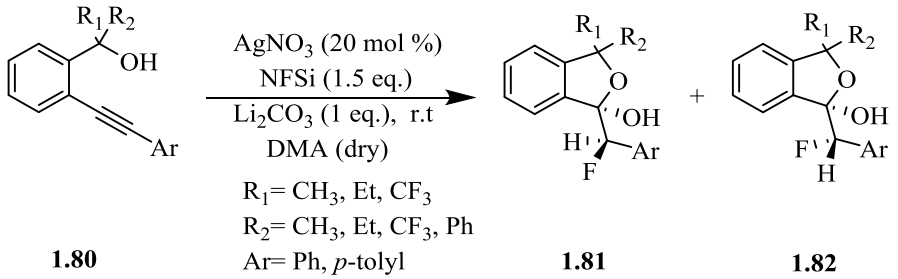
The project will outline approaches to the synthesis of heterocyclic species such as isochromenes and benzofurans. The methodology will be developed for the cyclisation of alcohols, amines and amides using electrophilic reagents. To achieve this, the electrophilic reagents iodine and *N*-fluorobenzensulfonimide will be investigated using a range of different reaction conditions, such as solvent and temperature, for halocyclisation reactions that deliver halogenated heterocycles.

The work in Chapter 2 focuses on the synthesis of a variety of alkyne substrates **(1.79)** using one of the most popular coupling methods, the Sonogashira cross-coupling (**Scheme 1.23)**. These alkynes are the key starting materials required for the iodocyclisation/ fluorocyclisation reactions using internal nucleophiles.



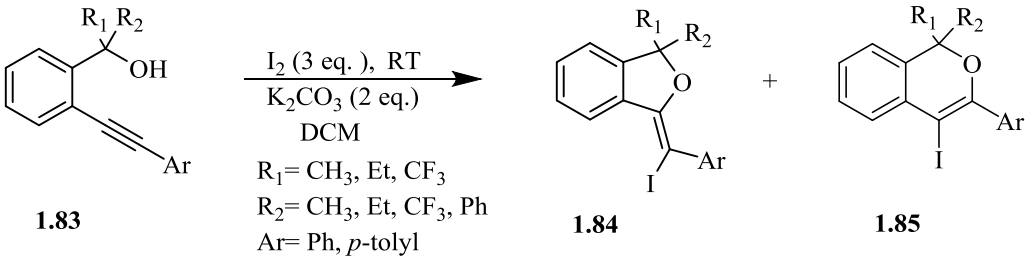
Scheme 1.23: Sonogashira cross-coupling

The aim in Chapter 3 is to design new fluorocyclisation procedures for aromatic alkynes containing tertiary alcohol groups **(1.80)** that act as the internal nucleophiles. The possibility of using $AgNO_3$ as a cheap, readily available catalyst is also extremely attractive. NFSi was chosen as the fluorinating reagent since it is a selective, shelf-stable and easy to handle source of electrophilic fluorine (**Scheme 1.24)**.



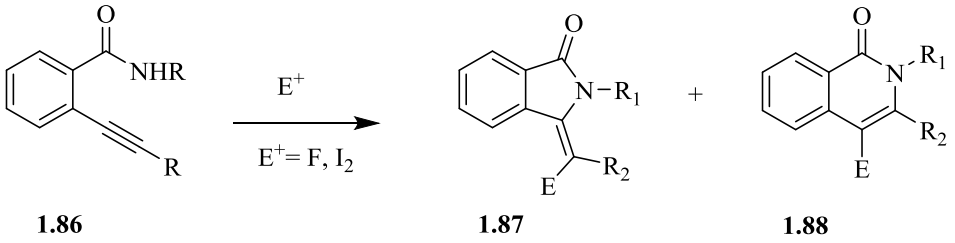
Scheme 1.24*: Fluorocyclisation of aromatic alkynes containing tertiary alcohol groups*

In Chapter 4, iodocyclisation reactions of the same aromatic alkynes in a couple of solvents will be presented. In this interesting reaction, the regioselectivity of the products will be studied, as either 6-endo or 5-exo-dig cyclisation products **(1.84)** and **(1.85)** can be formed. The regioselectivity will depend on the functional groups present and the reaction conditions (**Scheme 1.25).**



Scheme 1.25*: Iodocyclisation reactions*

Finally, in Chapter 5 attempts to prepare new alkynyl aromatics containing amines or amides **(1.86)** as internal nucleophiles for fluorocyclisation and iodocyclisation reactions under similar conditions to those used for the alkyne-containing tertiary alcohol substrates will be described (**Scheme 1.26)**.



Scheme 1.26*: Halocyclisation reactions*

1.7 References

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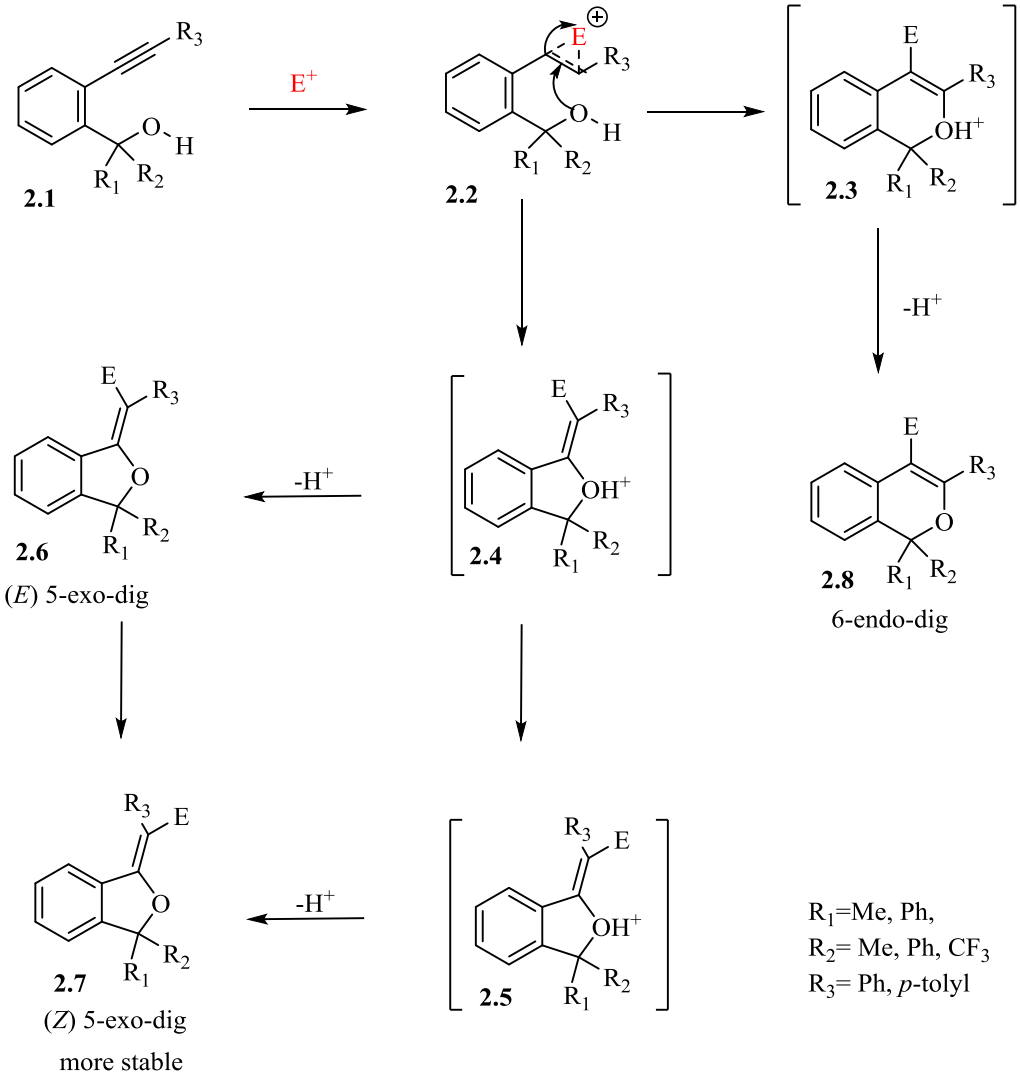
Chapter 2

Synthesis of Alkyne Containing Tertiary Alcohol Targets and Protocyclisation Reactions

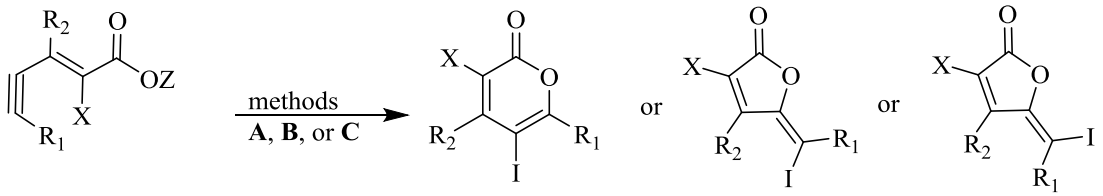
2.1 Introduction

Previous studies have shown that the synthesis of oxygen-containing heterocycles, such as isochromenes and dihydroisobenzofurans, can be achieved through a cyclisation reaction of 2-alkynyl aromatics **(2.1)**.[1,2] These methods have been highly successful in organic synthesis. The reactions start through the activation of the alkyne with an electrophile (E^+), after which the alcohol (nucleophile, Nu^-) attacks the electron-deficient carbon of the alkyne. Finally, deprotonation yields the heterocycles **(2.6), (2.7),** and **(2.8)** (**Scheme 2.1**).



Scheme 2.1: *Synthesis of isochromenes and dihydroisobenzofurans*

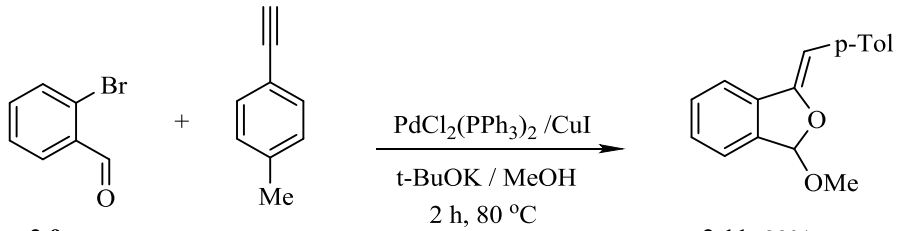
This basic approach, using the cyclisation of alcohols with electrophilic reagents, can give either five-membered cyclised products **(2.6)/(2.7)** or the six-membered cyclised product **(2.8)** under different reaction conditions. In an alternative example, using enynoates**,** a mixture of *E*- and *Z*-iodoethylidenefuranone isomers can be formed by a 5-exo-dig cyclisation or 6-membered ring iodopyranone products. In this case, the selectivity of the iodolactonisation depended not only on the solvent but also the structures of the starting materials **(Scheme 2.2)**.[2]



Z = H, Me; X = Br; R_1 = n-C_5H_{11}, (Z)-MeCH=CMe; R_2 = H, C_5H_{11}
method **A**: I_2 (3.0 eq.), $NaHCO_3$ (3.0 eq.), CH_3CN, 1.5h, r.t
method **B**: NIS (1.1 eq.), $KHCO_3$ (1.0 eq.), CH_3CN, 2.5h, r.t
method **C**: ICl (1.0 eq.), CH_2Cl_2, 1h, r.t

Scheme 2.2: *Cyclisation reactions*

However, the cyclisation reaction can also be achieved through a different approach. For example, dihydroisobenzofurans have been successfully prepared by Dell'Acqua's[3] group using a Pd-mediated Sonogashira coupling reaction of a terminal alkyne **(2.10)** with 2-bromobenzaldehyde **(2.9)**. The palladium catalyst functions as the activating electrophile on the alkynyl-coupled product from the Sonogashira reaction to give a cyclised product **(2.11)** in excellent yield (82%) at 80°C in 2 h (**Scheme 2.3**).



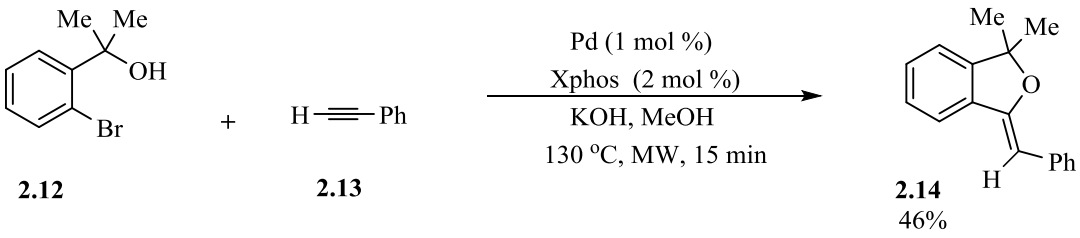
2.9 **2.10** **2.11** 82%

Scheme 2.3: *Metal-catalysed cyclisation reaction*

More recently, other groups have taken inspiration from this work to generate cyclised products. In 2014, Buxaderas and co-workers[4] used this palladium-catalysed protocyclisation route to effect the reaction of a terminal alkyne **(2.13)** with an aryl halide

tertiary alcohol **(2.12)** in the presence of Pd (1 mol %) and a strong base under microwave radiation at 130 ˚C for 15 minutes to generate (*Z*)-3-benzylidene-1,1-dimethyl-1,3-dihydroisobenzofuran **(2.14)** in modest yield (46%) (

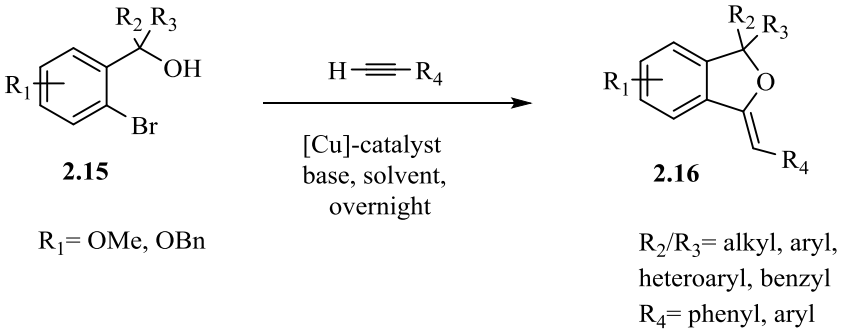
Scheme 2.4).



Scheme 2.4: *Palladium-catalysed protocyclisation*

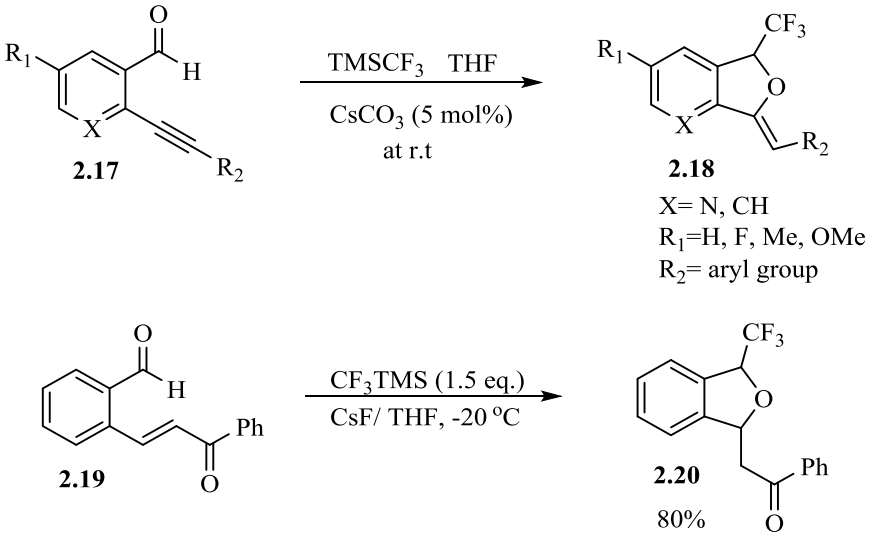
Following this, Satyanarayana's group[5] demonstrated a very similar cyclisation, which was carried out using terminal acetylenes with aryl halide tertiary alcohols **(2.15)** but in the absence of a palladium catalyst, providing additional flexibility when planning synthetic routes. This reaction was carried out for a longer time at 110 ˚C with $CsCO_3$ as a strong base to give the cyclisation products **(2.16)** in good yields (> 89%) (

Scheme 2.5).



Scheme 2.5: *Protocyclisation in the absence of a palladium catalyst*

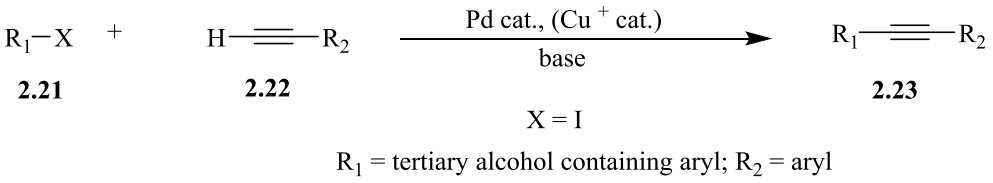
In the literature,[6,7] a number of publications have reported a nucleophilic addition/ intramolecular cyclisation approach using $TMSCF_3$. Cyclised dihydroisobenzofuran products **(2.18)** were synthesised by Gong and co-workers in 2013 using alkyne **(2.17)** in THF at room temperature. Following this, in 2014, Xu and co-workers investigated the use of $TMSCF_3$ with CsF at -20 ˚C, which gave the cyclisation product **(2.20)** in good yield (80%) (**Scheme 2.6**).



Scheme 2.6: *Nucleophilic addition/ intramolecular cyclisation*

2.2 Targets for the Iodocyclisation/ Fluorocyclisation Reactions

The key starting materials required for the iodocyclisation/fluorocyclisation reactions with internal nucleophiles were the alkyne-containing tertiary alcohol substrates **(2.23)** (Scheme 2.7). Many studies in the literature and research groups have tried the electrophilic cyclisation with the alkyne-containing primary and secondary alcohol substrates while previous studies on tertiary alcohol substrates were rare. Therefore, the aim of the work in this chapter focussed on the preparation of a variety of alkyne-containing tertiary alcohol substrates **(2.23)** as starting materials for the cyclisation reactions using a common coupling reaction, namely the Sonogashira cross-coupling.



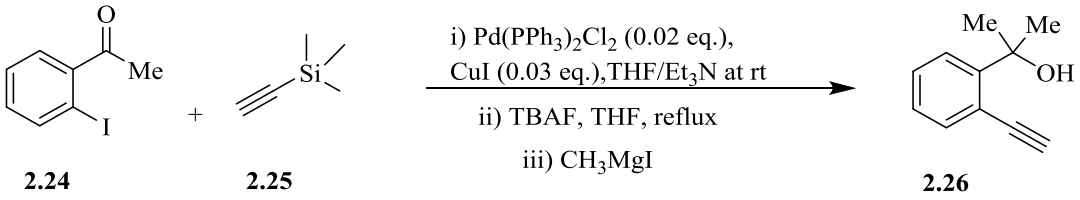
Scheme 2.7: *Sonogashira cross-coupling*

Transition-metal-catalysed cross-coupling reactions can easily be considered cornerstones in the field of organic synthesis. Among them, the palladium-catalysed sp^2-sp coupling reactions between aryl or alkenyl halides or triflates **(2.21)** and terminal alkynes **(2.22)** (Scheme 2.7) [8] is one of the most important methods by which to prepare aryl alkynes, which are precursors for natural products, pharmaceuticals, and molecular organic materials. In fact, it should be noted that alkynyl alcohols have two functional groups, an alcohol and an alkyne, which makes them highly attractive as building blocks.

However, synthetic routes to these alkynes are rare, especially those containing a tertiary alcohol. Propargylic alcohols **(2.26)** undergo a variety of Pd-catalysed transformations, and Sonogashira coupling forms an important class of these reactions. These alcohols can be synthesised from a broad range of terminal alkynes and aldehydes or, indeed, the more sterically encumbered ketones. The traditional method involves stoichiometric deprotonation of an alkyne *via* Grignard formation to access the metallated alkyne, which can then be used as a nucleophile to add into the electrophilic carbonyl.[9]

In 2009 Saá and co-workers[10] reported that the aromatic alkyne 2-(2-ethynylphenyl)propan-2-ol **(2.26)** could be prepared in three steps in up to an 86% yield. According to this literature procedure, the product was prepared by the Sonogashira coupling of 1-(2-iodophenyl)ethanone with trimethylsilylacetylene **(2.25)** (1.5 eq.) using $Pd(PPh_3)_2Cl_2$ (0.02 eq.) and CuI (0.03 eq.) in THF/Et_3N at room temperature, then desilylation with TBAF (1.25 eq.) in THF, and the addition of methyl magnesium iodide (2 eq.) in THF (

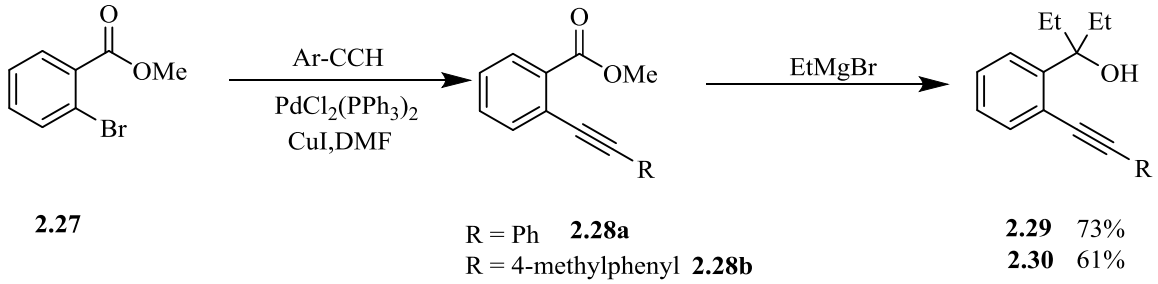
Scheme 2.8).



Scheme 2.8: *Synthesis of aromatic alkyne 2-(2-ethynylphenyl)propan-2-ol **(2.26)***

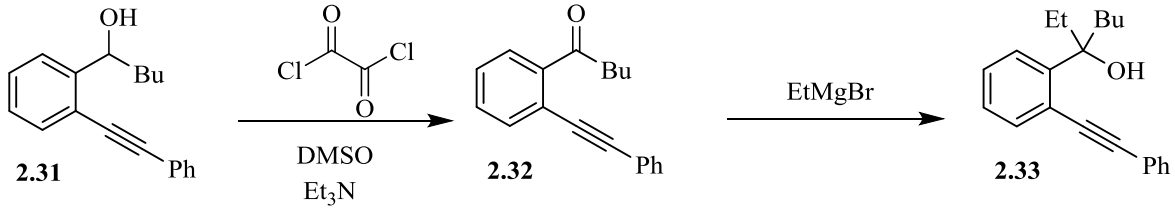
In 2009, Larock *et al.*[11] demonstrated the synthesis of compounds bearing a tertiary alcohol 3-[2-(phenylethynyl)phenyl]pentan-3-ol **(2.29)** and 3-[2-(p-tolylethynyl)phenyl]pentan-3-ol **(2.30)** by Sonogashira coupling of methyl-2-iodobenzoate **(2.26)** and the appropriate terminal alkyne, followed by the addition of EtMgBr. Broad scope, high tolerance to functional groups and a simple procedure make this method highly interesting.

For the general procedure of the Sonogashira coupling,[12] $PdCl_2(PPh_3)_2$, CuI, and phenylacetylene or *p*-tolylacetylene were added to a solution of methyl 2-bromobenzoate **(2.26)** (obtained by esterification of commercially available 2-bromobenzoic acid) in anhydrous DMF at room temperature, and the reaction allowed to proceed for 18 h to give intermediates **(2.27)** (isolated yield 96%) and **(2.28)** (isolated yield 89%) (**Scheme 2.9**).



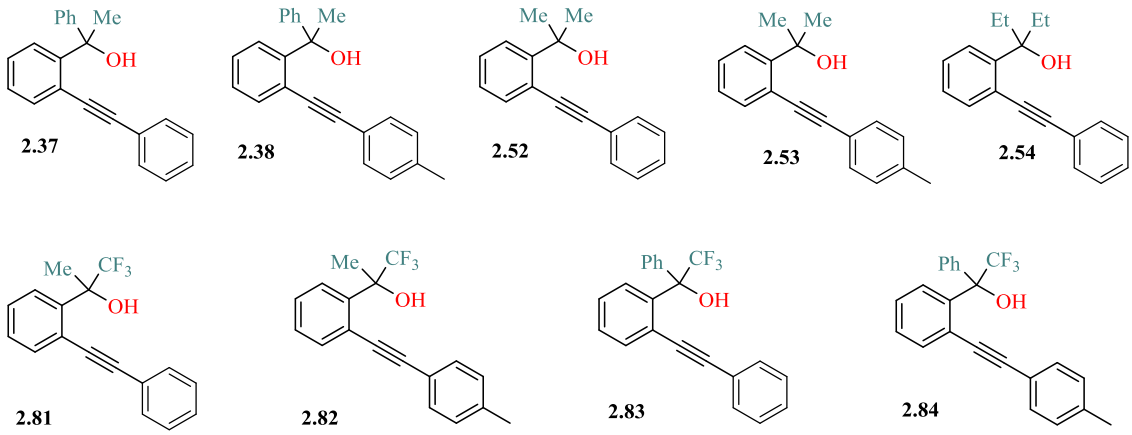
Scheme 2.9: *Synthesis of alkyne tertiary alcohol*

In the second step, that of introducing the ethyl group by EtMgBr addition, a solution of EtMgBr was prepared in anhydrous Et_2O from Mg and EtBr which was then added dropwise to a solution of the alkynyl ester **(2.28a)** and **(2.28b)** in anhydrous benzene, and the reaction allowed to proceed for 1 h. The crude reaction product was purified by column chromatography to give products **(2.29)** (isolated yield 73%) and **(2.30)** (isolated yield 61%) (**Scheme 2.9**). Larock and co-workers also used the secondary alcohol **(2.31)** to prepare the asymmetric tertiary alcohol **(2.33)** (**Scheme 2.10**).



Scheme 2.10: *Synthesis of alkynyl tertiary alcohol*

Our targets were a series of known (**2.52**, **2.53** and **2.54**) [14] and new alkynyl-containg tertiary alcohol substrates which would allow a comparison of alkyl, phenyl and trifluoromethyl substitutents on the cyclisation reactions (**Scheme 2.11**).

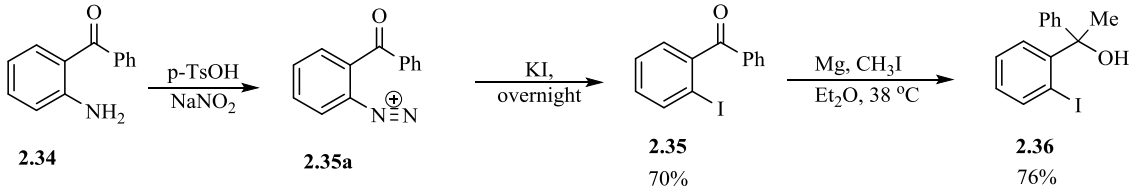


Scheme 2.11: *Alkynyl-containg tertiary alcohol substrates*

2.3 Synthetic Approaches to Alkyne Starting Materials - Sonogashira Coupling

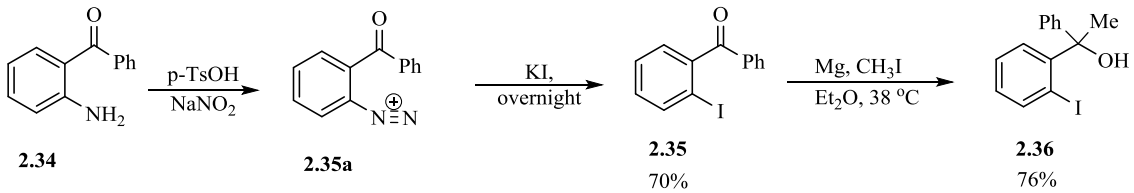
2.3.1 Preparation of 1-Phenyl-[1-(2-arylethynyl)phenyl]ethanol

The initial preparations of the new alkynyl tertiary alcohol products **(2.37)**, and **(2.38)** were carried out via three steps. The first step started with the preparation of 2-iodobenzophenone **(2.35)** (



2.34 **2.35a** **2.35** 70% **2.36** 76%

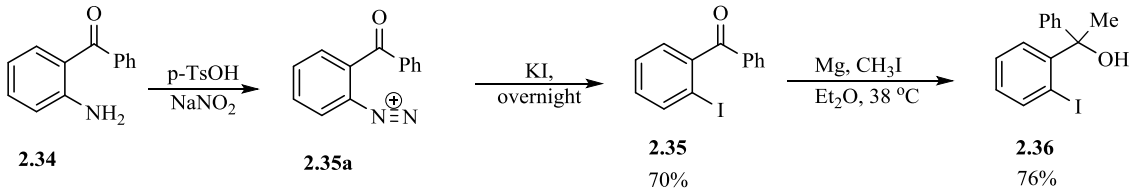
Scheme 2.12) via a diazotisation reaction of 2-aminobenzophenone **(2.34)** with potassium iodide, sodium nitrite and *p*-toluene sulfonic acid monohydrate in acetonitrile at low temperature, giving a 70% isolated yield after purification by column chromatography. The characterisation data for this known compound were in agreement with those in the literature. [5]



2.34 **2.35a** **2.35** 70% **2.36** 76%

Scheme 2.12: *Preparation of 1-phenyl-[1-(arylethynyl)phenyl]ethanol*

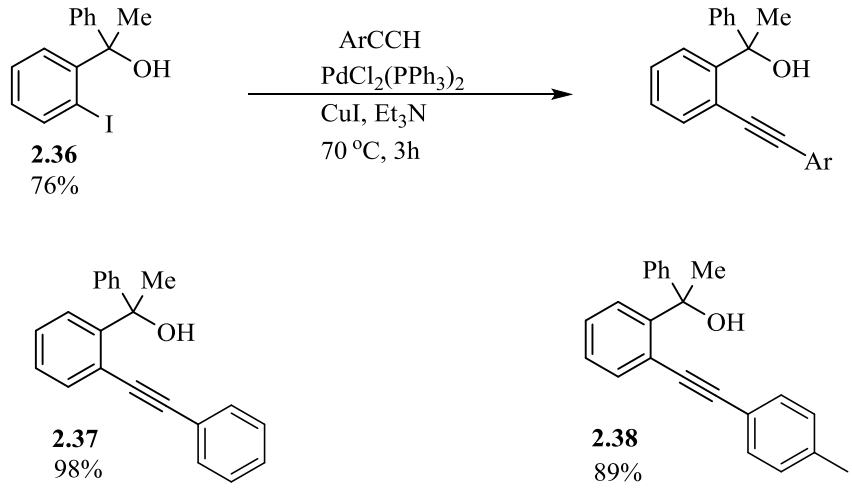
In the second step, the Grignard reagent CH_3MgI, freshly prepared from MeI and Mg in dry Et_2O, was reacted successfully with 2-iodobenzophenone **(2.35)** in dry Et_2O by heating under reflux for 3 h to produce the desired tertiary alcohol product (



2.34 **2.35a** **2.35** 70% **2.36** 76%

Scheme 2.12). 1-(2-Iodophenyl)-1-phenylethanol **(2.36)** was obtained in a 76% yield after purification by column chromatography; the characterisation data for this known compound were in agreement with those in the literature. [3]

For the Sonogashira reaction, 1-(2-iodophenyl)-1-phenylethanol **(2.36)** (1 eq.) was reacted with the terminal alkynes phenylacetylene and 1-ethynyl-4-methylbenzene (3 eq.) in the presence of bis(triphenylphosphine)palladium(II) dichloride [Pd $(PPh_3)_2Cl_2$] (2 mol %) and CuI (4 mol%) as a catalyst in dry Et_3N at 70°C overnight to give the alkynyl tertiary alcohol products **(2.37)** (isolated yield 98%) and **(2.38)** (isolated yield 89%) (**Scheme 2.13**).



Scheme 2.13: *Preparation of 1-phenyl-[1-(arylethynyl)phenyl]ethanol*

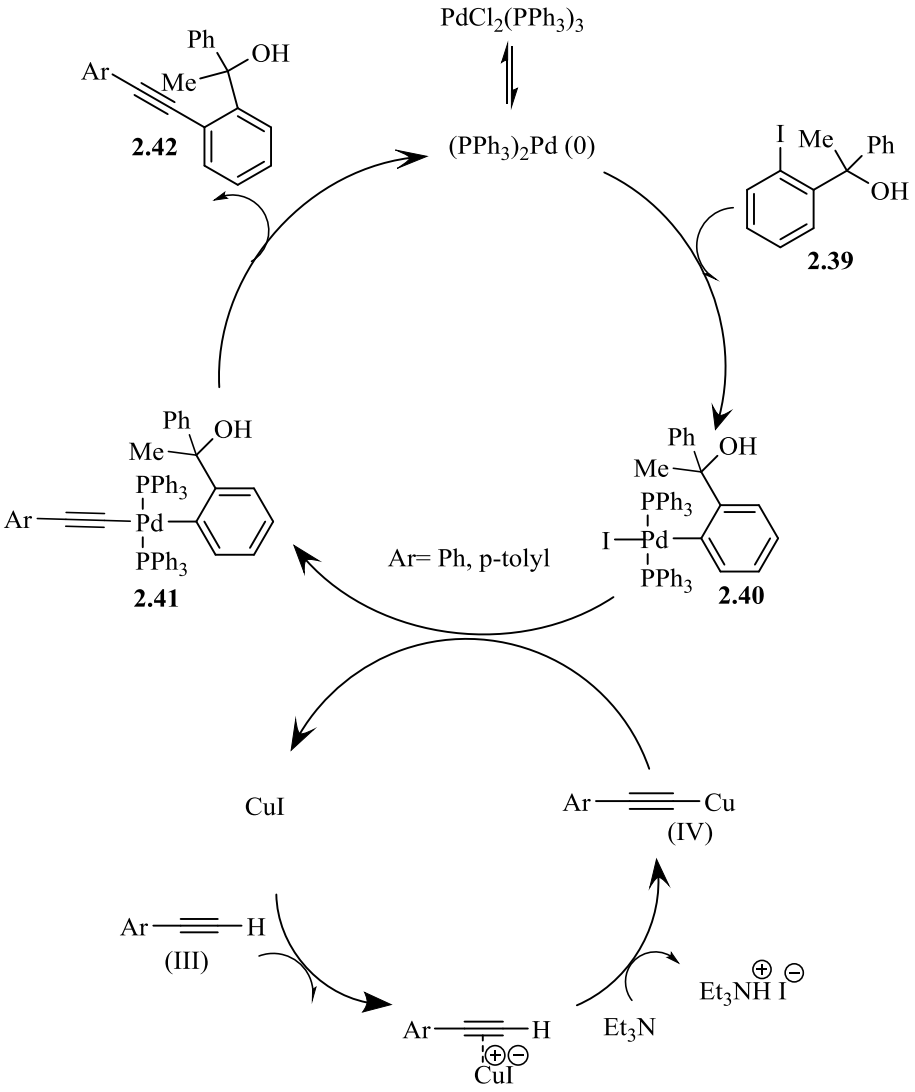
The crude products had few impurities and, therefore, purification by column chromatography was relatively straightforward, resulting in good isolated yields. These high yields, containing no unreacted starting material, could have been as a result of the electronic effect of the phenyl group of the alkynyl tertiary alcohols playing a significant role in reducing the reactivity of the alcohol group.

The identities of the new alkynyl tertiary alcohol products **(2.37)** and **(2.38)** were confirmed by ^{1}H and ^{13}C NMR spectroscopies, as well as ASAP mass spectrometry. The ^{1}H NMR provided valuable structural information about the methyl and the hydroxyl groups in the products; in particular, singlet peaks at 3.94 ppm and 4.03 ppm are assigned to the hydroxyl protons. In addition, there are two singlet peaks at 1.96 ppm and 2.32 ppm representing the methyl substituents for the 1-phenyl-[1-(2-p-tolylethynyl)phenyl] ethanol **(2.38)**, and one singlet peak was observed at 1.97 ppm for 1-phenyl-[1-(2-phenylethynyl)phenyl]ethanol **(2.37)**. Also, the ^{1}H NMR spectra showed multiplets between 7.07 ppm and 7.69 ppm for the aromatic protons. As expected, the ^{13}C NMR spectra showed peaks at 30.1 ppm **(2.37)** and 21.5 and 30.0 ppm **(2.38)**, representing the methyl substituents. Moreover, peaks at 87.6 ppm and 96.5 ppm due to the alkynyl C≡C

carbon atoms for both **(2.37)** and **(2.38)** were present. These peaks are of particular significance in demonstrating that the Sonogashira cross-coupling had been successful in generating the alkyne carbon resonances of alkyne-containing tertiary alcohol substrates. The accurate mass spectral data gave peaks for $[MH]^+$.

2.3.2 The Proposed Mechanism - Sonogashira Coupling

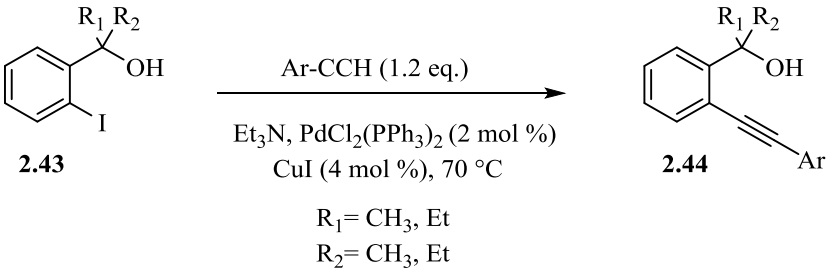
As can be seen from the mechanism below, a palladium(II) pre-catalyst is activated by reduction to the palladium(0) compound under the appropriate reaction conditions. This active palladium(0) catalyst reacts with the 2-iodobenzene substrates **(2.39)** *via* oxidative addition to give the organopalladium compound **(2.40)**. This intermediate reacts, in a transmetallation reaction, with the Cu-alkynyl species (IV) produced in the copper cycle to result in species **(2.41)** after expelling copper halide. The desired products **(2.42)** are obtained and the Pd(0) catalyst regenerated through a reductive elimination process (**Scheme 2.14**).



Scheme 2.14: *The Sonogashira cross-coupling mechanism*

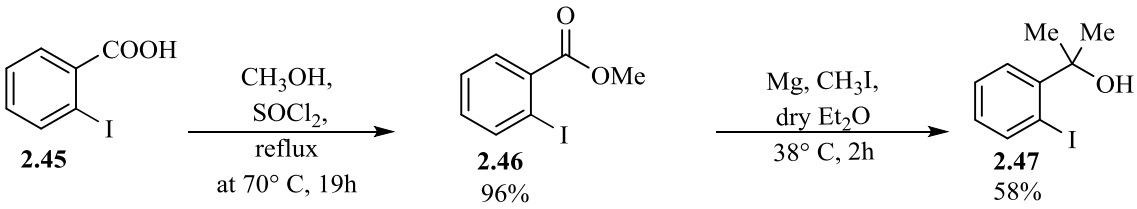
2.4 Synthetic Approaches to the Alkyne-Containing Tertiary Alcohols

After the successful synthesis of 1-phenyl-[1-(2-arylethynyl)phenyl]ethanols **(2.37)** and **(2.38)** in excellent yields, we sought to expand the route by exploring the reactions of 2-iodobenzyl tertiary alcohols **(2.43)** with terminal aryl acetylenes through Sonogashira cross-coupling reactions to generate alkyne-containing tertiary alcohol substrates **(2.44)** (**Scheme 2.15)**. The preparations of 2-(2-(phenylethynyl)phenyl)propan-2-ol **(2.52)**, 2-(2-(*p*-tolylethynyl)phenyl)propan-2-ol **(2.53)**, and (2-(phenylethynyl)phenyl)pentan-3-ol **(2.54)** from 2-iodobenzoic acid **(2.45)** were attempted through Grignard and Sonogashira reactions.



Scheme 2.15: *Sonogashira cross-coupling*

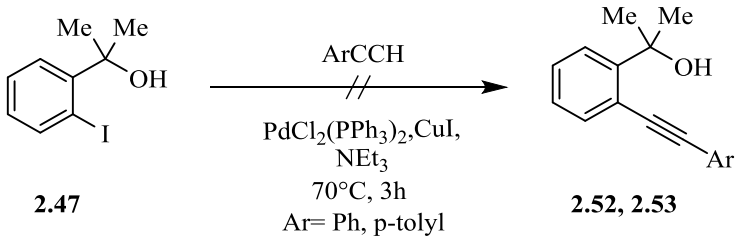
For all reactions, the first step, esterification of 2-iodobenzoic acid **(2.45)** (1 eq.), was achieved in MeOH at 0 °C in the presence of thionyl chloride (1.4 eq.) to give methyl-2-iodobenzoate **(2.46)** as a yellow oil, in virtually quantitative yield (96%), where no further purification of the product was required. The characterisation data for this known compound were in agreement with those in the literature.[11]



Scheme 2.16: *Preparation of 2-(2-iodophenyl)propan-2-ol*

The Grignard reagent CH_3MgI was freshly prepared and was reacted successfully with methyl-2-iodobenzoate in dry Et_2O heated at reflux for 3 h to afford the desired tertiary alcohol product 2-(2-iodophenyl)propan-2-ol **(2.47)** in a 58% isolated yield (**Scheme 2.16**). The product was characterised by ^1H and ^{13}C NMR spectroscopies and ASAP mass spectrometry, whose data were consistent with those in the literature. [13] Interestingly, when applying the Sonogashira step, where the 2-(2-iodophenyl) propan-2-ol **(2.47)** was reacted with 2-phenylacetylene or 1-ethynyl-4-methylbenzene (1 eq.), $[Pd(PPh_3)_2Cl_2]$ (2

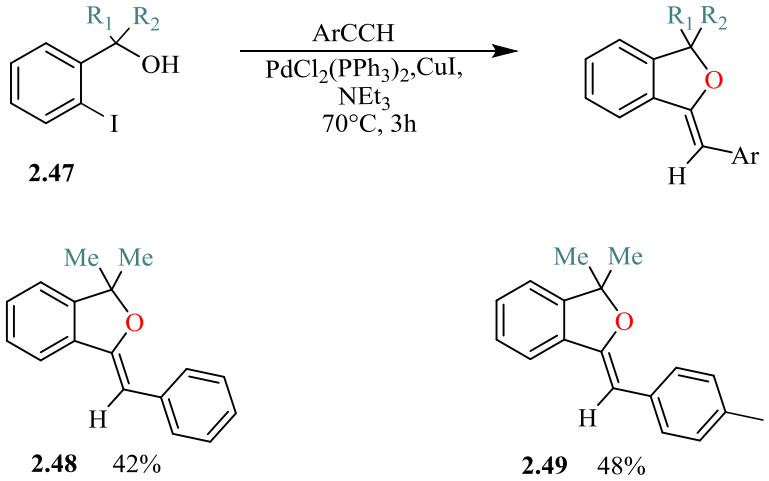
mol %) and CuI (4 mol%) in dry Et_3N at 70 °C for 3 h, the desired products **(2.52)** and **(2.53)** were not obtained **(Scheme 2.17).**



Scheme 2.17 *Unsuccessful coupling reaction*

2.4.1 Protocyclisation Reactions

As highlighted above, attempts to subject some of the 2-phenyl-tertiary alcohols to the Sonogashira cross-coupling reactions under the "standard" conditions used in this work did not generate the desired alkynyl-derivatised tertiary alcohols **(2.52)** **(Scheme 2.18)**. In particular, whilst the ASAP mass spectra revealed the desired peaks for the protonated MH^+ parent ions, ^{13}C NMR spectroscopy of the products generated did not show the typical alkynyl carbon resonances. In the HMQC ^{13}C-^{1}H correlation spectra, all of the proton signals between 5.78 and 5.86 ppm correlated to carbon signals between 95.7 and 95.8 ppm, indicating that tertiary alcohol products had not been formed.

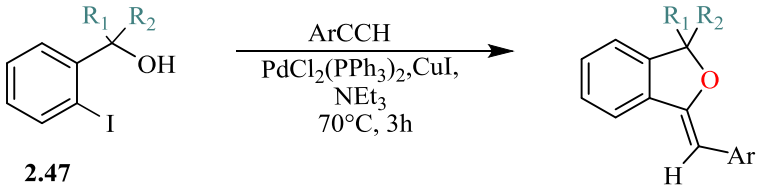


Scheme 2.18: *Palladium-catalysed protocyclisation*

Hence, when 2-(2-iodophenyl)propan-2-ol **(2.47)** was reacted with the terminal alkynes 2-phenylacetylene or *p*-tolylacetylene (1.2 eq.) in the presence of $[Pd(PPh_3)_2Cl_2]$ (2 mol %) and CuI (4 mol %) in dry Et_3N at 70°C for 3 h the protocyclised 5-membered ring products were produced in reasonable yields: benzofuran product **(2.48)** (42%)

benzofuran product **(2.49)** (48%) (**Scheme 2.18**) after purification by column chromatography.

Table 2-1: *Cyclised 5-membered ring products*



2.47

Product	R_1	R_2	Ar	Lowest δ_H ArH ppm	Highest δ_H ArH ppm	δ_H CH_3 ppm	δ_H CH ppm	δc CH ppm	MS
2.48	CH_3	CH_3	Ph	7.10(dd)	7.71(dd)	1.60	5.86	95.7	MH^+
2.49	CH_3	CH_3	*p*-tolyl	7.05(d)	7.56(d)	1.54, 2.25	5.78	95.8	MH^+

As can been seen from table above, the identities of the cyclised products **(2.48)** and **(2.49)** were confirmed by ^1H and ^{13}C NMR spectroscopies as well as ASAP accurate mass spectrometry. The ^1H NMR data provided valuable structural information about the cyclised 5-membered ring products. Typically, both of these compounds presented two singlet peaks between 1.54 ppm to 2.25 ppm for the methyl substituents (**Table 2-1**). In addition, singlet peaks were observed at 5.78 ppm and 5.86 ppm which correlated to alkenic carbon resonances in the ^1H-$^{!3}C$ HMQC NMR spectra. These results were similar to those of Buxaderas and co-workers[4] who used a terminal alkyne with an aryl halide tertiary alcohol for their palladium-catalysed protocyclisation reaction, as mentioned above in the introduction on page 4. **(Figure 2.1)** shows the ^1H NMR spectrum for one example. The downfield chemical shift for singlet peak at 5.78 ppm corresponds to the alkenic proton in the isobenzofuran product (3*Z*)-3-(benzylidene)-1,1-dimethyl-1,3-dihydro-2-isobenzofuran **(2.49)** This downfield shift has been shown to be diagnostic of the stereochemistry for this type of alkenyl isobenzofuran product, in this case identifying the product as the (Z) isomer. [14]

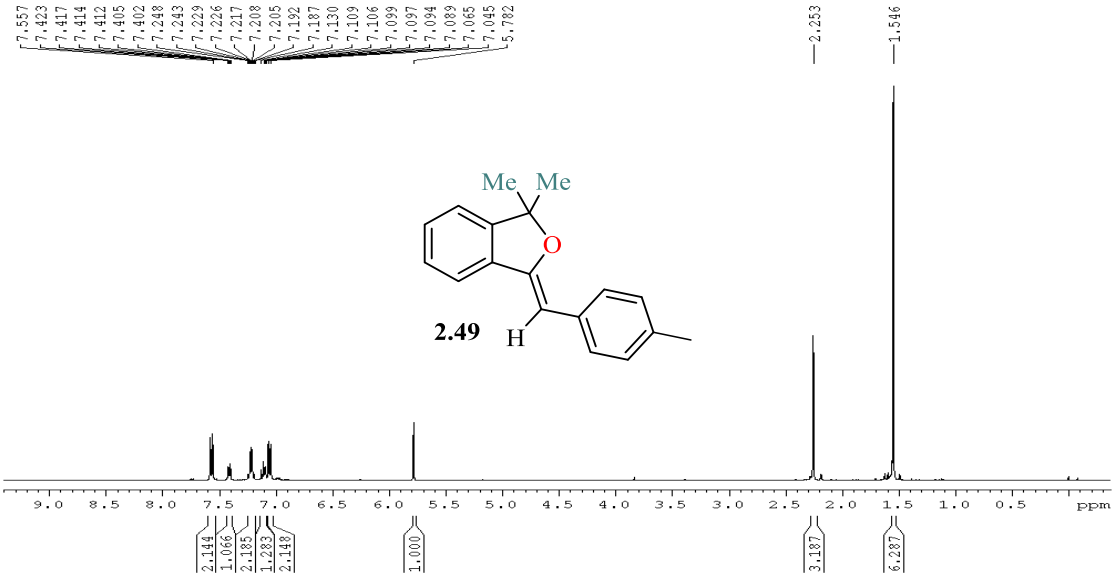
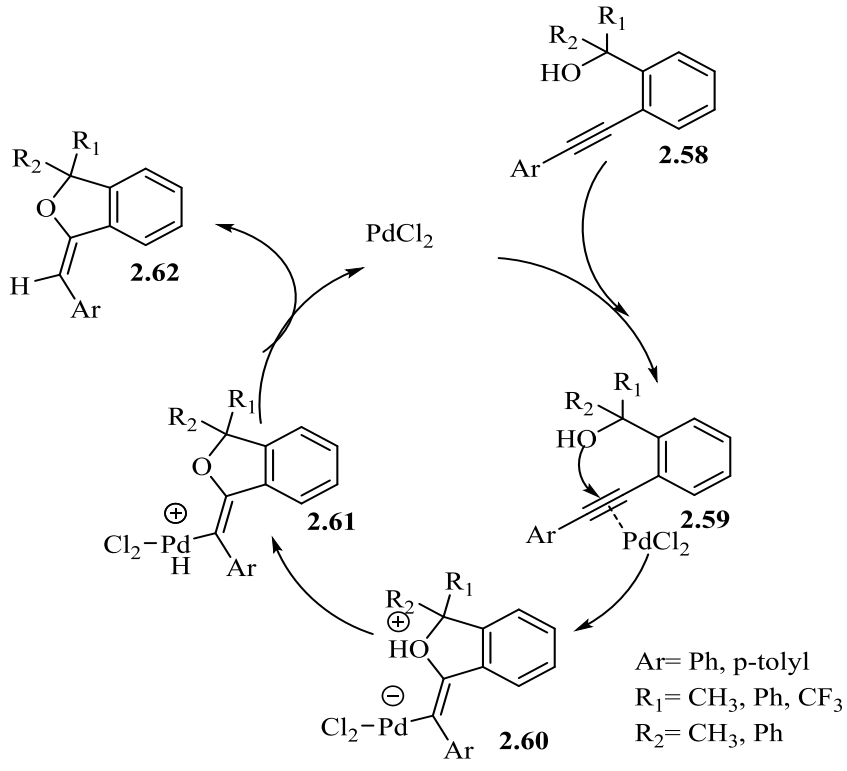


Figure 2.1: *^{1}H NMR spectra for (3Z)-3-(Benzylidene)-1,1-dimethyl-1,3-dihydro-2-isobenzofuran* ***(2.49)***



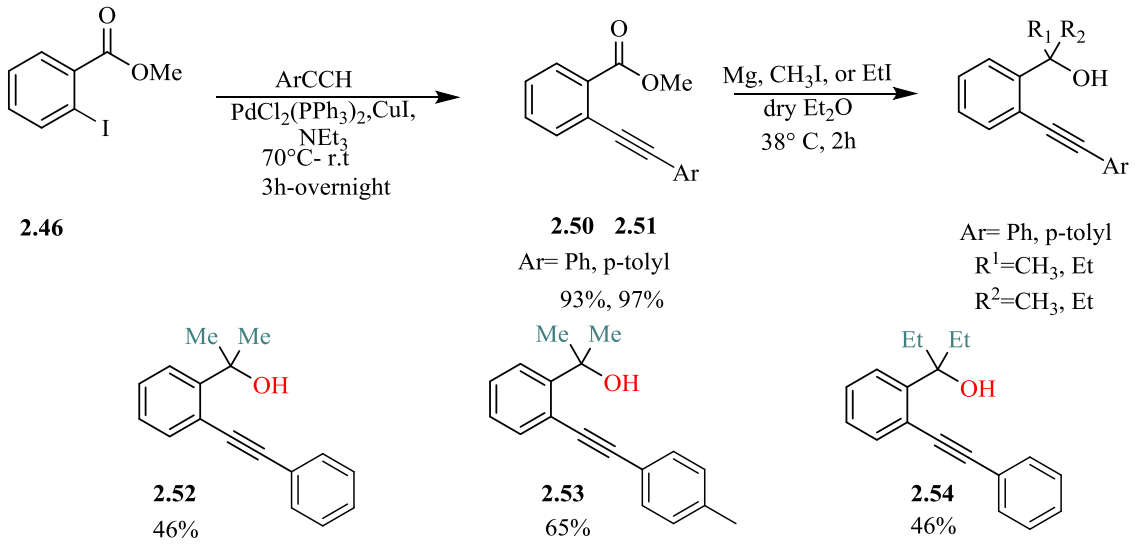
Scheme 2.19 *The possible mechanism for cyclised 5-membered ring products*

Here, the triple bond in the desired product **(2.58)** from the Sonogashira coupling is activated by the palladium catalyst to nucleophilic attack by the tertiary alcohol which, after proto-depalladation, results in the cyclised dihydroisobenzofuran product **(2.62)**

(**Scheme 2.19**). This was not a problem encountered for 1-(2-iodophenyl)-1-phenylethanol **(2.36)** suggesting that the phenyl group changes the nucleophilicity of the alcohol reducing the tendency to cyclisation.

2.4.2 Alternative Strategy for Preparing the Alkyne-Containing Tertiary Alcohols

As an alternative route, in the first step methyl-2-iodobenzoate **(2.46)** was reacted with the terminal alkynes phenylacetylene and 1-ethynyl-4-methylbenzene in the presence of $[Pd(PPh_3)_2Cl_2]$ (2 mol %) and CuI (4 mol %) in dry Et_3N at 70 °C for 3 h to give methyl 2-(phenylethynyl)benzoate (**2.50**) and methyl 2-(p-tolylethynyl)benzoate **(2.51)** via the Sonogashira cross-coupling reaction in excellent isolated yields (93 % and 97 %, respectively) **(Scheme 2.20)** after purification by column chromatography. The characterisation data were in agreement with those in the literature.[14,15]

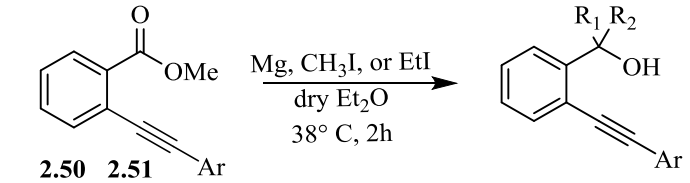


Scheme 2.20: *Preparation of 2-aryl-tertiary alcohols*

In the second step, freshly prepared Grignard reagent CH_3MgI was reacted successfully with product **(2.50)** or **(2.51)** in dry Et_2O by heating under reflux for 3 h to produce the desired tertiary alcohol products **(2.52)**, and **(2.53)** in reasonable isolated yields (46 % and 65 %, respectively) (**Scheme 2.20**). A similar Grignard reaction between the methyl 2-(phenylethynyl)benzoate **(2.50)** and EtMgBr, allowed (2 tertiary alcohol products **(2.54)** to be prepared in an isolated yield of 46 %. In general, the ^1H NMR spectra of the products showed peaks in the aromatic region that showed a downfield shift from 7.12 to 7.66 ppm. These peaks were representative of the phenyl aromatic rings for all products. The ^1H NMR spectra for the pure products exhibited singlet peaks between 2.57 and 3.38

ppm corresponding to the hydroxyl group (**Figure 2.2**). In addition, singlet peaks were observed between 1.70 ppm and 2.35 ppm for the methyl substituents for products **(2.52)** and **(2.53)**, while the ^{1}H NMR spectra of product **(2.54)** showed a triplet peak at 0.85 ppm and quartets at 2.02 ppm and 2.53 ppm for the ethyl substituents (**Table 2-2**). As can be seen from the ^{1}H NMR spectra for one example, the alkyne-containing tertiary alcohol **(2.53)** (**Figure 2.2**) the ^{1}H NMR spectrum showed the chemical shift of a δ_H singlet peak at 3.38 ppm that corresponded to the hydroxyl group.

Table 2-2: *Characterisation data for 2-phenyl-tertiary alcohols*



2.50 **2.51**

Ar= Ph, p-tolyl

93%, 97%

Product	R_1	R_2	Ar	Lowest δ_H ArH ppm	Highest δ_H ArH ppm	δ_H CH_3 ppm	δ_H OH ppm	δ_C C≡C ppm
2.52	CH_3	CH_3	Ph	7.12	7.48	1.70	3.20	89.3, 95.5
2.53	CH_3	CH_3	*p*-tolyl	7.15	7.55	1.78, 2.35	3.38	88.7, 95.8
2.54	Et	Et	Ph	7.28	7.66	0.85	2.57	89.3, 94.5

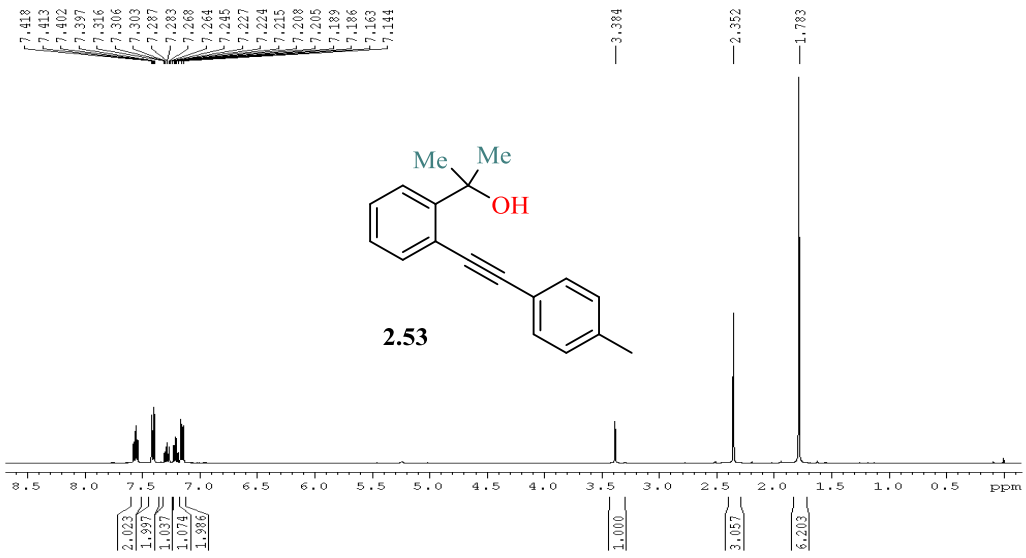
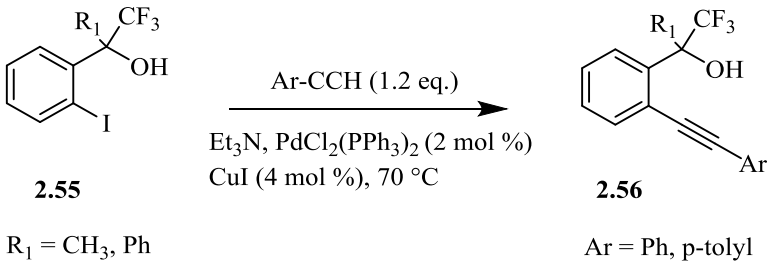


Figure 2.2: *^{1}H NMR spectra for 2-(2-(p-tolylethynyl)phenyl)propan-2-ol* ***(2.53)***

As mentioned above, this result was confirmed by ^{1}H-^{13}C HMQC NMR spectra which showed that the alcohol proton resonances did not show correlations to carbon resonances. Further, the ^{13}C NMR spectra showed peaks from 88.7 to 95.5 ppm for alkyne carbon resonances confirming that the C≡C bond was present, and ASAP mass spectrometry ananlysis showed molecular ion peaks corresponding to M-H^+ (**Table 2-2**).

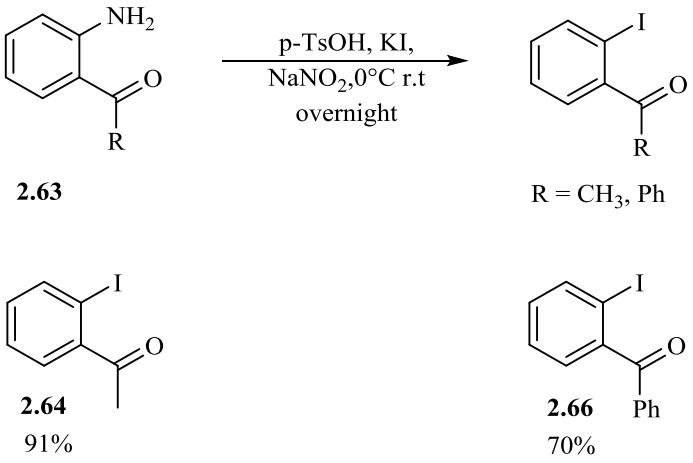
2.5 Preparation of 1,1,1-trifluoro-[2-(2-arylethynyl)phenyl]propan-2-ol and 2,2,2-trifluoro-1-phenyl-[1-(2-arylethynyl)phenyl]ethanol.

Following the successful syntheses of the alkynyl-aryl-propan-2-ol derivatives (**2.52)** and **(2.53)**, a series of related alkynyl tertiary alcohols with trifluoromethyl substituents were targeted: **(2.81)**, **(2.82)**, **(2.83),** and **(2.84)**. It was anticipated that the trifluoromethyl groups would reduce the nucleophilicity of the alcohols such that the unwanted protocyclisations seen for the propanol derivatives (Section 2.4.1) could be avoided. So, attempts to synthesise the alkyne-containing tertiary alcohol substrates started with the treatment of various 1,1,1-trifluoro-2-(2-iodophenyl)propan-2-ol substrates (1 eq.) with the same aryl acetylene reagents (1.2 eq.) using [$Pd(PPh_3)_2Cl_2$] (2 mol %), and CuI (4 mol %) in dry Et_3N at 70 °C to target the desired alkyne-derivatised substrates (**2.56**) (**Scheme 2.21**).



Scheme 2.21 *Other attempts to prepare the alkyne-containing tertiary alcohols substrates*

2-Iodoacetophenone **(2.64)** and 2-iodobenzophenone **(2.66)** **(Scheme 2.22*)*** were initially synthesised as starting materials. In the diazotisation reactions, 2-aminoacetophenone or 2-aminobenzophenone **(2.63)** were reacted with potassium iodide, sodium nitrite and *p*-toluene sulfonic acid monohydrate in acetonitrile at low temperature to give 2-iodoacetophenone **(2.64)** (91% isolated yield) and 2-iodobenzophenone **(2.66)** (70% isolated yield) as orange liquids (**Scheme 2.22)** after purification by column chromatography. All of the characterisation data were in agreement with those in the literature.[16,17]



Scheme 2.22: *Preparation of* ***(2.64)*** and ***(2.36)***

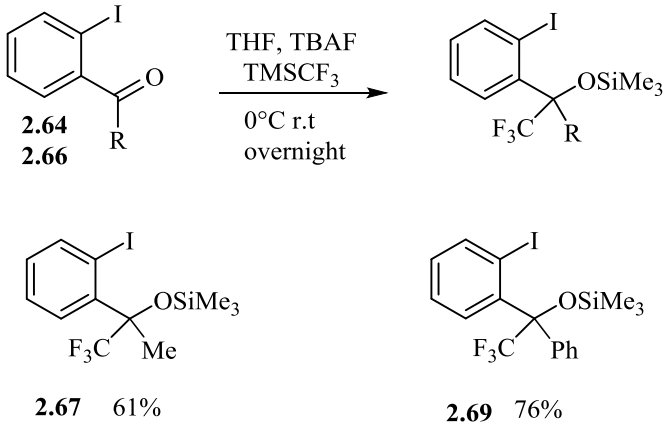
Table 2-3: *Improvement of the yield for 2-iodoacetophenone* ***(2.64)***

Entry	Time/ atmosphere	Mass of SM (g)	Moles of SM	Isolated Yield %
1	4.5 hours/under N_2	0.90	6.7	42
2	Overnight/under N_2	4.5	33.5	68
3	4.5 hours	4.5	33.5	65
4	Overnight	4.5	33.5	88
5	Overnight	4.82	33.5	91

Diazotisation reactions conditions: 2-aminoacetophenone or 2-aminobenzophenone (**2.63**) were reacted with KI, $NaNO_2$ and *p*-TsOH in MeCN at low temperature.

The yield of 2-iodoacetophenone **(2.64)** was initially poor, so this reaction was carried out several times under a range of different reaction conditions to improve the results, as summarised in the Table 2-3. The isolated yields were improved from 42% when a closed system was used with a short reaction time to 91% (**Table 2-3**) after reaction in an open system overnight. It appears that merely increasing the reaction time encouraged the conversion to the desired product. In the next step in the reaction sequence, $TMSCF_3$ (2 eq.) was added to 2-iodoacetophenone **(2.64)** or 2-iodobenzophenone **(2.66)** (1 eq.) in dry

THF, and the mixtures cooled to 0 °C before TBAF (0.03 eq.) was added. The mixtures were allowed to warm to room temperature and stirred for 48 h to give the pure intermediates 1,1,1-trifluoro-2-(2-iodophenyl)-2-trimethylsiloxypropane **(2.67)** (61%) and trimethyl(2,2,2-trifluoro-1-(2-iodophenyl)-1-phenylethoxy)silane **(2.69)** (76%) as products (**Scheme 2.23**).



Scheme 2.23: *Preparation of 1,1,1-trifluoro-2-(2-iodophenyl)-2-trimethylsiloxypropane **(2.67)**, and trimethyl(2,2,2-trifluoro-1-(2-iodophenyl)-1-phenylethoxy)silane **(2.69)***

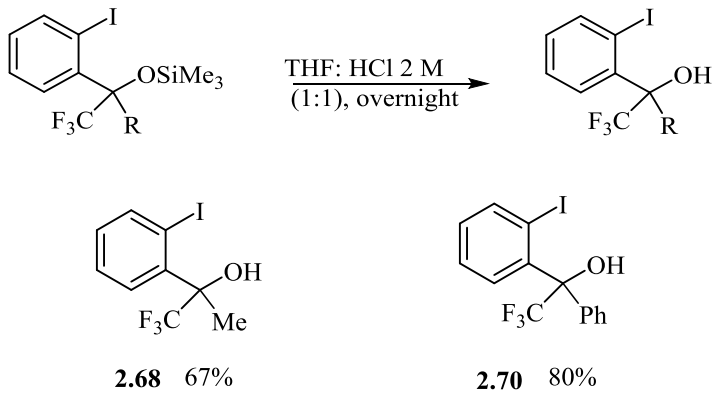
***Table* 2-4:** *The Characterisation data of **(2.67)** and **(2.69)** products*

Product	R	δ_H $OSiMe_3$ ppm	δ_H CH_3 ppm	δc $OSiMe_3$ ppm	δc CH_3 ppm	δ_C CI ppm	δ_C CF_3 ppm	δ_F ^{19}F ppm
2.67	CH_3	0.00	1.82	0.0	23.0	92.0	127.3	-78.2
2.69	Ph	0.00	-	0.0	-	97.6	123.6	-72.5

As can been see from table above, there are some interesting characterisation data for products **(2.67)** and **(2.69).** Their identities were confirmed by ^1H and ^{13}C NMR spectroscopies, as well as ASAP accurate mass spectrometry. The ^{19}F NMR data provided valuable information about the products. Commonly, both of these compounds presented singlet peaks at -78.2 and -72.5 ppm for the CF_3 substituents (**Table 2-4**).

For both products, the ^1H NMR spectra provide valuable structural information about the $OSiMe_3$ groups in the products; in particular, the singlet peaks at 0.00 ppm were assigned to the nine protons referring to $OSiMe_3$ groups. In addition, there was a singlet peak at

1.82 ppm representing the methyl substituent for **(2.67)**, and, as expected, the ^{13}C NMR spectra showed a peak at 23.0 ppm representing the methyl substituent. These products were washed with THF:HCl 2M (1:1) (100 mL), and the mixtures were stirred overnight. The mixtures were extracted with Et_2O (2 x 30 mL), the combined organic layers dried, and the solvent removed *in vacuo* to give the crude products as yellow oils. These were purified by column chromatography to give 1,1,1-trifluoro-2-(2-iodophenyl)propan-2-ol **(2.68)** (67%), and 1-(2-iodophenyl)-1-phenyl-2,2,2-trifluoroethanol **(2.70)** (80%) (***Scheme* 2.24**).



2.68 67% **2.70** 80%

Scheme* 2.24:** *Preparation of 1,1,1-trifluoro-2-(2-iodophenyl)propan-2-ol **(2.68)**, and 1-(2-iodophenyl)-1-phenyl-2,2,2-trifluoroethanol **(2.70)

***Table 2-5:** The Characterisation data of **(2.68)** and **(2.70)** products*

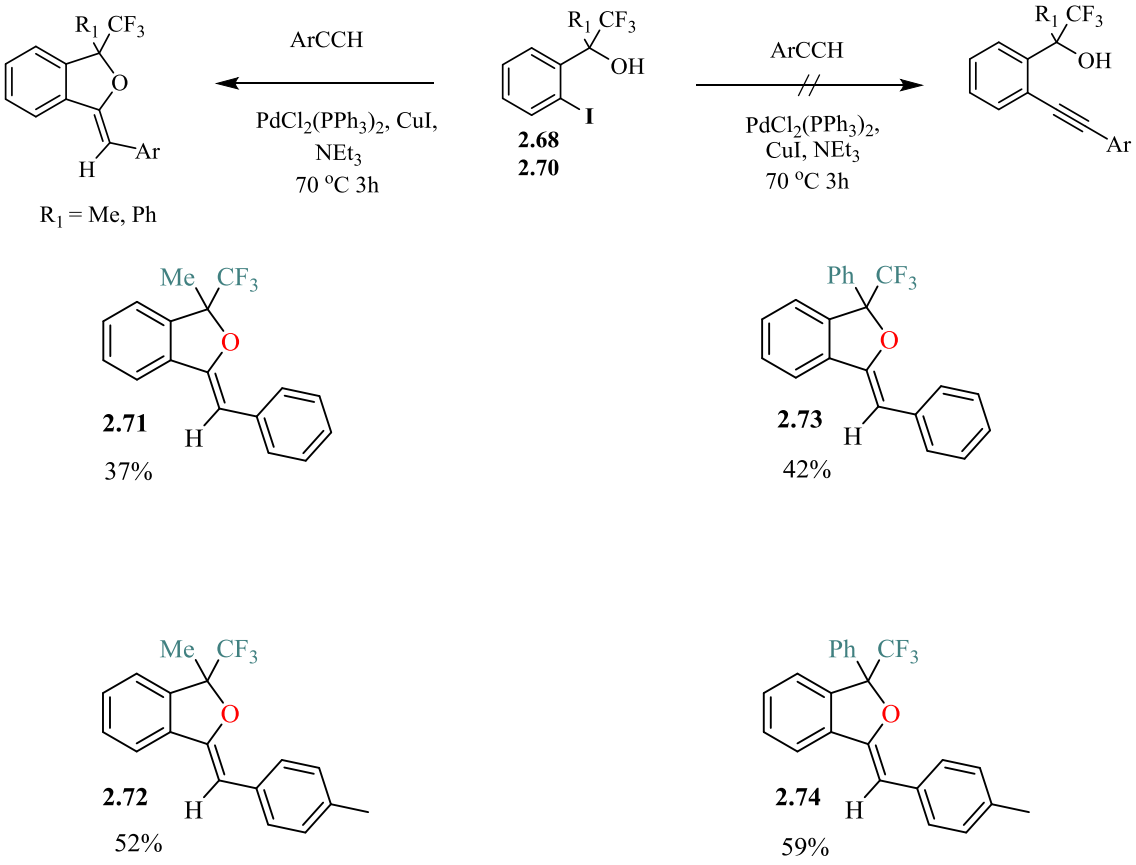
Product	R	δ_H CH_3 ppm	δ_H OH ppm	δc CH_3 ppm	δ_C CI ppm	δ_C CF_3 ppm	δ_F ppm
2.68	CH_3	1.91	3.45	23.6	92.0	127.1	-78.0
2.70	Ph	-	3.59	-	96.3	128.2	-72.3

The Table 2-5 reports some of the characterisation data for the products **(2.68)** and **(2.70)**. Their identities were confirmed by ^1H and ^{13}C NMR spectroscopies, as well as ASAP accurate mass spectrometry. The ^{19}F NMR data provided valuable structural information about the products. Commonly, both of these compounds present singlet peaks at -78.0 and -72.3ppm for the CF_3 substituents (**Table 2-5**). The ^1H NMR spectra also provided valuable structural information about the methyl and the OH groups in the products; singlet peaks between 3.45 ppm to 3.59 ppm were assigned to the hydroxyl protons. Also,

there was a singlet peak at 1.91 ppm representing the methyl substituents for **(2.68)**. In addition, the ^{13}C NMR spectra showed peaks at 23.6 ppm representing the methyl substituents.

2.5.1 Protocyclisation following Sonogashira Cross-Coupling Reactions

However, as seen in the failed attempts to form **(2.52)** and **(2.53)** through the Pd-catalysed Sonogashira reactions of 2-iodophenyl-propan-2-ol, the use of the Sonogashira cross-coupling protocol with products **(2.68)**, and **(2.70)** did not afford the desired alkynyl tertiary alcohols but rather gave cyclised functionalised dihydroisobenzofuran products **(2.71)** (37%), **(2.72)** (52%), **(2.73)** (42%), and **(2.74)** (59%), **(Scheme 2.25).**



Scheme 2.25 *Dihydroisobenzofuran products from Sonogashira cross-coupling reactions*

Some of these dihydroisobenzofuran products were found to have δ_H singlet peaks between 1.75 and 2.27 ppm representing the methyl protons, while others had δ_F singlet peaks between -76.9 ppm to -79.9 ppm representing the CF_3 units. In general, the peaks in the aromatic region were observed from 7.09 to 7.76 ppm; these peaks were representative of the phenyl rings. The ASAP mass spectrum showed a molecular ion peak corresponding to $[MH^+]$. Some of the data for these species have been summarised

in (***Table* 2-6**). For each of the cyclised products, the ^{1}H NMR spectra show a singlet peak between 5.78 ppm and 6.06 ppm corresponding to the alkenyl protons; these assignments were confirmed by ^{1}H-^{13}C HMQC NMR spectra which showed the protons correlating to the carbon signals between 98.0 and 99.0 ppm.

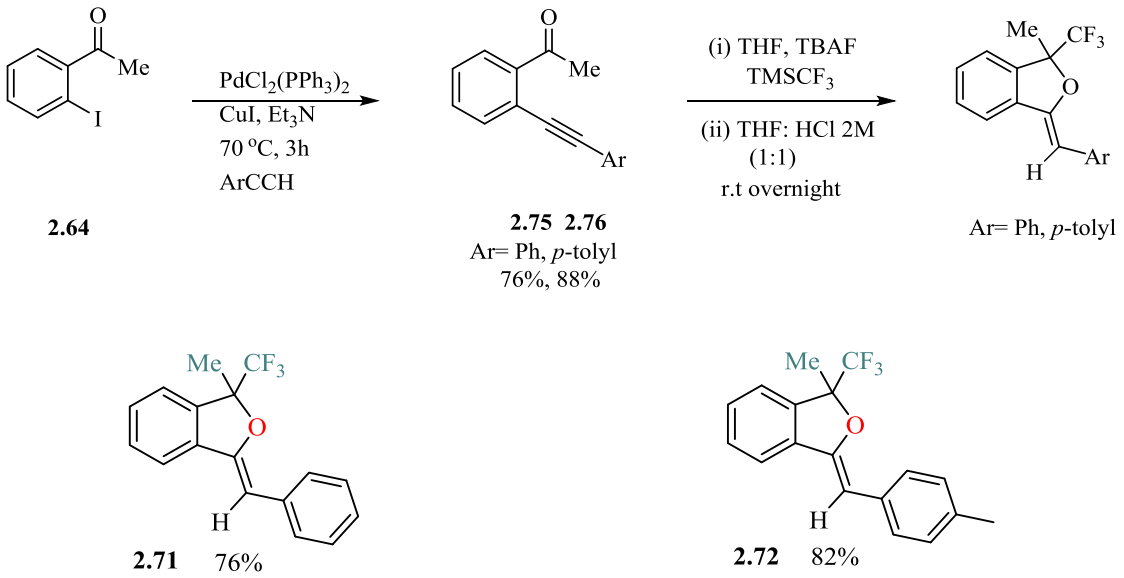
***Table* 2-6:** Characterisation data for the dihydroisobenzofuran products

Prod.	R_1	Ar	Lowest δ_H ArH ppm	Highest δ_H ArH ppm	δ_H CH_3 ppm	δ_H CH ppm	δ_C CF_3 ppm	δc CH ppm	δ_F ppm
2.71	CH_3	Ph	7.19	7.73	1.83	6.01	128.4	98.6	-79.9
2.72	CH_3	*p*-tolyl	7.09	7.55	1.75, 2.27	5.90	128.5	98.5	-79.2
2.73	Ph	Ph	7.13	7.74	-	5.99	128.1	98.0	-77.8
2.74	Ph	*p*-tolyl	7.21	7.76	-	6.06	125.3	99.0	-76.9

This palladium-catalysed protocyclisation following the alkyne-coupling may be due to CuI or the palladium catalyst functioning as the activating electrophile on the alkynyl-coupled product from the Sonogashira reaction as discussed for the aryldialkyl tertiary alcohols in Section 2.4.1 above. As mentioned in the introduction, Buxaderas and co-workers[4] used such a palladium-catalysed protocyclisation route to allow for the reaction of a terminal alkyne. Satyanarayana's group[5] also demonstrated a very similar cyclisation. Here, protocyclisations for both trifluoromethylated tertiary alcohols suggests that the electronic influence of the substituents on the nucleophilicity of the alcohol are not controlling the reaction and this unwanted reactivity may arise from steric effects in these substrates.

2.5.2 Protocyclisation Reactions via Nucleophilic addition/ Intramolecular Cyclisation Reaction of 2-alkynylacetophenone with $TMSCF_3$ under Mild Reaction Conditions

In an alternative approach to make the CH_3/CF_3 alkynyl tertiary alcohols **(2.81)** and **(2.82)** from the reaction of the alkynyl methyl ketone intermediates (**2.75**) and (**2.76**) with Ruppert's reagent, unfortunately the same cyclised dihydroisobenzofuran products, **(2.71)** (76%) and **(2.72)** (82%), were formed (**Scheme 2.26**).

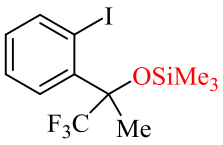


Scheme 2.26: *Cyclisation following the reaction of 2-alkynylacetophenone and $TMSCF_3$ under mild reaction conditions*

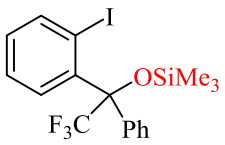
In the first step, 2-iodoacetophenone **(2.64)** (1 eq.) was reacted with the appropriate alkyne (1.2 eq.), $[Pd(PPh_3)_2Cl_2]$ (2 mol %), CuI (4 mol %) in dry Et_3N (80 ml) at 70 °C to room temperature overnight to give the known products 2-(phenylethynyl)acetophenone **(2.75)** (isolated yield 76%), and 2-(*p*-tolylethynyl)acetophenone **(2.76)** (isolated yield 88 %), respectively (**Scheme 2.26**); the characterisation data for these species were in agreement with those reported in the literature.[18,19] Unfortunately, the reactions of these ketones with $TMSCF_3$ followed by an acidic work-up, gave the dihydroisobenzofuran products via a protocyclisation step. The data for **(2.71)** and **(2.72)** were identical to those obtained via the palladium-catalysed protocyclisation route.

2.5.3 Successful Alternative Strategy for Preparing the Alkyne-Containing Trifluoromethyl Tertiary Alcohols

As an alternative approach for preparing the alkyne-containing tertiary (CH_3/CF_3) species **(2.81)** and **(2.82)**, and the (Ph/CF_3) compounds **(2.83)** and **(2.84)**, a Sonogashira-deprotection strategy {using the previously prepared intermediates 1,1,1-trifluoro-2-(2-iodophenyl)-2-trimethylsiloxypropane **(2.67)** and trimethyl(2,2,2-trifluoro-1-(2-iodophenyl)-1-phenylethoxy)silane species (**2.69**)} was found to work smoothly and eliminate the cyclisation steps seen previously (**Scheme 2.27**).



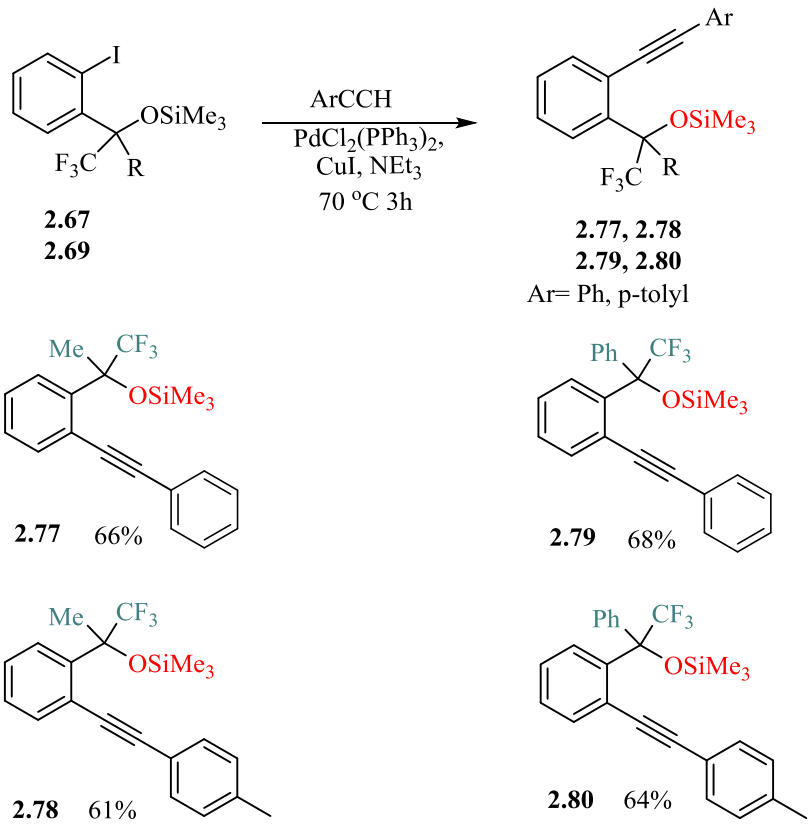
2.67 61%



2.69 76%

Scheme 2.27*: Synthesis of silane species*

The Sonogashira reactions using compounds **(2.67)** or **(2.69)**, in which the OH group was effectively protected as a trimethylsilyl ether in dry Et_3N with either 2-phenylacetylene or 1-ethynyl-4-methylbenzene (1.2 eq.) gave the alkyne-functionalised species (**2.77)** (66 % isolated yield), (**2.78)** (61 % isolated yield), (**2.79)** (68 % isolated yield), and **(2.80)** (64 % isolated yield) (**Scheme 2.28)**.



Scheme 2.28: *The Sonogashira reactions*

The Table 2-7 reports some of the characterisation data of the products **(2.77), (2.78), (2.79)**, and **(2.80)**. Their identities were confirmed by ^{1}H, ^{13}C, and ^{19}F NMR spectroscopies, as well as ASAP accurate mass spectrometry. The ^{1}H NMR provided valuable structural information about the methyl and the $OSiMe_3$ groups in the products; in particular, singlet peaks between 0.21 ppm and 0.26 ppm were assigned to the nine protons corresponding to the $OSiMe_3$ groups. In addition, there were two singlet peaks at 2.09 ppm and 2.33 ppm representing the methyl substituents on **(2.78)** and one singlet peak was observed at 2.06 ppm for **(2.77)**, while product **(2.80)** showed one singlet peak at 2.29 ppm for the methyl substituent. As expected, the ^{13}C NMR spectra showed peak between 19.5 ppm to 21.1 ppm representing the methyl substituents.

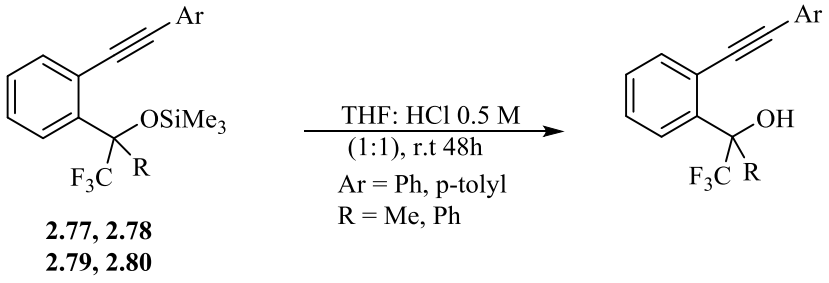
Further, the ^{13}C NMR spectra showed peaks that would normally appear from 82.5 to 94.4 ppm, confirming that the C≡C bond was present. These peaks are significant in that they demonstrate that the Sonogashira cross-coupling had been successful in generating the alkyne-containing tertiary alcohol substrates. The ^{19}F NMR data provided valuable structural information about the products. Commonly, all of these compounds present

singlet peaks between -69.7 ppm to -79.8 ppm for the CF_3 units. The ASAP mass spectrum showed molecular ion peaks corresponding to the $[M-H]^+$ on (**Table 2-7**).

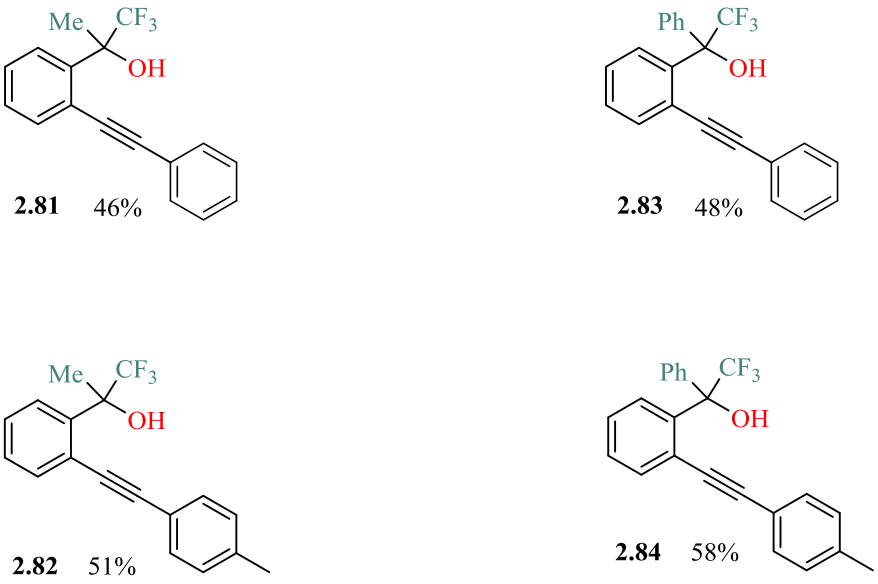
Table 2-7: Characterisation data for the *silane species*

Prod.	R_1	R_2	Ar	δ_H $OSiMe_3$ ppm	δ_H CH_3 ppm	δ_H Ar-CH_3 ppm	δ_C $OSiMe_3$ ppm	δc CH_3 ppm	δc Ar-CH_3 ppm	δ_C CF_3 ppm	δ_F ppm
2.80	CF_3	CH_3	Ph	0.21	2.06	-	0.1	21.1	-	125.6	-79.8
2.81	CF_3	CH_3	*p*-tolyl	0.22	2.09	2.33	0.2	21.1	19.5	123.0	-76.4
2.82	CF_3	Ph	Ph	0.25	-	-	0.3	-	-	123.0	-69.7
2.83	CF_3	Ph	*p*-tolyl	0.26	-	2.29	0.0	-	20.2	125.0	-69.9

Ultimately, the synthesis of the **(2.81)**, **(2.82)**, **(2.83)** and **(2.84)** tertiary alcohols required the use of the silyl protecting group ($OSiMe_3$), which is easily removed under mild acidic conditions. This was removed via treatment with THF:HCl (0.5 M) at room temperature for 48 h to give the desired tertiary alcohols 1,1,1-trifluoro-[2-(2-phenylethynyl)phenyl]propan-2-ol **(2.81)** (46 % isolated yield) and 1,1,1-trifluoro-[2-(2-p-tolylethynyl)phenyl]propan-2-ol **(2.82)** (51 % isolated yield) (**Scheme 2.29**). The pure alcohols **(2.83)** (48 % isolated yield) and **(2.84)** (58 % isolated yield) were obtained using more forcing conditions than those needed for the analogous methyl/CF_3 tertiary alcohols, namely by washing with THF:HCl 1.0 M (1:1) and stirring at room temperature for 48 h (**Scheme 2.29**).



2.77, 2.78
2.79, 2.80



Scheme 2.29: *Preparation of 2-phenyl-tertiary alcohols*

The identities of all the alkyne tertiary alcohols products were confirmed by ^{1}H, ^{13}C and ^{19}F NMR spectroscopies, as well as ASAP mass spectrometry. Some of the associated NMR data have been summarised in (**Table 2-8**) for these new alkynyl-derivatised tertiary alcohols.

Table 2-8: *Characterisation data for trimethylsilyl-alkynyl tertiary alcohols products*

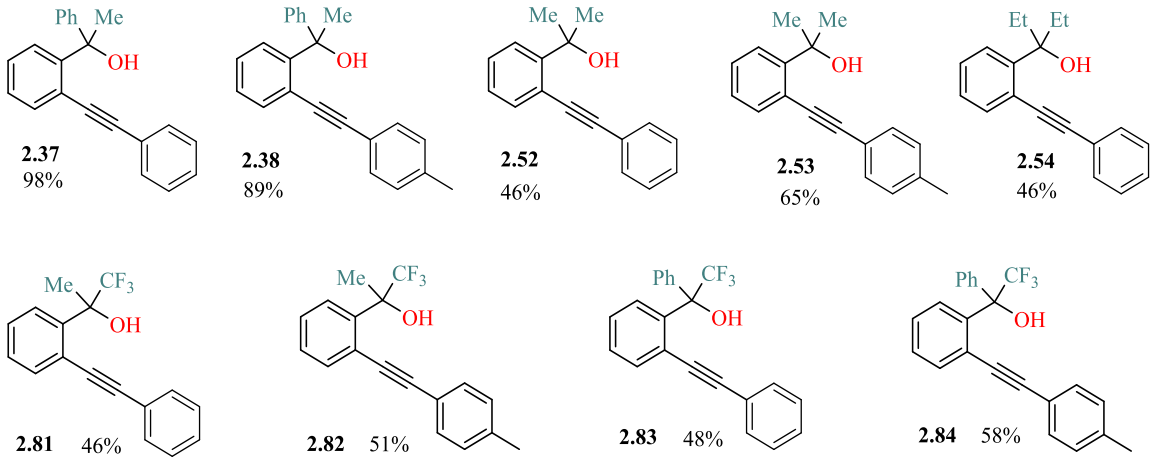
	R_1	Ar	Lowest δ_H ArH ppm	Highest δ_H ArH ppm	δ_H CH_3 ppm	δ_H OH ppm	δ_C C≡C ppm	δ_C CF_3 ppm	δ_F CF_3	MS
2.84	CH_3	Ph	7.27	7.53	1.82	5.12	86.4, 95.1	125.6	-80.2	MH^+
2.85	CH_3	*p*-tolyl	7.09	7.52	1.81, 2.32	5.23	85.7, 95.5	123.5	-80.3	MH^+
2.86	Ph	Ph	7.01	7.83	-	5.03	86.7, 95.3	125.9	-70.5	$[M\text{-}OH]^+$
2.87	Ph	*p*-tolyl	7.09	7.81	2.35	5.16	85.9, 95.8	123.8	-70.7	$[M\text{-}OH]^+$

In general, the ^{1}H NMR spectra of the products showed peaks in the aromatic region that were observed from 7.01 to 7.83 ppm; these peaks are representative of the phenyl aromatic rings. The ^{1}H NMR spectra for the pure products exhibited a singlet peak between 5.03 and 5.16 ppm corresponding to the hydroxyl group. This result was confirmed by ^{1}H-^{13}C HMQC NMR spectra which showed that the alcohol proton resonances did not show correlations to carbon resonances. Further, the ^{13}C NMR C≡C peaks were present from 85.7 to 95.8 ppm, and in the ^{19}F NMR spectra a single peak

appeared at -80 ppm or -70 ppm for the CF_3 groups. In addition, ASAP mass spectrometry showed molecular ion peaks corresponding to $[MH]^+$ or $[MH\text{-}OH_2]^+$ (**Table 2-8**).

2.6 Conclusions

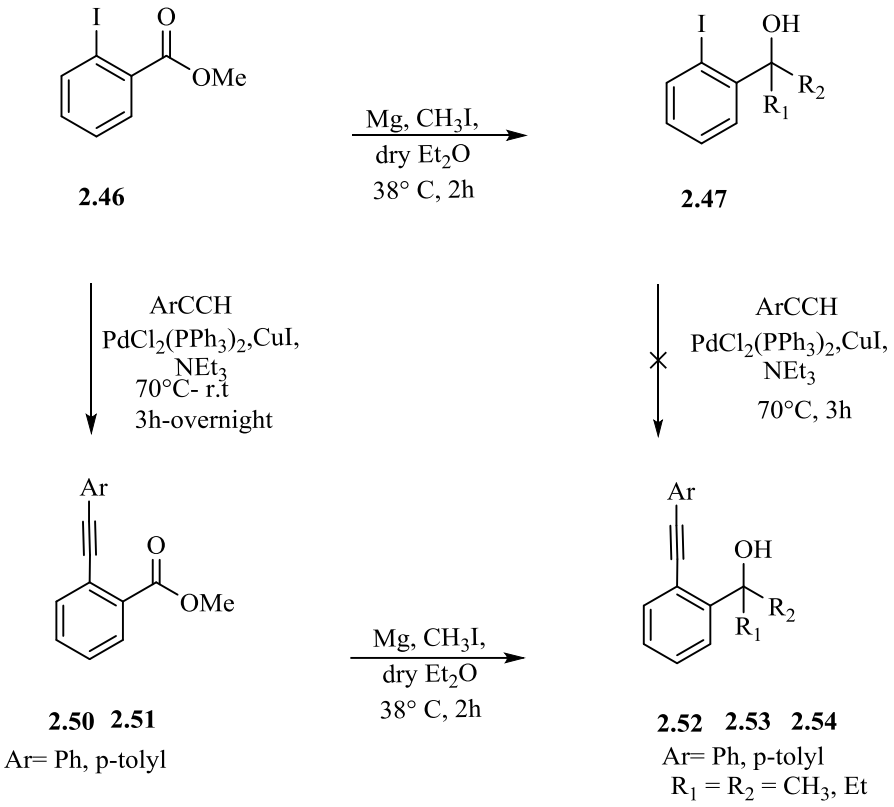
In this chapter, the preparation of a series of alkyne-containing tertiary alcohol substrates **(2.37)**, **(2.38)**, **(2.52)** **(2.53)**, **(2.54)**, **(2.81)**, **(2.82)**, **(2.83)** and **(2.84)** have been demonstrated. These have been targeted as starting materials to allow an investigation of iodocyclisation/fluorocyclisation reactions in order to generate cyclised products. For these studies, it was necessary for the substrates to contain both an internal nucleophile and an alkyne group. As the work developed, it became necessary to adopt a number of different synthetic strategies (***Scheme* 2.30**).



***Scheme* 2.30:** *Alkyne-containing tertiary alcohol substrates*

Strategy (a) products **(2.37)** and **(2.38)**. We initially focussed on the Sonogashira coupling to affect the reaction between the terminal alkynes and aryl iodides that contained tertiary alcohols. This coupling reaction required the support of copper salts as co-catalysts along with a [Pd] catalyst in the presence of amine bases. This procedure afforded the target alkyne-containing tertiary alcohols, generating excellent yields of products **(2.37)** and **(2.38)**.

Strategy (b) products **(2.50)** and (**2.51)**. Here, under Sonogashira reaction conditions, the tertiary alcohols were coupled to the alkynes but then underwent protocyclisation reactions to generate dihydroisobenzofuran derivatives (**2.48)** and **(2.49)**.



Scheme 2.31: *Preparation of 2-phenyl-tertiary alcohol alkyl substrates by strategy (b)*

So, an alternative reaction sequence was developed in which the Grignard reagent addition and the Sonogashira coupling steps were reversed to afford **(2.50)** and **(2.51)** **(Scheme 2.31)**. Presumably, the dialkyl aryl tertiary alcohols here were more nucleophilic than the alkyl diaryl tertiary alcohols, leading to protocyclisation under Sonogashira reaction conditions.

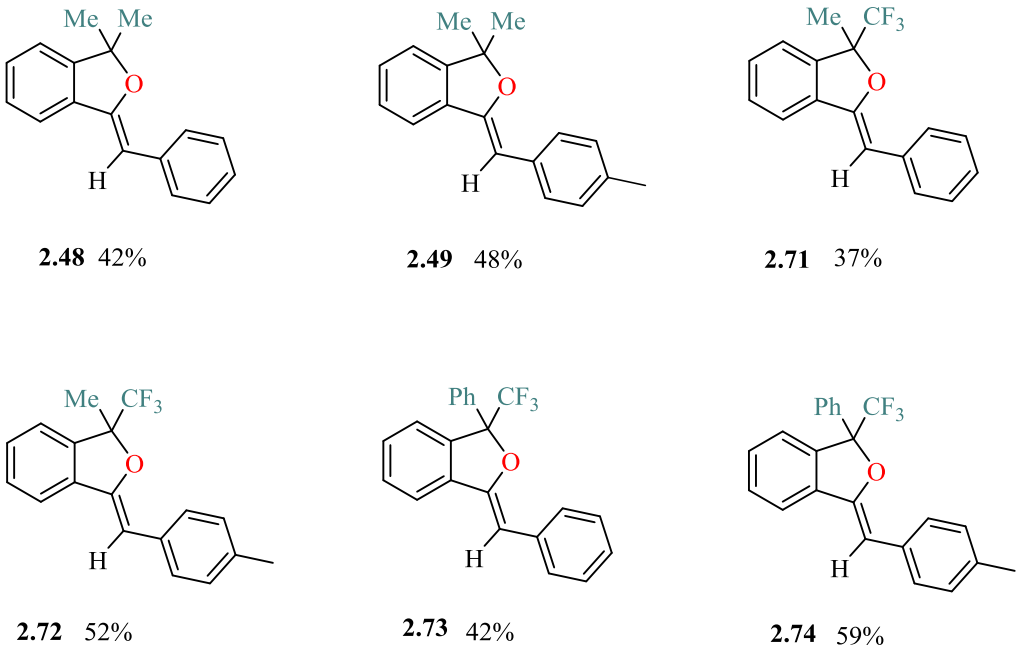
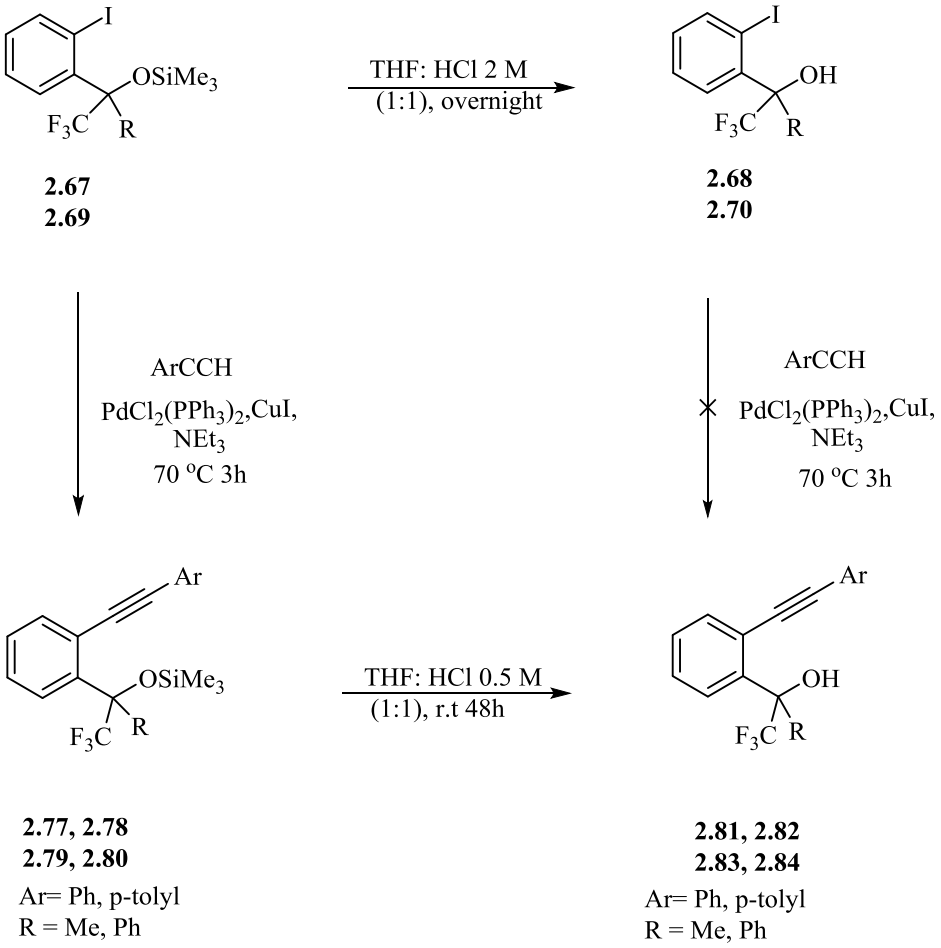


Figure 2.3: *Protocyclisation products*

Strategy (c) products **(2.81)**, **(2.82)**, **(2.83)** and **(2.84)**. Neither of the previous two strategies worked in the synthesis of these trifluoromethyl-derivatised tertiary alcohols. The use of the Sonogashira reaction of 2-iodo-aryl-trifluoro-propan-2-ol or -ethanol as the final step in the reaction sequence resulted in alkyne coupling followed by protocyclisation to give trifluoromethyl-derivatised dihydroisobenzofuran products **(2.71)**, **(2.72)**, **(2.73)**, and **(2.74)** (**Figure 2.3**).



Scheme 2.32: *Preparation of trifluoromethyl-2-phenyl-tertiary alcohol substrates*

The same protocyclised products were generated in the reaction of Ruppert's reagent with alkynyl-ketone substrates. However, the desired tertiary alcohols were finally generated by using trimethylsilyl-protected tertiary alcohol intermediates for the Sonogashira coupling followed by deprotection under less acidic conditions (**Scheme 2.32**).

All the products have been identified by NMR spectroscopy (^{1}H, ^{13}C, ^{19}F, ^{1}H-^{13}C HMQC, NOESY, COSY$_{45}$) and accurate mass spectrometry. Whilst the data obtained for (3*Z*)-3-(benzylidene)-1,1-dimethyl-1,3-dihydroisobenzofuran **(2.48)** were consistent with those reported in the literature,[20,21] **(2.37)**, **(2.38)**, **(2.49)**, **(2.71)**, **(2.72)**, **(2.73)**, and **(2.74)** were unknown compounds. Data for all the cyclised products have been discussed above. Unfortunately, as all the products were oils, crystals suitable for single crystal X-ray structural determinations could not be obtained to allow their molecular structures to be investigated. Overall, either the alkyne-containing tertiary alcohol products or the cyclised products could be obtained. It is reasonable to say that the reaction outcomes were strongly dependent on the nature of the functional groups in the starting materials.

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Chapter 3

Silver-catalysed fluorocyclisation of alkynes containing tertiary alcohols

3.1 Introduction

The inclusion of a fluorine atom or fluorinated substituents can have a significant impact upon the properties of organic molecules due to its small size, the fact that it is isosteric with an hydroxyl group, and has a high electronegativity, which influences the electronics and polarity of fluorinated molecules and the strength of the C-F bond, which itself has an impact upon the metabolic stabilities of these compounds.[1] Since heterocyclic compounds often form the core structure in drug candidate molecules, fluorinated heterocycles are highly desirable targets for the pharmaceutical industry[2] because the incorporation of fluorine can enhance their biological activities.[3,4]

The synthesis and functionalization of isochromenes and isoquinolines have been major objectives of research for over one hundred years because they are commonly found in natural products, and are often used as building blocks for pharmaceutical compounds.[5] For instance, 4-fluoroisoquinolines **(3.1)** have been used as antiproliferative drugs, as myosin inhibitors, and to reduce intraocular pressure. However, the synthesis of 4-fluoroisoquinolines is quite rare (**Figure 3.1**).[6]

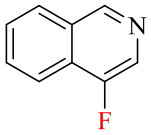


Figure 3.1: *4-fluoroisoquinolines*

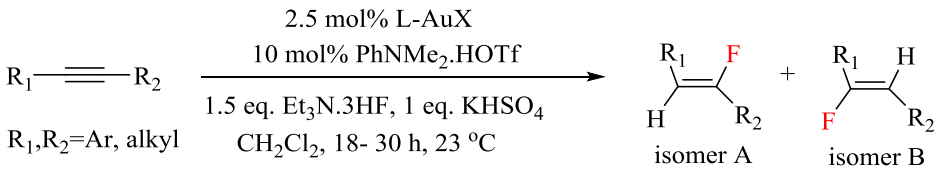
As a result, the development of efficient and mild methods to incorporate fluorine into a diverse range of molecules has received increasing attention in organic synthesis, whilst the exploration of new synthetic strategies for the synthesis of fluorinated heterocycles has also attracted attention.[7] The most significant conceptual advances over the past decade in the area of fluorination, broadly defined, were made in the reactions that led to the formation of C-F and C-CF_3 bonds, most prominently by organo- and transition-metal catalysis.[8,9] However, it has been found that the most challenging transformation remains the formation of the parent C-F bond, primarily due to the high hydration energy of fluoride, strong metal–fluorine bonds, and the highly polarized nature of bonds to fluorine.[9]

An alternative strategy is electrophilic fluorination by using a strong base to generate a nucleophilic carbanion to attack the F^+ reagent. The most popular reagents used for electrophilic fluorination are the fluoraza reagents, which have been discussed by various

groups in the literature relating to the synthesis of fluorinated heterocycles.[10] However, many fluorination reactions still lack general predictability and practicality. For example, commonly employed electrophilic fluorinating reagents are often not cost efficient on a manufacturing scale.[11] Even nucleophilic methods often require expensive reagents or catalysts, which reduce the practicality of modern fluorination reactions for large-scale synthesis. Despite these limitations, modern fluorination methods have made fluorinated molecules more readily available than ever before. In particular, modern methods have started to have an impact on research areas that require large amounts of material, such as drug discovery. [12]

3.1.1 The Hydrofluorination of Alkynes

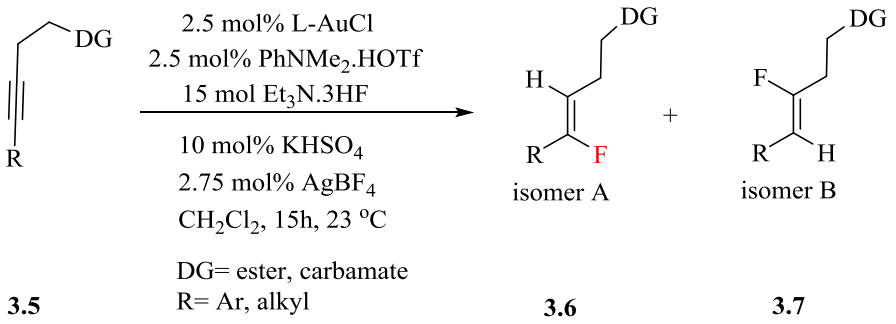
The synthesis of fluoroalkenes **(3.3)** and **(3.4)** by alkyne hydrofluorination was first accomplished with polymer-supported triethylamine trihydrofluoride or tetrabutylammonium dihydrogen trifluoride. Transition metal-mediated hydrofluorination was demonstrated by Sadighi and co-workers by gold-mediated hydrofluorination of substituted alkynes **(3.2)** with triethylamine/hydrogen fluoride (**Scheme 3.1**).[13]



3.2 **3.3** **3.4**

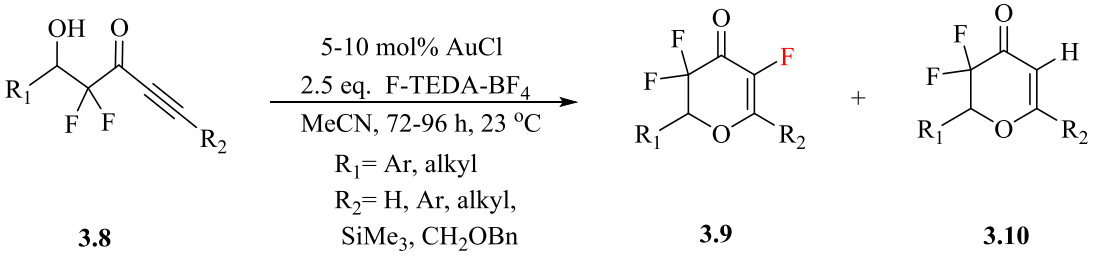
Scheme 3.1: *Monofluoroalkene synthesis by Au-catalysed hydrofluorination of alkynes*

Subsequently, a gold-catalysed N-directed synthesis of monofluoroalkenes **(3.6)** and **(3.7)** from disubstituted alkynes **(3.5)** and triethylamine/hydrogen fluoride was shown to yield a > 50:1 regioselectivity by Miller and co-workers.[14] The reaction can also be directed by ester groups, but the associated regioselectivity is lower (1:1.5) in favour of isomer B in some cases (**Scheme 3.2**).



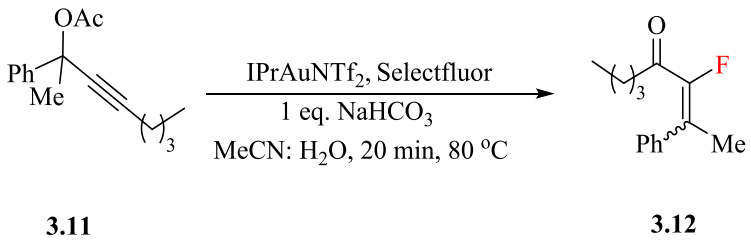
Scheme 3.2: *Au-catalysed directed hydrofluorination of alkynes*

The silver-mediated electrophilic fluorodestannylation of alkenyl stannanes reported by Tius *et al*. demonstrated that the synthesis of fluoroalkenes can be accomplished via electrophilic fluorination.[15] Gouverneur and co-workers reported the gold-catalysed cyclization/fluorination of propargyl ketones with F-TEDA-BF_4 to afford cyclic α-fluorovinylogous esters (**Scheme 3.3**) with the proto deaurated product accounting for most of the by-product. [16]



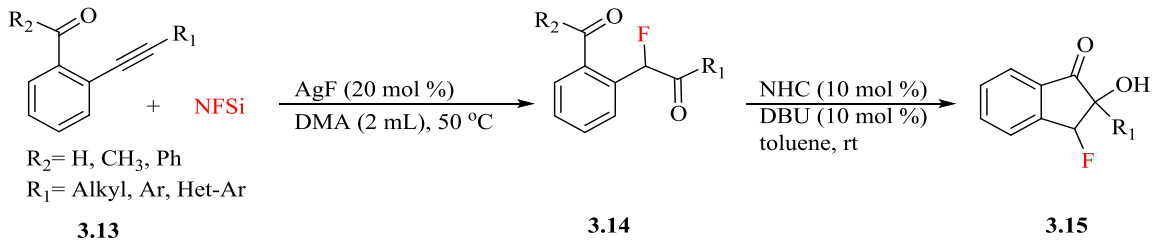
Scheme 3.3: *Au-catalysed fluorination of ketones*

Intermediates of the gold-carbene-catalysed rearranged propargyl acetate **(3.11)** can also be fluorinated electrophilically to afford the corresponding α-fluoroenone in 84% yield as a 1.5: 1 mixture of *E: Z* isomers **(3.12)**, as described by de Haro and Nevado [17] (**Scheme 3.4**).



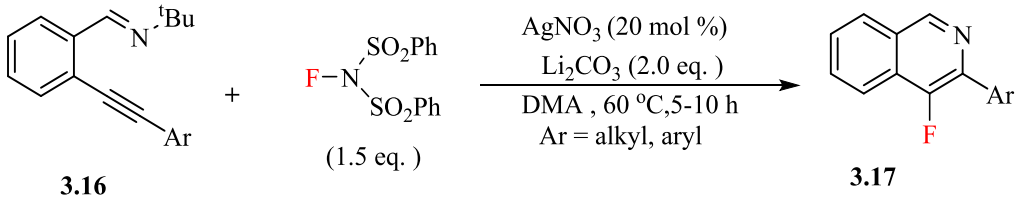
Scheme 3.4: *Domino gold-catalysed rearrangement and fluorination of propargyl acetates*

In 2017, Wang *et al.*[18] reported a silver-catalysed direct fluorination reaction for rapid assembly of α-fluoroketone derivatives **(3.14)** from carbonyl-directed alkynes **(3.13)** with the commercially available electrophilic fluorinating reagent NFSi. The transformation could be accomplished under simple and mild conditions with high regioselectivity, which provides chemists with an alternative method for designing α-fluoroketones. Meanwhile, the fluorine-containing 1,5-dicarbonyl compounds **(3.14)** may also be further applied to construct other valuable synthetic units (**Scheme 3.5**).



Scheme 3.5*: Silver-catalysed direct fluorination reaction*

Liu and Xu [9] reported silver-catalyzed aminofluorination of alkynes. This reaction was carried out with 20% mol $AgNO_3$, 1.5 eq of NFSi, and 2 eq of Li_2CO_3 in DMA (*N*,*N*-dimethylacetamide), and the desired products **(3.17)** were produced in excellent yields (**Scheme 3.6**).

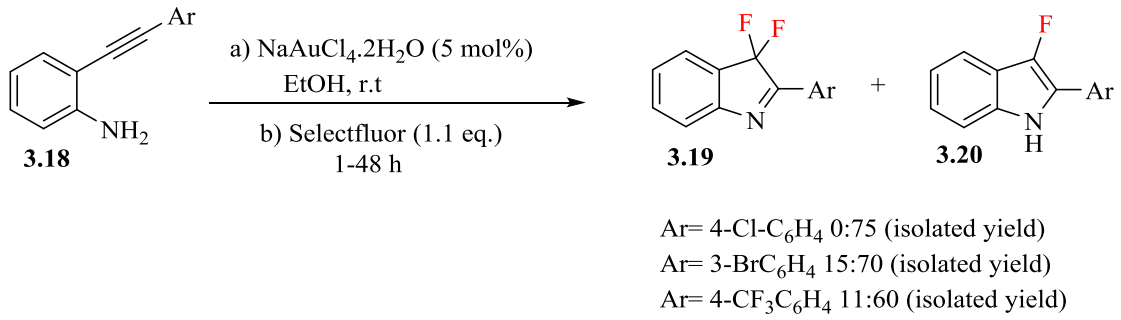


Scheme 3.6: *Silver-catalyzed aminofluorination of Alkyne reaction*

3.1.2 Preparation of Difluorinated Compounds

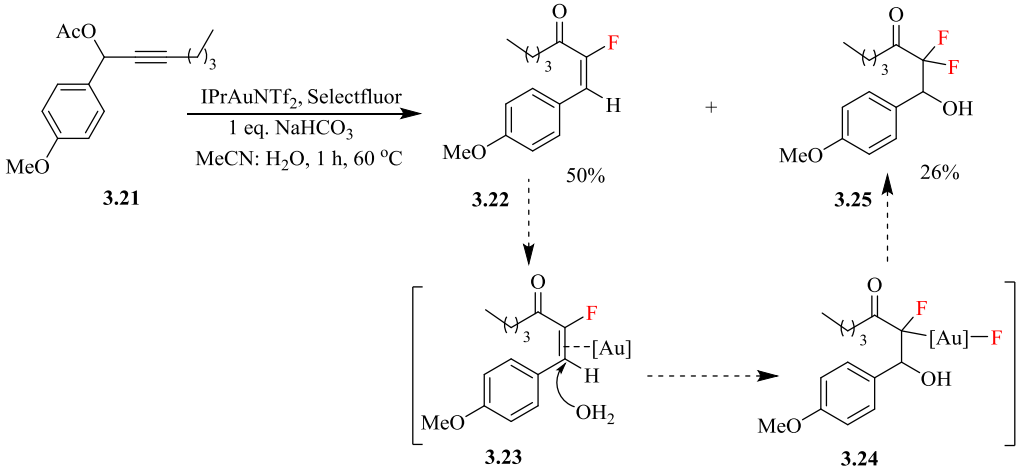
A two-step, one-pot Au-catalysed cyclization/electrophilic fluorination of unprotected 2-alkynylanilines **(3.18)** with Selectfluor was reported by Arcadi and Michelet, [19] allowing for a convenient synthesis of the difluorinated product **(3.19)** together with the monofluorinated product **(3.20)** in good yields under mild conditions (**Scheme 3.7**). The reaction proceeded smoothly by only using 1.1 eq. of Selectfluor in ethanol and did not require any base, acid, or N-protection group. Whilst mixtures of mono- and di-

fluorinated adducts were obtained using 3-Br- and 4-CF_3-substituted aryl-alkynes, just the monofluorinated indole was isolated in 75% yield for the 4-Cl-aryl-alkyne.



Scheme 3.7*: One-pot Au-catalysed cyclization/electrophilic fluorination*

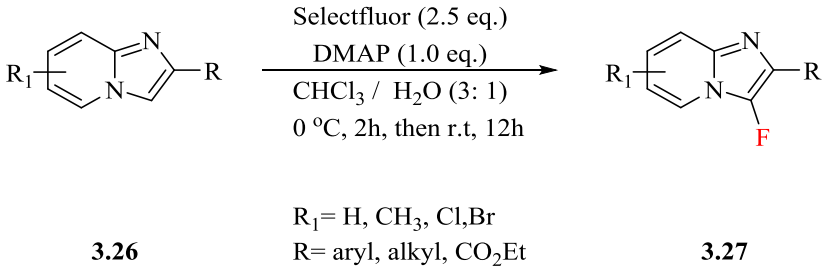
In 2010, de Haro and Nevado [17] demonstrated that the reaction of *p*-methoxyphenyl substituted propargyl acetate **(3.21)** with $IPrAuNTf_2$ (5 mol%), Selectfluor (2 eq.), 20:1 $CH_3CN–H_2O$ afforded not only the isomeric α-fluoroenones **(3.22)** in 50% isolated yield (2:1 Z:E ratio), but also the bis fluorinated compound **(3.25)** in 26% isolated yield (**Scheme 3.8**).



Scheme 3.8*: Preparation of α-fluoroenones*

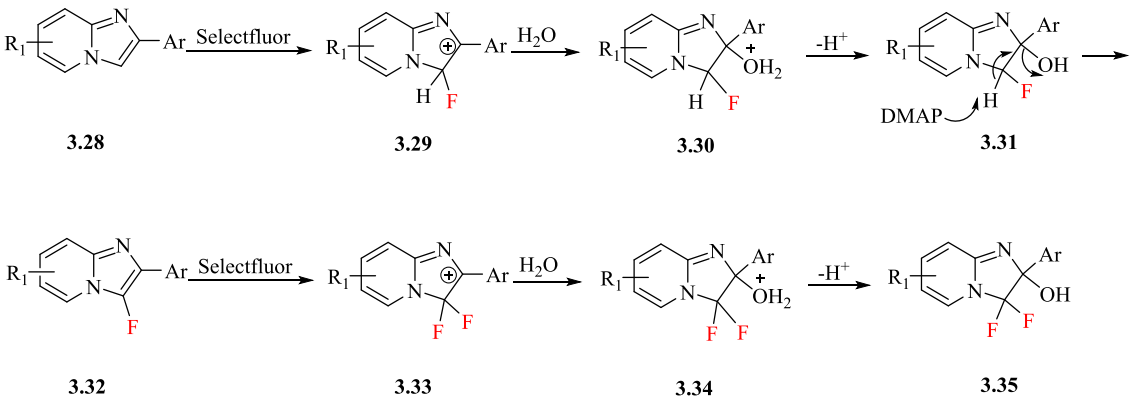
Efficient regioselective monofluorination of imidazo[1,2-a] pyridine with Selectfluor in aqueous conditions was developed by Sun and coworkers.[21] Various substituents on the aryl rings at the 2-position of the imidazo[1,2-a]pyridines **(3.26)** were tolerated in the reaction, which gave the corresponding 3-fluorinated imidazo[1,2-a]pyridines **(3.27)** in moderate to good yields. Addition of DMAP to the reaction mixtures benefited

monofluorination and the difluorination was distinctly suppressed. The reaction might proceed through an electrophilic fluorination mechanism (**Scheme 3.9**).



Scheme 3.9*: Synthesis of 3-fluoroimidazo[1,2-α]pyridines*

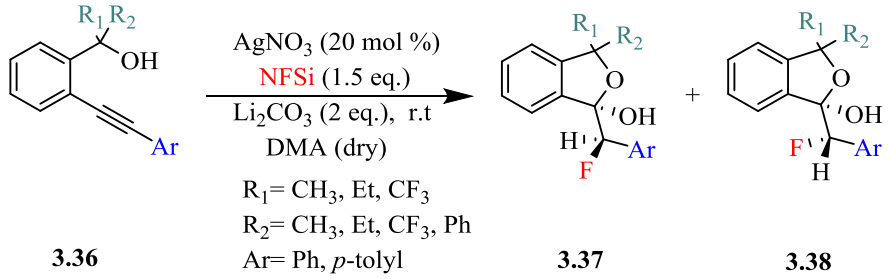
Initially, the reaction of imidazo[1,2-a]pyridine **(3.26)** with Selectfluor yields the unstable 3-fluorinated cation **(3.29)**, which reacts with water to form **(3.30)**. Deprotonation of **(3.30)** generates intermediate **(3.31)**, the proton of which is extracted by DMAP to rapidly furnish the monofluorinated product **(3.32)**. DMAP might also limit the reactivity of Selectfluor to a certain extent. When the reaction was run without DMAP, product **(3.32)** would react further, by a similar process, to produce the unstable 3,3-difluorinated cation **(3.33)**, which is attacked by H_2O followed by deprotonation to form the difluorohydroxylated product **(3.35)** (**Scheme 3.10**).



Scheme 3.10: *Regioselective monofluorination of aryl substituted imidazol[1,2-alpyridines in a solvent mixture of $CHCl_3$ and water.*

3.1.3 Aims

The aim of the work in this chapter was to design new fluorocyclisation procedures for aromatic alkynes containing tertiary alcohol groups **(3.36)** that could act as the internal nucleophiles. NFSi was chosen as the fluorinating reagent. This reagent is selective, shelf stable and an easy to handle source of electrophilic fluorine. This electrophilic reagent was used under Liu's conditions;[9] 20 mol% silver nitrate as a catalyst with Li_2CO_3 as a base at room temperature (**Scheme 3.**).



3.36 **3.37** **3.38**

Scheme 3.11: *Fluorocyclisation of aromatic alkynes containing tertiary alcohol groups*

It was hoped that these conditions could be applied successfully to give new monofluorinated dihydroisobenzofuran products **(3.37)** and **(3.38)**. Thus, these reaction conditions were tested on the series of tertiary alcohols. The reaction pathway involves a ring-closure process for the construction of the new C−O and C−F bonds. The key starting materials required for these fluorocyclisation reactions were the alkyne-containing tertiary alcohol substrates (**Table 3-1)**, as described in Chapter 2.

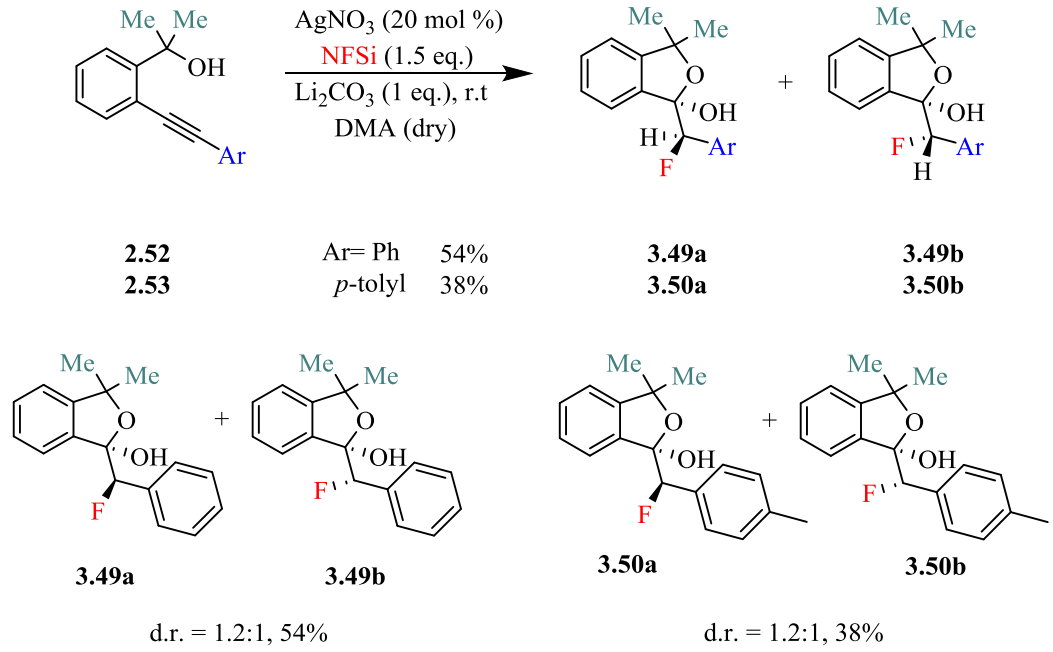
Table 3-1*: Alkyne-containing tertiary alcohol substrates*

SM No.	R_1	R_2	Ar
2.52	Me	Me	Ph
2.53	Me	Me	p-tolyl
2.54	Et	Et	Ph
2.37	Me	Ph	Ph
2.38	Me	Ph	p-tolyl
2.81	Me	CF_3	Ph
2.82	Me	CF_3	p-tolyl
2.83	Ph	CF_3	Ph
2.84	Ph	CF_3	p-tolyl

3.2 Silver-catalysed Fluorocyclisation Reactions under Mild Conditions

3.2.1 Fluorocyclisation Reactions of the Dimethyl Tertiary Alcohols

Initial investigations focussed on validating the ring closure. At the outset of this study, the first silver-catalysed fluorocyclisation reaction of the dimethyl tertiary alcohols **(2.52)** and **(2.53)** (2.0 eq.) was carried out in dry DMA using a catalytic amount of $AgNO_3$ (20 mol%) as the promoter, followed by the addition of NFSi (1.5 eq.), and Li_2CO_3 (2.0 eq.) at room temperature, and the reaction allowed to proceed overnight under nitrogen (**Scheme 3.**).



Scheme 3.12: *Monofluorinated dihydroisobenzofuran products*

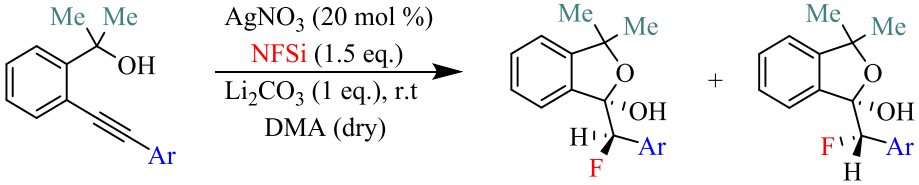
It was found that the desired monofluorinated dihydroisobenzofuran products were obtained as 1.2:1 mixtures **(3.49a)** & **(3.49b)** (54 % isolated yield) or **(3.50a)** & **(3.50b)** (38 % isolated yield) which were detected in the crude reaction mixtures using ^{19}F NMR spectroscopy.

3.2.1.1 Characterisation of Monofluorinated Diastereoisomeric Products

After purification by column chromatography, the identities of these monofluorinated dihydroisobenzofuran products **(3.49a)** & **(3.49b)** and **(3.50a)** & **(3.50b)** were confirmed by ^{1}H, ^{13}C, ^{19}F NMR spectroscopies as well as ASAP accurate mass spectrometry (**Table 3-2**). The ^{1}H NMR spectra provided valuable structural information about these mixtures

via the presence of two singlet peaks between 2.69 ppm to 3.19 ppm representing the hydroxyl protons, and two singlet peaks between 1.28 to 2.32 ppm representing the dimethyl substituents. In addition, the ^{1}H NMR spectra showed four doublet peaks at 5.53 and 5.69 ppm ($^{2}J_{HF}$ = 45.3 Hz, C*H*F) for the CHF units. The ^{13}C NMR spectra showed the related peaks at 94.3 (d, $^{1}J_{CF}$ = 180.9 Hz, CHF) and 96.3 (d, $^{1}J_{CF}$ = 180.9 Hz, CHF) or 94.2 (d, $^{1}J_{CF}$ = 179.9 Hz, CHF) and 96.1 (d, $^{1}J_{CF}$ = 179.9 Hz, CHF), representing the CHF units for each monofluorinated dihydroisobenzofuran products (**3.49a)** & **(3.49b)** or **(3.50a)** & **(3.50b)**. Moreover, the ^{19}F NMR spectrum gave two singlet peaks, which indicated a ratio of 1.2:1, at -182.5 and -191.2 ppm or -181.4 and -191.3 ppm. The ASAP accurate mass spectrometry revealed daughter ions for [M-OH]$^{+}$.

Table 3-2*: The NMR data for monofluorinated dihydroisobenzofuran products*



2.52
2.53

Ar= Ph 54%
p-tolyl 38%

3.49a
3.50a

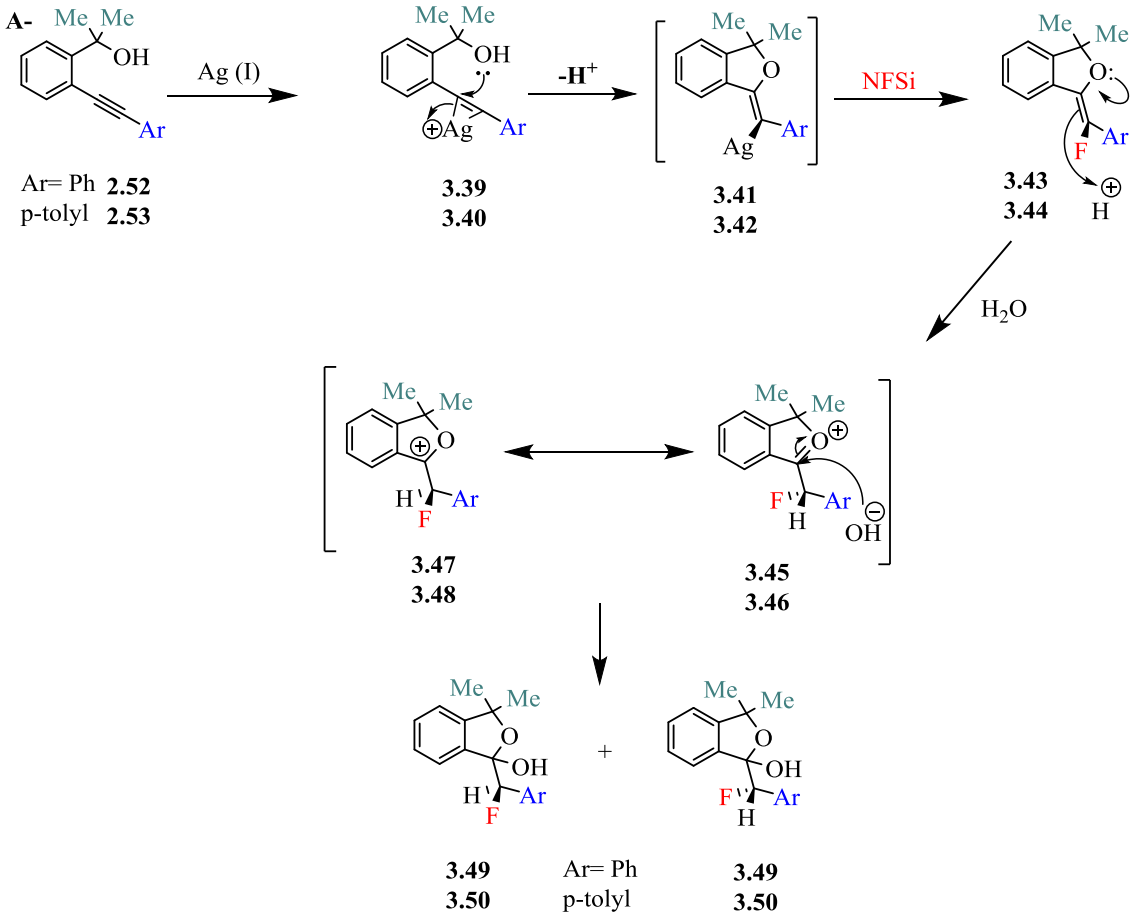
3.49b
3.50b

P	Ar	δ_H OH ppm	δ_H CHF ppm	δ_C CHF ppm	$^{1}J_{CF}$ Hz	δ_C COH ppm	$^{2}J_{CF}$ Hz	δ_F ppm
3.49a	Ph	2.83	5.58	94.3	180.9	105.5	26.0	-182.5
3.49b	Ph	3.19	5.69	96.3	180.9	105.9	26.0	-191.2
3.50a	*p*-tolyl	2.69	5.53	94.2	179.9	105.6	26.0	-181.4
3.50b	*p*-tolyl	2.84	5.65	96.1	179.9	105.9	26.0	-191.3

3.2.1.2 The Proposed Mechanism

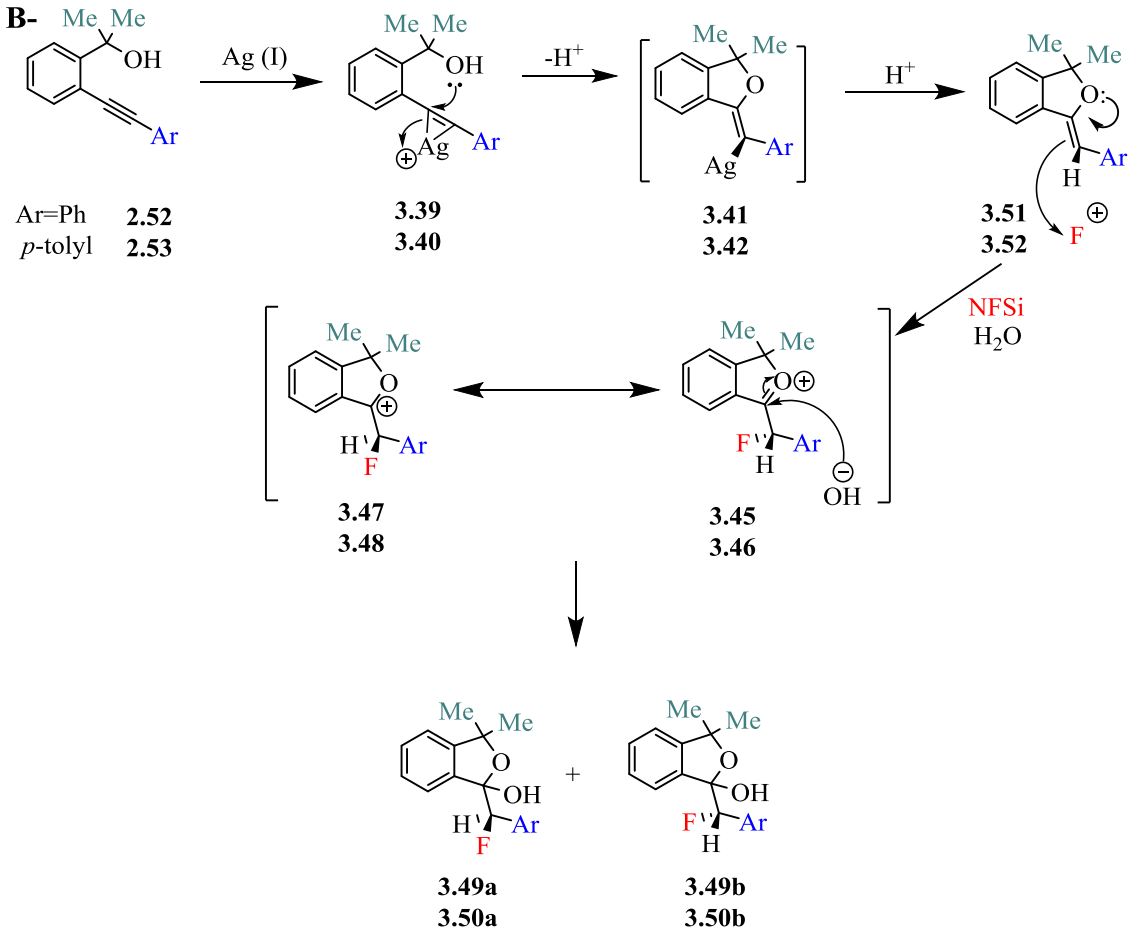
There are two possible mechanisms for these reactions which are shown in (**Scheme 3.8)**, which both of start through activation of the carbon-carbon triple bond by coordination to the electrophilic silver cation to form an intermediate species **(3.39)** or **(3.40)** in which the electron-deficient carbon of the alkyne is attacked by the internal alcohol nucleophile to give intermediates **(3.41)** or **(3.42)**.

In mechanism (A) (**Scheme 3.8**) fluorodemetallation generates the fluorinated enol ethers **(3.43)** or **(3.44)** which, on aqueous workup, form the pairs of diastereoisomers (**3.49a)** & **(3.49b)** or **(3.50a)** & **(3.50b)**.



Scheme 3.8: *Possible mechanism A*

In a second mechanism, (B), (**Scheme 3.**), the Ag catalyst acts in an essentially identical manner to a Pd catalyst to catalyse a protocyclisation reaction and form the enol ethers (**3.51** or **3.52**). Then the enol ethers would react with the electrophilic fluorinating reagent (NFSi) to form the pair of diastereoisomers **(3.45)** or **(3.46)** and **(3.47)** or **(3.48)**, which on aqueous workup forms the pairs of diastereoisomers (**3.49a)** & **(3.49b)** or **(3.50a)** & **(3.50b)**.

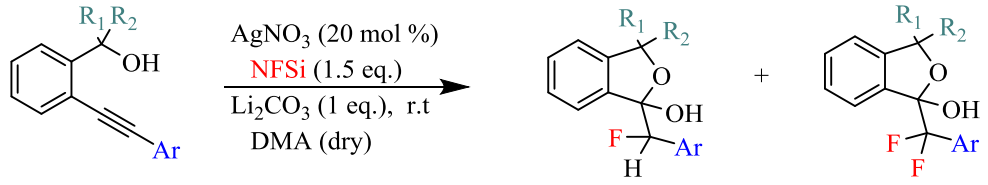


Scheme 3.14: *Possible mechanism B*

3.2.2 Fluorocyclisation Reaction of the (Et, Ph and CF_3) Tertiary Alcohols

In contrast to these straightforward results for the fluorination of dimethyl tertiary alcohols **(2.52**, **2.53)**, using the same reaction conditions for the other alcohol substrates (Table 3-1: **2.54**, **2.37**, **2.38**, **2.81**, **2.82**, **2.83** and **2.84)** the silver catalysed fluorocyclisation reaction gave mixtures of products with complicated NMR spectra.

Interestingly, for the aromatic alkynes containing tertiary alcohol starting materials **(2.54**, **2.37** and **2.38)**, the ^{19}F NMR spectra of the crude reaction products showed peaks in two distinct ranges: (a) peaks in the -180 to -190 ppm region for the monofluorinated dihydroisobenzofuran products; (b) peaks in the -100 to -120 ppm region for the difluorinated products (**Scheme 3.15)**.



2.37 $R_1 = CH_3$, R_2 = Ph, Ar = Ph
2.38 $R_1 = CH_3$, R_2 = Ph, Ar = *p*-tolyl
2.54 $R_1 = R_2$ = Et, Ar = Ph

3.53 **3.54**

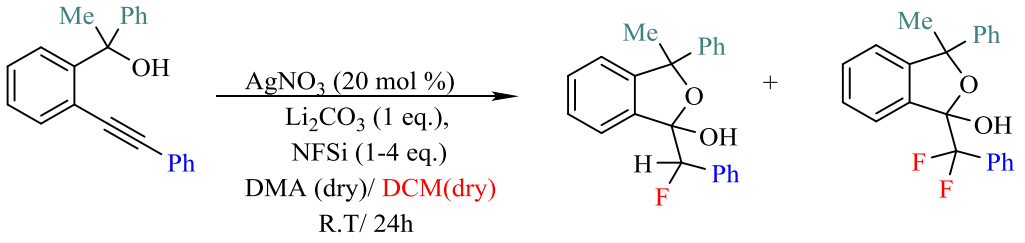
Scheme 3.9: *The monofluorinated and difluorinated dihydroisobenzofuran products*

For the CF_3-substituted tertiary alcohol starting materials **(2.81-2.84)**, the ^{19}F NMR spectra of the crude reaction products revealed virtually quantitative recovery of unreacted starting materials. However, these NMR spectra did reveal trace amounts of three groups of products with ^{19}F NMR signals: (a) in the -180 to -190 ppm region; (b) in the -100 to -120 ppm region; (c) in the -160 to -170 ppm region. Peaks in region (a) indicated of monofluorinated dihydroisobenzofuran products comparable to those observed **(3.49**, **3.50)** in the fluorination of dimethyl substrates. However, the resonances are very complicated due to the presence of three chiral centres. Peaks in region (b) were mutually-coupled suggesting difluorinated products whilst those in region (c) suggested the formation of fluoroalkenyl products. For the other substrates, although there was no evidence for the fluoroalkenyl products, the NMR spectra suggested both mono- and di-fluorinated products. Therefore, using **2.37** as a test substrate, attempts were made to force the silver-catalysed fluorination to yield just the difluorinated products.

3.2.2.1 Optimisation of the Ag-catalysed Fluorocyclisation Reactions with NFSi

Firstly, the fluorocyclisation reactions were investigated using differing amounts of NFSi and with different solvents under the standard reaction conditions. This showed that there were no significant changes in the conversions (**Table 3-3**).

Table 3-3: *Optimization of fluorocyclisations with amount of NFSi*



2.37 **3.57** **3.58**

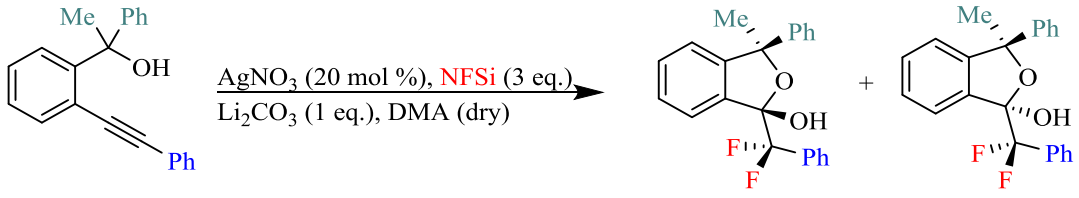
Entry	NFSi (eq)	Monofluoro product % [a]	Difluoro product % [a]
1	1	78	22
2	1.5	75	25
3	3	75	25
4	4	72	28

[a] Conversion calculated by ^{19}F NMR spectroscopy

3.2.2.2 Optimisation of Ag-catalysed Fluorocyclisation Reactions with different Temperatures and Reaction Times

At this point, longer reaction times and heating the reaction mixture were attempted. Initially, the temperature of the reaction mixture was increased to 80 °C for 72 h using 3 eq. of NFSi to give the difluorinated products (entry 3) (**Table 3-4**). Under these conditions there was no evidence of the monofluorinated dihydroisobenzofuran product.

Table 3-4: *Optimization of fluorocyclisation reactions with time and temperature*



2.37 **3.58a** **3.58b**

Entry	Temperature (°C)	Time (h)	Monofluoro product %	Difluoro product %
1	r.t	overnight	75	25
2	r.t	24	75	25
3	80	72	0	100
4	50	72	0	100
5	**50**	**24**	**0**	**100**
6	50	6	75	25

Then, it was decided to reduce the reaction time and the temperature to establish the best reaction conditions. As it can be seen from the Table above (entry 5), a 100% conversion to the difluorinated dihydroisobenzofuran product was obtained by heating at 50 °C with 3 eq. NFSi dissolved in dry DMA for 24 hrs. The ^{19}F NMR spectrum displayed two pairs of mutually-coupled doublets δ_F -103.3 (1F, d, $^2J_{FF}$ = 251.3 Hz, CF_AF_B), -103.2 (1F, d, $^2J_{FF}$ = 251.5 Hz, CF_AF_B), -111.7 (1F, d, $^2J_{FF}$ = 251.5 Hz, CF_AF_B), -112.7 (1F, d, $^2J_{FF}$ = 251.4 Hz, CF_AF_B) indicating a mixture of the difluorinated dihydroisobenzofuran products **(3.58a)** & **(3.58b)** (**Figure 3.2**). the ^{19}F NMR spectrum gave two singlet peaks, which indicated a ratio of 2:1.

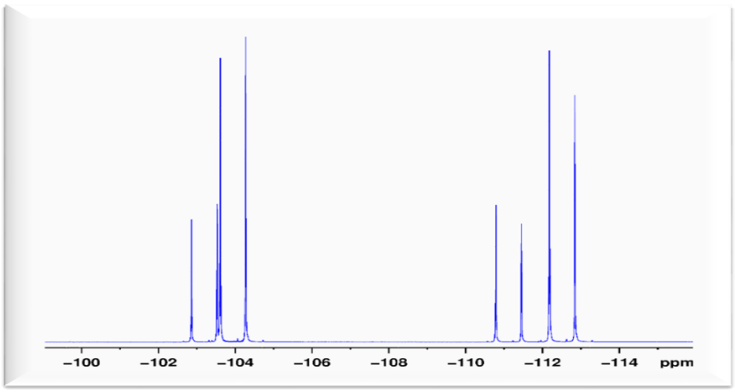
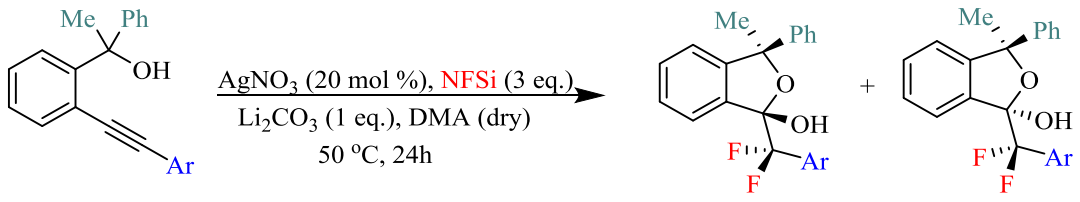


Figure 3.2: *The ^{19}F NMR spectra of the difluorinated dihydroisobenzofuran products*

The new fluorination protocol was applied successfully to give the difluorinated dihydroisobenzofuran products **(3.58a)** & **(3.58b)** and **(3.60a)** & **(3.60b)**. The crude reaction products were purified by column chromatography (**Scheme 3.10**).

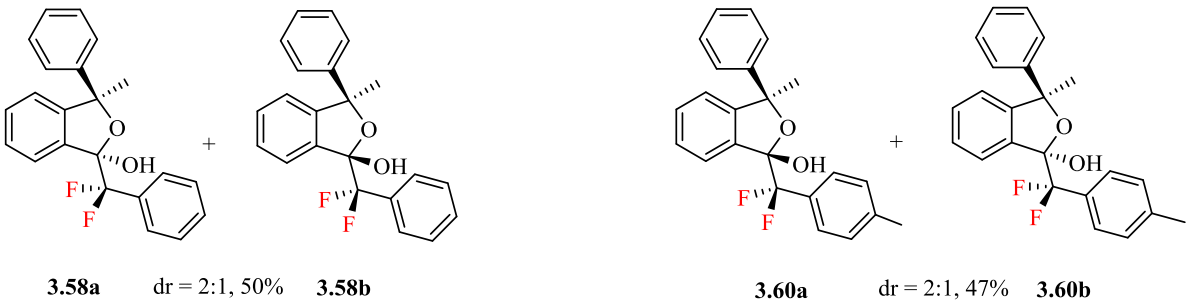


2.37
2.38

Ar = Ph, *p*-tolyl

3.58a
3.60a

3.58b
3.60b



Scheme 3.10: *The difluorinated diastereomeric products*

The identities of all the difluorinated dihydroisobenzofuran products **(3.58a)** & **(3.58b)** and **(3.60a)** & **(3.60b)** were confirmed by ^{1}H, ^{13}C, ^{19}F NMR spectroscopies as well as by ASAP mass spectrometry. Some of the NMR data have been summarised (**Table 3-5**).

Table 3-5: *The NMR data for the difluorinated dihydroisobenzofuran products*

P	Ar	δ_H CH_3 ppm	δ_H CH_3 ppm	δ_H OH ppm	δ_C CF_2 ppm	$^{1}J_{CF}$ Hz	δ_F ppm	$^{2}J_{FF}$ Hz
3.58a	Ph	1.81	-	3.29	119.8	247.1	-104.2 -112.8	251.4
3.58b	Ph	1.58	-	3.17	119.8	247.1	-103.5 -111.5	251.5
3.60a	*p*-tolyl	1.82	2.27	3.23	119.8	247.1	-103.4 -112.7	251.4
3.60b	*p*-tolyl	1.62	2.22	3.19	119.8	247.1	-103.3 -111.7	251.5

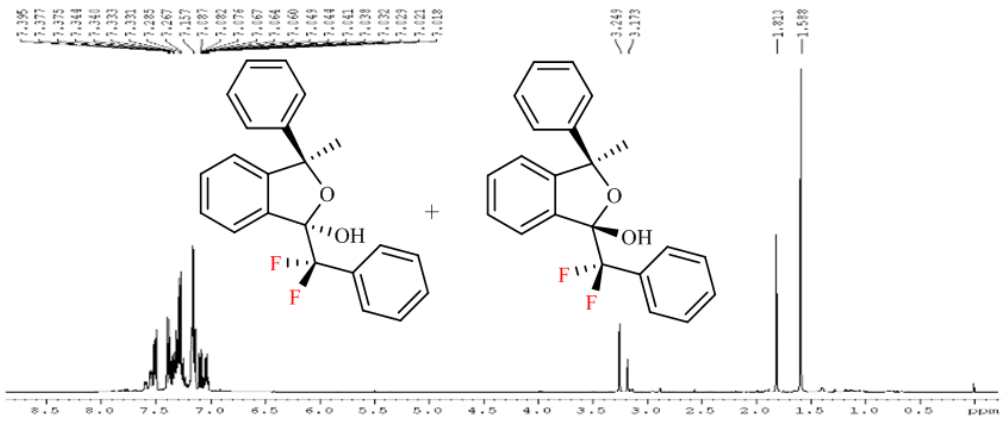


Figure 3.3: *The ^{1}H NMR spectra of the difluorinated dihydroisobenzofuran products*

Using one of the difluorinated dihydroisobenzofuran products **(3.58a) & (3.58b)** as an example. The ^{1}H NMR spectra showed upfield chemical shift signals at 1.58 ppm and 1.81 ppm, respectively, corresponding to the methyl group, and broad singlets at 3.17 ppm and 3.29 ppm for the hydroxyl group, for each of the diastereomers (**Figure 3.3**). In the ^{19}F NMR spectrum, doublet peaks at -103 ppm and -112 ppm with fluorine-fluorine coupling constants of 251 Hz are assigned to the diastereomeric fluorine atoms. In the ^{13}C NMR spectroscopy, two triplets at 119.8 ppm ($^{1}J_{CF}$ = 247.1 Hz) and 106.0 ppm (t, $^{2}J_{CF}$ = 33.6 Hz, COH), were observed due to the CF_2 unit and the COH unit next to the CF_2 for the major diastereomer, but the comparable weak multiplets could not be observed for the minor diastereomer. The accurate mass spectrometric data gave the major species as $(MH\text{-}OH_2)^{+}$.

After recrystallization from dichloromethane/chloroform (1:3) the major diastereomer 1-[difluoro(phenyl)methyl]-3-methyl-3-phenyl-1,3-dihydroisobenzofuran-1-ol **(3.58a)** was isolated as white crystals in a 39% yield, and ^{1}H (**Figure 3.4**), ^{19}F and ^{13}C NMR spectroscopy were performed allowing the resonances for the two diastereomers to be identified.

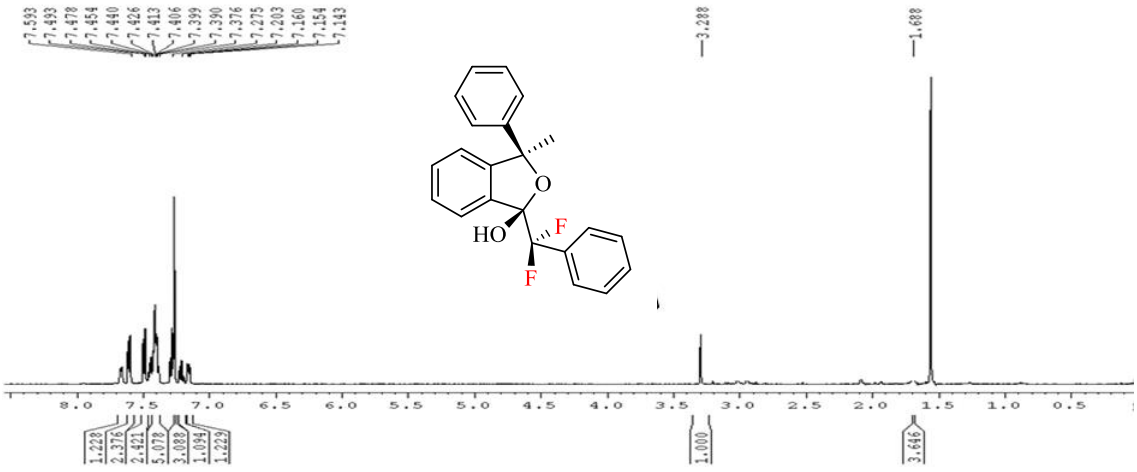


Figure 3.4: *The ^{1}H NMR spectrum of the 1-[difluoro(phenyl)methyl]-3-methyl,3-phenyl-1,3-dihydro-2-benzofuran-1-ol* ***(3.58a)***

Single crystals suitable for an X-ray crystallographic structural determination were obtained for 1-[difluoro(phenyl)methyl]-3-methyl-3-phenyl-1,3-dihydroisobenzofuran-1-ol **(3.58a)** which showed that there was one unique molecule in the unit cell (**Figure 3.5**). The key bond lengths and angles for **(3.58a)** are presented in (**Table 3-6**).

Table 3-6: *Key bond lengths (Å) and angles (◦) for* ***(3.58a)***

Bond lengths (Å)		Angles (◦)	
F(1)-C(7)	1.381(4)	F(2)-C(7)-F(1)	104.8(3)
F(2)-C(7)	1.374(4)	F(2)-C(7)-C(1)	110.8(3)
O(1)-C(8)	1.438(4)	F(1)-C(7)-C(1)	109.8(3)
O(1)-C(15)	1.462(4)	F(2)-C(7)-C(8)	107.5(3)
O(2)-C(8)	1.392(4)	F(1)-C(7)-C(8)	107.0(3)
		C(8)-O(1)-C(15)	112.3(3)

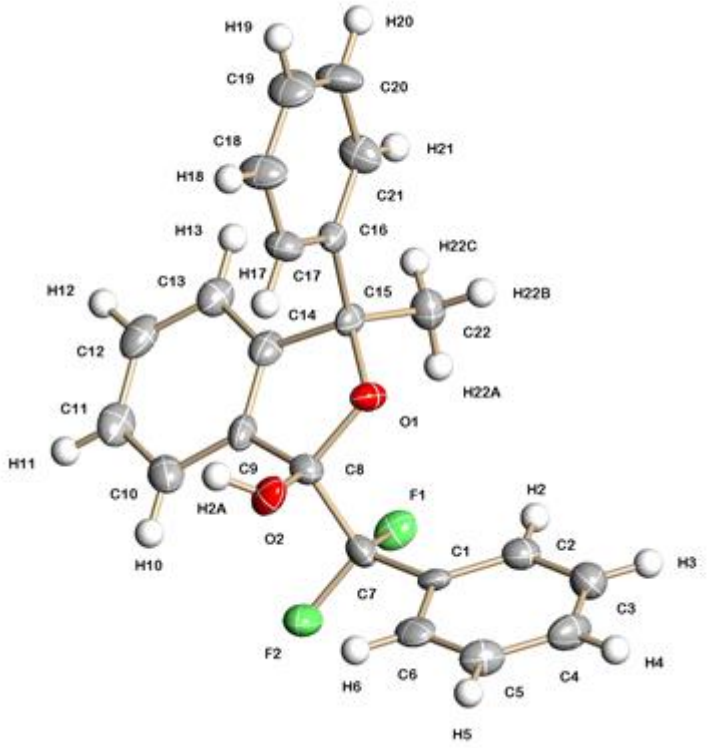


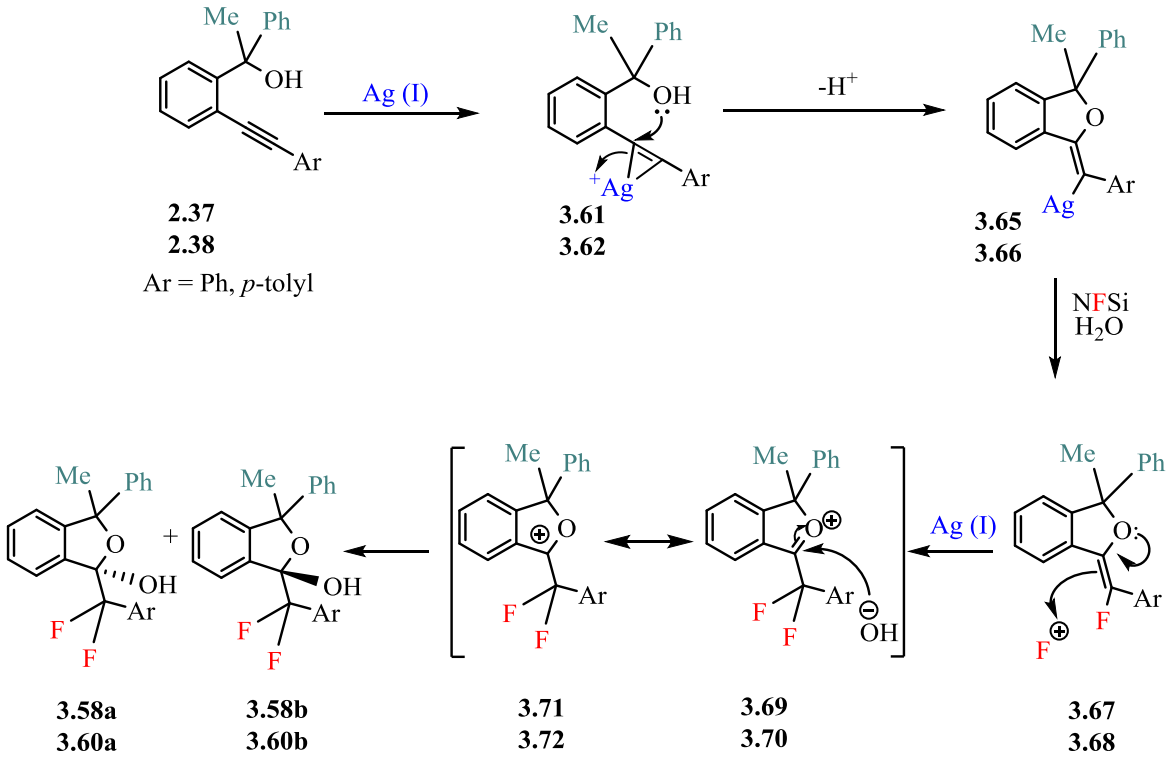
Figure 3.5: *Solid state structure of the 1-[difluoro(phenyl)methyl]-3-methyl-3-phenyl-1,3-dihydroisobenzofuran-1-ol* **(3.58a)**

The structural data supports the assignments of the ^{1}H, ^{19}F and ^{13}C NMR spectroscopic data. As expected, the 5-membered ring for **(3.58a)** is quite strained. The C(8)-O(1)-C (15) bond angle of 112.3(3)^{o} shows that there is significant strain in the 5-membered ring, which is partially relieved by the adoption of an envelope conformation in which the oxygen atom sits either above or below the plane of the ring. The F(1)-C(7) and F(2)-C(7) bond lengths are typical for CF_2 units which is consistent with a difluorinated dihydroisobenzofuran product **(3.58a)**.

3.2.2.3 Proposed Mechanism

In a typical electrophilic cyclisation, the synthesis of oxygen-containing heterocycles such as isochromenes and dihydroisobenzofurans can be achieved through a cyclisation reaction of 2-alkynyl aromatics, and the mechanism here is very similar to that discussed in the formation of the monofluorinated dihydroisobenzofurans (**Schemes 3.17 and 3.18**). These reactions start through activation of the alkyne **(2.37)** or **(2.38)** with electrophiles (Ag^+), and then the alcohol attacks the electron deficient carbon of the alkyne. Finally, deprotonation yields the heterocyclic intermediates (**3.65**) or (**3.66**). The formation of the difluorinated products indicates that the monofluorinated intermediates **(3.67)** and **(3.68)** must be formed in a fluorodemetallation reaction (cf Mechanism A, **Scheme 3.13**). These fluorinated enol ethers react with a second equivalent of NFSi before the final diastereomeric products are produced on aqueous work up

***Scheme* 3.11**.



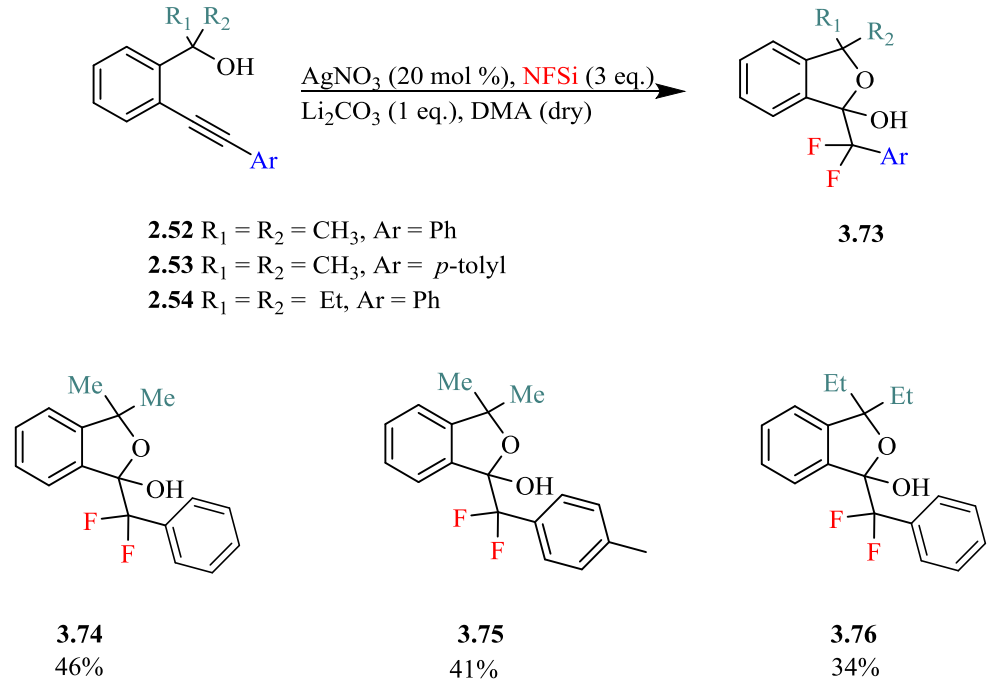
Scheme 3.11: *Proposed mechanism for formation of the difluorinated cyclised products*

The possible explanation for this result is that at elevated temperatures and with large amounts of NFSi, the fluorodemetallation reaction occurs more rapidly than the protodemetallation reaction postulated for the generation of the monofluorinated dihydroisobenzofurans (Mechanism B; **Scheme 3.17**) leading to the fluorinated enol ether that reacts readily with the electrophilic reagent leading, ultimately, to the difluorinated products.

3.3 Silver-catalysed Fluorocyclisation Reactions at 50 °C

3.3.1 Fluorocyclisation Reaction of the Alkyl-alkyne Containing Tertiary Alcohols

Under these new conditions, we next examined the scope of this fluorination reaction. The reaction of alkyne containing tertiary alcohols **(2.52)**, **(2.53)** and **(2.54)** at 50 °C with 3 eq. NFSi, $AgNO_3$ (20 % mol) in dry DMA gave good reactivity to afford the corresponding difluorinated dihydroisobenzofuran products in moderate yields (***Scheme 3.12***).



Scheme 3.12*: The difluorinated dihydroisobenzofurans*

The identities of the difluorinated dihydroisobenzofuran products **(3.74)**, **(3.75)** and **(3.76)** were confirmed by ^{1}H, ^{19}F and ^{13}C NMR spectroscopy, as well as by mass spectrometry. In (**Table 3-7**) below, there are some characterisation data. For example,

the ^{19}F NMR spectrum of the benzofuran products **(3.74)** showed two doublet peaks at -104 ppm and -112 ppm with a fluorine-fluorine coupling constant of 251 Hz, which confirmed that one difluorinated dihydroisobenzofuran product had been formed by this reaction (**Figure 3.6**).

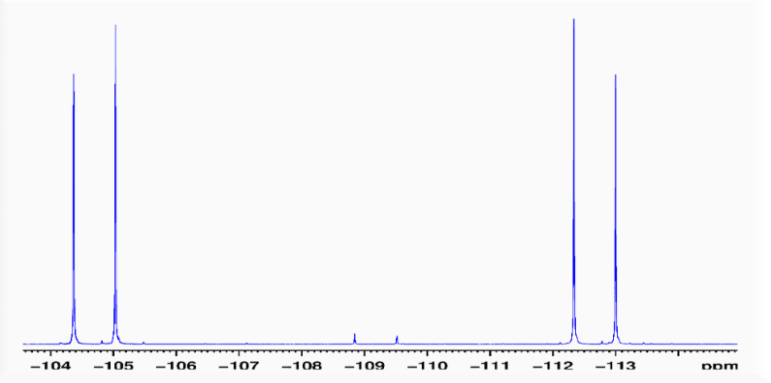


Figure 3.6*: The ^{19}F NMR spectrum of the difluorinated dihydroisobenzofuran products*

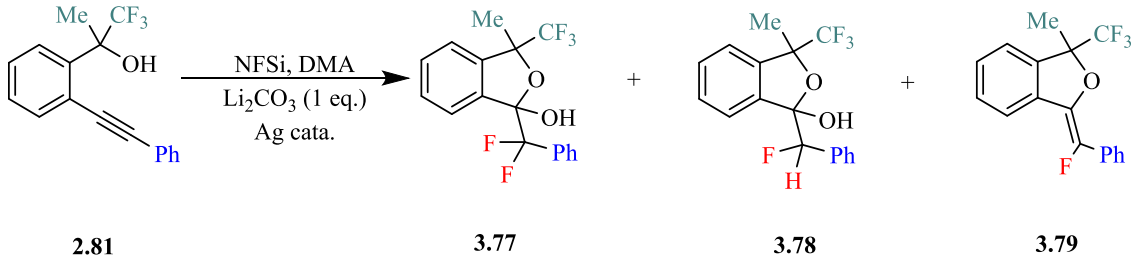
Table 3-7: *Characterisation data for the difluorinated dihydroisobenzofuran products **(3.74)**, **(3.75)** and **(3.76)***

P	R_1	R_2	Ar	δ_H CH_3 ppm	δ_H CH_3 ppm	δ_H OH ppm	δ_C CF_2 ppm	$^1J_{CF}$ Hz	δ_F ppm	$^2J_{FF}$ Hz
3.74	CH_3	CH_3	Ph	1.21	1.42	3.14	119.6	247.1	-104.0 -112.3	251.5
3.75	CH_3	CH_3	*p*-tolyl	1.33	1.51	3.24	119.6	247.8	-104.6 -112.6	250.5
3.76	Et	Et	Ph	-	-	3.07	119.6	247.1	-103.8 -111.4	250.8

3.3.2 Attempted Fluorocyclisation Reactions of the Trifluoromethylated Tertiary Alcohols

In the first instance, the fluorination reaction was carried out using the same conditions that had been used for the dialkylaryl and alkyldiaryl substrates, leaving a large amount of unreacted starting material. In order to increase the conversion, it was also carried out with DMA as a solvent at 80 ^oC for 72 hours. This product mixture was difficult to characterise via ^1H NMR spectroscopy because it also included various unidentified products. However, some species were identified from the ^{19}F NMR spectra by comparison to the data for the species identified in the previous reaction. This suggested

a difluorinated **(3.77)** product (55%), a monofluorinated **(3.78)** product (36%) and a very low conversion to the fluorinated alkene **(3.79)** product (9%) (Entry 3) (***Table 3-8***) However, the purification was impossible because of the complex mixture of products. Increasing the reaction time and reaction temperature did not improve the outcome (Entry 4).



2.81 **3.77** **3.78** **3.79**

Table 3-8: *The monofluorinated, difluorinated and alkene products from the CF_3 substrates for different amounts of NFSi, time and temperatures in DMA*

Entry	NFSi eq.	Temp. (◦C)	Time	Difluoro[a] %	Monofluoro[a] %	Fluoroalkene[a] %
1	1.5	R.T	18 h	0.6	1.2	7
2*	3	50	24 h	52	43	5
3*	3	80	72 h	55	36	9
4*	5	100	Week	46	29	15

[a] Conversion calculated by ^{19}F NMR spectrum, * Contained many unidentified products

Finally (Table 3-9), this reaction was attempted with a different silver(I) species, AgF, as catalyst (Entry 3), without any other silver catalyst (Entry 2) or with a stoichiometric amount of silver nitrate (Entry 1). These indicated that silver nitrate was necessary to achieve a reasonable conversion, but even with a stoichiometric amount of silver nitrate the complex product mixture proved too difficult to separate and pure products could not be isolated. It is unclear whether these failures with the trifluoromethylated substrates are due to steric or electronic effects arising from the fluorinated substituent.

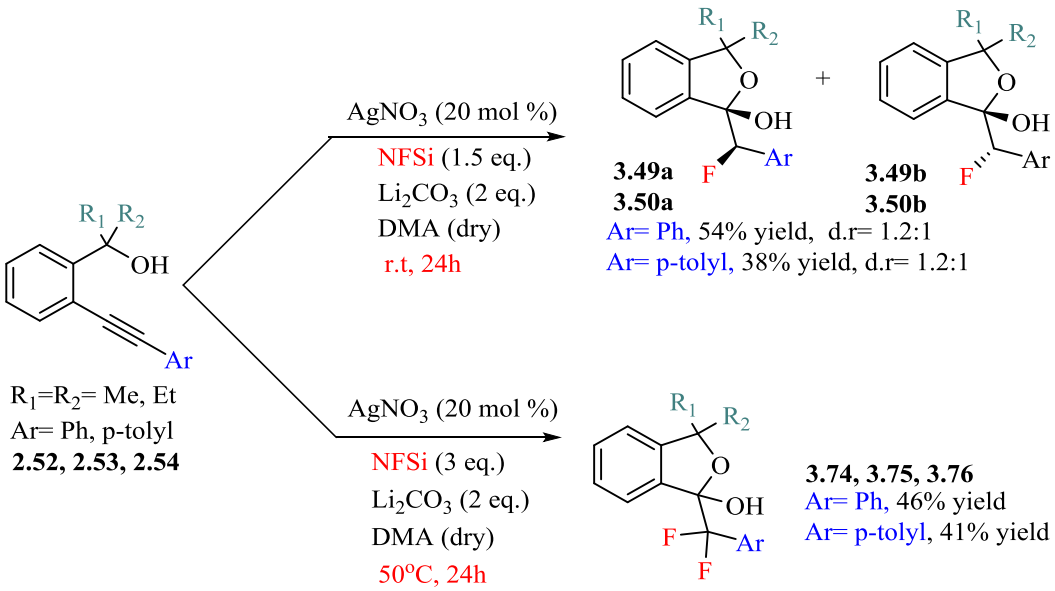
Table 3-9: *Optimisation of Ag-catalysed Fluorocyclisation Reactions*

Entry	Ag^+ eq.	Difluoro[a] %	Monofluoro[a] %	Fluoroalkene[a] %	Unreacted SM[a] %
1*	$AgNO_3$ (1eq.)	55	33	12	0
2	Without Ag^+	8	2	8	65
3	AgF (20 mol %)	15	9	1	75

[a] Conversion calculated by ^1H NMR spectroscopy comper to unreacted starting material, * There are many unidentified products

3.4 Conclusions

In this chapter, it has been demonstrated that the fluorocyclisation via the electrophilic fluorinating reagent NFSi in combination with $AgNO_3$ using alkynes containing tertiary alcohols can give either monofluorinated dihydroisobenzofuran products or difluorinated dihydroisobenzofuran products. These outcomes could be obtained selectively depending on the amount of NFSi used in the reaction and the temperature. We sought to expand the methodology for Ag-catalysed electrophilic fluorination of alkynes by developing new avenues for regiospecific control that would expand both the utility and substrate scope of the reaction.

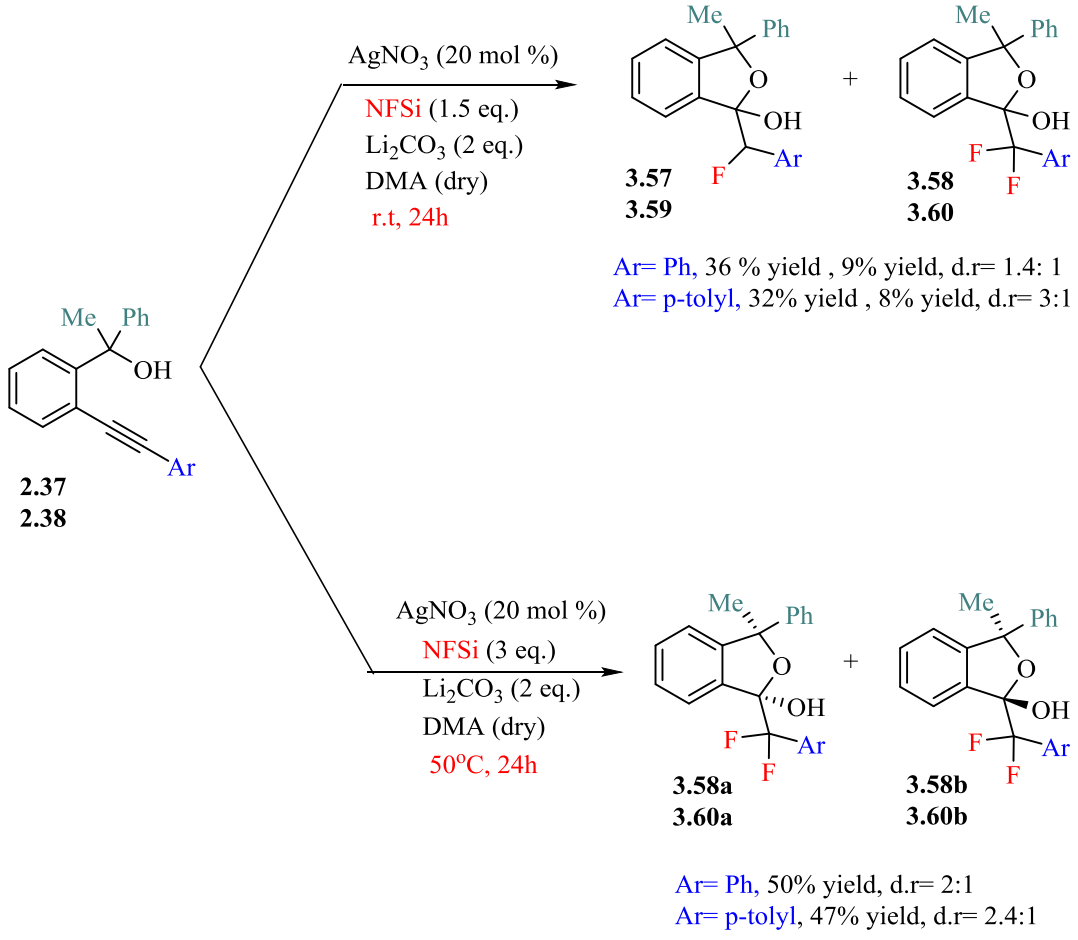


Scheme 3.13: *Monofluorinated dihydroisobenzofuran diastereoisomers and difluorinated dihydroisobenzofuran products*

Under mild conditions, the dialkylaryl tertiary alcohol containing alkynes (**2.52**), (**2.53**) and (**2.54**) with NFSi, $AgNO_3$ and Li_2CO_3, combine to give monofluorinated

dihydroisobenzofuran products (**3.49a)** & **(3.49b)** and **(3.50a)** & **(3.50b)**. In contrast, the same starting materials could give different selectivity and provide difluorinated dihydroisobenzofuran products (**3.74), (3.75)** and **(3.76)** by maintaining a reaction temperature of 50 ˚C (**Scheme 3.13**).

In contrast, the diarylalkyl tertiary alcohol containing alkynes (**2.37)** and **(2.38)** gave mixtures of monofluorinated and difluorinated dihydroisobenzofuran products **(3.57)** & **(3.58)** and **(3.59)** & **(3.60)** at room temperature. However, in a similar manner to the regioselectivity seen for the dialkylaryl alcohol substrates, diastereomeric mixtures of the difluorinated dihydroisobenzofuran products **(3.58a)** & **(3.58b)** and **(3.60a)** & **(3.60b)**, were obtained by maintaining a reaction temperature of 50 ˚C (**Scheme 3.20**). Importantly, the identity of one of these diastereomers **(3.58a)** was confirmed by single crystal X-ray crystallography.



Scheme 3.20: *Monofluorinated, and difluorinated dihydroisobenzofuran products*

3.5 References

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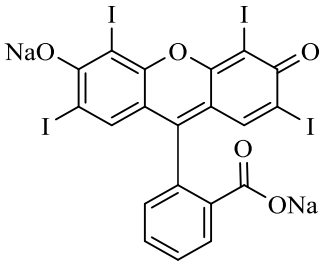
Chapter 4

Iodocyclisation Reactions

4.1 Introduction

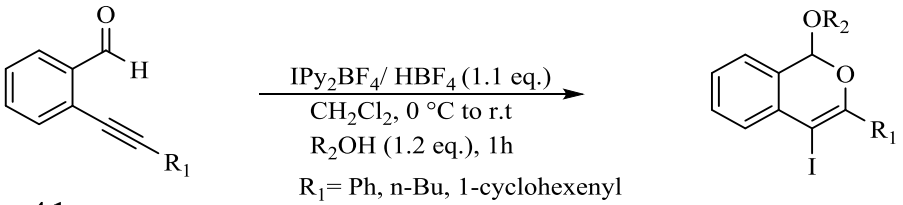
Halogenated heterocycles are highly valued intermediates with a wide range of applications in the pharmaceutical and agrochemical industrial sectors.[1] Although the organoiodine moiety is virtually absent in nature, the incorporation of an iodine atom into molecules greatly affects their biological activities, [2] including anti-hypertensive, anti-inflammatory, anti-ulcer and anti-leukemic properties.[3] The synthesis and functionalisation of chromenes, isochromenes, indoles, quinolines and isoquinolines have been the major objectives of research for over one hundred years because they are commonly found in natural products, and are often used as building blocks for pharmaceutical compounds (**Scheme 4.1**).[4,5] For these reasons, organoiodine compounds have been the object of considerable research, including iodocyclisation reactions to deliver iodinated heterocycles.[6]



Erythrosine

Scheme 4.1: *Organiodine compounds*

The synthesis of isochromenes and isoquinolines has been achieved by the electrophilic cyclisation of 2-alkynyl aromatics. One of the most common methods to have been used in electrophilic cyclisations is iodocyclisation using electrophilic reagents. In 2003, Barluenga's[7] group reported the application of this approach (**Scheme 4.2**).

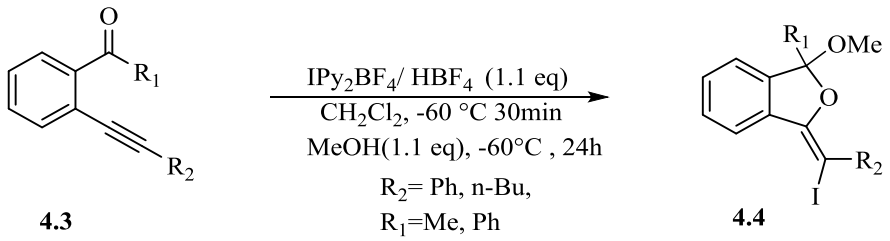


4.1 **4.2**

Scheme 4.2: *Six-membered heterocyclic products using IPy_2BF_4*

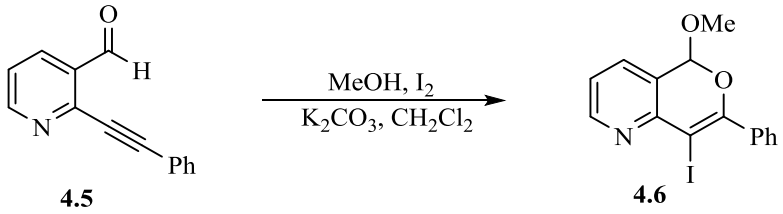
The carbonyl functionalised alkynes **(4.1)** have been successfully reacted with bis(pyridine)iodonium tetrafluoroborate (IPy_2BF_4) in the presence of an external nucleophile to produce iodocyclisation products. In fact, either 6-endo **(4.2)** or (*E*)-5-

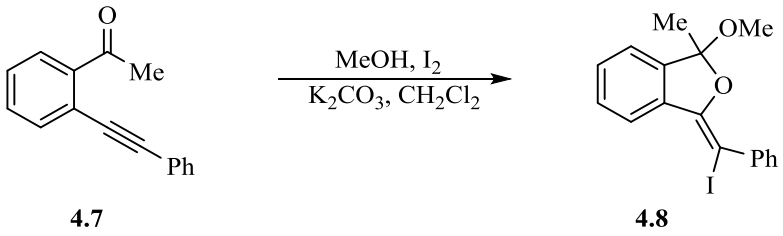
exo-dig cyclisation **(4.4)** products can be formed; the regioselectivity of the products is dependent on the groups present. The cyclisation of carbonyl groups onto alkynes, promoted by IPy_2BF_4 as the iodinating reagent, and using external alcohols as the nucleophiles at room temperature, gave six-membered heterocyclic products when acetylenic aldehydes were used as the starting materials. In contrast, employing alkynylaryl ketones **(4.3)** as substrates for the iodine cyclisation with IPy_2BF_4 gave five-membered heterocycles as the products **(4.4)** (**Scheme 4.3**). [7]



Scheme 4.3: *The five-membered heterocyclic products using IPy_2BF_4*

In both cases, the iodinating reagent is activated by the addition of HBF_4. Using this approach, the methoxyketone gave only moderate yields, most probably because of partial decomposition under acidic media. In this case, the cyclisation follows the more common 5-exo-dig cyclisation mode, furnishing a five-membered ring rather than the 6-endo cyclisation noticed for aldehydes.[8]

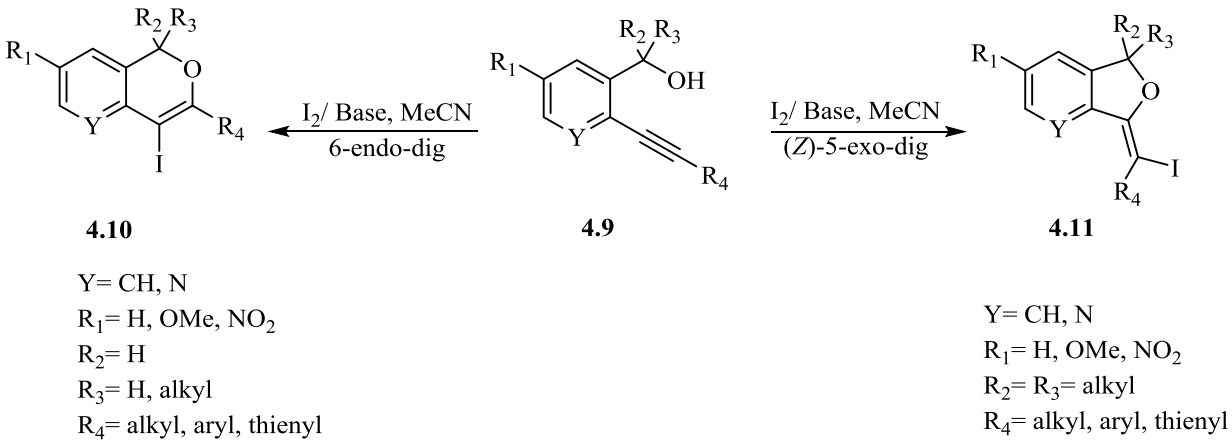




Scheme 4.4: *The 6-endo-dig or (*E*)-5-exo-dig cyclisation products*

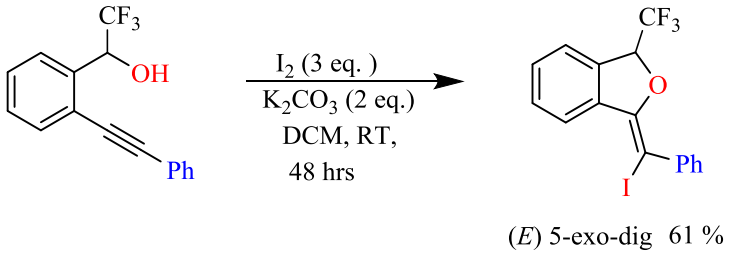
In a similar approach to that described by Barluenga, Larock *et al*. used either aldehydes **(4.5)** or ketones **(4.7)** in the presence of alcohols as external nucleophiles, but using iodine as the electrophilic reagent, to generate 6-endo-dig **(4.6)** or (*E*)-5-exo-dig **(4.8)** cyclisation products depending on the starting materials (**Scheme 4.4**).[9,10]

On the other hand, by using alcohols **(4.9)** as the internal nucleophilic substrates, both 6-endo-dig **(4.10)** and 5-exo-dig **(4.11)** cyclisation products could be formed (**Scheme 4.5**). Larock's group stated that the formation of the five-membered ring and the six-membered ring cyclised products were dependent on the substituents on the starting materials. They showed that tertiary alcohols would normally lead to five-membered ring products while primary and secondary alcohols would lead to six-membered ring cyclised products.[1]



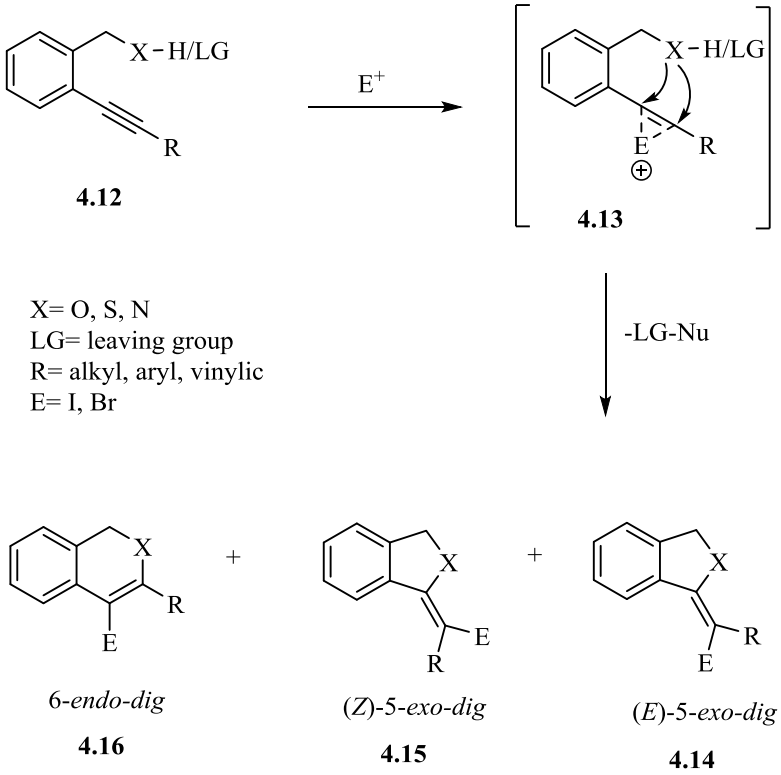
Scheme 4.5: The five-membered ring and the six-membered ring cyclised products

The synthesis of five-membered ring product has been demonstrated by Hope's group using primary alcohols and secondary alcohols. [11] The reaction was carried out using I_2 (3 eq.), K_2CO_3 (2 eq.) in DCM at room temperature for 48 hrs. The use of trifluoromethylated secondary alcohols allowed the fluoroalkyl group to direct the position of nucleophilic attack (5-exo-dig rather than 6-endo-dig) (**Scheme 4.6**).



Scheme 4.6: *The synthesis of five-membered ring products*

The mechanism for the synthesis of heterocycles using such electrophilic reagents is shown in (**Scheme 4.7**).[4] In a general electrophilic cyclisation, the addition of the electrophilic source to the C (sp) bonds of alkynes **(4.12)** will give the intermediate **(4.13)**, which activates the carbon-carbon bond towards nucleophilic attack. Then three different 6- or 5- membered products can be formed **(4.14)**, **(4.15)**, and **(4.16)**.



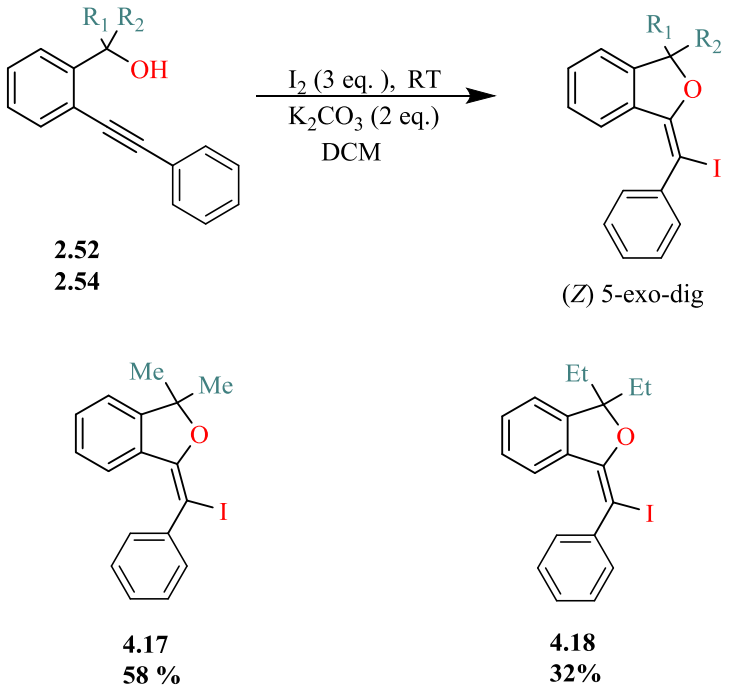
Scheme 4.7: *General mechanism of electrophilic cyclisation*

Interestingly, there was no evidence in the literature that the choice of reaction solvent played a significant role in the regioselectivities of the products. Thus, the aim of the work in this chapter is focussed on the development of the regioselectivities for the iodocyclisation reactions in two directions: (i) iodocyclisation reactions of aromatic alkynes containing tertiary alcohol groups, since most of the work in the literature had focussed on primary or secondary alcohols and (ii), establishing any influence of the solvent on these iodocyclisation reactions.

4.2 Iodocyclisation Reactions of Alkyne-Containing Tertiary Alcohol Substrates in DCM

4.2.1 Iodocyclisation Reactions of 2-(1-(arylethynyl)phenyl)propan-2-ol and (2-(phenylethynyl)phenyl)pentan-3-ol

In previous work in the group,[11] optimisation studies found that I_2 (3 eq.) as the electrophile in the presence of K_2CO_3 (2 eq.) as a base in dry DCM at room temperature for 48 h gave the best conversions in the iodocyclisation reactions of secondary alcohols containing aromatic alkynes. For direct comparison purposes, the alkyne-containing aryldialkyl tertiary alcohol substrates **(2.52)** and **(2.54)** were reacted under these iodocyclisation reaction conditions and gave (*Z*) 5-membered ring cyclised products, (*Z*)-dihydroisobenzofuran **(4.17)** (isolated yield 58%) and dihydroisobenzofuran **(4.18)** (isolated yield 32%) (**Scheme 4.8**).



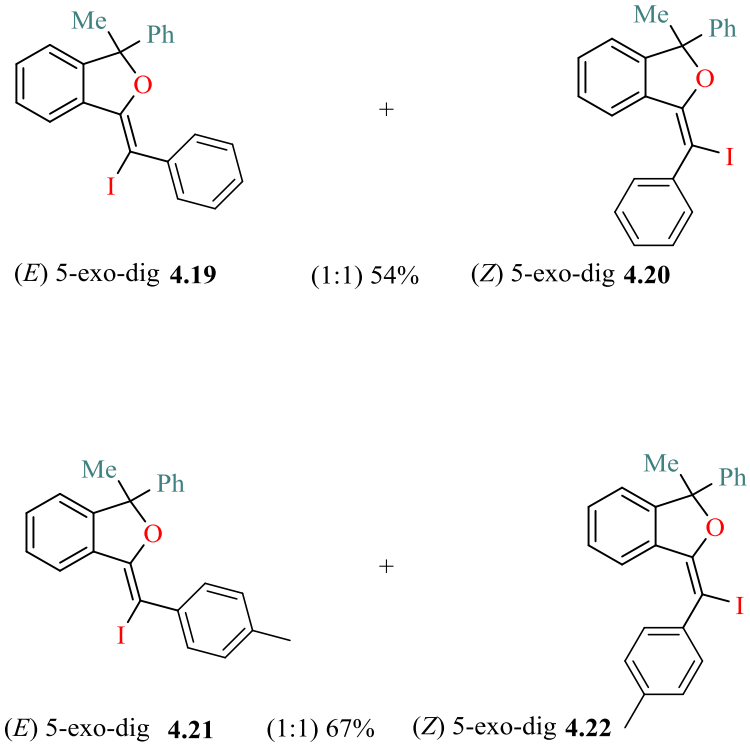
Scheme 4.8: *Iodocyclisation reactions*

In terms of characterisation, Hope's group found that the absence of diagnostic low-field peaks in the aromatic region of the ^{1}H NMR spectra for these products **(4.17)** and **(4.18)**, together with high field aromatic peaks (6.40 and 6.42 ppm, respectively) and δ_{CI} resonances characteristic of dihydroisobenzofuran 5-membered iodocyclisation products (63.1 and 65.9 ppm, respectively), allowed identification of the products as the (Z) 5-exo-dig regioisomers, chemical shifts in line with reported by Larock.[12]

In contrast with the reaction of the monomethyl secondary alcohol, the Thorpe-Ingold effect can be used to explain the regioselectivity observed here. Three substituents on the alcohol carbon lead to enhanced reactivity of the nucleophile by compressing the bond angle of the CCR_2OH group and pushing the nucleophile closer to the alkyne.

4.2.2 Iodocyclisation Reactions of 1-phenyl-[1-(arylethynyl)phenyl]ethanol

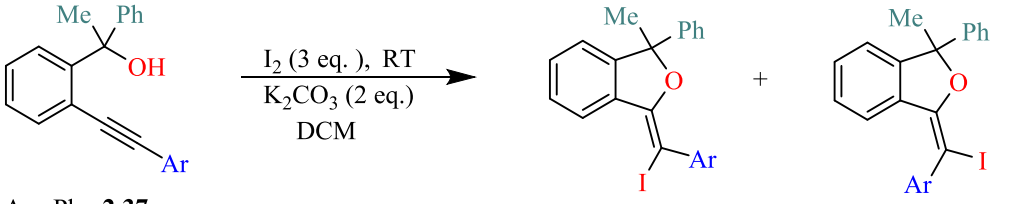
In contrast, as can be seen from the scheme below, the iodocyclisation reactions of the alkyne-containing diarylalkyl tertiary alcohol substrates **(2.37)** and **(2.38)** under mild conditions for 48 h in a DCM solvent generated a mixture, in a 1:1 ratio, of (*E*)- and (*Z*)-dihydroisobenzofuran **(4.19)** and **(4.20)** (isolated yield 54%), and (*E*)- and (*Z*)-dihydroisobenzofuran **(4.21)** and **(4.22)** (isolated yield 67%) (**Scheme 4.9**).



Scheme 4.9: *The iodocyclisation reactions of the diarylmethyl tertiary alcohol substrates*

The identity of all products **(4.19)** and **(4.20)**, and **(4.21)** and **(4.22)** were confirmed by ^{1}H and ^{13}C NMR spectroscopies, as well as ASAP accurate mass spectrometry. Some of the associated NMR data have been highlighted in (Table 4.1) below.

Table 4-1: *NMR data for iodocyclisation products*



Ar= Ph= **2.37**
Ar= p-tolyl= **2.38**

(*E*) 5-exo-dig
4.19, 4.21

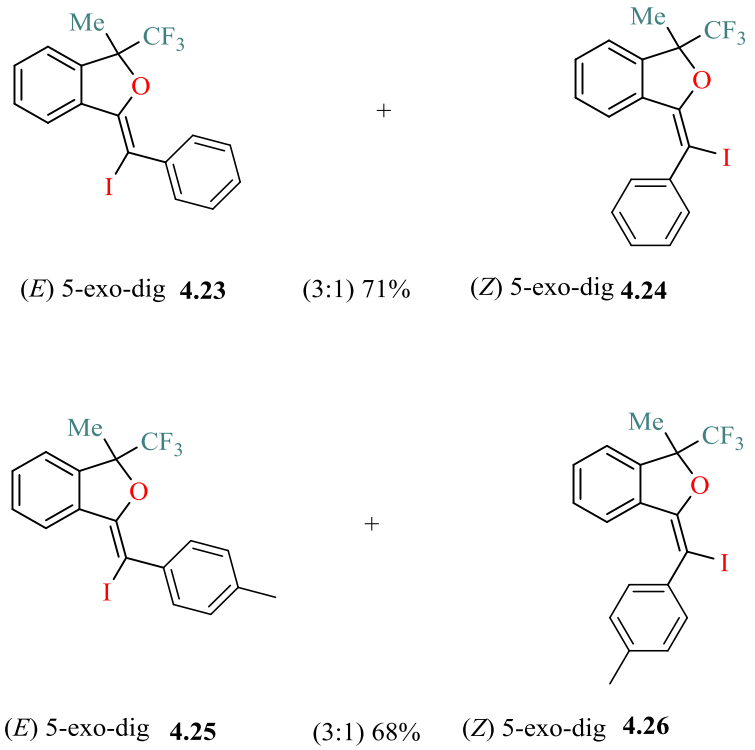
(*Z*) 5-exo-dig
4.20, 4.22

Products	Ar	δ_H lowest frequency aromatic proton peaks ppm	δ_H highest frequency aromatic proton peaks ppm	δ_C CI ppm
4.19	Ph	6.82	8.67	63.9
4.20	Ph	6.34	7.50	65.6
4.21	*p*-tolyl	6.88	8.67	64.4
4.22	*p*-tolyl	6.42	7.50	66.4

In the litertuare,[12] it is possible to identify characteristic resonances in the ^{1}H and ^{13}C NMR spectra associated with the (*E*) 5-exo-dig and (*Z*) 5-exo-dig products. For the (*E*) 5-exo-dig products, the lowest frequency aromatic proton peaks appeared around 6.8 ppm, whilst the highest frequency aromatic proton peaks appear above 8.7 ppm (**Table 4-1**). In addition, the ^{1}H NMR spectra of (*E*) 5-exo-dig products showed singlet peaks at 1.76 and 1.80 ppm, indicative of the methyl substituents. Further, the ^{13}C NMR spectra reveal peaks at 63.9 and 64.4 ppm which can be assigned to C-I. In contrast, for the (*Z*) 5-exo-dig products the lowest frequency aromatic proton peaks appeared around 6.4 ppm whilst the highest frequency aromatic proton peaks appeared around 7.5 ppm (**Table 4-1**). In addition, the ^{1}H NMR spectra of the (*Z*) 5-exo-dig products showed singlet peaks at 1.91 and 1.94 ppm, indicative of the methyl substituents. In the ^{13}C NMR spectra, peaks for C-I appeared at 65.6 ppm and 66.4 ppm.

4.2.3 Iodocyclisation Reactions of 1,1,1-trifluoro-[2-(2-arylethynyl) phenyl]propan-2-ol

Interestingly, using the alkyne-containing trifluoromethylated tertiary alcohols, **(2.84)** and **(2.85)** in the iodocyclisation reactions under the same mild reaction conditions gave a different regioselectivity: A 3:1 ratio of the *(E)* and *(Z)* 5-exo-dig products, *(E)*- and *(Z)* -dihydroisobenzofuran **(4.23)** & **(4.24)** **(**isolated yield 71%), and (*E*)- and (*Z*) dihydroisobenzofuran **(4.25)** & **(4.26)** **(**isolated yield 68%) (**Scheme 4.10**).

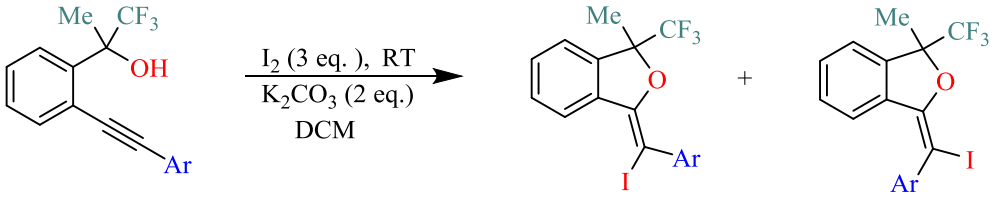


Scheme 4.10*: The iodocyclisation reactions of methyl/CF_3 substrates*

By ^{1}H, ^{13}C and ^{19}F NMR spectroscopies as well as ASAP mass spectrometry, the identity of all the iodinated products **(4.23)** & **(4.24)**, and **(4.25)** & **(4.26)** were confirmed **Table 4-2**. The presence of two singlet peaks (-80.4 and -80.7 ppm) in the ^{19}F NMR spectra confirmed the crude products to be a mixture of regioisomers in both cases. Commonly, for the (*E*) 5-exo-dig products the lowest frequency aromatic proton peaks appeared around 7.0 ppm, and the highest frequency aromatic proton peaks appeared around 8.7 ppm. Also, the ^{1}H NMR spectra show the presence of a singlet peak in each case between 1.55 to 1.71 ppm representing the methyl substituents, which are to low frequency of the analogous resonances in the dihydroisobenzofuran products without an electron-withdrawing CF_3 substituent. In addition, the ^{13}C NMR spectra reveal peaks between 19.2

to 21.5 ppm assigned to the same substituents. The peaks at 65.2 and 66.8 ppm can be assigned to the C-I groups (**Table 4-2**).

Table 4-2: *NMR data for iodocyclisation products*



Ar= Ph= **2.84**
Ar= p-tolyl= **2.85**

(*E*) 5-exo-dig
4.23, 4.25

(*Z*) 5-exo-dig
4.24, 4.26

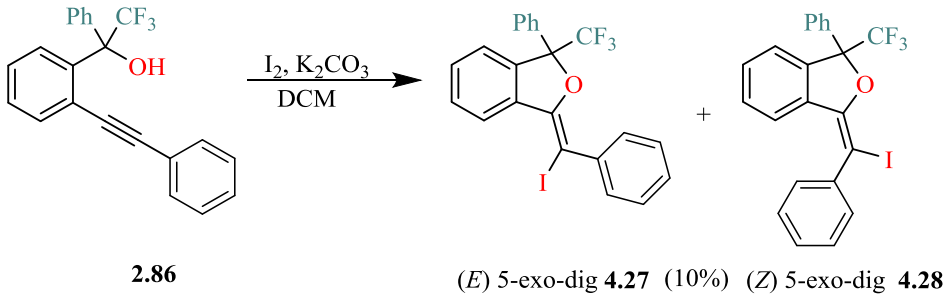
Products	Ar	δ_H lowest frequency aromatic proton peaks ppm	δ_H highest frequency aromatic proton peaks ppm	δ_C CI ppm	δ_F CF_3 ppm
4.23	Ph	7.15	8.69	65.2	-80.4
4.24	Ph	6.35	7.54	65.4	-80.7
4.25	*p*-tolyl	7.08	8.66	66.8	-80.4
4.26	*p*-tolyl	6.41	7.43	67.0	-80.7

On the other hand, for the (*Z*) 5-exo-dig products, the lowest frequency aromatic proton peaks appeared around 6.4 ppm, and the highest frequency aromatic proton peaks appeared around 7.5 ppm (**Table 4-2**) which were matched with the litertuare. The ^{1}H NMR spectra showed the presence of a singlet peak in each case between 1.71 ppm to 2.28 ppm, representing the methyl substituents. In addition, the ^{13}C NMR spectra revealed peaks between 19.3 ppm to 21.7 ppm that could be assigned to the same substituents. Further, the ^{13}C NMR peaks due to C-I appeared at 65.4 and 67.0 ppm.

4.2.4 Iodocyclisation Reactions of 2,2,2-trifluoro-1-phenyl-[1-(2- arylethynyl)-phenyl]ethanol.

In order to explore the potential of the iodocyclisation reactions of alkyne-containing tertiary alcohol (phenyl/ CF_3) substrates, the reaction (**2.86)** and **(2.87)** with I_2 (3 eq.) and K_2CO_3 (2 eq.) in dry DCM at room temperature for 48 h was attempted. However, this gave only a 10% conversion to a mixture of the *(E)*- and *(Z)* 5-exo-dig products (in a 3:1

ratio) with 90% unreacted starting material remaining for both substrates (**2.86)** and **(2.87)** (**Scheme 4.11**).



2.86

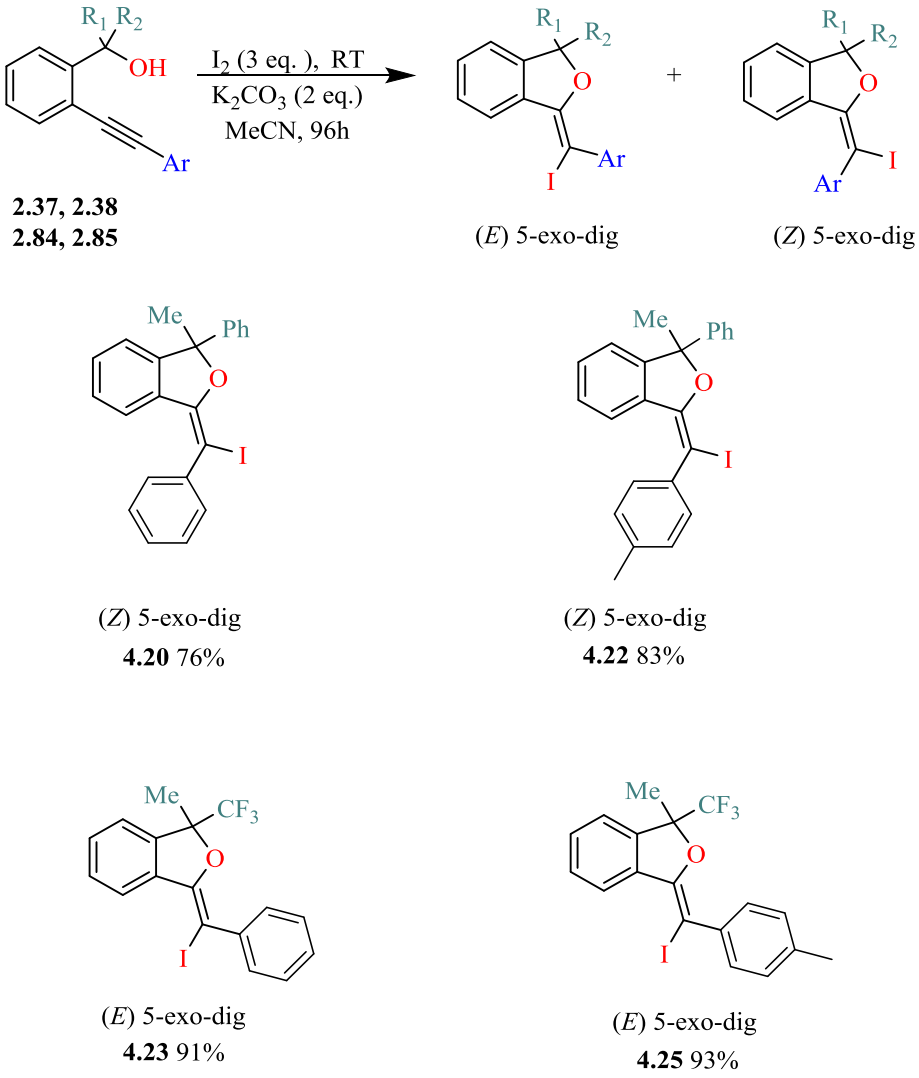
(*E*) 5-exo-dig **4.27** (10%) (*Z*) 5-exo-dig **4.28**

Scheme 4.11: *The iodocyclisation reactions of phenyl/CF_3 substrates*

This reaction was also carried out at 40 ˚C with increased amounts of I_2 (6 eq.), and K_2CO_3 (4 eq.) in DCM for 48 h, but this just gave a 5% conversion to the *(E)*- and *(Z)* 5-exo-dig products (in a 3:1 ratio) with 95% of unreacted starting material remaining. In both cases, an inseparable mixture of the (*E*)- and (*Z*)-regioisomers of 3-(iodo(phenyl)methylene)-1-phenyl-1-(trifluoromethyl)-1,3-dihydroisobenzofuran **(4.27)** & **(4.28)** were obtained along with the unreacted starting material. Unfortunately, the NMR spectra were too complicated to fully assign and it proved impossible to isolate the products that had been formed by column chromatography.

4.3 Iodocyclisation Reactions of Alkyne-Containing Tertiary Alcohol Substrates in MeCN

The same regioselectivity [(*Z*) 5-exo-dig] was observed in the iodocyclisation reactions of the alkyne-containing aryldialkyl tertiary alcohol substrates **(2.52)** and **(2.54)** in dry MeCN, albeit that the reaction time needed to be increased to 96 h to achieve similar conversions. In marked contrast, in dry MeCN, the iodocyclisation reactions of the alkyne-containing tertiary alcohol substrates (R_1 = CH_3, R_2 = Ph) **(2.37)** and **(2.38)** generated only the (*Z*)-5-exo-dig products **(4.20)** and **(4.22)** rather than the 1:1 mixture of (*E*) and (*Z*) 5-exo-dig products obtained in DCM. Alternatively, the trifluoromethyl alkyne-containing tertiary alcohol substrates (**2.84)** and (**2.85)** generated only the (*E*) 5-exo-dig products **(4.23)** and **(4.25)** rather than the 3:1 mixture of (*E*) and (*Z*) 5-exo-dig products obtained in DCM (**Scheme 4.12**).



Scheme 4.12*: The iodocyclisation reactions*

^{1}H, ^{13}C and ^{19}F NMR spectroscopies, as well as ASAP mass spectrometry, were used to identify the iodinated products **(4.20), (4.22), (4.23)** and **(4.25)** and the data have been summarised in (**Table 4-3**). The ^{19}F NMR spectra reveal singlet peaks at -80.4 ppm for the CF_3 substituents. These compounds showed the characteristic singlet around 2.0 and 1.5 ppm representing the methyl substituents in the ^{1}H NMR spectra for the phenyl-substituted and trifluoromethyl-substituted dihydroisobenzofurans, respectively. In addition, the ^{13}C NMR spectra revealed peaks at 28.0 and 19.2 ppm which could be assigned to the same substituents, respectively. The peaks between 63.6 ppm and 65.8 ppm could be identified as being due to C-I. (**Table 4-3**).

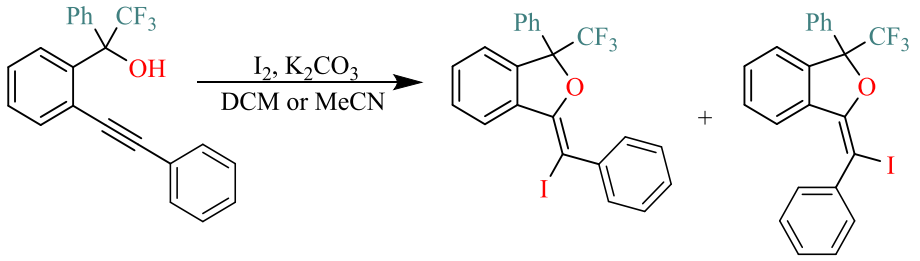
Table 4-3: *NMR data for iodocyclisation products*

	R	Ar	δ_H CH_3 ppm	δ_H $ArCH_3$ ppm	δ_C CH_3 ppm	δ_C $ArCH_3$ ppm	δ_C CI ppm	δ_F CF_3 ppm
4.20	Ph	Ph	1.92	-	28.0	-	63.6	-
4.22	Ph	*p*-tolyl	2.01	2.40	28.0	21.4	64.4	-
4.23	CF_3	Ph	1.54	-	19.2	-	65.4	-80.4
4.25	CF_3	*p*-tolyl	1.57	2.27	19.2	20.1	65.8	-80.4

In the ^{1}H NMR spectra, for the (*Z*) 5-exo-dig phenyl-substituted dihydroisobenzofurans the lowest frequency aromatic proton peaks appeared at 6.50 ppm to 6.83 ppm and the highest frequency aromatic H peaks at 7.47 ppm to 7.55 ppm. In the ^{13}C NMR spectra, diagnostic resonances at ca. 64 ppm could be identified as due to C-I for the (*Z*)-regioisomer. In contrast, in the ^{1}H NMR spectra, for the (*E*) 5-exo-dig trifluoromethyl-substituted dihydroisobenzofurans the lowest frequency aromatic H peaks appeared at 7.05 ppm to 7.09 ppm, and the highest frequency aromatic H peaks were apparent above 8.67 ppm. In the ^{13}C NMR spectra, diagnostic resonances at ca. 66 ppm could be identified as due to C-I for the (*E*)-regioisomer.

Having identified poor conversion in the iodocyclisation reactions of the Ph/CF_3 substrates in DCM, it was hoped that using MeCN at higher temperatures and for longer reaction times might improve the conversions for these substrates. A variety of conditions were investigated, but conversions of only 5-27%, with between 73 and 95% unreacted starting material were observed. (**Table 4-4**).

Table 4-4: *The iodocyclisation reactions of phenyl/ CF_3 substrates*



2.86 (*E*) 5-exo-dig **4.27** (*Z*) 5-exo-dig **4.28**

Entry	I_2 (eq.)	K_2CO_3 (eq.)	Solvent (dry)	Time	Temp. (^OC)	*% **2.86**	**% **4.27**& **4.28**	*E* : *Z* Ratio
1	3	2	DCM	48 h	RT	90	10	3 : 1
2	6	4	DCM	48 h	40	95	5	3 : 1
3	6	4	MeCN	1 week	RT	85	15	3 : 1
4	6	4	MeCN	48 h	60	77	23	3 : 1
5	6	4	MeCN	1 week	60	73	27	3 : 1

* Amount of unreacted starting material, **Conversion for product mixtures

Analysis by ^{1}H NMR and ^{19}F NMR spectroscopy showed a complex mixture of products that could not be purified by column chromatography. Significantly, none of the changes in reaction conditions had any notable impact upon the reaction outcome.

4.4 Discussion

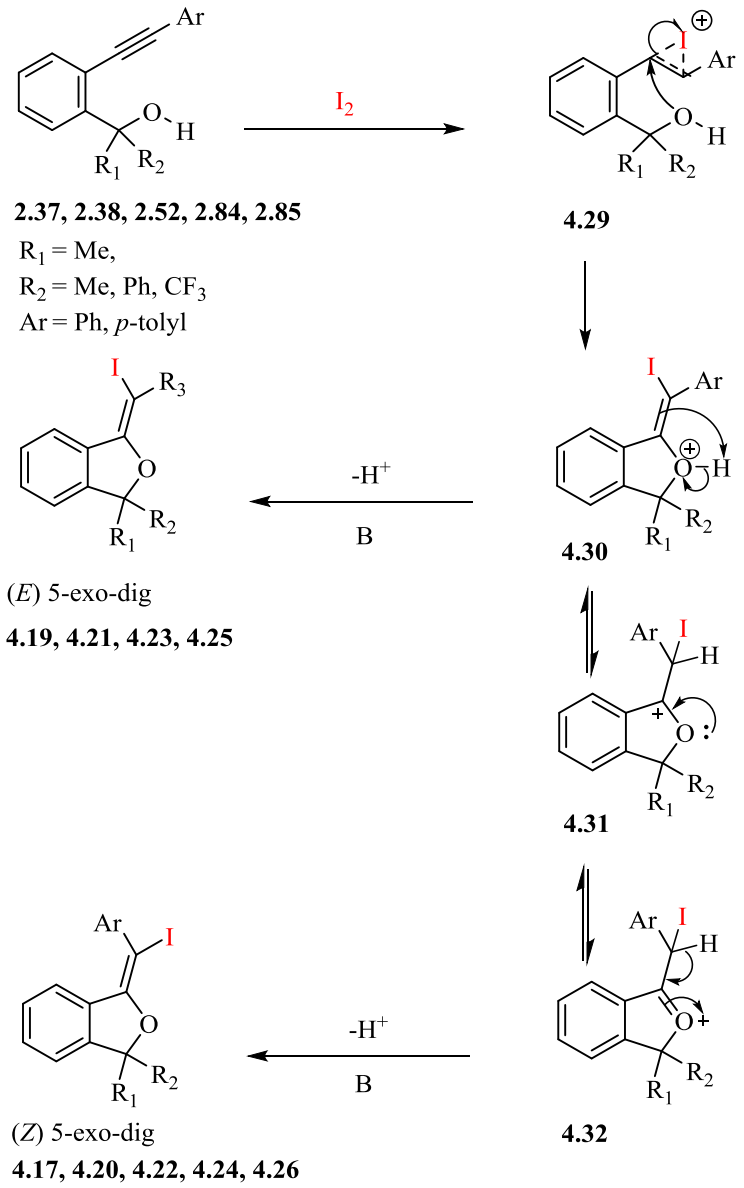
All of the products obtained from these reactions were oils, which precluded stereochemical identification via single crystal X-ray crystallography. However, NMR spectroscopic techniques allowed their identification using a variety of characteristic peak positions. In all cases, the iodocyclisation reactions afforded single products in MeCN, whilst in DCM mixtures of the two regioisomers were obtained which could not be separated by column chromatography.

The possible mechanism [12] of the iodocyclisation reactions is shown in (**Scheme 4.13**). The reaction involves coordination of iodine to the alkyne, which leads to electrophilic activation of the alkyne carbon-carbon triple bond and generation of an iodonium intermediate **(4.29)**. 5-exo-dig nucleophilic attack by the hydroxyl group then takes place

via the intramolecular cyclisation modes. Deprotonation of intermediates **(4.30)** or **(4.32)** leads to the dihydroisobenzofuran products **(4.19)/(4.21)/(4.23)/(4.25)** [(*E*) regioisomer] or **(4.17)(4.20)/(4.22)/(4.24)/(4.26)** [(*Z*) regioisomer] respectively.

From this work, it can be seen that the outcome of the iodocyclisation reactions of tertiary alcohols can be influenced by a number of factors; the solvent, the reaction time and the substituents at the tertiary alcohol carbon centre each have an impact upon the stability of the intermediate **(4.31**) to internal rearrangement to generate, following proton loss, either the (*E*) 5-exo-dig or (*Z*) 5-exo-dig products (**Scheme 4.13)**. For 2-(1-(arylethynyl)phenyl)propan-2-ol (R_1 = R_2 = Me), in line with Larock's observations,[12] rearrangement to (**4.32**) must be fast in comparison to proton loss from (**4.30**) leading to exclusively the (*Z*) regioisomer in both DCM and MeCN. They proposed that this "unexpected" stereochemistry arose due to the equilibration of the originally formed predicted stereoisomer to that of the observed isomer. This, they suggest, indicates that the *Z*-isomer would need to be more stable than the *E*-isomer. However, clearly, for both the 1-phenyl-[1-(arylethynyl)phenyl]ethanol (R_1 = CH_3, R_2 = Ph) and the 1,1,1-trifluoro-[2-(2-arylethynyl) phenyl]propan-2-ol (R_1 = CH_3, R_2 = CF_3) substrates in dry DCM, mixtures, indeed different ratios of mixtures, of the (*E*) 5-exo-dig and (*Z*) 5-exo-dig products were obtained. Whilst, only one (but different) regioisomer was observed in each case when dry MeCN was used.

The longer reaction time, over 96 h, necessary in the dry MeCN solvent used for the iodocyclisation reactions of 1-phenyl-[1-(arylethynyl)phenyl]ethanol (R_1 = CH_3, R_2 = Ph) appears to favour production of the (*Z)*-regioisomers **(4.20)** and **(4.22)** (isolated yields 76% and 83%, respectively). This would imply that the observed *Z*-isomer would need to be more stable than the mechanistically predicted *E*-isomer, allowing generation of exclusively the (*Z*) 5-exo-dig product, in line with the conclusions from Larock's report.[12]



Scheme 4.13*: The proposed mechanism for the 5-exo-dig cyclisation reactions*

On the other hand, (*E*)-dihydroisobenzofuran **(4.23)** and (*E*)-dihydroisobenzofuran **(4.25)** were formed in high isolated yields of 93% and 91%, respectively. This different reactivity and selectivity shows that the fluoroalkylated substituents influence the isomerisation, allowing highly selective generation of the (*E*) regioisomer. This might be because of the electron-withdrawing effect of fluorine destabilising the positive charge on oxygen in intermediate (**4.30**) encouraging immediate proton loss to form the (*E*) regioisomers.

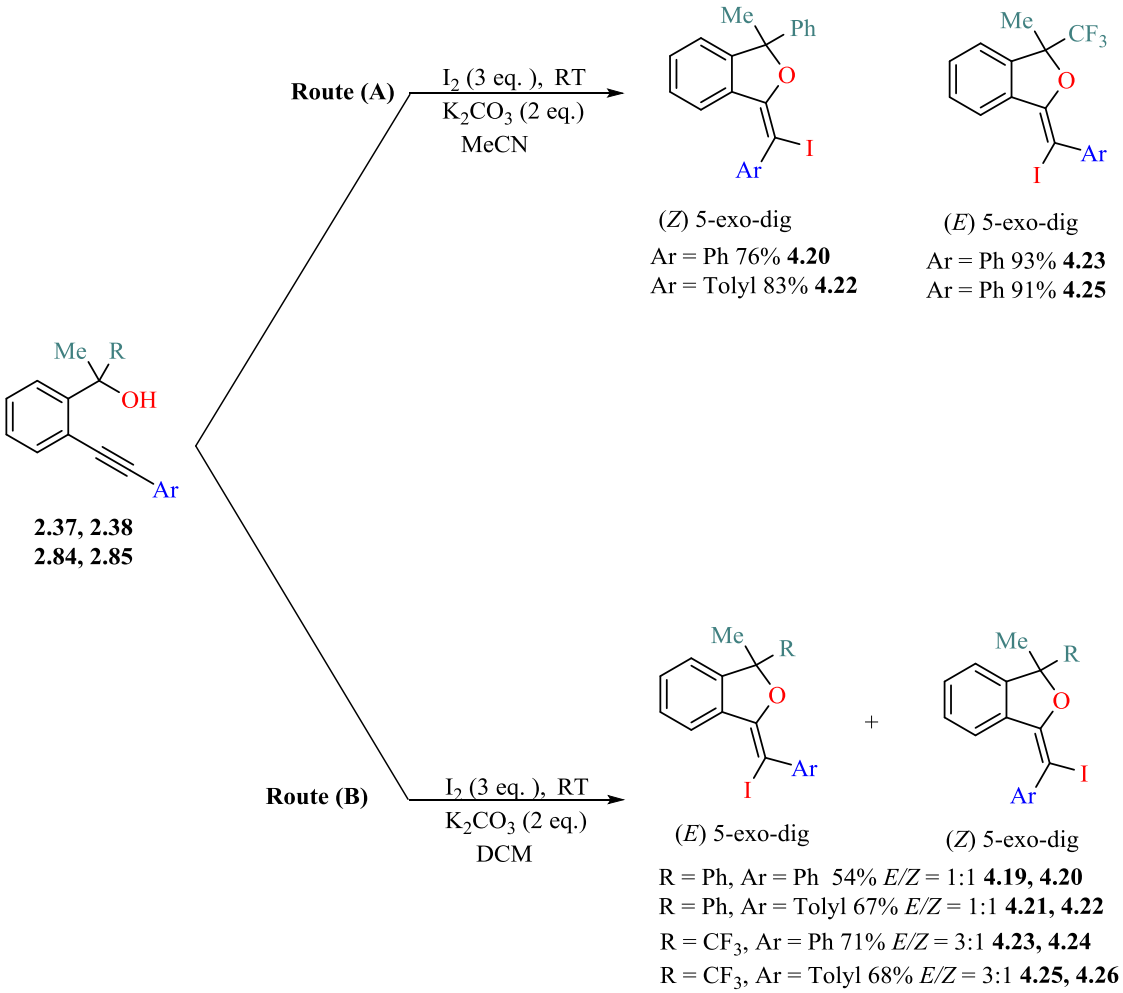
4.5 Conclusion

Through the work in this chapter, iodocyclisation products have been prepared via a simple and efficient method. For 2-(1-(arylethynyl)phenyl)propan-2-ol and (2-(phenylethynyl)phenyl)pentan-3-ol substrates the products were found to be the same as those reported by Larock in both MeCN and CH_2Cl_2 as solvents.

Interestingly, quite high yields with a selectivity to only one stereoisomer were obtained via iodocyclisation reactions in dry MeCN albeit for quite long reaction times. By using the alkyne-containing tertiary alcohol substrates **(2.37)** and **(2.38)** (R_1 = Me, R_2 = Ph), good yields of the *(Z)* 5-exo-dig products **(4.29)** and **(4.30)** could be obtained, whilst using substrates **(2.84)** and **(2.85)** (R_1 = Me, R_2 = CF_3) allowed excellent yields of the *(E)* 5-exo-dig products **(4.31)** and **(4.32)** to be obtained.

In contrast, the same starting materials gave mixtures of the *(E)* and *(Z)* 5-exo-dig products in dry DCM; the ratios of products obtained were found to be dependent upon the substrate used. By using the alkyne-containing tertiary alcohols **(2.37)** and **(2.38)** (R_1 = Me, R_2 = Ph) 1:1 mixtures of the *(E)* and *(Z)* 5-exo-dig products **(4.19)** & **(4.20)**, and **(4.21)** & **(4.22)** were obtained. In contrast, the alkyne-containing tertiary alcohols **(2.84)** and **(2.85)** (R_1 = Me, R_2 = CF_3) resulted in a 3:1 ratio of the *(E)* and *(Z)* 5-exo-dig products **(4.23)** & **(4.24)**, and **(4.25)** & **(4.26)** **()**.

On the other hand, very poor conversions were obtained for the iodocyclisation reactions, in either MeCN or DCM, using sterically hindered substrates (with phenyl and CF_3 substituents on the tertiary alcohol carbon atom), which were similar to the issues observed during the fluorocyclisation studies with these substrates (Chapter 3).



Scheme 4.14: *Iodocyclisation reactions*

4.6 References

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Chapter 5

Synthesis of alkyne-containing tertiary amine substrates

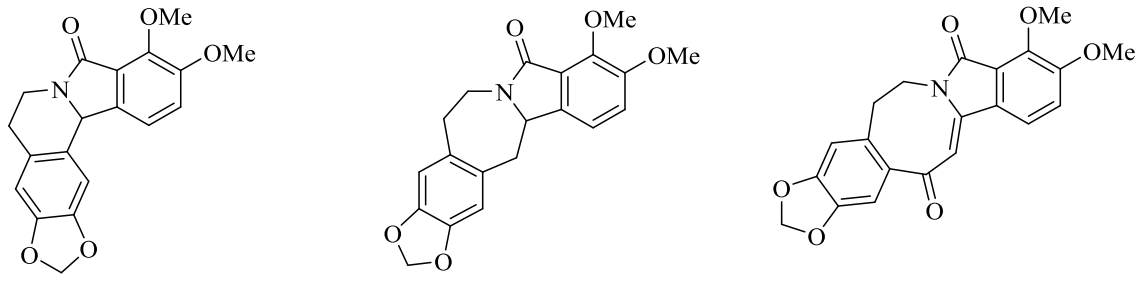
5.1 Introduction

Nitrogen heterocycles are a well-known class of compounds whose interest lies in the fact of their excellent biological activity. In addition, these compounds are very useful synthetic intermediates and can function as suitable building blocks for the synthesis of other biologically active compounds, such as natural products. As an example, many compounds with an isoquinoline core can be found in a number of natural compounds, whilst others have played important roles in the medical applications. For example, (**Figure 5.1**) Berberine **(5.1)** is an antitumor compound, and Lamellarin **(5.2)** is an anticancer alkaloid for inhibition of human topoisomerase.[1-3]

5.1 **5.2**

Figure 5.1: *Drug compounds with isoquinoline cores*

Heterocyclic groups often form the core structure in drug candidate molecules and, for this reason, isoindoline and isoindolinone compounds have attracted scientific interest for decades. Shamma and co-workers reported the synthesis of related drugs, such as Nuevamine **(5.3)**, Lennoxamine(III) **(5.4)** and Magallanesine(V) **(5.5)** (**Figure 5.2**), with *N*-heterocyclic cores, and which display a range of biological activities including anti-hypertensive, anti-psychotic, antiulcer, vasodilatory, antiviral and anti-leukemic properties.[4]



5.3 **5.4** **5.5**

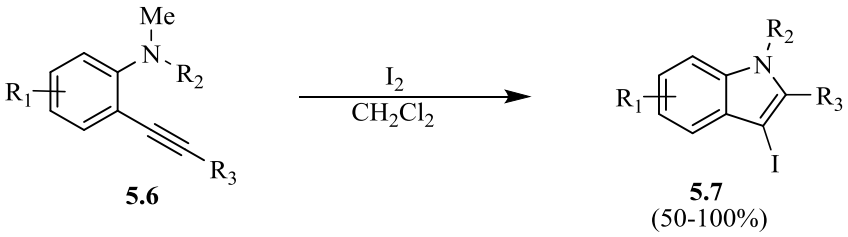
Figure 5.2: *(±)-Nuevamine, (±)-lennoxamine and magallanesine*

Many synthetic methods,[5,6] including transition-metal-catalysed intramolecular cyclisation, have been successfully employed in the synthesis of nitrogen-containing heterocycles. However, some of these approaches are either incompatible with the desired functionality or sometimes restricted by a lack of regioselectivity. Isoquinolines can be synthesised from the transition metal-catalysed hydroamination of alkynes.

As outlined in Chapters 3 and 4, more than 20% of commercial drugs contain fluorine, whilst iodine is often a key group in bioactive molecules.[7,8] Here, building upon the fluorocyclisation and iodocyclisation strategies used to form oxygen-containing heterocycles, the work in this chapter was directed towards developing the iodocyclisation and fluorocyclisation methods of various alkyne-contacting amines and amides to synthesis new *N*-heterocyclic derivatives.

5.2 Electrophilic Cyclisation Reactions Leading to *N*-heterocycles via Nitrogen Nucleophiles

Several research groups have reported interesting approaches to producing nitrogen-containing heterocycles. In 2006, Larock *et al.*[9,10] reported that the 3-iodoindoles **(5.7)** could be synthesised in excellent yields by coupling of terminal acetylenes with *N*,*N*-dialkyl-2-iodoanilines in the presence of a Pd/Cu catalyst, followed by an electrophilic cyclisation of the resulting *N*,*N*-dialkyl-2-(1-alkynyl)anilines **(5.6)** using I_2 in CH_2Cl_2 (**Scheme 5.1**).

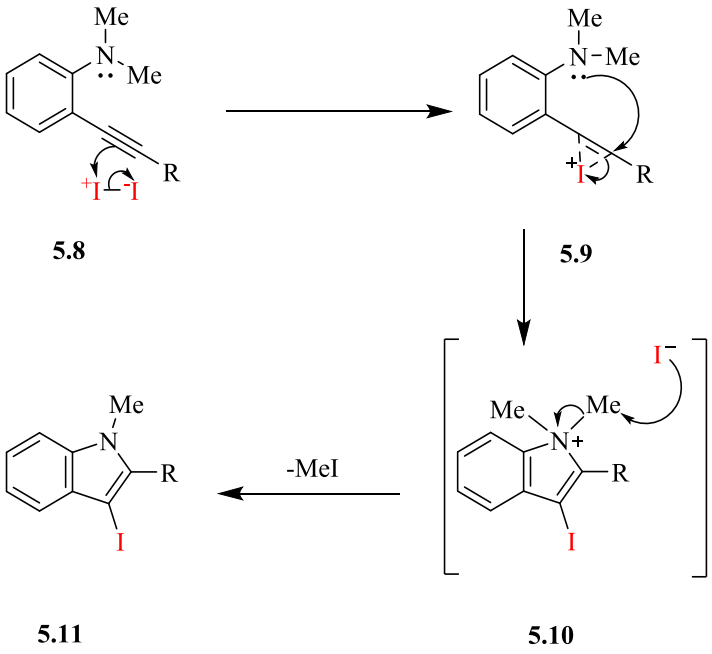


5.6 **5.7** (50-100%)

R_1= H, Me, MeO, NO_2, CO_2Et, CO_2Me
R_2= Me, *n*-Bu, cyclohexyl
R_3= *n*-C_6H_{13}, *t*-Bu, Ph, *c*-Hexyl

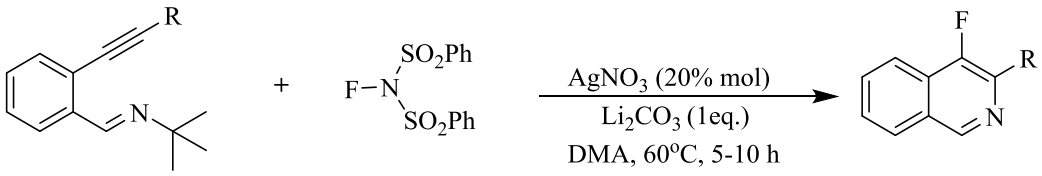
Scheme 5.1: *Electrophilic cyclisation*

When this reaction was carried out in an NMR tube using a CD_2Cl_2 solvent, MeI, cyclohexene and cyclohexyl iodide were observed in the ^1H NMR spectrum.[11] These results suggest that the loss of the alkyl group (either R_2 = Me, *n*-Bu) can occur by either an S_N1 or S_N2 type mechanism (**Scheme 5.2**), or perhaps the loss of the cyclohexyl group occurs by an E2 elimination instead.



Scheme 5.2: *Mechanism of electrophilic cyclisation*

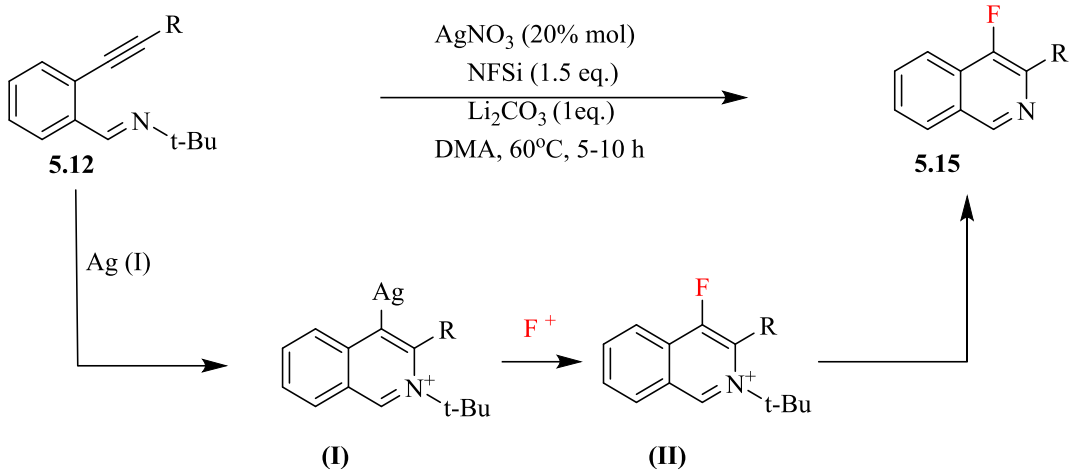
In the literature,[12] isoquinolines have been prepared using classical methods. For instance, Liu and Xu have reported the silver-catalysed oxidative fluorination of the alkyne-containing imine **(5.12)**. The fluorinated isoquinolines **(5.13)** were prepared from electrophilic fluorination by using a fluorinating reagent, NFSi, in the presence of $AgNO_3$ and a strong base, Li_2CO_3, in DMA, to generate a nucleophilic carbanion to attack the F^+ reagent **Scheme 5.3**.



5.12 **5.13**

Scheme 5.3: *Silver-Catalysed aminofluorination of alkynes*

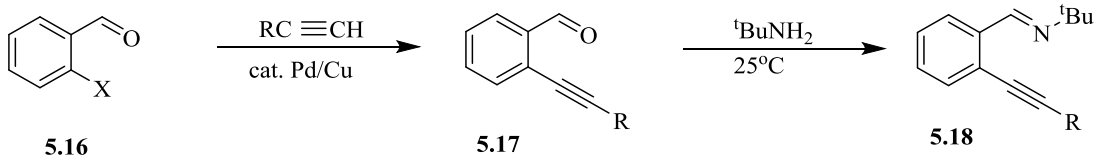
Further mechanistic studies have suggested that the fluorinated intermediate isoquinolinium, derived from oxidative fluorination of the sp^2 C-Ag bond of (**I**) by F^+, is stable at 0 °C **Scheme 5.4**. However, this intermediate gradually decomposed to the isoquinoline by releasing isobutene at room temperature.[13] Inspired by this understanding, it was envisioned that further transformation of active isoquinolinium (**II**) could lead to a diverse range of fluorinated isoquinoline derivatives **(5.15)**



Scheme 5.4: *Mechanism of transition-metal-catalysed fluorocyclisation*

5.3 Towards Alkyne-containing Secondary Amines for Cyclisation

In 2002, Larock *et al.*[14,15] demonstrated that the (*E*)-*N*-tert-butyl-1-(2-(arylethynyl) phenyl)methanimine **(5.18)** can be prepared in two steps. Firstly, the *o*-(1-alkynyl)benzaldehydes **(5.17)** is prepared via a Sonogashira palladium/copper-catalysed cross coupling in MeCN. Then, the o-(1-alkynyl) benzaldehydes **(5.16)** are reacted with tert-butylimines at 25 °C (**Scheme 5.5**).

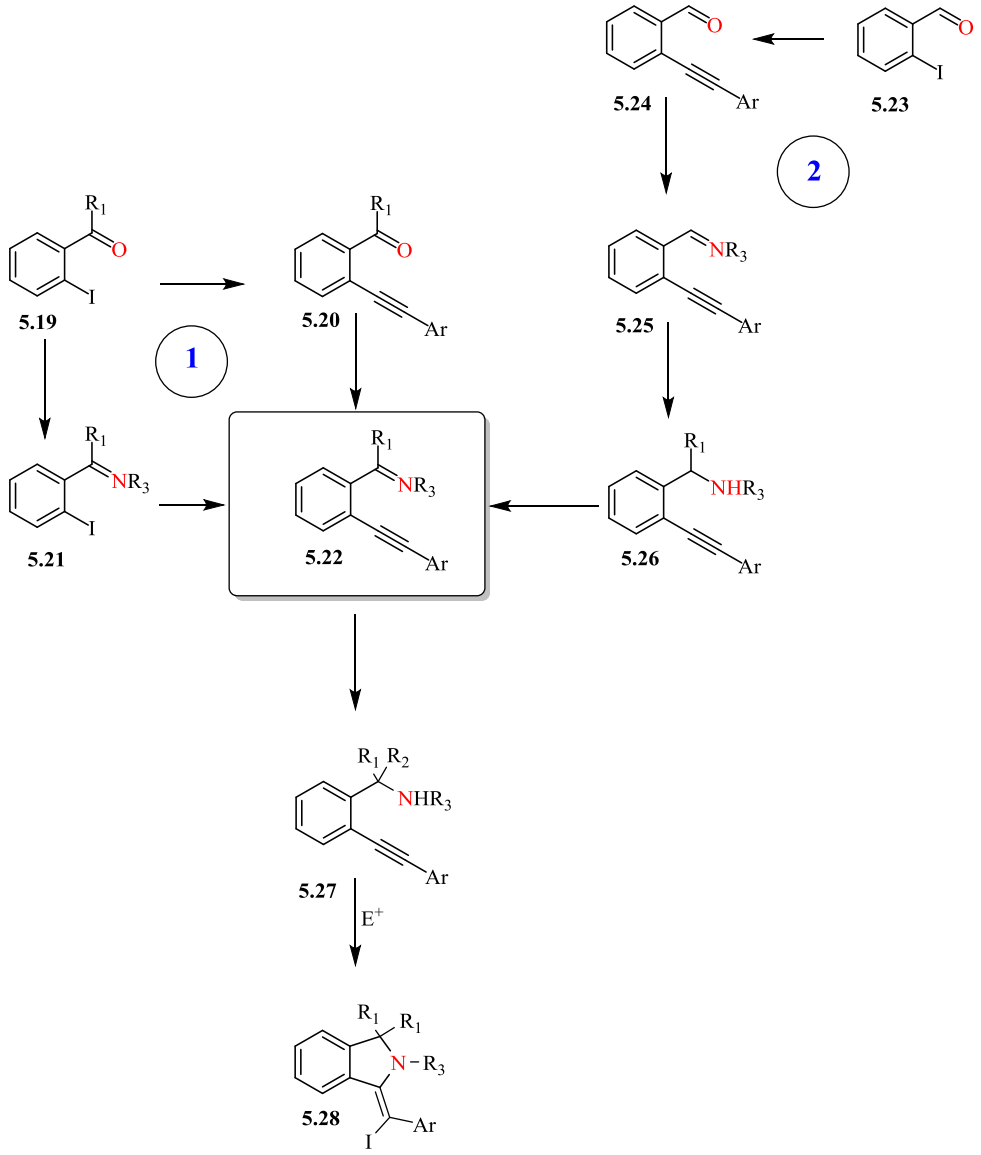


Scheme 5.5: *Alkynes containing imines.*

5.4 Targets for the Iodocyclisation/ Fluorocyclisation Reactions

By analogy to the tertiary alcohol alkynyl substrates used for the fluoro- and iodo-cyclisation studies, we targeted secondary amines (**5.27**) (**Scheme 5.6**) to allow flexibility (R_1, R_2 and R_3) and allow a direct comparison with the alcohol cyclisation studies. However, even the simplest substrates ($R_1 = R_2 = Me$) have not been described previously in the literature. There are a number of potential synthetic approaches that could be envisaged for the synthesis of the desired starting material, and here the work towards two synthetic routes will be described (**Scheme 5.6**). Route (1) was investigated for R_1 =

Me, Ph; R_3 = ^{t}Bu, Bn, C_6H_4-OMe, C_6H_4-NO_2, C_6H_4-F; Ar = Ph. Route (2) was investigated for R_1 = Et, CF_3 and R_3 = Bn, C_6H_4-OMe, and Ar = Ph.

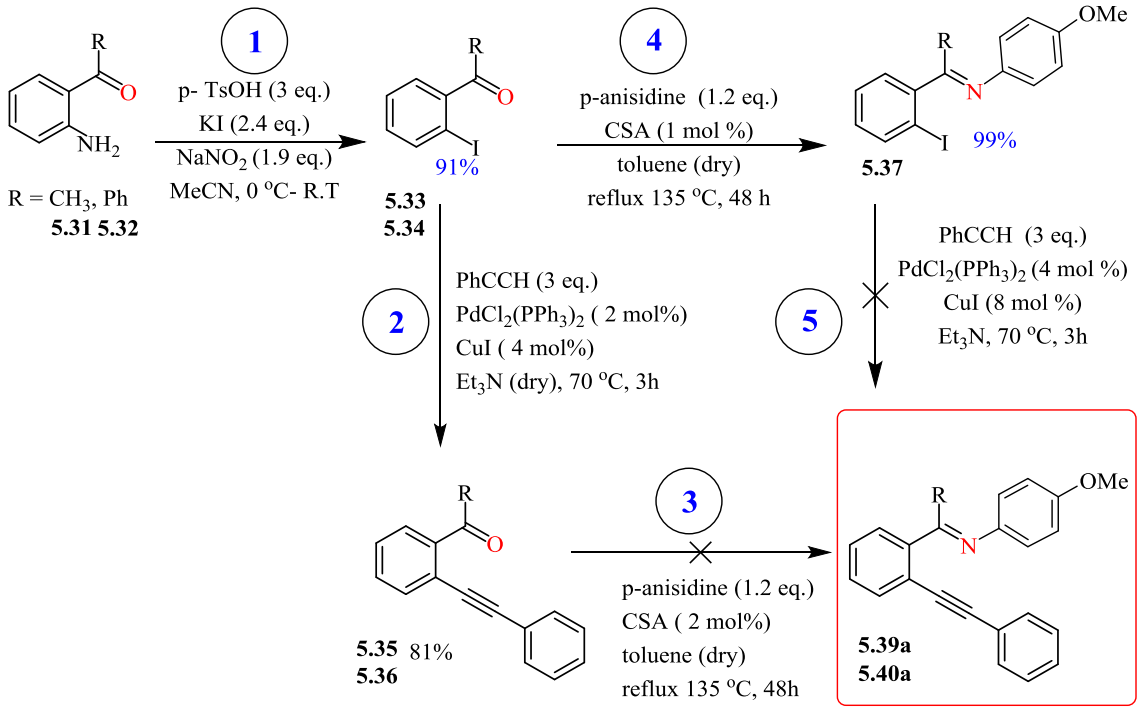


Scheme 5.6: *Synthetic routes to alkynes containing secondary amines for cyclisation.*

5.4.1 Attempt to Synthesise Alkynes-containing Secondary Amines - Route 1

Following the literature,[16] Step (1) (**Scheme 5.7**), 2-aminoacetophenone **(5.31)** or 2-aminobenzophenone **(5.32)** underwent diazotisation reactions with potassium iodide, sodium nitrite and *p*-toluenesulfonic acid monohydrate in acetonititrile at low temperature to give 2-iodoacetophenone **(5.33)** or 2-iodobenzophenone **(5.34)** (isolated yields of 91% and 70%, respectively). The ^{1}H and ^{13}C NMR spectroscopic and mass

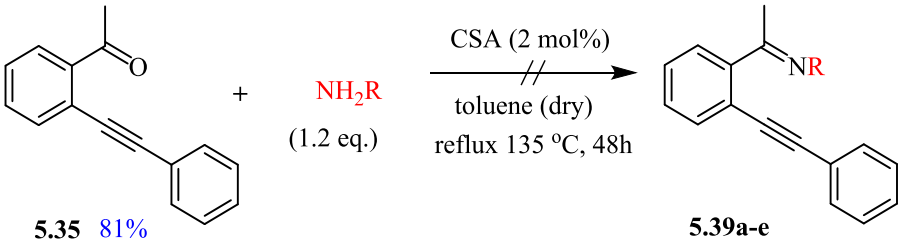
spectrometric data recorded to characterise the products were in excellent agreement with those in the literature.[17,18]



Scheme 5.7: *Attempted synthesis of alkyne-containing ketimines*

In Step (2), 2-iodoacetophenone **(5.33)** or 2-iodobenzophenone **(5.34)** was reacted with phenylacetylene (3.0 eq.) via the Sonogashira reaction {[$Pd(PPh_3)_2Cl_2$] (4 mol %), CuI (8 mol %) in dry Et_3N at 70 °C overnight} to give 2-(phenylethynyl)acetophenone **(5.35)** and phenyl(2-(phenylethynyl)phenyl)methanone **(5.36)** (isolated yields of 81% and 76%, respectively) (**Scheme 5.7**). The ^1H and ^{13}C NMR spectroscopic and mass spectrometric data used to characterise the products were in excellent agreement with those in the literature.[18]

Although the cross-coupling reactions were successful, in Step (3) the condensation reaction with *p*-anisidine, either for 18 h or 48 h, failed to generate the desired products **(5.39a)** and **(5.40a)**. Analysis of the crude reaction mixtures by ^1H NMR spectroscopy failed to show any of the desired products, and only unreacted starting materials were recovered. In order to establish whether this failure was just the result of using *p*-anisidine, the reactions of (**5.35**) with a series of alkyl and aryl amines {4-fluoroaniline, 4-nitroaniline, phenylmethanamine and 2-methylpropan-2-amine} targeting a range of ketimines **(5.39a-e)** (**Scheme 5.8**) was investigated, but in all cases no reaction was observed and only starting materials were recovered in each case.



R = C_6H_4-OMe, ^{t}Bu, Bn, C_6H_4-NO_2, C_6H_4-F

Scheme 5.8: *Attempted syntheses of alkyne-containing ketimines*

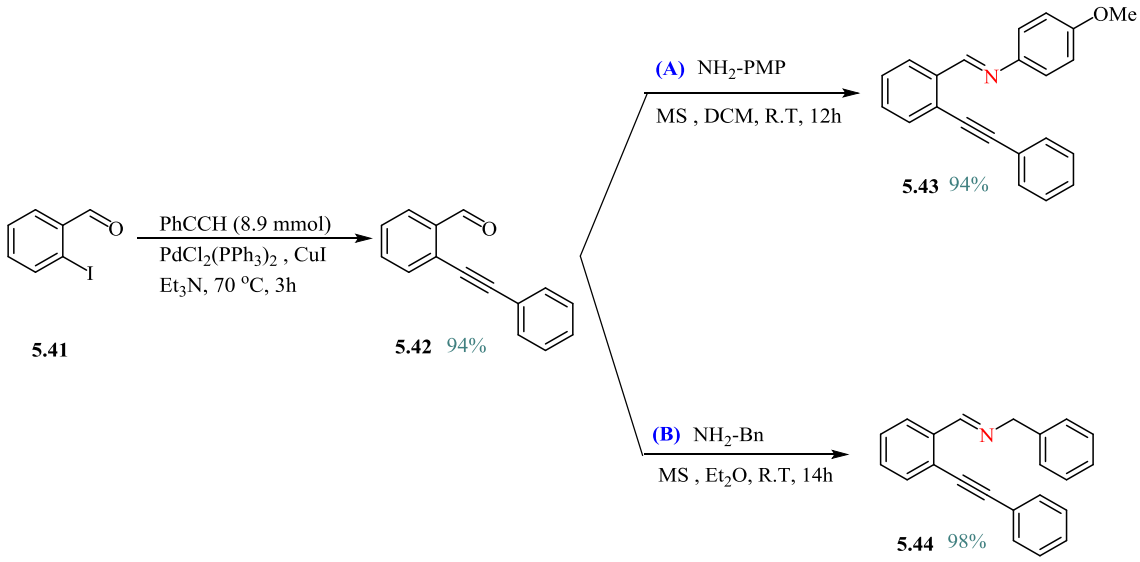
In a final attempt, a different set of reaction conditions reported in the literature[19] were attempted; phenyl(2-(phenylethynyl)phenyl)methanone **(5.36)** was reacted with *p*-anisidine, Et_3N and $TiCl_4$ in CH_2Cl_2 at 45 °C overnight. However, again, the reaction was unsuccessful. In general, [2] it is well established that ketones react more slowly than aldehydes. However, neither higher temperatures nor longer reaction times could improve this reaction to give the desired product. It is possible that the presence of the ortho-alkynyl group could be impacting upon the reaction due to steric effects.

Following the failure of Step (3) the alternative approach, reversing the two steps (condensation followed by Sonogashira coupling), was attempted. In Step (4), a mixture of *o*-iodoacetophenone **(5.33)** (1.0 eq.), *p*-anisidine (1.2 eq.) and CSA (1.0 mol %) in dry toluene was heated to reflux (130 °C) for 48 h using a Dean-Stark apparatus to give the desired product, 1-(2-iodophenyl)-*N*-(4-methoxyphenyl)ethan-1-imine **(5.37)** as a mixture of two geometrical isomers (*E*/*Z* = 1:1) in a 99% isolated yield (**Scheme 5.7**). Alternatively, 2-iodobenzophenone **(5.34)** (1.0 eq.), *p*-anisidine (1.2 eq.), Et_3N and $TiCl_4$ were heated in CH_2Cl_2 at 45 °C overnight to give the desired product 1-(2-iodophenyl)-*N*-(4-methoxyphenyl)-1-phenylmethanimine **(5.38)** in a 98% isolated yield. The ^{1}H and ^{13}C NMR spectroscopic and mass spectrometric data were in excellent agreement with those reported in the literature,[19] and the successful synthesis of these ketimines supports the suggestion that the ortho-alkynyl group was the reason for the failure of Step (3). Unfortunately, all attempts to prepare **(5.39a)** or **(5.40a)** from **(5.37)** or **(5.38)** using the standard Sonogashira cross-coupling reaction conditions {phenylacetylene (3.0 eq.), [Pd(PPh_3)$_2$$Cl_2$] (4 mol %), CuI (8 mol %), in dry Et_3N at 70 °C for 3 h Step (5)}, or for a longer reaction time {24 h} or with larger catalyst loadings {[Pd(PPh_3)$_2$$Cl_2$] (8 mol %), and CuI (16 mol %)} failed and only unreacted starting materials were recovered. (**Scheme 5.7**). According to the literature, Cacchi and Fabrizi [20] reported that the palladium catalysed coupling chemistry is flexible but also unpredictable at times. These

reactions strongly depend on a number of factors such as the nature of the starting material, bases, additives, solvents, and temperature.

5.4.2 Attempt to Synthesise Alkyne-containing Secondary Amines - Route 2

Following the failures in Route 1, which appeared to be related to the formation of the ketimines, and in view of the precedent reported in the literature for the preparation of *o*-alkynyl-imines[21,22] an alternative strategy starting from 2-iodobenzaldehyde was investigated (**Scheme 5.6**). Initially, Step (1) was started through the preparation of 2-(phenylethynyl)benzaldehyde **(5.42)** from the Sonogashira coupling of 2-iodobenzaldehyde **(5.41)** and phenylacetylene (**Scheme 5.9).** The ^{1}H and ^{13}C NMR spectroscopic and mass spectrometric data to characterise the product were in agreement with those in the literature.[23]

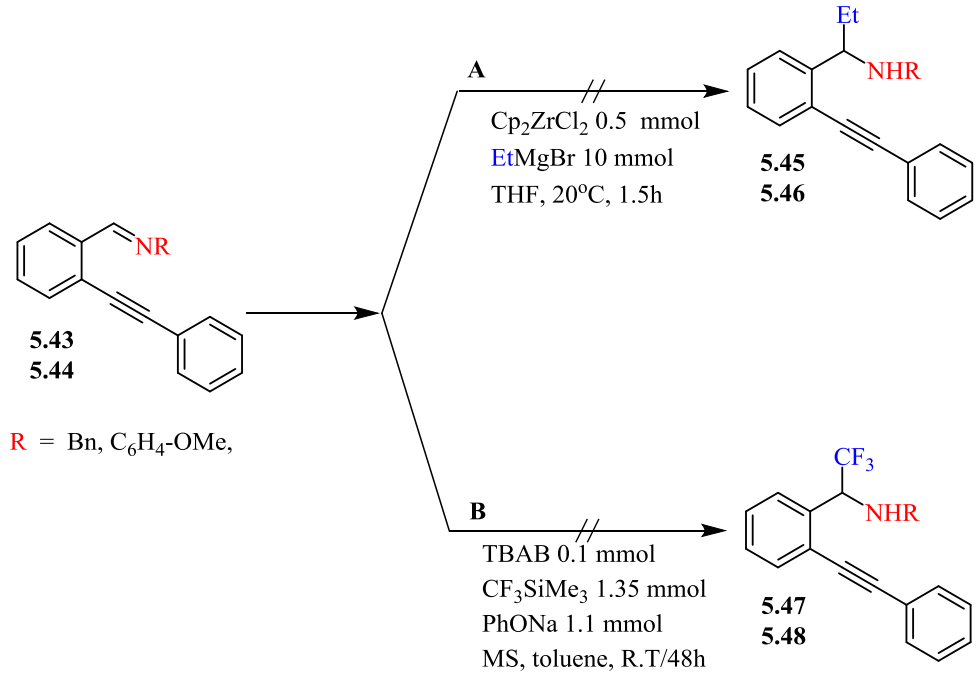


Scheme 5.9*: Synthesis of alkyne-containing imines*

For step (2), the attempt was made to prepare a different set of imine products. Therefore, two different routes were used, as can be seen from the scheme above. For route (A), a solution of 2-(phenylethynyl)benzaldehyde **(5.42)** in DCM were added to 4-methoxyaniline and MS 4Å (20 mg), and the mixture was stirred at room temperature for 12 h. The mixture was filtered, and the solvent was removed under reduced pressure to give (*E*)-*N*-(4-methoxyphenyl)-1-(2-(phenylethynyl)phenyl)methanimine **(5.43)** (94%) as a yellow oily product (**Scheme 5.9).** For route (B), a solution of 2-(phenylethynyl)benzaldehyde **(5.42)** in Et_2O was added to benzylamine (eq.) and MS 4Å (0.4 g) and the mixture was stirred at room temperature for 14 h. The mixture was filtered,

and the solvent was removed under reduced pressure to give (*E*)-*N*-benzyl-1-(2-(phenylethynyl)phenyl)methanimine **(5.44)** (98%) as a yellow oily product (**Scheme 5.9)**

The products **(5.43)** and **(5.44)** were characterised by ^{1}H and ^{13}C NMR spectroscopies as well as ASAP accurate mass spectrometry. The most significant peaks in the ^{1}H NMR spectra indicated the presence of imine protons, which appeared around 9 ppm, whilst the methoxy group appeared as a singlet peak at 3.62 ppm, and the CH_2 group of the benzyl as a doublet peaks at 4.87 ppm (2H, d, $^{4}J_{HH}$ = 1.2, CH_2). The ^{13}C NMR spectra showed a peak at 55.8 ppm for the OMe group for **(5.43)**, while the alkynyl carbons appeared at 87.6 and 95.4 ppm. For **(5.44)** the peaks associated with the CH_2 of the benzyl group appeared at 63.9 ppm, while the alkynyl carbons appeared at 85.4 and 93.8 ppm. All the characterisation data were in agreement with those in the literature.[24,25]



Scheme 5.10: *Attempted synthesis of alkyne-containing secondary amines*

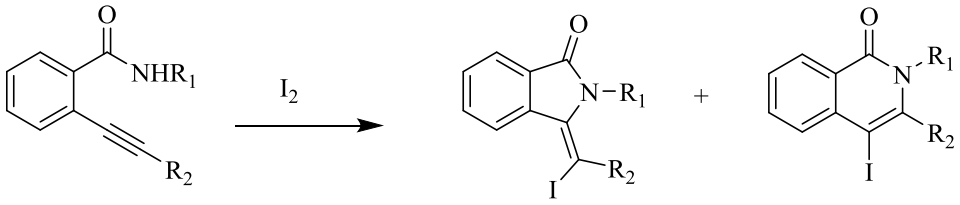
The most challenging steps were the attempted syntheses of alkynyl secondary amines **(5.45), (5.46)**, (**5.47**) and (**5.48**). Previously,[26] it has been reported that imines react with Grignard reagents in the presence of Cp_2ZrCl_2 as a catalyst step (A) **(Scheme 5.10)**, whilst in step (B), CF_3SiMe_3 (1.0 eq.) and TBAB were used with 5 Å molecular sieves in dry toluene followed by PhONa (1.0 eq.) at room temperature for 48 h to prepare **(5.47)** and **(5.48).** No evidence for the desired products was obtained from either approach.

5.5 Towards Alkyne-containing Secondary Amides for Cyclisation

5.5.1 Introduction

Since all attempts to prepare alkynyl secondary amines as substrates for electrophilic cyclisation studies had failed, an alternative class of substrates, alkynyl amides, was targeted. Although there have been three reports of iodocyclisation reactions involving this class of substrate, there have been no similar reports on fluorocyclisation studies.

In 2005, Larock *et al.*[27] reported that the isoindolinones **(5.50a)** and isoquinolinones **(5.50b)** were formed in high yields from *o*-(1-alkynyl)benzamides **(5.49)** through an electrophilic cyclisation process that was carried out with 0.30 mmol of the *o*-(1-alkynyl)benzamide, 3 eq. of I_2, and 3 eq. of $NaHCO_3$ in CH_3CN at room temperature to give *N*-cyclisation regioselectively (**Scheme 5.11**).



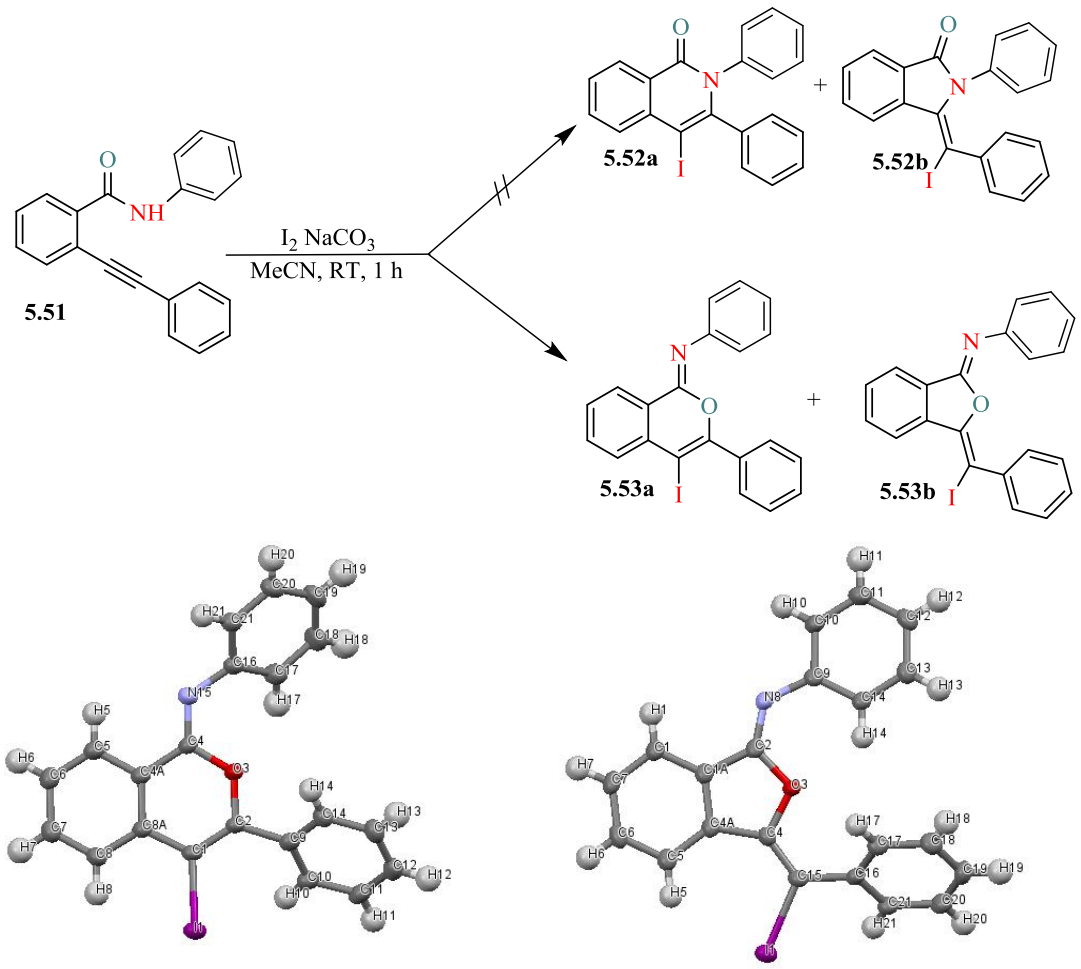
5.49
R_1= H, Me, Ph, Bu
R_2= H, Ph, TMS, 1-*c*-hexenyl

5.50a
(8-90%)

5.50b
(6-74%)

Scheme 5.11*: Electrophilic cyclisation*

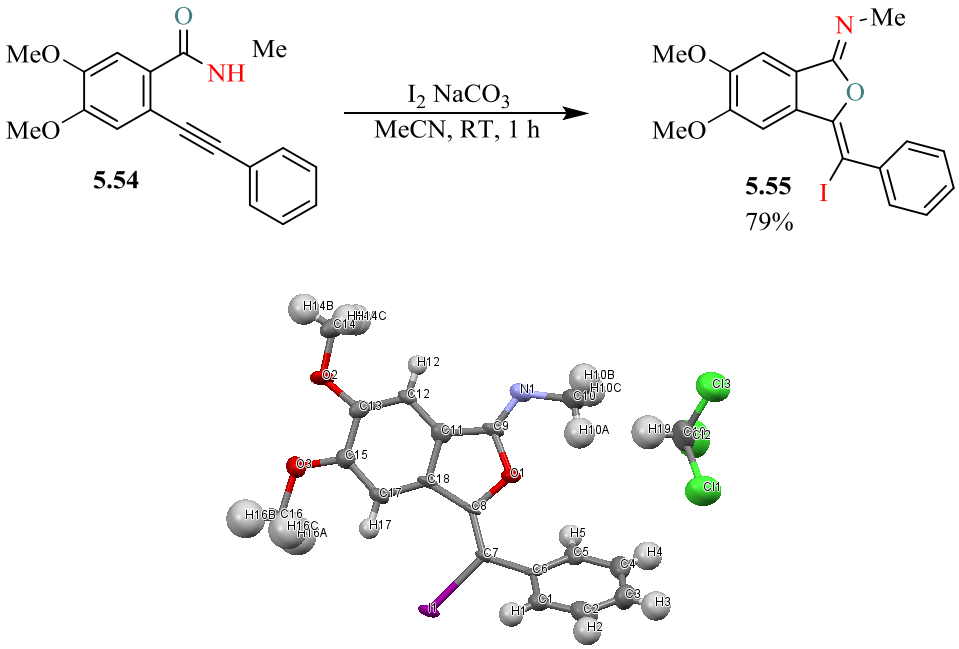
In marked contrast, in 2012, Opatz and co-workers[28] reported that the aromatic alkyne **(5.51)** (one of Larock's substrates) reacted smoothly with iodine in MeCN in the presence of $NaHCO_3$ through cyclisation via the O-atom of amide group to yield five-membered **(5.53a)** and six-membered **(5.53b)** cyclic imidates (**Scheme 5.12).** Crystals suitable for an X-ray structural analysis were grown for the 5-membered ring and the 6-membered ring products **(5.53a)** and **(5.53b)**, confirming O-cyclisation. The authors postulated that the O/N-selectivity here might have arisen due to steric effects.



5.53a **5.53b**

Scheme 5.12: *The literature X-ray sttractures of lectrophilic cyclisation*

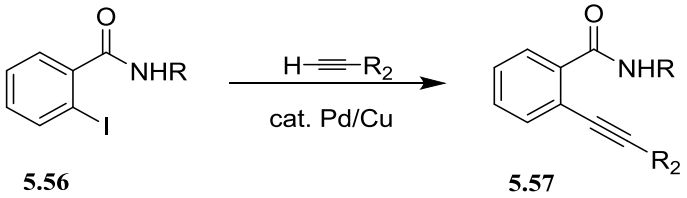
Following this, Larock's group [29] demonstrated a very similar cyclisation reaction carried out through the electrophilic cyclisation of 2-(1-alkynyl)-benzamides affording high yields of cyclic imidates instead of the previously reported isoindolin-1-ones, where cyclisation proceeds via the oxygen of the carbonyl group rather than the nitrogen of the amide functionality. X-ray crystallography and spectroscopic techniques have been used to characterise the products. A correction was provided in order to rectify the previous mis-assignment of the structure. The absence of any diagnostic signals for the C=O bonds in a lactam at δ >160 ppm in the ^{13}C NMR spectra of all of the 5- and 6-membered ring-containing products ruled out the previously claimed *N*-cyclisation (**Scheme 5.13**).



Scheme 5.13: *The literature X-ray sttractures of O-cyclisation*

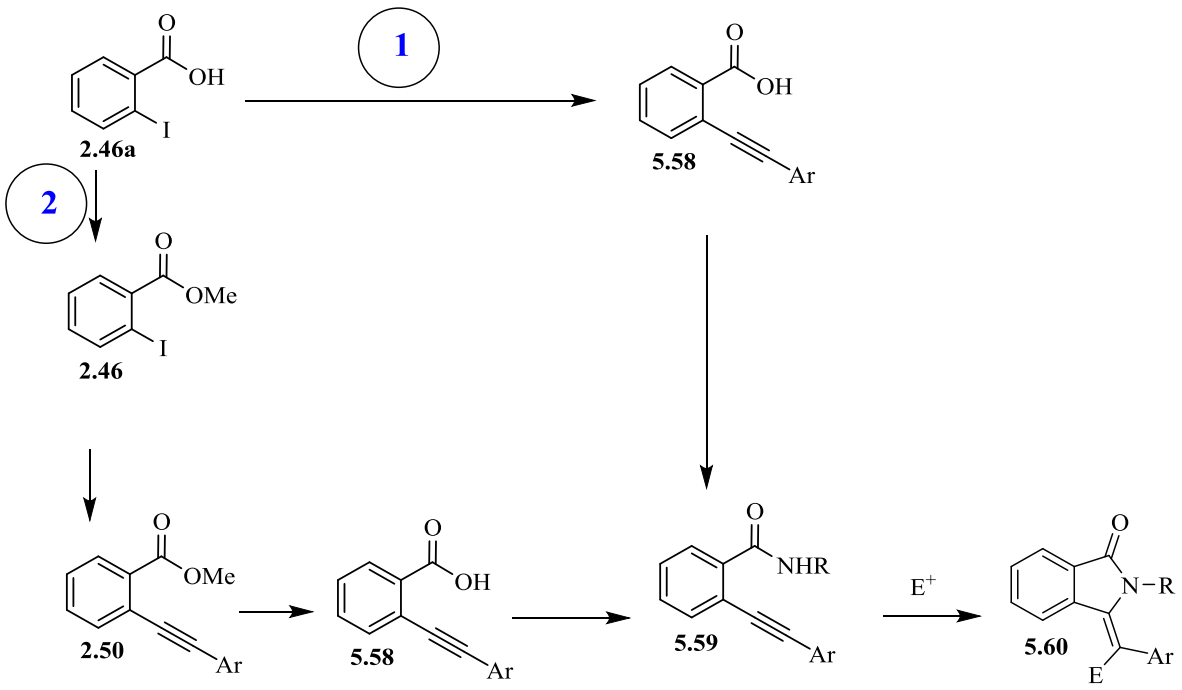
5.5.2 Targets for the Iodocyclisation/Fluorocyclisation Reactions

Larock reports[27] a general procedure for the preparation of the *o*-(1-alkynyl)benzamides **(5.57)** through the Sonogashira cross-coupling reaction of an aryl iodide **(5.56)** and a terminal alkyne in the presence of $PdCl_2(PPh_3)_2$ and CuI in Et_3N (**Scheme 5.14**).



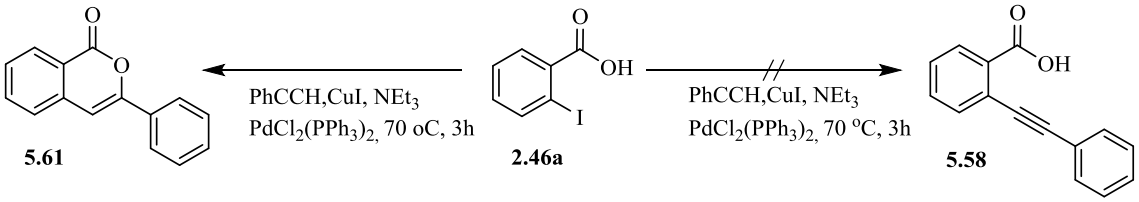
Scheme 5.14: *Sonogashira cross-coupling*

We chose not to follow this. The reasons behind this were, firstly, our worries about protocyclisation issues, and further that we wanted a generic route allowing variation in R (to give a series of substrates) at the end of the sequence. Thus, we tried different routes to synthesise a series of benzamides **(5.59)** incorporating alkyne groups for cyclisation where R = Bn, C_6H_4-4-OMe, C_6H_4-4-Me, C_6H_4-4-Cl, C_6H_4-4-F and Ar = Ph (**Scheme 5.15**).



Scheme 5.15: *Synthetic routes to benzamides for cyclisation*

Unfortunately, in Route (1), the Sonogashira coupling of 2-iodobenzoic acid **(2.46a)** with phenylacetylene, gave the protocyclised 3-phenyl-1H-isochromen-1-one **(5.61)** rather than the desired product (**Scheme 5.16**). It was purified by column chromatography using ethyl acetate /petroleum ether (1:9) (yield 90 %). All the characterisation data were in agreement with those in the literature.[30] Therefore, an alternative route was devised to eliminate the possibility of such a protocyclisation reaction.



Scheme 5.16: *Cyclised product*

In the first step in Route (2), esterification of 2-iodobenzoic acid (1 eq.) in MeOH at 0 °C in the presence of thionyl chloride (1.4 eq.) gave methyl-2-iodobenzoate **(2.46)** (96%), which required no further purification and acted effectively as a protected benzoic acid. Then, using the Sonogashira cross-coupling protocol, methyl-2-(phenylethynyl)benzoate **(2.50)** was synthesised in excellent yield after purification by column chromatography. All the characterisation data were in agreement with those in the literature.[31,32]

Removal of the methyl group was easily achieved by treatment of a solution of methyl 2-(phenylethynyl)benzoate **(2.50)** in methanol with aqueous NaOH (2.7 eq.) at room temperature for 14 h. The data used to characterise the pure white solid product **(5.58)** were in agreement with those in the literature.[33] Recrystallisation of the product from dichloromethane/hexane yielded white crystals suitable for a single crystal X-ray diffraction study (**Figure 5.3**). The analysis revealed a single unique molecule of 2-(phenylethynyl)benzoic acid in the unit cell. Selected bond lengths and bond angles are listed in (**Table 5-1**) and revealed nothing unusual or unexpected about the structure.

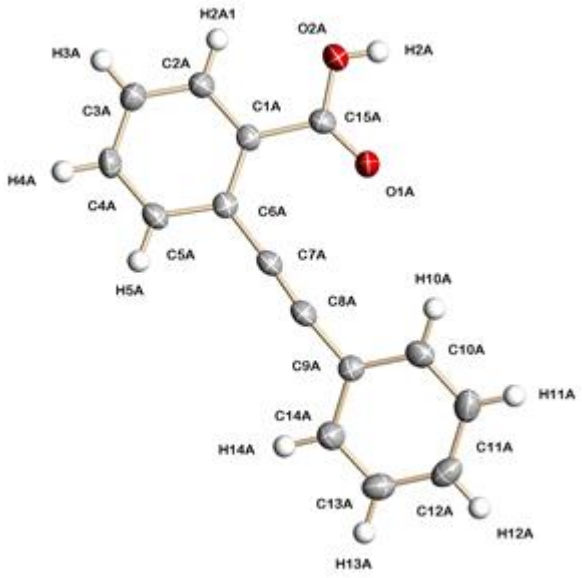
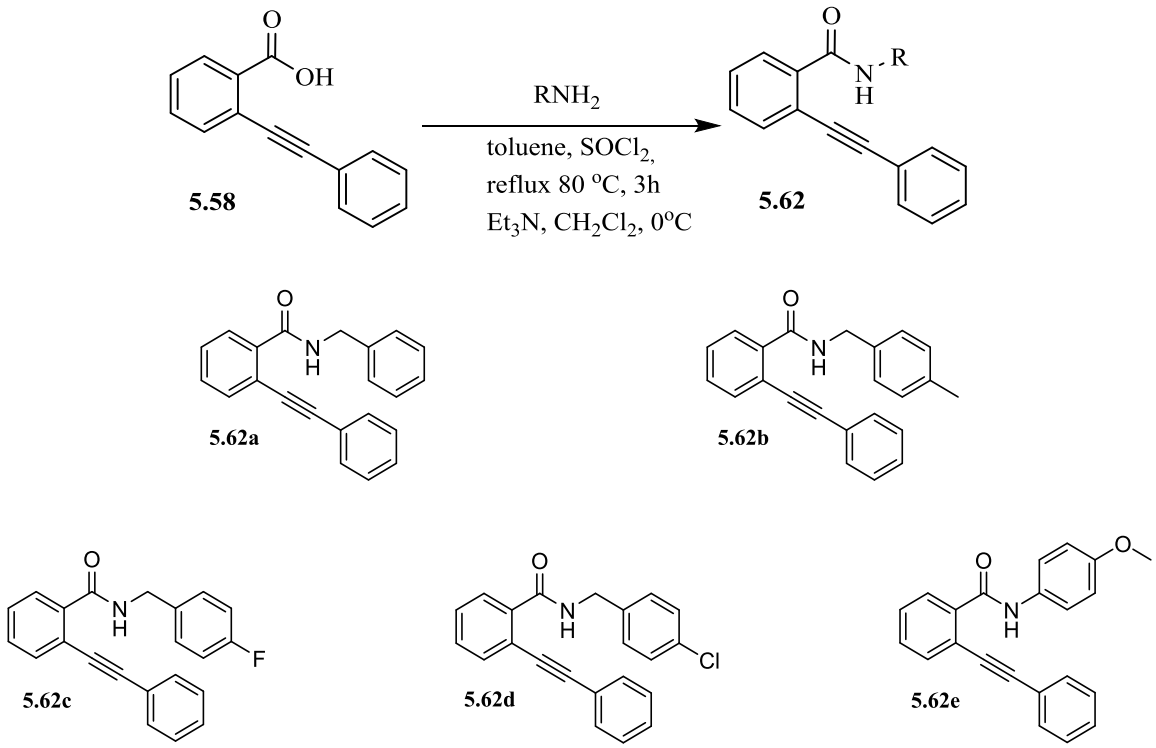


Figure 5.3: *Solid state structure of 2-(phenylethylnyl)benzoic acid **(5.58)***

Table 5-1: *Bond lengths and bond angles of **(5.58)***

Bond lengths (Å)		**Angles (◦)**	
O(1)-C(15)	1.262(2)	O(1)-C(15)-O(2)	123.19(17)
O(2)-C(15)	1.268(2)	O(1)-C(15)-C(1)	118.41(17)
C(1)-C(15)	1.490(2)	O(2)-C(15)-C(1)	118.34(17)
C(7)-C(8)	1.193(2)	C(8)-C(7)-C(6)	179.2(2)
		C(7)-C(8)-C(9)	174.42(19)

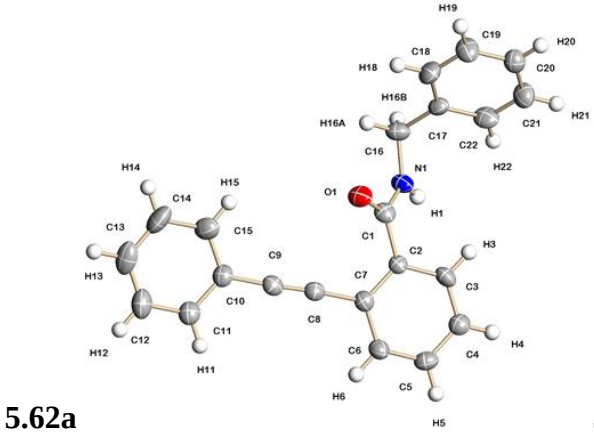
2-(Phenylethylnyl)benzoic acid **(5.58)** was chlorinated with $SOCl_2$ at 80 ^oC in toluene for 3 h, before reaction with a series of amines in the presence of Et_3N at room temperature for 1 h. This afforded a series of alkynyl amides **(5.62a-e)** including benzylamine, 4-methyl benzylamine, 4-fluorobenzylamine, 4-chlorobenzylamine and 4-methoxyaniline (isolated yields 78 %, 80 %, 73 %, 67 %, 74 % respectively) (**Scheme 5.17**).



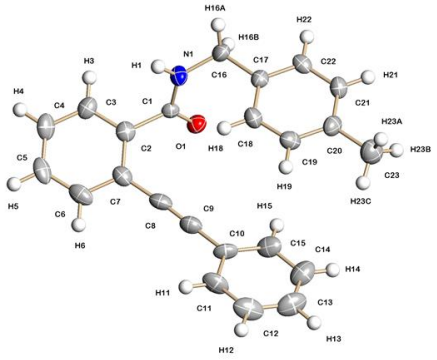
Scheme 5.17*: Synthesis of alkynyl amides*

The identity of the new alkynyl products **(5.62a,b,c,e)** was confirmed by ^{1}H and ^{13}C NMR spectroscopies, as well as ASAP mass spectrometry. The ^{1}H NMR spectra provide valuable structural information about the CH_2 group in the products **(5.62a, b, c)**. Common to all of these compounds are peaks between 8.06 ppm to 8.10 ppm indicating the presence of amide protons, and AB multiplet peaks between 4.58 ppm to 4.66 ppm for the benzyl protons. As expected, the ^{13}C NMR spectrum showed peaks above 44.7 ppm, representing the same substituent, together with two alkynyl quaternary carbon resonances. Moreover, peaks at 86.4 ppm and 94.7 ppm were due to the presence of alkynyl C≡C carbon atoms. For product **(5.62e)** the resonances for the alkynyl C≡C carbon atoms were seen at 87.3 ppm and 96.4 ppm and the OMe carbon atom at 55.5 ppm in the ^{13}C NMR spectrum, and the amide proton and OMe protons at 9.11 ppm and 3.81 ppm respectively in the ^{1}H NMR spectrum.

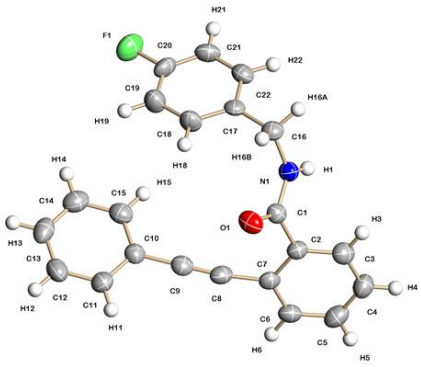
Whilst *N*-(4-chlorobenzyl)-2-(phenylethynyl)benzamide **(5.62d)** was an oil, recrystallisation from dichloromethane/hexane, dichloromethane/chloroform or acetonitrile/chloroform yielded white crystals suitable for single crystal X-ray diffraction studies for **(5.62a, b, c** and **e)** respectively (**Figure 5.4**). Selected bond lengths and bond angles are listed in Table 5.2.



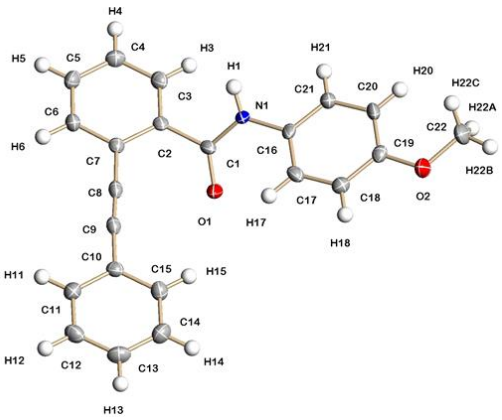
5.62a



5.62b



5.62c



5.62e

Figure 5.4: *Solid state structures of* ***(5.62a, b, c*** *and* ***e)***

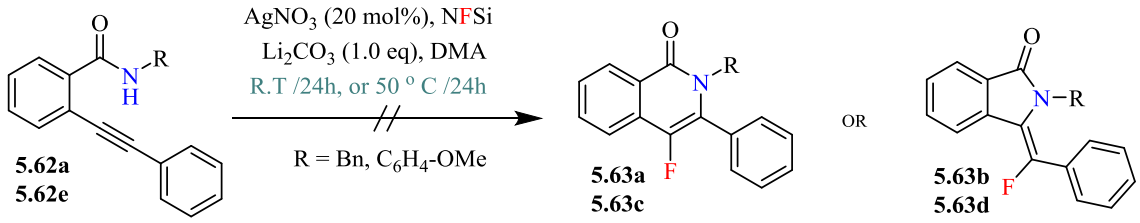
Table 5-2: *Bond lengths and bond angles of* ***(5.62a, b, c*** *and* ***e)***

	5.62a	**5.62b**	**5.62c**	**5.62e**
O(1)-C(1)	1.239(6)	1.215(6)	1.234(4)	1.230(2)
N(1)-C(1)	1.349(6)	1.340(7)	1.336(4)	1.350(3)
N(1)-C(16)	1.449(5)	1.450(7)	1.455(4)	1.425(3)
C(20)-H(20)	0.9500	-	-	-
C(20)-C(23)	-	1.520(10)	-	-
F(1)-C(20)	-	-	1.375(4)	-
C(8)-C(9)	1.195(6)	1.217(10)	1.186(5)	1.194(3)
C(1)-N(1)-C(16)	123.3(4)	121.9(5)	123.5(3)	126.0(2)
O(1)-C(1)-N(1)	121.1(4)	123.2(5)	124.4(4)	122.7(2)
C(19)-C(20)-H(20)	120.5	-	-	-
C(21)-C(20)-H(20)	120.5	-	-	-
C(19)-C(20)-C(23)	-	120.5(7)	-	-
C(21)-C(20)-C(23)	-	121.1(6)	-	-
C(19)-C(20)-F(1)	-	-	117.9(4)	-
C(21)-C(20)-F(1)	-	-	118.4(4)	-
C(9)-C(8)-C(7)	176.6(5)	173.6(7)	173.0(4)	178.0(2)
C(8)-C(9)-C(10)	177.0(5)	176.4(7)	179.1(4)	175.8(2)

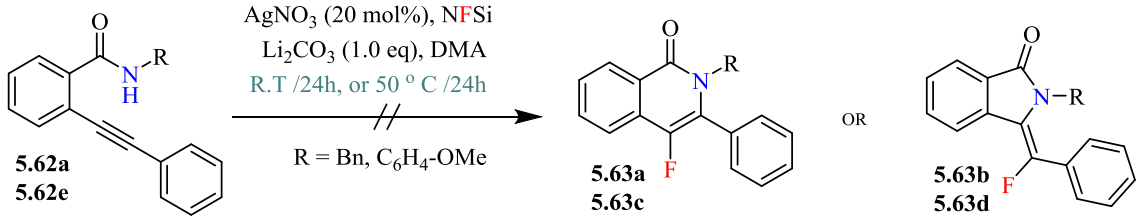
The data for the crystal structures of **(5.62a, b, c, e)** are in agreement with the ^{1}H, ^{19}F and ^{13}C NMR spectroscopic data. As expected, in each of the compounds the C(1)-N(1)-C(16) bond angle of [123 °], the O(1)-C(1)-N(1) bond angle of [123 °], the O(1)-C(1) bond length of [1.23 Å] and the N(1)-C(1) bond length of [1.34 Å] were similar, which confirmed the structures of the desired products (**Table 5-2**).

5.6 The Attempted Silver-catalysed Fluorocyclisation of Aromatic Alkynes containing Amides

At the outset of this study, the first silver-catalysed fluorocyclisation reactions of **(5.62a,e)** were carried out in dry DMA using a catalytic amount of $AgNO_3$ (0.4 eq.) as the promoter, followed by the addition of NFSi (1.5 eq.) and Li_2CO_3 (2.0 eq.) at room temperature and stirring overnight under nitrogen. However, ^{1}H NMR spectroscopy did not reveal the desired product(s) and only unreacted starting material was recovered



Scheme 5.18.



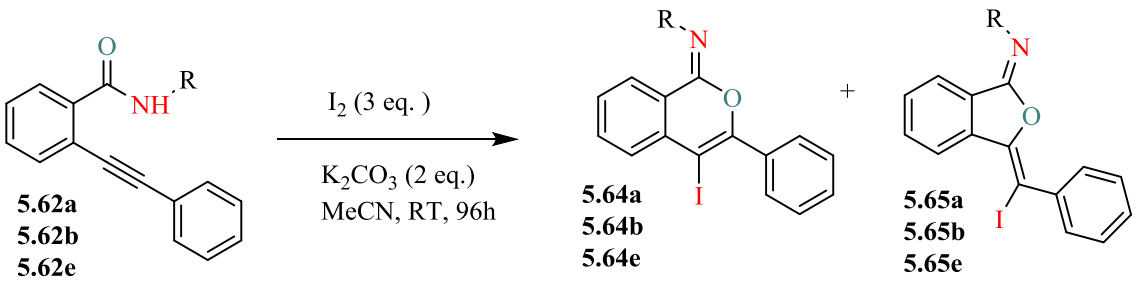
Scheme 5.18: Attempted silver-catalysed fluorocyclisations

In an attempt to force these reactions, the mixtures were heated at 50 °C for 24 h. Analysis by ^{1}H and ^{19}F NMR spectroscopies showed a complex mixture of unidentified products but without any evidence for the desired products. Unfortunately, it did not prove possible to separate the products by column chromatography and, due to time constraints, these reactions were not studied further.

5.7 Iodocyclisation Reactions under Mild Conditions in Various Solvents

In Chapter 4, the iodocyclisation reactions of alkynyl-derivatised tertiary alcohols were shown to be dependent upon both the alcohol substituents and the reaction solvent. Here, similar comparative studies on the iodocyclisation reactions of the alkynyl-derivatised amides are investigated.

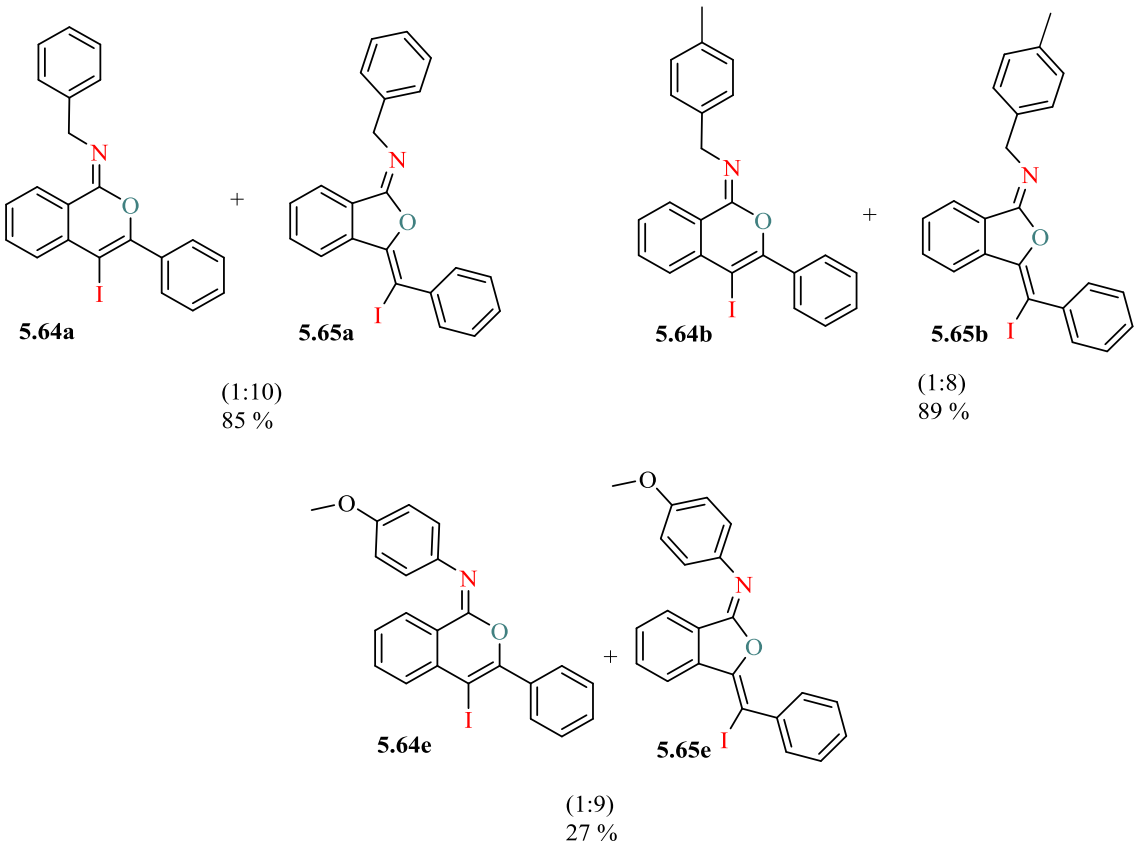
Using our reaction conditions, I_2 (3.0 eq.), K_2CO_3 (2.0 eq.) in MeCN, but allowing the reaction to continue for longer, it was found that the reactions of **(5.62a, b, e)** generated 1:10, 1:8 and 1:9 (respectively) ratios of mixtures of the O-cyclised six- and five-membered ring products **(5.64a)** & **(5.65b)**, **(5.64b)** & **(5.65b)**, and **(5.64e)** & **(5.65e)** (isolated yield 85%, 89% and 27%, respectively) (**Scheme 5.19**). IR, spectrometry was used to identify the iodinated products by comparison with the corresponding five- and six-membered O-cyclised ring products analysed by Larock and co-workers.[27,29] The five- membered ring products generally exhibit a carbonyl absorption band at 1712-1702 cm^{-1}, whilst in the six-membered ring products the carbonyl absorption band occurs at 1668-1666 cm^{-1}.



5.62a
5.62b
5.62e

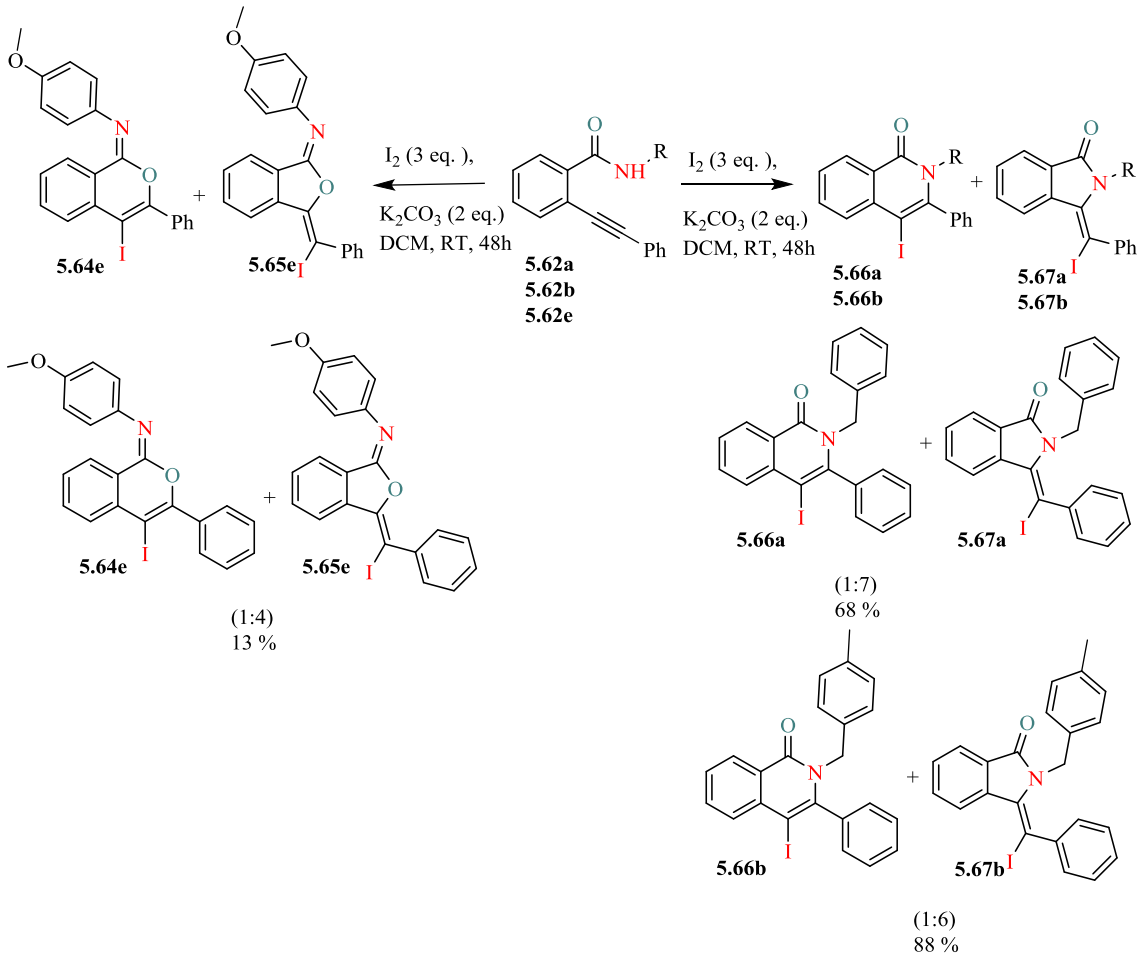
5.64a
5.64b
5.64e

5.65a
5.65b
5.65e



Scheme 5.19*: Iodocyclisation reactions under mild conditions in MeCN*

As seen for the iodocyclisation reactions previously (Chapter 4) changing the solvent from MeCN to DCM, under the same reaction conditions above for 48 h, had a significant impact on the reaction products **(Scheme 5.20)**. For the aryl amide **(5.62e)** mixtures, in a low yield, the O-cyclised six- and five-membered ring products **(5.64e)** & **(5.65e)** were generated in a 1:4 ratio. However, for the benzyl amides **(5.62a,b)** O-cyclisation was not observed and mixtures of the N-cyclised six- and five-membered ring products **(5.66a)** & **(5.67a)** and **(5.66b)** & **(5.67b)** (isolated yields of 68% and 88% respectively) in ratios of 1:7 and 1:6 (respectively) were formed.



Scheme 5.20: *Iodocyclisation under mild conditions in DCM*

IR, ^{1}H and ^{13}C NMR spectroscopies and ASAP mass spectrometry were used to identify the iodinated products by comparison with the corresponding five- and six-membered O-cyclised ring products analysed by Larock and co-workers.[27,29] The isoindolinones have been distinguished from isoquinolinones on the basis of their IR spectra. The five-membered ring products generally exhibit a carbonyl absorption band at 1712-1702 cm^{-1}, whilst in the six-membered ring products the carbonyl absorption band occurs at 1668-1666 cm^{-1}. For the benzyl-substituted species AB doublets in the ^{1}H NMR spectra around 4.5 ppm and peaks above 50 ppm in the ^{13}C NMR spectra were observed providing valuable information about the CH_2 groups in the mixtures of products.

It was noticed that the N-cyclised products could be differentiated from the O-cyclised products through the presence of diagnostic signals in the ^{13}C NMR spectra of these compounds. For comparison of the characteristic chemical shifts in the ^{13}C NMR spectroscopy, peaks at 153 ppm, representing C=N, were observed for **(5.64a) & (5.65a),**

(5.64b) & (5.65b) and **(5.64e)** & **(5.65e)**, while peaks around 191 ppm, representing the C=O, group were observed for **(5.66a)** & **(5.67a)** and **(5.66b)** & **(5.67b)** (**Figure 5.5**).

(a) (b)

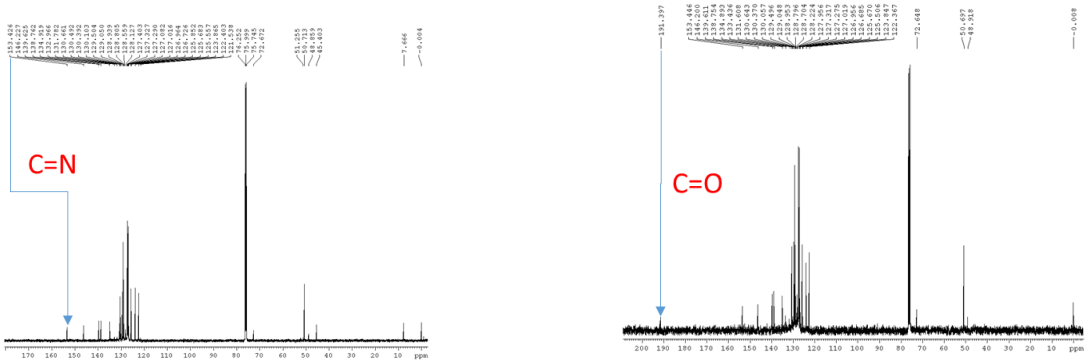


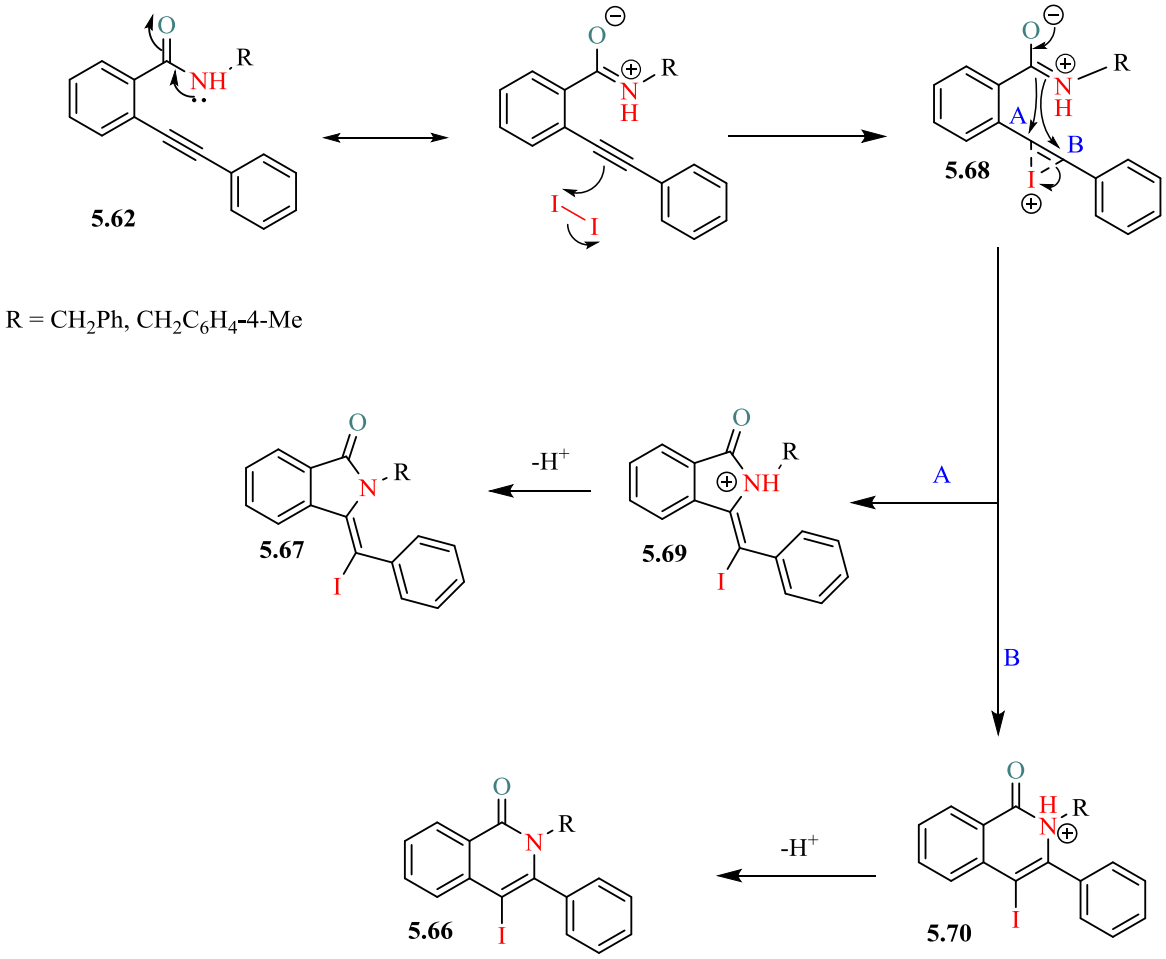
Figure 5.5: *^{13}C NMR spectra of the iodocyclisations of (a)- **(5.64a)** & **(5.65a)** and (b)- **(5.66b)** & **(5.67b)***

5.8 Proposed Mechanism of the Iodocyclisation

Two different mechanisms for the iodocyclisation reactions showing different regioselectivity to give five- and six-membered heterocycles are in presented in (**Scheme 5.19**, and **Scheme 5.20)**, respectively. The reaction was carried out under mild conditions in dry DCM in the presence of a base to coordinate an iodine equivalent to the alkyne, which leads to electrophilic activation of the alkyne carbon-carbon triple bond to generate iodonium as an intermediate **(5.68)**. Nucleophilic intramolecular cyclisation through attack by the amide nitrogen group then takes place to give either six-membered rings or five-membered rings (

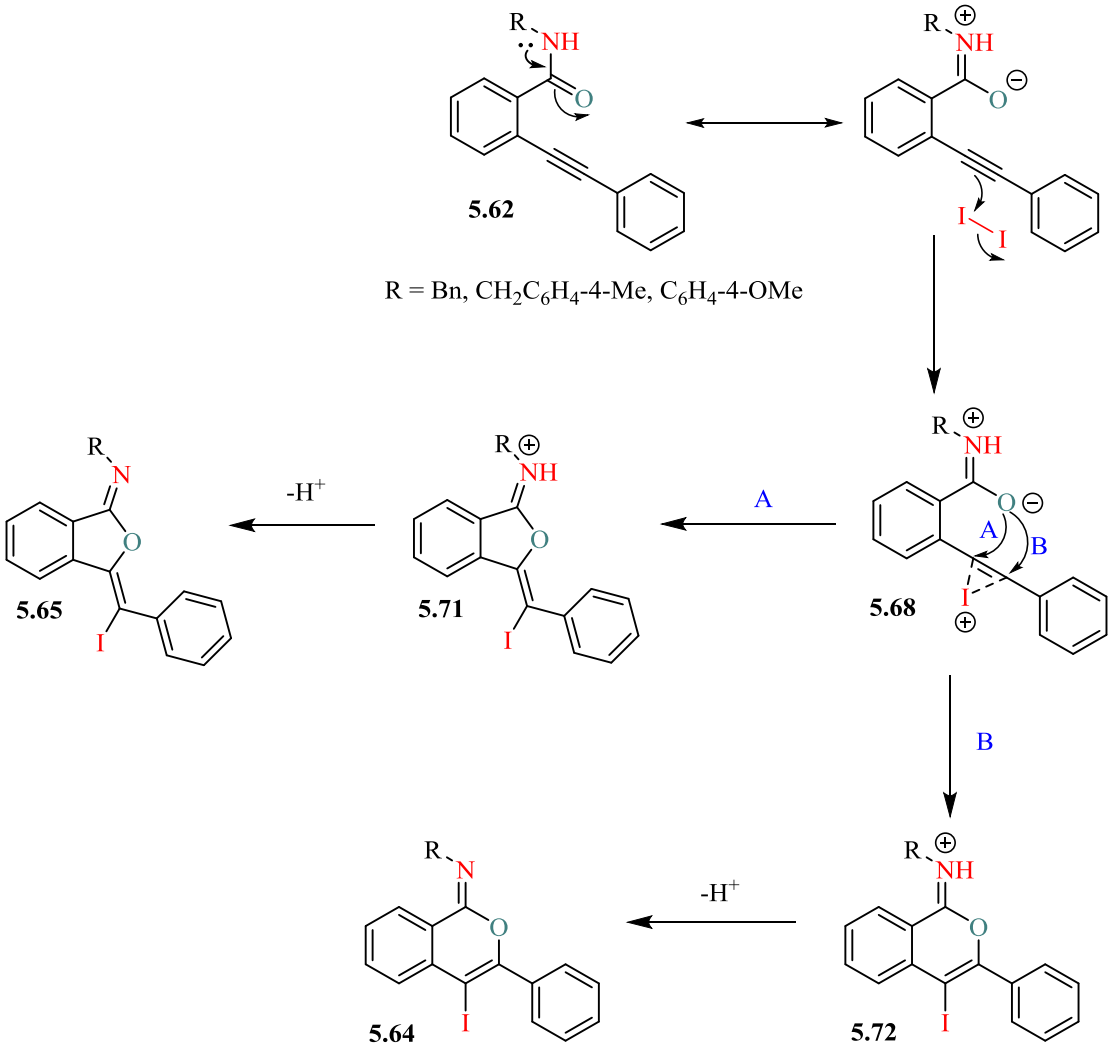
Scheme 5.21). Deprotonation of intermediates **(5.69)** and **(5.70)** leads to the N-heterocyclic products **(5.67)** and **(5.66)**.

In contrast to the variety of selectivities for the iodocyclisation reactions of tertiary alcohols in Chapter 4, for these amides there was no evidence for (*Z*)-5-exo-dig cyclisation. Similar selectivity to give just the (*E*)-5-exo-dig products has been reported previously by Opatz[28] and Larock.[29]



Scheme 5.21: *Proposed mechanism for iodocyclisation in DCM*

In contrast, in dry MeCN the same iodonium intermediate **(5.68)** undergoes nucleophilic intramolecular cyclisation through attack by the hydroxyl group to generate either six-membered rings or five-membered rings (**Scheme 5.22).** Deprotonation of intermediates **(5.71)** and **(5.72)** leads to the O-heterocyclic products **(5.65)** and **(5.64).**

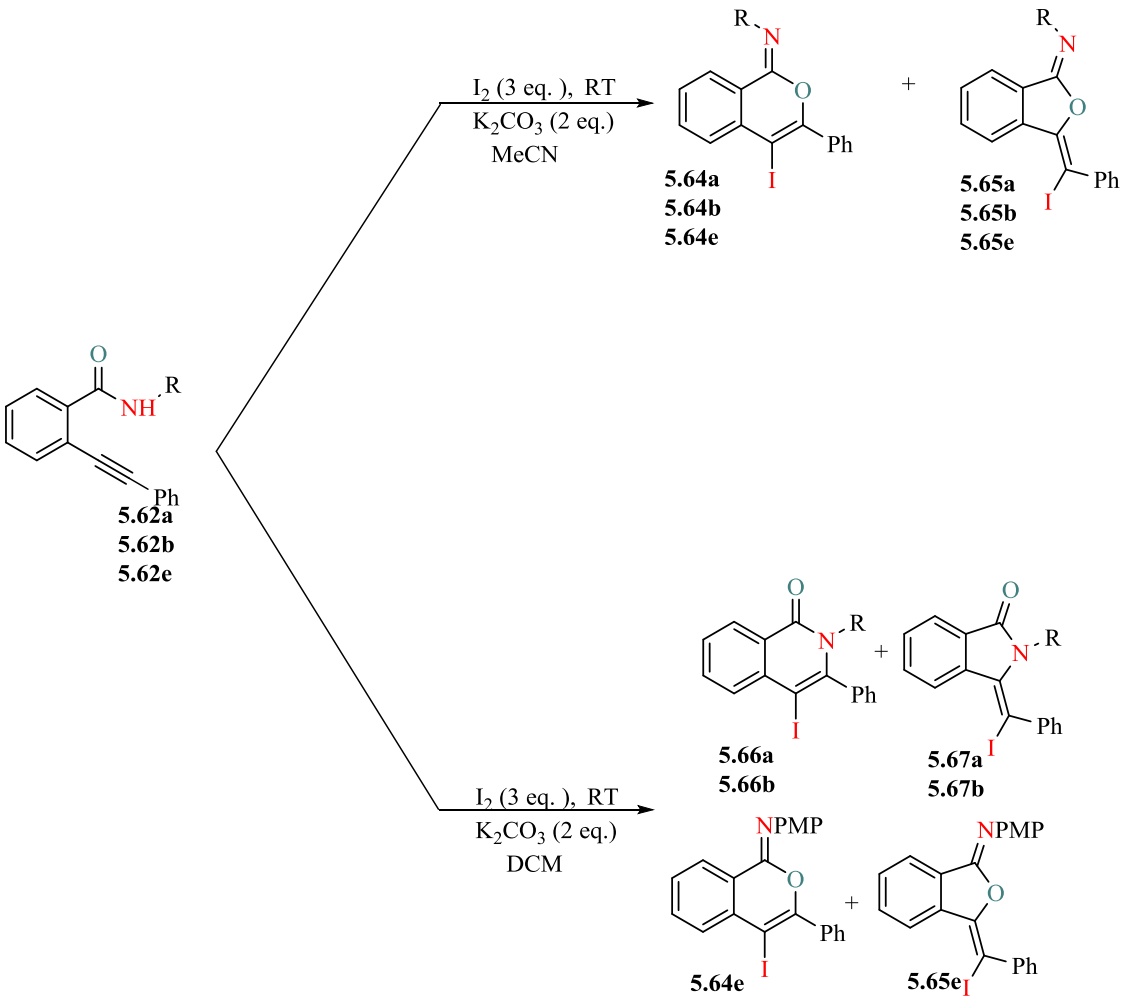


Scheme 5.22: *Proposed mechanism for iodocyclisation in MeCN*

5.9 Conclusion

In this chapter, the formation of alkyne-containing amines and amides as substrates for fluorocyclisation/iodocyclisation reactions have been targeted. Two different routes to alkynyl secondary amines failed to generate the desired target products. However, terminal alkynes containing benzyl or aryl amides have been prepared in excellent yields **(5.62a-e)**. Recrystallization of four of these have given white crystals suitable for single crystal X-ray diffraction analysis. These confirmed that the target substrates had been formed. Under mild conditions, using NFSi, $AgNO_3$ and Li_2CO_3, the fluorocyclisation of the intramolecular alkyne substrates **(5.62a)** and **(5.62e)** were unsuccessful. However, iodocyclisation reactions, using a simple and efficient method, of the substituted alkynes

(5.62a, b, e) in both CH_2Cl_2 and MeCN have been demonstrated. Here, different regioselectivities were identified in the different solvents. In both CH_2Cl_2 and MeCN inseparable mixtures of five- and six-membered ring heterocycles were formed. For the aryl amide (**5.62e)** poor yields of O-heterocycle mixtures were obtained in both solvents. However, for the benzyl amides **(5.62a,b)** mixtures of O-heterocycles were obtained MeCN whilst mixtures of N-heterocycles were obtained in DCM. Presumably, the relative nucleophilicities of the oxygen and nitrogen centres in these amides are influenced by both the electronic influence of the N-substituent and interactions with the solvent (**Scheme 5.23).**



Scheme 5.23: *Iodocyclisation reactions*

5.10 References

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Chapter 6

Experimental

6.1 General Information

Proton, ^{19}F and ^{13}C NMR spectra were recorded on Bruker DPX-300, Bruker DPX-400 or Bruker DPX-500 instruments. The samples were measured for solutions in the stated solvent at ambient temperature if not mentioned otherwise. To specify the signal multiplicity the following abbreviations are used: s = singlet, d = doublet, t = triplet, q = quartet, qn = quintet and m = multiplet. Shifts δ are reported in parts per million (ppm) to low field of tetramethylsilane (TMS) as an external standard for ^{1}H and ^{13}C NMR spectra and calibrated against the residual solvent peak. The specified deuterated solvent was used. The following spectrometer frequencies were used:

Bruker DPX-300 spectrometer: ^{1}H: 300.13 MHz

^{13}C: 75.47 MHz

^{19}F: 283.57 MHz

Bruker DPX-400 spectrometer: ^{1}H: 400.13 MHz

^{13}C: 100.61 MHz

^{19}F: 376.50 MHz

Bruker DPX-500 spectrometer: ^{1}H: 500.13 MHz

^{13}C: 125.75 MHz

Atmospheric Solids Analysis Probe (ASAP) mass spectra were recorded on a Waters Xevo QToF mass spectrometer. X-ray crystallography data were collected on a Bruker Apex SMART 2000 diffractometer using graphite-monochromated Mo-Kα radiation (λ = 0.71073 Å).

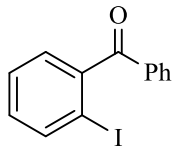
X-ray diffraction of single crystals was performed by Mr. Kuldip Singh at the University of Leicester using Bruker APEX 2000 CCD diffractometer. The data were corrected for Lorentz and polarisation effects and empirical absorption corrections applied. Structure solution by direct methods and structure refinement based on full-matrix least-squares on F^2 employed SHELXTL version 6.10.[1] H atoms were included in calculated positions (C-H = 0.96 _ 1.00 Å) riding on the bonded atom with isotropic displacement parameters

set to 1.5 U_{eq} (C) for methyl H atoms and 1.2 U_{eq} (C) for all other H atoms. All non H atoms were refined with anisotropic displacement parameters.

Dry solvents such as diethyl ether, tetrahydrofuran (THF) and triethylamine were dried by the distillation under nitrogen after heating the solvents at reflux over CaH_2. Then, they were stored in sealed ampoules over 4Å molecular sieves under an atmosphere of dry nitrogen. Where a reaction was carried out at an elevated temperature, the temperature stated is the oil bath temperature. Acetonitrile, dichloromethane, ethyl acetate, diethyl ether (fraction from petroleum ether 40-60) were not subjected to any further purification and were used as received (Fisher Scientific Co). Commercial compounds were used as received without any further purification unless stated otherwise. Starting materials were used as received from Sigma-Aldrich, Apollo Scientific, Alfa Aesar, Fluorochem, Acros Organics and Manchester Organics, Bis(triphenylphosphine)palladium(II) dichloride was prepared by the literature route.[2]

6.2 Experimental procedures for Chapter 2

6.2.1 Synthesis of 2-Iodobenzophenone (2.35) [3]

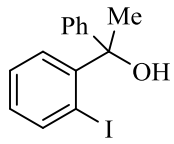


2.35

2-Aminobenzophenone (1.31 g, 6.7 mmol) was added to a stirred solution of p-toluenesulfonic acid monohydrate (3.8 g, 20.1 mmol) in acetonitrile (24 ml) under nitrogen. The resulting suspension of protonated amine was cooled to 0 °C, and an aqueous solution (4 ml) of potassium iodide (2.78 g, 16.75 mmol) and sodium nitrite (0.92 g, 13.4 mmol) was carefully added. The resulting brown solution was warmed to room temperature, and stirred overnight under nitrogen. The reaction mixture was quenched with a saturated sodium bicarbonate solution (15 ml) and a saturated aqueous sodium thiosulfate solution (6 ml) was added. The resulting yellow solution was extracted with ether (3 x 10 ml) and washed with brine (10 ml). The combined organic phases were dried over anhydrous magnesium sulphate, and concentrated *in vacuo* to afford the crude product (2.91 g). This crude product was purified by using column chromatography (Et_2O/ hexane 5:1) to give the pure product as an orange oil (1.42 g, 70 %). The characterisation data were in agreement with the literature. ^{1}H NMR (400 MHz; $CDCl_3$)

δ_H 7.16 (1H, td, $^3J_{HH}$ = 7.7 Hz, $^4J_{HH}$ = 1.7 Hz, Ar*H*), 7.28 (1H, dd, $^3J_{HH}$ = 7.6 Hz, $^4J_{HH}$ = 1.6 Hz, Ar*H*), 7.44 (3H, t, $^3J_{HH}$ = 7.6 Hz, Ar*H*), 7.59 (1H, t, $^3J_{HH}$ = 7.3 Hz, Ar*H*), 7.73 (2H, dd, $^3J_{HH}$ = 8.2 Hz, $^4J_{HH}$ = 1.3 Hz, Ar*H*), 7.91 (1H, dd, $^3J_{HH}$ = 8.1 Hz, $^4J_{HH}$ = 0.9 Hz, Ar*H*); $^{13}C\{^1H\}$ NMR (100 MHz; $CDCl_3$) δ_C 91.1 (CI), 126.7 (CH), 127.8 (CH), 129.6 (CH), 129.8 (CH), 130.0 (CH), 132.6 (CH), 134.5 (C), 138.6 (CH), 143.3 (C), 196.1 (CO). m/z (ASAP): 308.9781 ($[MH]^+$, $C_{13}H_{10}IO$ requires 308.9776, 100 %).

6.2.2 Synthesis of 1-(2-iodophenyl)-1-phenylethanol (2.36) [4]



2.36

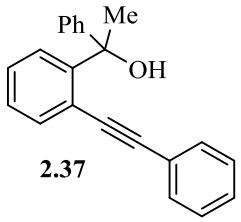
In a 250 mL three-necked flask with a reflux condenser and a dropping funnel were placed magnesium turnings (1.12 g, 0.046 mol) in dry diethyl ether (10 ml). To this was added a solution of methyl iodide (2.07 ml, 0.033 mol) in dry diethyl ether (10 ml) drop wise over 30 min at a rate to maintain the mixture at a gentle reflux. After the reaction mixture had started to reflux spontaneously, dry diethyl ether (10 ml) was added and was allowed to cool to room temperature before it was transferred to a new three-necked flask using a transfer tube needle and the remaining magnesium turnings were washed with dry diethyl ether (5 ml). A solution of 2-iodobenzophenone (4.62 g, 0.015 mol) in dry diethyl ether (10 ml) was added at 0 °C (ice/H_2O) drop wise over 10 min. The dropping funnel was washed by addition of dry diethyl ether (5 ml). The solution was allowed to warm to room temperature overnight, and then it was heated to reflux at 38 °C for 3 hours with monitoring by TLC (using 10% ethyl acetate in petroleum ether as a mobile phase). After the reaction had been judged to have finished, the reaction mixture was allowed to cool to room temperature. This solution was then poured slowly into an ice-cold, saturated solution of ammonium chloride (30 ml) and then water (50 ml) was added and the mixture stirred for 20 minutes. The solution was filtered through Celite, separated and the aqueous phase washed with diethyl ether (2 x 100 ml). The combined organic phases were dried over K_2CO_3 and concentrated *in vacuo* to give the crude product (4.50 g). The crude product was purified using column chromatography (DCM/ hexane 20: 1) to obtain pure product as a yellow oil (3.72 g, 76 %). The characterisation data were in agreement with the literature. ^1H NMR (400 MHz; $CDCl_3$) δ_H 1.98 (3H, s, C*H*$_3$), 3.22 (1H, s, O*H*), 6.91 (1H, td, $^3J_{HH}$ = 7.6, $^4J_{HH}$ = 1.6 Hz, Ar*H*), 7.29 (5H, m, Ar*H*), 7.43 (1H, td, $^3J_{HH}$ = 7.5 Hz, $^4J_{HH}$ = 1.3 Hz, Ar*H*), 7.82 (1H, dd, $^3J_{HH}$ = 7.9 Hz, $^4J_{HH}$ = 1.6 Hz, Ar*H*), 7.98 (1H, dd, $^3J_{HH}$

= 7.8, $^4J_{HH}$ = 1.3 Hz, Ar*H*); $^{13}C\{^1H\}$ NMR (100 MHz; $CDCl_3$) δ_C 30.6 (CH_3), 78.1 (C), 96.3 (CI), 126.4 (CH), 127.0 (CH), 127.9 (CH), 128.2 (CH), 128.6 (CH), 129.1 (CH), 142.3 (CH), 147.1 (C), 147.4 (C). m/z (ASAP): 306.9982 ($[MH\text{-}OH_2]^+$, $C_{14}H_{12}I$ requires 306.9984, 100 %).

6.2.3 General Procedure for the Reaction in Scheme 2.13

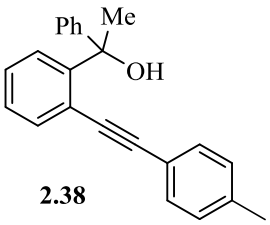
1-(2-Iodophenyl)-1-phenylethanol (2.39 g, 7.4 mmol), phenylacetylene (2.26 ml, 22.2 mmol) or 1-ethylnyl-4-methylbenzene (1.21 ml, 10.5 mmol), $[Pd(PPh_3)_2Cl_2]$ (0.12 g, 0.17 mmol), CuI (0.059 g, 0.3 mmol) and dry Et_3N (40 ml) were charged into a dry three – necked flask. After stirring under nitrogen at 70 °C for 3h , it was allowed to cool to r.t overnight with stirring, then H_2O (30 ml) and Et_2O (30 ml) were added to the reaction mixture. The precipitate was filtered off and the solution was extracted with Et_2O (3 x 20 ml). The combined organic layers were dried over $MgSO_4$ (anhydrous), and the solvent was removed *in vacuo* to give the crude product.

6.2.4 Characterisation Data for Products in Scheme 2.13



2.37

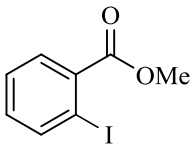
The crude product (2.4 g) was purified by column chromatography using DCM: Hexane (20:1) to give the pure product of 1- phenyl-[1-(2-phenylethynyl)phenyl]ethanol **(2.37)** as an orange oil (1.5 g, 98 %). ^1H NMR (400 MHz; $CDCl_3$) δ_H 1.97 (3H, s, C*H*$_3$), 3.94 (1H, s, O*H*), 7.16 (2H, m, Ar*H*), 7.26 (9H, m, Ar*H*), 7.39 (1H, td, $^3J_{HH}$ = 7.7 Hz, $^4J_{HH}$ = 1.5 Hz, Ar*H*), 7.56 (1H, dd, $^3J_{HH}$ = 7.5 Hz, $^4J_{HH}$ = 1.3 Hz, Ar*H*), 7.69 (1H, dd, $^3J_{HH}$ = 8.0 Hz, $^4J_{HH}$ = 1.02 Hz, Ar*H*); $^{13}C\{^1H\}$ NMR (100 MHz; $CDCl_3$) δ_C 30.0 (CH_3), 88.2 (C) , 96.2 (C), 120.9 (C), 122.4 (C), 125.7 (CH), 126.1 (CH), 126.4 (C), 126.7 (CH), 127.2 (CH), 127.9 (CH), 128.2 (CH), 128.3 (CH), 128.5 (CH), 131.3 (CH), 134.5 (CH), 148.5(C), 148.8 (C). m/z (ASAP): 299.1444 ($[MH]^+$, $C_{22}H_{19}O$ requires 299.1436, 99 %).



2.38

The crude product (1.5 g) was purified by column chromatography using DCM/petroleum ether (20:1) to give the pure product of 1-phenyl-[1-(2-p-tolylethynyl)phenyl] ethanol **(2.38)** as an orange oil (1.02 g, 89 %). ^{1}H NMR (400 MHz; $CDCl_3$) δ_H 1.96 (3H, s, C*H*$_3$), 2.32 (3H, s, C*H*$_3$), 4.03 (1H, s, O*H*), 7.07 (3H, s, Ar*H*), 7.28 (8H, m, Ar*H*), 7.51 (1H, dd, $^{3}J_{HH}$ = 7.5 Hz, $^{4}J_{HH}$ = 1.3 Hz, Ar*H*), 7.67 (1H, dd, $^{3}J_{HH}$ = 7.9 Hz, $^{4}J_{HH}$ = 1.0 Hz, Ar*H*); ^{13}C{^{1}H} NMR (100 MHz; $CDCl_3$) δ_C 21.5 (CH_3), 30.1 (CH_3), 87.6 (C), 96.5 (C), 119.3 (C), 121.0 (C), 125.3 (CH), 125.9 (C), 126.1 (CH), 126.7 (CH), 127.2 (CH), 127.9 (CH), 128.2 (CH), 129.0 (CH), 131.1 (CH), 134.4 (CH), 138.7 (C), 148.61 (C), 148.7(C). m/z (ASAP): 313.1596 ($[MH]^+$, $C_{23}H_{21}O$ requires 313.1592, 100 %).

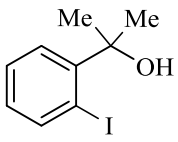
6.2.5 Synthesis of Methyl-2-iodobenzoate (2.46) [5]



2.46

Thionyl chloride (11 ml, 0.146 mol) was added slowly to a solution of 2-iodobenzoic acid (25.08 g, 0.101 mol) in MeOH (151 ml) at 0 °C. After stirring for 30 min at 0 °C the cooling bath was removed and the reaction mixture was heated to reflux at 70 °C overnight (19 h). All volatiles were removed on a rotary evaporator. The residue was dissolved in ethyl acetate (50 ml) and washed three times with brine (50 ml). The combined organic phases were dried over $MgSO_4$, filtered and the solvent was removed on a rotary evaporator to give the product methyl-2-iodobenzoate as an orange oil (25.509 g, 96 %). The characterisation data were in agreement with the literature. ^{1}H NMR (400 MHz; $CDCl_3$) δ_H 3.93 (3H, s, C*H*$_3$), 7.14 (1H, td, $^{3}J_{HH}$ = 7.5 Hz, $^{4}J_{HH}$ 1.6, Hz, Ar*H*), 7.39 (1H, td, $^{3}J_{HH}$ = 7.5 Hz, $^{4}J_{HH}$ = 1.1 Hz, Ar*H*), 7.79 (1H, dd, $^{3}J_{HH}$ = 7.6 Hz, $^{4}J_{HH}$ = 1.8 Hz, Ar*H*), 7.99 (1H, dd, $^{3}J_{HH}$ = 8.0 Hz, $^{4}J_{HH}$ = 1.1 Hz, Ar*H*).^{13}C{^{1}H} NMR (100 MHz; $CDCl_3$) δ_C 52.4 (CH_3), 94.0 (CI), 127.8 (CH), 130.9 (CH), 132.6 (CH), 135.1 (C), 141.3 (CH), 166.9 (CO). m/z (ASAP): 262.9567 ($[MH]^+$, $C_8H_8IO_2$ requires 262.9569, 100 %).

6.2.6 Synthesis of 2-(2-iodophenyl) propan-2-ol (2.47) [6]



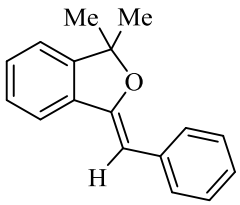
2.47

In a 250 mL three-necked flask with a reflux condenser and a dropping funnel were placed magnesium turnings (4.74 g, 0.19 mol) in dry diethyl ether (17.5 ml). To this was added a solution of methyl iodide (8.7 ml, 0.139 mol) in dry diethyl ether (12.5 ml) drop wise over 30 min at a rate to maintain the mixture at a gentle reflux. After the reaction had started to reflux spontaneously, dry diethyl ether (10 ml) was added to the reaction mixture. After addition, the reaction mixture was allowed to cool to room temperature before it was transferred to a new three-necked flask using a transfer tube needle and the remaining magnesium turnings were washed with dry diethyl ether (6.5 ml). A solution of methyl 2-iodobenzoate (16.46 g, 0.0628 mol) in dry diethyl ether (10 ml) was added at 0 °C (ice/H_2O) drop wise over 10 min. The dropping funnel was washed by addition of dry diethyl ether (7 ml). The solution was allowed to warm to room temperature overnight, and then it was heated to reflux at 49 °C for 3 hours with monitoring by TLC (using 10% ethyl acetate in petroleum ether as a mobile phase). After the reaction had been judged to have finished, the reaction mixture was allowed to cool to room temperature. This solution was then poured slowly into an ice-cold, saturated solution of ammonium chloride (75 ml) and then water (100 ml) was added and the mixture was stirred for 20 minutes. The solution was filtered through Celite, separated and the aqueous phase washed with diethyl ether (4 x 100 ml). The combined organic phases were dried over K_2CO_3 and concentrated *in vacuo* to give the crude product (12.3 g). The crude product was purified using column chromatography (ethyl acetate/petroleum ether 1: 9) to obtain 2-(2-iodophenyl)propan-2-ol as a yellow oil (9.10 g, 58 %). The characterisation data were in agreement with the literature. ^{1}H NMR (400 MHz; $CDCl_3$) δ_H 1.75 (6H, s, C*H*$_3$), 2.51 (1H, s, O*H*), 6.89 (1H, td, $^3J_{HH}$ = 7.6 Hz, $^4J_{HH}$ = 1.7 HZ, Ar*H*), 7.31 (1H, td, $^3J_{HH}$ = 7.4 Hz, $^4J_{HH}$ = 1.3 Hz, Ar*H*), 7.62 (1H, dd, $^3J_{HH}$ = 7.9 Hz, $^4J_{HH}$ = 1.7 Hz, Ar*H*), 7.95 (1H, dd, $^3J_{HH}$ = 7.8 Hz, $^4J_{HH}$ = 1.4 Hz, Ar*H*); ^{13}C{^{1}H} NMR (100 MHz; $CDCl_3$) δ_C 29.8 (CH_3), 73.6 (CI), 93.1 (C), 126.7 (CH), 128.1 (CH), 128.6 (CH), 142.7 (CH), 148.5 (C). m/z (ASAP): 244.9517 ([MH-OH_2]$^+$, $C_9H_{10}I$ requires 244.9529, 99 %).

6.2.7 General Procedure for the Reaction in Scheme 2.18

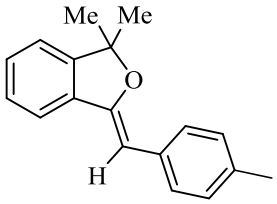
2-(2-Iodophenyl)propan-2-ol (0.96 g, 3.7 mmol), phenylacetylene (0.49 ml, 4.45 mmol) or 1-ethylnyl-4-methylbenzene (1.13 ml, 8.9 mmol), [$Pd(PPh_3)_2Cl_2$] (0.12 g, 0.17 mmol), CuI (0.059 g, 0.3 mmol) and dry Et_3N (20 ml) were charged into a dry three–necked flask. After stirring at 70 °C under nitrogen for 3 h, the reaction mixture was cooled to room temperature, then H_2O (10 ml) and Et_2O (10 ml) were added. The precipitate was filtered off and the solution was extracted with Et_2O (3 x 10 ml). The combined organic layers were dried over $MgSO_4$ (anhydrous), and the solvent was removed *in vacuo* to give the crude product.

6.2.8 Characterisation Data for Products in Scheme 2.18



2.48

The crude product (0.90 g) was purified by column chromatography using diethyl ether/ hexane (1:9) to give the pure product of (3Z)-3-(benzylidene)-1,1-dimethyl-1,3- dihydroisobenzofuran **(2.48)** [5,6] as orange oil (0.19 g, 42 %). The characterisation data were in agreement with the literature. ^{1}H NMR (400 MHz; $CDCl_3$) δ_H 1.60 (6H, s, C*H*$_3$), 5.86 (1H, s, CH), 7.10 (1H, dd, $^3J_{HH}$ = 7.9 Hz, $^4J_{HH}$ = 1.3 Hz, ArH), 7.18 (1H, m, ArH), 7.35 (4H, m, Ar*H*), 7.53 (1H, m, Ar*H*), 7.71 (2H, dd, $^3J_{HH}$ = 8.1 Hz, $^4J_{HH}$ = 1.7 Hz, Ar*H*); ^{13}C{^{1}H} NMR (100 MHz; $CDCl_3$) δ_C 28.4 (CH_3), 89.1 (C), 95.7 (CH), 120.0 (CH), 120.4 (CH), 125.7 (CH) 127.7 (CH), 128.0 (CH), 128.2 (CH), 128.7 (CH), 134.1 (C), 136.7 (C), 147.5 (C), 154.0 (CO). m/z (ASAP): 237.1271 ([MH]$^+$, $C_{17}H_{17}O$ requires 237.1279, 100 %).



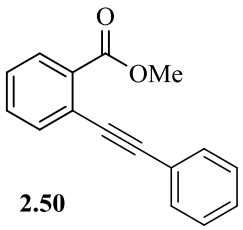
2.49

The crude product (1.51 g) was purified by column chromatography using diethyl ether/hexane (1:9) to give the pure product of (Z)-1,1-dimethyl-3-(4-methylbenzylidene)-1,3-dihydroisobenzofuran **(2.49)** as a red oil (0.71 g, 48 %). ^{1}H NMR (400 MHz; $CDCl_3$) δ_H 1.54 (6H, s, C*H*$_3$), 2.25 (3H, s, C*H*$_3$), 5.78 (1H, s, C*H*), 7.05 (2H, d, $^3J_{HH}$ = 7.9 Hz, ArH), 7.10 (1H, m, ArH), 7.21 (2H m, ArH), 7.41 (1H, m, ArH), 7.56 (2H, d, $^3J_{HH}$ = 8.1 Hz, ArH); ^{13}C{^{1}H} NMR (100 MHz; $CDCl_3$) δ_C 21.2 (CH_3), 28.5 (CH_3), 88.9 (C), 95.7 (CH), 119.8 (CH), 120.4 (CH), 124.6 (CH) 127.7 (CH), 128.0 (CH), 128.5 (CH), 133.9 (C), 134.2 (C), 134.7 (C), 147.4 (C), 153.6 (CO). m/z (ASAP): 251.1426 ([MH]$^+$, $C_{18}H_{19}O$ requires 251.1436, 99 %).

6.2.9 General Procedure for the Reaction in Scheme 2.20

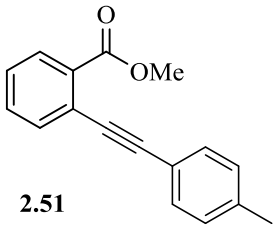
Methyl-2-iodobenzoate (5.79 g, 22.2 mmol), phenylacetylene (2.94 ml, 26.7 mmol) or 1-ethylnyl-4-methylbenzene (2.26 ml, 17.8 mmol), $[Pd(PPh_3)_2Cl_2]$ (0.36 g, 0.51 mmol), CuI (0.17 g, 0.9 mmol) and dry Et_3N (120 ml) were stirred at 70 °C under nitrogen overnight. The reaction mixture was allowed to cool to room temperature, before H_2O (45 ml) and Et_2O (45 ml) were added. The precipitate was filtered off and the solution was extracted with Et_2O (3 x 30 ml). The combined organic layers were dried over $MgSO_4$ (anhydrous), and the solvent was removed to give the crude product.

6.2.10 Characterisation Data for Products in Scheme 2.20 [7,8]



2.50

The crude product (5.64 g) was purified by column chromatography using diethyl ether/petroleum ether (1:9) to give the pure product of methyl-2-(phenylethynyl)benzoate **(2.50)** [7] as an orange oil (4.88 g, 93%). The characterisation data were in agreement with the literature. ^{1}H NMR (400 MHz; $CDCl_3$) δ_H 3.94 (3H, s, C*H*$_3$), 7.34 (4H, m, Ar*H*), 7.46 (1H, td, $^3J_{HH}$ = 7.6 Hz, $^4J_{HH}$ = 1.3 Hz, Ar*H*), 7.57 (2H, m, Ar*H*), 7.63 (1H, dd, $^3J_{HH}$ = 7.7 Hz, $^4J_{HH}$ = 1.3 Hz, Ar*H*), 7.9 (1H ,dd, $^3J_{HH}$ = 7.9 Hz, $^4J_{HH}$ = 1.3 Hz, Ar*H*); ^{13}C{^{1}H} NMR (100 MHz; $CDCl_3$) δ_C 52.1 (OCH_3), 88.2 (C), 94.3 (C), 120.8 (C), 123.3 (C), 127.8 (CH) 128.3 (CH), 128.5 (CH), 128.7 (CH), 130.47 (CH), 131.7 (CH), 133.9 (CH), 138.6 (C), 166.6 (CO). m/z (ASAP): 237.0906 ($[MH]^+$, $C_{16}H_{13}O_2$ requires 237.0916, 99 %)



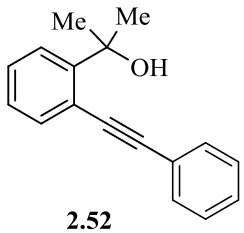
2.51

The crude product (3.75 g) was purified by column chromatography using diethyl ether/petroleum ether (1:9) to give the pure product of methyl-2-(p-tolylethynyl)benzoate **(2.51)** [8] as an orange oil (3.6 g, 97 %). The characterisation data were in agreement with the literature. ^{1}H NMR (400 MHz; $CDCl_3$) δ_H 2.37 (3H, s, C*H*$_3$), 3.96 (3H, s, OC*H*$_3$), 7.16 (2H, d, $^3J_{HH}$ = 8.2 Hz, Ar*H*), 7.36 (1H, td, $^3J_{HH}$ = 7.6 Hz, $^4J_{HH}$ = 1.3 Hz, Ar*H*), 7.47 (3H ,m, Ar*H*), 7.63 (1H, dd, $^3J_{HH}$ = 7.7 Hz, $^4J_{HH}$ = 1.0 Hz, Ar*H*), 7.9 (1H, dd, $^3J_{HH}$ = 7.8 Hz, $^4J_{HH}$ = 1.0 Hz, Ar*H*); ^{13}C{^{1}H} NMR (100 MHz; $CDCl_3$) δ_C 21.5 (CH_3), 52.1 (OCH_3), 87.6 (C), 94.6 (C), 120.2 (C), 123.9 (C), 125.1 (C), 127.6 (CH), 129.1 (CH), 130.4 (CH), 131.6 (CH), 131.8 (CH), 133.9 (CH), 138.7 (C), 166.8 (CO). m/z (ASAP): 251.1071 ($[MH]^+$, $C_{17}H_{15}O_2$ requires 251.1072, 100 %).

6.2.11 General Procedure for the Reaction in Scheme 2.20

In a 250 mL three-necked flask with a reflux condenser and a dropping funnel were placed magnesium turnings (1.12 g, 0.046 mol) in dry diethyl ether (10 ml). To this was added a solution of methyl iodide (2.07 ml, 0.033 mol) in dry diethyl ether (10 ml) drop wise over 30 min at a rate to maintain the mixture at a gentle reflux. After the reaction had started to reflux spontaneously, dry diethyl ether (10 ml) was added to the reaction mixture. After addition, the reaction mixture was allowed to cool to room temperature before it was transferred to a new three-necked flask using a transfer tube needle and the remaining magnesium turnings were washed with dry diethyl ether (5 ml). A solution of methyl (2-phenylethynyl)benzoate (3.54 g, 0.015 mol) or methyl 2-(p-tolylethynyl)benzoate (3.75 g, 0.015 mol) in dry diethyl ether (10 ml) was added at 0 °C (ice/H_2O) drop wise over 10 min. The dropping funnel was washed by addition of dry diethyl ether (5 ml). The solution was allowed to warm to room temperature overnight, and then it was heated to reflux at 38 °C for 3 hours with monitoring by TLC (using 10% ethyl acetate in petroleum ether as a mobile phase). After the reaction had been judged to have finished, the reaction mixture was allowed to cool to room temperature. This solution was then poured slowly into an ice-cold, saturated solution of ammonium chloride (30 ml) and then water (50 ml) was added and the mixture stirred for 20 minutes. The solution was filtered through Celite, separated and the aqueous phase washed with diethyl ether (2 x 100 ml). The combined organic phases were dried over K_2CO_3 and concentrated *in vacuo* to give the crude product.

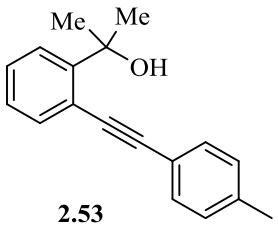
6.2.12 Characterisation Data for Products in Scheme 2.20 [6]



2.52

The crude product (3.39 g) was purified using column chromatography (ethyl acetate/petroleum ether 1:9) to obtain the pure product of 2-(2-(phenylethynyl)phenyl)propan-2-ol **(2.52)** [9] as a yellow oil (1.63 g, 46 %). The characterisation data were in agreement with the literature. ^{1}H NMR (400 MHz; $CDCl_3$) δ_H 1.70 (6H, s, C*H*$_3$), 3.20 (1H, s, O*H*), 7.12 (1H, td, $^3J_{HH}$ = 7.5 Hz, $^4J_{HH}$ = 1.3 Hz, Ar*H*), 7. 2 (1H, td, $^3J_{HH}$ = 7.8 Hz, $^4J_{HH}$ = 1.5 Hz, Ar*H*), 7.25 (3H, m, Ar*H*), 7.42 (2H, dd, $^3J_{HH}$ = 7.3 Hz, $^4J_{HH}$ = 1.9 Hz, Ar*H*), 7.48 (2H, t, $^3J_{HH}$ = 7.7 Hz, Ar*H*); ^{13}C{^{1}H} NMR (100 MHz; $CDCl_3$) δ_C 30.0 (CH_3), 73.27 (C), 89.3 (C), 95.5 (C), 119.3 (C), 122.9 (C), 124.7 (CH) 126.7

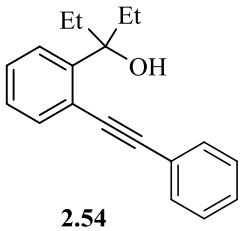
(CH), 128.5 (CH), 128.6 (CH), 131.1 (CH), 131.2 (CH), 134.4 (CH), 150.1 (C). m/z (ASAP): 237.1280 ([MH]$^+$, $C_{17}H_{17}O$ requires 237.1279, 100 %).



2.53

The crude product (3.63 g) was purified using column chromatography (ethyl acetate/petroleum ether 1:9) to obtain the pure product of 2-(2-(p-tolylethynyl)phenyl) propan-2-ol **(2.53)** as a yellow oil (2.47 g, 65 %). The characterisation data were in agreement with the literature. ^{1}H NMR (400 MHz; $CDCl_3$) δ_H 1.78 (6H, s, C*H*$_3$), 2.35(3H, s, C*H*$_3$), 3.38 (1H, s, O*H*), 7.15 (2H, d, $^3J_{HH}$ = 7.9 Hz, Ar*H*), 7.20 (1H, td, $^3J_{HH}$ = 7.5 Hz, $^4J_{HH}$ = 1.3 Hz, Ar*H*), 7.28 (1H, td, $^3J_{HH}$ = 7.7 Hz, $^4J_{HH}$ = 1.5 Hz, Ar*H*), 7.40 (2H, d, $^3J_{HH}$ = 8.1 Hz, Ar*H*), 7.55 (2H, td, $^3J_{HH}$ = 6.3 Hz, $^4J_{HH}$ = 1.2 Hz, Ar*H*); ^{13}C{^{1}H} NMR (100 MHz; $CDCl_3$) δ_C 21.5 (CH_3), 29.9 (CH_3), 73.2 (C), 88.7 (C), 95.8 (C), 119.5 (C), 119.8 (C), 124.7 (CH) 126.7 (CH), 128.4 (CH), 129.3 (CH), 131.1 (CH), 134.3 (CH), 138.8 (C), 150.0 (C). m/z (ASAP): 251.1438 ([MH]$^+$, $C_{18}H_{19}O$ requires 251.1436, 100 %).

6.2.13 Synthesis of (2-(Phenylethnyl)phenyl)pentan-3-ol (2.54) [6]



2.54

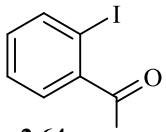
EtMgBr (37.5 ml, 37.5 mmol, 1M in THF) was charged into a three-necked flask with diethyl ether (10 ml) at 0 ^{o}C and methyl 2-(phenylethynyl)benzoate (3.544 g, 15 mmol) was charged into a dropping funnel with diethyl ether (10 ml). The methyl 2-(phenylethynyl)benzoate solution was added dropwise to the three-necked flask over 20 minutes the mixture was warmed to RT and stirred overnight. The mixture was stirred and heated to reflux for 1.5 h. after cooling to RT, the mixture was extracted with diethyl ether (3 x 15 ml) and H_2O (20 ml). The combined organic layers were dried over $MgSO_4$ (anhydrous), and the solvent was removed *in vacuo* to give the crude product (3.89 g). It was purified by column chromatography using ethyl acetate/ petroleum ether (40-60 ^{o}C) (1:9) to give the pure product as a brown oil (1.83 g, 46 %).^{1}H NMR (400 MHz; $CDCl_3$) δ_H 0.85 (6H, t, J_{HH} = 7.7 Hz, C*H*$_3$), 2.02 (2H, ABq, J_{HH} = 7.7 Hz, C*H*$_2$), 2.53 (2H, ABq, J_{HH} = 7.7 Hz, C*H*$_2$), 2.57 (1H, s, OH), 7.28 (1H, td, $^3J_{HH}$ = 7.5 Hz, $^4J_{HH}$ = 1.2 Hz, Ar*H*), 7.39 (4H, m, Ar*H*), 7.56 (2H, m, Ar*H*), 7.62 (1H, dd, $^3J_{HH}$ = 7.5 Hz, $^4J_{HH}$ = 1.3 Hz, Ar*H*), 7.66 (1H, dd, $^3J_{HH}$ = 7.9 Hz, $^4J_{HH}$ = 1.1 Hz, Ar*H*); ^{13}C{^{1}H} NMR (100 MHz; $CDCl_3$) δ_C 8.1 (CH_3), 33.1 (CH_2), 78.5 (C), 89.7 (C), 94.4 (C), 119.4

(C), 123.2 (C), 126.3 (CH), 127.1 (CH), 127.8 (CH), 128.3 (CH), 128.5 (CH), 131.1 (CH), 134.5 (CH), 147.0 (C). m/z (ASAP): 265.1583 ($[MH]^+$, $C_{19}H_{21}O$ requires 265.1591, 100 %).

6.2.14 General Procedure for the Reaction in Scheme 2.22

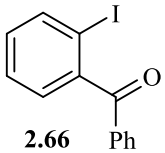
2-Aminoacetophenone or 2-Aminobenzophenone (4.85 g, 0.033 mol) was added to a stirred solution of *p*-toluenesulfonic acid monohydrate (19.3g, 0.1 mol) in acetonitrile (120 ml) under nitrogen. The resulting suspension of protonated amine was cooled to 0 °C, and an aqueous solution (20 ml) of potassium iodide (13.90 g, 0.08 mol) and sodium nitrite (4.6 g, 0.065 mol) was carefully added. The resulting brown solution was warmed to room temperature, and stirred overnight under nitrogen. The reaction mixture was quenched with a saturated sodium bicarbonate solution (120 ml) and a saturated aqueous sodium thiosulfate solution (30 ml) was added. The resulting yellow solution was extracted with ether (3 x 150 ml) and washed with brine (20 ml). The combined organic phases were dried over anhydrous magnesium sulphate, and concentrated *in vacuo* to afford the crude product.

6.2.15 Characterisation Data for Products in Scheme 2.22 [10,11]



2.64

The crude product (9.11 g) was extracted with HCl 2M (3 x 50 ml), dried, and concentrated, to give the pure product of 2-iodoacetophenone **(2.64)** as an orange liquid (7.51 g, 91%). The characterisation data were in agreement with the literature. ^{1}H NMR (400 MHz; $CDCl_3$) δ_H 2.54 (3H, s, C*H*$_3$), 7.07 (1H, td, $^3J_{HH}$ = 7.6 Hz, $^4J_{HH}$ = 1.7 Hz, Ar*H*), 7.33 (1H, td, $^3J_{HH}$ = 7.5 Hz, $^4J_{HH}$ = 1.0 Hz, Ar*H*) 7.39 (1H, dd, $^3J_{HH}$ = 7.6 Hz, $^4J_{HH}$ = 1.7 Hz, Ar*H*) 7.86 (1H, dd, ^3J_v = 7.9 Hz, $^4J_{HH}$ = 0.8 Hz, Ar*H*); ^{13}C{^{1}H} NMR (100 MHz; $CDCl_3$) δ_C 28.4 (CH_3), 89.9 (CI), 127.0 (CH), 127.3 (CH), 130.7 (CH), 139.8 (CH), 143.1 (C), 200.7 (CO). m/z (ASAP): 246.9616 ($[MH]^+$, C_8H_8IO requires 246.9620, 99 %).



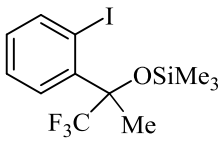
2.66

The crude product (2.91 g) was purified by using column chromatography (Et_2O/ hexane 5:1) to give the pure product of 2-iodobenzophenone **(2.66)** [11] as an orange oil (1.42 g, 70 %). The characterisation data were in agreement with the literature. ^{1}H NMR (400 MHz; $CDCl_3$) δ_H 7.16 (1H, td, $^3J_{HH}$ = 7.7 Hz, $^4J_{HH}$ = 1.7 Hz, Ar*H*), 7.28 (1H, dd, $^3J_{HH}$ = 7.6 Hz, $^4J_{HH}$ = 1.6 Hz, Ar*H*), 7.44 (3H, t, $^3J_{HH}$ = 7.6 Hz, Ar*H*) 7.59 (1H, t, $^3J_{HH}$ = 7.3 Hz, Ar*H*), 7.73 (2H, dd, $^3J_{HH}$ = 8.2 Hz, $^4J_{HH}$ = 1.3 Hz, Ar*H*), 7.91 (1H, dd, $^3J_{HH}$ = 8.1 Hz, $^4J_{HH}$ = 0.9 Hz, Ar*H*); ^{13}C{^{1}H} NMR (100 MHz; $CDCl_3$) δ_C 91.1 (CI), 126.7 (CH), 127.8 (CH), 129.6 (CH), 129.8 (CH), 130.0 (CH), 132.6 (CH), 134.5 (C), 138.6 (CH), 143.3 (C), 196.1 (CO). m/z (ASAP): 308.9781 ($[MH]^+$, $C_{13}H_{10}IO$ requires 308.9776, 100 %).

6.2.16 General Procedure for the Reaction in Scheme 2.23

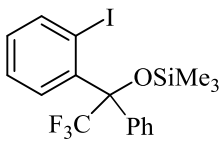
TBAF (50 mg, 0.2 mmol) was added drop wise to a solution of $TMSCF_3$ (15.74 g, 14.9 mmol) and 2-iodoacetophenone (7.87 g, 7.4 mmol) in dry THF (80 ml) at 0 °C under nitrogen, and the mixture stirred for 20 minutes. After being allowed to warm to room temperature, the reaction mixture was stirred for a further 48 hours. The reaction mixture was hydrolysed with H_2O (70 ml) and then extracted with diethyl ether (3 x 50 ml). The combined organic layers were washed with water (3 x 50 ml) and brine (50 ml), dried over $MgSO_4$ (anhydrous) and the solvent removed *in vacuo* to give the crude product.

6.2.17 Characterisation Data for Products in Scheme 2.23



2.67

The crude product (10.89 g) was purified by column chromatography using DCM: petroleum ether 40-60 (1:50) to give the pure product of 1,1,1-trifluoro-2-(2-iodophenyl)-2-trimethylsiloxypropane **(2.67)** as a yellow oil (7.61 g, 61 %). ^{1}H NMR (400 MHz; $CDCl_3$) δ_H 0.0 (9H, s, $OSiMe_3$), 1.82 (3H, s, C*H*$_3$), 6.75 (1H, td, $^3J_{HH}$ = 7.7 Hz, $^4J_{HH}$ = 1.6, Hz, Ar*H*), 7.14 (1H, td, $^3J_{HH}$ = 7.6 Hz, $^4J_{HH}$ = 1.5 Hz, Ar*H*), 7.38 (1H, d, $^3J_{HH}$ = 8.2 Hz, Ar*H*), 7.89 (1H, dd, $^3J_{HH}$ = 7.8 Hz, $^4J_{HH}$ = 1.3 Hz, Ar*H*); ^{13}C{^{1}H} NMR (100 MHz; $CDCl_3$) δ_C 0.0 ($OSiMe_3$), 23.0 (CH_3), 76.4 (q, $^2J_{CF}$ = 32.3 Hz, C-CF_3), 92.0 (CI), 124.3 (C), 127.3 (q, $^1J_{CF}$ = 282 Hz, CF_3), 128.0 (CH), 129.3 (CH), 130.0 (CH), 138.8 (C), 143.7 (CH). ^{19}F NMR (376 MHz; $CDCl_3$) δ_F -78.2 (s, CF_3). m/z (ASAP): 298.9542 ($[M- OSiMe_3]^+$, $C_9H_7F_3I$ requires 298.9545, 100 %).



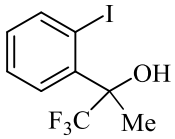
2.69

The crude product as a brown oil (1.46 g) was purified by column chromatography ethylacetate/petroleum ether (1:9) to give the pure product of trimethyl(2,2,2-trifluoro-1-(2-iodophenyl)-1-phenylethoxy)silane **(2.69)** as an orange oil (1.42 g, 76%).^{1}H NMR (400 MHz; $CDCl_3$) δ_H 0.00 (9H, s, $OSiMe_3$), 6.94 (1H, td, $^{3}J_{HH}$ = 7.5 Hz, $^{4}J_{HH}$ = 1.5, Hz, Ar*H*), 7.26 (5H, m, Ar*H*), 7.35 (1H, td, $^{3}J_{HH}$ = 7.4 Hz, $^{4}J_{HH}$ = 1.4 Hz, Ar*H*), 7.68 (1H, m, Ar*H*), 7.92 (1H, dd, $^{3}J_{HH}$ = 7.8 Hz, $^{4}J_{HH}$ = 1.3 Hz, Ar*H*); $^{13}C\{^{1}H\}$ NMR (100 MHz; $CDCl_3$) δ_C 0.02 ($OSiMe_3$), 83.3 (q, $^{2}J_{CF}$ = 32.3 Hz, C-CF_3), 97.6 (CI), 123.6 (q, $^{1}J_{CF}$ = 282.3 Hz, CF_3), 127.4 (CH), 127.8 (CH), 128.1 (CH), 128.2 (CH), 129.1 (CH), 129.2 (CH), 129.8 (CH), 140.4 (C), 143.8 (C). ^{19}F NMR (376 MHz; $CDCl_3$) δ_F -72.5 (s, CF_3). m/z (ASAP): 234.0649 ($[M\text{-}I\text{-}OSiMe_3]^+$, $C_{14}H_9F_3$ requires 234.2401, 100 %).

6.2.18 General Procedure for the Reaction in Scheme 2.24

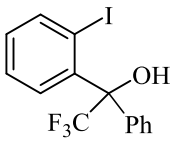
This product was washed with THF: HCl 2M (1:1) (100 mL) and stirred overnight. The mixture was extracted with Et_2O (2 x 30 mL), the combined organic layers dried, and the solvent removed *in vacuo* to give the crude product.

6.2.19 Characterisation Data for Products in Scheme 2.24



2.68

The crude product (1.96 g) was purified by column chromatography using DCM:petroleum ether 40-60 (1: 50) to give the pure product of 1,1,1-trifluoro-2-(2-iodophenyl)propan-2-ol **(2.68)** [12] as a colourless oil (1.76 g, 67 %). The characterisation data was in agreement with the literature. ^{1}H NMR (400 MHz; $CDCl_3$) δ_H 1.91 (3H, s, C*H*$_3$), 3.45 (1H, s, O*H*), 6.98 (1H, td, $^{3}J_{HH}$ = 7.4 Hz, $^{4}J_{HH}$ = 1.6, Hz, Ar*H*), 7.3 (1H, td, $^{3}J_{HH}$ = 8.2 Hz, $^{4}J_{HH}$ = 1.3 Hz, Ar*H*), 7.53 (1H, d, $^{3}J_{HH}$ = 8.1 Hz, Ar*H*), 8.03 (1H, dd, $^{3}J_{HH}$ = 8.01 Hz, $^{4}J_{HH}$ = 1.2 Hz, Ar*H*); $^{13}C\{^{1}H\}$ NMR (100 MHz; $CDCl_3$) δ_C 23.6 (CH_3), 76.1 (q, $^{2}J_{CF}$ = 32.3 Hz, C-CF_3), 92.0 (CI), 124.2 (C), 127.1 (q, $^{1}J_{CF}$ = 282 Hz, CF_3), 129.3 (CH), 129.9 (CH), 130.1 (CH), 138.8 (C), 143.7 (CH). ^{19}F NMR (376 MHz; $CDCl_3$) δ_F -78.0 (s, CF_3). m/z (ASAP): 298.9560 ($[MH\text{-}OH_2]^+$, $C_9H_7F_3I$ requires 298.9545, 100 %).



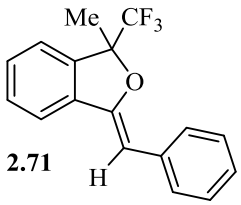
2.70

The crude product of 1-(2-iodophenyl)-1-phenyl-2,2,2-trifluoroethanol **(2.70)** as a brown oil (1.39 g) was purified by column chromatography ethylacetate/petroleum ether (2:8), and to give pure product as an orange oil (1.25 g, 80 %).^{1}H NMR (400 MHz; $CDCl_3$) δ_H 3.59 (1H, s, O*H*), 7.05 (1H, td, $^{3}J_{HH}$ = 7.6 Hz, $^{4}J_{HH}$ = 1.5, Hz, Ar*H*), 7.35 (5H, m, Ar*H*), 7.45 (1H, td, $^{3}J_{HH}$ = 7.6 Hz, $^{4}J_{HH}$ = 1.4 Hz, Ar*H*), 7.79 (1H, m, Ar*H*), 7.98 (1H, dd, $^{3}J_{HH}$ = 7.8 Hz, $^{4}J_{HH}$ = 1.3 Hz, Ar*H*); $^{13}C\{^{1}H\}$ NMR (100 MHz; $CDCl_3$) δ_C 81.4 (q, $^{2}J_{CF}$ = 32.3 Hz, C-CF_3), 96.3 (CI), 127.7 (CH), 128.2 (q, $^{1}J_{CF}$ = 282.3 Hz, CF_3), 128.6 (CH), 128.7 (CH), 128.8 (CH), 129.1 (CH), 130.2 (CH), 137.3 (C), 139.7 (C), 143.6 (CH). ^{19}F NMR (376 MHz; $CDCl_3$) δ_F -72.3 (s, CF_3). m/z (ASAP): 360.9770 ($[MH\text{-}OH_2]^+$, $C_{14}H_9F_3I$ requires 360.9767, 100 %).

6.2.20 General Procedure for the Reaction in Scheme 2.25

1,1,1-Trifluoro-2-(2-iodophenyl)propan-2-ol (1.16 g, 3.7 mmol), phenylacetylene (0.5 ml, 4.45 mmol) or 1-ethylnyl-4-methylbenzene (0.5 ml, 4.45 mmol), $[Pd(PPh_3)_2Cl_2]$ (0.12 g, 0.17 mmol), CuI (0.059 g, 0.3 mmol) and dry Et_3N (20 ml) were charged into a dry three – necked flask. After stirring at 70 °C under nitrogen for 3 h. The reaction mixture was cooled to room temperature, then H_2O (10 ml) and Et_2O (10 ml) were added to the reaction mixture. The precipitate was filtered off and the solution was extracted with Et_2O (3 x 10 ml). The combined organic layers were dried over $MgSO_4$ (anhydrous), and the solvent was removed *in vacuo* to give the crude product

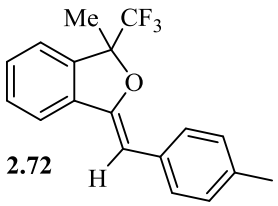
6.2.21 Characterisation Data for Products in Scheme 2.25



2.71

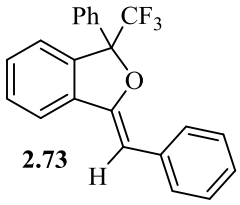
The crude product (1.03 g) was purified by column chromatography using diethyl ether/hexane (1:9) to give pure product of (3Z)-1-(benzylidene)-3-methyl-3-(trifluoromethyl)-1,3- dihydroisobenzofuran **(2.71)** as a yellow oil (0.19 g, 37%). ^{1}H NMR (400 MHz; $CDCl_3$) δ_H 1.81 (3H, s, C*H*$_3$), 5.99 (1H, s, C*H*), 7.17 (1H, td, $^{3}J_{HH}$ = 7.48 Hz, $^{4}J_{HH}$ =1.20 Hz Ar*H*), 7.36 (5H, m, Ar*H*), 7.53 (1H, td, $^{3}J_{HH}$ = 7.6 Hz, $^{4}J_{HH}$ =1.02 Hz, Ar*H*), 7.73 (2H, dd, $^{3}J_{HH}$ = 8.71 Hz, $^{4}J_{HH}$ =1.8, Ar*H*); $^{13}C\{^{1}H\}$ NMR (100 MHz; $CDCl_3$) δ_C 20.5 (CH_3), 88.0 (q, $^{2}J_{CF}$ = 32.7 Hz, C-CF_3), 95.0 (CH), 120.0 (CH), 122.3 (CH), 123.8 (CH), 125.5(C), 127.8 (q, $^{1}J_{CF}$ = 282.3 Hz, CF_3), 128.6 (CH), 129.2 (CH),

130.0 (CH), 130.8 (CH), 133.7 (C), 135.08 (C), 153.4 (CO). ^{19}F NMR (376 MHz; $CDCl_3$) δ_F -79.9 (s, CF_3). m/z (ASAP): 291.0994 ($[MH]^+$, $C_{17}H_{14}OF_3$ requires 291.0997, 100 %).



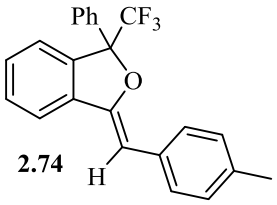
2.72

The crude product (1.03 g) was purified by column chromatography using diethyl ether/hexane (1:9) give pure product of (E)-1-(p-tolyl)methylene-3-methyl-3-(trifluoromethyl)-1,3 dihydroisobenzofuran **(2.72)** as an orange oil (0.58 g, 52 %).^{1}H NMR (400 MHz; $CDCl_3$) δ_H 1.82 (3H, s, C*H*$_3$), 2.35 (3H, s, C*H*$_3$), 5.98(1H, s, C*H*), 7.13 7.16 (2H, d, $^3J_{HH}$ = 8.2 Hz, Ar*H*), 7.37 (2H, d, $^3J_{HH}$ = 6.9 Hz, Ar*H*), 7.4 (1H, m, Ar*H*), 7.55 (1H, d, $^3J_{HH}$ = 7.9 Hz, Ar*H*), 7.62 (2H, d, $^3J_{HH}$ = 8.1 Hz, Ar*H*); ^{13}C{^{1}H} NMR (100 MHz; $CDCl_3$) δ_C 20.6 (CH_3), 21.6 (CH_3), 73.4 (q, $^2J_{CF}$ = 32.3 Hz, C-CF_3), 118.8 (C), 119.9 (CH), 122.3 (CH), 128.3 (CH), 128.9 (CH), 129.1 (q, $^1J_{CF}$ = 282.3 Hz, CF_3), 129.2 (CH), 129.2 (CH), 132.4 (CH), 135.8 (C), 137.8 (C), 139.5(C), 152.6 (CO). ^{19}F NMR (376 MHz; $CDCl_3$) δ_F -79.2 (s, CF_3). m/z (ASAP): 305.1152 ($[MH]^+$, $C_{18}H_{16}OF_3$ requires 305.1153, 100 %).



2.73

The crude product (2.4 g) was purified by column chromatography using ethyl acetate: petroleum ether 40-60 (1: 20) to give pure (3*Z*)-1-(benzylidene)-3-phenyl-3-(trifluoromethyl)-1,3-dihydroisobenzofuran **(2.73)** as a yellow oil (0.52 g, 42%). ^{1}H NMR (400 MHz; $CDCl_3$) δ_H 5.99 (1H, s, C*H*), 7.13 (1H, t, $^3J_{HH}$ = 7.6 Hz, Ar*H*), 7.30 (7H, m, Ar*H*), 7.49 (1H, d, $^3J_{HH}$ = 7.9 Hz, Ar*H*), 7.58 (1H, d, $^3J_{HH}$ = 7.3 Hz, Ar*H*), 7.68 (2H, d, $^3J_{HH}$ = 7.2 Hz, Ar*H*), 7.74 (2H, d, $^3J_{HH}$ = 7.8 Hz, Ar*H*); ^{13}C{^{1}H} NMR (100 MHz; $CDCl_3$) δ_C 89.5 (q, $^2J_{CF}$ = 32.3 Hz, C-CF_3), 98.0 (CH), 119.17 (CH), 118.6 (C), 122.5 (CH), 125.1 (CH), 125.2 (CH), 127.1 (CH), 127.4 (CH), 127.6 (CH), 128.1 (q, $^1J_{CF}$ = 282.3 Hz, CF_3), 128.3 (CH), 129.1 (CH) 130.9 (CH), 134.0 (C), 134.2 (C), 136.1 (C), 152.0 (CO). ^{19}F NMR (376 MHz; $CDCl_3$) δ_F -77.8 (s, CF_3). m/z (ASAP): 353.1143 ($[MH]^+$, $C_{22}H_{16}F_3O$ requires 353.1153, 99 %).



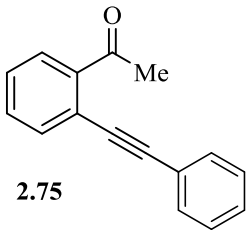
2.74

The crude product (2.4 g) was purified by column chromatography using ethyl acetate: petroleum ether 40-60 (1: 20) to give pure (3E)-1-(p-tolyl)methylene)-3-phenyl-3-(trifluoromethyl)-1,3- dihydroisobenzofuran **(2.74)** as a yellow oil (0.801 g, 59 %). ^{1}H NMR (400 MHz; $CDCl_3$) δ_H 6.06 (1H, s, C*H*), 7.21 (2H, t, $^{3}J_{HH}$ = 7.8 Hz, Ar*H*), 7.39 (5H, m, Ar*H*), 7.57 (1H, d, $^{3}J_{HH}$ = 7.8 Hz, Ar*H*), 7.66 (1H, d, $^{3}J_{HH}$ = 7.5 Hz, Ar*H*), 7.72 (2H, d, $^{3}J_{HH}$ = 8.1 Hz, Ar*H*), 7.76 (2H, d, $^{3}J_{HH}$ = 7.2 Hz, Ar*H*); ^{13}C{^{1}H} NMR (100 MHz; $CDCl_3$) δ_C 21.3 (CH_3), 90.1 (q, $^{2}J_{CF}$ = 32.3 Hz, C-CF_3), 99.0 (CH), 120.0 (CH), 123.6 (C), 125.3 (q, $^{1}J_{CF}$ = 282.3 Hz, CF_3), 126.1 (CH), 128.4 (CH), 128.6 (CH),129.0 (CH), 129.1 (CH), 129.3 (CH), 130.1 (CH), 132.4 (CH), 135.2 (C), 135.4 (C), 136.2 (C), 137.1 (C), 152.4 (CO). ^{19}F NMR (376 MHz; $CDCl_3$) δ_F -76.9 (s, CF_3). m/z (ASAP): 367.1315 ($[MH]^+$, $C_{23}H_{16}F_3O$ requires 367.1310, 100 %).

6.2.22 General Procedure for the Reaction in Scheme 2.26

2-Iodoacetophenone (3.64 g, 14.8 mmol), phenylacetylene (1.96 ml, 17.8 mmol) or 1-ethylnyl-4-methylbenzene (2.26 ml, 17.8 mmol), $[Pd(PPh_3)_2Cl_2]$ (0.12 g, 0.17 mmol), CuI (0.059 g, 0.3 mmol) and dry Et_3N (80 ml) were charged into a dry three–necked flask. After stirring under nitrogen at 70 °C overnight, the reaction mixture was allowed to cool to room temperature and H_2O (30 ml) and Et_2O (30 ml) were added. The precipitate was filtered off, and the solution was extracted with Et_2O (3 x 20 ml). The combined organic layers were dried over $MgSO_4$ (anhydrous), and the solvent was removed *in vacuo* to give the crude product.

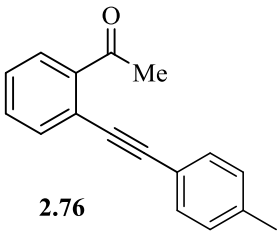
6.2.23 Characterisation Data for Products in Scheme 2.26 [11,12]



2.75

The crude product (3.11 g) was purified by column chromatography using diethyl ether/petroleum ether (1:9) to give the pure product 1-(2-(phenylethynyl)phenyl)ethan-1-one **(2.75)** as a yellow oil (2.5 g, 76%). The characterisation data was in agreement with the literature. ^{1}H NMR (400 MHz; $CDCl_3$) δ_H 2.79 (3H, s, CH_3), 7.31 (1H, m, Ar*H*), 7.51 (4H, m, Ar*H*), 7.42 (2H, td, $^{3}J_{HH}$ = 7.7 Hz, $^{4}J_{HH}$ = 1.4 Hz, Ar*H*), 7.66 (1H, dd, $^{3}J_{HH}$ = 7.7 Hz, $^{4}J_{HH}$ = 1.1 Hz, Ar*H*), 7.73 (1H, dd, $^{3}J_{HH}$ = 7.8

Hz, $^{4}J_{HH}$ = 1.2 Hz, Ar*H*); $^{13}C\{^{1}H\}$ NMR (100 MHz; $CDCl_3$) δ_C 29.9 (CH_3), 88.5 (C), 95.0 (C),121.7 (C), 122.9 (C), 128.2 (CH), 128.0 (CH), 128.7 (CH), 131.3 (CH), 131.5 (CH), 132.5 (CH), 133.9 (CH), 140.8 (C), 200.3 (CO). m/z (ASAP): 221.0965 ($[MH]^+$, $C_{16}H_{13}O$ requires 221.0966, 100 %).



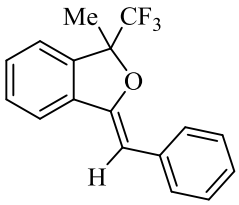
2.76

The crude product (3.11 g) was purified by column chromatography using diethyl ether/petroleum ether (1:9) to give the pure product of 2-(p-tolylethynyl)acetophenone **(2.76)** as a yellow oil (3.01 g, 88 %). The characterisation data was in agreement with the literature. ^{1}H NMR (400 MHz; $CDCl_3$) δ_H 2.33 (3H, s, C*H*$_3$), 2.74 (3H, s, C*H*$_3$), 7.13 (2H, td, $^{3}J_{HH}$ = 7.9 Hz, $^{4}J_{HH}$ = 1.3 Hz, Ar*H*), 7.33 (4H, m, Ar*H*), 7.53 (1H, dd, $^{3}J_{HH}$ = 7.6 Hz, $^{4}J_{HH}$ = 1.3 Hz, Ar*H*), 7.72 (1H, dd, $^{3}J_{HH}$ = 7.9 Hz, $^{4}J_{HH}$ = 1.4 Hz Ar*H*); $^{13}C\{^{1}H\}$ NMR (100 MHz; $CDCl_3$) δ_C 21.5 (CH_3), 29.9 (CH_3), 87.9 (C), 95.3 (C), 119.8 (C), 121.9 (C), 129.6 (CH), 129.2 (CH), 129.4 (CH), 131.4 (CH), 132.3 (CH), 133.7 (CH), 138.9 (C), 140.6 (C), 200.1 (CO). m/z (ASAP): 235.1123 ($[MH]^+$, $C_{17}H_{15}O$ requires 235.1123, 100 %).

6.2.24 General Procedure for the Reaction in Scheme 2.26

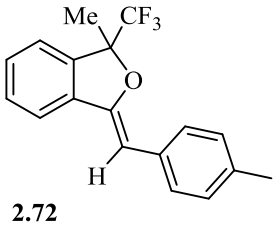
TBAF (50 mg, 0.2 mmol) was added drop wise to a solution of $TMSCF_3$ (1.5 g, 11.09 mmol) and 2-(phenylethynyl)acetophenone (1.0 g, 4.5 mmol) or 2-(*p*-tolylethynyl) acetophenone (1.0 g, 4.25 mmol) in dry THF (10 ml) at 0°C under nitrogen, and the mixture stirred for 20 minutes. After being allowed to warm to room temperature, the reaction mixture was stirred for a further 3 hours before it was hydrolysed with H_2O (15 ml) and then extracted with diethyl ether (3 x 20 ml). The combined organic layers were washed with water (2 x 50 ml) and brine (50 ml), were dried over $MgSO_4$ (anhydrous) and the solvent removed *in vacuo* to give the intermediate as a brown oil (1.29 g). This product was dissolved in THF: HCl 2 M (1:1) (100 ml) and stirred overnight. The mixture was extracted with Et_2O (2 x 30 mL), the combined organic layers dried, and the solvent removed *in vacuo* to give the crude product.

6.2.25 Characterisation Data for Products in Scheme 2.26



2.71

The crude product (1.31 g) was purified by column chromatography ethyl acetate/petroleum ether (1:29) to give the pure product of 1-(phenylmethylidene)-3-(trifluoromethyl)-1,3-dihydroisobenzofuran **(2.71)** as a yellow oil (1.03 g, 76%). ^{1}H NMR (400 MHz; $CDCl_3$) δ_H 1.83 (3H, s, C*H*$_3$), 6.01(1H, s, C*H*), 7.19 (1H, td, $^{3}J_{HH}$ = 7.4 Hz, $^{4}J_{HH}$ = 1.1, Hz, Ar*H*), 7.36 (4H, m, Ar*H*), 7.47 (1H, m, Ar*H*), 7.57 (1H, td, $^{3}J_{HH}$ = 7.7 Hz, $^{4}J_{HH}$ = 1.0 Hz, Ar*H*), 7.73 (2H, dd, $^{3}J_{HH}$ = 7.9 Hz, $^{4}J_{HH}$ = 1.3 Hz, Ar*H*); ^{13}C{^{1}H} NMR (100 MHz; $CDCl_3$) δ_C 20.5 (CH_3), 87.7 (q, $^{2}J_{CF}$ = 32.3 Hz, C-CF_3), 98.6 (CH), 120.0 (CH), 122.3 (CH), 126.2 (C), 128.4 (q, $^{1}J_{CF}$ = 282.3 Hz, CF_3), 129.0 (CH), 129.2 (CH), 129.7 (CH), 129.9 (CH), 130.3 (CH) 135.4 (C), 137.9 (C), 153.2 (CO). ^{19}F NMR (376 MHz; $CDCl_3$) δ_F -79.9 (s, CF_3). m/z (ASAP): 291.1009 ($[MH]^+$, $C_{17}H_{14}F_3O$ requires 291.0997, 100 %).



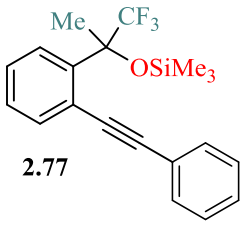
2.72

The crude product (1.31 g) was purified by column chromatography ethyl acetate/petroleum ether (1:29) to give the pure product of 1-(p-tolylmethylidene)-3-(trifluoromethyl)-1,3-dihydroisobenzofuran **(2.72)** as a yellow oil (0.87 g, 82%). ^{1}H NMR (400 MHz; $CDCl_3$) δ_H 1.75 (3H, s, C*H*$_3$), 2.27 (3H, s, C*H*$_3$), 5.90 (1H, s, C*H*), 7.09 (2H, d, $^{3}J_{HH}$ = 7.9 Hz, Ar*H*), 7.30 (2H, m, Ar*H*), 7.37 (1H, m, Ar*H*), 7.48 (1H, td, $^{3}J_{HH}$ = 7.7 Hz, $^{4}J_{HH}$ = 1.0 Hz, Ar*H*), 7.55 (2H, d, $^{3}J_{HH}$ =7.5 Hz, Ar*H*); ^{13}C{^{1}H} NMR (100 MHz; $CDCl_3$) δ_C 20.6 (CH_3), 21.2 (CH_3), 87.5 (q, $^{2}J_{CF}$ = 32.2 Hz, C-CF_3), 98.5 (CH), 119.8 (CH), 122.3 (CH), 125.7 (C), 128.3 (CH), 128.5 (q, $^{1}J_{CF}$ = 282.2 Hz, CF_3), 128.9 (CH), 129.1 (CH), 129.9 (CH), 132.4 (C), 135.8 (C), 137.8 (C), 152.6 (CO). ^{19}F NMR (376 MHz; $CDCl_3$) δ_F -79.2 (s, CF_3). m/z (ASAP): 305.1161 ($[MH]^+$, $C_{18}H_{16}F_3O$ requires 305.1153, 99 %).

6.2.26 General Procedure for the Reaction in Scheme 2.28

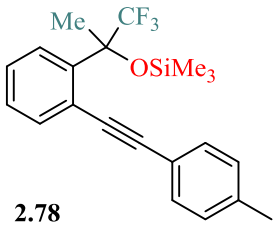
1,1,1-Trifluoro-2-(2-iodophenyl)-2-trimethylsiloxypropane (0.95 g, 2.46 mmol), arylacetylene (2.96 mmol) or (3.33 mmol), [$Pd(PPh_3)_2Cl_2$] (0.12 g, 0.17 mmol), CuI (0.059 g, 0.3 mmol) and dry Et_3N (15 ml) were charged into a dry three–necked flask. After stirring at 70 °C under nitrogen for 3 h. The reaction mixture was cooled to room temperature, then H_2O (10 ml) and Et_2O (10 ml) were added. The precipitate was filtered off and the solution was extracted with Et_2O (3 x 10 ml). The combined organic layers were dried over $MgSO_4$ (anhydrous) and the solvent was removed *in vacuo* to give a crude intermediate (0.79 g).

6.2.27 Characterisation Data for Products in Scheme 2.28



2.77

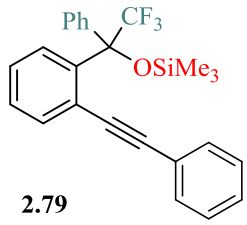
The crude product was purified by column chromatography using ethyl acetate/petroleum ether 40-60 (1:9) to give the pure product of trimethyl(1,1,1-trifluoro-2-(2-(phenylethynyl)phenyl)propan-2-yl)oxy)silane **(2.77)** as a brown oil (0.19 g, 66 %). ^{1}H NMR (400 MHz; $CDCl_3$) δ_H 0.21 (9H, s, $OSiMe_3$), 2.06 (3H, s, C*H*$_3$), 7.24 (5H, m, Hz, Ar*H*), 7.35 (2H, m, Ar*H*), 7.40 (1H, dd, $^3J_{HH}$ = 6.9 Hz, $^4J_{HH}$ = 1.8 Hz, Ar*H*), 7.61 (1H, dd, $^3J_{HH}$ = 6.8 Hz, $^4J_{HH}$ = 1.7 Hz, Ar*H*); ^{13}C{^{1}H} NMR (100 MHz; $CDCl_3$) δ_C 0.1 ($OSiMe_3$), 21.1 (CH_3), 76.4 (q, $^2J_{CF}$ = 32.3 Hz, C-CF_3), 88.1 (C), 92.0 (C), 118.5 (C), 120.0 (C), 125.6 (q, $^1J_{CF}$ = 282.3 Hz, CF_3), 126.3 (CH), 126.4 (CH), 126.5 (CH), 127.6 (CH), 129.1 (CH), 132.6 (CH), 133.3 (CH), 138.5(C).^{19}F NMR (376 MHz; $CDCl_3$) δ_F -79.8 (s, CF_3). m/z (ASAP): 363.1387 ([MH]$^+$, $C_{20}H_{22}F_3OSi$ requires 363.1392, 100 %).



2.78

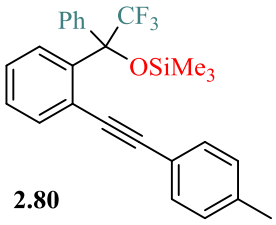
The crude product was purified by column chromatography using ethyl acetate/petroleum ether 40-60 (1:9) to give the pure product of trimethyl(1,1,1-trifluoro-2-(2-(p-tolylethynyl)phenyl)propan-2-yl)oxy)silane **(2.78)** as an orange oil (0.31 g, 61 %). ^{1}H NMR (400 MHz; $CDCl_3$) δ_H 0.22 (9H, s, $OSiMe_3$), 2.09 (3H, s, C*H*$_3$), 2.33 (3H, s, C*H*$_3$), 7.09 (2H, d, $^3J_{HH}$ = 7.9 Hz, Ar*H*), 7.23 (2H, m, Ar*H*), 7.37 (2H, d, $^3J_{HH}$ = 7.9 Hz, Ar*H*), 7.45 (1H, t, $^3J_{HH}$ = 6.9 Hz, Ar*H*), 7.50 (1H , m, Ar*H*); ^{13}C{^{1}H} NMR (100 MHz; $CDCl_3$) δ_C 0.2 ($OSiMe_3$), 19.5 (CH_3), 21.1 (CH_3), 76.4 (q, $^2J_{CF}$ = 32.3 Hz, C-CF_3), 87.4 (C), 92.2 (C), 118.5 (C), 120.2 (C), 123.0 (q, $^1J_{CF}$ = 282 Hz, CF_3), 125.8 (C), 126.2 (CH), 127.4 (CH), 129.5 (CH), 130.4 (CH), 132.3

(CH), 133.2 (CH), 136.5 (C), 138.4 (C). ^{19}F NMR (376 MHz; $CDCl_3$) δ_F -79.3 (s, CF_3). m/z (ASAP): 377.1540 ($[MH]^+$, $C_{21}H_{24}F_3OSi$ requires 377.1549, 99 %).



2.79

The crude product was purified by column chromatography using ethyl acetate/petroleum ether 40-60 (1:9) to give the pure product of trimethyl(2,2,2-trifluoro-1-phenyl-1-(2-(phenylethynyl)phenyl)ethoxy)silane **(2.79)** as an orange oil (0.28 g, 68 %). ^{1}H NMR (400 MHz; $CDCl_3$) δ_H 0.25 (9H, s, $OSiMe_3$), 7.02 (2H, s, Ar*H*), 7.19 (4H, m, Ar*H*), 7.29 (3H, m, Ar*H*), 7.49 (2H, td, $^3J_{HH}$ = 6.8 Hz, $^4J_{HH}$ = 1.5 Hz, Ar*H*), 7.57 (2H, m, Ar*H*), 7.85 (1H, td, $^3J_{HH}$ = 7.3 Hz, $^4J_{HH}$ = 1.9 Hz, Ar*H*); ^{13}C{^{1}H} NMR (100 MHz; $CDCl_3$) δ_C 0.3 ($OSiMe_3$), 81.4 (q, $^2J_{CF}$ = 32.3 Hz, C-CF_3), 87.5 (C) , 94.4 (C), 123.0 (q, $^1J_{CF}$ = 282.3 Hz, CF_3), 125.4 (CH), 126.2 (CH), 126.3 (CH), 126.8 (CH), 127.2 (CH), 127.3 (CH), 128.1 (CH), 128.2 (CH), 130.2 (CH), 134.3 (CH), 137.6 (C), 139.2 (C), 139.9 (C), 140.2 (C).^{19}F NMR (376 MHz; $CDCl_3$) δ_F -69.7 (s, CF_3). m/z (ASAP): 425.1557 ($[MH]^+$, $C_{25}H_{24}F_3OSi$ requires 425.1549, 100 %).



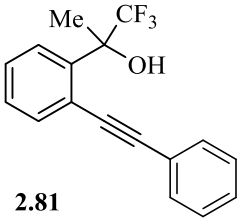
2.80

The crude product was purified by column chromatography using ethyl acetate/petroleum ether 40-60 (1:9) to give the pure product of trimethyl(2,2,2-trifluoro-1-phenyl-1-(2-(p-tolylethynyl)phenyl)ethoxy)silane **(2.80)** as an orange oil (0.196 g, 64%). ^{1}H NMR (400 MHz; $CDCl_3$) δ_H 0.26 (9H, s, $OSiMe_3$), 2.29 (1H, s, C*H*$_3$), 6.94 (1H, td, $^3J_{HH}$ = 7.5 Hz, $^4J_{HH}$ = 1.3 Hz, Ar*H*), 7.06 (2H, dd, $^3J_{HH}$ = 7.8 Hz, $^4J_{HH}$ = 1.0 Hz Ar*H*), 7.29 (8H, m, Ar*H*), 7.68 (1H, td, $^3J_{HH}$ = 7.8 Hz, $^4J_{HH}$ = 1.8 Hz, Ar*H*), 7.91 (1H, dd, $^3J_{HH}$ = 7.9 Hz, $^4J_{HH}$ = 1.2 Hz, Ar*H*); ^{13}C{^{1}H} NMR (100 MHz; $CDCl_3$) δ_C 0.2 ($OSiMe_3$), 20.2 (CH_3), 81.1 (q, $^2J_{CF}$ = 32.3 Hz, C-CF_3), 82.5 (C), 96.4 (C), 117.8 (C), 125.0 (q, $^1J_{CF}$ = 282.3 Hz, CF_3), 126.0 (CH), 126.1 (CH), 126.5 (CH), 126.9 (CH), 127.0 (CH), 127.3 (CH), 127.4 (CH), 127.8 (CH), 128.2 (CH), 137.6 (C), 137.8 (C), 139.1 (C), 139.6 (C), 142.6 (C).^{19}F NMR (376 MHz; $CDCl_3$) δ_F -69.9 (s, CF_3). m/z (ASAP): 438.5712 ($[MH]^+$, $C_{26}H_{26}F_3OSi$ requires 438.5725, 100 %).

6.2.28 General Procedure for the Reaction in Scheme 2.29

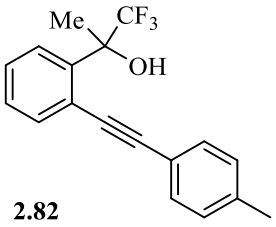
The products above were washed with THF: HCl 0.5 M (1:1) (80 mL) and stirred at room temperature for 48 h. The mixture was extracted with Et_2O (2 x 30 mL), the combined organic layers dried, and the solvent removed *in vacuo* to give the crude product.

6.2.29 Characterisation Data for Products in Scheme 2.29



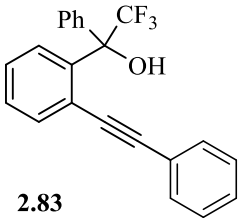
2.81

The crude product was purified by column chromatography using DCM: petroleum ether 40-60 (1:2) to give the pure product of 1,1,1-trifluoro-[2-(2-phenylethynyl)phenyl]propan-2-ol **(2.81)** as an orange oil (0.19 g, 46 %). ^{1}H NMR (400 MHz; $CDCl_3$) δ_H 1.82 (3H, s, C*H*$_3$), 5.12 (1H, s, O*H*), 7.27 (5H, m, Hz, Ar*H*), 7.44 (3H, m, Ar*H*), 7.53 (1H, m, Ar*H*); ^{13}C{^{1}H} NMR (100 MHz; $CDCl_3$) δ_C 21.7 (CH_3), 78.0 (q, $^2J_{CF}$ = 32.3 Hz, C-CF_3), 86.4 (C), 95.1 (C), 119.5 (C), 125.6 (q, $^1J_{CF}$ = 282.3 Hz, CF_3), 127.3 (CH), 127.4 (CH), 127.5 (CH), 127.6 (CH), 128.1 (CH), 130.4 (CH), 133.7 (CH), 138.8 (C), 142.8 (C). ^{19}F NMR (376 MHz; $CDCl_3$) δ_F -80.2 (s, CF_3). m/z (ASAP): 291.0995 ([MH]$^+$, $C_{17}H_{14}OF_3$ requires 291.0997, 100 %).



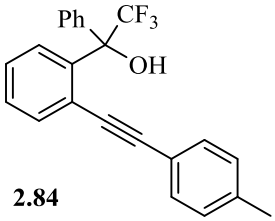
2.82

The crude product was purified by column chromatography using DCM:petroleum ether 40-60 (1:2) to give the pure product of 1,1,1-trifluoro-[2-(2-p-tolylethynyl)phenyl]propan-2-ol **(2.82)** as a yellow oil (0.31 g, 51 %). ^{1}H NMR (400 MHz; $CDCl_3$) δ_H 1.81 (3H, s, C*H*$_3$), 2.32 (3H, s, C*H*$_3$), 5.23 (1H, s, O*H*), 7.09 (2H, d, $^3J_{HH}$ = 7.9 Hz, Ar*H*), 7.21 (2H, m, Ar*H*), 7.34 (2H, d, $^3J_{HH}$ = 7.9 Hz, Ar*H*), 7.43 (1H, t, $^3J_{HH}$ = 6.9 Hz, Ar*H*), 7.52 (1H , m, Ar*H*); ^{13}C{^{1}H} NMR (100 MHz; $CDCl_3$) δ_C 20.5 (CH_3), 22.7 (CH_3), 76.3 (q, $^2J_{CF}$ = 32.3 Hz, C-CF_3), 85.7 (C), 95.5 (C), 117.8 (C), 119.7 (C), 123.5 (q, $^1J_{CF}$ = 282 Hz, CF_3), 126.3 (C), 127.2 (CH), 127.4 (CH), 128.3 (CH), 129.2 (CH), 130.3 (CH), 133.7 (CH), 138.2 (C), 138.4 (C). ^{19}F NMR (376 MHz; $CDCl_3$) δ_F -80.3 (s, CF_3). m/z (ASAP): 305.1164 ([MH]$^+$, $C_{18}H_{16}OF_3$ requires 305.1153, 99 %).



2.83

The crude product was purified by column chromatography using DCM: petroleum ether 40-60 (1: 9) to give the pure product of 2,2,2-trifluoro-1-phenyl -[1-(2- phenylethynyl)phenyl]ethanol **(2.83)** as a yellow oil (0.28 g, 48 %). ^{1}H NMR (400 MHz; $CDCl_3$) δ_H 5.03 (1H, s, O*H*), 7.01 (2H, s, Ar*H*), 7.18 (2H, m, Ar*H*), 7.28 (6H, m, Ar*H*), 7.47 (2H, td, $^{3}J_{HH}$ = 6.8 Hz, $^{4}J_{HH}$ = 1.5 Hz, Ar*H*), 7.56 (1H, m, Ar*H*), 7.83 (1H, td, $^{3}J_{HH}$ = 7.3 Hz, $^{4}J_{HH}$ = 1.9 Hz, Ar*H*); ^{13}C{^{1}H} NMR (100 MHz; $CDCl_3$) δ_C 81.1 (q, $^{2}J_{CF}$ = 32.3 Hz, C-CF_3), 87.5 (C) , 94.4 (C), 123.8 (q, $^{1}J_{CF}$ = 282.3 Hz, CF_3), 124.4 (CH), 126.2 (CH), 126.3 (CH), 126.8 (CH), 127.2 (CH), 127.3 (CH), 128.1 (CH), 128.2 (CH), 130.2 (CH), 134.3 (CH), 134.7 (C), 139.2 (C), 139.9 (C), 150.4 (C).^{19}F NMR (376 MHz; $CDCl_3$) δ_F -70.5 (s, CF_3). m/z (ASAP): 335.1045 ([MH-OH_2]$^{+}$, $C_{22}H_{14}F_3$ requires 335.1048, 100 %).



2.84

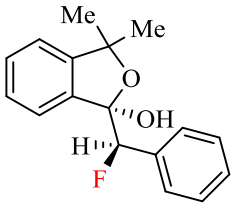
The crude product was purified by column chromatography using DCM: petroleum ether 40-60 (1: 9) to give the pure product of 2,2,2-trifluoro-1- phenyl -[1-(2-p-tolylethynyl)phenyl] ethanol **(2.84)** as a yellow oil (0.196 g, 58%). ^{1}H NMR (400 MHz; $CDCl_3$) δ_H 2.29 (1H, s, C*H*$_3$), 5.16 (1H, s, O*H*), 6.94 (1H, td, $^{3}J_{HH}$ = 7.5 Hz, $^{4}J_{HH}$ = 1.3 Hz, Ar*H*), 7.06 (2H, dd, $^{3}J_{HH}$ = 7.8 Hz, $^{4}J_{HH}$ = 1.0 Hz Ar*H*), 7.29 (8H, m, Ar*H*), 7.68 (1H, td, $^{3}J_{HH}$ = 7.8 Hz, $^{4}J_{HH}$ = 1.8 Hz, Ar*H*), 7.91 (1H, dd, $^{3}J_{HH}$ = 7.9 Hz, $^{4}J_{HH}$ = 1.2 Hz, Ar*H*); ^{13}C{^{1}H} NMR (100 MHz; $CDCl_3$) δ_C 20.2 (CH_3), 82.1 (q, $^{2}J_{CF}$ = 32.3 Hz, C-CF_3), 96.4 (C), 117.8 (C), 125.0 (q, $^{1}J_{CF}$ = 282.3 Hz, CF_3), 126.0 (CH), 126.1 (CH), 126.5 (CH), 126.9 (CH), 127.0 (CH), 127.3 (CH), 127.4 (CH), 127.8 (CH), 128.2 (CH), 137.6 (C), 137.8 (C), 139.1 (C), 139.6 (C), 142.6 (C).^{19}F NMR (376 MHz; $CDCl_3$) δ_F -70.8 (s, CF_3). m/z (ASAP): 350.1045 ([MH-OH_2]$^{+}$, $C_{23}H_{16}F_3$ requires 350.1048, 100 %).

6.3 Experimental procedures for Chapter 3

6.3.1 General Procedure for the Reaction in Scheme 3.12

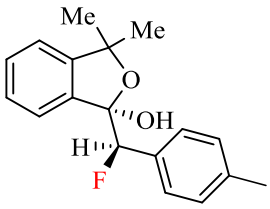
2-(2-(Phenylethynyl)phenyl)propan-2-ol **(2.52)** (0.47 g, 1.0 mmol) or 2-(2-(*p*-tolylethynyl)phenyl)propan-2-ol **(2.53)** (0.52 g, 1.0 mmol) was dissolved in dry DMA (15 mL) and $AgNO_3$ (0.07 g, 0.2 mmol), NFSi (0.96 g, 1.5 mmol), and Li_2CO_3 (0.15 g, 1.0 mmol) were added. The mixture was left to stir at r.t overnight under nitrogen. The reaction mixture was quenched with H_2O (20 mL), then it was extracted with Et_2O (3 x 15 mL). The solvent was removed from the combined organic layers *in vacuo* and a saturated solution of LiCl (15 mL) was added and the mixture was left to stir for 10 min. The mixture was extracted with Et_2O (3 x 15 mL), the combined layers were dried using $MgSO_4$, and the solvent was removed *in vacuo* to give the crude product.

6.3.2 Characterisation Data for Products in Scheme 3.12, and Table 3-2



(3.49a) (3.49b)

This crude product was purified by column chromatography ethyl acetate: petroleum ether 40-60 (1: 9) to give the product, a yellow oil (0.31 g, 54 %) as a 1.2:1 ratio of a mixture of 1-[anti-fluoro(phenyl)methyl]-3,3-dimethyl-1,3-dihydro-2-benzofuran-1-ol and 1-[syn-fluoro(phenyl)methyl]-3,3-dimethyl-1,3-dihydroisobenzofuran-1-ol isomers **(3.49a)** & **(3.49b)**. ^{1}H NMR (400 MHz; $CDCl_3$) δ_H 1.28 (3H, s, C*H*$_3$), 1.29 (3H, s, C*H*$_3$), 1.55 (6H, s, C*H*$_3$), 2.83 (1H, s, OH), 3.19 (1H, s, OH), 5.58 (1H, d, $^{2}J_{HF}$ = 45.3 Hz, C*H*F), 5.69 (1H, d, $^{2}J_{HF}$ = 45.3 Hz, C*H*F), 7.10 (2H, m, Ar*H*), 7.32 (8H, m, Ar*H*), 7.40 (8H, m, Ar*H*), 7.49 (2H, m, Ar*H)*; ^{13}C{^{1}H} NMR (100 MHz; $CDCl_3$) δ_C 28.3 (CH_3), 28.3 (CH_3), 30.9 (CH_3), 31.0 (CH_3), 86.5 (C), 86.6 (C), 94.3 (d, $^{1}J_{CF}$ = 180.9 Hz, CHF), 96.3 (d, $^{1}J_{CF}$ = 180.9 Hz, CHF), 105.5 (d, $^{2}J_{CF}$ = 26.0 Hz, C), 105.9 (d, $^{2}J_{CF}$ = 26.0 Hz, C), 120.5 (CH), 120.6 (CH), 123.1 (CH), 123.5 (CH), 127.1 (C), 127.2 (CH), 127.7 (CH), 127.8 (CH), 127.9 (CH), 128.1 (CH), 128.2(CH), 128.3 (CH), 128.5 (CH), 129.1 (CH), 129.9 (CH), 130.1 (CH), 134.9 (C), 135.1 (C), 136.9 (C), 148.2 (C). ^{19}F NMR (376 MHz; $CDCl_3$) δ_F -182.5 (s, CF), -191.2 (s, CF). m/z (ASAP): 273.1107 ($[MH]^+$, $C_{17}H_{18}FO_2$ requires 273.1291, 99 %).



(3.50a) (3.50b)

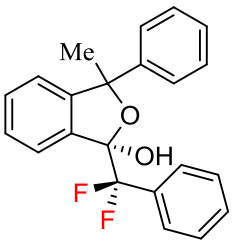
This crude product was purified by column chromatography ethyl acetate: petroleum ether 40-60 (1: 9) to give the product, a yellow oil (0.22 g, 38 %) as a 1.2:1 ratio of a mixture of 1-[anti-fluoro(4-methylphenyl)methyl]-3,3-dimethyl-1,3-dihydro-2-benzofuran-1-ol and 1-[syn-fluoro(4-methylphenyl)methyl]-3,3-dimethyl-1,3-dihydroisobenzofuran-1-ol isomers **(3.50a)** & **(3.50b)**. ^{1}H NMR (400 MHz; $CDCl_3$) δ_H 1.31 (6H, s, C*H*$_3$), 1.54 (6H, s, C*H*$_3$), 2.32 (6H, s, C*H*$_3$), 2.69 (1H, s, OH), 2.84 (1H, s, OH), 5.53 (1H, d, $^{2}J_{HF}$ = 45.9 Hz, C*H*F), 5.65 (1H, d, $^{2}J_{HF}$ = 45.3 Hz, C*H*F), 7.10 (6H, m, Ar*H*), 7.32 (2H, m, Ar*H*), 7.36 (4H, m, Ar*H*), 7.40 (3H, m, Ar*H*), 7.49 (1H, dd, $^{3}J_{HH}$ = 7.0 Hz, $^{4}J_{HH}$ = 1.9 Hz, Ar*H*); ^{13}C{^{1}H} NMR (100 MHz; $CDCl_3$) δ_C 21.3 (CH_3), 21.4 (CH_3), 28.3 (CH_3), 28.4 (CH_3), 31.0 (CH_3), 86.5 (C), 86.6 (C), 94.2 (d, $^{1}J_{CF}$ = 179.9 Hz, CHF), 96.1 (d, $^{1}J_{CF}$ = 179.9 Hz, CHF), 105.6 (d, $^{2}J_{CF}$ = 26.0 Hz, C), 105.9 (d, $^{2}J_{CF}$ = 26.0 Hz, C), 120.5 (CH), 120.6 (CH), 123.1 (CH), 123.5 (CH), 127.1 (CH), 127.2 (CH), 127.7 (CH), 127.8 (CH), 127.9 (CH), 128.2 (CH), 128.1(CH), 128.3 (CH), 129.1 (CH), 131.8 (d, $^{3}J_{CF}$ = 3.2 Hz, C), 132.0 (d, $^{3}J_{CF}$ = 3.2 Hz, C),137.3 (C), 137.7 (C), 138.3 (C), 138.8 (C), 148.2 (C), 148.3 (C). ^{19}F NMR (376 MHz; $CDCl_3$) δ_F -181.4 (s, CF), -191.3 (s, CF). m/z (ASAP): 269.1351 ([MH-OH_2]$^{+}$, $C_{17}H_{19}FO$ requires 269.1342, 100 %).

6.3.3 General Procedure for the Reaction in Scheme 3.16

1-Phenyl-[1-(2-phenylethynyl)phenyl]ethanol **(2.37)** (0.30 g, 1.0 mmol) or 1-phenyl-[1-(2-p-tolylethynyl)phenyl] ethanol **(2.38)** (0.31 g, 1.0 mmol) was dissolved in dry DMA (8 mL) and $AgNO_3$ (0.035 g, 0.2 mmol), NFSi (0.94 g, 3.0 mmol), and Li_2CO_3 (0.075 g, 1.0 mmol) were added. The mixture was left to stir at 50 ^{o}C 24h under nitrogen. The solvent was removed *in vacuo* under high pressure and high temperature to give the crude product.

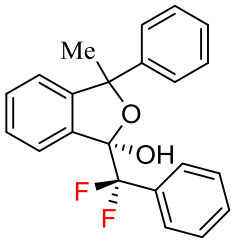
6.3.4 Characterisation Data for Products in Scheme 3.16, and Table 3-5

This crude product was purified by column chromatography ethyl acetate: petroleum ether 40-60 (1: 9) to give the product as a yellow oil (0.176 g, 50 %) in a 2:1 ratio of a mixture of 1-[difluoro(phenyl)methyl]-3-methyl,3-phenyl-1,3-dihydroisobenzofuran-1-



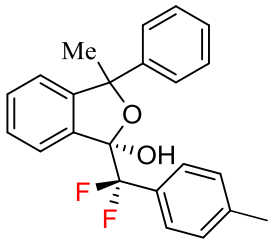
(3.58a) (3.58b)

ol isomers **(3.58a)** & **(3.58b)**. ^{1}H NMR (400 MHz; $CDCl_3$) δ_H 1.58 (3H, s, C*H*$_3$), 1.81 (3H, s, C*H*$_3$), 3.17 (1H, s, OH), 3.29 (1H, s, OH), 7.05 (1H, m, Ar*H*), 7.08 (1H, td, $^{3}J_{HH}$ = 7.3 Hz, $^{4}J_{HH}$ = 1.3 Hz, Ar*H*), 7.15 (5H, m, Ar*H*), 7.28 (9H, m, Ar*H*), 7.38 (2H, td, $^{3}J_{HH}$ = 7.0 Hz, $^{4}J_{HH}$ = 1.3 Hz, Ar*H*), 7.50 (2H, d, $^{3}J_{HH}$ = 7.2 Hz, Ar*H*), 7.54 (1H, d, $^{3}J_{HH}$ = 7.2 Hz, Ar*H*), 7.58 (1H, td, $^{3}J_{HH}$ = 7.1 Hz, Ar*H*); ^{13}C{^{1}H} NMR (100 MHz; $CDCl_3$) δ_C 27.5 (CH_3), 30.7 (CH_3), 90.4 (C), 90.5 (C), 106.0 (t, $^{2}J_{CF}$ = 33.6 Hz, COH), 119.8 (t, $^{1}J_{CF}$ = 247.1 Hz, CF_2), 121.7 (CH), 122.1 (CH), 122.3 (CH), 124.5 (CH), 125.1 (CH), 125.4 (CH), 126.0 (CH), 126.3 (CH), 127.6 (t, $^{3}J_{CF}$ = 6.5 Hz, CH), 127.9 (CH), 128.1 (CH), 128.3 (CH), 128.4 (CH), 130.1 (CH), 130.2 (CH), 130.3 (CH), 130.6 (CH), 133.5 (t, $^{2}J_{CF}$ = 26.5 Hz, C), 134.9 (C), 136.1 (C), 143.3 (C) 145.2 (C), 147.2 (C), 147.8 (C). ^{19}F NMR (376 MHz; $CDCl_3$) δ_F -103.5 (1F, d, $^{2}J_{FF}$ = 251.3 Hz, CF_AF_B), -104.2 (1F, d, $^{2}J_{FF}$ = 251.5 Hz, CF_AF_B), -111.5 (1F, d, $^{2}J_{FF}$ = 251.5 Hz, CF_AF_B), -112.8 (1F, d, $^{2}J_{FF}$ = 251.4 Hz, CF_AF_B). m/z (ASAP): 335.1248 ([MH-OH_2]$^+$, $C_{22}H_{18}F_2O$ requires 335.1247, 99 %).



(3.58a)

This crude product was purified by column chromatography ethyl acetate: petroleum ether 40-60 (1: 9) to give the product 1-[difluoro(phenyl)methyl]-3-methyl,3-phenyl-1,3-dihydroisobenzofuran-1-ol **(3.58a)** as a white solid (0.089 g, 39%). Crystals suitable for a single crystal X-ray diffraction study were grown from a dichloromethane solution of the complex layered with chloroform. Mp: (135-137 ◦C) ^{1}H NMR (400 MHz; $CDCl_3$) δ_H 1.68 (3H, s, C*H*$_3$), 3.28 (1H, s, OH), 7.15 (1H, m, Ar*H*), 7.20 (1H, td, $^{3}J_{HH}$ = 7.2 Hz, $^{4}J_{HH}$ = 1.2 Hz, Ar*H*), 7.27 (3H, s, Ar*H*), 7.40 (5H, m, Ar*H*), 7.48 (2H, dd, $^{3}J_{HH}$ = 7.9 Hz, $^{4}J_{HH}$ = 1.5 Hz, Ar*H*), 7.47 (2H, d, $^{3}J_{HH}$ = 7.2 Hz, Ar*H*), 7.59 (1H, d, $^{3}J_{HH}$ = 7.0 Hz, Ar*H*); ^{13}C{^{1}H} NMR (100 MHz; $CDCl_3$) δ_C 30.7 (CH_3), 90.5 (C), 106.0 (t, $^{2}J_{CF}$ = 33.6 Hz, COH), 119.8 (t, $^{1}J_{CF}$ = 247.1 Hz, CF_2), 122.1 (CH), 124.5 (CH), 125.4 (CH), 126.3 (CH), 127.6 (t, $^{3}J_{CF}$ = 6.5 Hz, CH), 128.1 (CH), 128.4 (CH), 130.2(CH), 130.6 (CH), 133.5 (t, $^{2}J_{CF}$ = 26.5 Hz, C), 136.1 (C), 145.2 (C), 147.8 (C). ^{19}F NMR (376 MHz; $CDCl_3$) δ_F -103.7 (1F, d, $^{2}J_{FF}$ = 251.3 Hz, CF_AF_B), -112.4 (1F, d, $^{2}J_{FF}$ = 251.4 Hz, CF_AF_B). m/z (ASAP): 335.1248 ([MH-OH_2]$^+$, $C_{22}H_{18}F_2O$ requires 335.1247, 99 %).



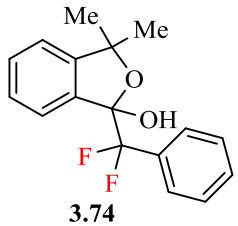
(3.60a) (3.60b)

This crude product was purified by column chromatography ethyl acetate: petroleum ether 40-60 (1: 9) to give the product, a yellow oil (0.168 g, 47%) as 2:1 a ratio of a mixture of 1-[difluoro(4-methylphenyl)methyl]-3-methyl,3-phenyl-1,3-dihydroisobenzofuran-1-ol isomers **(3.60b)** & **(3.60a)**. ^{1}H NMR (400 MHz; $CDCl_3$) δ_H 1.62 (3H, s, C*H*$_3$), 1.82 (3H, s, C*H*$_3$), 2.22 (3H, s, C*H*$_3$), 2.27 (3H, s, C*H*$_3$), 3.19 (1H, s, OH), 3.23 (1H, s, OH), 6.96 (1H, d, $^{3}J_{HH}$ = 7.3 Hz, Ar*H*), 7.05 (1H, d, $^{3}J_{HH}$ = 7.2 Hz, Ar*H*), 7.11 (3H, m, Ar*H*), 7.18 (5H, m, Ar*H*), 7.22 (1H, d, $^{3}J_{HH}$ = 7.8 Hz, Ar*H*), 7.29 (2H, td, $^{3}J_{HH}$ = 7.1 Hz, $^{4}J_{HH}$ = 1.2 Hz, Ar*H*), 7.33 (1H, td, $^{3}J_{HH}$ = 7.2 Hz, $^{4}J_{HH}$ = 1.1 Hz, Ar*H*), 7.40 (5H, d, $^{3}J_{HH}$ = 7.9 Hz, Ar*H*), 7.55 (1H, d, $^{3}J_{HH}$ = 7.1 Hz, Ar*H*), 7.60 (1H, d, $^{3}J_{HH}$ = 7.2 Hz, Ar*H*); ^{13}C{^{1}H} NMR (100 MHz; $CDCl_3$) δ_C 21.3 (CH_3), 27.5 (CH_3), 29.5 (CH_3), 30.7 (CH_3), 87.8 (C), 87.9 (C), 90.3 (C), 90.4 (C), 106.0 (t, $^{2}J_{CF}$ = 33.6 Hz, COH), 119.8 (t, $^{1}J_{CF}$ = 247.1 Hz, CF_2), 121.7 (CH), 122.1 (CH), 122.3 (C), 124.5 (C), 125.1 (CH), 125.4 (CH), 126.0 (C), 126.3 (C), 126.5 (CH), 126.6 (CH), 127.6 (t, $^{3}J_{CF}$= 6.5 Hz, CH), 127.9 (CH), 128.1 (CH), 128.3 (CH), 128.4 (CH), 130.1 (CH), 130.2 (CH), 130.3 (CH), 130.6 (CH), 133.5 (t, $^{2}J_{CF}$ = 26.5 Hz, C), 134.9 (C), 136.1 (C), 143.3 (C) 145.2 (C), 147.23 (C), 147.8 (C). ^{19}F NMR (376 MHz; $CDCl_3$) δ_F -103.3 (1F, d, $^{2}J_{FF}$ = 251.3 Hz, CF_AF_B), -103.2 (1F, d, $^{2}J_{FF}$ = 251.5 Hz, CF_AF_B), -111.7 (1F, d, $^{2}J_{FF}$ = 251.5 Hz, CF_AF_B), -112.7 (1F, d, $^{2}J_{FF}$ = 251.4 Hz, CF_AF_B). m/z (ASAP): 349.1414 ($[MH\text{-}OH_2]^+$, $C_{23}H_{20}F_2O$ requires 349.1404, 99 %).

6.3.5 General Procedure for the Reaction in Scheme 3.18

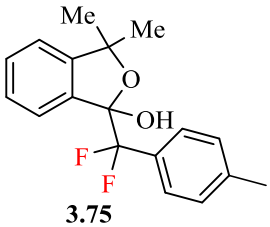
2-(2-(Phenylethynyl)phenyl)propan-2-ol **(2.52)** (0.23 g, 1.0 mmol) or 2-(2-(*p*-tolylethynyl)phenyl) propan-2-ol **(2.53)** (0.26 g, 1.0 mmol), 2-(2-(phenylethynyl)phenyl)propan-2-ol **(2.54)** (0.264 g, 1.0 mmol) was dissolved in dry DMA (8 mL) and $AgNO_3$ (0.035 g, 0.2 mmol), NFSi (0.96 g, 3.0 mmol), and Li_2CO_3 (0.075 g, 1.0 mmol) were added. The mixture was left to stir at 50 ^{o}C 24h under nitrogen. The solvent was removed *in vacuo* under high pressure and high temperature to give the crude product.

6.3.6 Characterisation Data for Products in Scheme 3.18, and Table 3-7



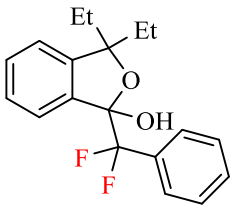
3.74

This crude product was purified by column chromatography ethyl acetate: petroleum ether 40-60 (1: 9) to give the product 1-[difluoro(phenyl)methyl]-3,3-dimethyl-1,3- dihydroisobenzofuran-1-ol **(3.74)** as a yellow oil (0.131 g, 46 %). ^{1}H NMR (400 MHz; $CDCl_3$) δ_H 1.21 (3H, s, C*H*$_3$), 1.42 (3H, s, C*H*$_3$), 3.14 (1H, s, OH), 6.98 (1H, td, $^{3}J_{HH}$ = 7.6 Hz, $^{4}J_{HH}$ = 0.9 Hz, Ar*H*), 7.28 (5H, m, Ar*H*), 7.44 (2H, d, $^{3}J_{HH}$ = 7.0 Hz, Ar*H*), 7.49 (1H, d, $^{3}J_{HH}$ = 7.2 Hz, Ar*H*), 7.42 (2H, d, $^{3}J_{HH}$ = 7.9 Hz, Ar*H*); ^{13}C{^{1}H} NMR (100 MHz; $CDCl_3$) δ_C 27.9 (CH_3), 30.8 (CH_3), 86.6 (C), 105.4 (t, $^{2}J_{CF}$ = 33.6 Hz, COH), 119.6 (t, $^{1}J_{CF}$ = 247.1 Hz, CF_2), 120.5 (CH), 123.9 (CH), 127.2 (t, $^{3}J_{CF}$ = 6.5 Hz, CH), 127.7 (CH), 128.1(CH), 129.9(CH), 130.5 (CH), 134.1 (t, $^{2}J_{CF}$ = 26.5 Hz, C), 135.1 (C), 148.2 (C). ^{19}F NMR (376 MHz; $CDCl_3$) δ_F -104 (1F, d, $^{2}J_{FF}$ = 251.5 Hz, CF_AF_B), -112.3 (1F, d, $^{2}J_{FF}$ = 251.5 Hz, CF_AF_B). m/z (ASAP): 273.1104 ([MH-OH_2]$^+$, $C_{17}H_{16}F_2O$ requires 273.1091, 100 %).



3.75

This crude product was purified by column chromatography ethyl acetate: petroleum ether 40-60 (1: 9) to give the product 1-[difluoro(4-methylphenyl)methyl]-3,3-dimethyl-1,3-dihydroisobenzofuran-1-ol **(3.75)** as a yellow oil (0.127 g, 41%). ^{1}H NMR (400 MHz; $CDCl_3$) δ_H 1.33 (3H, s, C*H*$_3$), 1.51 (3H, s, C*H*$_3$), 2.33 (3H, s, C*H*$_3$), 3.24 (1H, s, OH), 7.08 (1H, dd, $^{3}J_{HH}$ = 7.7 Hz, $^{4}J_{HH}$ = 1.1 Hz, Ar*H*), 7.15 (2H, d, $^{3}J_{HH}$ = 7.9 Hz, Ar*H*), 7.36 (1H, d, $^{3}J_{HH}$ = 7.4 Hz, $^{4}J_{HH}$ = 1.4 Hz, Ar*H*), 7.39 (1H, dd, $^{3}J_{HH}$ = 7.4 Hz, $^{4}J_{HH}$ = 1.2 Hz, Ar*H*), 7.42 (2H, d, $^{3}J_{HH}$ = 7.9 Hz, Ar*H*), 7.58 (1H, d, $^{3}J_{HH}$ = 7.6 Hz, Ar*H*); ^{13}C{^{1}H} NMR (100 MHz; $CDCl_3$) δ_C 21.3 (CH_3), 27.3 (CH_3), 30.8 (CH_3), 87.5 (C), 105.4 (t, $^{2}J_{CF}$ = 33.5 Hz, COH), 119.6 (t, $^{1}J_{CF}$ = 247.8 Hz, CF_2), 120.4 (CH), 124.1 (CH), 127.5 (t, $^{3}J_{CF}$ = 6.3 Hz, CH), 128.2 (CH), 129.8 (CH), 130.1 (CH), 130.3 (t, $^{2}J_{CF}$ = 26.5 Hz, C), 136.9 (C), 140.2 (C). ^{19}F NMR (376 MHz; $CDCl_3$) δ_F -104.6 (1F, d, $^{2}J_{FF}$ = 250.5 Hz, CF_AF_B), -112.6 (1F, d, $^{2}J_{FF}$ = 250.5 Hz, CF_AF_B). m/z (ASAP): 287.1253 ([MH-OH_2]$^+$, $C_{18}H_{17}F_2O$ requires 287.1247, 100 %).



3.76

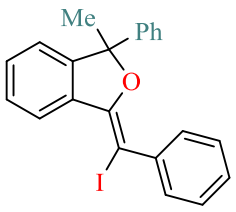
This crude product was purified by column chromatography ethyl acetate: petroleum ether 40-60 (1: 9) to give the product 1-[difluoro-(phenyl)methyl]-3-methyl-3,3-diethyl,1,3- dihydroisobenzofuran-1-ol **(3.76)** (0.109 g, 34 %) as a yellow oil. ^{1}H NMR (400 MHz; $CDCl_3$) δ_H 0.68 (3H, t, $^{3}J_{HH}$ = 7.3 Hz C*H*$_3$), 0.93 (3H, t, $^{3}J_{HH}$ = 7.4 Hz C*H*$_3$), 1.02 (2H, ABt, $^{3}J_{HH}$ = 7.4 Hz, C*H*$_2$), 1.47 (1H, ABt, $^{3}J_{HH}$ = 7.1 Hz, C*H*$_2$), 1.72 (2H, ABt, $^{3}J_{HH}$ = 7.4 Hz, C*H*$_2$), 1.87 (2H, ABt, $^{3}J_{HH}$ = 7.6 Hz, C*H*$_2$), 3.07 (1H, s, OH), 7.04 (1H, td, $^{3}J_{HH}$ = 7.3 Hz, $^{4}J_{HH}$ = 1.2 Hz, Ar*H*), 7.23 (1H, td, $^{3}J_{HH}$ = 7.1 Hz, $^{4}J_{HH}$ = 1.3 Hz, Ar*H*), 7.38 (8H, m, Ar*H*), 7.51 (3H, m, Ar*H*), 7.57 (2H, d, $^{3}J_{HH}$ = 7.1 Hz, Ar*H*), 7.61 (1H, d, $^{3}J_{HH}$ = 7.1 Hz, Ar*H*); ^{13}C{^{1}H} NMR (100 MHz; $CDCl_3$) δ_C 8.2 (CH_3), 8.4 (CH_3), 10.3 (CH_3), 31.0 (CH_2), 31.2 (CH_2), 32.3 (CH_2), 73.8 (C), 87.2 (C), 93.3 (C), 94.2 (C), 105.4 (t, $^{2}J_{CF}$ = 33.6 Hz, COH), 119.6 (t, $^{1}J_{CF}$ = 247.1 Hz, CF_2), 120.7 (CH), 123.1 (CH), 127.3 (t, $^{3}J_{CF}$ = 6.5 Hz, CH), 127.7 (CH), 128.1(CH), 129.6(CH), 130.1 (CH), 133.1 (t, $^{2}J_{CF}$ = 26.5 Hz, C), 136.4 (C), 146.4 (C), 146.5 (C). ^{19}F NMR (376 MHz; $CDCl_3$) δ_F -103.2 (1F, d, $^{2}J_{FF}$ = 251.5 Hz, CF_AF_B), -103.8 (1F, d, $^{2}J_{FF}$ = 250.8 Hz, CF_AF_B), -111.4 (1F, d, $^{2}J_{FF}$ = 251.3 Hz, CF_AF_B), -112.0 (1F, d, $^{2}J_{FF}$ = 251.1 Hz, CF_AF_B). m/z (ASAP): 301.1416 ([MH-OH_2]$^{+}$, $C_{19}H_{19}F_2O$ requires 301.1404, 100 %).

6.4 Experimental procedures for Chapter 4

6.4.1 General Procedure for the Reaction in Scheme 4.9

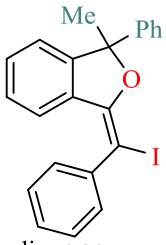
1-Phenyl-[1-(2-phenylethynyl)phenyl]ethanol **(2.37)** (1 eq.) (0.298 g, 1 mmol), or 1-phenyl-[1-(2-p-tolylethynyl)phenyl] ethanol **(2.38)** (1 eq.) (0.312 g, 1 mmol), I_2 (3 eq.) (0.761 g, 3 mmol), K_2CO_3 (2 eq.) (0.276 g, 2 mmol), and dry DCM (30 mL) were charged into a three- necked flask. After stirring under N_2 at R.T for 48 h, a saturated solution of NaS_2O_3 (10 mL) was added and the mixture was stirred for 5 min. before being extracted with DCM (3 x 10 mL). The combined organic layers were dried over $MgSO_4$ (anhydrous), and the solvent was removed in *vacuo* to give the crude product.

6.4.2 Characterisation Data for Products in Scheme 4.9, and Table 4-1



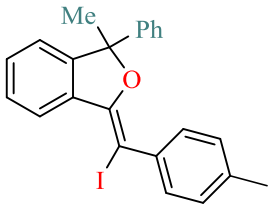
(*E*) 5-exo-dig **4.19**

+



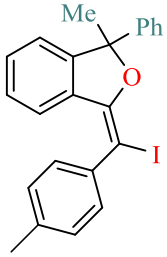
(*Z*) 5-exo-dig **4.20**

The crude product (0.356g) was purified by column chromatography using ethyl acetate/ hexane (1/15) to give the pure product as a yellow oil (0.230 g, 54 %) as a 1:1 ratio of a mixture of *(E)* and *(Z)* -1-(Iodo(phenyl)methylene)-3,3 methyl(phenyl)-1,3-dihydroisobenzofuran isomers **(4.19)** & **(4.20)**. ^{1}H NMR (400 MHz; $CDCl_3$) δ_H 1.76 (3H, s, C*H*$_3$), 1.91 (3H, s, C*H*$_3$), 6.34 (1H, d, $^{3}J_{HH}$ = 7.7 Hz, Ar*H*), 6.82 (1H, td, $^{3}J_{HH}$ = 7.3 Hz, $^{4}J_{HH}$ = 1.2 Hz, Ar*H*), 7.15 (5H, m, Ar*H*), 7.25 (3H, m, Ar*H*), 7.34 (9H, m, Ar*H*), 7.36 (2H, td, $^{3}J_{HH}$ = 7.4 Hz, $^{4}J_{HH}$ = 1.1 Hz, Ar*H*), 7.44 (2H, d, $^{3}J_{HH}$ = 7.6 Hz, Ar*H*), 7.46 (2H, dd, $^{3}J_{HH}$ = 7.4 Hz, $^{4}J_{HH}$ = 1.1 Hz, Ar*H*), 7.52 (2H, dd, $^{3}J_{HH}$ = 7.7 Hz, $^{4}J_{HH}$ = 1.2 Hz, Ar*H*), 8.68 (1H, d, $^{3}J_{HH}$ = 7.6 Hz, Ar*H*); ^{13}C{^{1}H} NMR (100 MHz; $CDCl_3$) δ_C 27.4 (CH_3), 28.0 (CH_3), 63.9 (CI), 65.6 (CI), 89.6 (C), 96.4 (C), 121.8 (CH), 123.1 (CH), 124.8 (CH), 125.1 (CH), 125.9 (CH), 126.1 (CH), 127.0 (CH), 127.4 (CH), 127.6 (CH), 127.7 (CH), 127.9 (CH), 128.0 (CH), 128.2 (CH), 128.3 (CH), 128.4 (CH), 128.5 (CH), 128.9 (CH), 129.1 (CH), 129.7 (CH), 129.8 (CH), 130.5 (C). 130.6 (C), 141.0 (C), 143.9 (C), 149.8 (C). m/z (ASAP): 298.1363 ([MH-I]$^{+}$, $C_{22}H_{18}O$ requires 298.1358, 100 %).



(*E*) 5-exo-dig **4.21**

+



(*Z*) 5-exo-dig **4.22**

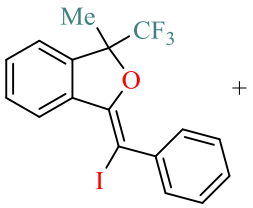
The crude product (0.441g) was purified by column chromatography using ethyl acetate/ hexane (1/15) to give the pure product as an orange oil (0.294 g, 67%) as a 1:1 ratio of a mixture of *(E)* and *(Z)* -1-(Iodo(4-methylphenyl)methylene)-3,3 methyl(phenyl)-1,3-dihydroisobenzofuran isomers **(4.21)** & **(4.22)**. ^{1}H NMR (400 MHz; $CDCl_3$) δ_H 1.80 (3H, s, C*H*$_3$), 1.94 (3H, s, C*H*$_3$), 2.26 (3H, s, C*H*$_3$), 2.33 (3H, s, C*H*$_3$), 6.42 (1H, d, $^{3}J_{HH}$ = 7.9 Hz, Ar*H*), 6.88 (1H, td, $^{3}J_{HH}$ = 7.3 Hz, $^{4}J_{HH}$ = 1.5 Hz Ar*H*), 7.03 (2H, d, $^{3}J_{HH}$ = 7.8 Hz, Ar*H*), 7.14 (6H, m, Ar*H*), 7.21 (3H, t, $^{3}J_{HH}$ = 7.8 Hz,, Ar*H*), 7.28 (6H, m, Ar*H*), 7.32 (2H, td, $^{3}J_{HH}$ = 7.8 Hz, $^{4}J_{HH}$ = 1.0 Hz, Ar*H*), 7.34 (2H, d, $^{3}J_{HH}$ = 7.9 Hz, Ar*H*), 7.43 (2H, d, $^{3}J_{HH}$ = 7.9 Hz, Ar*H*), 8.68 (1H, d, $^{3}J_{HH}$ = 7.8 Hz, Ar*H*); ^{13}C{^{1}H}

NMR (100 MHz; $CDCl_3$) δ_C 21.2 (CH_3), 21.4 (CH_3), 27.5 (CH_3), 28.0 (CH_3), 64.4 (CI), 66.4 (CI), 89.1 (C), 89.5 (C), 121.8 (CH), 123.2 (CH), 124.9 (CH), 125.1 (CH), 126.1 (CH), 126.6 (CH), 127.4 (CH), 127.5 (CH), 127.7 (CH), 128.3 (CH), 128.4 (CH), 128.5 (CH), 128.6 (CH), 129.0 (CH), 129.2 (CH), 129.7 (CH), 129.8 (CH), 129.8 (CH), 130.3 (C), 130.4 (C), 132.3 (C), 136.8 (C), 138.0 (C), 138.2 (C), 139.4 (C), 143.7 (C), 144.0 (C), 149.8 (C), 150.1 (C), 155.0 (C). m/z (ASAP): 312.1508 ($[MH-I]^+$, $C_{23}H_{19}O$ requires 312.1514, 100 %).

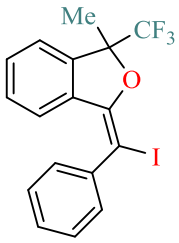
6.4.3 General Procedure for the Reaction in Scheme 4.10

1,1,1-Trifluoro-[2-(2-phenylethynyl)phenyl]propan-2-ol **(2.84)** (1 eq.) (0.290 g, 1 mmol), or 1,1,1-trifluoro-[2-(2-p-tolylethynyl)phenyl]propan-2-ol **(2.85)** (1 eq.) (0.304 g, 1 mmol), I_2 (3 eq.) (0.761 g, 3 mmol), K_2CO_3 (2 eq.) (0.276 g, 2 mmol), and dry DCM (30 mL) were charged into a three- necked flask. After stirring under N_2 at R.T for 48 h, a saturated solution of NaS_2O_3 (10 mL) was added and the mixture was stirred for 5 min. The mixture was extracted with DCM (3 x 10 mL). The combined organic layers were dried over $MgSO_4$ (anhydrous), and the solvent was removed in *vacuo* to give the crude product.

6.4.4 Characterisation Data for Products in Scheme 4.10, and Table 4-2



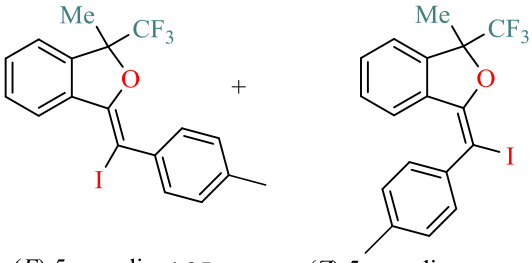
(*E*) 5-exo-dig **4.23**



(*Z*) 5-exo-dig **4.24**

The crude product (0.396 g) was purified by column chromatography using ethyl acetate/ hexane (1/15) to give the pure product as a pink oil (0.295 g), (71 %) as a 3:1 ratio of a mixture of *(E)* and *(Z)* -1-(iodo(phenyl)methylene)-3,3-methyl(trifluoromethyl)-1,3-dihydroisobenzofuran isomers **(4.23)** & **(4.24)** .^{1}H NMR (400 MHz; $CDCl_3$) δ_H 1.59 (3H, s, C*H*$_3$), 1.76 (3H, s, C*H*$_3$), 6.35 (1H, d, $^3J_{HH}$ = 7.9 Hz, Ar*H*), 7.01 (1H, td, $^3J_{HH}$ = 7.3 Hz, $^4J_{HH}$ = 1.9 Hz, Ar*H*), 7.15 (2H, m, Ar*H*), 7.28 (5H, m, Ar*H*), 7.41 (2H, td, $^3J_{HH}$ = 7.3 Hz, $^4J_{HH}$ = 1.0 Hz, Ar*H*), 7.47 (5H, m, Ar*H*), 7.54 (1H, m, Ar*H*), 8.69 (1H, d, $^3J_{HH}$ = 7.9 Hz, Ar*H*); $^{13}C\{^1H\}$ NMR (100 MHz; $CDCl_3$) δ_C 19.2 (CH_3), 19.3 (CH_3), 65.2 (CI), 65.4 (CI), 84.5 (q, $^2J_{CF}$ = 32.3 Hz, C-CF_3), 84.7 (q, $^2J_{CF}$ = 32.5 Hz, C-CF_3), 121.3 (C), 121.4 (C), 121.9 (CH), 122.1 (CH), 124.2 (C), 125.0 (C), 126.5 (CH), 126.7 (CH), 126.8 (CH), 126.9 (CH), 127.6 (CH), 128.0 (CH), 128.2

(CH), 128.3 (CH), 128.5 (CH), 128.8 (CH), 129.1 (CH), 129.2 (CH), 130.2 (C), 132.7 (C), 139.2 (q, $^{1}J_{CF}$ = 282.3 Hz, CF_3), 139.8 (q, $^{1}J_{CF}$ = 282.3 Hz, CF_3), 140.2 (C), 140.3 (C), 151.4 (C), 153.6 (C). ^{19}F NMR (376 MHz; $CDCl_3$) δ_F -80.4 (s, CF_3), δ_F -80.7 (s, CF_3). m/z (ASAP): 415,9895 ($[MH]^+$, $C_{17}H_{12}F_3IO_2$ requires 415.9885, 100 %).



(*E*) 5-exo-dig **4.25** (*Z*) 5-exo-dig **4.26**

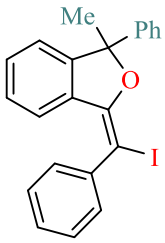
The crude product (0.394g) was purified by column chromatography using ethyl acetate/ hexane (1/15) to give the pure product as a purple oil (0.288 g), (68 %) as a 3:1 ratio of a mixture of *(E)* and *(Z)* -1-(iodo(4-methylphenyl)methylene)-3,3-methyl(trifluoromethyl)-1,3-dihydroisobenzofuran isomers **(4.25)** & **(4.26)** . ^{1}H NMR (400 MHz; $CDCl_3$) δ_H 1.55 (3H, s, C*H*$_3$), 1.71 (3H, s, C*H*$_3$), 2.25 (3H, s, C*H*$_3$), 2.28 (3H, s, C*H*$_3$), 6.41 (1H, d, $^{3}J_{HH}$ = 7.9 Hz, Ar*H*), 7.04 (2H, d, $^{3}J_{HH}$ = 7.8 Hz, Ar*H*), 7.08 (2H, d, $^{3}J_{HH}$ = 7.7 Hz, Ar*H*), 7.12 (1H, m, Ar*H*), 7.15 (1H, m, Ar*H*), 7.28 (1H, d, $^{3}J_{HH}$ = 7.8 Hz, Ar*H*), 7.29 (1H, d, $^{3}J_{HH}$ = 7.7 Hz, Ar*H*), 7.35 (2H, d, $^{3}J_{HH}$ = 7.8 Hz, Ar*H*), 7.37 (2H, d, $^{3}J_{HH}$ = 7.7 Hz, Ar*H*), 7.41 (1H, td, $^{3}J_{HH}$ = 7.9 Hz, $^{4}J_{HH}$ = 1.2 Hz , Ar*H*), 7.43 (1H, td, $^{3}J_{HH}$ = 7.9 Hz, $^{4}J_{HH}$ = 1.2 Hz , Ar*H*), 8.66 (1H, d, $^{3}J_{HH}$ = 7.9 Hz, Ar*H*); ^{13}C{^{1}H} NMR (100 MHz; $CDCl_3$) δ_C 20.3 (CH_3), 20.6 (CH_3), 21.5 (CH_3), 21.7 (CH_3), 66.8 (CI), 67.0 (CI), 81.6 (q, $^{2}J_{CF}$ = 32.5 Hz, C-CF_3), 86.1 (q, $^{2}J_{CF}$ = 32.5 Hz, C-CF_3), 118.8 (C), 119.9 (C), 122.4 (CH), 122.5 (CH), 123.8 (CH), 123.9 (CH), 125.1 (C), 125.4 (C), 126.1 (CH), 126.2 (CH), 126.9 (CH), 127.6 (CH), 128.3 (CH), 128.4 (CH), 131.0 (C), 131.4 (C), 138.6 (q, $^{1}J_{CF}$ = 282.3 Hz, CF_3), 139.5 (q, $^{1}J_{CF}$ = 282.3 Hz, CF_3), 140.8 (C), 141.2 (C), 152.9 (C), 154.5 (C). ^{19}F NMR (376 MHz; $CDCl_3$) δ_F -80.4 (s, CF_3), δ_F -80.7 (s, CF_3). m/z (ASAP): 431.0130 ($[MH]^+$, $C_{17}H_{12}F_3IO_2$ requires 431.0120, 100 %).

6.4.5 General Procedure for the Reaction in Scheme 4.12

1-Phenyl-[1-(2-phenylethynyl)phenyl]ethanol **(2.37)** (1 eq.) (0.298 g, 1 mmol), or 1-phenyl-[1-(2-p-tolylethynyl)phenyl] ethanol **(2.38)** (1 eq.) (0.312 g, 1 mmol), or 1,1,1-trifluoro-[2-(2-phenylethynyl)phenyl]propan-2-ol **(2.84)** (1 eq.) (0.290 g, 1 mmol), or

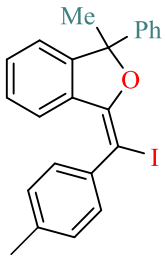
1,1,1-trifluoro-[2-(2-p-tolylethynyl)phenyl]propan-2-ol **(2.85)** (1 eq.) (0.304 g, 1 mmol), I_2 (3 eq.) (0.761 g, 3 mmol), K_2CO_3 (2 eq.) (0.276 g, 2 mmol), and dry MeCN (30 mL) were charged into a three- necked flask. After stirring under N_2 at R.T for 96 h, a saturated solution of NaS_2O_3 (10 mL) was added and the mixture was stirred for 5 min. The mixture was extracted with Et_2O (3 x 10 mL). The combined organic layers were dried over $MgSO_4$ (anhydrous), and the solvent was removed in *vacuo* to give the crude product.

6.4.6 Characterisation Data for Products in Scheme 4.12, and Table 4-3



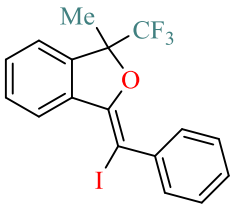
(*Z*) 5-exo-dig
4.20

The crude product (0.387 g) was purified by column chromatography using ethyl acetate/ hexane (1/15) to give the pure product (*Z*) -1-(iodo(phenyl)methylene)-3,3-methyl(phenyl)-1,3-dihydroisobenzofuran **(4.20)** as a yellow oil (0.324 g, 76 %). ^{1}H NMR (400 MHz; $CDCl_3$) δ_H 1.92 (3H, s, C*H*$_3$), 6.34 (1H, d, $^3J_{HH}$ = 7.9 Hz, Ar*H*) 6.83 (1H, td, $^3J_{HH}$ = 7.4 Hz, $^4J_{HH}$ = 1.0 Hz, Ar*H*), 7.26 (8H, m, Ar*H*), 7.45 (2H, d, $^3J_{HH}$ = 7.1 Hz, Ar*H*), 7.47 (2H, d, $^3J_{HH}$ = 7.9 Hz, Ar*H*); ^{13}C{^{1}H} NMR (100 MHz; $CDCl_3$) δ_C 28.0 (CH_3), 63.6 (CI), 89.6 (C), 121.8 (CH), 123.1 (CH), 125.3 (CH), 125.9 (CH), 127.6 (CH), 128.0 (CH), 128.3 (CH), 128.5 (CH), 128.7 (CH), 129.1 (CH), 130.1 (C), 130.6 (C), 134.3 (C) . 143.9 (C), 149.8 (C) . m/z (ASAP): 298.1361 ([MH-I]$^+$, $C_{22}H_{18}O$ requires 298.1358, 100 %).



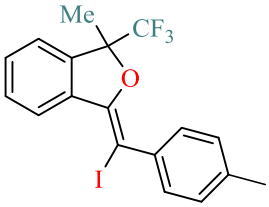
(*Z*) 5-exo-dig
4.22

The crude product (0.441 g) was purified by column chromatography using ethyl acetate/ hexane (1/15) to give the pure product (*Z*) -1-(iodo(4-methylphenyl)methylene)-3,3-methyl(phenyl)-1,3-dihydroisobenzofuran **(4.22)** as an orange oil (0.365 g, 83 %). ^{1}H NMR (400 MHz; $CDCl_3$) δ_H 2.01 (3H, s, C*H*$_3$), 2.40 (3H, s, C*H*$_3$), 6.50 (1H, d, $^3J_{HH}$ = 7.6 Hz, , Ar*H*) 6.95 (1H, td, $^3J_{HH}$ = 7.4 Hz, $^4J_{HH}$ = 1.8 Hz , Ar*H)*), 7.20 (4H, m, Ar*H*), 7.28 (1H, m, Ar*H*), 7.35 (4H, m, Ar*H*), 7.55(2H, dd, $^3J_{HH}$ = 7.9 Hz, $^4J_{HH}$ = 1.3 Hz , Ar*H)*; ^{13}C{^{1}H} NMR (100 MHz; $CDCl_3$) δ_C 21.4 (CH_3), 28.0 (CH_3), 64.4 (CI), 89.5 (C), 121.8 (CH), 123.2 (CH), 124.9 (CH), 127.5 (CH), 127.7 (CH), 127.9 (CH), 128.5 (CH), 129.0 (CH), 129.7(CH), 130.4 (C), 138.0 (C), 138.2 (C), 144.0 (C), 149.8 (C), 155.0 (C). m/z (ASAP): 312.1508 ([MH-I]$^+$, $C_{23}H_{19}IO$ requires 312.1514, 100 %).



(*E*) 5-exo-dig **4.23**

The crude product (0.407g) was purified by column chromatography using ethyl acetate/ hexane (1/15) to give the pure product (*E*) -1-(iodo(phenyl)methylene)-3-(trifluoromethyl)-1,3-dihydroisobenzofuran **(4.23)** as a pink oil (0.391 g), (93 %). ^{1}H NMR (400 MHz; $CDCl_3$) δ_H 1.54 (3H, s, C*H*$_3$), 7.09 (1H, td, $^{3}J_{HH}$ = 7.4 Hz, $^{4}J_{HH}$ = 1.1 Hz, Ar*H*) 7.23 (3H, m, Ar*H*), 7.35 (1H, td, $^{3}J_{HH}$ = 7.6 Hz, $^{4}J_{HH}$ = 1.0 Hz, Ar*H*), 7.44 (3H, m, Ar*H*), 8.67 (1H, d, $^{3}J_{HH}$ = 7.8 Hz, Ar*H*); ^{13}C{^{1}H} NMR (100 MHz; $CDCl_3$) δ_C 19.2 (CH_3), 65.4 (CI), 84.7 (q, $^{2}J_{CF}$ = 32.5 Hz, C-CF_3), 97.5 (C), 121.4 (CH), 124.2 (C), 126.5 (CH), 126.7(CH), 127.4 (CH), 127.5 (CH), 128.5 (CH), 128.8 (CH), 130.2 (C), 139.8(q, $^{1}J_{CF}$ = 282.3 Hz, CF_3), 140.3 (C), 153.6 (C). ^{19}F NMR (376 MHz; $CDCl_3$) δ_F -80.4 (s, CF_3). m/z (ASAP): 415.9895 ($[MH]^+$, $C_{17}H_{12}F_3IO_2$ requires 415.9885, 100 %).

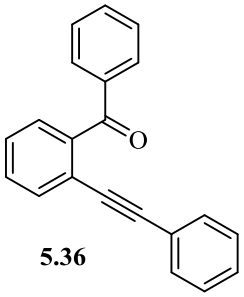


(*E*) 5-exo-dig **4.25**

The crude product (0.392 g) was purified by column chromatography using ethyl acetate/ hexane (1/15) to give the pure product (*E*) -1-(iodo(4-methylphenyl)methylene)-3-(trifluoromethyl)-1,3-dihydroisobenzofuran **(4.25)** as a purple oil (0.389 g), (91 %). ^{1}H NMR (400 MHz; $CDCl_3$) δ_H 1.57 (3H, s, C*H*$_3$), 2.27 (3H, s, C*H*$_3$), 7.05 (2H, d, $^{3}J_{HH}$ = 7.8 Hz, , Ar*H*) 7.12 (1H, s, Ar*H*), 7.28 (1H, d, $^{3}J_{HH}$ = 7.9 Hz, Ar*H*), 7.36 (2H, d, $^{3}J_{HH}$ = 7.9 Hz, Ar*H*), 7.44 (1H, td, $^{3}J_{HH}$ = 7.9 Hz, $^{4}J_{HH}$ = 1.2 Hz , Ar*H*), 8.67 (1H, d, $^{3}J_{HH}$ = 7.9 Hz, Ar*H*); ^{13}C{^{1}H} NMR (100 MHz; $CDCl_3$) δ_C 19.2 (CH_3), 20.1 (CH_3), 65.8 (CI), 84.6 (q, $^{2}J_{CF}$ = 32.5 Hz, C-CF_3), 117.7 (C), 121.2(CH), 124.2 (CH), 125.0 (C), 126.5 (CH), 127.5 (CH), 128.7(CH), 131.2 (C), 138.4 (q, $^{1}J_{CF}$ = 282.3 Hz, CF_3), 140.1 (C), 150.1 (C). ^{19}F NMR (376 MHz; $CDCl_3$) δ_F -80.4 (s, CF_3). m/z (ASAP): 431.0130 ($[MH]^+$, $C_{17}H_{12}F_3IO_2$ requires 431.0120, 100 %).

6.5 Experimental procedures for Chapter 5

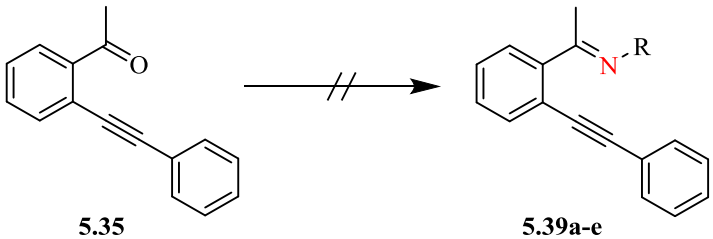
6.5.1 Synthesis of Phenyl(2-(phenylethynyl)phenyl)methanone (5.36) [13,14]



5.36

(2-Iodophenyl)(phenyl)methanone (2.279 g, 7.4 mmol), phenylacetylene (2.26 ml, 22.2 mmol), $[Pd(PPh_3)_2Cl_2]$ (0.23 g, 0.34 mmol), CuI (0.118 g, 0.6 mmol) and dry Et_3N (40 ml) were charged into a dry three–necked flask. After stirring under nitrogen at 70 °C for 5 h, the reaction mixture was allowed to cool to room temperature and left to stir overnight. H_2O (30 ml) and Et_2O (30 ml) were added. The precipitate was filtered off, and the solution was extracted with Et_2O (3 x 20 ml). The combined organic layers were dried over $MgSO_4$ (anhydrous), and the solvent was removed *in vacuo* to give the crude product (3.01 g). It was purified by column chromatography using diethyl ether/petroleum ether (1:9) to give the pure product as a brown oil (2.5 g, 76%). ^{1}H NMR (400 MHz; $CDCl_3$) δ_H 7.39 (1H, m, Ar*H*), 7.40 (2H, m, Ar*H*), 7.45 (1H, td, $^3J_{HH}$ = 7.7 Hz, $^4J_{HH}$ = 1.4 Hz, Ar*H*), 7.51 (2H, dd, $^3J_{HH}$ = 7.7 Hz, $^4J_{HH}$ = 1.1 Hz, Ar*H*), 7.59 (2H, m, Ar*H*), 7.61 (1H, m, Ar*H*), 7.66 (1H, m, Ar*H*), 7.67 (1H, m, Ar*H*), 7.70 (1H, m, Ar*H*), 7.75 (2H, dd, $^3J_{HH}$ = 7.8 Hz, $^4J_{HH}$ = 1.2 Hz, Ar*H*); $^{13}C\{^1H\}$ NMR (100 MHz; $CDCl_3$) δ_C 93.3 (C), 99.0 (C), 127.4 (C), 128.1 (CH), 128.3 (CH), 128.4 (CH), 128.6 (CH), 129.7 (CH), 130.3 (CH), 132.0 (CH), 132.3 (CH), 132.4 (CH), 133.5 (C), 134.5 (CH), 138.9 (C), 141.8 (C), 196.3 (CO). m/z (ASAP): 283.0965 ($[MH]^+$, $C_{21}H_{14}O$ requires 283.0966, 100 %). Data are consistent with those reported in the literature.

6.5.2 General Procedure for the Reaction in Scheme 5.8

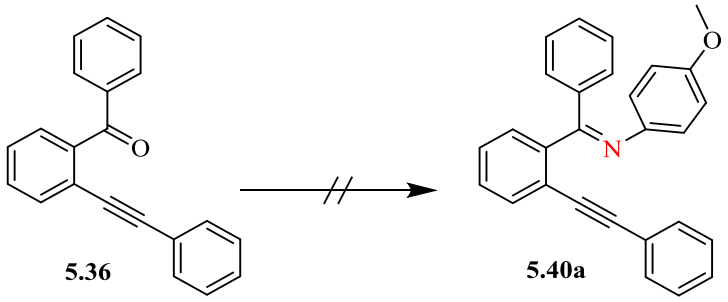


5.35 5.39a-e

A mixture of 2-(phenylethynyl)acetophenone (1.1 g, 5.0 mmol), p-anisidine (0.74g, 6.0 mmol) and CSA (10 mg) in toluene (10 mL) was heated to reflux (130 ◦C) for 24 h using a Dean-Stark apparatus. The solvent was removed under reduced pressure. This reaction

was also carried out using the same reaction conditions for 48 h, and using different amines, 4-fluoroaniline, 4-nitroaniline, phenylmethanamine and 2-methylpropan-2-amine. ^{1}H NMR spectroscopy showed 100 % presence of the starting material. The desired product was not observed.

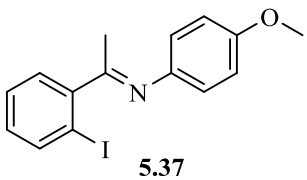
6.5.3 Synthesis of (*E*)-*N*-(4-methoxyphenyl)-1-phenyl-1-(2-(phenylethynyl)phenyl) methanimine



5.36 **5.40a**

Phenyl(2-(phenylethynyl)phenyl)methanone (2.82 g, 10 mmol), p-anisidine (3.69 g, 30 mmol) and (4.17 mL, 30 mmol) of Et_3N were dissolved in CH_2Cl_2 (50 mL) under an atmosphere of N_2. The mixture was cooled by an ice-salt bath. A solution of $TiCl_4$ (10 mL, 10 mmol) was introduced via syringe to the rapidly stirred mixture. After stirring for 1h, the ice bath was removed. The temperature of the solution was raised to 45 ◦C and stirring was continued overnight. The solvent was evaporated to give the crude product as a brown oil. ^{1}H NMR spectroscopy showed 100 % recording of the starting material. The desired product was not observed.

6.5.4 Synthesis of *N*-[1-(2-Iodophenyl)ethylidene]-4-methoxyaniline (5.37) [15]

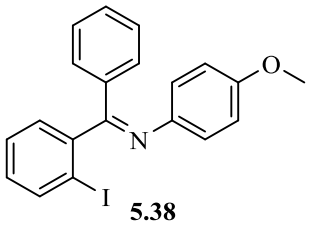


5.37

A mixture of 2-iodoacetophenone (1.23 g, 5.0 mmol), p-anisidine (0.74 g, 6.0 mmol) and CSA (10 mg) in toluene (10 mL) was heated to reflux (130 ◦C) for 48 h using a Dean-Stark apparatus. The solvent was removed under reduced pressure to give the product N-[1-(2-iodophenyl)ethylidene]-4-methoxyaniline as a brown oil as a 1:1 ratio of two geometrical isomers *(E)* and *(Z)*, (1.751 g, 99 %). The spectral data of the mixture of *E*,*Z*- isomers are given below. ^{1}H NMR (400 MHz; $CDCl_3$) δ_H 2.09 (3H, s, C*H*$_3$), 2.40 (3H, s, C*H*$_3$), 2.56 (3H, s, C*H*$_3$), 3.71 (3H, s, C*H*$_3$), 6.54 (2H, d, $^{3}J_{HH}$ = 7.8 Hz, Ar*H*), 6.63 (2H, d, $^{3}J_{HH}$ = 7.8 Hz, Ar*H*), 6.81 (6H, m, Ar*H*), 6.94 (1H, t, $^{3}J_{HH}$ = 7.5

Hz, Ar*H*), 7.10 (1H, td, $^{3}J_{HH}$ = 7.1 Hz, Ar*H*), 7.28 (2H, m, Ar*H*), 7.60 (1H, d, $^{3}J_{HH}$ = 7.7 Hz, Ar*H*), 7.77 (1H, d, $^{3}J_{HH}$ = 7.5 Hz, Ar*H*); $^{13}C\{^{1}H\}$ NMR (100 MHz; $CDCl_3$) δ_C 20.0 (CH_3), 27.0 (CH_3), 54.1 (OCH_3), 54.4 (OCH_3), 92.6 (CI), 92.9 (CI), 112.5 (CH), 113.2 (CH), 119.6 (CH), 121.0 (CH), 126.5 (CH), 126.8 (CH), 127.20 (CH), 127.25 (CH), 128.2 (CH), 128.7 (CH), 138.5 (C), 139.8 (C), 141.9 (CH), 142.4 (CH), 144.0 (C), 145.5 (C), 154.9 (C), 155.3 (C), 168.9 (C), 170.0 (C). m/z (ASAP): 352.0197 ($[MH]^+$, $C_{15}H_{14}INO$ requires 352.0198, 100 %). Data are consistent with those reported in the literature.

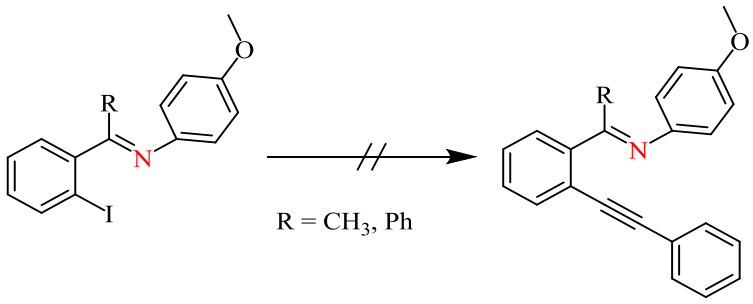
6.5.5 Synthesis of (2-Iodophenyl)(phenyl)methylene]-4-methoxyaniline (5.38)



5.38

2-Iodobenzophenone (1.82 g, 10 mmol), p-anisidine (3.69 g, 30 mmol) and (4.17 mL, 30 mmol) of Et_3N were dissolved in CH_2Cl_2 (50 mL) under an atmosphere of N_2. The mixture was cooled by an ice-salt bath. A solution of $TiCl_4$ (10 mL, 10 mmol) was introduced via syringe to the rapidly stirred mixture. After stirring for 1h, the ice bath was removed. The temperature of the solution was raised to 45 ◦C and stirring was continued for overnight. The solvent was evaporated to give the product as a brown oil (2.41g, 98 %). ^{1}H NMR (400 MHz; $CDCl_3$) δ_H 3.67 (3H, s, C*H*$_3$), 6.62 (1H, d, $^{3}J_{HH}$ = 7.7 Hz, Ar*H*), 6.67 (4H, m, Ar*H*), 6.74 (1H, d, $^{3}J_{HH}$ = 7.5 Hz, Ar*H*), 6.93 (1H, m, Ar*H*), 7.22 (1H, d, $^{3}J_{HH}$ = 7.7 Hz, Ar*H*), 7.33 (1H, d, $^{3}J_{HH}$ = 7.5 Hz, Ar*H*), 7.63 (1H, d, $^{3}J_{HH}$ = 7.8 Hz, Ar*H*), 11.84 (2H, s, Ar*H*); $^{13}C\{^{1}H\}$ NMR (100 MHz; $CDCl_3$) δ_C 54.7 (OCH_3), 92.6 (CI), 112.6 (CH), 113.7 (CH), 116.2 (CH), 121.4 (CH), 126.8 (CH), 127.3 (CH), 128.6 (CH), 129.3 (CH), 129.6.5 (C), 137.0 (C), 137.4 (C), 138.1 (C), 152.4 (C). m/z (ASAP): 414.0349 ($[MH]^+$, $C_{20}H_{16}INO$ requires 414.0355, 100 %).

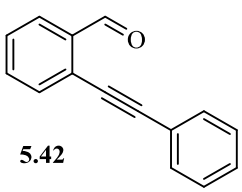
6.5.6 General Procedure for the Reaction in Scheme 5.9



N-[1-(2-Iodophenyl)ethylidene]-4-methoxyaniline (2.59 g, 7.4 mmol) or (2-iodophenyl)(Phenyl)methylene]-4-methoxyaniline (3.05 g, 7.4 mmol), phenylacetylene (2.26 ml, 22.2 mmol), $[Pd(PPh_3)_2Cl_2]$ (0.12 g, 0.17 mmol), CuI (0.059 g, 0.3 mmol) and dry Et_3N (40 ml) were charged into a dry three – necked flask. After stirring under nitrogen at 70 °C for 3h, then H_2O (30 ml) and Et_2O (30 ml) were added to the reaction mixture. The precipitate was filtered off and the solution was extracted with Et_2O (3 x 20 ml). The combined organic layers were dried over $MgSO_4$ (anhydrous), and the solvent was removed *in vacuo* to give the crude product (2.8 g). ^1H NMR spectroscopy showed 100 % recording of the starting materials. The desired products were not observed.

This reaction was also carried out using $[Pd(PPh_3)_2Cl_2]$ (0.24 g, 0.34 mmol), CuI (0.118 g, 0.6 mmol) stirring under nitrogen at 70 °C for 3h and using $[Pd(PPh_3)_2Cl_2]$ (0.12 g, 0.17 mmol), CuI (0.059 g, 0.3 mmol) stirring under nitrogen at 70 °C for 24h.

6.5.7 Synthesis of 2-(phenylethynyl)benzaldehyde (5.42) [16]

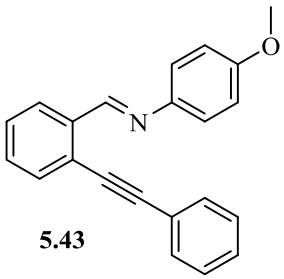


5.42

2-Iodobenzaldehyde (1.72 g, 7.4 mmol), phenylacetylene (1.0 ml, 8.9 mmol), $[Pd(PPh_3)_2Cl_2]$ (0.12 g, 0.17 mmol), CuI (0.059 g, 0.3 mmol) and dry Et_3N (40 ml) were charged into a dry three – necked flask. After stirring under nitrogen at 70 °C for 3h , the reaction mixture was stirred at r.t overnight, before H_2O (30 ml) and Et_2O (30 ml) were added. The precipitate was filtered off and the solution was extracted with Et_2O (3 x 20 ml). The combined organic layers were dried over $MgSO_4$ (anhydrous), and the solvent was removed in *vacuo* to give the crude product. It was purified by column chromatography using Et_2O:hexane (1:9) to give the pure product as an orange oil (1.74 g, 94 %). ^1H

NMR (400 MHz; $CDCl_3$) δ_H 7.36 (3H, m, Ar*H*), 7.42 (1H, td, $^3J_{HH}$ = 7.4 Hz, $^4J_{HH}$ = 1.3 Hz, Ar*H*), 7.55 (3H, , m, Ar*H*), 7.62 (1H, dd, $^3J_{HH}$ = 7.7 Hz, $^3J_{HH}$ = 1.0 Hz, Ar*H*), 7.93 (1H, dd, $^3J_{HH}$ = 7.8 Hz, $^4J_{HH}$ = 1.1 Hz, Ar*H*), 10.62 (1H, d, $^3J_{HH}$ = 0.79 Hz, C*H*); $^{13}C\{1H\}$ NMR (100 MHz; $CDCl_3$) δ_C 84.9 (C), 96.3 (C), 122.7 (C), 127.2 (CH), 128.5 (CH), 128.6 (CH), 128.7 (CH), 129.0 (CH), 131.7 (CH), 133.2 (CH), 133.7 (C), 135.8 (C), 191.6 (C). m/z (ASAP): 207.0812 ($[MH]^+$, $C_{15}H_{10}O$ requires 207.0810, 100 %). Data are consistent with those reported in the literature.

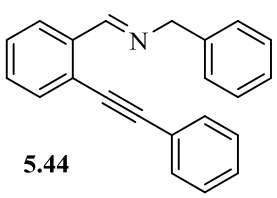
6.5.8 Synthesis of (E)-*N*-(4-methoxyphenyl)-1-(2-(phenylethynyl)phenyl)methanimine (5.43) [17,18]



5.43

To a solution of 2-(phenylethynyl)benzaldehyde) (0.206 g, 1.0 mmol) in DCM (1 mL), benzylamine (0.123 g, 1.0 mmol) and MS 4Å (20 mg) were added and the mixture was stirred at room temperature for 12 h. The mixture was filtered and the solvent was removed under reduced pressure to give the product as a yellow oil (0.291 g, 94 %). ^1H NMR (400 MHz; $CDCl_3$) δ_H 3.62 (3H, s, C*H*$_3$), 6.77 (2H, d, $^3J_{HH}$ = 7.9 Hz, Ar*H*), 7.36 (2H, m, Ar*H*), 7.40 (3H, m, Ar*H*), 7.43 (3H, m, Ar*H*), 7.47 (1H, m, Ar*H*), 7.49 (1H, m, Ar*H*), 8.12 (1H, td, $^3J_{HH}$ = 7.9 Hz, $^4J_{HH}$ = 1.9 Hz Ar*H*), 8.98 (1H, s, N*H*); $^{13}C\{^1H\}$ NMR (100 MHz; $CDCl_3$) δ_C 55.8 (OCH_3), 87.6 (C), 95.4 (C), 115.2 (CH), 122.5 (CH), 127.1 (C), 128.3 (CH), 128.4 (CH), 128.6 (CH), 128.8 (CH), 130.2 (CH), 132.2 (CH), 132.7 (C), 134.6 (C), 134.9 (CH), 144.9 (C), 159.5 (C), 160.2 (CN). m/z (ASAP): 311.1342 ($[MH]^+$, $C_{22}H_{17}NO$ requires 311.1338, 100 %. Data are consistent with those reported in the literature.

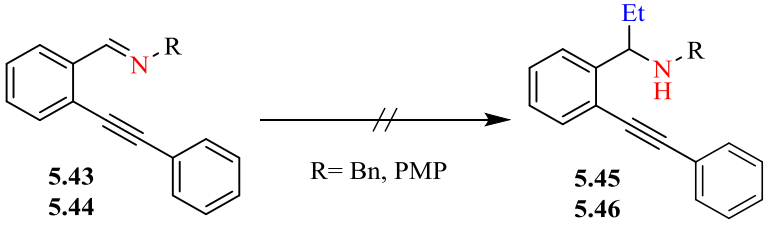
6.5.9 Synthesis of (*E*)-*N*-benzyl-1-(2-(phenylethynyl)phenyl)methanimine (5.44) [19,20]



5.44

To a solution of 2-(phenylethynyl)benzaldehyde) (0.206 g, 1.0 mmol) in Et_2O (0.4 mL), benzylamine (0.130 mL,1.2 mmol) and MS 4 Å (0.4 g) were added and the mixture was stirred at room temperature for 14 h. The mixture was filtered and the solvent was removed under reduced pressure to give the imine product as a yellow oil (0.289 g, 98 %). ^{1}H NMR (400 MHz; $CDCl_3$) δ_H 4.87 (2H, d, $^3J_{HH}$ = 1.2, C*H*$_2$), 7.29 (1H, m, Ar*H*), 7.33 (8H, m, Ar*H*), 7.50 (2H, m, Ar*H*), 7.53 (2H, m, Ar*H*), 8.13 (1H, m, Ar*H*), 8.97 (1H, s, N*H*); ^{13}C{^{1}H} NMR (100 MHz; $CDCl_3$) δ_C 63.9 (CH_2), 85.4 (C), 93.8 (C), 121.8 (CH), 123.1 (C), 125.4 (CH), 125.6 (C), 128.6 (CH), 128.9 (CH), 129.0 (CH), 129.2 (CH),130.5 (CH), 130.7 (CH), 131.5 (CH), 133.8 (CH), 135.9 (C), 138.2 (C), 159.3 (CN). m/z (ASAP): 296.1441 ($[MH]^+$, $C_{22}H_{17}N$ requires 296.1439, 100 %). Data are consistent with those reported in the literature.

6.5.10 General Procedure for the Reaction in Scheme 5.10

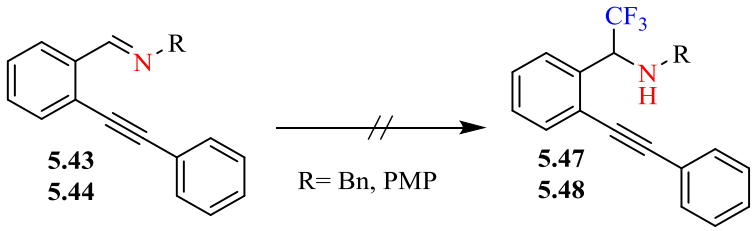


5.43
5.44

5.45
5.46

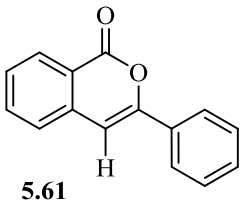
Cp_2ZrCl (29.2 mg, 0.5 mmol) and (*E*)-N-benzyl-1-(2-(phenylethynyl)phenyl)methanimine (0.295 g, 5 mmol) or *(E)-N*-(4-methoxyphenyl)-1-(2-(phenylethynyl)phenyl)methanimine (1.55 g, 5 mmol) were dissolved in THF (5 mL) in schlenk flask. The ethyl grignard reagent (1 M in THF, 2 eq.) (3.5 mL, 17.5 mmol) was added and the reaction mixture was stirred for 3 h at R.T. The reaction was carefully quenched with 15% NaOH (5 mL). Then the phases were separated and the aqueous phase was extracted with ether (3 x 10 mL). The combined organic layer were washed with a saturated solution of $NaCO_3$, dried with Na_2SO_4, and the solvent was removed in *vacuo* to give the crude product (0.325 g). It was purified by column chromatography using ethyl acetate /petroleum ether (1:9). Analysis by ^{1}H NMR spectroscopy showed a complex mixture of products.

6.5.11 General Procedure for the Reaction in Scheme 5.10



(*E*)-*N*-benzyl-1-(2-(phenylethynyl)phenyl)methanimine (0.295 g, 1 mmol) or *(E)*-*N*-(4-methoxyphenyl)-1-(2-(phenylethynyl)phenyl)methanimine (0.155 g, 1 mmol) and TBAB (0.031 g, 0.1 mmol) were charged into a three-necked flask with 5 Å molecular sieves and dry toluene (4 mL). CF_3SiMe_3 (0.222 mL, 1.5 mmol) was charged into the mixture followed by PhONa (0.063 g, 1.1 mmol). The mixture was stirred at R.T under nitrogen for 48 h. The mixture was washed with a saturated solution of Na_2CO_3 (10 mL) and extracted with ethyl acetate (3 x 10 mL). The combined organic layers were dried over $MgSO_4$, and the solvent was removed in *vacuo* to give the crude product (0.351 g). It was purified by column chromatography using ethyl acetate /petroleum ether (2:8). Analysis by ^1H and ^{19}F NMR spectroscopy showed a complex mixture of products.

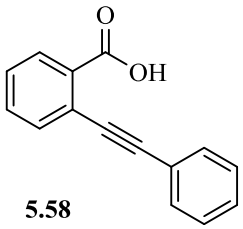
6.5.12 Synthesis of 2-(phenylethylnyl)benzoic acid (5.67) [21]



5.61

Using 2-iodobenzoic acid (1.83 g, 7.4 mmol), phenylacetylene (1.13 ml, 8.9 mmol), $[Pd(PPh_3)_2Cl_2]$ (0.12 g, 0.17 mmol), CuI (0.059 g, 0.3 mmol) and dry Et_3N (40 ml) were charged into a dry three – necked flask. After stirring under nitrogen at 70 °C for 3h, H_2O (20 ml) and EtOAc (20 ml) were added to the reaction mixture. The precipitate was filtered off and the solution was extracted with EtOAc (3 x 20 ml). The combined organic layers were dried over $MgSO_4$ (anhydrous), and the solvent was removed in *vacuo* to give the crude product. It was purified by column chromatography using ethyl acetate /petroleum ether (1:9) to give the pure product as an orange oil (1.47 g, 90 %). ^1H NMR (400 MHz; $CDCl_3$) δ_H 6.68 (1H, s, CH), 7.42 (5H, m, Ar*H*), 7.65 (1H, td, $^3J_{HH}$ = 7.7 Hz, $^4J_{HH}$ = 1.2 Hz, Ar*H*), 7.83 (2H, td, $^3J_{HH}$ = 7.8 Hz, $^4J_{HH}$ = 1.1 Hz, Ar*H*), 8.31 (1H, dd, $^3J_{HH}$ = 7.9 Hz, $^4J_{HH}$ = 1.1 Hz, Ar*H*). Data are consistent with those reported in the literature.

6.5.13 Synthesis of 2-(phenylethylnyl)benzoic acid (5.66) [22,23]



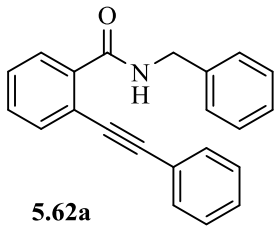
5.58

To a stirred solution of methyl-2-(phenylethynyl)benzoate (3.27 g, 13.84 mmol) in methanol (60 mL), an aqueous NaOH solution (38 mL,1.0 M, 2.7 eq.) was added at ambient temperature and the reaction mixture was stirred for 14 h before being concentrated under reduced pressure. This was subsequently diluted with water (120 mL) and washed with Et_2O (3 x 30 mL). The aqueous phase was acidified (pH = 1‑2) with HCl (1 M) and extracted with EtOAc (3 x 50 mL). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure to afford the pure white solid product (3.84 g, 76%). Crystals suitable for a single crystal X-ray diffraction study were grown from a dichloromethane solution of the complex layered with hexane. Mp: 126-127 ◦C. ^{1}H NMR (400 MHz; $CDCl_3$) δ_H 7.30 (3H, m, Ar*H*), 7.43 (1H, td, $^3J_{HH}$ = 7.8, $^4J_{HH}$ = 1.2 Hz, Ar*H*), 7.58 (3H, m, Ar*H*), 7.70 (1H, d, $^3J_{HH}$ = 7.7 Hz, Ar*H*), 8.15 (1H, dd, $^3J_{HH}$ = 7.9, $^4J_{HH}$ = 1.1 Hz, Ar*H*); ^{13}C{^{1}H} NMR (100 MHz; $CDCl_3$) δ_C 88.0 (C), 95.5 (C), 123.1 (C), 124.4 (C), 128.0 (CH), 128.4 (CH), 128.7 (CH), 130.5 (C), 131.4 (CH), 131.8 (CH), 132.6 (CH), 134.2 (CH), 171.1 (CO). m/z (ASAP): 233.0762 ($[MH]^+$, $C_{15}H_{11}O_2$ requires 223.0759, 100 %). Data are consistent with those reported in the literature.

6.5.14 General Procedure for the Reaction in Scheme 5.17

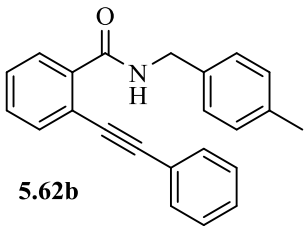
To a stirred solution of 2-(phenylethylnyl)benzoic acid (0.44 g, 2 mmol) in toluene (10 mL), $SOCl_2$ (0.87 mL, 12 mmol) was added and the reaction mixture was stirred at 80 ◦C for 3 h. The reaction mixture was concentrated under reduced pressure, before DCM (4 mL) and Et_3N (5 mL) were added and the solution cooled to 0 ◦C before benzylamine (0.218 mL, 2 mmol) was added. This solution was stirred at R.T for 1 h. This was washed with a $NaHCO_3$ solution and extracted with Et_2O (3 x 5 mL). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure to afford the product.

6.5.15 Characterisation Data for Products in Scheme 5.17, and Table 5-2



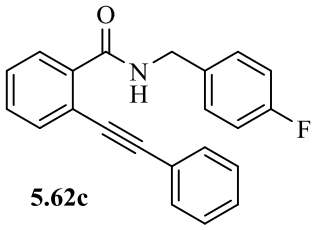
5.62a

N-benzyl-2-(phenylethynyl)benzamide **(5.62a)** was ontained as a pure white solid (0.48 g, 78 %). Crystals suitable for a single crystal X-ray diffraction study were grown from a dichloromethane solution of the complex layered with hexane. Mp: 130-132 ◦C. ^{1}H NMR (400 MHz; $CDCl_3$) δ_H 4.66 (2H, m $_{A,B}$, CH_AH_B), 7.12 (2H, td, $^{3}J_{HH}$ = 7.0, $^{4}J_{HH}$ = 1.1 Hz, Ar*H*), 7.22 (5H, m, Ar*H*), 7.29 (1H, td, $^{3}J_{HH}$ = 7.5, $^{4}J_{HH}$ = 1.4, Ar*H*), 7.34 (2H, m, Ar*H*), 7.40 (2H, m, Ar*H*), 7.56 (1H, m, Ar*H*), 7.79 (1H, s, Ar*H*), 8.10 (1H, m, N*H*); ^{13}C{^{1}H} NMR (100 MHz; $CDCl_3$) δ_C 44.7 (CH_2), 87.7 (C), 95.7 (C), 119.8 (CH), 122.1 (CH), 127.4 (C), 128.4 (CH), 128.6 (CH), 128.9 (CH), 129.0 (CH), 129.2 (CH), 130.5 (CH), 130.7 (C), 131.5 (CH), 133.8 (CH), 135.2 (CH), 138.1 (C), 166.1 (CO). m/z (ASAP): 312.1362 ([MH]$^+$, $C_{22}H_{18}NO$ requires 312.1359, 100 %).



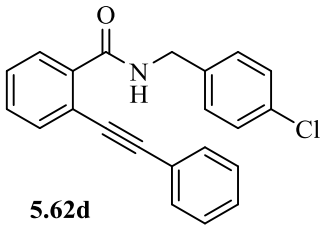
5.62b

N-(4-methylbenzyl)-2-(phenylethynyl)benzamide **(5.62b)** was ontained as a brown oil. This product was washed with EtOAc : HCl 1.0 M (1:2) (100: 200 mL) and stirred at room temperature for 24 h. The mixture was extracted with EtOAc (2 x 10 mL), the combined organic layers dried over $MgSO_4$, and the solvent removed *in vacuo* to give a pure white solid product (0.37 g, 80 %). Crystals suitable for a single crystal X-ray diffraction study were grown from a dichloromethane solution of the complex layered with chloroform. Mp: 121-123 ◦C. ^{1}H NMR (400 MHz; $CDCl_3$) δ_H 2.30 (3H,s, CH_3) , 4.64 (2H, m $_{A,B}$, CH_AH_B), 7.04 (2H, dd, $^{3}J_{HH}$ = 7.0, $^{4}J_{HH}$ = 1.2 Hz, Ar*H*), 7.10 (2H, dd, $^{3}J_{HH}$ = 7.9, $^{3}J_{HH}$ = 1.5, Ar*H*), 7.23 (4H, m, Ar*H*), 7.33 (1H, td, $^{3}J_{HH}$ = 7.8, $^{4}J_{HH}$ = 1.6, Ar*H*), 7.44 (2H, m, Ar*H*), 7.58 (1H, m, Ar*H*), 7.80 (1H, s, Ar*H*), 8.13 (1H, m, N*H*); ^{13}C{^{1}H} NMR (100 MHz; $CDCl_3$) δ_C 20.0 (CH_3), 44.8 (CH_2), 86.4 (C), 94.7 (C), 118.5 (CH), 120.8 (CH), 127.2 (C), 127.4 (CH), 127.7 (CH), 127.8 (CH), 128.4 (CH), 129.2 (CH), 129.5 (CH), 130.4 (C), 132.5 (CH), 133.7 (C), 134.0 (C), 136.1 (C), 164.9 (CO). m/z (ASAP): 326.1549 ([MH]$^+$, $C_{23}H_{19}NO$ requires 326.1545, 100 %).



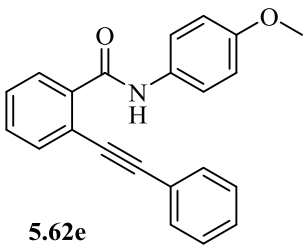
5.62c

N-(4-fluorobenzyl)-2-(phenylethynyl)benzamide **(5.62c)** was ontained as a brown oil. This product was washed with EtOH : HCl 1.0 M (1:2) (100: 200 mL) and stirred at room temperature for 24 h. The mixture was extracted with EtOAc (2 x 10 mL), the combined organic layers dried over $MgSO_4$, and the solvent removed *in vacuo* to give a pure white solid product (0.34 g, 73 %). Crystals suitable for a single crystal X-ray diffraction study were grown from a acetonitrile solution of the complex layered with chloroform. Mp: 170-172 ◦C. Sample was not soluble enough to obtain a NMR spectra. m/z (ASAP): 330.1282 ($[MH]^+$, $C_{22}H_{16}FNO$ requires 330.1294, 100 %).



5.62d

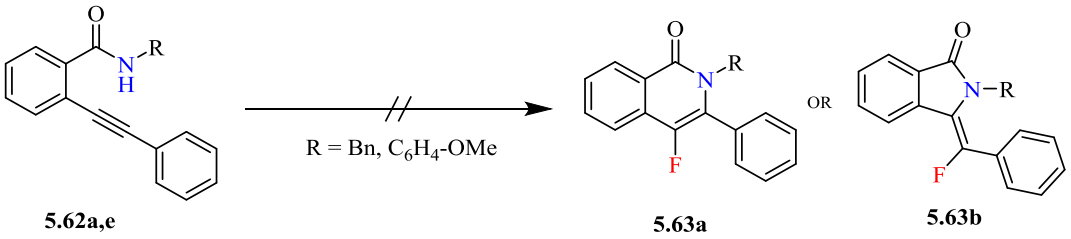
N-(4-chlorobenzyl)-2-(phenylethynyl)benzamide **(5.62d)** was ontained as a brown oil. This product was washed with EtOH : HCl 1.0 M (1:2) (100: 200 mL) and stirred at room temperature for 24 h. The mixture was extracted with $CHCl_3$ (2 x 10 mL), the combined organic layers dried over $MgSO_4$, and the solvent removed *in vacuo* to give a pure white solid product (0.36 g, 74 %). mp 110-112 ◦C. ^{1}H NMR (400 MHz; $CDCl_3$) δ_H 4.58 (2H, m $_{A,B}$, CH_AH_B), 7.06 (2H, dd, $^3J_{HH}$ = 7.0, $^4J_{HH}$ = 1.9 Hz, Ar*H*), 7.11 (2H, td, $^3J_{HH}$ = 7.0, $^4J_{HH}$ = 1.9 Hz, Ar*H*), 7.22 (4H, m, Ar*H*), 7.28 (1H, td, $^3J_{HH}$ = 7.0, $^4J_{HH}$ = 1.8, Ar*H*), 7.38 (2H, m, Ar*H*), 7.52 (1H, m, Ar*H*), 7.72 (1H, s, Ar*H*), 8.06 (1H, m, N*H*); ^{13}C{^{1}H} NMR (100 MHz; $CDCl_3$) δ_C 44.7 (CH_2), 86.4 (C), 94.8 (C), 127.4 (C), 127.5 (CH), 127.9 (CH), 128.0 (CH), 128.1 (CH), 128.5 (CH), 129.2 (CH),129.7 (CH), 130.2 (CH), 131.4 (C), 132.4 (CH), 132.5 (CH), 133.8 (C), 135.4 (C), 140.5 (C), 165.0 (CO). m/z (ASAP): 346.0994 ($[MH]^+$, $C_{22}H_{16}ClNO$ requires 346.0999, 100 %).



5.62e

N-(4-Methoxyphenyl)-2-(phenylethynyl)benzamide **(5.62e)** [24] was ontained as a pure white solid (0.38 g, 67 %). Crystals suitable for a single crystal X-ray diffraction study were grown from a acetonitrile solution of the complex layered with chloroform. Mp: 155-157 ◦C. ^{1}H NMR (400 MHz; $CDCl_3$) δ_H 3.81 (3H, s, C*H*$_3$), 7.26 (1H, s, Ar*H*), 7.37 (4H, m, Ar*H*), 7.49 (4H, m, Ar*H*), 7.57 (2H, m, Ar*H*), 7.65 (1H, m, Ar*H*), 8.14 (1H, m, Ar*H*), 9.11 (1H, s, N*H*); ^{13}C{1H} NMR (100 MHz; $CDCl_3$) δ_C 55.5 (CH_3), 87.3 (C), 96.4 (C), 114.2 (CH), 119.5 (C), 121.7 (CH), 121.8 (C), 128.1 (CH), 128.6 (CH), 129.1 (CH), 129.3 (CH), 130.2 (CH),130.8 (CH), 131.1 (C), 131.6 (CH), 133.4 (CH), 135.9 (C), 156.5 (C), 164.2 (CO). m/z (ASAP): 328.1342 ($[MH]^+$, $C_{22}H_{17}NO_2$ requires 328.1338, 100 %).

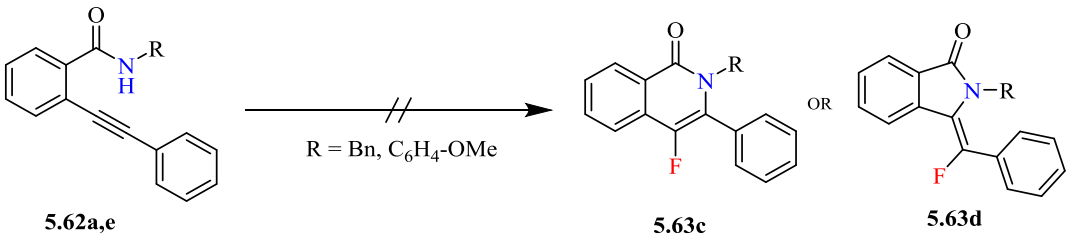
6.5.16 General Procedure for the Reaction in Scheme 5.18



5.62a,e **5.63a** **5.63b**

N-Benzyl-2-(phenylethynyl)benzamide (0.311 g, 1.0 mmol), or *N*-(4-methoxyphenyl)-2-(phenylethynyl)benzamide (0.327 g, 1.0 mmol), was dissolved in dry DMA (7 mL), and $AgNO_3$ (0.035 g, 0.2 mmol), NFSi (0.48 g, 1.5 mmol), and Li_2CO_3 (0.075 g, 1.0 mmol) were added. The mixture was left to stir at r.t overnight under nitrogen. The reaction mixture was quenched with H_2O (20 mL), and extracted with Et_2O (3 x 15 mL). The combined organic layers were dried over $MgSO_4$ and the solvent was removed *in vacuo*. A saturated solution of LiCl (5 mL) was added and the mixture was left to stir for 10 min. The mixture was extracted with Et_2O (3 x 10 mL), the mixture was dried using $MgSO_4$, and the solvent was removed *in vacuo* to give the crude product (0.308 g). ^{1}H NMR spectroscopy showed 100 % recording of the starting material. The desired product was not observed.

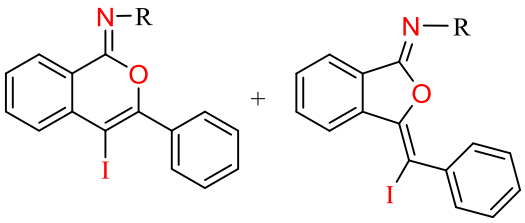
6.5.17 General Procedure for the Reaction in Scheme 5.18



5.62a,e **5.63c** **5.63d**

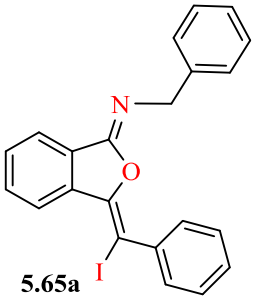
N-Benzyl-2-(phenylethynyl)benzamide (0.311 g, 1.0 mmol), or *N*-(4-methoxyphenyl)-2-(phenylethynyl)benzamide (0.327 g, 1.0 mmol), was dissolved in dry DMA (8 mL), $AgNO_3$ (0.035 g, 0.2 mmol), NFSi (0.96 g, 3.0 mmol), and Li_2CO_3 (0.075 g, 1.0 mmol) were added. The reaction mixture was left to stir at 50° C 24 h under nitrogen. The solvent was removed *in vacuo* to give crude product (0.331 g). Analysis by ^1H and ^{19}F NMR spectroscopy showed a complex mixture of products that could not be purified.

6.5.18 General Procedure for the Reaction in Scheme 5.19



N-Benzyl-2-(phenylethynyl)benzamide (1 eq.) (0.311 g, 1 mmol), I_2 (3 eq.) (0.761 g, 3 mmol), K_2CO_3 (2 eq.) (0.276 g, 2 mmol), and dry MeCN (30 mL) were charged into a three-necked flask. After stirring under N_2 at R.T for 96 h, a saturated solution of NaS_2O_3 (10 mL) was added to the mixture and it was stirred for 5 min. The mixture was extracted with Et_2O (3 x 10 mL), the combined organic layers were dried over $MgSO_4$ (anhydrous), and the solvent was removed *in vacuo*.

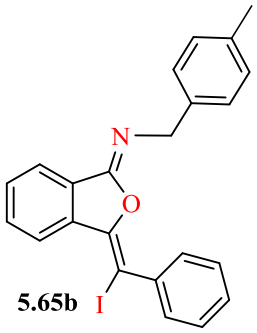
6.5.19 Characterisation Data for Products in Scheme 5.19



5.65a

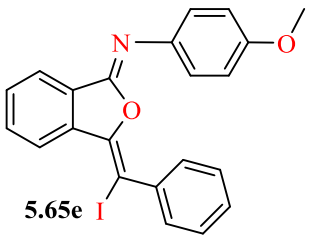
Attempted purification by column chromatography (EtOAc: petroleum ether) (2:8) gave an inseparable mixture (0.407 g, 85 %), in a 1:10 ratio of (*Z*)-*N*-benzyl-4-iodo-3-phenyl-1H-isochromen-1-imine **(5.64a)**, (1*Z*,3*E*)-*N*-benzyl-3-(iodo(phenyl)methylene)isobenzofuran-1(3*H*)-imine **(5.65a)**. The characterisation data are given for the major compound **(5.65a)** in

the mixture. ^{1}H NMR (400 MHz; $CDCl_3$) δ_H 4.53 (2H, s, C*H*$_2$), 7.14 (1H, m, Ar*H*), 7.20 (4H, d, $^{3}J_{HH}$ = 7.8 Hz, Ar*H*), 7.31 (2H, t, $^{3}J_{HH}$ = 7.7 Hz, Ar*H*), 7.39 (1H, m, Ar*H*), 7.48 (3H, t, $^{3}J_{HH}$ = 7.3 Hz, Ar*H*), 7.57 (1H, d, $^{3}J_{HH}$ = 7.6 Hz, Ar*H)*, 7.87 (1H, d, $^{3}J_{HH}$ = 7.7 Hz, Ar*H*), 8.73 (1H, d, $^{3}J_{HH}$ = 7.9 Hz, Ar*H*), ^{13}C{^{1}H} NMR (100 MHz; $CDCl_3$) δ_C 50.7 (CH_2), 72.6 (CI), 122.4 (CH), 123.8 (CH), 125.5 (CH), 125.8 (CH), 127.0 (CH), 128.1 (CH), 128.9 (CH), 130.3 (CH), 130.6 (CH), 131.7 (C), 132.9 (C), 134.9 (CH), 138.7 (C), 139.6 (C), 146.2 (C), 153.4 (CN). IR (selected bonds, cm^{-1}): 1666 ($\upsilon_{C=N}$). m/z (ASAP): 438.0358 ([MH]$^{+}$, $C_{22}H_{16}INO$ requires 438.0355, 100 %).



5.65b

Attempted purification by column chromatography (EtOAc: petroleum ether) (2:8) gave an inseparable mixture (0.317 g, 89 %), in a 1:8 ratio of 4-iodo-2-(4-methylbenzyl)-3-phenylisoquinolin-1(2*H*)-one **(5.64b)**, (*E*)-3-(iodo(phenyl)methylene)-2-(4-methylbenzyl)isoindolin-1-one **(5.65b)**. The characterisation data are given for the major compound **(5.65b)** in the mixture. ^{1}H NMR (400 MHz; $CDCl_3$) δ_H 2.23 (3H, s, C*H*$_3$) 4.49 (2H, s, C*H*$_2$), 7.00 (2H, d, $^{3}J_{HH}$ = 7.9 Hz, Ar*H)*, 7.07 (2H, d, $^{3}J_{HH}$ = 7.9 Hz, Ar*H)*, 7.22(2H, m, Ar*H)*, 7.31 (3H, t, $^{3}J_{HH}$ = 7.8 Hz, Ar*H*), 7.38 (1H, m, Ar*H*), 7.46 (2H, t, $^{3}J_{HH}$ = 7.5 Hz, Ar*H*), 7.50 (1H, d, $^{3}J_{HH}$ = 7.2 Hz, Ar*H)*, 7.84 (1H, d, $^{3}J_{HH}$ = 7.6 Hz, Ar*H*), 8.73 (1H, d, $^{3}J_{HH}$ = 7.9 Hz, Ar*H*); ^{13}C{^{1}H} NMR (100 MHz; $CDCl_3$) δ_C 20.0 (CH_3), 50.5 (CH_2), 72.3 (CI), 122.2 (CH), 122.3 (CH), 126.8 (CH), 127.9 (CH), 128.1 (CH), 128.3 (CH), 128.6 (CH), 128.8 (CH), 130.8 (C), 132.8 (CH), 135.2 (C), 135.8 (C), 139.7 (C), 146.3 (C), 153.1 (C), 158.9 (CN). IR (selected bonds, cm^{-1}): 1665 ($\upsilon_{C=N}$). m/z (ASAP): 452.0338 ([MH]$^{+}$, $C_{23}H_{18}INO$ requires 452.0355, 100 %).

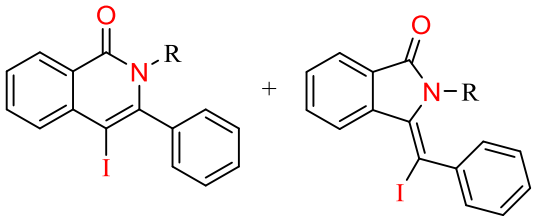


5.65e

Attempted purification by column chromatography (EtOAc: petroleum ether) (2:8) gave an inseparable mixture (0.132 g, 27 %), in a 1:9 ratio of (*Z*)-4-iodo-*N*-(4-methoxyphenyl)-3-phenyl-1*H*-isochromen-1-imine **(5.64e)**, (1*Z*,3*Z*)-3-(iodo(phenyl)methylene)-*N*-(4-methoxyphenyl)isobenzofuran-1(3*H*)-imine **(5.65e)**. The characterisation data are given for the major compound **(5.65e)** in the mixture. ^{1}H NMR (400 MHz; $CDCl_3$) δ_H 3.72 (3H,

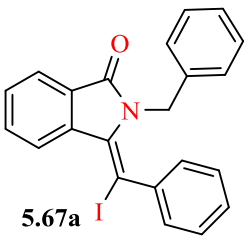
s, C*H*$_3$), 6.67 (2H, d, $^3J_{HH}$ = 7.7 Hz, Ar*H*), 7.19 (1H, s, Ar*H)*, 7.25 (1H, d, $^3J_{HH}$ = 7.9 Hz, Ar*H)*, 7.33 (3H, m, $^3J_{HH}$ = 7.9 Hz, Ar*H*), 7.55 (3H, m, Ar*H*), 7.60 (1H, t, $^3J_{HH}$ = 7.6 Hz, Ar*H*), 7.94 (1H, d, $^3J_{HH}$ = 7.7 Hz, Ar*H*), 8.77 (1H, d, $^3J_{HH}$ = 7.9 Hz, Ar*H*); $^{13}C\{^1H\}$ NMR (100 MHz; $CDCl_3$) δ_C 45.3 (CH_3), 54.3 (CI), 112.6 (CH), 122.5 (CH), 123.8 (CH), 125.5 (CH), 125.8 (CH), 127.0 (CH), 128.1 (CH), 128.9 (CH), 130.3 (CH), 130.6 (CH), 131.7 (C), 132.9 (C), 134.9 (C), 138.7 (C), 139.6 (C), 146.2 (C), 153.4 (CN). IR (selected bonds, cm^{-1}): 1668 ($\upsilon_{C=N}$). m/z (ASAP): 454.0298 ($[MH]^+$, $C_{22}H_{16}INO_2$ requires 454.0304, 100 %).

6.5.20 General Procedure for the Reaction in Scheme 5.20



N-benzyl-2-(phenylethynyl)benzamide (1 eq.) (0.311 g, 1 mmol), I_2 (3 eq.) (0.761 g, 3 mmol), K_2CO_3 (2 eq.) (0.276 g, 2 mmol), and dry DCM (30 mL) were charged into a three-necked flask. After stirring under N_2 at R.T for 48 h, a saturated solution of NaS_2O_3 (10 mL) was added to the mixture and stirred for 5 min. the mixture was extracted with DCM (3 x 10 mL). The combined organic layers were dried over $MgSO_4$ (anhydrous), and the solvent was removed *in vacuo*.

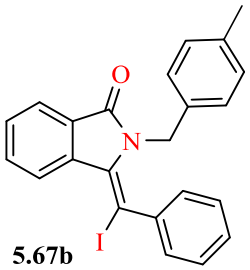
6.5.21 Characterisation Data for Products in Scheme 5.20



5.67a

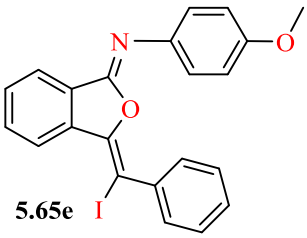
Purification by column chromatography (EtOAc: petroleum ether) (1:9) gave an inseparable mixture 0.326 g, 68 %), in a 1:7 the ratio of 2-benzyl-4-iodo-3-phenylisoquinolin-1(2*H*)-one **(5.66a)**, (*E*)-2-benzyl-3-(iodo(phenyl)methylene)isoindolin-1-one **(5.67a)**. The characterisation data are given for the major compound **(5.67a)** in the mixture. ^1H NMR (400 MHz; $CDCl_3$) δ_H 4.52 (2H, s, C*H*$_2$), 7.13 (1H, m, Ar*H*), 7.19 (5H, m, Ar*H*), 7.37 (1H, m, Ar*H*), 7.45 (2H, t, $^3J_{HH}$ = 7.7 Hz, Ar*H*), 7.49 (1H, d, $^3J_{HH}$ = 7.9 Hz, Ar*H)*, 7.54 (2H, t, $^3J_{HH}$ = 7.9 Hz, Ar*H)*, 7.83 (1H, d, $^3J_{HH}$ = 7.9 Hz, Ar*H*), 8.71 (1H, d, $^3J_{HH}$ = 7.8 Hz, Ar*H*); $^{13}C\{^1H\}$ NMR (100 MHz; $CDCl_3$) δ_C 50.7 (CH_2), 72.6 (CI), 122.3 (CH), 122.5 (CH), 123.8 (CH), 125.5 (CH), 127.1 (CH), 128.2 (CH), 128.9 (CH), 129.6 (CH), 130.0 (C), 130.4 (C), 134.7 (CH), 137.1 (C), 139.6 (C), 146.2 (C), 153.4

(CH), 191.3 (CO). IR (selected bonds, cm^{-1}): 1712 ($\upsilon_{C=O}$). m/z (ASAP): 438.0338 ($[MH]^+$, $C_{22}H_{16}INO$ requires 438.0355, 100 %).



5.67b

Purification by column chromatography (EtOAc: petroleum ether) (1:9) gave an inseparable mixture (0.312 g, 88 %), in a 1:6 ratio of4-iodo-2-(4-methylbenzyl)-3-phenylisoquinolin-1(2*H*)-one **(5.66b)** (*E*)-3-(iodo(phenyl)methylene)-2-(4-methylbenzyl)isoindolin-1-one **(5.67b)**. The characterisation data are given for the major compound **(5.67b)** in the mixture. ^{1}H NMR (400 MHz; $CDCl_3$) δ_H 2.21 (3H, s, C*H*$_3$) 4.47 (2H, s, C*H*$_2$), 6.98 (2H, d, $^3J_{HH}$ = 7.5 Hz, Ar*H)*, 7.06 (2H, d, $^3J_{HH}$ = 7.6 Hz, Ar*H)*, 7.21(2H, d, $^3J_{HH}$ = 7.2 Hz, Ar*H)*, 7.30 (3H, t, $^3J_{HH}$ = 7.5 Hz, Ar*H*), 7.37 (1H, m, Ar*H*), 7.44 (2H, d, $^3J_{HH}$ = 7.5 Hz, Ar*H*), 7.49 (2H, d, $^3J_{HH}$ = 7.9 Hz, Ar*H)*, 7.82 (1H, d, $^3J_{HH}$ = 7.6 Hz, Ar*H*), 8.71 (1H, d, $^3J_{HH}$ = 7.9 Hz, Ar*H*); ^{13}C{^{1}H} NMR (100 MHz; $CDCl_3$) δ_C 20.0 (CH_3), 50.4 (CH_2), 72.4 (CI), 122.2 (CH), 122.3 (CH), 126.8 (CH), 127.9 (CH), 128.1 (CH), 128.3 (CH), 128.6 (CH), 128.8 (CH), 130.8 (C), 132.8 (CH), 135.2 (C), 135.8 (C), 139.6 (C), 146.2 (C), 153.3 (C), 190.9 (CO). IR (selected bonds, cm^{-1}): 1702 ($\upsilon_{C=O}$). m/z (ASAP): 452.0338 ($[MH]^+$, $C_{23}H_{18}INO$ requires 452.0355, 100 %).



5.65e

Purification by column chromatography (EtOAc: petroleum ether) (1:9) gave an inseparable mixture (0.067 g, 13 %), in a 1:4 ratio of (*Z*)-4-iodo-*N*-(4-methoxyphenyl)-3-phenyl-1*H*-isochromen-1-imine **(5.64e)**, (1*Z*,3*Z*)-3-(iodo(phenyl)methylene)-*N*-(4-methoxyphenyl)isobenzofuran-1(3*H*)-imine **(5.65e)**, The characterisation data are given for the major compound **(5.56e)**. in the mixture. ^{1}H NMR (400 MHz; $CDCl_3$) δ_H 3.72 (3H, s, C*H*$_3$), 6.67 (2H, d, $^3J_{HH}$ = 7.7 Hz, Ar*H*), 7.19 (1H, s, Ar*H)*, 7.25 (1H, d, $^3J_{HH}$ = 7.9 Hz, Ar*H)*, 7.33 (3H, m, $^3J_{HH}$ = 7.9 Hz, Ar*H*), 7.55 (3H, m, Ar*H*), 7.60 (1H, t, $^3J_{HH}$ = 7.6 Hz, Ar*H*), 7.94 (1H, d, $^3J_{HH}$ = 7.7 Hz, Ar*H*), 8.77 (1H, d, $^3J_{HH}$ = 7.9 Hz, Ar*H*); ^{13}C{^{1}H} NMR (100 MHz; $CDCl_3$) δ_C 45.3 (CH_3), 54.3 (CI), 112.6 (CH), 122.5 (CH), 123.8 (CH), 125.5 (CH), 125.8 (CH), 127.0 (CH), 128.1 (CH), 128.9 (CH), 130.3 (CH), 130.6 (CH), 131.7 (C), 132.9 (C), 134.9

(C), 138.7 (C), 139.6 (C), 146.2 (C), 153.4 (CN). IR (selected bonds, cm^{-1}): 1668 ($\upsilon_{C=N}$). m/z (ASAP): 454.0326 ($[MH]^+$, $C_{22}H_{16}INO_2$ requires 454.0304, 100 %).

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Appendix

A1 Crystal Data and Structure refinement for (3.58a)

Identification code	16147	
Empirical formula	C24 H22 F2 O3	
Formula weight	396.42	
Temperature	150(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	C2/c	
Unit cell dimensions	a = 25.316(4) Å	α= 90°.
	b = 8.0211(14) Å	β= 104.626(4)°.
	c = 19.987(4) Å	γ = 90°.
Volume	3927.1(12) $Å^3$	
Z	8	
Density (calculated)	1.341 Mg/m^3	
Absorption coefficient	0.100 mm^{-1}	
F(000)	1664	
Crystal size	0.17 x 0.15 x 0.04 mm^3	
Theta range for data collection	1.66 to 25.00°.	
Index ranges	-30<=h<=30, -9<=k<=9, -23<=l<=23	
Reflections collected	13809	
Independent reflections	3469 [R(int) = 0.1541]	
Completeness to theta = 25.00°	99.9 %	
Absorption correction	Empirical	
Max. and min. transmission	0.983 and 0.728	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3469 / 0 / 237	
Goodness-of-fit on F^2	0.768	
Final R indices [I>2sigma(I)]	R1 = 0.0624, wR2 = 0.1130	
R indices (all data)	R1 = 0.1601, wR2 = 0.1311	
Largest diff. peak and hole	0.259 and -0.251 $e.Å^{-3}$	

A2 Crystal Data and Structure refinement for (5.58)

Identification code	18046	
Empirical formula	C15 H10 O2	
Formula weight	222.23	
Temperature	150(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	Pbcn	
Unit cell dimensions	a = 24.511(5) Å	α= 90°.
	b = 17.358(4) Å	β= 90°.
	c = 10.567(2) Å	γ = 90°.
Volume	4496.0(16) $Å^3$	
Z	16	
Density (calculated)	1.313 Mg/m^3	
Absorption coefficient	0.087 mm^{-1}	
F(000)	1856	
Crystal size	0.27 x 0.22 x 0.12 mm^3	
Theta range for data collection	1.44 to 26.00°.	
Index ranges	-30<=h<=30, -21<=k<=21, -12<=l<=13	
Reflections collected	33180	
Independent reflections	4419 [R(int) = 0.0924]	
Completeness to theta = 26.00°	100.0 %	
Absorption correction	Empirical	
Max. and min. transmission	0.983 and 0.445	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	4419 / 0 / 307	
Goodness-of-fit on F^2	0.947	
Final R indices [I>2sigma(I)]	R1 = 0.0493, wR2 = 0.0970	
R indices (all data)	R1 = 0.0853, wR2 = 0.1077	
Largest diff. peak and hole	0.183 and -0.187 $e.Å^{-3}$	

A3 Crystal Data and Structure refinement for (5.62a)

Identification code	18062	
Empirical formula	C22 H17 N O	
Formula weight	311.37	
Temperature	150(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)	
Unit cell dimensions	a = 10.328(4) Å	α= 90°.
	b = 5.0421(17) Å	β= 104.126(7)°.
	c = 16.191(5) Å	γ = 90°.
Volume	817.7(5) $Å^3$	
Z	2	
Density (calculated)	1.265 Mg/m^3	
Absorption coefficient	0.077 mm^{-1}	
F(000)	328	
Crystal size	0.49 x 0.12 x 0.06 mm^3	
Theta range for data collection	1.30 to 24.99°.	
Index ranges	-12<=h<=12, -5<=k<=5, -19<=l<=18	
Reflections collected	5956	
Independent reflections	1607 [R(int) = 0.1908]	
Completeness to theta = 24.99°	99.9 %	
Absorption correction	Empirical	
Max. and min. transmission	0.981 and 0.704	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	1607 / 1 / 217	
Goodness-of-fit on F^2	0.885	
Final R indices [I>2sigma(I)]	R1 = 0.0636, wR2 = 0.0967	
R indices (all data)	R1 = 0.1060, wR2 = 0.1096	
Absolute structure parameter	?	
Largest diff. peak and hole	0.234 and -0.251 e.$Å^{-3}$	

A4 Crystal Data and Structure refinement for (5.62b)

Identification code	18043	
Empirical formula	C23 H19 N O	
Formula weight	325.39	
Temperature	150(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	Pna2(1)	
Unit cell dimensions	a = 9.152(3) Å	α= 90°.
	b = 9.712(3) Å	β= 90°.
	c = 19.531(7) Å	γ = 90°.
Volume	1735.9(10) $Å^3$	
Z	4	
Density (calculated)	1.245 Mg/m^3	
Absorption coefficient	0.076 mm^{-1}	
F(000)	688	
Crystal size	0.24 x 0.12 x 0.10 mm^3	
Theta range for data collection	2.09 to 25.00°.	
Index ranges	-10<=h<=10, -11<=k<=9, -23<=l<=23	
Reflections collected	7893	
Independent reflections	1568 [R(int) = 0.1644]	
Completeness to theta = 25.00°	99.6 %	
Absorption correction	Empirical	
Max. and min. transmission	0.970 and 0.161	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	1568 / 1 / 227	
Goodness-of-fit on F^2	0.955	
Final R indices [I>2sigma(I)]	R1 = 0.0743, wR2 = 0.1489	
R indices (all data)	R1 = 0.1091, wR2 = 0.1625	
Absolute structure parameter	?	
Largest diff. peak and hole	0.374 and -0.237 $e.Å^{-3}$	

A5 Crystal Data and Structure refinement for (5.62c)

Identification code	18044	
Empirical formula	C22 H16 F N O	
Formula weight	329.36	
Temperature	150(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	Pbca	
Unit cell dimensions	a = 17.320(5) Å	α= 90°.
	b = 8.625(2) Å	β= 90°.
	c = 23.026(6) Å	γ = 90°.
Volume	3439.4(16) $Å^3$	
Z	8	
Density (calculated)	1.272 Mg/m^3	
Absorption coefficient	0.085 mm^{-1}	
F(000)	1376	
Crystal size	0.32 x 0.16 x 0.15 mm^3	
Theta range for data collection	1.77 to 26.00°.	
Index ranges	-21<=h<=21, -10<=k<=10, -27<=l<=28	
Reflections collected	25439	
Independent reflections	3384 [R(int) = 0.2339]	
Completeness to theta = 26.00°	99.9 %	
Absorption correction	Empirical	
Max. and min. transmission	0.962 and 0.384	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3384 / 0 / 226	
Goodness-of-fit on F^2	0.836	
Final R indices [I>2sigma(I)]	R1 = 0.0641, wR2 = 0.1117	
R indices (all data)	R1 = 0.1804, wR2 = 0.1453	
Largest diff. peak and hole	0.243 and -0.217 $e.Å^{-3}$	

A6 Crystal Data and Structure refinement for (5.62e)

Identification code	18055	
Empirical formula	C22 H17 N O2	
Formula weight	327.37	
Temperature	150(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)/c	
Unit cell dimensions	a = 19.328(4) Å	α= 90°.
	b = 5.0797(10) Å	β= 112.474(4)°.
	c = 18.091(4) Å	γ = 90°.
Volume	1641.3(6) $Å^3$	
Z	4	
Density (calculated)	1.325 Mg/m^3	
Absorption coefficient	0.085 mm^{-1}	
F(000)	688	
Crystal size	0.40 x 0.11 x 0.08 mm^3	
Theta range for data collection	2.26 to 25.99°.	
Index ranges	-23<=h<=23, -6<=k<=6, -22<=l<=22	
Reflections collected	12098	
Independent reflections	3226 [R(int) = 0.1008]	
Completeness to theta = 25.99°	99.8 %	
Absorption correction	Empirical	
Max. and min. transmission	0.983 and 0.449	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3226 / 0 / 227	
Goodness-of-fit on F^2	0.853	
Final R indices [I>2sigma(I)]	R1 = 0.0551, wR2 = 0.0961	
R indices (all data)	R1 = 0.1118, wR2 = 0.1106	
Largest diff. peak and hole	0.213 and -0.233 $e.Å^{-3}$	

Conferences Attended

- Poster presentation: Midlands Meeting 7/04/2017 - University of Leicester
- Poster presentation: Departmental Research Day 4/07/2017 - University of Leicester
- Poster presentation: Main Group Interest Group Meeting 1/09/2017- Burlington House, London
- Poster presentation: 7th Annual RSC Fluorine Subject Group Postgraduate Meeting 18-19 September 2017, Tilton and Smithland Suite, John Foster Hall/ Leicester
- Poster presentation: Organ fluorine Chemistry: Synthetic Methods and Applications 9 /02/2018 SCI/ 14/15 Belgrave Square/ London/ SW1X 8PS.
- Poster presentation: the 22nd International Symposium on Fluorine Chemistry22-27-July -2018, Oxford University Examination Schools/ 75-81 High Street/ Oxford OX1 4BG

Short Courses

- (Basic Impedance Spectroscopy) Instructor by Mark Orazem 232nd Electrochemical Society Meeting/ Gaylord National Resort and Convention Centre, National Harbour, MD/ October 1st to October 5th 2017
- Introduction to Mass Spectrometry Course the 39t BMSS ANNUAL MEETING CHURCHILL COLLEGE CAMBRIDGE 10-13 September 2018.