University College London

Functionalisation of saturated heterocycles via aerobic C-H activation to form C-C bonds

by

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in the
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Declaration of Authorship

I, Nehaal Ahmed, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.
Abstract

This project is focused on the transformation of heterocycles by exploiting their interaction with oxygen in air as a means to construct C–C bonds via radical addition. Chapter one introduces fundamental information about radical reactivity, C–H bond transformations and aerobic C–H activation work. Furthermore, the reactions of radical acceptors used in this thesis are introduced alongside current methods for functionalising heterocycles. Chapter two describes the research and development section of this work, where an optimised reaction is developed for the C–C bond formation of heterocycles via an aerobic oxidation pathway. Alkynyl hypervalent iodine and acetylenic triflone radical acceptors are shown to be compatible with differing success in the designed reaction conditions. Following this, exemplification of the alkynylation reaction is demonstrated by reaction scope studies for both the heterocycles and radical acceptors. The method was also shown to be compatible with vinyl triflones allowing access to vinyl heterocycles in one step. The use of the products formed was demonstrated by novel transformations to generate privileged scaffolds and fundamental building blocks of varying oxidation levels. Mechanistic studies are carried out to confirm both the aerobic and radical nature of the developed reaction conditions. Future directions are also highlighted as a result of the findings in this thesis, finally the last chapter contains the experimental results and characterisations of compounds mentioned within the thesis.
Impact Statement

The main aim of this research project is to devise a synthetic method for the transformation of heterocycles via an aerobic oxidation pathway. While there are many pathways which can provide routes to C–H activation, aerobic oxidation is relatively unexplored in the diverse field of C–C bond formation. Existing methodologies can involve the use of precious metal catalysts, toxic initiators, and intricate reaction conditions to achieve successful transformations; aerobic C–H activation provides alternative reaction conditions focusing on utilising oxygen present in the atmosphere to alleviate the need of these valuable resources.

Previously this method has successfully been well documented in the formation of a wide variety of unsymmetrical ketones and acyl hydrazides via C-H functionalisation of aldehydes. The work was also extended to include C–N bond formation at the $\alpha$-position of ethers, highlighting a departure from traditional methods employed to functionalise ethers. Within this thesis, a protocol for the formation of alkynyl and vinyl heterocycles through an aerobic oxidation pathway is developed. An emphasis is placed on reducing the equivalents of substrate used and minimising the additives present in the reaction conditions. An efficient chain reaction is developed, allowing access to a wide portfolio of $sp^3$–C(H) functionalised heterocycles. Substrates ranging from 5-membered heterocycles and 6-membered sugars are shown to be compatible while also aliphatic ether derivatives allow facile reactivity to occur. The products synthesised fit into the remit of increasing methods allowing the functionalisation of $sp^3$-rich heterocycles, where they considered likely to reduce attrition in the drug discovery process, while also reducing the use of toxic/expensive transition metals.
“How long will this last, this delicious feeling of being alive, of having penetrated the veil which hides beauty and the wonders of celestial vistas? It doesn't matter, as there can be nothing but gratitude for even a glimpse of what exists for those who can become open to it.”

Alexander Shulgin
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<td>ACS</td>
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<td>Azobisisobutyronitrile</td>
</tr>
<tr>
<td>aq.</td>
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<tr>
<td>BDE</td>
<td>Bond Dissociation Energy</td>
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<tr>
<td>BHT</td>
<td>Butylated hydroxytoluene</td>
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<tr>
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<td>tert-Butyloxycarbonyl</td>
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<td>br.</td>
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<tr>
<td>Bu</td>
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<td>Benziodoxol(on)es</td>
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<td>CBz</td>
<td>Benzyloxycarbonyl</td>
</tr>
<tr>
<td>CFL</td>
<td>Compact fluorescent lamp</td>
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<td>Diastereomeric excess</td>
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<tr>
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<td>EDG</td>
<td>Electron Donating Group</td>
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<tr>
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<tr>
<td>eq.</td>
<td>Equivalents</td>
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<td>ES</td>
<td>Electrospray</td>
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<tr>
<td>Et</td>
<td>Ethyl</td>
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<tr>
<td>Abbreviation</td>
<td>Full Form</td>
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<tr>
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<tr>
<td>EWG</td>
<td>Electron withdrawing group</td>
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<tr>
<td>HFIP</td>
<td>1,1,1,3,3,3-Hexafluoro-2-propanol</td>
</tr>
<tr>
<td>HRMS</td>
<td>High resolution mass spectrometry</td>
</tr>
<tr>
<td>iPr</td>
<td>Isopropyl</td>
</tr>
<tr>
<td>IR</td>
<td>Infrared</td>
</tr>
<tr>
<td>J</td>
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</tr>
<tr>
<td>m</td>
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</tr>
<tr>
<td>m.p.</td>
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<tr>
<td>MO</td>
<td>Molecular orbital</td>
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<tr>
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<tr>
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</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>SOMO</td>
<td>Singly occupied molecular orbital</td>
</tr>
<tr>
<td>t</td>
<td>Triplet</td>
</tr>
<tr>
<td>TAC</td>
<td>Trisaminocyclopropenium</td>
</tr>
<tr>
<td>TBHP</td>
<td>Tert-butyl hydroperoxide</td>
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<td>TCICA</td>
<td>Trichloroisocyanuric acid</td>
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<td>TEMPO</td>
<td>2,2,6,6-Tetramethylpiperidin-1-yl)oxyl</td>
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<td>Ts</td>
<td>Tosylate</td>
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<td>Abbreviation</td>
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</tr>
<tr>
<td>UCL</td>
<td>University College London</td>
</tr>
<tr>
<td>UV</td>
<td>Ultraviolet</td>
</tr>
<tr>
<td>VSEPR</td>
<td>Valence shell electron pair repulsion</td>
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Chapter 1

Introduction

1.1 Free Radical

Traditionally, the electronic configuration of carbon-based molecules consists of paired electrons as bonding pairs. According to Pauli’s exclusion principle each electron in this pair consists of an electron in opposite spin orientations of $\pm \frac{1}{2}$ in each orbital. Free radicals refer to a class of atoms or molecules that include the presence of at least one unpaired valence electron. Most radicals are inherently highly reactive paramagnetic species. They are represented in chemical equations, mechanisms, and structures as a single dot. In reaction mechanisms the movement of each electron is represented by a single-headed arrow.

1.1.1 First evidence of radical formation

The history of the radical dates to the early 1900s, where the triphenylmethyl radical 2 was formed by abstraction of Cl• from triphenylmethyl chloride 1 by silver metal.\(^1\) The triphenylmethyl radical is relatively stable but reacts with itself reversibly in solution. It was hypothesised that the product of the dimerization of triphenylmethyl was hexaphenylethane 3, however NMR studies in 1968 showed that it was, in fact an unsymmetrical ‘head-tail’ dimer 4 (Scheme 1).\(^2\)

![Scheme 1: Formation of the triphenylmethyl radical 2 and the subsequent dimer.](image)
The initial reaction towards a trivalent carbon species was scepticism, but studies by Hofeditz and Paneth in 1929 provided evidence of the methyl radical through gaseous state studies by thermal decomposition of tetramethyllead 5 under argon. Further evidence followed in 1933 when Kharasch observed the ‘peroxide effect’, where the addition of hydrogen bromide to allyl bromide 6 followed an anti-Markovnikov addition to yield 1,3-dibromopropane 8 in the presence of peroxides (Scheme 2). This contrasted with the result in the absence of peroxides where a slower ionic reaction over 10 days resulted in 1,2-dibromopropane 7, confirming the presence of an alternative radical mechanism initiated by peroxide. Eventually the properties behind the free radical became better understood, and in modern day chemistry, it is widely accepted as a powerful and efficient tool in synthetic chemistry.

Scheme 2: An illustration of the thermal decomposition of tetramethyllead, alongside the addition of HBr to allyl bromide 6 showcasing differing reactivity of ionic and radical transformation.
1.1.2 Radical properties

1.1.2.1 Structure

The structure of a radical is defined by the location in space of each atom directly attached to the radical centre. In the case of three atoms bonded to carbon atom on which the radical is centered, the configuration could either be planar or pyramidal. A planar configuration consists of each atom directly attached to radical centre and the centre itself which all exist in the same plane (Scheme 3). For trigonal pyramidal radicals, the radical centre is at the apex and three atoms are at the corners of the trigonal base, resembling a tetrahedron.

Scheme 3: The potential configuration of radicals dependent on the properties of substituents, when \( R^{1,2,3} = H \) expect planar radicals but when \( R^{1,2,3} = F \) pyramidal radicals are observed. \(*X = \) electronegative atom such as F.

Almost all carbon-centered radicals have trigonal pyramidal configuration, however they can vary widely depending on how close their configurations are to being planar in geometry. A \( \pi \)-type radical is often described as having almost a planar arrangement of attached atoms, this is because the orbital in which the electron is centered is close to being a \( p \) orbital. On the other hand, a radical can also have a pyramidal configuration, this can be thought of as approaching \( sp^3 \) hybridisation and is described as a \( \sigma \)-type radical. The geometry of these radicals varies depending on how electronegative a substituent is, in the case of a methyl radical it is planar, but if the hydrogen atoms are replaced progressively with fluorine atoms, we can expect the structure to produce pyramidal radicals. This structure deviates further from planarity until a trifluoromethyl radical is reached, this F–C–F bond angle is like those found in tetrahedral geometries. The pyramidal geometry is favoured for electronegative...
substituents such as fluorine as there is additional stabilisation offered by hyperconjugation between the orbital that contains the lone pair and the C-F antibonding orbital. In a planar geometry the orbitals are perpendicular, and no overlap occurs (Scheme 3). More can be learnt about radical configurations through analysis of $\alpha^{13}$C hyperfine coupling constants, which can be obtained from the electron spin resonance spectra of $^{13}$C-enriched radicals.

### 1.1.2.2 Stability and MO model

Bond dissociation energies can help give an idea of how likely radicals are to form, they can also give an idea of the stability of those radicals once they have formed. If we compare the BDE (bond dissociation enthalpy) of C–H bonds from methane H$_3$C–H up to isobutane Me$_3$C–H, a simple trend is apparent. C–H bonds decrease in strength in R-H when R goes from primary to secondary to tertiary. Tertiary alkyl radicals are therefore the most stable, whereas methyl radicals are the least stable (Scheme 4).

![Scheme 4](image)

Scheme 4: The relationship between bond strength and the corresponding stability of the resulting radicals.

Hyperconjugation can explain this observation, in the case of a methyl radical that is trigonal planar, the unpaired electron is contained in a p orbital perpendicular to the molecular plane. The trigonal planar geometry allows for the sigma orbital on adjacent carbons to align and overlap with the p orbital. This interaction allows for electron
donation into the electron deficient p orbital. The effect of hyperconjugation increases as we increase the number of R substituents on the methyl group as the amount of orbital overlap is also increased.

Radical species can also be stabilised through conjugation with electron-withdrawing groups (EWGs) via delocalisation of the unpaired electron, or by adjacent electron-donating groups (EDGs) where the neighbouring heteroatom can donate electron density into the partially empty singly occupied molecular orbital (SOMO) of the radical species. The orbital in which the lone electron (radical) resides in is termed the SOMO. Neighbouring EDGs or EWGs can often change the characteristic behaviour of the radical centre. MO theory (Scheme 5) can be used to determine the behaviour of differing radical species. The presence on a neighbouring EDG to the radical centre can increase the relative energy of the SOMO and create a nucleophilic type radical. Conversely, EWGs decrease the overall energy of the SOMO generating an electrophilic radical. This concept can be referred to as polarity matching, where radicals favourably couple with partners of opposite polarity, through a polarity-matched process (nucleophile + electrophile). ⁹

Scheme 5: Molecular orbital diagram exhibiting the electronic representation of both nucleophilic and electrophilic radicals.
1.1.3 Forming Free Radicals

1.1.3.1 Homolysis

The breaking of a single covalent bond to give one electron to each atom that formed the bond is termed homolysis. To carry out this bond cleavage, activation energy needs to be supplied in the form, most commonly in the form of thermal or photochemical energy.

\[ \text{X-Y} \rightarrow \text{X}^- + \text{Y}^- \]

Scheme 6: General homolytic fission, creating two radical species.

The amount of energy typically required to carry out this cleavage is termed BDE and is a measure of how strong the bond is. Typical BDEs in stable organic molecules range from 200 kJ mol\(^{-1}\) (C–I) to more than 400 kJ mol\(^{-1}\) (C–H);\(^{10}\) these bonds are far too strong to undergo homolysis at a reasonable rate in standard conditions (room temperature and pressure). Only particularly weak bonds are useful as thermal radical sources at moderate temperature (e.g. 92 °C for dibenzoyl peroxide 11). An example of a commonly used initiator species is dibenzoyl peroxide 11, which has a low bond energy of 142 kJ mol\(^{-1}\) owing to a weak O–O bond (Scheme 7), this allows for facile formation of the corresponding free radical species 12 at relatively low temperatures.

\[
\text{PhCO}_2\text{O} \quad \xrightarrow{\text{hv or heat}} \quad 2\text{PhCO}_2\text{.}
\]

Scheme 7: Homolytic fission of the O–O bond in benzoyl peroxide 11 to form radical species 12.

1.1.3.2 Single Electron Transfer (SET)

An alternative method for the generation of a radical species from a spin-paired molecule is the addition or removal of a single electron, known as reduction or
oxidation respectively. For molecules that undergo reduction, they contain low-lying antibonding orbitals for the electron to go into, these include carbonyl compounds and aromatic systems. Ketyl radicals 14 are a common example of a radical anion formed by the addition of an electron to a ketone 13.11 A complementary example of an oxidative single electron transfer can be demonstrated the formation of the electrophilic dimethylmalonate radical 16, this SET is facilitated by Mn$^{3+}$ acting as an oxidising agent (Scheme 8).12

Scheme 8: Formation of the corresponding ketyl radical 14 from benzophenone 13 (top). The formation of the malonate radical species 16 from dimethyl malonate 15 is also shown (bottom).

1.1.4 Typical Reactions of Radicals

Radical reactions can generally be divided into two class: Unimolecular processes and bimolecular processes; the latter can be subdivided into radical-molecule reactions and radical-radical reaction types. These processes are briefly described below in this section.

1.1.4.1 Unimolecular Radical Processes

Unimolecular radical processes involve the intramolecular fragmentation of a bond influenced by the presence of a single electron. This fragmentation can take place in two processes termed $\alpha$-scission and $\beta$-scission, the term describes the location of the initial radical relative to the broken bond. Radical cyclisation is also another example
of a unimolecular radical process as it involves a single molecule and an intramolecular cyclisation.

\[
\begin{align*}
\text{\textbullet X-Y} & \quad \xrightarrow{\alpha-\text{Scission}} \quad \text{X} + \text{Y}\cdot \\
\text{\textbullet X-Y-Z} & \quad \xrightarrow{\beta-\text{Scission}} \quad \text{X=Y} + \text{Z}\cdot
\end{align*}
\]

Scheme 9: General \(\alpha\)-scission process resulting in a species with a non-bonding lone pair of electrons (top). General \(\beta\)-scission process, resulting in the formation of a new \(\pi\)-bond (bottom).

**\(\alpha\)-Scission**

\(\alpha\)-Scission describes the cleavage of a \(\sigma\)-bond \(\alpha\) to the radical centre. The most commonly encountered example of \(\alpha\)-scission is the cleavage of acyl radicals to liberate carbon monoxide and an alkyl radical. The relative rate of fragmentation depends on the stability of the formed alkyl radical. Another example of \(\alpha\)-scission involves the formation of an isonitrile 18 and stabilised sulphur-centred radical 19 in the sugar molecule 17 (Scheme 10).\(^{13}\)

\[
\begin{align*}
\text{AcO} & \quad \text{O} & \quad \text{N} & \quad \text{C} & \quad \text{SSnBu}_3 \\
\text{AcO} & \quad \text{OAc} & \quad \text{OAc} & \quad \text{OAc} & \quad \text{OAc}
\end{align*}
\]

Scheme 10: \(\alpha\)-Scission taking place on a sugar molecule 17 to release a stabilised sulphur-centered radical 19 and form an isonitrile group.

**\(\beta\)-Scission**

\(\beta\)-Scission involves the cleavage of a \(\sigma\)-bond \(\beta\) to the radical centre, forming a new \(\pi\) bond. The reaction is thermodynamically favoured if the breaking \(\sigma\)-bond is particularly weak. Other factors which can alter the rate of reaction include strain-release, in the
case of cyclopropylcarbinyl radical 20 β-scion is rapid due to the release of ring strain in the three-membered ring. Stereoelectronic alignment is particularly important in β-scion and this applies to cyclic systems (Scheme 11) where the efficiency of orbital overlap may determine the ease of β-scion and the structure of the final product.  

Scheme 11: Scheme showing the overlap between the SOMO and the exocyclic C–C bond (red) in 20 is more efficient than the overlap between the SOMO and endocyclic bond (blue), which enables rapid β-scion to take place and give 21.

1.1.4.2 Bimolecular Radical Processes

Bimolecular radical processes can take place between either a free radical and spin-paired molecule or two free radical containing molecules.

Radical-molecule interactions

Radicals can abstract hydrogen or other atoms from many types of reagents and solvents. This is a particularly important example of an atom or group transfer reaction. Since these reactions involve the breaking and formation of bonds, the process is governed by thermodynamics and best proceeds if the overall reaction is exothermic.

Scheme 12: General radical abstraction process
Radicals are also capable of addition reactions. For synthetic purposes, additions to alkenes are particularly important while most radicals are also highly reactive towards singlet oxygen. Mechanistically this can be thought of as being the reverse of β-scission and so by analogy the radical is formed with both the SOMO and new σ-bond in the same plane.

\[
\begin{array}{c}
A^* \\
\text{addition} \\
\beta - \text{scission} \\
B=C \\
\rightarrow A-B-C^* \\
\end{array}
\]

Scheme 13: General radical addition process, which is the reverse of β-scission.

**Radical-Radical interactions**

Radical-radical interactions have extremely low activation energies and hence radical recombination takes place rapidly. The rate of reaction in solution is diffusion-controlled and depends strongly on the concentration of radicals in solution. Other important factors which dictate the relative rate of reaction include steric hindrance about the radical centre and the number of C–H positions available β- to the radical centre.\(^{15}\) The radical-radical interactions can take place via recombination of two radical species to form a spin-paired molecule or through a disproportionation step where two-spin paired species are formed.

\[
\begin{array}{c}
\cdot 23 \\
\text{recombination} \\
\cdot 23 \\
\rightarrow 24 \\
\cdot 25 \\
\text{disproportionation} \\
\cdot H 25 \\
\rightarrow 26 + 27 \\
\end{array}
\]

Scheme 14: Possible termination processes which include both recombination of propyl radicals 23 and the disproportionation of ethyl radicals 25 to generate ethane 26 and ethene 27.
1.1.5 Chain Reactions

Free radical chain reactions are a powerful method for synthetic chemists to achieve transformations that may otherwise be inaccessible through ionic pathways. In addition to this, radical chemistry can provide certain advantages over conventional ionic paths. Radicals are generally more tolerant of functional groups, for example one issue with carbanions as nucleophiles is unwanted basicity, however neutral alkyl radicals avoid epimerisation of sensitive centres such as those which are adjacent to a carbonyl group. This advantage circumvents the need of protecting group chemistry which can often be cumbersome and inefficient.\textsuperscript{16-17} Due to these reasons, radical chain reactions are successfully applied over a vast range of molecules and solvents of differing polarities, ranging from polar carbohydrates to lipophilic steroids and peptides, with more confidence than in corresponding ionic reaction systems.\textsuperscript{18}

1.1.5.1 Initiation

Every free radical reaction begins with an initial step where free radicals are generated. There is one important factor to note, at any given time there is a small concentration of the free radical present. There is also an overall net increase in free radicals over time. It is common for many radical reactions to contain an initiator species which is sensitive to a combination of thermal, sonochemical or photochemical degradation.\textsuperscript{19} This will trigger the formation of an initial radical species and the start of a chain reaction. The appropriate choice of initiator is decided by the operating temperature and the approximate half-life of the decomposition reaction. Further criteria include selecting an initiating radical species which has the correct character for the reaction at hand, for example powerful electrophilic alkoxy radicals are required to induce cleavage of the $\alpha$–$\pi$ bonds of amines and ethers or the alkyl $\pi$–$\pi$ bond of esters. Conversely, abstraction from the acyl group of an ester would require a nucleophilic alkyl radical. Azobisisobutyronitrile (AIBN) \textsuperscript{28} (Scheme 15) is an example of a commonly used radical inhibitor, its structural features provide many advantages over other initiators such as being activated by both photochemical and thermal means, safety when handling and low operational temperatures when compared to...
peroxide based initiators. The disadvantage of using AIBN is the docile reactivity of the produced cyanoisopropyl radical 29, which will only initiate homolytic cleavage of weak bonds. To circumvent the low reactivity, often tributyltin hydride (Bu₃SnH) is used in tandem with AIBN,¹⁹ where the cleavage of the weak Sn–H bond takes place by the cyanoisopropyl radical 29 to generate a tin-centered radical 31. Tin-centered radicals are excellent for the selective cleavage of C–X (X = I, Br, Cl) bonds which are commonly reactive centres in organic molecules, this is due to the relative bond strength of the stronger Sn–halogen bond compared to a Sn–C bond which is weak. Overall it is unlikely the tin centered radical will participate in unwanted addition reactions, however they are often avoided due to their toxicity.²⁰

![Scheme 15: Photochemical or thermal degradation of AIBN 28 generates cyanoisopropyl radicals 29 where abstraction of an H atom from tributyltin hydride 30 generates the tin-centered radical 31.](image)

1.1.5.2 Propagation

During the propagation steps, there is no net increase or decrease in the amount of radical species. A chain process requires a propagation cycle, in which at least two sets of propagation reactions repeat alternatively until all the starting material is consumed or the subsequent termination pathways dominate. Chain carriers are continuously regenerated through reaction with starting materials and initiators, driving product formation from the respective starting materials. An example of a propagation cycle is shown below in the Hoffman-Löffler-Freytag reaction, where the photolysis of protonated N-chloroamine 34 takes place to give a nitrogen centered radical 35 which can undergo a 1,5-translocation via a 6-membered transition state to generate the
corresponding alkyl radical 35 (Scheme 16). This alkyl radical can then undergo an abstraction process with the protonated $N$-chloroamine starting material to generate a $\delta$-chloroamine 37 which can then subsequently be cyclised to a pyrrolidine 38. This is a historic example of a remote intramolecular free radical C–H functionalisation, which outlines how discriminant reactivity in radical chain reactions has contributed significantly to the use of radical chemistry in modern day synthesis.

Scheme 16: Hoffman-Löffler-Freytag reaction to generate pyrrolidine derivatives via a radical chain reaction.

1.1.5.3 Termination

Termination in a radical chain process takes place when an alternative radical-radical reaction pathway involving at least one of the chain carriers in a propagation cycle.
occurs, this prevents further reactivity of the radical species in propagation cycle. Termination involves a radical-radical interaction (1.1.4.2) which often results in either a combination or disproportionation pathway. In solution, radical termination steps are diffusion-controlled processes. Therefore, to prevent unwanted termination reactions from taking place, the reaction conditions can be manipulated to achieve optimum results. Careful selection of initiator species based on half-life, portion-wise addition of initiator and a dilute reaction concentration can ensure unwanted termination products are avoided. Another aspect which is often important includes conducting the reaction under an inert atmosphere as oxygen in air can intercept the propagation cycle and form a peroxy radical, this will remove the species from the cycle and form unwanted by-products.

Termination processes can be useful in deciphering whether a reaction proceeds through an ionic or radical mechanism. 2,2,6,6-Tetramethylpiperidin-1-yloxyl (TEMPO) 41 (Scheme 17) is a typical radical scavenger which has a low energy barrier involving radical-radical interactions to allow for recombination pathways to dominate. TEMPO is commonly used as a tool in radical mechanistic studies, where its presence in a radical reaction allows the formation of a TEMPO-adduct species which can shed light on any intermediate radicals.

Scheme 17: Trapping of radical intermediate 40 using TEMPO 41.
1.2 C–H Bond Activation

Direct C–H bond activation has long been credited as the ‘holy grail’ of organic chemistry. Discriminatively activating an inert C–H bond is fundamentally powerful tool in synthesis for a multitude of reasons: (i) C–H bonds are ubiquitous; (ii) C–H activation enables shorter synthetic routes, removing the need for laborious syntheses utilising protecting and directing groups; and (iii) it allows for an atom economical process which reduces waste. Modern methods for C–H functionalisation include: (i) C–H activation via an oxidative addition step, carbon-metal intermediate through $\sigma$-bond metathesis, and concerted metalation deprotonation; (ii) usage of singlet carbenes or nitrenes to allow C–H insertion; and (iii) C–H bond homolysis via single electron transfer (SET) traditionally involving radical initiators or utilising first-row transition metal species such as iron or cobalt followed by radical functionalisation (Scheme 18).

Oxidative addition

![Scheme 18: Traditional methods of C–H activation.](image)

While traditional methods of C–H activation allow access to a plethora of complicated molecules, many protocols requires the usage of harsh reagents and/or additives to activate otherwise unreactive C–H bonds. Organometallic C–H bond activation often requires the usage of precious metals such as palladium and up to stoichiometric amounts of oxidants (e.g. H$_2$O$_2$, MnO$_2$ or PhI(OAc)$_2$). Carbenes and nitrenes are high energy materials, which require intricate reaction conditions (temperature
control/limited scalability) and constant monitoring alongside prior installation of the leaving group such as azides, iminoiodanes or sulfonamides to generate the reactive carbene/nitrene species. Radical initiators are generally toxic or shock sensitive and can be difficult to work with on a larger scale, reducing their appeal to industrial scale reactions. C–H activation processes using green oxidants while giving consistent and predictable site selectivity has been highlighted as one of the top three research areas by ACS Green Chemistry Institute Pharmaceutical Roundtable, further outlining the demand for new and sustainable methods for C–H activation. To achieve this goal, the synthetic organic community have developed elegant strategies for organometallic C–H activation by incorporating earth abundant metals such as iron or copper or alleviating the use of metals altogether. Perhaps one of the most sustainable and recent methods for C–H activation involve dioxygen and its ability to initiate C–H bond homolysis. While air has been used in homogenous catalytic oxidation of both organic and inorganic compounds, its presence in traditional C–H bond activation is scarce and presents an opportunity for further research into aerobic C–H activation.

1.2.1 Dioxygen, auto-oxidation & application in aerobic C–H activation

Dioxygen can exist as either the singlet (\( ^1\text{O}_2 \)) or triplet (\( ^3\text{O}_2 \)) electronic state. The electronic configuration of the triplet state consists of two unpaired electrons (Scheme 19) and is the ground energy state, therefore this energy state is often termed a ‘biradical’ as the unpaired electrons occupy two degenerate SOMOs (single occupied molecular orbitals). Atmospheric oxygen contains mostly triplet oxygen, however the higher energy singlet oxygen state is also present through atmospheric photosensitisation and UV absorption. Singlet oxygen has no SOMO present as all of it’s electrons are paired and can be thought of as a double bonded connecting two oxygen atoms. Consequently singlet (\( ^1\text{O}_2 \)) oxygen can behave as a dienophile in Diels-Alder type reactions. Importantly, dioxygen is able to interact with a carbon based radical to generate a peroxy radical, this interaction can allow for subsequent abstraction of a H atom bringing about the start of a chain reaction. This is often thought of as being problematic in a radical chain reaction, as addition of dioxygen to
a carbon-based radical (acting as a chain carrier) in a propagation step is likely to terminate the desired cycle or lead to unwanted by-products. As such, many radical reactions are carried out under inert conditions, preventing this interaction between atmospheric dioxygen and any radical intermediates.

Scheme 19: Molecular orbital diagram of triplet dioxygen ($^3\text{O}_2$).

Auto-oxidation is defined as the spontaneous oxidation of organic or inorganic systems in air. In an organic system, it is typically used to describe the propagation reactions in a chain reaction cycle in which dioxygen react with carbon radical species to form a peroxy radical. This peroxy radical can further abstract a hydrogen atom to form a peroxide product and regenerate further carbon radicals (Scheme 20). Initial C–H bond homolysis is achieved through the use of UV light or a radical initiator. This process if often inhibited, with many chemicals or solvents containing inhibitors such as BHT (2,6-di-tert-butyl-4-methylphenol) to prevent this process from happening. Importantly, there are examples in the literature of dioxygen interacting with C–H bonds to generate carbon radicals without the need for initiators or UV light. This type of radical generation allows for clean and efficient C–H activation, with very few examples in literature limited largely to the aldehyde auto-oxidation process.
Scheme 20: Dioxygen initiated C–H activation (top) followed by propagation steps in the radical pathway (bottom).

In order for the C–H bond to be susceptible to dioxygen-induced homolysis, a relatively low BDE (bond dissociation energy) is required such as those observed with aldehydic C–H bonds or α–C–H bonds in ethers (350-400 kJ/mol).\textsuperscript{36,37} The dioxygen-induced carbon radical formation can then be further trapped with the corresponding acceptor, such as alkenes, alkynes or azodicarboxylates (dependant on polarity matching rules) to allow for functionalisation utilising just atmospheric oxygen.

1.2.2 Aldehydes as a source of acyl radicals

One of the first examples using aldehydes as a source of acyl radical via the aerobic oxidation process was achieved by Caddick and co-workers.\textsuperscript{38} The authors show the reaction of aldehydes 43 with a range of vinyl sulfonates 44 under mild aerobic oxidation conditions that take place at just room temperature, furnishing several unsymmetrical ketones 45 in reasonable yields up to 70% (Scheme 21). The authors also follow up on this work, highlighting the use of water as a compatible ‘green’ solvent, producing similar yields of ketones.

Scheme 21: Metal/initiator-free hydroacylation of vinyl sulfonates 44.
The group prove the mechanistic pathway follows a radical route by showing the
reactions were completely inhibited in the presence of a radical scavenger such as
butylated hydroxytoluene (BHT). By confirming that the mechanism follows a radical
pathway, the group proposed the reaction is initiated by generation of an acyl radical
through the interaction of an aldehyde with oxygen in air. Following this work, further
publications highlighted the versatility of aldehydes as an acyl radical sources by
expanding the scope of hydroacylation to include α,β-unsaturated esters 46, vinyl
phosphonates and azodicarboxylates 48. Both diisopropyl azodicarboxylate (DIAD)
and diethyl azodicarboxylate (DEAD) showed compatibility with aliphatic and
aromatic aldehydes via an aerobic C–H activation pathway. The efficiency of the
radical chain reaction was further demonstrated with excellent yields being achieved
when employing aldehydes as the limiting reagent (Scheme 22).

Scheme 22: Metal/initiator-free hydroacylation of α,β-unsaturated esters 46 (top) and
azodicarboxylates 48 (bottom).

The general hydroacylation reaction was tolerant of a variety of functionalities attached
to the aldehyde moiety. This is an attractive feature of the reaction as it allows it to
be used in the synthesis of more complex scaffolds where a variety of functional
groups are likely to exist.

The mechanism for the aerobic hydroacylation pathway achieved by both Caddick and
Chudasama groups is initiated by the interaction of oxygen in air with an aldehyde 43
to form an acyl radical 50 (Scheme 23). Acyl radicals are nucleophilic in nature and by
following polarity-matching rules they can efficiently take part in radical addition to
electron-deficient unsaturated bonds 51 to give the corresponding electrophilic radical adduct species 52. This species 52 can abstract a hydrogen atom from the starting aldehyde, allowing efficient radical chain turnover and driving the formation of product 53 from the aldehyde.

Scheme 23: Proposed mechanism for the hydroacylation of aldehydes via aerobic C–H activation.

This work on aldehydes has been well demonstrated with the trapping of aerobically generated acyl radicals from aldehydes. Since aldehydes have been well studied in the past, the focus of this project will be on heterocyclic systems such as ethers, acetals or sugar derivatives and how aerobic C–H radical generation can be achieved.

1.2.3 Ethereal radicals

Ethereal radicals refer to species in which a radical exists on a carbon atom α- to an oxygen atom in an ether. This is because the alpha position is most commonly accessed experimentally, with a BDE of THF α–C–H shown to be 390 kJ/mol relative to the BDE of the β–C–H which is at ca. 410 kJ/mol. The formation of the α-THF radical has been experimentally observed to be consistent with C–O bond length shortening, outlining electron delocalisation of an oxygen lone pair with the SOMO. This effect is why ethereal radicals are nucleophilic in nature, and outline potential for α- ethereal radical species to react with electrophilic acceptors. The BDE’s of ethers
and acetals can vary depending on the structure,\textsuperscript{43} tertiary C–H bonds such as the one present in 2-methyltetrahydrofuran have lower BDE’s due to increased stability of the radical through hyperconjugation (Scheme 24). The presence of stabilising groups such as phenyl groups can also stabilise and lower BDE’s through $\pi$-conjugation.

\begin{center}
\textbf{Scheme 24:} Mean BDE of $\alpha$–C–H bonds in ethers and acetals.
\end{center}

\begin{center}
\begin{tabular}{c|c}
\hline
BDE: (kJ/mol) & 391.6 & 384.1 & 381.2 & 359.0 \\
\hline
\end{tabular}
\end{center}

\begin{center}
\textbf{Scheme 25:} (Top) Proposed pathway for insertion of singlet oxygen into (S)-2-methyltetrahydrofuran \textbf{54} to give (R)-2-hydroperoxy-2-methyltetrahydrofuran \textbf{55}. (Bottom) Proposed pathway for ethereal radical formation via interaction of C–H bond with triplet oxygen.
\end{center}

In 2017, work by Su \textit{et al.} investigated the mechanism of dioxygen induced oxidation of enantiopure (S)-2-methyltetrahydrofuran \textbf{54}.\textsuperscript{44} They reported minimal loss of enantiomeric purity when singlet oxygen ($^1\text{O}_2$) was inserted into the $\alpha$–C–H bond (Scheme 25). The authors attempted to prove this by isolating singlet $^1\text{O}_2$•THF chemical reaction products after photo irradiation of a THF solution in the presence of a singlet O$_2$ photosensitiser, e.g. meso-tetraphenylporphyrin. This led the authors to suggest a direct insertion pathway of singlet oxygen into the C–H bond, with no formation of any intermediate species. This was an intriguing result, as to date the direct interaction of oxygen with a C–H bond was assumed to always take place through a radical pathway. Owing to the fact that no radical intermediates was observed in the direct insertion pathway of singlet oxygen into C–H bonds, It was then
suggested triplet oxygen ($^3\text{O}_2$) is responsible for the radical pathway that takes place in the formation of organic radical species 57 observed in the auto-oxidation process. It is important to note, an alternative diffusion-based mechanism to explain the stereochemistry of product 55 was not proposed. The aerobically generated peroxy-radical could also diffuse away and approach the THF ring system from the top face giving product 55.

### 1.2.4 Generation of ethereal radicals

The typical method for C–H radical functionalisation in organic molecules involves homolysis of a C-X type bond ($X = \text{Cl, Br or I}$). A potential side-reaction to be vary of with $\propto$-C-X bonds of ethers is ionic elimination to yield the respective oxocarbenium cation 59 (Scheme 26). Therefore, reactions conditions must be tailored to avoid this.

![Scheme 26: Facile elimination of $\propto$-halo functionality in ethers to yield oxocarbenium cation 59.](image)

Therefore, C–H abstraction processes are generally employed to access ethereal radicals. The relatively low BDE of $\propto$-C–H of ethers allows the use of traditional radical initiation methods to access the $\propto$-ethereal radicals (Scheme 27). This includes peroxide-based initiators and triethylborane-air mediated C–H abstraction.  

![Scheme 27: Traditional methods for ethereal radical formation via C–H bond homolysis](image)
1.2.5 The importance of Sp$_3$-C–H functionalised heterocycles

Saturated heterocycles are important motifs that are prevalent in numerous pharmaceuticals and natural products. The importance is highlighted by the piperidine ring, which is long known in the medicinal chemistry setting as the most abundant saturated heterocycle system in small-molecule therapeutic agents. The tetrahydrofuran scaffold is present in both DNA and RNA and is common in drug design targeting nucleic acids. THF based nucleoside analogs also make up the largest class of DNA methyltransferase inhibitors, which are routinely used in the treatment of a variety of cancers (Scheme 28).

![Scheme 28: Tetrahydrofuran-containing polymerase and kinase inhibitors receptively.](image)

There is also a growing interest in the use of sp$_3$-rich heterocycle heterocyclic scaffolds for pharmaceutical applications where they are considered likely to reduce attrition in the drug discovery pipeline. Their widespread use in the industry is held back by the difficulty in synthesising these molecules from readily available precursors. Most small-molecule pharmaceuticals contain between one and four ring systems due to the lower conformational entropy to be overcome upon target binding. Saturated rings however in some cases can be inherently more drug-like than planar aromatic heterocycles; saturation increases water solubility and imparts desirable three-dimensional occupancy of a target site, toxic metabolites due to arene oxidation are also avoided. Departure from exclusively aromatic rings such as benzene, pyridines and imidazoles also allows for greater stereochemical diversity for a small increase in molecular weight and increased structural novelty (stereoisomerism) which can assist in the patentability process.
1.2.6 Existing methods of radical C–H functionalisation of ethereal systems

Traditional methods for radical C–H functionalisation of heterocyclic ether systems can take place through metal-catalysed coupling reactions usually containing a peroxide based radical initiator or metal-free coupling reactions which solely utilise initiators. Work by Lie et al.\textsuperscript{55} demonstrates a copper-catalysed coupling strategy between α-amino carbonyl compounds \textit{60} and ethers \textit{61} in the presence of TBHP (\textit{tert}-butyl hydrogen peroxide) to achieve C(sp\textsuperscript{3})-H bond activation (Scheme 29) in reasonable yields (50-82\%). The reaction conditions tolerates 25 different α-amino carbonyl compounds containing an electron-donating (methoxy) or withdrawing group (halogens) on the aromatic ring. Similarly, many ester groups are compatible such as methyl esters, phenyl esters and pthalimide groups. A temperature of 50 °C is required to promote initiation of the ethereal radical by TBHP (1.2 eq.) alongside a catalytic loading of 2% CuCl\textsubscript{2}. Unfortunately, a large excess of ether is required (15 eq.) which is problematic as it limits the sustainability and scalability of the reaction.

\[
\begin{align*}
\text{ArHN} & \quad \xrightarrow{\text{CuCl}_2, \text{TBHP}} \quad \text{R}^1 \quad \xrightarrow{50 \degree \text{C}, 12 \text{~h}} \quad \text{ArHN} \\
\text{R}^1 & = \text{OPh, OEt, NHPH, NMePH} \\
\text{Heterocycles:} & \quad \text{S, O, O, O, } \\
& \quad \text{O, } \\
& \quad \text{f} \\
\end{align*}
\]

Scheme 29: Optimised reaction conditions for C(sp\textsuperscript{3})-H bond activation of ethers.

The authors also proposed a mechanism where the \textit{tert}-butoxy radical is generated by heat in the presence of Cu\textsuperscript{+}, which then allows subsequent abstraction of an α-hydrogen atom from ether \textit{56} to generate the ethereal radical \textit{57} (Scheme 30). This nucleophilic radical is then able to react with 1-phenyl-2-(phenylamino)ethenone \textit{60} to give a radical cation \textit{64}. Hydrogen abstraction from the generated cation \textit{64} in the presence of Cu\textsuperscript{2+}(OH) allows for formation of the desired product \textit{65} and regenerates the copper species Cu\textsuperscript{2+}.\textsuperscript{55}
Regioselective cross-coupling between ethers and coumarins or flavones under oxidative conditions was demonstrated by Zhou et al.\textsuperscript{56} THF was successfully functionalised with a coumarin moiety in the presence of 10 mol\% FeCl\textsubscript{3} as a catalyst, utilising TBHP (3 eq.) as an initiator and 1 eq. of DABCO as a ligand to afford the corresponding product 68 in a 62\% yield (Scheme 31). Few examples were showcased, with electronically varied coumarins reacting well with various ethers to give the ether-coumarin adducts in moderate yields. Substitution of the ester moiety took place solely on the electron rich $\alpha$-position of the coumarin ester. No adduct was observed when a nitro group was present on the coumarin moiety, perhaps due to degradation of the functional group when exposed to a large excess of radical initiator (3 eq.) or lack of compatibility with electron-poor groups. The reaction also takes place at high temperature (120 °C) and so scalability is an issue due to the relatively low boiling points of the substrates (THF - 66 °C, THP - 88 °C, 1,4-dioxane - 101 °C).

Scheme 31: C–H activation of coumarin derivatives with ethers.

Scheme 30: Proposed mechanism for the C(Sp\textsuperscript{3})-H bond activation of ethers.
This reaction was then extended to flavone type systems 69 where 10 mol% CuO was identified as a more compatible metal catalyst, whilst keeping the rest of the original conditions for coumarin functionalisation the same (Scheme 32). In this case, coupling took place at the electron deficient $\beta$-position of the flavone 69, giving good yields ranging from 68-78%, although diversification of the flavone system was not explored in depth besides a few minor electronic modifications.\textsuperscript{56}

Scheme 32: C–H activation of flavanone derivatives with ethers.

While there are many further examples in the literature of C–H activation of heterocyclic ethers which utilise transition metals and radical initiators to form C–C bonds, perhaps the most pioneering work has been published in recent times taking advantage of visible light or photoredox catalysis methods. Work by MacMillan \textit{et al.}\textsuperscript{57} showcased a mild method for catalytic photoredox C–H functionalisation of ethers with heteroarenes via a Minisci type process (Scheme 33). THP (tetrahydropyran) 71 was successfully arylated with a wide range of isoquinolines 72 while utilising an iridium photocatalyst ([$\text{Ir(dF(CF}_3)_{ppy})_2(\text{dtbbpy})$]PF$_6$) and a household 26W lamp (CFL). Other additives include sodium persulfate to help cycle the radical process and TFA (trifluoroacetic acid) to allow protonation of the heteroarenes in the Minisci radical addition. The scope was wide ranging, showing compatibility with C-6 and C-4 bromo substituted isoquinolines 74 and C-2 chloro substituted quinolones and quinoxalines 78. The reaction was also tolerant of substituted pyridine 75 and various pyrimidine derivatives, giving excellent yields ranging from 60-85% for a mild method taking place at only 23 °C. THF derivatives also coupled well with isoquionlines, and regioselective
arylation of tetrahydrofurfuryl acetate 76 was possible at the α-methylene carbon atom in an impressive 77% yield.57

![Chemical structure 1](image1)

**Examples:**

![Chemical structures 2](image2)

Scheme 33: Photoredox mediated coupling between ethers and heteroarenes.

Recent work by Lambert *et al.* demonstrated an elegant strategy for a highly regioselective electrophotocatalytic C–H functionalisation of ethers.58 The reaction is catalysed by a trisaminocyclopropenium (TAC) 79 ion at mild electrochemical potential with visible light irradiation. The TAC electrophotocatalyst is able to convert to the open shell photoabsorptive TAC radical dication via anodic oxidation (Scheme 34). Once the radical cation is photoexcited, the radical cation is sufficiently strong enough to allow hydrogen atom abstraction to take place ($E_{\text{Red}} = 3.33\text{V vs SCE}$).

![Chemical structures 3](image3)

Scheme 34: Electrophotocatalysis with a trisaminocyclopropenium radical cation (TAC).
The authors demonstrate the utility of TAC 79 by activating ethers to undergo coupling with various electron deficient quinolines 80 and 81 in good yields ranging from 40-80% depending on the complexity of the substrate (Scheme 35). A reasonable 8 mol% catalyst is employed, which is acceptable for an organocatalyst, however long irradiation times (36 h) perhaps reduce the usefulness of the method. Most impressively, only one regioisomer is observed when employing 2-methyl THF showing preference for primary C–H bonds over secondary, the authors reason the steric difference between the two positions outweighs the greater stability of the intermediate secondary carbon radical give 81.58

Scheme 35: A broad range of substrates are shown to be compatible with TAC electrophotocatalysis, with only one regioisomer observed when applicable.

No reaction is observed when only tertiary C–H bonds are present in the α–C–H position. The authors then further apply the methodology to electron-deficient alkenes (vinyl sulfones and acrylate esters) and alkynes (propargylic esters), showing excellent compatibility and regioselectivity with only one regioisomer observed and yields from 32-72% (Scheme 35). Finally, azole systems 82 are also tolerated in high
yields (50-89%) and one regiosomer is observed in all cases. This highlights a significant development on the previously mentioned pioneering work of MacMillan et al.\textsuperscript{57} as a larger scope is appraised outside of electron-deficient heteroarenes, without the need for expensive Iridium based photocatalysts.

Recently published work reported in the Chudasama group has shown a procedure for α-C(\textit{sp}^3)–H amination of ethereal compounds through use of azodicarboxylates as the sole nitrogen source.\textsuperscript{59} Ethereal radical intermediates (Scheme 36, \textit{57}) are accessed solely through the use of atmospheric oxygen and fluorinated alcohols such as HFIP and 2,2,2-trifluoroethanol (TFE), which are shown to greatly increase the susceptibility of azodicarboxylates to undergo reactions with radical intermediates \textit{via} H-bonding. This was shown to be the case computationally, where Fukui function calculations indicate a H-bonding interaction adjacent to the N=N bond of the azodicarboxylate \textit{83}.

Scheme 36: Optimised reaction conditions and proposed mechanism for α-C(\textit{sp}^3)–H amination of ethereal compounds with azodicarboxylates. THF \textit{56} and diisopropyl azodicarboxylate (DIAD \textit{83}) are shown as representative examples.
This process results in a decrease in energy of the LUMO of the N=N bond, allowing for increased susceptibility to nucleophilic attack from ethereal radicals and vastly increasing the efficiency of the reaction. As well as providing a lower energy pathway for radical attack, the H-bonding interaction between THF and HFIP allows for access to higher reaction temperatures (boiling point – 100 °C), a significant increase of 34 °C in comparison to neat THF.

All readily available azodicarboxylates (i.e. DIAD, DEAD etc) were shown to be compatible with the reaction conditions, achieving good to excellent yields (72-94%) resulting in azodicarboxylate adducts with carbamate esters (methyl, isopropyl, benzyl, etc.) that could be removed under basic, acidic or hydrogenation conditions. Further to this, a broad portfolio of molecules were functionalised including cyclic acetals, acyclic ethers and even a sulfur based heterocycle in tetrahydrothiophene (THT) in moderate to excellent yields (49-94%). Overall, the work represents a simplistic and powerful method for α-C(sp³)–H amination of ethereal compounds and the synergy between HFIP and DIAD provides room for further investigation between the interaction of fluorinated alcohols with electrophilic π-type systems.59

With successful formation of aerobic ethereal C–N bonds achieved, it was postulated that the aerobic heterocycle C–H activation protocol could be adapted to the goal of forming aerobically constructed C–C bonds. It was speculated that the H-bonding abilities of HFIP could serve to make C–H bonds more prone to rupture alongside lowering the LUMO of any π-acceptors to further increase susceptibility to nucleophilic radical attack.
1.2.7 The use of HFIP as a C–H activation solvent

HFIP (1,1,1,3,3,3-hexafluoro-2-propanol) is a versatile fluorinated alcohol which has recently gained popularity in the synthesis community.\textsuperscript{60,61} Its unique properties allow use of the alcohol as either an acid promoter, a solvent and/or additive which has significant advantages over other alcohols such as isopropyl alcohol or ethanol. The presence of the strong electron-withdrawing trifluoromethyl groups endow HFIP with properties such as strong hydrogen-bond donation (HBD) ability, high polarity and ionising power, low nucleophilicity, increased Brønsted acidity of the hydroxyl proton and the ability to solvate anions and stabilise cations.\textsuperscript{60,61}

One of the key properties that contributes to the major work in this thesis (Chapter 2, Section 3.2) is the ability of HFIP to act as a hydrogen bond donor. The mild acidity of HFIP (pK\textsubscript{a} – 9.3) aids the ability of the solvent to function as a hydrogen bond donor. This phenomenon is amplified by higher-order aggregates which increase the hydrogen bond ability of the solvent. Works by Berkessel \textit{et al} named this the “booster effect”, they measured an enhanced complexation constant K\textsubscript{c} = [complex]/[HFIP][1,4-dioxane] of 33 L mol\textsuperscript{-1}, which is significantly larger than that of the methyl ester of HFIP (0.76 L mol\textsuperscript{-1}).\textsuperscript{62} This is due to the H-bonding from the terminal hydrogen atom of an oligomeric structure such as trimer 85 (Scheme 37). These oligomers were observed in crystal structures and computational studies.

\begin{center}
\textbf{Scheme 37: H-bonding abilities of HFIP, the boiling point of the THF-HFIP complex is 100 °C which is considerably higher than the boiling point of neat THF (66 °C).}
\end{center}
1.3 Radical Acceptors

1.3.1 Hypervalent iodine reagents as radical acceptors

Hypervalent iodine reagents (87 and 88) represent an intriguing classing of electrophilic acceptors. The iodine atom can be substituted with a variety of functional groups including alkynes, alkenes, heteroarenes and trifluoromethyl functionalities. The non-classical 4-electron-3-centre bond of hypervalent iodine is weaker than the normal bonds (Scheme 38), allowing this class of molecules to confer exceptional reactivity as electrophilic acceptors. Both the electrophilic nature of the iodine atom and the reactivity of the relatively weak C-I bond allows for convenient access to electrophilic synthons starting from nucleophiles. The high reactivity of these reagents can be problematic however, with degradation of the scaffold possible in the presence of a strong base, transition metal or high temperatures. In this content, benziodoxol(on)es (BX) 89 are a class of cyclic hypervalent iodine reagents that have shown increase stability due to the iodine atom being connected a heterocycle. BX reagents also benefit from the trans-effect in the hypervalent bond, this is a well-known phenomenon defined as the extent to which the ligand weakens the bond trans to itself in the equilibrium state of the complex.65

\[
\text{Scheme 38: Reactivity of hypervalent iodine reagents and different classes of BX reagents 90-98.}
\]

Ethynylbenziodoxol(on)es (EBX) reagents 95 were first introduced by Ochai and Zhandkin and are increasingly used in synthesis.66,67 From 2015 onwards, an increasing number of reports highlighted the exceptional reactivity of EBXs and
confirmed the importance of EBXs as a reagent of choice to undergo alkynylation reactions under oxidative conditions. The high stability of EBX-TIPS 97 ([Triisopropylsilyl]ethynyl]-1,2-benziodoxol-3(1H)-one) tolerates a range of reaction conditions. The bulky silyl protecting group is effective at shielding the triple bond, limiting side reactions in numerous processes and can give access to versatile terminal acetylenes which can be accessed easily after silyl deprotection. Recent work by Waser et al., showcased an example of the first oxidative C–H alkynylation of arylcycloproanes 99 utilising EBX 98 as an alkynylating reagent.69 Arylcyclopropanes have been shown to form a reactive radical cation using an appropriate copper catalyst alongside a strong oxidant or photoredox metal catalysis, however these methods usually result in ring-opening reactions promoted by the release of ring strain.

Scheme 39: C–H or C–C alkynylation of cyclopropanes via aryl radical cations generated through direct light activation.
The optimised reaction (Scheme 39) found that variation of the aryl group on the cyclopropane could result in either the ring opened C–C oxyalkynylated product or direct C–H alkynylation. The cyclopropyl radical was generated through photochemical means by using a Kessil 440nm lamp and between 1.5-2.5 equivalents of Ph-EBX. The methodology was successfully applied to a range of arylcyclopropanes for the C–H functionalisation reaction showing excellent functional group tolerance for substituents in the meta and para position, with yields between 44 and 92%. Para-substituted EBX reagents were less effective presumably due to the steric clash between the requisite dimethyl group in the para-positions of the arylcyclopropane. The scope for the alternative C–C oxalkynylation pathway was wider ranging showing varied functional group tolerance and reasonable yields between 40-70% (Scheme 39).

Interestingly, the authors speculate the switch of chemoselectivity when introducing a second ortho-methyl group on the arene ring is due to the strong steric interaction with the cyclopropane, and hence the less favoured perpendicular conformation becomes lower in energy leading to the C–H alkynylation product. The authors then go on to confirm the confirmational analysis of radical cation conformations via DFT studies to support their findings.

Another example of the utility of EBX reagents is showcased by recent work by Zhang and co-workers, through a stereoselective C-glycosylation by photocatalytic decarboxylative alkynylation on the anomeric position. They utilise a carboxylic acid group in the anomeric position of the sugar molecule 105, which in the optimised reaction is decarboxylated using potassium carbonate, an iridium photocatalyst, 34 W blue LEDs at a mild operating temperature of 40 °C (Scheme 40). Most impressively, they observed a diastereoselectivity of $\beta:\alpha > 99/1$ and can functionalise the C-glycoside with a range of arene groups via the EBX payload 95 including electron-donating moieties such as methoxy 107 and alkyl 108 functionalities in yields up to 83%. Electron-withdrawing groups are also tolerated such as a cyano 108 (55%), acyl 109 (56%) and trifluoromethyl groups 110 (61%). However, alkyl groups such as TIPS 107 (20%) and n-pentyl 112 (22%) were found to be low yielding. Similar
diastereoselectivities were observed when applying the method to other anomeric acids in sugars (Scheme 40), however functionalisation of deoxyribosyl acid 115 was less selective giving a $\beta:\alpha$ ratio of 1:2 respectively.

Scheme 40: Substrate scope of stereoselective C-glycosylation using EBX reagents.\textsuperscript{70}

1.3.2 Acetylenic triflones as radical acceptors

Acetylenic triflones 117 are a versatile class of radical acceptors, known for their exceptional reactivity as an electrophilic terminal alkyne source.\textsuperscript{71} They are a well investigated class of radical acceptors where additions generally proceed with high regioselectivity at the terminal position. The presence of the triflone functional group only enhances the efficiency of the radical chain process as once radical addition takes place onto the alkynyl triflone, $\cdot$SO$_2$CF$_3$ 118 is liberated as a leaving group (Scheme
41), which further fragments into the highly reactive $\cdot$CF$_3$ radical 119. The trifluoromethyl radical can then take part in most H-abstraction processes to further the generation of reactive radical species. This is due to the low-lying SOMO in the highly electrophilic radical and compared to the methyl radical it is 440 times quicker to react with styrene.$^{72}$ The factor which governs the high reactivity is the pyramidalization of the CF$_3$ radical (Section 1.1.2.1).

![Scheme 41: General reactivity of acetylenic triflones.](image)

Select examples:

121, 60% ($dr$ = 72:28)

122, 49% ($dr$ = 73:27)

123, 54% ($dr$ = 72:28)

124, 63% ($dr$ = 72:28)

125, 24% ($dr$ = 71:29)

126, 57% ($dr$ = 72:28)

Scheme 42: Substrate scope where the acetylenic R group 117 is varied to provide structural diversity.

Work by Studer and co-workers, highlights the versatility of the acetylenic triflones where they construct highly substituted cyclopentanes through 1,1,2-trifunctionalisation of terminal alkynes via a radical addition-translocation-cyclisation strategy.$^{73}$ They employ 20 mol% BPO (benzoyl peroxide) as a radical initiator and a
carefully selected terminal alkyne scaffold 120 in the presence of acetylenic triflone 117 (Scheme 42). Through a radical cascade mechanism, they are successfully able to generate substituted cyclopentanes in good yields between 50-75%. Variation of the R group on the acetylenic triflone allows access to a diverse portfolio of substituents including electron withdrawing substituents 121-122, electron donating groups 123-124 and heterocycles such as thiophene 125 and benzofuran 126.

The authors were also able to alter the scaffold to tolerate different malonic esters, where steric effects related to the esters did not impact the yields observed. Impressively, the methodology was applied to more complicated bicyclic systems 130 and spiroannellated bicycles 131; although these reactions were not found to be particularly diastereoselective. The authors speculate the 5-exo-cyclisation forming the 5-membered ring occurs with complete selectivity, however poor selectivity is observed for the trapping of the cyclised radical with triflone 117. Whilst the 1,2-difunctionalisation of π-systems is very well explored in the field of radical chemistry, alkyne trifunctionalisation is rare, outlining the strong reactivity of acetylenic triflones in radical cascade mechanisms.

![Scheme 43](image)

Select examples:

- 128, 64% (dr = 72:28)
- 129, 50% (dr = 79:21)
- 130, 70% (dr = 51:49)
- 131, 65% (dr = 66:34)

Scheme 43: Further exemplification of the methodology on varied malonic esters 128 and 129, bicyclic system 130 and spiroannellated bicycle 131. 73
1.4 Aims

The main goal of this project is to take advantage of the aerobic auto-oxidation mechanism, which is largely viewed as a nuisance degradation process, and apply it in a pathway where it can be manipulated to form desirable products. The key aspiration is to develop optimised methodologies for the formation of heterocyclic entities by using oxygen in air for C–H activation. This can be achieved by identifying heterocyclic moieties that are susceptible to oxidation in air via a radical pathway, and then picking appropriate radical trapping agents to allow the formation of new C–C bonds in chain reaction process. A particular emphasis will be placed on the formation of C–C bonds via regiospecific C–H bond functionalisation as this area is relatively unexplored in the literature and could lead to the development of a important novel methodologies.

![Scheme 44: General radical pathway involving radical trap T.](image)

Polarity matching rules will be used to identify appropriate radical trapping agents (i.e., the use of electrophilic trapping agents would be used to trap a heterocyclic nucleophilic radical). Emphasis will be placed on reducing the equivalents of heterocycle used to improve the atom economy of the process and make it an attractive choice over existing methodologies in the literature. Functionalisation to create new reactive centres in the heterocycles such as alkynes or alkenes will be explored with a goal to create methodology which is completely independent of initiators or precious metal catalysts commonly used in the field of C–H functionalisation.
Exploiting Auto-oxidation of Heterocycles for C-C Bond Formation – R&D

2.1 Introduction

Saturated heterocycles represent important motifs that are present in numerous pharmaceuticals and natural products. There is a growing interested in the use of sp$^3$-rich heterocyclic scaffolds for pharmaceutical applications where they are considered likely to reduce attrition in the drug discovery pipeline (Chapter 1, 2.1.5).$^{49,53}$ Their widespread use is still held back by the difficulties in synthesis of these molecules from readily available precursors. Approaches which can functionalise heterocycles directly in one step can be demanding and limited in scope. The direct sp$^3$ C–H functionalisation of saturated heterocycles is a potentially useful and valuable strategy which could allow a plethora of compounds to be synthesised from readily available precursors, with C–C bond formation arguably being the most important and valuable transformation. However, current available methods for the direct C–H activation of saturated heterocycles require: (i) the presence of precious and/or toxic transition metal catalysts;$^{74,75}$ (ii) complicated directing group scaffolds/protecting groups, which necessitate additional installation and removal steps;$^{76,77}$ (iii) external additives or initiators which can be used up to stoichiometric quantities than then must be separated from the product;$^{28,78}$ (iv) high energy materials such as diazo compounds, which can have storage issues or be difficult to handle.$^{79,80}$ To overcome these limitations and improve overall sustainability, new methodologies than enable simple and sustainable C–H functionalisation of sp$^3$-rich heterocycles are required.$^{81}$

Radical-based C–H bond activation is a potentially discriminant and versatile strategy for the functionalisation of saturated heterocycles.$^{82,83}$ However, existing approaches, whilst effective, typically employ specialised initiators and/or careful management of
reaction conditions to achieve this in a controlled fashion.\textsuperscript{84–86} Aerobic C–H activation, utilising oxygen in air to promote radical-based C–H bond rupture, represents a potentially ideal approach, but importantly to date has not been exploited for the formation of C–C bonds on saturated heterocycles. To explore this idea, tetrahydrofuran (THF) was initially examined as a candidate for C–H activation as THF derivatives are highly sought after whilst having a reasonably low BDE (391 kJ mol\textsuperscript{-1}).\textsuperscript{87} The interaction of molecular oxygen with the $\alpha$-C(sp\textsuperscript{3})-H in THF is known to result in the generation of a nucleophilic radical intermediate 57 (Scheme 45), which then reacts with a second equivalent of oxygen to form a peroxy radical and completes the chain reaction by C–H activation of THF to form a peroxide species, re-generating the radical intermediate 57 (Scheme 45).\textsuperscript{44,88–90} With this knowledge in hand, the initial plan involved finding a suitable trapping agent so an alternative chain reaction to afford THF derivatives with a new C–C bond could take place. This could form a general strategy for the preparation of $\alpha$-functionalised ethers, which are important scaffolds in drug discovery, representing more than 20\% of the top 200 small molecule drugs in the pharmaceutical industry (Scheme 45).\textsuperscript{91}

\begin{center}
\textbf{Scheme 45:} Aerobic oxidation of THF 56 to form a peroxide species via reactive nucleophilic radical intermediate 57 (top). Bioactive $\alpha$-functionalised ethers scaffolds present in pharmaceuticals.\textsuperscript{92–94}
\end{center}
2.2 Initial investigation of electrophilic radical acceptors

As electron-poor alkynes were expected to be highly reactive towards the nucleophilic ethereal radical, a range of alkyne reaction partners bearing leaving groups that could propagate a chain reaction cycle were tested (Scheme 46). The expected alkynyl-THF products would also then provide a synthetically versatile scaffold, which could be readily manipulated to achieve further molecular complexity through transformations of the triple bond. The initial reaction conditions were set based on previous work in the Chudasama group,\(^5^9\) where HFIP was found to be pivotal in forming a THF-HFIP complex which has an approximate boiling point of 100 °C compared to the boiling point of THF (66 °C). This allows access to higher temperatures which aids in accelerating the oxidative process and forming the subsequent THF radical. Another important parameter included limiting the amount of substrate to only five equivalents of heterocycle, with the goal of avoiding usage of a vast excess of heterocycle as done by previous reports on THF functionalisation mentioned in Chapter 1 Section 2.1.7.

![Scheme 46: Choice of electrophilic radical acceptors trialled in the initial study.](image-url)

Compounds 134–136 are readily available and have previously demonstrated success with radical chain reactions. Compounds 137 and 96 were synthesised (Scheme 47 and 48). Recent work by Alcarazo and co-workers outlined the utility of sulphur-based alkynyl dibenzothiophenium salt 137 for alkynylation reactions,\(^9^5\) these scaffolds have been shown to have a strong functional group tolerance and wide-ranging substrate scopes.\(^9^6,^9^7\) Whilst reports on radical compatibility of such sulphonium salts are scarce, it presented an opportunity for further study. Dibenzothiophenium triflate salt 137 was synthesised by treating dibenzothiophene 138 (Scheme 47) with hydrogen peroxide to obtain the corresponding S-oxide 139, which was subsequently reacted...
with one equivalent of triflic anhydride and TMS-protected alkyne to generate alkynyl dibenzothiophenium triflate 137.

\[
\begin{align*}
\text{S} & \quad \text{TfOH, } H_2O_2 \quad \text{S} \\
& \quad \text{ii) TMS} \quad \text{S} \\
& \quad \text{TMS} \quad \text{Ph} \\
\end{align*}
\]

Scheme 47: Synthesis of alkynyl dibenzothiophenium triflate.

Acceptor 96 represents a class of ethynylbenziodoxol(on)es (EBX) reagents, which were discussed in Chapter 1 section 2.1.8 and have increasingly been used in radical synthesis methods since 2009. The presence of a leaving group (2-iodobenzoic acid) also enables more controlled reactivity and decreased the likelihood of polymerisation. Acceptor 96 (Scheme 48) was synthesised by refluxing 2-iodobenzoic acid 140 in sodium periodate and aqueous acetic acid (30%) to give intermediate 141 which was activated with trimethylsilyl trifluoromethanesulfonate and functionalised with the corresponding TMS alkyne to give 96 in 82% yield.

\[
\begin{align*}
\text{COOH} & \quad \text{NaI0}_4 \quad \text{aq AcOH 30\%} \quad \text{Refux, 4 h} \\
& \quad \text{TMS} \quad \text{TMS} \\
& \quad \text{S} \quad \text{TMS} \quad \text{Ph} \\
\end{align*}
\]

Scheme 48: Synthesis of TMS-EBX (trimethylsilyl ethynylbenziodoxol(on)e)

With the radical acceptors in hand, reaction with THF 56 in HFIP was trialled (Table 1). Unfortunately, vinyl phosphonate 134 and vinyl sulfonate 135 were prone to polymerisation. TLC analysis of both reaction mixtures led to immobile baseline spots on the TLC plate and crude NMR analysis showing broad peaks in the aliphatic region of both reaction mixtures. Similar degradation of dimethyl 2-ethylidenemalonate 136 was observed by both NMR and TLC. This was hypothesised to be due to the acidic nature of HFIP (pKa – 9) and high temperature involved (80 °C). The hypothesis was tested by independently stirring acceptors 134-136 in neat HFIP at 80 °C, which led to subsequent degradation and polymerisation of the vinyl starting materials.
Table 1: A variety of electron deficient alkenes and alkynes were trialled as radical acceptors. *= yield via internal standard using pentachlorobenzene.

Incomplete conversion of salt 137 was observed in the reaction conditions due to the poor solubility of the dibenzothiophenium salt in the THF-HFIP mixture, giving no alkynylation. Increasing the temperature to 100 °C had no effect on the solubility of the salt and trying an alternative fluorine-based solvent such as TFE (trifluoroethanol), did not remedy the issue.

The highly reactive TMS-EBX 96 was then subjected to the reaction conditions (Scheme 49), with NMR analysis showing the complete consumption of TMS-EBX
within 4 hours and the formation of the desired THF-TMS alkyne adduct 138 in a promising 78% NMR yield (via use of pentachlorobenzene as an internal standard). Unfortunately, the volatile nature of the product made isolation difficult, independent attempts to work-up the reaction in pentane (boiling point – 36 °C) and carry out column chromatography in pentane led to no desired product being isolated. Literature preps for volatile alkyne isolation do exist, allowing for this with the usage of dicobalt octacarbonyl (Co$_2$(CO)$_8$) as an alkyne protecting group due to the high affinity of cobalt for alkynes, although this was not appraised at this stage due to an extra protecting group step. Instead, a bulkier silyl group, i.e. TIPS (triisopropylsilyl), on the EBX scaffold was synthesised 97 and appraised in the reaction conditions, in the hope of decreasing the volatility of the desired adduct whilst showcasing reaction scope. Similarly, this acceptor worked reasonably well with a 71% NMR yield of 139 (via internal standard using pentachlorobenzene) but the product remained volatile enough to evaporate during either work-up and/or column chromatography in pentane.

Scheme 49: Various EBX reagents showing promising functionalisation of THF. Adducts 138 and 139 were volatile and direct isolation was not possible. Ph-EBX 98 yielded an isolable product 140 and unwanted side-product 141.
Finally, the THF-phenyl alkyne product analogue 140 (Scheme 49) was synthesised as this would presumably be isolable via either an ethyl acetate work-up or via column chromatography. To do this, Ph-EBX 98 was synthesised and subjected to the reaction conditions with THF. This returned a 60% isolated yield of the desired alkyne adduct 140 after classical aqueous work-up in ethyl acetate and provided an example of C–C bond formation on THF under aerobic C–H activation conditions.

Upon further analysis of the reaction mixture obtained when reacting 98 with THF and HFIP, an interesting side-product 141 was isolated. A mechanism for its formation is postulated (Scheme 50). It is thought that HFIP protonates the oxygen on 98, allowing for water to attack the alkyne and subsequently break the weak C-I bond 142. Keto-enol tautomerization then likely takes place to allow formation of a carbene-type C=I bond 143 which is stabilised by the carbonyl group. The C=I bond then deprotonates the carboxylic acid, facilitating nucleophilic attack of the weak C-I(+) bond by the carboxylate to give rearranged product 141, thus outlining the need to remove water from the reaction and ensure dry conditions throughout. Temperature and stirring rate are other factors which could potentially contribute towards the undesired formation of adduct 141,59 alongside the amount of HFIP used. This will be discussed in more detail below. Overall, an excellent preliminary result was observed with an alkyne acceptor with the potential to improve yield through reaction optimisation.

Scheme 50: Postulated mechanism for the formation of rearranged product 141.
2.3 Reaction Optimisation

Initially, the equivalents of THF were reduced from five to three to one respectively (Table 2, entries 1-3), however, this resulted in below optimal yields of desired product 140, with a one to one equivalence giving incomplete conversion of Ph-EBX 98. The reaction was also attempted in the dark, in case visible light was driving the formation of rearranged product 141, however, this was not the case and an identical yield was observed with visible light present (Table 2, entries 4 and 1 (respectively)). In an attempt to reduce the amount of undesired rearranged product 141, the amount of HFIP was first decreased from 2.0 mmol to 1.0 mmol in order to lower the acidity of the reaction mixture, pleasingly the amount of 141 decreased by almost a half while also slightly increasing the amount of desired adduct 140 (Table 2, entry 5). Use of other fluorinated alcohols such as TFE (trifluoroethanol) and perfluoro-tertbutyl alcohol were also explored and proved to be unfruitful, leading to large amounts of undesired adduct 141 (Table 2, entry 6-9).

![Chemical Structures](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Temp</th>
<th>Solvent</th>
<th>THF (equivs)</th>
<th>Other conditions</th>
<th>Yield (140) (%)</th>
<th>Yield (141) (%)</th>
<th>Ph-EBX (%) Conversion</th>
</tr>
</thead>
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<td>HFIP (2.0 mmol)</td>
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<td>58</td>
<td>20</td>
<td>100</td>
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<tr>
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<td>80</td>
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<td></td>
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<td>In the dark</td>
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<td>80</td>
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<td></td>
<td>62</td>
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</tr>
<tr>
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<td>80</td>
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<td></td>
<td></td>
</tr>
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<td>100</td>
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<tr>
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<td>5</td>
<td>MgSO₄ (3 eq.)</td>
<td>70</td>
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<td></td>
</tr>
</tbody>
</table>

Table 2: Optimisation table for the radical C−H functionalisation of THF 56 with Ph-EBX 98.
To further understand why complete conversion to desired adduct 140 was not obtained, a variety of controls were also set up with Ph-EBX and HFIP independently (Table 2, entries 10-14). The general trend showed at higher temperatures promotion of rearranged product 141 increased approximately linearly, however attempting to carry out the reaction at lower temperatures (Table 2, entries 15-17) resulted in the opposite trend with no reaction taking place at room temperature. This highlighted that higher temperatures were crucial for a larger yield of the desired THF alkyne adduct 140. The desired product 140 was also independently subjected to THF and HFIP at 80 °C and showed no degradation (Table 2, entry 18) outlining a stable product relative to the reaction conditions.

Since both temperature and solvent parameters were explored, another factor which could lead to adduct 141 was the presence of water. Drying agents such as MgSO₄ and 4Å molecular sieves were employed, with both agents being dried/activated in an oven for 24 hours at 80 °C prior to being employed (Table 2, entries 19-22). Both THF and HFIP were also stored with molecular sieves and FPT (freeze, pump, thawed) to remove any remaining water. Pleasingly this led to a significant decrease in the formation of rearranged product 141, with either drying agent giving similar yields of desired adduct 140. The reaction was also subject to addition of radical inhibitor TEMPO ((2,2,6,6-tetramethylpiperidin-1-yl)oxyl) to ensure the reaction pathway proceeded via a radical mechanism, this led to a trace amount of desired adduct 140 suggesting that the reaction is likely to proceed via a radical pathway. With the optimised conditions in-hand (Table 2, entry 21), a reaction scope plan was set up with a variety of promising heterocycles prone to auto-oxidation and/or those with low C–H bond energies that could be functionalised by alkynyl EBX reagents.
2.4 Reaction Scope

Given the success of benziodoxol(on)e based acceptors, such as Ph-EBX, TMS-EBX and TIPS-EBX in functionalising THF, further EBX based acceptors 146 and 147 (Scheme 51) were synthesised to appraise functionalising THF with the optimised reaction conditions using scaffolds of higher complexity like trans-alkenes and heterocyclic functionalities including indoles.\(^{100,101}\) Both alkene and indole moieties represent important scaffolds and could enable access to a wide range of molecules; traditionally these acceptors require precious metal catalysts such as palladium or iridium to allow direct C–H functionalisation.

![Scheme 51: Vinyl-BX 146 and Indole-BX 147 were synthesised from existing literature methods.\(^{100,101}\)](image)

Addition of Vinyl-BX 147 (Scheme 51) to HFIP in THF however led to complete degradation of 147 (Scheme 52) to a variety of side products including polymerisation of the alkene moiety, likely induced by the presence of HFIP. Repeating the reaction without HFIP, resulted in the formation of trans-alkene 148 (Scheme 52), a known side product caused by visible light cleavage of vinyl-BX and resulted in incomplete conversion of Vinyl-BX 147,\(^{100}\) no polymerisation was observed outlining HFIP was responsible for initial side reaction. Repeating the reaction in the dark and without the presence of HFIP did not lead to any desired product.
Scheme 52: Novel Vinyl-BX 147 and Indole-BX 146 acceptors were subjected to the optimised reaction conditions to give unwanted side products 148 and 149 respectively.

Given this result, more optimisation on alkene type acceptors could influence reactivity by placing emphasis on the introduction of an electron-withdrawing group on the phenyl alkene. This could allow for better polarity matching with the nucleophilic ethereal radical and reducing the reactivity of the trans-alkene moiety. Similarly, 146 (Scheme 52) Indole-BX represents a newer class of EBX reagents, allowing for more complex functionalities on the hypervalent iodine scaffold, however, previous work in the literature use a rhodium catalyst to facilitate C–H functionalisation. Subjecting 146 to the optimised reaction conditions, showed the formation of only one product via TLC and NMR - indole dimer 149. Attempting the reaction with the addition of Cu(OAc)₂ also gave dimer 149 with incomplete conversion of the Indole-BX reagent.

With more diverse EBX scaffolds such as 146 and 147 proving to be incompatible with the optimised conditions, the focus was then turned to carrying out a reaction scope to ensure the conditions were compatible with other heterocycles. Subjecting 2-methyl THF to the optimised reaction conditions described in Table 2 resulted in a mixture of two products 151 and 152-a/b (Scheme 53), with the substituted product being the major one. This is a result of this product being formed through a more stable tertiary
radical intermediate; stabilised by hyperconjugation. Both products, however, were inseparable by column due to identical polarities. Pleasingly, functionalisation of the 6-membered tetrahydropyran was also possible giving 153, this was especially promising for future work on similar 6-membered type sugar structures such as arabinose and more complex ring systems. Tetrahydrothiophene (THT) 154 (Scheme 53) also allowed functionalisation in the α–C–H position giving the corresponding alkynyl heterocycle in the trialkled reaction conditions, showcasing an organosulfur example, and not limiting the scope to oxygen-based heterocycles only. The reaction of Ph-EBX with THF and HFIP was also repeated with radical inhibitor TEMPO, and only a trace amount of product 154 was observed, outlining this likely proceeded via a radical mechanism.

Scheme 53: Initial screening of simple substrates under the optimised reaction conditions for Ph-EBX. Ratio of 150:151-a/b is 1.7:1:0.5.

Following the successful reactions of oxygen-based heterocycles above, other chemically similar candidates such as isochroman 156, dihydrobenzofuran 157, benzyl phenyl ether 158 and 2,2-dimethyl-1,3-dioxolane 159 were trialled (Scheme 54). Unfortunately, these heterocycles were not reactive with Ph-EBX, showing no reaction even after 48 h. Given the higher boiling points of isochroman (228 °C) and dihydrobenzofuran (188 °C), the temperature of the reaction was increased to 120 °C in the hope of forming desired product, with literature precedent for α–C–H functionalisation of these molecules at this temperature range. This did not prove to be successful, with starting materials observed and a 15% increase of unwanted rearranged by-product 141 promoted by the higher temperature. In order to
understand why these molecules were not reactive with Ph-EBX, isochroman 156 was reacted with HFIP and DIAD under previously published conditions (Scheme 54). DIAD has proven to be an excellent electrophilic radical acceptor, with its electrophilicity enhanced by the presence of HFIP.\(^{59}\) The reaction gave the desired product 160 within 6 h in a high yield of 92%. This experiment shows that generation of the isochroman α-C(sp3)−H radical takes place, however it is likely that Ph-EBX is not a suitable reaction partner for the radical, with DIAD showing significant reactivity. This is corroborated with literature work, who have also struggled to make similar adducts from Ph-EBX.\(^{102}\)

Scheme 54: Substrate screen of oxygen based heterocyclic molecules leading to sole formation of rearranged by-product 141. Reacting isochroman 156 with DIAD gives 160 in high yield, outlining incompatibility of Ph-EBX with isochroman 156.\(^*\) Attempted at 120 °C over 48 hours.

With analogous oxygen-based heterocycles proving to be unreactive, the scope focus was shifted towards nitrogen heterocycles. Nitrogen functionalised heterocycles have proven to be valuable building blocks in the pharmaceutical industry.\(^{103−105}\) Each nitrogen heterocycle was protected at the N-H position to prevent any unwanted ionic nucleophilic side reactions taking place. N-Boc pyrrolidine 161, N-Boc pyridine 162, N-Boc azepane 163 and N-Boc morpholine 164 were initially submitted to the
optimised reaction with HFIP and Ph-EBX (Scheme 55). No reaction was observed between Ph-EBX and the N-Boc heterocycles, with crude NMRs showing no symmetry breaking of the ring systems. This was confirmed by TLC and work-up, which returned only starting materials and rearranged by-product 141. N-Boc pyrrolidine 161 has previously shown radical reactivity with DIAD & HFIP,\(^5^9\) although in this case no reaction was observed highlighting incompatibility issues with Ph-EBX as a radical partner. Carboxybenzyl protecting groups were also explored on both the pyrrolidine 165 and pyridine 166, this did not prove to be successful, with no reaction taking place in the desired position.

![Scheme 55: Substrate screen of N-based heterocycles, showing no formation of $\alpha$–C–H functionalised product.](image)

With Ph-EBX proving to be unreactive to a wide range of simple heterocyclic molecules, a modification was attempted to increase the reactivity of the Ph-EBX scaffold. Recent work by Zhang and co-workers utilised a N-acetylbenziodazole skeleton when synthesising their hypervalent trifluoromethylthio-iodine(III) reagent 167 (Scheme 56).\(^1^0^7\) They reported that HFIP forms hydrogen bonds with the two carbonyl oxygen atoms of the N-acetyl skeleton, and thus the nitrogen and sulphur atoms in the hydrogen-bonded adduct are more electron-deficient and reactive, this was confirmed by DFT studies.
Scheme 56: Enhanced activity of novel-BX reagent via strong H-bonding abilities of HFIP.\textsuperscript{107}

The proposed synthesis of the modified Ph-EBX scaffold is shown (Scheme 57), with the first step starting from 2-iodobenzamide \textbf{168} to \textbf{169} existing in the literature and giving the cyclised N-acetylbenziodazole skeleton in 88\% yield.\textsuperscript{108} Subjecting \textbf{169} to TMS triflate and TMS protected phenyl alkyne however did not result in transfer of the iodine hydroxyl group. In fact, \textbf{169} showed very poor solubility in DCM and a few other solvents which were trialled such as acetonitrile and toluene. Only partial solubility in methanol was possible, which is incompatible with TMS triflate. It was envisaged that TMS triflate may help the solubility of \textbf{169} once added to the reaction mixture due to the polar nature of the triflate group, although this was not observed with solid material still present in the reaction flask. Any attempt to directly acylate \textbf{169} in order to aid solubility, led directly to decomposition of \textbf{169}.

Scheme 57: Work by Zhang \textit{et al.} utilise the N-acetylbenziodazole skeleton \textbf{167} to H-bond to HFIP,\textsuperscript{107} a similar synthesis was attempted to form \textbf{170}, however was unsuccessful due to insolubility of \textbf{169}.
Another synthetic route was devised based on work by Barber and Henderson (Scheme 58), this route allows for cyclisation to take place stepwise and form the soluble acylated N-acetylbenziodazole skeleton 172. Unfortunately, cyclisation to 172 proved to be problematic, acylation did not take place on the amide 171, this was confirmed by NMR where two N-H protons were seen. Attempting to acylate the amide first and then cyclise also did not prove to be successful as the amide N-H proton was still present in the NMR alongside two acetate groups that did not match the desired product 172. No NMR data is provided for 171 and 172 from Henderson et al. making it difficult to reproduce the desired intermediates and so this synthesis route was abandoned and focus shifted towards an alternative acetylenic acceptor.

Scheme 58: Synthetic route to 170 devised based on work by Barber and Henderson, this route was unsuccessful as cyclisation of 171 to 172 was not observed.

In the future, following a recent publication by Waser and Borrel, a more effective umpolung synthesis of this novel acceptor could be attempted. Current methodologies rely on the usage of alkynyl-boronic esters in a trifluoroethanol/dichloromethane mixture to obtain high yields. In this context, potential modification of the alkyne group is a tedious process as it requires isolation and purification of the reagent for each step. This can be especially problematic in the case of non-crystalline alkyl-substituted EBXs as they are purified by column chromatography, which usually leads to a substantial loss of yield.
The authors then employ the usage of alkynyl-trifluoroborate salts 174 as they were found to be more nucleophilic than silyl alkyne precursors and do not have the stability issues associated with alkynyl-boronic esters. By using these alkynyl-trifluoroborate salts they were successfully able to develop a method for the formation of EBX-based reagents 95 in excellent yields ranging up to 95% with a purity no less than 95% of all synthesised reagents (Scheme 59). Importantly, this reaction took place in only one hour and required only a basic work-up and pentane wash of the crude solid to afford EBX reagents. This methodology could then be applied to the analogous tosylated N-acetylbenziodazole skeleton 175 which could be transformed to the corresponding product 170 and submitted to analogous reaction conditions, this could in term improve the reactivity of the scaffold in the C–C bond formation methodology highlighted above.
2.5 Acetylenic triflone as a radical acceptor in aerobic C–C bond formation

In Chapter One Section 2.1.9, the potential utility of acetylenic triflone 117 in radical C–C bond formation reactions was highlighted. Based upon this, and the varying reactivity of EBX reagents as reaction partners for heterocyclic C–H bond functionalisation, they were then trialled as radical acceptors in the THF C–C bond formation reaction. The synthesis of acetylenic triflones is generally robust and requires one step via deprotonation of a terminal acetylene followed by addition of triflic anhydride to furnish the corresponding acetylenic triflone 117. Importantly, based on a procedure by Yu et al.,\textsuperscript{112} a reverse addition of the deprotonated acetylide to diluted triflic anhydride in diethyl ether via cannula transfer was shown to be an effective and high yielding method to prepare the corresponding acetylenic triflones (Scheme 117). By following this protocol, pure phenyl acetylenic triflone 176 was synthesised in 88% yield and trialled in analogous conditions to the ones developed in section 3.1.2 (Scheme 60). Introduction of 176 to HFIP and THF 56 at 80 °C led to a promising 68% yield, identical to the yields observed in the optimised reaction conditions for Ph-EBX.

![Scheme 60: General synthesis of acetylenic triflone 117 (top) and application of phenyl acetylenic triflone 176 to a radical chain THF C–C bond formation reaction (bottom).](image)

With this knowledge in hand, the reaction was studied in more detail to better optimise THF 56 towards the acetylenic triflone 176 (Table 3). Initially, we wanted to understand why full consumption of acetylenic triflone 176 only led to a 68% yield of the alkynyl-THF adduct 140. Firstly, the effect of the concentration of HFIP on the highly reactive
acetylenic triflone 176 was studied by independently stirring HFIP and acetylenic triflone at 80 °C. Degradation of acetylenic triflone was observed at higher concentrations (2.0 mmol, entry 1) in comparison with lower concentrations (entries 2 and 3) to phenyl acetylene and triflone by-products. This outlined that a highly concentrated reaction mixture could be detrimental to the yield of desired adduct 140. It was also important to consider the use of HFIP overall as reducing the concentration of HFIP would be beneficial to the overall sustainability and appeal of the protocol. Following this, the effect of temperature on degradation was considered (entry 3-5) by independently stirring HFIP and acetylenic triflone, where it was found that increasing temperature did influence the overall degradation of the triflone, albeit not a substantial amount at 80 °C (entries 3, 5%). Temperature was found to be a key parameter in maximising the yield of the desired adduct 140 as carrying out the reaction at lower temperatures (entries 6-8) led to a significant decrease in triflone conversion and subsequently the amount of product 140. This was to be expected as the formation of THF radicals and subsequent peroxides under aerobic conditions is a function of temperature.\textsuperscript{113} Following application of these results and attempting the reaction with 0.4 mmol of HFIP, 5 equivalents of THF and one equivalent of acetylenic triflone at 80 °C (entry 9) led to an exceptional 93% yield of the desired acetylenic THF-adduct.

To confirm the presence of a radical mechanism reacting THF 56 and acetylenic triflone 176 under an argon atmosphere and by bubbling argon through the solution three times led to no formation of 140 (entry 13) confirming oxygen in air is vital for the formation of THF radicals in this reaction. Other parameters were also explored such as removal of HFIP altogether (entry 10), however, this led to a significant reduction in yield as the reaction could only be carried out at the boiling point of THF (66 °C). Other fluorinated solvents such as 2,2,2-trifluoroethanol and perfluoro-\textit{tert}-butanol were trialled as substitutes for HFIP but were found to be less effective (entries 14 and 15), and acidic substitutes such as acetic acid were also trialled but once again proved not be as high yielding (entry 16).

Overall, optimisation led to a substantial increase in yield whilst decreasing the amount of HFIP. The difference in yields between employment of phenylacetylenic triflone 176 and Ph-EBX 98, is likely due to the leaving group $\cdot\text{SO}_2\text{CF}_3$ which aids the radical chain
process, as decomposition of this radical releases SO$_2$ and •CF$_3$. The generated trifluoromethyl radical is highly reactive and an excellent candidate for subsequent H abstraction of THF, propagating the chain reaction further. In the CF$_3$ radical the fluorine atom acts as electron-withdrawing group via the inductive effect but also as a weak pi donor through the interaction of the fluorine lone pair with the radical centers SOMO. Compared to the methyl radical the CF$_3$ radical is pyramidal with a large inversion barrier, electrophilic and significant more reactive.$^{72}$ Overall, from the optimisation study, the acetylenic triflone shows more potential as a radical partner in the reactivity of THF radicals as compared to Ph-EBX.

![Diagram](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Temp</th>
<th>Solvent (in THF)</th>
<th>Other conditions</th>
<th>Yield (A) %</th>
<th>Triflone (%) Conversion</th>
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</thead>
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<tr>
<td>1</td>
<td>80</td>
<td>HFIP (2.0 mmol)</td>
<td>Control – No THF</td>
<td>18</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>80</td>
<td>HFIP (1.0 mmol)</td>
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</tr>
<tr>
<td>3</td>
<td>80</td>
<td>HFIP (0.40 mmol)</td>
<td>Control – No THF</td>
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<tr>
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</tr>
<tr>
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</tr>
<tr>
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<td>0</td>
</tr>
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<td>CF$_3$CH$_2$OH (0.40 mmol)</td>
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<td>15</td>
<td>80</td>
<td>Tert-C$_4$F$_9$OH (0.40 mmol)</td>
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<tr>
<td>16</td>
<td>80</td>
<td>AcOH (0.40 mmol)</td>
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<td>42</td>
<td>100</td>
</tr>
</tbody>
</table>
Table 3: Optimisation table for radical C–H functionalisation of THF 56 with phenyl acetylenic triflone 176.

2.6 Application of optimised methodology to heterocycles

With the optimised conditions in hand, the generality of the procedure to \( \alpha \)-alkynlate various heterocycles was then explored. Heterocycles were selected based on their likely susceptibility to aerobic activation based on the bond dissociation energy of their \( \alpha-C-H \) bond(s).\textsuperscript{36,114,115} Another indication which could potentially hint at the ability to oxidise under aerobic conditions included the presence of radical inhibitors such as BHT (butylated hydroxytoluene) in the storage of these molecules which are commercially available, this is especially helpful when there’s a lack of information on the strength of an \( \alpha-C-H \) bond. Hence, all heterocycles used in this methodology were freshly distilled and degassed before usage to remove any radical inhibitors.

2.6.1 5-Membered THF derivatives

Initial investigation began on 2-methyl THF, which is usually derived from sugar via furfural (Scheme 61). As expected, a complex mixture 151 and 152-a/b was obtained when submitting 2-methyl THF to HFIP and phenylacetylenic triflone 176, the complex mixture being due to the competing formation of both secondary and tertiary \( \alpha-C-H \) radicals. Pleasingly, this proceeded in an 86% yield and gave a ratio of products of 151:152-a:152-b of 1.7:1:0.5, analysed with the help of 2D NMR data. Similarly, application of the reaction to 2,5-dimethyltetrahydrofuran gave a mixture of isomers 177 in a 3:1 ratio with an overall yield of 97%. The reaction conditions were found to be tolerant of ketone functionalities and these were applied to 178 and 179 in good yields. It was especially interesting to observe that no mixture of products was obtained when functionalising 2-methyltetrahydro-3-furanone, compared to 2-methyl THF as they both have a potential tertiary radical centre.
Another intriguing observation included the isolation of a single diastereomer for product 178. The reaction was also shown to be compatible with ester functional groups giving products 180, 181 and 182 in good yields. Whilst simple alkyl-substituted THF derivates do not show much regioselectivity in the reactions, substrates bearing a carbonyl group (either within the THF ring or adjacent to it) typically undergo alkynylation with high regioselectivity with alkynylation not taking place adjacent to the carbonyl group (i.e. 178, 179 and 182). This observation can likely be explained by the presence of the adjacent carbonyl group which would reduce the potential nucleophilicity of the radical centre and provide less of a polarity match with the radical acceptor phenylacetylenic triflone 176. Overall, while simple THF based molecules such as 2-methyl THF and 2,5-dimethyltetrahydrofuran are known to undergo aerobic oxidation, the examples on ketones and ester based THFs represents the first known examples of aerobic C–H activation on these type of molecules.
In an attempt to functionalise a more structurally complicated 5-membered sugar triol 185, the synthesis of the sugar was successfully completed (Scheme 62). The synthetic methodology was based on previous work in the Sheppard group,\textsuperscript{116} where the hydrazone moiety is hydrolysed and then reduced and protected to give sugar 185 in a reasonable overall yield.

![Scheme 62: Synthesis of protected THF-triol based on works by Sheppard et al.\textsuperscript{116}](image)

Unfortunately, the protected THF-triol was unstable to the reaction conditions and all 5 equivalents had degraded in the presence of HFIP and heat. This gave a complex mixture of inseparable products and crude NMR analysis did not outline the presence of key peaks associated with the formation of 185.

### 2.6.2 6-Membered heterocycles

![6-Membered heterocycles](image)
Scheme 63: Application of optimised methodology to 6-membered heterocycles. \( ^\circ \) 30 h, 10 eq. THP. \(^g\) Major diastereomer isolated, 99:1 dr, 48 h.

The scope of the reaction was then moved towards 6-membered heterocyclic derivatives, while 5-membered THF ring derivatives are known to auto-oxidise, 6-membered ring systems are generally unexplored (Scheme 63). Application of the optimised reaction conditions to tetrahydropyran (THP) led to functionalisation affording 153 in 64% yield. A longer reaction time (30 h) and 10 equivalents were required for optimal yield of 153 when using THP; this is presumably due to the slower rate of formation of THP \( \alpha \)-C(sp\(^3\))-H radicals.\(^{117}\) Monofunctionalisation of 1,4-dioxane was also possible through the method, giving the acetylenic dioxane moiety 186 in 71% yield. Interestingly, a mixture of products 187 and 188 was obtained when submitting 1,4-thioxane to the reaction conditions, where the major product resulted in functionalisation adjacent to the sulphur moiety. This is presumably due to the weaker \( \alpha \)-C–H bond adjacent to the sulphur in comparison to the oxygen heteroatom, leading to a more facile formation of the radical species.

Scheme 64: Synthesis of protected sugar 191 (top),\(^{118}\) followed by diagram for the generation of a major diastereomer (bottom).

Following the promising results on THP and dioxane, the next step was applying the method to a 6-membered sugar derivative, which was synthesised from the readily
available protected sugar derivative 190 (Scheme 64) and was subsequently hydrogenated to give the starting material 191. Pleasingly, the functionalisation reaction proceeded with 99% stereoselectivity for a single diastereomer, of which 90% of this diastereomer was separable via column chromatography. A possible explanation for the observed stereoselectivity can be rationalised by realising axial attack is preferred on the lowest energy conformed of the ring. The THP-radical is effectively similar to having an oxonium ion within the 6-membered ring, therefore the lone pair on the oxygen atom and new formed C–C bond need to be generated antiperiplanar for the lowest energy TS, where overall axial attack is preferred for this transition state giving 189.

2.6.3 Miscellaneous examples

Scheme 65: Miscellaneous examples including straight chain alkanes and acetals.

Further exemplification of the reaction conditions included examples such as tetrahydrothiophene (THT) which was readily converted to 154 in 72% yield. Importantly, the presence of HFIP (and temperature) was deemed detrimental to the reaction conditions where over-oxidation of THT to the corresponding aldehyde and
thiol were observed in this setting and in agreement with similar observations by Kokotos et al.\textsuperscript{120} where deconstructive ring cleavage occurs. Straight chain ethers such as diethyl ether and dimethoxyethane were also compatible with the reaction conditions giving 155 and 192 in reasonable yields. In the case of diethyl ether a lower temperature (60 °C) was required due to its extremely low boiling point; this also demonstrates that lower temperatures can still lead to efficient C–H functionalisation. Acetylenic acetal 193 was also successfully synthesised giving monoalkynylation and the desired product in 65% yield. Unfortunately, application of the method to the THF-containing natural product ambroxide scaffold to give 195 was unsuccessful due to the poor solubility of ambroxide in HFIP, attempts to increase the concentration of HFIP in the reaction conditions up to 2 mmol and the temperature to 100 °C did not improve the solubility of the substrate.

Using readily available cyclopentyl methyl ether (CPME) led unexpectedly to the formation of enyne 194, presumably via HFIP-assisted elimination of methanol from the initial C–H alkynylated product. Following this result, an attempt to repeat the generation of enyne on the analogous cyclohexane methyl ether did not result in any C–H functionalisation taking place, and hence no subsequent elimination to enyne 198 was observed (Scheme 66).

Scheme 66: Attempted generation of enyne 198 via cyclohexane methyl ether.

2.6.4 Nitrogen based heterocycles

While the general methodology to this point has shown to be applicable to a variety of oxygen-based heterocycles and acyclic ethers, nitrogen-based heterocycles represent a key class of molecules to target due to their heavy prevalence in both industry and pharmaceuticals. To date however, very little evidence exists for the auto-oxidation of nitrogen-based molecules in the presence of oxygen in air. Interestingly, these class of molecules have comparable C–H bond energies to oxygen based
heterocycles such as THF and THP (Scheme 67),\textsuperscript{121} which could potentially hint towards the formation of $\alpha$-radical species such as the nucleophilic radical generated with THF. Although BDEs are used as a general guidance for selecting potential candidates prone to auto-oxidation, this does not always translate to successful reactivity. Alongside this, protecting groups are employed in the case of radical functionalisation of $N$-heterocycles to prevent any ionic reactivity at the nitrogen atom.

Scheme 67: BDEs of N-Heterocycles in comparison to oxygen based heterocycles, showing a roughly similar range for BDE of $\alpha$–C–H protons.\textsuperscript{121}

The initial investigation began by submitting $N$-boc pyrrolidine and $N$-boc piperidine to the optimised conditions previously developed in Chapter 2 section 3.2 (Scheme 68). No reaction was observed via TLC and crude NMR analysis, where almost no consumption of the acetylenic triflone had taken place. This potentially highlighted that formation of the alpha radical was not taking place. To remedy this, the conditions were altered to allow for higher-temperatures and longer reaction times to promote the generation of a radical species, but this did not increase consumption of acetylenic triflone.\textsuperscript{176} Another factor which was explored was the role of the protecting group (PG); $N$-Ts, $N$-CBz and $N$-Me (Scheme 68) protecting groups were trialled to no avail. In analogous C–H activation work on N-heterocycles, most protecting groups were found to be compatible and play no major role in the outcome of functionalised products but were nonetheless explored.\textsuperscript{46,57} Altering the protecting group did not lead to any functionalised product and consumption of the acetylenic triflone was minimal, further highlighting the incompatibility of the substrates 199-206 with the reaction conditions.
PG\(^1\) = Me \(^{199}\), Boc \(^{200}\), CBz \(^{201}\) and Ts \(^{202}\)
PG\(^2\) = Me \(^{203}\), Boc \(^{204}\), CBz \(^{205}\) and Ts \(^{206}\)

Scheme 68: Initial trial of protected pyrrolidine and piperidine in the reaction conditions.

Following these results, the introduction of a heteroatom was explored in the \(N\)-heterocycle such as morpholine and thiomorpholine (Scheme 69) to observe any differences in reactivity. Pleasingly, \(N\)-Boc morpholine was selectively functionalised in the reaction conditions to give a single product \(^{215}\) in 58% yield. Assignment of the product proved to be tricky as functionalisation could potentially take place either adjacent to the oxygen or nitrogen in \(N\)-boc morpholine \(^{212}\). Functionalisation was confirmed to be adjacent to the nitrogen atom due to the rotameric nature of Boc group via \(^1\)H NMR, the sample was heated to 60 °C to help resolve the rotamers present (Scheme 70) and clear correlation was seen by HSQC between the carbon adjacent to the nitrogen atom and the proton of the functionalised \(\alpha\)-\(C\)-\(H\) position. It is also interesting to note that the largest coupling constant observed in the multiplet at 4.9 ppm is 3.2 Hz, indicating that the \(\alpha\)-\(C\)-\(H\) in the functionalised position is equatorial and the corresponding acetylenic bond is axial. The lack of a larger axial-axial coupling constant (7-11 Hz) in the region also proves this. This is likely due to a minimal competing 1,3 interaction between the axial protons on morpholine and the lack of protons on the \(\alpha\)-acetylene carbon (Scheme 70).

PG\(^3\) = Me \(^{207}\), Boc \(^{208}\), CBz \(^{209}\) and Ts \(^{210}\)
PG\(^4\) = Me \(^{211}\), Boc \(^{212}\), CBz \(^{213}\) and Ts \(^{214}\)

Scheme 69: Trial of \(N\)-heterocycles with other heteroatoms present in the scaffold.
Unfortunately, no reactivity or consumption of triflone was observed when altering the protecting group on morpholine to either Me\textsubscript{211}, Ts\textsubscript{212} and Cbz\textsubscript{213} protecting groups. Similarly for the protected thiomorpholine examples\textsubscript{207-210}, complete degradation of all five equivalents of starting material was observed due to unwanted ring-opening reactions adjacent to the sulphur. Attempting the reaction without the presence of HFIP as previously carried out in Chapter\textsubscript{2} section\textsubscript{3.1.2} led to minimal consumption of acetylenic triflone\textsubscript{176} when monitored by TLC and crude NMR and no formation of the desired acetylenic product.
Scheme 70: Rotameric resolution of functionalised N-boc morpholine 215 via high-temperature $^1$H NMR experiments (top). Predicted conformation of 215 based on relaxed grid molecular mechanics search performed by A. Aliev (bottom).

Given the success of the reaction with N-boc morpholine, the analogous 7-membered 1,4-oxazepane 216 was trialled (Scheme 71). The potential product could give functionalisation on the $\alpha$–C–H closest to the oxygen atom suggesting an influence of the oxygen heteroatom in the reaction. Disappointingly, no reaction was observed with 216, with minimal consumption of acetylenic triflone observed.

Scheme 71: No reactivity observed with N-Boc-oxazepane 216 with acetylenic triflone 176.

Overall, with the exception of N-Boc morpholine, nitrogen heterocycles were found to be generally incompatible with the developed reaction conditions for aerobic C–H functionalisation. Interestingly, while their BDEs are within the same range of successful candidates such as THF, they were found to not be prone to aerobic C–H activation, although introducing a protecting group will alter the BDEs of these molecules. Importantly, in the trial reactions set out above, consumption of acetylenic triflone was always found to be minimal, outlining that the formation of the $\alpha$-radical in these N-heterocycles did not take place under aerobic conditions. Whilst other factors such as competing H-abstraction could take place given aerobic generation of an $\alpha$-radical, this is unlikely to be a major pathway given the equivalents of substrate employed in this reaction. This hypothesis was tested by introducing TEMPO into the reactions of N-Boc pyrrolidine and piperidine, where no observation of TEMPO adducts was observed via LCMS analysis and crude NMR. This outlines that aerobic generation of the $\alpha$-radical does not take place or is extremely inefficient in these conditions.
2.6.5 Unsuccessful substrates

Benzyl phenyl ethers are an example of a substrate with generally low BDEs in comparison to THF. For example, in the case of benzyl phenyl ether 158 the BDE is known to be 359 kJmol\(^{-1}\) in comparison with THF (391.6 kJmol\(^{-1}\)).\(^{122}\) This is due to the stabilisation offered by the adjacent phenyl group as well as the adjacent oxygen heteroatom. Therefore, benzylic ethers 156-158 (Scheme 72) were trialled in the optimised reaction conditions in the hopes of alkynylating the benzylic position. Unfortunately, no such reactivity was observed and minimal consumption of triflone was seen for 156-158. Pthalan 217 led to a complex mixture of products, due to its rapid and uncontrollable auto-oxidation pathway.\(^{123}\)

![Scheme 72: A range of heterocyclic substrates which proved to be incompatible with the developed methodology for aerobic C–H functionalisation.](image)

It is likely that the generated radical is not nucleophilic enough to allow attack of the acetylenic triflone, this is corroborated by Chapter 2 section 3.1.2 where DIAD is found to react with benzylic ether 156. It is likely the extremely electrophilic behaviour of DIAD enhanced with HFIP provides a stronger polarity match allowing it to undergo attack by a benzylic radical which is not highly nucleophilic. Further to this, fused ether systems such as 219 and 220 also demonstrated little reactivity, proving to be unreactive in the conditions for up to 72 h. Given the higher boiling points of these systems,
fused ethers, temperatures up to 100 °C were tested, however did not aid the lack of auto-oxidation observed. Benzofuran-3(2H)-one 220 also followed the reactivity pattern observed in section 3.3.1 where functionalisation did not take place adjacent to any carbonyl functional groups. Overall benzylic ethers and aromatic fused heterocyclic systems were not compatible with the developed reaction conditions. This is supported with the literature where very few successful C–H functionalisation are observed with these scaffolds even when employing the use of precious metal catalysts and initiators.83,102,120
2.6.6 Overall overview

Scheme 73: Overall substrate scope for the reaction of a range of heterocyclic and straight chain ether molecules with acetylenic triflone 176. \(^a\) 89% yield on a gram scale. \(^b\) 1.7 : 1 : 0.5 : \(150 : 151\)-a/b. \(^c\) 3 : 1 mixture of isomers. \(^d\) Single stereoisomer obtained. \(^e\) 1 : 0.35 : 0.85 \(180a/b:181:8h\). \(^f\) 30 h, 10 eq. THP. \(^g\) Major diastereomer isolated, 99 : 1 dr, 48 h. \(^h\) No HFIP, 60 °C. CPME = cyclopentyl methyl ether.
2.7 Further exemplification

Scheme 74: Substrate scope showcasing a variety of acetylenic THF products formed via the aerobically generated THF radical from 56. *No HFIP and 24 h reaction time.

Given the success in functionalising a range of heterocyclic species under aerobic C–H activation conditions, attention was then turned to altering the functional groups attached to the acetylenic triflone. A variety of acetylenic triflones 117 were synthesised and reacted with THF under the optimal C–H functionalisation conditions developed (Scheme 74). Electron-rich aryl alkynes furnished the desired adducts 222-225 in excellent yields, where methoxy and alkyl substituents on the aryl ring were shown to be compatible with the conditions at hand. Introduction of halogen moieties onto the aryl ring, in either para- (226), meta- (227) or ortho- (228) positions relative
to the alkyne handle allowed subsequent C–C bond formation in yields up to 86%. Aromatic halogen functionalities are especially useful in this reaction due to their ability to serve as useful handles for further reactivity in C–C bond coupling reactions.\textsuperscript{125} The medicinally relevant trifluoromethyl functional group \textsuperscript{229} was also compatible, providing the respective alkynyl THF scaffold in 88% yield.

Pleasingly, the method also allowed for derivatisation to other aromatic rings such as the electron-rich thiophene which yielded the corresponding THF-alkynyl thiophene adduct \textsuperscript{230} in 72% yield. In this reaction, it was important to exclude HFIP due to polymerisation of the alkynyl thiophene triflone starting material and hence a longer reaction time of 24 hours was required as the temperature was adjusted to account for this (70 °C). Naphthalene was also shown to be compatible in the reaction conditions yielding the corresponding acetylenic product \textsuperscript{231} in 65% yield. Finally, the scope was extended to aliphatic substituents on the alkynyl triflone showing compatibility with the radical chain process. Both straight-chain and branched groups were trialled, giving products \textsuperscript{232} and \textsuperscript{233} in good yield. Overall, application of the methodology to variety of acetylenic triflones was proven to be successful, giving access to privileged heterocyclic and acyclic alkyne scaffolds in a simple and high yielding manner.

2.8 Alkenyl Triflones

Following the success of alkynyl triflone acceptors under the aerobic C–H activation conditions, the synthesis of alkenyl triflones was attempted based on the works of Fuchs \textit{et al}, (Scheme 75).\textsuperscript{126} The authors had originally employed HF-Pyridine to transform triflone \textsuperscript{176} to the subsequent vinyl fluoride, although these reaction conditions were instead emulated using TBAF/AcOH to provide a safer and milder route towards the desired product \textsuperscript{234}. The corresponding lithium halides were also used to convert triflone \textsuperscript{176} to the respective vinyl halides \textsuperscript{235} and \textsuperscript{236}. The original authors of the work confirm the stereochemistry of the vinyl halides by further reacting them with t-BuLi and subsequent quenching with water to give the disubstituted
styrene derivatives with known $J_{\text{HCCH}}$ couplings. These metalations are known to occur with retention of stereochemistry.

![Scheme 75: Conversion of phenyl acetylenic triflone 176 to vinyl halides 234-236.](image)

Initially, vinyl bromide 235 was reacted with THF under the previously optimised conditions for acetylenic triflones. This gave product 237 in a good 62\% yield, however upon further analysis complete conversion of vinyl bromide 235 was not observed via TLC or crude NMR data. Allowing the reaction to proceed for a total of 30 hours did not remedy this conversion issue, with ca 75\% conversion observed via NMR. A similar pattern of incomplete conversion was observed for both fluoro 234 and iodo vinyl triflones 236. Using a mixture of AcOH/HFIP, was found to improve the conversion of these reactions allowing full consumption of vinyl triflones in the reaction conditions, good yields were then observed for the formation of THF-alkene adducts 237-241 (Scheme 76). Using vinyl bromide triflone 235 in the newly optimised conditions led to a 78\% isolated yield of adduct 237. Applying these conditions to the analogous vinyl fluoride afforded the THF-alkene 238 in 67\% yield and finally to a vinyl iodide analogue to give 239 in 72\% yield. The stereochemistry of 238 was assigned based on the three-bond $J_{\text{HCFC}}$ coupling constants of 37 Hz which is typical for vinyl fluorides. NOEs were used to aid assignment of the iodo-olefin 239 (Scheme 76). Finally, application to simple 1,2-disubstitued vinyl triflones also provided 240 and 241 in good yields, also proceeding via retention of vinyl triflone geometry to furnish the corresponding (E) isomers (Scheme 76).
Scheme 76: Reactivity of vinyl triflones under aerobic C–H activation conditions to give the corresponding vinyl THF scaffolds 237-241 (top). NOE of vinyl iodide 239 confirming the stereochemistry of corresponding (E) isomer (bottom).
2.9 Further derivatisation of acetylenic and vinyl THF products

Following the development of optimised reaction conditions for both vinyl and acetylenic triflones, the attention was then turned towards outlining the utility of these molecules. Alkynes are versatile building blocks which can be transformed into a range of products with varying oxidation levels. The simplest example includes hydrogenation of product 140 into the corresponding straight chain alkane 242 in 97% yield (Scheme 77). Introducing trichloroisocyanuric acid to the acetylenic THF product also generated the interesting dichlorinated ketone 243, outlining the formation of a novel halogenated building block in a high yield reaction (94%). Finally, the commonly employed Suzuki coupling of vinyl THF iodide 239 using the medicinally relevant 3,5-bis(trifluoromethyl)phenylboronic acid allowed facile formation of the coupling vinyl THF product 244 in an excellent yield of 92%. Pleasingly the reaction proceeded with retention of stereochemistry to give access to a structurally diverse molecule. The exemplification further highlights the high yielding transformation of a simple THF molecule under aerobic activation conditions to generate novel building blocks such as 242-244 in two steps overall.

Scheme 77: Further diversification of the products synthesised under the developed aerobic C–C bond formation methodology, highlighting the further utility of the method.
2.10 Mechanistic Studies

Scheme 78: Two proposed mechanistic pathways for the reactivity observed with THF 56 and phenyl acetylenic triflone 176.

To gain a deeper understanding of the THF reaction with acetylenic triflone 176, mechanistic studies were carried out. Two mechanistic pathways were proposed which would lead to corresponding acetylenic THF product 140. The proposed mechanisms for the formation of the final product 140 is shown above (Scheme 78). Path A begins with $\alpha$-addition of the aerobically generated THF radical 57 to afford vinyl radical 245, followed by rapid $\beta$-elimination to generate desired adduct 140. Importantly, this also leads to fragmentation of trifluoromethylsulfonyl radical 246 to sulphur dioxide and the highly reactive trifluoromethyl radical, which can aid in the efficiency of the chain reaction by abstraction the $\alpha$–C–H proton of THF 56. Another possible reaction pathway could take place through initial $\beta$-addition to form the corresponding $\alpha$-trifluoromethylsulfonyl vinyl radical 247, which could then fragment to a vinylidene carbene species 248 and the trifluromethylsulfonyl radical 246. The highly reactive vinylidene carbene species 248 could then rapidly undergo a Fritch-Buttenberg-Weichell (FBW) type 1,2-rearrangement to generate the observed acetylenic product 140. $^{131,142}$
Scheme 79: Mechanistic study involving $^{13}$C labelled phenyl acetylenic triflone $^{13}$C-$249$ under the optimised reaction conditions.

Carbon-13 labelling studies were carried out to gain insight on the route of the mechanism, phenyl acetylenic triflone $249$ was synthesised from phenylacetylene-$2^{-13}$C. The labelled triflone was then submitted to the reaction conditions to afford $250$ (Scheme 79), upon analysis of the $^{13}$C NMR spectrum, an intense $^{13}$C signal is visible at 89ppm corresponding to the alpha position on the acetylenic product $250$ (highlighted in red). This suggests that alpha addition of the THF radical $57$ takes place onto phenyl acetylenic triflone $176$ to afford the corresponding vinyl triflone intermediate $245$, i.e. Path A - $\alpha$-addition.

To further gain insight to the mechanism, a kinetic isotope effect (KIE) experiment was performed using liquid chromatography-mass spectrometry (LCMS) analysis. The reaction of phenyl acetylenic triflone with both THF and THF-$d_8$ provided both products $140$ and $140_d$ respectively (Scheme 80). The product ratio was then determined via LCMS analysis by integrating the peak areas of the extracted ion chromatograms (EICs) for the non-deuterated and deuterated species. As a result of this method, the KIE was calculated to give a $K_{H}/K_{d}$ value of 3.53 (see experimental section for calculations). This indicates that breakage of the initial $\alpha$–C–H proton of THF is likely involved in the turnover limiting step, with a much faster reaction possible with the C–H bond than with the C-D bond in deuterated THF-$d_8$. 

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$Ph\equiv\rightarrow$ i) $n$-BuLi, -78 °C
ii) Tf$_2$O, -78 °C

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Scheme 80: Deuterium labelling experiment involving THF and THF-$d_6$, through LCMS analysis a kinetic isotopic effect of 3.53 is calculated. Indicating that breakage of the $\alpha$–C–H proton of THF is involved in the turnover limiting step.

Finally, the radical nature of the reaction was confirmed with the use of the radical trap TEMPO (2,2,6,6-tetramethylpiperidin-1-yl)oxyl). THF 56 was reacted with acetylenic triflone 176 in the presence of an equivalent amount of TEMPO (0.25 mmol) at 80 °C. No C–H functionalisation product 140 was formed (Scheme 81). The presence of the THF-TEMPO adduct 251 was detected via LCMS; it could not be isolated as intermediate 251 was unstable to all forms of work-up and purification. Importantly, attempting the reaction in an argon atmosphere whilst bubbling argon through the reaction mixture led to no observation of the acetylenic product 140. This highlights that oxygen in air is vital for the formation of the initial THF-radical species which allows propagation of the radical chain reaction to take place.
Scheme 81: Radical trapping of THF 56 by TEMPO in the presence of acetylenic triflone 176, forming 251 in-situ, which was detected by LCMS (top). Using an argon atmosphere led to no formation of the acetylenic THF product 140 (bottom).

Overall, through mechanistic studies an insight into the radical pathway was explored; $^{13}$C-labelling experiments provided evidence for an $\alpha$-addition pathway, KIE experiments outlined the cleavage of the $\alpha$–C–H proton was likely the turnover limiting step and radical inhibition experiments outlined the presence of both an aerobic and radical mechanism.
3.1 Conclusion

In summary, an aerobic approach for $\alpha$-C($sp^3$)-H functionalisation of heterocycles utilising acetylenic and vinyl triflones has been developed, enabled using HFIP. The use of atmospheric oxygen to generate reactive radical species feeds into the sought after goal of simplification and dematerialisation of C–H activation transformations. A broad library of acetylenic and vinyl heterocycles were efficiently prepared. Acetylenic and vinyl heterocycles offer opportunity for further synthetic manipulations as shown in the novel transformations to generate privileged building blocks in only two overall steps. The radical nature of the mechanism was studied through the use of $^{13}$C labelling studies, kinetic isotope effect experiments and radical traps. It is maintained that the use of auto-oxidation to access reactive radical species without the use of precious metals or initiators is largely unexplored and can be a powerful method when used in C–H bond functionalisation methodologies.
3.2 Future Directions

Following the success of utilising the aerobic oxidation pathway of the heterocycles described in this work, further application towards a radical arylation method could be devised to generate privileged arylated scaffolds. Preliminary results using THF in HFIP (Scheme 82) alongside 2-(tetrahydrofuran-2-yl)benzo[d]thiazole 252 allowed for facile addition of the aerobically generated THF radical and subsequent elimination of the chlorine leaving group giving 253 in 94% yield. Following this, reacting with the analogous 2-(tetrahydrofuran-2-yl)benzo[d]oxazole 254 also furnished the respective THF-addition product 255 in 71% yield. In these reaction conditions, 10 equivalents of THF and a higher temperature of 90 °C are used as poor conversion of the aromatic heterocycle is observed when employing 5 equivalents of heterocycle.

![Scheme 82](image)

Scheme 82: Provision results showing a radical addition/elimination mechanism to generate arylated scaffolds 253 and 254.

This idea could then be applied to more complex substrates (Scheme 83) by optimising the reaction conditions for a range of leaving groups or stabilising functionalities which would allow for addition of the nucleophilic THF radical onto the aromatic system. This would be an especially appealing method as unwanted ionic reactivity is avoided; protecting complex aromatic scaffolds from side-reactions of ionic nucleophilic species.
Heteroaryl sources:

Scheme 83: Potential aromatic scaffolds which could allow nucleophilic addition of an aerobically generated THF radical.
General Experimental

Chemicals

All reagents were purchased from Merck or AlfaAesar and were used as received without further purification unless otherwise stated. All ethers were freshly distilled and degassed before usage in the reactions described below to remove radical inhibitors such as BHT.

Chromatography

All reactions were monitored by thin-layer chromatography (TLC) on pre-coated silica gel plates. Silica gel plates were initially examined under short wave UV light and then developed using aqueous potassium permanganate stain. Flash column chromatography was carried out with pre-loaded GraceResolv™ flash cartridges on a Biotage® Isolera Spektra One flash chromatography system.

Spectroscopy

Quoted yields refer to chromatographically and spectroscopically pure compounds unless otherwise stated. $^1$H NMR spectra were recorded at 400, 500 600 or 700 MHz and $^{13}$C NMR at 126, 151 or 176 MHz on a Bruker Avance III 600 or Bruker Avance Neo 700 spectrometer. The chemical shifts (δ) for $^1$H and $^{13}$C are quoted relative to residual signals of the solvent on the parts per million (ppm) scale. In the case of multiple rotamers, only the major has been assigned. Coupling constants ($J$ values) are reported in Hertz (Hz) and are reported as $J_{H,H}$. Signal multiplicities in $^{13}$C NMR were determined using the distortionless enhancement by polarisation transfer (DEPT) spectral editing technique.

LCMS used for kinetic isotope effect experiments

LCMS was performed using a Waters Acquity uPLC connected to Waters Acquity Single Quad Detector (SQD). All samples were run with the following parameters. Column: Hypersil Gold C4, 1.9 μm, 2.1 μm × 50 μm. Wavelength: 254 nm. Mobile Phase: 50:50 Water (0.1% Formic Acid): MeCN (0.1% Formic Acid) Gradient over 4 min (to 5:95 Water (0.1% Formic Acid): MeCN (0.1% Formic Acid). Flow Rate: 0.6 mL/min. MS Mode: ES+. Scan Range: m/z = 150 – 300. Scan time: 0.25 s. Data obtained in continuum mode. The electrospray source of the MS was operated with a capillary voltage of 3.5 kV and a cone voltage of 50 V. Nitrogen was used
as the nebulizer and desolvation gas at a total flow of 600 L/h. Ion series were generated by integration of the total ion chromatogram (TIC) over the appropriate range.
Preparation of Reagents

(((Trifluoromethyl)sulfonyl)ethynyl)benzene – 176

![Chemical Structure](image)

To a stirring solution of phenylacetylene (2.41 mL, 22.0 mmol, 1.1 eq.) in dry Et$_2$O (100 mL) was added $n$-BuLi (13.8 mL, 1.6 M in hexanes, 1.1 eq.) over 30 min at -78 °C under an argon atmosphere. After being stirred for 0.5 h at -78 °C, the corresponding lithium acetylide was slowly transferred via cannula transfer to a solution of triflic anhydride (3.36 mL, 20.0 mmol, 1.0 eq.) in dry Et$_2$O (50 mL) at -78 °C. The reaction was stirred at -78 °C for 30 min before being quenched with water. The aqueous layer was extracted with ether, and the combined organic layers were washed with brine, dried over MgSO$_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (0-10% EtOAc/cyclohexane) to afford 176 as a pale yellow oil (3.65g, 16.0 mmol) in 88% yield. $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.70 (d, $J = 7.5$ Hz, 2 H, H-3), 7.64 (t, $J = 7.5$, Hz, 1 H, H-1), 7.47 (t, $J = 7.2$ Hz, 2 H, H-2); $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 133.9 (CH, Ar-C), 133.5 (CH, Ar-C), 129.2 (CH, Ar-C), 119.1 (C, q, $J = 323.1$ Hz, C-7), 115.9 (C-Ar), 100.9 (C-5), 77.4 (C-6); IR (thin film): 3072, 2852, 2175, 2104, 1596, 1489, 1445 cm$^{-1}$. Known compound.$^{124}$
2-oxo-2-phenylethyl 2-iodobenzoate – 141

Rearranged product observed as a yellow oil from the reaction of THF 56 with Ph-EBX 98 (Scheme 50 – Major side-product 50%). \(^1\)H NMR (700 MHz, CDCl\(_3\)) \(\delta\) 8.06 (dd, \(J = 7.8, 1.7\) Hz, 1H, H-Ar), 8.02 (dd, \(J = 8.0, 1.0\) Hz, 1H, H-Ar), 7.99 – 7.94 (m, 2H, H-Ar), 7.71 – 7.59 (m, 1H, H-Ar), 7.54 – 7.48 (m, 2H, H-Ar), 7.45 (td, \(J = 7.6, 1.1\) Hz, 1H, H-Ar), 7.19 (td, \(J = 7.7, 1.7\) Hz, 1H, H-Ar), 5.60 (s, 2H, H-3). \(^{13}\)C NMR (176 MHz, CDCl\(_3\)) \(\delta\) 191.9 (C=O, C-4), 165.9 (C=O, C-2), 141.6 (CH, C-Ar), 134.3 (C, C-Ar), 134.2 (C, C-Ar), 134.1 (CH, C-Ar), 133.2 (CH, C-Ar), 131.8 (CH, C-Ar), 129.1 (CH, C-Ar), 128.2 (CH, C-Ar), 128.0 (CH, C-Ar), 94.6 (C-I, C-1), 66.9 (CH\(_2\), C-3). IR (thin film): 2983, 2912, 1754, 1688, 1544 cm\(^{-1}\). Known compound. \(^{132}\)
General Procedure for aerobic C-H functionalisation of heterocycles – Method A (Alkynylation)

To a solution of heterocycle/ether (1.25 mmol, 5.0 eq.) in HFIP (0.40 mmol) was added (((trifluoromethyl)sulfonyl)ethynyl)benzene \(176\) (0.25 mmol, 1.0 eq). The reaction mixture was stirred at 80 °C for 16 h and then poured over sat. aq. NaHCO\(_3\) (5 mL). The organics were extracted with EtOAc (3 x 10 mL), dried over MgSO\(_4\), filtered and the solvent removed under reduced pressure. The resultant crude residue was purified as described below.
2-(Phenylethynyl)tetrahydrofuran – 140

Following application of method A, purification by column chromatography (0-15% EtOAc/cyclohexane) afforded 2-(phenylethynyl)tetrahydrofuran 140 as a clear oil (0.957g, 5.50 mmol, 89%). $^1$H NMR (CDCl$_3$, 700 MHz): $\delta$ 7.43 (dd, 7.0, 3.0 Hz, 2H, H-Ar), 7.34–7.29 (m, 3H, H-Ar), 4.81 (dd, $J = 7.2$ Hz, 5.0 Hz, 1H, H-4), 4.08–4.01 (m, 1H, H-1), 3.86 (td, $J = 8.0$, 5.5 Hz, 1H, H-1), 2.29–2.20 (m, 1H, H-2), 2.17–2.07 (m, 2H, H2-3), 2.00–1.91 (m, 1H, H-3); $^{13}$C NMR (176 MHz, CDCl$_3$) $\delta$ 131.8 (CH, C-Ar), 128.3 (CH, C-Ar), 128.4 (CH, C-Ar), 123.0 (C, C-Ar), 89.2 (C, C-6), 84.6 (C, C-5), 68.7 (CH, C-1), 68.1 (CH$_2$, C-4), 33.6 (CH$_2$, C-3), 25.6 (CH$_2$, C-2); IR (thin film): 2929, 2209, 1602, 1558, 1521 cm$^{-1}$. Known compound. $^{133}$
Following application of method A, purification by column chromatography (0-15% EtOAc/cyclohexane) afforded 2-methyl-2-(phenylethynyl)tetrahydrofuran 150 and 2-methyl-5-(phenylethynyl)tetrahydrofuran 151-a and 151-b as an inseparable yellow oil (40 mg, 0.22 mmol, 86%). Assignment for each regioisomer/diastereomer is provided below. Product ratio: 1.7:1.0:5 150:151-a:151-b respectively. These ratios were calculated using NMR integrations of key protons such as the propargylic C-H.

150: ¹H NMR (500 MHz, CDCl₃): δ 7.44–7.39 (m, 2H), 7.30–7.26 (m, 3H), 4.03–3.94 (m, 2H), 2.09–2.18 (m, 3H), 1.86 (dt, J = 12.4, 8.4 Hz, 1H), 1.68 (s, 3H). ¹³C NMR (126 MHz, CDCl₃): δ 131.8 (CH), 128.3 (CH), 128.2 (CH), 123.2 (C) 92.5 (C), 82.9 (C), 76.5 (C), 67.8 (CH₂), 40.3 (CH₂), 27.8 (CH₃), 25.8 (CH₂).

151-a: ¹H NMR (500 MHz, CDCl₃): δ 7.44–7.39 (m, 2H), 7.30–7.26 (m, 3H), 4.92 (dd, J = 7.2, 5.8 Hz, 1H), 4.33–4.24 (m, 1H), 2.36–2.27 (m, 2H), 2.17–2.13 (m, 1H), 1.51 (m, 1H), 1.28 (d, J = 8.1 Hz, 3H). ¹³C NMR (126 MHz, CDCl₃): δ 131.8 (CH), 128.3 (CH), 128.2 (CH), 123.2 (C), 89.7 (C), 84.4 (C), 75.2 (CH), 68.5 (CH), 34.0 (CH₂), 33.2 (CH₂), 20.9 (CH₃).

151-b: ¹H NMR (500 MHz, CDCl₃): δ 7.44–7.39 (m, 2H), 7.30–7.26 (m, 3H), 4.73 (dd, J = 7.2, 6.1 Hz, 1H), 4.08–4.03 (m, 1H), 2.27–2.23 (m, 2H), 2.17–2.12 (m, 1H), 1.76–1.66 (m, 1H), 1.35 (d, J = 6.1 Hz, 3H). ¹³C NMR (126 MHz, CDCl₃): δ 131.8 (CH), 128.3 (CH), 128.2 (CH), 123.2 (C), 89.6 (C), 84.5 (C), 76.4 (CH), 68.7 (CH), 33.9 (CH₂), 33.1 (CH₂), 21.6 (CH₃).

IR (thin film): 3002, 2899, 2199, 1567, 1540, 1521 cm⁻¹. HRMS (ESI) calcd for C₁₄H₁₄O [M+H]⁺ 186.1039; observed 186.1032.
2,5-Dimethyl-2-(phenylethynyl)tetrahydrofuran (unidentified mixture of 3:1 cis/trans isomers) – 177

Following application of method A, purification by column chromatography (0-15% EtOAc/cyclohexane) afforded 2,5-dimethyl-2-(phenylethynyl)tetrahydrofuran 177 (3:1 mixture of cis/trans isomers) as a yellow liquid (48 mg, 0.24 mmol, 97%). $^1$H NMR (700 MHz, CDCl$_3$): δ 7.45–7.37 (m, 2H), 7.31–7.27 (m, 3H), 4.31 (dq, $J$ = 12.7, 6.2 Hz, 0.75H), 4.22 (dq, $J$ = 8.2, 6.1 Hz, 0.25H), 2.35 (ddd, $J$ = 9.4, 6.4, 4.0 Hz, 0.25H), 2.29 (ddd, $J$ = 12.2, 8.5, 6.0 Hz, 0.75H), 2.21 (ddt, $J$ = 12.7, 8.5, 6.4 Hz, 0.75H), 2.16–2.11 (m, 0.25H), 1.94 (m, 1H), 1.91–1.82 (m, 0.25H), 1.63 (s, 2.25H), 1.61 (s, 0.75H), 1.57–1.52 (m, 0.75H), 1.36 (d, $J$ = 6.1 Hz, 0.75H), 1.28 (d, $J$ = 6.1 Hz, 2.25H). $^{13}$C NMR (176 MHz, CDCl$_3$) δ 131.8 (CH), 131.7 (CH), 128.3 (CH), 128.1 (CH), 128.1 (CH), 123.4 (C), 123.2 (C), 93.8 (C), 93.1 (C), 82.7 (C), 82.5 (C), 76.6 (C), 76.3 (C), 75.3 (CH), 41.5 (CH$_2$), 40.4 (CH$_2$), 34.3 (CH$_2$), 33.1 (CH$_2$), 28.7 (CH$_3$), 28.4 (CH$_3$), 22.4 (CH$_3$), 21.4 (CH$_3$). IR (thin film): 3011, 2921, 2215, 1600, 1540, 1512 cm$^{-1}$. HRMS (ESI) calc for C$_{14}$H$_{16}$O [M+H]$^+$ 201.1274; observed 201.1268.
5-(phenylethynyl)dihydrofuran-3(2H)-one – 179

Following application of method A, purification by column chromatography (0-15% EtOAc/cyclohexane) afforded 5-(phenylethynyl)dihydrofuran-3(2H)-one 179 as a clear oil (40 mg, 0.21 mmol, 84%). $^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.44–7.40 (m, 2H, H-Ar), 7.38–7.29 (m, 3H, H-Ar), 5.30 (dd, $J = 7.6$, 5.2 Hz, 1H, H-4), 4.16 (d, $J = 16.8$ Hz, 1H, H-1), 3.98 (d, $J = 16.8$ Hz, 1H, H-1), 2.85 (dd, $J = 17.8$, 7.7 Hz, 1H, H-3), 2.68 (dd, $J = 17.8$, 5.2 Hz, 1H, H-3). $^{13}$C NMR (126 MHz, CDCl$_3$): $\delta$ 213.0 (C=O, C-2), 132.0 (CH, C-Ar), 129.1 (CH, C-Ar), 128.5 (CH, C-Ar), 121.9 (C, C-Ar), 87.1 (C, C-6), 86.2 (C, C-5), 69.8 (CH$_2$, C-1), 67.8 (CH, C-4), 43.9 (CH$_2$, C-3); IR (thin film): 2911, 2901, 2206, 1724, 1613, 1558, 1543 cm$^{-1}$. HRMS (ESI) calcd for C$_{12}$H$_{10}$O$_2$ [M+H]$^+$ 187.0675; observed 187.0643.
2-Methyl-5-(phenylethynyl)dihydrofuran-3(2H)-one – 178

Following application of method A, purification by column chromatography (0-15% EtOAc/cyclohexane) afforded 2-(phenylethynyl)-1,4-dioxane 178 as a yellow oil (39 mg, 0.20 mmol, 78%). $^1$H NMR (CDCl$_3$, 400 MHz): δ 7.42 (dd, $J = 7.5$, 2.0 Hz, 2H, H-Ar), 7.34–7.31 (m, 3H, H-Ar), 5.35 (dd, $J = 8.4$, 3.0 Hz, 1H, H-5), 4.20 (q, $J = 6.9$ Hz, 1H, H-2), 2.87 (dd, $J = 17.9$, 8.4 Hz, 1H, H-4), 2.70 (dd, $J = 17.9$, 3.0 Hz, 1H, H-4), 1.34 (d, $J = 7.0$ Hz, 3H, H-1); $^{13}$C NMR (101 MHz, CDCl$_3$) δ 214.7 (C=O, C-Ar), 131.9 (CH, C-Ar), 129.1 (CH, C-Ar), 128.4 (CH, C-Ar), 121.9 (C, C-Ar), 86.9 (C, C-7), 86.4 (C, C-6), 73.3 (CH, C-5), 65.2 (CH, C-2), 43.3 (CH$_2$, C-4), 15.6 (CH$_3$, C-1); IR (thin film): 2915, 2899, 2211, 1723, 1613, 1560, 1543 cm$^{-1}$. HRMS (ESI) calcd for C$_{13}$H$_{12}$O$_2$ [M+H]$^+$ 201.0910; observed 201.0903.
(2R)-4-Oxo-5-(phenylethynyl)tetrahydrofuran-2-yl)methyl acetate and (2-(phenylethynyl)tetrahydrofuran-2-yl)methyl acetate – 180-a, 180-b and 181.

Following application of method A, purification by column chromatography (0-15% EtOAc/cyclohexane) afforded ((2R)-4-oxo-5-(phenylethynyl)tetrahydrofuran-2-yl)methyl acetate 180-a + 180-b and (2-(phenylethynyl)tetrahydrofuran-2-yl)methyl acetate 181 as an inseparable yellow oil (39 mg, 0.15 mmol, 61%). Assignment for each regioisomer/diastereomer is provided below. Product ratio is 1:0.35:0.85 180-a:180-b:181 respectively. These ratios were calculated using NMR integrations of key protons such as the propargylic C-H.

180-a: $^1$H NMR (CDCl$_3$, 700 MHz): $\delta$ 7.47–7.38 (m, 2H), 7.34–7.27 (m, 3H), 4.95 (t, $J$ = 6.2 Hz, 1H), 4.42 (qd, $J$ = 7.0, 3.6 Hz, 1H), 4.18 (dd, $J$ = 11.6, 3.6 Hz, 1H), 4.01–3.97 (m, 1H), 2.17–2.14 (m, 1H), 2.09 (s, 3H), 2.00-1.91 (m, 2H), 1.75–1.70 (m, 1H). $^{13}$C NMR (176 MHz, CDCl$_3$): $\delta$ 171.2 (br C=O), 131.9 (CH), 128.5 (CH), 128.4 (CH), 122.8 (C), 85.0 (C), 88.5 (C), 76.6 (CH), 69.4 (CH), 27.9 (CH$_2$), 25.8 (CH$_2$), 21.06 (CH$_3$).

180-b: $^1$H NMR (CDCl$_3$, 700 MHz): $\delta$ 7.47–7.38 (m, 2H), 7.34–7.27 (m, 3H), 4.86 (dd, $J$ = 7.1, 5.1 Hz, 1H), 4.29 (dd, $J$ = 11.4, 3.7 Hz, 1H), 4.12 (dd, $J$ = 11.4, 6.8 Hz, 1H), 4.08–4.04 (m, 1H), 2.25–2.00 (m, 3H), 2.08 (s, 3H), 1.91 (dq, $J$ = 12.6, 8.2 Hz, 1H). $^{13}$C NMR (176 MHz, CDCl$_3$): $\delta$ 171.2 (br C=O), 131.8 (CH), 128.6 (CH), 128.4 (CH), 122.8 (C), 88.9 (C), 84.9 (C), 77.7 (CH), 69.4 (CH), 67.0 (CH$_2$), 29.8 (CH$_2$), 28.1 (CH$_2$), 22.8 (CH$_3$).

181: $^1$H NMR (CDCl$_3$, 700 MHz): $\delta$ 7.47–7.38 (m, 2H), 7.34–7.27 (m, 3H), 4.38 (d, $J$ = 11.3 Hz, 1H), 4.22 (d, d, $J$ = 11.3 Hz, 1H), 4.08–4.04 (m, 2H), 2.28–2.20 (m, 3H), 2.13 (s, 3H), 2.11–2.05 (m, 1H). $^{13}$C NMR (176 MHz, CDCl$_3$): $\delta$ 170.9 (C=O), 131.9 (CH), 128.6 (CH), 128.4 (CH), 122.6 (C), 88.8 (C), 84.9 (C), 77.2 (C), 68.2 (C), 66.4 (C), 36.0 (CH$_2$), 33.5 (CH$_2$), 21.1 (CH$_3$).
IR (thin film): 2901, 2211, 1745, 1600, 1565, 1547 cm\(^{-1}\). HRMS (ESI) calcd for C\(_{15}\)H\(_{16}\)O\(_3\) [M+H]\(^+\) 245.1172; observed 245.1161.
Ethyl 5-(phenylethynyl)tetrahydrofuran-2-carboxylate – 182

Following application of method A, purification by column chromatography (0-15% EtOAc/cyclohexane) afforded ethyl 5-(phenylethynyl)tetrahydrofuran-2-carboxylate 182 as a clear oil (46 mg, 0.18 mmol, 76%). $^1$H NMR (500 MHz, CDCl$_3$) δ 7.46–7.38 (m, 2H, H-Ar), 7.37–7.27 (m, 3H, H-Ar), 5.12–5.06 (m, 1H, H-4), 4.67 (dd, $J$ = 8.3, 5.3 Hz, 1H, H-7), 4.23 (dq, $J$ = 11.9, 7.1 Hz, 1H, H-2), 4.20 (dq, $J$ = 11.9, 7.1 Hz, 1H, H-2), 2.53–2.41 (m, 1H, H-5), 2.38–2.27 (m, 1H, H-6), 2.18–2.05 (m, 2H, H5-6), 1.29 (t, $J$ = 7.1 Hz, 3H, H-1). $^{13}$C NMR (126 MHz, CDCl$_3$) δ 172.8 (C=O, C-3), 131.9 (CH, C-Ar), 128.5 (CH, C-Ar), 128.4 (CH, C-Ar), 122.7 (C, C-Ar), 88.0 (C, C-9), 85.4 (C, C-8), 70.2 (CH, C-7), 61.2 (CH$_2$, C-2), 32.9 (CH$_2$, C-5), 29.9 (CH$_2$, C-6), 14.3 (CH$_3$, C-1); IR (thin film): 2921, 2199, 1743, 1575, 1547 cm$^{-1}$; HRMS (ESI) calcd for C$_{15}$H$_{16}$O$_3$ [M+H]$^+$ 245.1172; observed 245.1170.
2,2-Dimethyl-4-(phenylethynyl)-1,3-dioxolane – 193

Following application of method A, purification by column chromatography (0-15% EtOAc/cyclohexane) afforded 2,2-dimethyl-4-(phenylethynyl)-1,3-dioxolane 193 as a clear oil (46 mg, 0.18 mmol, 76%). $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.48–7.41 (m, 2H, H-Ar), 7.31 (m, 3H, H-Ar), 4.95 (t, $J$ = 6.4 Hz, 1H, H-4), 4.24 (dd, $J$ = 8.0, 6.3 Hz, 1H, H-5), 4.02 (dd, $J$ = 8.0, 6.3 Hz, 1H, H-5), 1.55 (s, 3H, H-6/7), 1.42 (s, 3H, H-6/7); $^{13}$C NMR (151 MHz, CDCl$_3$) $\delta$ 131.9 (CH, C-Ar), 128.8 (CH, C-Ar), 128.4 (CH, C-Ar), 122.4 (C, C-Ar), 110.5 (C, C-Ar), 86.3 (C, C-2), 86.0 (C, C-3), 70.2 (CH, C-4), 66.2 (CH$_2$, C-5), 26.4 (CH$_3$, C-6/7), 26.2 (CH$_3$, C-6/7). IR (thin film): 3001, 2923, 2204, 1601, 1575, 1557 cm$^{-1}$. Known compound.$^{133}$
2-(Phenylethynyl)tetrahydro-2H-pyran – 153

Following application of method A (10 equivalents of THP), purification by column chromatography (0-15% EtOAc/cyclohexane) afforded 2-(phenylethynyl)tetrahydro-2H-pyran 153 as a clear oil (30 mg, 0.16 mmol, 64%). $^1$H NMR (CDCl$_3$, 600 MHz): δ 7.45–7.44 (m, 2H, H-Ar), 7.31–7.29 (m, 3H, H-Ar), 4.52 (dd, $J = 7.9, 2.7$ Hz, 1H, H-5), 4.06–4.04 (m, 1H, H-1), 3.57–3.53 (m, 1H, H-1), 1.93–1.90 (m, 2H, H-4), 1.79–1.76 (m, 1H, H-3), 1.61–1.59 (m, 3H, H-2/3); $^{13}$C NMR (151 MHz, CDCl$_3$) δ 131.9 (CH, C-Ar), 128.4 (CH, C-Ar), 128.4 (CH, C-Ar), 122.9 (C, C-Ar), 88.2 (C, C-7), 85.3 (C, C-6), 67.6 (CH, C-5), 66.8 (CH$_2$, C-1), 32.3 (CH$_2$, C-4), 25.8 (CH$_2$, C-3), 22.0 (CH$_2$, C-2); IR (thin film): 2945, 2901, 2211, 1608, 1562, 1553 cm$^{-1}$. Known compound. 102
(2R,3S,4R,6S)-2-(acetoxymethyl)-6-(phenylethynyl)tetrahydro-2H-pyran-3,4-diyl diacetate and (2R,3S,4R,6R)-2-(acetoxymethyl)-6-(phenylethynyl)tetrahydro-2H-pyran-3,4-diyl diacetate – 189 and 189-b

Following application of method A, purification by column chromatography (0-25% EtOAc/cyclohexane) afforded single diastereomer (2R,3S,4R,6S)-2-(acetoxymethyl)-6-(phenylethynyl)tetrahydro-2H-pyran-3,4-diyl diacetate 189 as a yellow oil (41 mg, 0.11 mmol, 41%). A inseparable mixture of 189 and 189-b was also isolated, the yield and data quoted is of the pure diasteromer 189. 1H NMR (CDCl₃, 600 MHz): δ 1H NMR (600 MHz, CDCl₃) δ 7.53–7.46 (m, 2H, H-Ar), 7.38–7.29 (m, 3H, H-Ar), 5.43 (ddd, J = 11.6, 9.5, 5.0 Hz, 1H, H-3), 5.11 (br d, J = 4.4 Hz, 1H, H-1), 5.01 (t, J = 9.7 Hz, 1H, H-4), 4.35 (dd, J = 12.3, 4.2 Hz, 1H, H-6), 4.23 (ddd, J = 9.9, 4.2, 2.1 Hz, 1H, H-5), 4.10 (dd, J = 12.3, 2.1 Hz, 1H, H-6), 2.34 (ddd, J = 12.8, 5.0, 1.5 Hz, 1H, H-2), 2.10 (s, 3H, H-7), 2.07 (m, 1H, H-2), 2.04 (s, 3H, H-7), 2.03 (s, 3H, H-7). 13C NMR (151 MHz, CDCl₃) δ 171.0 (C=O, C-7), 170.4 (C=O, C-7), 170.1 (C=O, C-7), 132.1 (CH, C-Ar), 129.1 (CH, C-Ar), 128.5 (CH, C-Ar), 121.9 (C, C-Ar), 88.7 (C, C-9), 84.6 (C, C-8), 71.4 (CH, C-5), 70.1 (CH, C-3), 69.4 (CH, C-4), 64.7 (CH, C-1), 62.5 (CH, C-6), 35.6 (CH₂, C-2), 21.2 (CH₃, C-7), 21.0 (CH₃, C-7), 20.9 (CH₃, C-7). IR (thin film): 2961, 2867, 2214, 1741, 1501, 1440 cm⁻¹. HRMS (ESI) calced for C₂₀H₂₂O₇ [M+H]⁺ 375.1444; observed 375.1436.
Following application of method A, purification by column chromatography (0-15% EtOAc/cyclohexane) afforded 2-(phenylethynyl)-1,4-dioxane 186 as a yellow oil (33 mg, 0.18 mmol, 71%). $^1$H NMR (CDCl$_3$, 600 MHz): δ 7.45 (dd, $J = 6.2$, 1.8 Hz, 2H, H-Ar), 7.31–7.29 (m, 3H, H-Ar), 4.57 (dd, $J = 8.2$, 1.6 Hz, 1H, H-4), 3.95–3.92 (m, 2H, H-3), 3.77–3.68 (m, 4H, H-2/3); $^{13}$C NMR (151 MHz, CDCl$_3$) δ 132.0 (CH, C-Ar), 128.9 (CH, C-Ar), 128.4 (CH, C-Ar), 122.2 (CH$_2$, C-Ar), 86.7 (C, C-6), 84.4 (C, C-5), 70.7 (CH, C-4), 66.6 (CH$_2$, C-3), 66.5 (CH$_2$, C-1/2), 66.0 (CH$_2$, C-1/2); IR (thin film): 2905, 2892, 2199, 1613, 1560, 1546 cm$^{-1}$. Known compound. $^{133}$
**tert-Butyl 3-(phenylethynyl)morpholine-4-carboxylate– 215**

Following application of method A, purification by column chromatography (0-15% EtOAc/cyclohexane) afforded **tert-butyl-2-(phenylethynyl)morpholine-4-carboxylate 215** as a yellow oil (42 mg, 0.15 mmol, 58%). $^1$H NMR (CDCl$_3$, 600 MHz): δ 7.45–7.43 (m, 2H, H-Ar), 7.31–7.29 (m, 3H, H-Ar), 4.94 (br s, 1H, H-4), 3.99 (dd, $J$ = 11.2, 3.1 Hz, 1H, H-3) 3.92 (dd, $J$ = 11.4, 3.1 Hz, 1H, H-1), 3.74 (d, $J$ = 13.1 Hz, 1H, H-2), 3.66 (dd, $J$ = 11.2, 3.2 Hz, 1H, H-3), 3.50 (td, $J$ = 11.7, 2.7 Hz, 1H, H-1), 3.40 (td, $J$ = 12.6, 3.2 Hz, 1H, H-2), 1.50 (s, 9H, N-Boc); $^{13}$C NMR (151 MHz, CDCl$_3$) δ 154.7 (C=O, N-Boc), 132.0 (CH, C-Ar), 128.3 (CH, C-Ar), 128.2 (CH, C-Ar), 123.0 (C, C-Ar), 86.2 (C, C-6), 83.4 (C, C-5), 80.8 (C, N-Boc), 70.2 (CH$_2$, C-3), 67.0 (CH$_2$, C-1), 45.6 (CH, C-4), 40.7 (CH$_2$, C-2), 28.5 (CH$_3$, N-Boc); IR (thin film): 2912, 2888, 2203, 1619, 1560, 1531 cm$^{-1}$. HRMS (ESI) calcd for C$_{17}$H$_{21}$NO$_3$ [M+H]$^+$ 288.1605; observed 288.1593. NMR run at 60 ºC to resolve rotamers.
3-(Phenylethynyl)-1,4-oxathiane and 2-(phenylethynyl)-1,4-oxathiane – 187 + 188

Following application of method A, purification by column chromatography (0-15% EtOAc/cyclohexane) afforded 3-(phenylethynyl)-1,4-oxathiane and 2-(phenylethynyl)-1,4-oxathian 187 and 188 as an inseparable mixture of regioisomers – yellow oil (30 mg, 0.15 mmol, 59%). 187 (major): ¹H NMR (600 MHz, CDCl₃) δ 7.51–7.38 (m, 2H, H-Ar), 7.36–7.27 (m, 3H, H-Ar), 4.20 (d, J = 8.9 Hz, 1H, H-3), 4.05 (ddd, J = 11.8, 4.7, 2.9 Hz, 1H, H-2), 3.93–3.79 (m, 3H, H-2/3/4), 2.85 (ddd, J = 13.6, 8.9, 2.9 Hz, 1H, H-1), 2.72 (ddd, J = 13.6, 4.7, 2.2 Hz, 1H, H-1); ¹³C NMR (151 MHz, CDCl₃) δ 132.0 (CH, C-Ar), 129.6 (CH, C-Ar), 128.4 (CH, C-Ar), 122.7 (C, C-Ar), 85.4 (C, C-6), 84.5 (C, C-5), 72.8 (CH₂, C-3), 68.5 (CH₂, C-2), 30.4 (CH, C-4), 27.1 (CH₂, C-1); IR (thin film): 2918, 2221, 1619, 1560, 1531 cm⁻¹. HRMS (ESI) calcd for C₁₂H₁₂O₃ [M+H]⁺ 205.0682; observed 205.0680.
Following application of method A with the exclusion of HFIP, purification by column chromatography (0-15% EtOAc/cyclohexane) afforded 2-(phenylethynyl)tetrahydrothiophene 154 as a yellow oil (34 mg, 0.18 mmol, 72%). $^1$H NMR (CDCl$_3$, 500 MHz): $^1$H NMR (500 MHz, CDCl$_3$) δ 7.40 (ddd, $J$ = 6.0, 2.4, 1.6 Hz, 2H, H-Ar), 7.29–7.26 (m, 3H, H-Ar), 4.27 (t, $J$ = 5.8 Hz, 1H, H-4), 3.16–3.09 (m, 1H, H-1), 2.93 (dd, $J$ = 10.1, 6.6 Hz, 1H, H-1), 2.30–2.13 (m, 3H, H-2/3), 2.12–2.04 (m, 1H, H-2). $^{13}$C NMR (126 MHz, CDCl$_3$) δ 131.8 (CH, C-Ar), 128.3 (CH, C-Ar), 128.1 (CH, C-Ar), 123.4 (C, C-Ar), 90.8 (C, C-6), 83.0 (C, C-5), 39.1 (CH, C-4), 37.1 (CH$_2$, C-1), 33.0 (CH$_2$, C-3), 30.6 (CH$_2$, C-2). IR (thin film): 3002, 2931, 2209, 1602, 1558 cm$^{-1}$. Known compound. 134
(3-Ethoxybut-1-yn-1-yl)benzene – 155

Following application of method A, purification by column chromatography (0-15% EtOAc/cyclohexane) afforded (3-ethoxybut-1-yn-1-yl)benzene 155 as a clear oil (25 mg, 0.14 mmol, 57%). $^1$H NMR (CDCl$_3$, 500 MHz): δ 7.45-7.43 (m, 2H, H-Ar), 7.31-7.29 (m, 3H, H-Ar), 4.39 (q, $J$ = 6.6 Hz, 1H, H-3), 3.85 (dq, $J$ = 14.0, 7.0 Hz, 1H, H-2), 3.51 (dq, $J$ = 14.0 Hz, 7.0, 1H, H-2), 1.53 (d, $J$ = 6.6 Hz, 3H, H-4), 1.26 (t, $J$ = 7.0 Hz, 3H, H-1); $^{13}$C NMR (126 MHz, CDCl$_3$) δ 131.8 (CH, C-Ar), 128.4 (CH, C-Ar), 123.0 (C, C-Ar), 89.6 (C, C-6), 84.8 (C, C-5), 65.6 (CH, C-3), 64.3 (CH$_2$, C-2), 22.4 (CH$_3$, C-4), 15.4 (CH$_3$, C-1); IR (thin film): 2930, 2902, 2185, 1603, 1548, 1521 cm$^{-1}$. Known compound. 135
(3,4-Dimethoxybut-1-yn-1-yl)benzene – 192

Following application of method A, purification by column chromatography (0-15% EtOAc/cyclohexane) afforded (3,4-dimethoxybut-1-yn-1-yl)benzene 192 as a yellow oil (36 mg, 0.19 mmol, 76%). $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.48–7.42 (m, 2H, H-Ar), 7.38–7.28 (m, 3H, H-Ar), 4.41 (dd, $J = 7.4$, 3.8 Hz, 1H, H-3), 3.68 (dd, $J = 10.5$, 7.4 Hz, 1H, H-2), 3.64 (dd, $J = 10.5$, 3.8 Hz, 1H, H-2), 3.53 (s, 3H, H-1), 3.45 (s, 3H, H-4); $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 132.0 (CH, C-Ar), 128.7 (CH, C-Ar), 128.4 (CH, C-Ar), 122.5 (C, C-Ar), 87.0 (C, C-6), 85.1 (C, C-5), 75.1 (CH, C-3), 71.3 (CH$_2$, C-2), 59.5 (CH$_3$, C-1), 57.0 (CH$_3$, C-4); IR (thin film): 2920, 2903, 2197, 1548, 1521 cm$^{-1}$. Known compound.$^{13}$
Following application of method A, purification by column chromatography (0-15% EtOAc/cyclohexane) afforded (cyclopent-1-en-1-ylethynyl)benzene 194 as a clear oil (37 mg, 0.22 mmol, 89%). $^1$H NMR (500 MHz, MeOD) $\delta$ 7.43–7.36 (m, 2H, H-Ar), 7.35–7.27 (m, 3H, H-Ar), 6.09 (ddd, $J = 4.6, 2.6, 2.1$ Hz, 1H, H-4), 2.50 (m, 4H, H-1/3), 1.96 (m, 2H, H-2). $^{13}$C NMR (126 MHz, MeOD) $\delta$ 138.6 (CH, C-4), 132.3 (CH, C-Ar), 129.4 (CH, C-Ar), 129.0 (CH, C-5), 126.0 (CH, C-Ar), 125.0 (C, C-Ar), 91.3 (C, C-7), 87.4 (C, C-6), 37.3 (CH$_2$, C-1/3), 34.1 (CH$_2$, C-1/3), 24.3 (CH$_2$ C-2). IR (thin film): 2944, 2204, 1651, 1550, 1527, 1496 cm$^{-1}$. Known compound.$^{136}$
General Procedure for aerobic C-H functionalisation of THF – Method B (Alkynylation)

To a solution of THF (1.25 mmol, 5.0 eq.) in HFIP (0.40 mmol) was added the respective acetylenic triflone 176 (60 mg, 0.25 mmol, 1.0 eq). The reaction mixture was stirred at 80 °C for 16 h and then poured over sat. aq. NaHCO₃ (5 mL). The organics were extracted with EtOAc (3 × 10 mL), dried over MgSO₄, filtered and the solvent removed under reduced pressure. The resultant crude residue was purified as described below.
Following application of method B, purification by column chromatography (0-15% EtOAc/cyclohexane) afforded 2-((4-methoxyphenyl)ethynyl)tetrahydrofuran 140 as a yellow oil (35 mg, 0.17 mmol, 69%). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.41–7.32 (m, 2H, H-8), 6.86–6.77 (m, 2H, H-9), 4.79 (dd, $J = 7.1, 5.2$ Hz, 1H, H-4), 4.06–3.96 (m, 1H, H-1), 3.85 (td, $J = 8.0, 5.5$ Hz, 1H, H-1), 3.80 (s, 3H, H-11), 2.36–2.17 (m, 1H, H-3), 2.14–2.00 (m, 2H, H-2/3), 1.99–1.85 (m, 1H, H-2); $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 159.7 (C, C-10), 133.3 (CH, C-8), 115.1 (C, C-7), 114.0 (CH, C-10), 87.8 (C, C-6), 84.5 (C, C-5), 68.8 (CH$_2$, C-1), 68.0 (CH, C-4), 55.4 (CH$_3$, C-11), 33.6 (CH$_2$, C-3), 25.6 (CH$_2$, C-2); IR (thin film): 2930, 2903, 2234, 1568, 1501 cm$^{-1}$. Known compound.$^{133}$
2-((4-Ethylphenyl)ethynyl)tetrahydrofuran – 223

Following application of method B, purification by column chromatography (0-15% EtOAc/cyclohexane) afforded 2-((4-ethylphenyl)ethynyl)tetrahydrofuran 223 as a yellow oil (39 mg, 0.23 mmol, 90%). $^1$H NMR (400 MHz, CDCl$_3$) δ 7.41–7.31 (m, 2H, H-8), 7.12 (d, $J$ = 8.4 Hz, 2H, H-9), 4.81 (dd, $J$ = 7.1, 5.0 Hz, 1H, H-4), 4.06–3.96 (m, 1H, H-1), 3.90–3.80 (m, 1H, H-1), 2.63 (q, $J$ = 7.6 Hz, 2H, H-11), 2.27–2.17 (m, 1H, H-3), 2.14–2.01 (m, 2H, H-2/3), 1.99–1.89 (m, 1H, H-2), 1.22 (t, $J$ = 7.6 Hz, 3H, H-12); $^{13}$C NMR (126 MHz, CDCl$_3$) δ 144.8 (C, C-10), 131.8 (CH, C-8), 127.9 (CH, C-9), 120.1 (C, C-7), 88.4 (C, C-6), 84.8 (C, C-5), 68.8 (CH, C-4), 68.0 (CH$_2$, C-1), 33.6 (CH$_2$, C-3), 28.9 (CH$_2$, C-11), 25.6 (CH$_2$, C-2), 15.5 (CH$_3$, C-12); IR (thin film): 2942, 2913, 2217, 1558, 1511 cm$^{-1}$. Known compound.$^{137}$
2-((4-Pentylphenyl)ethynyl)tetrahydrofuran – 224

Following application of method B, purification by column chromatography (0-15% EtOAc/cyclohexane) afforded 2-((4-pentylphenyl)ethynyl)tetrahydrofuran 224 as a clear oil (51 mg, 0.21 mmol, 84%). $^1$H NMR (600 MHz, CDCl$_3$) $\delta$ 7.34 (d, $J = 8.2$ Hz, 2H, H-8), 7.10 (d, $J = 8.3$ Hz, 2H, H-9), 4.80 (dd, $J = 7.2$, 5.1 Hz, 1H, H-4), 4.08–3.96 (m, 1H, H-1), 3.85 (td, $J = 8.0$, 5.5 Hz, 1H, H-1), 2.60–2.54 (m, 2H, H-11), 2.28–2.17 (m, 1H, H-3), 2.13–2.03 (m, 2H, H-2/3), 1.98–1.87 (m, 1H, H-2), 1.58 (tt, $J = 15.0$, 7.4 Hz, 3H, H-15), 1.30 (tt, $J = 15.4$, 8.2, 2.3 Hz, 5H, H-13/14), 0.88 (t, $J = 7.1$ Hz, 3H, H-15). $^{13}$C NMR (151 MHz, CDCl$_3$) $\delta$ 143.5 (C, C-10), 131.7 (CH, C-8), 128.5 (CH, C-9), 120.0 (C, C-7), 88.4 (C, C-6), 84.8 (C, C-5), 68.8 (CH, C-4), 68.0 (CH$_2$, C-1), 35.9 (CH$_2$, C-11), 33.6 (CH$_2$, C-3), 31.6 (CH$_2$, C-12), 31.1 (CH$_2$, C-13), 25.6 (CH$_2$, C-2), 22.7 (CH$_2$, C-14), 14.2 (CH$_3$, C-15); IR (thin film): 2934, 2911, 2902, 2205, 1560, 1512 cm$^{-1}$. Known compound.$^{138}$
2-(M-tolylethynyl)tetrahydrofuran – 225

Following application of method B, purification by column chromatography (0-15% EtOAc/cyclohexane) afforded 2-(m-tolylethynyl)tetrahydrofuran 225 as a yellow oil (38 mg, 0.20 mmol, 80%). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.28–7.22 (m, 2H, H-Ar), 7.18 (t, $J = 7.5$ Hz, 1H, H-Ar), 7.11 (d, $J = 7.7$ Hz, 1H, H-Ar), 4.81 (dd, $J = 7.2$, 5.0 Hz, 1H, H-4), 4.07–3.94 (m, 1H, H-1), 3.92–3.79 (m, 1H, H-1), 2.31 (s, 3H, H-13), 2.27–2.18 (m, 1H, H-3), 2.09–2.02 (m, 2H, H-2/3), 2.00–1.90 (m, 1H, H-2). $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 138.0 (C, C-Ar), 132.5 (CH, C-Ar), 129.3 (CH, C-Ar), 128.9 (CH, C-Ar), 128.2 (CH, C-Ar), 122.8 (C, C-Ar), 88.8 (C, C-6), 84.8 (C, C-5), 68.8 (CH, C-4), 68.1 (CH$_2$, C-1), 33.6 (CH$_2$, C-3), 25.6 (CH$_2$, C-2), 21.3 (CH$_3$, C-13). IR (thin film): 2911, 2902, 2213, 1559, 1512 cm$^{-1}$. Known compound.$^{133}$
2-((4-Bromophenyl)ethynyl)tetrahydrofuran – 226

Following application of method B, purification by column chromatography (0-15% EtOAc/cyclohexane) afforded 2-((4-bromophenyl)ethynyl)tetrahydrofuran 226 as a yellow oil (60 mg, 0.24 mmol, 96%). $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.45–7.38 (m, 2H, H-9), 7.33–7.26 (m, 2H, H-8), 4.78 (dd, $J$ = 7.2, 5.1 Hz, 1H, H-4), 4.05–3.94 (m, 1H, H-1), 3.85 (ddd, $J_1$ = 8.3, 7.7, 5.5 Hz, 1H, H-1), 2.27–2.18 (m, 1H, H-3), 2.14–2.01 (m, 2H, H-2/3), 2.00–1.89 (m, 1H, H-1); $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 133.3 (CH, C-8), 131.6 (CH, C-9), 122.7 (C, C-10), 121.9 (C, C-7), 90.4 (C, C-6), 83.6 (C, C-5), 68.7 (CH$_2$, C-1), 68.2 (CH, C-4), 33.5 (CH$_2$, C-3), 25.7 (CH$_2$, C-2); IR (thin film): 2929, 2909, 2215, 1540, 1522 cm$^{-1}$. Known compound.$^{138}$
2-((3-Fluorophenyl)ethynyl)tetrahydrofuran – 227

Following application of method B, purification by column chromatography (0-15% EtOAc/cyclohexane) afforded 2-((3-fluorophenyl)ethynyl)tetrahydrofuran 227 as a yellow oil (36 mg, 0.19 mmol, 76%). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.29–7.18 (m, 2H, H-11/12), 7.12 (ddd, $J = 9.5$, 2.5, 1.4 Hz, 1H, H-8), 7.05–6.96 (m, 1H, H-10), 4.80 (dd, $J = 7.2$, 5.0 Hz, 1H, H-4), 4.06–3.94 (m, 1H, H-1), 3.92–3.81 (m, 1H, H-1), 2.31–2.17 (m, 1H, H-3), 2.14–2.03 (m, 2H, H-2), 2.01–1.89 (m, 1H, H-1); $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 162.4 (d, $J = 246.4$ Hz, C-9), 129.9 (d, $J = 8.6$ Hz, C-11), 127.7 (d, $J = 3.0$ Hz, C-12), 124.8 (d, $J = 9.4$ Hz, C-7), 118.6 (d, $J = 22.8$ Hz, C-8), 115.7 (d, $J = 21.2$ Hz, C-10), 90.3 (C, C-6), 83.4 (C, C-5), 68.6 (CH$_2$, C-1), 68.1 (CH, C-4), 33.5 (CH$_2$, C-3), 25.6 (CH$_2$, C-2). IR (thin film): 2930, 2230, 1555, 1512 cm$^{-1}$. Known compound.
Following application of method B, purification by column chromatography (0-15% EtOAc/cyclohexane) afforded 2-((2-chlorophenyl)ethynyl)tetrahydrofuran 15a as a yellow oil (37 mg, 0.18 mmol, 73%). \(^1\)H NMR (600 MHz, CDCl\(_3\)) \(\delta\) 7.45 (dd, \(J = 7.6, 1.8\) Hz, 1H, H-12), 7.37 (dd, \(J = 8.0, 1.2\) Hz, 1H, H-9), 7.22 (td, \(J = 7.7, 1.8\) Hz, 1H, H-11), 7.18 (td, \(J = 7.5, 1.3\) Hz, 1H, H-10), 4.87 (dd, \(J = 7.4, 4.5\) Hz, 1H, H-4), 4.08–3.97 (m, 1H, H-1), 3.88 (td, \(J = 8.2, 5.6\) Hz, 1H, H-1), 2.28–2.19 (m, 1H, H-3), 2.17–2.08 (m, 2H, H-2/3), 1.99–1.90 (m, 1H, H-2). \(^13\)C NMR (151 MHz, CDCl\(_3\)) \(\delta\) 136.1 (C, C-Ar), 133.5 (CH, C-Ar), 129.5 (CH, C-Ar), 129.3 (CH, C-Ar), 126.5 (CH, C-Ar), 122.8 (C, C-Ar), 94.7 (C, C-6), 81.4 (C, C-5), 68.7 (CH\(_2\), C-1), 68.1 (CH, C-4), 33.5 (CH\(_2\), C-3), 25.5 (CH\(_2\), C-2); IR (thin film): 2929, 2910, 2214, 1543, 1502 cm\(^{-1}\). Known compound.\(^{137}\)
2-((4-(Trifluoromethyl)phenyl)ethynyl)tetrahydrofuran – 229

Following application of method B, purification by column chromatography (0-15% EtOAc/cyclohexane) afforded 2-((4-(trifluoromethyl)phenyl)ethynyl)tetrahydrofuran 229 as a yellow oil (52 mg, 0.22 mmol, 88%). $^1$H NMR (600 MHz, CDCl$_3$) $\delta$ 7.56–7.54 (m, 2H, H-9), 7.53–7.51 (m, 2H, H-8), 4.81 (dd, $J$ = 7.3, 5.0 Hz, 1H, H-4), 4.05–3.94 (m, 1H, H-1), 3.87 (td, $J$ = 7.8, 5.5 Hz, 1H, H-1), 2.31–2.17 (m, 1H, H-3), 2.15–2.02 (m, 2H, H-2/3), 1.99–1.88 (m, 1H, H-2). $^{13}$C NMR (151 MHz, CDCl$_3$) $\delta$ 132.1 (CH, C-8), 130.0 (q, C, $J_{F,C}$ = 32.7 Hz, C-10), 126.8 (CH C-7), 125.3 (q, CH, $J_{F,C}$ = 3.7 Hz, C-9), 124.0 (d, CH, $J_{F,C}$ = 272.2 Hz, C-11), 91.8 (C, C-6), 83.3 (C, C-5), 68.6 (CH$_2$, C-1), 68.3 (CH, C-4), 33.4 (CH$_2$, C-3), 25.7 (CH$_2$, C-2); IR (thin film): 2949, 2907, 2222, 1543, 1502 cm$^{-1}$. Known compound.$^{133}$

![NMR spectrum](image-url)
2-(Thiophen-2-ylethynyl)tetrahydrofuran – 230

Following application of method B, purification by column chromatography (0-15% EtOAc/cyclohexane) afforded 2-(thiophen-2-ylethynyl)tetrahydrofuran 230 as a brown oil (32 mg, 0.18 mmol, 72%). $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.29–7.13 (m, 2H, H-8/10), 6.94 (dd, $J$ = 5.1, 3.6 Hz, 1H, H-9), 4.82 (dd, $J$ = 7.3, 4.9 Hz, 1H, H-4), 4.07–3.94 (m, 1H, H-1), 3.85 (td, $J$ = 7.9, 5.5 Hz, 1H, H-2), 2.28–2.16 (m, 1H, H-3), 2.14–2.04 (m, 2H, H-2/3), 1.99–1.89 (m, 1H, H-2). $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 132.3 (CH, C-8), 127.2 (CH, C-9), 127.0 (CH, C-10), 122.9 (C, C-7), 93.1 (C, C-5), 77.9 (C, C-6), 68.8 (CH$_2$, C-1), 68.2 (CH, C-4), 33.4 (CH$_2$, C-3), 25.7 (CH$_2$, C-2); IR (thin film): 3067, 2926, 2209, 1518, 1463 cm$^{-1}$. Known compound.$^{138}$
Following application of method B, purification by column chromatography (0-15% EtOAc/cyclohexane) afforded 2-((6-methoxynaphthalen-2-yl)ethynyl)tetrahydrofuran 231 as a yellow oil (41 mg, 0.16 mmol, 65%). $^1$H NMR (500 MHz, CDCl₃) δ 7.88 (s, 1H, H-Ar), 7.67 (d, J = 9.0 Hz, 1H, H-Ar), 7.64 (d, J = 8.7 Hz, 1H, H-Ar), 7.44 (dd, J = 8.5, 1.6 Hz, 1H, H-Ar), 7.14 (dd, J = 8.9, 2.5 Hz, 1H, H-Ar), 7.09 (d, J = 2.5 Hz, 1H, H-Ar), 4.85 (dd, J = 7.2, 5.1 Hz, 1H, H-4), 4.08–4.00 (m, 1H, H-1), 3.91 (s, 3H, H-3), 3.96–3.84 (m, 1H, H-1), 2.33–2.20 (m, 1H, H-3), 2.17–2.07 (m, 2H, H-2/3), 2.01–1.91 (m, 1H, H-2). $^{13}$C NMR (126 MHz, CDCl₃) δ $^{13}$C NMR (126 MHz, CDCl₃) δ 134.9 (C, C-Ar), 134.3 (C, C-Ar), 131.6 (CH, C-Ar), 129.4 (CH, C-Ar), 129.3 (CH, C-Ar), 128.5 (CH, C-Ar), 126.8 (CH, C-Ar), 119.5 (C, C-Ar), 105.9 (C, C-6), 88.8 (C, C-5), 68.9 (CH₂, C-1), 68.1 (CH, C-4), 55.5 (CH₃, C-7), 33.6 (CH₂, C-3), 25.7 (CH, C-2); IR (thin film): 3012, 2930, 2199, 1555, 1503 cm⁻¹. HRMS (ESI) calcd for C₁₇H₁₆O₂ [M+H]+ 253.1223; observed 253.1199.
2-(oct-1-yn-1-yl)tetrahydrofuran – 232

Following application of method B, purification by column chromatography (0-15% EtOAc/cyclohexane) afforded 2-(oct-1-yn-1-yl)tetrahydrofuran 232 as a yellow oil (31 mg, 0.16 mmol, 63%). $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 4.60-4.53 (m, 1H, H-4), 3.98–3.89 (m, 1H, H-1), 3.78 (td, $J = 7.8, 6.1$ Hz, 1H, H-1), 2.19 (td, $J = 7.1, 1.8$ Hz, 2H, H-2/3), 2.16–2.08 (m, 1H, H-3), 2.05–1.97 (m, 1H, H-2), 1.96–1.80 (m, 2H, H-7), 1.54–1.44 (m, 2H, H-8), 1.36-1.25 (m, 6H, H-9/10/11), 0.88 (t, $J = 7.0$ Hz, 3H, H-12). $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 85.4 (C, C-5), 80.1 (C, C-6), 68.6 (CH$_2$, C-1), 67.7 (CH, C-4), 33.7 (CH$_2$, C-3), 31.4 (CH$_2$, C-7), 28.7 (CH$_2$ C-8), 28.6 (CH, C-9), 25.5 (CH$_2$, C-2), 22.6 (CH$_2$, C-10), 18.9 (CH$_2$, C-11), 14.1 (CH$_3$, C-12); IR (thin film): 3022, 2991, 2204. Known compound.$^{134}$
Following application of method B, purification by column chromatography (0-15% EtOAc/cyclohexane) afforded 2-(3,3-dimethylbut-1-yn-1-yl)tetrahydrofuran 233 as a clear oil (27 mg, 0.18 mmol, 72%). 1H NMR (500 MHz, CDCl3) δ 4.52 (dd, J = 7.0, 5.8 Hz, 1H, H-4), 3.98–3.89 (m, 1H, H-1), 3.81–3.71 (m, 1H, H-1), 2.21–2.04 (m, 1H, H-3), 2.05–1.92 (m, 2H, H-2/3), 1.93–1.78 (m, 1H, H-2), 1.20 (s, 9H, H-8). 13C NMR (126 MHz, CDCl3) δ 93.5 (C, C-6), 78.3 (C, C-5), 68.6 (CH, C-4), 67.7 (CH2, C-1), 33.8 (C, C-3), 31.1 (CH3, C-8), 27.0 (C, C-7), 25.4 (CH2, C-2); IR (thin film): 3002, 2920, 2221 cm⁻¹. Known compound.
General Procedure for aerobic C-H functionalisation of heterocycles – Method C (vinyl triflone)

To a solution of heterocycle (1.25 mmol, 5.0 eq.) in HFIP (0.40 mmol) and glacial acetic acid (0.40 mmol) was added vinyl triflone (0.25 mmol, 1.0 eq.). The reaction mixture was stirred at 80 °C for 16 h and then poured over sat. aq. NaHCO₃ (5 mL). The organics were extracted with EtOAc (3 × 10 mL), dried over MgSO₄, filtered and the solvent removed under reduced pressure. The resultant crude residue was purified as described below. Note: the alkenyl triflones were made in accordance with literature procedures. ¹⁴₀
(Z)-2-(2-Bromo-2-phenylvinyl)tetrahydrofuran – 237

Following application of method B, purification by column chromatography (0-15% EtOAc/cyclohexane) gave (Z)-2-(2-bromo-2-phenylvinyl)tetrahydrofuran 237 as a yellow oil (49 mg, 0.20 mmol, 78%). $^1$H NMR (CDCl$_3$, 700 MHz): δ 7.54–7.50 (m, 2H, H-Ar), 7.37–7.31 (m, 3H, H-Ar), 6.35 (d, $J = 7.0$ Hz, 1H, H-5), 4.81 (q, $J = 7.0$ Hz, 1H, H-4), 3.96 (dt, $J = 8.2$, 6.9 Hz, 1H, H-1), 3.85 (td, $J = 7.9$, 6.2 Hz, 1H, H-1), 2.32 (ddt, $J = 12.5$, 7.2, 5.4 Hz, 1H, H-3), 2.03–1.93 (m, 2H, H-2/3), 1.70 (dq, $J = 12.4$, 7.9 Hz, 1H, H-2); $^{13}$C NMR (176 MHz, CDCl$_3$) δ 139.4 (C, C-Ar), 133.0 (CH, C-5), 128.9 (CH, C-Ar), 128.4 (CH, C-Ar), 127.7 (C, C-6), 125.6 (CH, C-Ar), 79.6 (CH, C-4), 68.5 (CH$_2$, C-1), 31.9 (CH$_2$, C-3), 26.2 (CH$_2$, C-2); IR (thin film): 2932, 2902, 1623, 1555, 1532 cm$^{-1}$. Known compound.\(^{139}\)
(Z)-2-(2-Fluoro-2-phenylvinyl)tetrahydrofuran – 238

Following application of method B, purification by column chromatography (0-15% EtOAc/cyclohexane) gave (Z)-2-(2-fluoro-2-phenylvinyl)tetrahydrofuran 238 as a colourless oil (31 mg, 0.16 mmol, 67%). $^1$H NMR (CDCl$_3$, 700 MHz): $\delta$ 7.52 (dd, $J = 8.4, 1.5$ Hz, 2H, H-8), 7.39–7.30 (m, 3H, H-9/10), 5.50 (dd, $J = 36.9, 8.2$ Hz, 1H, H-5), 4.94–4.88 (m, 1H, H-4), 3.98–3.92 (m, 1H, H-1), 3.82 (td, $J = 8.1, 6.0$ Hz, 1H, H-1), 2.24–2.19 (m, 1H, H-3), 2.05–1.92 (m, 2H, H-2/3), 1.72–1.64 (m, 1H, H-2); $^{13}$C NMR (176 MHz, CDCl$_3$) $\delta$ 157.7 (CF, d, $J_{F,C} = 250.7$ Hz, C-6), 132.1 (C, d, $J_{F,C} = 28.2$ Hz, C-7), 129.2 (CH, C-10), 128.6 (CH, d, $J_{F,C} = 1.9$Hz, C-9), 124.5 (CH, d, $J_{F,C} = 7.2$ Hz, C-8), 107.6 (C, d, $J_{F,C} = 11.7$ Hz, C-5), 73.0 (CH, C-4), 68.1 (CH$_2$, C-1), 32.8 (CH$_2$, C-3), 26.2 (CH$_2$, C-2); IR (thin film): 3011, 2983, 1625, 1575, 1532 cm$^{-1}$. Known compound.$^{139}$
(Z)-2-(2-iodo-2-phenylvinyl)tetrahydrofuran – 239

Following application of method B, purification by column chromatography (0-15% EtOAc/cyclohexane) gave (Z)-2-(2-iodo-2-phenylvinyl)tetrahydrofuran 239 as a yellow oil (54 mg, 0.18 mmol, 72%). $^1$H NMR (CDCl$_3$, 500 MHz): $\delta$ $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.73–7.48 (m, 2H, H-Ar), 7.45–7.19 (m, 3H, H-Ar), 6.35 (d, $J$ = 7.0 Hz, 1H, H-5), 4.81 (m, 1H, H-Ar4), 3.96 (m, 1H, H-1), 3.85 (m, 1H, H-1), 2.38–2.18 (m, 1H, H-3), 2.07–1.84 (m, 2H, H-2/3), 1.83–1.53 (m, 1H, H-2). $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 139.4 (CH, C-5), 133.0 (C, C-6), 128.9 (C, C-Ar), 128.3 (CH, C-Ar), 127.7 (CH, C-Ar), 125.5 (CH, C-Ar), 79.6 (C, C-4), 68.5 (CH$_2$, C-1), 31.9 (CH$_2$, C-3), 26.2 (CH, C-2). 3023, 2981, 2904, 1635, 1550, 1532 cm$^{-1}$. Known compound.$^{139}$
Following application of method B, purification by column chromatography (0-15% EtOAc/cyclohexane) gave \((E)-2\text{-styryltetrahydrofuran} 240\) as a yellow oil (31 mg, 0.18 mmol, 71%). \(^1\)H NMR (600 MHz, CDCl\(_3\)) \(\delta 7.38\) (d, \(J = 7.6\) Hz, 2H, H-Ar), 7.30 (t, \(J = 7.6\) Hz, 2H, H-Ar), 7.22 (t, \(J = 7.2\) Hz, 1H, H-Ar), 6.58 (d, \(J = 15.8\) Hz, 1H, H-6), 6.20 (dd, \(J = 15.8, 6.6\) Hz, 1H, H-5), 4.47 (q, \(J = 6.9\) Hz, 1H, H-4), 3.99–3.93 (m, 1H, H-1), 3.88–3.78 (m, 1H, H-1), 2.13 (td, \(J = 12.4, 7.2\) Hz, 1H, H-3), 2.01–1.92 (m, 2H, H-2/3), 1.71 (dq, \(J = 12.4, 7.7\) Hz, 1H, H-2). \(^1^3\)C NMR (151 MHz, CDCl\(_3\)) \(\delta 137.0\) (C, C-Ar), 130.7 (CH, C-5/6), 130.6 (CH, C-5/6), 128.7 (CH, C-Ar), 127.6 (CH, C-Ar), 126.6 (CH, C-Ar), 79.8 (CH, C-4), 68.3 (CH\(_2\), C-1), 32.5 (CH\(_2\), C-3), 26.1 (CH\(_2\), C-2). IR (thin film): 2926, 2900, 1629, 1554, 1515 cm\(^{-1}\). Known compound.\(^{140}\)
(E)-2-(4-pentylstyryl)tetrahydrofuran—241

Following application of method B, purification by column chromatography (0-15% EtOAc/cyclohexane) gave (E)-2-(4-pentylstyryl)tetrahydrofuran 241 as a yellow oil (35 mg, 0.15 mmol, 58%). δ¹H NMR (500 MHz, CDCl₃): δ 7.29 (d, J = 8.1 Hz, 2H, H-8), 7.11 (d, J = 8.0 Hz, 2H, H-9), 6.55 (d, J = 15.8 Hz, 1H, H-6), 6.15 (dd, J = 15.8, 6.7 Hz, 1H, H-5), 4.46 (q, J = 6.9 Hz, 1H, H-4), 4.00–3.92 (m, 1H, H-1), 3.90–3.79 (m, 1H, H-1), 2.61–2.52 (m, 2H, H-11), 2.11 (dt, J = 12.0, 5.6 Hz, 1H, H-3), 1.99–1.87 (m, 2H, H-2/3), 1.70 (dq, J = 12.0, 7.6 Hz, 1H, H-2), 1.66–1.55 (m, 3H, H-Pen), 1.34–1.30 (m, 5H, H-Pen), 0.95–0.83 (m, 3H, H-Pen). ¹³C NMR (126 MHz, CDCl₃) δ 142.6 (C, C-10), 134.4 (CH, C-6), 130.6 (CH, C-5), 129.7 (CH, C-Ar), 128.7 (CH, C-Ar), 126.5 (CH, C-Ar), 79.9 (CH, C-4), 68.3 (CH₂, C-1), 35.8 (CH₂, C-11), 32.6 (CH₂, C-3), 31.6 (CH₂, C-12), 31.2 (CH₂, C-13), 26.1 (CH₂, C-2), 22.7 (CH₂, C-14), 14.2 (CH₃, C-15). IR (thin film): 2926, 2900, 1629, 1554, 1515 cm⁻¹. HRMS (ESI) calcd for C₁₇H₂₄O [M+H]+ 245.1822; observed 245.1813.
2-phenethyltetrahydrofuran – 242

2-(phenylethynyl)tetrahydrofuran 140 (0.50 mmol, 121mg) in THF (5 mL) was added to a flask containing 10% Pd on C (20 mg) under a N₂ atmosphere. The N₂ was evacuated and H₂ was purged through the flask and bubbled through the solution. The resultant solution was stirred for 16 h under a H₂ atmosphere at room temperature. The resultant solution was filtered through celite and the filter cake was washed with ethyl acetate. The resulting solution was concentrated and gave 2-phenethyltetrahydrofuran 242 as a yellow liquid (43 mg, 0.49 mmol, 97%). ¹H NMR (500 MHz, CDCl₃) δ 7.32–7.25 (m, 2H), 7.24–7.15 (m, 3H), 3.94–3.86 (m, 1H), 3.82 (qn, J = 7.4 Hz, 1H), 3.73 (td, J = 7.9, 6.4 Hz, 1H), 2.81–2.73 (m, 1H), 2.66 (ddd, J = 13.8, 10.0, 6.3 Hz, 1H), 2.02-1.95 (m, 1H), 1.93–1.83 (m, 3H), 1.82-1.73 (m, 1H), 1.48 (dq, J = 11.8, 7.7 Hz, 1H). ¹³C NMR (126 MHz, CDCl₃) δ 142.4 (C), 128.5 (CH), 128.4 (CH), 125.8 (CH), 78.8 (CH), 67.8 (CH₂), 37.6 (CH₂), 32.8 (CH₂), 31.5 (CH₂), 25.9 (CH₂). Known compound.¹⁴¹
2,2-dichloro-1-phenyl-2-(tetrahydrofuran-2-yl)ethan-1-one – 243

Trichloroisocyanuric acid (116 mg, 0.5 mmol) was added to a stirring solution of 2-(phenylethynyl)tetrahydrofuran 140 (0.5 mmol) in MeCN/H$_2$O (2 mL, 10:1). Once the reaction was complete (TLC), the solvent was removed under reduced pressure before the residue was purified by column chromatography (0-10% EtOAc/cyclohexane) to give the dihalohydroxyketone 243 as a clear liquid (116 mg, 92%). $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 8.26 – 8.20 (m, 2H, H-Ar), 7.58 (t, $J = 7.4$ Hz, 1H, H-Ar), 7.46 (t, $J = 7.8$ Hz, 2H, H-Ar), 4.88 (t, $J = 7.2$ Hz, 1H, H-4), 4.06 – 3.93 (m, 2H, H-1), 2.33 (dtd, $J = 12.1$, 7.9, 4.3 Hz, 1H, H-3), 2.19 (dq, $J = 13.0$, 8.3 Hz, 1H, H3), 2.13 – 2.03 (m, 1H, H-2), 1.97 (dqn, $J = 12.1$, 8.3 Hz, 1H, H-2). $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 188.6 (C=O, C-6), 133.4 (C, C-Ar), 132.8 (CH, C-Ar), 130.8 (CH, C-Ar), 128.2 (CH, C-Ar), 89.0 (C, C-5), 83.4 (CH, C-4), 70.6 (CH$_2$, C-1), 28.9 (CH$_2$, C-3), 26.3 (CH$_2$, C-2); IR (thin film): 2965, 1677, 1600, 1250, 1199 cm$^{-1}$; HRMS (ESI) calcd for C$_{12}$H$_7$Cl$_2$O$_2$ [M$^{35}$Cl+H]$^+$ 259.0287; observed 259.0282.
(Z)-2-(2-(3,5-bis(trifluoromethyl)phenyl)-2-phenylvinyl)tetrahydrofuran – 244

![](image)

In a sealed tube, (Z)-2-(2-iodo-2-phenylvinyl)tetrahydrofuran 239 (75 mg, 0.25 mmol), Pd(PPh₃)₄ (10 mg), K₂CO₃ (100 mg, 0.75 mmol), 3,5-bis(trifluoromethyl)phenylboronic acid (71 mg, 0.275 mmol) were mixed together in dioxane:water (10:1, 1.5 mL) and heated at 70 °C for 16 h under an argon atmosphere. The resultant mixture was cooled to rt and water (10 mL) was added, the resulting mixture was extracted with diethyl ether (3 x 30 mL). The combined organics were dried over MgSO₄, filtered and the solvent removed under reduced pressure. The resultant crude residue was purified by column chromatography (0-10% EtOAc/cyclohexane) to afford (Z)-2-(2-(3,5-bis(trifluoromethyl)phenyl)-2-phenylvinyl)tetrahydrofuran 244 as a clear oil (89 mg, 0.23 mmol). ¹H NMR (500 MHz, CDCl₃) δ 7.86 (s, 1H, H-10), 7.69 (s, 2H, H-8), 7.31 (m, 3H, H-Ph), 7.22–7.15 (m, 2H, H-Ph), 6.19 (d, J = 9.0 Hz, 1H, H-5), 4.15–4.07 (m, 1H, H-4), 4.01–3.91 (m, 1H, H-1), 3.75 (td, J = 8.0, 5.9 Hz, 1H, H-1), 2.09-1.99 (m, 2H, H-3), 1.94-1.85 (m, 1H, H-2), 1.80-1.71 (m, 1H, H-2). ¹³C NMR (151 MHz, CDCl₃) δ 141.7 (C), 141.3 (C), 140.6 (C), 132.4 (CH), 131.6 (C, q, J₁,F₂ = 33.3 Hz, C-8), 130.2 (br s, CH, C-10), 128.7 (CH, C-Ph), 128.4 (C), 127.7 (C), 123.5 (CF₃, q, J₁,F₂ = 272.7 Hz, C-9), 121.7–121.5 (m, CH), 76.3 (CH, C-4), 68.4 (CH₂, C-1), 33.2 (CH₂, C-3), 26.5 (CH₂, C-2); HRMS (ESI) calcd for C₂₀H₁₆F₆O [M+H]⁺ 387.1178; observed 387.117.
Mechanistic studies

$^{13}$C Labelled (((trifluoromethyl)sulfonyl)ethynyl)benzene – $^{13}$C-249

$^1$H NMR 700 MHz, CDCl$_3$ δ 7.71–7.68 (m, 2 H), 7.64–7.61 (m, 1 H), 7.50–7.47 (m, 2 H); $^{13}$C NMR (126 MHz, CDCl$_3$) δ 133.9 (CH, d, $J = 2.9$ Hz), 133.5 (br s, CH), 129.2 (CH), 119.2 (C, qd, $J = 323.1, 25.0$ Hz), 115.92 (C, d, $J = 10.6$ Hz), 100.9 (m, C), 77.4 ($^{13}$C).

Synthesis as described above (Page 5)
$^{13}$C Labelled 2-(phenylethynyl)tetrahydrofuran – $^{13}$C-250

$^{1}$H NMR (CDCl$_3$, 700 MHz): $\delta$ 7.45–7.41 (m, 2H), 7.34–7.29 (m, 3H), 4.81 (dt, $J = 7.1$, 4.9 Hz, 1H), 4.09–3.96 (m, 1H), 3.89–3.84 (m, 1H), 2.29–2.20 (m, 1H), 2.17–2.07 (m, 2H), 2.00–1.91 (m, 1H); $^{13}$C NMR (176 MHz, CDCl$_3$) $\delta$ 131.9 (CH, d, $J = 2.6$ Hz), 128.4 (CH, br s), 128.3 (CH), 122.9 (C, $J = 12.5$ Hz), 89.2 ($^{13}$C), 86.02 (C, d, $J = 355.7$ Hz), 68.7 (CH, d, $J = 77.5$ Hz), 68.1 (CH$_2$, d, $J = 2.1$ Hz), 33.6 (CH$_2$), 25.6 (CH$_2$).
Kinetic Isotope Experiments

MS data for 2-(Phenylethynyl)tetrahydrofuran, non-deuterated

MS data for 2-(Phenylethynyl)tetrahydrofuran, deuterated

In a seal tubed containing (0.625 mmol) THF and (0.625 mmol) THF-d8 was added HFIP (0.4 mmol) and (((trifluoromethyl)sulfonyl)ethynyl)benzene (60 mg, 0.25 mmol, 1.0 eq). The reaction was heated at 80 °C for 16 h. After this time, the product ratio was determined via LCMS analysis by integrating the peak areas of the extracted ion chromatograms (EICs) for the non-deuterated and deuterated species in a similar manner as described previously.\textsuperscript{83}
LCMS Total Ion Count

EIC at 173.23 Da (THF, non-deuterated H⁺ adduct)

Height = 63715984
Area = 6036667.0

EIC at 180.27 Da (THF-d7 deuterated H⁺ adduct)

Height = 19001804
Area = 1705952.125

Adduct with H⁺: d0/d7 = 6036667/1705952 = 3.53 = Kinetic Isotope effect
Tempo Radical Trapping experiment:

To a solution of THF (0.1 mL, 1.25 mmol, 5.0 eq.) in HFIP (0.4 mmol) was added (trifluoromethyl)sulfonyl)ethynyl)benzene 6a (60 mg, 0.25 mmol, 1.0 eq.) and TEMPO (0.25 mmol, 1.0 eq.). The reaction mixture was stirred at 80 °C for 16 h and then analysed via LCMS.

LCMS Total ion count

EIC at 228.0 Da

MS trace at 0.53-0.68


