Synthesis of Fluorinated Heterocycles by Electrophilic Cyclisations of Alkynes

Thesis submitted for the degree of Doctor of Philosophy at the University of Leicester

Jinglei He

Department of Chemistry, University of Leicester

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Abstract

Fluorinated heterocyclic compounds are a highly desirable target for the pharmaceutical industry because heterocyclic compounds often form the core structure in drug candidate molecules and the incorporation of fluorine often enhances their biological activity. The aim of this project was to design new and efficient procedures to fluorinated heterocycles using aromatic alkynes containing internal nucleophiles.

In Chapter 2 a series of known and new alkynes were synthesised by Sonagashira reactions of terminal alkynes with aryl iodides and the reactivity of these alkynes with electrophilic fluorinating reagents was studied. The alkynes were reacted with Selectfluor to generate difluorinated ketones and a diketone byproduct was also produced in some of the reactions. The introduction of an ortho-substituent (\(-\text{NO}_2\), \(-\text{CH}_2\text{OH}\), \(-\text{CHO}\), \(-\text{CH}_2\text{OAc}\)) on the aryl rings had a significant impact on these reactions and, in most cases, no difluoroketone products could be isolated.

In Chapter 3 iodoncyclisations of the alkynes with internal nucleophiles were studied as the model reactions for electrophilic cyclisation. When \(\text{Py}_2\text{I}^+\text{BF}_4^-\) was used as the electrophilic iodinating reagent, 6-membered rings were normally obtained. However, when iodine was used as the electrophilic iodinating reagent, either 6- or 5-membered rings could be obtained as the main products depending on the internal nucleophile. For example, the fluoroalkylated secondary alcohols underwent 6-endo-dig cyclisations with \(\text{Py}_2\text{I}^+\text{BF}_4^-\), whilst the reaction of the same substrate with iodine gave predominately the (\(E\)) 5-exo-dig iodocyclised products.

Palladium-catalysed protocyclisations with a range of aromatic alkyne substrates, including secondary and tertiary alcohols, carboxylic acid and secondary amine, are described in Chapter 4. A new fluorocyclisation for tertiary alcohols using \(N\)-fluorobenzenesulfonylimide and silver nitrate was developed successfully and three different types of fluorinated products (monofluorinated alcohol, difluorinated alcohol and monofluorinated alkene) were obtained depending upon the tertiary alcohol and the amount of \(N\)-fluorobenzenesulfonylimide.
Acknowledgements

I would like to take the opportunity to thank my supervisors; Prof. Eric Hope and Dr. Alison Stuart for their continued enthusiasm during these four years. The last four years are the most suffered years in my life so far, not only the pressures from the PhD researches, and also lots of difficulties from my family and social life. During these years, my father continuously received injustice judgement, my grandma suffered from gastric cancer and I lost my fiancée. I have to admit that I am not strong enough to conquer all the difficulties and pressures, not only once I lost my faith and behaved extremely bad. I must thank Prof. Hope and Dr. Stuart for their patience and encouragement, I definitely would have fallen at the first hurdle, long ago, without their unselfish assistance and understanding.

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### Abbreviations

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<thead>
<tr>
<th>Abbreviation</th>
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<tbody>
<tr>
<td>Å</td>
<td>Angstrom (0.1 nM)</td>
</tr>
<tr>
<td>Ar</td>
<td>Aryl Fragment</td>
</tr>
<tr>
<td>ASAP</td>
<td>Atmospheric Solids Analysis Probe</td>
</tr>
<tr>
<td>Bn</td>
<td>Benzyl Fragment</td>
</tr>
<tr>
<td>ca.</td>
<td>circa</td>
</tr>
<tr>
<td>cf.</td>
<td>conferatur</td>
</tr>
<tr>
<td>d</td>
<td>Doublet</td>
</tr>
<tr>
<td>DCM</td>
<td>Dichloromethane</td>
</tr>
<tr>
<td>DMA</td>
<td>Dimethylacetamide</td>
</tr>
<tr>
<td>dt</td>
<td>Double of Triplets</td>
</tr>
<tr>
<td>ee</td>
<td>Enantiomeric Excess</td>
</tr>
<tr>
<td>eq.</td>
<td>Equivalents</td>
</tr>
<tr>
<td>g</td>
<td>Grams</td>
</tr>
<tr>
<td>H</td>
<td>Hours</td>
</tr>
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<td>I</td>
<td>iso</td>
</tr>
<tr>
<td>J</td>
<td>Joules</td>
</tr>
<tr>
<td>m</td>
<td>multiplet</td>
</tr>
<tr>
<td>m/z</td>
<td>Mass/Charge Ratio</td>
</tr>
<tr>
<td>Me</td>
<td>Methyl Fragment</td>
</tr>
<tr>
<td>MeCN</td>
<td>Acetonitrile</td>
</tr>
<tr>
<td>MHz</td>
<td>Mega Herts</td>
</tr>
<tr>
<td>min</td>
<td>Minutes</td>
</tr>
<tr>
<td>MOM</td>
<td>Methoxymethyl Fragment</td>
</tr>
<tr>
<td>mp</td>
<td>Melting Point</td>
</tr>
<tr>
<td>Acronym</td>
<td>Definition</td>
</tr>
<tr>
<td>---------</td>
<td>----------------------------------</td>
</tr>
<tr>
<td>MS</td>
<td>Mass Spectrometry</td>
</tr>
<tr>
<td>NMR</td>
<td>Nuclear Magnetic Resonance</td>
</tr>
<tr>
<td>OAc</td>
<td>Acetate</td>
</tr>
<tr>
<td>OTf</td>
<td>Triflate</td>
</tr>
<tr>
<td>pKa</td>
<td>Acid Dissociation Constant</td>
</tr>
<tr>
<td>ppm</td>
<td>Parts Per Million</td>
</tr>
<tr>
<td>Pr</td>
<td>Propyl Fragment</td>
</tr>
<tr>
<td>pTol</td>
<td>para-tolyl Fragment</td>
</tr>
<tr>
<td>Py</td>
<td>Pyridyl Fragment</td>
</tr>
<tr>
<td>q</td>
<td>Quartet</td>
</tr>
<tr>
<td>s</td>
<td>Singlet</td>
</tr>
<tr>
<td>SET</td>
<td>Single Electron Transfer</td>
</tr>
<tr>
<td>tBu</td>
<td>t-butyl Fragment</td>
</tr>
<tr>
<td>THF</td>
<td>Tetrahydrofuran</td>
</tr>
<tr>
<td>t</td>
<td>Triplet</td>
</tr>
<tr>
<td>o</td>
<td>Degrees</td>
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Chapter 1
Chapter 1 Introduction

1.1 Introduction

Finding new synthetic routes to fluorinated heterocycles has become a popular topic in recent years because 20-25% of all drugs contain at least one fluorine atom. The incorporation of fluorine into biologically-active compounds often increases the bioavailability and lipophilicity of drugs, and enhances the binding affinity of the drugs for the enzyme’s active site. Surprisingly, the reactions of alkynes with fluorinating reagents have been rarely reported. The aim of the work in this thesis is therefore to understand this type of reaction and to investigate suitable reaction conditions for obtaining fluorinated heterocyclic products.

1.2 The use and importance of fluorine in drug development

Small molecule natural products have had a significant impact on pharmaceutical development. Many recently developed drugs, such as the taxoids and the Vinca alkaloids, are illustrative examples of the utility of natural sources in clinically based oncology. However, considering that organofluorine compounds are virtually absent as natural products, it is interesting that 20–25% of drugs in the pharmaceutical pipeline contain at least one fluorine atom.

One of the earliest synthetic fluorinated drugs is the antineoplastic agent, 5-fluorouracil (1.1), an antimetabolite first synthesised in 1957. It shows high anticancer activity by inhibiting the enzyme thymidylate synthase to prevent thymidine formation. Since the advent of 5-fluorouracil, fluorine substitution is commonly used in contemporary medicinal chemistry to improve metabolic stability, bioavailability and protein–ligand interactions. The strategic use of fluorine substitution in drug design has culminated with the production of some of the key drugs available on the market such as Fluoxetine (antidepressant), Faslodex (anticancer), Flurithromycin (antibacterial) and Efavirenz (antiviral). These fluorinated drugs
have become the most common and effective drugs in their treatment areas. Some of the previous less effective drugs or drugs that had side effects have been replaced by these new fluorinated molecules.

In the case of the antidepressant Fluoxetine (Eli Lilly), sold as a racemic mixture and commonly known as Prozac®, a trifluoromethyl group is attached to one of its aryl rings (1.2). It was approved by the Food and Drug Administration (FDA) in December 1987, and has become the most prescribed antidepressant drug worldwide, achieving annual sales in the region of one billion US dollars. In 1994, the FDA approved the drug for use in the treatment of both obsessive-compulsive disorder (OCD) and bulimia. Studies have shown that depression is linked to low levels of the neurotransmitter 5-hydroxytryptamine (5-HT), also known as serotonin. Fluoxetine acts by selectively inhibiting the reuptake of serotonin, thereby allowing the neurotransmitter to activate its specific receptor. Structure–activity relation studies have shown that the trifluoromethyl group in the para-position of the phenolic ring increased the potency for inhibiting 5-HT uptake by 32 times, compared to the non-fluorinated parent compound. 1.3 The trifluoromethyl group at this position creates a steric bulk which allows the phenoxy ring to adopt a conformation which favours binding to the serotonin transporter. 1.4

Faslodex (1.3) and Tamoxifen (1.4) are two anticancer drugs. Tamoxifen has been used very successfully in the treatment of hormone-dependent breast cancer since the 1970’s, and it is an oestrogen antagonist in breast tissue. However, it also acts as an oestrogen agonist in the bones and endometrium, and it has been linked to some undesirable side effects such as an increased risk of endometrial cancer. Faslodex® (AstraZeneca), also known as fulvestrant, was developed as a pentafluorinated 7α-alkylsulfinyl analogue of 17β-oestradiol to address the drawbacks of Tamoxifen. It is an oestrogen receptor antagonist, but has no agonist activity. Fulvestrant acts by competitively binding with oestradiol to the oestrogen receptors in breast tissue, reducing proliferation of the cancer cells. 1.5
Erythromycin is a macrolide antibiotic which is effective against a wide range of bacteria and is used to treat a series of infections including bronchitis and legionellosis. It is especially important for treatment of patients with penicillin anaphylaxis. As the drug decomposes under the acidic conditions of the stomach, Erythromycin is unsuitable for the treatment of gastritis caused by Helicobacter pylori infection. Flurithromycin (Pharmacia) (1.5), launched in 1997, is a fluorinated analogue of Erythromycin developed with the aim of improving its
stability under acidic conditions. In the treatment of gastritis, even of peptic ulcers, Flurithromycin has a longer biological half-life, better bioavailability and reaches higher tissue concentrations than Erythromycin \textit{in vivo}. \textsuperscript{1.6, 1.7}

Efavirenz (1.6) (Bristol-Myers Squibb, trade names Sustiva\textsuperscript{®} and Stocrin\textsuperscript{®}) is a non-nucleoside reverse transcriptase inhibitor used in the treatment of HIV. As there is no cure for the HIV infection, the current strategy is to suppress the replication of the virus for as long as possible. With a trifluoromethyl group on the tertiary stereogenic centre in a heteroaliphatic ring, Efavirenz acts by binding to the reverse transcriptase enzyme remote from the active site, altering its conformation, and hence inhibiting the enzyme. In order to minimise the development of drug resistance, current treatment guidelines recommend the use of a combination of two nucleoside reverse transcriptase inhibitors with either a protease inhibitor or a non-nucleoside reverse transcriptase inhibitor. In 2001, the Efavirenz-based combination therapies were found to be the most active against the retrovirus, and were better tolerated by patients. \textsuperscript{1.8, 1.9} Structure–activity relationship studies showed that the presence of the trifluoromethyl group improved drug potency by lowering the pKa of the cyclic carbamate, which makes a key hydrogen bonding interaction with the protein. \textsuperscript{1.10}

Drugs with a fluorine substituent can also be used as mechanism-based inhibitors. Although the incorporation of a single fluorine atom into a molecule causes minimal steric perturbation, the high electronegativity of fluorine may result in unusual metabolic pathways, leading to inhibition of the target enzyme. Trifluridine (Viroptic1) (1.7) is an antiviral drug used for the treatment of eye infections caused by viral herpes. It can cause irreversible inhibition of thymidylate synthase (TS). Trifluridine acts by irreversibly forming a covalent bond with thymidylate synthase to inhibit this enzyme and then causes apoptotic cell death, which affects rapidly dividing cells such as viral or cancer cells. \textsuperscript{1.11}

One of the other mechanism-based inhibitors of thymidylate synthase (TS) is 5-fluorouracil (1.1). 5-Fluorouracil is used in standard therapy for treatment of a variety of malignancies
including gastrointestinal cancers, breast cancer and head and neck cancer. Because of the short biological half-life of the drug and its irregular absorption profile, 5-fluorouracil is administered by continuous infusion or by intravenous bolus. Unfortunately, the drug also displays neurotoxic and cardiotoxic side effects.  

Another important class of fluorinated mechanism-based inhibitors is the nucleoside reverse transcriptase inhibitors used in the treatment of HIV and AIDS. These drugs are structurally similar in size and shape to their non-fluorinated analogues and, hence, are incorporated into the growing viral DNA strand. They are phosphorylated but the lack of a hydroxyl group in the 3’-position leads to chain termination. It is also known that fluorination on the carbohydrate ring can affect its conformation, in particular the degree of puckering, which in turn can affect enzyme recognition.

There are several key features that are important for drugs to be effective. For the case of an orally administered drug, it must be able to withstand physiological pH in the stomach long enough to cross into the bloodstream and to be transported in sufficient quantity to the site of action. It must then perform its desired task efficiently, and finally be metabolised at an appropriate rate into non-toxic materials. For fluorine substituents to become useful, they have to improve one or several criteria from the list above and then contribute to the drug efficiency.

The effect of fluorine on physicochemical and conformational properties can be allocated into four different aspects. The perturbation of pKa can strongly adjust the binding affinity and the pharmacokinetic properties of a pharmaceutical agent. Since fluorine is the most electronegative element, its inclusion in a molecule has a very strong effect on the acidity or basicity of the functional groups and as such can then modify the bioavailability of the orally administered drug. Secondly, for passive transport of an oral administered drug to be absorbed and distributed, the rate is dependent on the permeability of the cell membrane. For a drug molecule to pass through the membrane, its lipophilicity must be such that it can pass
into but not become trapped in the lipid core. Lipophilicity is expressed as a partition coefficient (log P) between octanol and water. Fluorine substituents on drug molecules will largely affect this partition coefficient and depending on the different types of fluorine substituent, lipophilicity can be either increased or decreased to make the drug efficient in passive transport. Thirdly, as the fluorine van der Waals radius lies between that of oxygen and hydrogen, substitution of a hydrogen or hydroxyl group for a fluorine in biologically active molecules exerts only a minor steric demand at receptor sites. However, since a trifluoromethyl group has a similar van der Waals volume to an iso-propyl group, the molecular conformation will be changed, and then combined with the high electronegativity of fluorine. Lastly, in comparison with hydrogen bonding, the participation of fluorine in electrostatic interactions is widely accepted and may contribute to the enhanced binding affinity of organofluorine compounds at the enzyme’s active site.

Due to the major successes of fluorinated compounds in medicinal chemistry, it may be predicted that the number and application of fluorine containing drugs will continue to increase.

1.3 Making NF reagents

Since the presence of fluorine in medicinal and plant-protection compounds can deeply influence their biological properties, the development of new synthetic methods that employ a variety of fluorinating reagents has been researched. These reagents may be classified as sources of fluoride ion (F⁻) or fluorine radicals (F⁻) and as compounds that can deliver electrophilic fluorine (F⁺). In traditional methods, these fluorine containing chemicals are made from hydrogen fluoride or other sources of the fluoride ion (e.g. pyridine·HF, Bu₄N⁺ HF₂⁻), activated alkali metal fluorides, as well as SF₄ and (diethylamino)sulfur trifluoride (DAST), which can convert carbon-oxygen bonds to carbon-fluorine bonds. The fluorination of electron-rich centres, in particular, a direct conversion of C-H to C-F linkages, is usually not feasible with HF-based chemistry and, therefore, electrophilic
fluorination needs to be used for this purpose. Under certain conditions elemental fluorine can be a useful synthetic reagent, and a regioselective introduction of fluorine using elemental fluorine has in principle been demonstrated for many organic substrates, including carbanions, enolates, olefins, and certain aromatics (Scheme 1.1). However it is, in general, difficult to achieve high yields, and there are only a few industrial-scale fluorination processes that are based on elemental fluorine, such as the synthesis of 5-fluorouracil (1.1).

![Scheme 1.1]

The difficulties associated with direct fluorination have stimulated the development of alternative sources of electrophilic fluorine. Perchloryl fluoride (FCIO₃), xenon difluoride (XeF₂), trifluoromethyl hypofluorite (CF₃OF), and various acyl and perfluoroacyl hypofluorites (RC(O)OF and RfC(O)OF), are examples of electrophilic fluorinating reagents. These compounds display the classical reactivity in the addition of electrophilic fluorine to carbanions and enolates as well as in the electrophilic fluorinations of aromatics.

While FCIO₃, XeF₂, and the hypofluorites are generally more selective electrophilic fluorinating reagents than elemental fluorine, their widespread use has been limited. While perchloryl fluoride has been employed in the industrial scale fluorination of steroidal enolates, with organic compounds this fluoride can become a dangerous oxidant. Xenon difluoride is a valuable laboratory fluorinating reagent but is not economical for use on a large scale. The hypofluorites are also very powerful oxidising as well as fluorinating agents. While CF₃OF can be stored at room temperature, acetyl and perfluoroacetyl hypofluorites are less stable and are usually generated in situ from their acetate salts and elemental fluorine.
A number of new NF fluorinating agents have emerged as generally safer and easier to handle, selective sources of electrophilic fluorine. These are either neutral $R_2NF$ compounds or quaternary ammonium $R_3N^+FA^-$ salts where $A^-$ is a non-nucleophilic anion. Most of the electrophilic NF reagents need to be prepared from elemental fluorine, with the only exceptions being a few substrates that have been prepared by electrochemical fluorination (ECF), $^{1,24}$ cobalt trifluoride fluorination, $^{1,25}$ or transfer fluorination. $^{1,26}$

The three most popular and commercially available NF reagents are Selectfluor ($R_3N^+FA^-$ salts), N-Fluorobenzenesulfonimide (NFSi) ($R_2NF$ compounds) and N-Fluoropyridinium salts ($R_3N^+FA^-$ salts). To make the Selectfluor or the N-Fluoropyridinium salts, fluorination of an amine precursor, in the presence of an equimolar amount of an alkali metal salt of a weakly nucleophilic anion, leads to the NF reagent and an alkali metal fluoride byproduct. For example, Umemoto’s $N$-fluoropyridinium triflate $^{1,27}$ and Selectfluor $^{1,28}$ are synthesised by this method (Scheme 1.2).

![Scheme 1.2](image)

The synthesis of N-Fluorobenzenesulfonimide (NFSi) involves fluorination of the parent acid of the desired reagent using elemental fluorine with concomitant formation of HF (Scheme 1.3).$^{1,29-1,31}$
Here, the R₂N- and R₃N⁺- organonitrogen fragments are chosen to be good leaving groups, thus promoting a reactivity of the bound fluorine with nucleophiles, as illustrated below for the quaternary salt reagents (Scheme 1.4).

\[ R_3N^+ - F + Nu^- \xrightarrow{\delta^+} R_3N \cdots F \cdots Nu \xrightarrow{\delta^-} R_3N + F - Nu \]

**Scheme 1.4**

Single electron transfer (SET) pathways are also possible and this reaction is usually indicated by a quantitative conversion of aqueous iodide solutions to iodine (Scheme 1.5).

\[ R_3N^+ F + I^- \xrightarrow{H_2O, H^+} R_3NH^+ + \frac{1}{2} I_2 + F^- \]

**Scheme 1.5**

The current known NF reagents display a wide range of oxidising and fluorinating power towards nucleophiles. Systems that can be fluorinated include benzene and activated aromatics, stabilised carbanions, activated olefins (aryl-substituted alkenes, alkyl and silyl enol ethers, enol acetates and enamines), certain organometallics, and aliphatic sulfides.

### 1.4 Application of NF reagents

The classical method for introducing fluorine into aromatic compounds is via the Balz-Schiemann reaction.\(^1\,^2\,^3\) This constitutes the replacement of an aryl-NH₂ by the fluorine atom through a diazonium salt. Alternatively, the exchange of other halogen atoms or the nitro group for fluorine with alkali metal fluorides has been employed as well. Due to the limitation of these reactions, new ways to selectively introduce fluorine into biologically
Active aromatic compounds by electrophilic fluorination has been found to provide a useful complement to the traditional methods.  

(a) via electrophilic aromatic substitution

\[
\begin{align*}
\text{F}^+ &= \begin{array}{c}
\text{Cl} \\
\text{N} \\
\text{Cl} \\
\text{F} \\
\text{BF}_4
\end{array} \\
\end{align*}
\]

(b) monosubstituted aromatics

\[
\begin{align*}
\text{R} &= \\
\text{F} &= \\
\text{BF}_4 &= \\
\text{N} &= \\
\text{Cl} &= \\
\text{F} &= \\
\text{Cl} &= \\
\text{R} &= \\
\text{F} &= \\
\text{(o,p)} &= \\
\end{align*}
\]

(c) disubstituted aromatics

\[
\begin{align*}
\text{F}^+ &= \begin{array}{c}
\text{N} \\
\text{Tf} \\
\end{array} \\
\text{Selectfluor} &= \begin{array}{c}
\text{N} \\
\text{Tf} \\
\end{array}
\end{align*}
\]

Scheme 1.6

Reagents such as N-fluoropyridinium salts, N-fluorobenzenesulfonimide and Selectfluor have been employed in electrophilic aromatic substitution reactions. Compounds with varying degrees of activation toward electrophilic aromatic substitution can be used including phenols, anisole, acetanilide, xylene, toluene, benzene and naphthalene. Different reactivity was observed, and the reactions can be carried out in a variety of solvents (halocarbons, CH₃CN) or in the substrate itself, and the products are usually mixtures of o/p-.
isomers. Mono-fluorinated products are obtained in most cases, but multiple fluorination has been observed in some reactions with the more reactive reagents such as Selectfluor and \(N\)-fluoropyridinium salts (Scheme 1.6). \(^{1.28, 1.36}\)

Directed ortho-lithiation, \(^{1.34}\) followed by electrophilic fluorination, has been successfully applied to the synthesis of regioisomerically pure ortho-fluorinated aromatic compounds. A range of carbon, oxygen, and sulfur ortho-metallating directing groups on aromatic compounds have been used to prepare o-lithiated substrates. These react readily with \(N\)-fluorobenzenesulfonylimide, \(^{1.34}\) and \(N\)-fluoro-o-benzenesulfonylimide, to yield the selectively fluorinated aromatics.

Two \(a, a\)-difluoro-isomers were formed at the same time by reacting the steroid with NFSi/KOtBu under thermodynamic reaction conditions with 62 % and 10 % isolated yields respectively (Scheme 1.7). These diastereoisomers were used as the key intermediates to prepare fluorinated vitamin D analogues. \(^{1.37}\)

![Scheme 1.7](image)

Various examples in the literature describe the direct \(a\)-fluorination of neutral \(\beta\)-dicarbonyl compounds with different electrophilic fluorinating agents. \(^{1.38-1.40}\) NF reagents have proved to be effective and safe for this transformation (Scheme 1.8).
One of the most exciting applications of the NF reagent is for enantioselective fluorinations, e.g. Selectfluor and NFSi have been utilised to prepare a new class of chiral \([N-F]^+\) reagents. The N-Fluoroammonium derivatives (1.8a-b) of \(p\)-chlorobenzoylquinine are shown in Scheme 1.9, and they were made by transfer fluorination using the NF reagents. 1.41-1.44

\[
\begin{align*}
\text{(1.8a)} & \quad \text{OMe} \quad \text{H} \quad \text{N}^+ \quad \text{BF}_4^- \quad \text{Cl} \\
\text{(1.8b)} & \quad \text{OMe} \quad \text{H} \quad \text{N}^+ \quad (\text{PhSO}_2)_2\text{N}^- \quad \text{Cl}
\end{align*}
\]

Scheme 1.9
These reagents were tested in the enantioselective fluorination of the trimethylsilyl enol ether of methyl and benzyl indanones, and the results were excellent with up to 98 % yield and with up to 85 % ee (Table 1.1).  

![Chemical structure](image)

\[
\text{[N-F]}^+ \xrightarrow{\text{MeCN, -40 °C}} \text{R} \xrightarrow{(1.8)} \text{R} = \text{Me or Bn}
\]

<table>
<thead>
<tr>
<th>[N-F]⁺</th>
<th>R</th>
<th>Yield %</th>
<th>ee %</th>
</tr>
</thead>
<tbody>
<tr>
<td>(1.8a)</td>
<td>Me</td>
<td>90</td>
<td>64</td>
</tr>
<tr>
<td>(1.8b)</td>
<td>Me</td>
<td>91</td>
<td>62</td>
</tr>
<tr>
<td>(1.8a)</td>
<td>Bn</td>
<td>98</td>
<td>84</td>
</tr>
<tr>
<td>(1.8b)</td>
<td>Bn</td>
<td>94</td>
<td>85</td>
</tr>
</tbody>
</table>

**Table 1.1**

Furthermore, the development of enantioselective catalysis using chiral Lewis acid catalysts, such as the taddol-modified (taddol = \(\alpha,\alpha',\alpha''\)-tetraaryl-2,2-dimethyl-1,3-dioxolan-4,5-dimethanl) titanium complexes (1.9a) and (1.9b), in combination with Selectfluor provided further improvement in the enantioselective fluorination of β-keto esters (Scheme 1.10).
At the beginning of my PhD in 2012, there was only one report outlining the direct fluorination of alkynes by Zupan. $\alpha,\alpha$-Difluoroketones were synthesised by reacting various phenylacetylenes with Selectfluor or Accufluor (NFTh) in MeCN/H$_2$O at reflux (Scheme 1.11). Higher yields were obtained with NFTh reaction, but NFTh is not as commonly used as Selectfluor, and NFTh is not even commercially available nowadays. 1.46, 1.47
1.5 Electrophilic alkyne activation depending on the \( \pi \)-electrophiles

Electrophilic alkyne activation with iodine (and other halogens) and with metal complexes has attracted the interest of a number of organic chemists,\(^{1.48-1.52}\) because the activation brings about many important molecular transformations, such as cyclisation, cycloisomerisation and cycloaddition.

In the cyclisation of carbon-carbon multiple bonds (such as alkynes), promoted by different electrophiles, different pathways have been reported. For example, the cyclisation of the 2-alkynyl azide aromatics (1.10) in the presence of a combined catalyst, \( \text{AuCl}_3 \) and \( \text{AgSbF}_6 \), in THF gave the corresponding isoquinolines in good yields.\(^{1.53}\) Alternatively, the cyclisation of (1.10) catalysed by TfOH afforded the Huisgen 1,3-dipolar cycloaddition products, triazoles (1.12), without the formation of the corresponding isoquinolines (Scheme 1.12).\(^{1.53a}\)
The similar Pd-catalysed cyclisations have been reported as well (Scheme 1.13). Protocyclised products (1.15) and (1.16) could be formed using the same palladium catalyst. Related substrates, with carboxylate and amine nucleophiles, are cyclised in a similar pathway, using palladium catalysts to form lactones and imines respectively. In each of these cases, proto-demetallation occurs on work-up.
In contrast, cyclisation of these substrates with iodinated reagents as the electrophile provides iodo-functionalised heterocycles, where further elaboration at the iodine can be envisaged. For example, the reaction of the 2-alkynyl azide aromatics with iodine or other iodonium donors, gave highly substituted cyclisation products, 1,3-disubstituted 4-iodoisoquinolines, in good to high yields. The reaction proceeds through the formation of an iodonium ion intermediate followed by nucleophilic cyclisation of the azide and subsequent elimination of N₂ (Scheme 1.14).
Further functionality has been introduced in cascade reactions for alkynyl substrates without internal nucleophiles, as reported by two groups. Barluenga et al used IPy$_2$BF$_4$ as the electrophile in the presence of alcohols for the cyclisation of aldehydes to O-heterocyclic products (Scheme 1.15).\textsuperscript{1.58, 1.59} In similar work, Larock et al used iodine in the presence of alcohols for the cyclisation of aldehydes and ketones (Scheme 1.16).\textsuperscript{1.60, 1.61}

\begin{center}
\begin{tikzpicture}
\begin{scope}
\node at (0,0) {\textbf{Scheme 1.15}};
\node[draw,shape=circle,fill=black,inner sep=1pt] (A) at (0,0) {\textbf{R}};
\node[draw,shape=circle,fill=black,inner sep=1pt] (B) at (1,0) {\textbf{OR}};
\node[draw,shape=circle,fill=black,inner sep=1pt] (C) at (2,0) {\textbf{IPy$_2$BF$_4$ (1.5 eq.),}};
\node[draw,shape=circle,fill=black,inner sep=1pt] (D) at (3,0) {\textbf{HBF$_4$Et$_2$O (1.2 eq.).}};
\node[draw,shape=circle,fill=black,inner sep=1pt] (E) at (4,0) {\textbf{R$_1$OH}};
\node[draw,shape=circle,fill=black,inner sep=1pt] (F) at (5,0) {\textbf{DCM, 0 °C to RT}};
\node[draw,shape=circle,fill=black,inner sep=1pt] (G) at (6,0) {\textbf{(1.18)}};
\node[draw,shape=circle,fill=black,inner sep=1pt] (H) at (7,0) {\textbf{DCM, 0 °C to RT}};
\node[draw,shape=circle,fill=black,inner sep=1pt] (I) at (8,0) {\textbf{(1.19)}};
\node[draw,shape=circle,fill=black,inner sep=1pt] (J) at (9,0) {\textbf{57- 87 %}};
\node[draw,shape=circle,fill=black,inner sep=1pt] (K) at (10,0) {\textbf{R = Ph, $n$-Bu, 1-$c$-hexenyl; R$_1$ = Me, $i$-Pr, $t$-Bu}};
\end{scope}
\end{tikzpicture}
\end{center}

\begin{center}
\begin{tikzpicture}
\begin{scope}
\node at (0,0) {\textbf{Scheme 1.16}};
\node[draw,shape=circle,fill=black,inner sep=1pt] (A) at (0,0) {\textbf{Y}};
\node[draw,shape=circle,fill=black,inner sep=1pt] (B) at (1,0) {\textbf{Nu (1.2 eq.)}};
\node[draw,shape=circle,fill=black,inner sep=1pt] (C) at (2,0) {\textbf{I$_2$ (2.5 eq.),}};
\node[draw,shape=circle,fill=black,inner sep=1pt] (D) at (3,0) {\textbf{K$_2$CO$_3$ (1.0 eq.)}};
\node[draw,shape=circle,fill=black,inner sep=1pt] (E) at (4,0) {\textbf{DCM}};
\node[draw,shape=circle,fill=black,inner sep=1pt] (F) at (5,0) {\textbf{(1.20)}};
\node[draw,shape=circle,fill=black,inner sep=1pt] (G) at (6,0) {\textbf{(1.21)}};
\node[draw,shape=circle,fill=black,inner sep=1pt] (H) at (7,0) {\textbf{Y = H, Me; NuH = MeOH, EtOH, PhOH, etc.}};
\node[draw,shape=circle,fill=black,inner sep=1pt] (I) at (8,0) {\textbf{21- 100 %}};
\end{scope}
\end{tikzpicture}
\end{center}

Alkyne activation with iodine, iodonium salts, metal complexes or protons takes place at a very early stage in these reactions, and the reaction pathways to form the cationic intermediates are different depending upon the catalyst and reagent. To clarify why the reaction takes a different pathway depending on the electrophiles, DFT calculations were carried out by Yamamoto and co-workers.\textsuperscript{1.53b} Computed enthalpies of formation and selected structural parameters of the optimised structures for the complexes between the alkyne (1.22) and the electrophiles (Brønsted acids, iodine, iodonium compounds, gold and silver complexes) are shown in Table 1.2. Selected structural parameters of the optimised structures of initial intermediates between diaryl acetylene (1.22) and various electrophilic reagents were calculated. Optimisations were done on the B3LYP/SDD level of theory.
Table 1.2

Comparing the binding energies of the actual catalysts (not the naked cations), the gold complexes demonstrated stronger interactions (ca. 28-38 kcal mol\(^{-1}\)), which can be considered as the most promising activators of the triple bond (ca. 18-30 kcal mol\(^{-1}\) for silver...
salts, *ca.* 1-8 kcal mol$^{-1}$ for Brønsted acids, *ca.* 3-22 kcal mol$^{-1}$ for interhalogen compounds). However, the enthalpies of formation of the naked cations, H$^+$, I$^+$, Au$^+$ and Ag$^+$ are much greater than those of the catalysts or reagents. In addition, these cations demonstrate strong asymmetrical binding that shows itself in a large difference between angles $c$ and $d$, and interatomic distances $a$ and $b$ resulting in two possible iodonium ions (e.g. (1.23) and (1.24) for naked I$^+$ (Scheme 1.17). Cyclisation of (1.23) would yield isoquinoline (1.25), whereas nucleophilic attack on (1.24) would result in addition to the triple bond and formation of product (1.26). The stabilities of the iodonium ions (1.23) and (1.24) are quite similar, therefore, under the reaction conditions interconversion between these two structures is possible. Hence, the chemoselectivity can only be regulated at a later stage of the reaction. There are two possible approaches: (i) Adjusting the properties of the base (to deprotonate (1.23)), and (ii) reducing the nucleophilic strength of the counterion (retarding formation of (1.26)) which will hopefully improve the chemoselectivity of the overall transformation in favour of (1.25) (the product via cyclisation).

Scheme 1.17
Computation for the other three H\(^+\), Au\(^+\) and Ag\(^+\) naked cations were also carried out, but only in the case of Ag\(^+\) and I\(^-\) could the two different structures be found. In the other two cases, the structures of the initial species formed from (1.22) and the cations could not be evaluated, since the optimisation calculations invariably produced the corresponding cyclisation products (Table 1.2).

In the case of reactions which adopt “symmetrical” coordination, the triple bond activation will also result in a different process, which is [3+2] cycloaddition reaction leading to triazoles (Scheme 1.18).

![Scheme 1.18](image)

This type of reaction would be mostly expected for catalysts with strong symmetrical coordination, such as AuCl and HX (X = Cl, I, Br, etc.). The Bronsted acids adopt “symmetrical” geometries and, therefore, the reaction of (1.22) with TfOH afforded triazoles (Scheme 1.12). On the other hand, the non-symmetrical coordination would favour the formation of isoquinolines (Scheme 1.12 and 1.14). PyI\(^+\), AuCl\(_3\) and AuPMMe\(_3\)\(^+\) adopt “non-symmetrical” or “slightly non-symmetrical” geometries. Isoquinolines are obtained selectively and triazoles are not formed. Hence, based on this computational study, the
addition of a phosphine ligand may be recommended to disfavour triazoles in favour of isoquinolines.

According to the theoretical predictions, the only exception to these ‘rules’ are the reactions with iodine. The covalent bond of iodine is more easily polarisable as compared to the others, which may be the reason why the reactions with iodine produced isoquinolines (Scheme 1.14).

The structural feature of (1.22) is specific in that there are two possible pathways for the attack of the nucleophilic N3 group to the alkyne, resulting in either isoquinolines or triazoles as the main product. However, if a nucleophile (rather than N3) is used that has no alternative diversity, the different electrophiles such as coinage metal complex, I2 and Brønsted acids must provide similar isoquinolines, and the only difference may be whether I or H is attached in the products.

1.6 Potential synthesis of fluorinated heterocycles

The cyclisation of alkynes with nucleophiles tethered through an aromatic ring represents a powerful tool for the formation of O-/N-heterocyclic scaffolds. As well as iodine or iodonium reagents, other electrophilic halogen compounds (Br+ or Cl+) have been reported as the reagents in the reaction of electrophilic halogen cyclisation. 1.62-1.64 For example, the products (1.28a), (1.28b) and (1.29) can be afforded, depending on the different catalyst or reagent used, either E (E = I, Br, Cl, etc.) or H (via metal-catalysed or acid-catalysed) will be incorporated in the products (Scheme 1.19).
In a comparison of the four main halogens (F₂, Cl₂, Br₂, I₂), fluorine is the smallest halogen and has the highest electronegativity. Therefore, in terms of reactivity, it normally follows the general trend: F < Cl < Br < I, with iodine normally forming the strongest interactions. There are only a few reports about the reactions of electrophilic fluorinating reagents with alkynes.

The first reaction between electrophilic fluorinating reagents and alkyne systems was reported by Zupan and co-workers. The Selectfluor reaction (Scheme 1.20), ¹⁴⁶,¹⁴⁷ indicated that electrophilic fluorinating reagents have the ability to react with alkynes, even though triple bonds are less reactive toward electrophilic reagents than double bonds by as much as a factor of ten. ¹⁶³ Four different R groups were tested and the effect of the substituent R on the
relative rate of fluorine addition was examined. It was found that the substitution of hydrogen \( (1.30a) \) with a methyl substituent \( (1.30d) \) greatly increased the reactivity. No transformation of phenylacetylene in a mixture with phenylpropyne was observed, which means that phenylacetylene is at least 100 times less reactive. \(^{1.65,1.66}\) However, substitution of the methyl group with a larger tert-butyl \( (1.30c) \) or phenyl group \( (1.30b) \) slightly decreased the reactivity (Table 1.3).

<table>
<thead>
<tr>
<th>Compound</th>
<th>R</th>
<th>( K_{rel} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>( (1.30a) )</td>
<td>H</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>( (1.30b) )</td>
<td>Ph</td>
<td>0.56</td>
</tr>
<tr>
<td>( (1.30c) )</td>
<td>C(CH(_3))(_3)</td>
<td>0.63</td>
</tr>
<tr>
<td>( (1.30d) )</td>
<td>Me</td>
<td>1</td>
</tr>
</tbody>
</table>

Table 1.3

A similar reaction of Selectfluor with alkynes was reported by Nevado’s group in 2011 (Scheme 1.21), \(^{1.67}\) but a gold catalyst was used to enhance the reactions. In addition, a fluorinated cyclised reaction was introduced in the same paper and product \( (1.33) \) is the first fluorinated cyclised product found in my literature review.

Scheme 1.21
More methodologies for the preparation of fluorinated heterocyclic compounds have been reported since 2011. Metal catalysts were required for almost all of those reactions and they are summarised below.

For \(N\)-heterocyclic products, another gold-catalysed fluorocyclisation reaction was introduced by Fensterbank’s group (Table 1.4). Various gold catalysts were tested for the reaction in this report. The reaction in entry 1 using \( \text{Ph}_3\text{PAuCl} \) as the catalyst was chosen as the best catalyst for this reaction.

![Catalyst Diagram](image)

<table>
<thead>
<tr>
<th>Catalyst</th>
<th>(1.35a) yield %</th>
<th>(1.35b) yield %</th>
<th>(1.35c) yield %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 ( \text{Ph}_3\text{PAuCl} )</td>
<td>75</td>
<td>17</td>
<td>0</td>
</tr>
<tr>
<td>2 ( \text{AuCl} )</td>
<td>46</td>
<td>0</td>
<td>7</td>
</tr>
<tr>
<td>3 ( \text{AuCl}_3 )</td>
<td>14</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>4 ( \text{IPrAuCl} )</td>
<td>65</td>
<td>13</td>
<td>0</td>
</tr>
<tr>
<td>5 (biphenyl)((-\text{Bu})_2\text{PAuCl})</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>6 ( \text{PhO}_2\text{PAuCl} )</td>
<td>35</td>
<td>7</td>
<td>0</td>
</tr>
<tr>
<td>7 (2,4-di-(-\text{BuPhO})_3\text{PAuCl})</td>
<td>35</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>8 ( \text{t-Bu}_3\text{PAuCl} )</td>
<td>35</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>9 dppm(AuCl)_2</td>
<td>43</td>
<td>0</td>
<td>14</td>
</tr>
<tr>
<td>10 ( \text{Ph}_3\text{PAuNTf}_2 )</td>
<td>35</td>
<td>0</td>
<td>11</td>
</tr>
<tr>
<td>11 [\text{Ph}_3\text{PAu}]\text{SbF}_6 )</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

**Table 1.4**

Another gold-catalysed reaction was reported by Arcadi’s group (Scheme 1.22), and difluorinated cyclised products were formed using two different gold catalysts. Monofluorinated cyclised products could also be formed via a two-step procedure using one equivalent of Selectfluor.
Silver-catalysed fluorocyclisations were reported by Liu’s group during 2012-2013 (Scheme 1.23).\textsuperscript{1.74,1.75} Fluorinated \textit{N}-isoquinolines (1.41) were formed by using the silver catalyst in combination with NFSi and the aromatic imine (1.40).

Gold catalysts have also been used to form O-heterocyclic products (Scheme 1.24).\textsuperscript{1.76} Hammond’s group reported that, when \((p\text{-CF}_3\text{C}_6\text{H}_4)_3\text{PAuCl}\) (5 %) was used as the catalyst, a difluorinated product (1.43) was formed in 61 % isolated yield. On the other hand, when Selectfluor (1.2 eq.) and a different gold catalyst was used, a monofluorinated product (1.45) and a protonated cyclised product (1.46) (1/0.8) were formed instead.
A carbocyclic product was formed using HBF$_4$.Et$_2$O as the fluoride reagent in Rodriguez’s group (Scheme 1.25).$^{1,77}$ A slightly different type of fluorocyclic product (1.48) was formed by this surprising simple synthetic route.

1.7 Aim of research

Fluorinated heterocyclic compounds are an important aspect of modern chemistry research. The aim of this project was to investigate and develop new synthetic routes to fluorinated heterocycles using aromatic alkynes containing internal nucleophiles. Three different methods for cyclisation were studied. Initially, iodocyclisations using I$_2$ and IPy$_2$BF$_4$ were used to prepare a series of trifluoromethylated heterocycles. Metal-catalysed cyclisations
were also studied and finally, fluorocyclisations using a silver-catalysed reaction provided a convenient access to new fluorinated heterocycles.

In chapter 2 a series of aromatic alkynes were reacted with Selectfluor in order to investigate the relative reactivity of the alkyne substrates. These reactions were carried out in CH$_3$CN/H$_2$O in order to form the difluoroketones following on from Zupan’s work.

In chapter 3 a series of aromatic alkynes containing an internal alcohol were prepared. The iodon cyclisation of these alkynes were then investigated using both I$_2$/K$_2$CO$_3$ and IPy$_2$BF$_4$. When IPy$_2$BF$_4$ was used as the electrophile, the 6-membered trifluoromethylated heterocycle (1.51) was obtained as expected (Scheme 1.26). Surprisingly, however, the 5-membered trifluoromethylated heterocycle (1.50) was produced when iodine was used as the electrophile. These different reactions can probably be rationalised by the fact that I$_2$ coordinates symmetrically to the alkyne whereas PyI$^+$ is slightly non-symmetrical.

Finally, alkynes containing internal alcohols were used to develop electrophilic fluorocyclisation reactions in chapter 4. Fluorinated N-heterocyclic products were reported by Liu and formed by a silver-catalysed reaction between imine and NFSi (Scheme 1.23). Based
on Liu’s procedure, fluorinated $O$-heterocyclic products were produced successfully, and the results are discussed in chapter 4. In the meanwhile, metal-catalysed protocyclisation reactions were also studied in order to investigate the potential of forming fluorinated cyclised products using palladium catalysts.

1.8 References


Chapter 2
Chapter 2 - Reactions of alkynes with Selectfluor in the presence of water

2.1 Introduction

Studies of electrophilic additions to alkyne systems have received scrutiny in recent years. However, since the onset of the project, electrophilic fluorinating reagents, have still not been applied frequently in this area. This may be because electrophilic fluorinating reagents have strong oxidising properties which may cause difficulties, and instead of fluorinating reagents, other halogen reagents have been used more frequently. The overall aim of the work in this thesis was to research the potential of a fluorination-cyclisation sequence from alkyne systems. Therefore, the reactivity of electrophilic fluorinating reagents with alkynes became the first thing to study in my project.

The reactions of electrophilic fluorinating reagents with alkyne systems have been reported recently, but metal catalysts are usually required for this type of reaction (Scheme 2.1).

However, the direct reaction between electrophilic fluorinating reagents and alkynes have only been reported rarely. When the project started in 2011, for any knowledge about direct electrophilic fluorination on alkynes, Zupan’s research was the only and most appropriate information that was available in the literature. Reactions using two different electrophilic fluorinating reagents, Accufluor and Selectfluor, with alkynes had been reported by Zupan’s group. Both reactions gave similar results under similar reaction conditions. The Selectfluor reaction is reported in more detail below because this fluorinating reagent is commercially available and is more commonly used in fluorination reactions.
In Zupan’s reaction (Scheme 2.2), \(^{2,10}\) the alkynes were reacted with Selectfluor and water under reflux for around 20 - 30 h to form the difluoroketone products (Table 2.1). Compound (2.9d) had the highest reactivity and the internal alkynes were much more reactive than the terminal alkynes.
The effect of substituents on the Relative Rates of formation of α,α-difluoro ketones from acetylenes with Selectfluor $^{2,10}$

<table>
<thead>
<tr>
<th>Compound</th>
<th>R</th>
<th>$K_{rel}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>(2.9a)</td>
<td>H</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>(2.9b)</td>
<td>Ph</td>
<td>0.56</td>
</tr>
<tr>
<td>(2.9c)</td>
<td>C(CH$_3$)$_3$</td>
<td>0.63</td>
</tr>
<tr>
<td>(2.9d)</td>
<td>CH$_3$</td>
<td>1</td>
</tr>
</tbody>
</table>

The aim of this chapter was to repeat the work in Zupan’s report and extend it to get more specific data. The reactions of various alkynes were examined to establish the ability of Selectfluor as an electrophilic fluorinating reagent to fluorinate alkynes in the presence of water. The alkynes used in this study are listed below (Figure 2.1).

Two symmetrical diaryl alkynes, (2.11) and (2.12), were used to repeat Zupan’s work. After that, asymmetric systems with a NO$_2$ group in the ortho or para positions ((2.13) and (2.14)) were designed. Compound (2.15) was used to modify the electron density of the aromatic ring as the reactions with (2.13) and (2.14) were not as good as expected. In the next step, more asymmetric alkynes with alkyl based groups on the other side of the alkynes were used ((2.16), (2.17), (2.18) and (2.19)). In the end, ortho-benzyl (2.20) and similar ortho-substituted compounds ((2.21), (2.22), and (2.23)) were used to test the difluoroketone formation reactions.
Figure 2.1
2.2 Synthesis of alkyne substrates

Alkynes (2.11) and (2.16) were purchased and used as supplied. The rest of the alkynes were generally made via Sonagashira coupling reactions. The iodobenzene substrates were reacted with acetylene substrates (1.2 eq.), \([\text{Pd(PPh}_3\text{)}_2\text{Cl}_2]\) (2 mol %) and \(\text{CuI}\) (4 mol %) in Et\(_3\text{N}\) at 70 °C in all the Sonagashira coupling reactions (Figure 2.2).

![Figure 2.2](image)

Compounds (2.12), (2.13), (2.14), (2.17), (2.18), (2.20) and (2.21) were prepared by a Sonagashira reaction directly in 35 – 99% yields (Scheme 2.3). In most of the reactions, the
di-alkyne byproducts were also formed and the pure products were isolated by column chromatography.

In the majority of these syntheses, the aryl iodide starting materials were commercially available. However, in the synthesis of (2.21), 2-iodobenzaldehyde (2.31) was prepared by a pyridinium chlorochromate (PCC) oxidation of 2-iodobenzylalcohol (2.30) in 99 % yield (Scheme 2.4).
Scheme 2.4

Compound (2.15) was made from (2.14) through reduction with SnCl₂ and protection with p-toluenesulfonylchloride in 19 % overall yield (Scheme 2.5).

Scheme 2.5

In the synthesis of (2.23), 2-iodobenzylalcohol was MOM protected in 38 % yield (Scheme 2.6) before the Sonagashira coupling.

Scheme 2.6
Compounds (2.19) and (2.22) were made from (2.18) and (2.20) respectively by reaction with acetyl chloride and pyridine in 49 % and 78 % yields (Scheme 2.7).

Scheme 2.7

Compounds (2.15) and (2.19) are new compounds. All of the other products are known and their characterisation data are in agreement with that published in the literature (chapter 5). The desired acetylenic products were identified by their multinuclear NMR data ($^1$H, $^{13}$C). In all cases, except for the symmetrical alkynes (2.11) and (2.12), two quaternary carbon peaks around 80 - 100 ppm were assigned to the alkynic carbons in the $^{13}$C-$^1$H NMR spectrum. All the peaks from the R1/ R2 groups could also be detected.

2.3 Synthesis of difluoroketone

In this type of reaction, Selectfluor was chosen to be the electrophilic fluorinating reagent because it has high stability, low toxicity and was commercially available. $^{2,25}$ It is categorised as R$_3$N$^+$-F reagent, and these fluorinating reagents are safer, milder, more stable and less expensive to produce, compared to previous electrophilic fluorinating reagents.

Initially, the fluorination of diphenylacetylene (2.11) was investigated using Zupan’s reaction conditions (Scheme 2.8). In addition to the desired product (2.34), a byproduct (2.35) was
observed in the crude reaction mixture by $^1$H NMR spectroscopy. Column chromatography allowed the separation of the desired difluoroketone (2.34) from the diketone (2.35). A similar crude reaction mixture was obtained in the fluorination of 1,2-di-$p$-tolylethyne (2.12) generating, after column chromatography, the desired difluoroketone (2.36) and the related diketone (2.37). These had not been reported previously in the literature. 2.10, 2.11

\[
\text{Scheme 2.8}
\]

Attempts to convert the difluoroketones (2.34) and (2.36) into the diketones by their reaction with Selectfluor and water failed, demonstrating that these byproducts are generated directly
from the alkyne during the reaction. These byproducts might be formed by single-electron transfer (SET),\textsuperscript{2,26,2,27} in which a radical fluorination had occurred and was followed by a rapid loss of HF to generate the diketones. However, the diketone byproduct could not be detected in the preparation of product (2.38).

The first three reactions (Scheme 2.8) provided the desired products and the byproducts in relatively good yields. Compound (2.38) was the only product from the reaction of (2.16) and no diketone byproduct was observed. In the reaction of an asymmetric alkyne, a single regioisomer is formed that is consistent with the product reported by Zupan’s group in the fluorination of 1-phenyl-prop-1-ynne.\textsuperscript{2,10} The difluoroketones were characterised by multinuclear NMR spectroscopy. A number of triplets in the $^{13}$C\textsubscript{1H} NMR spectra were assigned to the CF$_2$, C=O and $\alpha$-C atoms and these species also showed a sharp singlet at -98 ppm in the $^{19}$F\textsubscript{1H} NMR spectrum. In addition to undertaking the reactions with Selectfluor, another electrophilic fluorinating reagent (NFSI) was also examined for the fluorination of (2.11). However, NFSI did not react with compound (2.11) at all, presumably since NFSI is a weaker electrophilic fluorinating reagent.

The proposed mechanism for the synthesis of the difluoroketones is shown in Scheme 2.9. The electron-rich alkyne will attack the electrophilic fluorine from Selectfluor first, and then the temporary positive centre will attract the nucleophile. Thus, the carbon-carbon triple bond will be converted to an alkene structure, with the fluorine atom and the nucleophile attached to the two ends of the alkene. In the case of OH$^-$ as the nucleophile, an enol will be formed which should be in equilibrium with the ketone. However, in reality, the reaction does not stop after formation of the alkene. The enol is highly nucleophilic and reacts with a further equivalent of F$^+$ cation ultimately forming the difluoroketone product.
The diketone byproduct might be generated by single-electron transfer (SET) from radical fluorination by Selectfluor. Selectfluor has been reported to have oxidation properties.\textsuperscript{2.26,2.27} When Selectfluor was reacted with the electron-rich centre (alkyne), a rapid loss of HF could take place leading to the formation of the non-fluorinated byproducts in some cases. A radical alkene system would be the intermediate in the formation of the diketone byproducts in these type of reactions.
Unfortunately, when substituents were present on the aromatic ring, the florination did not proceed well (Scheme 2.10). Reactions using the starting alkynes (2.13) and (2.15) gave none of the desired products. However, the $^{19}$F NMR spectrum of the crude product indicated that some of the fluorinated products might have been formed, but the $^1$H NMR spectrum was too messy to identify any products obtained. Nothing useful was separated by column chromatography.
chromatography afterwards. A similar situation was observed using substrate (2.14). Two singlets were observed at -97.5 ppm and -112.2 ppm in the $^{19}$F NMR spectrum indicating that two fluorinated products had been formed. The $^1$H NMR spectrum of the crude product from the reaction of (2.14) showed some significant peaks, which also indicated that two fluorinated products and the diketone byproduct may have been formed in the reaction. However, these compounds could not be separated by column chromatography. In the fluorination of (2.17), the similarly complicated $^1$H and $^{19}$F NMR spectra of the crude reaction mixture was obtained. This time, product (2.39) with characteristic $^{19}$F and $^{13}$C NMR spectral data was separated as a pure compound in a very low yield by column chromatography. Since isomers could be formed from these asymmetric starting compounds, the reactions and purifications became much more complicated.

In Scheme 2.11, the reactions using functionalised alkynes (2.18) and (2.19) are summarised. The crude product from the reaction of the alcohol substituted alkyne (2.18) could not be purified by column chromatography, and the desired product was not observed in the $^1$H NMR spectrum of the crude product. Presumably the hydroxyl group became an internal nucleophile involved in the reaction leading to different products. After the addition of the acetyl protecting group, the fluorination of (2.19) gave the desired product (2.40) in low yield, and a byproduct which was identified by NMR spectroscopy as a mixture of two isomers (2.41) and (2.42). In this reaction, the regioselectivity of the fluorination was the same as that in the fluorination of (2.16) (Scheme 2.8). The mixture of (2.41) and (2.42) could not be separated, as the two species are in equilibrium. The relative ratios of the two isomers observed in the NMR spectrum were different depending on whether CDCl$_3$ (1:1 ratio) or d$_6$-acetone (1:9 ratio) was used as the solvent. Since CDCl$_3$ is slightly acidic, it is possible that pH influences this equilibrium.
In the $^1$H NMR spectrum, an extra methyl singlet peak at 1.93 ppm could be observed for the isolated product (2.40), indicating that the acetyl protecting group was still on the product, whereas the extra methyl peak had been replaced by OH peaks in the $^1$H NMR spectrum of the mixture (2.41) and (2.42). Two sets of peaks could be observed for this mixture accounting for the two different products. From the $^{19}$F NMR spectrum, one singlet peak could be observed for (2.40) at -99.3 ppm, and one singlet (-98.2 ppm) and two AB pattern doublets (-120.72 and -103.39 ppm with 233.1 Hz coupling constants) could be observed for the mixture of (2.41) and (2.42). The singlet indicated the presence of product (2.41) and the AB pattern doublets indicated (2.42) had been formed as a cyclised product. In addition, on deprotection with base, difluoroketone (2.40) gave the same mixture of isomers, (2.41) and (2.42), in the same ratios (Scheme 2.12).
In the reaction of the MOM protected benzyl alcohol (2.23) with Selectfluor (Scheme 2.13), the MOM group was not detected in the crude product, and no single product could be isolated after purification by column chromatography. However, the similar pattern in the crude $^{19}$F NMR spectrum (one singlet and two AB pattern doublets) indicated that the products may be similar to the two isomers formed from the reaction using compound (2.19).

The MOM group was not observed in crude $^1$H NMR spectrum. The pattern in the crude $^{19}$F NMR spectrum indicated that the products formed may be similar to the two isomers formed from compound (2.19).

The last three reactions shown in Scheme 2.14 were undertaken as these types of ortho-substituted substrates are important substrates for forming cyclised products and they were used as the main starting compounds to form iodocyclised heterocyclic products in chapter 3. However, these reactions gave none of the desired products at all. The NMR spectra of these three crude products were too complicated to analyse and none of the starting materials could be observed in the crude NMR spectra. Selectfluor did react with these compounds, mixtures, including several non-fluorinated products, were formed (no fluorinated products were isolated), which possibly because the substituents at the ortho-position had a sufficiently
large steric effect to inhibit attack by the electrophilic reagent, or the radical fluorination had occurred leading to SET, and several non-fluorinated products were generated.

\[
\begin{align*}
\text{Selectfluor (3.0 eq.)} & \quad \text{Inseparable, complicated reaction mixture.} \\
\text{H}_2\text{O}/\text{MeCN, reflux, 20 h} & \quad \text{No single product isolated by column chromatography.}
\end{align*}
\]

Scheme 2.14

2.4 Discussion and Conclusions

A series of known and new alkynes were synthesised by Sonagashira reactions of terminal alkynes with aryl iodides and isolated in 35-99 % yields. These alkynes have been fully characterised by NMR spectroscopy.

The relative influence of various functional groups (R₁ and R₂) towards the electrophilic cyclisation reactions of alkynes bearing a nucleophile was recently defined by Larock. A number of factors affect the cyclisation including both electronic (the relative nucleophilicity of the functional groups, polarisation of the carbon-carbon triple bond, and cationic nature of the intermediate) and steric effects (hindrance and geometrical alignment of the functional groups), as well as the nature of the electrophilic source. In most cases, only one of the two possible products was obtained. However, in the cases where a mixture of both possible
products was obtained, one of them was always obtained in a higher amount. These workers concluded that there is a hierarchy of functional group reactivity towards the electrophilic cyclisation.

These electrophilic cyclisation reactions are similar to the reactions in this work except that the nucleophile here is external water. Therefore, the functional group hierarchy as defined by Larock \(^2\text{.29}\) could also apply to these experiments, since the position on the alkyne to be attacked by the fluorinating reagent would be affected by the same factors.

The work on the fluorination of alkynes reported by Zupan has been extended to a wider series of alkynes. In contrast to Zupan’s report, in some cases, a diketone byproduct has been identified and isolated during these reactions. The introduction of an ortho-substituent (-NO\(_2\), -CH\(_2\)OH, -CHO, -CH\(_2\)OAc) on the aryl rings has a significant impact on these reactions such that, in most cases, no difluoroketone products could be isolated. It is possible that this is a result of steric congestion. In comparison with the conclusion by Larock, in the attempted fluorinations of the nitro-benzyl substituted alkyne \((2.13)\), the benzyl alcohol \((2.20)\), benzyl aldehyde \((2.21)\), benzyl acetate \((2.22)\) and the very low yield in the fluorination of nitro-benzyl \((2.17)\), the ortho- groups may be too big and too close to the alkyne functional groups such that steric effects (hindrance and geometrical alignment of the functional groups) will influence the reactivity. More complicated radical fluorination might also be occurring in these cases to generate the inseparable crude mixtures. In addition, in one series of reactions, deprotection of a primary alcohol occurred during the fluorination to generate a difluoroketone-alcohol which exists in equilibrium with its internally cyclised hemi-acetal.

In conclusion, the direct fluorination on the alkynes is relatively difficult. The desired difluoroketone products were not formed if the substituents on the two sides of the alkyne \((R_1\) and \(R_2)\) were too big or too reactive. The desired difluoroketone products were only formed while the substituents next to the alkyne were small and had no obvious steric effects. Apart from the steric effect, there are other aspects which may also influence the reactivity of
fluorination, e.g., SET could take place presumably to generate some non-fluorinated byproducts.

2.5 References


Chapter 3
Chapter 3 Iodocyclisation

3.1 Introduction

Synthesising heterocycles is an area of significant interest in modern chemistry and O- or N-heterocyclic structures have been identified as the basic core structure in many drugs or materials in the pharmaceutical or industrial areas. Various synthetic routes have been introduced in Chapter 1 including transition metal-catalysed cyclisation methodologies of which Pd and Pt are the most common transition metals that have been used in forming heterocycles. 3.1

In comparison with these transition metal-catalysed cyclisation reactions, the synthesis of heterocycles using electrophilic halogen reagents has become attractive and interesting in the last few years. 3.2 These methodologies are efficient and the presence of the residual halogen atoms in these heterocycles are usually highly suitable for further transformations. The mechanisms of the electrophilic cyclisation are shown below (Scheme 3.1).

In a typical electrophilic cyclisation, the addition of the electrophilic source to the C (sp) bonds of alkynes (3.1) will give intermediate (3.2), which activates the carbon-carbon bond towards nucleophilic attack. A salt (3.3) will be produced by the nucleophilic anti attack of the heteroatom on the intermediate, and then an SN2 displacement by the Nu’ present in the reaction mixture will remove the leaving group bound to the heteroatom to generate the heterocyclic products (3.4). In Case 1, 5-endo-dig cyclisation will normally occur as the sterically-hindered effect for 4-exo-dig cyclisation is huge, and a 5-membered product (3.4) will be formed. In Case 2, with the starting compound (3.5) following similar mechanisms, 6-endo-dig and 5-exo-dig cyclisations are available to take place, and three different 6- or 5-membered products (3.7), (3.8) and (3.9) can be theoretically formed.
Case 1

\[ \begin{align*}
&\text{(3.1)} \\
&\text{(3.2)} \\
&\text{(3.3)} \\
&\text{(3.4)} \\
&\text{(3.5)} \\
&\text{(3.6)} \\
&\text{(3.7)} \\
&\text{(3.8)} \\
&\text{(3.9)} \\
\end{align*} \]

5-endo-dig

Case 2

\[ \begin{align*}
&\text{(3.1)} \\
&\text{(3.2)} \\
&\text{(3.3)} \\
&\text{(3.4)} \\
&\text{(3.5)} \\
&\text{(3.6)} \\
&\text{(3.7)} \\
&\text{(3.8)} \\
&\text{(3.9)} \\
\end{align*} \]

6-endo-dig

\[ \begin{align*}
X &= \text{O, NR} \\
E &= \text{Electrophilic reagents} \\
\text{LG} &= \text{Leaving group} \\
\text{Nu} &= \text{Nucleophile} \\
\end{align*} \]

Scheme 3.1

Iodocyclisations are the most common methodologies that have been used in these electrophilic cyclisations. Various electrophilic iodinated reagents have been reported to generate many types of heterocycles in good to excellent yields. Compared to
iodocyclisations, fluorocyclisation reactions are virtually unknown and only a few reports
could be found in the literature. In addition, the difficulty of the direct electrophilic
fluorination of alkyne systems had been discovered from the studies of the reactivity of
electrophilic fluorinating reagents with alkynes in Chapter 2. Therefore, before starting an
investigation into fluorocyclisations, the more common electrophilic cyclisations were
studied first by repeating some iodocyclisations from the literature. Some new fluorinated
heterocycles were then generated by using iodocyclisation reactions.

Reagent = I₂, Br₂, ICl, PhSeBr
E = I, Br, PhSe
R₁ = SePh, SeBu, SMe, SPh
R₂ = H, Me, OMe, F

\[
\begin{align*}
\text{Reagent} & \rightarrow \text{DCM, RT} \\
(3.1a) & \rightarrow (3.4a) (50 - 95 \%) \\
(3.1b) & \rightarrow (3.4b) (74 - 86 \%)
\end{align*}
\]

\[
X = \text{Br, I} \\
R = \text{c-C}_3\text{H}_5, p-\text{MeC}_6\text{H}_4, p-\text{tBuC}_6\text{H}_4
\]

\[
\begin{align*}
(3.1c) & \rightarrow (3.4c) (10 - 87 \%)
\end{align*}
\]

R₁ = SO₂Me, CO₂Me, CO₂t-Bu
R₂ = Ph, Bn, Bu, 3-thienyl
R₃ = H, Me

\textbf{Scheme 3.2}
Three examples of the reaction in **Case 1** are listed in Scheme 3.2. In the first example, products (3.4a) have been reported by Manarin’s group in good to excellent yields. The electrophilic reagents used in these reactions included I₂, Br₂, ICl, PhSeBr, from which iodo- or bromo-substituents or other five-membered ring cyclised products could be generated. In the second example, NIS and NBS were used as the electrophilic reagents to generate the products (3.4b). In this case, the enolate resonance structures, \( \text{N}=\text{COH} \leftrightarrow \text{NHC}=\text{O} \), acted as the X-(H/LG) substituents within the cyclisation reaction. In the third example, five-membered ring iodocyclised N-heterocycles (3.4c) were formed by Barluenga’s group.

Three examples of the reactions in **Case 2** are listed in Scheme 3.3. The formation of the bromo-cyclised product (3.8a) was reported by Sofia’s group, where only the (E) 5-exo-dig product was formed. However, in examples 2 and 3, 6-endo-dig products (3.7b) and (3.7c) were generated with different halogen or other electrophilic reagents. Trace amounts of the (E) 5-exo-dig product (3.8b) were observed in the second example. However, in the third example, depending upon the different substituents and electrophilic reagents either the (E) 5-exo-dig (3.8c) or 6-endo-dig (3.7c) products were obtained as the main products.
Among all the electrophilic cyclisations, iodocyclisation is the most common cyclisation of alkynes with electrophilic halogen reagents. One advantage of these iodocyclisation reactions is that functionalisation could be achieved by applying further transformation on the iodine group in the iodocyclised products (e.g. Sonagashira coupling reactions) to generate more complicated compounds. The reactions reported by Barluenga’s and Larock’s groups provide several examples of iodocyclisations via two different routes.\(^\text{3.2, 3.9-3.11}\) Most of the results of
Barluenga’s research on iodocyclisations are listed below (Scheme 3.4). External nucleophiles were usually used in Barluenga’s iodocyclisations.

\[\text{Scheme 3.4}\]

Throughout, IPy2BF4 has been used as the electrophilic reagent, and the substrates, aldehydes or ketones, do not contain nucleophiles. Instead, the reactions were slightly different in that
the additional nucleophiles were added during the reaction processes. Alcohols were used as these nucleophiles in reaction 1, and in reaction 2, with the presence of B(OMe)$_3$, IPy$_3$BF$_4$ was acting as the electrophilic source and Lewis acid as well. In reaction 3, some of the carbon based nucleophiles, such as silyl-masked or electron-rich arenes, were adapted in such reactions as well. Using ketones as the starting compounds in reaction 4, the different 5-membered products (3.15) ($^E$ 5-exo-dig) were formed. Throughout, no reactions of preformed nucleophilic starting materials have been reported by Barluenga’s group, there is no evidence for the external nucleophiles reacting directly with the activated alkynes and the nucleophiles used for the cyclisations have only been generated in situ.

Scheme 3.5 summarises the reactions reported by Larock’s group. Here, the much more common and cheaper electrophilic reagent, iodine, was used. In a similar approach to that described by Barluenga, in the first example aldehydes or ketones, in the presence of alcohols as external nucleophiles, were iodo-cyclised with iodine. Both 6-endo-dig and ($^E$) 5-exo-dig cyclisations occurred in these reactions and, according to his report, the ($^E$) 5-membered products (3.18) were favoured over the 6-membered products (3.17). In contrast, using benzyl alcohols as the nucleophilic substrates, both 6-endo-dig and ($^Z$) 5-exo-dig cyclisation products were formed. Here, Larock stated that the formation of the 6-/5-membered products (3.20) and (3.21) was dependent on the substituents of the starting compounds. Tertiary alcohols would normally lead to the 5-membered products (3.21), and primary or secondary alcohols would normally lead to the 6-membered products (3.20). In his report, the only primary alcohol used was with the $n$-Bu alkynyl-substituent, and only the 6-membered product could be observed.
In addition, (Z) 5-membered products (3.21) would be formed rather than (E) 5-membered products (3.22) in this second class of reaction as the (Z) 5-membered products (3.21) are more stable. The hypothesised mechanism for the reaction (Scheme 3.6) indicated that an isomerisation would take place, transforming the intermediate (3.22) into the (Z) 5-membered products (3.21).
3.2 Preparation of alkyne substituents

A variety of alkynes were prepared as the starting materials for use in the iodocyclisation reactions (Figure 3.1). Throughout, the Sonagashira coupling reaction was the key reaction in making these species. The compounds, aldehydes (3.23), (3.41), (3.42), alcohols (3.24), (3.25), (3.26), (3.27), (3.39) and carboxylic acid (3.36) were known products and their characterisation data is in agreement with that published in the literature. All the other new
products (3.28), (3.29), (3.30), (3.31), (3.32), (3.33), (3.34), (3.35), (3.37), (3.38) and (3.40) were identified by their multinuclear NMR data and accurate mass spectral data.

**Aldehydes**

(3.23)

(3.41)

(3.42)

(3.23), (3.41) and (3.42) were prepared to synthesise other starting materials for the iodocyclisations.

**Primary alcohols**

(3.24)

(3.25)

(3.26)

(3.23), (3.25) and (3.26) were prepared to synthesise other starting materials for the iodocyclisations.

**Secondary alcohols**

(3.27)

(3.28)

(3.29)

(3.30)

(3.31)

(3.32)
The syntheses of compounds (3.23) and (3.24) were described in Chapter 2. The related alkynes, (3.25) and (3.26) were made by similar Sonagashira coupling reactions with 96 % and 91 % isolated yields respectively (Scheme 3.7).
Many of the other compounds were made from compound (3.23) with good to excellent yields. Compound (3.27) was made from the reaction of (3.23) with methylmagnesium bromide in THF in a 97 % isolated yield (Scheme 3.8).

Similarly, compound (3.28) was made from (3.23) with trifluoromethyltrimethylsilane (CF<sub>3</sub>SiMe<sub>3</sub>) and tetrabutylammonium fluoride (TBAF) in THF and isolated in 99 % yield (Scheme 3.9).
Compounds (3.29) and (3.30) were made similarly from different aldehyde substrates (Scheme 3.10). Using 1-ethynyl-4-methylbenzene or oct-1-yne, Sonagashira coupling reactions were used to form aldehydes (3.41) and (3.42) (87 % and 87 % isolated yields). Nucleophilic addition of the trifluoromethyl group gave the final alcohol products in 97 % and 58 % isolated yields respectively.

\[
\begin{align*}
  \text{Sonagashira coupling} \\
  + \ \text{H-C≡C-CH₃} \\
  \rightarrow \ \text{HC(O)CH₃} \quad 87 \%
\end{align*}
\]

\[
\begin{align*}
  \text{Scheme 3.10}
\end{align*}
\]

Singlet peaks in the \(^{19}\text{F}\) NMR spectra could be observed for all CF₃ secondary alcohols (3.28), (3.29) and (3.30) at -77.6 ppm. Similarly, there was a quartet at 5.5 ppm in the \(^{1}\text{H}\) NMR spectrum due to the benzylic proton coupling to the CF₃ group (\(^{3}J_{HF} = 6.5\) Hz), which indicated that the CF₃ substituent had been successfully reacted with the aldehyde.
Compounds (3.31), (3.32), (3.33), (3.34) and (3.35) were all made via Reformatsky addition reactions using either BrCF₂COOEt or BrCH₂COOEt in the presence of activated zinc dust in 63-92% yields (Schemes 3.11 & 3.12).

AB patterns could be observed in the ¹⁹F NMR spectra for the alcohols (3.31), (3.33) and (3.34), which displayed two doublets around -120 and -113 ppm with ²J_FF coupling constants around 260 Hz. Closely related AB patterns for the protons in alcohols (3.32) and (3.35) could be observed in their ¹H NMR spectra, with coupling constants (²J_HH ≈ 16 Hz, ³J_HH ≈ 9 Hz) and (²J_HH ≈ 16 Hz, ³J_HH ≈ 3 Hz) around 2.6 and 3.0 ppm respectively.
As a direct Sonagashira reaction could not be used on 2-iodobenzoic acid to form compound (3.36), a protection/deprotection strategy was used. 2-iodobenzoic acid was converted to its methylester (98 % isolated yield), followed by the Sonagashira coupling reaction to form compound (3.44) (99 % isolated yield). Finally, deprotection with sodium hydroxide gave the desired product (3.36) in an overall 72 % isolated yield (Scheme 3.13).
Scheme 3.13

Tertiary alcohols (3.37), (3.38) were made from the appropriate alkynyl esters via Grignard addition reactions (43 % and 18 % isolated yield). Alkynyl ester (3.45) was made by Sonagashira coupling reaction using 2-iodomethylbenzoate and 1-ethynyl-4-methylbenzene in a 99 % isolated yield (Scheme 3.14). The yields of these Grignard addition reactions were very low, possibly because MeMgI was generated in situ for which the yield was not determined. Nevertheless, sufficient alkynyl tertiary alcohols were prepared for the subsequent cyclisation reactions, so no attempts were made to improve these yields.

Scheme 3.14
A single crystal X-ray structural determination has been carried out for compound (3.37) (Figure 3.2). The C8-C9 bond length of 1.118 Å, confirmed the presence of a carbon-carbon triple bond. The bond angle C17-C1-C16 was 111.3 °, which is larger than the normal tetrahedral bond angle 109.5 °. The presence of two methyl groups reduced the bond angles C17-C1-O1 to 103.2 ° and C16-C1-O1 to 107.3 ° due to the Thorpe-Ingold effect.

![Figure 3.2 X-ray crystal structure for (3.37)](image)

A similar Grignard addition reaction was applied to form compound (3.39) (39 % isolated yield). The yield was slightly higher as a commercial sample of the Grignard reagent EtMgBr was used (Scheme 3.15).

![Scheme 3.15](image)
Compound (3.46) was made first from the reaction of compound (3.23) with \( p \)-toluenesulfonamide (NH\(_2\)Ts) (94 % isolated yield). Then (3.46) was reacted with trifluoromethyltrimethylsilane (CF\(_3\)SiMe\(_3\)), tetra-\( n \)-butylammonium bromide (TBAB) and PhONa to form compound (3.40) in 50 % isolated yield (Scheme 3.16). The reaction needed to be carried out under rigorously anhydrous conditions, such that 5Å molecular sieves were added in both steps. The second step was similar to the reaction used to form compound (3.28), however, since the imine group is sensitive to hydrolysis, tetrabutylammonium bromide (TBAB) was used instead of TBAF as a stronger phase transfer catalyst, and PhONa was added as a precursor to enhance the reactivity.

![Scheme 3.16](image)

Single crystal X-ray structural determinations have been carried out for compounds (3.46) and (3.40) (Figures 3.3 and 3.4). The length between C8-C9 is 1.200 Å and 1.194 Å for (3.46) and (3.40) respectively, indicating that these bonds are carbon-carbon triple bonds.
The length between C1-N1 and the bond angle between C2-C1-N1 in compound (3.46) were 1.280 Å and 121.4 ° indicative of a sp² hybridised carbon. In contrast, in compound (3.40),
the addition of the CF₃ substituent increased the C-N distance and reduced the C-C-N angle to 1.456 Å and 114.86 ° reflective of the change to sp³ hybridisation.

3.3 Iodocyclisation Reactions with I₂ and IPy₂BF₄

Based upon the iodocyclisation reactions reported by Barluenga’s and Larock’s groups, both I₂ and IPy₂BF₄ have been used as electrophilic iodinating reagents.

3.3.1 Reactions of aldehydes together with external nucleophiles

In the beginning, as iodine seemed to be more economic and environmentally friendly, one of Larock’s reaction was repeated in which the known product (3.47) was generated and a fluorine-containing nucleophile was used to generate the new product (3.48) (Scheme 3.17). Although the reactions were successful, the yields were not high (51 % and 35 % isolated yields respectively). The lower yield for product (3.48) presumably arose from the lower nucleophilicity of the trifluoroethoxy compared to the methoxy group.

![Scheme 3.17](image-url)
The significant characterisation data for products (3.47) and (3.48) are summarised in Table 3.1.

<table>
<thead>
<tr>
<th>Product</th>
<th>$\delta_C$ Cl</th>
<th>$\delta_C$ CHO</th>
<th>$\delta_H$ CHO</th>
<th>$\delta_H$ Lowest field aromatic H</th>
</tr>
</thead>
<tbody>
<tr>
<td>(3.47)</td>
<td>73.8 ppm</td>
<td>100.0 ppm</td>
<td>5.95 ppm</td>
<td>7.54 ppm</td>
</tr>
<tr>
<td>(3.48)</td>
<td>74.5 ppm</td>
<td>98.8 ppm</td>
<td>6.17 ppm</td>
<td>7.55 ppm</td>
</tr>
</tbody>
</table>

Table 3.1

These compounds were generally unstable as a result of their acetal structures. So an alternative strategy that eliminated this issue was investigated, the cyclisation of alcohols.

3.3.2 Trifluoromethyl substituted alcohol, primary alcohol and methyl substituted alcohol

The trifluoromethyl alcohol (3.28) was used as the starting compound to investigate iodocyclisation reactions with I$_2$ and I$^+$ regents (Scheme 3.18). Trifluoromethyl groups are commonly found in the structure of drugs, since it can enhance the drug’s reactivity and the efficacy of an orally administered drug.

Using iodine as the reagent generated product (3.49) in a 24 % isolated yield, while product (3.50) was obtained in a 67 % isolated yield using the bispyridine iodonium cation. Mass spectrometry revealed that both products had the same accurate mass, but the $^1$H and $^{13}$C NMR data for both were different.
Iodocyclisation reactions with the iodonium reagent and preformed alcohols have not been reported in the literature. In contrast, Larock, using iodine, has described the formation of either 5- or 6-membered heterocycles dependent upon the alcohol. \(^{3.11}\)

By analogy of the NMR data of products (3.49) and (3.50) with those reported by Larock for the 6-membered isochromene species \(^{3.11}\) and those obtained for isochromenes (3.47) and (3.48) (Scheme 3.17, page 20), the product from cyclisation of (3.28) with the iodonium cation can be identified as the trifluoromethyl isochromene (3.50). In particular, resonances associated with the aromatic protons cover a range from 7.0-7.6 ppm and the quaternary (Cl) carbon is seen at 73 ppm. In marked contrast, the \(^1\)H NMR spectrum for (3.49) reveals an unusually low field aromatic proton resonance (1H) at 8.72 ppm and the quaternary (Cl) carbon is seen at 67 ppm. These data do not correlate with those reported by Larock for the (Z) 5-membered products, \(^{3.11}\) typically observed after the iodocyclisation of tertiary alcohols for which there are unusually high field proton resonances at ca. 6.4 ppm and for which the quaternary (Cl) carbon is seen at ca. 62 ppm. In addition, the CHO resonances for (3.49) and (3.50) show subtle differences, \(\delta_H \ 5.51 \ (^{3}J_{HF} = 5.6 \ Hz) \) and \(\delta_C \ 79.7 \ (^{2}J_{CF} = 33 \ Hz) \) for the
former and $\delta_H$ 5.50 ($^3J_{HF} = 7.1$ Hz) and $\delta_C$ 75.2 ($^2J_{CF} = 32$ Hz) for the latter, where the $^3J_{HF}$ coupling constant, in particular, varies with the ring size and provides a simple guide to the configuration of the iodocyclised product.

Confirmation of the structure for (3.49) came from a single crystal structural determination for crystals grown by recrystallisation from hot toluene (Figure 3.5).

![Figure 3.5 X-ray structure for (3.49)](image)

Bond length (Å) C9-I1: 2.093(3); C2-C9: 1.343(4); C2-O1: 1.390(4); I1-H8: 2.855. Bond angle (°) C4-C1-O1: 105.0(3).

**Figure 3.5 X-ray structure for (3.49)**

The structure revealed that (3.49) has an (E) 5-exo-dig configuration. This configuration can be used to rationalise some of the NMR data. The different chemical shifts in the $^{13}$C NMR resonance for the CHO carbon between (3.49) (79.7 ppm) and (3.50) (75.2 ppm) arisen from the change from a 5- to 6-membered ring. Similarly, the related but opposite variation in the Cl resonances arised from a cyclic to an exo-cyclic position for the iodine. Most importantly, the unusually low field shift in the aromatic region for (3.49) may be influenced by the close
orientation of H8 and iodine. Note that it is not simply a question of I-H distance since that is similar in the 6-membered ring (see Figure 3.6 and 3.7).

There are three important conclusions from this work. Firstly, alcohol substrates with internal nucleophiles have been iodocyclised for the first time with the bispyridine iodonium cation. Secondly, both 5- and 6-membered ring heterocycles with a CF3 substituent have been readily prepared. Thirdly, in contrast with the observation of Larock with butyl (or ethyl) substituted alcohols, the trifluoromethyl secondary alcohol does not iodocyclise to the isochromene (3.50) with iodine, but rather it undergoes a 5-exo-dig cyclisation to generate the trifluoromethyl hydroisobenzofuran (3.49). The observation of the (E)-isomer of (3.49) (including an X-ray structurally characterised example), also contrasts with the generation of (Z)-isomers, reported by Larock. 3.11 However, as noted by Larock, it is the (E)-isomer that would be predicted, mechanistically, following an 5-exo-dig cyclisation of the iodonium intermediate formed by activation of the alkyne. Computational calculations by Larock indicate that in his system the (Z)-isomers are thermodynamically more stable than the (E)-isomers allowing him to propose that the observed configuration of the products in his reactions arises from isomerisation of the predicted (E)-isomers after cyclisation. In this work, it would appear that the fluoroalkyl group not only changes the position of nucleophilic attack (5-exo-dig rather than 6-endo-dig) following activation of the alkyne with iodine, but also influences any subsequent isomerisation of the hydroisobenzofuran formed.

Further studies of the isomeric products have been undertaken and the optimised reaction conditions for the iodocyclisation of the CF3 secondary alcohol (3.28) and the primary alcohol (3.24) were obtained (Table 3.2). From these experiments, reacting 3.0 eq. of I2 and 2.0 eq. of K2CO3 with the alcohol in DCM at RT for 48 h (entry 5) provided the best reaction conditions for the iodocyclisation of (3.28) with iodine. It should also be noted that in the reaction using MeCN as the solvent, the same (E) 5-exo-dig cyclisation product was obtained.
Table 3.2

For the Py$_2$I$^+$/BF$_4^-$ promoted reaction, the original reaction condition using 1.5 eq. of IPy$_2$BF$_4$ and 1.2 eq. of HBF$_4$.Et$_2$O in DCM at RT for 3 h (entry 13), turned out to be highly effective. The product was obtained in a 98 % isolated yield.

Related optimisation studies were also carried out using the primary alcohol (3.24). As reported by Larock, using iodine, only the 6-membered isochromene was generated. The optimum conditions (entry 17) mirrored those in entry 5. The isochromene could also be formed using the IPy₂BF₄ reagent, although in a much lower yield (entry 19).

![Chemical structures and reactions](image)

**Scheme 3.19**

Extending these reactions to the p-tolyl alkynyl primary alcohol (3.25) gave similar results. Using iodine, the isochromene was formed in a 56 % yield and, with IPy₂BF₄, the isochromene could only be isolated in a 17 % yield. For the latter, the NMR spectrum of the
crude product suggested the presence of some (Z)-dihydroisobenzofuran (3.54) ($\delta_H$ 6.43), in line with Larock’s findings, but this could not be isolated pure. For the hexyl substituted alcohol (3.26), no desired products could be observed in the $^1$H NMR spectra of the crude products from either the I$_2$ or IPy$_2$BF$_4$ reactions (Scheme 3.19).

Scheme 3.20

The trifluoromethyl secondary alcohols with both tolyl and hexyl substituents on the alkynes were evaluated next. For the tolyl substituted compound (3.29), both I$_2$ and Py$_2$I$^+$ gave the anticipated products (Scheme 3.20). Using Py$_2$I$^+$BF$_4$ the 6-endodig product (3.57) was generated as the main product in a 63 % isolated yield. The $^1$H and $^{13}$C NMR data for (3.57)
correlated closely with those for (3.50) indicating formation of the isochromene product. Single crystals suitable for X-ray structural determination were grown by recrystallisation from hot toluene and the solid state structure (Figure 3.6) confirmed the assignment from the NMR data.

Bond length (Å) C1-I1: 2.103(4); C2-C1: 1.335(5); C2-O1: 1.392(4); I1-H6: 2.866. Bond angle (°) C4-C3-O1: 113.5(3).

Figure 3.6 X-ray structure for (3.57)

The NMR spectrum for the crude product obtained using iodine as the reagent indicated a mixture of products. By comparison with the data from the reactions alocohol (3.28), these data indicated a mixture of the isochoromene (3.57) and both the (E) and (Z)-isomers of the hydroisobenzofuran (3.55) and (3.56). All attempts at separating the mixture by column chromatography were unsuccessful.

Integrations in the ¹H NMR spectrum indicated that the (E)-hydroisobenzofuran (3.55) was the major product. Using pure hexane as the eluant for column chromatography concentrated this major isomer and slow evaporation of the hexane generated a yellow crystalline solid. The NMR data, particularly the low field resonance aromatic proton (8.71 ppm) and the ¹³C resonance of the C-I group (67.1 ppm) correlated closely with those of (3.49). Crystals suitable for X-ray crystallography confirmed this assignment (Figure 3.7). Whilst there was
no evidence for isochromene from the iodocyclisation of (3.28) with iodine, the formation of a small amount of the isochromene here is consistent with Larock’s observation of increased conversion to the isochromene in the iodocyclisation of the p-tolyl and p-anisoyl substituted alkyne-primary alcohols. cf. For (3.29), enhanced electron donation from the methyl group should promote enhanced 6-membered ring formation in comparison to that for (3.28).

Bond length (Å) C1-I1: 2.091(4); C2-C1: 1.325(5); C2-O1: 1.391(4); I1-H4: 2.881. Bond angle (°) C8-C9-O1: 104.7(3).

**Figure 3.7 X-ray structure for (3.55)**

For the hexyl substituent compound (3.30) (Scheme 3.21), only the reaction with iodine gave identifiable products. The $^1$H NMR spectrum of the crude reaction mixture following the reaction of (3.30) with Py$_2$I$^+$/BF$_4$ gave no signals characteristic of iodocyclised products, and no pure species could be isolated following column chromatography. Following the reaction with iodine, three different products were observed in the $^1$H NMR spectrum of the crude reaction mixture. ((E) 5-exo-dig product (3.58), (Z) 5-exo-dig product (3.59) and 6-endo-dig product (3.60)), and the ratio of these three products was 4.5/4.5/1. After column chromatography, product (3.59) was separated in a 15 % isolated yield, and was fully characterised. The CHO resonance at $\delta_H$ 5.51 ($^3J_{HF} = 5.9$ Hz) indicated the 5-membered ring
structure, and the aromatic proton resonance at 7.63 ppm indicated the (Z)-isomer structure. Furthermore, three different CHO resonances in the $^1$H spectrum of the crude reaction mixture at $\delta_H$ 5.51 ($^3J_{HF} = 5.9$ Hz), 5.56 ($^3J_{HF} = 6.0$ Hz) and 5.37 ($^3J_{HF} = 7.4$ Hz) indicated the (Z), (E)-isomers and the 6-membered isochromene.

Since mixtures of products, both isochromenes and hydroisobenzofurans, had been observed in the $^1$H NMR spectra of the crude reaction mixtures from both the reactions of (3.29) and (3.30) with iodine, the reaction of the original, phenyl-substituted, trifluoromethyl-substituted secondary alcohol (3.28) was repeated and the resultant mixture analysed carefully (Scheme 3.22).

The primary product in the reaction mixture, the (E)-trifluoromethyl hydroisobenzofuran, was isolated in a similar 61 % (cf. 70 %, entry 5, Table 3.2, page 26) isolated yield. However, very careful analysis of the $^1$H NMR spectrum of the crude reaction mixture showed very
weak CHO resonances at $\delta_H 5.61 \left( J_{HF} = 7.3 \text{ Hz} \right)$ and $\delta_H 5.68 \left( J_{HF} = 5.9 \text{ Hz} \right)$ ppm indicating the different coupling constants for 5- and 6-membered rings. The spectrum also displayed the characteristic high field aromatic proton resonance for the (Z)-isomer (6.39 ppm). Furthermore, three CF$_3$ resonances around $\delta_F -77.8$ ppm were observed in the $^{19}$F NMR spectrum of the crude reaction mixture. These significant resonances indicated that the (Z)-trifluoromethyl hydroisobenzofuran (3.61) and the isochromene (3.50) had been formed with 10 % and 5 % conversions respectively.

![Scheme 3.22](image)

Although Larock had reported that alkyl-substituted (-Bu) secondary alcohols could be iodocyclised with iodine, attempts to react the methyl-substituted secondary alcohol (3.27) with either iodine or Py$_2$I$^+$BF$_4^-$ under the optimised conditions, failed to give any evidence for iodocyclised reaction products, although (3.27) had been fully consumed in these reactions. The reasons behind these failures are unclear (Scheme 3.23).
3.3.3 Extension to reactions with other secondary alcohols

As the secondary trifluoromethyl alcohol gave different products (5-exo-dig or 6-endo-dig products as the main products) on iodocyclisation with iodine or IPy2BF4 respectively, whilst the secondary methyl alcohol did not appear to undergo iodocyclisation reactions, it was interesting to know whether this chemistry could be extended to other secondary alcohols, either fluorinated or non-fluorinated. The secondary alcohols (3.31), (3.32), (3.33), (3.34) and (3.35) generated by Reformatsky reactions were tested under both sets of reaction conditions.

Compound (3.31) with both I2 and Py2I+BF4+ reactions gave the iodocyclised products (3.62) and (3.63) in 57 % and 73 % isolated yields respectively (Scheme 3.24). In line with the observations for (3.28) with iodine, the major product was the (E) 5-exo-dig product, whilst with Py2I+BF4+ the major product was the 6-endo-dig product. In the reaction with iodine, there was no evidence in the 1H NMR spectrum of the crude reaction mixture for either of the other two isomers observed in the reaction with (3.28).
Similarly, reactions with alkyne (3.33) gave the anticipated products (3.64) and (3.65) in 57 % and 48 % isolated yields respectively (Scheme 3.25).

Scheme 3.24

Scheme 3.25
Products (3.62), (3.63), (3.64) and (3.65) all contain diastereotopic fluorine atoms displaying large (ca. 260 Hz) fluorine-fluorine coupling constants typical for acyclic pairs of sp\(^3\)-hybridised fluorines.\(^{3,12}\) Both (3.62) and (3.64) display the characteristic low field aromatic proton resonances for the \((E)\) 5-exo-dig isomers (at 8.69 ppm) whilst (3.63) and (3.65) show the larger \(J_{HF}\) coupling constants for their CHO protons ((3.63): \(J_{HF} = 16.6\) and 6.5 Hz; (3.65): \(J_{HF} = 16.4\) and 6.6 Hz; (3.62): \(J_{HF} = 15.3\) and 4.4 Hz; (3.64): \(J_{HF} = 14.7\) and 4.8 Hz). Finally, the diagnostic shifts in the \(\delta_{CI}\) between the 5- and 6-membered ring compounds are also seen here ((3.63): \(\delta_{CI} = 73.2\); (3.65): \(\delta_{CI} = 72.8\); (3.62): \(\delta_{CI} = 65.9\); (3.64): \(\delta_{CI} = 66.4\)).

As observed for the trifluoromethyl derivative functionalized with a hexyl group on the alkyne, reactions of (3.34) with either iodine or \(\text{Py}_2\Gamma\text{BF}_4^+\) gave no evidence for iodocyclisation (Scheme 3.26). It may be concluded that secondary alcohols containing alkynes with a hexyl group are not suitable for these iodocyclisations, and it is interesting that Larock only reported diaryl alkynes in his work on iodocyclisations.

![Scheme 3.26](image)

For the CH\(_2\)CO\(_2\)Et alcohols, with either phenyl or tolyl substituents (3.32) and (3.35) (Scheme 3.27), no identifiable products could be isolated from their reaction with \(\text{Py}_2\Gamma\text{BF}_4^+\),
an observation that matches the reactivity of the methyl alcohol (3.27). These results suggest that this iodonium reagent is only compatible with fluoroalkylated secondary alcohols.

\[
\begin{align*}
&\text{(3.32)} & & \text{I}_2 (3.0 \text{ eq.}), \\
& & & \text{K}_2\text{CO}_3 (2.0 \text{ eq.}) \\
& & & \text{DCM} \\
\text{DCM} & & \text{IPy}_2\text{BF}_4 (1.5 \text{ eq.}), \\
& & & \text{HBF}_4\cdot\text{Et}_2\text{O} (1.2 \text{ eq.}) \\
\end{align*}
\]

No desired product obtained after further purification

\[
\begin{align*}
&\text{(3.66)} & & 6\% \\
+ & \text{(3.67)} & & 16\% \\
\end{align*}
\]

\[
\begin{align*}
&\text{(3.35)} & & \text{I}_2 (3.0 \text{ eq.}), \\
& & & \text{K}_2\text{CO}_3 (2.0 \text{ eq.}) \\
& & & \text{DCM} \\
& & & \text{DCM} \\
& & & \text{IPy}_2\text{BF}_4 (1.5 \text{ eq.}), \\
& & & \text{HBF}_4\cdot\text{Et}_2\text{O} (1.2 \text{ eq.}) \\
\end{align*}
\]

No desired product obtained after further purification

\[
\begin{align*}
&\text{(3.68)} & & 46\% \\
+ & \text{(3.69)} & & 12\% \\
\end{align*}
\]

Scheme 3.27

However, in contrast to the failure to obtain any isolable products from the reaction of the methyl alcohol (3.27) with iodine, (3.32) and (3.35) both gave two products on reaction with
iodine that could be separated, in relatively poor yields, by column chromatography. In both cases, one of the products had low field CI resonances characteristic of the isochromene iodo
cyclisation, allowing (3.66) and (3.68) to be identified as the 6-endo-dig cyclisation products. The complete absence of the characteristic low field aromatic proton resonance for the second products suggested that the (E) hydroisobenzofuran products had not been isolated. However, the diagnostic high field aromatic proton resonances at 6.36 and 6.43 ppm respectively correlated well with data reported by Larock, indicating that (3.67) and (3.69) were the (Z) hydroisobenzofurans, presumably formed via a similar 5-exo-dig iodo
cyclisation followed by isomerisation mechanism.

3.3.4 Discussion of NMR Data

As many of the products from these iodo
cyclisations were oils, the trends in the NMR data have been summarised (Table 3.3), to allow a consideration of the isomers (5-exo-dig or 6-endo-dig).

As the crystal structures of products (3.49), (3.55) and (3.57) have been obtained, the 5-exo-dig structures of (3.49) and (3.55), the 6-endo-dig structure of (3.57) can be confirmed. Based on the NMR data of products (3.49) and (3.55), it can be concluded that for the (E) 5-exo-dig products, the lowest frequency aromatic H peaks would normally appear from ~7.10 to ~7.20 ppm, and the highest frequency aromatic H peaks would appear above 8.50 ppm. However, for the (Z) 5-exo-dig products, the highest frequency aromatic H peaks would appear below 8.0 ppm. Further, the $^{13}$C CI peaks would normally appear from ~64.0 to ~67.0 ppm, and the $^{13}$C CHO peaks would appear from ~79.0 to ~81.0 ppm for the 5-exo-dig products. Finally, the $^{3}J_{HF}$ coupling constants of the 5-exo-dig products are generally smaller than those in the 6-endo-dig products.
### 6-endo-dig

![6-endo-dig](image)

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<th>Highest frequency ¹H aromatic peak/ ppm</th>
<th>δC CI/ ppm</th>
<th>δC CHO/ ppm</th>
<th>³J_HH coupling constants</th>
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### (E) 5-exo-dig

![5-exo-dig](image)

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Table 3.3

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</table>

Products (3.49), (3.55), (3.58), (3.62) and (3.64) followed the same trends, and they could be assigned as the (E) 5-exo-dig structures. Although the NMR data for products (3.54), (3.56), (3.59), (3.61), (3.67) and (3.69) are not fully observed, they could be assigned as the (Z) 5-exo-dig structures.

Based on product (3.57), it could be concluded that for the 6-endo-dig products, the lowest frequency aromatic peaks would normally appear at ~7.00 ppm in the ¹H NMR spectrum, and the highest frequency aromatic peaks would appear around ~7.40 to ~7.60 ppm. The CI peaks in the ¹³C NMR spectrum would normally appear from ~72.0 to ~73.0 ppm, and the CHO peaks would appear from ~75.0 to ~77.0 ppm. Products (3.47) and (3.48) show slightly different CHO chemical shifts due to their acetal structures. And products (3.47), (3.48), (3.50), (3.52), (3.53), (3.57), (3.60), (3.63), (3.65), (3.66) and (3.68) followed the same trends for the 6-endo-dig structures.

Some of the characteristic peaks for products (3.52), (3.53) and (3.54) were slightly different from the others, as these products were formed from primary alcohol compounds. The CHO ³JHF coupling constants for products (3.62), (3.63), (3.64) and (3.65) were different and the
spin multiplicities for these four products were doublets of doublets as they coupled with the next two geminal-coupled fluorines. However, they still followed the trends that the coupling constants for the 5-membered products were still smaller than those for the 6-membered products.

3.3.5 Extension to iodocyclisation reactions of carboxylic acids and tertiary alcohols

Comparison with previous work (Scheme 3.3, reaction for (3.5b)) suggests I$_2$ reaction would give just one product. For comparison purpose, acid (3.36) was reacted under both iodocyclisation conditions (Scheme 3.28).

The reaction of (3.36) with Py$_2$I$^+$/BF$_4^+$ afforded a single product in good yield, whilst iodine gave a mixture of two isomers that could be separated by column chromatography. The introduction of the carbonyl group removed a number of the key NMR indicators for the products in these reactions, but the minor product from the iodine reaction displayed a low field resonance at 8.9 ppm in its $^1$H NMR spectrum, suggesting an (E) inden-1-one structure (3.71).

Single crystals of (3.71) were grown by recrystallisation using hot petroleum ether (40-60), and the structural data (Figure 3.8) confirmed that (E) 5-endo-dig iodocyclisation had taken place. In the $^{13}$C NMR spectrum the $\delta_{C1}$ for (3.71) occurs at higher frequency than that for the major product (3.70) (80 and 77 ppm respectively) which does not help in the characterisation of the latter. However, since isochromen-1-ones have almost exclusively been seen previously in electrophilic cyclisations, the 6-endo-dig cyclisation to give (3.70) is believed to occur in these reactions.
Scheme 3.28

Bond length (Å) C1-I1: 2.094(4); C2-C1: 1.319(5); C2-O1: 1.418(4); I1-H6: 2.896. Bond angle (°) C4-C3-O1: 107.7(3).

Figure 3.8 X-ray structure for (3.71)
Iodocyclisation reactions using tertiary alcohol compounds were reported by Larock’s group (Scheme 3.5, reaction 2), and the diethyl tertiary alcohol iodocyclisation with I₂ gave the (Z) 5-membered product in his report.

Reactions of either the dimethyl- (3.37) or diethyl- (3.39) tertiary alcohols with either iodine or Py₂I⁺BF₄⁻ gave single iodocyclised products in modest yields after column chromatography (Schemes 3.29 and 3.30). The absence of the diagnostic low field peak in the aromatic region of the ¹H NMR spectra for these products, together with high field aromatic peaks (6.40 and 6.42 ppm respectively) and δ CI resonances characteristic of dialkylisobenzofuran, 5-membered iodocyclisation products (63.1 and 65.9 ppm respectively), allowed identification as the (Z) 5-exo-dig products in line with Larock’s report.

In contrast with the reaction of the monomethyl secondary alcohol (Scheme 3.21, page 33), the Thorpe–Ingold effect might be the reason that these reactions succeed. Two substituents...
on a carbon lead to enhanced reactivity of the nucleophile by compressing the bond angle of the CCR₂OH group and pushing the nucleophile close to the alkyne by this steric effect.

### 3.3.6 Iodocyclisation of an amine substrate

To expand the research width, not only oxygen heterocyclic products should be studied, but nitrogen heterocyclic products should be studied as well. Nitrogen-containing heterocyclic rings are commonly used in chemical and pharmaceutical industries, as they are the core structure for many important chemicals.

The trifluoromethyl, tosyl-protected, amine (3.40) was chosen as a model test substrate that is similar to the secondary alcohol (3.28) and it was tested under both sets of reaction conditions (Scheme 3.31).

![Reaction Scheme 3.31](image)

The reaction of (3.40) with iodine gave a single iodocyclised product (3.74) in a 79 % isolated yield after column chromatography. Establishing, from a single example, whether a 6-endo-dig or 5-exo-dig cyclisation had occurred here is difficult. A relatively low field resonance (8.54 ppm) in the ¹H NMR spectrum could indicate a 5-membered ring.
Assignment of (3.74) as the 5-exo-dig product is tentative, and further work in the cyclisation of amines would be necessary to confirm this. The reaction with Py$_2$I$^+$BF$_4^+$ did not work for the amine, and only starting material could be recovered at the end of the reaction.

3.4 Discussion and conclusions

Both iodine and Py$_2$I$^+$BF$_4^+$ can be used for the iodocyclisation of alkynes with internal nucleophiles, but the selectivity, which tends to be good, and the mechanism of these reactions can be different depending on the substrate and the reagent. Tertiary alcohols, in line with Larock’s observations, give predominately (Z) 5-exo-dig iodocyclisations, with both reagents. Primary alcohols, again in line with Larock’s observations, give predominately 6-endo-dig iodocyclisations, although using iodine as a reagent gave substantially better yields. Carboxylic acids similarly gave 6-endo-dig iodocyclisations, although here iodine performed less well than Py$_2$I$^+$BF$_4^+$ in terms of yield and selectivity.

Non-fluorinated secondary alcohols gave conflicting results. Products from iodocyclisation with Py$_2$I$^+$BF$_4^+$ could not be identified. With iodine, the CH$_2$CO$_2$Et derivatised species (3.32) and (3.35) gave mixtures of 6-endo-dig and (Z) 5-exo-dig iodocyclisations, again in line with Larock’s observations. However, no identifiable products could be obtained using the methyl substituted alcohol suggesting that this is not a substrate amenable to these types of reactions. This might be because the size of the methyl substituent is not big enough to enhance the nucleophilicity by steric effect.

In marked contrast, the fluoroalkylated secondary alcohols gave different reactivities and selectivities. 6-endo-dig cyclisations were readily achieved using Py$_2$I$^+$BF$_4^+$ as the reagent. Using iodine gave predominately the (E) 5-exo-dig iodocyclisations. Larock has proposed that, in the iodine promoted reactions, isomerisation of the expected (E) iodoalkene to the (Z) iodoalkene product occurs. Clearly, here, the fluoroalkylated substituents influence this isomerisation allowing highly selective generation of the (E) iodoalkenes. Considering our
The proposed mechanism of these reactions (Scheme 3.32) suggests that the reagents impact upon the site of the intramolecular nucleophilic attack. The reactions with Py$_2$I$^+$BF$_4^+$ are carried out under acidic conditions whilst those with iodine are carried out in the presence of base. Perhaps, in the former, the nucleophile is the alcohol whilst in the latter the alcohol is deprotonated and the nucleophile is the alkoxide. Clearly, the difference in reactivity of the fluorine-containing and non-fluorine-containing substrates with Py$_2$I$^+$BF$_4^+$ indicates that the electron withdrawing influence of fluorine has an influence on this situation.
With iodine, the (E)/ (Z)-selectivity in the 5-exo-dig iodo cyclisations suggests that the electronegative fluorine atoms inhibit the isomerisation identified by Larock allowing selective formation of the (E) 5-exo-dig products here.

Although both iodine and IPy$_2$BF$_4$ iodo cyclisations reach 100 % conversion at the end of the reactions, according to all experimental data, the average yield of all iodocyclised products using iodine was higher than those using IPy$_2$BF$_4$. However, as the reactions using iodine need longer time (48 h), it is hard to conclude which electrophilic iodinating reagent is stronger.

The Thorpe–Ingold effect influences the reactions to a large extent. Increasing the size of the two R substituents on the CCR$_2$OH will increase the reactivity of the nucleophile. The bond angle of the CCR$_2$OH group is compressed, which enables the nucleophile to become closer to the alkyne. The reactions of the mono-methyl secondary alcohol (3.27) and dimethyl tertiary alcohol (3.37) showed the direct comparison.

The iodocyclisation reactions not only depend on the substituents on the alcohols (primary, secondary or tertiary), but also the substituents attached to the alkynes. In my project, the cyclised products could not be formed from nearly all hexyl substituted alcohols. These reactions were complicated by the large alkyl group giving unidentifiable crude products.

### 3.5 References


Chapter 4
Chapter 4 Protocyclisation and Fluorocyclisation

4.1 Introduction

The CF₃ and CF₂CO₂Et substituted iodocyclised products discussed in Chapter 3 could be used as substrates for further functionalisation, e.g. Sonagashira coupling reactions at iodine, in order to form more complex structures, which could be applied to pharmaceutical or industrial chemistry. However, a different approach to preparing fluorine-substituted heterocycles, based on fluorocyclisation using electrophilic fluorinating reagents (Scheme 4.1) was investigated.

![Proposed fluorocyclisation](image)

Scheme 4.1

Whilst the fluorocyclisation of alkenes is well established, the number and range of fluorocyclisation reactions with alkynes has been relatively unexplored until the last three years. Fluorocyclisation using electrophilic fluorinating reagents in combination with gold catalysts were reported in 2014 (Scheme 4.2). Either monofluorinated products, (4.3) & (4.7), or difluorinated products, (4.2) & (4.5), could be obtained selectively depending on the amount of Selectfluor used in the reaction. This was not surprising since difluorinated products were formed in the early reactions of F⁺ reagents with alkynes (Chapter 2). Interestingly, in the reaction of the acid-functionalised substrate (4.6), the competitive protocyclised product was obtained in a 1:1 ratio with the desired product, probably because of the absence of base in this reaction. Exclusively, five-membered ring heterocycles were reported using Selectfluor with both oxygen and nitrogen nucleophiles.
Elsewhere, Nevado’s group \(^4^3\) used the amino-substituted alkynes (4.9) as the substrate for gold-catalysed fluoro-cyclisation and it could be envisaged that either 5- or 6-membered heterocyclic products could be formed (Scheme 4.3, top reaction). Here, a 5-membered ring was formed exclusively and presumably it reacted further with water to form (4.10).
In a different type of fluorocyclisation, the 6-membered isoquinoline (4.12) was formed (Scheme 4.3, bottom reaction). A different electrophilic fluorinating reagent (NFSi) was used in this reaction with an imine and a silver catalyst. Various R substituents in (4.11) were used (phenyl, ethyl acetate, propyl, etc.) to undergo the silver-catalysed fluorocyclisations in good to excellent yields (56-87%). The only exception was using tBu as the R substituent, and no desired product was obtained from this starting material.

In 2014, Rodriguez’s group reported the first example of a fluorocyclisation of alkynes using a nucleophilic fluorinating reagent (Scheme 4.4). A 6-membered fluorinated cyclised product (4.14) was formed by this synthetic route. However, nucleophilic fluorocyclisations have not been studied in this project.
4.2 Fluorocyclisation reactions

4.2.1 Attempted fluorocyclisation reactions with Selectfluor

Throughout the successful electrophilic fluorocyclisation reactions, a metal catalyst was essential and gold catalysts were used in almost all of the reported reactions. In Chapter 2, it was shown that alkynes could react with just F⁺ reagents and water was used as the nucleophile to attack the activated alkynes. In this work, the aim was to use the carboxylic acid and the benzyl alcohol as the internal nucleophiles in order to form the fluorocyclised products. Since the fluorinations of alkynes worked without a catalyst in Chapter 2, the fluorocyclisation was investigated initially without a metal catalyst (Table 4.1).

![Diagram](4.15)

<table>
<thead>
<tr>
<th>Selectfluor/ eq.</th>
<th>Additive/ eq.</th>
<th>Temp./°C</th>
<th>Time/ h</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2.2 (dry)</td>
<td>Reflux</td>
<td>24</td>
<td>No signals were observed in the ¹⁹F NMR spectra indicating that fluorinated products were not formed. However, starting materials could not be recovered after purification.</td>
</tr>
<tr>
<td>2</td>
<td>2.2 (dry)</td>
<td>40</td>
<td>24</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>1.2 (dry)</td>
<td>100</td>
<td>24</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>2.2 (dry) K₂CO₃ (1.2)</td>
<td>40-100*</td>
<td>Overnight</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>2.2 (dry) K₂CO₃ (1.2)</td>
<td>50-100*</td>
<td>24</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>2.2 (dry) K₂CO₃ (1.2)</td>
<td>50-100*</td>
<td>4</td>
<td></td>
</tr>
</tbody>
</table>

*(4.15) and K₂CO₃ in MeCN at 40 or 50 °C for 30 min first, then the Selectfluor was charged and the reaction temperature was raised to 100 °C till the end of the reaction.

![Diagram](4.16)

<table>
<thead>
<tr>
<th>Selectfluor/ eq.</th>
<th>Additive/ eq.</th>
<th>Temp./°C</th>
<th>Time/ h</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>7</td>
<td>3.0</td>
<td>RT</td>
<td>Overnight</td>
<td>No signals were observed in the ¹⁹F NMR spectra indicating that fluorinated products were not formed. However, starting materials could not be recovered after purification.</td>
</tr>
<tr>
<td>8</td>
<td>3.0 (dry)</td>
<td>100</td>
<td>Overnight</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>2.2 (dry)</td>
<td>Reflux</td>
<td>Overnight</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>2.2 (dry)</td>
<td>80</td>
<td>24</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>1.2 (dry)</td>
<td>100</td>
<td>24</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>2.2 (dry)</td>
<td>100</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>2.2 (dry) K₂CO₃ (1.2)</td>
<td>100</td>
<td>6</td>
<td></td>
</tr>
</tbody>
</table>

Table 4.1
The reactions designed in Table 4.1 followed on from the studies in Chapters 2 and 3, but electrophilic fluorinating reagents were used instead of electrophilic iodinating reagents. The results in Table 4.1 demonstrated that attempts to fluorocyclise two substrates, which had been successfully iodocyclised in Chapter 3, were unsuccessful both with and without a base. This may be due to the weaker electrophilicity of the fluorinating reagent or other reactions occurred during the process. For example, Selectfluor can also be used as an oxidant, and Popplewell’s group \(^{4.9}\) reported a radical fluorination of a benzaldehyde at the benzylic position initiated by a single-electron transfer (SET), followed by the rapid loss of HF to yield an amide product (Scheme 4.5).

![Scheme 4.5](image)

**Scheme 4.5**

### 4.2.2 Palladium-catalysed protocyclisation

A number of palladium catalysts have been used in protocyclisation reactions. \(^{4.10-14}\) Both O-/N-heterocyclic products have been formed with good isolated yields using PdCl₂(MeCN)₂ as the metal catalyst (Scheme 4.6). \(^{4.10}\) In the products (4.18) and (4.20), the final step in the reaction is thought to be a protodemettallation to recover the catalyst and the postulated reaction mechanism is shown in Figure 4.1.
Initially, a cationic intermediate would be formed and the desired product would be obtained after the palladium complex had been replaced by the proton. Since the palladium catalysts worked so well in protocyclisation reactions, it was envisaged that a fluorocyclised product may be formed if an electrophilic fluorinating reagent was involved in the reaction. No palladium-catalysed fluorocyclisation reactions had been reported previously, and so this new synthetic route was tested.
Before attempting any fluorocyclisations, a number of the substrates used for the iodocyclisations (Figure 4.2) were first investigated for protocyclisation using the Pd catalyst. Not only would some of these reactions generate a number of new fluorinated heterocycles, but they would also give the spectroscopic data to establish whether competitive protocyclisation had occurred during the attempted fluorocyclisations.

The carboxylic acid (4.15), tertiary alcohol (4.23) and trifluoromethyl substituted secondary alcohol (4.16) were reacted by the palladium-catalysed cyclisation process. Products (4.25), (4.26) and (4.27) were formed in reasonable to excellent isolated yields (Scheme 4.7). The singlet peaks of the protons attached to the alkenes for the products were observed around 6 ppm in the $^1H$ NMR spectra, which indicated that the desired products had been formed. The 6-membered ring products (4.25), and 5-membered ring products (4.26) and (4.27) had been prepared previously by different synthetic routes and the characterisation data was in agreement with the literature. In the literature, products (4.26) and (4.27) were assigned to be the ($Z$) 5-membered isomers as nuclear overhauser effect (NOE) was observed from the proton of the alkene and the closest aromatic proton. In addition, as discussed for the trifluoromethyl substituted 5-membered ring iodocyclised product in Chapter 3, the
characteristic CHO coupling constant in $^1$H NMR data for product (4.27) ($^3J_{HF} = 5.9$ Hz) can be used to indicate the 5-membered ring structure.

Compared to the carboxylic acid (4.15) and the secondary alcohol (4.27), the increased nucleophilicity of the tertiary alcohol as well as the Thorpe-Ingold effect of the dimethyl substituent in (4.23) might cause the protocyclisation to proceed to a higher conversion.

![Scheme 4.7](attachment:scheme.png)

The CF$_2$CO$_2$Et substituted secondary alcohols, (4.21) and (4.22), were then cyclised using the palladium-catalysed protocol (Scheme 4.8). The new protocyclised products were formed for both reactions. In contrast, although the CF$_3$-substituted heterocycle (4.27) was formed in an excellent 67 % yield, there were problems faced in the isolation of CF$_2$CO$_2$Et-substituted heterocycles (4.28) and (4.29). The isolated yields for (4.28) and (4.29) were low and in the case of (4.29), only an impure product was obtained due to problems with purification by column chromatography.
Two sets of proton peaks were observed around 6 ppm in the $^1$H NMR spectra, which indicated that the desired protocyclised products had been obtained. The proton attached to the alkene group was a singlet, and for the proton $\alpha$ to the CF$_2$CO$_2$Et groups coupled to the F atoms, doublets of doublets were observed.

The characteristic coupling constants for the CHO proton in $^1$H NMR spectra for both products (4.28) and (4.29) ($^3J_{HF} = 13.7$ Hz, $^3J_{HF} = 5.5$ Hz and $^3J_{HF} = 13.6$ Hz, $^3J_{HF} = 5.6$ Hz respectively) are similar to these for the CF$_2$CO$_2$Et-substituted 5-membered ring iodocyclised products (Chapter 3), although products (4.28) and (4.29) are new compounds, they can be similarly assigned to be the 5-membered ring compounds.
The secondary amine (4.25) was also reacted by the palladium-catalysed cyclisation protocol (Scheme 4.9) and the protocyclised N-heterocyclic substrate (4.30) was formed in 49 % isolated yield. Similar $^1$H NMR proton signals were observed compared to the secondary alcohol reactions, however, peak of the additional proton had been shifted to around 5.6 ppm, which might be due to the different electronegativity of the N-heterocyclic substrate. Product (4.30) was assigned to be the 5-membered indole structure, as the CHN coupling constant ($^3J_{HF} = 7.4 \text{ Hz}$) was similar to that for the iodocyclised 5-membered product ($^3J_{HF} = 6.8 \text{ Hz}$).

In addition, a similar reaction was described in Hiroya’s report, $^4$ the (Z) 5-membered product (4.30a) is the only product obtained from the protocyclisation reaction of the primary amine (4.25a) (Scheme 4.10). Furthermore, resonances associated with the aromatic protons (7.06-7.59 ppm) for (4.30) were similar to those (6.90-7.80 ppm) for (4.30a) also indicating the indole structure.

All the products were identified by NMR spectroscopy ($^1$H, $^{13}$C and $^{19}$F) and accurate mass spectrometry. As all the products were oils, crystals suitable for single crystal X-ray structural determinations could not be obtained and the molecular structure investigated. (4.25) is a known 6-membered ring product, whilst (4.26) and (4.27) are known 5-membered
ring products. From all NMR data, it could be concluded that (Z) 5-membered products had been formed as the major products from the secondary amine, secondary and tertiary alcohols.

All of the reactions proceeded at room temperature, whereas higher temperatures had normally been applied in the literature reactions. Some of the products were obtained with very high isolated yields, but others were not as good as expected. Therefore, increasing the temperature may increase the yields in these reactions. The primary alcohol substrates were not tested, so far, and the palladium-catalysed cyclisation reactions could be applied to secondary and tertiary alcohols as well as a secondary amine substrate to form both O-/N-heterocyclic products.

4.2.3 Attempted palladium-catalysed fluorocyclisation reactions

Based on the palladium-catalysed cyclisation reactions, a new reaction using Selectfluor, PdCl$_2$(MeCN)$_2$ and Et$_3$N in THF was designed. The aim of this process was to replace the palladium complex with the F$^+$ reagent, or the F$^+$ reagent could be attached to the palladium complex first instead of proton, which then could lead to the desired product in the end (Scheme 4.11).

Substrate (4.15) was used as the starting compound to test the reactions as it would be easy to tell if any protocyclised byproducts had been formed. The first reaction allowed an overnight palladium-catalysed cyclisation reaction to take place first to form the intermediate product (4.31), and then the fluorinating reagent was charged into the reaction mixture in order to fluorodemetallate. In the second attempt, all of the reagents were charged in a one-pot reaction, and the intermediate product (4.32) might be formed. The reactions were run under dry conditions using an inert atmosphere of nitrogen. However, the crude $^1$H NMR spectra were complicated and the desired products could not be identified. Surprisingly, there was no sign of the protocyclised products in the crude NMR spectra either. Both reactions did not work.
4.2.4 Silver-catalysed fluorocyclisations

During the course of this work, Liu reported the fluorocyclisation of a tert-butyl imine using NFSi in the presence of AgNO₃ as a catalyst (Scheme 4.3, bottom reaction). Although the substrates and mechanism of this reaction are different to those used in this study, the possibility of using AgNO₃ as a cheap, readily available catalyst was attractive. Therefore, Liu’s cyclisation reaction conditions were checked using the same tBu-substituted imine, before using these reaction conditions on the series of secondary and tertiary alcohols.
Isoquinoline (4.34) was isolated in 68 % yield (Scheme 4.12). The spectroscopic data was consistent with that reported by Liu, and crystals suitable for X-ray structural determination were grown from hot petroleum ether (40-60) and the molecular structure is shown in Figure 4.3.

![Figure 4.3 X-ray structure for (4.34)](image)

The mechanism proposed by Liu was different to the electrophilic halogen cyclisation mechanism proposed in the iodocyclisation reactions in Chapter 3. In Liu’s hypothesised reaction mechanism, tBu is eliminated from the intermediate, and an oxidative fluorination of the sp² C-Ag bond by the F⁺ reagent had occurred and formed the sp² C-F bond (Scheme 4.13). Crucially, the addition of Li₂CO₃ was necessary to mop up the proton formed in the elimination of the tBu group so as to avoid formation of the protocyclised product. A similar iodocyclisation reaction using the imine as the starting substrate was reported by Larock’s group, using I₂ and NaHCO₃ in acetonitrile at RT under mild conditions to form the analogous iodocyclised product (4.43). The reaction mechanism is shown in Figure 4.4.
In both reactions, cationic intermediates are formed, (4.36) and (4.42). Iodine is sufficiently electrophilic to generate the iodonium intermediate (4.40) by itself (Figure 4.4). However, the metal catalyst is necessary to generate the silver-alkene intermediate, and then NFSi could be used to replace the Ag group to form the desired product (4.37) in Scheme 4.13. As shown in Figure 4.4, a proton would be generated in the final step and therefore, the presence of base in both reactions is necessary to prevent the formation of the protocyclised products.
The first attempts at the silver-catalysed fluorocyclisation reactions on the benzoic acid (4.15) and the trifluoromethyl benzyl alcohol (4.16) were unsuccessful (Table 4.2). Unfortunately, none of the desired products were formed when (4.15) and (4.16) were reacted with NFSi, in the presence of AgNO₃ and base at either RT or 60 °C. Additionally, in entry 4, K₂CO₃ and the acid were allowed to react together for 1 h to ensure that the salt had been formed. However, none of the desired products were observed in this reaction.

In contrast, reactions of the dimethyl tertiary alcohols (4.23) and (4.43) generated cyclised products, as mixtures of two diastereoisomers. However, these cyclised products formed an aliphatic C-F bond rather than the alkene C-F bond (Scheme 4.14). In both cases (R₁ = Ph and tolyl), the isomers could not be separated, and after column chromatography, a mixture of diastereoisomers were obtained in 52 % and 35 % isolated yields respectively.
Products (4.44) and (4.45) were characterised by accurate mass spectrometry and by multinuclear NMR ($^1$H, $^{13}$C, $^{19}$F) spectroscopies. $^1$H NMR spectroscopy revealed characteristic peaks at around 2.8 and 3.2 ppm for the OH protons. In addition, two doublets ($^2J_{HF} = 45.3$ Hz) were observed at 5.6-5.7 ppm for the two CHF units. $^{13}$C NMR spectroscopy revealed two doublets ($^1J_{CF} = 180.9$ Hz) at 94.3 and 96.2 ppm for the CHF units, and two doublets ($^2J_{CF} = 27.1$ Hz) for the COH units next to the CHF. $^{19}$F NMR spectroscopy revealed two singlets in a 1:1 ratio at -183 and -191 ppm for the fluorine substituents in each diastereomer. Accurate MS gave daughter ions for [MH-OH$_2$]$^+$. The molecular ions obtained were always 17 units less than those calculated for the parent ions.

As all the products were oils, crystals suitable for single crystal X-ray structural determinations could not be obtained and the molecular structure investigated. It was difficult to conclude whether 5- or 6-membered products had been formed. However, following the trends for the iodocyclisation and protocyclisation reactions, products (4.44) and (4.45) were assigned to be the 5-membered ring products.

Two possible mechanisms have been outlined in Schemes 4.15 and 4.16. Scheme 4.15 shows the mechanism proposed by Liu in order to form the desired monofluorinated product (4.46). Upon aqueous workup, however, it is possible that the enol reacted with the water to form the pair of diastereomers.
Scheme 4.15

Scheme 4.16
In Scheme 4.16, however, the Ag catalyst may act just like the Pd catalyst to catalyse the protocyclisation reaction and form product (4.47). The enol ether may then react with the electrophilic fluorinating reagent to form the pair of diastereomers.

A similar reaction had been described (Scheme 4.3, top reaction), that gave similar monofluorinated cyclised products. In this case, the reaction was under mild conditions and the diastereomers could be formed during the reaction. Further studies have not been carried out by Nevado’s group, however, their work provides further evidence to support the structures assigned to isomers (4.44) and (4.45).

\[
\begin{align*}
\text{Ph} & \quad \text{Ph} \\
\text{NHTs} & \quad \text{Ph}_3\text{PAuSbF}_6 (5 \%) \\
\text{Selectfluor (2.0 eq.)} & \quad \text{NaHCO}_3 (1.0 \text{ eq.}) \\
\text{MeCN/H}_2\text{O (20/1)} & \quad 80 ^\circ \text{C}, 1.5 \text{ h}
\end{align*}
\]

Scheme 4.3, top reaction

In addition, if the amount of NFSi was doubled to 3.0 equivalents, different products were obtained, which the difluorinated cyclised products have also been reported by Liu (Scheme 4.17). The extra proton given by NaBH₄ allowed a second fluorination to form the difluorinated product (4.49). Compared to the tBu substituent on the starting material used for the monofluorination, the R₁ substituent was not been removed in forming the final product. The formation of the difluorinated products mainly depended on the amount of NFSi and the additional NaBH₄ in Liu’s report.
In order to try to distinguish between the two possible mechanisms outlined in Schemes 4.15 and 4.16, compounds (4.23) and (4.43) were also reacted with 3 equivalents of NFSi to see if the difluorinated cyclised products could be formed (Scheme 4.18). In both cases the difluorinated cyclised products were isolated in moderate yields (36-45 %) after purification by column chromatography.
The difluorinated products were characterised by $^1$H, $^{13}$C and $^{19}$F NMR spectroscopy. In the $^{19}$F NMR spectra there were two doublets at -105 and -113 ppm with coupling constants of 250 Hz for the fluorine-fluorine coupling. Broad singlets were observed at 3.09 ppm in the $^1$H NMR spectra for the OH signals. $^{13}$C NMR spectroscopy revealed two triplets at 119.7 ($^1J_{CF} = 247.0$ Hz) and 105.4 ppm ($^2J_{CF} = 33.6$ Hz) for the CF$_2$ unit and the COH unit next to the CF$_2$. The accurate mass data gave the molecular weight of (MH-OH$_2$)$^+$ as well.

The formation of the difluorinated products indicates that the monofluorinated product is formed first via the mechanism outlined in Scheme 4.14. The monofluorinated enol must then react with a second equivalent of NFSi, as shown in Scheme 4.19, in order to form the difluorinated cyclised product.

The diethyl tertiary alcohol (4.52) was also reacted under the same silver-catalysed fluorocyclisation conditions with both 1.5 and 3.0 equivalents of NFSi (Scheme 4.20).
Interestingly, when (4.52) was reacted with 1.5 equivalents of NFSi, the monofluorinated alkene (4.53) and the difluorinated product (4.54) were isolated in 22 % and 18 % yields respectively. In this reaction, only a trace amount of the monofluorinated alcohols (4.55a) and (4.55b) were detected by $^{19}$F NMR spectroscopy.

Three sets of fluorine peaks were observed in the $^{19}$F NMR spectrum of the crude product (two singlet peaks at -181.0 and -191.0 ppm, two doublet peaks at -103.6 and -111.8 ppm, and a singlet at -163.4 ppm), which indicated that three different fluorinated products had been formed.

Scheme 4.20
The first two fluorine singlet peaks appeared in the similar positions compared to those for the dimethyl products (4.44a/4.44b) and (4.45a/4.45b), and indicated that the same monofluorinated alcohols (4.55a/4.55b) had been formed. The two doublets indicated that the difluorinated product (4.54) had been formed. The third singlet peak at -163.4 ppm indicated that the desired monofluorinated alkene (4.53) had been isolated for the first time. Neither of the OH and the CHF signals were observed in the 1H NMR spectrum, whilst the 13C NMR spectroscopy revealed a doublet at 144.2 ppm (1J\textsubscript{CF} = 243.1 Hz) for a quaternary carbon and was assigned to be the CF unit. Finally, the accurate mass spectrometry data also gave the correct MH\(^+\) molecular ion.

When (4.52) was reacted with 3.0 equivalents of NFSi, the difluorinated cyclised product was isolated in 15 % yield and only a trace amount of the monofluorinated alkene and the monofluorinated alcohols were observed in the 19F NMR spectrum of the crude product.

It is difficult to explain the differences in the reactivity of the dimethyl tertiary alcohols (4.23) and (4.43), with the diethyl tertiary alcohol (4.52) which formed a mixture of the monofluorinated alkene and the difluorinated product instead of the monofluorinated alcohols which were produced with the dimethyl substrates. In the case of the formation of the monofluorinated alkene (4.53), it would follow the mechanism of Liu’s reaction, but this type of product was not observed in the dimethyl alcohol reactions.

The reaction conditions for the successful fluorocyclisations of tertiary alcohols were also applied to the methyl secondary alcohol (4.56) for a direct comparison between secondary and tertiary alcohols. Since the trifluoromethyl secondary alcohol (4.16) had failed to undergo a fluorocyclisation under the standard reaction conditions, the reaction temperature was raised to 60 °C (Scheme 4.21). However, no fluorinated products were isolated from the reactions using either 1.5 or 3.0 equivalents of NFSi and the starting materials were not recovered. Unfortunately, since the methyl secondary alcohol did not work, only the Thorpe-Ingold effect could be assigned here to explain the differences in the reactivity.
Finally, a CF₃ substituted secondary amine (4.24) was also tested in the silver-catalysed reactions using both 1.5 and 3.0 equivalents of NFSi (Scheme 4.22). Interestingly, only the desired monofluorinated products were formed as a mixture of the (Z) and (E) 5-membered rings. After purification by column chromatography on an alumina column, products (4.57) and (4.58) were both isolated in 19 % yield when 1.5 equivalents of NFSi was used. When 3.0 equivalents of NFSi were used products (4.57) and (4.58) were isolated in 52 % and 9 % respectively.

No CHF peaks or OH peaks were observed in the ¹H NMR spectra of both products (4.57) and (4.58). In the ¹⁹F NMR spectrum of (4.57), a singlet was present at -113.7 ppm, and a singlet was obtained at -182.5 ppm in the ¹⁹F NMR spectrum of (4.58). The CHN coupling
constants for products (4.57) and (4.58) ($^3J_{HF} = 6.3$ Hz and $^3J_{HF} = 6.6$ Hz respectively) were similar to those for the iodocyclised and the protocyclised 5-membered indole products. Products (4.57) and (4.58) were assigned to be the (Z) and (E) 5-membered ring products. It should be noted that, as the $\delta_{C-Cl}$ peaks for the iodocyclised (Z) 5-membered products would normally occur to lower field than those for the iodocyclised (E) 5-membered products. So, in this reaction, the product (4.57) with the lower $\delta_{C-Cl}$ CF peak frequency (154.7 ppm) was assigned to be the (Z) 5-membered product and the other product (4.58) (133.1 ppm) was assigned to be the (E) 5-membered product. The accurate mass spectra also gave the same and correct parent ions for the two products.

4.2.5 Metal catalysed fluorocyclisations of tertiary alcohols

Following the success of the silver-catalysed fluorocyclisations of the tertiary alcohols, it was decided to investigate whether the Pd catalyst and/or Selectfluor would also promote these fluorocyclisations. Four smaller scale reactions were tested and the results are shown in Table 4.3.

Runs 2-5 were the smaller scale reactions compared to the original silver-catalysed reaction with NFSi. Using the palladium catalyst in Run 3, the monofluorinated diastereomers (4.44) were formed as the major products. The two doublets for the protons in the monofluorinated products were observed in the $^1$H NMR spectrum of the crude product, and the doublets for the two coupled fluorines in the difluorinated product were observed in the $^{19}$F NMR spectrum as well. None of the starting material was observed, and the $^1$H and $^{19}$F NMR spectra of the crude product were very similar to that for the crude product from the original reaction (Run 1). The reaction using Selectfluor and the palladium catalyst (Run 2) also gave a similar result with 100 % conversion, with no starting material observed in the $^1$H NMR spectrum of the crude product, and both mono- and di-fluorinated products (4.44) and (4.45) were observed in the $^{19}$F NMR spectrum of the crude product. In Run 4, the starting material was still observed in the $^1$H NMR spectrum of the crude product, and a singlet at 5.9 ppm
indicated that the protocyclised product had been formed as well as both the mono- and di-fluorinated products. The signals for both the mono- and di-fluorinated products in the $^{19}$F NMR spectrum were strong, but it was hard to distinguish which was the major product.

In conclusion, both electrophilic fluorinating reagents (Selectfluor and NFSi) and both metal catalysts (palladium and silver) could be used to promote the metal-catalysed fluorocyclisation reaction with the tertiary alcohol substrates. NFSi was the better electrophilic fluorinating reagent in these reactions, and the palladium catalyst gave a similar effect compared to the silver catalyst. However, only the starting material \((4.23)\) was recovered in Run 5 when there was no catalyst present to promote the reaction.

![Reaction Scheme](image)

<table>
<thead>
<tr>
<th>Run</th>
<th>NF reagent</th>
<th>Catalyst</th>
<th>Conversion</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>NFSi</td>
<td>AgNO$_3$</td>
<td>100 %</td>
<td>((4.44)) in 52 % isolated yield, trace amount of ((4.50)).</td>
</tr>
<tr>
<td>2</td>
<td>Selectfluor</td>
<td>AgNO$_3$</td>
<td>100 %</td>
<td>((4.44)) as the major product, trace amount of ((4.50)).</td>
</tr>
<tr>
<td>3</td>
<td>NFSi</td>
<td>PdCl$_2$(MeCN)$_2$</td>
<td>100 %</td>
<td>Both ((4.44)) and ((4.50)) were observed.</td>
</tr>
<tr>
<td>4</td>
<td>Selectfluor</td>
<td>PdCl$_2$(MeCN)$_2$</td>
<td>60 %</td>
<td>Both ((4.44)) and ((4.50)) were observed, and protocyclised product ((4.26)) was also observed.</td>
</tr>
<tr>
<td>5</td>
<td>NFSi</td>
<td>-</td>
<td>-</td>
<td>Only starting material ((4.23)) was recovered.</td>
</tr>
</tbody>
</table>

**Table 4.3**

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A mechanism for the Pd-catalysed reaction is proposed in Scheme 4.23. In the first step it was postulated that the PdL₂ catalyst would react with the alkyne substrate to form the anionic intermediate which would react with the fluorinating reagent to form the desired fluorocyclised product (4.46). Product (4.46) could either react with water in the aqueous workup to form the pair of diastereomers (4.44a) and (4.44b) or it could react with the excess electrophilic fluorinating reagent to form the difluorinated product (4.50).

4.3 Discussion and conclusions

All of the palladium-catalysed protocyclisation reactions proceeded at room temperature with a range of aromatic alkyne substrates including secondary and tertiary alcohols, a carboxylic
acid and a secondary amine. The reaction conditions were unoptimised and higher reaction temperatures might be required to improve some of the isolated yields. These reactions were studied in order to help understand metal-catalysed fluorocyclisations and to identify any protocyclised products potentially formed as unwanted side products in the fluorocyclisations.

A new fluorocyclisation reaction was developed successfully for tertiary alcohols using N-fluorobenzenesulfonimide and silver nitrate. Three different types of fluorinated products were obtained depending upon the tertiary alcohol and the amount of NFSi.

When the dimethyl tertiary alcohols, (4.23) and (4.43), underwent the silver-catalysed fluorocyclisations, the monofluorinated alcohol diastereomers were obtained as the major products with 1.5 equivalents of NFSi. The difluorinated alcohol, however, was obtained as the major product with 3.0 equivalents of NFSi.

Surprisingly, when the diethyl tertiary alcohol (4.52) was reacted with 1.5 equivalents of NFSi in the presence of silver nitrate, the desired monofluorinated alkene and the difluorinated fluorocyclised product were both isolated in 22 % and 18 % yields respectively. When 3.0 equivalents of NFSi was reacted with the diethyl tertiary alcohol the difluorinated fluorocyclised product was isolated as the main product but only in a low isolated yield.

Unfortunately, the silver-catalysed fluorocyclisations did not work with the trifluoromethyl and the methyl-substituted secondary alcohols and the carboxylic acid. The trifluoromethyl substituted secondary amine (4.24) was also reacted under the standard silver-catalysed fluorocyclisation reaction conditions with both 1.5 and 3.0 equivalents of NFSi. The desired (Z) and (E) 5-membered fluorocyclised products were obtained in a 1:1 ratio when using 1.5 equivalents of NFSi, and the (Z) 5-membered product became the major product when using 3.0 equivalents of NFSi. The mono- or di-fluorinated alcohols were not formed after the water extraction workup. This might arise from the different reactivities of the N- and O-heterocycles.
Finally, the dimethyl tertiary alcohol (4.23) was tested using both NFSi and Selectfluor as well as silver and palladium catalysts in small scale reactions. Interestingly, using either NF reagent with either metal catalyst gave the monofluorinated diastereomers as well as the difluorinated product. However, the palladium-catalysed fluorocyclisatoin with Selectfluor was less selective and also formed the protocyclised product. These reactions also established that the fluorocyclisations did not work unless a palladium or silver catalyst was present.

The formation of fluorinated heterocyclic products is important for both pharmaceutical and industrial chemistry. The fluorinated O- and N-heterocycles are the key structure for many different drugs and chemicals. Only a few samples were studied for this metal-catalysed fluorocyclisation reaction so far and more reactions need to be tested in future to fully understand this reaction.

4.4 References

Chapter 5
Chapter 5 – Experimental

5.1 General Experimental Information

Proton, $^{19}$F and $^{13}$C NMR spectra were recorded on Bruker DRX 400 and Bruker AM 300 spectrometers at ambient temperatures. They were referenced to external SiMe₄ (¹H), external CFCl₃ (¹⁹F) and to external SiMe₄ (¹³C) using the high frequency positive convention. All chemical shifts are quoted in $\delta$ (ppm) and coupling constants in Hertz. The specified deuterated solvent was used. The following spectrometer frequencies were used:

Bruker AM 300 spectrometer: $^1$H at 300.13 MHz
$^{19}$F{¹H} at 283.57 MHz
$^{13}$C{¹H} at 75.47 MHz

Bruker DRX 400 spectrometer: $^1$H at 400.13 MHz
$^{19}$F{¹H} at 376.46 MHz
$^{13}$C{¹H} at 100.62 MHz

Electron impact (EI) mass spectra were recorded on a Kratos concept 1 H, double focussing, forward geometry mass spectrometer, Atmospheric Solids Analysis Probe (ASAP) mass spectra were recorded on a Xevo QTof mass spectrometer (Waters). X-ray crystallography data were collected on a Bruker Apex SMART 2000 diffractometer using graphite monochromated Mo-Kα radiation ($\lambda = 0.71073$ Å).

Where a reaction was carried out at an elevated temperature, the temperature stated is the oil bath temperature.

Starting materials were used as received from Sigma-Aldrich, Apollo Scientific, Alfa Aesar, Fluorochem, Acros Organics and Manchester Organics.
Dried dichloromethane (DCM), acetonitrile (MeCN), tetrahydrofuran (THF), ethyl acetate and diethyl ether were available in the lab supplies. Triethylamine (Et₃N) and dimethylacetamide (DMA) were dried by the distillation after refluxing the solvents with CaCl₂ overnight.

Activated zinc was prepared via the following procedure: Zinc dust (5.0 g, < 10 µm, 98+ %) was washed with 17 % HCl (20 mL) for 10 seconds and the acid was removed by suction filtration. The zinc dust was then washed with water (20 mL), ethanol (20 mL) and diethyl ether (20 mL) before it was dried under vacuum at 120 °C for 2 h. The activated zinc dust was stored and handled under a nitrogen atmosphere.

5.2 Experimental for Chapter 2

**General method A:** Iodobenzene substrates (1.0 eq.), phenylacetylene derivatives (1.2 eq.), [Pd(PPh₃)₂Cl₂] (0.02 eq.), CuI (0.04 eq.) and dry Et₃N were charged into a dry three-necked flask. After stirring at 70 °C under nitrogen for 3 h, water (15 mL) and diethyl ether (15 mL) were added to the reaction mixture. The precipitate was filtered off and the solution was extracted with Et₂O (3 x 10 mL). The combined organic layers were dried over MgSO₄ (anhydrous), and the solvent was removed to give the crude product.

1. 1,2-Di-tolylethyne (2.12)

![1,2-Di-tolylethyne](image)

After **General method A** using 4-iodotoluene (1.61 g, 7.40 mmol), 1-ethynyl-4-methylbenzene (1.13 mL, 8.90 mmol), [Pd(PPh₃)₂Cl₂] (0.12 g, 0.17 mmol), CuI (0.059 g, 0.30 mmol) and Et₃N (30 mL), the crude product (1.59 g) was purified by column chromatography using diethyl ether/hexane (1/9) to give pure 1,2-di-tolylethyne as a brown
oil (1.16 g, 76 %). The characterisation data was in agreement with the literature.\(^5\)\(^1\)H NMR
(400 MHz; CDCl\(_3\)) \(\delta\)H 2.29 (6H, s, CH\(_3\)), 7.07 (4H, d, \(^3\)J\(_{HH}\) = 7.8 Hz, ArH), 7.34 (4H, d, \(^3\)J\(_{HH}\) = 7.8 Hz, ArH); \(^13\)C NMR (100 MHz; CDCl\(_3\)) \(\delta\)C 21.5 (CH\(_3\)), 88.9 (C), 120.4 (C), 129.1 (CH),
131.4 (CH), 138.2 (C).

2. 1-Nitro-2-(phenylethynyl)benzene (2.13)

![1-Nitro-2-(phenylethynyl)benzene](image)

After **General method A** using 1-iodo-2-nitrobenzene (2.76 g, 11.1 mmol), phenylacetylene
(1.5 mL, 13.35 mmol), \([\text{Pd(PPh}_3\text{)_2Cl}_2]\) (0.18 g, 0.255 mmol), CuI (0.089 g, 0.45 mmol) and
Et\(_3\)N (40 mL), a small amount of the crude product (0.50 g) was purified by column
chromatography using diethyl ether/hexane (1/9) to give pure 1-nitro-2-(phenylethynyl)benzene as an orange oil (0.327 g, 65 %). The characterisation data was in
agreement with the literature.\(^5\)\(^2\) \(^1\)H NMR (400 MHz; CDCl\(_3\)) \(\delta\)H 7.40 (3H, m, ArH), 7.48
(2H, td, \(^3\)J\(_{HH}\) = 7.8 Hz, \(^4\)J\(_{HH}\) = 1.4 Hz, ArH), 7.62 (3H, m, ArH), 8.10 (1H, dd, \(^3\)J\(_{HH}\) = 8.3 Hz,
\(^4\)J\(_{HH}\) = 1.2 Hz, ArH); \(^13\)C NMR (100 MHz; CDCl\(_3\)) \(\delta\)C 84.8 (C), 97.2 (C), 118.8 (C), 122.4
(C), 124.7 (CH), 128.5 (CH), 128.5 (CH), 129.3 (CH), 132.0 (CH), 132.8 (CH), 134.6 (CH),
149.7 (CNO\(_2\)).

3. 1-Nitro-4-(phenylethynyl)benzene (2.14)

![1-Nitro-4-(phenylethynyl)benzene](image)

After **General method A** using 1-iodo-4-nitrobenzene (2.76 g, 11.1 mmol), phenylacetylene
(1.5 mL, 13.35 mmol), \([\text{Pd(PPh}_3\text{)_2Cl}_2]\) (0.18 g, 0.255 mmol), CuI (0.0885 g, 0.45 mmol) and
Et\(_3\)N (30 mL), a small amount of the crude product (0.515 g) was purified by column
chromatography using diethyl ether/hexane (1/9) to give pure 1-nitro-4-(phenylethynyl)benzene as an brown oil (0.178 g, 35 %). The characterisation data was in agreement with the literature. 5.3 1H NMR (400 MHz; CDCl₃) δH 7.31 (3H, m, ArH), 7.48 (2H, m, ArH), 7.59 (2H, d, 3JHH = 6.9 Hz, ArH), 8.14 (2H, d, 3JHH = 6.9 Hz, ArH); 13C NMR (100 MHz; CDCl₃) δC 87.6 (C), 94.7 (C), 122.1 (C), 123.6 (CH), 128.6 (CH), 129.3 (CH), 130.3 (C), 131.9 (CH), 132.3 (CH), 147.0 (CNO₂).

4(a). (4-(Phenylethynyl)aniline (2.32)

After General method A using 1-iodo-4-nitrobenzene (2.76 g, 11.1 mmol), phenylacetylene (1.50 mL, 13.35 mmol), [Pd(PPh₃)₂Cl₂] (0.18 g, 0.255 mmol), CuI (0.0885 g, 0.45 mmol) and Et₃N (50 mL), the crude product (3.02 g) was placed into a round bottom flask with tin (II) chloride dehydrated (12.53 g, 55.5 mmol) and EtOH (120 mL). The mixture was stirred at RT for 2 h and the solvent was removed vacuo. KOH (3M, 120 mL) and chloroform (30 mL) were added into the reaction mixture and the precipitate was filtered off. After extracting the solution with chloroform (3 x 10 mL), the organic phase was dried over MgSO₄ (anhydrous), and the solvent was removed to give the crude product (2.56 g). Purification by column chromatography using chloroform/petroleum ether (40- 60°C) (1/1) gave the desired product (4-(phenylethynyl)aniline as a brown oil (1.29 g, 60 %). The characterisation data was in agreement with the literature. 5.4 1H NMR (400 MHz; CDCl₃) δH 3.74 (2H, s, NH₂), 6.56 (2H, td, 3JHH = 8.6 Hz, 4JHH = 2.2 Hz, ArH), 7.25 (5H, m, ArH), 7.42 (2H, d, 3JHH = 6.4 Hz, ArH); 13C NMR (100 MHz; CDCl₃) δC 87.3 (C), 90.1 (C), 112.7 (C), 114.8 (CH), 123.9 (C), 127.6 (CH), 128.3 (CH), 131.4 (CH), 133.0 (CH), 146.6 (C).
4(b). 4-Methyl-N-(4-(phenylethynyl)phenyl)benzenesulfonamide (2.15)

![Structure](image)

The 4-(phenylethynyl)aniline (1.29 g, 6.66 mmol), dry pyridine (1 mL, 12.4 mmol), p-toluenesulfonylchloride (1.63 g, 8.55 mmol) and DCM (40 mL) were charged into a dry three-necked flask at 0°C. After warming to RT and stirring under nitrogen overnight, H2O (20 mL) was added to the reaction mixture and the solution was extracted with Et2O (3 x 10 mL). The combined organic layers were dried over MgSO4 (anhydrous) and the solvent was removed to give the crude product (1.82 g). Hot toluene was used to recrystallise the crude product and after cooling in the fridge overnight, it gave the desired product (4-methyl-N-(4-(phenylethynyl)phenyl)-benzenesulfonamide as a brown oil (0.43 g, 19 %). 1H NMR (400 MHz; CDCl3) δH 2.30 (3H, s, CH3), 6.92 (1H, s, NH), 6.99 (2H, td, 3JHH = 8.7 Hz, 4JHH = 2.2 Hz, ArH), 7.16 (2H, d, 3JHH = 8.0 Hz, ArH), 7.25 (3H, m, ArH), 7.32 (2H, d, 3JHH = 8.7 Hz, ArH), 7.41 (2H, m, ArH), 7.62 (2H, d, 3JHH = 8.4 Hz, ArH); 13C NMR (100 MHz; CDCl3) δC 21.6 (CH3), 88.6 (C), 89.7 (C), 120.0 (C), 120.8 (CH), 123.1 (C), 127.3 (CH), 128.4 (CH), 129.8 (CH), 131.5 (CH), 132.7 (CH), 135.9 (C), 136.5 (C), 144.2 (C).

5. 1-Nitro-2-(oct-1-ynyl)benzene (2.17)

![Structure](image)

After **General method A** using 1-iodo-2-nitrobenzene (1.84 g, 7.4 mmol), 1-octyne (1.32 ml, 8.9 mmol), [Pd(PPh3)2Cl2] (0.12 g, 0.17 mmol), CuI (0.059 g, 0.30 mmol) and Et3N (30 mL), a small amount of the crude product (0.78 g) was purified by column chromatography using diethyl ether/hexane (1/9) to give pure 1-nitro-2-(oct-1-ynyl)benzene as a brown oil (0.571 g, 73 %). The characterisation data was in agreement with the literature. 1H NMR (400 MHz; CDCl3) δH 0.94 (3H, t, 3JHH = 7.0 Hz, CH2CH3), 1.34 (4H, m, CH2CH2CH3), 1.50 (2H, quintet, 3JHH = 7.4 Hz, CH2CH2CH2CH3), 1.66 (2H, quintet, 3JHH = 7.3 Hz, CH2CH2C), 2.50
(2H, t, $^3J_{HH} = 7.1$ Hz, CH$_2$C), 7.41 (1H, td, $^3J_{HH} = 7.8$ Hz, $^4J_{HH} = 1.6$ Hz, ArH), 7.53 (1H, td, $^3J_{HH} = 7.5$ Hz, $^4J_{HH} = 1.3$ Hz, ArH), 7.59 (1H, dd, $^3J_{HH} = 7.8$ Hz, $^4J_{HH} = 1.5$ Hz, ArH), 7.98 (1H, dd, $^3J_{HH} = 8.2$ Hz, $^4J_{HH} = 1.1$ Hz, ArH); $^{13}$C NMR (100 MHz; CDCl$_3$) δC 14.0 (CH$_3$), 19.8 (CH$_2$), 22.5 (CH$_2$), 28.3 (CH$_2$), 28.6 (CH$_2$), 31.3 (CH$_2$), 75.9 (C), 99.5 (C), 119.4 (C), 124.3 (CH), 127.8 (CH), 132.4 (CH), 134.8 (CH), 150.2 (C).

6. 4-Tolylbut-3-yn-1-ol (2.18)

After **General method A** using 4-iodotoluene (3.23 g, 14.8 mmol), 3-butyn-1-ol (1.35 mL, 17.8 mmol), [Pd(PPh$_3$)$_2$Cl$_2$] (0.24 g, 0.34 mmol), CuI (0.118 g, 0.60 mmol) and Et$_3$N (40 mL), the crude product (3.31 g) was purified by column chromatography using ethyl acetate/hexane (3/7) to give pure 4-tolylbut-3-yn-1-ol as a brown oil (2.18 g, 99 %). The characterisation data was in agreement with the literature. $^5$-$^6$ $^1$H NMR (400 MHz; CDCl$_3$) δH 1.82 (1H, s, OHH), 2.26 (3H, s, CH$_3$), 2.61 (2H, t, $^3J_{HH} = 6.3$ Hz, CH$_2$), 3.73 (2H, t, $^3J_{HH} = 6.3$ Hz, OCH$_2$), 7.02 (2H, d, $^3J_{HH} = 8.0$ Hz, ArH), 7.23 (2H, d, $^3J_{HH} = 8.0$ Hz, ArH); $^{13}$C NMR (100 MHz; CDCl$_3$) δC 21.4 (CH$_3$), 23.9 (CH$_2$), 61.2 (CH$_2$), 82.6 (C), 85.5 (C), 120.2 (C), 129.0 (CH), 131.5 (CH), 138.0 (C).

7. 4-Tolylbut-3-ynyl acetate (2.19)

Acetyl chloride (0.57 mL, 8.0 mmol) was added dropwise to a cooled (ice bath) stirred solution of 4-tolylbut-3-yn-1-ol (1.19 g, 8.0 mmol) and pyridine (0.64 mL, 8.0 mmol) in dry DCM (30 mL). The mixture was then removed from the ice bath. After stirring at RT overnight, the mixture was washed with H$_2$O (2 x 20 mL), dilute HCl (2 x 20 mL) and 2M NaOH (2 x 20 mL). Water (20 mL) was added and 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 to give the crude product (1.35 g). Purification by column chromatography using ethyl acetate/hexane (3/7) gave 4-tolylbut-3-ynyl acetate as an orange oil (0.748 g, 49%). \[^1\text{H NMR (400 MHz; CDCl}_3\text{) }\delta \text{H 2.11 (3H, s, CH}_3\text{), 2.36 (3H, s, CH}_3\text{), 2.76 (2H, t, J_HH = 7.0 Hz, CH}_2\text{), 4.27 (2H, t, J_HH = 7.0 Hz, OCH}_2\text{), 7.11 (2H, d, J_HH = 7.8 Hz, ArH), 7.31 (2H, d, J_HH = 8.1 Hz, ArH); }\[^1\text{C NMR (100 MHz; CDCl}_3\text{) }\delta \text{C 19.9 (CH}_2\text{), 20.9 (CH}_3\text{), 21.4 (CH}_3\text{), 62.5 (CH}_2\text{), 84.6 (C), 120.3 (C), 129.0 (CH), 131.5 (CH), 138.0 (C), 170.9 (CO).}\]

8. (2-(Phenylethynyl)phenyl)methanol (2.20)

![Image](image_url)

After **General method A** using 2-iodobenzyl alcohol (1.73 g, 7.4 mmol), phenylacetylene (1.0 mL, 8.9 mmol), [Pd(PPh\textsubscript{3})\textsubscript{2}Cl\textsubscript{2}] (0.12 g, 0.17 mmol), CuI (0.059 g, 0.3 mmol) and dry Et\textsubscript{3}N (40 mL), the crude product (1.93 g) was purified by column chromatography using diethyl ether/hexane (1/9) to give pure 2-(phenylethynyl)benzyl alcohol as an orange oil (0.94 g, 60%). The characterisation data was in agreement with the literature. \[^{5,7,8}\ ]\[^1\text{H NMR (400 MHz; CDCl}_3\text{) }\delta \text{H 2.13 (1H, s, OH), 4.95 (2H, s, CH}_2\text{), 7.32 (2H, td, J_HH = 7.5 Hz, J_HH = 1.4 Hz, ArH), 7.39 (3H, m, ArH), 7.51 (2H, m, ArH), 7.56 (2H, m, ArH); }\[^1\text{C NMR (100 MHz; CDCl}_3\text{) }\delta \text{C 64.1 (CH}_2\text{), 86.7 (C), 94.2 (C), 121.4 (C), 122.9 (C), 127.3 (CH), 127.5 (CH), 128.5 (CH), 128.6 (CH), 128.8 (CH), 131.6 (CH), 132.2 (CH), 142.6 (C).}\]

9(a). 2-Iodobenzaldehyde (2.31)

![Image](image_url)

2-Iodobenzyl alcohol (3.00 g, 12.8 mmol), pyridinium chlorochromate (3.32 g, 15.4 mmol) and DCM (150 mL) were charged into a round bottom flask. After stirring at RT overnight, the solvent was removed. A pad of silica gel was used to filter the residue using hexane/ethyl
acetate (2/1). The solvent was removed to give pure 2-iodobenzaldehyde as a white solid (2.96 g, 99 %). The characterisation data was in agreement with the literature. $^{5.9a}$ mp 30-31 °C (Lit., $^{5.9a}$ 30-31 °C). $^1$H NMR (400 MHz; CDCl$_3$) $\delta$H 7.21 (1H, td, $^3$J$_{HH}$ = 7.6 Hz, $^4$J$_{HH}$ = 1.8 Hz, ArH), 7.39 (1H, tt, $^3$J$_{HH}$ = 7.3 Hz, $^4$J$_{HH}$ = 0.9 Hz, ArH), 7.81 (1H, dd, $^3$J$_{HH}$ = 7.8 Hz, $^4$J$_{HH}$ = 1.8 Hz, ArH), 7.88 (1H, dd, $^3$J$_{HH}$ = 8.0 Hz, $^4$J$_{HH}$ = 1.0 Hz, ArH), 10.00 (1H, d, $^4$J$_{HH}$ = 0.8 Hz; CH); $^{13}$C NMR (100 MHz; CDCl$_3$) $\delta$C 100.7 (C), 128.7 (CH), 130.3 (CH), 135.2 (C), 135.5 (CH), 140.7 (CH), 195.7 (CO).

9(b). 2-(Phenylethynyl)benzaldehyde (2.21)

After General method A using 2-iodobenzaldehyde (1.72 g, 7.4 mmol), phenylacetylene (1.0 mL, 8.9 mmol), [Pd(PPh$_3$)$_2$Cl$_2$] (0.12 g, 0.17 mmol), CuI (0.059 g, 0.3 mmol) and dry Et$_3$N (40 mL), the crude product (2.00 g) was purified by column chromatography using diethyl ether/hexane (1/9) to give pure 2-(phenylethynyl)benzaldehyde as an orange oil (0.96 g, 62 %). The characterisation data was in agreement with the literature. $^{5.9b}$ $^1$H NMR (400 MHz; CDCl$_3$) $\delta$H 7.31 (3H, m, ArH), 7.37 (1H, t, $^3$J$_{HH}$ = 7.5 Hz, ArH), 7.49 (3H, m, ArH), 7.57 (1H, dd, $^3$J$_{HH}$ = 7.8 Hz, $^4$J$_{HH}$ = 1.2 Hz, ArH), 7.87 (1H, dd, $^3$J$_{HH}$ = 7.8 Hz, $^4$J$_{HH}$ = 1.3 Hz, ArH), 10.57 (1H, d, $^4$J$_{HH}$ = 0.6 Hz; CH); $^{13}$C NMR (100 MHz; CDCl$_3$) $\delta$C 84.9 (C), 96.4 (C), 122.4 (C), 126.9 (C), 127.3 (CH), 128.5 (CH), 128.6 (CH), 129.1 (CH), 131.7 (CH), 133.2 (CH), 133.8 (CH), 135.9 (C), 191.7 (CO).
10. 2-(Phenylethynyl)benzyl acetate (2.22)

\[
\begin{align*}
\text{Acetyl chloride (0.36 mL, 5.0 mmol) was added dropwise to a solution of 2-} \\
(\text{phenylethynyl})\text{benzyl alcohol (0.848 g, 4.0 mmol) and pyridine (0.32 mL, 4.0 mmol) stirring} \\
\text{in dry DCM (30 mL) at 0 °C. The mixture was then removed from the ice bath and allowed} \\
\text{to warm to RT. After stirring at RT under nitrogen overnight, the mixture was washed with} \\
H_2O (2 x 20 mL), \text{dilute HCl (2 x 20 mL) and 2M NaOH (2 x 20 mL). Water (20 mL) was} \\
\text{added and the mixture was extracted with DCM (3 x 10 mL). The combined organic layers} \\
\text{were dried over MgSO}_4 \text{ (anhydrous), and the solvent was removed to give the crude product} \\
(0.92 g). \text{Purification by column chromatography using ethyl acetate/hexane (1/4) gave pure} \\
2-(\text{phenylethynyl})\text{benzyl acetate as an orange oil (0.793 g, 78 %). The characterisation data} \\
\text{was in agreement with the literature.} ^5 \text{10} \text{1H NMR (400 MHz; CDCl}_3 \text{)} \delta_H 2.15 (3H, s, CH}_3, \\
5.40 (2H, s, CH}_2), 7.38 (5H, m, ArH), 7.45 (1H, d, }^3\text{J}_\text{HH} = 7.6 \text{ Hz, ArH}), 7.57 (3H, m, ArH); \\
^{13}\text{C NMR (100 MHz; CDCl}_3 \text{)} \delta_C 21.0 \text{ (CH}_3), 64.8 \text{ (CH}_2), 86.5 \text{ (C), 94.4 (C), 122.8 (C), 123.0} \\
\text{(C), 128.1 (CH), 128.4 (CH), 128.5 (CH), 128.5 (CH), 131.6 (CH), 132.3 (CH), 137.5 (C), 170.8 (CO).}\n\end{align*}
\]

11(a). 1-Iodo-2-((methoxymethoxy)methyl)benzene (2.33)

\[
\begin{align*}
\text{2-Iodobenzyl alcohol (2.34 g, 10 mmol), 60 % NaH (0.6 g, 15 mmol) and THF (30 mL) were} \\
\text{charged into a dry three-necked flask. After stirring at RT for 20 min,} \\
\text{chloro(methoxy)methane (1 mL, 13.2 mmol) was added dropwise. The mixture was stirred} \\
\text{and heated at reflux for 3 h, and then water (15 mL) and Et}_2\text{O (15 mL) were added. The} \\
\text{mixture was extracted with Et}_2\text{O (3 x 10 mL), the combined organic layers were dried over} \\
\text{MgSO}_4 \text{, and the solvent was removed to give the crude product (3.36 g). The crude product}\n\end{align*}
\]
was purified by column chromatography using ethyl acetate/hexane (1/9) to give pure 1-iodo-2-((methoxymethoxy)methyl)benzene as a brown oil (1.07 g, 38 %). The characterisation data was in agreement with the literature. 5.11 H NMR (400 MHz; CDCl3) δH 3.37 (3H, s, OCH3), 4.52 (2H, s, OCH2), 4.70 (2H, s, OCH2), 6.92 (1H, td, 3JHH = 7.6 Hz, 4JHH = 1.7 Hz, ArH), 7.28 (1H, td, 3JHH = 7.5 Hz, 4JHH = 1.1 Hz, ArH), 7.38 (1H, dd, 3JHH = 7.6 Hz, 4JHH = 1.7 Hz, ArH), 7.72 (1H, dd, 3JHH = 7.9 Hz, 4JHH = 1.1 Hz, ArH); 13C NMR (100 MHz; CDCl3) δC 55.6 (CH3), 73.8 (CH2), 96.2 (CH2), 98.0 (C), 128.3 (CH), 128.9 (CH), 129.2 (CH), 139.3 (CH), 140.3 (C).

11(b). 1-((Methoxymethoxy)methyl)-2-(phenylethynyl)benzene (2.23)

After General method A using 1-iodo-2-((methoxymethoxy)methyl)benzene (1.07 g, 3.83 mmol), phenylacetylene (0.575 mL, 5.0 mmol), [Pd(PPh3)2Cl2] (0.12 g, 0.17 mmol), CuI (0.059 g, 0.3 mmol) and dry Et3N (20 mL), the crude product (1.39 g) was purified by column chromatography using ethyl acetate/hexane (1/9) to give pure 1-((methoxymethoxy)methyl)-2-(phenylethynyl)benzene as an orange oil (0.71 g, 73 %). The characterisation data was in agreement with the literature. 5.11 H NMR (400 MHz; CDCl3) δH 3.46 (3H, s, OCH3), 4.83 (2H, s, OCH2), 4.88 (2H, s, OCH2), 7.35 (5H, m, ArH), 7.56 (4H, m, ArH); 13C NMR (100 MHz; CDCl3) δC 55.4 (CH3), 67.8 (CH2), 87.0 (C), 93.8 (C), 96.3 (CH2), 122.1 (C), 123.2 (C), 127.5 (CH), 127.9 (CH), 128.4 (CH), 128.5 (CH), 131.6 (CH), 132.1 (CH), 132.2 (CH), 139.7 (C).

Synthesis of α,α-Difluoro Ketones with Selectfluor/ H2O

General method B: 1,2-Acetylene substrates (1.0 eq.) were refluxed with Selectfluor (2.2-5.0 eq.) and H2O (20.0 eq.) in MeCN for 22-30 h. After removing the solvent, H2O (15 mL)
and DCM (15 mL) were added to the reaction mixture. The precipitate was filtered off and the aqueous phase was extracted with DCM (3 x 10 mL). The combined organic layers were dried over MgSO₄ (anhydrous), and the solvent was removed to give the crude product.

1. 2,2-Difluoro-1,2-diphenylethanone (2.34) and diphenylethane-1,2-dione (2.35)

![Chemical Structure](image)

After General method B using 1,2-diphenylacetylene (0.178 g, 1.0 mmol), Selectfluor (0.709 g, 2.2 mmol) and H₂O (0.36 g, 20.0 mmol) in MeCN (20 mL) for 22 h, the crude product (0.248 g) was purified by column chromatography using diethyl ether/hexane (1/9) to recover unreacted 1,2-diphenylacetylene (0.030 g, 17%).

2,2-Difluoro-1,2-diphenylethanone was also obtained as a colourless oil (0.100 g, 0.405 mmol, 41%). The characterisation data was in agreement with the literature. ⁵.¹⁸ᵃ ¹H NMR (400 MHz; CDCl₃) δ_H 7.36 (6H, m, ArH), 7.50 (2H, m, ArH), 7.94 (2H, td, ³_J_HH = 8.5 Hz, ⁴_J_HH = 1.0 Hz, ArH); ¹³C NMR (100 MHz; CDCl₃) δ_C 117.0 (t, ¹_J_CF = 251.0 Hz, CF₂), 125.7 (t, ³_J_CF = 2.7 Hz, CH), 128.7 (CH), 128.8 (CH), 130.9 (CH), 132.2 (CH), 132.9 (C), 133.2 (t, ²_J_CF = 20.3 Hz, C), 134.2 (CH), 189.0 (t, ²_J_CF = 31.2 Hz, CO); ¹⁹F NMR (376 MHz; CDCl₃) δ_F -97.45 (s).

The byproduct, diphenylethane-1,2-dione, was also isolated as a yellow solid (0.016 g, 0.074 mmol, 7%). The characterisation data was in agreement with the literature. ⁵.¹⁸ᵇ ¹H NMR (400 MHz; CDCl₃) δ_H 7.45 (4H, t, ³_J_HH = 7.8 Hz, ArH), 7.59 (2H, tt, ³_J_HH = 7.4 Hz, ⁴_J_HH = 1.3 Hz, ArH), 7.91 (4H, dd, ³_J_HH = 8.3 Hz, ⁴_J_HH = 1.2 Hz, ArH); ¹³C NMR (100 MHz; CDCl₃) δ_C 129.0 (CH), 129.9 (CH), 133.0 (C), 134.9 (CH), 194.6 (CO).
The reaction was repeated using NFSI (0.694 g, 2.2 mmol) instead of Selectfluor, but no reaction had occurred after 22 h. Therefore, Selectfluor was used in all of the reactions afterwards.

2. 2,2-Difluoro-1,2-di-tolylethanone (2.36) and bis(4-methylphenyl)ethane-1,2-dione (2.37)

After General method B using 1,2-di-tolylethylene (0.206 g, 1.0 mmol), Selectfluor (0.709 g, 2.2 mmol) and H₂O (5 mL) in MeCN (45 mL) for 30 h, the crude product (0.223 g) was purified by column chromatography using ethyl acetate/hexane (1/9) to give pure 2,2-difluoro-1,2-di-tolylethanone as an orange oil (0.148 g, 57 %). ¹H NMR (400 MHz; CDCl₃) δH 2.30 (3H, s, CH₃), 2.32 (3H, s, CH₃), 7.17 (4H, m, ArH), 7.41 (2H, d, ³J_HH = 8.3 Hz, ArH), 7.84 (2H, d, ³J_HH = 8.3 Hz, ArH); ¹³C NMR (100 MHz; CDCl₃) δC 21.3 (CH₃), 21.8 (CH₃), 117.1 (t, ¹JC = 245.0 Hz, CF₂), 125.5 (t, ³JC = 6.0 Hz, CH), 129.3 (CH), 129.5 (CH), 129.6 (C), 129.7 (C), 130.44 (CH), 141.1 (C), 145.3 (C), 188.7 (t, ²JC = 31.2 Hz, CO); ¹⁹F NMR (376 MHz; CDCl₃) δF -96.98 (CF₂).

The purification by column chromatography also gave unreacted starting material (0.0336 g, 16 %), and byproduct, bis(4-methylphenyl)ethane-1,2-dione (0.0193 g, 8 %). The characterisation data was in agreement with the literature.⁵¹¹H NMR (400 MHz; CDCl₃) δH 2.36 (6H, s, CH₃), 7.22 (4H, d, ³J_HH = 8.0 Hz, ArH), 7.78 (4H, d, ³J_HH = 8.2 Hz, ArH); ¹³C NMR (100 MHz; CDCl₃) δC 21.9 (CH₃), 129.7 (CH), 130.0 (CH), 130.7 (C), 146.1 (C), 194.5 (CO).

The reaction was repeated using 3 equivalents of Selectfluor under exactly the same reaction conditions. Under these conditions, the starting material (0.0025 g, 1 %), the desired product
2,2-difluoro-1,2-di-tolylethanone, (0.145 g, 56 %), and the byproduct bis(4-methyl-phenyl)ethane-1,2-dione, (0.0169 g, 7 %) were obtained.

3. 2,2-Difluoro-1-phenylhexan-1-one (2.38)

After General method B using 1-phenyl-1-hexyne (0.158 g, 1.0 mmol), Selectfluor (0.709 g, 2.2 mmol), H2O (5 mL) and MeCN (45 mL) for 30 h, the crude product (0.163 g) was purified by column chromatography using ethyl acetate/hexane (1/9) to give the 2,2-difluoro-1-phenylhexan-1-one as a brown oil (0.0603 g, 32 %). The characterisation data was in agreement with the literature. 5.20 1H NMR (400 MHz; CDCl3) δH 0.85 (3H, t, 3JHH = 7.3 Hz, CH3), 1.32 (2H, sextet, 3JHH = 7.3 Hz, CH2), 1.45 (2H, quintet, 3JHH = 7.7 Hz, CH2), 2.10 (2H, m, CH2), 7.41 (2H, t, 3JHH = 7.7 Hz, ArH), 7.54 (1H, tt, 3JHH = 7.4 Hz, 4JHH = 0.6 Hz, ArH), 8.03 (2H, dd, 3JHH = 8.3 Hz, 4JHH = 0.8 Hz, ArH); 13C (400 MHz; CDCl3) δC 13.8 (CH3), 22.5 (CH2), 23.5 (t, 3JCF = 3.0 Hz, CH2), 33.8 (t, 2JCF = 23.0 Hz, CH2), 119.9 (t, 1JCF = 251.0 Hz, CF2), 128.6 (CH), 130.1 (t, 4JCF = 2.7 Hz, CH), 132.4 (C), 134.2 (CH), 189.7 (t, 2JCF = 31.2 Hz, CO); 19F NMR (376 MHz; CDCl3) δF -100.17 (s).

Some of the starting material (0.0039 g, 18 %) was also recovered from the column and the anticipated byproduct (1-phenylhexane-1,2-dione) was not observed in this reaction.

When the reaction was repeated with 3.0 equivalent of Selectfluor, the desired product was obtained in 78 % yield. No starting material or byproduct were observed.
4. 2,2-Difluoro-1-(2-nitrophenyl)octan-1-one (2.39)

After **General method B** using 1-nitro-2-(oct-1-ynyl)benzene (0.462 g, 2.0 mmol), Selectfluor (2.13 g, 6.0 mmol), H₂O (0.72 g, 40.0 mmol) and MeCN (50 mL), for 30 h), the crude product (0.301 g) was purified by column chromatography using ethyl acetate/hexane (1/9) to give the desired product, 2,2-difluoro-1-(2-nitrophenyl)octan-1-one, (0.0306 g, 0.107 mmol, 5 %) as a yellow liquid. ¹H NMR (400 MHz; CDCl₃) δH 0.83 (3H, t, ³JHH = 7.0 Hz, CH₃), 1.29 (6H, m, CH₂CH₂CH₂CH₂CH₃), 1.53 (2H, m, CF₂CH₂CH₂), 2.19 (2H, m, CF₂CH₂), 7.41 (1H, dd, ³JHH = 7.5 Hz, ⁴JHH = 1.4 Hz, ArH), 7.63 (1H, td, ³JHH = 7.9 Hz, ⁴JHH = 1.5 Hz, ArH), 7.73 (1H, td, ³JHH = 7.5 Hz, ⁴JHH = 1.2 Hz, ArH), 8.16 (1H, dd, ³JHH = 8.2 Hz, ⁴JHH = 1.0 Hz, ArH); ¹³C NMR (100 MHz; CDCl₃) δC 14.0 (CH₃), 20.8 (CH₂), 22.5 (CH₂), 29.0 (CH₂), 31.5 (CH₂), 32.9 (t, ³JC = 3.0 Hz, CH₂), 118.6 (t, ¹JC = 251 Hz, CF₂), 124.1 (CH), 128.6 (CH), 131.6 (CH), 132.5 (C), 134.7 (CH), 146.4 (CNO₂), 193.2 (t, ²JC = 31.2 Hz, CO); ¹⁹F NMR (376 MHz; CDCl₃) δF -104.28 (s).

Another two byproducts were also obtained. The amounts of these two products are 0.0133 g (2 % isolated yield) and 0.0254 g (4 % isolated yield). One of the byproducts may be 1,1-difluoro-1-(2-nitrophenyl)octan-2-one. The other one may be the byproduct, 1-(2-nitrophenyl)octane-1,2-dione. However, from the current NMR data, they cannot be characterised fully.
5. 4,4-Difluoro-3-oxo-4-tolylbutyl acetate (2.40), the mixture of 2,2-difluoro-4-hydroxy-1-(4-methylphenyl)butan-1-one (2.41) and 3,3-difluoro-2-(4-methylphenyl)oxolan-2-ol (2.42)

After General method B using 4-tolylbut-3-ynyl acetate (0.382 g, 2.0 mmol), Selectfluor (2.13 g, 6.0 mmol), H₂O (5 mL) and MeCN (45 mL) for 30 h, the crude product (0.355 g) was purified by column chromatography using ethyl acetate/hexane (3/7) to give the desired product, 3,3-difluoro-4-oxo-4-p-tolylbutyl acetate (0.148 g, 30 %) as a brown oil. ¹H NMR (400 MHz; CDCl₃) δ_H 1.91 (3H, s, C_H₃), 2.36 (3H, s, C_H₃), 2.51 (2H, tt, 3J_HH = 17.0 Hz, 3J_HF = 6.6 Hz, CH₂), 4.27 (2H, t, 3J_HH = 6.6 Hz, OCH₂), 7.22 (2H, d, 3J_HH = 8.6 Hz, ArH), 7.92 (2H, d, 3J_HH = 8.2 Hz, ArH); ¹³C NMR (100 MHz; CDCl₃) δ_C 20.7 (CH₃), 21.8 (CH₃), 33.4 (t, 2J_CF = 23.0 Hz, CH₂), 4.27 (2H, t, 3J_HH = 6.6 Hz, OCH₂), 7.22 (2H, d, 3J_HH = 8.6 Hz, ArH), 7.92 (2H, d, 3J_HH = 8.2 Hz, ArH); ¹⁹F NMR (376 MHz; CDCl₃) δ_F -99.29(s).

Purification also gave a second product which was a mixture of two isomers, 2,2-difluoro-4-hydroxy-1-p-tolylbutan-1-one and 3,3-difluoro-2-p-tolyltetrahydrofuran-2-ol (0.0921 g, 23 %) as a white solid. The ratio of two isomers was approximately 1:2. ¹H NMR (400 MHz; CDCl₃) δ_H 1.49 (1H, s, O_H), 2.30 (3H, s, CH₃), 2.37 (3H, s, CH₃), 2.44 (2H, m, CH₂), 2.66 (2H, m, CH₂), 2.84 (1H, s, O_H), 4.14 (2H, m, OCH₂), 4.24 (2H, m, OCH₂), 7.13 (2H, d, 3J_HH = 7.9 Hz, ArH), 7.23 (2H, d, 3J_HH = 8.1 Hz, ArH), 7.43 (2H, d, 3J_HH = 8.2 Hz, ArH), 7.94 (2H, d, 3J_HH = 8.3 Hz, ArH); ¹³C NMR (100 MHz; CDCl₃) δ_C 21.2 (CH₃), 21.8 (CH₃), 31.8 (t, 2J_CF = 24.0 Hz, CH₂), 37.2 (CH₂), 56.4 (CH₂), 63.2 (CH₂), 126.7 (CH), 128.9 (CH), 129.5 (CH), 130.4 (CH), 133.2 (C), 139.3 (C); ¹⁹F NMR (376 MHz; CDCl₃) δ_F -120.72 (1F, d, 2J_FF = 233.1 Hz, CF₄F₂), -103.39 (1F, d, 2J_FF = 233.1 Hz, CF₄F₂), -98.20 (2F, s, CF₂).
6. Deprotection of 4,4-Difluoro-3-oxo-4-tolylbutyl acetate

3,3-Difluoro-4-oxo-4-p-tolylbutyl acetate (0.142 g, 0.579 mmol) was reacted with ethanol (20 mL) and NaOH (2M, 25 mL) to deprotect the acetyl group. The mixture was stirred at RT for 3 h. After removing the ethanol, the residue was extracted with Et<sub>2</sub>O (3 x 10 mL) and the combined organic layers were dried over MgSO<sub>4</sub> (anhydrous), and the solvent was removed to give the crude product (0.0687 g, 58%).

The crude product contained the same mixture of the two isomers which was obtained as the second product in the previous reaction.

Purification by column chromatography using ethyl acetate/hexane (3/7) could not be used to separate the two products. The <sup>1</sup>H NMR spectrum showed the ratio of two products was approximately 1:9 when d<sup>6</sup> acetone was used as the solvent. However, the ratio changed to about 1:1 if CDCl<sub>3</sub> was used as the NMR solvent, because CDCl<sub>3</sub> is slightly acidic and changes the ratio of the isomers.

5.3 Experimental for Chapter 3

**General method C:** Benzaldehyde derivatives (1.0 eq.), CF<sub>3</sub>SiMe<sub>3</sub> (1.5 eq.) and dry THF were charged into a three-necked flask at 0 °C. TBAF (0.2 eq.) was added dropwise to the mixture and the mixture was stirred for 5 min at 0 °C. The mixture was then removed from the ice bath and allowed to warm to RT. After stirring at RT under nitrogen for 3 h, HCl (10 mL, 0.5 M) was added. After stirring for a further 30 min, water (15 mL) was added, and the mixture was extracted with Et<sub>2</sub>O (3 x 10 mL). The combined organic layers were dried over MgSO<sub>4</sub> (anhydrous), and the solvent was removed to give the crude product.
General method D: In a dry 100 mL three-necked flask equipped with a dropping funnel and magnetic stirring bar, activated zinc dust (2.5 eq.) was suspended in dry THF and stirred vigorously under nitrogen. The temperature was raised to 40 °C, and trimethylsilyl chloride (0.27 eq.) was added. The temperature was then raised to 55 °C for 15 min. After switching off the heater, ethyl bromodifluoroacetate or ethyl bromoacetate (2.0 eq.) in dry THF was added dropwise over 20 min and the reaction mixture stirred for 10 min. The prepared Reformatsky reagent was transferred into another dry 100 mL three-necked flask equipped with a dropping funnel and magnetic stirring bar under nitrogen. The benzaldehyde derivative (1.0 eq.) in dry THF was added dropwise over 10 min at RT. After stirring the reaction mixture at RT under nitrogen for 4 h, 2M HCl (50 mL) was added and the mixture stirred for a further 15 min. The mixture was then extracted with diethyl ether (3 x 20 mL). The combined organic layers were then washed with 10 % NaCl solution (50 mL) and water (50 mL), and dried over MgSO₄ (anhydrous) to give the crude product.

General method E: A solution of MeI (3.3 eq.) in diethyl ether was added dropwise into a three-necked flask charged with magnesium (4.7 eq.) and diethyl ether until the reaction mixture started to reflux. After adding more diethyl ether to the three-necked flask, the remainder of the MeI solution was added at a rate that kept the reaction mixture at reflux. The mixture was kept stirring for a further 15 min and was then transferred to a second three-necked flask at 0 °C. The benzoate derivative (1.0 eq.) was charged into a second dropping funnel with diethyl ether. The benzoate solution was added dropwise to the second three-necked flask over 20 min. The mixture was warmed to RT and stirred overnight. On the next day, the mixture was heated at reflux for 1.5 h. After cooling to RT, the mixture was extracted with diethyl ether (3 x 15 mL) and washed with H₂O (20 mL). The combined organic layers were dried over MgSO₄ (anhydrous), and the solvent was removed to give the crude product.
1. 2-(p-Tolylethynyl)benzaldehyde (3.41)

After General method A using 2-iodobenzaldehyde (1.72 g, 7.4 mmol), 1-ethynyl-4-methylbenzene (1.13 mL, 8.9 mmol), [Pd(PPh3)2Cl2] (0.12 g, 0.17 mmol), CuI (0.059 g, 0.3 mmol) and dry Et3N (40 mL), the crude product (2.16 g) was purified by column chromatography using diethyl ether/hexane (1/9) to give pure 2-(p-tolylethynyl)benzaldehyde as a yellow solid (1.42 g, 87 %). The characterisation data was in agreement with the literature. 5.12 mp 38-40 °C (lit., 5.12 36-42 °C). 1H NMR (400 MHz; CDCl3) δH 2.42 (3H, s, CH3), 7.22 (2H, d, 3JHH = 7.9 Hz, ArH), 7.46 (3H, m, ArH), 7.60 (1H, td, 3JHH = 7.7 Hz, 4JHH = 1.3 Hz, ArH), 7.66 (1H, dd, 3JHH = 7.7 Hz, 4JHH = 0.7 Hz, ArH), 7.97 (1H, dd, 3JHH = 7.8 Hz, 4JHH = 0.8 Hz, ArH), 10.68 (1H, s, CHO); 13C NMR (100 MHz; CDCl3) δC 21.6 (CH3), 84.3 (C), 96.7 (C), 116.7 (C), 119.3 (C), 127.2 (CH), 128.4 (CH), 129.3 (CH), 131.6 (CH), 133.2 (CH), 133.8 (CH), 135.8 (C), 139.4 (C), 191.8 (CHO).

2. 2-(Oct-1-yn-1-yl)benzaldehyde (3.42)

After General method A using 2-iodobenzaldehyde (1.72 g, 7.4 mmol), 1-octyne (1.0 mL, 8.9 mmol), [Pd(PPh3)2Cl2] (0.12 g, 0.17 mmol), CuI (0.059 g, 0.3 mmol) and dry Et3N (40 mL), the crude product (1.99 g) was purified by column chromatography using diethyl ether/hexane (1/9) to give pure 2-(oct-1-yn-1-yl)benzaldehyde as a brown oil (1.38 g, 87 %). The characterisation data was in agreement with the literature. 5.13 1H NMR (400 MHz; CDCl3) δH 0.93 (3H, t, 3JHH = 7.0 Hz, CH3), 1.36 (4H, m, CH2CH2CH3), 1.49 (2H, m, CCH2CH2CH2), 1.66 (2H, quintet, 3JHH = 7.4 Hz, CCH2CH2), 2.50 (2H, t, 3JHH = 7.1 Hz, CCH2), 7.40 (1H, m, ArH), 7.53 (2H, m, ArH), 7.91 (1H, d, 3JHH = 7.6 Hz, ArH), 10.56 (1H, d, 4JHH = 0.8 Hz, CHO); 13C NMR (100 MHz; CDCl3) δC 14.0 (CH3), 19.6 (CH2), 22.6 (CH2), 25.2 (CH2), 78.9 (CH), 127.2 (CH), 128.4 (CH), 129.3 (CH), 131.6 (CH), 132.8 (CH), 133.8 (CH), 135.8 (C), 139.4 (C), 191.8 (CHO).
28.5 (CH₂), 28.6 (CH₂), 31.3 (CH₂), 76.4 (C), 98.3 (C), 126.9 (CH), 127.9 (CH), 128.0 (C), 133.3 (CH), 133.7 (CH), 136.0 (C), 192.2 (CHO).

3. 1-(2-(Phenylethynyl)phenyl)ethan-1-ol (3.27)

MeMgBr solution (0.5 mL, 1.5 mmol, 3M in diethyl ether) was charged into a three-necked flask with 2-(phenylethynyl)benzaldehyde (0.206 g, 1.0 mmol) stirring in dry THF (20 mL) at -25 °C. The mixture was stirred for 5 min and warmed to RT overnight under nitrogen. Saturated NH₄Cl solution (15 mL) was added to the mixture and stirred for 5 min, followed by Et₂O (100 mL). The precipitate was filtered off and the solution was extracted with Et₂O (3 x 10 mL). The combined organic layers were dried over MgSO₄ (anhydrous), and the solvent was removed to give the crude product (0.224 g). The crude product was purified by column chromatography using diethyl ether/hexane (1/4) to give pure 1-(2-(phenylethynyl)phenyl)ethan-1-ol as an orange oil (0.216 g, 97 %). The characterisation data was in agreement with the literature. 

$^1$H NMR (400 MHz; CDCl₃) $\delta$H 1.50 (3H, d, $^3J_{HH} = 6.5$ Hz, CH₃), 2.07 (1H, s, OH), 5.35 (1H, q, $^3J_{HH} = 6.5$ Hz, CH), 7.18 (1H, m, ArH), 7.29 (4H, m, ArH), 7.45 (3H, m, ArH), 7.50 (1H, dt, $^3J_{HH} = 7.8$ Hz, $^4J_{HH} = 0.6$ Hz, ArH); $^{13}$C NMR (100 MHz; CDCl₃) $\delta$C 24.0 (CH₃), 68.5 (CH), 87.0 (C), 94.4 (C), 120.3 (C), 123.1 (C), 124.7 (CH), 127.1 (CH), 128.4 (CH), 128.5 (CH), 128.9 (CH), 131.5 (CH), 132.3 (CH), 147.6 (C).
4. 2,2,2-Trifluoro-1-(2-(phenylethynyl)phenyl)ethanol (3.28)

![Chemical Structure]

After General method C using 2-(phenylethynyl)benzaldehyde (0.42 g, 2.0 mmol), CF₃SiMe₃ (0.37 mL, 2.5 mmol), TBAF (0.2 mL) and dry THF (20 mL), the crude product (0.57 g) was purified by column chromatography using ethyl acetate/hexane (1/20) to remove all the starting materials, and pure ethyl acetate to elute the desired product, 2,2,2-trifluoro-1-(2-(phenylethynyl)phenyl)ethanol as a brown oil (0.56 g, 99 %). ¹H NMR (400 MHz; CDCl₃) δ H 2.94 (1H, s, OH), 5.63 (1H, q, ³J HF = 6.5 Hz, CH), 7.29-7.32 (4H, m, ArH), 7.36 (1H, dd, ³J HH = 7.8 Hz, ⁴J HH = 1.7 Hz, ArH), 7.45 (2H, m, ArH), 7.50 (1H, dd, ³J HH = 7.1 Hz, ⁴J HH = 2.0 Hz, ArH), 7.59 (1H, d, ³J HH = 7.6 Hz, ArH); ¹³C NMR (100 MHz; CDCl₃) δ C 70.7 (q, ²J CF = 32.3 Hz, CH), 86.1 (C), 94.7 (C), 122.6 (C), 123.0 (q, ¹J CF = 282.8 Hz, CF₃), 125.9 (C), 127.5 (CH), 128.5 (CH), 128.8 (CH), 128.8 (CH), 129.2 (CH), 131.6 (CH), 132.4 (CH), 135.6 (C); ¹⁹F NMR (376 MHz; CDCl₃) δ F -77.6 (s, CF₃). m/z (ASAP) 277.0833 (MH⁺). C₁₆H₁₂F₃O requires 277.0840, 100 %.

5. 2,2,2-Trifluoro-1-(2-(p-tolylethynyl)phenyl)ethanol-1-ol (3.29)

![Chemical Structure]

After General method C using 2-(p-tolylethynyl)benzaldehyde (0.66 g, 3.0 mmol), CF₃SiMe₃ (0.59 mL, 4.0 mmol), TBAF (0.2 mL) and dry THF (30 mL), the crude product (1.01 g) was purified by column chromatography using ethyl acetate/hexane (3/7) to remove all the starting materials, and pure ethyl acetate was used to elute the desired product 2,2,2-trifluoro-1-(2-(p-tolylethynyl)phenyl)ethanol-1-ol as a brown oil (0.86 g, 99 %). ¹H NMR (400
MHz; CDCl₃) δ₇H 0.84 (3H, s, CH₃), 2.85 (1H, s, OH), 5.55 (1H, q, ³JHF = 6.7 Hz, CH), 7.03 (1H, d, ³JHH = 7.9 Hz, ArH), 7.26 (4H, m, ArH), 7.42 (2H, m, ArH), 7.50 (1H, d, ³JHH = 7.3 Hz, ArH); ¹³C NMR (100 MHz; CDCl₃) δC 21.5 (CH₃), 70.7 (q, ²JCF = 31.6 Hz, CH), 85.5 (C), 94.9 (C), 119.5 (C), 123.2 (q, ¹JC = 282.8 Hz, CF₃), 125.9 (C), 127.5 (CH), 128.6 (CH), 129.3 (CH), 131.5 (CH), 132.4 (CH), 132.4 (CH), 135.5 (C), 139.1 (C); ¹⁹F NMR (376 MHz; CDCl₃) δF -77.6 (s, CF₃). m/z (ASAP) 291.0995 (MH⁺. C₁₇H₁₄F₃O requires 291.0997, 100 %).

6. 2,2,2-Trifluoro-1-(2-(oct-1-yn-1-yl)phenyl)ethan-1-ol (3.30)

![Structure](image)

After General method C using 2-(oct-1-yn-1-yl)benzaldehyde (0.64 g, 3.0 mmol), CF₃SiMe₃ (0.59 mL, 4.0 mmol), TBAF (0.2 mL) and dry THF (30 mL), the crude product (0.89 g) was purified by column chromatography using ethyl acetate/hexane (3/7) to remove all the starting materials, and pure ethyl acetate to elute the desired product 2,2,2-trifluoro-1-(2-(p-tolylethynyl)phenyl)ethan-1-ol as a brown oil (0.49 g, 58 %). ¹H NMR (400 MHz; CDCl₃) δH 0.84 (3H, t, ³JHH = 6.9 Hz, (CH₂)₅CH₃), 1.26 (4H, m, CH₂CH₂CH₂CH₃CH₂CH₃), 1.38 (2H, m, CH₂CH₂CH₂CH₂CH₂CH₃), 1.54 (2H, m, CH₂CH₂CH₂CH₂CH₂CH₂CH₃), 2.37 (2H, t, ³JHH = 7.0 Hz, CH₂CH₂CH₂CH₂CH₂CH₂CH₃), 2.85 (1H, s, OH), 5.51 (1H, q, ³JHF = 6.4 Hz, CH), 7.27 (2H, m, ArH), 7.37 (1H, m, ArH), 7.49 (1H, d, ³JHH = 7.3 Hz, ArH); ¹³C NMR (100 MHz; CDCl₃) δC 14.1 (CH₃), 19.5 (CH₂), 22.5 (CH₂), 28.5 (CH₂), 28.6 (CH₂), 31.3 (CH₂), 70.8 (q, ²JCF = 31.8 Hz, CH), 76.5 (C), 96.6 (C), 123.2 (q, ¹JC = 283.0 Hz, CF₃), 125.9 (C), 127.3 (CH), 127.9 (CH), 129.1 (CH), 132.5 (CH), 135.4 (C); ¹⁹F NMR (376 MHz; CDCl₃) δF -77.6 (s, CF₃). m/z (ASAP) 285.1455 (MH⁺. C₁₆H₂₀F₃O requires 285.1466, 100 %).
7. Ethyl 2,2-difluoro-3-hydroxy-3-(2-(phenylethynyl)phenyl)propanoate (3.31)

After **General method D** using activated zinc dust (0.8 g, 12.5 mmol, in 10 mL THF), trimethylsilyl chloride (0.15 mL, 1.35 mmol), ethyl bromodifluoroacetate (1.25 mL, 10 mmol, in 10 mL THF) and 2-(phenylethynyl)benzaldehyde (1.05 g, 5 mmol, in 10 mL THF), the crude product (2.15 g) was purified by column chromatography using ethyl acetate/hexane (1/3) to give ethyl 2,2-difluoro-3-hydroxy-3-(2-(phenylethynyl)phenyl)propanoate as a yellow solid (1.52 g, 92 %). mp 83-85 °C. $^1$H NMR (400 MHz; CDCl$_3$) $\delta$H 1.31 (3H, t, $^3$J$_{HH}$ = 7.2 Hz, OCH$_2$CH$_3$), 3.03 (1H, br s, OH), 4.35 (2H, m, OCH$_2$CH$_3$), 5.89 (1H, dd, $^3$J$_{HF}$ = 16.0 Hz, $^3$J$_{HF}$ = 5.9 Hz, CF$_A$F$_B$CHOH), 7.40 (4H, m, ArH), 7.58 (4H, m, ArH), 7.66 (1H, d, $^3$J$_{HH}$ = 7.5 Hz, ArH); $^{13}$C NMR (100 MHz; CDCl$_3$) $\delta$C 13.8 (CH$_3$), 63.2 (CH$_2$), 71.6 (dd, $^2$J$_{CF}$ = 27.7 Hz, $^2$J$_{CF}$ = 23.6 Hz, CH), 86.5 (C), 94.6 (C), 114.0 (dd, $^1$J$_{CF}$ = 260.1 Hz, $^1$J$_{CF}$ = 255.1 Hz, CF$_A$F$_B$), 122.8 (C), 123.1 (C), 128.1 (CH), 128.5 (CH), 128.6 (CH), 128.7 (CH), 129.0 (CH), 131.6 (CH), 132.2 (CH), 136.1 (C), 163.5 (t, $^2$J$_{CF}$ = 31.4 Hz, CO); $^{19}$F NMR (376 MHz; CDCl$_3$) $\delta$F -120.6 (1F, d, $^2$J$_{FF}$ = 265.4 Hz, CF$_A$F$_B$), -113.3 (1F, d, $^2$J$_{FF}$ = 265.4 Hz, CF$_A$F$_B$). m/z (ASAP) 331.1140 (MH$^+$). C$_{19}$H$_{17}$F$_2$O$_3$ requires 331.1146, 100 %).
8. Ethyl 3-hydroxy-3-(2-(phenylethynyl)phenyl)propanoate (3.32)

After **General method D** using activated zinc dust (0.8 g, 12.5 mmol, in 10 mL THF), trimethylsilyl chloride (0.15 mL, 1.35 mmol), ethyl bromoacetate (1.25 mL, 11.3 mmol, in 10 mL THF) and 2-(phenylethynyl)benzaldehyde (1.05 g, 5 mmol, in 10 mL THF), the crude product (1.76 g) was purified by column chromatography using ethyl acetate/hexane (1/2) to give ethyl 3-hydroxy-3-(2-(phenylethynyl)phenyl)propanoate as a yellow solid (0.99 g, 68 %). mp 82-84 °C. $^1$H NMR (400 MHz; CDCl$_3$) δ$_H$ 1.29 (3H, t, $^3$J$_{HH}$ = 7.2 Hz, OCH$_2$CH$_3$), 2.71 (1H, dd, $^2$J$_{HH}$ = 16.1 Hz, $^3$J$_{HH}$ = 9.8 Hz, CH$_3$H$_B$CO), 3.02 (1H, dd, $^2$J$_{HH}$ = 16.4 Hz, $^3$J$_{HH}$ = 2.7 Hz, CH$_A$H$_BCO$), 3.45 (1H, br s, O$_H$), 4.23 (2H, AB q, $^3$J$_{HH}$ = 7.2 Hz, OCH$_2$CH$_3$), 5.69 (1H, dd, $^3$J$_{HH}$ = 9.8 Hz, $^3$J$_{HH}$ = 2.6 Hz, CH$_2$CHOH), 7.30 (1H, td, $^3$J$_{HH}$ = 7.6 Hz, $^4$J$_{HH}$ = 1.3 Hz, ArH), 7.39 (4H, m, ArH), 7.55 (3H, m, ArH), 7.63 (1H, dt, $^3$J$_{HH}$ = 7.8 Hz, $^4$J$_{HH}$ = 0.6 Hz, ArH); $^{13}$C NMR (100 MHz; CDCl$_3$) δ$_C$ 14.2 (CH$_3$), 42.4 (CH$_2$), 60.9 (CH$_2$), 68.7 (CH), 86.6 (C), 95.1 (C), 120.3 (C), 123.0 (C), 125.2 (CH), 127.4 (CH), 128.4 (CH), 128.5 (CH), 128.9 (CH), 131.5 (CH), 132.1 (CH), 144.3 (C), 172.6 (CO). m/z (ASAP) 295.1343 (MH$^+$. C$_{19}$H$_{19}$O$_3$ requires 295.1334, 100 %).
9. Ethyl 2,2-difluoro-3-hydroxy-3-(2-(p-tolylethynyl)phenyl)propanoate (3.33)

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\text{structures}
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After **General method D** using activated zinc dust (0.8 g, 12.5 mmol, in 10 mL THF), trimethylsilyl chloride (0.15 mL, 1.35 mmol), ethyl bromodifluoroacetate (1.25 mL, 10 mmol, in 10 mL THF) and 2-(p-tolylethynyl)benzaldehyde (1.1 g, 5 mmol, in 10 mL THF), the crude product (1.98 g) was purified by column chromatography using ethyl acetate/hexane (1/9) to give ethyl 2,2-difluoro-3-hydroxy-3-(2-(p-tolylethynyl)phenyl)propanoate as a yellow solid (1.24 g, 72 %). mp 83-86 °C; \(^1\)H NMR (400 MHz; CDCl\(_3\)) \(\delta_H\) 1.31 (3H, t, \(J_{HH} = 7.2\) Hz, OCH\(_2\)CH\(_3\)), 2.41 (3H, s, CH\(_3\)), 3.08 (1H, br s, OH), 4.34 (2H, m, OCH\(_2\)CH\(_3\)), 5.88 (1H, dd, \(J_{HF} = 15.9\) Hz, \(J_{HF} = 7.6\) Hz, CFAFBCHOH), 7.20 (2H, d, \(J_{HH} = 7.8\) Hz, ArH), 7.40 (2H, m, ArH), 7.48 (2H, dd, \(J_{HH} = 6.5\) Hz, \(J_{HF} = 1.6\) Hz, ArH), 7.57 (1H, dd, \(J_{HH} = 7.2\) Hz, \(J_{HF} = 1.8\) Hz, ArH), 7.64 (1H, d, \(J_{HH} = 7.5\) Hz, ArH); \(^{13}\)C NMR (100 MHz; CDCl\(_3\)) \(\delta_C\) 13.8 (CH\(_3\)), 21.5 (CH\(_3\)), 63.2 (CH\(_2\)), 71.7 (dd, \(J_{CF} = 28.2\) Hz, \(J_{CF} = 24.1\) Hz, CH), 85.9 (C), 94.8 (C), 114.1 (dd, \(J_{CF} = 259.6\) Hz, \(J_{CF} = 255.6\) Hz, CFAFB), 119.7 (C), 123.3 (C), 128.1 (CH), 128.4 (CH), 128.9 (CH), 129.2 (CH), 131.5 (CH), 132.1 (CH), 136.0 (C), 139.0 (C), 163.6 (t, \(J_{CF} = 31.8\) Hz, CO); \(^{19}\)F NMR (376 MHz; CDCl\(_3\)) \(\delta_F\) -120.5 (1F, d, \(J_{FF} = 257.2\) Hz, CFAFB), -113.4 (1F, d, \(J_{FF} = 257.2\) Hz, CFAFB). m/z (ASAP) 345.1299 (MH\(^+\). C\(_{20}\)H\(_{19}\)F\(_2\)O\(_3\) requires 345.1302, 100 %).
After **General method D** using activated zinc dust (0.8 g, 12.5 mmol, in 10 mL THF), trimethylsilyl chloride (0.15 mL, 1.35 mmol), ethyl bromodifluoroacetate (1.25 mL, 10 mmol, in 10 mL THF) and 2-(oct-1-yn-1-yl)benzaldehyde (1.073 g, 5 mmol, in 10 mL THF), the crude product (1.99 g) was purified by column chromatography using ethyl acetate/hexane (1/4) to give ethyl 2,2-difluoro-3-hydroxy-3-(2-(oct-1-yn-1-yl)phenyl)propanoate as a yellow oil (1.06 g, 63 %). $^1$H NMR (400 MHz; CDCl$_3$) $\delta$H 0.93 (3H, t, $^3$J$_{HH}$ = 6.9 Hz, CH$_2$CH$_2$CH$_2$CH$_2$CH$_2$CH$_3$), 1.32 (3H, t, $^3$J$_{HH}$ = 7.2 Hz, OCH$_2$CH$_3$), 1.33 (4H, m, CH$_2$CH$_2$CH$_2$CH$_2$CH$_2$CH$_2$CH$_3$), 1.48 (2H, m, CH$_2$CH$_2$CH$_2$CH$_2$CH$_2$CH$_2$CH$_3$), 1.65 (2H, quintet, $^3$J$_{HH}$ = 7.3 Hz, CH$_2$CH$_2$CH$_2$CH$_2$CH$_2$CH$_3$), 2.46 (2H, t, $^3$J$_{HH}$ = 7.1 Hz, CH$_2$CH$_2$CH$_2$CH$_2$CH$_2$CH$_3$), 3.10 (1H, br s, OH), 4.24 (2H, m, OCH$_2$CH$_3$), 5.72 (1H, dd, $^3$J$_{HF}$ = 16.4 Hz, $^3$J$_{HF}$ = 7.7 Hz, CHO), 7.33 (2H, m, ArH), 7.10 (1H, dd, $^3$J$_{HH}$ = 7.1 Hz, $^4$J$_{HH}$ = 1.9 Hz, ArH), 7.54 (1H, d, $^3$J$_{HH}$ = 7.4 Hz, ArH); $^{13}$C NMR (100 MHz; CDCl$_3$) $\delta$C 13.8 (CH$_3$), 14.0 (CH$_3$), 19.5 (CH$_2$), 22.5 (CH$_2$), 28.5 (CH$_2$), 28.6 (CH$_2$), 31.3 (CH$_2$), 63.0 (CH$_2$), 71.9 (dd, $^2$J$_{CF}$ = 28.2 Hz, $^2$J$_{CF}$ = 24.1 Hz, CH), 77.9 (C), 96.2 (C), 114.1 (t, $^1$J$_{CF}$ = 258.0 Hz, CF$_A$F$_B$), 123.8 (C), 127.8 (CH), 128.0 (CH), 128.8 (CH), 132.4 (CH), 135.8 (C), 163.5 (t, $^2$J$_{CF}$ = 32.9 Hz, CO); $^{19}$F NMR (376 MHz; CDCl$_3$) $\delta$F -120.5 (1F, d, $^2$J$_{FF}$= 268.4 Hz, CF$_A$F$_B$), -113.2 (1F, d, $^2$J$_{FF}$= 268.4 Hz, CF$_A$F$_B$). m/z (ASAP) 339.1758 (MH$^+$. C$_{19}$H$_{25}$F$_2$O$_3$ requires 339.1772, 100 %).
11. Ethyl 3-hydroxy-3-(2-(p-tolylethynyl)phenyl)propanoate (3.35)

After **General method D** using activated zinc dust (0.8 g, 12.5 mmol, in 10 mL THF), trimethylsilyl chloride (0.15 mL, 1.35 mmol), ethyl bromoacetate (1.25 mL, 11.3 mmol, in 10 mL THF) and 2-(p-tolylethynyl)benzaldehyde (1.1 g, 5 mmol in 10 mL THF), the crude product (1.89 g) was purified by column chromatography using ethyl acetate/hexane (1/4) to give ethyl 3-hydroxy-3-(2-(p-tolylethynyl)phenyl)propanoate as a yellow solid (1.31 g, 85 %). mp 85-88 °C; ¹H NMR (400 MHz; CDCl₃) δ 1.19 (3H, t, ³JHH = 7.2 Hz, OCH₂CH₃), 2.30 (3H, s, CH₃), 2.60 (1H, dd, ²JHH = 16.2 Hz, ³JHH = 9.9 Hz, CH₃H₂CO), 2.92 (1H, dd, ²JHH = 16.2 Hz, ³JHH = 2.9 Hz, CH₃H₂CO), 3.35 (1H, br s, OH), 4.13 (2H, AB q, ³JHH = 7.1 Hz, OCH₂CH₃), 5.57 (1H, dd, ²JHH = 9.6 Hz, ³JHH = 2.7 Hz, CH₂CHOH), 7.09 (2H, d, ³JHH = 7.8 Hz, ArH), 7.19 (1H, td, ³JHH = 7.6 Hz, ³JHH = 1.3 Hz, ArH), 7.29 (1H, td, ³JHH = 7.7 Hz, ⁴JHH = 1.3 Hz, ArH), 7.35 (2H, d, ³JHH = 8.1 Hz, ArH), 7.32 (1H, dd, ³JHH = 7.5 Hz, ⁴JHH = 1.1 Hz, ArH), 7.54 (1H, dt, ³JHH = 7.8 Hz, ⁴JHH = 0.6 Hz, ArH); ¹³C NMR (100 MHz; CDCl₃) δC 14.2 (CH₃), 21.5 (CH₃), 42.4 (CH₂), 60.8 (CH₂), 68.7 (CH), 86.0 (C), 95.4 (C), 119.9 (C), 120.5 (C), 125.2 (CH), 127.3 (CH), 128.7 (CH), 129.2 (CH), 131.4 (CH), 132.0 (CH), 138.7 (C), 144.2 (C), 172.6 (CO); m/z (ASAP) 309.1489 (MH⁺. C₂₀H₂₁O₃ requires 309.1491, 100 %).

12(a). Methyl 2-iodobenzoate (3.43)

Thionyl chloride (2.2 mL, 30 mmol) was added dropwise over 20 min to a solution of 2-iodobenzoic acid (5.0 g, 20 mmol) in MeOH (30 mL) at 0 °C. The reaction mixture was
warmed to RT and then refluxed overnight. After cooling to RT, the reaction mixture was washed with brine (20 mL) and extracted with ethyl acetate (3 x 15 mL). The combined organic layers were dried over MgSO4 (anhydrous), and the solvent was removed to give the pure methyl 2-iodobenzoate (5.15 g, 98 %). The characterisation data was in agreement with the literature. 5.15a 1H NMR (400 MHz; CDCl3) δH 3.93 (3H, s, OCH3), 7.15 (1H, td, 3JHH = 7.6 Hz, 4JHH = 1.8 Hz, ArH), 7.40 (1H, td, 3JHH = 7.6 Hz, 4JHH = 1.2 Hz, ArH), 7.89 (1H, dd, 3JHH = 7.8 Hz, 4JHH = 1.8 Hz, ArH), 7.99 (1H, dd, 3JHH = 8.1 Hz, 4JHH = 1.1 Hz, ArH); 13C NMR (100 MHz; CDCl3) δC 52.5 (OCH3), 94.1 (Cl), 127.9 (CH), 130.9 (CH), 132.9 (CH), 135.1 (C), 141.3 (CH), 166.9 (CO).

12(b). Methyl 2-(phenylethynyl)benzoate (3.44)

After General method A using methyl 2-iodobenzoate (1.939 g, 7.4 mmol), ethynylbenzene (1.0 mL, 8.9 mmol), [Pd(PPh3)2Cl2] (0.12 g, 0.17 mmol), CuI (0.059 g, 0.3 mmol) and dry Et3N (40 mL), the crude product (2.30 g) was purified by column chromatography using ethyl acetate/petroleum ether 40-60 °C (1/9) to give pure methyl 2-(phenylethynyl)benzoate (1.73 g, 99 %). The characterisation data was in agreement with the literature. 5.15b 1H NMR (400 MHz; CDCl3) δH 3.96 (3H, s, OCH3), 7.37 (4H, m, ArH), 7.49 (1H, td, 3JHH = 7.5 Hz, 4JHH = 1.4 Hz, ArH), 7.58 (2H, m, ArH), 7.65 (1H, dd, 3JHH = 7.8 Hz, 4JHH = 1.3 Hz, ArH), 7.97 (1H, dd, 3JHH = 7.8 Hz, 4JHH = 1.4 Hz, ArH); 13C NMR (100 MHz; CDCl3) δC 52.2 (OCH3), 88.2 (C), 94.3 (C), 123.4 (C), 123.7 (C), 127.9 (CH), 128.4 (CH), 128.5 (CH), 130.5 (CH), 131.7 (CH), 131.8 (CH), 131.9 (C), 134.0 (CH), 166.7 (CO).
12(c). 2-(Phenylethynyl)benzoic acid (3.36)

Methyl 2-(phenylethynyl)benzoate (1.620 g, 6.9 mmol) and a 1M solution of NaOH (2.744 g, 68.6 mmol) were charged into a round bottom flask with THF (50 mL) at RT. The mixture was stirred overnight and was then extracted with ethyl acetate (3 x 15 mL). The aqueous layer was acidified with 2M HCl to pH 1, and extracted with ethyl acetate (3 x 15 mL). The second combined organic layers were dried over MgSO$_4$ (anhydrous), and the solvent was removed to give 2-(phenylethynyl)benzoic acid as a white solid (1.13 g, 74 %). The characterisation data was in agreement with the literature. $^5$ mp 126-128 °C (lit., $^5$ 126-128 °C). $^1$H NMR (400 MHz; CDCl$_3$) $\delta_H$ 7.31 (3H, m, ArH), 7.42 (1H, td, $^3$J$_{HH}$ = 7.7 Hz, $^4$J$_{HH}$ = 1.2 Hz, ArH), 7.57 (3H, m, ArH), 7.69 (1H, dd, $^3$J$_{HH}$ = 7.8 Hz, $^4$J$_{HH}$ = 0.9 Hz, ArH), 8.14 (1H, dd, $^3$J$_{HH}$ = 7.9 Hz, $^4$J$_{HH}$ = 1.1 Hz, ArH); $^{13}$C NMR (100 MHz; CDCl$_3$) $\delta_C$ 88.0 (C), 95.5 (C), 123.1 (C), 124.4 (C), 128.0 (CH), 128.4 (CH), 128.7 (CH), 130.6 (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 %).

13. 2-(2-(Phenylethynyl)phenyl)propan-2-ol (3.37)

After General method E using MeI (2.07 mL, 33 mmol), magnesium (1.12 g, 46.5 mmol), methyl 2-(phenylethynyl)benzoate (3.54 g, 15 mmol) and diethyl ether (40 mL), the crude product (3.32 g) was purified by column chromatography using ethyl acetate/petroleum ether (40-60) (1/9) to give pure 2-(2-(phenylethynyl)phenyl)propan-2-ol as a yellow solid (1.51 g,
43 %). Crystals suitable for X-ray crystallography were grown from hot petroleum ether (40-60). mp 80-85 °C; 1H NMR (400 MHz; CDCl3) δH 1.80 (6H, s, CH3), 3.23 (1H, s, OCH3), 7.24 (1H, td, JHH = 7.5 Hz, JHH = 1.2 Hz, ArH), 7.32 (1H, td, JHH = 7.7 Hz, JHH = 1.5 Hz, ArH), 7.36 (3H, m, ArH), 7.55-7.65 (4H, m, ArH); 13C NMR (100 MHz; CDCl3) δC 30.0 (CH3), 73.2 (C), 89.3 (C), 95.6 (C), 119.4 (C), 122.9 (C), 124.7 (CH), 126.7 (CH), 128.5 (CH), 128.6 (CH), 131.2 (CH), 131.2 (CH), 134.4 (CH), 150.1 (C). m/z (ASAP) 237.1283 (MH+). C17H17O requires 237.1279, 20 %), 219.1135 ((MH-OH2)+, 100%).

14(a). Methyl 2-(p-tolylethynyl)benzoate (3.45)

After General method A using methyl 2-iodobenzoate (3.878 g, 14.8 mmol), 1-ethynyl-4-methylbenzene (1.83 mL, 17.8 mmol), [Pd(PPh3)2Cl2] (0.24 g, 0.34 mmol), CuI (0.118 g, 0.6 mmol) and dry Et3N (40 mL), the crude product (4.25 g) was purified by column chromatography using ethyl acetate/petroleum ether 40-60 °C (1/9) to give pure methyl 2-(p-tolylethynyl)benzoate as an orange oil (3.66 g, 99 %). 1H NMR (400 MHz; CDCl3) δH 2.37 (3H, s, CH3), 3.96 (3H, s, OCH3), 7.16 (2H, d, JHH = 8.3 Hz, ArH), 7.36 (1H, td, JHH = 7.8 Hz, JHH = 1.3 Hz, ArH), 7.47 (2H, d, JHH = 8.3 Hz, ArH), 7.49 (1H, m, ArH), 7.63 (1H, dd, JHH = 7.7 Hz, JHH = 1.0 Hz, ArH), 7.96 (1H, dd, JHH = 7.9 Hz, JHH = 1.4 Hz, ArH); 13C NMR (100 MHz; CDCl3) δC 21.6 (CH3), 52.2 (OCH3), 87.6 (C), 94.6 (C), 120.3 (C), 123.9 (C), 127.7 (CH), 129.1 (CH), 130.5 (CH), 131.7 (CH), 131.8 (CH), 131.8 (C), 133.9 (CH), 138.7 (C), 166.8 (CO). m/z (ASAP) 251.1062 (MH+). C17H15O2 requires 251.1072, 100 %).
14(b). 2-(2-(p-Tolylethynyl)phenyl)propan-2-ol (3.38)

\[
\text{\begin{center}
\includegraphics[width=0.2\textwidth]{structures/2-(2-(p-Tolylethynyl)phenyl)propan-2-ol.png}
\end{center}}
\]

After **General method E** using MeI (3.8 mL, 60 mmol), magnesium (2.038 g, 84.9 mmol), methyl 2-(p-tolylethynyl)benzoate (6.98 g, 27.9 mmol) and diethyl ether (40 mL), the crude product (6.435 g) was purified by column chromatography using ethyl acetate/petroleum ether (40-60) (1/9) to give pure 2-(2-(p-tolylethynyl)phenyl)propan-2-ol as a brown solid (1.259 g, 18 %). mp 85-87 °C; \(^1\)H NMR (400 MHz; CDCl\(_3\)) \(\delta\)H 1.79 (6H, s, CH\(_3\)), 2.38 (3H, s, CH\(_3\)), 3.33 (1H, s, OH), 7.18 (2H, d, \(^3J_{HH} = 7.9\) Hz, Ar\(H\)), 7.23 (1H, td, \(^3J_{HH} = 7.5\) Hz, \(^4J_{HH} = 1.4\) Hz, Ar\(H\)), 7.31 (1H, td, \(^3J_{HH} = 7.5\) Hz, \(^4J_{HH} = 1.6\) Hz, Ar\(H\)), 7.42 (2H, dt, \(^3J_{HH} = 8.1\) Hz, \(^4J_{HH} = 1.7\) Hz, Ar\(H\)), 7.57 (2H, dt, \(^3J_{HH} = 7.8\) Hz, \(^4J_{HH} = 1.4\) Hz, Ar\(H\)); \(^13\)C NMR (100 MHz; CDCl\(_3\)) \(\delta\)C 21.5 (CH\(_3\)), 29.9 (CH\(_3\)), 73.2 (C), 88.6 (C), 95.8 (C), 119.6 (C), 119.8 (C), 124.7 (CH), 126.6 (CH), 128.4 (CH), 129.3 (CH), 131.1 (CH), 134.3 (CH), 138.9 (C), 150.0 (C). m/z (ASAP) 251.1429 (MH\(^+\). C\(_{18}\)H\(_{19}\)O requires 251.1436, 30 %), 233.1288 ((MH-\(\text{OH}_2\))^+. 100 %)

15. 3-(2-(phenylethynyl)phenyl)pentan-3-ol (3.39)

EtMgBr (37.5 mL, 37.5 mmol, 1M in THF) was charged into a three-necked flask with diethyl ether (10 mL) at 0 °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 in 20 min. The mixture was warmed to RT and stirred overnight. On the next day, the mixture was
stirred under reflux for 1.5 h. After cooling to RT, the mixture was extracted with diethyl ether (3 x 15 mL) and H2O (20 mL). The combined organic layers were dried over MgSO4 (anhydrous), and the solvent was removed to give the crude product (3.80 g). It was purified by column chromatography using ethyl acetate/petroleum ether (40-60) (1/9) to give pure 3-(2-(phenylethynyl)phenyl)pentan-3-ol as a brown oil (1.53 g, 39 %). 1H NMR (400 MHz; CDCl3) δ H 0.79 (6H, t, 3JHH = 7.5 Hz, CH3), 1.96 (2H, ABt, 3JHH = 7.4 Hz, CH2), 2.49 (2H, ABt, 3JHH = 7.5 Hz, CH2), 2.50 (1H, s, OH), 7.23 (1H, td, 3JHH = 7.5 Hz, 4JHH = 1.3 Hz, ArH), 7.35 (4H, m, ArH), 7.51 (2H, m, ArH), 7.57 (1H, dd, 3JHH = 7.6 Hz, 4JHH = 1.4 Hz, ArH), 7.60 (1H, dd, 3JHH = 8.1 Hz, 4JHH = 1.2 Hz, ArH); 13C NMR (100 MHz; CDCl3) δC 8.1 (CH3), 33.1 (CH2), 78.5 (C), 89.7 (C), 94.5 (C), 119.4 (C), 123.2 (C), 126.4 (CH), 127.1 (CH), 127.9 (CH), 128.2 (CH), 128.5 (CH), 131.2 (CH), 134.5 (CH), 146.9 (C). m/z (ASAP) 265.1596 (MH+. C19H21O requires 265.1592, 100%).

16. (Z)-4-Methyl-N-(2-(phenylethynyl)benzylidene)benzenesulfonamide (3.46)

Molecular sieves (5Å) were charged into a three-necked flask at 200 °C under vacuum for 4 h. 2-(Phenylethynyl)benzaldehyde (5.80 g, 20.2 mmol) and NH2Ts (3.596 g, 21.0 mmol) were charged into the flask with dry toluene (50 mL). The mixture was refluxed under nitrogen for 48 h. After cooling to RT, the mixture was filtered and the solvent was removed to give the crude product (8.843 g). The crude product was washed with petroleum ether (40-60) and the precipitate was filtered to give the pure (Z)-4-methyl-N-(2-(phenylethynyl)-benzylidene)benzenesulfonamide as a brown solid (6.856 g, 94 %). Crystals suitable for X-ray crystallography were grown from hot petroleum ether (40-60). mp >300 °C; 1H NMR (400 MHz; CDCl3) δ H 2.41 (3H, s, CH3), 7.33 (2H, d, 3JHH = 8.0 Hz, ArH), 7.40 (4H, m, ArH), 7.57 (3H, m, ArH), 7.62 (1H, dd, 3JHH = 7.8 Hz, 4JHH = 0.9 Hz, ArH), 7.91 (2H, dt, 3JHH = 8.3 Hz, 4JHH = 1.7 Hz, ArH), 8.17 (1H, dd, 3JHH = 7.9 Hz, 4JHH = 1.1 Hz, ArH), 9.62 (1H, s,
$^{13}$C NMR (100 MHz; CDCl$_3$) $\delta$C 21.6 (CH$_3$), 85.9 (C), 97.6 (C), 122.1 (C), 128.3 (C), 128.4 (CH), 128.5 (CH), 128.6 (CH), 128.7 (CH), 129.2 (CH), 129.8 (CH), 131.8 (CH), 132.8 (CH), 134.3 (CH), 134.7 (C), 144.7 (C), 168.4 (CHN). One of the quaternary carbon missing. m/z (ASAP) 360.1048 (MH$^+$. C$_{22}$H$_{18}$NO$_2$S requires 360.1058, 100 %).

17. 4-Methyl-N-(2,2,2-trifluoro-1-(2-(phenylethynyl)phenyl)ethyl)benzenesulfonamide (3.40)

(Z)-4-Methyl-N-(2-(phenylethynyl)benzylidene)benzenesulfonamide (3.23 g, 9.0 mmol) and TBAB (0.290 g, 0.9 mmol) were charged into a three-necked flask with 5Å molecular seives and dry toluene (40 mL). CF$_3$SiMe$_3$ (2 mL, 13.5 mmol) was charged into the mixture followed by PhONa (0.575 g, 9.9 mmol). The mixture was stirred at RT under nitrogen for 48 h. The mixture was washed with a saturated solution of Na$_2$CO$_3$ (20 mL) and extracted with ethyl acetate (3 x 10 mL). The combined organic layers were dried over MgSO$_4$ (anhydrous), and the solvent was removed to give the crude product (4.142 g). It was purified by column chromatography using ethyl acetate/petroleum ether (40-60) (2/8) followed by recrystallisation using DCM/petroleum ether (40-60) (1/4) to give pure 4-methyl-N-(2,2,2-trifluoro-1-(2-(phenylethynyl)phenyl)ethyl)benzene-sulfonamide as a pink/ white solid (1.935 g, 50 %). Crystals suitable for X-ray crystallography were grown from hot petroleum ether (40-60). mp 158-160 °C; $^1$H NMR (400 MHz; CDCl$_3$) $\delta$H 2.23 (3H, s, CH$_3$), 5.55 (1H, dq, $^3$J$_{HH}$ = 9.5 Hz, $^3$J$_{HF}$ = 7.7 Hz, CHCF$_3$), 5.83 (1H, d, $^3$J$_{HH}$ = 9.6 Hz, NH), 6.98 (2H, d, $^3$J$_{HH}$ = 8.0 Hz, ArH), 7.18 (3H, m, ArH), 7.35 (4H, m, ArH), 7.50 (3H, m, ArH), 7.53 (1H, d, $^3$J$_{HH}$ = 8.4 Hz, ArH); $^{13}$C NMR (100 MHz; CDCl$_3$) $\delta$C 21.4 (CH$_3$), 57.1 (q, $^2$J$_{CF}$ = 32.7 Hz, CH), 86.0 (C), 95.4 (C), 122.3 (C), 123.4 (C), 125.4 (q, $^1$J$_{CF}$ = 282.2 Hz, CF$_3$), 127.1 (CH), 127.5 (CH), 128.6 (CH), 128.7 (CH), 128.9 (CH), 129.0 (CH), 129.4 (CH), 131.7 (CH), 132.5 (CH), 171
133.3 (C), 136.5 (C), 143.7 (C). $^{19}$F NMR (376 MHz; CDCl$_3$) $\delta$ -73.7 (s, CF$_3$). m/z (ASAP) 430.1069 (MH$^+$; C$_{23}$H$_{19}$NO$_2$SF$_3$ requires 430.1089, 100 %).

**Synthesis of heterocyclic products via iodocyclisation**

**General method F:** Dry DCM, IPy$_2$BF$_4$ (1.5 eq.) and HBF$_4$.Et$_2$O (1.2 eq.) were charged into a three-necked flask at 0 °C under nitrogen. After stirring for 20 min, the alkynol substrate (1.0 eq.) was added to the reaction mixture. After stirring for 15 min, the mixture was warmed to RT. After stirring for 3 h at RT, a saturated solution of NaHCO$_3$ (10 mL) was added, and the mixture was vigorously stirred for a further 5 min. The mixture was then extracted with DCM (10 mL) and the combined organic layers were washed with a saturated solution of NaS$_2$O$_3$ (10 mL) and water (10 ml). The aqueous phase was extracted with DCM (3 x 10 mL). The combined organic layers were dried over MgSO$_4$ (anhydrous), and the solvent was removed to give the crude product.

**General method G:** The alkynol substrate (1.0 eq.), I$_2$ (3.0 eq.), K$_2$CO$_3$ (2.0 eq.) and dry DCM were charged into a three-necked flask. After stirring under nitrogen at RT for 48 h, a saturated solution of NaS$_2$O$_3$ (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 to give the crude product.

**1. 4-Iodo-1-methoxy-3-phenyl-1H-isochromene (3.47)**

![](attachment:image.png)

2-(Phenylethynyl)benzaldehyde (0.21 g, 1.0 mmol), MeOH (0.038 g, 1.2 mmol), I$_2$ (0.305 g, 1.2 mmol), K$_2$CO$_3$ (0.138 g, 1.0 mmol) and dry DCM (20 mL) were charged into a three-necked flask. After stirring under nitrogen at RT for 21 h, a saturated solution of NaS$_2$O$_3$ (10...
mL) and water (10 mL) were used to wash the reaction mixture. The mixture was extracted with DCM (3 x 10 mL), and the combined organic layers were dried over MgSO₄ (anhydrous). The solvent was removed to give the crude product (0.309 g), which was purified by column chromatography using ethyl acetate/hexane (1/15) to give pure 4-iodo-1-methoxy-3-phenyl-1H-isochromene as a purple oil (0.186 g, 51%). The characterisation data was in agreement with the literature. 

5.21 ¹H NMR (400 MHz; CDCl₃) δH 3.58 (3H, s, OCH₃), 5.95 (1H, s, OCH), 7.13 (1H, dd, 3J_HH = 7.5 Hz, 4J_HF = 0.9 Hz, ArH), 7.26 (1H, td, 3J_HH = 7.5 Hz, 4J_HH = 1.0 Hz, ArH), 7.38 (4H, m, ArH), 7.54 (3H, m, ArH), 13C NMR (100 MHz; CDCl₃) δC 56.0 (CH₃), 73.8 (CI), 100.0 (CH), 125.5 (CH), 127.2 (C), 127.8 (CH), 128.0 (CH), 129.3 (CH), 129.7 (CH), 129.9 (CH), 130.0 (CH), 131.4 (C), 137.5 (C), 151.8 (C).

2. 4-Iodo-3-phenyl-1-(2,2,2-trifluoroethoxy)-1H-isochromene (3.48)

2-(Phenylethynyl)benzaldehyde (0.21 g, 1.0 mmol), CF₃CH₂OH (0.120 g, 1.2 mmol), I₂ (0.3046 g, 1.2 mmol), K₂CO₃ (0.138 g, 1.0 mmol) and dry DCM (15 mL) were charged into a three-necked flask. After stirring under nitrogen at RT for 21 h, a saturated solution of NaS₂O₃ (10 mL) was added to the mixture and stirred for 5 min. The mixture was extracted with DCM (3 x 10 mL) and the combined organic layers were dried over MgSO₄ (anhydrous). The solvent was removed to give the crude product (0.359 g) which was purified by column chromatography using ethyl acetate/hexane (1/9) to give the pure 4-iodo-3-phenyl-1-(2,2,2-trifluoroethoxy)-1H-isochromene as a purple oil (0.154 g, 35%). ¹H NMR (400 MHz; CDCl₃) δH 4.04 (1H, dq, 2J_HH = 12.6 Hz, 3J_HF = 8.8 Hz, OCH₂H₃B), 4.04 (1H, dq, 2J_HH = 12.6 Hz, 3J_HF = 8.4 Hz, OCH₂H₃B), 6.17 (1H, s, OCHO), 7.29 (1H, td, 3J_HH = 7.5 Hz, 4J_HH = 1.1 Hz, ArH), 7.37 (3H, m, ArH), 7.42 (2H, td, 3J_HH = 7.6 Hz, 4J_HH = 1.3 Hz, ArH), 7.48 (2H, m, ArH), 7.55 (1H, d, 3J_HH = 7.9 Hz, ArH); ¹³C NMR (100 MHz; CDCl₃) δC 64.5 (q, 2J_CF = 34.6 Hz, CH₂), 74.5 (CI), 94.4 (C), 98.8 (CH), 122.4 (q, 1J_CF = 285.5 Hz, CF₃), 125.8 (CH), 128.1 (CH),
128.2 (CH), 129.5 (CH), 129.8 (CH), 130.0 (CH), 130.5 (CH), 131.2 (C), 137.1 (C), 151.1 (C); $^{19}$F NMR (376 MHz; CDCl$_3$) $\delta_{F}$ -73.9 (s, CF$_3$). Product decomposed quickly, cannot get mass spectrum.

3. (E)-1-(Iodo(phenyl)methylene)-3-(trifluoromethyl)-1,3-dihydroisobenzofuran (3.49)

![Chemical structure](image)

After General method G using 2,2,2-trifluoro-1-(2-(phenylethynyl)phenyl)ethanol (0.280 g, 1.0 mmol), I$_2$ (0.761 g, 3.0 mmol), K$_2$CO$_3$ (0.276 g, 2.0 mmol) and dry DCM (30 mL), the crude product (0.38 g) was purified by column chromatography using ethyl acetate/hexane (1/15) to give pure (E)-1-(iodo(phenyl)methylene)-3-(trifluoromethyl)-1,3-dihydroisobenzofuran as a pale yellow solid (turned to purple in air) (0.247 g, 61%). Crystals suitable for X-ray crystallography were grown from hot toluene. mp 55-60 °C. $^1$H NMR (400 MHz; CDCl$_3$) $\delta$$_H$ 5.51 (1H, q, $^3$$J$$_{HF}$ = 5.7 Hz, CF$_3$CHO), 7.19 (1H, m, Ar$H$), 7.29 (2H, t, $^3$$J$$_{HH}$ = 7.4 Hz, Ar$H$), 7.47 (5H, m, Ar$H$), 8.72 (1H, d, $^3$$J$$_{HH}$ = 8.0 Hz, Ar$H$); $^{13}$C NMR (100 MHz; CDCl$_3$) $\delta$$_C$ 66.7 (Cl), 79.7 (q, $^2$$J$$_{CF}$ = 33.3 Hz, CH), 122.8 (q, $^1$$J$$_{CF}$ = 282.8 Hz, CF$_3$), 122.9 (CH), 126.3 (CH), 127.8 (CH), 128.0 (CH), 128.2 (CH), 129.5 (CH), 130.2 (CH), 134.0 (C), 136.3 (C), 141.2 (C), 151.9 (C); $^{19}$F NMR (376 MHz; CDCl$_3$) $\delta_{F}$ -77.76 (s, CF$_3$). m/z (ASAP) 402.9801 (MH$^+$, C$_{16}$H$_{11}$F$_3$I requires 402.9807, 45 %), 276.0757 ((MH-I)$^+$, 100 %).

The reaction was repeated, and some side products were also observed. The $^1$H NMR spectrum of the crude product, indicated that a small amount of (Z)-1-(iodo(phenyl)methylene)-3-(trifluoromethyl)-1,3-dihydroisobenzofuran (3.61) (~10 %) and 4-iodo-3-phenyl-1-(trifluoromethyl)-1H-isochromene (3.50) (~5 %) were formed in the reaction as well.
After **General method G** using 2,2,2-trifluoro-1-(2-(phenylethynyl)phenyl)ethanol (0.138 g, 0.5 mmol), I₂ (0.383 g, 1.5 mmol), K₂CO₃ (0.138 g, 1.0 mmol) and dry MeCN (30 mL), the crude product (0.37 g) was purified by column chromatography using ethyl acetate/hexane (1/15) to give (E)-1-(iodo(phenyl)methylene)-3-(trifluoromethyl)-1,3-dihydroisobenzofuran as a pale yellow solid (turned to purple in air) (0.14 g, 69%).

**4. 4-Iodo-3-phenyl-1-(trifluoromethyl)-1H-isochromene (3.50)**

![Chemical structure](image)

After **General method F** using dry DCM (30 mL), IPY₂BF₄ (0.558 g, 1.5 mmol), HBF₄.Et₂O (0.163 ml, 1.2 mmol) and 2,2,2-trifluoro-1-(2-(phenylethynyl)phenyl)ethanol (0.280 g, 1.0 mmol), the crude product (0.399 g) was purified by column chromatography using ethyl acetate/hexane (1/15) to give the pure 4-iodo-3-phenyl-1-(trifluoromethyl)-1H-isochromene as a yellow oil (turned to purple in air) (0.273 g, 67 %). 

1H NMR (400 MHz; CDCl₃) \(\delta\) 5.51 (1H, q, \(^3J_{HF} = 7.3\) Hz, CF₃CHO), 7.05 (1H, d, \(^3J_{HH} = 7.5\) Hz, ArH), 7.24 (1H, td, \(^3J_{HH} = 7.5\) Hz, \(^4J_{HH} = 1.1\) Hz, ArH), 7.36 (3H, m, ArH), 7.39 (1H, td, \(^3J_{HH} = 7.6\) Hz, \(^4J_{HH} = 1.2\) Hz, ArH), 7.49 (1H, dd, \(^3J_{HH} = 7.9\) Hz, \(^4J_{HH} = 1.0\) Hz, ArH), 7.57 (2H, m, ArH); 13C NMR (100 MHz; CDCl₃) \(\delta\) 72.9 (Cl), 75.2 (q, \(^2J_{CF} = 32.0\) Hz, CH), 121.7 (C), 123.5 (q, \(^1J_{CF} = 288.5\) Hz, CF₃), 126.4 (CH), 128.0 (CH), 128.2 (CH), 129.9 (CH), 130.3 (CH), 130.4 (CH), 130.5 (CH), 132.6 (C), 136.0 (C), 152.8 (C); 19F NMR (376 MHz; CDCl₃) \(\delta\) -77.88 (s, CF₃). m/z (ASAP) 401.9730 (MH⁺). C₁₆H₁₀F₃IO requires 401.9729, 6 %), 276.0767 ((MH-I)⁺, 100 %).
After **General method G** using 2-(phenylethynyl)benzyl alcohol (0.208 g, 1.0 mmol), I₂ (0.761 g, 3.0 mmol), K₂CO₃ (0.276 g, 2.0 mmol) and dry DCM (30 mL), the crude product (0.327 g) was purified by column chromatography using diethyl ether/hexane (1/1) to give pure 4-iodo-3-phenyl-1\(H\)-isochromene as a brown oil (0.211 g, 62%). The characterisation data was in agreement with the literature.  

\[
\begin{align*}
\text{H NMR (400 MHz; CDCl}_3\text{) } & \delta_H 5.15 (2H, s, OCCH₂), 6.94 (1H, dd, 3\textbf{J}_{HH} = 7.5 Hz, 4\textbf{J}_{HH} = 0.8 Hz, ArH), 7.16 (1H, td, 3\textbf{J}_{HH} = 7.4 Hz, 4\textbf{J}_{HH} = 1.2 Hz, ArH), 7.28 (1H, td, 3\textbf{J}_{HH} = 7.6 Hz, 4\textbf{J}_{HH} = 1.2 Hz, ArH), 7.33 (3H, m, ArH), 7.39 (1H, dd, 3\textbf{J}_{HH} = 7.8 Hz, 4\textbf{J}_{HH} = 0.8 Hz, ArH), 7.57 (2H, m, ArH); \\
\text{C NMR (100 MHz; CDCl}_3\text{) } & \delta_C 69.6 (CH₂), 73.4 (CI), 123.4 (CH), 127.7 (CH), 127.8 (CH), 128.5 (C), 128.6 (CH), 128.7 (CH), 129.6 (CH), 130.4 (CH), 133.6 (C), 136.6 (C), 156.5 (C).
\end{align*}
\]

After **General method G** using 2-(phenylethynyl)benzyl alcohol (0.208 g, 1.0 mmol), I₂ (0.761 g, 3.0 mmol), K₂CO₃ (0.276 g, 2.0 mmol) and dry MeCN (30 mL) for 48 h, the crude product (0.32 g) was purified by column chromatography using diethyl ether/hexane (4/6) to give pure 4-iodo-3-phenyl-1\(H\)-isochromene as a brown oil (0.031 g, 9%). A 24 h reaction gave a 34% yield of the desired product. However, three other reactions using 0.2 equivalent I₂/ 1.0 equivalent of K₂CO₃, 1.2 equivalent of I₂/ 1.0 equivalent of K₂CO₃ and 1.2 equivalent of I₂/ none of K₂CO₃, gave no desired products.

After **General method F** using dry DCM (15 mL), IPy₂BF₄ (0.558 g, 1.5 mmol), HBF₄·Et₂O (0.163 ml, 1.2 mmol) and 2-(phenylethynyl)benzyl alcohol (0.208 g, 1.0 mmol), the crude product (0.287 g) was purified by column chromatography using diethyl ether/hexane (3/7) to give pure 4-iodo-3-phenyl-1\(H\)-isochromene as a brown oil (turned to purple in air) (0.072 g, 22%).
After General method G using (2-(p-tolylethynyl)phenyl)methanol (0.222 g, 1.0 mmol), I₂ (0.761 g, 3.0 mmol), K₂CO₃ (0.276 g, 2.0 mmol) and dry DCM (30 mL), the crude product (0.306 g) was purified by column chromatography using diethyl ether/hexane (1/1) to give pure 4-iodo-3-(p-tolyl)-1H-isochromene as a brown oil (0.196 g, 56%). The characterisation data was in agreement with the literature. 5.22 ¹H NMR (400 MHz; CDCl₃) δH 2.42 (3H, s, CH₃), 5.23 (2H, s, OCH₂), 7.03 (1H, dd, 3JHH = 7.3 Hz, 4JHH = 0.6 Hz, ArH), 7.25 (3H, m, ArH), 7.37 (1H, td, 3JHH = 7.6 Hz, 4JHH = 1.2 Hz, ArH), 7.49 (1H, dd, 3JHH = 7.6 Hz, 4JHH = 0.9 Hz, ArH), 7.58 (2H, d, 3JHH = 8.2 Hz, ArH); ¹³C NMR (100 MHz; CDCl₃) δC 21.5 (CH₃), 69.6 (CH₂), 72.9 (CI), 123.4 (CH), 127.5 (CH), 128.5 (CH), 128.6 (CH), 128.7 (CH), 129.2 (C), 130.4 (CH), 133.6 (C), 133.8 (C), 139.8 (C), 156.5 (C).

After General method F using dry DCM (15 mL), IPy₂BF₄ (0.558 g, 1.5 mmol), HBF₄.Et₂O (0.163 ml, 1.2 mmol) and (2-(p-tolylethynyl)phenyl)methanol (0.222 g, 1.0 mmol), the crude product (0.306 g) was purified by column chromatography using diethyl ether/hexane (1/1) to give 4-iodo-3-(p-tolyl)-1H-isochromene (0.0603 g, 17 %), and a mixture of 4-iodo-3-(p-tolyl)-1H-isochromene and (Z)-1-(iodo(p-tolyl)methylene)-1,3-dihydroisobenzofuran as a brown oil (0.0851 g, 25 %). The two isomers could not be separated. However, some peaks in the NMR spectra indicated the second product in this reaction. ¹H NMR (400 MHz; CDCl₃) δH 2.32 (3H, s, CH₃), 5.35 (2H, s, OCH₂), 6.43 (1H, d, 3JHH = 8.0 Hz, ArH), the rest of the aromatic peaks were overlapping with those for the main product, and therefore, cannot be distinguished; ¹³C NMR (100 MHz; CDCl₃) δC 21.4 (CH₃), 73.3 (CH₂), 77.3 (CI), 121.3 (CH), 123.2 (CH), 125.4 (C), 127.7 (CH), 128.5 (CH), 128.9 (CH), 129.8 (CH), 138.0 (C), 138.3 (C), 139.3 (C), 142.2 (C).
7. \((E)-1-(\text{iodo}(p\text{-tolyl})\text{methylene})-3-(\text{trifluoromethyl})-1,3\text{-dihydroisobenzofuran (3.55)}\)

![Chemical Structure](image)

After **General method G** using 2,2,2-trifluoro-1-(2-(p-tolylenyl)phenyl)ethanol (0.290 g, 1.0 mmol), \(I_2\) (0.761 g, 3.0 mmol), \(K_2CO_3\) (0.276 g, 2.0 mmol) and dry DCM (30 mL) to give the crude product (0.346 g). According to the \(^1\)H NMR spectrum of the crude product, three different products were formed, \((E)-1-(\text{iodo}(\text{phenyl})\text{methylene})-3-(\text{trifluoromethyl})-1,3\text{-dihydroiso-benzofuran as the main product, (Z)-1-(\text{iodo}(p\text{-tolyl})\text{methylene})-3-(\text{trifluoromethyl})-1,3\text{-dihydroisobenzofuran and 4-iodo-3-(p-tolyl)-1-(trifluoromethyl)-1H-isochromene. The ratio of these three products was approximately 8/1/1, respectively. Purification by column chromatography using diethyl ether/hexane (1/50) still gave a mixture (0.260 g, 63 %). These three products could not be separated even using pure hexane. However, after a second column, a small amount of a yellow solid was obtained from the side of the collection flask, which was identified as \((E)-1-(\text{iodo}(\text{phenyl})\text{methylene})-3-(\text{trifluoromethyl})-1,3\text{-dihydroisobenzofuran, with nearly 100\% purity. Crystals suitable for X-ray crystallography were grown from hexane. mp 58-61 °C. \(^1\)H NMR (400 MHz; CDCl\(_3\)) \(\delta_H\) 2.30 (3H, s, \(CH_3\)), 5.51 (1H, q, \(^3J_{HF} = 5.6\) Hz, \(\text{CF}_3\text{CHO}\)), 7.10 (2H, d, \(^3J_{HH} = 8.5\) Hz, \(\text{ArH}\)), 7.38 (2H, d, \(^3J_{HH} = 8.3\) Hz, \(\text{ArH}\)), 7.45 (3H, m, \(\text{ArH}\)), 8.71 (1H, d, \(^3J_{HH} = 8.2\) Hz, \(\text{ArH}\)); \(^{13}\)C NMR (100 MHz; CDCl\(_3\)) \(\delta_C\) 21.2 (\(\text{CH}_3\)), 67.1 (\(\text{CI}\)), 79.3 (q, \(^2J_{CF} = 33.2\) Hz, \(\text{CH}\)), 122.9 (\(\text{CH}\)), 125.6 (q, \(^1J_{CF} = 281.5\) Hz, \(\text{CF}_3\)), 126.2 (\(\text{CH}\)), 128.7 (\(\text{CH}\)), 129.4 (\(\text{CH}\)), 130.0 (\(\text{CH}\)), 130.0 (\(\text{CH}\)), 134.0 (\(\text{C}\)), 136.2 (\(\text{C}\)), 137.8 (\(\text{C}\)), 138.3 (\(\text{C}\)), 151.7 (\(\text{C}\)); \(^{19}\)F NMR (376 MHz; CDCl\(_3\)) \(\delta_F\) -77.77 (s, \(\text{CF}_3\)). \(m/z\) (ASAP) 416.9948 (MH\(^+\)). \(C_{17}H_{13}F_3\) requires 416.9963, 54 %), 290.0896 ((MH-I\(^+\)), 100 %).

Some other peaks were also observed from the \(^1\)H NMR spectrum. (400 MHz; CDCl\(_3\)) \(\delta_H\) 2.34 (3H, s, \(\text{CH}_3\)), 2.35 (3H, s, \(\text{CH}_3\)), 5.68 (1H, q, \(^3J_{HF} = 5.7\) Hz, \(\text{CF}_3\text{CHO}\)), 6.46 (2H, d, \(^3J_{HH} = 7.8\) Hz, \(\text{ArH}\)). These peaks are associated with \((Z)-1-(\text{iodo}(p\text{-tolyl})\text{methylene})-3-\)
(trifluoromethyl)-1,3-dihydroisobenzofuran (3.56) and 4-iodo-3-(p-tolyl)-1-(trifluoromethyl)-1H-isochromene (3.57). Unfortunately, the rest of the peaks were too weak to be resolved.

8. 4-Iodo-3-(p-tolyl)-1-(trifluoromethyl)-1H-isochromene (3.57)

After General method F using dry DCM (30 mL), IPy$_2$BF$_4$ (0.558 g, 1.5 mmol), HBF$_4$.Et$_2$O (0.163 ml, 1.2 mmol) and 2,2,2-trifluoro-1-(2-(p-tolylethynyl)phenyl)ethanol (0.290 g, 1.0 mmol), the crude product (0.412 g) was purified by column chromatography using ethyl acetate/hexane (1/15) to give the pure 4-iodo-3-(p-tolyl)-1-(trifluoromethyl)-1H-isochromene as yellow solid (turned to purple in air) (0.264 g, 63 %). Crystals suitable for X-ray crystallography were grown by slow evaporation of a hexane solution containing the product. mp 53-56 °C. $^1$H NMR (400 MHz; CDCl$_3$) δ$_H$ 2.34 (3H, s, CH$_3$), 5.50 (1H, q, $^3$J$_{HF}$ = 7.1 Hz, CF$_3$CHO), 7.05 (1H, d, $^3$J$_{HH}$ = 7.45 Hz, ArH), 7.17 (2H, d, $^3$J$_{HH}$ = 7.5 Hz, ArH), 7.24 (1H, td, $^3$J$_{HH}$ = 7.5 Hz, $^4$J$_{HH}$ = 1.1 Hz, ArH), 7.39 (1H, td, $^3$J$_{HH}$ = 7.6 Hz, $^4$J$_{HH}$ = 1.2 Hz, ArH), 7.40 (3H, m, ArH); $^{13}$C NMR (100 MHz; CDCl$_3$) δ$_C$ 21.5 (CH$_3$), 72.4 (Cl), 75.2 (q, $^2$J$_{CF}$ = 33.2 Hz, CH), 121.7 (C), 126.3 (CH), 126.5 (q, $^1$J$_{CF}$ = 286.1 Hz, CF$_3$), 128.1 (CH), 128.6 (CH), 130.2 (CH), 130.3 (CH), 130.5 (CH), 132.8 (C), 133.0 (C), 140.1 (C), 152.9 (C); $^{19}$F NMR (376 MHz; CDCl$_3$) δ$_F$ -77.84 (s, CF$_3$). m/z (ASAP) 416.9964 (MH$^+$). C$_{17}$H$_{13}$F$_3$IO requires 416.9963, 38 %. 290.0897 ((MH-I)$^+$, 100 %).
9. (Z)-1-(1-Iodoheptylidene)-3-(trifluoromethyl)-1,3-dihydroisobenzofuran (3.59), (E)-1-(1-Iodoheptylidene)-3-(trifluoromethyl)-1,3-dihydroisobenzofuran (3.58) and 3-hexyl-4-iodo-1-(trifluoromethyl)-1H-isochromene (3.60)

\[
\begin{align*}
\text{CF}_3 & \quad \text{O} \\
(\text{Z}) & + \\
\text{CF}_3 & \quad \text{O} \\
(\text{E}) & + \\
\text{CF}_3 & \quad \text{O} \\
& \quad + \\
\end{align*}
\]

After General method G using 2,2,2-trifluoro-1-(2-(oct-1-yn-1-yl)phenyl)ethanol (0.285 g, 1.0 mmol), I₂ (0.761 g, 3.0 mmol), K₂CO₃ (0.276 g, 2.0 mmol) and dry DCM (30 mL) to give the crude product (0.407 g). Three products were observed from the ¹H NMR spectrum of the crude product, (Z)-1-(1-iodoheptylidene)-3-(trifluoromethyl)-1,3-dihydroisobenzofuran, (E)-1-(1-iodoheptylidene)-3-(trifluoromethyl)-1,3-dihydroisobenzofuran and 3-hexyl-4-iodo-1-(trifluoro-methyl)-1H-isochromene, in an approximately 4.5/4.5/1 ratio. Purification by column chromatography using ethyl acetate/hexane (1/39) still gave a mixture of the three products, (0.17 g, 42 %), but also some of the pure (Z)-1-(1-iodoheptylidene)-3-(trifluoromethyl)-1,3-dihydroisobenzofuran as a pale yellow oil (turned to purple in air) (0.062 g, 15 %). ¹H NMR (400 MHz; CDCl₃) δH 0.82 (3H, t, ³J_HH = 7.1 Hz, CH₃), 1.26 (4H, m, CH₂CH₃), 1.34 (2H, m, CH₂CH₂CH₃), 1.58 (2H, m, CH₂CH₂CH₂CH₂CH₃), 2.85 (2H, AB dt, CH₂CH₂CH₂CH₂CH₂CH₃), 5.51 (1H, q, ³J_HF = 5.9 Hz, CF₃CH₂O), 7.38 (3H, m, ArH), 7.63 (1H, d, ³J_HH = 7.8 Hz, ArH); ¹³C NMR (100 MHz; CDCl₃) δC 14.0 (CH₃), 22.6 (CH₂), 28.3 (CH₂), 29.3 (CH₂), 31.7 (CH₂), 37.7 (CH₂), 76.9 (CI), 79.2 (q, ²J_CF = 33.8 Hz, CH), 122.8 (CH), 123.5 (CH), 124.2 (q, ¹J_CF = 278.3 Hz, CF₃), 129.1 (CH), 130.2 (CH), 131.4 (C), 136.1 (C), 153.7 (C); ¹⁹F NMR (376 MHz; CDCl₃) δF -78.10 (s, CF₃). m/z (ASAP) 411.0439 (MH⁺). C₁₆H₁₉F₃IO requires 411.0433, 100 %).
10. (E)-Ethyl-2,2-difluoro-2-(3-(iodo(phenyl)methylene)-1,3-dihydroisobenzofuran-1-yl)-acetate (3.62)

After **General method G** using ethyl-2,2-difluoro-3-hydroxy-3-(2-(phenylethynyl)phenyl)-propanoate (0.330 g, 1.0 mmol), I₂ (0.761 g, 3.0 mmol), K₂CO₃ (0.276 g, 2.0 mmol) and dry DCM (30 mL), the crude product (0.416 g) was purified by column chromatography using ethyl acetate/hexane (2/8) to give (E)-ethyl 2,2-difluoro-2-(3-(iodo(phenyl)methylene)-1,3-dihydroisobenzofuran-1-yl)acetate as yellow oil (turned to purple in air) (0.260 g, 57 %). ¹H NMR (400 MHz; CDCl₃) δ H 1.08 (3H, t, 3JHH = 7.1 Hz, OCH₂CH₃), 4.13 (2H, m, OCH₂CH₃), 5.66 (1H, dd, 3JHF = 15.3 Hz, ³JHH = 4.4 Hz, CF₂CHO), 7.12 (1H, tt, ³JHH = 7.4 Hz, ⁴JHH = 1.3 Hz, ArH), 7.24 (2H, tt, ³JHH = 7.5 Hz, ⁴JHH = 1.8 Hz, ArH), 7.42 (5H, m, ArH), 8.69 (1H, d, ³JHH = 8.1 Hz, ArH); ¹³C NMR (100 MHz; CDCl₃) δ C 13.7 (CH₃), 63.3 (CH₂), 65.9 (CI), 81.4 (dd, ²JCF = 32.2 Hz, ²JCF = 28.2 Hz, CH), 112.3 (dd, ¹JCF = 260.6 Hz, ¹JCF = 254.6 Hz, CF₆F₆), 123.1 (CH), 126.1 (CH), 127.6 (CH), 127.8 (CH), 129.1 (CH), 130.1 (CH), 130.3 (CH), 134.2 (C), 137.2 (C), 141.3 (C), 152.1 (C), 162.3 (t, ²JCF = 31.0 Hz, CO); ¹⁹F NMR (376 MHz; CDCl₃) δ F -121.67 (1F, d, ²JFF = 249.1 Hz, CF₆F₆), -112.9 (1F, d, ²JFF = 249.1 Hz, CF₆F₆), m/z (ASAP) 456.0031 (MH⁺. C₁₉H₁₅F₂O₃ requires 456.0034, 3 %), 330.1047 ((MH-I)⁺, 100 %).
11. Ethyl 2,2-difluoro-2-(4-iodo-3-phenyl-1H-isochromen-1-yl)acetate (3.63)

![Chemical Structure]

After **General method F** using dry DCM (30 mL), IPy₂BF₄ (0.558 g, 1.5 mmol), HBF₄·Et₂O (0.163 ml, 1.2 mmol) and ethyl 2,2-difluoro-3-hydroxy-3-(2-(phenylethynyl)phenyl)propanoate (0.330 g, 1.0 mmol), the crude product (0.535 g) was purified by column chromatography using ethyl acetate/hexane (1/9) to give ethyl 2,2-difluoro-2-(4-iodo-3-phenyl-1H-isochromen-1-yl)acetate as a yellow oil (turned to purple in air) (0.332 g, 73 %). ¹H NMR (400 MHz; CDCl₃) δH 1.14 (3H, t, ³JHH = 7.1 Hz, OCH₂CH₃), 4.20 (2H, q, ³JHH = 7.1 Hz, OCH₂CH₃), 5.68 (1H, dd, ³JHF = 16.6 Hz, ³JHF = 6.5 Hz, CF₂CHO), 7.06 (1H, d, ³JHH = 7.4 Hz, ArH), 7.23 (1H, td, ³JHH = 7.5 Hz, ⁴JHH = 1.2 Hz, ArH), 7.39 (4H, m, ArH), 7.46 (1H, dd, ³JHH = 7.9 Hz, ⁴JHH = 1.0 Hz, ArH), 7.52 (2H, m, ArH); ¹³C NMR (100 MHz; CDCl₃) δC 13.8 (CH₃), 63.5 (CH₂), 73.2 (Cl), 77.2 (t, ²JC = 27.5 Hz, CH), 113.0 (t, ¹JC = 260.7 Hz, CF₂), 121.8 (C), 126.5 (CH), 127.9 (CH), 128.1 (CH), 129.7 (CH), 130.0 (CH), 130.2 (CH), 130.3 (CH), 132.7 (C), 136.3 (C), 153.2 (C), 163.0 (t, ²JC = 30.4 Hz, CO); ¹⁹F NMR (376 MHz; CDCl₃) δF -119.6 (1F, d, ²JFF = 263.3 Hz, CF₃F₂B), -112.3 (1F, d, ²JFF = 263.3 Hz, CF₃F₂B). m/z (ASAP) 456.0012 (MH⁺. C₁₉H₁₅F₂IO₃ requires 456.0034, 29 %), 330.1005 ((MH-I)⁺, 100 %).
12. (E)-Ethyl 2,2-difluoro-2-(3-(iodo(p-tolyl)methylene)-1,3-dihydroisobenzofuran-1-yl)-acetate (3.64)

After **General method G** using ethyl 2,2-difluoro-3-hydroxy-3-(2-(p-tolylethynyl)phenyl)-propanoate (0.344 g, 1.0 mmol), I₂ (0.761 g, 3.0 mmol), K₂CO₃ (0.276 g, 2.0 mmol) and dry DCM (30 mL), the crude product (0.451 g) was purified by column chromatography using ethyl acetate/hexane (2/8) to give (E)-ethyl 2,2-difluoro-2-(3-(iodo(phenyl)methylene)-1,3-dihydroisobenzofuran-1-yl)acetate as a yellow oil (turned to purple in air) (0.268 g, 57 %). 

$^1$H NMR (400 MHz; CDCl₃) δ $^1H$ 1.09 (3H, t, $^3J_{HH} = 7.2$ Hz, OCH₂CH₃), 2.27 (3H, s, CH₃), 4.14 (2H, q, $^3J_{HH} = 7.1$ Hz, OCH₂CH₂), 5.65 (1H, dd, $^3J_{HF} = 14.7$ Hz, $^3J_{HF} = 4.8$ Hz, CF₂CHO), 7.04 (2H, d, $^3J_{HH} = 7.9$ Hz, ArH), 7.22 (1H, m, ArH), 7.38 (1H, m, ArH), 7.46 (3H, m, ArH), 8.69 (1H, d, $^3J_{HH} = 7.9$ Hz, ArH); $^{13}$C NMR (100 MHz; CDCl₃) δC 13.7 (CH₃), 21.2 (CH₃), 63.3 (CH₂), 66.4 (C₁), 81.4 (dd, $^2J_{CF} = 31.7$ Hz, $^2J_{CF} = 29.7$ Hz, CH), 112.3 (dd, $^1J_{CF} = 260.1$ Hz, $^1J_{CF} = 255.1$ Hz, CF₃), 123.1 (CH₁), 126.1 (CH), 128.5 (CH), 129.1 (CH), 130.1 (CH), 130.3 (CH), 134.3 (C), 137.2 (C), 137.5 (C), 138.4 (C), 151.8 (C), 162.3 (t, $^2J_{CF} = 32.0$ Hz, CO); $^{19}$F NMR (376 MHz; CDCl₃) δF -121.2 (1F, d, $^2J_{FF} = 259.1$ Hz, CF₃), -112.2 (1F, d, $^2J_{FF} = 259.1$ Hz, CF₃). m/z (ASAP) 470.0182 (MH⁺. C₂₀H₁₇F₂ΙO₃ requires 470.0191, 3 %), 344.1176 ((MH-I)⁺, 100 %).

A very small amount of (Z)-ethyl 2,2-difluoro-2-(3-(iodo(p-tolyl)methylene)-1,3-dihydroisobenzofuran-1-yl)acetate was also observed in the crude $^1$H NMR spectrum.
13. Ethyl 2,2-difluoro-2-(4-iodo-3-(p-tolyl)-1H-isochromen-1-yl)acetate (3.65)

After General method F using dry DCM (30 mL), IPy2BF₄ (0.558 g, 1.5 mmol), HBF₄.Et₂O (0.163 ml, 1.2 mmol) and ethyl 2,2-difluoro-3-hydroxy-3-(2-(p-tolylethynyl)phenyl)propanoate (0.344 g, 1.0 mmol), the crude product (0.555 g) was purified by column chromatography using ethyl acetate/hexane (1/9) to give ethyl 2,2-difluoro-2-(4-iodo-3-(p-tolyl)-1H-isochromen-1-yl)acetate as a yellow oil (turned to purple in air) (0.226 g, 48 %). ¹H NMR (400 MHz; CDCl₃) δ H 1.15 (3H, t, ³JHH = 7.2 Hz, OCH₂CH₃), 2.33 (3H, s, CH₃), 4.20 (2H, q, ³JHH = 7.2 Hz, OCH₂CH₃), 5.67 (1H, dd, ³JHF = 16.4 Hz, ⁴JHF = 6.6 Hz, CF₂CHO), 7.05 (1H, d, ³JHH = 7.7 Hz, ArH), 7.14 (2H, d, ³JHH = 7.9 Hz, ArH), 7.22 (1H, td, ³JHH = 7.5 Hz, ⁴JHH = 1.2 Hz, ArH), 7.36 (1H, td, ³JHH = 7.6 Hz, ⁴JHH = 1.2 Hz, ArH), 7.46 (3H, m, ArH); ¹³C NMR (100 MHz; CDCl₃) δ C 13.8 (CH₃), 21.5 (CH₃), 63.5 (CH₂), 72.8 (CH), 77.2 (t, ²JC= 29.2 Hz, CH), 112.9 (t, ¹JC= 260.5 Hz, CF₂), 121.9 (C), 126.4 (CH), 127.9 (CH), 128.5 (CH), 130.0 (CH), 130.2 (CH), 130.3 (CH), 132.9 (C), 133.4 (C), 134.0 (C), 153.3 (C), 163.3 (t, ²JC= 31.2 Hz, CO); ¹⁹F NMR (376 MHz; CDCl₃) δ F -119.3 (1F, d, ²JFF= 264.6 Hz, CF₂F₂B), -112.3 (1F, d, ²JFF= 264.6 Hz, CF₂F₂B). m/z (ASAP) 470.0185 (MH⁺, C₂₀H₁₇F₂O₃ requires 470.0191, 12 %), 344.1163 ((MH-I)⁺, 100 %).
14. Ethyl 2-(4-iodo-3-phenyl-1H-isochromen-1-yl)acetate (3.66) and (Z)-ethyl 2-(3-(iodo(phenyl)methylene)-1,3-dihydroisobenzofuran-1-yl)acetate (3.67)

After General method G using ethyl 3-hydroxy-3-(2-(phenylethynyl)phenyl)propanoate (0.294 g, 1.0 mmol), I2 (0.761 g, 3.0 mmol), K2CO3 (0.276 g, 2.0 mmol) and dry DCM (30 mL), the crude product (0.391 g) was purified by column chromatography using ethyl acetate/hexane (2/8) to give 2-(4-iodo-3-phenyl-1H-isochromen-1-yl)acetate as a yellow oil (turned to purple in air) (0.023 g, 6 %). 1H NMR (400 MHz; CDCl3) δH 1.20 (3H, t, JHH = 7.0 Hz, OCH2CH3), 2.74 (1H, dd, JHH = 15.3 Hz, JHH = 4.6 Hz, CH2CO), 3.12 (1H, dd, JHH = 15.4 Hz, JHH = 9.2 Hz, CH2CHO), 4.12 (2H, m, OCH2CH3), 5.71 (1H, dd, JHH = 9.2 Hz, JHH = 4.6 Hz, CH2CHO), 6.96 (1H, t, JHH = 7.2 Hz, ArH), 7.18 (1H, dt, JHH = 7.5 Hz, JHH = 1.1 Hz, ArH), 7.31 (4H, m, ArH), 7.44 (1H, dd, JHH = 7.8 Hz, JHH = 0.9 Hz, ArH), 7.56 (2H, m, ArH); 13C NMR (100 MHz; CDCl3) δC 14.2 (CH3), 39.2 (CH2), 61.0 (CH2), 72.6 (CI), 75.2 (CH), 123.2 (CH), 127.8 (CH), 128.0 (CH), 128.8 (CH), 129.5 (CH), 129.6 (CH), 130.4 (CH), 130.7 (C), 132.4 (C), 136.6 (C), 153.7 (C), 170.2 (CO); m/z (ASAP) 420.0205 (MH+). C19H17IO3 requires 420.0222, 49 %), 295.1168 ((MH-I)+, 100 %).

The second product, (Z)-ethyl 2-(3-(iodo(phenyl)methylene)-1,3-dihydroisobenzofuran-1-yl)acetate was isolated, as a yellow oil (turned to purple in air) (0.067 g, 16 %). 1H NMR (400 MHz; CDCl3) δH 1.24 (3H, t, JHH = 7.2 Hz, CH2CH3), 2.77 (1H, dd, JHH = 15.6 Hz, JHH = 6.1 Hz, CH2CO), 2.89 (1H, dd, JHH = 15.7 Hz, JHH = 6.9 Hz, CH2CHO), 4.17 (2H, m, CH2CH3), 5.90 (1H, t, JHH = 6.5 Hz, CH2CHO), 6.36 (1H, d, JHH = 7.9 Hz, ArH), 6.92 (1H, m, ArH), 7.16 (2H, m, ArH), 7.31 (5H, m, ArH); 13C NMR (100 MHz; CDCl3) δC 14.3 (CH3), 41.1 (CH2), 61.0 (CH2), 64.1 (Cl), 80.2 (CH), 121.6 (CH), 123.2 (CH), 128.3 (CH), 128.4
(CH), 129.0 (CH), 129.1 (CH), 130.5 (CH), 130.7 (C), 140.8 (C), 144.4 (C), 155.7 (C), 169.9 (CO); m/z (ASAP) 420.0251 (MH⁺. C₁₀H₁₇IO₃ requires 420.0222, 5 %), 294.1202 ((MH-I)+, 100 %).

15. Ethyl 2-(4-iodo-3-(p-tolyl)-1H-isochromen-1-yl)acetate (3.68) and (Z)-ethyl 2-(3-(iodo(o-tolyl)methylene)-1,3-dihydroisobenzofuran-1-yl)acetate (3.69)

After General method G using ethyl 3-hydroxy-3-(2-(p-tolylethynyl)phenyl)propanoate (0.308 g, 1.0 mmol), I₂ (0.761 g, 3.0 mmol), K₂CO₃ (0.276 g, 2.0 mmol) and dry DCM (30 mL), the crude product (0.429 g) was purified by column chromatography using ethyl acetate/hexane (2/8) to give ethyl 2-(4-iodo-3-(p-tolyl)-1H-isochromen-1-yl)acetate as a yellow oil (turned to purple in air) (0.199 g, 46 %). ¹H NMR (400 MHz; CDCl₃) δH 1.20 (3H, t, ³JHH = 7.1 Hz, OCH₂CH₃), 2.31 (3H, s, CH₃), 2.73 (1H, dd, ²JHH = 15.3 Hz, ³JHH = 4.8 Hz, CH₂CO), 3.09 (1H, dd, ²JHH = 15.5 Hz, ³JHH = 9.1 Hz, CH₂CHO), 4.14 (2H, m, OCH₂CH₃), 5.68 (1H, dd, ³JHH = 9.2 Hz, ³JHH = 4.6 Hz, CH₂CHO), 6.93 (1H, dd, ³JHH = 7.4 Hz, ⁴JHH = 0.5 Hz, ArH), 7.12 (2H, d, ³JHH = 7.9 Hz, ArH), 7.16 (1H, td, ³JHH = 7.5 Hz, ⁴JHH = 1.2 Hz, ArH), 7.29 (1H, td, ³JHH = 7.7 Hz, ⁴JHH = 1.2 Hz, ArH), 7.42 (1H, dd, ³JHH = 7.8 Hz, ⁴JHH = 1.0 Hz, ArH), 7.46 (2H, dt, ³JHH = 8.1 Hz, ⁴JHH = 1.6 Hz, ArH); ¹³C NMR (100 MHz; CDCl₃) δC 14.2 (CH₃), 21.5 (CH₃), 39.1 (CH₂), 61.0 (CH₂), 72.1 (Cl), 75.1 (CH), 123.2 (CH), 127.8 (CH), 128.1 (C), 128.5 (CH), 128.8 (CH), 129.5 (CH), 130.4 (CH), 132.6 (C), 133.6 (C), 139.7 (C), 153.7 (C), 170.2 (CO); m/z (ASAP) 435.0133 (MH⁺. C₂₀H₂₀IO₃ requires 435.0121, 49 %), 309.1312 ((MH-I)+, 100 %).
A mixture of ethyl 2-(4-iodo-3-(p-tolyl)-1H-isochromen-1-yl)acetate with (Z)-ethyl 2-(3-iodo(o-tolyl)methylene)-1,3-dihydroisobenzofuran-1-yl)acetate was also obtained as a yellow oil (turned to purple in air) (0.052 g, 12 %). Since it was an inseparable mixture, only some of the data of the second product could be obtained, $^1$H NMR (400 MHz; CDCl$_3$) $\delta$H 1.24 (3H, t, $^3$J$_{HH} = 7.1$ Hz, CH$_2$CH$_3$), 2.33 (3H, s, CH$_3$), 2.77 (1H, dd, $^2$J$_{HH} = 15.8$ Hz, $^3$J$_{HH} = 6.3$ Hz, CH$_2$CO), 2.88 (1H, dd, $^2$J$_{HH} = 15.6$ Hz, $^3$J$_{HH} = 6.9$ Hz, CH$_2$CHO), 4.16 (2H, m, CH$_2$CH$_3$), 5.89 (1H, t, $^3$J$_{HH} = 6.3$ Hz, CH$_2$CHO), 6.43 (1H, d, $^1$J$_{HH} = 8.0$ Hz, ArH), 7.18 (7H, m, ArH), $^{13}$C NMR (100 MHz; CDCl$_3$) $\delta$C 14.1 (CH$_3$), 21.4 (CH$_3$), 41.1 (CH$_2$), 61.0 (CH$_2$), 64.5 (Cl), 80.1 (CH), 121.6 (CH), 123.2 (CH), 137.9 (C), 138.3 (C), 144.3 (C), 155.5 (C), 169.9 (CO); m/z (ASAP) 435.0241 (MH$^+$, C$_{20}$H$_{20}$I$_3$ requires 435.0222, 5 %), 309.1102 ((MH-I)$^+$, 100 %).

16. 4-Iodo-3-phenyl-1H-isochromen-1-one (3.70) and (E)-3-[iodo(phenyl)methylidene]-1,3-dihydro-2-benzofuran-1-one (3.71)

After General method G using 2-(phenylethynyl)benzoic acid (0.222 g, 1.0 mmol), I$_2$ (0.761 g, 3.0 mmol), K$_2$CO$_3$ (0.276 g, 2.0 mmol) and dry DCM (30 mL), the crude product (0.318 g) was purified by column chromatography using ethyl acetate/petroleum ether (40-60) (1/9) to give pure 4-iodo-3-phenyl-1H-isochromen-1-one as a brown oil (0.134 g, 39 %). $^1$H NMR (400 MHz; CDCl$_3$) $\delta$H 7.48 (3H, m, ArH), 7.59 (1H, td, $^3$J$_{HH} = 7.6$ Hz, $^4$J$_{HH} = 1.2$ Hz, ArH), 7.70 (2H, m, ArH), 7.83 (1H, td, $^3$J$_{HH} = 7.2$ Hz, $^4$J$_{HH} = 1.4$ Hz, ArH), 7.90 (1H, dd, $^3$J$_{HH} = 8.2$ Hz, $^4$J$_{HH} = 0.6$ Hz, ArH), 8.31 (1H, dd, $^3$J$_{HH} = 7.9$ Hz, $^4$J$_{HH} = 0.9$ Hz, ArH); $^{13}$C NMR (100 MHz; CDCl$_3$) $\delta$C 77.1 (Cl), 120.3 (C), 128.1 (CH), 129.3 (CH), 129.8 (CH), 130.0 (CH), 130.2 (CH), 131.6 (CH), 135.3 (C), 135.7 (CH), 138.2 (C), 154.9 (C), 161.6 (CO). m/z (ASAP) 348.9734 (MH$^+$, C$_{15}$H$_{10}$O$_2$I requires 348.9726, 100 %).
(E)-3-[iodo(phenyl)methylidene]-1,3-dihydro-2-benzofuran-1-one was obtained as a brown solid (0.056 g, 16 %). Crystals suitable for X-ray crystallography were grown by slow evaporation of a toluene solution containing the product. $^1$H NMR (400 MHz; CDCl$_3$) $\delta_H$

7.23 (1H, tt, $^3J_{HH} = 7.4$ Hz, $^4J_{HH} = 1.3$ Hz, Ar$H$), 7.32 (2H, m, Ar$H$), 7.48 (2H, m, Ar$H$), 7.58 (1H, td, $^3J_{HH} = 7.5$ Hz, $^4J_{HH} = 0.8$ Hz, Ar$H$), 7.75 (1H, td, $^3J_{HH} = 7.7$ Hz, $^4J_{HH} = 1.3$ Hz, Ar$H$), 7.89 (1H, dt, $^3J_{HH} = 7.6$ Hz, $^4J_{HH} = 0.9$ Hz, Ar$H$), 8.87 (1H, dt, $^3J_{HH} = 8.0$ Hz, $^4J_{HH} = 0.7$ Hz, Ar$H$); $^{13}$C NMR (100 MHz; CDCl$_3$) $\delta_C$ 80.3 (Cl), 124.9 (CH), 125.9 (CH), 126.2 (C), 128.1 (CH), 129.0 (CH), 130.1 (CH), 130.8 (CH), 134.3 (CH), 138.5 (C), 140.1 (C), 144.4 (C), 165.5 (CO). m/z (ASAP) 348.9727 (MH$^+$. C$_{15}$H$_{10}$O$_2$I requires 348.9726, 100 %).

After **General method F** using dry DCM (15 mL), IPy$_2$BF$_4$ (0.558 g, 1.5 mmol), HBF$_4$Et$_2$O (0.163 ml, 1.2 mmol) and (2-(Phenylethynyl)benzoic acid (0.222 g, 1.0 mmol)), the crude product (0.372 g) was purified by column chromatography using ethyl acetate/petroleum ether (40-60) (1/9) to give pure 4-iodo-3-phenyl-1$H$-isochromen-1-one as a brown oil (turned to purple in air) (0.265 g, 76 %).

17. (Z)-3-(iodo(phenyl)methylene)-1,1-dimethyl-2,3-dihydro-1$H$-indene (3.72)

After **General method G** using 2-(2-(phenylethynyl)phenyl)propan-2-ol (0.236 g, 1 mmol), I$_2$ (0.761 g, 3.0 mmol), K$_2$CO$_3$ (0.276 g, 2.0 mmol) and dry DCM (30 mL), the crude product (0.388 g) was purified by column chromatography using ethyl acetate/petroleum ether (40-60) (1/9) to give pure (Z)-3-(iodo(phenyl)methylene)-1,1-dimethyl-2,3-dihydro-1$H$-indene as a brown oil (0.211 g, 58 %). $^1$H NMR (400 MHz; CDCl$_3$) $\delta_H$ 1.66 (6H, s, CH$_3$), 6.40-6.96 (2H, m, Ar$H$), 7.14 (1H, dt, $^3J_{HH} = 7.6$ Hz, $^4J_{HH} = 0.8$ Hz, Ar$H$), 7.23 (1H, dd, $^3J_{HH} = 7.4$ Hz, $^4J_{HH} = 0.8$ Hz, Ar$H$), 7.38 (5H, m, Ar$H$); $^{13}$C NMR (100 MHz; CDCl$_3$) $\delta_C$ 28.4 (CH$_3$), 63.1 (Cl), 87.4 (C), 120.6 (CH), 121.9 (CH), 123.2 (CH), 127.6 (CH), 128.2 (CH), 129.0 (CH), 129.9
(C), 130.7 (CH), 141.2 (C), 150.6 (C), 155.1 (C). Product decomposed quickly, so the mass spectrum could not be recorded.

After **General method F** using dry DCM (15 mL), IPy2BF4 (0.558 g, 1.5 mmol), HBF4.Et2O (0.163 ml, 1.2 mmol) and 2-(2-(phenylethynyl)phenyl)propan-2-ol (0.236 g, 1 mmol), the crude product (0.505 g) was purified by column chromatography using ethyl acetate/petroleum ether (40-60) (1/19) to give the pure (Z)-3-(iodo(phenyl)methylene)-1,1-dimethyl-2,3-dihydro-1H-indene as a brown oil (0.206 g, 57%).

18. (Z)-1,1-Diethyl-3-(iodo(phenyl)methylene)-2,3-dihydro-1H-indene (3.73)

![Chemical structure](attachment:chemical_structure.png)

After **General method F** using dry DCM (30 mL), IPy2BF4 (0.558 g, 1.5 mmol), HBF4.Et2O (0.163 ml, 1.2 mmol) and 3-(2-(phenylethynyl)phenyl)pentan-3-ol (0.264 g, 1.0 mmol), the crude product (0.437 g) was purified by column chromatography using ethyl acetate/petroleum ether (40-60) (1/9) to give (Z)-1,1-diethyl-3-(iodo(phenyl)methylene)-2,3-dihydro-1H-indene as a brown oil (0.123 g, 32%). The characterisation data was in agreement with the literature. 5.22 1H NMR (400 MHz; CDCl3) δH 0.77 (6H, t, 3JHH = 7.3 Hz, CH3), 1.86 (2H, ABt, 3JHH = 7.3 Hz, CH2), 2.07 (2H, ABt, 3JHH = 7.3 Hz, CH2), 6.42 (1H, d, 3JHH = 7.9 Hz, ArH), 6.96 (1H, t, 3JHH = 7.3 Hz, ArH), 7.05 (1H, d, 3JHH = 7.6 Hz, ArH), 7.23 (1H, t, 3JHH = 7.6 Hz, ArH), 7.38 (5H, m, ArH); 13C NMR (100 MHz; CDCl3) δC 7.7 (CH3), 32.6 (CH2), 32.7 (CH2), 65.9 (Cl), 92.7 (C), 121.1 (CH), 122.9 (CH), 127.5 (CH), 128.1 (CH), 128.8 (CH), 128.9 (CH), 130.8 (CH), 132.0 (C), 141.3 (C), 147.5 (C). Product decomposed quickly, so the mass spectrum could not be recorded.

After **General method G** using 3-(2-(phenylethynyl)phenyl)pentan-3-ol (0.264 g, 1 mmol), I2 (0.761 g, 3.0 mmol), K2CO3 (0.276 g, 2.0 mmol) and dry DCM (30 mL), the crude
Product (0.352 g) was purified by column chromatography using ethyl acetate/petroleum ether (40-60) (1/19) to give pure (Z)-1,1-diethyl-3-(iodo(phenyl)methylene)-2,3-dihydro-1H-indene as a brown oil (0.081 g, 21%).

19. 1-[(Iodo(phenyl)methylidene)-2-(4-methylbenzenesulfonyl)-3-(trifluoromethyl)-2,3-dihydro-1H-isoindole (3.74)

After General method G using 4-methyl-N-(2,2,2-trifluoro-1-(2-(phenylethynyl)phenyl)ethyl)benzene-sulfonamide (0.430 g, 1 mmol), I₂ (0.761 g, 3.0 mmol), K₂CO₃ (0.276 g, 2.0 mmol) and dry DCM (30 mL), the crude product (0.534 g) was washed with petroleum ether (40-60) to give pure 1-[(ido(phenyl)methylidene)-2-(4-methylbenzenesulfonyl)-3-(trifluoromethyl)-2,3-dihydro-1H-isoindole as a brown solid (0.401 g, 72 %). mp 184-186 °C; ¹H NMR (400 MHz; CDCl₃) δ 2.28 (3H, s, CH₃), 5.32 (1H, q, JHF = 6.8 Hz, CHCF₃), 7.01 (2H, d, JHH = 8.3 Hz, ArH), 7.19 (2H, d, JHH = 8.3 Hz, ArH), 7.26 (2H, m, ArH), 7.35-7.45 (4H, m, ArH), 7.56 (2H, dt, JHH = 7.3 Hz, JHF = 1.3 Hz, ArH), 8.54 (1H, d, JHH = 7.9 Hz, ArH); ¹³C NMR (100 MHz; CDCl₃) δC 21.5 (CH₃), 64.5 (q, JCF = 32.8 Hz, CHCF₃), 93.4 (CI), 110.0 (C), 121.0 (t, JCF = 280.5 Hz, CF₃), 124.1 (CH), 125.6 (CH), 127.3 (CH), 127.9 (CH), 128.2 (CH), 128.7 (CH), 129.2 (CH), 129.5 (CH), 130.2 (CH), 133.4 (C), 134.5 (C), 137.8 (C), 144.5 (C), 144.7 (C). ¹⁹F NMR (376 MHz; CDCl₃) δF -73.6 (s, CF3). m/z (ASAP) 556.0041 (MH⁺). C₂₃H₁₈NO₂F₃S requires 556.0055, 100 %.

Based on the General method F, reacting IPy₂BF₄ with 4-methyl-N-(2,2,2-trifluoro-1-(2-(phenylethynyl)phenyl)ethyl)benzenesulfonamide gave only the starting material back.
5.4 Experimental for Chapter 4

1. \((E)-N\text{-}\text{tert}\text{-}\text{Butyl}\text{-}1\text{-}\text{(2\text{-}(\text{phenylethynyl})\text{phenyl})\text{methanimine}}\) (4.33)

\[\text{N} \quad \text{tBu}\]

2-(Phenylethynyl)benzaldehyde (0.795 g, 3.85 mmol), \(H_2O\) (0.96 mL, 0.25 mL/mmol) and \text{tert}-butylamine (1.1 mL, 11.55 mmol) were charged into a round bottom flask and stirred overnight. \text{tert}-butylamine was removed via vacuum and the mixture was extracted with diethyl ether (3 x 15 mL) and washed with \(H_2O\) (20 mL). The combined organic layers were dried over \(\text{MgSO}_4\) (anhydrous), and the solvent was removed to give \((E)-N\text{-}\text{tert}-\text{butyl}\text{-}1\text{-}(\text{2\text{-}(\text{phenylethynyl})\text{phenyl})\text{methanimine}}\) as a brown solid (0.969 g, 96 %). The characterisation data was in agreement with the literature. \(^{5,17}\) Crystals suitable for X-ray crystallography were grown from hot toluene. \(m_p\) 53-55 °C (Lit., \(^{5,17}\) 54-56 °C). \(^1\text{H NMR}\) (400 MHz; \(\text{CDCl}_3\)) \(\delta H\) 1.34 (9H, s, \(\text{CH}_3\)), 7.37 (5H, m, \(\text{ArH}\)), 7.54 (3H, m, \(\text{ArH}\)), 8.07 (1H, dt, \(3J_{\text{HH}} = 9.2\) Hz, \(4J_{\text{HH}}\) = 3.8 Hz, \(\text{ArH}\)), 8.93 (1H, s, \(\text{HC}=-\text{N}\)); \(^{13}\text{C NMR}\) (100 MHz; \(\text{CDCl}_3\)) \(\delta C\) 29.8 (\(\text{CH}_3\)), 57.8 (C), 86.7 (C), 94.8 (C), 123.1 (C), 123.9 (C), 126.0 (CH), 128.5 (CH), 128.5 (CH), 128.6 (CH), 129.7 (CH), 131.5 (CH), 132.2 (CH), 137.8 (C), 154.2 (C=\text{N}). \(m/z\) (ASAP) 262.1586 (MH\(^+\)). \(\text{C}_{19}\text{H}_{20}\text{N}\) requires 262.1596, 100 %.

\textbf{Synthesis of heterocyclic products via palladium cyclisation}

\textbf{General method H:} The alkynol substrate (1.0 eq.), \(\text{PdCl}_2(\text{MeCN})_2\) (0.1 eq.) and \(\text{Et}_3\text{N}\) were charged into a three-necked flask with dry THF. The mixture was stirred at RT under nitrogen overnight. The mixture was washed with brine (20 mL) and extracted with diethyl ether (3 x 15 mL). The combined organic layers were dried over \(\text{MgSO}_4\) (anhydrous), and the solvent was removed \textit{in vacuo} to give the crude product.
1. 3-Phenyl-1H-isochromen-1-one (4.25)

After General method H using 2-(phenylethynyl)benzoic acid (0.222 g, 1 mmol), PdCl₂(MeCN)₂ (0.025 g, 0.1 mmol), Et₃N (0.5 mL) and dry THF (20 mL), the crude product (0.146 g) was purified by column chromatography using ethyl acetate/petroleum ether (40-60) (1/9) to give pure 3-phenyl-1H-isochromen-1-one as a colourless oil (0.0756 g, 34 %). The characterisation data was in agreement with the literature. ¹H NMR (400 MHz; CDCl₃) δH 6.95 (1H, s, OCC₃), 7.47 (5H, m, ArH), 7.72 (1H, td, ³JHH = 7.6 Hz, ⁴JHH = 1.4 Hz, ArH), 7.88 (2H, dt, ³JHH = 6.6 Hz, ⁴JHH = 1.7 Hz, ArH), 8.31 (1H, dd, ³JHH = 8.0 Hz, ⁴JHH = 0.8 Hz, ArH); ¹³C NMR (100 MHz; CDCl₃) δC 101.8 (CH), 120.6 (C), 125.3 (CH), 126.0 (CH), 128.2 (CH), 128.9 (CH), 129.7 (CH), 130.0 (CH), 132.0 (C), 134.9 (CH), 137.6 (C), 153.7 (C), 162.3 (CO). m/z (ASAP) 223.0771 (MH⁺). C₁₅H₁₁O₂ requires 223.0759, 100 %.

2. (Z)-1,1-Dimethyl-3-(phenylmethylidene)-1,3-dihydro-2-benzofuran (4.26)

After General method H using 2-(2-(phenylethynyl)phenyl)propan-2-ol (0.236 g, 1 mmol), PdCl₂(MeCN)₂ (0.025 g, 0.1 mmol), Et₃N (0.5 mL) and dry THF (20 mL) to give the pure (Z)-1,1-dimethyl-3-(phenylmethylidene)-1,3-dihydro-2-benzofuran as a colourless oil (0.244g, 99 %). The characterisation data was in agreement with the literature. ¹H NMR (400 MHz; CDCl₃) δH 1.65 (6H, s, CH₃), 5.89 (1H, s, OCCC), 7.13 (1H, tt, ³JHH = 7.4 Hz, ⁴JHH = 1.2 Hz, ArH), 7.21 (1H, m, ArH), 7.33 (4H, m, ArH), 7.53 (1H, m, ArH), 7.75 (2H, dd, ³JHH = 8.5 Hz, ⁴JHH = 1.3 Hz, ArH); ¹³C NMR (100 MHz; CDCl₃) δC 28.5 (CH₃), 89.1 (C), 95.8 (CH), 120.0 (CH), 120.5 (CH), 125.1 (CH), 127.8 (CH), 128.0 (CH), 128.3 (CH), 128.8 (CH), 134.1 (C), 192
136.8 (C), 147.5 (C), 154.3 (C). m/z (ASAP) 235.1130 (MH⁺. C₁₇H₁₇O requires 235.1133, 20 %).

3. (Z)-1-(Phenylmethylidene)-3-(trifluoromethyl)-1,3-dihydro-2-benzofuran (4.27)

After General method H using 2,2,2-trifluoro-1-(2-(phenylethynyl)phenyl)ethan-1-ol (0.280 g, 1 mmol), PdCl₂(MeCN)₂ (0.025 g, 0.1 mmol), Et₃N (0.5 mL) and dry THF (20 mL), the crude product (0.284 g) was purified by column chromatography using petroleum ether (40-60) /DCM (1/2) to give (Z)-1-(phenylmethylidene)-3-(trifluoromethyl)-1,3-dihydro-2-benzofuran as a brown oil (0.191 g, 67 %). The characterisation data was in agreement with the literature. ¹H NMR (400 MHz; CDCl₃) δH 5.85 (1H, q, ³JₜH = 5.9 Hz, C₅H₇CF₃), 6.04 (1H, s, OCCH), 7.20 (1H, tt, ³JₜH = 7.4 Hz, ⁴JₜH = 1.1 Hz, ArH), 7.38 (3H, m, ArH), 7.48 (2H, d, ³JₜH = 6.8 Hz, ArH), 7.61 (1H, d, ³JₜH = 8.7 Hz, ArH), 7.73 (2H, d, ³JₜH = 8.2 Hz, ArH); ¹³C NMR (100 MHz; CDCl₃) δC 81.5 (q, ²JCF = 34.0 Hz CHCF₃), 99.1 (CH), 120.1 (CH), 122.9 (CH), 123.0 (q, ¹JₜCF = 280.2 Hz CF₃), 126.3 (CH), 128.4 (CH), 128.5 (CH), 129.2 (CH), 130.2 (CH), 133.0 (C), 135.1 (C), 135.7 (C), 153.9 (C); ¹⁹F NMR (376 MHz; CDCl₃) δF -77.9 (s, CF₃). m/z (ASAP) 277.0837 (MH⁺. C₁₆H₁₂F₃O requires 277.0840, 100 %).
4. Ethyl 2,2-difluoro-2-[(Z)-3-(phenylmethylidene)-1,3-dihydro-2-benzofuran-1-yl]acetate (4.28)

After **General method H** using ethyl 2,2-difluoro-3-hydroxy-3-(2-(phenylethynyl)-phenyl)propanoate (0.338 g, 1 mmol), PdCl$_2$(MeCN)$_2$ (0.025 g, 0.1 mmol), Et$_3$N (0.5 mL) and dry THF (20 mL), the crude product (0.223 g) was purified by column chromatography using ethyl acetate/petroleum ether (40-60) (1/9) to give ethyl 2,2-difluoro-2-[(Z)-3-(phenylmethylidene)-1,3-dihydro-2-benzofuran-1-yl]acetate as a brown oil (0.0799 g, 24%).

$^1$H NMR (400 MHz; CDCl$_3$) $\delta$H 1.27 (3H, t, $^3$J$_{HH}$ = 7.1 Hz, CH$_2$CH$_3$), 4.33 (2H, q, $^3$J$_{HH}$ = 7.1 Hz, CH$_2$CH$_3$), 6.00 (1H, dd, $^3$J$_{HF}$ = 13.7 Hz, $^3$J$_{HF}$ = 5.5 Hz, CHF$_2$), 6.00 (1H, s, OCCCH), 7.17 (1H, tt, $^3$J$_{HH}$ = 7.5 Hz, $^4$J$_{HH}$ = 1.1 Hz, ArH), 7.38-7.50 (5H, m, ArH), 7.58 (1H, d, $^3$J$_{HH}$ = 7.6 Hz, ArH), 7.66 (2H, d, $^3$J$_{HH}$ = 7.2 Hz, ArH); $^{13}$C NMR (100 MHz; CDCl$_3$) $\delta$C 13.8 (CH$_3$), 63.3 (CH$_2$), 83.3 (t, $^2$J$_{CF}$ = 30.5 Hz, CHF$_2$), 98.5 (CH), 113.2 (t, $^1$J$_{CF}$ = 256.6 Hz, CF$_2$), 120.0 (CH), 123.2 (CH), 126.1 (CH), 128.3 (CH), 128.4 (CH), 129.1 (CH), 129.9 (CH), 133.8 (C), 135.3 (C), 135.8 (C), 154.1 (C), 162.4 (CO); $^{19}$F NMR (376 MHz; CDCl$_3$) $\delta$F -121.0 (1F, d, $^2$J$_{FF}$ = 263.9 Hz, CF$_3$F$\beta$), -112.6 (1F, d, $^2$J$_{FF}$ = 263.9 Hz, CF$_3$F$\alpha$). m/z (ASAP) 331.3309 (MH$^+$. C$_{19}$H$_{17}$F$_2$O$_3$ requires 331.3311, 100 %).
5. Ethyl 2,2-difluoro-2-[(Z)-3-[4-methylphenyl)methylidene]-1,3-dihydro-2-benzofuran-1-yl]acetate (4.29)

After **General method H** using ethyl 2,2-difluoro-3-hydroxy-3-(2-(p-tolylethynyl)phenyl)propanoate (0.344 g, 1 mmol), PdCl₂(MeCN)₂ (0.025 g, 0.1 mmol), Et₃N (0.5 mL) and dry THF (20 mL), the crude product (0.192 g) was purified by column chromatography using ethyl acetate/petroleum ether (40-60) (1/9) to give ethyl 2,2-difluoro-2-[(Z)-3-[4-methylphenyl)methylidene]-1,3-dihydro-2-benzofuran-1-yl]acetate as a brown oil (0.030 g, 9%).

The product could not be separated pure by column chromatography. The NMR spectra are not clean, however, significant peaks can be identified.

$^1$H NMR (400 MHz; CDCl₃) $\delta$H 1.29 (3H, t, $^3$J₃H₂H = 6.9 Hz, CH₂CH₃), 2.38 (3H, s, CH₃), 4.33 (2H, q, $^3$J₃H₂H = 7.1 Hz, CH₂CH₃), 5.98 (1H, s, OCC), 5.99 (1H, dd, $^3$JHF = 13.6 Hz, $^3$JHF = 5.6 Hz, CHCF₂); $^{13}$C NMR (100 MHz; CDCl₃) $\delta$C 13.8 (CH₃), 21.3 (CH₃), 63.3 (CH₂), 83.2 (t, $^2$JCF = 30.4 Hz CHCF₂), 98.5 (CH), 111.7 (t, $^1$JCF = 256.6 Hz, CF₂), 167.7 (CO); $^{19}$F NMR (376 MHz; CDCl₃) $\delta$F -121.0 (1F, d, $^2$JFF = 265.5 Hz, CF₂F), -112.6 (1F, d, $^2$JFF = 265.5 Hz, CF₃F₈).
6. 2-(4-Methylbenzenesulfonyl)-(Z)-1-(phenylmethylidene)-3-(trifluoromethyl)-2,3-dihydro-1H-isoindole (4.30)

After **General method H** using 4-methyl-N-(2,2,2-trifluoro-1-(2-(phenylethynyl)phenyl)ethyl)benzenesulfonamide (0.128 g, 0.3 mmol), PdCl₂(MeCN)₂ (0.0075 g, 0.03 mmol), Et₃N (0.15 mL) and dry THF (20 mL), the crude product (0.125 g) was washed with petroleum ether (40-60) to give pure 3-phenyl-2-tosyl-1-(trifluoromethyl)-1,2-dihydroisoquinoline as a brown solid (0.0635 g, 49%). mp 154-156 °C; ¹H NMR (400 MHz; CDCl₃) δH 2.30 (3H, s, CH₃), 5.61 (1H, q, ³JHF = 7.4 Hz, CHCF₃), 5.69 (1H, s, CH), 7.06 (2H, d, ³JHH = 7.9 Hz, ArH), 7.22 (1H, m, ArH), 7.26 (3H, m, ArH), 7.42 (3H, m, ArH), 7.59 (4H, m, ArH); ¹³C NMR (100 MHz; CDCl₃) δC 21.4 (CH₃), 57.1 (q, ²JCF = 32.8 Hz, CHCF₃), 95.4 (CH), 122.7 (t, ¹JCF = 280.5 Hz, CF₃), 124.1 (C), 127.1 (CH), 127.6 (CH), 128.6 (CH), 128.7 (CH), 128.9 (CH), 129.0 (CH), 129.4 (CH), 131.7 (CH), 132.6 (CH), 132.9 (C), 133.3 (C), 136.6 (C), 140.7 (C), 143.6 (C). ¹⁹F NMR (376 MHz; CDCl₃) δF -73.7 (s, CF₃). m/z (ASAP) 430.1100 (MH⁺). C₂₃H₁₉NSF₃O₂ requires 430.1089, 100 %).

**Synthesis of heterocyclic products via fluorocyclisation**

**General method I:** The alcohol/imine substrate (1.0 eq.), AgNO₃ (0.2 eq.), NFSi (1.5 eq.), Li₂CO₃ (1.0 eq.) and dry DMA were charged into a three-necked flask and stirred under nitrogen overnight. The mixture was extracted with diethyl ether (3 x 15 mL) and washed with H₂O (20 mL), the combined organic layer solvent was removed in vacuo and a saturated solution of LiCl (15 mL) was added. After stirring the mixture for 5 min, it was extracted with diethyl ether (3 x 15 mL). The combined organic layers were dried over MgSO₄ (anhydrous), and the solvent was removed in vacuo to give the crude product.
General method J: The alcohol/imine substrate (1.0 eq.), AgNO₃ (0.2 eq.), NFSi (3.0 eq.), Li₂CO₃ (1.0 eq.) and dry DMA were charged into a three-necked flask and stirred under nitrogen overnight. The mixture was extracted with diethyl ether (3 x 15 mL) and washed with H₂O (20 mL), the combined organic layer solvent was removed in vacuo and a saturated solution of LiCl (15 mL) was added. After stirring the mixture for 5 min, it was extracted with diethyl ether (3 x 15 mL). The combined organic layers were dried over MgSO₄ (anhydrous), and the solvent was removed in vacuo to give the crude product.

1. 4-Fluoro-3-phenylisoquinoline (4.34)

After General method I using (E)-N-tert-butyl-1-(2-(phenylethynyl)phenyl)methanimine (0.261 g, 1.0 mmol), AgNO₃ (0.035 g, 0.2 mmol), NFSi (0.48 g, 1.5 mmol), Li₂CO₃ (0.075 g, 1.0 mmol) and dry DMA (15 mL), the crude product (0.403 g) was purified by column chromatography using diethyl ether/petroleum ether (40-60) (2/8) to give pure 4-fluoro-3-phenylisoquinoline as a brown solid (0.152 g, 68 %). The characterisation data was in agreement with the literature. Crystals suitable for X-ray crystallography were grown by slow evaporation of a petroleum ether (40-60) solution containing the product. mp 64-68 °C (Lit., 64-68 °C); ¹H NMR (400 MHz; CDCl₃) δH 7.42 (1H, tt, 3JHH = 7.4 Hz, 4JHH = 2.0 Hz, ArH), 7.52 (2H, tt, 3JHH = 7.4 Hz, 4JHH = 1.7 Hz, ArH), 7.61 (1H, td, 3JHH = 7.6 Hz, 4JHH = 1.1 Hz, ArH), 7.74 (1H, td, 3JHH = 7.7 Hz, 4JHH = 1.0 Hz, ArH), 7.98 (1H, dt, 3JHH = 8.4 Hz, 4JHH = 1.1 Hz, ArH), 8.10 (2H, m, ArH), 8.13 (1H, dd, 3JHH = 8.5 Hz, 4JHH = 0.8 Hz, ArH), 9.14 (1H, s, HC=N); ¹³C NMR (100 MHz; CDCl₃) δC 120.0 (d, 4JCF = 4.8 Hz, CH), 127.0 (CH), 127.4 (d, 2JCF = 16.2 Hz, C), 127.9 (CH), 128.5 (CH), 128.6 (CH), 129.0 (d, 3JCF = 6.4 Hz, CH), 129.5 (C), 130.7 (CH), 135.8 (d, 3JCF = 4.7 Hz, C), 136.7 (d, 2JCF = 9.4 Hz, C), 147.7 (d, 4JCF = 4.9 Hz, CH), 152.4 (d, 1JCF = 264.6 Hz, CF). ¹⁹F NMR (376 MHz; CDCl₃) δF -137.7 (s, CF). m/z (ASAP) 224.0865 (MH⁺. C₁₅H₁₁FN requires 224.0876, 100 %).
2. 1-[Anti-fluoro(phenyl)methyl]-3,3-dimethyl-1,3-dihydro-2-benzofuran-1-ol (4.44a) and 1-[syn-fluoro(phenyl)methyl]-3,3-dimethyl-1,3-dihydro-2-benzofuran-1-ol (4.44b) isomers

After General method I using (2-(2-(phenylethynyl)phenyl)propan-2-ol (0.473 g, 2.0 mmol), AgNO₃ (0.07 g, 0.4 mmol), NFSi (0.96 g, 3.0 mmol), Li₂CO₃ (0.15 g, 2.0 mmol) and dry DMA (15 mL), the crude product (0.542 g) was purified by column chromatography using ethyl acetate/petroleum ether (40-60) (1/9) to give 1-[(R)-fluoro(phenyl)methyl]-3,3-dimethyl-1,3-dihydro-2-benzofuran-1-ol and 1-[(S)-fluoro(phenyl)methyl]-3,3-dimethyl-1,3-dihydro-2-benzofuran-1-ol isomers as a brown oil (0.285 g, 52%).

Since two diastereomers are formed, there are two sets of peaks in the ¹H, ¹⁹F and ¹³C NMR spectra. ¹H NMR (400 MHz; CDCl₃) δH 1.28 (3H, s, CH₃), 1.29 (3H, s, CH₃), 1.55 (6H, s, CH₃), 2.88 (1H, br s, OH), 3.24 (1H, br s, OH), 5.63 (1H, d, 2JHF = 45.3 Hz, CHF), 5.64 (1H, d, 2JHF = 45.3 Hz, CHF), 7.10 (2H, m, ArH), 7.32 (8H, m, ArH), 7.40 (8H, m, ArH), 7.48 (2H, m, ArH); ¹³C NMR (100 MHz; CDCl₃) δC 28.3 (CH₃), 28.3 (CH₃), 30.9 (CH₃), 31.0 (CH₃), 86.5 (C), 86.6 (C), 94.3 (d, 1JCF = 180.9 Hz, CHF), 96.2 (d, 1JCF = 180.9 Hz, CHF), 105.8 (d, 2JCF = 26.0 Hz, C), 105.9 (d, 2JCF = 27.1 Hz, C), 120.5 (CH), 120.6 (CH), 123.1 (CH), 123.9 (CH), 127.2 (C), 127.3 (CH), 127.7 (CH), 127.8 (CH), 127.9 (CH), 128.1 (CH), 128.2 (CH), 128.3 (CH), 128.5 (CH), 128.9 (CH), 129.9 (CH), 130.0 (CH), 134.9 (C), 135.1 (C), 137.2 (C), 148.2 (C); ¹⁹F NMR (376 MHz; CDCl₃) δF -182.5 (s, CF), -191.2 (s, CF). m/z (ASAP) 255.1182 ((MH-OH₂)+. C₁₇H₁₆OF requires 255.1185, 100%).
3. 1-\([\text{Anti-fluoro(4-methylphenyl)methyl}]\)-3,3-dimethyl-1,3-dihydro-2-benzofuran-1-ol (4.45a) and 1-\([\text{syn-fluoro(4-methylphenyl)methyl}]\)-3,3-dimethyl-1,3-dihydro-2-benzofuran-1-ol (4.45b) isomers

After General method I using 2-\((\text{p}-\text{tolylethynyl})\)propan-2-ol (0.250 g, 1.0 mmol), AgNO₃ (0.035 g, 0.2 mmol), NFSi (0.48 g, 1.5 mmol), Li₂CO₃ (0.075 g, 1.0 mmol and dry DMA (15 mL), the crude product (0.284 g) was purified by column chromatography using ethyl acetate/petroleum ether (40-60) (1/9) to give 1-\((\text{R})\)-fluoro(4-methylphenyl)methyl]-3,3-dimethyl-1,3-dihydro-2-benzofuran-1-ol and 1-\((\text{S})\)-fluoro(4-methylphenyl)methyl]-3,3-dimethyl-1,3-dihydro-2-benzofuran-1-ol isomers as a brown oil (0.0992 g, 35 %).

Since two diastereomers are formed, there are two sets of peaks in the \(^1\text{H},^{19}\text{F}\) and \(^{13}\text{C}\) NMR spectra. \(^1\text{H}\) NMR (400 MHz; CDCl₃) \(\delta_H 1.32 (6\text{H}, \text{s, } CH_3), 1.55 (6\text{H}, \text{s, } CH_3), 2.33 (6\text{H}, \text{s, } CH_3), 2.84 (1\text{H}, \text{s, } \text{OH}), 3.18 (1\text{H}, \text{s, } \text{OH}), 5.58 (1\text{H}, \text{d, } ^2J_{HF} = 45.2 \text{ Hz, } CHF), 5.59 (1\text{H}, \text{d, } ^2J_{HF} = 45.2 \text{ Hz, } CHF), 7.11 (6\text{H}, \text{m, } ArH), 7.34 (9\text{H}, \text{m, } ArH), 7.45 (1\text{H}, \text{dd, } ^3J_{HH} = 6.4 \text{ Hz, } ^4J_{HH} = 1.7 \text{ Hz, } ArH); ^{13}\text{C}\) NMR (100 MHz; CDCl₃) \(\delta_C 21.2 (\text{CH}_3), 21.3 (\text{CH}_3), 28.3 (\text{CH}_3), 28.4 (\text{CH}_3), 31.0 (\text{CH}_3), 86.4 (\text{C}), 86.5 (\text{C}), 94.3 (\text{d, } ^1J_{CF} = 179.6 \text{ Hz, } CHF), 96.1 (\text{d, } ^1J_{CF} = 179.6 \text{ Hz, } CHF), 105.6 (\text{d, } ^2J_{CF} = 25.5 \text{ Hz, } COH), 105.9 (\text{d, } ^2J_{CF} = 28.7 \text{ Hz, } COH), 120.5 (\text{CH}), 123.0 (\text{CH}), 123.9 (\text{CH}), 127.2 (\text{CH}), 127.3 (\text{CH}), 127.9 (\text{CH}), 128.0 (\text{CH}), 128.1 (\text{CH}), 128.2 (\text{CH}), 128.5 (\text{CH}), 128.6 (\text{CH}), 128.8 (\text{CH}), 129.9 (\text{CH}), 131.8 (\text{d, } ^3J_{CF} = 3.2 \text{ Hz, } C), 132.0 (\text{d, } ^3J_{CF} = 3.2 \text{ Hz, } C), 137.2 (\text{C}), 137.3 (\text{C}), 138.3 (\text{C}), 138.8 (\text{C}), 148.2 (\text{C}), 148.3 (\text{C}); ^{19}\text{F}\) NMR (376 MHz; CDCl₃) \(\delta_F -181.4 (\text{s, CF}), -190.3 (\text{s, CF}). m/z (ASAP) 269.1331 ((\text{MH-OH})^+). C_{18}H_{18}OF requires 269.1342, 100 %).
4. 1-[Difluoro(phenyl)methyl]-3,3-dimethyl-1,3-dihydro-2-benzofuran-1-ol (4.50)

After **General method J** using 2-(2-phenylethynyl)propyl propan-2-ol (0.236 g, 1.0 mmol), AgNO₃ (0.035 g, 0.2 mmol), NFSi (0.96 g, 3.0 mmol), Li₂CO₃ (0.075 g, 1.0 mmol) and dry DMA (15 mL), the crude product (0.630 g) was purified by column chromatography using ethyl acetate/petroleum ether (40-60) (1/9) to give pure 1-[difluoro(phenyl)methyl]-3,3-dimethyl-1,3-dihydro-2-benzofuran-1-ol as a brown oil (0.131 g, 45 %). ¹H NMR (400 MHz; CDCl₃) δ H 1.32 (3H, s, CH₃), 1.54 (3H, s, CH₃), 3.09 (1H, s, OH), 7.10 (1H, d, ³JHH = 6.9 Hz, ArH), 7.39 (5H, m, ArH), 7.54 (2H, dd, ³JHH = 6.8 Hz, ⁴JHH = 1.6 Hz, ArH), 7.61 (1H, d, ³JHH = 0.6 Hz, ArH); ¹³C NMR (100 MHz; CDCl₃) δ C 27.9 (CH₃), 30.9 (CH₃), 87.7 (C), 105.4 (t, ²JC = 33.6 Hz, COH), 119.7 (t, ¹JC = 247.0 Hz, CF₂), 119.7 (CH), 124.3 (CH), 127.4 (t, ³JC = 6.5 Hz, CH), 127.7 (CH), 128.2 (CH), 130.1 (CH), 130.3 (CH), 133.2 (t, ²JC = 25.5 Hz, C), 135.2 (C), 148.5 (C); ¹⁹F NMR (376 MHz; CDCl₃) δ F -104.8 (1F, d, ²JFF = 251.5 Hz, FₐFₖ), -112.9 (1F, d, ²JFF = 251.5 Hz, FₐFₖ). m/z (ASAP) 273.1078 ((MH-OH₂)+. C₁₇H₁₅OF₂ requires 273.1091, 100 %).

5. 1-[Difluoro(4-methylphenyl)methyl]-3,3-dimethyl-1,3-dihydro-2-benzofuran-1-ol (4.51)

After **General method J** using 2-(2-(p-tolylethynyl)phenyl)propyl propan-2-ol (0.250 g, 1.0 mmol), AgNO₃ (0.035 g, 0.2 mmol), NFSi (0.96 g, 3.0 mmol), Li₂CO₃ (0.075 g, 1.0 mmol) and dry DMA (15 mL), the crude product (0.667 g) was purified by column chromatography using ethyl acetate/petroleum ether (40-60) (1/9) to give pure 1-[difluoro(4-methylphenyl)methyl]-
3,3-dimethyl-1,3-dihydro-2-benzofuran-1-ol as a brown oil (0.109 g, 36 %). $^1$H NMR (400 MHz; CDCl$_3$) $\delta$H 1.34 (3H, s, CH$_3$), 1.53 (3H, s, CH$_3$), 2.35 (3H, s, CH$_3$), 3.10 (1H, br s, OH), 7.10 (1H, dt, $^3$J$_{HH}$ = 7.7 Hz, $^4$J$_{HH}$ = 0.8 Hz, ArH), 7.17 (2H, d, $^3$J$_{HH}$ = 7.9 Hz, ArH), 7.36 (1H, dd, $^3$J$_{HH}$ = 7.4 Hz, $^4$J$_{HH}$ = 1.3 Hz, ArH), 7.40 (1H, dd, $^3$J$_{HH}$ = 3.8 Hz, $^4$J$_{HH}$ = 1.5 Hz, ArH), 7.42 (2H, dt, $^3$J$_{HH}$ = 7.5 Hz, $^4$J$_{HH}$ = 1.3 Hz, ArH), 7.59 (1H, d, $^3$J$_{HH}$ = 7.3 Hz, ArH); $^{13}$C NMR (100 MHz; CDCl$_3$) $\delta$C 21.3 (CH$_3$), 28.0 (CH$_3$), 30.9 (CH$_3$), 87.6 (C), 105.4 (t, $^2$J$_{CF}$ = 32.4 Hz, C), 119.8 (t, $^1$J$_{CF}$ = 248.7 Hz, CF$_2$), 120.4 (CH), 124.3 (CH), 127.3 (t, $^3$J$_{CF}$ = 6.4 Hz, CH), 128.1 (CH), 130.3 (CH), 130.3 (CH), 130.3 (t, $^2$J$_{CF}$ = 26.4 Hz, C), 135.3 (C), 140.1 (C), 148.5 (C); $^{19}$F NMR (376 MHz; CDCl$_3$) $\delta$F -104.4 (1F, d, $^2$J$_{FF}$ = 249.0 Hz, CF$_A$F$_B$), -112.5 (1F, d, $^2$J$_{FF}$ = 249.0 Hz, CF$_A$F$_B$). m/z (ASAP) 287.1249 ((MH-OH$_2$)$^+$. C$_{18}$H$_{17}$OF$_2$ requires 287.1247, 100 %).

6. (E)-1,1-Diethyl-3-[fluoro(phenyl)methylidene]-1,3-dihydro-2-benzofuran (4.53), 1-[difluoro-(phenyl)methyl]-3,3-diethyl-1,3-dihydro-2-benzofuran-1-ol (4.54) and 3,3-diethyl-1-[fluoro-(phenyl)methyl]-1,3-dihydro-2-benzofuran-1-ol (4.55a &b) isomers

After General method I using 3-(2-(phenylethynyl)phenyl)pentan-3-ol (0.264 g, 1.0 mmol), AgNO$_3$ (0.035 g, 0.2 mmol), NFSi (0.48 g, 1.5 mmol), Li$_2$CO$_3$ (0.075 g, 1.0 mmol) and dry DMA (15 mL), the crude product (0.206 g) was purified by column chromatography using ethyl acetate/petroleum ether (40-60) (1/9) to give pure (E)-1,1-diethyl-3-[fluoro(phenyl)methylidene]-1,3-dihydro-2-benzofuran as a brown oil (0.061 g, 22 %). $^1$H NMR (400 MHz; CDCl$_3$) $\delta$H 0.75 (6H, t, $^3$J$_{HH}$ = 7.4 Hz, CH$_3$), 1.88 (2H, ABt, $^3$J$_{HH}$ = 7.4 Hz, CH$_2$), 2.05 (2H, ABt, $^3$J$_{HH}$ = 7.3 Hz, CH$_2$), 7.12 (1H, dd, $^3$J$_{HH}$ = 6.8 Hz, $^4$J$_{HH}$ = 1.0 Hz, ArH), 7.23 (1H, tt, $^3$J$_{HH}$ = 7.5 Hz, $^4$J$_{HH}$ = 1.0 Hz, ArH), 7.38 (4H, m, ArH), 7.87 (3H, m, ArH); $^{13}$C NMR (100 MHz; CDCl$_3$) $\delta$C 7.8 (CH$_3$), 32.9 (CH$_2$), 95.2 (C), 120.7 (CH), 123.7 (CH), 123.8 (CH), 126.4 (CH), 128.3 (CH), 128.4 (CH), 128.5 (CH), 132.7 (C), 134.3 (C), 140.9 (C), 201
143.9 (C), 144.2 (d, $J_{CF} = 243.1$ Hz, CF).  $^{19}$F NMR (376 MHz; CDCl$_3$) δ$_F$ -163.4 (s, CF). m/z (ASAP) 283.1485 (MH$^+$). C$_{19}$H$_{20}$FO requires 283.1498, 100 %.

1-[Difluoro-(phenyl)methyl]-3,3-diethyl-1,3-dihydro-2-benzofuran-1-ol was obtained as a brown oil (0.0571 g, 18 %). $^1$H NMR (400 MHz; CDCl$_3$) δ$_H$ 0.69 (3H, t, $J_{HH} = 7.4$ Hz, CH$_3$), 0.94 (3H, t, $J_{HH} = 7.4$ Hz, CH$_3$), 1.46 (1H, ABt, $J_{HH} = 7.4$ Hz, CH$_2$), 1.71 (2H, m, CH$_2$), 1.89 (1H, ABt, $J_{HH} = 7.4$ Hz, CH$_2$), 3.00 (1H, s, OH), 7.06 (1H, dd, $J_{HH} = 6.4$ Hz, $J_{HH} = 1.5$ Hz, ArH), 7.39 (5H, m, ArH), 7.61 (3H, m, ArH); $^{13}$C NMR (100 MHz; CDCl$_3$) δ$_C$ 8.3 (CH$_3$), 8.4 (CH$_3$), 31.1 (CH$_2$), 32.3 (CH$_2$), 93.3 (C), 105.2 (t, $J_{CF} = 33.6$ Hz, COH), 119.8 (t, $J_{CF} = 247.8$ Hz, CF$_2$), 122.3 (CH), 124.4 (CH), 127.3 (t, $J_{CF} = 6.4$ Hz, CH), 128.2 (CH), 130.0 (CH), 131.7 (CH), 131.8 (CH), 131.9 (C), 136.4 (C), 146.4 (C); $^{19}$F NMR (376 MHz; CDCl$_3$) δ$_F$ -103.6 (1F, d, $J_{FF} = 250.5$ Hz, CF$_A$F$_B$), -111.8 (1F, d, $J_{FF} = 250.5$ Hz, CF$_A$F$_B$). m/z (ASAP) 301.1398 ((MH-OH$_2$)$^+$). C$_{19}$H$_{19}$OF$_2$ requires 301.1404, 100 %.

A very tiny amount of 3,3-diethyl-1-[fluoro-(phenyl)methyl]-1,3-dihydro-2-benzofuran-1-ol isomers was also detected by $^{19}$F NMR spectroscopy, but it could not be isolated. $^{19}$F NMR (376 MHz; CDCl$_3$) δ$_F$ -181.0 (s, CF), -190.1 (s, CF).

After General method J using (3-(2-(phenylethynyl)phenyl)pentan-3-ol (0.264 g, 1.0 mmol), AgNO$_3$ (0.035 g, 0.2 mmol), NFSi (0.96 g, 3.0 mmol), Li$_2$CO$_3$ (0.075 g, 1.0 mmol) and dry DMA (15 mL), the crude product (0.792 g) was purified by column chromatography using ethyl acetate/petroleum ether (40-60) (1/9) to give pure 1-[difluoro-(phenyl)methyl]-3,3-diethyl-1,3-dihydro-2-benzofuran-1-ol as a brown oil (0.0476 g, 15 %). From $^{19}$F NMR spectroscopy, ($E$)-1,1-diethyl-3-[fluoro(phenyl)methylidene]-1,3-dihydro-2-benzofuran (δ$_F$ = -163.4 ppm) and 3,3-diethyl-1-[fluoro-(phenyl)methyl]-1,3-dihydro-2-benzofuran-1-ol isomers (δ$_F$ = -181.0 and -190.1 ppm) were also detected as minor products.
7. \((Z)\) 1-[Fluoro(phenyl)methylidene]-2(4-methylbenzenesulfonyl)-3-(trifluoromethyl)-2,3-dihydro-1H-isooindole (4.57) and \((E)\)-1-[fluoro(phenyl)methylidene]-2(4-methylbenzene-sulfonyl)-3-(trifluoromethyl)-2,3-dihydro-1H-isooindole (4.58)

After **General method I** using 4-methyl-N-(2,2,2-trifluoro-1-(2-(phenylethynyl)phenyl)ethyl)benzene-sulfonamide (0.215 g, 0.5 mmol), AgNO\(_3\) (0.0175 g, 0.1 mmol), NFSi (0.24 g, 0.75 mmol), Li\(_2\)CO\(_3\) (0.0375 g, 0.5 mmol) and dry DMA (15 mL), the crude product (0.211 g) was purified by column chromatography using ethyl acetate/petroleum ether (40-60) (1/9) to give pure 4-fluoro-3-phenyl-2-tosyl-1-(trifluoromethyl)-1,2-dihydroisoquinoline as a white solid (0.0423 g, 19 %). mp 168-170 °C. 

\(^1\)H NMR (400 MHz; CDCl\(_3\)) \(\delta\) H 2.17 (3H, s, CH\(_3\)), 5.36 (1H, q, \(^3\)J\(_{HF}\) = 6.3 Hz, CH\(_{CF3}\)), 6.94 (2H, d, \(^3\)J\(_{HH}\) = 8.1 Hz, Ar\(_H\)), 7.15 (4H, m, Ar\(_H\)), 7.36 (4H, m, Ar\(_H\)), 7.57 (1H, d, \(^3\)J\(_{HH}\) = 7.8 Hz, Ar\(_H\)), 7.89 (2H, dd, \(^3\)J\(_{HH}\) = 6.8 Hz, \(^4\)J\(_{HH}\) = 1.6 Hz, Ar\(_H\)); \(^{13}\)C NMR (100 MHz; CDCl\(_3\)) \(\delta\) C 21.4 (CH\(_3\)), 66.2 (q, \(^2\)J\(_{CF}\) = 33.0 Hz, CH), 123.7 (q, \(^1\)J\(_{CF}\) = 280.1 Hz, CF\(_3\)), 123.8 (CH), 123.9 (d, \(^3\)J\(_{CF}\) = 15.6 Hz, CH), 124.2 (d, \(^3\)J\(_{CF}\) = 15.6 Hz, C), 127.5 (CH), 127.6 (CH), 127.9 (CH), 128.2 (CH), 128.4 (CH), 129.3 (CH), 129.9 (d, \(^4\)J\(_{CF}\) = 9.9 Hz, CH), 131.2 (d, \(^2\)J\(_{CF}\) = 26.9 Hz, C), 130.8 (C), 132.3 (C), 136.4 (C), 144.7 (C), 154.7 (d, \(^1\)J\(_{CF}\) = 255.9 Hz, CF). \(^{19}\)F NMR (376 MHz; CDCl\(_3\)) \(\delta\) F -74.9 (3F, s, CF\(_3\)), -113.7 (1F, s, CF). m/z (ASAP) 448.0994 (MH\(^+\)). C\(_{23}\)H\(_{18}\)F\(_4\)N\(_2\)SO\(_2\) requires 448.0994, 100 %.

\((E)\)-1-(Fluoro(phenyl)methylene)-2-tosyl-3-(trifluoromethyl)isoindoline was also obtained as a white solid (0.0424 g, 19 %). mp 145-146 °C. \(^1\)H NMR (400 MHz; CDCl\(_3\)) \(\delta\) H 2.24 (3H, s, CH\(_3\)), 5.46 (1H, q, \(^3\)J\(_{HF}\) = 6.6 Hz, CH\(_{CF3}\)), 7.01 (2H, d, \(^3\)J\(_{HH}\) = 8.1 Hz, Ar\(_H\)), 7.23 (4H, m, Ar\(_H\)), 7.37 (3H, m, Ar\(_H\)), 7.47 (2H, d, \(^3\)J\(_{HH}\) = 8.3 Hz, Ar\(_H\)), 7.77 (2H, d, \(^3\)J\(_{HH}\) = 7.4 Hz, Ar\(_H\)); \(^{13}\)C NMR (100 MHz; CDCl\(_3\)) \(\delta\) C 21.4 (CH\(_3\)), 66.1 (q, \(^2\)J\(_{CF}\) = 33.4 Hz, CH\(_{CF3}\)), 119.1 (CH), 119.6 (CH), 123.7 (q, \(^1\)J\(_{CF}\) = 282.2 Hz, CF\(_3\)), 124.1 (CH), 127.9 (CH), 128.1 (CH), 128.6
(CH), 129.2 (CH), 129.6 (CH), 129.7 (CH), 131.1 (C), 133.0 (C), 133.1 (d, \(^{1}J_{CF} = 244.5\) Hz, CF), 135.1 (C), 137.1 (C), 138.8 (C), 144.5 (C). \(^{19}\)F NMR (376 MHz; CDCl\(_3\)) \(\delta_{F} -74.9\) (3F, s, CF\(_{3}\)), -182.5 (1F, s, CF). m/z (ASAP) 448.0963 (MH\(^{+}\). C\(_{23}\)H\(_{18}\)F\(_{4}\)NSO\(_{2}\) requires 448.0994, 100 %).

A tiny amount of 2-(phenylethynyl)benzaldehyde (0.006 g, 3 %) was also detected and identified following the purification by column chromatography, which means that some part of the 4-methyl-\(N\)-(2,2,2-trifluoro-1-(2-(phenylethynyl)phenyl)ethyl)benzene-sulfonamide decomposed during the reaction or on the column.

After General method J using 4-methyl-\(N\)-(2,2,2-trifluoro-1-(2-(phenylethynyl)phenyl)ethyl)benzene-sulfonamide (0.215 g, 0.5 mmol), AgNO\(_{3}\) (0.0175 g, 0.1 mmol), NFSi (0.48 g, 1.5 mmol), Li\(_{2}\)CO\(_{3}\) (0.0375 g, 0.5 mmol) and dry DMA (15 mL), the crude product (0.476 g) was purified by column chromatography using ethyl acetate/petroleum ether (40-60) (1/9) to give pure 4-fluoro-3-phenyl-2-tosyl-1-(trifluoromethyl)-1,2-dihydroisoquinoline as a white solid (0.117 g, 52 %), and (E)-1-(fluoro(phenyl)methylene)-2-tosyl-3-(trifluoromethyl)isoindoline as a white solid (0.0199 g, 9 %).

5.5 References


### Appendix: X-ray crystallography

#### Crystal data and structure refinement for (3.37)

<table>
<thead>
<tr>
<th>Identification code</th>
<th>14116</th>
</tr>
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<tr>
<td>Empirical formula</td>
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</tr>
<tr>
<td>Formula weight</td>
<td>490.61</td>
</tr>
<tr>
<td>Temperature</td>
<td>150(2) K</td>
</tr>
<tr>
<td>Wavelength</td>
<td>0.71073 Å</td>
</tr>
<tr>
<td>Crystal system</td>
<td>Orthorhombic</td>
</tr>
<tr>
<td>Space group</td>
<td>Iba2</td>
</tr>
<tr>
<td>Unit cell dimensions</td>
<td>$a = 11.642(4)$ Å, $\alpha = 90^\circ$. $b = 32.278(11)$ Å, $\beta = 90^\circ$. $c = 7.384(3)$ Å, $\gamma = 90^\circ$.</td>
</tr>
<tr>
<td>Volume</td>
<td>2774.7(17) Å³</td>
</tr>
<tr>
<td>Z</td>
<td>4</td>
</tr>
<tr>
<td>Density (calculated)</td>
<td>1.174 Mg/m³</td>
</tr>
<tr>
<td>Absorption coefficient</td>
<td>0.073 mm⁻¹</td>
</tr>
<tr>
<td>F(000)</td>
<td>1048</td>
</tr>
<tr>
<td>Crystal size</td>
<td>0.19 x 0.12 x 0.07 mm³</td>
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<tr>
<td>Theta range for data collection</td>
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<td>$-13 \leq h \leq 13$, $-38 \leq k \leq 38$, $-8 \leq l \leq 8$</td>
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<td>Reflections collected</td>
<td>9800</td>
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<tr>
<td>Independent reflections</td>
<td>2442 [R(int) = 0.2089]</td>
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<tr>
<td>Completeness to theta = 24.99°</td>
<td>99.9 %</td>
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<tr>
<td>Absorption correction</td>
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<td>Refinement method</td>
<td>Full-matrix least-squares on F²</td>
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<td>Data / restraints / parameters</td>
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<td>Goodness-of-fit on F²</td>
<td>0.775</td>
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<td>Final R indices [I&gt;2sigma(I)]</td>
<td>R1 = 0.0650, wR2 = 0.1000</td>
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<tr>
<td>R indices (all data)</td>
<td>R1 = 0.1357, wR2 = 0.1187</td>
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<tr>
<td>Largest diff. peak and hole</td>
<td>0.207 and -0.207 e.Å⁻³</td>
</tr>
</tbody>
</table>

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Crystal data and structure refinement for (3.46)

Identification code  15032
Empirical formula  C22 H17 N O2 S
Formula weight  359.43
Temperature  150(2) K
Wavelength  0.71073 Å
Crystal system  Monoclinic
Space group  P2(1)/n
Unit cell dimensions  
\[ a = 9.523(5) \text{ Å} \quad \alpha = 90^\circ. \]
\[ b = 19.757(10) \text{ Å} \quad \beta = 102.276(9)^\circ. \]
\[ c = 9.830(5) \text{ Å} \quad \gamma = 90^\circ. \]
Volume  1807.1(16) Å³
Z  4
Density (calculated)  1.321 Mg/m³
Absorption coefficient  0.195 mm⁻¹
F(000)  752
Crystal size  0.18 x 0.13 x 0.10 mm³
Theta range for data collection  2.06 to 26.00°
Index ranges  -11<=h<=11, -24<=k<=24, -12<=l<=12
Reflections collected  13944
Independent reflections  3551 [R(int) = 0.0854]
Completeness to theta = 26.00°  100.0 %
Absorption correction  Empirical
Max. and min. transmission  0.928 and 0.558
Refinement method  Full-matrix least-squares on F²
Data / restraints / parameters  3551 / 0 / 236
Goodness-of-fit on F²  0.968
Final R indices [I>2sigma(I)]  R1 = 0.0545, wR2 = 0.1205
R indices (all data)  R1 = 0.0783, wR2 = 0.1297
Largest diff. peak and hole  0.366 and -0.440 e.Å⁻³
Crystal data and structure refinement for (3.40)

Identification code 15060
Empirical formula C23 H18 F3 N O2 S
Formula weight 429.44
Temperature 150(2) K
Wavelength 0.71073 Å
Crystal system Monoclinic
Space group P2(1)/n
Unit cell dimensions
a = 8.6871(14) Å \( \alpha = 90^\circ \).
b = 17.207(3) Å \( \beta = 102.597(3)^\circ \).
c = 14.002(2) Å \( \gamma = 90^\circ \).
Volume 2042.7(6) Å³
Z 4
Density (calculated) 1.396 Mg/m³
Absorption coefficient 0.205 mm⁻¹
F(000) 888
Crystal size 0.24 x 0.14 x 0.05 mm³
Theta range for data collection 1.90 to 26.00°.
Index ranges -10 <= h <= 10, -21 <= k <= 21, -17 <= l <= 17
Reflections collected 15785
Independent reflections 4016 [R(int) = 0.0570]
Completeness to theta = 26.00° 100.0 %
Absorption correction Empirical
Max. and min. transmission 0.928 and 0.760
Refinement method Full-matrix least-squares on F²
Data / restraints / parameters 4016 / 0 / 272
Goodness-of-fit on F² 0.973
Final R indices [I>2sigma(I)] R1 = 0.0467, wR2 = 0.1064
R indices (all data) R1 = 0.0658, wR2 = 0.1139
Largest diff. peak and hole 0.361 and -0.295 e.Å⁻³
### Crystal data and structure refinement for (3.49)

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<td>Formula weight</td>
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<tr>
<td>Temperature</td>
<td>150(2) K</td>
</tr>
<tr>
<td>Wavelength</td>
<td>0.71073 Å</td>
</tr>
<tr>
<td>Crystal system</td>
<td>Triclinic</td>
</tr>
<tr>
<td>Space group</td>
<td>P-1</td>
</tr>
</tbody>
</table>
| Unit cell dimensions                  | a = 8.542(2) Å  
|                                       | b = 9.360(2) Å  
|                                       | c = 9.479(2) Å  
|                                       | α = 70.024(4)°  
|                                       | β = 87.158(4)°  
|                                       | γ = 83.365(4)°  |
| Volume                                | 707.5(3) Å³ |
| Z                                     | 2 |
| Density (calculated)                  | 1.888 Mg/m³ |
| Absorption coefficient                | 2.292 mm⁻¹ |
| F(000)                                | 388 |
| Crystal size                          | 0.31 x 0.24 x 0.06 mm³ |
| Theta range for data collection       | 2.29 to 26.00° |
| Index ranges                          | -10<=h<=10, -11<=k<=11, -11<=l<=11 |
| Reflections collected                 | 5549 |
| Independent reflections               | 2761 [R(int) = 0.0303] |
| Completeness to theta = 26.00°        | 98.7 % |
| Absorption correction                 | Empirical |
| Max. and min. transmission            | 0.862 and 0.522 |
| Refinement method                     | Full-matrix least-squares on F² |
| Data / restraints / parameters         | 2761 / 0 / 190 |
| Goodness-of-fit on F²                  | 1.033 |
| Final R indices [I>2sigma(I)]         | R1 = 0.0312, wR2 = 0.0762 |
| R indices (all data)                   | R1 = 0.0349, wR2 = 0.0782 |
| Largest diff. peak and hole            | 0.914 and -0.824 e.Å⁻³ |
### Crystal data and structure refinement for (3.57)

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<td>Empirical formula</td>
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</tr>
<tr>
<td>Formula weight</td>
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</tr>
<tr>
<td>Temperature</td>
<td>150(2) K</td>
</tr>
<tr>
<td>Wavelength</td>
<td>0.71073 Å</td>
</tr>
<tr>
<td>Crystal system</td>
<td>Monoclinic</td>
</tr>
<tr>
<td>Space group</td>
<td>P2(1)/c</td>
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<tr>
<td>Unit cell dimensions</td>
<td>a = 12.998(3) Å, α = 90°</td>
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<tr>
<td></td>
<td>b = 8.8647(18) Å, β = 101.921(4)°</td>
</tr>
<tr>
<td></td>
<td>c = 13.450(3) Å, γ = 90°</td>
</tr>
<tr>
<td>Volume</td>
<td>1516.3(5) Å³</td>
</tr>
<tr>
<td>Z</td>
<td>4</td>
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<tr>
<td>Density (calculated)</td>
<td>1.823 Mg/m³</td>
</tr>
<tr>
<td>Absorption coefficient</td>
<td>2.142 mm⁻¹</td>
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<tr>
<td>F(000)</td>
<td>808</td>
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<tr>
<td>Crystal size</td>
<td>0.34 x 0.27 x 0.04 mm³</td>
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<td>Theta range for data collection</td>
<td>1.60 to 26.00°</td>
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<td>-16&lt;=h&lt;=16, -10&lt;=k&lt;=10, -16&lt;=l&lt;=16</td>
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<tr>
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<tr>
<td>Independent reflections</td>
<td>2985 [R(int) = 0.0739]</td>
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<td>Completeness to theta = 26.00°</td>
<td>99.9 %</td>
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<td>Absorption correction</td>
<td>Empirical</td>
</tr>
<tr>
<td>Max. and min. transmission</td>
<td>0.981 and 0.693</td>
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<td>Refinement method</td>
<td>Full-matrix least-squares on F²</td>
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<td>Data / restraints / parameters</td>
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<tr>
<td>Goodness-of-fit on F²</td>
<td>0.934</td>
</tr>
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<td>Final R indices [I&gt;2sigma(I)]</td>
<td>R1 = 0.0376, wR2 = 0.0699</td>
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<td>R indices (all data)</td>
<td>R1 = 0.0531, wR2 = 0.0747</td>
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<tr>
<td>Largest diff. peak and hole</td>
<td>0.640 and -0.702 e.Å⁻³</td>
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Crystal data and structure refinement for (3.55)

Identification code 13082
Empirical formula C17 H12 F3 I O
Formula weight 416.17
Temperature 150(2) K
Wavelength 0.71073 Å
Crystal system Monoclinic
Space group P2(1)/c
Unit cell dimensions
\[ a = 8.790(4) \text{ Å} \quad \alpha = 90^\circ. \]
\[ b = 19.562(9) \text{ Å} \quad \beta = 104.522(8)^\circ. \]
\[ c = 9.296(4) \text{ Å} \quad \gamma = 90^\circ. \]
Volume 1547.3(13) Å³
Z 4
Density (calculated) 1.787 Mg/m³
Absorption coefficient 2.099 mm⁻¹
F(000) 808
Crystal size 0.33 x 0.22 x 0.08 mm³
Theta range for data collection 2.08 to 26.00°
Index ranges -10<=h<=10, -24<=k<=24, -11<=l<=11
Reflections collected 11945
Independent reflections 3045 \[ R(\text{int}) = 0.0604 \]
Completeness to theta = 26.00° 99.9 %
Absorption correction Empirical
Max. and min. transmission 0.928 and 0.699
Refinement method Full-matrix least-squares on F²
Data / restraints / parameters 3045 / 0 / 200
Goodness-of-fit on F² 1.036
Final R indices [I>2sigma(I)] R1 = 0.0395, wR2 = 0.0812
R indices (all data) R1 = 0.0527, wR2 = 0.0856
Largest diff. peak and hole 0.974 and -0.970 e.Å⁻³
Crystal data and structure refinement for (3.71)

Identification code 14065
Empirical formula C15 H9 I O2
Formula weight 348.12
Temperature 150(2) K
Wavelength 0.71073 Å
Crystal system Monoclinic
Space group P2(1)/n
Unit cell dimensions
\[ a = 13.306(3) \text{ Å} \quad \alpha = 90^\circ. \]
\[ b = 5.6844(11) \text{ Å} \quad \beta = 105.813(3)^\circ. \]
\[ c = 16.978(3) \text{ Å} \quad \gamma = 90^\circ. \]
Volume 1235.6(4) Å³
Z 4
Density (calculated) 1.871 Mg/m³
Absorption coefficient 2.581 mm⁻¹
F(000) 672
Crystal size 0.25 x 0.12 x 0.08 mm³
Theta range for data collection 1.73 to 26.00°
Index ranges -16≤h≤16, -6≤k≤7, -20≤l≤20
Reflections collected 9141
Independent reflections 2409 [R(int) = 0.0645]
Completeness to theta = 26.00° 100.0 %
Absorption correction Empirical
Max. and min. transmission 0.928 and 0.660
Refinement method Full-matrix least-squares on F²
Data / restraints / parameters 2409 / 0 / 163
Goodness-of-fit on F² 0.967
Final R indices [I>2sigma(I)] R1 = 0.0331, wR2 = 0.0596
R indices (all data) R1 = 0.0418, wR2 = 0.0624
Largest diff. peak and hole 0.793 and -0.637 e.Å⁻³
Crystal data and structure refinement for (4.33)

Identification code 14126
Empirical formula C19 H19 N
Formula weight 261.35
Temperature 150(2) K
Wavelength 0.71073 Å
Crystal system Monoclinic
Space group P2(1)
Unit cell dimensions a = 5.882(2) Å  \(\alpha = 90^\circ\).
b = 8.123(4) Å  \(\beta = 96.067(10)^\circ\).
c = 15.960(7) Å  \(\gamma = 90^\circ\).
Volume 758.4(6) Å³
Z 2
Density (calculated) 1.144 Mg/m³
Absorption coefficient 0.066 mm⁻¹
F(000) 280
Crystal size 0.18 x 0.16 x 0.08 mm³
Theta range for data collection 2.57 to 24.99°.
Index ranges -6<=h<=6, -9<=k<=9, -18<=l<=18
Reflections collected 5539
Independent reflections 1426 [R(int) = 0.1515]
Completeness to theta = 24.99° 99.8 %
Absorption correction Empirical
Max. and min. transmission 0.981 and 0.529
Refinement method Full-matrix least-squares on F²
Data / restraints / parameters 1426 / 1 / 184
Goodness-of-fit on F² 0.843
Final R indices [I>2sigma(I)] R1 = 0.0638, wR2 = 0.1175
R indices (all data) R1 = 0.1436, wR2 = 0.1458
Largest diff. peak and hole 0.185 and -0.202 e.Å⁻³
### Crystal data and structure refinement for (4.34)

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<td>Wavelength</td>
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<tr>
<td>Crystal system</td>
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</tr>
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<td>Space group</td>
<td>P2(1)2(1)2(1)</td>
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<tr>
<td>Unit cell dimensions</td>
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</tr>
<tr>
<td>a</td>
<td>6.4233(16) Å</td>
</tr>
<tr>
<td>b</td>
<td>7.5287(18) Å</td>
</tr>
<tr>
<td>c</td>
<td>22.223(6) Å</td>
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<td>Density (calculated)</td>
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<td>F(000)</td>
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<td>Crystal size</td>
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<td>Theta range for data collection</td>
<td>1.83 to 25.00°</td>
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<td>Reflections collected</td>
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<tr>
<td>Independent reflections</td>
<td>1888 [R(int) = 0.0754]</td>
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<tr>
<td>Completeness to theta = 25.00°</td>
<td>100.0 %</td>
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<td>Absorption correction</td>
<td>Empirical</td>
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<tr>
<td>Max. and min. transmission</td>
<td>0.981 and 0.351</td>
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<td>Refinement method</td>
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