N → *S* Acyl Transfer in Peptides and Regioselective Dihalohydration Reactions of Propargylic Alcohols

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in partial fulfilment of the requirements for the degree of

DOCTOR OF PHILOSOPHY

Declaration

I, Samantha Mary Gibson 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.

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Abstract

This thesis describes results obtained during the investigation of peptide thioester formation and regioselective dihalohydration reactions of propargylic alcohols.

Chapter 1 explores the formation of peptide thioesters via *N* → *S* acyl transfer. Firstly, native chemical ligation (NCL) will be introduced as a powerful tool to join a peptide thioester and a peptide fragment containing an *N* terminal cysteine. The challenges of making a peptide thioester will be discussed. Following this, the synthesis of model peptides will be reported, including the first synthesis of boronocysteine. The model peptides are then used to investigate the rate of peptide thioester formation. Alongside this, the effects of guanidine hydrochloride and the thiol additive will be explored.

Chapter 2 describes regioselective dihalohydration reactions of propargylic alcohols. Previous research in this area will be reviewed, including previous work within the Sheppard group involving dichloro- and diiodohydration reactions. Following this, the development of the dibromohydration reaction will be detailed which was used to synthesise a wide range of dibromoketoalcohols and dibromolactols. These products have been further manipulated to give a wide variety of products. The difluorohydration reactions of propargylic alcohols will be briefly explored.

Chapter 3 details the experimental procedures and compound characterisation for the results discussed in Chapters 1 and 2.

Publications

- Expanding the scope of N → S acyl transfer in native peptide sequences; Cowper, B., Shariff, L., Chen, W., Gibson, S. M., Di, W.-L., Macmillan, D.; *Org. Biomol. Chem.* **2015**, *13*, 7469

- Synthesis of Boronocysteine; Gibson, S. M., Macmillan, D., Sheppard T. D.; Manuscript accepted for publication in Synlett

- Dihalohydration of Alkynols as a Route to Diverse Halogenated Molecules; Gibson, S. M., D'Oyley, J. M., Sanders, K., Aliev, A. E., Sheppard, T. D.; Manuscript in preparation

Publications not covered in this thesis:

- A lactate-derived chiral aldehyde for determining the enantiopurity of enantioenriched primary amines; Gibson, S. M., Lanigan, R. M., Benhamou, L., Aliev, A. E., Sheppard, T. D.; *Org. Biomol. Chem.* **2015**, *13*, 9050

- Intercepting the Gold-Catalysed Meyer-Schuster Rearrangement by Controlled Protodemetallation: A Regioselective Hydration of Propargylic Alcohols; Pennell, M. N., Kyle, M. P., Gibson, S. M., Male, L., Turner, P. G., Grainger, R. S., Sheppard, T. D.; *Adv. Synth. Catal.* **2016**, *358*, 1519

Contents

Abbreviations

Ac	Acetyl
AcOH	Acetic acid
APCI	Atmospheric pressure chemical ionisation
B_2pin_2	Bis(pinacolato)diboron
Boc	*Tert*-butyloxycarbonyl
BINAP	2,2′-Bis(diphenylphosphino)-1,1′-binaphthalene
Bpin	Pinacolato boron
Bu	Butyl
BuOH	Butanol
C	Cysteine
Cbz	Carboxybenzyl
CI	Chemical ionisation
Cy	Cyclohexyl
Cys	Cysteine
Da	Dalton
DAST	Diethylaminosulfur trifluoride
DBA	Dibromoisocyanuric acid
DBU	1,8-Diazabicyclo(5.4.0)undec-7-ene
DIBAL-H	Diisobutylaluminium hydride
DIPEA	Diisopropylethylamine
DMAP	4-(Dimethylamino)pyridine
DMF	Dimethylformamide
DMN	1,5-Dimethoxynaphthalene
DMSO	Dimethylsulfoxide
dr	Diastereomeric ratio
DTT	Dithiothreitol
E	Glutamic acid
EDT	1,2-Ethanedithiol
ee	Enantiomeric excess
EI	Electron ionisation
Eq.	Equivalents
ESI	Electrospray ionisation
Et_3N	Triethylamine
EtOAc	Ethyl acetate

EtOH	Ethanol
Fmoc	9-Fluorenylmethyloxycarbonyl
G or Gly	Glycine
GuHCl	Guanidine hydrochloride
h	Hour(s)
HBTU	*O*-(Benzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate
H	Histidine
HPLC	High performance liquid chromatography
HRMS	High resolution mass spectrometry
hv	light
i	Iso
IBCF	Isobutyl chloroformate
IPCF	Isopropenyl chloroformate
K	Lysine
L	Leucine
LCMS	Liquid chromatography–mass spectrometry
lit	Literature
M	Methionine
m-	Meta-
MeCN	Acetonitrile
MeOH	Methanol
MESNa	Sodium 2-Mercaptoethanesulfonate
MIDA	*N*-Methyliminodiacetic acid
min	Minute(s)
mp	Melting point
MPA	3-Mercaptopropionic acid
MW	Microwave
n	Normal
NBS	*N*-Bromosuccinimide
NCL	Native chemical ligation
NCS	*N*-Chlorosuccinimide
NIS	*N*-Iodosuccinimide
NMM	*N*-Methyl morpholine
NMP	*N*-Methyl-2-pyrrolidone
NMR	Nuclear magnetic resonance

nOe	Nuclear Overhauser effect
NSI	Nano electrospray
o-	Ortho-
p-	Para-
PEG	Polyethylene glycol
PG	Protecting group
PMB	*Para*-methoxybenzyl
ppm	Parts per million
PPTS	Pyridinium *p*-toluenesulfonate
Pr	Propyl
S	Serine
SPPS	Solid phase peptide synthesis
t or *tert*	Tertiary
TBAF	Tetra-*n*-butylammonium fluoride
TBTU	2-(1*H*-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate
TCEP	Tris(2-carboxyethyl)phosphine
TCICA	Trichloroisocyanuric acid
TFA	Trifluoroacetic acid
TLC	Thin layer chromatography
TMEDA	Tetramethylethylenediamine
TOF	Time of flight
$TsNBr_2$	*N*,*N*-Dibromo-*p*-toluenesulfonamide
v	Volume
w	Weight
Y	Tyrosine

Acknowledgements

When I was a lot younger, I used to marvel at my Nanna's seemingly never ending knowledge. She always told me "no one knows everything," but she hasn't met Tom. I'm incredibly grateful for Tom's knowledge of all things chemistry and his ability to make everything seem ok, even when nothing has worked for what feels like forever. It's been great to work with someone who also enjoys a drink every now and then, even if he occasionally runs away from the pub so he can't be coerced into staying – I suppose everyone needs to have something to improve on.

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I'm incredibly lucky to have a brilliant family – whether we're related through blood or love, or in some cases, both. Despite not really understanding what I'm doing, they've supported and encouraged me throughout my PhD and I'm incredibly grateful to them. Special shout out to my grandparents for giving me the right amount of intellect,

stubbornness and drive to finish this, and to my niece Abbie, for reminding me with every smile that there's more to life than a thesis.

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*Excluding the three peaks challenge, cycling in London or Glastonbury

Chapter 1 *N* → *S* Acyl Transfer in Native Peptide Sequences

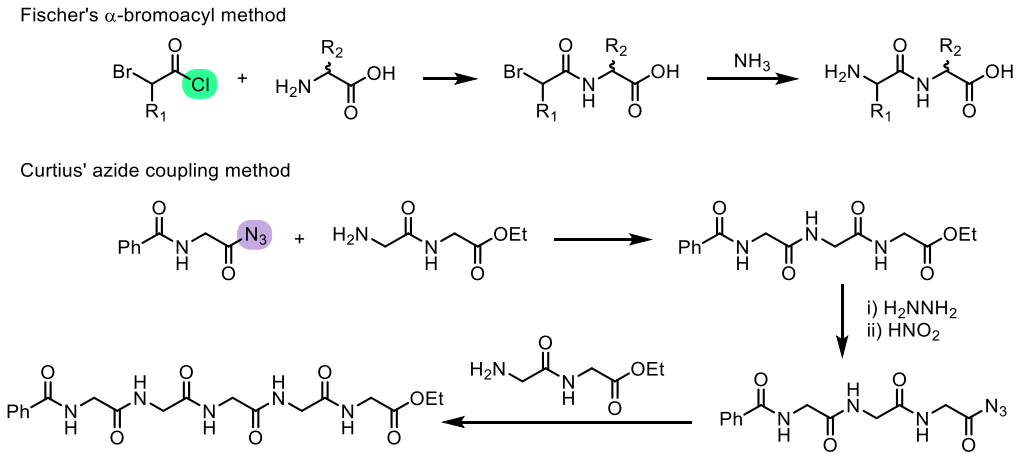
1.1 Introduction

1.1.1 Peptide synthesis

Peptides are implicated in a plethora of biological functions and are ubiquitous in living systems, and as such, synthetic peptides have been incredibly important in a variety of fields including biology, biomedicine and drug discovery.[1] Due to this, peptide synthesis has been investigated for over a century,[2] and has continued to inspire chemists. The development of strategies for peptide synthesis have been reviewed extensively,[3–7] and so will be discussed briefly below.

1.1.1.1 Solution phase peptide synthesis

Initial research into peptide structure was conducted by Fischer and Fourneau in 1901. They demonstrated that proteins are comprised of amino acids connected by an amide bond.[2] Fischer then went on to develop solution phase peptide synthesis by coupling α-bromoacyl chlorides and amino acids followed by treatment with ammonia (Scheme 1.1)[8] and was able to synthesise an octadecapeptide consisting of glycine and leucine.[9] Around the same time, Curtius developed an azide coupling method and used this to synthesise a range of benzoylglycine peptides (Scheme 1.1).[10]



Scheme 1.1 Early methods of peptide synthesis used by Fischer[8] and Curtius[10]

Both methods rely on forming an activated acyl compound, however, they were both limited by the lack of an amine protecting group that was easily removed. This was overcome in 1931 by Bergmann and Zervas who developed the carboxybenzyl

protecting group (Cbz, Scheme 1.2)[11] which is readily removed with hydrogenolysis. This revolutionised the field of peptide synthesis and encouraged work on the total chemical synthesis of peptides and proteins. For example, oxytocin (Figure 1) was synthesised in this way by du Vigneaud *et al.* in 1953,[12] which was the first synthesis of a biologically active peptide.

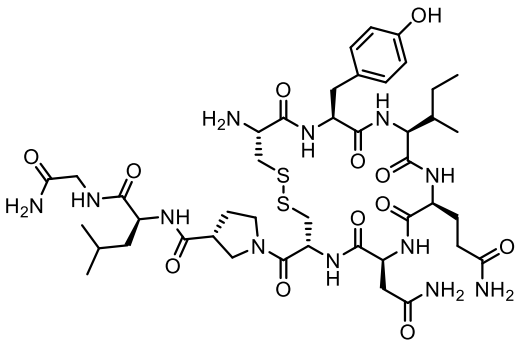
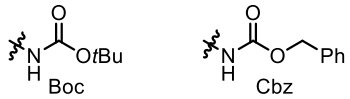


Figure 1 Oxytocin

Shortly afterwards, the *tert*-butyloxycarbonyl group (Boc, Scheme 1.2) was introduced; an orthogonal protecting group to Cbz, which provided chemists with an enhanced tool kit for the synthesis of peptides. Since then, numerous protecting groups for the termini and side groups of amino acids have been developed.[13,14]



Scheme 1.2 Two of the first amino protecting groups

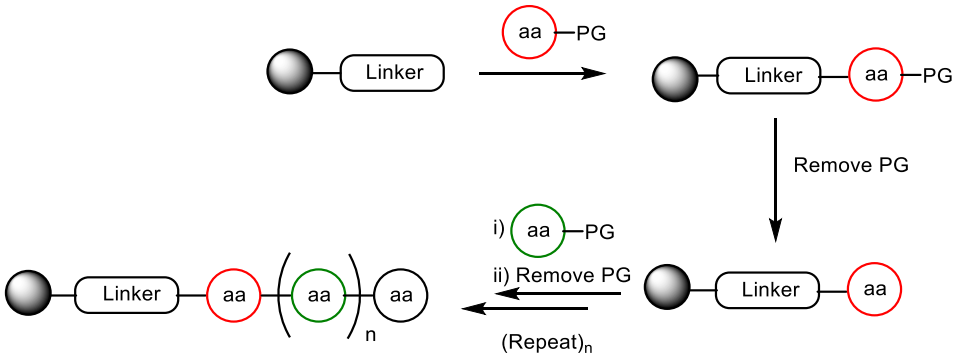
Whilst these advantages were significant, it is important to note that the presence of hydrophobic protecting groups can reduce the solubility of the peptides, leading to the formation of aggregates.[15] Another limitation of solution phase peptide synthesis is the requirement to isolate and purify the peptide product between coupling steps. This makes the process operationally intensive and reduces the yield of the product. Due to these limiting factors, it is impractical to make long peptides by solution phase peptide synthesis.

1.1.1.2 Solid Phase Peptide Synthesis

In 1963, the limitations of solution phase peptide synthesis were addressed by Merrifield's development of solid phase peptide synthesis (SPPS).[16] This novel approach used a resin consisting of cross linked styrene-divinylbenzene polymers on

which an amino acid can be anchored. Since then, numerous resins have been developed, each offering particular characteristics in regard to their swelling properties and the desired *C*-terminal functionality of the peptide.[17]

An amino acid is attached to the resin, commonly via a linker or a handle that provides the required functionality for effective coupling and prevents racemisation of the initial amino acid. The amino acid is anchored by the *C*-terminus, and peptide synthesis proceeds from the *C*- to *N*-terminus. The initial amino acid can be coupled to the resin, or alternatively, a preloaded resin can be used. The protecting group can be removed and the free amine can react with the activated carboxylic acid of the subsequent amino acid (Scheme 1.3). The deprotection and coupling steps can be repeated until the desired peptide has been attained, after which side chain protecting groups are removed and the peptide is cleaved from the resin.



Scheme 1.3 Solid Phase Peptide Synthesis

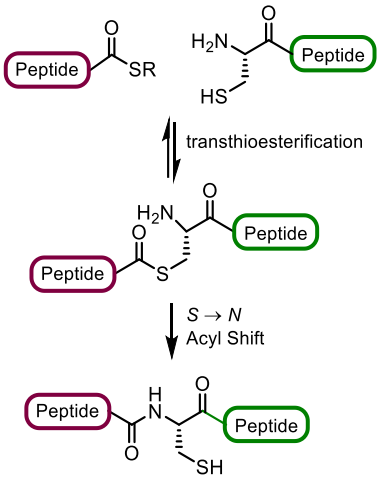
The advantages of this method are that impurities can be rapidly removed by washing and filtering the resin. This also allows an excess of reagents to be used, encouraging the coupling reactions to reach completion. Due to the operationally simple process, SPPS can be automated. It is also worth noting that this method allows the incorporation of amino acids with post translational modifications and unnatural amino acids.

Using this strategy, it is possible to create peptides around 50 amino acids in length; much longer than would be possible by solution phase peptide synthesis. Whilst SPPS marked a significant improvement in the synthesis of peptides, the length of the resulting chains was still prohibitive in the design of larger peptides and proteins. This can be attributed primarily to the formation of aggregates, addition or deletion of amino acids in the growing peptide chain and an increase in the number of side reactions as the peptide chain increases in length.[1] New methods were required if

chemists were to ever achieve the longstanding goal of synthesising large proteins *ab initio*.

1.1.1.3 Native Chemical Ligation

Native chemical ligation allows convergent syntheses of larger peptides, overcoming the limitations of SPPS. The introduction of native chemical ligation (NCL) in 1994[18] has provided a facile route to synthesise a native peptide bond between two unprotected peptide or protein fragments, which circumvents any problematic solubility issues.[19] The ligation requires two fragments; generally a *C*-terminal thioester and an *N*-terminal cysteine component (Scheme 1.4). The two polypeptides undergo reversible transthioesterification to generate an *S*-peptide. An intramolecular $S \rightarrow N$ acyl shift occurs to generate a native peptide bond between the two fragments.



Scheme 1.4 Native Chemical Ligation (NCL) of a *C*-terminal thioester fragment (purple) and an *N*-terminal cysteine fragment (green)

The requirement for a *C*-terminal thioester can be challenging and time consuming, and for this reason routes to access thioesters have been explored.

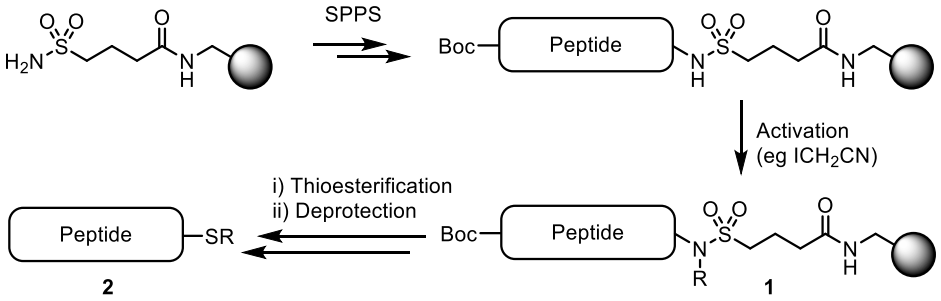
1.1.1.4 *C*-Terminal thioester formation

There are various methods to synthesise *C*-terminal peptide thioesters. Some of these will be detailed below.

1.1.1.4.1 Safety catch linkers

Early work in the field used Boc SPPS, though the harsh cleavage conditions, for example HF, are commonly considered a major disadvantage.[18] For this reason, routes to *C*-terminal peptide thioesters using Fmoc SPPS have been explored.

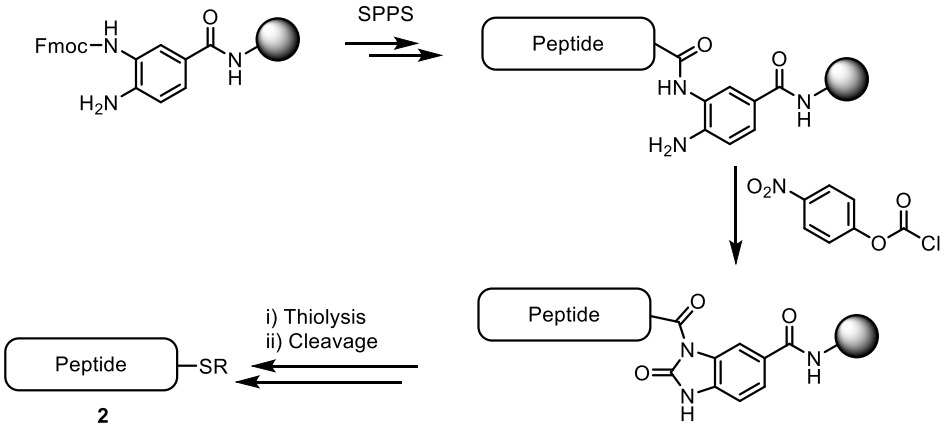
However, problems can arise as resin-bound thioesters are not stable to the repeated exposure to piperidine.[20] A popular route is via the use of a sulfonamide "Safety Catch" resin, for example 4-sulfamylbutyryl linker. Safety catch linkers are named for the requirement of two different reactions for cleavage to occur. Fmoc SPPS can be used to synthesise the peptide chain and then the sulfonamide is activated by alkylation, for example with iodoacetonitrile, to give **1**.[21] Addition of a thiol nucleophile results in cleavage to generate a peptide thioester which can then be deprotected to generate the unprotected *C*-terminal thioester **2** (Scheme 1.5).



Scheme 1.5 Thioester formation via a sulfonamide safety catch resin[21]

Variations of this method have been used by numerous groups,[21–24] however, the success is often dependent on the nature of the peptide.

Another popular safety-catch linker is the 3,4-diaminobenzoic acid (Dbz) handle (Scheme 1.6).[25] Following chain elongation by Fmoc SPPS, *p*-nitrophenylchloroformate is used to generate an N-acylurea peptide which can be subjected to thiolysis and cleavage to give thioester peptide **2**.



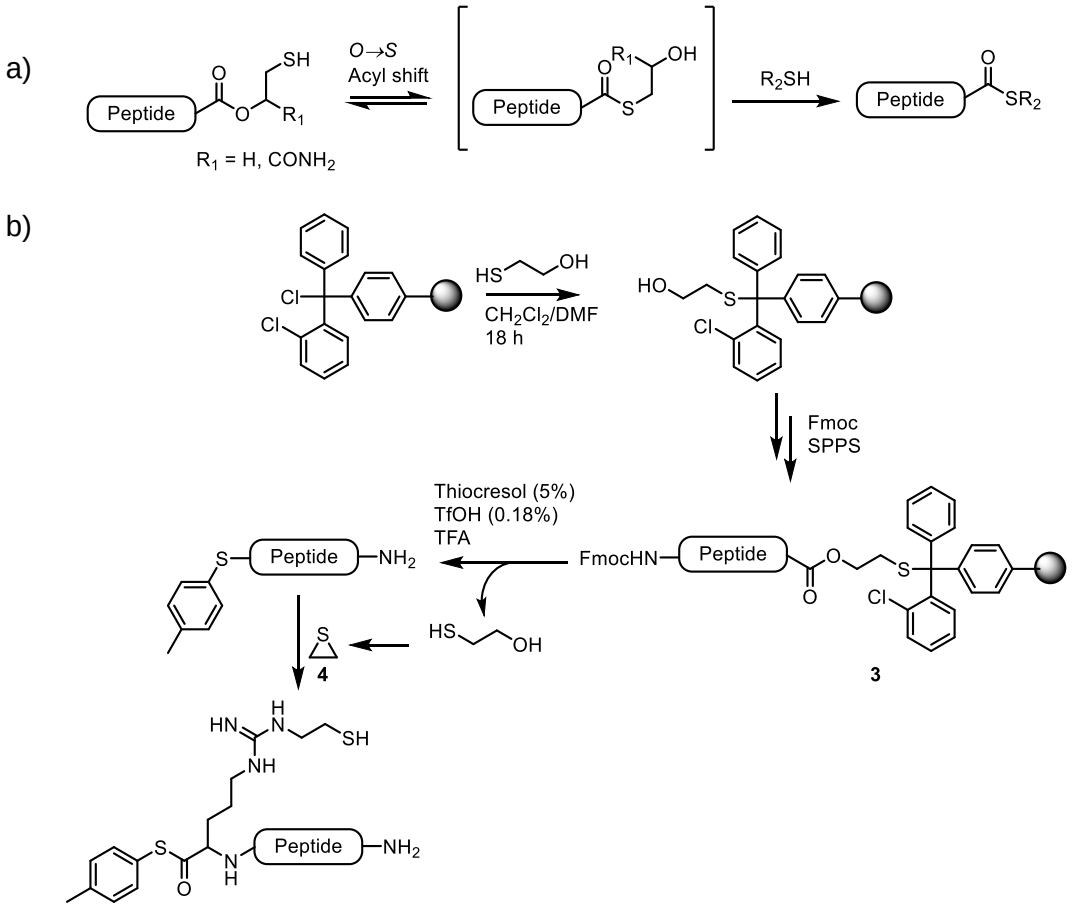
Scheme 1.6 *N*-acyl urea formation via Dbz linker[25]

There are drawbacks associated with the safety catch resin technique, including the

incompatibility of post-translational modifications to the alkylating activation step and low yields.[26]

1.1.1.4.2 *O* → *S* Acyl shift

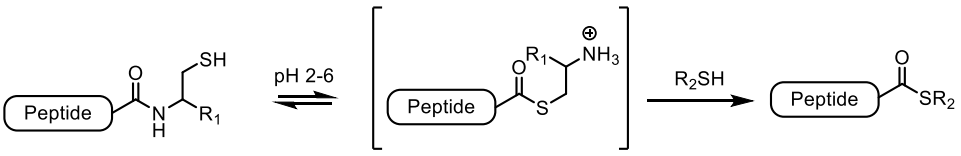
Peptide thioester synthesis has been achieved by an *O* → *S* acyl shift (Scheme 1.7a). It has been demonstrated that this strategy is efficient for starting peptides with various *C*-terminal functionality, including mercaptoethanol esters,[27] phenolic esters[28] and a 2-hydroxymercaptopropanoate ester.[29] However, hydrolysis of the starting ester can be problematic,[30] compounding the low yields obtained. Issues with residue compatibility were also observed. For example, peptide ester **3** is synthesised on a resin, using a mercaptoethanol handle (Scheme 1.7b). It has been observed that released mercaptoethanol forms ethylene sulphide **4**. This alkylated the guanidino side-chain of arginine residues, thus limiting the utility of this approach.[27]



Scheme 1.7 a) Schematic thioester formation via *O* → *S* acyl shift b) Previously reported *O* → *S* acyl shift and the problematic alkylation of the guanidine side chain of arginine residues by ethylene sulfide[27]

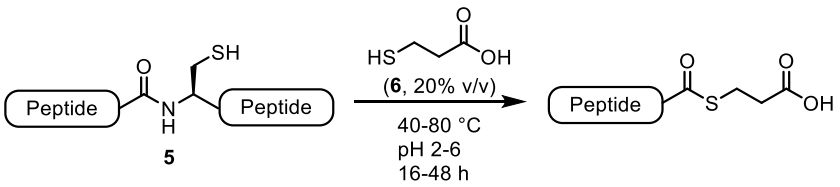
1.1.1.4.3 *N* → *S* Acyl shift

One strategy to synthesise peptide thioesters makes use of an *N* → *S* acyl shift, which is the reverse step of NCL. A peptide with a *C*-terminal cysteine residue can undergo an *N* → *S* acyl shift to the less stable *S*-peptide (Scheme 1.8). An additional thiol can trap this thioester form, resulting in a *C*-terminal thioester and the release of the original thiol-containing amino acid (commonly cysteine).



Scheme 1.8 Schematic thioester formation via *N* → *S* acyl shift

Previously within the Macmillan group, it was identified that subjecting peptide **5** to 3-mercaptopropionic acid (MPA, **6**) led to fragmentation to furnish a *C*-terminal thioester (Scheme 1.9).[31] It was noted that this occurred preferentially at His-Cys, Gly-Cys or Cys-Cys residues.



Scheme 1.9 Previously reported thioester formation from the Macmillan group[31]

However, the use of MPA was not ideal, leading to complicated product analyses and in some cases complicating product purification. Hydrolysis of the thioester product was also observed. For these reasons, other thiol additives were explored with the aim of optimising thioester formation whilst overcoming these limitations. To this end, the combination of 2-mercaptoethanesulfonate (MESNa, Figure 2) in the presence of acetic acid and TCEP was identified as an improved set of conditions.[32] However, the rate of thioester formation was still plagued by the long reaction times required for full conversion from starting peptide to thioester. The extended reaction times led to hydrolysis of the thioester product, thus reducing the yield. Therefore, additional investigation into the optimum conditions for the thioester formation have been explored.

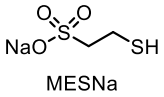
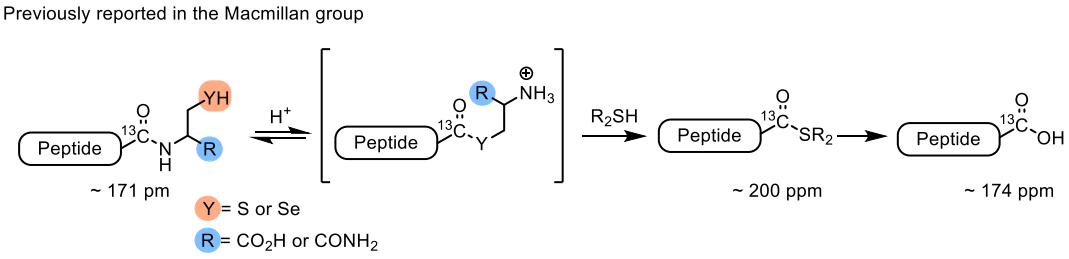


Figure 2 The structure of MESNa

Further work within the Macmillan group has investigated the rate of thioester formation by *N* → *S* acyl shift for a model peptide containing a terminal cysteine or selenocysteine.[33] The functionality at the *C*-terminus has also been investigated, comparing the difference between peptides ending with a carboxylic acid and those ending with a carboxamide (Scheme 1.10).[33]



Scheme 1.10 Previously reported investigation into the rate of thioester formation for cysteine or selenocysteine and carboxylic acid or carboxamide terminated peptides[33]

The reaction was easily monitored by using a ^{13}C-labelled residue, in this case glycine. The starting peptide has a characteristic peak at 171 ppm in the ^{13}C NMR spectrum, whereas the thioester product has a peak at 200 ppm (Scheme 1.10). In many cases, hydrolysis of the thioester product was observed, noted by a peak at 174 ppm. The hydrolysed product is assumed to come from the thioester, as it is only observed after significant thioester formation. Furthermore, attempts to hydrolyse the starting peptide by heating it in AcOH were unsuccessful.[34] During the investigation, it was discovered that thioester formation was faster for carboxylic acid terminated peptide **7** than the carboxamide analogue **8** (Figure 3).

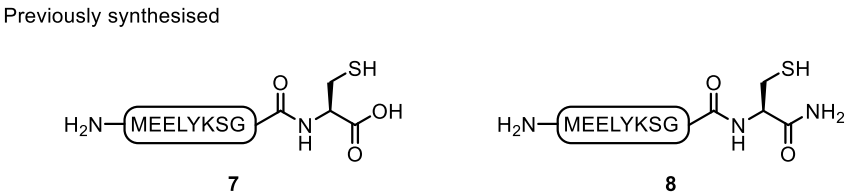


Figure 3 Structures of previously synthesised model peptides and proposed model peptides to explore the factors that influence thioester formation

Currently, only these two analogues, **7** and **8**, have been used to investigate the factors influencing *N* → *S* acyl shift; the effect of other *C*-terminal analogues remains to be seen.

1.2 Aims

The aim of this project will be to determine the factors governing the rate of thioester formation via *N* → *S* acyl shift. This would lead to an improved method of synthesising peptide thioesters that can be used in NCL. One factor that has already been shown to be important is the functionality at the *C*-terminus of the peptide. However, it has also been found that the thioester product is prone to hydrolysis under the reaction conditions, therefore, increasing the rate of the reaction would limit this hydrolysis.

To investigate this, the rate of thioester formation will be measured for model peptides with various *C*-terminus functionality, for example, these could be methyl ester terminated peptide **9**, boronic acid peptide **10** or phosphinic acid peptide **11** (Figure 4).

The rate of thioester formation of these *C*-terminal analogues will be monitored by ^{13}C NMR and compared to previously reported carboxylic acid peptide **7** and carboxamide analogue **8**.[33] This will provide a better understanding of the factors that influence this reaction, so that optimum starting materials can be designed to accelerate the reaction; thereby limiting hydrolysis and increasing efficiency.

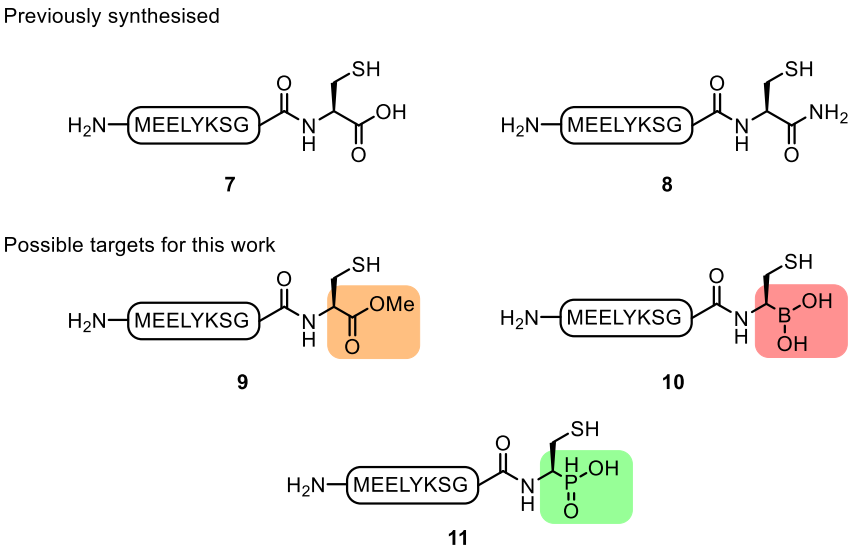
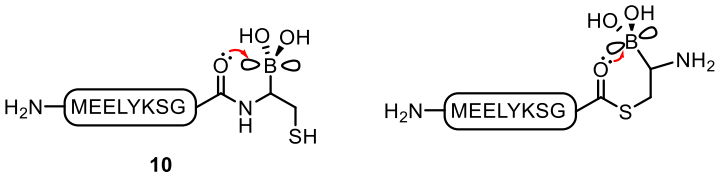


Figure 4 Synthetic targets to investigate the rate of thioester formation via *N* → *S* acyl shift

It is envisaged that the vacant p orbital of the boronic acid would allow for activation of the carbonyl group via donation from the oxygen lone pair. This could be from the starting peptide or from the *S*-peptide intermediate (Figure 5a). The synthesis of boronic acid peptide **10** would first require the synthesis of the α-amino boronic acid

analogue of cysteine, boronocysteine **12** (Figure 5b). Whilst boronic acid analogues of some amino acids are known (see Section 1.3.2), the synthesis of boronocysteine has not been reported.

a)



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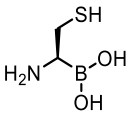
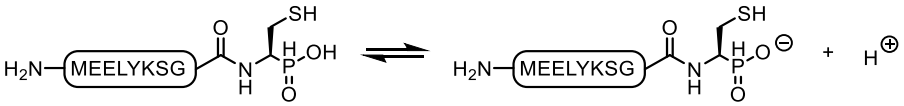


Boronocysteine
12

Figure 5 a) Potential methods of activation of the carbonyl by having a boronic acid terminated peptide; b) boronocysteine **12**

Phosphinic acids have previously been used as isosteres for carboxylic acids[35] as they're monoacidic.[36] Subjecting phosphinic acid peptide **11** (Figure 6a) to thioester forming conditions could reveal if the ability to become charged is important during the reaction. The synthesis of phosphinic acid peptide **11** would first require the synthesis of phosphinocysteine **13** (Figure 6b).

a)



b)

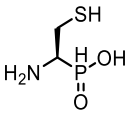


Figure 6 a) Formation of charged peptide species; b) phosphinocysteine **13**

1.3 Synthesis of peptides

1.3.1 Synthesis of model peptide as a *C*-terminal methyl ester

The aim of this part of work was to understand the factors that are important in the rate of thioester formation via *N* → *S* acyl shift. This was to be explored by subjecting *C*-terminal methyl ester peptide **9** to thioester formation conditions and comparing the rate of the reaction to peptides with different *C*-terminal functionality, and so efforts began on synthesising methyl ester peptide **9** (Figure 7). As discussed in Section 1.1.1.4, thioester formation can be easily monitored by using a ^{13}C-labelled residue, in this case glycine.

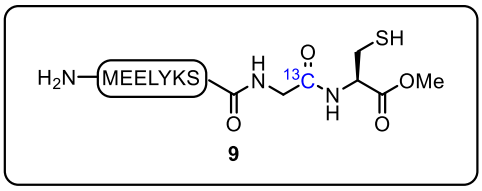
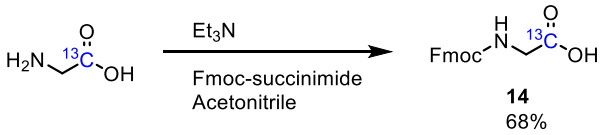


Figure 7 Methyl ester peptide **9**

Peptide methyl esters have previously been synthesised,[37–39] and so our synthesis followed previously reported strategies. Firstly, ^{13}C-labelled Fmoc-glycine **14** was synthesised by the reaction of ^{13}C-labelled glycine with Fmoc-succinimide (Scheme 1.11), which gave **14** in 68% yield.



Scheme 1.11 Synthesis of ^{13}C-labelled Fmoc-Glycine

Labelled glycine **14** was incorporated into the model peptide **7** (Figure 8), which was synthesised using hydroxybenzotriazole (HOBt) and *O*-(Benzotriazol-1-yl)-*N,N,N′,N′*-tetramethyluronium hexafluorophosphate (HBTU) as coupling reagents with a NovaSyn TGT resin preloaded with cysteine. The peptide was isolated in 94% yield. Carboxamide terminated peptide **8** was not synthesised during this work, but had previously been synthesised by Anna Adams using a Rink amide resin.[33] With two of the required peptide variants in hand, efforts began on the synthesis of the model peptide as the methyl ester **9**, however this was found to be more challenging than anticipated.

H—M-E-E-L-Y-K-S-G-C—OH

7

H—M-E-E-L-Y-K-S-G-C—NH_2

8

H—M-E-E-L-Y-K-S-G-C—OMe

9

Figure 8 Structure of model peptides synthesised with ^{13}C labelled glycine

Methyl esters of peptides have previously been synthesised[40] using standard Fmoc solid phase peptide synthesis and hydroxymethylbenzoic acid (HMBA) resin (Figure 9). The methyl ester is formed by nucleophilic cleavage from the resin. The advantage of this strategy is that one common precursor can give rise to different *C*-terminal functionality based on the nucleophile used; for example ammonia has been used to generate amides[41] or hydrazine to produce hydrazides.[42]

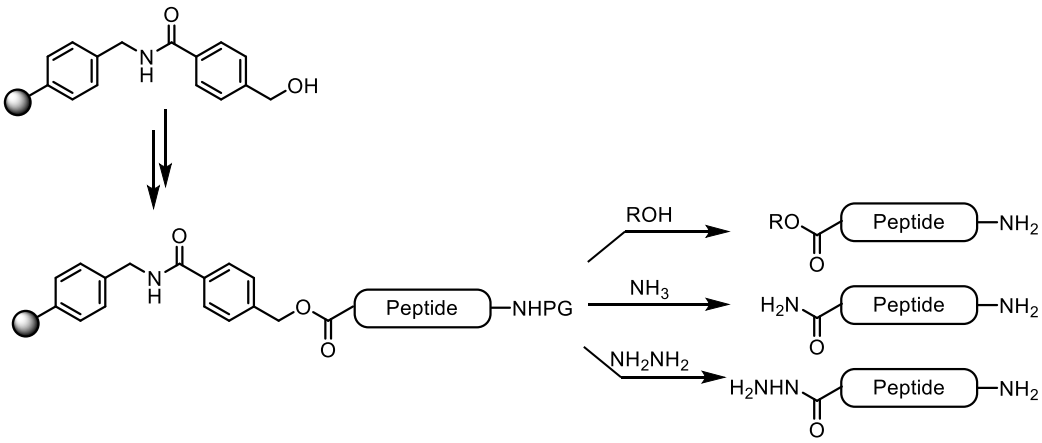


Figure 9 Use of HMBA resin and subsequent peptide cleavage with various nucleophiles

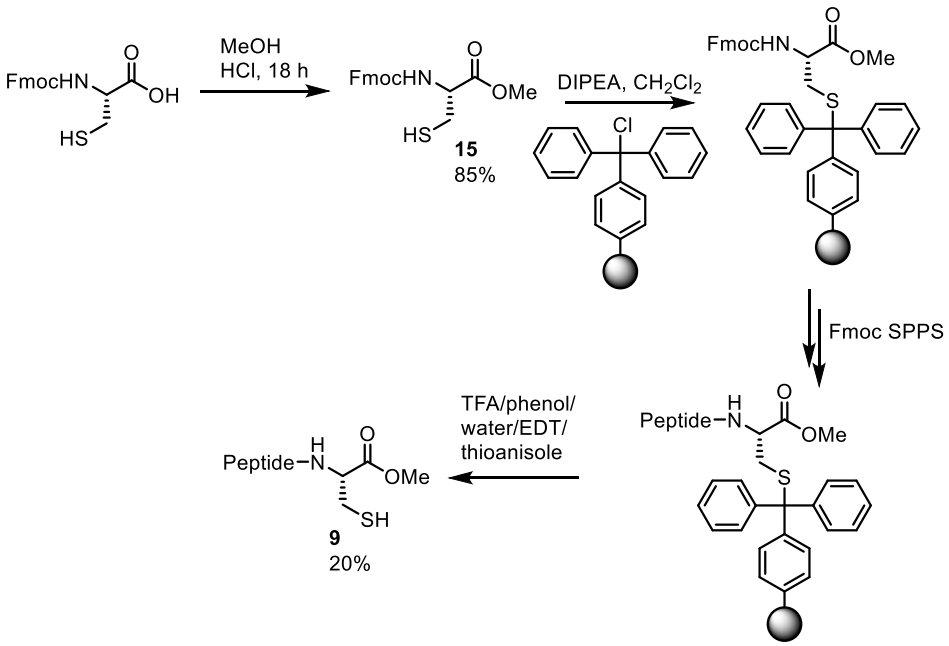
The first strategy employed during this work used HMBA-aminomethyl (AM) resin. Standard attachment protocols for this resin use either 1-(mesitylene-2-sulphonyl)-3-nitro-1*H*-1,2,4-triazole (MSNT) and methyl imidazole (MeIm) or the formation of a symmetrical anhydride using diisopropylcarbodiimide (DIC) and 4-dimethylaminopyridine (DMAP). Both strategies were tried in this work. After peptide elongation using HBTU/HOBt and subsequent cleavage of protecting groups, the peptide was cleaved from the resin using a mixture of DIPEA:MeOH:DMF (1:5:5). However, cleavage of both of these peptides gave < 1 mg of desired peptide **9**. LCMS analysis of the resulting peptides showed a significant amount of peptide with a cysteine deletion, denoted by a mass difference of 103 Da. This implied that using HBTU/HOBt to couple the second residue, in this case glycine, led to the coupling of

glycine to the resin. Following this observation, HBTU/HOBt was used to attach the first cysteine residue. The efficiency of the attachment using all three methods was determined by treating a known amount of coupled resin with piperidine and measuring the absorbance at 290 nm (Table 1).[43]

	1st Coupling	2nd Coupling	Cleavage procedure	Purified Yield
Symmetrical Anhydride	31%	46%	DIPEA:MeOH:DMF (1:5:5)	< 1 mg
MSNT/ MeIm	24%	44%	DIPEA:MeOH:DMF (1:5:5)	< 1 mg
HBTU/HOBt	38%	38%	Et_3N:MeOH:THF (1:5:5), KCN	2 mg (impure)

Table 1 Estimation of level of first amino acid attachment

It has previously been reported that the use of a cleavage cocktail of Et_3N:MeOH:THF (1:5:5) with KCN can cleave peptide methyl esters from HMBA resin;[40] whilst this method did give more crude product, it was not possible to purify it sufficiently by HPLC. As using HMBA-AM resin gave poor yields of peptides, an alternative method applied by Diaz-Rodriguez was employed.[37] Cysteine methyl ester **15** was first synthesised (Scheme 1.12) and subsequently attached to a trityl chloride resin via the thiol side chain. This strategy was particularly favourable as it may allow for the attachment of other cysteine analogues via the side chain, facilitating incorporation into a peptide.



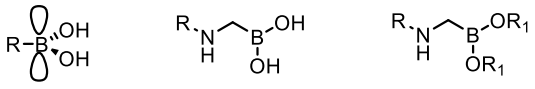
Scheme 1.12 Synthesis of model peptide **9** [H-MEELYKSGC-OMe]

After peptide elongation and cleavage of protecting groups, the peptide was cleaved from the resin using reagent K (TFA:phenol:thioanisole:H_2O:ethane dithiol (EDT), 82.5:5:5:5:2.5). Purification by HPLC gave peptide **9** in 20% yield.[44] With the methyl ester in hand, attention turned to synthesising boronic acid terminated peptide **10**.

1.3.2 Synthesis of model peptide as a *C*-terminal boronic acid

1.3.2.1 Introduction to boronic acids

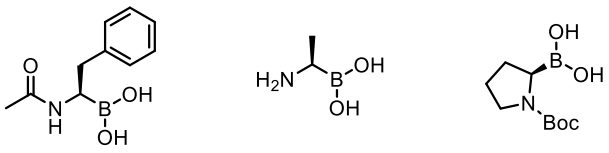
Boronic acids are trivalent boron-containing compounds in which boron is bonded to one alkyl substituent, with the two remaining substituents being hydroxyl groups (Figure 10). As the boron atom is sp^2 hybridised, this leaves a vacant p orbital, which is responsible for the Lewis acidic behaviour of boronic acids. α-Amino boronic acids have an amine α to the boron and are analogues of α-amino acids. Boronic acids are known to form oligomers and so are often manipulated as boronic esters (Figure 10).



boronic acid | α-amino boronic acid | α-amino boronic ester

Figure 10 Boronic acid structure

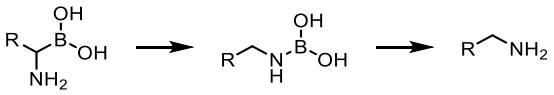
Some boronic acid derivatives of naturally occurring amino acids have previously been synthesised, such as boronophenylalanine,[45] boronoalanine[46] and boronoproline[47] (Figure 11). Both boronophenylalanine and boronoalanine were synthesised for their inhibitory effects on chymotrypsin and peptidoglycan synthesis respectively. Boronoproline was synthesised as a potential bifunctional catalyst for organic reactions.[47] Boronocysteine, however, has not previously been synthesised.



Boronophenylalanine Boronoalanine Boronoproline

Figure 11 Previously synthesised boronic amino acids

During the syntheses of these boronic acid compounds, it was observed that the free amino boronic acid was prone to a 1,3-rearrangement to the homologated amine (Scheme 1.13), which can be prevented by manipulating the α-amino boronic acids as a hydrochloride salt, or using suitable protecting groups on the nitrogen atom.[45]



Scheme 1.13 1,3-Rearrangemet of α-amino boronic acid to amine

1.3.2.1.1 Applications of α-amino boronic acids and derivatives

In addition to providing potential solutions to some of the issues faced within NCL, α-aminoboronic acids have been shown to be incredibly useful in their own right. The important uses of α-aminoboronic acids have only been established in the last few decades. These include biomedical applications, their utility as building blocks and their use in sensing applications. These will be discussed further below.

α-Aminoboronic acids and derivatives as therapeutics

The utilisation of α-amino boronic acids mainly arises from their incorporation into a peptide. One such example is bortezomib (marketed as Velcade®) which is the first successful therapeutic containing boron (Figure 12).[48] Velcade® is used to treat multiple myeloma (cancer of plasma cells) and mantle cell lymphoma (cancer of the lymph nodes).[49]

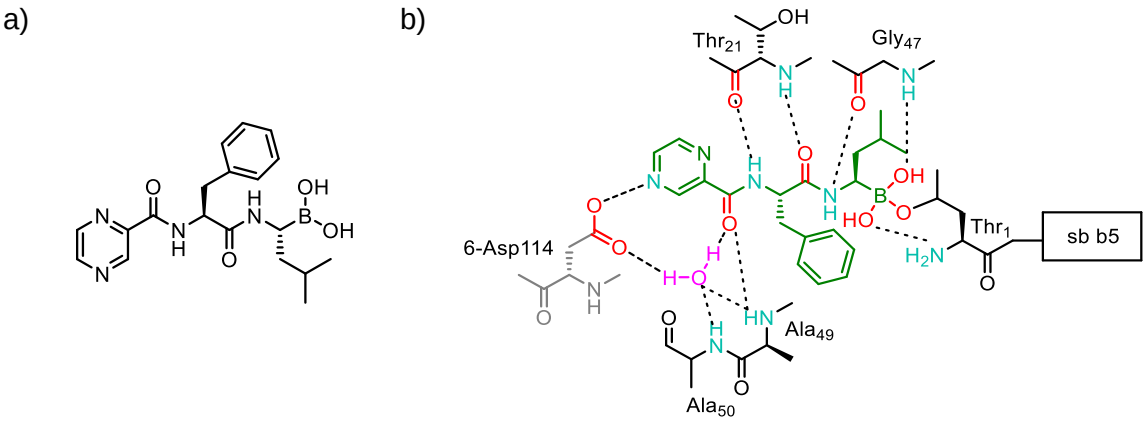
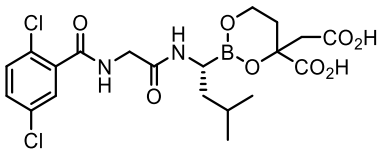


Figure 12 Bortezomib (Velcade®) a) Structure b) Critical interactions of bortezomib with residues of proteasome[50]

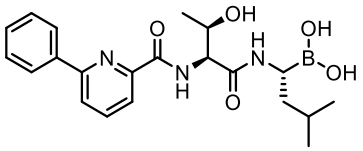
Velcade® gave a lifeline for sufferers of these cancers when it was approved in 2003, as it was the first therapeutic agent for these conditions that worked by proteasome

inhibition. The boronic acid moiety specifically forms a (pseudo)covalent bond with the hydroxyl group of a threonine residue on the 26S proteasome.[51,52] This proteasome is responsible for controlled protein degradation, and so inhibition leads to the accumulation of proteins, many of which are involved in cell cycle regulation. The accumulation of these proteins leads to apoptosis. Cancerous cells are more susceptible to cell death in this way, due to the exploitation of the proteasome to induce rapid proliferation.[53] Velcade® was particularly promising for patients who were no longer responding to initial chemotherapy, though, resistance to Velcade® has also been reported.[54]

The therapeutic success of Velcade® led to the development of second-generation proteasome inhibitor ixazomib (marketed as Ninlaro®, Figure 13). Ninlaro® was approved by the FDA in November 2015 and is administered orally, after which it is hydrolysed to the active boronic acid.[53] It has also recently received attention for the treatment of breast cancer.[55] Another orally available treatment of multiple myeloma containing a boronic acid is Delanzomib (Figure 13).



Ixazomib



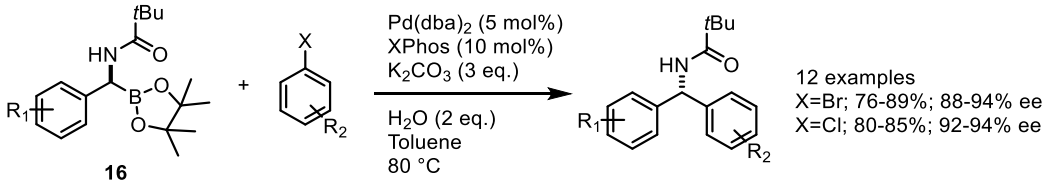
Delanzomib

Figure 13 Second generation proteasome inhibitors

Aside from therapeutics, α-amino boronic acids have been patented for their use in liquid detergents containing proteolytic enzymes. α-Amino boronic acids are used to inhibit the proteolytic enzymes to ensure that they don't degrade other enzymes in the detergent.[56]

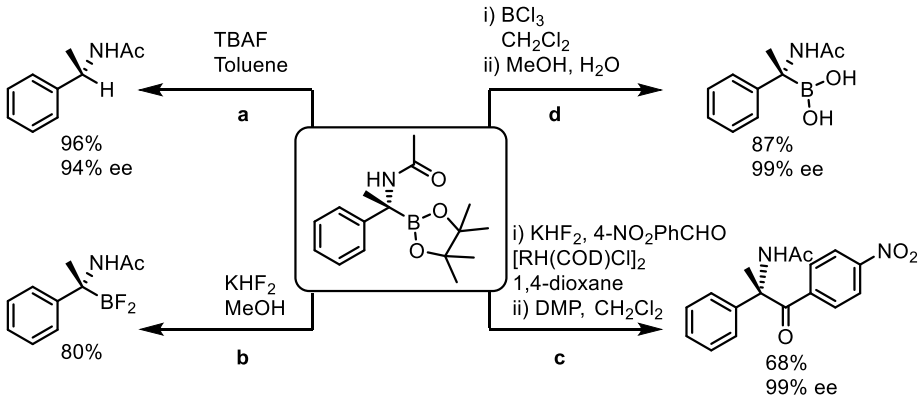
α-Aminoboronic acids and derivatives as building blocks

Ohmura *et al.* found that they could couple enantioenriched α-(acylamino)benzyl boronic esters **16** with aryl bromides and chlorides in a Suzuki-Miyaura coupling with an inversion of stereochemistry (Scheme 1.14). Boronic ester **16** was synthesised via Matteson's asymmetric homologation (see Section 1.3.2.1.3).



Scheme 1.14 Invertive Suzuki-Miyaura coupling of α-(acylamino)benzylboronic esters[57]

Hu *et al.* have shown that α-amino tertiary boronic esters are amenable to a range of transformations; protodeboronation (Scheme 1.15a), synthesis of difluoroborane (Scheme 1.15b), the synthesis of α-acetylaminoketone (Scheme 1.15c) and transformation to the corresponding boronic acid (Scheme 1.15d).[58]



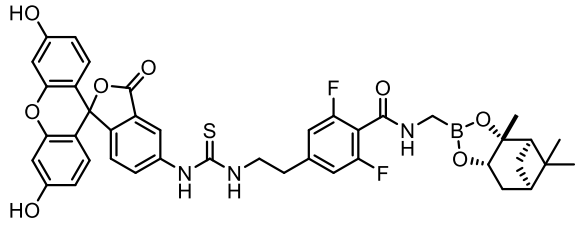
Scheme 1.15 Transformations of chiral α-amino tertiary boronic ester[58]

This shows that α-aminoboronic acids are versatile compounds that can be further manipulated to allow access to a range of different functionalities.

α-Aminoboronic acids and derivatives as sensing molecules

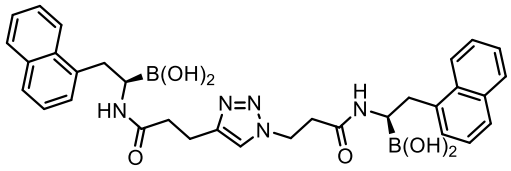
The binding interactions that are responsible for the selectivity of boronic acid derived therapeutics have also been exploited in the development of chemical tracers. Figure 14a shows **17**, a fluorescent tracer that has been developed for the identification of inhibitors of penicillin binding proteins and β-lactamases, which have a role in antibiotic use and resistance.[59] Compound **18** (Figure 14b) has shown fluorescent intensity changes when bound to different carbohydrates.[60]

a)



17

b)



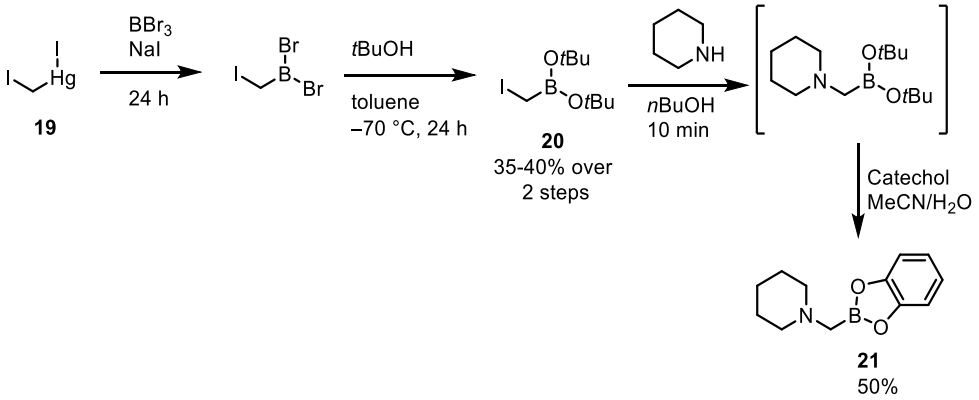
18

Figure 14 Fluorescent tracers for a) penicillin binding proteins and β-lactamases[59] and b) carbohydrate sensing[60]

Despite the range of uses of α-aminoboronic acids, synthetic routes to access them are somewhat elusive. Synthetic routes that have been used will be discussed below.

1.3.2.1.2 Synthesis of α-amino boronic acids

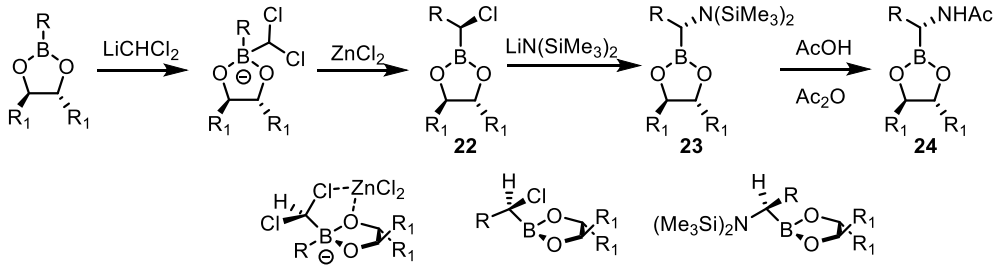
The first synthesis of α-amino boronic acids was by Matteson in 1966 (Scheme 1.16).[61] It relied on the reaction of iodomethylmercuric iodide[62] **19** with boron tribromide. Treatment with *tert*-butanol in the presence of sodium iodide gave di-*tert*-butyl (iodomethyl)boronate **20**. Displacement using piperidine followed by hydrolysis of the boronic ester and subsequent formation of the catechol ester gave **21** in 50% yield.



Scheme 1.16 First synthesis of α-amino boronic acids[61,63]

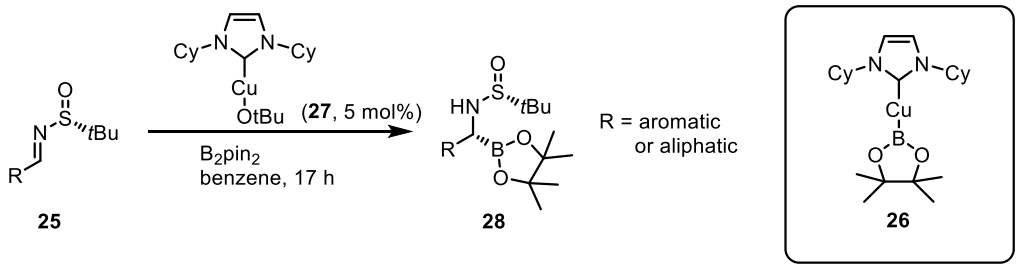
1.3.2.1.3 Asymmetric synthesis of α-chloro boronic esters

Matteson continued work on α-aminoboronic esters and devised a route to enantioenriched α-amino boronic esters from α-chloro boronic esters (Scheme 1.17).[64] This route involved the insertion of (dichloromethyl)lithium into pinanediol boronic esters that rearrange in the presence of zinc chloride to give α-chloro boronic ester **22**. The Lewis acid prevents epimerisation of the α-chloro boronic ester by chelation of the chloride and oxygen. This chelation coupled with the steric hindrance provided by the boronic ester favours the selective displacement of one chloride and is responsible for the asymmetric induction.[65] Lithium hexamethyldisilylamide can then displace the chloride and the resulting silylated boronic ester **23** is treated with acetic anhydride and acetic acid to give the desired acetylated α-amino boronic ester **24**. This can give the desired product in high diastereoselectivity, often over 100:1 dr.[65] Whilst this route provides good yields, the scope is limited as the α-amino boronic acid side chain is derived from the starting alkyl boronic acid. It is also worth noting that this method was reported to be unsuccessful when applied to compounds with α-sulfur substituents.



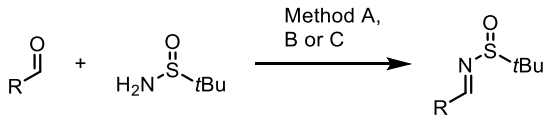
Scheme 1.17 Asymmetric synthesis of α-amino boronic esters showing how chelation of chloride and oxygen to zinc result in diastereoselectivity[64]

A more recently published strategy for the asymmetric synthesis of α-amino boronic acids relies on the formation of *tert*-butyl sulfinimine **25** (Scheme 1.18).[66] Copper-boron species **26** is generated from copper catalyst **27** and bis(pinacolato)diboron (B_2pin_2).[67] From species **26**, asymmetric addition of boron to *tert*-butyl sulfinimines **25** occurred and gave α-amino boronate esters **28** in isolated yields of 52-81%, with dr from 95:5 to >99:1. Both branched and unbranched aliphatic sulfinimines were tolerated, as well as electron poor and electron rich aromatic sulfinimines.[66]



Scheme 1.18 Synthesis of α-amino boronic esters from *tert*-butyl sulfinimines[66]

The starting sulfinimines are easily accessed from the corresponding aldehyde via condensation with *tert*-butyl sulfinamide in the presence of a Lewis acid dehydrating agent (Scheme 1.19).[68] Use of magnesium sulfate ($MgSO_4$) with pyridinium *p*-toluenesulfonate (PPTS) requires 2-3 equivalents of aldehyde, though this can be lowered to 1.1 equivalent if copper sulfate ($CuSO_4$) is used. The condensation of particularly unreactive aldehydes or ketones can be achieved with titanium ethoxide ($Ti(OEt)_4$) (Scheme 1.19).[68]



Method A	$MgSO_4$ (5 eq.), PPTS (5 mol%), CH_2Cl_2
Method B	$CuSO_4$ (2 eq.), CH_2Cl_2
Method C	$Ti(OEt)_4$ (2 eq.), THF

Scheme 1.19 Synthesis of *tert*-butyl sulfinimines[68]

1.3.2.2 Synthesis of boronocysteine

To examine the rate of thioester formation from model peptide **10**, the synthesis of boronocysteine must first be developed (Figure 15). For this, a free thiol is needed to attach boronocysteine to the trityl chloride resin, as was used for the synthesis of methyl ester peptide **9** (Section 1.3.1). The amine group should be protected to prevent deborylation (Section 1.3.2.1). The boronic acid will also need to be protected; pinacol was chosen for this.

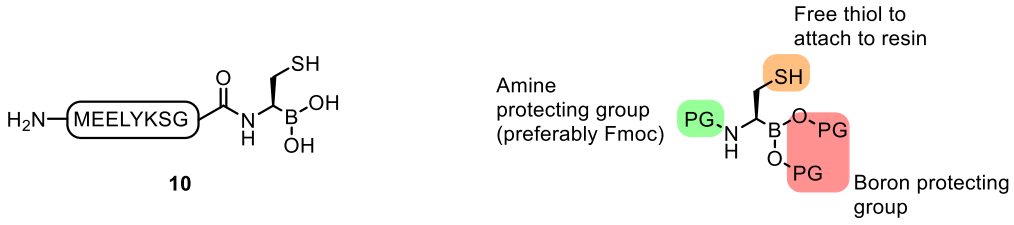
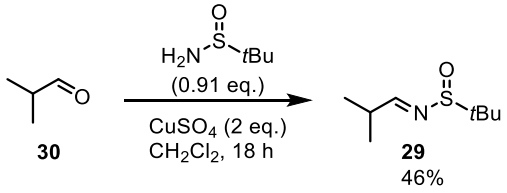


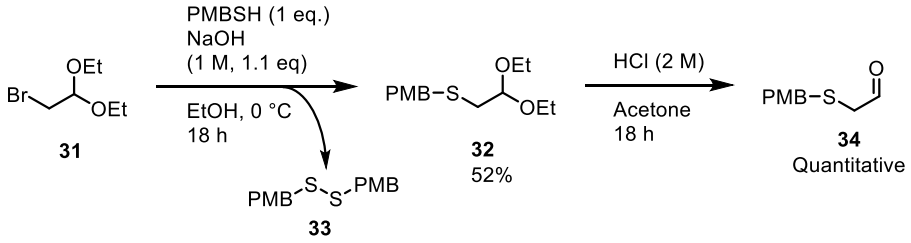
Figure 15 Boronic acid peptide **10** and boronocysteine

The proposed synthetic route to boronocysteine relied on Beenen's procedure.[66] To test the synthetic route, previously reported compound **29**, made by Beenen *et al.* was synthesised. Sulfinimine **29** (Scheme 1.20) was isolated in 46% yield from the reaction of isobutyraldehyde **30** with *tert*-butyl sulfinamide using $CuSO_4$ in CH_2Cl_2.



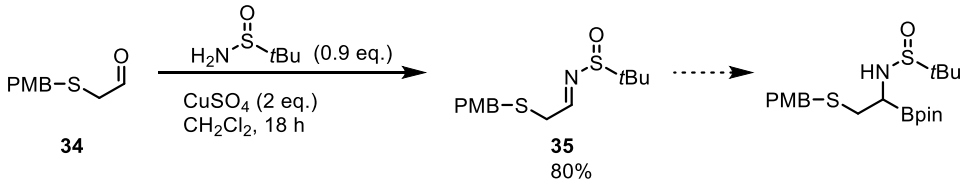
Scheme 1.20 Condensation of isobutyraldehyde and *tert*-butyl sulfinamide

Encouraged by this result, efforts began on the synthetic route to boronocysteine outlined in Scheme 1.21. At this stage, racemic starting materials were used, with the view to synthesise enantiopure boronocysteine after the synthetic route has been optimised. The synthesis of boronocysteine began with the nucleophilic substitution of bromo acetal **31** with *para*-methoxybenzyl mercaptan (PMBSH).[69] Initial attempts yielded the desired PMB-protected acetal **32** in an acceptable yield of 30%, though a large amount of by-product formed which was confirmed to be the disulfide dimer of the PMB mercaptan **33**, isolated in 44% yield. Increasing the amount of solvent and dropwise addition of thiol suppressed dimerisation giving desired product **32** in 52% yield. Acetal **32** was readily deprotected using HCl in acetone to give the corresponding aldehyde **34** in quantitative yield.



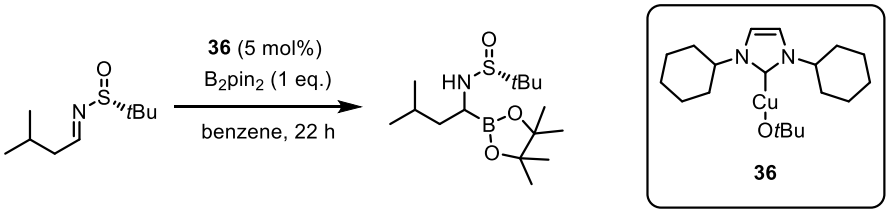
Scheme 1.21 Synthetic route towards boronocysteine

Condensation of **34** with *tert*-butyl sulfinamide in the presence of $CuSO_4$ gave the *tert*-butyl sulfinimine **35** in 80% yield. Next, it was envisaged that nucleophilic borylation of *tert*-butyl sulfinimine **35** would give pinacol boron ester (Scheme 1.22).



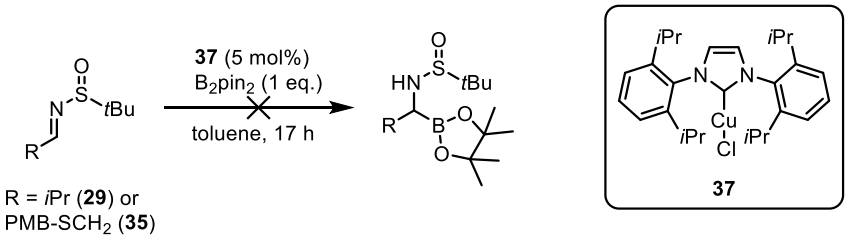
Scheme 1.22 Condensation of aldehyde **34** followed by envisaged nucleophilic addition to sulfinimine **35**

This was based around the procedure used by Beenen *et al.*, who reported the use of catalyst **36** (Scheme 1.23).[66] This catalyst has previously been used to achieve the diboration of aldehydes, however, the synthesis must be undertaken in a glove box and it is difficult to remove residual amounts of tetrahydrofuran.[67]



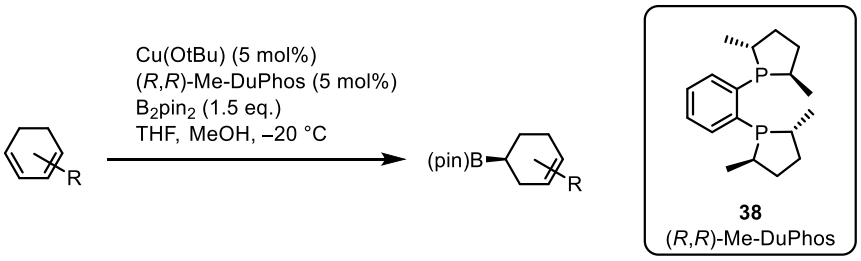
Scheme 1.23 Synthesis of *tert*-butyl sulfinamide reported by Beenen *et al.* [66]

Due to the reported difficulties of synthesising catalyst **36**, and the need to handle it in a glove box, it was decided that more stable catalyst **37** would be trialled. Unfortunately, the attempted borylation of imine **29** or **35** using catalyst **37** was unsuccessful (Scheme 1.24).



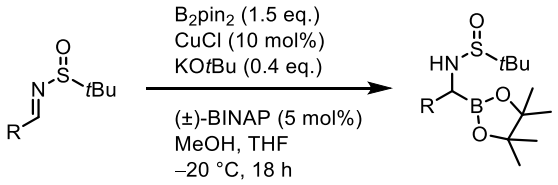
Scheme 1.24 Attempted borylation reaction using catalyst **37**

Sasaki *et al.* have previously reported a Cu(I) catalysed borylation reaction using the *in situ* generation of Cu(O*t*Bu) from CuCl and K(O*t*Bu).[70] In this case, enantioselectivity is achieved by the use of chiral ligand (*R*,*R*)-Me-DuPhos (**38**, Scheme 1.25).



Scheme 1.25 Copper catalysed borylation reported by Sasaki *et al.*[70]

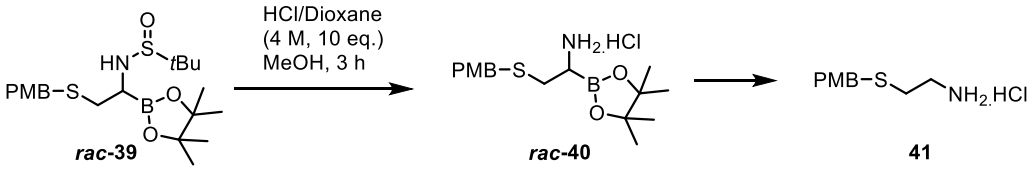
This method was used in the synthesis of boronocysteine, using racemic BINAP as the ligand, and gave the desired protected thiol product **39** in 60% yield (Scheme 1.26). Only one diastereoisomer was observed. Interestingly, this method was unsuccessful for the isopropyl sulfinimine **29**, potentially due to steric hindrance.



Sulfinimine	Product (Yield)
29 (R = *i*Pr)	No reaction
35 (R = PMB-SCH_2)	***rac*-39** (60%)

Scheme 1.26 Copper catalysed borylation reaction

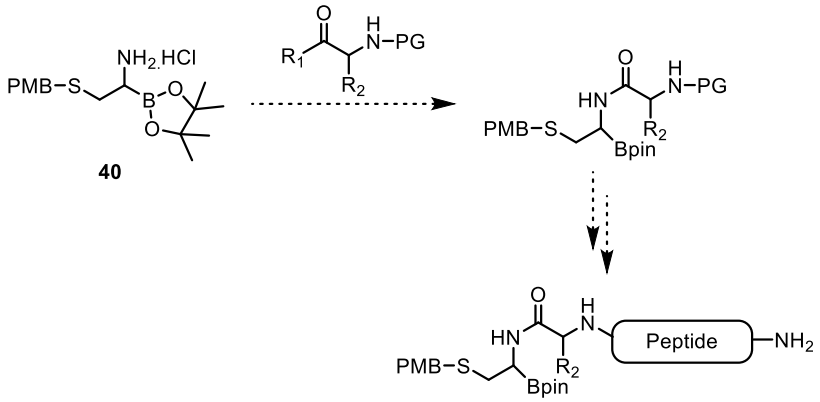
Cleavage of the sulfinyl group was elicited using 4 M HCl in dioxane with MeOH. Originally, the reaction was left overnight, with either 1, 1.5 or 10 equivalents of HCl. However, it was found that the product (**40**) was prone to rearrangement (see Section 1.3.2) to give deborylated product **41**, despite the reported stability of HCl salts of α-amino boronates[45] (Scheme 1.27). Reducing the reaction time to 3 hours allowed the isolation of desired product **40**, however, NMR analysis showed that deborylation of the isolated product occurred on storage overnight, leaving only compound **41**.



Scheme 1.27 Cleavage of sulfinyl group followed by deborylation

Using the methodologies developed thus far, it is possible to synthesise protected boronocysteine; a molecule that has not been previously reported. Next, the protected HCl salt **40** needed to be coupled to another amino acid, which could then be

incorporated into a peptide (Scheme 1.28). Owing to the observed instability of **40**, sulfinamide **39** was treated with 10 equivalents of HCl for 3 hours and then the salt **40** was used immediately in the coupling reactions that are described below.



Scheme 1.28 Envisaged coupling of HCl salt **40** with an amino acid and subsequent elongation to form a peptide

1.3.2.2.1 Coupling of α-amino boronate

Whilst there are a handful of papers in which α-amino boronic esters have been coupled to amino acids or short peptides,[71–73] it is important to note that all previously reported strategies have used Boc protected amino acids. Whilst it would be desirable to use Fmoc protected amino acids, initial attempts were conducted using amino acids with Boc protecting groups.

After observing the decomposition of HCl salt **40**, there was concern that the same degradation would be observed during the coupling of the HCl salt to other compounds. The borylated and deborylated compounds were easily distinguishable by ^{1}H NMR, as deborylated compounds have 2 × 2H triplets in the region of 2.5-3.5 ppm (Figure 16a), whereas pinacol boron esters had 3 × 1H peaks in the same region (Figure 16b). Observation of these protons was used to indicate if deborylation had occurred during the various coupling strategies.

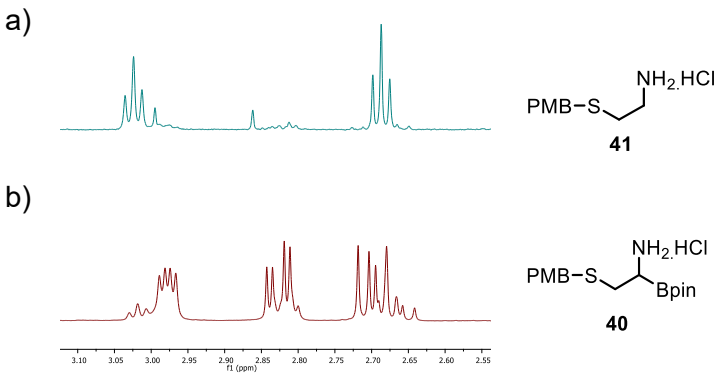
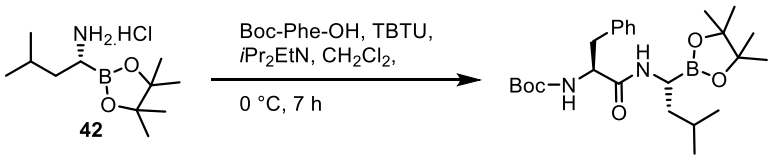


Figure 16 Comparison of ^{1}H NMR of a) deborylated HCl salt (**41**) and b) HCl salt with pinacol boronic ester intact (**40**)

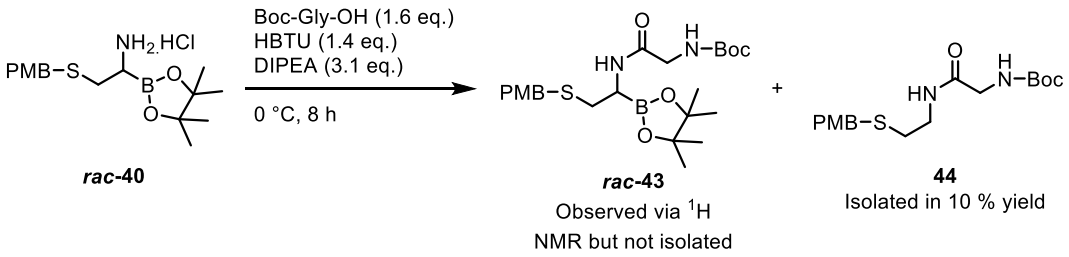
Uronium salts

Beenen *et al.*[66] used the protocol patented by Millennium Pharmaceuticals[74] to couple boronic ester HCl salt **42** to Boc-phenylalanine using TBTU (Scheme 1.29).



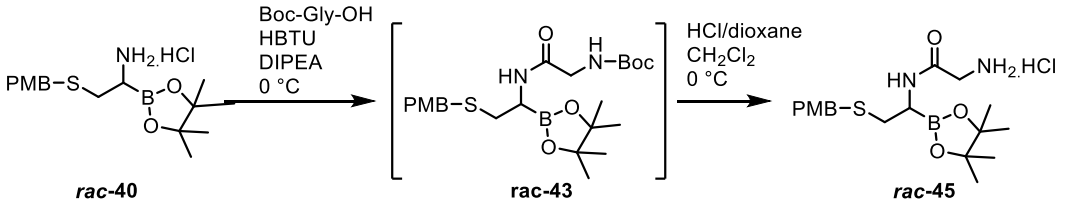
Scheme 1.29 Coupling of amine hydrochloride with Boc-Phe reported by Beenen *et al.*[66]

Based on this, HBTU was used during an attempt to couple boronocysteine and Boc-glycine at 0 °C (Scheme 1.30). This strategy resulted in some borylated product **43** and some deborylated product **44**, in an approximately 1:1 ratio, based on the crude ^{1}H NMR spectrum. Column chromatography was used to separate the two compounds, however, only the deborylated product **44** was isolated in 10% yield. Deborylated HCl salt **41** was not observed.



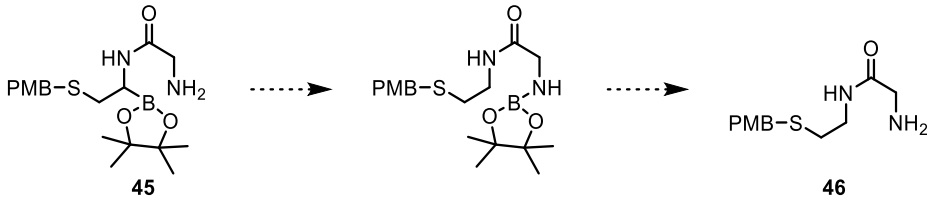
Scheme 1.30 Attempted coupling of **40** with Boc-Gly-OH using HBTU and DIPEA

In an attempt to overcome this purification issue, the reaction was repeated, followed by HCl cleavage of the Boc protecting group of the crude compound (Scheme 1.31).



Scheme 1.31 Attempted coupling of HCl salt **40** with Boc-Gly-OH followed by immediate deprotection of Boc group

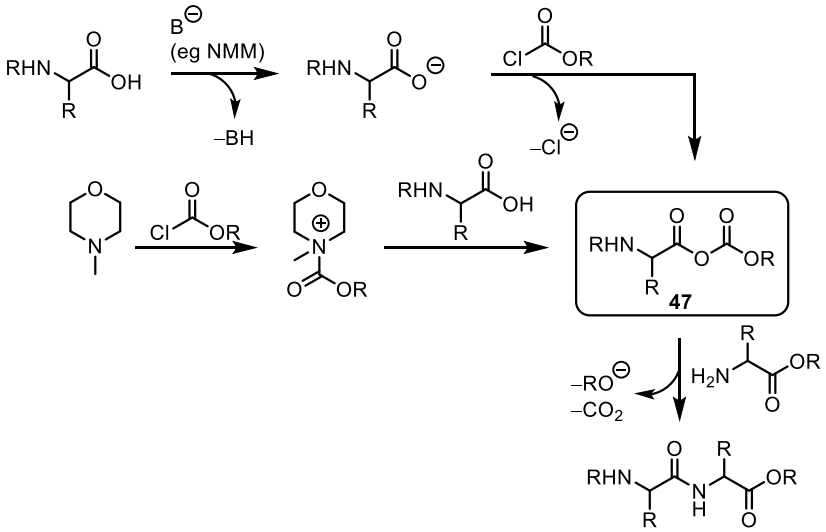
Unfortunately, this didn't aid purification and the two products could not be separated. It is possible that a 1,6 shift of **45**, similar to the 1,3 rearrangement discussed earlier,[75] could take place, causing the desired product to undergo a rearrangement to the deborylated product **46** (Scheme 1.32). Due to these issues, other methods were explored.



Scheme 1.32 Potential rearrangement of boronic ester **45** with deprotected amine

Chloroformates

Chloroformates have been widely used in peptide coupling reactions.[76–78] Initially, the chloroformate forms a mixed carbonic anhydride **47**, with the *N*-protected amino acid (Scheme 1.33). *N*-Methyl morpholine (NMM) is normally the base of choice, used both to deprotonate the amino acid and, as evidence suggests, as a participant in the reaction.[4] Isobutyl chloroformate (IBCF) is the chloroformate mostly used in peptide synthesis, as the bulky *iso*-butyl group reduces the occurrence of side reactions.[77]

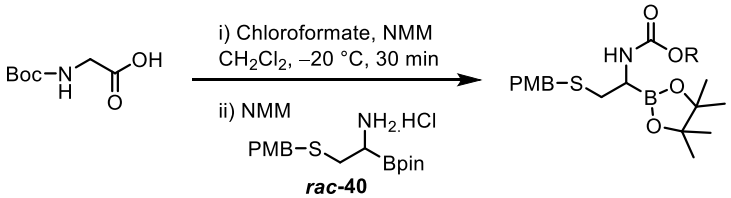


Scheme 1.33 Peptide coupling using chloroformates via formation of mixed carbonic anhydride

There are two examples in the literature where α-amino boronic esters have been coupled with amino acids using chloroformates. In both, the initial activation step has been carried out at −20 °C for either 5 minutes[79] or 30 minutes[80] and both used IBCF.

During this work, both IBCF and isopropenyl chloroformate (IPCF) were used. Whilst IBCF has been used previously, it was envisaged that the volatile by-products (acetone and carbon dioxide) formed using IPCF would aid product purification.

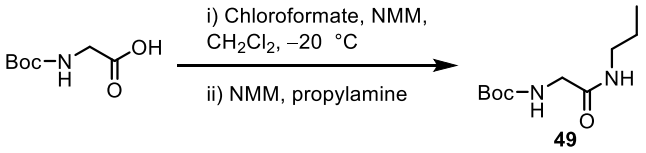
Attempts began on coupling HCl salt **40** to Boc-Gly-OH with both IBCF and IPCF. Initial activation of Boc-Gly-OH took place at −20 °C for 30 minutes, before addition of HCl salt **40** and overnight stirring (Scheme 1.34). However, with both IBCF and IPCF, the product formed was the respective carbamate **48**, indicating that 30 minutes was not sufficient to form the activated mixed anhydride, and instead the nucleophile reacted directly with the chloroformate.



Chloroformate	R	Yield	Product
IBCF		Not purified	***rac*-48a**
IPCF		77%	***rac*-48b**

Scheme 1.34 Initial attempts at coupling **40** with Boc-Gly-OH using IBCF or IPCF

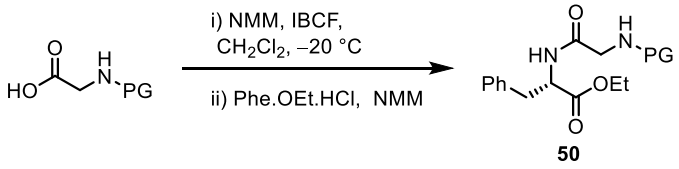
Therefore, the activation step was monitored by thin layer chromatography (TLC) using propylamine as the nucleophile. Based on this, activation using IPCF took 3 hours, whereas IBCF required 5 hours (Scheme 1.35). However, the reaction with IPCF gave product **49** in 35% yield compared with 86% yield with IBCF. Based on this, further coupling reactions were only done with IBCF.



Chloroformate	Time	Yield
IPCF	3 h	35%
IBCF	5 h	86%

Scheme 1.35 Coupling of Boc-Gly-OH with propylamine to determine required activation time

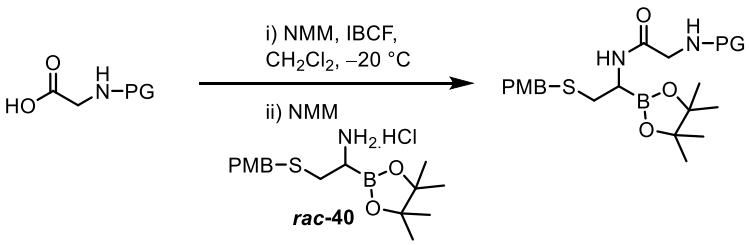
Armed with the required activation time for Boc-Gly-OH, it remained to be seen if the reaction would work with a nucleophile with more resemblance to the HCl salt that would be used. As a substitute, *L*-phenylalanine ethyl ester hydrochloride (Phe.OEt-HCl) was used, which successfully gave compound **50a** in 70% yield (Scheme 1.36). It would be preferable to use Fmoc-Glycine (Fmoc-Gly-OH). To see how general the use of IBCF was, the same reaction was repeated using Fmoc-Gly-OH. Gratifyingly, the reaction with Phe.OEt.HCl proceeded in even better yield than the Boc alternative, giving the Fmoc protected product **50b** in 90% yield (Scheme 1.36).



Protecting Group (PG)	Yield	Product
Boc	70%	**50a**
Fmoc	90%	**50b**

Scheme 1.36 Coupling of *N*-protected glycine with Phe.OEt.HCl with IBCF

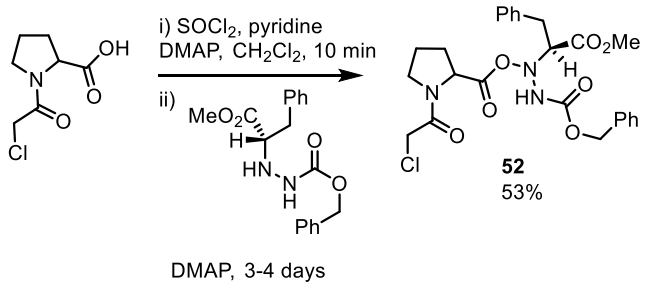
Encouraged by these results, it was decided to try using the protected boronocysteine HCl salt **40** with both Boc-Gly-OH and Fmoc-Gly-OH. The reaction with Boc-Gly-OH gave a promising yield of 89%, however, the reaction using Fmoc-Gly-OH did not proceed (Scheme 1.37).



Protecting Group (PG)	Yield	Product
Boc	89%	***rac*-51**
Fmoc	NR	N/A

Scheme 1.37 Coupling of HCl salt **40** with *N*-protected glycine

Whilst this route had looked promising, multiple attempts to make **51** showed that it was unreliable and so another strategy was tried. In an attempt to couple a hindered nucleophile to a proline derivative, Lenman *et al.* had tried a variety of coupling methods, including IBCF and uronium salts, all of which had failed.[81] They did, however, achieve success by proceeding via an acid chloride, generating **52** in 53% yield (Scheme 1.38).



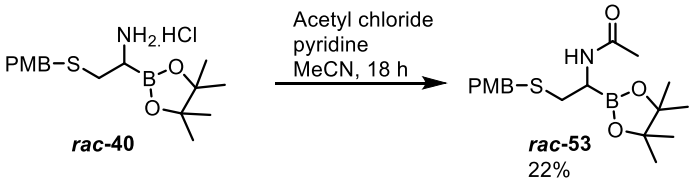
Scheme 1.38 Previously reported coupling of hindered nucleophile and an acid chloride[81]

Based on this, it was decided to attempt to perform our coupling reactions using acid chlorides rather than chloroformates.

Acid chlorides

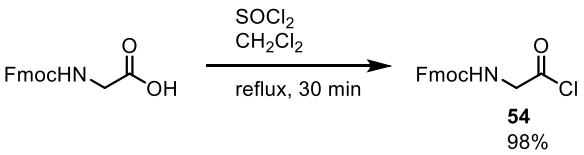
The use of acid chlorides in peptide coupling was first reported in 1903.[82] Whilst this method has gained a bad reputation due to the possibility of hydrolysis, potential side reactions or the racemisation of amino acids due to the release of HCl, the high reactivity of acid chlorides makes them an attractive possibility to overcome coupling issues.

Initially, amine hydrochloride **40** was coupled with acetyl chloride in the presence of pyridine to check the viability of this approach (Scheme 1.39). Gratifyingly, the desired α-amido boronic ester **53** was obtained, albeit in a poor yield of 22%.



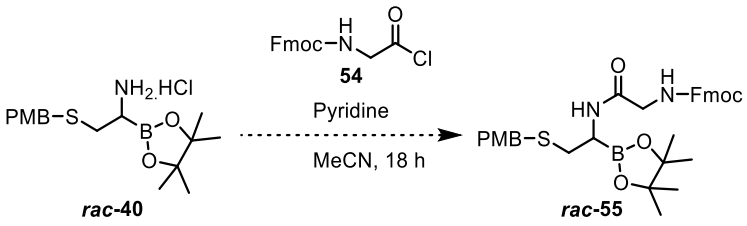
Scheme 1.39 Effective coupling of HCl salt **40** and acetyl chloride

With this somewhat encouraging result, endeavours began on coupling HCl salt **40** to an *N*-protected glycine residue. Fmoc-Gly-Cl **54** was synthesised in 98% yield by treating Fmoc-Gly-OH with $SOCl_2$ (Scheme 1.40).



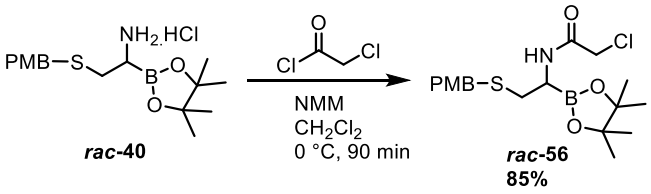
Scheme 1.40 Synthesis of Fmoc-Gly-Cl

Treatment of HCl salt **40** with pyridine and Fmoc-Gly-Cl resulted in a complex crude NMR spectrum, however, it was possible to distinguish three separate protons around 2.5-3.5 ppm, implying that the boronic ester was still intact. Attempts to purify this compound by column chromatography resulted in a complex mixture of compounds that could not be sufficiently separated. Compound **55** was potentially isolated in a crude form, though attempts to repeat the reaction to allow the isolation of a pure sample proved to be unreliable and full characterisation was not possible (Scheme 1.41).



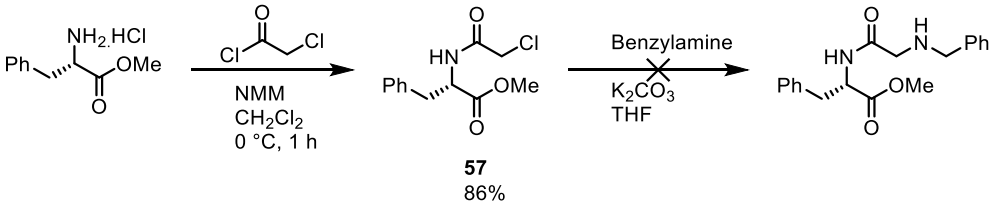
Scheme 1.41 Coupling of Fmoc-Gly-Cl and HCl salt **40** with pyridine in acetonitrile

It was considered if another, although slightly longer, route would be more successful. The reaction of HCl salt **40** with chloroacetyl chloride gave desired amide product **56** in 85% yield (Scheme 1.42).



Scheme 1.42 Coupling of HCl salt **40** with chloroacetyl chloride

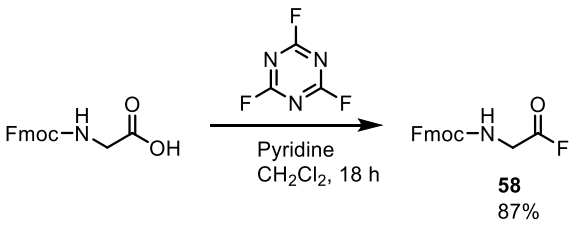
To optimise this procedure, the analogous reaction using phenylalanine methyl ester hydrochloride was attempted first (Scheme 1.43). Initial coupling of the hydrochloride salt of Phe.OMe with chloroacetyl chloride gave the desired product **57** in excellent yield, however, attempts to couple this with benzylamine were unsuccessful. As this route would add an extra step in synthesising desired Fmoc-protected coupled product, it was not explored further.



Scheme 1.43 Coupling of phenylalanine salt with chloroacetyl chloride, followed by unsuccessful displacement attempt

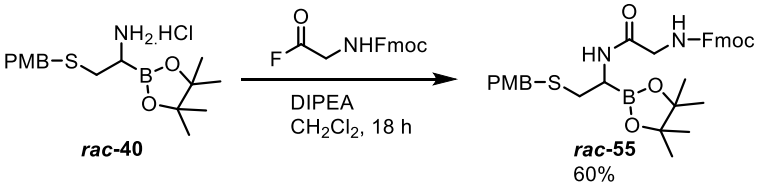
Acid fluorides

Following the capricious result using Fmoc-Gly-Cl, an analogous reaction with Fmoc-Gly-F was investigated. Amino acid fluorides have increased stability to hydrolysis and therefore do not need to be used in high excess.[83] It was hoped that this would aid purification of the desired product. Fmoc-Gly-F **58** was synthesised in 87% yield from Fmoc-Gly-OH and cyanuric fluoride (Scheme 1.44).



Scheme 1.44 Synthesis of Fmoc-Gly-F

Addition of this to HCl salt **40** (Scheme 1.45) gave desired product **55** in 60% yield on a 25 µmol scale. All that remained was to increase the scale of this reaction, however, attempts to scale up by a factor of 3 were unsuccessful. Disappointingly, numerous attempts to synthesise **55** on the same scale were also unsuccessful. During these attempts, analysis of the crude NMR spectra revealed that only a small amount of **55** had formed, and attempts to purify it led to a loss of material.

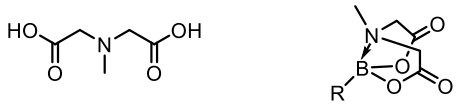


Scheme 1.45 Coupling of HCl salt **40** with Fmoc-Gly-F **58**

It was considered that the inconsistent results may be due to the instability of HCl salt **40** and coupled product **55**. Instability problems could be prevented by using the *N*-methyliminodiacetic acid (MIDA) protecting group developed by Burke.[84]

1.3.2.2.2 MIDA Protected boronate

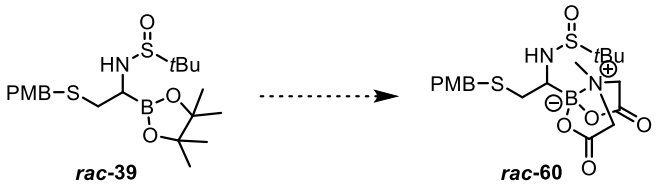
MIDA boronates (**59**) were synthesised in 1986 by Mancilla and Contreras, via the reaction of boronic acids and *N*-methyliminodiacetic acid (MIDA, Figure 17).[85] MIDA boronates have since been popularised by the Burke group and are known to tolerate oxidations,[86] sodium borohydride reductions[87] and triflic acid,[86] and they are also reported to be stable on exposure to air.[88] They are also stable at temperatures over 120 °C.[89]



N-Methyliminodiacetic acid **59**

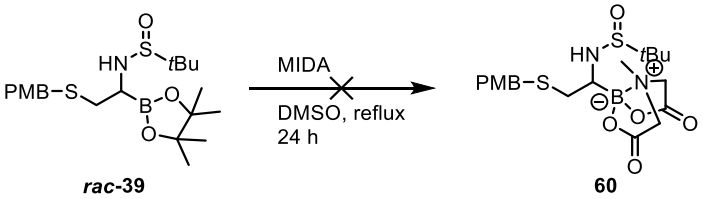
Figure 17 Structure of *N*-methyliminodiacetic acid (MIDA) and a MIDA boronate

It was envisaged that the additional stability of a MIDA protected boronate would allow efficient and reproducible coupling to an amino acid derivative. The most attractive route to MIDA protected **60** was directly from pinacol protected sulfinamide **39** that had already been synthesised (Scheme 1.46).



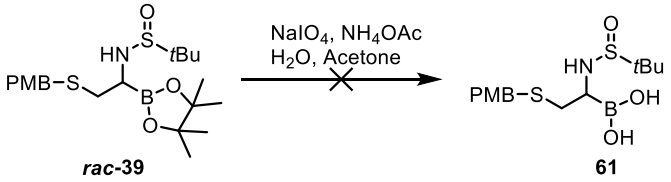
Scheme 1.46 Envisaged transformation of pinacol protected **39** to MIDA protected **60**

Initial attempts began on exchanging the pinacol protecting group for MIDA in one step, as demonstrated by Woerly *et al.*[90] However, after refluxing **39** with MIDA for 24 hours, solely starting material remained (Scheme 1.47).



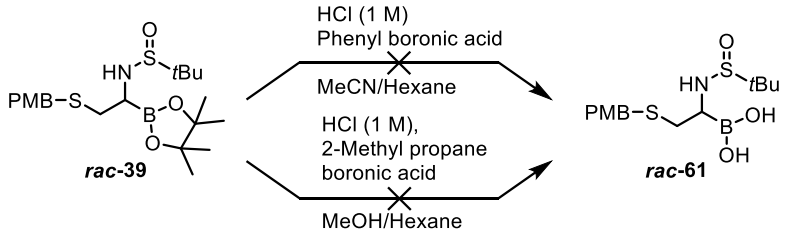
Scheme 1.47 Attempted transformation of pinacol protected **39**

Following this, it was decided that a two-step approach via the boronic acid may be necessary to arrive at MIDA protected **60**, and so attempts began on the deprotection of pinacol protected **39**. Suzuki *et al.* reported oxidative hydrolysis of pinacol boronic esters using NH_4OAc and $NaIO_4$,[91] though when this strategy was applied to **39**, a complex mixture of products was obtained, possibly due to sulfur oxidation (Scheme 1.48).



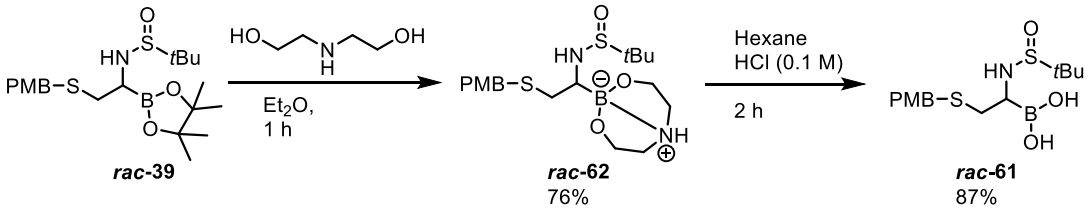
Scheme 1.48 Attempted deprotection of *tert*-butyl sulfinimide boronic ester **39** using $NaIO_4$

Both Eidam *et al.*[92] and Touchet *et al.*[93] achieved the deprotection of a pinacol protected boronate via transesterification with a sacrificial boronic acid in a biphasic mixture. However, in our hands, the use of either phenyl boronic acid or 2-methylpropylboronic acid were unsuccessful, with a complex mixture of products formed in both cases (Scheme 1.49).



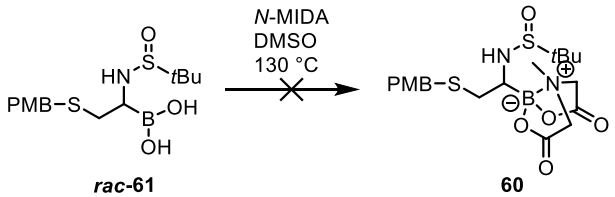
Scheme 1.49 Unsuccessful deprotection of *tert*-butyl sulfinimide boronic ester **39**

Another route, though containing an extra step, had been reported by Sun *et al.,* who have shown that pinacol boronic esters can undergo transesterification with diethanolamine to form tetrahedral boron-diethanolamine adducts.[94] Gratifyingly, this route was successful with **39** and gave **62** in 76% yield. Treating this with HCl in a biphasic mixture of ether and hexane gave boronic acid **61** in 87% yield. Given the high yields of these two reactions, the inclusion of an extra step was not viewed as an issue.



Scheme 1.50 Transformation of boronic ester **39** to boronic acid **61** via diethanolamine adduct **62**

Next began the efforts to protect the free boronic acid with MIDA (Scheme 1.51). Refluxing boronic acid **61** with MIDA in DMSO unfortunately gave a complex mixture of products that could not be separated, but are possibly a range of degradation products.

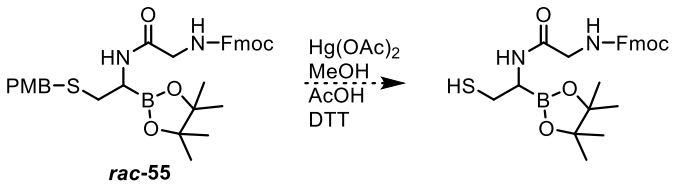


Scheme 1.51 Unsuccessful formation of MIDA boronate **60** from boronic acid **61**

To be able to use boronocysteine to investigate thioester formation via *N* → *S* acyl shift, it remained to be seen if the thiol protecting group could be removed to give a free thiol. This was attempted with the sample of **55** that was available.

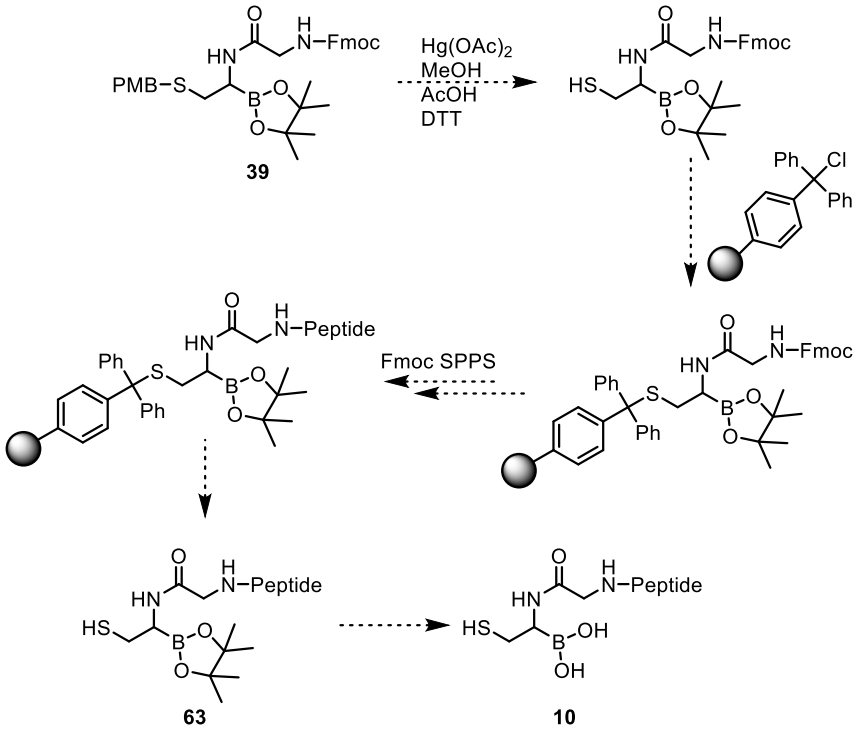
1.3.2.2.3 PMB Deprotection

It was hoped that the PMB protecting group could be removed using mild methods. To that end, protected boronoCys-Gly **55** was treated with 10% acetic acid in the presence of $Hg(OAc)_2$ and dithiothreitol (DTT) (Scheme 1.52).[95] NMR analysis showed that multiple reactions had taken place after 2 h, however, it was not possible to purify the crude mixture to identify the different species.



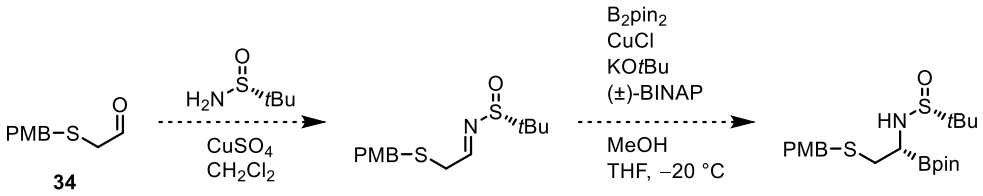
Scheme 1.52 Attempted removal of PMB group

At this point, it was questioned if the generation of boronocysteine was possible. If reliable conditions to remove the PMB protecting group could be found, pre-coupled boronocysteine would still need to be attached to a trityl chloride resin, as used in Section 1.3.1. Following this, it was envisaged that SPPS could be used to generate the model peptide, which could be used in *N* → *S* acyl shift as the boronic ester **63**, or potentially as the boronic acid **10**.



Scheme 1.53 Envisaged synthesis of *C*-terminal boronic acid peptide

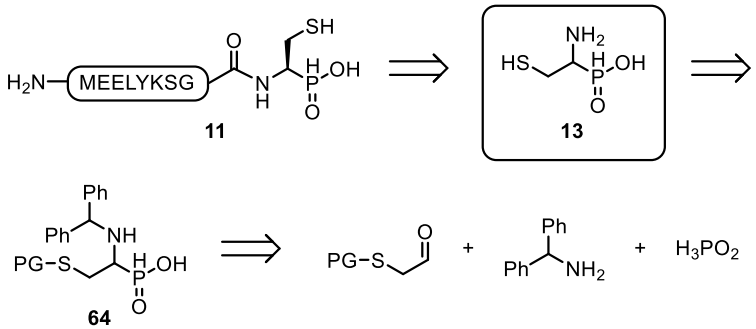
With the lack of success and reproducibility of coupling HCl salt to glycine, synthesising MIDA boronate **60**, and the deprotection of the thiol protecting group, it was considered that this was due to degradation (mainly deborylation). As stated previously, Matteson's method was unsuccessful with thiol containing side chains, and so it is postulated that this is due to the problematic stability of the products, which have been observed during this work. Furthermore, to form model peptide **10**, the synthesis would need repeating to generate the enantiopure form of boronocysteine using (*R*)-*tert*-butyl sulfinamide (Scheme 1.54). This would then need to be incorporated into a peptide and subjected to the thioester formation conditions. Due to this, it was decided that efforts to synthesise model peptide **10** would be halted. Nevertheless, this is the first ever reported synthesis of racemic protected boronocysteine.



Scheme 1.54 Potential synthesis of enantiopure boronocysteine precursor

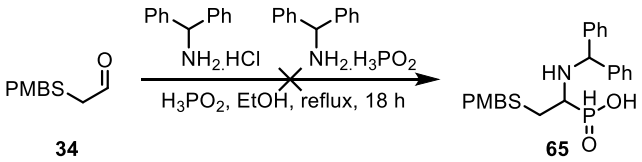
1.3.3 Synthesis of model peptide as a *C*-terminal phosphinate

Another potential *C*-terminal derivative is phosphinic acid **11** (Scheme 1.55). Phosphinic acid **11** is monoacidic, as is the carboxylic acid peptide, and so could reveal if this is important during *N* → *S* acyl shift. This would require the synthesis of phosphinocysteine **13** from diphenylmethylaminoalkylphosphonous acid **64**, which could be synthesised from an aldehyde, diphenylmethylamine and hypophosphorous acid (Scheme 1.55).



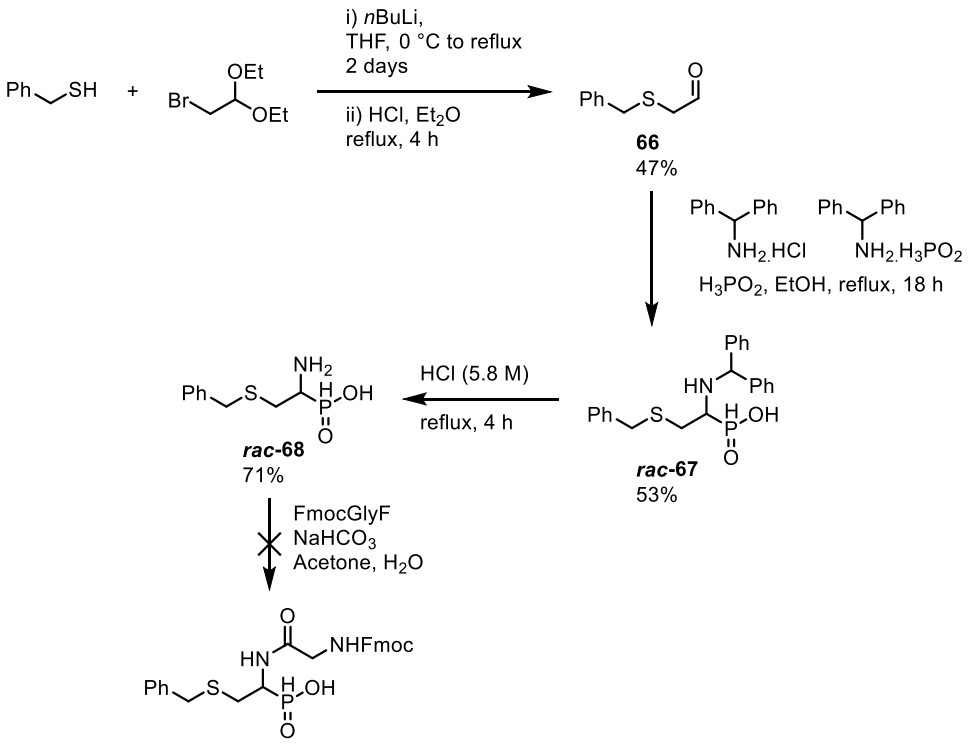
Scheme 1.55 Proposed synthetic route to *C*-terminal phosphinate model peptide

Initially, the synthesis of phosphinocysteine began from aldehyde **34**, that had already been synthesised in this project (Section 1.3). This was subjected to the conditions reported by Baylis *et al.*[96] in the attempt to generate phosphinic acid **65** (Scheme 1.56). Unfortunately, this was unsuccessful and only starting material remained.



Scheme 1.56 Attempted synthetic route towards phosphinocysteine

This route was unsuccessful for the synthesis of phosphinocysteine with a PMB protecting group, however, Baylis *et al.* have reported the synthesis of phosphinocysteine with a benzyl sulfur protecting group. To this end, nucleophilic substitution of bromodiethoxyethane and the subsequent deprotection to give aldehyde **66** proceeded in 47% yield over two steps (Scheme 1.57). Synthesis of phosphinic acid **67** proceeded in a moderate yield of 53%. Refluxing **67** in HCl for four hours gave α-amino **68** in 71% yield. However, attempts to couple **68** to FmocGlyF were unsuccessful. Due to the lack of time, this route to generate phosphinocysteine was not further explored.

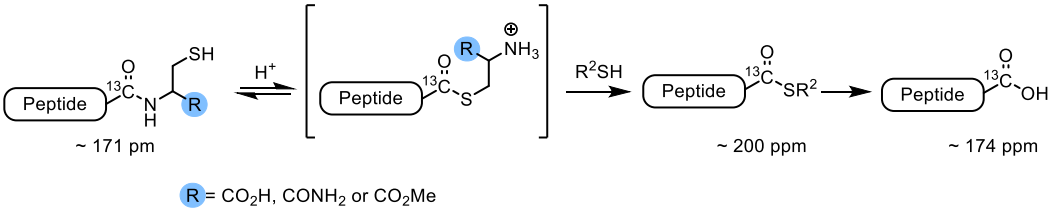


Scheme 1.57 Attempted synthetic route towards phosphinocysteine

1.4 Study of peptides in thioester formation via *N* → *S* acyl shift

1.4.1 Effect of peptide *C*-terminal functionality

To increase validity of the results, previously reported experiments were repeated (Scheme 1.59).



Scheme 1.58 Thioester formation from a model peptide with varying *C*-terminal functionality

The rate of thioester formation from the carboxylic acid peptide **7** [H-MEELYKSGC-OH] and carboxamide peptide **8** [H-MEELYKSGC-NH_2] in the presence of 2-mercaptoethanesulfonate (MESNa, 10% w/v), tris(2-carboxyethyl)phosphine hydrochloride (TCEP.HCl) (0.5% w/v) and sodium phosphate buffer (0.1 M, pH 5.8) at 60 ºC was monitored by ^{13}C NMR over 24 hours (Figure 18). The formation of the hydrolysed product can be observed after 48 hours.

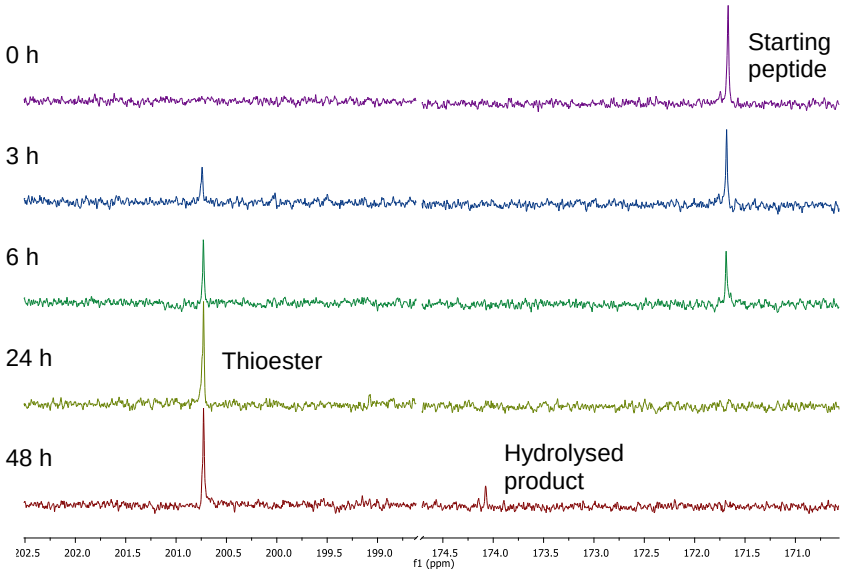


Figure 18 ^{13}C NMR analysis of Gly $^{13}C_1$ labelled peptide **7** [H-MEELYKSGC-OH] with a *C*-terminal carboxylic acid undergoing thioester formation

The resultant rates were found to be in excellent agreement with previous data, (Figure 19).[33] The rate of thioester formation was also monitored for the carboxamide

and methyl ester. The results can be seen in Figure 19.

Whilst the thioester formation rate of the carboxylic acid is clearly faster than for the methyl ester or carboxamide, the difference between methyl ester and carboxamide is not so apparent. It is only after 48 hours that there appears to be a significant difference between the amount of thioester formed in each case.

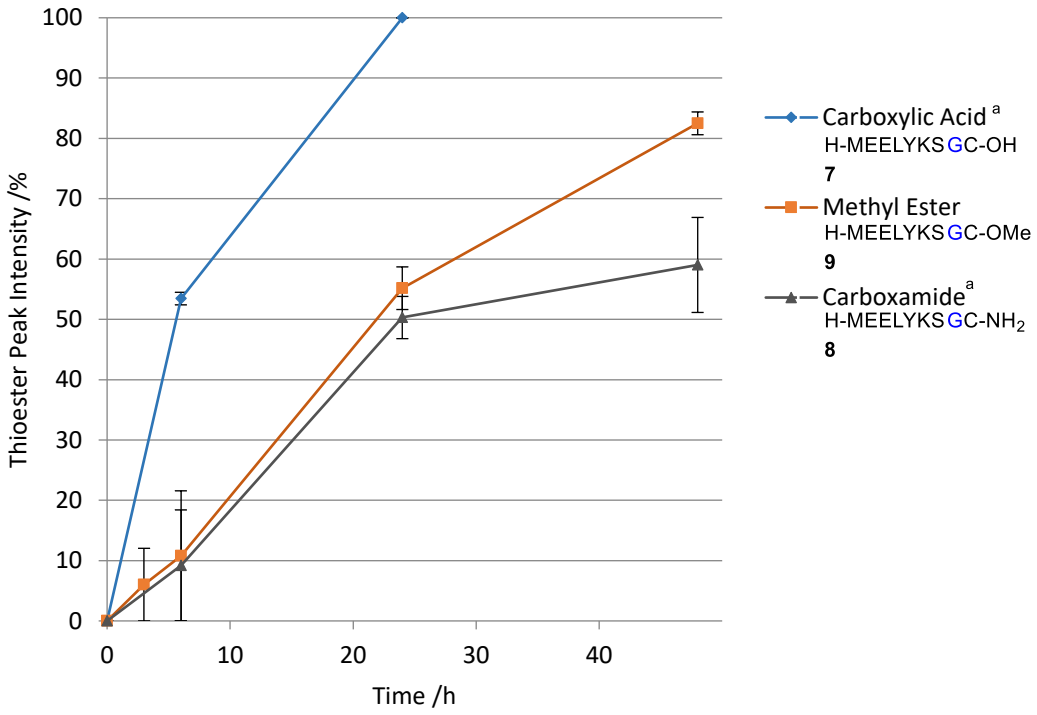


Figure 19 Rate of thioester formation of model peptide prepared as *C*-terminal carboxylic acid **7** [H-MEELYKSGC-OH], carboxamide **8** [H-MEELYKSGC-NH_2] or methyl ester **9** [H-MEELYKSGC-OMe] on exposure to MESNa (10% w/v), TCEP.HCl (0.5% w/v) in 0.1 M sodium phosphate buffer (pH 5.8). The reaction mixture was split into aliquots which were analysed independently for each time point. [a]Uses some data reported by Anna Adams[33]

It has previously been suggested that the difference in rate of thioester formation between the carboxylic acid and the carboxamide terminated model peptide could be due to the pKa of the amine group and the subsequent effect this has on the equilibrium between *N*- and *S*-peptide (Figure 20).[34] Reported pKa values of the carboxylic acid, carboxamide and methyl ester of glycine are shown in Figure 20. Assuming there is some correlation between the glycine series and cysteine, it would be expected that the pKa of the amino group would decrease from the carboxylic acid terminated peptide to the carboxamide, with the methyl ester amino group having the lowest pKa. This would be expected to be reflected in the differences in thioester formation between the three different peptides, which does not appear to be the case.

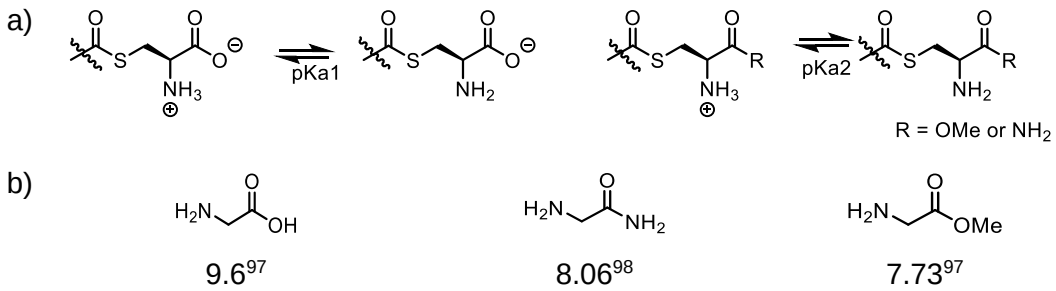


Figure 20 a) Increased pKa of amino group could favour *S*-peptide formation for carboxylic acid peptide derivative if pKa1>pKa2, b) Reported pKa values of glycine derivatives

A major difference between the carboxylic acid and the methyl ester or carboxamide is the ability to form zwitterions. The formation of carboxylate anion and ammonium cation is energetically favourable in solution, as it increases the sites for water-solute interactions.[99] This could encourage the formation of the *S*-peptide, and therefore increase the rate of the reaction.

Based on these results, the best substrate that was used was the carboxylic acid terminated peptide **7**. Using this starting material, the reaction is much quicker, limiting the amount of hydrolysed product. It must be noted that these model peptides are soluble in the reaction mixture. Many peptide starting materials are insoluble, and in these cases, chaotropic agents are required to solubilise the starting peptide. It is generally accepted that the need for chaotropic agents reduces the rate of the reaction, however, this has not yet been explored in depth.

1.4.2 Effect of chaotropic agents

A widely-encountered issue with thioester forming reactions is the decreased rate in the presence of guanidine hydrochloride (GuHCl). GuHCl, typically 6 M, is added to solubilise peptides. Since a significant quantity of the model peptide was to hand, the relationship between GuHCl concentration and the rate of thioester formation was explored. The rate was measured in the presence of 3, 4, 5 and 6 M GuHCl for carboxylic acid peptide **7**, and in the presence of 6 M GuHCl for methyl ester peptide **9** (Figure 21). Whilst 3 M GuHCl appears to have little impact on the rate of thioester formation, as the concentration increases to 6 M, the rate of thioester formation decreases, failing to reach 100% conversion after 48 hours. It is interesting to note that 6 M GuHCl slows both the carboxylic acid and the methyl ester to a similar degree. After 24 hours, the carboxylic acid had reached 56% conversion rather than 100% in the absence of GuHCl, and after 48 hours for the methyl ester the GuHCl

reaction had formed 50% thioester, compared with 78% without GuHCl. The data shows that as the concentration of GuHCl is increased beyond 4 M, the rate of thioester formation decreases.

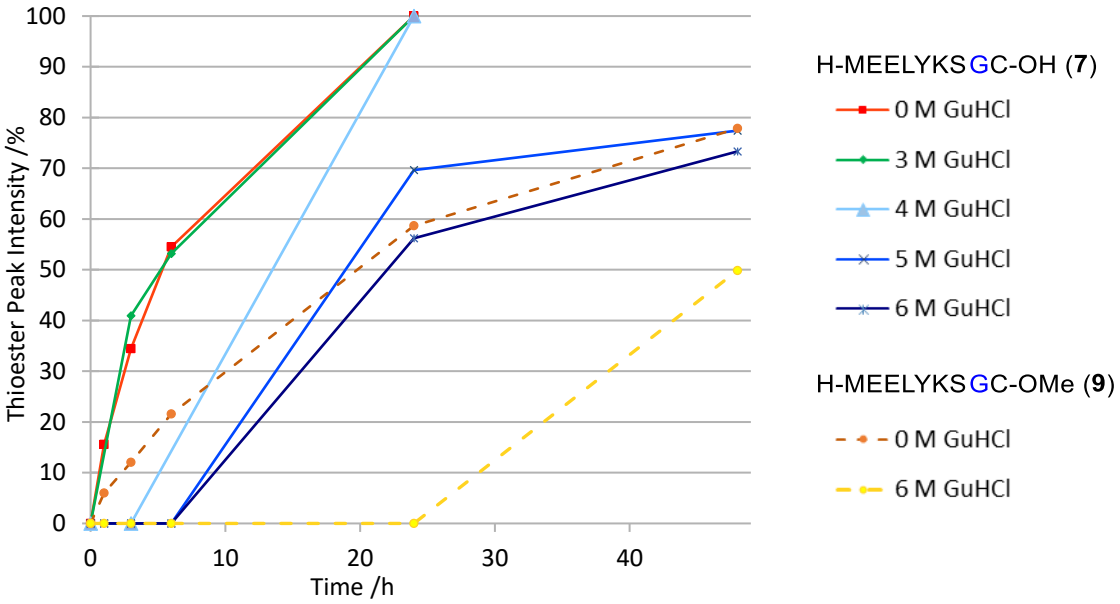


Figure 21 Rate of thioester formation of model peptide prepares as *C*-terminal carboxylic acid **7** [H-MEELYKSGC-OH] (solid line), or methyl ester **9** [H-MEELYKSGC-OMe] (dashed line) on exposure to MESNa (10% w/v), TCEP (0.5% w/v) in 0.1 M sodium phosphate buffer (pH 5.8). The reaction mixture was split into aliquots which were analysed independently at each time point

It was considered that these decreased rates of thioester formation were related to the amount of H_2O present in GuHCl. The concentrations tested required a large amount of GuHCl, therefore, the volume of H_2O present is significantly affected. The volume of H_2O in each 0.6 mL aliquot is shown in Table 2. As there is a large difference between the volume of H_2O in each aliquot, it was considered that this might be responsible for the decreased rate of thioester formation, and not in fact the increasing concentration of GuHCl. To test this, the thioester formation reactions were repeated using urea, sucrose and PEG 20,000 in solutions with the same H_2O content as 6 M GuHCl (Figure 22).

GuHCl concentration /M	Volume of H_2O per sample /µL	% H_2O
3	421	70
4	364	61
5	320	53
6	316	53

Table 2 Volume of H_2O present in varying GuHCl concentrations. Calculated for each 0.6 mL aliquot

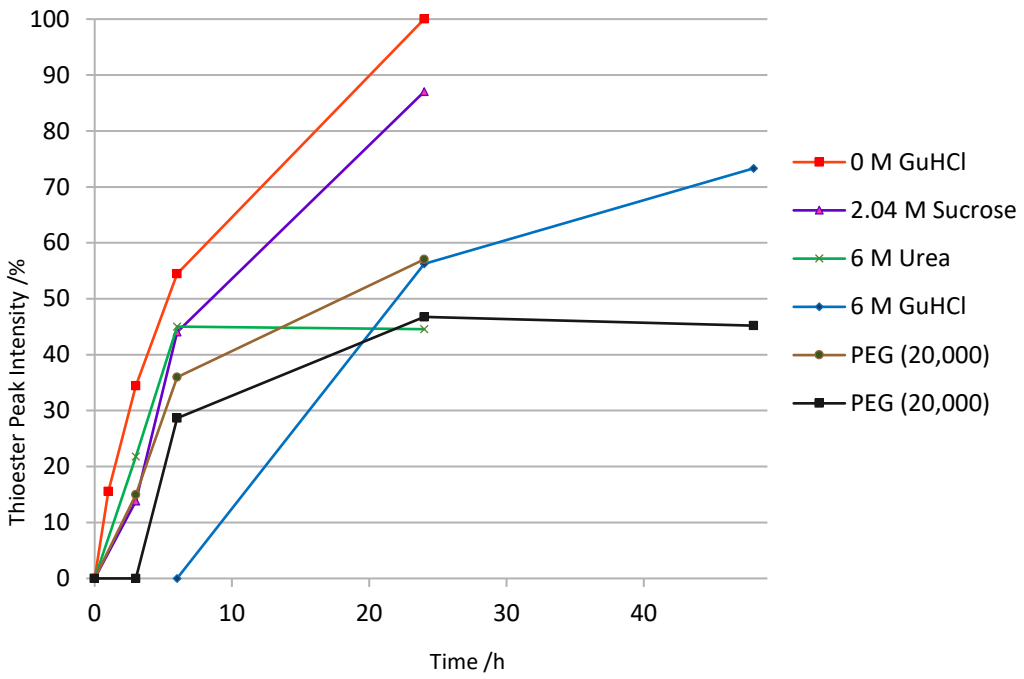
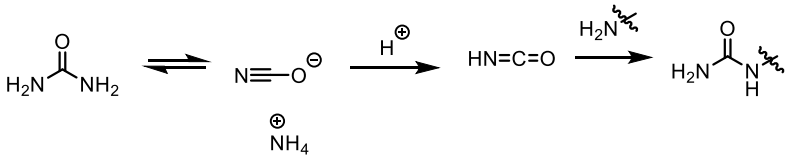


Figure 22 Rate of thioester formation of model peptide prepared as *C*-terminal carboxylic acid **7** [H-MEELYKSGC-OH] on exposure to MESNa (10% w/v), TCEP.HCl (0.5% w/v) in 0.1 M sodium phosphate buffer (pH 5.8) and GuHCl, PEG, urea or sucrose. The reaction mixture was split into aliquots which were analysed independently at each time point

Previous work exploring the rate of thioester formation has taken the first time point at 6 hours, due to the slow nature of the reaction. However, by taking time points at 3 hours it can be seen that the amount of thioester formed at this point varies greatly depending on the conditions. Over the first 6 hours, there appears to be good agreement with the urea and sucrose data, both of which have formed thioester after 3 hours and are similar with the control results in the presence of H_2O alone. The lag before the formation of the thioester product is apparent in the presence of PEG and GuHCl.

It was observed that between 6 and 24 hours, the relative amount of thioester present in the urea reaction decreased. LCMS analysis of the sample at 24 hours showed none of the expected masses, but instead showed that carbamylation of the starting material, thioester and hydrolysed product had taken place, indicated by mass increases by 43 Da (either once or twice). This is due to the formation of isocyanic acid which reacts with the lysine residue and the *N* terminus, as shown in Scheme 1.59.[100]



Scheme 1.59 Formation of isocyanic acid responsible for peptide carbamylation

It is also important to note that there are two sets of data for the experiments with PEG. The differences between the two are attributed to the viscous nature of the samples, making accurate dispensing of the peptide sample difficult.

The marked differences in thioester formation between the different agents implies that H_2O concentration is not the sole reason for the slower rate, and that the properties of sucrose, urea, PEG and GuHCl are likely to be culpable.

It is well known that both urea and GuHCl solubilise peptides. It has previously been reported that the mechanisms by which urea and guandinium act, however, are different.[101] Urea is proposed to form hydrogen bonds with NH and CO moieties present in amide bonds (Figure 23a), whereas guanidinium interacts via stacking interactions with itself and other planar groups.[101] This is supported by the cocrystal structure of diglycine with GuHCl in which guanidinium doesn't form hydrogen bonds to the peptide backbone, but does interact with the free carboxylic acid (Figure 23b).[102] It was also observed in 1970 that GuHCl has better solubilising effects in the presence of aromatic groups.[103] Reports can be found for the stabilisation of proteins by sucrose, which is attributed to the inhibition of oxidation and deamidation, though this is significant when storing a peptide for over 12 weeks,[104] thus unlikely to be a factor in our case.

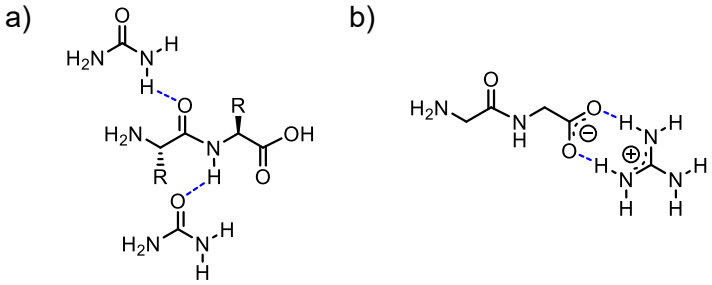


Figure 23 Previously reported interactions of a) urea[101] and b) guanidinium[102] with peptides

In molecular crowding experiments, PEG has been shown to disrupt hydrophobic interactions of proteins.[105] Molecular crowding studies have been conducted using PEG and the effect it has on DNA has been examined. During these studies, it was

found that PEG caused restructuring of the H_2O molecules hydrating DNA.[106] A similar effect could be seen here, as the most marked differences in thioester rate are seen in the presence of agents that are known to disrupt hydrophobic interactions.

Another potential explanation for the reduced rate of thioester formation in the presence of 6 M GuHCl could be due to the formation of a hydrogen bonded sheet with MESNa (Figure 24), which are known to form between the guanidinium protons and the sulfonate oxygen atoms.[107–109] It is possible that these networks form, effectively decreasing the amount of MESNa available, thereby causing a decrease in reaction rate. To explore this, the rate of thioester formation was observed, using a thiol that does not contain a sulfonate, both with and without 6 M GuHCl.

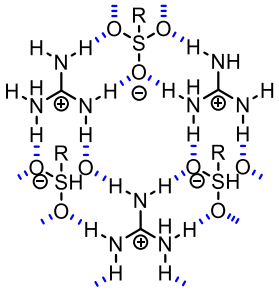
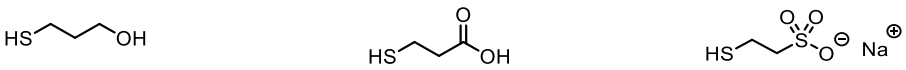


Figure 24: Guanidinium sulfonate sheet, with hydrogen bonds shown in blue

1.4.3 Effect of thiol

To test if the identity of the thiol influenced the rate of thioester formation, the reaction was conducted using mercaptopropanol and mercaptopropionic acid (Figure 25).

If hydrogen bonding between MESNa and GuHCl were responsible for the slower rate of thioester formation, it would be expected that the addition of 6 M GuHCl would have a smaller effect on the reaction with 3-mercaptopropionic acid and an even smaller effect on 3-mercaptopropanol.



3-Mercaptopropanol 3-Mercaptopropionic acid MESNa

Figure 25 The structures of 3-mercaptopropanol, 3-mercaptopropionic acid and MESNa

The reaction profile of all three thiols in the absence of GuHCl are similar (Figure 26). However, the presence of 6 M GuHCl has the most drastic effect on

mercaptopropanol, followed by mercaptopropionic acid and finally MESNa, which is the reverse of what would be expected if solely hydrogen bonding was responsible for the reduced rate.

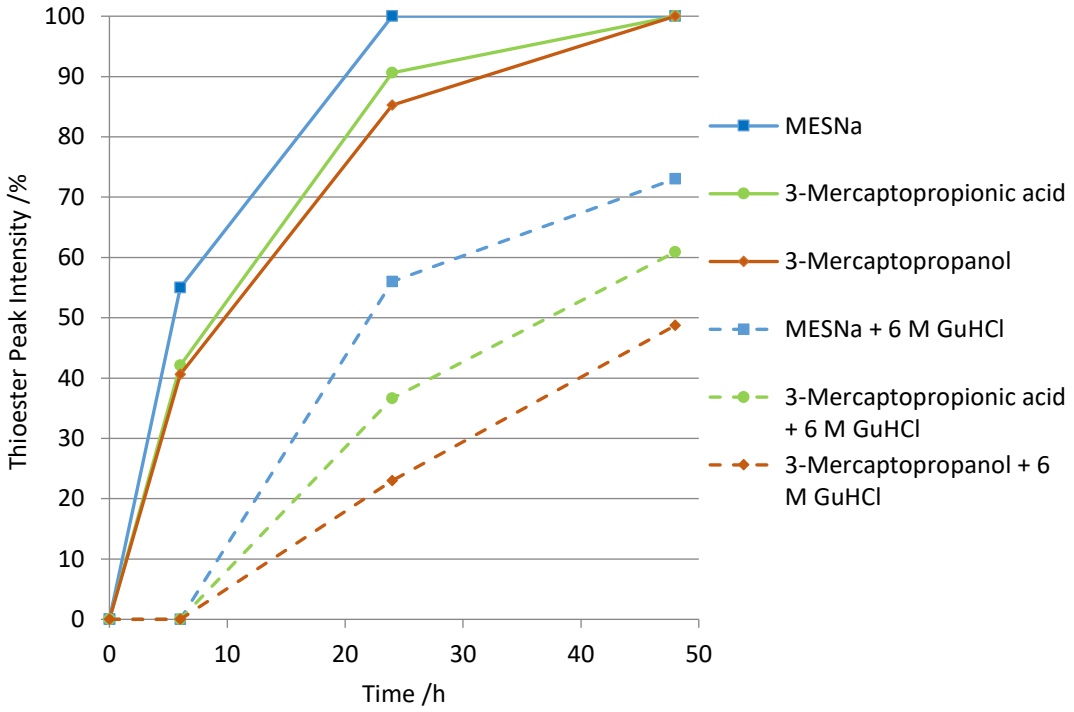


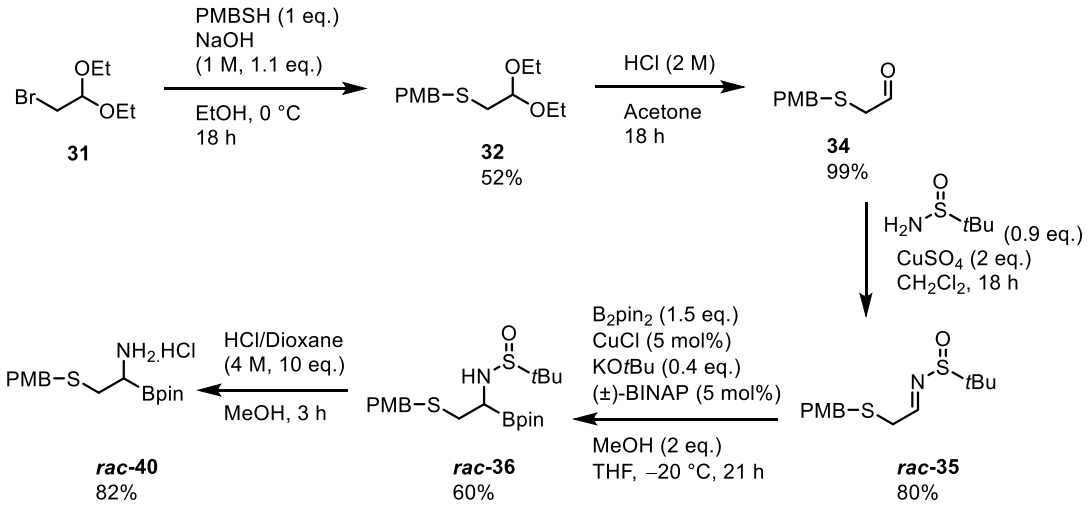
Figure 26 Rate of thioester formation of model peptide prepared as *C*-terminal carboxylic acid **7** [H-MEELYKSGC-OH] on exposure to thiol additive (10% w/v), TCEP.HCl (0.5% w/v) in 0.1 M sodium phosphate buffer (pH 5.8) without (solid line) and with (dashed line) 6 M GuHCl. The reaction mixture was split into aliquots which were analysed independently at each time point

The rate of thioester formation appears to be associated with the solubility of the thiol additive; the reaction is slowest for 3-mercaptopropanol, which is the least soluble, and fastest for MESNa, which is the most soluble under the reaction conditions. This effect is more pronounced in the presence of GuHCl. The rate may be slower due to the interaction of GuHCl with the peptide, effectively shielding the peptide from nucleophilic attack of the thiol. This shielding effect will further exacerbate the reduced rate of the less soluble thiols.

1.5 Conclusions & Future Work

1.5.1 Synthesis of boronocysteine

The first route to synthesise protected racemic boronocysteine has been developed (Scheme 1.60), although the synthetic utility of this was questioned due to the observed instability of the molecule, which could explain the lack of literature precedent for making similar compounds. In fact, this is the first synthesis of an α-aminoboronic acid with a heteroatom-containing side chain. Nevertheless, a protected boronocysteine can be synthesised, and with the current interest in boron chemistry, it's possible that a strategy to overcome the stability issues may be found. Methods could then be sought to deprotect the boronocysteine and couple it to another molecule. The reaction could then be developed to synthesise enantiopure boronocysteine.



Scheme 1.60 The first synthesis of protected boronocysteine

1.5.2 Rate of thioester formation

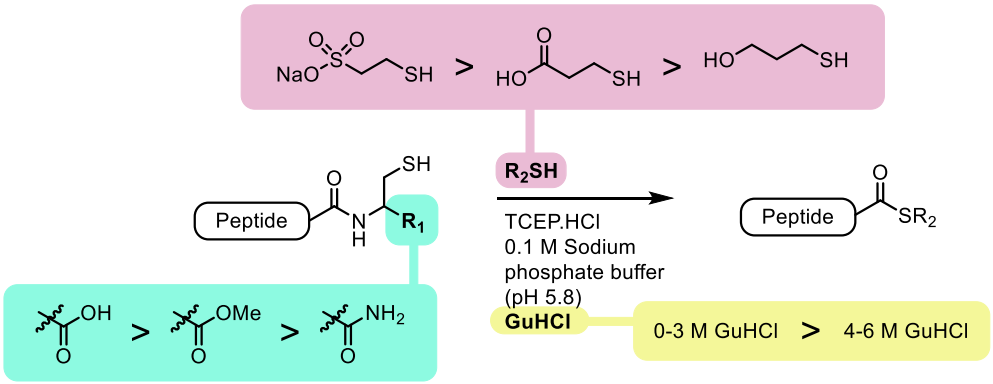
Factors that are important in thioester formation have been explored, namely the functionality of the *C*-terminus, the effect of varying GuHCl concentrations and the effect of different thiols. From these, it has been shown that a *C*-terminal carboxylic acid peptide undergoes thioester formation much faster than a *C*-terminal methyl ester or carboxamide peptide.

It is widely recognised that the rate of thioester formation is reduced when GuHCl is required to solubilise a peptide. However, during this work it has been shown that in the case of the model peptide, having a GuHCl concentration of less than 4 M has a

minimal effect on the rate of thioester formation. Being able to use a concentration below 4 M GuHCl allows the reaction to proceed quickly, hence limiting the hydrolysis of the thioester product which reduces the yield of the reaction.

Whilst exploring the effect of the thiol additive, it was observed that 6 M GuHCl had the most dramatic effect on mercaptopropanol and then mercaptopropionic acid. The effect of 6 M GuHCl was smallest when using MESNa.

Out of the conditions trialled, it has been shown that MESNa is the best reagent to use with a carboxylic acid terminated peptide, and that if GuHCl is required, it should be kept to below 4 M if possible.

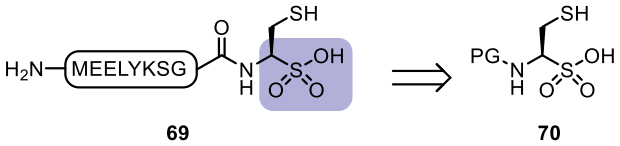


Scheme 1.61 Exploration of factors affecting the rate of thioester formation

There are other targets that could be synthesised to investigate *N* → *S* acyl shift, including phosphonic acid or sulfonic acid peptides. As it is hypothesised that the carboxylic acid terminated peptide is a superior starting material due to its ability to form a zwitterion, the investigation of monobasic sulfonic acid peptide or dibasic phosphonic acid peptide may reveal if this is important.

1.5.3 Synthesis of model peptide as a sulfonic acid

Another potential analogue is sulfonic acid peptide **69**, which could be synthesised from protected sulfonocysteine **70** (Scheme 1.62).

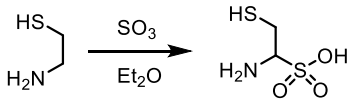


69 **70**

Scheme 1.62 Sulfonic acid model peptide via sulfonocysteine **70**

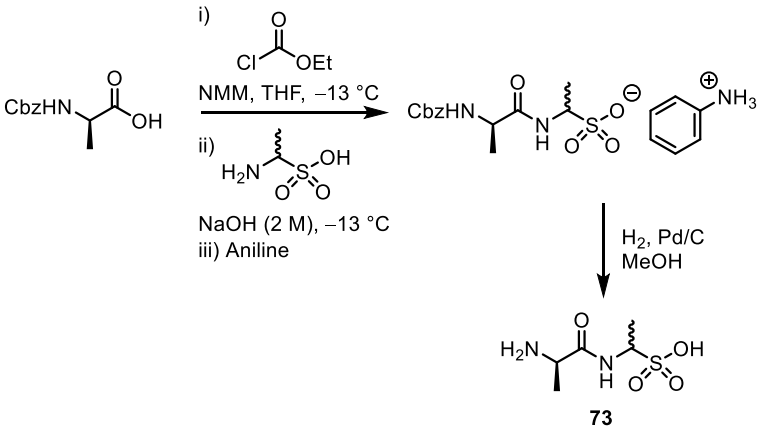
Sulfonocysteine (**71**) has previously been synthesised from amine **72** using Sulfan (Scheme 1.63a).[110] Whilst there are reports of α-amino sulfonic acids not being stable,[111] Shiba *et al.* have used Cbz chemistry to synthesise dipeptide **73** (Scheme 1.63b).[112]

a)



72 ***rac*-71**

b)



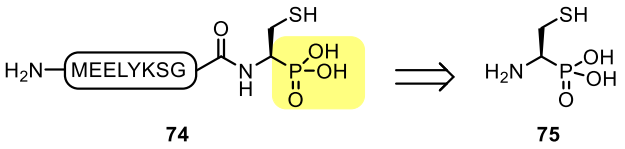
73

Scheme 1.63 Previously reported synthesis of a) sulfonocysteine **71**[110] and b) sulfonodipeptide **73**[112]

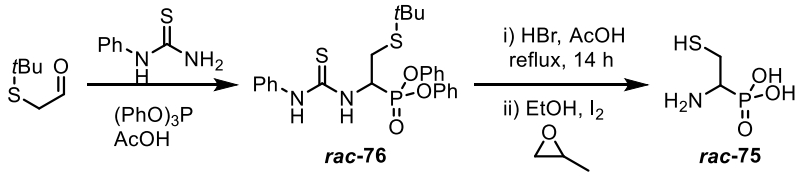
1.5.4 Synthesis of model peptide as a phosphonic acid

Phosphonic acid peptide **74** could be synthesised from phosphonocysteine **75** (Scheme 1.64). Phosphonocysteine **75** has previously been synthesised via thioureiodoalkane phosphonate **76** (Scheme 1.64b).[113,114]

a)



b)



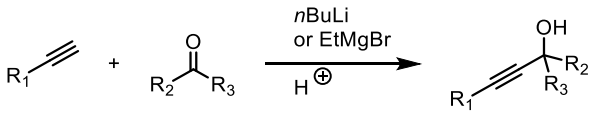
Scheme 1.64 a) Phosphonic acid model peptide via phosphonocysteine **75**; b) Previously synthesised phosphonocysteine[113]

Chapter 2 Regioselective Dihalohydration Reactions of Propargylic Alcohols

2.1 Introduction

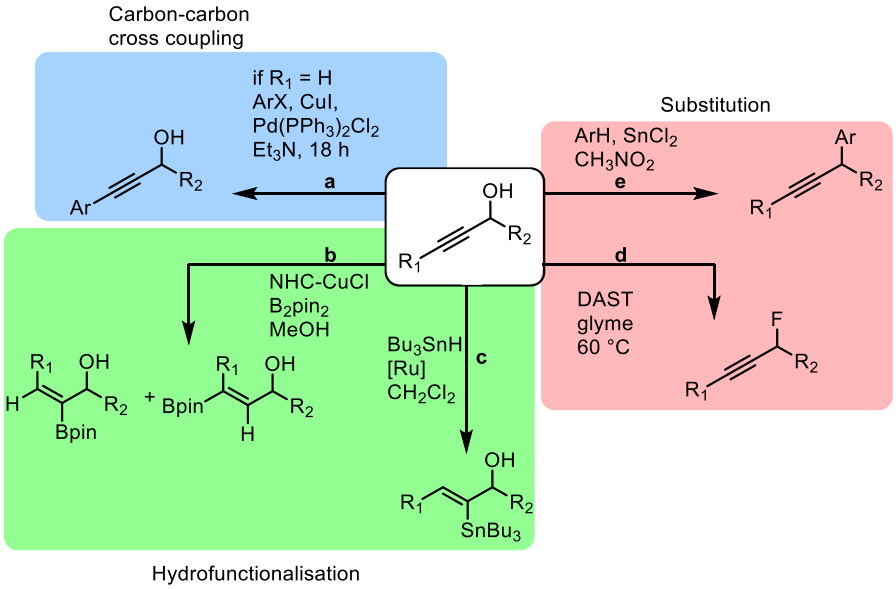
2.1.1 Synthesis and reactions of propargylic alcohols

Propargylic alcohols are incredibly versatile intermediates, due to the presence of both alcohol and alkyne functionality. These synthetic intermediates can be readily made by the nucleophilic attack of a deprotonated terminal alkyne on an aldehyde or ketone (Scheme 2.1). Recently, the utility of these building blocks has been enhanced through the development of methodologies that allow the asymmetric synthesis of propargylic alcohols.[115–117]



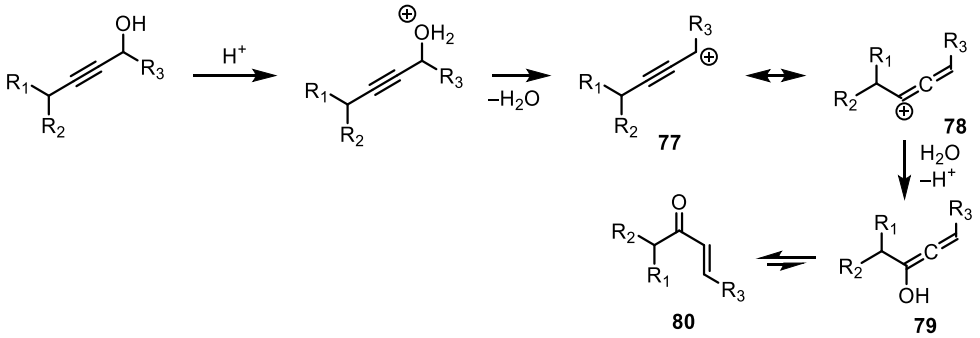
Scheme 2.1 General synthesis of propargylic alcohols

Numerous transformations of propargylic alcohols have been reported, many of which arise from alkyne activation induced by transition metal catalysts. These include well known Sonogashira couplings of terminal alkynes (Scheme 2.2a)[118] and hydroboration of propargylic alcohols catalysed by a Cu(I)-NHC complex (Scheme 2.2b).[119] Ruthenium catalysed *trans*-hydrostannation (Scheme 2.2c) has also been reported.[120] This method was developed from the analogous hydrostannation of alkynes, however it was found that a different ruthenium catalyst was required to obtain good regioselectivities from propargylic alcohols. The hydroxyl functionality has also been utilised to access allenes via a palladium catalysed carbonylation reaction[121] or can be substituted by fluoride (Scheme 2.2d)[122] or aryl groups (Scheme 2.2e)[123]



Scheme 2.2 Selected examples of reactions of propargylic alcohols: a) Sonogashira coupling;[118] b) Hydroboration;[119] c) Hydrostannation;[120] d) Diethylaminosulfur trifluoride (DAST) fluorination[122] and e) $SnCl_2$ catalysed substitution[123]

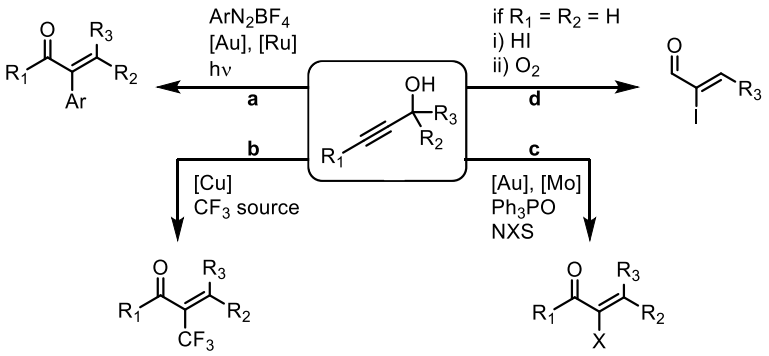
A well-known transformation of propargylic alcohols is the Meyer Schuster rearrangement which enables the formation of enones (Scheme 2.3).[124] During this, a molecule of H_2O is lost to give propargylic carbocation **77**, which is a resonance form of vinyl carbocation **78.** Vinyl cation **78** is subsequently attacked by a molecule of H_2O. Tautomerisation of **79** gives α,β-unsaturated ketone **80**.



Scheme 2.3 Meyer Schuster reaction of propargylic alcohols

This route to enones was first reported by Meyer and Schuster in 1922, but since then, the proposed vinyl cation intermediate has been functionalised with aryl groups,[125] trifluoromethyl groups[126] or halogens[127,128] to give α-substituted enones (Scheme 2.4). These transformations often require a transition metal catalyst to activate the alkyne. This route has been used to synthesise α-haloenones, which have well documented uses as synthetic intermediates and in cross coupling

reactions.[129] Much less has been published on routes to α,α-dihaloketones, however, despite their varied uses, which will be discussed below.

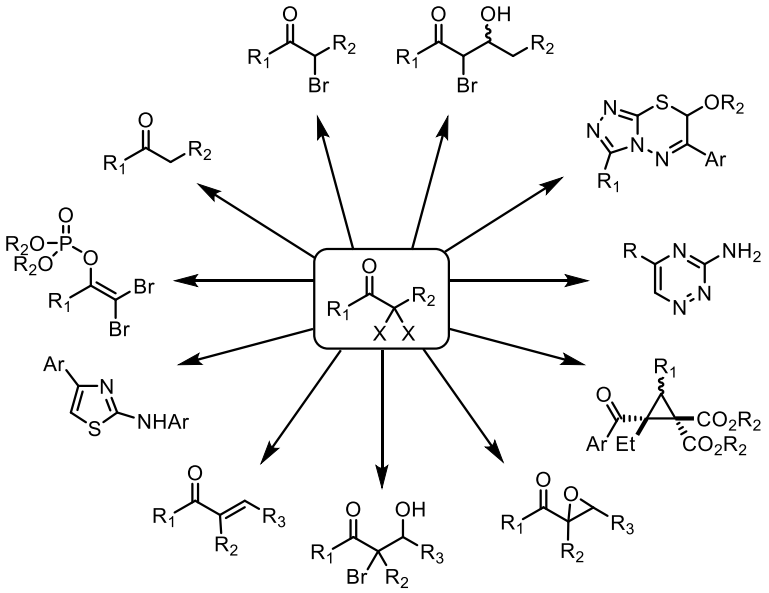


Scheme 2.4 Functionalisation of vinyl cation intermediate with a) Aryl groups[125] b) Trifluoromethyl groups[126] or c) and d) Halogens[127,128]

2.1.2 Uses of α,α-dihaloketones

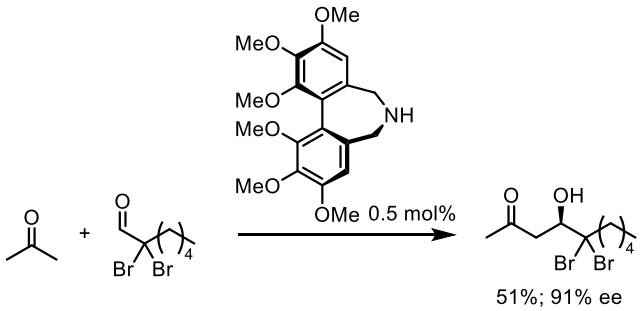
2.1.2.1 Uses of α,α-dihaloketones in organic synthesis

α,α-Dihaloketones have been used in the synthesis of a variety of compounds. Their synthetic importance arises from the presence of two versatile functional groups in close proximity. This allows for a rapid increase in molecular complexity and provides a wide scope for further transformations (Scheme 2.5) which will be discussed below.



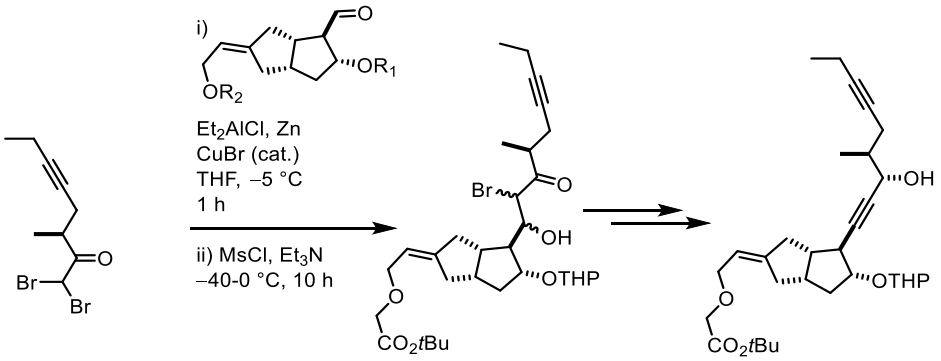
Scheme 2.5 The structure and reactivity of an α,α-dihaloketone

Asymmetric aldol reactions of α,α-dibromoaldehydes and ketones have been demonstrated (Scheme 2.6).[130]



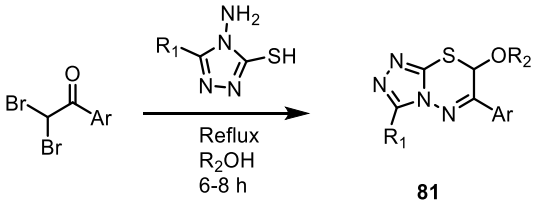
Scheme 2.6 Asymmetric aldol reaction of α,α-dibromoaldehyde and acetone[130]

Aldol reactions of α,α-dibromoketones have been employed in the synthesis of prostacyclin analogues[131] which have antithrombotic properties, and in the synthesis of compounds with antimicrobial properties.[132]



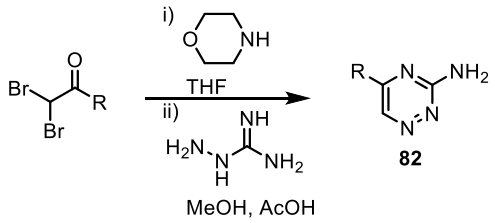
Scheme 2.7 Asymmetric aldol reactions of α,α-dibromoketones[131]

The reaction of α,α-dibromoacetophenones with 3-alkyl/phenyl-4-amino-5-mercapto-*s*-triazoles has been used to generate a variety of analogues of **81**, some of which had comparable biological activities to commercially available antibiotics and antifungal agents (Scheme 2.8).[132]



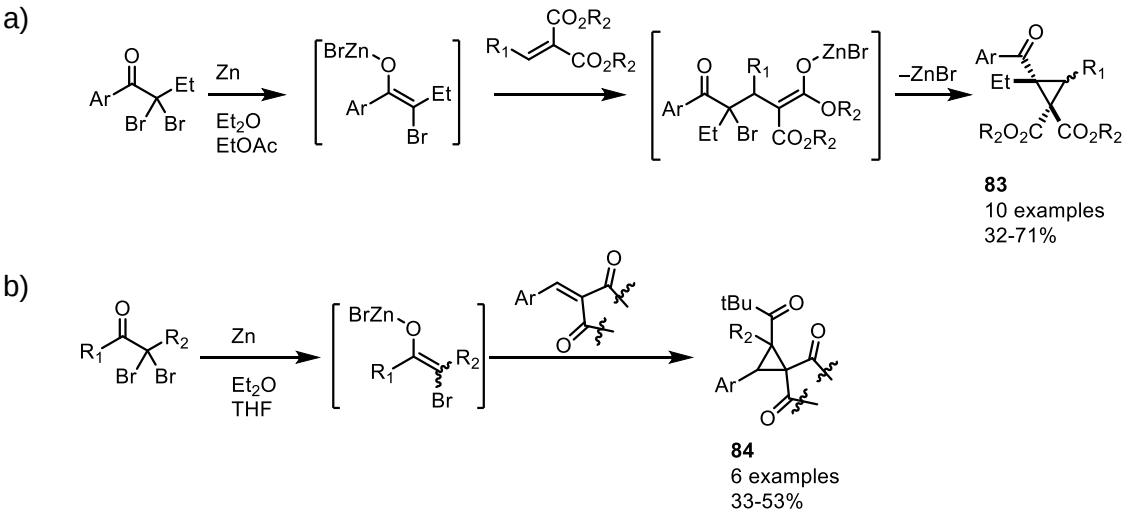
Scheme 2.8 The use of α,α-dibromoacetophenones in the synthesis of antifungal and antibacterial compounds[132]

The nucleophilic displacement of α,α-dibromoketones with morpholine to give the corresponding ketoaminals and the subsequent condensation with aminoguanidine has been used in the synthesise of triazines (**82**, Scheme 2.9).[133] Triazines have received interest for their use as building blocks in agrochemical[134] and medicinal fields.[135]



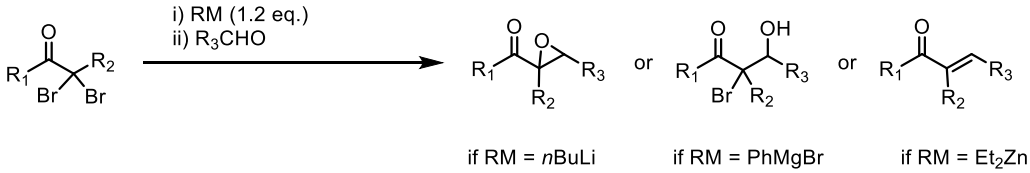
Scheme 2.9 Nucleophilic displacement of α,α-dibromoketones with excess morpholine and subsequent condensation with aminoguanidine[133]

Shchepin *et al.* have utilised α,α-dibromoketones to access cyclopropane dicarboxylates **83** via Reformatsky reactions (Scheme 2.10a).[136] Furthermore, the zinc enolates derived from α,α-dibromoketones have also been used to generate spirocyclic compounds containing cyclopropanes **84** (Scheme 2.10b).[137]



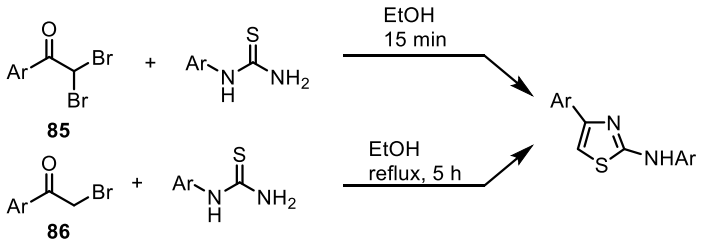
Scheme 2.10.Synthesis of a) Cyclopropane dicarboxylates via a Reformatsky reaction[136] and b) Cyclopropyl spirocyclic compounds[137]

α,α-Dibromoketones have been shown to form α-bromoenolates in the presence of *n*-butyllithium, phenylmagnesium bromide or diethylzinc via halogen-metal exchange.[138] It was found that the distribution of the products formed from the ensuing aldol reactions depended heavily on the organometallic reagent used. These are summarised in Scheme 2.11.



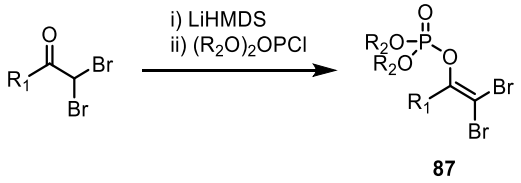
Scheme 2.11 Synthesis of α-bromoenolates and their reaction with aldehydes[138]

Aryl α,α-dibromoketones have been shown to be amenable to Hantzsch thiazole synthesis. During this work, it was found that thiazole formation from **85** was complete in 15 minutes at room temperature, whereas analogous α-bromoketone **86** required to be heated at reflux for 5 hours.[139] Prakash *et al.* also noted that the reactions of α,α-dibrominated ketones proceeded with fewer side reactions. This was attributed to increased reactivity of the ketone when adjacent to two electron withdrawing halogens.



Scheme 2.12 Hantzsch thiazole synthesis requires milder conditions for α,α-dibromoketones compared to α-bromoketones[139]

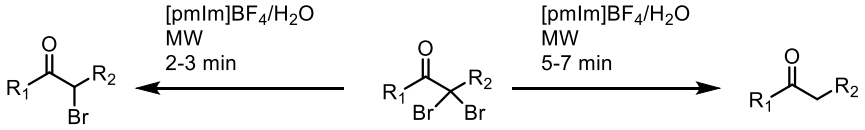
Recently, α,α-dibromoketones have been employed to synthesise tetrasubstituted alkenes bearing a phosphate moiety.[140] Tobrman's group generated α,α-dibromoketones which were enolised and reacted with dialkyl chlorophosphates to give dibromoenol phosphates **87** (Scheme 2.13).



Scheme 2.13 Formation of 1,1-dibromoalkenyl phosphates from α,α-dibromoketones[140]

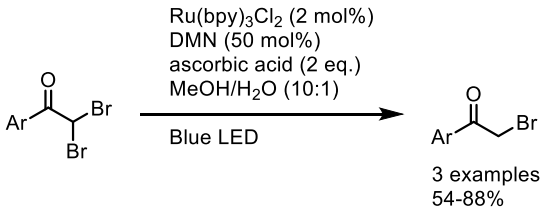
These dibromoalkenyl phosphates have since been applied in the synthesis of tetrasubstituted alkenes via modular and selective carbon-carbon bond forming reactions.[141]

Several de-bromination reactions of α,α-dibromoketones exist. Ranu *et al.* found that using ionic liquid 1-methyl-3-pentylimidazolium tetrafluoroborate ([pmIm]BF_4) under microwave irradiation, it was possible to form either monobromoketones or ketones depending on the reaction time (Scheme 2.14).[142]



Scheme 2.14 Selective de-bromination of α,α-dibromoketones[142]

Since then, de-bromination of α,α-dibromoketones has also been effected photocatalytically using a ruthenium catalyst (Scheme 2.15).[143]



Scheme 2.15 Photocatalytic de-bromination of α,α-dibromoketones[143]

2.1.2.1 Uses of α,α-dihaloketones in chemical biology

A practical use of geminal dihalides, such as α,α-dihaloketones, is as isosteric replacements for hydrated carbonyls. This has been exploited to modulate bacterial activity. Bacterial gene expression is regulated in response to fluctuations in the density of cell populations in a process called quorum sensing. Quorum sensing is used in a range of bacteria and controls many processes, including biofilm formation and antibiotic resistance. In quorum sensing bacteria, signalling molecules are produced, known as autoinducers. One of these, autoinducer-2, is ubiquitous in bacterial quorum sensing and therefore there has been much research into the modulation of autoinducer-2 mediated signalling.

α,α-Dihaloketones have been used as inhibitors of a repressor protein, LsrR, which is responsible for the regulation of biofilm production. LsrR sits on DNA, inhibiting the production of biofilms. In the presence of autoinducer-2, LsrR preferentially binds to autoinducer-2, thus allowing transcription of biofilm genes.[144] Many isomers of autoinducer-2 exist, but it has previously been reported that LsrR binds to 3-hydrated form **88a**.[145] Investigation into analogues showed that dibromo compound **88b** binds

to LsrR with the same affinity as **88a** and dichloro compound **88c** with slightly less potency. Interestingly, LsrR did not bind to difluoroketone **88d**.[144] This was explained by the reduced size of difluoroketone **88d**. Also, calculation of the electrostatic surface potential revealed a positive potential on the opposite side of the C-X bond for the bromo and chloro compounds. It was postulated that this would allow the halogen to act as an electrophile and partake in halogen bonding. The same was not observed for the fluoro compound **88d**, demonstrating the unique properties of α,α-dibromoketones.

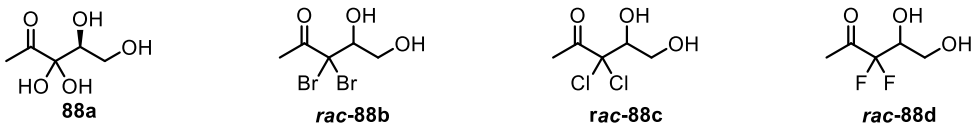
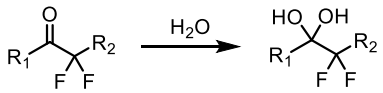


Figure 27 Structures of one isomer of autoinducer-2 (**88a**) and dihaloautoinducer-2 (**88b-d**)

In the case of α,α-difluoroketones, it has been observed that the carbonyl group can readily react with H_2O to form hydrates **90** (Scheme 2.16).[146] This reactivity is attributed to the presence of the electron withdrawing fluorine atoms. When this motif is within a peptide-like structure, the hydrates mimic the transition state of peptide hydrolysis, allowing them to inhibit proteases, such as HIV-1 aspartic protease.[147]



89 90

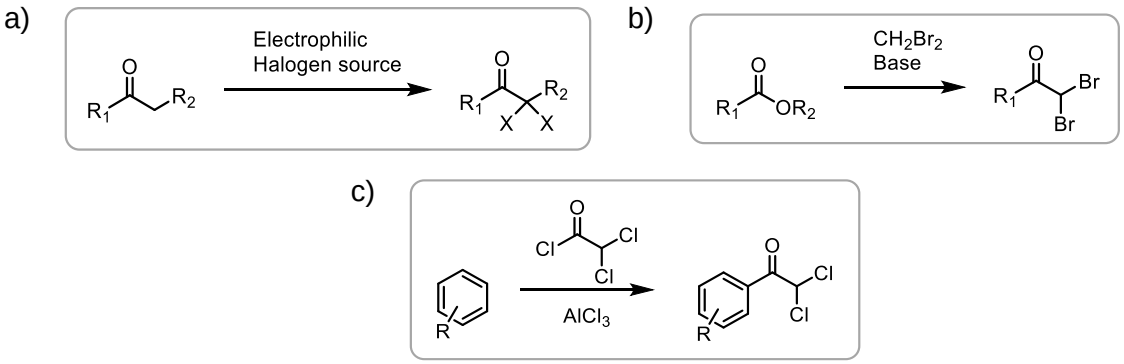
Scheme 2.16 Peptide hydrolysis mimic formed by hydrated α,α-difluoroketone[146]

There are many uses for α,α-dibromoketones, though the current syntheses are somewhat limited. These will be discussed below.

2.1.3 Synthesis of α,α-dihaloketones

There are numerous routes to α,α-dihaloketones which rely on the presence of a preinstalled carbonyl moiety. A handful of these are depicted in Scheme 2.17, though this list is by no means exhaustive. Unfortunately, these strategies rely on halogenating a carbonyl compound and are generally limited by substrate scope. For example, electrophilic halogen sources have been used to generate dihaloketones[148] or dihaloaldehydes[149] (Scheme 2.17a). Many of these require elemental halogens or sodium hypohalides, which have toxicity issues. However, more recently, reagents such as *N*-bromosuccinimide (NBS) have been used. Chlorinated hydantoins have been used to dichlorinate aromatic ketones.[148] Nevertheless, there is not a universal strategy that works on a broad substrate scope and no examples exist that give α,α-dihalo-β-hydroxy ketones directly.

Esters can be made into dibromoketones on treatment with dibromomethane and a base;[150,151] however, this also causes homologation and has only been reported with dibromomethane, (Scheme 2.17b) hence limiting the substitution of the product. Aromatic dichloroketones have been synthesised via the acetylation of arenes, however this strategy is limited to the synthesis of aromatic dichloroketones (Scheme 2.17c).[152]



Scheme 2.17 A small selection of examples of syntheses of α,α-dihaloketones from a) a ketone[148] or aldehyde[149] b) from an ester, using CH_2Br_2[150] or c) via the acylation of arenes[152]

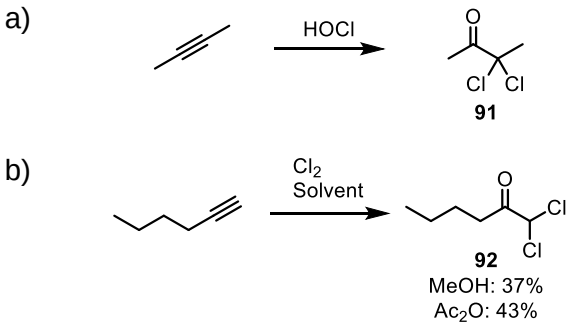
Due to the limitations of these previously reported methods, a mild and efficient route to generate a wide variety of α,α-dihalo-β-hydroxy ketones remains elusive. An attractive route to these compounds would be via the functionalisation of an alkyne which offers the opportunity to install two functional groups concurrently. Many alkynes are activated by transition metal catalysts, however, these methods are disfavoured due to costs of transition metals, and also the potentially expensive and

problematic requirement for removal of transition metals in the pharmaceutical industry.[153] The merit of generating α,α-dihaloketones from alkynes has been previously observed and these strategies will be discussed below. Examples of dihalohydration reactions have been reported with each of the halogens, however, the first dihalohydration reactions of alkynes were dichloro- and dibromohydration reactions. For clarity, the dihalohydration reactions will be discussed in turn based on the identity of the halogen.

2.1.3.1 Dichlorohydration and dibromohydration reactions of alkynes

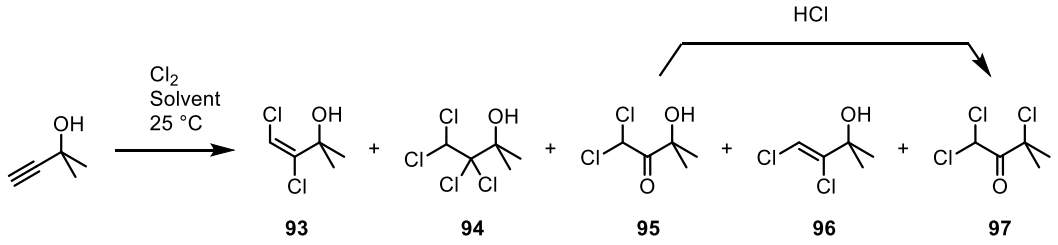
.

The first report of dichlorohydration of alkynes originates from 1895 and used hypochlorous acid to generate dichloroketone **91** (Scheme 2.18a). Unfortunately, the conditions used for this transformation were not given.[154] For the next 70 years, numerous groups generated dichlorohydrated products from alkynes either using hypochlorous acid directly[155] or by generating it *in situ* from chlorine and either MeOH[156] or acetic anhydride[157] (**92**, Scheme 2.18b).



Scheme 2.18 Early reports of dihalohydration reactions of an alkyne using a) hypochlorous acid[154] or b) chlorine in MeOH[156] or acetic anhydride[157]

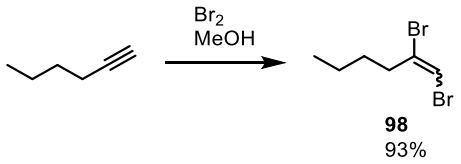
Hennion then applied this chemistry to propargylic alcohols (Scheme 2.19).[158] During this work, it was discovered that the solvent had a dramatic effect on the products that formed. Using carbon tetrachloride, the reaction gave **93** and **94** as the sole products. However, when MeOH, a nucleophilic solvent was used, competing solvent incorporation was observed to give a small amount of **95** and **96** as well as **93** and **94**. Conducting the reaction in H_2O gave **95** and a considerable amount of **97**, presumably from the reaction of HCl with the hydroxyl group of **95**,[158] demonstrating that this method is not practical for the dihalohydration of propargylic alcohols.



Solvent					
CCl_4	22%	45%	-	-	-
MeOH	20%	36%	11%	7%	-
H_2O	-	-	16%	-	30%

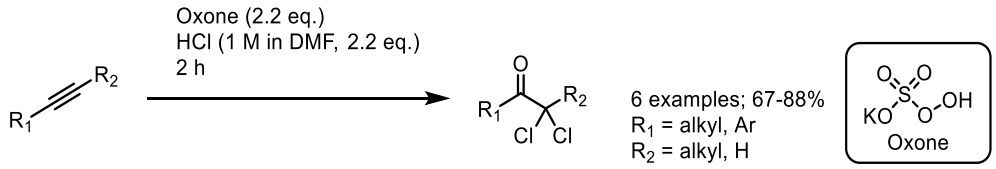
Scheme 2.19 Early reported dichlorohydration of a propargylic alcohol[158]

Verbanc and Hennion also tried the reaction with bromine; however, they were only able to isolate 1,2-dibromide **98** (Scheme 2.20).



Scheme 2.20 Unsuccessful dibromohydration of 1-hexyne using bromine[156]

The next progression of dichlorohydration reactions of alkynes occurred using potassium peroxymonosulfate, marketed as Oxone®. In 1992, Kim *et al.* used Oxone® as an oxidant with HCl in DMF to form α,α-dichloro ketones (Scheme 2.21).[159] They achieved isolated yields of 67-88% for 6 examples, including both phenylacetylenes and alkylacetylenes. They also tried using mCPBA as an oxidant, but found that Oxone® was superior.

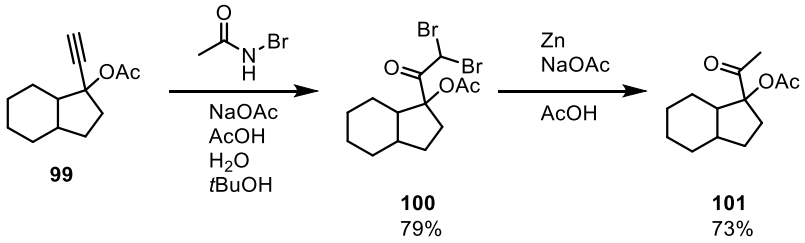


Scheme 2.21 Dichlorohydration of alkynes using Oxone®[159]

Later, in 1965, Reed treated both terminal and internal alkynes with *N*-chlorosuccinimide (NCS) in MeOH to give dichloromethyl ketals in good yields that were readily transformed to ketones under acidic conditions (Scheme 2.22).[160]

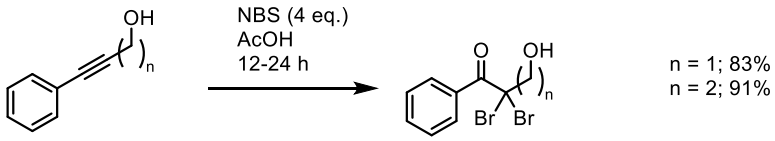
Scheme 2.22 NCS dichlorohydration of terminal and internal alkynes[160]

The dibromohydration of alkynes is generally achieved by generating hypobromous acid (HOBr) *in situ*. This has been achieved by several different routes. The first successful dibromohydration was of a terminal alkyne and was reported in 1947.[161] This method used *N*-bromoacetamide, sodium acetate and acetic acid to form hypobromous acid *in situ* and has since been used by Coles *et al.* to synthesise bicyclic cortical hormone analogues. In this case, acetylated ethynylhexahydroindanol **99** was treated with *N*-bromoacetamide, sodium acetate and acetic acid in H_2O and *tert*-butanol to give α,α-dibromoketone **100** (Scheme 2.23) in 79% yield, which was then de-brominated to give ketone **101**.[162] This demonstrated that the procedure was tolerated by esters, and presumably proceeds via the generation of hypobromous acid.[162] This strategy has been used by numerous groups, however, it is limited to terminal alkynes.[163–166]



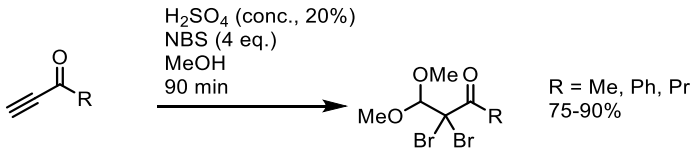
Scheme 2.23 Dibromohydration reaction of a terminal alkyne[162]

Following this, it was found in 1967 that *N*-bromosuccinimide (NBS) could be used to dibromohydrate alkynes.[167] Jovtscheff and Spassov used NBS in acetic acid to form α,α-dibromo ketones in excellent yields (Scheme 2.24). NBS would form hypobromous acid *in situ,*[168] and the authors attained similar yields when hypobromous acid was generated from H_2O, bromine and mercury oxide.[167] During this study, only two examples were given, suggesting a limited substrate scope.



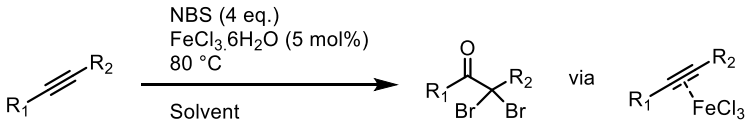
Scheme 2.24 First use of NBS as a bromine source in the dibromohydration of alkyne alcohols[167]

The generation of hypobromous acid from NBS has also elicited the dibromohydration of carbonyl conjugated alkynes and attained the opposite regioselectivity compared with non-conjugated alkynes (Scheme 2.25). Heasley *et al.* found that 20% sulphuric acid was required to give the dibromoketones as opposed to the dibrominated alkenes, which they attributed to decomposition resulting in Br_2 which adds to the alkyne.[169]

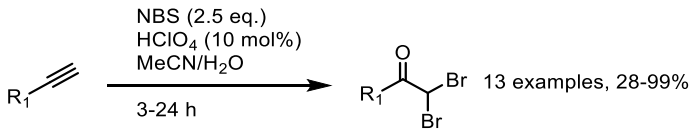


Scheme 2.25 Dibromohydration of carbonyl conjugated alkynes[169]

Other conditions that generate hypobromous acid from NBS have been reported, including in the presence of $FeCl_3.6H_2O$ (Scheme 2.26) which presumably activates the alkyne.[170–172] Dibromohydration reactions have also been achieved using NBS with catalytic perchloric acid; however, this has only been reported for terminal alkynes (Scheme 2.27).[140]

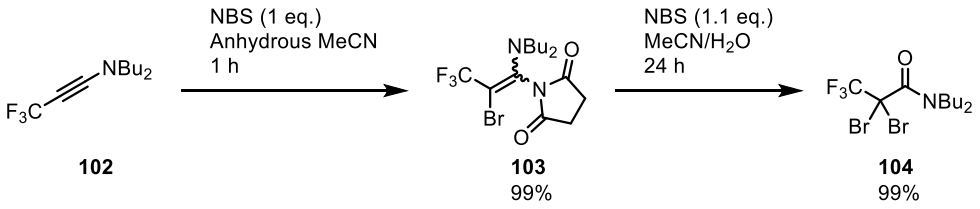


Scheme 2.26 Dibromohydration of alkynes via the generation of hypobromous acid with an iron catalyst in a solvent mixture of THF/H_2O[171,172] or MeOH[170]



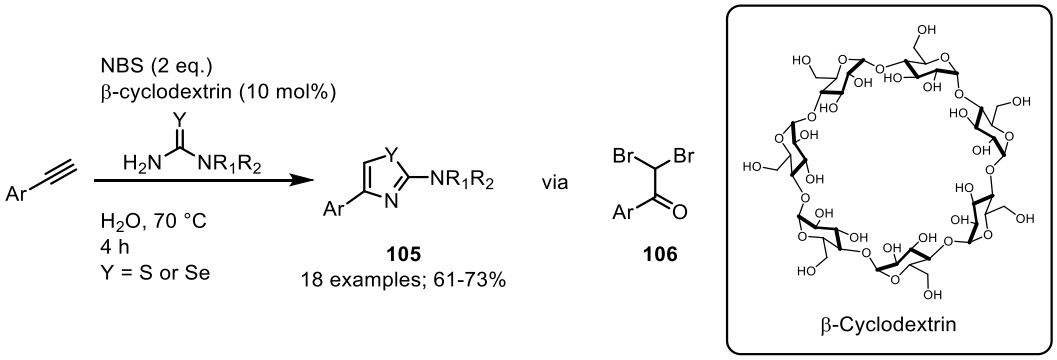
Scheme 2.27 Dibromohydration of terminal alkynes by generation of hypobromous acid from NBS in the presence of perchloric acid[140]

Dibromohydration using NBS has been shown to be effective in the transformation of trifluoromethylated ynamines to α,α-dibromoketones, albeit via a lengthy route (Scheme 2.28).[173] Reacting ynamine **102** with NBS under anhydrous conditions gives addition product **103**. Treating this with NBS again, but this time using MeCN and H_2O, α,α-dibromopropanamide **104** was isolated in quantitative yield.[173]



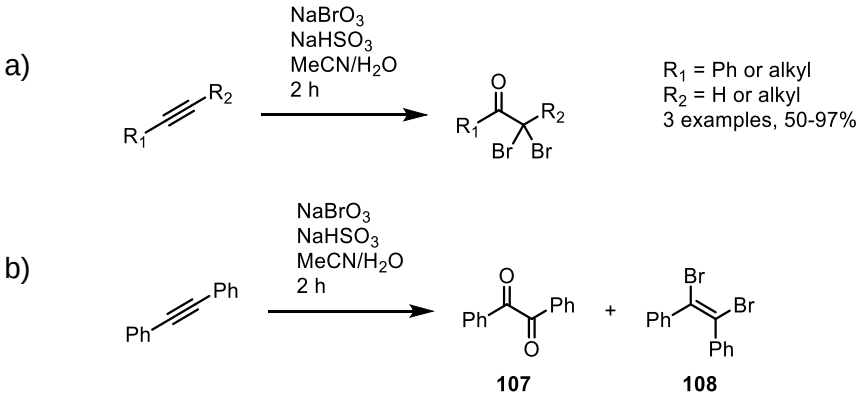
Scheme 2.28 Synthesis of α,α-dibromopropanamides[173]

Thiazoles and selenazoles have also been generated via NBS dibromohydration of actylenes (Scheme 2.29). Treatment of terminal acetylene and thiourea or selenourea with NBS and a catalytic amount of β-cyclodextrin at 70 °C gave thiazole or selenazole products **105**. These were formed from a tandem one pot protocol, proceeding through the *in situ* formation of α,α-dibromoketone **106** which then reacts with thiourea or selenourea.[174] The authors achieved good yields, but the substrate scope of the acetylene was limited to phenylacetylene and isomers of tolylacetylene and fluorophenylacetylene. The limited substrate scope was attributed to the requirement for the addition of thiourea to α,α-dibromoketone **106** to take place in a hydrophobic pocket present in β-cyclodextrin.



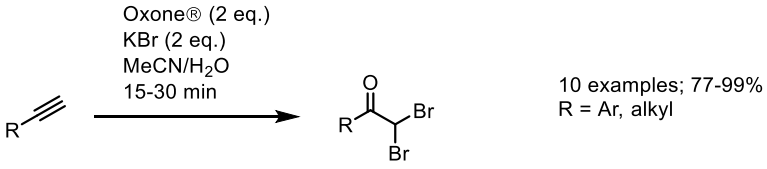
Scheme 2.29 Tandem one pot synthesis of thiazoles and selenazoles via the *in situ* formation of α,α-dibromoketones[174]

The majority of previously reported dibromohydration reactions have required the *in situ* generation of hypobromous acid. As shown above, many of these have used NBS, however, in 1994 Masuda *et al.* showed that sodium bromate and $NaHSO_3$ resulted in hypobromous acid that could be used for the dibromohydration of alkynes (Scheme 2.30a).[175] The authors showed only 3 examples in which this worked, and also noted that the reaction was unsuccessful with diphenylacetylene, instead generating benzil **107** and dibrominated alkene **108** (Scheme 2.30b).



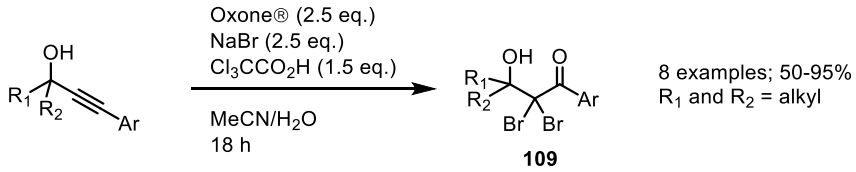
Scheme 2.30 Use of $NaBrO_3$ and $NaHSO_3$ for the *in situ* generation of hypobromous acid to give a) α,α-dibromoketones or b) benzil and dibrominated alkene[175]

Oxone® has been employed in the dichlorohydration of alkynes in 1992 (Scheme 2.21). Over 20 years later, in 2013, it was shown that Oxone® could also be used in dibromination reactions to generate dibrominated ketones in the presence of KBr (Scheme 2.31). Curiously, only terminal alkynes were discussed, implying a limited substrate scope.[176]



Scheme 2.31 Oxybromination of alkynes using Oxone® and KBr[176]

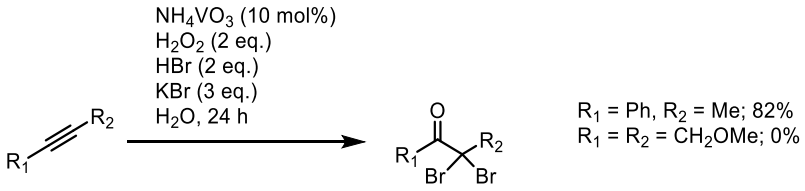
Aborways *et al.* found that subjecting propargylic alcohols to Oxone® and NaBr gave α,α-dibromo-β-hydroxyketones **109** (Scheme 2.32).[177] These reactions proceeded at room temperature, however the reactions were slow. The 8 examples given were tertiary alcohols bearing linear or cyclic alkyl groups.



Scheme 2.32 Formation of α,α-dibromoketones from propargylic alcohols[177]

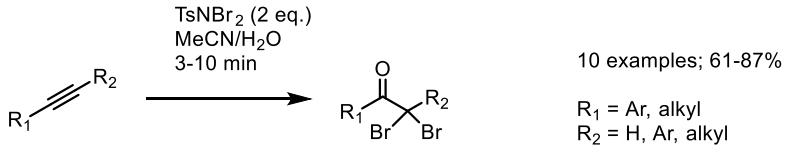
Vanadium haloperoxidases are found in marine algae and catalyse the oxidation of halides into the corresponding hypohalous acids in the presence of hydrogen peroxide.[178] Inspired by this, the dibromohydration of alkynes has been catalysed by ammonium metavanadate (NH_4VO_3) with hydrogen peroxide, HBr and KBr.[179]

However, this catalytic system was attempted on two alkynes and it was found to only work in a single case (Scheme 2.33). The choice of solvent proved to be crucial; α,α-dibromoketone was the major product when the reaction was conducted in H_2O, but was only observed in trace amounts when using a biphasic mixture of H_2O and $CHCl_3$.[179]



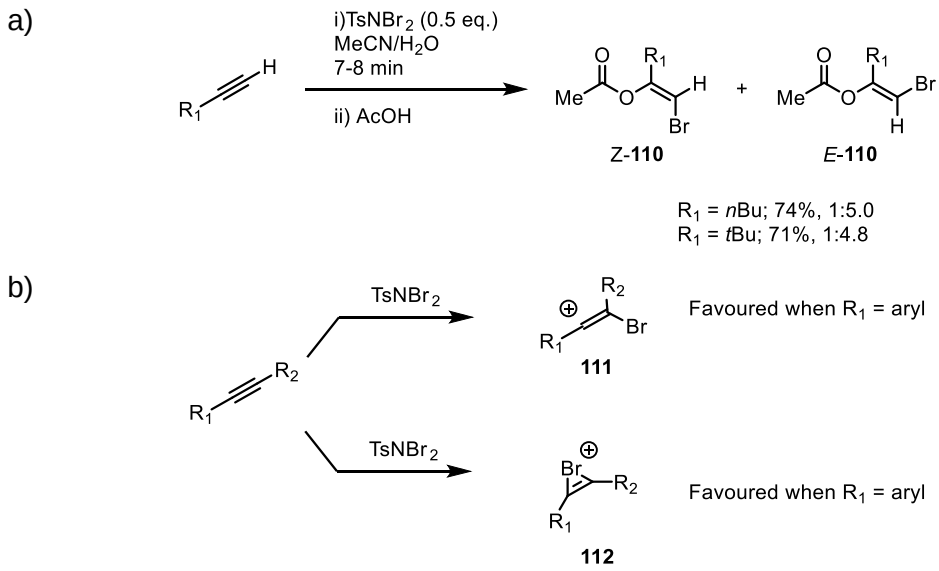
Scheme 2.33 Vanadium catalysed bromohydration[179]

In 2013, Chawla *et al.* used *N*,*N*-Dibromo-*p*-toluenesulfonamide ($TsNBr_2$) to generate α-α-dibromoketones from alkynes (Scheme 2.34).[153] The reaction was complete within 10 minutes at ambient temperature and could tolerate both terminal and internal alkynes.



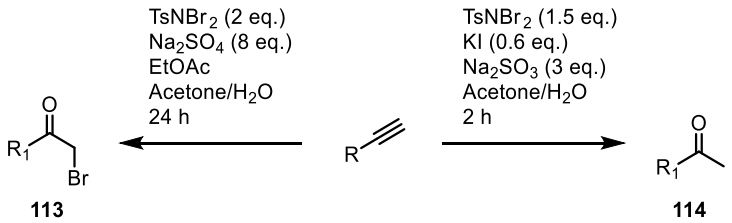
Scheme 2.34 Dibromohydration of alkynes using $TsNBr_2$[153]

The group found that reducing the amount of $TsNBr_2$ to 0.5 equivalents and adding a carboxylic acid resulted in the formation of haloenol acetates. When hex-1-yne or 3,3-dimethylbut-1-yne were subjected to these conditions, *Z*-**110** and *E*-**110** were isolated in 1:5.0 and 1:4.8 ratio respectively. This led the group to suggest that for aromatic alkynes, vinyl cation **111** formed, however, alkyl alkynes were more likely to proceed via cyclic bromonium cation **112**.[153]



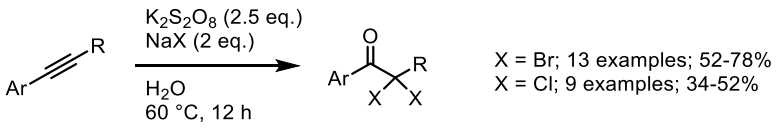
Scheme 2.35 a) Formation of haloenol acetates using $TsNBr_2$; b) Proposed intermediates formed by alkyne and $TsNBr_2$[153]

Rajbongshi *et al.* used $TsNBr_2$ in a one-pot oxybromination/de-bromination reaction to form α-brominated ketones **113** from alkynes in the presence of Na_2SO_4 and EtOAc (Scheme 2.36).[180] By adding KI to the reaction, it was possible to obtain the ketone **114** instead (Scheme 2.36). Both of these reactions were proposed to proceed via the α,α-dibromoketone, which was observed in small quantities in some cases, though the authors did not attempt to isolate it.



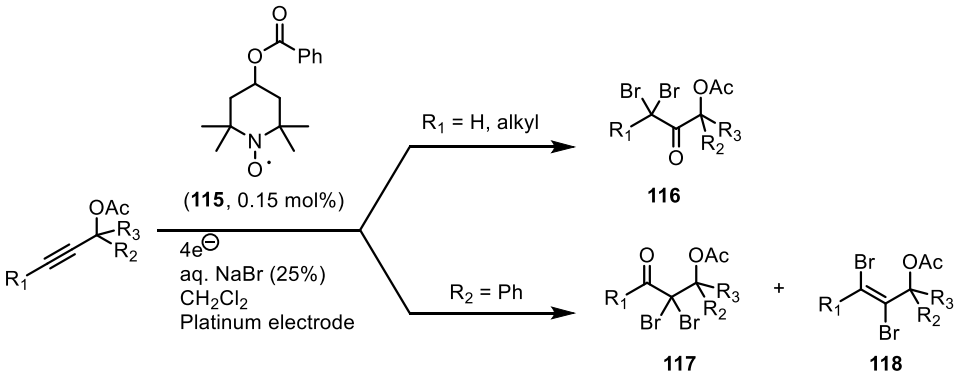
Scheme 2.36 $TsNBr_2$ mediated oxidative transformation of alkynes[180]

In 2014, the dihalohydration of alkynes was reported using potassium persulfate ($K_2S_2O_8$) and NaX to generate dibromo- or dichloroketones (Scheme 2.37).[181] The substrate scope mainly focussed on varying the aromatic substituent and most of the examples were terminal alkynes. The procedure was unsuccessful for aliphatic alkynes, in which case *trans*-1,2-dihalo alkenes were obtained. Whilst the reaction was successful for the transformation of internal alkynes, the yields were reduced significantly.



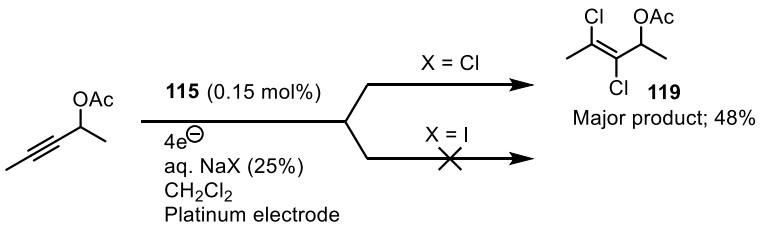
Scheme 2.37 Potassium persulfate mediated oxydihalogenation of alkynes[181]

The dibromohydration of acetylated propargylic alcohols has also been shown to occur via electrochemical means.[182] Inokuchi *et al.* used electrochemical oxybromination in the presence of a catalytic amount of *N*-oxyl compound **115** to synthesise α,α-dihaloketones from propargylic acetates. The acetoxy group was necessary for the reaction to proceed. They also found that the regioselectivity of the reaction was determined by the nature of R_1. If R_1 in Scheme 2.38 was H or alkyl, the reaction selectively gave regioisomer **116**, whereas if R_1 was phenyl, regioisomer **117** was the major product, with a small amount of alkene **118** being observed. In the absence of *N*-oxyl compound **115**, the reaction of an alkyl substituted alkyne gave the 1,2-dibromide compound as the major product and dibromoketone as the minor product.



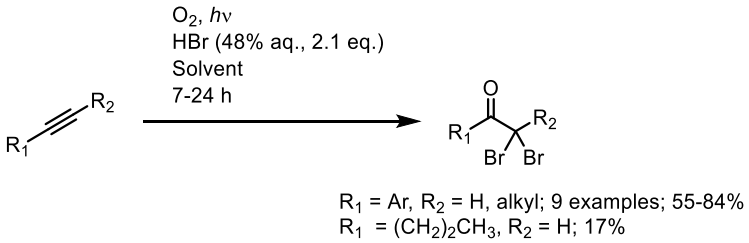
Scheme 2.38 Electrochemical oxybromination of propargylic acetates[182]

The analogous oxychlorination reaction was attempted using NaCl. However, the major product formed was the corresponding 1,2-dichloride **119** (Scheme 2.39). Attempts at iodination using NaI were unsuccessful and only starting material was recovered.



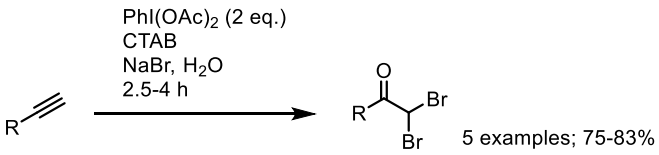
Scheme 2.39 Attempted electrochemical oxyhalogenation of propargylic acetates[182]

A more recent synthesis of α,α-dibromoketones used molecular oxygen, visible light and 48% HBr solution (Scheme 2.40).[183] Both electron withdrawing and electron donating aromatic groups were tolerated, as were diaromatic internal alkynes. One heterocyclic example was also given, with a 2-ethynylpyridine derived alkyne being converted to the corresponding α,α-dibromoketone in a modest yield of 55%. Only one aliphatic example (1-decyne) was reported with a low yield of 17% and it required changing the solvent to ethyl acetate.



Scheme 2.40 Aerobic photo-oxidative synthesis of α,α-dibromoketones[183]

The dibromohydration of terminal alkynes has also been shown to occur in lipophilic nanoreactors.[184] Upon addition of cationic surfactant cetyltrimethylammonium bromide (CTAB) to H_2O, a self-assembled nanoreactor forms. The addition of $PhI(OAc)_2$, alkyne and NaBr resulted in the formation of α,α-dibromoketone in yields of 75-83% (Scheme 2.41). The authors were encouraged by the reaction times of 2.5-4 hours and the acceptance of both electron donating and electron withdrawing groups. They also only observed one regioisomer. However, there was no mention of disubstituted alkynes.

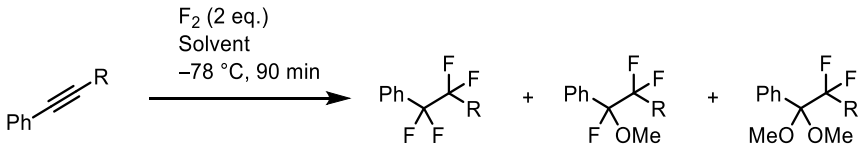


Scheme 2.41 Synthesis of α,α-dibromoketones using aqueous NaBr and cationic surfactant CTAB[184]

2.1.3.2 Difluorohydration reactions of alkynes

Less work on the difluorohydration of alkynes has been reported than on the dichlorination and dibromination, with the first reported concurrent addition of fluorine and solvent incorporation being observed by Merrit in 1967. The treatment of an alkyne with fluorine in trichlorofluoromethane produced **120** as the sole product (Scheme 2.42).[185] However, when MeOH was used as the solvent, fluoro ether **121**

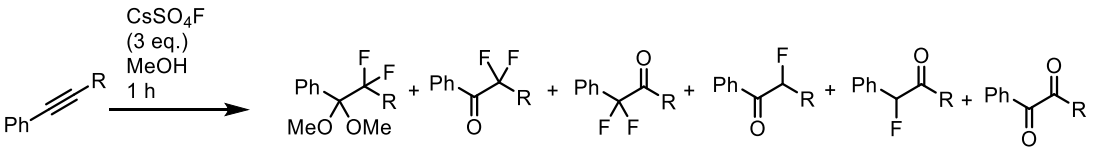
and difluoro ketal **122** were also isolated. Merrit also found that the amount of **120** decreased with the bulkiness of the alkyne, with terminal alkynes giving difluoroketal **122** as the major product (Scheme 2.42).[185]



Solvent	R	**120**	**121**	**122**
CCl_3F	Ph	100%	-	-
MeOH	Ph	23%	57%	20%
MeOH	H	13%	35%	52%

Scheme 2.42 First reported difluorohdration of an alkyne[185]

In 1987, Stavber and Zupan showed that cesium fluoroxysulfate could be used to fluorinate alkenes,[186] which led them to explore the fluorination of alkynes. During this work they observed solvent incorporation to give acetal **123** and difluoroketone **124** (Scheme 2.43) when R = H, Ph or *t*Bu.[187] When the reaction was conducted on pent-1-yn-1-ylbenzene (R = $(CH_2)_2CH_3$), corresponding **123** and **124** were formed in 31% and 25% yield respectively, but compounds **125**, **126**, **127** and **128** were also isolated. The range of products isolated was attributed to the formation of radical intermediates. This was verified by the observation that the use of nitrobenzene as a radical scavenger inhibited the reaction.



R	**123**	**124**	**125**	**126**	**127**	**128**
Ph	40	60				
H	50	50				
*t*Bu	54	46				
$(CH_2)_2CH_3$	31	25	25	5	10	4

Scheme 2.43 Cesium fluoroxysulfate as a fluorinating agent[187]

In 1995, F-TEDA-BF_4, or Selectfluor® (Figure 28) was used for the regioselective conversion of 1-substituted-2-phenyl acetylenes to give α,α-difluoroketones.[188] The authors conducted the reaction in acetonitrile and H_2O at reflux for 24 hours and isolated difluorinated ketone **129** as the sole product (Scheme 2.44). The regioselectivity of the reaction was the same for four acetylenes shown in Scheme 2.44, however, the reaction was unsuccessful for 1-decyne.[188]

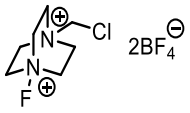
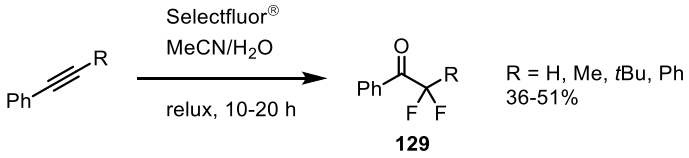
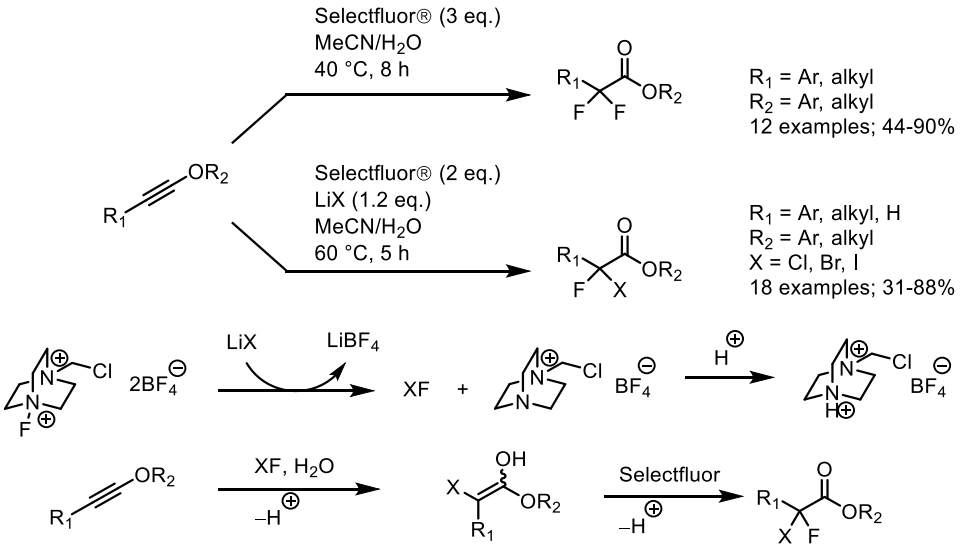


Figure 28 F-TEDA-BF_4 or Selectfluor®



Scheme 2.44 Difluorohydration of 1-phenylacetylenes[188]

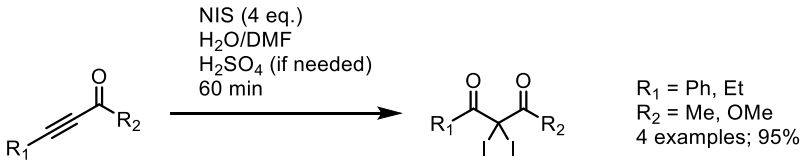
In 2015, the difluorination of ynol ethers was reported. Hu *et al.* found that it was possible to generate α,α-difluoro esters from ynol ethers using Selectfluor® in a mixture of acetonitrile and H_2O (Scheme 2.45).[189] The reaction required heating to 40 °C for 8 hours. They then went on to show that conducting the reaction in the presence of a lithium halide at 60 °C for 5 hours gave α,α-fluorohalo esters (Scheme 2.45).[189] The yields of both reactions varied greatly. The group proposed a mechanism based on Selectfluor oxidising the lithium halide to give active halogenating reagent XF. Halohydration of the alkyne can then take place, followed by electrophilic fluorination with Selectfluor (Scheme 2.45). The ability to sequentially add a halogen provides products that can be utilised to develop fluorinated α-amino acids.



Scheme 2.45 Synthesis of α,α-fluorohalo esters from ynol esters and the proposed mechanism of the reaction[189]

2.1.3.3 Diiodohydration of alkynes

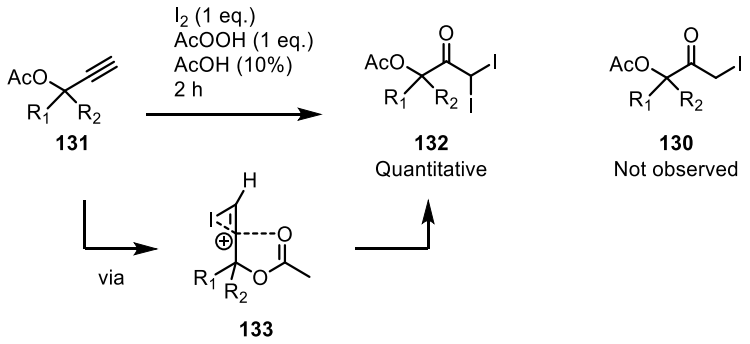
Diiodohydrations of alkynes have been successful when using *N*-iodosuccinimide (NIS) as an electrophilic source of iodine. This was first demonstrated in 1998 in the transformation of carbonyl conjugated alkynes in a solvent mixture of H_2O and DMF (Scheme 2.46).[169]



Scheme 2.46 Diodohydration of carbonyl conjugated alkynes[169]

NIS has since been used in the diiodohydration of propargylamides[190] and terminal aromatic alkynes.[171]

During the synthesis of an intermediate of artificial corticosteroids, Nitta *et al.* used a previously reported reaction[191] in the hope to synthesise enol acetate **130** (Scheme 2.47).[165] In fact, when they treated alkynyl acetate **131** with iodine, peracetic acid and acetic acid, they obtained diiodoketone **132** in quantitative yield. When the propargylic acetoxyl group was replaced with a hydroxyl group, the reaction was much slower and resulted in numerous products which weren't isolated or identified, demonstrating the need for the stabilisation of proposed intermediate **133** (Scheme 2.47).[165]

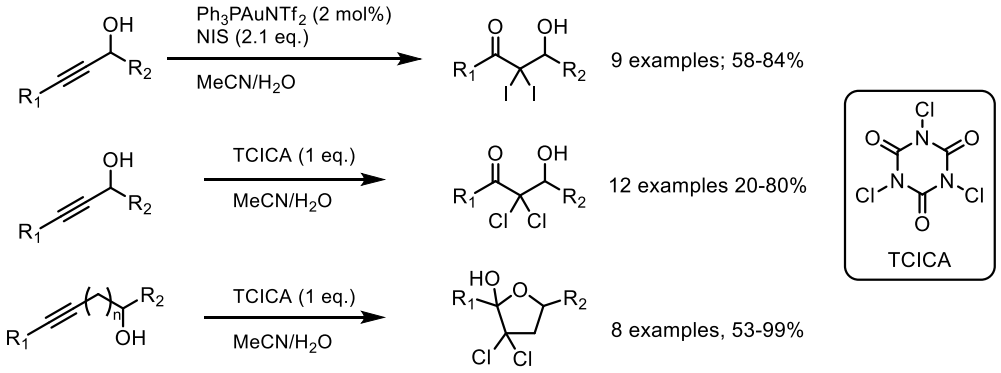


Scheme 2.47 Unexpected α,α-diiodoketone formation and the proposed carbonium intermediate, stabilised by neighbouring acetoxyl group[165]

Previously within the Sheppard group, the diiodohydration of propargylic alcohols was developed using *N*-iodosuccinimde (Scheme 2.48).[192] It was found during this work that a gold catalyst ($Ph_3PAuNTf_2$, Gagosz catalyst) was required for the diiodohydration reactions to proceed. A range of different α,α-diiodo-β-

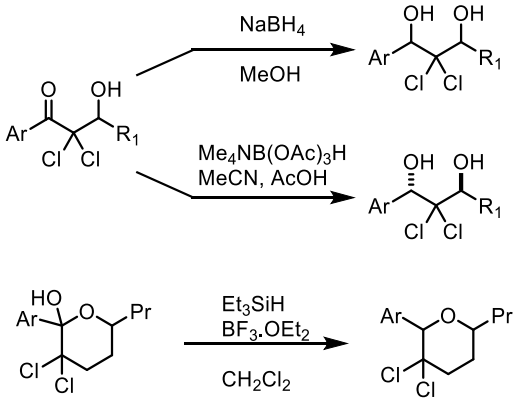
hydroxyketones were synthesised, including secondary and primary alcohols, though tertiary alcohols were not suitable substrates.

Following this, efforts were spent on developing the dichlorohydration of propargylic alcohols. It was found that trichloroisocyanuric acid (TCICA) effected the dichlorohydration reaction and that a gold catalyst was not necessary (Scheme 2.48). The substrate scope was larger than for the diiodohydration reactions, and tolerated primary, secondary and tertiary alcohols. Using alkynols, it was also possible to prepare lactol products (Scheme 2.48).[192]



Scheme 2.48 Dihalohydration reactions of propargylic alcohols previously reported within the Sheppard group[192]

A handful of further transformations were applied to the dichlorinated products, namely sodium borohydride reductions, triethylsilane reductions and an *anti*-selective reduction using sodium triacetyoxy borohydride (Scheme 2.49).

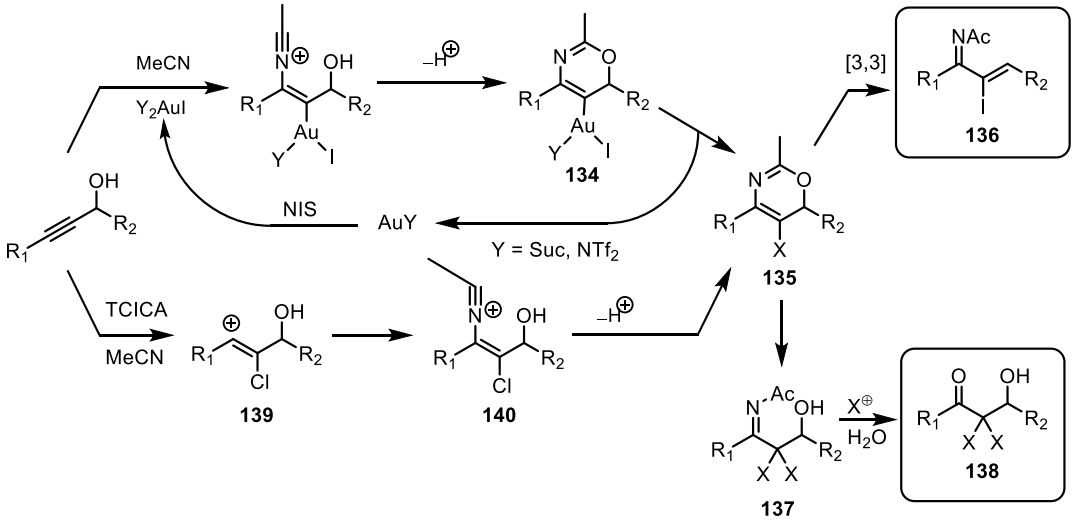


Scheme 2.49 Reduction reactions of dichlorinated products[192]

For the diiodohydration reactions, it was proposed that the alkyne was activated by the gold catalyst, which induces nucleophilic attack of MeCN. The intermediate undergoes cyclisation to give **134** (Scheme 2.50). Subsequent reductive elimination provides oxazine **135**. The gold salt can then be reoxidised by NIS. Oxazine **135** can

undergo a 6π-electrocyclic ring opening to give *N*-acyl imine **136**, which was observed when the reaction was conducted in the absence of H_2O. In the presence of H_2O, oxazine **135** is halogenated to give *N*-acyl imine **137** which is hydrolysed to the α,α-dihalo-β-hydroxyketone **138**.

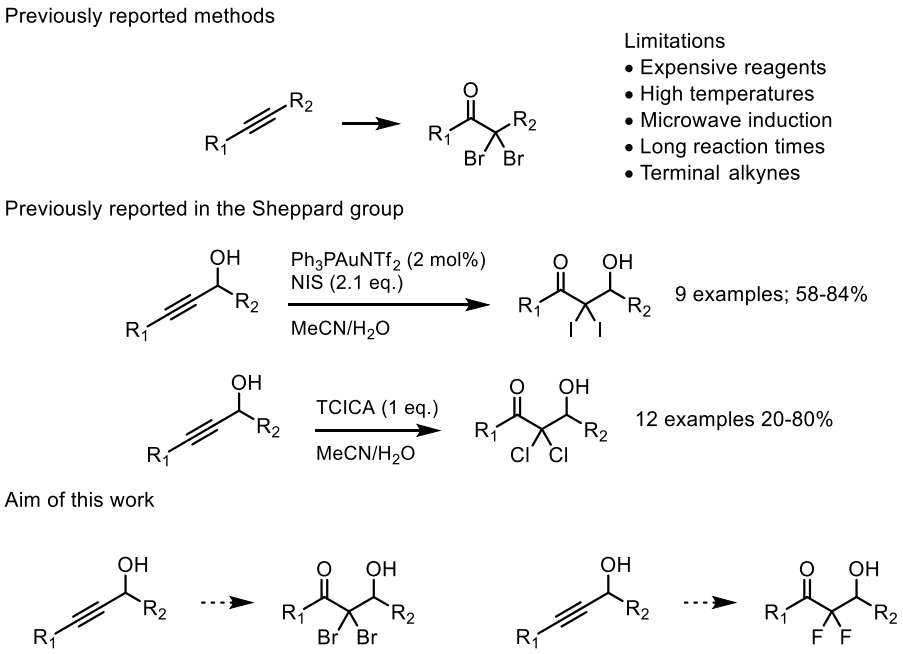
For the dichlorohydration reactions, the gold catalyst is not required to activate the alkyne so it is proposed that vinyl cation **139** forms which is followed by nucleophilic attack by MeCN to give **140**. Cyclisation to give oxazine **135** occurs and then the mechanism proceeds analogously to the diiodination.



Scheme 2.50 Proposed mechanism for the dihalohydration reactions developed within the Sheppard group

2.2 Aims

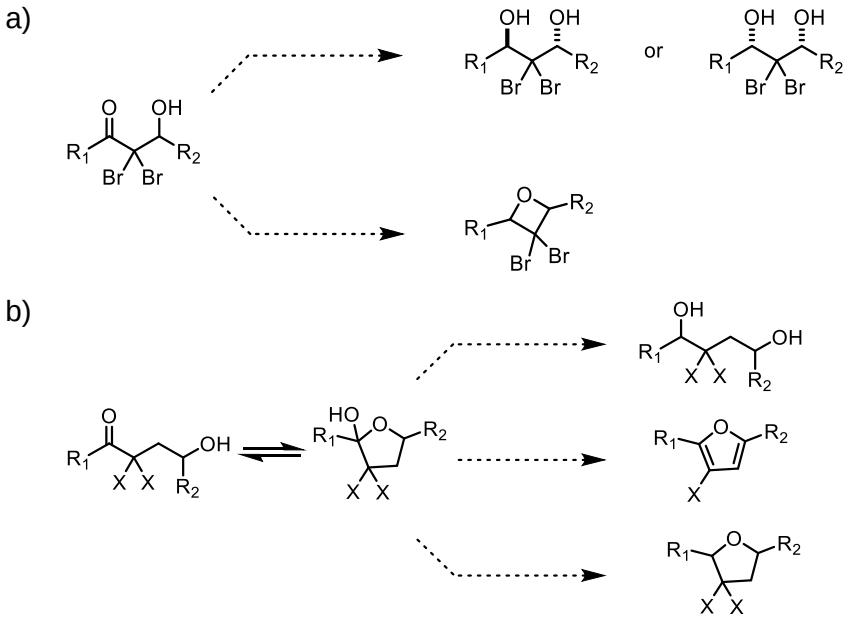
The direct transformation of alkynes into compouds with more versatile functionality within a close proximity allows access to more chemical complexity, even more so if applying this to propargylic alcohols. It has been demonstrated that this can be achieved by using α,α-dihalohydration reactions, however there are limitations with previously reported methods. Previously within the Sheppard group, methods to generate 2,2-diiodohydroxyketones and 2,2-dichlorohydroxyketones from propargylic alcohols have been developed (Scheme 2.51). The aim of this project is to develop the analogous dibromohydration and difluorohydration reactions, whilst trying to overcome previous limitations such as expensive reagents, high temperatures, the requirement for microwave induction or long reaction times. Additionally, most of the previously documented dibromohydration methods have focussed on non-propargylic alcohols, and in particular the transformation of terminal alkynes. It is hoped that a new method that will be successful for the transformation of propargylic alcohols will be found.



Scheme 2.51 Envisaged transformation of propargylic alcohols to α,α-dibromo- and α,α-difluoro-β-hydroxyketones

As the presence of a carbonyl and dihalide can be used in further functionalisation, derivatisation of the dihalohydroxyketones will be attempted to demonstrate the chemical diversity that can rapidly be accessed from these valuable compounds. These could include diastereoselective reduction of the α,α-dihalo-β-hydroxyketones,

or oxetane formation (Scheme 2.52a). Application of the dihalohydration reaction to homopropargylic alcohols should allow access to dihalolactols which could be further manipulated. For example, it may be possible to access halogenated furans and lactols (Scheme 2.52b).

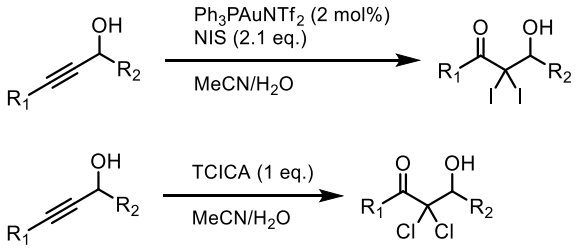


Scheme 2.52 Potential further transformations of dihalohydration products

2.3 Synthesis of dibromoketoalcohols

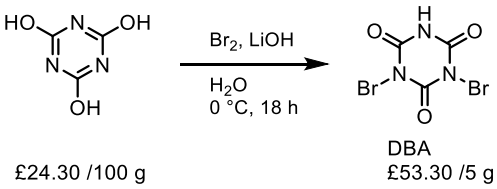
2.3.1 Background

Previously within the Sheppard group, the diiodohydration and dichlorohydration of propargylic alcohols was developed (Scheme 2.53).[192] It was found during this work that a gold catalyst was required for the diiodohydration reactions, but it was not needed for the dichlorohydration reactions. It was also discovered that the substrate scope of the chlorination reactions was much wider than the iodination reactions and included tertiary alcohols and aryl groups attached to the alcohol.



Scheme 2.53 Previously reported dihalohydration reactions of propargylic alcohols

Following these findings, attempts began on expanding the transformation to the analogous dibromohydration reactions, with an interest in the potential requirement of a catalyst and also the substrate scope of the reaction. The dichlorohydration reaction did not proceed when using NCS as an electrophilic source of chlorine, and so it was perhaps unsurprising that the dibromohydration reaction did not proceed using NBS both in the presence and absence of a gold catalyst. Next, it was decided to use dibromoisocyanuric acid (DBA, Scheme 2.54). DBA is commercially available but can also be made from cheap starting materials (Scheme 2.54).



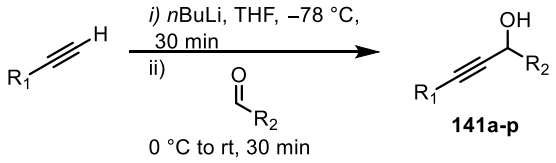
Scheme 2.54 Synthesis of dibromoisocyanuric acid. Cost of isocyanuric acid from Sigma

Previous work showed that desired dibromohydration reaction proceeded in the presence of DBA and that the reaction did not require a catalyst.[193] A small range of

α,α-dibromo-β-hydroxyketones were prepared, which will be presented below with the full substrate scope conducted as part of this work (Section 2.3.3).

2.3.2 Synthesis of propargylic alcohols

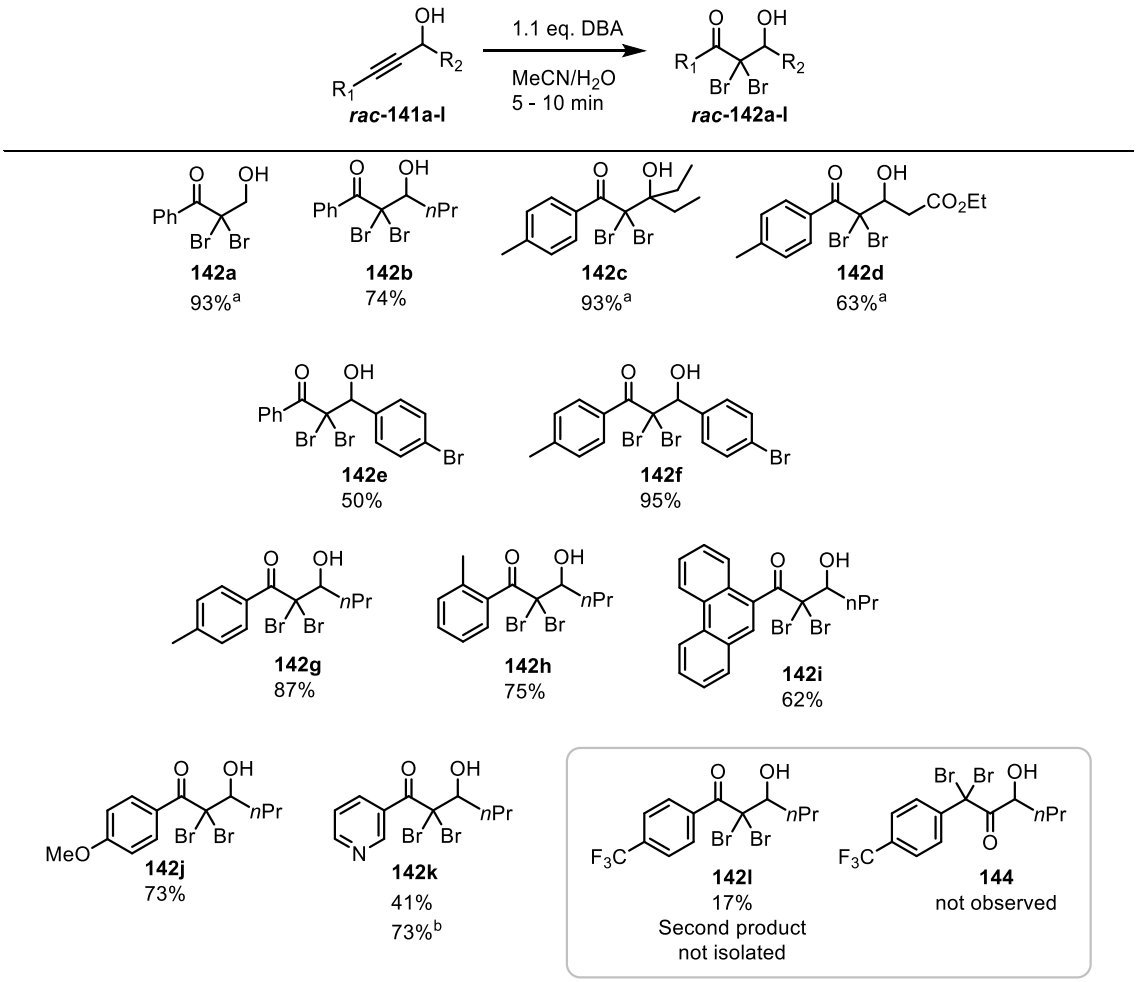
A range of propargylic alcohols **141** were prepared by the general procedure shown in Scheme 2.55.



Scheme 2.55 General procedure for the preparation of propargylic alcohols

2.3.3 Scope of dibromohydration reaction

Following the discovery within the Sheppard group that dibromohydration reactions of propargylic alcohols could be elicited using DBA,[193] the scope of this reaction was explored (Scheme 2.56). Pleasingly, the reaction proceeds with primary (**141a**), secondary (**141b**) and tertiary alcohols (**141c**); and also aromatic alcohols (**141e-f**). The reaction is successful with propargylic alcohols derived from both *para*- and *ortho*-tolylacetylene to give the desired product in good yields (**142g-h**). It was also found that increasing the steric bulk to a phenanthrene has little effect on the yield (**142i**). Unsurprisingly, the reaction is high yielding with an electron donating group on the aromatic ring (**142j**). It was unknown if the reaction of a propargylic alcohol containing an electron withdrawing group would proceed, or if the regioselectivity would be reversed in response to the reduced stabilisation of the resultant vinylic cation **143** (Figure 29). To this end, trifluoromethyl substituted propargylic alcohol **141l** was subjected to the standard reaction conditions and the desired product **142l** was isolated in 17% yield. Analysis of the crude NMR showed that no starting material remained and that α,α-dibromo-β-hydroxyketone **142l** was one of two major products, both present in an approximate 1:1 ratio. Unfortunately, the second product was not isolated following purification, however, analysis of the crude NMR spectrum suggested that it wasn't regioisomer **144** (Scheme 2.56).



Scheme 2.56 Successful dibromohydration reactions [a] Reactions completed by Jarryl D'Oyley[193] [b] 5 equivalents of DBA

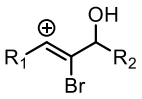
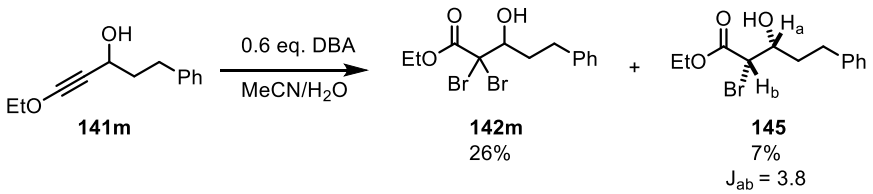


Figure 29 Proposed vinyl cation intermediate that would be stabilised when R_1 = electron donating and destabilised when R_1 = electron withdrawing

Gratifyingly, a pyridine substituent was tolerated, giving desired product **142k**, albeit in a lower yield of 41%. It is worth noting that under these reaction conditions 23% of the starting material was recovered, indicating reduced reactivity of the propargylic alcohol or potentially complexation with DBA or the formation of halogen bonds,[194] thus lowering the amount of electrophilic bromine available in the reaction. Repeating the reaction with 5 equivalents of DBA gave 100% conversion and 73% isolated yield.

When propargylic alcohol **141m** was subjected to the standard conditions of 1.1 equivalents of DBA, the major product was the expected α,α-dibromo-β-hydroxyester

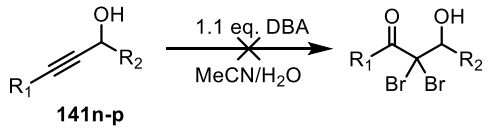
142m (53% yield), however, a trace amount of a monobrominated product was also observed. Lowering the amount of DBA to 0.6 equivalents of DBA allowed the isolation of the expected dibrominated product **142m** in 26% yield, but also the isolation of monobrominated product **145** in 7% yield (Scheme 2.57). Only the diastereomer shown in Scheme 2.57 was isolated, as determined by coupling constant analysis. The decomposition of α,α-dibromoketones on standing in air to give the monobrominated product has previously been observed[177] and so it is not possible to conclude if this was formed under the reaction conditions or is a degradation product. However, when **142m** was resubjected to the reaction conditions, only **142m** remained, implying that **145** is formed as a by-product.



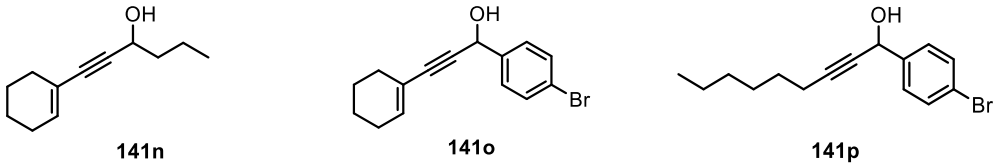
141m | **142m** 26% | **145** 7% J_{ab} = 3.8

Scheme 2.57 Treating propargylic alcohol **141m** with a lower amount of DBA allowed mono- and dibrominated products to be isolated

The scope of the dibromohydration reaction is wide when R_1 = aromatic, however some substrates were not tolerated. Cyclohexene derived propargylic alcohol **141n** gave a complex mixture of unidentified products, presumably due to the possibility of reaction with the alkene. Intrigued by this, propargylic alcohol **141o** was synthesised, in the hope of simplifying the NMR spectrum. Unfortunately, this still gave a complex mixture of products that could not be separated. A long aliphatic chain was not tolerated either, with the reaction of **141p** leading to a range of side reactions within which the desired dibrominated product could not be detected.



141n-p

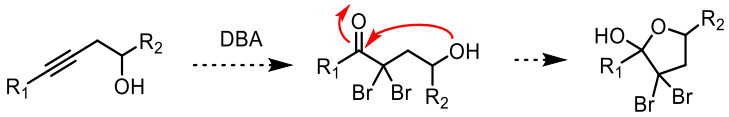


141n | **141o** | **141p**

Scheme 2.58 Unsuccessful dibromohydration reactions

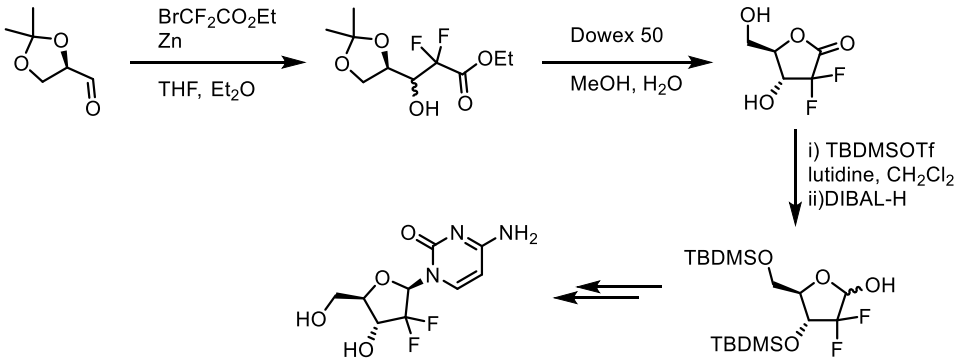
2.3.4 Synthesis of dihalolactols

It was envisaged that applying the dibromohydration reaction to a homopropargylic alcohol would allow cyclisation of the resultant α,α-dibromo-β-hydroxyketone to give a dibromolactol (Scheme 2.59).



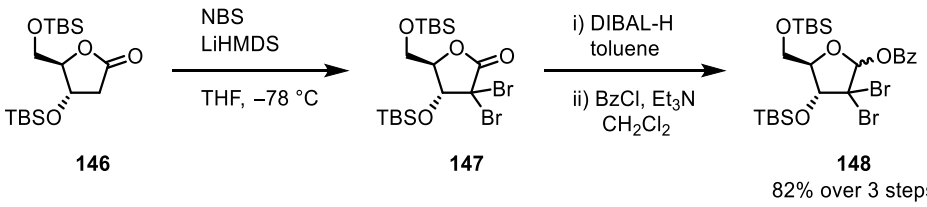
Scheme 2.59 Envisaged formation of dihalolactols via the dibromohydration of homopropargylic alcohols

Dihalolactols are small, highly functionalised compounds that are useful synthetic building blocks for pharmaceuticals. In particular, methods to develop difluorolactols have been explored as they are a key intermediate in the synthesis of fluorinated nucleoside analogue gemcitabine that has been used in the treatment of various cancers[195] and for its anti-HIV properties (Scheme 2.60).[196]



Scheme 2.60 The use of difluorolactols in the synthesis of gemcitabine[195]

Both dichlorolactols[197] and difluorolactols[196] have previously been synthesised, however, much less has been reported on the synthesis of dibromolactols. Recently, dibromination of dihydrofuranone **146** was reported to give dibrominated furanone **147**. This was then reduced and benzoylated to give dibromolactol **148** in 82% yield over 3 steps.[197]

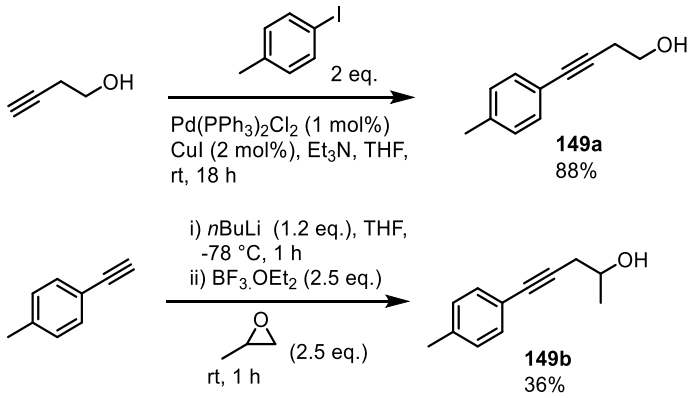


146 **147** **148**
82% over 3 steps

Scheme 2.61 Previously reported synthesis of a benzoylated dibromolactol[197]

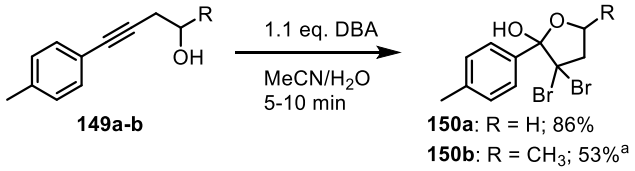
Dihalolactols have a large amount of synthetic utility, however, there are currently a limited number of methods to synthesise them. It would be advantageous to access these versatile dihalolactols in one step from homopropargylic alcohols, allowing the further transformation of them to be explored.

To this end, homopropargylic alcohol **149a** was synthesised via a Sonogashira coupling in excellent yield, whereas the synthesis of **149b** via opening of an epoxide only proceeded in 36% yield (Scheme 2.62).



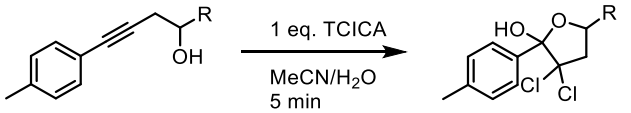
Scheme 2.62 Synthesis of homopropargylic alcohols **149a** and **149b**

Gratifyingly, both homopropargylic alcohols were acceptable substrates for the dibromohydration reaction and gave lactol products **150a** and **150b** in 86% and 53% yield respectively (Scheme 2.63). Lactol **150b** was isolated as an inseparable 1:2.5 mixture of diastereomers.



Scheme 2.63 Dibromohydration of homopropargylic alcohols [a] Isolated as a 1:2.5 inseparable mixture of diastereomers

Encouraged by the formation of these lactols, the previously reported method of dichlorohydration[192] was also used to generate dichlorolactols **151a** and **151b** in excellent yields of 83% and 89% respectively (Scheme 2.64).



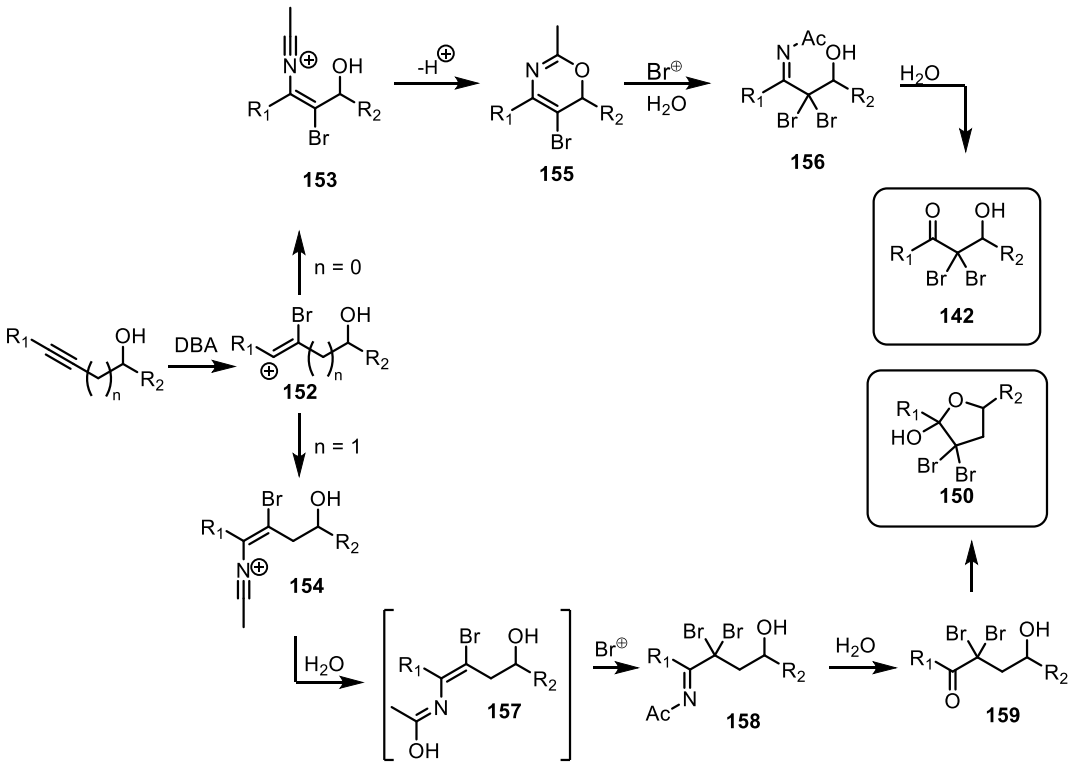
149a-b

151a: R = H; 83%
151b: R = CH_3; 89%

Scheme 2.64 Dichlorohydration of homopropargylic alcohols [a] Isolated as an inseparable 1:1.8 mixture of diastereomers

The proposed mechanism for the dibromohydration reaction of propargylic and homopropargylic alcohols is shown in Scheme 2.65. Nucleophilic attack of the alkyne to DBA occurs to give vinyl cation **152** which is then attacked by acetonitrile to give cation **153**, if the alcohol is propargylic, or cation **154** if the alcohol is homopropargylic. For propargylic alcohols, cyclisation occurs to give bromooxazine **155**, which is brominated again with the concurrent opening of the oxazine in the presence of H_2O to give imine **156**. The imine is then hydrolysed to give α,α-dibromo-β-hydroxyketone **142** as the product.

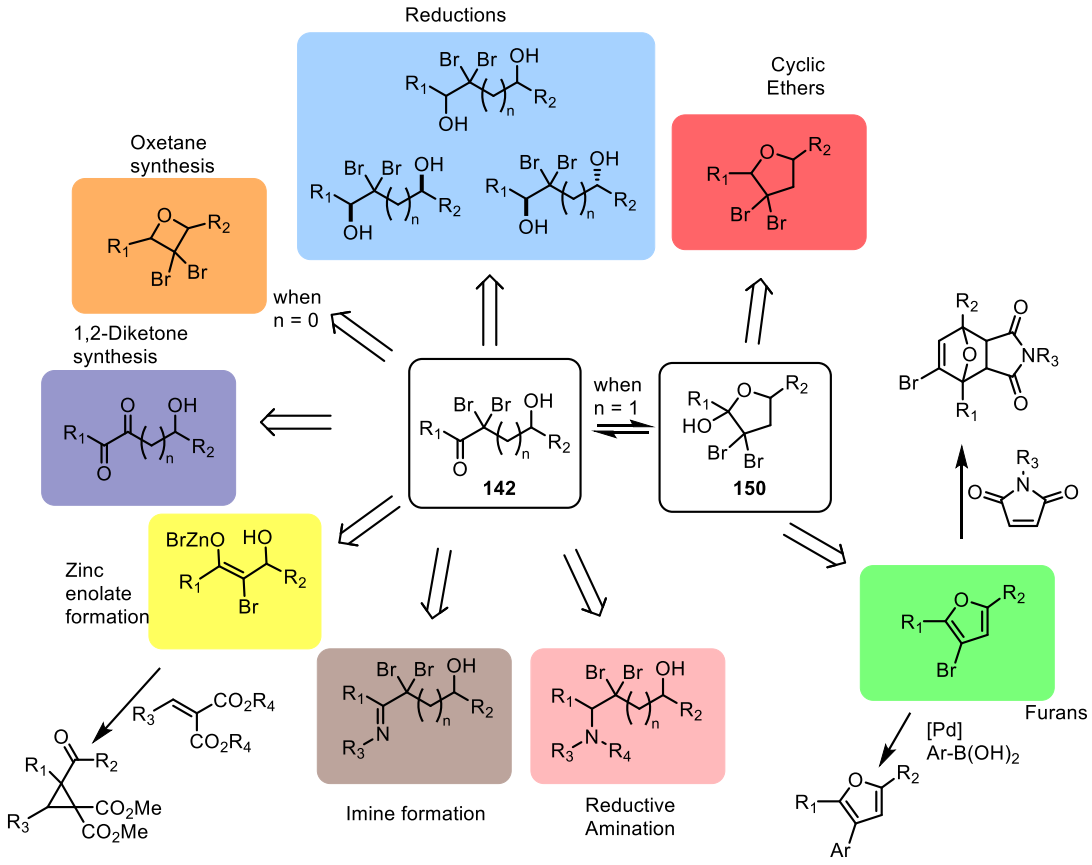
For homopropargylic alcohols, an oxazine won't form and instead H_2O will attack cation **154** to give acetimidic acid **157** which will rearrange to give more stable acetamide **158** and become brominated again in the process. From dibromoacetamide **158**, imine hydrolysis will occur to give α,α-dibromo-γ-hydroxyketone **159** which can cyclise to give the dibromolactol **150**.



Scheme 2.65 Proposed mechanism for the dibromohydration reactions of propargylic alcohols (n = 0) and homopropargylic alcohols (n = 1)

2.4 Further functionalisation of dibromoketoalcohol products

The wide scope of the dibromohydration reaction has been used to generate a variety of products. However, it was hoped that further functionalisation of these products would give access to more varied chemical functionality. Some of the envisaged transformations are shown in Scheme 2.66.



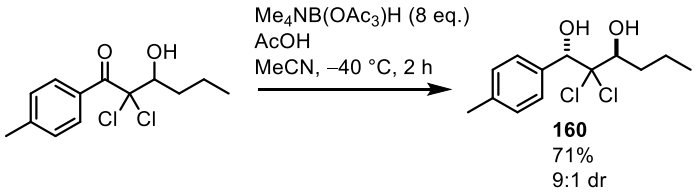
Scheme 2.66 Potential transformations of α-dibromoketone products, including reductions, oxetane synthesis, 1,2 diketone,[198] zinc enolate formation,[199] imine formation, reductive amination, furan synthesis followed by Suzuki-Miyaura couling[200] or Diels-Alder,[201] and cyclic ether synthesis

Below, the transformations that were attempted will be discussed.

2.4.1 Reductions of dibromoketoalcohol products

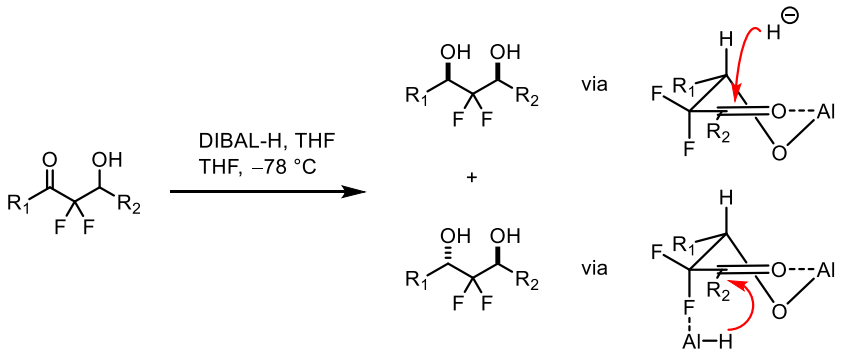
2.4.1.1 Diastereoselective synthesis of *syn*-1,3-diols

During the previously reported dichlorohydration reactions, it was found that diastereoselective reduction of the product could be achieved by using tetramethylammonium triacetoxyborohydride to give the *anti*-diol **160** (Scheme 2.67).[192]



Scheme 2.67 Previously reported diastereoselective reduction of dichlorohydroxyketone[192]

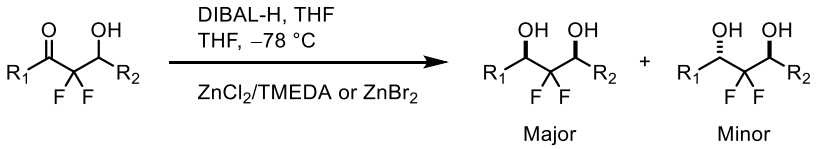
It was hoped that a strategy to elicit the complementary selectivity would be attainable. The *syn*-selective reduction of β-hydroxyketones has been well studied and generally proceeds via chelation control.[202] However, during investigations of the reduction of α,α-difluoro-β-hydroxyketones using DIBAL-H, it was found that *syn*-diols were not formed with high selectivity and in some cases, the *anti*-diol was the major product (Scheme 2.68).[203] This was attributed to the formation of a 6-membered cyclic chelation transition state as shown in Scheme 2.68. The axial α-fluorine interacts with the aluminium, resulting in hydride being delivered from the lower face as shown in Scheme 2.68, leading to the *anti*-product. Kuroboshi and Ishihara then explored methods of synthesising 2,2-difluorinated *syn*-diols.



Scheme 2.68 Previously reported DIBAL-H reductions of α,α-difluoro-β-hydroxyketones[203]

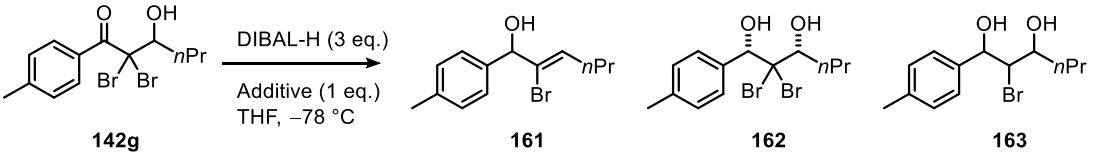
They found that using DIBAL-H with an additive of $ZnCl_2$/TMEDA or $ZnBr_2$ had a dramatic effect on the *syn*:*anti* ratio, in some cases improving it up to 96:4 in quantitative yields (Scheme 2.69).[203] This was explained by the ability of Lewis acids to weaken or prevent the F-Al interaction by coordinating to the α-fluorine.[203] It was suggested that the $ZnCl_2$/TMEDA complex would dissociate in solution to allow

TMEDA to coordinate to DIBAL-H , hence reducing the Lewis acidity of DIBAL-H. A complex of $ZnBr_2$/TMEDA would not dissociate to the same extent, and therefore was not effective.



Scheme 2.69 Previously reported DIBAL-H reductions of α,α-difluoro-β-hydroxyketones in the presence of an additive of $ZnCl_2$/TMEDA or $ZnBr_2$[203]

In response to this, a DIBAL-H reduction was attempted both with and without $ZnCl_2$ -TMEDA as an additive. In both cases, the reaction gave numerous products. Of these, **161**, **162** and **163** could be identified, and their compositions in the reactions with and without an additive can be seen in Scheme 2.70.

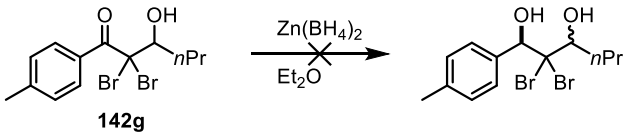


Additive	Conversion			
None	100%	1	2.5	1.7
$ZnCl_2$-TMEDA	100%	1	7.4	1.6

Scheme 2.70 NMR ratios of the products of DIBAL-H reduction of α,α-dibromo-β-hydroxyketone **142g** with and without $ZnCl_2$-TMEDA

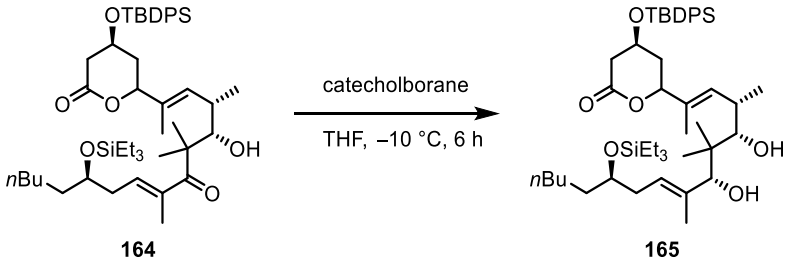
As mentioned earlier, the degradation of α,α-dibromoketones into the monobrominated products has previously been observed[177] and so it could be that these conditions encourage the degradation of α,α-dibromo-β-hydroxyketone **142g** into α-bromoketone which is then reduced, or it could be a result of the reaction conditions. Due to the problematic purification of the numerous products formed during this reaction, particularly the separation of bromohydrin **161** and dibrominated diol **162**, other routes to *syn*-diol **162** were explored.

Zinc borohydride has previously been used to reduce conjugated aldehydes preferentially over conjugated enones[204] and has been shown to provide *syn* selectivity during the reduction of β-hydroxyketones to form *syn*-1,3 diols.[205] Based on this, it was hoped that zinc borohydride would give the desired selectivity in the reduction of α,α-dibromo-β-hydroxyketone **142g**. Unfortunately, the reaction was unsuccessful and attempts gave only starting material (Scheme 2.71).



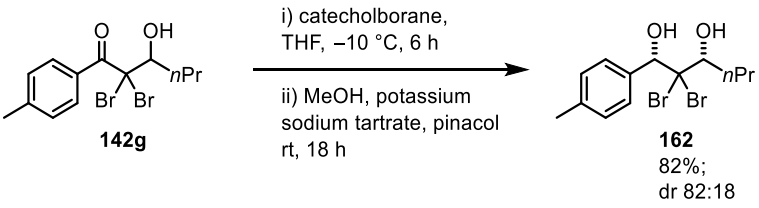
Scheme 2.71 Unsuccessful diastereoselective reduction of α,α-dibrominated hydroxyketone **142g** with $Zn(BH_4)_2$

Another strategy, previously shown to generate *syn*-1,3-diols, is the use of catecholborane. Catecholborane has been used in the synthesis of natural products consisting of *syn*-1,3-diols separated by an all-carbon quaternary centre (**164**, Scheme 2.72).[206] The authors' attempts at *syn* selective reduction using Et_2BOMe and $NaBH_4$ were unsuccessful, however, the use of catecholborane, as previously reported by Evans and Hoveyda,[207] gave the desired *syn*-1,3 diol **165**. Unfortunately, the yield and diastereoselectivity of this step were not given.



Scheme 2.72 Previously reported *syn*-selective reduction of β-hydroxyketone[206]

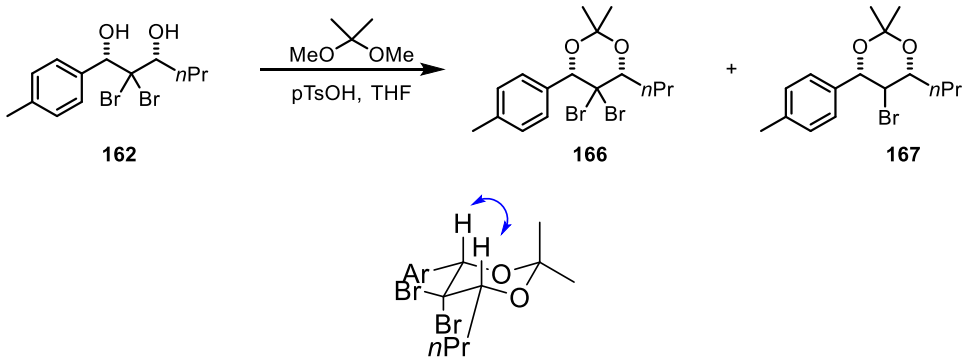
There were concerns that the densely substituted framework in **164** was responsible for the diastereoselectivity, and therefore the reaction would not be successful for simpler β-hydroxyketone **142g**. Pleasingly, catecholborane worked with our dibromoketoalcohol system and gave the desired diol **162** in 82% yield, with a good dr of 82:18 (Scheme 2.73). Whilst the two diastereomers could not be completely separated, a pure sample of the major isomer was isolated in 64% yield.



Scheme 2.73 Catecholborane *syn*-selective reduction of α,α-dibromo-β-hydroxyketone **142g**

In order to confirm the stereochemistry of **162**, acetonide **166** was formed (Scheme 2.74). Interestingly, the acetal formation resulted in a small amount of

monobrominated acetal **167**. Fortunately, the NMR signals for the dibrominated product could be observed clearly and using NMR spectroscopy, an nOe interaction was observed between protons shown in Scheme 2.74, confirming that the *syn* diol had been formed.

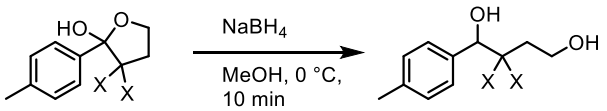


162 **166** **167**

Scheme 2.74 Determination of stereochemistry of *syn*-1,3-diol **162**

2.4.1.2 Preparation of 1,4-diols

Another envisaged transformation is the reduction of the dihalolactols to give 1,4-diols, which are important synthetic building blocks.[208] Reduction of the dihalolactols proceeded using sodium borohydride with success and both the dibrominated and dichlorinated lactols **150a** and **151a** were reduced to give 1,4-diols **168** and **169** in excellent yields (Scheme 2.75).

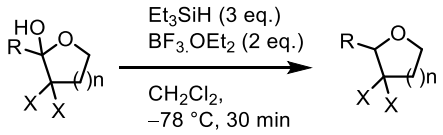


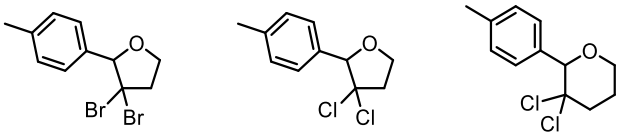
168: X = Cl; Quantitative
169: X = Br; 68%

Scheme 2.75 Sodium borohydride reduction of halogenated lactols

2.4.1.3 Preparation of cyclic ethers

Cyclic ethers could also be accessed from the halogenated lactols via triethylsilane reduction in the presence of boron trifluoride diethyl etherate (Scheme 2.76). Quantitative yields of tetrahydrofuran products **170** and **171** were obtained. Pleasingly, this strategy was also successful when applied to previously reported 6-membered lactol to generate tetrahydropyran **172** in 60% yield.



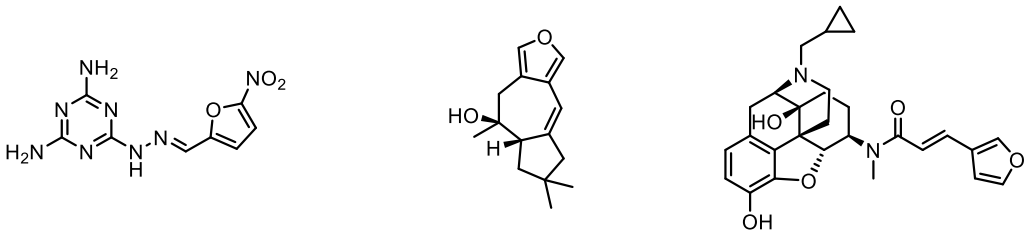


170 Quantitative | **171** Quantitative | **172** 60%

Scheme 2.76 Triethylsilane reduction of dihalogenated lactols

2.4.2 Furan synthesis

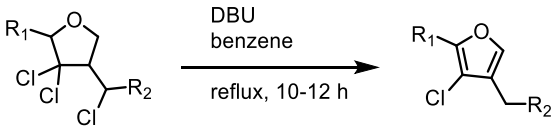
Furans are prevalent in natural products, and so it is not surprising that molecules containing furans have been found to have a wide range of pharmaceutical[209–212] and agrochemical applications (Figure 30).[213] For this reason, the synthesis of substituted furans has received considerable interest. It was envisaged that by creating furans from the synthesised lactol products, it would be possible to create 3-halofurans. The halofurans would be excellent starting points for further manipulation, for example in cross coupling reactions,[214,215] allowing a diverse range of furan products to be accessed rapidly.



Activity against trypanosomatid parasites[210] | Furoscrobiculin B Antifungal and antibacterial activity[211] | Nalfurafine Antipruritis activity[212]

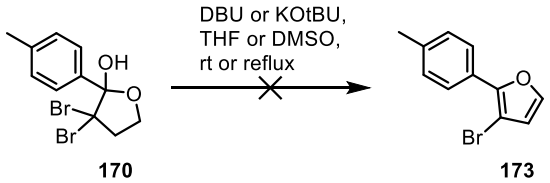
Figure 30 A selection of substituted furans that show medicinally relevant activity

Initially, inspiration came from the work of Ram and Kumar who used DBU for dehydrochlorination to form 3-chlorofurans (Scheme 2.77).[216]



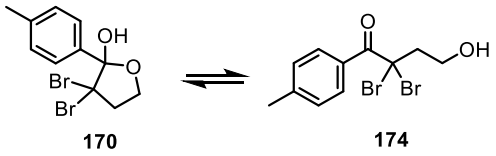
Scheme 2.77 Previously reported 3-chlorofuran synthesis[216]

It was decided that this strategy would be tried to generate 3-bromofuran **173**. Treating bromolactol **170** with DBU in THF gave a complex mixture of products, however, analysis of the crude NMR spectrum appeared to show the presence of a furan. Unfortunately, after purification by column chromatography, the furan could not be isolated. The reaction was repeated using DMSO as a solvent and also using KO*t*Bu instead of DBU in either THF or DMSO, and in all cases the furan product was present in the crude mixture but could not be isolated (Scheme 2.78).



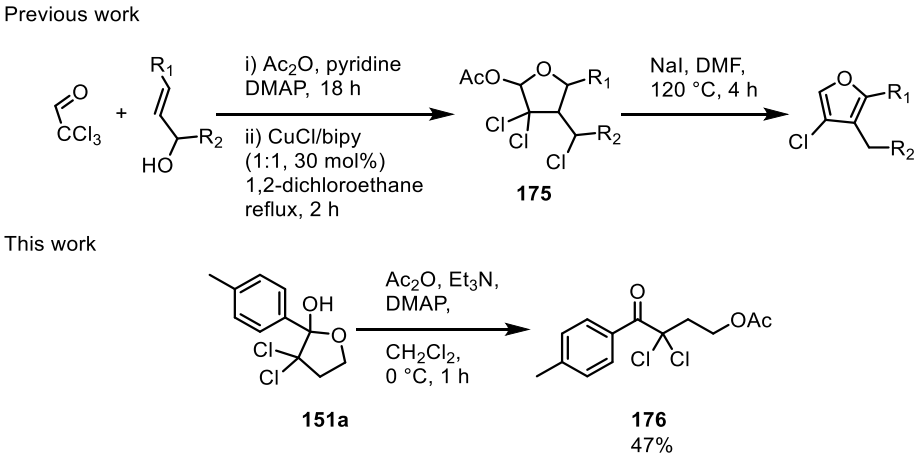
Scheme 2.78 Attempted synthesis of 3-bromofuran

The bromolactol **170** is likely to be in equilibrium with the open 4-hydroxybutanone form **174** (Scheme 2.79), which could account for the complex mixture of products observed.



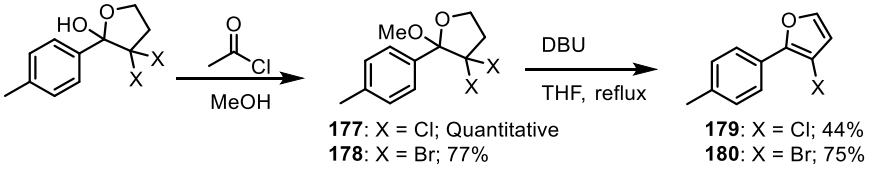
Scheme 2.79 Equilibrium of bromolactol **170** and 4-hydroxybutanone **174**

Converting the hydroxyl group into a better leaving group would encourage furan formation and also limit any possible side reactions that may occur with the open chain ketone. 3-Chlorofurans have been synthesised from 2-acetoxytetrahydrofurans **175** using NaI (Scheme 2.80),[217] so our first step toward the synthesis of a 3-halofuran was acetylation of dichlorolactol **151a**. However, and perhaps unsurprisingly, the major product was the acetylated open ketone **176** (Scheme 2.80).



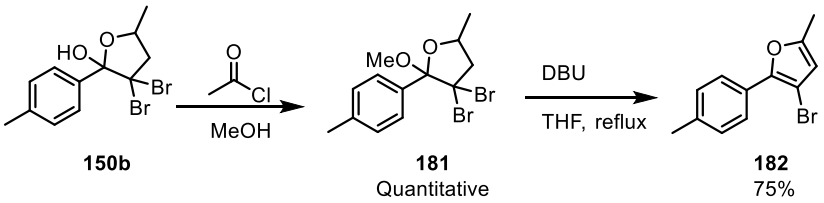
Scheme 2.80 Previously reported aromatisation of 2-acetoxytetrahydrofurans[217] and acetylation of dichlorolactol **151a**

Instead, 2-methoxytetrahydrofurans **177** and **178** were synthesised from both the dichloro- and dibromo-lactols, and refluxing them in THF with DBU resulted in the desired 3-halofurans in 44% and 75% yield respectively (Scheme 2.81). It was found that bromo-furan **180** was particularly unstable and degraded at room temperature within 36 hours.



Scheme 2.81 Furan synthesis from 3,3-dihalotetrahydrofurans

The same strategy was used to synthesise 2,4-substituted-3-bromofuran **182** in 75% yield (Scheme 2.82) which was found to be more stable.

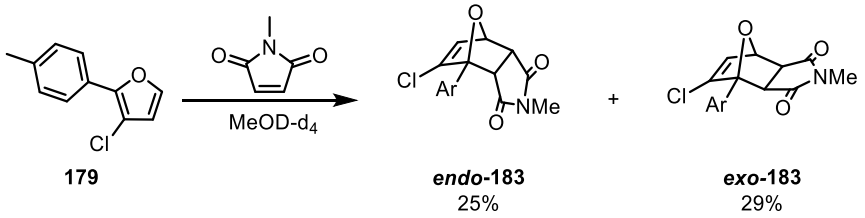


Scheme 2.82 Synthesis of 2,4-disubstituted bromofuran

2.4.2.1 Diels-Alder cyclisation

Recently in the Sheppard group, the synthesis of *endo*-cantharimides has been published using a Diels-Alder cyclisation of 3-alkoxyfurans and maleimides.[201] Keen

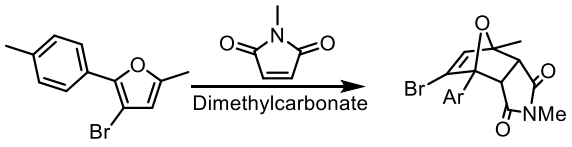
to explore how far we could functionalise our halofurans, we used these conditions. Initially this was done on a small scale in an NMR tube. Interestingly, this gave a mixture of *endo* and *exo* products in 25% and 29% yield respectively (Scheme 2.83). This contrasts with the original work in which the reaction was fairly *endo* selective. Analysis of the crude NMR spectrum showed that the ratio of *endo*:*exo* product was 7:3, implying that the isolated yields obtained are due to purification issues.



179 ***endo*-183** 25% ***exo*-183** 29%

Scheme 2.83 Diels Alder reaction of 3-chlorofuran and *N*-methyl maleimide

The previously published work used dimethylcarbonate as a solvent.[201] Applying this to 2,4-substituted furan **182**, solely the *endo* product **184** was observed, which was isolated in 84% yield (Scheme 2.84).



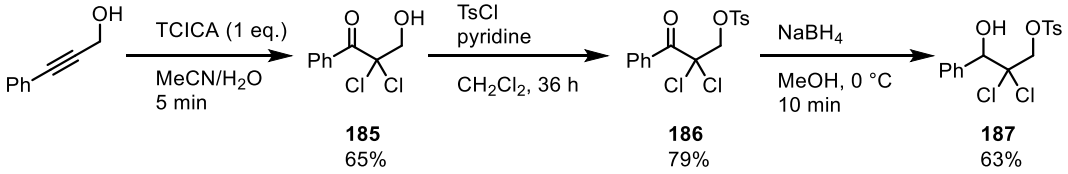
182 ***endo*-184** 84%

Scheme 2.84 Diels Alder reaction of 3-bromofuran and *N*-methyl maleimide

It is possible that either the solvent or substitution of the furan, or indeed both, are responsible for the selectivity that is observed in this Diels-Alder reaction. This could be more thoroughly investigated in the future.

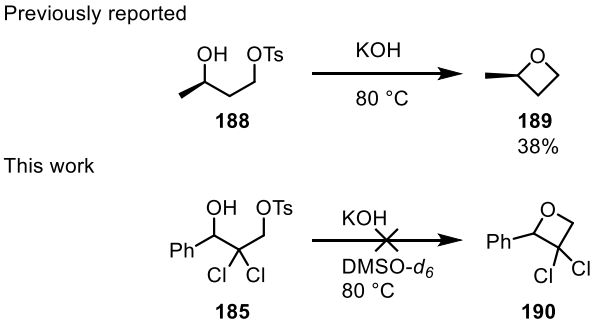
2.4.1 Oxetane synthesis

The ability of oxetanes to influence solubility, basicity, lipophilicity and stability of compounds,[218] and also act as isosteric replacement for *gem*-dimethyl groups or carbonyls,[219] has led to a relatively recent resurgence of interest in their synthesis. In light of this, it was considered whether a *gem*-dihalooxetane could be created from the dihalohydration products. To this end, α,α-dichloro-β-hydroxyketone **185** was synthesised, and the primary alcohol moiety converted to a tosyl group to give **186** in 79% yield (Scheme 2.85). Tosylated product **186** was then reduced to give **187** in 63% yield.



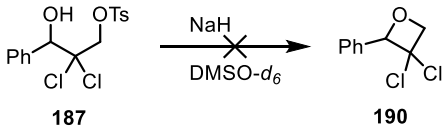
Scheme 2.85 Transformation of α,α-dichloro-β-hydroxyketone **185** to give tosylated product **187**

Previously, KOH has been used to generate oxetane **188** from primary tosylate **187** (Scheme 2.86).[220] Inspired by this, **185** was treated with KOH and heated at 80 °C in DMSO-d_6 (Scheme 2.86). However, only starting material remained after a week of heating.



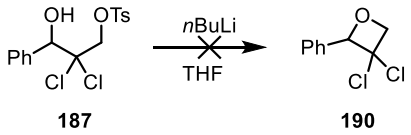
Scheme 2.86 Previously reported oxetane synthesis[220] and attempted oxetane synthesis from dichlorohydration product

Similarly, despite the literature precedent,[221] treating tosylate **187** with sodium hydride was unsuccessful, resulting in only starting material being present (Scheme 2.87).



Scheme 2.87 Unsuccessful oxetane synthesis

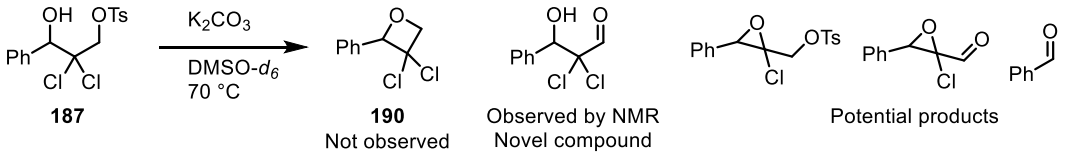
Oxetanes have previously been synthesised from tosylates on treatment with *n*BuLi in THF.[222] Using this synthetic route from tosylate **187** did lead to the consumption of starting material, however, analysis of the crude NMR spectrum showed the formation of a complex mixture of products, none of which appeared to be the desired oxetane **190** (Scheme 2.88).



187 190

Scheme 2.88 Unsuccessful oxetane synthesis

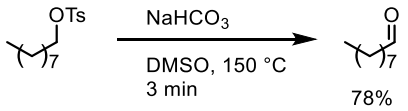
Following this, potassium carbonate was used (Scheme 2.89).[223] Again, the reaction was unsuccessful leaving almost exclusively unchanged starting material. Analysis of the ^{1}H and ^{13}C NMR spectra revealed that the minor product that had formed was an aldehyde.



187 **190** Not observed Observed by NMR Novel compound Potential products

Scheme 2.89 Unsuccessful oxetane synthesis

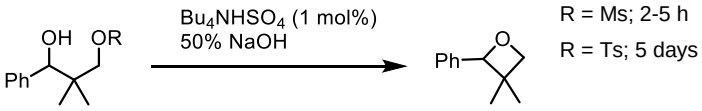
It has previously been observed that tosylates of primary alcohols can be prone to Kornblum oxidation to give aldehydes in the presence of sodium bicarbonate[224] and so this route was not continued (Scheme 2.90).



78%

Scheme 2.90 Previously reported Kornblum oxidation of primary tosylates into aldehydes[224]

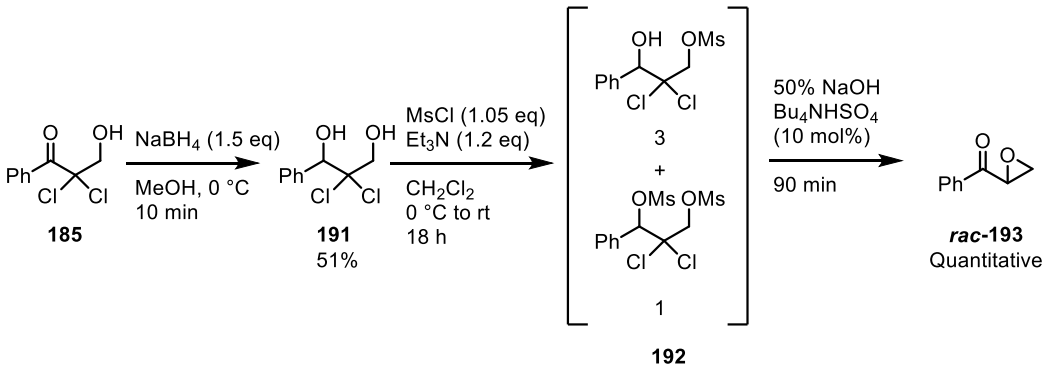
The suitability of using a tosylate for oxetane synthesis was therefore questioned, and so the mesylate was synthesised. This decision was further validated by Xiaming and Kellogg who found that using phase transfer catalysis to generate oxetanes generally took 5 days from the tosylate, or 2-4 hours from the analogous mesylate.[225]



Scheme 2.91 Previously reported phase transfer catalysis of tosylated or mesylated diols[225]

Xiaming and Kellogg tried various phase transfer catalysts based on a quaternary ammonium salt with NaOH and CH_2Cl_2. It was determined that Bu_4NHSO_4 was the best. They also found that the mesylate did not need to be purified for oxetane formation to occur. Inspired by this, α,α-dichloro-β-hydroxyketone **185** was reduced

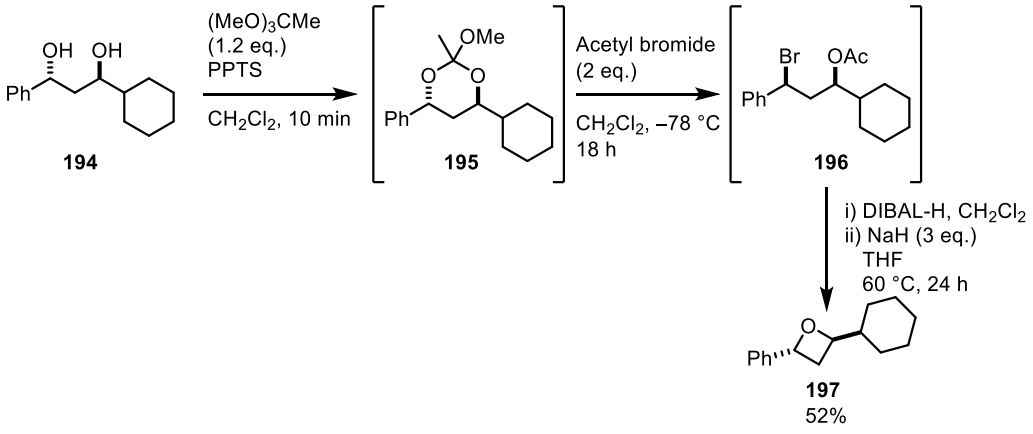
to the diol in 51% yield using $NaBH_4$ (Scheme 2.92). The diol was then subjected to mesylation, affording a mixture of mono- and dimesylated product in a 3:1 ratio. The mixture of products was subjected to aqueous NaOH in the presence of 10 mol% Bu_4NHSO_4. This reaction was clean, rendering chromatography unnecessary; but surprisingly the product was epoxyketone **193** which was isolated in quantitative yield. The mechanism by which this epoxide formed is not understood.



Scheme 2.92 Attempted oxetane synthesis

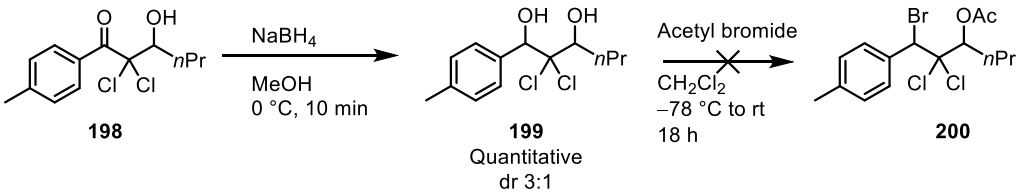
It was considered that difficulty in oxetane formation was arising from using a primary alcohol. Using a secondary alcohol may aid the process by encouraging a geometry that is more conducive to oxetane formation.

A procedure detailed by Aftab *et al.* initially converted diol **194** to acetoxy bromide derivative **196** as shown in Scheme 2.93.[226] The authors found that the diastereomeric ratio of the starting diol could be conferred to the acetoxy bromide if they first formed orthoester **195**. They were able to isolate acetoxy bromide **196** and reduce it with DIBAL-H to the hydroxy bromide which on treatment with NaH gave the desired oxetane **197** in 52% yield.



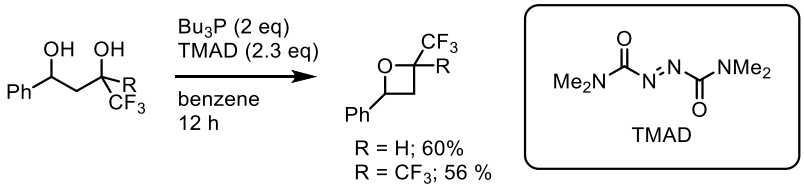
Scheme 2.93 Previously reported oxetane synthesis via acetoxy bromide **196**[226]

To investigate this potential route, α,α-dichloro-β-hydroxy ketone **198** was used to synthesise diol **199** in quantitative yield as a mixture of diastereoisomers (Scheme 2.94). Initially, oxetane synthesis was attempted on this mixture, with a view to selectively reducing α,α-dichloroketoalcohol **198** and separating the diastereomers if oxetane formation was successful. As selectivity wasn't a priority at this point, it was decided to first form and isolate acetoxy bromide **200**, made directly from the diol, rather than via the orthoester. Unfortunately, this acetoxy bromide **200** did not form, and a complex mixture of products was formed.



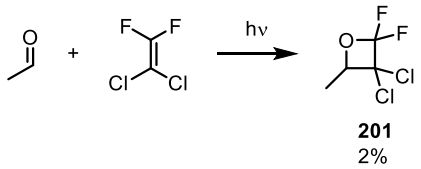
Scheme 2.94 Attempted synthesis of dichloroacetoxy bromide **200**

Other potential routes to oxetanes from 1,3 diols include making the analogous chloro acetoxy ester[227] or via a Mitsunobu cyclodehydration reaction (Scheme 2.95).[228]



Scheme 2.95 Previously reported oxetane synthesis via Mitsunobu cyclodehydration[228]

Whilst some routes to 3,3-difluorooxetanes have been reported,[146,229–231] the only reported 3,3-dichlorooxetane synthesis is from 1964 by a photoinitiated cycloaddition of acetaldehyde and 1,1-dichloro-2,2-difluoroethylene (Scheme 2.96).[231] This gave dichlorooxetane **201** in just 2% yield.



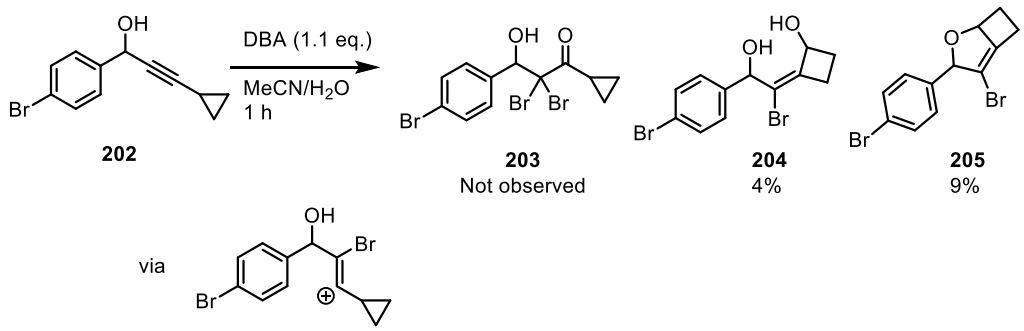
Scheme 2.96 Formation of 3,3-dichorooxetane via photocycloaddition[231]

It was unknown if the desired oxetane would be stable and if this was a factor in the apparent difficulty in synthesising it. It was also considered that the presence of two

bulky chlorine atoms may hamper the formation of an oxetane and so oxetane formation was not investigated further.

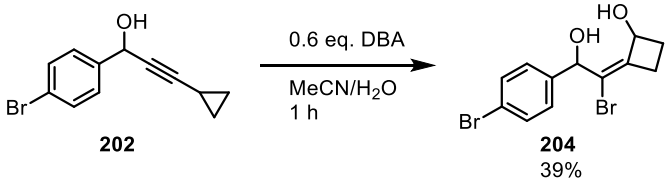
2.4.2 Cyclopropane ring expansion

Kate Sanders, a summer student in the Sheppard group, synthesised propargylic alcohol **202**, derived from cyclopropylacetylene, and subjected it to the dihalohydration reaction conditions (Scheme 2.97). Surprisingly, the expected dibromohydration product **203** was not observed, and in fact cyclobutanol **204** and dihydrofuran **205** were isolated in 4% and 9% yield respectively. It is worth noting, that this reaction took 1 hour for all the starting material to be consumed.



Scheme 2.97 Work done by Kate Sanders

Based on this previous result, it was hoped that reducing the amount of DBA to 0.6 equivalents would increase the yield of these two products. Doing so, allowed cyclobutanol **204** to be isolated in 39% yield (Scheme 2.98). Dihydrofuran **205** was not observed under these conditions.

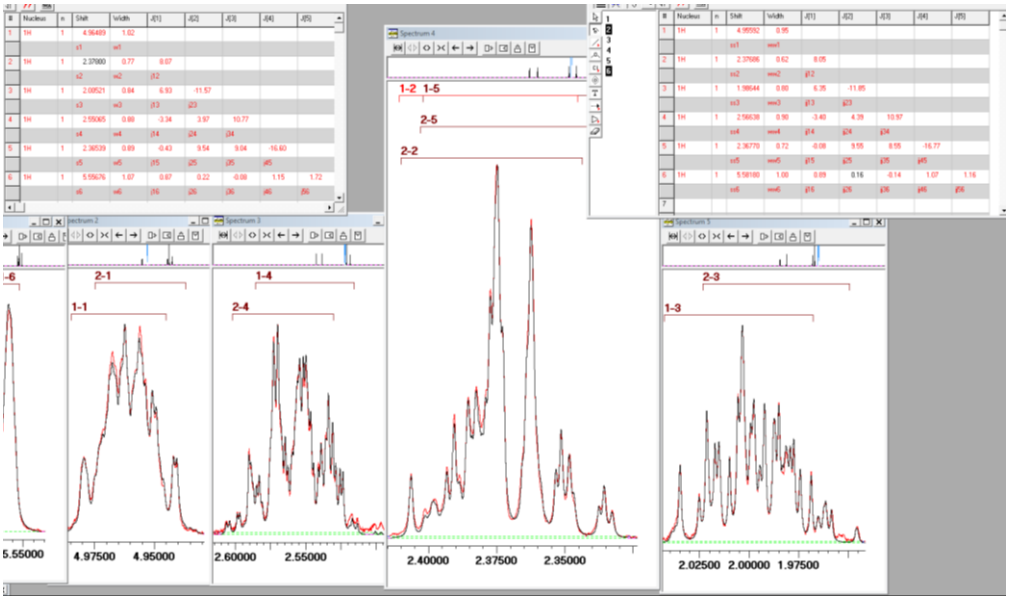


Scheme 2.98 Cyclopropyl ring expansion to give cyclobutanol **204**

Due to the strongly coupled spin system and overlapping of both isomers in nearly equal intensities, line shape analysis was used to verify the identity of the products and allow the chemical shifts and J couplings to be extracted. This was undertaken alongside DFT calculations by Dr Abil Aliev at University College London. The

spectral fittings can be seen in Figure 31a in red, which are in excellent agreement with the experimental spectrum, shown in black. Assignment of both **(*S*,*R*)/(*R*,*S*)-204** and **(*R*,*R*)/(*S*,*S*)-204** was done using nOe interactions as indicated in Figure 31b.

a)

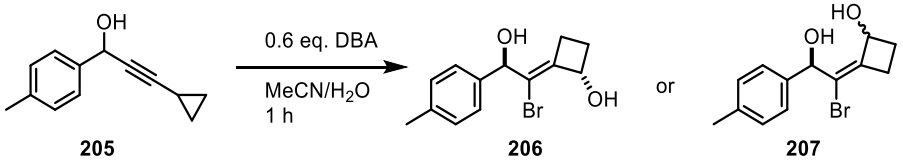


b)

(*R*,*S*)/(*S*,*R*)-204 (*R*,*R*)/(*S*,*S*)-204

Figure 31 a) Line shape analysis used to determine chemical shifts and J couplings of the 2 isomers of **204** b) Key nOe interactions that were used to determine the structures of **204**

This reaction was then applied to propargylic alcohol **205** (Scheme 2.99). The initial reaction was conducted on a 2 mmol scale and only isomer **206** was isolated in 7% yield. Increasing to a 4 mmol scale, only isomer **207** was isolated in 15% yield. The crude NMR spectra for both reactions were incredibly complex, potentially due to decomposition products, which makes it difficult to ascertain if the isolated product was the major product in each case. In both reactions, it was not possible to sufficiently purify the other compounds to determine their identity.



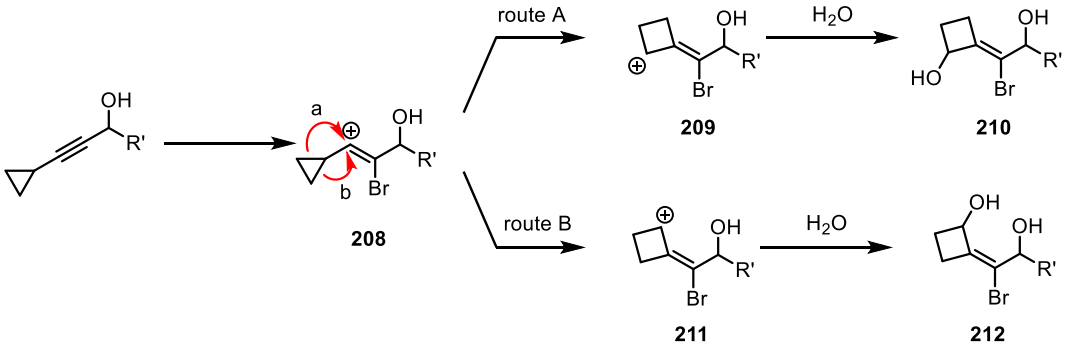
205 206 207

Reaction scale /mmol	Product (yield)	
2	**206** (7%)	Not observed
4	Not observed	**207** (15%)[a]

Scheme 2.99 [a]Isolated as a mixture of diastereomers, dr 1:1.6

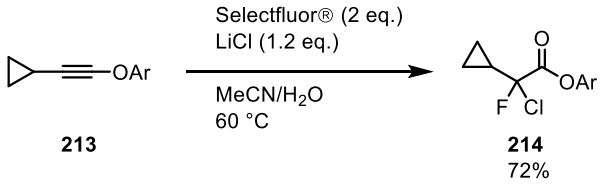
Interestingly, only the diastereomer of **206** shown in Scheme 2.99 was isolated, whereas both diastereomers of **207** were isolated with a dr of 1:1.6.

Mechanistically, it is proposed that vinylic cation **208** would form as previously described (Scheme 2.100). From here, it would be expected that the cyclopropyl ring will expand to give a cationic four-membered carbocycle, that can be trapped by a molecule of H_2O. It would be expected that ring expansion would proceed via route A, to give **209** with the cationic charge *cis* to the bromide, leading to **210**. However, in the case of **207**, route B was followed, resulting in the cationic charge (**211**), and subsequently the hydroxyl group, *trans* to the bromide (**212**).



Scheme 2.100 Proposed mechanism for cyclobutanol formation

The expansion of cyclopropyl rings has previously been observed, mainly in the presence of transition metal catalysts.[232,233] There is one report of a fluorohalogenative hydration of ynol ethers that used cyclopropane substituted starting material **213** (Scheme 2.101).[189] During this reaction, the authors stated that the formation of cyclopropyl product **214** indicated that the reaction was not proceeding by a radical mechanism, as the cyclopropyl ring remained intact. A competing radical mechanism could explain the complexity of the crude NMR spectra.

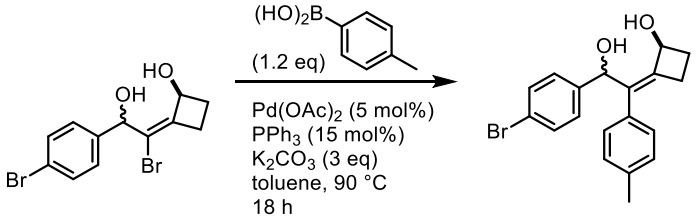


213 **214** 72%

Scheme 2.101 Previously reported Selectfluor® mediated difluorohydration of ynol ethers[189]

As the yields of these reactions are low and the composition of the crude reaction is complex, it is impossible to ascertain if the products and diastereomers isolated are indicative of the mechanism of this rearrangement or a symptom of the multiple possible reactions that can take place. Further exploration into this rearrangement would be advantageous.

Despite the complications of this reaction, it was possible to further derivatise the cyclobutanol products. The mixture of stereoisomers of **204** were subjected to a palladium catalysed Suzuki coupling to give tetrasubstituted alkene **215** in 33% yield. This further confirms the structure of **204**.

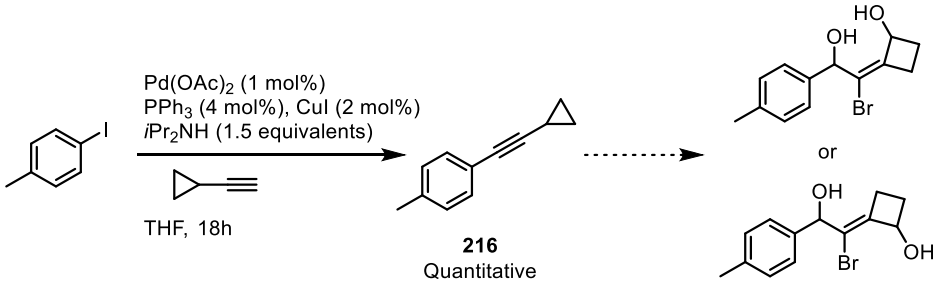


204 dr 1:1.1 **215** 33% dr 1:1

Scheme 2.102 Suzuki reaction of vinyl bromide **204** with 4-tolylboronic acid

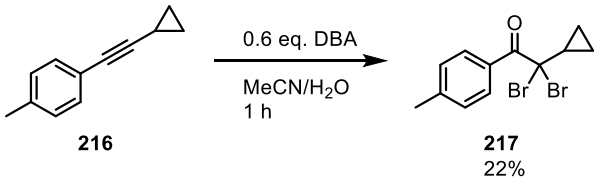
2.4.3 Cyclopropane ring expansion of cyclopropylacetylene derived alkynes

The cyclopropane ring expansion discovered during this work allows access to a complex molecular scaffold. It was envisaged that this reaction could be applied to an alkyne that doesn't contain a hydroxyl group. To investigate if the cyclopropane ring expansion occurred in alkynes, compound **216** was synthesised in quantitative yield via a Sonogashira coupling reaction (Scheme 2.103).



Scheme 2.103 Sonogashira coupling of 4-iodotoluene and cyclopropylacetylene

Alkyne **216** was then subjected to the standard cyclopropane expansion conditions (Scheme 2.104). In this case, **217** was isolated in 22% yield. However, it was not possible to isolate and characterise the other by products.



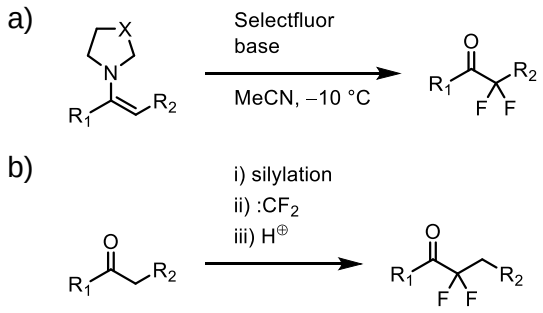
Scheme 2.104 Dibromohydration of alkyne **216**

It is difficult to conclude if this is due to a different reaction mechanism, or if it was just possible to isolate this product in this case. Further exploration into the scope of the reaction and isolation of all the products formed during the transformation of cyclopropyl alkynes with DBA could shed light on this result.

2.4.4 Synthesis of difluoroketoalcohols

The enhanced metabolic stability and increased lipophilicity of organofluorine compounds has led to their widespread use throughout the pharmaceutical industry.[234] It has been noted that the presence of two fluorine atoms in α,α-difluoroketones can aid the formation of hydrates, which results in increased

proteolytic stability.[235] However, common methods to synthesise α,α-difluoroketones require direct fluorination of ketones, which tend to require prior functionalisation (Scheme 2.105a)[236] or homologation of ketones with a CF_2 fragment (Scheme 2.105b).[235]

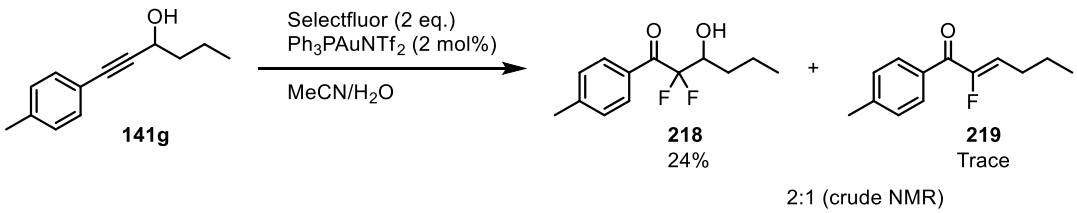


Scheme 2.105 Previously reported α,α-difluoroketone synthesis requiring previous functionalisation,[236] or homologation[235]

Current methods of difluorohydration of alkynes have been discussed, (see Section 2.1.3.2) however, the substrate scope explored has been fairly limited, therefore a mild method using easily handled reagents would be desirable.

Previously within the Sheppard group, it was found that Selectfluor® could be used as an electrophilic source of fluorine to give α,α-difluoro-β-hydroxy ketones from propargylic alcohols.[193] However, the reaction required a gold catalyst and overnight reflux to force the reaction.

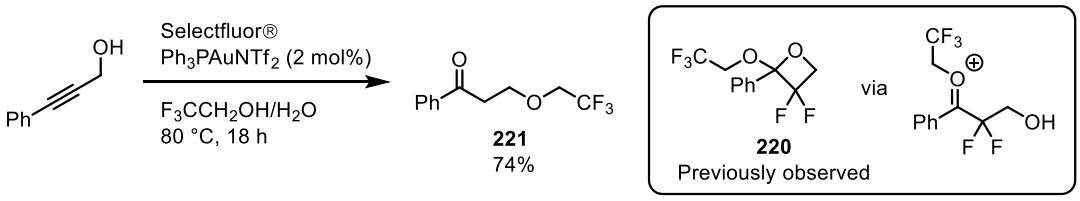
These conditions have been applied to propargylic alcohol **141g** to give α,α-difluoro-β-hydroxy ketone **218** in 24% yield (Scheme 2.106). Analysis of the crude NMR spectrum showed that, amongst other side products, fluoroenone **219** had formed in a 2:1 ratio of α,α-difluoro-β-hydroxy ketone **218**:fluoroenone **219**, however, following purification, fluoroenone **219** was only isolated in trace amounts. Further investigation into this will be necessary and the substrate scope will need to be explored.



Scheme 2.106 Difluorohydration reaction of propargylic alcohol **141g**

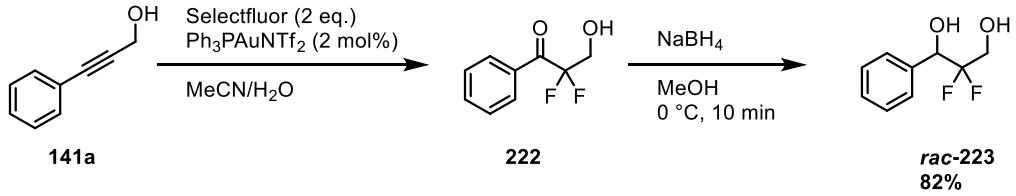
During the previous optimisation of the reaction, a range of temperatures, fluorine sources and solvents were tried. When trifluoroethanol was used as the solvent, analysis of the crude NMR was consistent with the formation of oxetane-acetal **220**, however this wasn't isolated.

The reaction was repeated as part of this work in an attempt to isolate oxetane **220**, however, conducting the reaction with trifluoroethanol, gave open ketone **221** instead. More exploration into this desired transformation will be required.



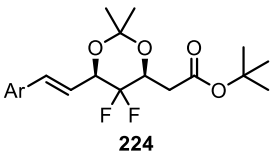
Scheme 2.107 Attempted difluorohydration reaction in a solvent mixture of trifluoroethanol/ H_2O

α,α-Difluoro-β-hydroxy ketone **222** has previously been synthesised in the group. It was treated with $NaBH_4$ to form 1,3-diol **223** in 82% yield (Scheme 2.108).



Scheme 2.108 $NaBH_4$ reduction of α,α-difluoro-β-hydroxy ketone **223**

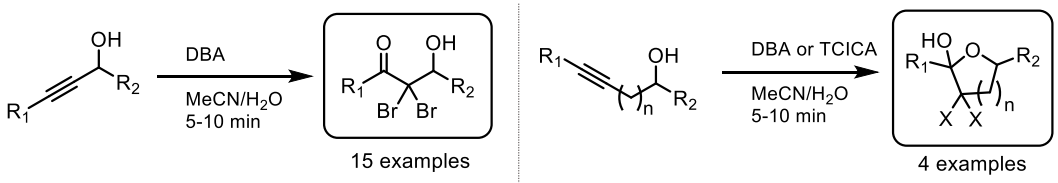
This high yielding reaction is encouraging, as difluorinated acetonides **224** have received interest as precursors in the synthesis of HMG-CoA reductase inhibitors which have a role in the treatment of hypercholesterolemia (Scheme 2.109).[237]



Scheme 2.109 Precursor in the synthesis of HMG-CoA reductase inhibitors[237]

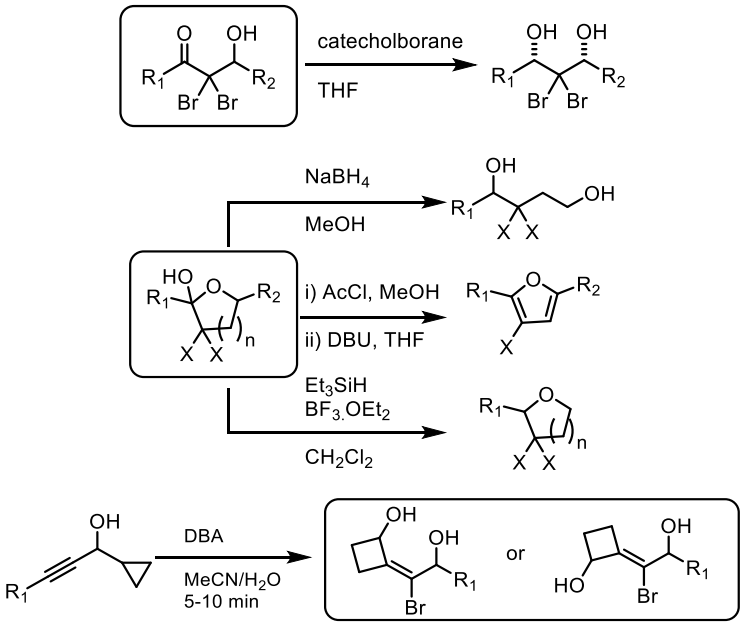
2.5 Conclusions & Future Work

A mild and regioselective dibromohydration reaction has been developed to convert propargylic alcohols to dibromoketoalcohols in good to excellent yield. Fifteen examples have been shown to proceed rapidly and at room temperature and the reaction appears to have a wide substrate scope. Using this strategy, it is possible to prepare cyclic lactols.



Scheme 2.110 Synthesis of dihaloketoalcohols and dihalolactols

The dibromoketoalcohols that are formed by this reaction are amenable to a plethora of further transformations. It has been shown that they can be reduced; either from the cyclic lactols to give either cyclic ethers or 1,4 diols, or from the 1,3 ketoalcohols to give 1,3 diols. It has also been shown that the production of syn 1,3 diols can be achieved diastereoselectively; a method that fits well alongside previous methods shown to work within the group.[192] The products can be used to generate 3-halofurans, both with and without substituents at the 5 position. Using this developed methodology on a propargylic alcohol derived from cyclopropylacetylene gave a cyclobutanol product that has been shown to partake in a Suzuki reaction.

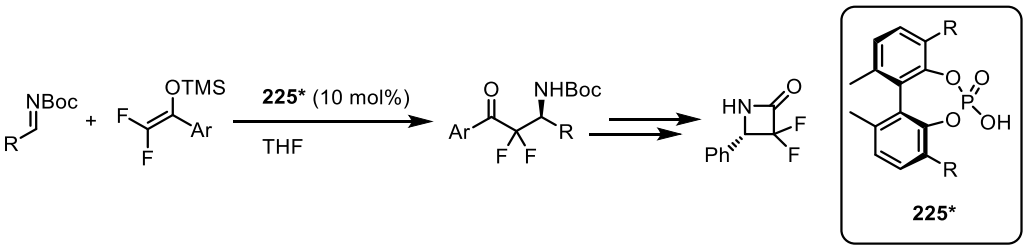


Scheme 2.111 Successful further transformations of dihalohydration products

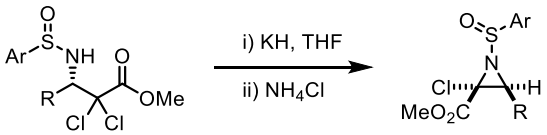
2.5.1 Dihalohydration reactions of propargylic amines

There have been previous reports of the synthesis of α,α-halo-β-amino carbonyl compounds and their subsequent transformations into β-lactams using catalyst **225*** (Scheme 2.112a)[238] and aziridines (Scheme 2.112b).[239]

a)

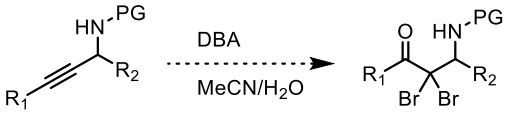


b)



Scheme 2.112 a) Synthesis of α,α-difluoro-β-amino ketones and their subsequent transformation into azetidines[238] b) Transformation of α,α-dichloro-β-amino esters

If the dibromohydration reaction, developed for propargylic alcohols, worked for propargylic amines (Scheme 2.113), this would provide another route to these products that can then be transformed into useful building blocks.

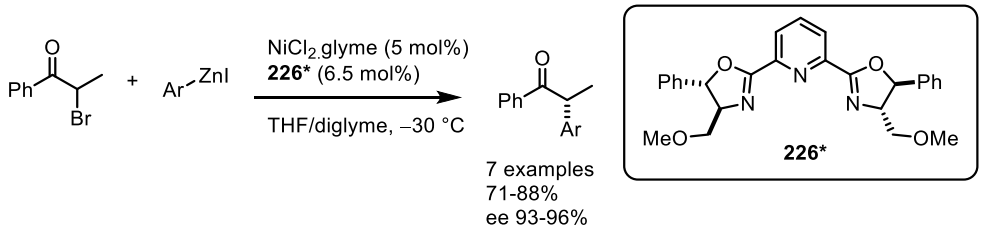


Scheme 2.113 Potential dibromohydration of propargylic amines

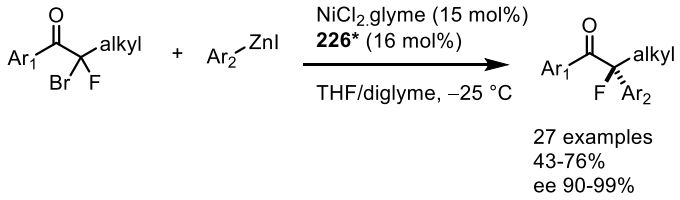
2.5.2 Cross coupling reactions

The importance of forming C-C bonds is well recognised in modern synthetic chemistry. Recently, Fu *et al.* have reported the nickel catalysed asymmetric cross coupling reactions of α-bromoketones to form ketones bearing an α-aryl substituent using catalyst **226*** (Scheme 2.114a).[240] More recently, the group have developed Negishi couplings of arylzinc reagents with α,α-bromofluoroketones to form tertiary α-fluoroketones (Scheme 2.114b).[241]

a)



b)



Scheme 2.114 Negishi cross couplings of a) α-bromoketones[240] and b) α,α-bromofluoroketones[241]

The previously reported methods have used starting materials of racemic α-haloketones to arrive at enantioenriched products. α,α-Dibromo-β-hydroxyketones could be substrates in this reaction, potentially giving enantioenriched products (Scheme 2.115).

Scheme 2.115 Potential Negishi coupling of α,α-dibromo-β-hydroxyketone

Chapter 3 Experimental

3.1 General Experimental procedures

All solvents and chemicals were used as received. Column chromatography was carried out using either Merck Geduran Si 60 (40-63 µm) silica gel or a Biotage purification system using Biotage or Grace silica columns. Analytical thin layer chromatography was carried out using Merck TLC Silica Gel 60 F_{254} aluminium-backed plates. Components were visualised using combinations of ultra-violet lights, potassium permanganate or ninhydrin.

Proton magnetic resonance spectra (^{1}H NMR) were recorded at 400, 500 or 600 MHz on a Bruker Avance spectrometer and are reported as follows: chemical shift δ in ppm (number of protons, multiplicity, coupling constant *J* in Hz, assignment). The solvent used was deuterated chloroform or deuterated methanol unless stated otherwise. Residual protic solvent was used as the internal reference, setting $CDCl_3$ to δ 7.26 and MeOD-d_4 to 3.31. The following abbreviations are used: s, singlet; d, doublet; t, triplet; q, quartet; m, mulitplet; br, broad or a combination of these.

Carbon magnetic resonance spectra (^{13}C NMR) were recorded at 100, 125 or 150 MHz on a Bruker Avance spectrometer using deuterated chloroform or deuterated methanol and using the central reference of $CDCl_3$ to δ 77.0 or MeOD-d_4 to δ 49.15 as the internal standard.

Mass Spectrometry data were collected on either TOF or magnetic sector analysers either at the Department of Chemistry, University College London or at the EPSRC UK National Mass Spectroscopy Facility at Swansea University. The ionization method is reported in the experimental data.

Automated solid phase peptide synthesis (SPPS) was carried out on a 0.05 mmol scale on an Applied Biosystems ABI 433A peptide synthesiser according to the manufacturers' instructions. The Fast-Moc™ protocol for SPPS was employed, using 10 equivalents of each standard Fmoc-protected amino acid in the sequence. When side chain protection was required, Fmoc-Glu(O*t*Bu)-OH, Fmoc-Tyr(*t*Bu)-OH and Fmoc-Ser(*t*Bu)-OH were used. Each coupling reaction was carried out using 0.45 M HBTU/HOBt in DMF, NMP for washes and 20% v/v piperidine in DMF for deprotection.

Semi-preparative reverse phase high performance liquid chromatography (HPLC) was carried out using a C_{18} column using a gradient of 5 → 60% acetonitrile in H_2O over 60 min.

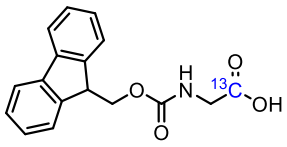
Ether refers to diethyl ether, petrol to petroleum ether (boiling point 40-60 °C) and brine refers to saturated sodium chloride in H_2O.

3.2 Experimental Part I

3.2.1 Synthesis of peptides

3.2.1.1 Synthesis of model peptide as *C*-terminal carboxylic acid

Fmoc-Gly($^{13}C_1$)-OH (14)[32]



Et_3N (0.92 mL, 6.6 mmol) was added to a solution of glycine ($^{13}C_1$) (493 mg, 6.48 mmol) in H_2O (6.2 mL). Fmoc-succinimide (2.13 g, 6.33 mmol) was dissolved in acetonitrile (6.2 mL) at 50 ºC. This was added to the glycine solution in one portion. Et_3N (0.50 mL, 3.6 mmol) was added to maintain pH 9 and the reaction mixture stirred for 35 min at room temperature. The reaction volume was reduced *in vacuo* by 70% and the resultant off-white concentrate added to HCl (1.5 M, 26 mL, 39 mmol). CH_2Cl_2 and EtOAc were added. The organic layer was separated and washed with HCl (1.5 M, 12 mL), H_2O (15 mL) and then brine (15 mL). The organic extract was dried ($MgSO_4$) and solvent removed *in vacuo* to give a white solid. The solid was washed with petrol and filtered to give **14** as a white solid (1.28 g, 68%, mp 172.6-173.5 °C (lit. 164-165 °C)[32]); **^{1}H NMR** (MeOD-d_4, 500 MHz) δ 7.80 (2H, d, J = 7.5, ArH), 7.67 (2H, d, J = 7.5, ArH), 7.38 (2H, t, J = 7.5, ArH), 7.32 (2H, t, J = 7.5, ArH), 4.34 (2H, d, J = 7.2, CHC**H**$_2$), 4.23 (1H, t, J = 7.2, C**H**CH$_2$), 3.84 (2H, d, J = 5.5, NHC**H**$_2$); **^{13}C NMR** (MeOD-d_4, 125 MHz) δ 173.6, 159.2, 145.3, 142.6, 128.8, 128.2, 126.3, 120.9, 68.2, 43.2, 42.9; **LRMS** (CI) 299 (16%, $[M+H]^+$), 207 (7%), 196 (10%), 179 (100%, $[Fmoc-CO_2]^+$), 121 (13%); **IR** ν_{max} (film/cm^{-1}) 3319 (O-H), 2952 (C-H), 1703 (C=O), 1685 (C=O), 1223

Model peptide synthesised as *C*-terminal carboxylic acid –

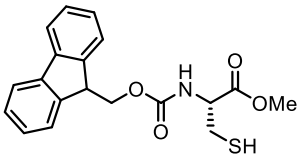
H-MEELYKSG($^{13}C_1$)C-OH (7)[33]

Fmoc-Cys(Trt)-NovaSyn TGT resin, loading = 0.19 mmol g^{-1} (263 mg, 0.05 mmol) was treated with piperidine in DMF (20% v/v, 15 min). The solution was filtered off and resin washed 10 times with DMF and CH_2Cl_2. The dried resin was coupled to **14** (75 mg, 0.25 mmol) with DIPEA (75 µL, 0.43 mmol) and HBTU/HOBt (0.45 M, 0.55

mL) in anhydrous DMF (0.55 mL) and the mixture shaken for 4 h. The resin was washed with DMF and CH_2Cl_2 and then automated SPPS was carried out on a 0.05 mmol scale. Following chain assembly, the resin was removed from the reaction vessel, washed 10 times with DMF and CH_2Cl_2, and dried. The dry resin was treated with a cleavage cocktail (4.0 mL) comprised of TFA (95% v/v), EDT (2.5% v/v) and H_2O (2.5% v/v) for 5 h at room temperature with gentle stirring. The resin was filtered off and the filtrate added to cold Et_2O (20 mL) to induce precipitation of the peptide. The mixture was vortexed, centrifuged (1500 rpm, 4 °C, 15 min) and then the supernatant removed. More Et_2O (20 mL) was added and the mixture was again vortexed, centrifuged and the supernatant removed to give the crude peptide. The white precipitate was dissolved in H_2O and then purified by semi-preparative reverse phase HPLC (gradient: 5–60% acetonitrile over 60 min). Fractions containing the product were identified by LC-MS and lyophilised to give **7** as a white fluffy solid (50 mg, 94%, t_R = 24.9 min). **^{13}C NMR** (D_2O, 125 MHz) δ 171.4; **LRMS** (ESI) 1061 ([M-H]$^+$)

3.2.1.2 Synthesis of model peptide as a *C*-terminal methyl ester

(*R*)-Methyl-((((9*H*-fluoren-9-yl)methoxy)carbonyl)amino)-3-mercaptopropanoate (15)[37]



HCl (12 M, 2 drops) was added to a solution of Fmoc-cysteine-OH (110 mg, 0.304 mmol) in MeOH (3 mL). The reaction was stirred at room temperature for 18 h. A white precipitate formed that was dissolved in acetone (5 mL) and the solvents removed *in vacuo* to give **15** as a white solid (79.8 mg, 75%). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.77 (2H, d, *J* = 7.5, ArH), 7.61 (2H, br d, *J* = 7.3, ArH), 7.41 (2H, t, *J* = 7.5, ArH), 7.32 (2H, t, *J* = 7.5, ArH), 5.79 (1H, d, *J* = 7.0, N**H**), 4.73-4.64 (1H, m, C**H**CO_2CH_3), 4.49-4.38 (2H, m, FmocC**H$_2$**), 4.24 (1H, t, *J* = 6.8, FmocC**H**), 3.79 (3H, s, OCH_3), 3.06 (1H, dd, *J* = 14.4, 4.7, 1 × C**H**$_2$SH), 3.00 (1H, dd, *J* = 14.4, 4.1, 1 × C**H**$_2$SH), 1.38 (1H, t, *J* = 8.9, S**H**); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 170.7, 155.8, 143.9, 141.5, 127.9, 127.2, 125.3, 120.2, 67.3, 55.4, 53.0, 47.3, 27.3; **LRMS** (CI) 358 (14%, $[M+H]^+$), 207 (7%), 179 (100%, $[Fmoc-CO_2]^+$)

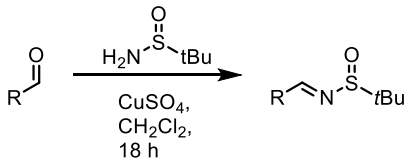
Model peptide synthesised as *C*-terminal carboxylic acid –

H-MEELYKSG($^{13}C_1$)C-OMe (9)

Trityl Chloride resin, loading = 1.40 mmol g^{-1} (35.7 mg, 0.05 mmol) was treated with DMF. A solution of **14** (79.8 mg, 0.224 mmol) in CH_2Cl_2 (1.5 mL) was added to the resin. DIPEA (156 µL, 0.896 mmol) was added and the resin was shaken for 2 days. MeOH (25 µL) was added and the resin shaken for a further 5 min. The resin was then washed with DMF and CH_2Cl_2 and treated with piperidine in DMF (20% v/v) for 15 min. The solution was filtered off and a solution of **15** (80.2 mg, 0.269 mmol) in anhydrous DMF (0.55 mL) with HBTU/HOBt (0.45 M, 0.55 mL) and DIPEA (75 µL) was added and the resin shaken for 5 h. The resin was washed with DMF and CH_2Cl_2 and elongated by automated SPPS as detailed in the General Experimental section. The resin was washed with DMF and CH_2Cl_2 and cleaved with Reagent K (4.0 mL; TFA (82.5% v/v), phenol (5% w/v), thioanisole (5% v/v), H_2O (5% v/v), EDT (2.5% v/v)) by stirring for 30 min. The resin was filtered off and the filtrate added to cold Et_2O to induce precipitation of the peptide. The precipitate was collected by centrifugation (1500 rpm, 4 °C, 15 min), the supernatant removed, and the precipitated peptide resuspended in Et_2O and centrifuged once more. The white precipitate was dissolved in H_2O and then purified by semi-preparative reverse phase HPLC (gradient: 5–60% acetonitrile over 60 min). Fractions containing the product were identified by LC-MS and lyophilised to afford pure peptide **9** as a white solid (11.8 mg, 20%; $t_{R=}$ 27.6 min). **^{13}C NMR** (D_2O, 125 MHz) δ 171.7; Calculated mass 1073.5, observed (ESI-MS) $[MH]^+$ 1074.4

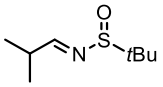
3.2.1.3 Synthesis of model peptide as a *C*-terminal boronic acid

General Procedure A: Synthesis of *tert*-butyl sulfinimines



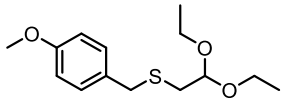
Reactions were carried out in flame dried glassware under an argon atmosphere. To a 0.5 M solution of (±)-*tert*-butyl sulfinamide in anhydrous CH_2Cl_2 was added $CuSO_4$ (2.2 eq.) followed by aldehyde (1.1 eq.). The reaction was stirred at room temperature for 18 h, before filtering through Celite. Solvents were removed *in vacuo* and the residue obtained was purified by column chromatography.

(*E*)-2-methyl-N-(2-methylpropylidene)propane-2-sulfinamide (29)[242]



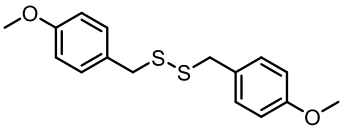
General Procedure A using *tert*-butyl sulfinamide (1.02 g, 8.25 mmol), CH_2Cl_2 (16 mL), $CuSO_4$ (2.92 g, 18.3 mmol) and isobutyraldehyde (830 µL, 9.10 mmol): pale orange oil, 660 mg, 46%. **^{1}H NMR** ($CDCl_3$, 600 MHz) *δ* 7.87 (1H, d, *J* = 4.4, NC**H**), 2.60 (1H, heptd, *J* = 6.9, 4.4, C**H**$(CH_3)_2$), 1.07 (9H, s, *t*Bu), 1.05 (3H, d, *J* = 6.9, 1 × CH(C**H**$_3)_2$), 1.04 (3H, d, *J* = 6.9, 1 × CH(C**H**$_3)_2$); **^{13}C NMR** *δ* ($CDCl_3$, 150 MHz) *δ* 173.5, 56.4, 34.9, 29.3, 18.91, 18.89; **LRMS** (CI) 199 (29%, $[M+Na]^+$), 176 (100%, $[M+H]^+$), 120 (96%); **IR** ν_{max} (film/cm^{-1}) 2964 (C-H), 1620 (C=N), 1083 (S=O)

(2,2-Diethoxyethyl)(4-methoxybenzyl)sulfane (32)[69,243]



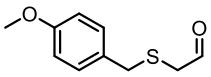
p-Methoxybenzyl mercaptan (3.83 mL, 27.5 mmol) was added to a stirred solution of bromoacetaldehyde diethyl acetal (3.76 mL, 25.0 mmol) in EtOH (110 mL) and NaOH (1 M, 50 mL) at 0 °C. The reaction was allowed to warm to rt and stirred for 2 days. A precipitate formed which was removed by filtration and the filtrate concentrated *in vacuo*. The residue was dissolved in Et_2O (25 mL) and washed with H_2O (25 mL) and then brine (20 mL). The organic layers were dried ($MgSO_4$) and concentrated *in vacuo* to give **32** as a pale yellow oil (3.56 g, 52%). **^{1}H NMR** ($CDCl_3$, 600 MHz) *δ* 7.25 (2H, d, *J* = 8.5, ArH), 6.83 (2H, d, *J* = 8.5, ArH), 4.54 (1H, t, *J* = 5.5, C**H**), 3.77 (3H, s, OCH_3), 3.74 (2H, s, ArC**H$_2$**), 3.64 (2H, dq, *J* = 9.3, 7.1, 2 × OCH_2), 3.51 (2H, dq, *J* = 9.3, 7.1, 2 × OCH_2), 2.57 (2H, d, *J* = 5.5, SC**H$_2$**CH), 1.21 (6H, t, J = 7.1, 2 × CH_2C**H$_3$**); **^{13}C NMR** ($CDCl_3$, 150 MHz) *δ* 158.7, 130.5, 130.3, 114.0, 103.5, 62.3, 55.4, 36.2, 34.0, 15.5; **IR** ν_{max} (film/cm^{-1}) 2973 (C-H), 1609 (C=C), 1509 (C=C)

1,2-Bis(4-methoxybenzyl)disulfane (33)[244,245]



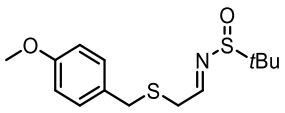
Following procedure for **32** gave **33** as a white solid (3.40 g, 44%, mp 98.5-100.1 ºC (lit. 75-78 ºC)[244]). **^{1}H NMR** ($CDCl_3$, 600 MHz) *δ* 7.17 (4H, d, *J* = 8.6, ArH), 6.86 (4H, d, *J* = 8.6, ArH), 3.80 (6H, s, OCH_3), 3.60 (4H, s, CH_2); **^{13}C NMR** ($CDCl_3$, 150 MHz) *δ* 159.1, 130.6, 129.5, 114.0, 55.4, 42.9; **LRMS** (ESI) 329.07 (100%, $[M+Na]^+$)

2-((4-Methoxybenzyl)sulfanyl)acetaldehyde (34)[69]



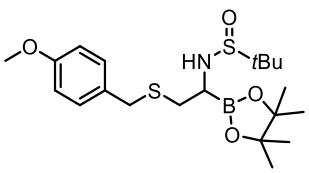
HCl (2 M, 15 mL) was added to **32** (1.94 g, 7.16 mmol) in acetone (15 mL) and the reaction stirred for 18 h. The solution was extracted with EtOAc (2 × 10 mL) and the organic layer washed with H_2O (10 mL) and then brine (10 mL). The organic layer was dried ($MgSO_4$), filtered, and concentrated *in vacuo* to give **34** as a colourless oil (1.39 g, 99%). **^{1}H NMR** ($CDCl_3$, 600 MHz) δ 9.40 (1H, t, J = 3.5, CHO), 7.21 (2H, d, J = 8.6, ArH), 6.85 (2H, d, J = 8.6, ArH), 3.79 (3H, s, OCH_3), 3.58 (2H, s, ArC**H$_2$**), 3.07 (2H, d, J = 3.5, C**H$_2$**CHO); **^{13}C NMR** ($CDCl_3$, 150 MHz) δ 194.1, 159.0, 130.5, 128.9, 114.2, 55.4, 40.3, 35.1; **IR** ν_{max} (film/cm^{-1}) 3006 (C-H), 2834 (C-H), 1714 (C=O), 1609, 1509

(*E*)-*N*-(2-((4-Methoxybenzyl)sulfanyl)ethylidene)-2-methylpropane-2-sulfinamide (35)



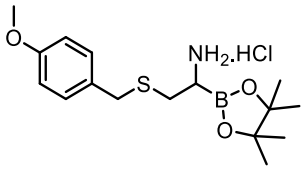
General Procedure A using *tert*-butyl sulfinamide (438 mg, 3.62 mmol), dry CH_2Cl_2 (7.3 mL), $CuSO_4$ (1.26 g, 7.95 mmol) and **34** (779 mg, 3.98 mmol): orange oil, 865 mg, 80%. **^{1}H NMR** ($CDCl_3$, 600 MHz) δ 7.98 (1H, t, J = 5.6, NCH), 7.23 (2H, d, J = 6.5, ArH), 6.85 (2H, d, J = 6.5, ArH), 3.79 (3H, s, OCH_3), 3.66 (2H, s, ArC**H$_2$**), 3.35 (1H, dd, J = 14.3, 6.0, 1 × SC**H**$_2$CH), 3.31 (1H, dd, J = 14.3, 5.3, 1 × SC**H**$_2$CH), 1.22 (9H, s, *t*Bu); **^{13}C NMR** ($CDCl_3$, 150 MHz) δ 164.2, 158.9, 130.3, 129.2, 114.1, 57.0, 55.4, 35.02, 34.3, 22.5; **LRMS** (CI) 420 (100%), 300 (37%, $[M+H]^+$), 240 (30%), 195 (32%, $[M-SOtBu]^+$), 121 (88%, PMB^+); **HRMS** Found 300.10877, $C_{14}H_{22}NO_2S_2$ requires 300.10865; **IR** ν_{max} (film/cm^{-1}) 2958 (C-H), 1609 (C=C), 1510 (C=N), 1458 (C=C), 1083 (S=O)

***N*-(2-((4-Methoxybenzyl)sulfanyl)-1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)ethyl)-2-methylpropane-2-sulfinamide (39)**



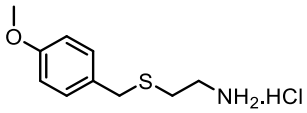
Using flame dried glassware under an argon atmosphere, CuCl (38.4 mg, 0.388 mmol), (±)-BINAP (111 mg, 0.178 mmol) and B_2pin_2 (1.33 g, 5.24 mmol) were dissolved in anhydrous THF (4 mL). KO*t*Bu (1 M in THF, 1.4 mL, 1.4 mmol) was added whilst stirring at room temperature. After 10 min, the reaction was cooled to −20 ºC and **35** (1.03 g, 3.45 mmol) was added followed by MeOH (300 µL, 7.41 mmol) and the reaction stirred for 18 h. Solvent was removed *in vacuo* and the resultant oil purified by column chromatography (20% EtOAc in CH_2Cl_2) to give **39** as an orange oil (878 mg, 60%). **^{1}H NMR** ($CDCl_3$, 600 MHz) *δ* 7.24 (2H, d, *J* = 8.6, ArH), 6.82 (2H, d, *J* = 8.6, ArH), 3.78 (3H, s, OCH_3), 3.71 (1H, d, *J* = 5.6, NH), 3.69 (2H, s, ArC**H$_2$**S), 3.22-3.17 (1H, m, CHB), 2.77 (1H, dd, *J* = 13.4, 6.3, 1 × SC**H**$_2$CH), 2.72 (1H, dd, *J* = 13.4, 7.9, 1 × SC**H**$_2$CH), 1.25 (s, 6H, 2 × pinacol-CH_3), 1.23 (s, 9H, *t*Bu), 1.20 (s, 6H, 2 × pinacol-CH_3); **^{13}C NMR** ($CDCl_3$, 150 MHz) *δ* 158.7, 130.1, 130.0, 114.0, 84.3, 56.2, 55.3, 41.3 (br), 35.2, 34.6, 25.0, 24.9, 22.6; **^{11}B NMR** ($CDCl_3$, 128 MHz) δ 31.83; **LRMS** (CI) 428 (41%, $[M+H]^+$), 371 (18%, $[M-tBu]^+$), 322 (38%, $[M-SOtBu]^+$), 121 (100%, PMB^+); **HRMS** Found 428.2095, $C_{20}H_{34}BNO_4S_2$ requires 428.2095; **IR** ν_{max} (film/cm^{-1}) 2977 (C-H), 2930 (C-H), 1609 (C=C), 1511 (C=C), 1544(C=C), 1369 (B-O)

2-((4-Methoxybenzyl)sulfanyl)-1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)ethanamine hydrochloride (40)



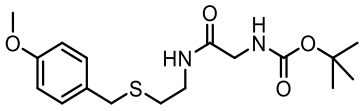
HCl in dioxane (4 M, 585 µL, 2.34 mmol) was added to a solution of **39** (99.7 mg, 0.233 mmol) in anhydrous MeOH (3 mL). The reaction was stirred for 3 h. The solvent was removed *in vacuo* to give an orange residue which was washed with Et_2O, sonicated, and centrifuged to isolate **40** as a pale brown solid (68.3 mg, 82%, mp 166-168 °C). **^{1}H NMR** (MeOD-d_4, 400 MHz) *δ* 7.29 (2H, d, *J* = 8.7, ArH), 6.89 (2H, d, *J* = 8.7, ArH) 3.80 (3H, s, OCH_3), 3.79 (2H, s, ArC**H$_2$**), 3.01 (1H, dd, *J* = 8.7, 4.7, CHB), 2.85 (1H, dd, *J* = 14.3,4.8, 1 × C**H**$_2$CH), 2.73 (1H, dd, *J* = 14.3, 8.8, 1 × C**H**$_2$CH), 1.33 (12H, s, 4 × CH_3); **^{13}C NMR** (MeOD-d_4, 100 MHz) *δ* 159.1, 129.9, 129.5, 113.7, 85.5, 74.4, 54.5, 35.1, 30.4, 23.8, 23.7; **LRMS** (CI) 323 (100%, $[M+H]^+$), 198 (18%, $[M-Bpin]^+$); **HRMS** Found 323.18359, $C_{16}H_{27}BNO_3S$ requires 323.1836; **IR** ν_{max} (solid/cm^{-1}) 2975 (C-H), 2958 (C-H), 2831 (C-H), 1607, 1583, 1411

2-((4-Methoxybenzyl)sulfanyl)ethanamine hydrochloride (41)[246]



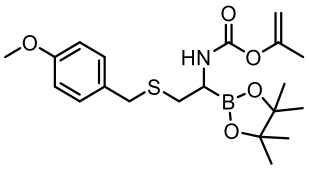
Following procedure for **40**, leaving the reaction mixture overnight gave **41** (mp 136.9-138.3 °C); **^{1}H NMR** (MeOD-d_4, 600 MHz) δ 7.27 (2H, d, J = 8.7, ArH), 6.87 (2H, d, J = 8.7, ArH), 3.77 (3H, s, OCH_3), 3.74 (2H, s, Ar**CH_2**), 3.01 (2H, t, J = 6.9, CH_2N), 2.68 (2H, t, J = 6.9, S**CH_2**CH_2); **^{13}C NMR** (MeOD-d_4, 150 MHz) δ 160.5, 131.2, 131.0, 115.1, 55.7, 39.7, 35.9, 29.1; **LRMS** (CI) 198 (16%, $[M+H]^+$), 121 (100%, PMB^+)

***Tert*-Butyl (2-((2-((4-methoxybenzyl)sulfanyl)ethyl)amino)-2-oxoethyl)carbamate (44)**



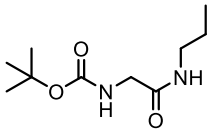
Using flame dried glassware and under an argon atmosphere, a solution of HCl salt **40** (30.3 mg, 84.2 µmol) in anhydrous CH_2Cl_2 (1.5 mL) was cooled to 0 °C. DIPEA (44 µL, 26 µmol) was added dropwise, followed by Boc-Gly-OH (24.3 mg, 139 µmol) and HBTU (49.7 mg, 131 µmol). The reaction was stirred at 0 °C for 8 h, and stored in the freezer for 18 h. Solvents were removed *in vacuo* to give an orange residue, which was dissolved in EtOAc (10 mL) and washed with H_2O (2 × 5 mL), phosphoric acid (1% in H_2O, 2 × 3 mL), potassium carbonate (2% in H_2O, 2 × 3 mL) followed by brine (2 × 3 mL). All aqueous layers were back extracted with EtOAc. The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo* to give an orange oil that was purified by column chromatography (25% EtOAc in petrol) to give **44** as a pale yellow oil (5 mg, 17%). **^{1}H NMR** (MeOD-d_4, 600 MHz) δ 7.25 (2H, d, J = 8.6, ArH), 6.85 (2H, d, J = 8.6, ArH), 3.77 (3H, s, OCH_3), 3.70 (2H, s, $ArCH_2S$), 3.67 (2H, br s, NHCOC**H$_2$**), 3.35 (2H, t, J = 7.0, SCH_2C**H$_2$**), 2.50 (2H, t, J = 7.0, S**CH_2**CH_2), 1.45 (9H, s, *t*Bu); **^{13}C NMR** (MeOD-d_4, 150 MHz) δ 172.6, 160.2, 158.4, 132.7, 131.1, 114.8, 80.8, 55.7, 44.6, 39.7, 35.8, 31.1, 28.7; **LRMS** (CI) 355 (6%, $[M+H]^+$), 299 (62%, $[M-tBu]^+$), 255 (13%, $[M-Boc]^+$), 241 (7%), 202 (13%), 121 (100%, PMB^+); **HRMS**: Found 355.16901, $C_{17}H_{27}N_2O_4S$ requires 355.16915; **IR** ν_{max} (film/cm^{-1}) 3369 (N-H), 2925 (C-H), 2854, 1703 (C=O), 1678 (C=O), 1511, 1452

Prop-1-en-2-yl(2-((4-methoxybenzyl)sulfanyl)-1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)ethyl)carbamate (48b)



Using flame dried glassware and under an argon atmosphere, NMM (72 µL, 0.65 mmol) was added to a solution of Boc-Gly-OH (87.5 mg, 0.50 mmol) in anhydrous CH_2Cl_2 (2 mL) at −20 °C. This was followed by IPCF (620 µL, 0.60 mmol). The solution was stirred for 30 min at −20 °C. A solution of HCl salt **40** (14.0 mg, 38.9 µmol) in CH_2Cl_2 (0.5 mL) was added, followed by NMM (22 µL, 0.20 mmol). The reaction was allowed to warm to rt and stirred for 18 h. The solution was diluted with EtOAc (5 mL) and washed with HCl (1 M, 2 × 3 mL), H_2O (2 × 3 mL), sat. sodium bicarbonate (2 × 3 mL) and H_2O (2 × 3 mL). All aqueous layers were back extracted with EtOAc. The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. The resultant oil was purified by column chromatography (2% MeOH in $CHCl_3$) using deactivated silica (35% H_2O w/w) to give **48b** as an orange oil (12.2 mg, 77%). **^{1}H NMR** ($CDCl_3$, 600 MHz) δ 7.22 (2H, d, J = 8.5, ArH), 6.83 (2H, d, J = 8.5), 5.34 (1H, br d, J = 5.2, NH), 4.70 (1H, br s, 1 × C=C**H**$_2$), 4.63 (1H, br s, 1 × C=C**H**$_2$), 3.79 (3H, s, OCH_3), 3.71 (1H, d, J = 13.3, 1 × SC**H**$_2$Ar), 3.68 (1H, d, J = 13.5, 1 × SC**H**$_2$Ar), 3.36-3.28 (1H, m, CHB), 2.87 (1H, dd, J = 13.5, 4.4, 1 × C**H**$_2$CH), 2.66 (1H, dd, J = 13.5, 7.4, 1 × C**H**$_2$CH), 1.92 (3H, s, C(CH_2)C**H**$_3$)), 1.27 (12H, s, 4 × C(C**H**$_3$)); **^{13}C NMR** ($CDCl_3$, 150 MHz) δ 158.7, 154.8, 153.0, 130.2, 130.1, 114.0, 101.3, 84.6, 55.4, 38.6 (br), 36.3, 29.8, 25.0, 24.9, 20.0; **LRMS** (ESI) 408 (54%, $[M+H]^+$), 382 (100%), 322 (38%, $[M-C_4H_5O_2]+$)

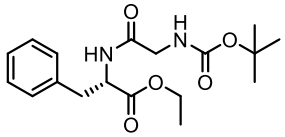
***tert*-Butyl (2-oxo-2-(propylamino)ethyl)carbamate (49)**[247]



Using flame dried glassware under an argon atmosphere, NMM (72 µL, 0.65 mmol) followed by IPCF (58 µL, 0.52 mmol) were added to a solution of Boc-Gly-OH (87.5 mg, 0.50 mmol) in anhydrous CH_2Cl_2 (2.5 mL) cooled to −20 °C. The reaction was stirred for 3 h at −20 °C. Propylamine (16 µL, 0.20 mmol) was added and the reaction stirred for 18 h. The reaction mixture was concentrated *in vacuo* and the resultant oil

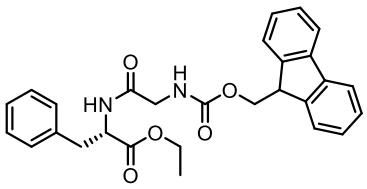
purified by column chromatography (10% MeOH in $CHCl_3$) using deactivated silica (35% H_2O w/w) to give **49** as a colourless oil (15.3 mg, 35%). **^{1}H NMR** ($CDCl_3$, 600 MHz) δ 6.35 (1H, s, BocN**H**), 5.31 (1H, s, N**H***i*Pr), 3.76 (2H, d, J = 4.5, BocNHC**H$_2$**), 3.21 (2H, q, J = 6.7, NHC**H$_2$**CH_2), 1.55-1.47 (2H, m, C**H$_2$**CH_3), 1.43 (9H, s, *t*Bu), 0.90 (3H, t, J = 7.4, CH_2C**H$_3$**); **^{13}C NMR** ($CDCl_3$, 150 MHz) δ 169.6, 156.3, 80.3, 44.5, 41.2, 28.4, 22.9, 11.4; **LRMS** (CI) 217 (100%, $[M+H]^+$), 161 (30%), 117 (8%, $[M-Boc]^+$)

Ethyl (tert-butoxycarbonyl)glycyl-*L*-phenylalaninate (50a)[248]



Using flame dried glassware and under an argon atmosphere, a solution of Boc-Gly-OH (87.5 mg, 0.50 mmol) in anhydrous CH_2Cl_2 (1.5 mL) was cooled to −20 °C. NMM (66 µL, 0.60 mmol) was added, followed by IBCF (58 µL, 0.45 mmol) and the solution stirred for 5 h at −20 °C. A solution of phenylalanine ethyl ester hydrochloride (46 mg, 0.20 mmol) and NMM (22 µL, 0.20 mmol) in CH_2Cl_2 (0.5 mL) was added and the reaction allowed to warm to rt and stirred for 18 h. The reaction mixture was concentrated *in vacuo* and the resultant oil purified by column chromatography (20% EtOAc in petrol) to give **50a** as a colourless oil (49.0 mg, 70%). **^{1}H NMR** ($CDCl_3$, 600 MHz) δ 7.26-7.19 (3H, m, ArH), 7.08 (2H, d, J = 6.9, ArH), 6.76 (1H, br d, J = 6.7, CHN**H**), 5.33 (1H, br s, CH_2N**H**), 4.81 (1H, m, C**H**NH), 4.08 (2H, q, J = 7.2, C**H$_2$**CH_3), 3.79 (1H, dd, J = 16.8, 5.2, 1 × $ArCH_2$), 3.70 (1H, dd, J = 16.8, 5.6, 1 × $ArCH_2$), 3.07 (2H, t, C**H$_2$**NH), 1.40 (9H, s, *t*Bu), 1.18 (3H, t, J = 7.2, CH_2C**H$_3$**); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 171.4, 171.3, 169.5, 135.9, 129.4, 128.6, 127.2, 80.2, 61.6, 53.3, 38.0, 28.4, 24.0, 14.3; **IR** ν_{max} (film/cm^{-1}) 3367 (N-H), 1739 (C=O), 1672 (C=O), 1505

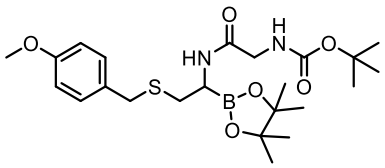
Ethyl (((9H-fluoren-9-yl)methoxy)carbonyl)glycyl-*L*-phenylalaninate (50b)[249]



Using flame dried glassware and under an argon atmosphere, NMM (66 µL, 0.60 mmol) followed by IPCF (58 µL, 0.45 mmol) were added to a solution of Fmoc-Gly-OH (148.7 mg, 0.50 mmol) in anhydrous CH_2Cl_2 (1.5 mL) cooled to −20 °C. The

solution was stirred for 4 h at −20 °C. A solution of phenylalanine ethyl ester hydrochloride (45.9 mg, 0.20 mmol) and NMM (22 µL, 0.20 mmol) in CH_2Cl_2 (0.5 mL) was added and the reaction allowed to warm to rt and stirred for 18 h. The reaction mixture was concentrated *in vacuo* and the resultant oil purified by column chromatography (10% EtOAc in petrol) to give **50b** as an off white gum (85.5 mg, 90%). **^{1}H NMR** ($CDCl_3$, 600 MHz) *δ* 7.77 (2H, d, *J* = 7.6, FmocH), 7.58 (2H, d, *J* = 7.2, FmocH), 7.40 (2H, t, *J* = 7.6, FmocH), 7.30 (2H, t, *J* = 7.2, FmocH), 7.17-7.25 (3H, m, ArH), 7.09 (2H, d, *J* = 7.3, ArH), 6.85 (1H, br s, N**H**CH), 5.79 (1H, br s, CH_2N**H**), 4.88 (1H, dd, *J* = 6.3, 5.9, C**H**NH), 4.37 (2H, d, *J* = 7.2, FmocCH_2), 4.20 (1H, t, *J* = 7.2, OCH_2C**H**), 4.13 (1H, q, *J* = 7.1, C**H**$_2$$CH_3$), 3.90 (1H, dd, *J* = 16.7, 5.4, 1 × C**H**$_2$NH), 3.85 (1H, dd, *J* = 16.7, 5.5, 1 × C**H**$_2$NH), 3.13 (1H, dd, *J* = 13.8, 5.9, 1 × C**H**$_2$Ar), 3.08 (1H, dd, *J* = 13.8, 6.3, 1 × C**H**$_2$Ar), 1.22 (3H, t, *J* = 7.1, CH_3); **^{13}C NMR** ($CDCl_3$, 150 MHz) *δ* 171.4, 168.7, 156.6, 143.9, 141.4, 135.7, 129.4, 128.7, 127.9, 127.3, 127.2, 125.2, 120.1, 67.4, 61.8, 53.3, 47.2, 44.5, 38.0, 14.2; **IR** ν_{max} (film/cm^{-1}) 3308 (N-H), 3065 (N-H), 2979 (C-H), 2938, 1722 (C=O), 1665 (C=O), 1519, 1448

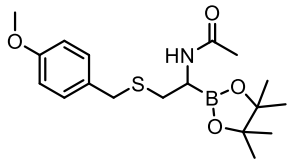
tert-Butyl (2-((2-((4-methoxybenzyl)sulfanyl)-1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)ethyl)amino)-2-oxoethyl)carbamate (51)



Using flame dried glassware under an argon atmosphere, Boc-Gly-OH (87.5 mg, 0.50 mmol) was dissolved in anhydrous CH_2Cl_2 (1.5 mL) and cooled to −20 °C. NMM (66 µL, 0.60 mmol) was added followed by IBCF (58 µL, 0.45 mmol) and the reaction stirred for 5 h at −20 °C. HCl salt **40** (23.4 mg, 65.1 µmol) was added followed by NMM (7 µL, 65 µmol) and the reaction allowed to warm to rt and stirred for 18 h. The reaction mixture was concentrated *in vacuo* and the resultant oil purified by column chromatography (2% MeOH in EtOAc) using deactivated silica (35% H_2O w/w) to give **51** as a pale yellow oil (27.9 mg, 89%). **^{1}H NMR** ($CDCl_3$, 600 MHz) *δ* 7.51 (1H, br s, CHN**H**), 7.21 (2H, d, *J* = 8.7, ArH), 6.82 (2H, d, *J* = 8.7, ArH), 5.29 (1H, br s, CH_2N**H**), 3.93 (2H, d, *J* = 5.7, NHC**H$_2$**), 3.78 (3H, s, OCH_3), 3.65 (2H, s, ArCH_2), 2.81 (1H, br d, *J* = 11.5, CHB), 2.75 (1H, dd, *J* = 14.1, 3.2, 1 × SC**H**$_2$CH), 2.46 (1H, dd, *J* = 14.1, 11.5, 1 × SC**H**$_2$CH), 1.44 (9H, s, Bu), 1.18 (6H, s, 2 × pinacol-CH_3), 1.16 (6H, s, 2 × pinacol-CH_3); **^{13}C NMR** ($CDCl_3$, 150 MHz) *δ* 174.9, 158.7, 130.3, 130.1, 114.1, 81.6, 55.4, 54.0, 41.4, 35.2, 33.6, 29.8, 28.4, 25.0, 24.9, 14.3; **LRMS** (CI) 481 (100%,

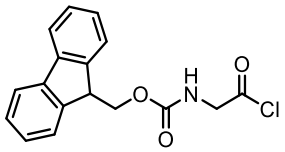
$[M+H]^+$); **HRMS** Found 480.2575, $C_{23}H_{37}BN_2O_6S$ requires 480.2574; **IR** (film/cm^{-1}) 2970 (C-H), 2926 (C-H), 1697 (br, C=O), 1609 (C=O), 1511, 1456

N-(2-((4-Methoxybenzyl)sulfanyl)-1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)ethyl)acetamide (55)



Acetyl chloride (65 µL, 0.42 mmol) was added to a solution of **40** (30 mg, 84 µmol) in acetonitrile (1 mL) followed by pyridine (40 µL, 0.50 mmol). The reaction was stirred for 18 h. Solvent was removed *in vacuo* and EtOAc (3 mL) added. The reaction mixture was filtered and the filtrate washed with H_2O (3 mL), phosphoric acid (1% in H_2O, 3 mL), potassium carbonate (2% in H_2O, 3 mL) and then brine (3 mL). All aqueous layers were back extracted with EtOAc. Removal of solvent *in vacuo* gave an orange oil which was purified by column chromatography (20% EtOAc in CH_2Cl_2) to give **55** as an orange oil (6.7 mg, 22%). **^{1}H NMR** ($CDCl_3$, 600 MHz) 7.21 (2H, d, *J* = 8.6, ArH), 7.00 (1H, br s, NH), 6.83 (2H, d, *J* = 8.6, ArH), 3.78 (3H, s, OCH_3), 3.66 (1H, d, *J* = 13.6, 1 × ArC**H**$_2$), 3.63 (1H, d, *J* = 13.6, 1 × ArC**H**$_2$), 2.81 (1H, dd, *J* =14.3, 2.8, 1 × C**H**$_2$CH), 2.65 (1H, br d, *J* = 12.2, C**H**B), 2.45 (1H, dd, *J* = 14.3, 12.8, 1 × C**H**$_2$CH), 2.05 (3H, s, C(O)C**H**$_3$), 1.16 (6H, s, 2 × pinacol-CH_3), 1.15 (6H, s, 2 × pinacol-CH_3); **^{13}C NMR** ($CDCl_3$, 150 MHz) *δ* 176.0, 158.8, 130.7, 130.1, 114.1, 80.4, 55.4, 44.4, 35.2, 34.2, 25.3, 24.9, 18.1; **LRMS** (CI) 366 (40%, $[M+H]^+$), 266 (51%), 243 (33%), 212 (57%, $[M-SPMB]^+$), 121 (100%, PMB^+); **HRMS** Found 366.19151, $C_{18}H_{28}BNO_4S$ requires 366.19103; **IR** ν_{max} (film/cm^{-1}) 3260 (N-H), 2960(C-H), 2924 (C-H), 2853 (C-H), 1609 (C=O), 1511

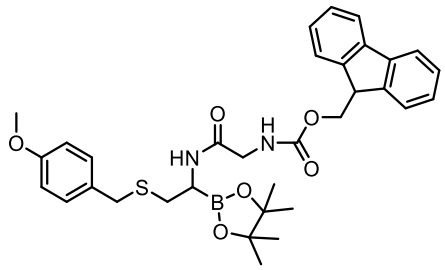
(9*H*-Fluoren-9-yl)methyl (2-chloro-2-oxoethyl)carbamate (54)[250]



Using flame dried glassware and under an argon atmosphere $SOCl_2$ (1.19 mL, 16.4 mmol) was added to a solution of Fmoc-Gly-OH (594 mg, 2.0 mmol) in anhydrous CH_2Cl_2 (10 mL). The reaction was stirred at reflux for 30 min. Solvent was removed

in vacuo and the residue diluted with CH_2Cl_2 and removed *in vacuo* again. This was repeated a further two times. The resultant white solid was recrystallised from hexane to give **54** as white needles (618 mg, 98%, mp 100.8-101.9 ºC (lit 107-108 ºC)[250]). **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 7.77 (2H, d, *J* = 7.4, ArH), 7.60 (2H, d, *J* = 7.3, ArH), 7.40 (2H, t, *J* = 7.3, ArH), 7.32 (2H, t, *J* = 7.4, ArH), 5.38 (1H, br s, NH), 4.42 (2H, d, *J* = 6.8, FmocCH_2), 4.24 (1H, t, *J* = 6.8, C**H**CH_2), 4.00 (2H, d, *J* = 5.2, C**H$_2$**NH); **^{13}C NMR** ($CDCl_3$, 125 MHz) δ 170.6, 156.4, 143.9, 141.4, 127.8, 127.2, 125.2, 120.1, 67.3, 52.5, 47.2; **IR** ν_{max} (solid/cm^{-1}) 3288 (N-H), 3039 (C-H), 2951 (C-H), 1713 (C=O), 1692 (C=O), 1548, 1445

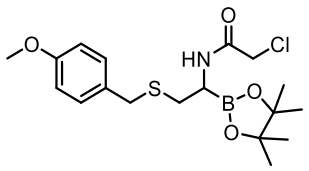
(9*H*-Fluoren-9-yl)methyl(2-((2-((4-methoxybenzyl)sulfanyl)-1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)ethyl)amino)-2-oxoethyl)carbamate (55)



Using flame dried glassware and under an argon atmosphere **54** (15.9 mg, 53.0 µmol) was added to a solution of HCl salt **40** (15.9 mg, 44.2 µmol) in anhydrous CH_2Cl_2 (1.5 mL) followed by DIPEA (15 µL, 88 µmol). The reaction was stirred for 18 h. The solution was washed with HCl (2 M, 2 × 3 mL), H_2O (2 × 3 mL), sodium bicarbonate (2 × 3 mL) and H_2O (2 × 3 mL). All aqueous layers were back extracted with CH_2Cl_2. The combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo* to give an orange residue which was purified by column chromatography (1% MeOH in $CHCl_3$) using deactivated silica (35% H_2O w/w) to give **55** as an orange gum (16.0 mg, 60%). **^{1}H NMR** ($CDCl_3$, 600 MHz) δ 7.77 (2H, d, *J* = 7.6, FmocH), 7.58 (2H, d, *J* = 7.4, FmocH), 7.40 (2H, t, *J* = 7.6, FmocH), 7.31 (2H, t, *J* = 7.4, FmocH), 7.18 (2H, d, *J* = 8.6, ArH), 7.03 (1H, br s, CHN**H**), 6.79 (2H, d, *J* = 8.6, ArH), 5.33 (1H, br s, CH_2N**H**), 4.46 (2H, d, *J* = 6.7, FmocCH_2), 4.22 (1H, d, *J* = 6.7, FmocCH_2C**H**), 3.98 (1H, dd, *J* = 17.3, 5.8, 1 × C**H$_2$**NH), 3.92 (1H, dd, *J* = 17.3, 5.7, 1 × C**H$_2$**NH), 3.74 (3H, s, OCH_3), 3.63 (2H, s, ArC**H$_2$**S), 2.89 (1H, br d, *J* = 10.0, CHB), 2.80 (1H, dd, *J* = 13.7, 3.4, 1 × C**H**$_2$CHB), 2.50 (1H, dd, *J* = 13.7, 11.6, 1 × C**H**$_2$CHB), 1.20 (6H, s, 2 × pinacol-CH_3), 1.19 (6H, s, 2 × pinacol-CH_3); **^{13}C NMR** ($CDCl_3$, 150 MHz) δ 173.0, 158.7, 156.5, 143.7, 141.4, 130.4, 130.1, 127.9, 127.3, 125.1, 120.2, 114.1, 82.2, 67.4, 55.4, 47.2, 42.3, 41.0 (br), 35.5, 33.7, 25.1, 24.9; **LRMS** (CI) 603 (3%, [M+H]$^+$), 503 (3%), 381

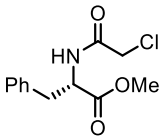
(9%), 325 (8%), 281 (7%), 207 (7%), 179 (100%, [Fmoc−CO_2]$^+$), 147 (8%), 121 (36%, PMB$^+$), 103 (17%); **HRMS** Found 603.27061, $C_{33}H_{39}BN_2O_6S$ requires 603.27001; **IR** ν_{max} (film/cm^{-1}) 3300 (N-H), 2970 (C-H), 2928 (C-H), 1711 (C=O), 1680 (C=O), 1610, 1536, 1511, 1462, 1450

2-Chloro-*N*-(2-((4-methoxybenzyl)sulfanyl)-1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)ethyl)acetamide (56)



Using flame dried glassware and under an argon atmosphere, a solution of **40** (82.3 mg, 0.193 mmol) in anhydrous CH_2Cl_2 (1 mL) was cooled to 0 °C. Chloroacetyl chloride (17 µL, 0.231 mmol) was added followed by the dropwise addition of NMM (30 µL, 0.270 mmol). The solution was allowed to warm to room temperature and stirred for 90 min. The reaction was cooled to 0 °C and HCl (0.2 M, 7 mL) added. The reaction mixture was diluted with EtOAc and the organic layer was separated, dried ($MgSO_4$), filtered and concentrated *in vacuo* to give a brown oil. On addition of Et_2O a brown solid formed which was filtered. The filtrate was concentrated *in vacuo* to give **56** as a brown oil (65.4 mg, 85%). **^{1}H NMR** ($CDCl_3$, 600 MHz) *δ* 7.66 (1H, br s, NH), 7.21 (2H, d, *J* = 8.7, ArH), 6.83 (2H, d, *J* = 8.7, ArH), 4.15 (2H, s, CH_2Cl), 3.78 (3H, s, OCH_3), 3.67 (2H, s, $ArCH_2$), 2.97 (1H, br d, *J* = 11.1, CHB), 2.76 (1H, dd, *J* = 14.0, 3.0, 1 × C**H**$_2$CHB), 2.52 (1H, dd, *J* = 14.0, 11.6, 1 × C**H**$_2$CHB), 1.21 (6H, s, 2 × pinacol-CH_3), 1.19 (6H, s, 2 × pincaol-CH_3); **^{13}C NMR** ($CDCl_3$, 150 MHz) *δ* 171.1, 158.8, 130.1 (2C), 114.1, 82.5, 55.4, 41.6 (br), 41.3, 35.4, 33.0, 24.9, 24.63; **LRMS** (CI) 402 (41%, [M+H]$^+$, ^{37}Cl), 404 (100%, [M+H]$^+$, ^{35}Cl); **HRMS** Found 399.1552, $C_{18}H_{28}BClNO_4S$ requires 399.1551; **IR** ν_{max} (film/cm^{-1}) 2923 (C-H), 1733 (C=O), 1661, 1593, 1494, 1434

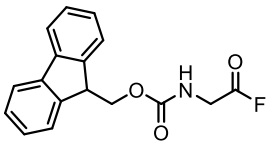
Methyl (2-chloroacetyl)-*L*-phenylalaninate (57)[251]



Using flame dried glassware and under an argon atmosphere, Phe.OMe-HCl (225

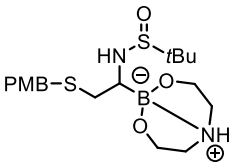
mg, 1.04 mmol) in anhydrous CH_2Cl_2 (2 mL) was cooled to 0 °C. To this was added chloroacetyl chloride (95 µL, 1.2 mmol) followed by the dropwise addition of NMM (154 µL, 1.40 mmol). The solution was stirred for 50 min and allowed to warm to room temperature. The reaction was cooled to 0 °C and HCl (0.2 M, 5 mL) added. The organic layer was separated, dried ($MgSO_4$) and concentrated *in vacuo* to give **57** as an orange oil (229 mg, 86%); **^{1}H NMR** ($CDCl_3$, 600 MHz) *δ* 7.32 (3H, m, ArH), 7.11 (2H, d, *J* = 6.8, ArH), 7.00 (1H, br d, *J* = 6.1, NH), 4.87 (1H, m, NHC**H**), 4.03 (2H, m, CH_2Cl), 3.74 (3H, s, OCH_3), 3.17 (1H, dd, *J* = 13.9, 5.6, 1 × C**H**$_2$Ar), 3.13 (1H, dd, *J* = 13.9, 5.9, 1 × C**H**$_2$Ar); **^{13}C NMR** ($CDCl_3$, 150MHz) *δ* 171.4, 165.8, 135.4, 129.4, 128.9, 127.5, 53.5, 52.7, 42.5, 37.9; **LRMS** (CI) 275 (34%, $[M+NH_4]^+$, ^{37}Cl), 273 (100%, $[M+NH_4]^+$, ^{35}Cl), 258 (4%, $[M+H]^+$, ^{37}Cl), 256 (13%, $[M+H]^+$, ^{35}Cl)

(9*H*-Fluoren-9-yl)methyl (2-fluoro-2-oxoethyl)carbamate (58)[252]



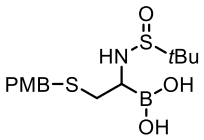
Using flame dried glassware and under an argon atmosphere, pyridine (810 µL, 10.0 mmol) was added to a solution of Fmoc-Gly-OH (2.97 g, 10.0 mmol) in anhydrous CH_2Cl_2 (50 mL) and anhydrous THF (15 mL). Cyanuric fluoride (1.72 mL, 20 mmol) was added dropwise and the reaction was stirred for 18 h. The precipitate and yellow solution were washed twice with ice water (2 × 50 mL) and then brine (50 mL). The organic layer was concentrated *in vacuo*. Addition of CH_2Cl_2 and hexane precipitated **58** as a yellow solid (2.59 g, 87%, mp 127.5-128.4 °C (lit. 134-135 °C)[252]). **^{1}H NMR** ($CDCl_3$, 600 MHz) *δ* 7.77 (2H, d, *J* = 7.6, ArH), 7.59 (2H, d, *J* = 7.4, ArH), 7.41 (2H, td, *J* = 7.4, 1.4, ArH), 7.32 (2H, td, *J* = 7.5, 1.0, ArH), 5.24 (1H, br s, NH), 4.47 (2H, d, *J* = 6.9, FmocC**H$_2$**), 4.24 (1H, t, *J* = 6.9, FmocC**H**CH_2), 4.19 (1H, d, *J* = 4.8, 1 × NHC**H**$_2$), 4.17 (1H, d, *J* = 4.8, 1 × NHC**H**$_2$); **^{13}C NMR** ($CDCl_3$, 150 MHz) *δ* 160.7 ($J_{C\text{-}F}$ = 362.9), 156.1, 143.6, 141.4, 127.9, 127.2, 125.0, 120.1, 67.6, 47.1, 41.4, 40.9; **IR** ν_{max} (solid/cm^{-1}) 3333 (N-H), 3212, 2970 (C-H), 1865, 1840 (C=O), 1678 (C=O), 1534

***N*-(2-((4-Methoxybenzyl)sulfanyl)-1-(tetrahydro-8 λ^4-[1,3,2]oxazaborolo[2,3-*b*][1,3,2]oxazaborol-8-yl)ethyl)-2-methylpropane-2-sulfinamide (62)**



Diethanolamine (46.4 mg, 0.440 mmol) was added to a solution of **39** (171 mg, 0.400 mmol) in Et_2O (2 mL) and the mixture was stirred for 2 h. A white precipitate formed which was filtered, washed (Et_2O) and dried to give **62** as a white solid (126 mg, 76%). **^{1}H NMR** ($CDCl_3$, 600 MHz) δ 7.24 (2H, d, *J* = 8.5, ArH), 6.82 (2H, d, *J* = 8.5, ArH), 4.02-3.95 (3H, m, 3 × OC**H**$_2$), 3.95-3.89 (1H, m, 1 × OC**H**$_2$), 3.86 (1H, m , CHB), 3.78 (3H, s, OCH_3), 3.69 (2H, s, ArC**H$_2$**S), 3.30 (1H, m, 1 × SC**H**$_2$CH), 3.18 (1H, m, 1 × SC**H**$_2$CH), 2.97-2.89 (2H, m, 2 × NC**H**$_2$), 2.81-2.72 (3H, m, 2 × NCH_2, N**H**CH_2), 1.28 (9H, s, *t*Bu); **^{13}C NMR** ($CDCl_3$, 150 MHz) δ 158.5, 131.1, 130.1, 113.9, 63.93, 63.89, 57.4, 55.4, 51.5, 51.4, 37.0, 35.2, 23.6, The signal for the carbon directly attached to boron was not observed; **^{11}B NMR** ($CDCl_3$, 128 MHz) δ 13.36; **LRMS** (CI) 415 (100%, $[M+H]^+$), 309 (97%, $[M-SOtBu]^+$), 294 (29%), 261 (9%), 196 (26%); **HRMS** Found 415.18912, $C_{18}H_{32}BN_2O_4S_2$ requires 415.18965

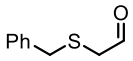
(1-((*tert*-Butylsulfinyl)amino)-2-((4-methoxybenzyl)sulfanyl)ethyl)boronic acid (61)



HCl in dioxane (4 M, 25 µL, 1 mmol) was added to a solution of **62** (35 mg, 83 µmol) in MeOH (1 mL). The reaction was stirred for 1 h and then diluted with EtOAc and H_2O. The organic layer was washed with H_2O (2 mL). The organic layer was dried ($MgSO_4$), filtered, and concentrated *in vacuo* to give **61** as a colourless oil (25.0 mg, 87%); **^{1}H NMR** (MeOD-d_4, 600 MHz) δ 7.28 (2H, d, *J* = 8.4, ArH), 6.89 (2H, d, *J* = 8.4), 3.80 (3H, s, OCH_3), 3.72 (2H, s, $ArSCH_2$), 3.09 (1H, br s, CHB), 2.72 (1H, br s, 1 × SC**H**$_2$CH), 2.71 (1H, br s, 1 × SC**H**$_2$CH), 1.19 (9H, s, *t*Bu); **^{13}C NMR** (MeOD-d_4, 150 MHz) δ 158.9, 132.0, 131.1, 114.8, 57.3, 55.7, 36.6 (br), 35.4, 30.4, 23.0;

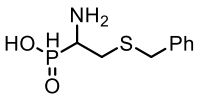
3.2.1.4 Synthesis of model peptide as a *C*-terminal phosphinate

2-(Benzylsulfanyl)acetaldehyde (66)[96]



Using flame dried glassware and under an argon atmosphere, benzyl mercaptan (650 µL, 5.0 mL) was dissolved in THF (5 mL) at 0 °C. *n*BuLi (1.6 M, 3.2 mL, 5.0 mmol) was added dropwise. After 1 h, bromoacetaldehyde diethyl acetal (910 µL, 6.0 mmol) was added dropwise and the solution allowed to warm to rt. The solution was then refluxed for 48 h. It was diluted with H_2O (10 mL) and extracted with Et_2O (3 × 10 mL). The combined organic phases were dried ($MgSO_4$), filtered, and concentrated *in vacuo* to give a colourless oil (122.6 mg). HCl (6 M, 1.5 mL) was added to the oil (122 mg, 0.51 mmol) in Et_2O (3.5 mL) and the reaction stirred at reflux for 4 h. The solution was diluted with H_2O and extracted with Et_2O (2 × 4 mL) and the organic layer washed with H_2O (5 mL) and then brine (5 mL). The organic layer was dried ($MgSO_4$), filtered, and concentrated *in vacuo* to give **66** as a colourless oil (74 mg, 87%); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 9.42 (1H, t, *J* = 3.3, CHO), 7.43-7.27 (5H, m, ArH), 3.63 (2H, s, CH_2Ph), 3.09 (2H, d, *J* = 3.3, C**H_2**CHO); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 194.0, 137.0, 129.4, 128.8, 127.6, 40.3, 35.6; **IR** ν_{max} (film/cm-1) 3016 (C-H), 2834, 1718 (C=O), 1602, 1512

(1-Amino-2-(benzylsulfanyl)ethyl)phosphinic acid (68)[96]

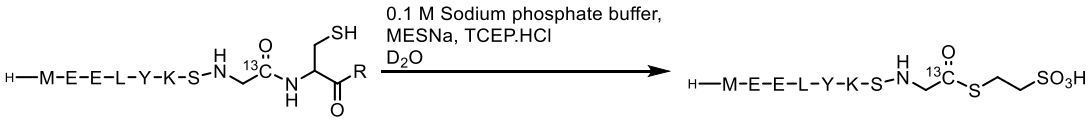


Aldehyde **66** (70 mg, 0.42 mmol) was dissolved in EtOH (1.5 mL). Aminodiphenylmethane phosphate (423 mg, 1.7 mmol) and aminodiphenylmethane hydrochloride (792 mg, 3.4 mmol) were added. H_3PO_2 (100% solution, 19 mg, 0.28 mmol) was added and the reaction stirred at reflux for 4 h. The resultant solid was filtered, washed with EtOH and then Et_2O and dried, to give a white insoluble solid (89 mg, mp 213-218 °C). The white solid (85 mg, 0.21 mmol) was added to HCl (18%, 4 mL) and refluxed for 4 h. Solvents were removed *in vacuo* and the resultant residue was dissolved in EtOH. Propylene oxide was added to induce precipitation. The precipitate was filtered, washed with EtOH, Et_2O and then dried to give **68** as a white solid (42 mg, 0.15 mmol, mp 221-224 °C (lit. 225-227 °C)[253]). **^{1}H NMR** (300 MHz,

D_2O) *δ* 7.42-7.28 (3H, m, 3 × ArH), (7.28-7.19 (2H, m, 2 × ArH), 6.13 (1H, br s, OH), 3.81 (2H, s, CH_2Ph), 3.13-2.89 (2H, m, C**H₂**CH), 2.66 (1H, ddd, *J* = 15.0, 11.1, 8.4, C**H**NH_2); **^{13}C NMR** (75 MHz, D_2O) δ 139.2, 129.6, 129.5, 127.9, 51.0, 35.9, 32.8; **^{31}P NMR** (121.5 MHz, D_2O) δ 31.5

3.2.2 Rate of thioester formation via *N* → *S* acyl shift

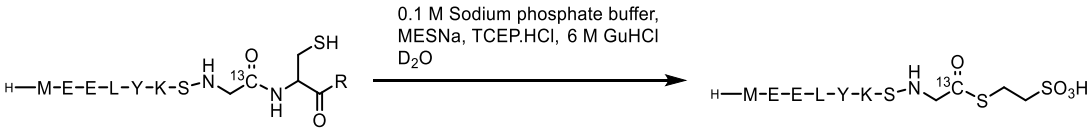
General Procedure B: Thioester Formation



Peptide **7**, **8** or **9** were dissolved to final concentrations of 1 mg mL^{-1} in 0.1 M sodium phosphate buffer (pH 5.8, prepared in D_2O) containing MESNa (10% w/v), and TCEP.HCl (0.5% w/v). Aliquots of 0.6 mL were dispensed into separate 1.5 mL Eppendorf tubes and shaken in an Eppendorf thermomixer at 60 ºC for 48 h. The contents of each Eppendorf tube were transferred to an NMR tube to obtain an independent estimation of reaction progress. The ^{13}C NMR spectra were acquired at 125 MHz using D_2O as an internal standard.

LCMS analysis at the end of each reaction was used to confirm the peptides present.

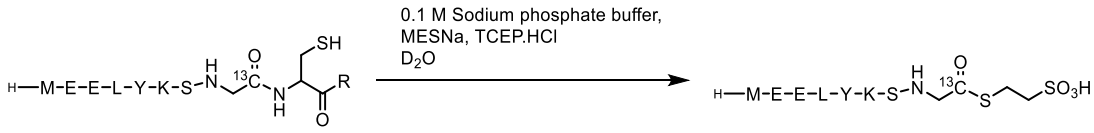
General Procedure C: Thioester Formation in the presence of GuHCl



0.1 M sodium phosphate buffer (pH 5.8) in GuHCl was prepared by a tenfold dilution of of 1 M sodium phosphate buffer into the corresponding concentration of GuHCl. Peptide **7** or **9** were dissolved to final concentrations of 1 mg mL^{-1} in 0.1 M sodium phosphate buffer (pH 5.8, prepared as detailed above) containing MESNa (10% w/v), and TCEP.HCl (0.5% w/v). Aliquots of 0.6 mL were dispensed into separate 1.5 mL Eppendorf tubes and shaken in an Eppendorf thermomixer at 60 ºC for 48 h. The contents of each Eppendorf tube were transferred to an NMR tube to obtain an independent estimation of reaction progress. The ^{13}C NMR spectra were acquired at 125 MHz using D_2O as an internal standard.

LCMS analysis at the end of each reaction was used to confirm the peptides present.

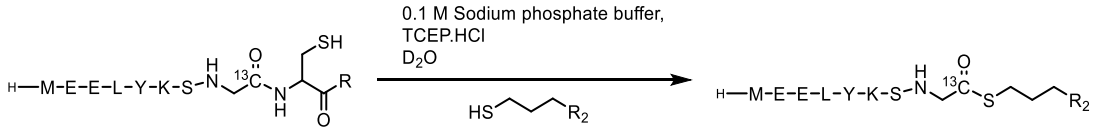
General Procedure D: Thioester Formation in the presence of urea, sucrose or PEG 20,000



0.1 M sodium phosphate buffer (pH 5.8) was prepared by a ten fold dilution of 1 M sodium phosphate buffer into either 6 M urea, 2.044 M sucrose or 26.26 mM PEG 20,000. Peptide **7** or **9** were dissolved to final concentrations of 1 mg mL^{-1} in 0.1 M sodium phosphate buffer (pH 5.8, prepared as detailed above) containing MESNa (10% w/v), and TCEP.HCl (0.5% w/v). Aliquots of 0.6 mL were dispensed into separate 1.5 mL Eppendorf tubes and shaken in an Eppendorf thermomixer at 60 ºC for 48 h. The contents of each Eppendorf tube were transferred to an NMR tube to obtain an independent estimation of reaction progress. The ^{13}C NMR spectra were acquired at 125 MHz using D_2O as an internal standard.

LCMS analysis at the end of each reaction was used to confirm the peptides present.

General Procedure E: Thioester Formation in the presence of 3-mercaptopropanol or 3-mercaptopropionic acid

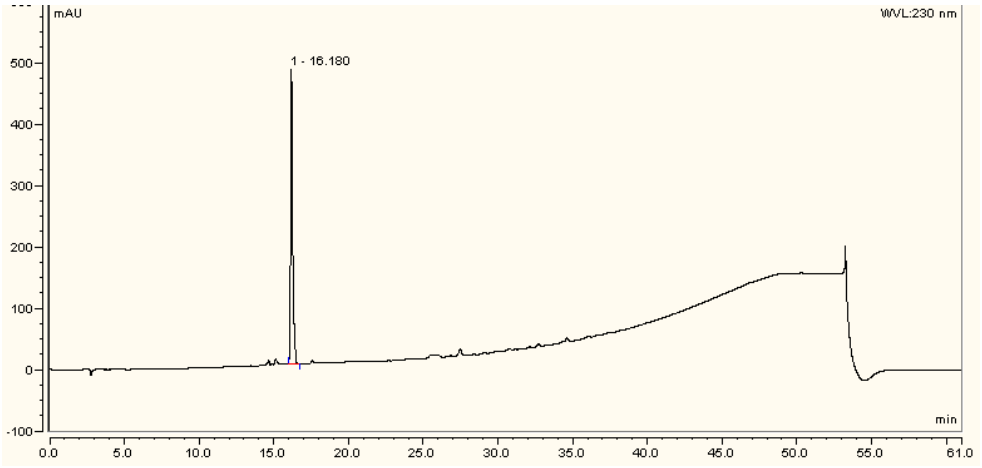


Peptide **7** was dissolved to a final concentration of 1 mg mL^{-1} in 0.1 M sodium phosphate buffer (pH 5.8, prepared in D_2O) containing 3-mercaptopropanol or 3-mercaptopropionic acid (10% w/v), and TCEP.HCl (0.5% w/v). Aliquots of 0.6 mL were dispensed into separate 1.5 mL Eppendorf tubes and shaken in an Eppendorf thermomixer at 60 ºC for 48 h. The contents of each Eppendorf tube were transferred to an NMR tube to obtain an independent estimation of reaction progress. The ^{13}C NMR spectra were acquired at 125 MHz using D_2O as an internal standard.

3.2.3 Analytical HPLC of Peptides

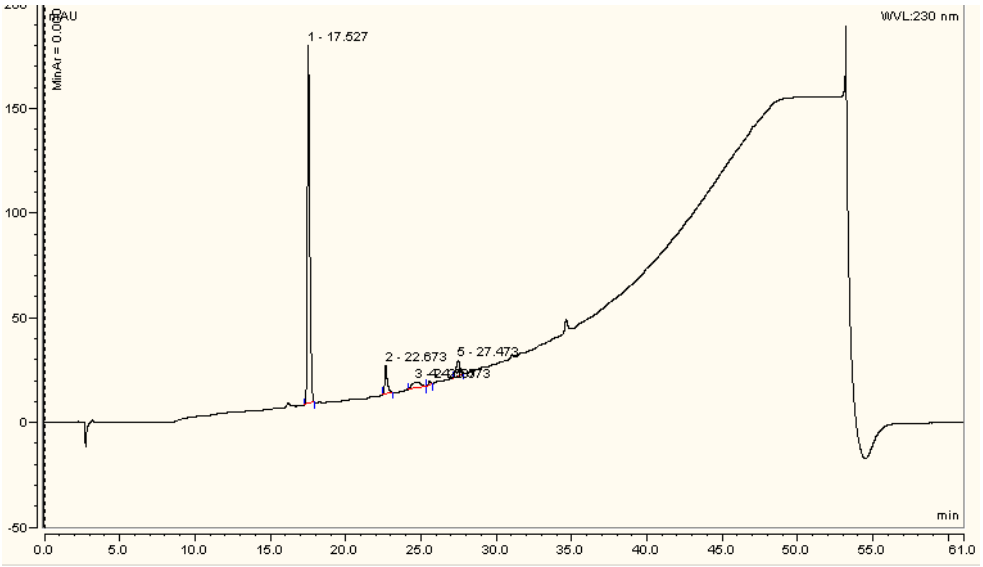
H-MEELYKSG($^{13}C_1$)C-OH (7)

t_R = 16.2 min, 5→95% acetonitrile in water over 60 min



H-MEELYKSG($^{13}C_1$)C-OMe (9)

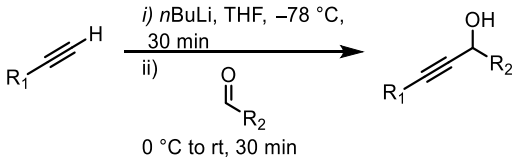
t_R = 17.5 min, 5→95% acetonitrile in water over 60 min



3.3 Experimental Part II

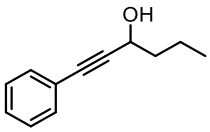
3.3.1 Preparation of propargylic alcohols

General Procedure F: Preparation of propargylic alcohols



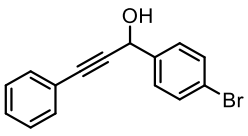
n-Butyllithium (1.6 M in hexanes, 1.2 eq.) was added dropwise to a stirred solution of alkyne (1 eq.) in anhydrous THF (1 mL.mmol^{-1}) at –78 ˚C under an argon atmosphere. After 30 min aldehyde (1 eq.) was added and the resulting solution was stirred for 5 min at 0 ˚C and then 30 min at rt. The reaction was quenched with aq. saturated NH_4Cl and the organic phase extracted with Et_2O. The combined organic phases were washed with brine, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by column chromatography to give the propargylic alcohol.

1-Phenylhex-1-yn-3-ol (141b)[254]



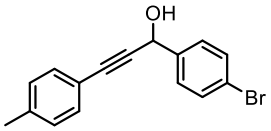
General Procedure F using phenylacetylene (2.03 g, 19.9 mmol), *n*-butyllithium (14.9 mL, 23.9 mmol), THF (20 mL) and butyraldehyde (1.44 g, 19.9 mmol): yellow oil, 3.33 g, 96%. **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 7.4-7.39 (2H, m, ArH), 7.35-7.28 (3H, m, ArH), 4.61 (1H, t, *J* = 6.6, CH), 1.86-1.72 (2H, m, CHC**H$_2$**), 1.65-1.49 (2H, m, C**H$_2$**CH_3), 0.99 (3H, t, *J* = 7.4, CH_3); **^{13}C NMR** ($CDCl_3$, 125 MHz) δ 131.8, 128.5, 128.4, 122.8, 90.3, 84.9, 62.9, 40.1, 18.6, 13.9; **LRMS** (CI) 174 (100%, $[M+H]^+$)

1-(4-Bromophenyl)-3-phenylprop-2-yn-1-ol (141e)[255]



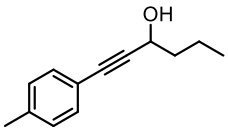
General Procedure F using phenylacetylene (204 mg, 2.00 mmol), *n*-butyllithium (1.50 mL, 2.40 mmol), THF (2 mL) and 4-bromobenzaldehyde (369 mg, 2.00 mmol): white solid, 235 mg, 41%, mp 71-73 °C (lit. 72-73 °C).[256] **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.56-7.43 (6H, m, ArH), 7.39-7.29 (3H, m, ArH), 5.66 (1H, d, J = 5.9, CH), 2.36 (1H, d, J = 5.9, OH); **^{13}C NMR** ($CDCl_3$, 150 MHz) δ 139.7, 131.9, 128.9, 128.5, 128.5, 128.4, 122.6, 122.2, 88.2, 87.1, 64.6; **LRMS** (CI) 287 (98%, $[M+H]^+$, ^{81}Br), 285 (100%, $[M+H]^+$, ^{79}Br), 236 (20%) 234 (21%), 218 (32%), 216 (30%)

1-(4-Bromophenyl)-3-(*p*-tolyl)prop-2-yn-1-ol (141f)[257]



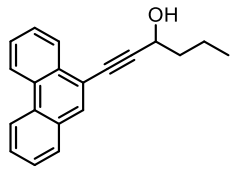
General Procedure F using *p*-tolylacetylene (291 mg, 2.51 mmol), *n*-butyllithium (1.88 mL, 3.01 mmol), THF (2.5 mL) and 4-bromobenzaldehyde (462 mg, 2.51 mmol): pale yellow solid, 512 mg, 68%, mp 97-98 °C. **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 7.55-7.50 (2H, m, ArH), 7.50-7.45 (2H, m, ArH), 7.36 (2H, d, J = 8.0, ArH), 7.13 (2H, d, J = 8.0, ArH), 5.64 (1H, s, CH), 2.52 (3H, s, CH_3); **^{13}C NMR** ($CDCl_3$, 125 MHz) δ 139.8, 139.1, 131.8, 131.7, 129.2, 128.5, 122.4, 119.1, 87.6, 87.3, 64.5, 21.6; **LRMS** (EI) 302 (34%, M^+, ^{81}Br), 300 (39%, M^+, ^{79}Br), 221 (100%, $[M-Br]^+$)

1-(*p*-Tolyl)hex-1-yn-3-ol (141g)[192]



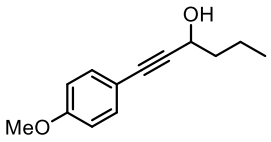
General Procedure F using *p*-tolylacetylene (3.88 g, 33.4 mmol), *n*-butyllithium (25 mL, 40.1 mmol), THF (33 mL) and butyraldehyde (2.41 g, 33.4 mmol): orange oil, 5.34 g, 85%. **^{1}H NMR** ($CDCl_3$, 600 MHz) δ 7.33 (2H, d, J = 8.0, ArH), 7.11 (2H, d, J = 8.0, ArH), 4.61 (1H, t, J = 6.6, CH), 2.35 (3H, s, CCH_3), 2.04 (1H, br s, OH), 1.85−1.71 (2H, m, CHC**H$_2$**), 1.61-1.49 (2H, m, C**H$_2$**CH_3), 0.99 (3H, t, CH_2C**H$_3$**); **^{13}C NMR** ($CDCl_3$, 150 MHz) δ 138.6, 131.7, 129.2, 119.7, 89.6, 85.0, 62.9, 40.1, 21.6, 18.7, 13.9; **LRMS** (EI) 188 (15%, M^+), 145 (90%), 143 (100%, $[M-OH]^+$), 115 (56%)

1-(Phenanthren-9-yl)-hex-1-yn-3-ol (141i)



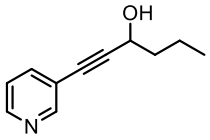
General Procedure F using 9-ethynylphenanthrene (217 mg, 1.07 mmol), *n*-butyllithium (804 µL, 1.29 mmol), THF (1.1 mL) and butyraldehyde (77.3 mg, 1.07 mmol): pale yellow solid, 285 mg, 97%, mp 80-81 °C. **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 8.70-8.63 (2H, m, ArH), 8.44-8.38 (1H, m, ArH), 7.99 (1H, br s, ArH), 7.84 (1H, dd, *J* = 7.9, 0.9, ArH), 7.71-7.63 (3H, m, ArH), 7.63-7.56 (1H, m, ArH), 4.80 (1H, t, *J* = 6.6, CH), 1.98-1.88 (2H, m, CHC**H$_2$**), 1.72-1.62 (2H, m, C**H$_2$**CH_3), 1.05 (3H, t, *J* = 7.4, CH_3); **^{13}C NMR** ($CDCl_3$, 125 MHz) δ 132.2, 131.2, 131.1, 130.4, 130.1, 128.6, 127.6, 127.1, 127.1, 127.0, 126.9, 122.8, 122.7, 119.1, 94.9, 83.1, 63.1, 40.2, 18.7, 13.9; **LRMS** (EI) 274 (52%, M^+), 231 (100%, $[M-CH_2CH_2CH_3]^+$) 202 (65%); **HRMS** Found 274.1351, $C_{20}H_{18}O$ requires 274.1352; **IR** ν_{max} (solid/cm^{-1}) 3360 (O-H), 3056 (C-H), 2955 (C-H), 2930 (C-H), 2196 (C≡C), 1450

1-(4-Methoxyphenyl)hex-1-yn-3-ol (141j)[258]



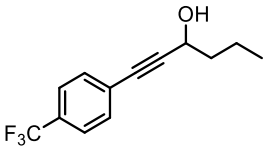
General Procedure F using 4-ethynylanisole (331 mg, 2.51 mmol), *n*-butyllithium (1.88 mL, 3.01 mmol), THF (2.5 mL) and butyraldehyde (181 mg, 2.51 mmol): orange oil, 497 mg, 97%. **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 7.36 (2H, d, *J* = 8.9, ArH), 6.83 (2H, d, *J* = 8.9, ArH), 4.59 (1H, t, *J* = 6.6, CH), 3.80 (3H, s, OCH_3), 1.94 (1H, br s, OH), 1.85-1.72 (2H, m, CHC**H$_2$**), 1.60-1.50 (2H, m, C**H$_2$**CH_3), 0.98 (3H, t, *J* = 7.4, CH_3); **^{13}C NMR** ($CDCl_3$, 125 MHz) δ 159.8, 133.3, 114.9, 114.0, 88.9, 84.9, 63.0, 55.4, 40.2, 18.6, 13.9; **LRMS** (EI) 204 (28%, M^+), 186 (21%, $[M-OH]^+$), 171 (18%), 161 (100%, $[M-CH_2CH_2CH_3]^+$)

1-(Pyridin-3-yl)hex-1-yn-3-ol (141k)



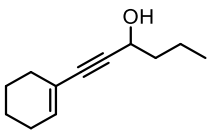
General Procedure F using 3-ethynylpyridine (129 mg, 1.25 mmol), *n*-butyllithium (940 µL, 1.50 mmol), THF (1.25 mL) and butyraldehyde (90.4 mg, 1.25 mmol): orange oil, 202 mg, 92%. **^{1}H NMR** ($CDCl_3$, 600 MHz) δ 8.71 (1H, br s, ArH), 8.53 (1H, dd, *J* = 4.9, 1.6, ArH), 7.72 (1H, dt, *J* = 7.9, 1.9, ArH), 7.25-7.22 (1H, m, ArH), 4.36 (1H, q, *J* = 6.6, CH), 2.76 (1H, br s, OH), 1.86-1.73 (2H, m, CHC**H$_2$**), 1.61-1.50 (2H, m, C**H$_2$**CH_3), 1.00 (3H, t, *J* = 7.4, CH_3); **^{13}C NMR** ($CDCl_3$, 150 MHz) δ 152.3, 148.6, 138.9, 123.2, 120.2, 94.3, 81.3, 62.6, 39.9, 18.7, 13.9; **LRMS** (ES+) 176 (100%, $[M+H]^+$); **HRMS** Found 176.1078, $C_{11}H_{14}NO$ requires 176.1075; **IR** ν_{max} (film/cm^{-1}) 3220 (O-H), 2957 (C-H), 2932 (C-H), 2871 (C-H), 2201 (C≡C), 1476

1-(4-(Trifluoromethyl)phenyl)hex-1-yn-3-ol (141l)[254]



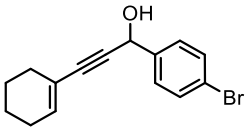
General Procedure F using 1-ethynyl-4-(trifluoromethyl)benzene (1.70 g, 10.0 mmol), *n*-butyllithium (7.5 mL, 12.0 mmol), THF (10 mL) and butyraldehyde (720 mg, 10.0 mmol): pale yellow liquid, 2.20 g, 91%. **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 7.56 (2H, d, *J* = 8.3, ArH), 7.52 (2H, d, *J* = 8.3, ArH), 4.62 (1H, t, *J* = 6.6, CH), 1.86-1.73 (2H, m, CHC**H$_2$**), 1.61-1.49 (2H, m, C**H$_2$**CH_3), 0.99 (3H, t, *J* = 7.4, CH_3); **^{13}C NMR** ($CDCl_3$, 150 MHz) 132.0, 130.1 (q, J_{CF} = 275.6), 125.2 (q, J_{CF} = 3.8), 124.9 (q, J_{CF} = 272.4) 92.7, 83.6, 62.8, 39.9, 18.6, 13.8; **LRMS** (EI) 242 (15%, M^+), 227 (11%), 213 (18%), 199 (100%, $[M-CH_2CH_2CH_3]^+$), 151 (37%)

1-(Cyclohex-1-en-1-yl)hex-1-yn-3-ol (141n)[259]



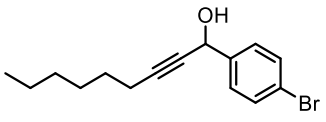
General Procedure F using 1-ethynylcyclohexene (530 mg, 5.0 mmol), *n*-butyllithium (3.75 mL, 6.00 mmol), THF (5 mL) and butyraldehyde (360 mg, 5.00 mmol): pale yellow liquid, 852 mg, 96%. **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 6.11-6.07 (1H, m, C=C**H**), 4.48 (1H, t, *J* = 6.6, C**H**OH), 2.09 (4H, m, 2 × CH_2), 1.71-1.55 (7H, m, 3 × CH_2, OH), 1.53-1.38 (2H, m, C**H$_2$**CH_3), 0.94 (3H, t, *J* = 7.4, CH_3); **^{13}C NMR** ($CDCl_3$, 125 MHz) δ 135.2, 120.2, 87.6, 86.7, 62.8, 40.2, 29.3, 25.7, 22.3, 21.5, 18.6, 13.8; **LRMS** (EI) 178 (34%, $[M]^+$), 149 (24%), 135 (100%, $[M-CH_2CH_2CH_3]^+$)

1-(4-Bromophenyl)-3-(cyclohex-1-en-1-yl)prop-2-yn-1-ol (141o)



General Procedure F using 1-ethynylcyclohexene (269 mg, 2.53 mmol), *n*-butyllithium (1.90 mL, 3.04 mmol), THF (2.5 mL) and 4-bromobenzaldehyde (466 mg, 2.53 mmol): yellow oil, 272 mg, 37%. **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 7.50 (2H, d, *J* = 8.4, ArH), 7.42 (2H, d, *J* = 8.4, ArH), 6.16-6.14 (1H, m, C=C**H**), 5.53 (1H, d, *J* = 6.0, C**H**OH), 2.18-2.07 (5H, m, 2 × CH_2, OH), 1.67-1.61 (2H, m, CH_2), 1.61-1.55 (2H, m, CH_2); **^{13}C NMR** ($CDCl_3$, 125 MHz) δ 140.1, 136.2, 131.7, 128.5, 122.3, 119.9, 89.0, 85.6, 64.5, 29.1, 25.7, 22.3, 21.5; **LRMS** (EI) 292 (30%, $[M]^+$, ^{81}Br), 290 (35%, $[M]^+$, ^{79}Br), 263 (48%), 261 (51%), 211 (60%, $[M-Br]^+$), 141 (70%), 45 (100%); **HRMS** Found 290.0256, $C_{15}H_{15}BrO$ requires 290.0301; **IR** ν_{max} (film/cm^{-1}) 3366 (O-H), 2930 (C-H), 2859 (C-H), 2182 (C≡C), 1586 (C=C)

1-(4-Bromophenyl)non-2-yn-1-ol (141p)

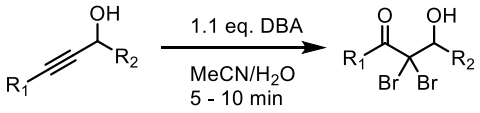


General Procedure F using oct-1-yne (278 mg, 2.53 mmol), *n*-butyllithium (1.90 mL, 3.04 mmol), THF (2.5 mL) and 4-bromobenzaldehyde (465 mg, 2.53 mmol): pale yellow oil, 468 mg, 63%. **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 7.49 (2H, d, *J* = 8.2, ArH), 7.41 (2H, d, *J* = 8.2, ArH), 5.40 (1H, d, *J* = 6.0, CH), 2.26 (2H, td, *J* = 7.2, 2.0, CH_2C), 2.15 (1H, d, *J* = 6.0, OH), 1.60-1.48 (2H, m, CH_2), 1.45-1.35 (2H, m, CH_2), 1.35-1.22 (4H, m, 2 × CH_2), 0.89 (3H, t, *J* = 7.0, CH_3); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 140.4, 131.7, 128.4, 122.2, 88.2, 79.6, 64.2, 31.3, 28.6, 28.5, 22.6, 18.8, 14.1; **LRMS** (EI) 296 (28%,

$[M]^+$, ^{81}Br), 294 (30%, $[M]^+$, ^{79}Br), 215 (100%, $[M-Br]^+$); **HRMS** Found 294.0615, $C_{15}H_{19}BrO$ requires 294.0614; **IR** ν_{max} (film/cm^{-1}) 3454 (O-H), 2954 (C-H), 2928 (C-H), 2858 (C-H), 2235 (C≡C), 1644 (C=O), 1584, 1568 (C=C), 1482 (C=C), 1465

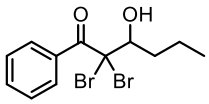
3.3.2 Preparation of α,α-dibromo-β-hydroxyketones

General Procedure G: Preparation of dibromohydroxyketones



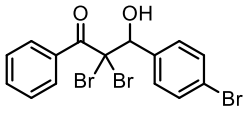
Dibromoisocyanuric acid (1.1 eq.) was added to a stirring solution of propargylic alcohol (1.0 eq.) in MeCN:H_2O (7:3, 2 mL.$mmol^{-1}$). The solution was stirred for 10 min after which solvent was removed *in vacuo* and the resultant residue purified by column chromatography (10% EtOAc in petrol) to give the dibromohydroxyketone.

2,2-Dibromo-3-hydroxy-1-phenylhexan-1-one (142b)



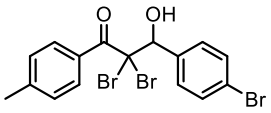
General Procedure G using **141b** (550 mg, 3.16 mmol), DBA (1.00 g, 3.47 mmol) and MeCN/H_2O (6.4 mL): yellow solid, 818 mg, 74%, mp 54-55 °C. **^{1}H NMR** ($CDCl_3$, 600 MHz) δ 8.37 (2H, m, ArH), 7.59 (1H, m, ArH), 7.48 (2H, m, ArH), 4.23 (1H, dd, *J* = 9.6, 1.4, CH), 3.34 (1H, br s, OH), 2.07 (1H, m, 1 × CHC**H**$_2$), 1.80 (1H, m, 1 × CHC**H**$_2$), 1.74 (1H, m, 1 × C**H**$_2$$CH_3$), 1.52 (1H, m, 1 × C**H**$_2$$CH_3$), 1.02 (3H, t, *J* = 7.4, CH_3); **^{13}C NMR** ($CDCl_3$, 150 MHz) δ 190.4, 133.9, 132.6, 131.5, 128.1, 77.2, 71.4, 34.9, 19.5, 14.1; **LRMS** (NSI) 375 (49%, $[M+Na]^+$, 2 × ^{81}Br), 373 (100%, $[M+Na]^+$, ^{79}Br, ^{81}Br), 371 (50%, $[M+Na]^+$, 2 × ^{79}Br); **HRMS** Found 370.9252, $C_{12}H_{14}Br_2O_2Na$ ($[M+Na]^+$) requires 370.9253; **IR** ν_{max} (solid/cm^{-1}) 3544 (O-H), 2955 (C-H), 2927 (C-H), 2864 (C-H), 1667 (C=O), 1594 (C=C), 1574 (C=C), 1445

2,2-Dibromo-3-(4-bromophenyl)-3-hydroxy-1-phenylpropan-1-one (142e)



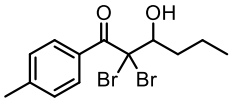
General Procedure G using **141e** (125 mg, 436 µmol), DBA (138 mg, 480 µmol), and MeCN/H_2O (870 µL): pale brown solid, 101 mg, 50%, mp 157-159 °C; **^{1}H NMR** ($CDCl_3$, 500 MHz) *δ* 8.39 (2H, d, *J* = 8.5, ArH), 7.63-7.59 (1H, m, ArH), 7.56 (2H, d, *J* = 8.6, ArH), 7.53 (2H, d, *J* = 8.6, ArH), 7.50-7.46 (2H, m, ArH), 5.41 (1H, d, *J* = 3.7, CH), 3.96 (1H, d, *J* = 3.7, OH); **^{13}C NMR** ($CDCl_3$, 125 MHz) *δ* 190.9, 135.5, 134.1, 132.4, 131.9, 131.6, 130.6, 128.1, 123.2, 77.8, 69.1; **LRMS** (NSI) 489 (11%, [M+Na]+, 3 × ^{81}Br), 487 (32%, [M+Na]+, 2 × ^{81}Br, ^{79}Br), 485 (35%, [M+Na]+, 2 × ^{79}Br, ^{81}Br), 483 (10%, [M+Na]+, 3 × ^{79}Br), 345 (100%); **HRMS** Found 482.8197, $C_{15}H_{11}Br_3O_2Na$ ([M+Na]$^+$) requires 482.8201; **IR** ν_{max} (solid/cm^{-1}) 3530 (O-H), 2923 (C-H), 2853 (C-H), 1657 (C=O), 1591 (C=C), 1574 (C=C), 1485

2,2-Dibromo-3-(4-bromophenyl)-3-hydroxy-1-(*p*-tolyl)propan-1-one (142f)



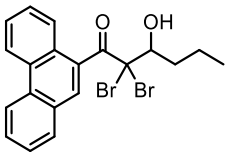
General Procedure G using **141f** (126 mg, 419 µmol), DBA (132 mg, 461 µmol) and MeCN/H_2O (840 µL): off white solid, 190 mg, 95%, mp 171-172 °C. **^{1}H NMR** ($CDCl_3$, 600 MHz) *δ* 8.32 (2H, d, *J* = 8.4, ArH), 7.56 (2H, d, *J* = 8.5, ArH), 7.53 (2H, d, *J* = 8.5, ArH), 7.28 (2H, d, *J* = 8.4, ArH), 5.40 (1H, br d, *J* = 2.4), 4.05 (1H, br d, *J* = 3.3, OH), 2.45 (3H, s, CH_3); **^{13}C NMR** ($CDCl_3$, 150 MHz) *δ* 190.6, 145.6, 135.6, 132.0, 131.9, 130.6, 129.6, 128.9, 123.3, 77.9, 69.2, 21.9; **LRMS** (CI) 480 (3%, [M]$^+$, 3 × ^{81}Br), 478 (6%, M$^+$, 2 × ^{81}Br, ^{79}Br), 476 (7%, [M]$^+$, ^{81}Br, 2 × ^{79}Br), 474 (3%, [M]$^+$, 3 × ^{79}Br), 413 (11%), 400 (51%, [M−Br]$^+$, 2 × ^{81}Br) 398 (100%, [M−Br]$^+$, ^{81}Br, ^{79}Br), 396 (54%, [M−Br]$^+$, 2 × ^{79}Br), 383 (16%), 381(31%), 379 (15%); **HRMS** Found 473.8459, $C_{16}H_{13}Br_3O_2$ requires 473.8466; **IR** ν_{max} (solid/cm^{-1}) 3554 (O-H), 1657 (C=O), 1598 (C=C), 1297, 1215

2,2-Dibromo-3-hydroxy-1-(*p*-tolyl)hexan-1-one (142g)



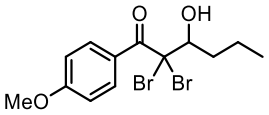
General Procedure G using **141g** (70 mg, 350 µmol), DBA (110 mg, 385 mmol) and MeCN/H_2O (750 µL): pale yellow solid, 111 mg, 87%, mp 71-73 °C; **^{1}H NMR** ($CDCl_3$, 600 MHz) δ 8.29 (2H, d, *J* = 8.4, ArH), 7.27 (2H, d, *J* = 8.4, ArH), 4.22 (1H, dd, *J* = 9.6, 1.6, CH), 3.46 (1H, br s, OH), 2.44 (3H, s, CCH_3), 2.12-2.02 (1H, m, 1 × CHC**H**$_2$), 1.85-1.76 (1H, m, 1 × CHC**H**$_2$), 1.76-1.69 (1H, m, 1 × C**H**$_2$$CH_3$), 1.59-1.47 (1H, m, 1 × C**H**$_2$$CH_3$), 1.02 (3H, t, *J* = 7.4, CH_2C**H**$_3$); **^{13}C NMR** ($CDCl_3$, 600 MHz) δ 190.1, 145.2, 131.7, 129.8, 128.9, 77.2, 71.5, 34.9, 21.9, 19.6, 14.1; **LRMS** (ES^+) 389 (34%, [M+Na^+], 2 × ^{81}Br), 387 (64%, [M+Na^+], ^{79}Br, ^{81}Br), 385 (31%, [M+Na^+], 2 × ^{79}Br), 367 (34%, $[M+H]^+$, 2 × ^{81}Br), 365 (100%, ^{79}Br, ^{81}Br), 363 (48%, 2 × ^{79}Br); **HRMS** Found 362.9579, $C_{13}H_{17}Br_2O_2$ requires 362.9595; **IR** ν_{max} (solid/cm^{-1}) 3502 (O-H), 2958 (C-H), 2865 (C-H), 1658 (C=O), 1600, 1565

2,2-Dibromo-3-hydroxy-1-(phenanthren-9-yl)hexan-1-one (142i)



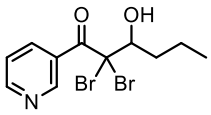
General Procedure G using **141i** (137 mg, 500 µmol), DBA (157 mg, 548 µmol) and MeCN/H_2O (1 mL): pale brown solid, 139 mg, 62%, mp 109-110 °C; **^{1}H NMR** ($CDCl_3$, 600 MHz) δ 8.74 (1H, d, *J* = 8.3, ArH), 8.71 (1H, d, *J* = 8.3, ArH), 7.99 (1H, dd, *J* = 9.9, 1.0, ArH), 7.91 (1H, dd, *J* = 8.2, 1.0, ArH), 7.76 (1H, ddd, *J* = 8.3, 7.0, 1.4, ArH), 7.71 (1H, ddd, *J* = 8.3, 7.0, 1.3, ArH), 7.69-7.65 (1H, m, ArH), 7.63 (1H, ddd, *J* = 8.3, 7.0, 1.3, ArH), 4.52-4.46 (1H, m, CH), 2.80 (1H, d, *J* = 7.5, OH), 1.85-1.71 (2H, m, C**H**$_2$CH), 1.60-1.50 (2H, m, **CH**$_2$$CH_3$), 1.05 (3H, t, *J* = 7.4, CH_3); **^{13}C NMR** ($CDCl_3$, 150 MHz) δ 195.9, 133.3, 131.2, 130.5, 130.0, 129.7, 129.3, 128.7, 127.8, 127.41, 127.39, 127.3, 126.4, 123.1, 122.8, 77.1, 75.0, 35.6, 19.4, 14.1; **LRMS** (EI) 452 (3%, $[M]^+$, 2 × ^{81}Br), 450 (7%, $[M]^+$, ^{79}Br, ^{81}Br), 448 (4%, $[M]^+$, 2 × ^{79}Br), 205 (100%, $[M-C_5H_9Br_2O]^+$); **HRMS** Found 447.9647, $C_{20}H_{18}Br_2O_2$ requires 447.9668; **IR** ν_{max} (solid/cm^{-1}) 3572 (O-H), 2957 (C-H), 1642 (C=O), 1447

2,2-Dibromo-3-hydroxy-1-(4-methoxyphenyl)hexan-1-one (142j)



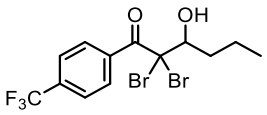
General Procedure G using **141j** (102 mg, 500 µmol), DBA (158 mg, 550 µmol) and MeCN/H_2O (1 mL): pale yellow solid, 138 mg, 73%, mp 81-84 °C; **^{1}H NMR** ($CDCl_3$, 600 MHz) *δ* 8.40 (2H, d, *J* = 9.1, ArH), 6.93 (2H, d, *J* = 9.1, ArH), 4.19 (1H, ddd, *J* = 9.6, 4.2, 1.6, CH), 3.90 (3H, s, OCH_3), 3.52 (1H, br d, *J* = 4.2, OH), 2.11-2.01 (1H, m, 1 × CHC**H**$_2$), 1.85-1.77 (1H, m, 1 × CHC**H**$_2$), 1.77-1.68 (1H, m, 1 × C**H**$_2$$CH_3$), 1.57-1.45 (1H, m, 1 × C**H**$_2$$CH_3$), 1.01 (3H, t, *J* = 7.3, CH_3); **^{13}C NMR** ($CDCl_3$, 150MHz) *δ* 189.0, 164.1, 134.2, 124.8, 113.3, 77.3, 71.4, 55.6, 34.8, 19.5, 14.0; **LRMS** (ES^+) 405 (12%, $[M+Na]^+$, 2 × ^{81}Br), 403 (26%, $[M+Na]^+$, ^{79}Br, ^{81}Br), 401 (11%, $[M+Na]^+$, 2 × ^{79}Br), 383 (48%, $[M+H]^+$, 2 × ^{81}Br), 381 (100%, $[M+H]^+$, ^{79}Br, ^{81}Br), 379 (50%, $[M+H]^+$, 2 × ^{79}Br); **HRMS** Found 378.9539, $C_{13}H_{17}Br_2O_3$ requires 378.9544; **IR** ν_{max} (solid/cm^{-1}) 3511 (O-H), 2957 (C-H), 1656 (C=O), 1596, 1568 (C=C), 1510 (C=C)

2,2-Dibromo-3-hydroxy-1-(pyridin-3-yl)hexan-1-one (142k)



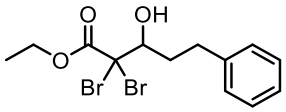
General Procedure G using **141k** (87 mg, 500 µmol), DBA (157 mg, 550 µmol) and MeCN/H_2O (1 mL). Purified by column chromatography using 1% MeOH in CH_2Cl_2: orange gum, 72 mg, 41%, orange gum (23% SM recovered); **^{1}H NMR** ($CDCl_3$, 500 MHz) *δ* 9.53 (1H, d, *J* = 1.4, ArH), 8.78 (1H, d, *J* = 3.6, ArH), 8.62 (1H, dt, *J* = 8.1, 2.0, ArH), 7.42 (1H, dd, *J* = 8.1, 4.8, ArH), 4.23 (1H, br d, *J* = 9.4, C**H**CH_2), 3.29 (1H, br s, OH), 2.11-1.97 (1H, m, 1 × CHC**H**$_2$), 1.84-1.74 (1H, m, 1 × CHC**H**$_2$), 1.73-1.67 (1H, m, 1 × C**H**$_2$$CH_3$), 1.60-1.44 (1H, m, 1 × C**H**$_2$$CH_3$), 1.02 (3H, t, *J* = 7.3, CH_3); **^{13}C NMR** ($CDCl_3$, 125 MHz) *δ* 189.1, 153.6, 152.1, 138.6, 128.7, 122.9, 76.8, 71.2, 34.8, 19.4, 14.0; **LRMS** (ESI) 354 (49%, $[M+H]^+$, 2 × ^{81}Br), 352 (100%, $[M+H]^+$, ^{79}Br, ^{81}Br), 350 (52%, $[M+H]^+$, 2 × ^{79}Br); **HRMS** Found 349.9383, $C_{11}H_{14}Br_2NO_2$ requires 349.9386; **IR** ν_{max} (film/cm^{-1}) 3113 (O-H), 2962 (C-H), 2927 (C-H), 2872 (C-H), 1681 (C=O), 1585 (C=C), 1417

2,2-Dibromo-3-hydroxy-1-(4-(trifluoromethyl)phenyl)hexan-1-one (142l)



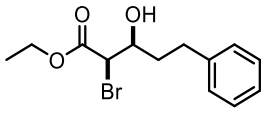
General Procedure G using **141l** (121 mg, 500 µL), DBA (157 mg, 550 µmol) and MeCN/H_2O (1 mL): yellow oil, 34.6 mg, 17%; **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 8.44 (2H, d, J = 8.3, ArH), 7.73 (2H, d, J = 8.3, ArH), 4.23 (1H, br d, J = 9.3, CH), 3.19 (1H, br s, OH), 2.10-2.00 (1H, m, 1 × CHC**H**$_2$), 1.82-1.74 (1H, m, 1 × CHC**H**$_2$) 1.74-1.67 (1H, m, 1 × C**H**$_2$$CH_3$), 1.59-1.46 (1H, m, 1 × C**H**$_2$$CH_3$), 1.02 (3H, t, J = 7.3, CH_3); **^{13}C NMR** ($CDCl_3$ 125 MHz) δ 189.4, 135.8, 134.7 (q, J_{CF} = 32.9), 131.6, 125.1 (q, J_{CF} = 3.7), 122.4 (q, J_{CF} = 273.0), 77.0, 71.2, 34.9, 19.4, 14.0; **LRMS** (EI) 401 (1%, $[M-H_2O]^+$, 2 × ^{81}Br), 399 (2%, $[M-H_2O]^+$, ^{79}Br, ^{81}Br), 397 (1%, $[M-H_2O]^+$, 2 × ^{79}Br), 348 (11%, $[M-CF_3]^+$, 2 × ^{81}Br), 346 (24%, $[M-CF_3]^+$, ^{79}Br, ^{81}Br), 344 (13%, $[M-CF_3]^+$, 2 × ^{79}Br), 230 (6%), 228 (14%), 226 (7%) 173 (100%, $[M-C_5H_9Br_2O]^+$); **HRMS** Found 433.9573, $C_{13}H_{17}Br_2F_3NO_2$ ($[M+NH_4]^+$) requires 433.9573; **IR** ν_{max} (film/cm^{-1}) 3562 (O-H), 2962 (C-H), 2933 (C-H), 2874 (C-H), 1678 (C=O), 1461

Ethyl 2,2-dibromo-3-hydroxy-5-phenylpentanoate (142m)



Dibromoisocyanuric acid (0.6 eq.) was added to a stirring solution of propargylic alcohol (1.0 eq.) in MeCN:H_2O (7:3, 2 mL.mmol^{-1}). The solution was stirred for 10 min after which solvent was removed *in vacuo* and the resultant residue purified by column chromatography (10% EtOAc in petrol) to give **142m** as a colourless oil (49 mg, 26%); **^{1}H NMR** ($CDCl_3$, 600 MHz) δ 7.35-7.27 (2H, m, ArH), 7.26-7.17 (3H, m, ArH), 4.34 (2H, q, J =7.1, C**H**$_2$$CH_3$), 4.05 (1H, dd, J = 9.9, 3.1, CH), 3.09-2.94 (2H, m, OH, 1 × CHC**H**$_2$), 2.77 (1H, ddd, J = 13.8, 9.0, 7.8, 1 × CHC**H**$_2$), 2.35-2.23 (1H, m, 1 × C**H**$_2$Ar), 2.08-1.95 (1H, m, 1 × C**H**$_2$Ar), 1.34 (3H, t, J = 7.1, CH_3); **^{13}C NMR** ($CDCl_3$, 150 MHz) δ 166.6, 141.3, 128.7, 128.6, 126.3, 76.8, 66.2, 64.2, 34.6, 32.1, 13.8; **LRMS** (CI) 400 (51%, $[M+NH_4]^+$, 2 × ^{81}Br), 398 (100%, $[M+NH_4]^+$, ^{79}Br, ^{81}Br), 396 (50%, $[M+NH_4]^+$, 2 × ^{79}Br); **HRMS** Found 395.9805, $C_{13}H_{20}Br_2NO_3$ ($[M+NH_4]^+$) requires 395.9804; **IR** ν_{max} (film/cm^{-1}) 3283 (O-H), 3027 (C-H), 2931 (C-H), 1727 (C=O), 1623, 1536 (C=C), 1496 (C=C), 1453

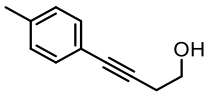
Ethyl 2-bromo-3-hydroxy-5-phenylpentanoate (145)



Dibromoisocyanuric acid (0.6 eq.) was added to a stirring solution of propargylic alcohol (1.0 eq.) in MeCN:H_2O (7:3, 2 mL.mmol^{-1}). The solution was stirred for 10 min after which solvent was removed *in vacuo* and the resultant residue purified by column chromatography (10% EtOAc in petrol) to give **145** as a colourless oil (10 mg, 7%); **^{1}H NMR** ($CDCl_3$, 600 MHz) δ 7.32-7.28 (2H, m, ArH), 7.23-7.19 (3H, m, ArH), 4.30-4.18 (3H, m, CHBr, C**H$_2$**CH_3), 3.90 (1H, dq, *J* = 7.9, 3.6, C**H**OH), 2.94 (1H, d, *J* = 3.6, OH), 2.86 (1H, ddd, *J* = 14.3, 9.4, 5.3, 1 × CHC**H$_2$**), 2.72 (1H, ddd, *J* = 13.8, 9.4, 7.8, 1 × CHC**H$_2$**), 2.02-1.92 (1H, m, 1 × C**H$_2$**Ar), 1.81-1.76 (1H, m, 1 × CH_2Ar), 1.29 (3H, t, *J* = 7.1, CH_3); **^{13}C NMR** ($CDCl_3$, 150 MHz) δ 169.5, 141.3, 128.62, 128.61, 126.2, 70.0, 62.6, 52.2, 35.9, 31.7, 14.0; **LRMS** (CI) 320 (98%, $[M+H]^+$, ^{81}Br), 318 (100%, $[M+H]^+$, ^{79}Br); **HRMS** Found 318.0699, $C_{13}H_{18}BrO_3$ requires 318.0699; **IR** ν_{max} (film/cm^{-1}) 3524 (O-H), 3026 (C-H), 2982 (C-H), 2934 (C-H), 1736 (C=O), 1495 (C=C), 1454 (C=C)

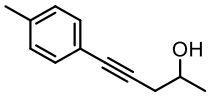
3.3.3 Preparation of homopropargylic alcohols

4-(*p*-Tolyl)but-3-yn-1-ol (149a)[260]



4-Iodotoluene (9.37 g, 43 mmol) and 4-pentyn-1-ol (2.17 g, 25.8 mmol) were dissolved in anhydrous THF (10 mL) under argon. $Pd(PPh_3)_2Cl_2$ (150 mg, 0.215 mmol), CuI (82 mg, 0.43 mmol) and Et_3N (30 mL, 215 mmol) were added and the reaction stirred for 18 h. The mixture was diluted with EtOAc (50 mL) and washed with H_2O (2 × 50 mL) and then brine (2 x 50 mL). The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo*. The resultant oil was purified by column chromatography (10% EtOAc in petrol) to give **149a** as a yellow oil (3.52g, 88%). **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 7.30 (2H, d, *J* = 8.1, ArH), 7.09 (2H, d, *J* = 8.1, ArH), 3.80 (2H, t, *J* = 6.3, C**H$_2$**OH), 2.67 (2H, t, *J* = 6.3, C**H$_2$**CH_2OH), 2.33 (3H, s, CH_3); **^{13}C NMR** ($CDCl_3$, 125 MHz) δ 138.0, 131.6, 129.1, 120.3, 85.6, 82.6, 61.3, 23.9, 21.5; **LRMS** (EI) 160 (91%, $[M]^+$) 129 (100%, $[M-CH_2OH]^+$), 115 (32%, $[M-CH_2CH_2OH]^+$)

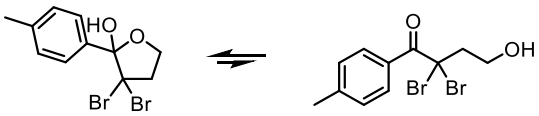
5-(*p*-Tolyl)pent-4-yn-2-ol (149b)[192]



n-Butyllithium (1.6 M in hexanes, 11.3 mL, 18 mmol) was added dropwise to a stirred solution of *p*-tolylacetylene (1.74 g, 15.0 mmol) in anhydrous THF (30 mL) at −78 ˚C under argon. After 1 h, $BF_3.OEt_2$ (5.33 g, 37.5 mmol) was added and the reaction stirred for 30 min. Propylene oxide (2.18 g, 37.5 mmol) was added and the resulting solution was stirred for 1 h at rt. The reaction was diluted with Et_2O (30 mL) and washed with NH_4Cl (2 × 50 mL). The organic layer was washed with H_2O (2 × 30 mL) then brine (2 × 30 mL). The organic layer was dried (Na_2SO_4), filtered and concentrated *in vacuo*. The resultant oil was purified by column chromatography (10% EtOAc in petrol) to give **149b** as a yellow oil (937 mg, 36%). ^{1}H NMR ($CDCl_3$, 600 MHz) *δ* 7.25 (2H, d, *J* = 8.1, ArH), 7.04 (2H, d, *J* = 8.1, ArH), 4.10-4.00 (1H, m, CH), 2.62 (1H, dd, *J* = 16.5, 5.1, 1 × CH_2), 2.55 (1H, dd, *J* = 16.5, 6.6, 1 × CH_2), 2.34 (3H, s, $ArCH_3$), 1.32 (3H, d, *J* = 6.2, $CHCH_3$); ^{13}C NMR ($CDCl_3$, 150 MHz) *δ* 138.1, 131.6, 129.1, 120.3, 85.4, 83.3, 66.7, 30.2, 22.5, 21.6; LRMS (EI) 174 (56%, $[M]^+$), 129 (100%, $[M-CH_3CHOH]^+$), 115 (92%, $[M-CH_2CH(OH)CH_3]^+$)

3.3.4 Preparation of dihalolactols

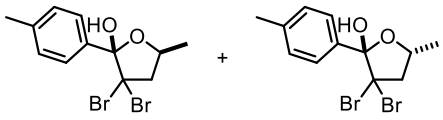
3,3-Dibromo-2-(*p*-tolyl)tetrahydrofuran-2-ol (150a)



General Procedure G using **149a** (2.00 g, 12.5 mmol), DBA (3.94 g, 13.8 mmol) and MeCN/H_2O (25 mL): white solid, 3.55 g, 84%, mp 116-117 °C; **^{1}H NMR** ($CDCl_3$, 500 MHz) *δ* 8.27 (2H, d, *J* = 8.4, minor ArH), 7.71 (2H, d, *J* = 8.2, major ArH), 7.26 (2H, d, *J* = 8.4, minor ArH), 7.21 (2H, d, *J* = 8.1, major ArH), 4.33-4.25 (1H, m, major 1 × OCH_2), 4.21-4.14 (1H, m, major 1 × OCH_2), 4.01 (2H, t, *J* = 6.2, minor C**H**$_2$OH), 3.46 (1H, dt, *J* = 13.5, 9.2, major 1 × CH_2CBr_2), 3.11-3.02 (1H, m, major 1 × CH_2CBr_2; 2H, m, minor CH_2CBr_2), 2.44 (3H, s, minor CH_3), 2.39 (3H, s, major CH_3); **^{13}C NMR** ($CDCl_3$, 125 MHz) *δ* 188.3, 144.8, 139.4, 135.4, 131.5, 129.3, 128.8, 128.4, 127.4, 108.6, 105.9, 68.0, 65.2, 61.6, 49.8, 47.1, 21.8, 21.3; **LRMS** (EI) 338 (4%, $[M]^+$, 2 × ^{81}Br), 336 (9%, $[M]^+$, ^{79}Br, ^{81}Br), 334 (5%, $[M]^+$, 2 × ^{79}Br), 136 (82%), 119 (100%);

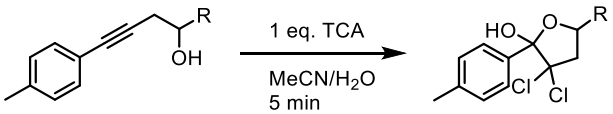
HRMS Found 333.9200 $C_{11}H_{12}Br_2O_2$ requires 333.9204; **IR** ν_{max} (solid/cm^{-1}) 3409 (O-H), 2971 (C-H), 2908 (C-H), 1401

3,3-Dibromo-5-methyl-2-(*p*-tolyl)tetrahydrofuran-2-ol (150b)



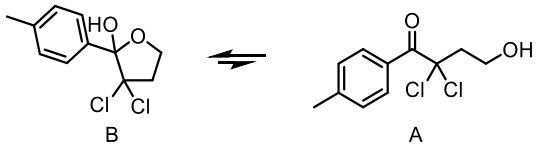
General Procedure G using **149b** (350 mg, 2 mmol), DBA (631 mg 2.2 mmol) and MeCN/H_2O (4 mL): Isolated as a mixture of diastereomers A:B 1:2.5; 294 mg, 42%, white solid, mp 98-99 °C; **^{1}H NMR** ($CDCl_3$, 600 MHz) δ 7.71 (2H, d, *J* = 8.2, minor ArH), 7.68 (2H, d, *J* = 8.2, major ArH), 7.21 (2H, d, *J* = 8.2, major ArH), 7.19 (2H, d, *J* = 8.2, minor ArH), 4.65 (1H, dp, *J* = 9.3, 6.0, major CH), 4.29 (1H, dqd, *J* = 9.8, 6.5, 3.4, minor CH), 3.74 (1H, s, major OH), 3.55 (dd, *J* = 14.1, 9.8, minor 1 × CH_2), 3.49 (1H, s, minor OH), 3.16 (1H, dd, *J* = 13.3, 6.0, major 1 × CH_2), 3.10 (1H, dd, *J* = 13.3, 9.3, major 1 x CH_2), 2.93 (1H, dd, *J* = 14.1, 3.4, minor 1 × CH_2), 2.40 (3H, s, minor $ArCH_3$), 1.49 (3H, d, *J* = 6.5, minor CHC**H**$_3$), 1.45 (3H, d, *J* = 6.0, major CHC**H**$_3$); **^{13}C NMR** ($CDCl_3$, 150 MHz) δ 139.3, 136.0, 135.4, 131.6, 128.4, 128.4, 127.5, 127.5, 106.4, 106.1, 74.7, 72.1, 68.8, 67.3, 54.4, 53.4, 22.4, 21.5, 21.4, 21.1; **LRMS** (CI) 370 (8%, $[M+NH_4]^+$, 2 × ^{81}Br), 368 (20%, $[M+NH_4]^+$, ^{79}Br, ^{81}Br), 366 (10%, $[M+NH_4]^+$, 2 × ^{79}Br), 335 (51%, $[M-CH_3]^+$, 2 × ^{81}Br), 333 (100%, $[M-CH_3]^+$, ^{79}Br, ^{81}Br), 331 (48%, $[M-CH_3]^+$, 2 × ^{79}Br); **HRMS** Found 365.9698, $C_{12}H_{18}Br_2NO_2$ ($[M+NH_4]^+$) requires 365.9699; **IR** ν_{max} (solid/cm^{-1}) 3342 (O-H), 2963 (C-H), 1913, 1510 (C=C)

<u>General Procedure H: Preparation of Dichlorolactols</u>



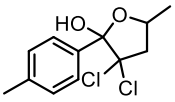
Trichloroisocyanuric acid (1 eq.) was added to a stirring solution of homopropargylic alcohol (1 eq.) in MeCN:H_2O (10:1, 4 mL.$mmol^{-1}$). After 30 min the solvent was removed *in vacuo* and the residue was purified by column chromatography to give the dichlorohydroxyketone.

3,3-Dichloro-2-(*p*-tolyl)tetrahydrofuran-2-ol (**151a**)



General Procedure H using **149a** (2.07 g, 8.92 mmol), TCICA (1.43 g, 8.92 mmol) and MeCN/H_2O (36 mL): Isolated as a mixture of isomers A:B 1:8.3; 1.83 g, 83%, white solid, mp 122-124 °C; **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 8.22 (2H, d, J = 8.4, minor ArH), 7.65 (2H, d, J = 8.2, major ArH), 7.30 (2H, d, J = 8.4, minor ArH), 7.22 (2H, d, J = 8.2, major ArH), 4.24 (1H, ddd, J = 9.2, 8.3, 7.1, major 1 × OCH_2), 4.15 (1H, ddd, J = 9.4, 8.3, 2.2, major 1 × OCH_2), 3.99 (2H, t, J = 6.3, minor C**H_2**OH), 3.50 (1H, br s, major OH), 3.20 (1H, dt, J = 13.1, 9.3, major 1 × CH_2CCl_2), 2.91 (1H, ddd, J = 13.1, 7.1, 2.2, major 1 × CH_2CCl_2), 2.84 (2H, t, J = 6.3, minor CH_2CCl_2), 2.47 (3H, s, minor CH_3), 2.41 (3H, s, major CH_3); **^{13}C NMR** ($CDCl_3$, 125 MHz) δ 188.2, 145.0, 139.3, 134.4, 131.4, 129.0, 128.8, 128.5, 127.4, 105.9, 91.1, 85.4, 64.5, 59.3, 47.4, 44.4, 21.8, 21.3; **LRMS** (EI) 250 (12%, M^+, 2 × ^{37}Cl), 248 (67%, M^+,^{35}Cl, ^{37}Cl), 246 (100%, M^+, 2 × ^{35}Cl), 229, 215, 194, 136; **HRMS** Found 246.02087, $C_{11}H_{12}Cl_2O_2$ requires 246.0209; **IR** ν_{max} (solid/cm^{-1}) 3360 (O-H), 3036 (C-H), 2973 (C-H), 2926 (C-H), 2910 (C-H), 1608 (C=O), 1510, 1482(C=C), 1441, 1400

3,3-Dichloro-5-methyl-2-(*p*-tolyl)tetrahydrofuran-2-ol (151b)[192]

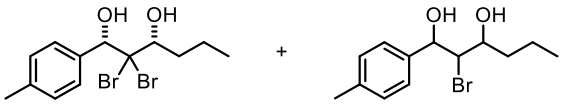


General Procedure H using **149b** (348 mg, 2.00 mmol), TCICA (465 mg, 2.00 mmol) and MeCN/H_2O (8 mmol): Isolated as a mixture of diastereomers A:B 1:1.8; 463 mg, 89%, pale yellow oil; **^{1}H NMR** ($CDCl_3$, 600 MHz) δ 7.67 (2H, d, J = 8.1, major ArH), 7.63 (2H, d, J = 8.2, minor ArH), 7.23-7.18 (4H, m, major ArH, minor ArH), 4.64-4.57 (1H, m, minor CH), 4.57-4.49 (1H, m, major CH), 3.29 (1H, dd, J = 13.7, 9.2, major 1 × CH_2), 3.16 (1H, br s, major OH), 3.09 (1H, br s, minor OH), 3.01 (1H, dd, J = 13.0, 5.9, minor 1 × CH_2), 2.88 (1H, dd, J = 13.0, 9.5, minor 1 × CH_2), 2.70 (1H, dd, J = 13.7, 3.3, major 1 × CH_2), 2.39 (3H, s, major $ArCH_3$), 2.38 (3H, s, minor $ArCH_3$), 1.49 (3H, d, J = 6.4, major CHC**H_3**), 1.47 (3H, d, J = 6.3, minor CHC**H_3**); **^{13}C NMR** ($CDCl_3$, 150 MHz) δ 139.4, 139.4, 134.9, 134.6, 128.5, 128.5, 127.3, 127.3, 106.5, 106.1, 91.8, 91.2, 74.0, 72.0, 51.8, 51.0, 22.7, 21.4, 21.4, 21.2; **LRMS** (CI) 264 (1%, $[M+H]^+$,

2 × ^{37}Cl), 262 (5%, $[M+H]^+$, ^{35}Cl, ^{37}Cl), 260 (6%, $[M+H]^+$, 2 × ^{35}Cl), 247 (14%, $[M-CH_3]^+$), 245 (65%, $[M-CH_3]^+$), 243 (100%, $[M-CH_3]^+$)

3.3.5 Reductions

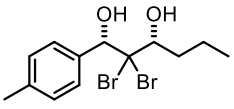
(1*S*,3*R*)-2,2-Dibromo-1-(*p*-tolyl)hexane-1,3-diol (162) and 2-Bromo-1-(p-tolyl)hexane-1,3-diol (163)



Method A: Using flame dried glassware and under an argon atmosphere, **142g** (36 mg, 0.10 mmol) was dissolved in THF (1 mL) and cooled to −78 °C. $ZnCl_2$-TMEDA (25 mg, 0.10 mmol) was added, followed by DIBAL-H (1 M in hexanes, 300 µL, 0.300 mmol). The reaction was stirred at −78 °C for 1 h. The reaction micture was poured into a mixture of HCl (6 M, 2 mL) and sat. NH_4Cl (2 mL). The organic layer was extracted with Et_2O (3 × 1 mL) and the combined organic layers were dried (Na_2SO_4), filtered and concentrated *in vacuo*. The resultant residue was purified by column chromatography (10% EtOAc in petrol).

Method B: Using flame dried glassware and under an argon atmosphere, **142g** (36 mg, 0.10 mmol) was dissolved in THF (1 mL) and cooled to −78 °C. DIBAL-H (1 M in hexanes, 300 µL, 0.300 mmol) was added. The reaction was stirred at −78 °C for 1 h. The reaction mixture was poured into a mixture of HCl (6 M, 2 mL) and sat. NH_4Cl (2 mL). The organic layer was extracted with Et_2O (3 × 1 mL) and the combined organic layers were dried (Na_2SO_4), filtered and concentrated *in vacuo*. The resultant residue was purified by column chromatography (10% EtOAc in petrol).

(162)

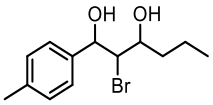


Method A: 12 mg, 33 µmol, 33%; **Method B**: 14 mg, 42 µmol, 42%

^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.53 (2H, d, J = 8.1, ArH), 7.18 (2H, d, J = 8.1, ArH), 5.23 (1H, s, ArCH), 3.40 (1H, d, J = 9.4, C**H**CH_2), 3.17 (1H, br s, OH), 2.37 (3H, s,

$ArCH_3$), 2.23-2.16 (1H, m, 1 × CHC**H**$_2$), 2.12 (1H, br s, OH), 1.72-1.64 (1H, m, 1 × CHC**H**$_2$), 1.64-1.54 (1H, m, 1 × C**H**$_2$$CH_3$), 1.42-1.37 (1H, m, 1 × C**H**$_2$$CH_3$), 0.93 (3H, t, *J* = 7.4, CH_2C**H**$_3$); **^{13}C NMR** ($CDCl_3$, 150 MHz) *δ* 138.8, 134.5, 128.8, 128.7, 91.0, 79.9, 77.6, 37.3, 21.4, 19.2, 14.0; **LRMS** (CI) 386 (49%, $[M+NH_4]^+$, 2 × ^{81}Br), 384 (100%, $[M+NH_4]^+$, ^{79}Br, ^{81}Br), 382 (50%, $[M+NH_4]^+$, 2 × ^{81}Br), 368 (4%, $[M]^+$, 2 × ^{81}Br), 366 (9%, $[M]^+$, ^{79}Br, ^{81}Br), 364 (5%, $[M]^+$, 2 × ^{79}Br); **HRMS** Found 363.9669, $C_{13}H_{18}Br_2O_2$ requires 363.9668; **IR** ν_{max} (film/cm^{-1}) 3412 (O-H), 2959 (C-H), 2925 (C-H), 1514, 1452

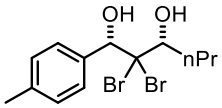
(163)



Method A: 7 mg, 24 µmol, 24%; **Method B**: 5 mg, 17 µmol, 17%

^{1}H NMR ($CDCl_3$, 600 MHz) *δ* 7.29 (2H, d, *J* = 8.1, ArH), 7.19 (2H, d, *J* = 8.1, ArH), 5.01 (1H, d, *J* = 6.2, ArCH), 4.22 (1H, dd, *J* = 6.2, 1.7, CHBr), 3.48 (1H, br t, *J* = 6.2, C**H**CH_2), 3.07 (1H, br s, OH), 2.07 (1H, br s, OH), 2.63 (3H, s, $ArCH_3$), 1.68-1.55 (1H, m, 1 × CHC**H**$_2$), 1.55-1.44 (1H, m, 1 × C**H**CH_2), 1.44-1.23 (2H, m, C**H**$_2$$CH_3$), 0.88 (3H, t, *J* = 7.4, CH_2C**H**$_3$); **^{13}C NMR** ($CDCl_3$, 150 MHz) *δ* 138.3, 137.2, 129.4, 126.5, 76.3, 72.3, 70.6, 39.0, 21.3, 18.7, 14.0; **LRMS** (CI) 306 (96%, $[M+NH_4]^+$, ^{81}Br), 304 (100%, $[M+NH_4]^+$, ^{79}Br), 288 (25%, M^+, ^{81}Br), 286 (28%, M^+, ^{79}Br); **HRMS** Found 286.0563, $C_{13}H_{19}BrO_2$ requires 286.0563; **IR** ν_{max} (film/cm^{-1}) 3351 (O-H), 2962 (C-H), 2923 (C-H), 1511, 1461

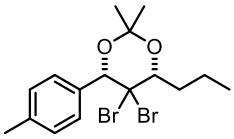
2,2-Dibromo-1-(*p*-tolyl)hexane-1,3-diol (162)



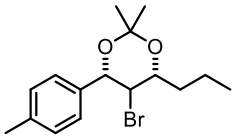
Using flame dried glassware and under an argon atmosphere, catecholborane (1 M in THF, 10 mL, 10 mmol) was added to a stirring solution of **142g** (182 mg, 0.497 mmol) in THF (35 mL) at –10 °C. The reaction was stirred at –10 °C for 6 h. MeOH (10 mL), saturated sodium potassium tartrate (10 mL) and pinacol (750 mg, 6.36 mmol) were added and the reaction was stirred for 18 h at rt. The reaction mixture was diluted with EtOAc (30 mL) and washed with NaOH (0.5 M) until the aqueous layer was colourless. The organic layer was washed with brine (2 × 50 mL), dried

(Na_2SO_4), filtered and concentrated *in vacuo*. The resultant residue was purified by column chromatography (20% EtOAc in petrol) to give **162** as a colourless oil (117 mg, 64%). **^{1}H NMR** ($CDCl_3$, 600 MHz) δ 7.52 (2H, d, *J* = 8.1, ArH), 7.18 (2H, d, *J* = 8.1, ArH), 5.21 (1H, s, ArCH), 3.42 (1H, br t, *J* = 8.0, C**H**CH_2), 3.31 (1H, br s, OH), 2.36 (3H, s, $ArCH_3$), 2.23-2.14 (1H, br d, *J* = 7.5, OH), 2.19 (1H, m, 1 × CHC**H**$_2$), 1.68 (1H, dtd, *J* = 14.3, 9.7, 4.8, 1 × CHC**H**$_2$), 1.64-1.53 (1H, m, 1 × C**H**$_2CH_3$), 1.41-1.33 (1H, m, 1 × C**H**$_2CH_3$), 0.93 (3H, t, *J* = 7.4, CH_2C**H$_3$**); **^{13}C NMR** ($CDCl_3$, 150 MHz) δ 138.8, 134.6, 128.8, 128.7, 90.8, 80.0, 77.7, 37.3, 21.4, 19.2, 14.0; **LRMS** (NSI) 386 (50%, $[M+NH_4]^+$, 2 × ^{81}Br), 384 (100%, $[M+NH_4]^+$, ^{79}Br, ^{81}Br), 382 (52%, $[M+NH_4]^+$, 2 × ^{79}Br) 227 (41%); **HRMS** Found 382.0016, $C_{13}H_{18}Br_2O_2+NH_4]^+$ requires 382.0012; **IR** ν_{max} (film/cm^{-1}) 3274 (O-H), 2959 (C-H), 2928 (C-H), 1516 (C=C), 1453

(4R,6S)-5,5-Dibromo-2,2-dimethyl-4-propyl-6-(p-tolyl)-1,3-dioxane (166) and (4R,6S)-5-Bromo-2,2-dimethyl-4-propyl-6-(p-tolyl)-1,3-dioxane (167)



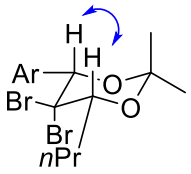
166 (A)



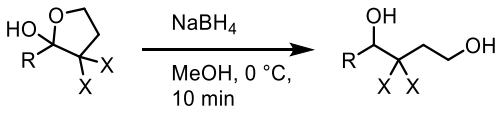
167 (B)

Using flame dried glassware and under an argon atmosphere, **162** (7 mg, 19 µmol) was dissolved in THF (1 mL). *p*-Tolylsulfonic acid (4 mg, 21 µmol) was added, followed by 2,2-dimethoxypropane (20 mg, 19 µmol). The reaction was refluxed for 18 h. The reaction mixture was diluted with sat. sodium bicarbonate (1 mL) and extracted with Et_2O (2 × 1 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated *in vacuo*. The resultant residue was purified by column chromatography (2% EtOAc in petrol) to give **166** and **167** as a colourless film in a 1:1.3 ratio (4 mg). **^{1}H NMR** ($CDCl_3$, 600 MHz) δ 7.53 (2H, d, *J* = 8.2, **A** ArH), 7.32 (2H, d, *J* = 8.1, B ArH), 7.20-7.15 (4H, m, A ArH, B ArH), 4.94 (1H, s, A ArCH), 4.82 (1H, d, *J* = 10.3, B ArCH), 4.03 (1H, ddd, *J* = 10.4, 8.4, 2.3, B C**H**CH_2), 3.89 (1H, dd, *J* = 9.3, 1.7, A C**H**CH_2), 3.69 (1H, t, *J* = 10.4, B CHBr), 2.37 (3H, s, A $ArCH_3$), 2.35 (3H, s, B $ArCH_3$), 2.11-2.01 (1H, m, A 1 × CHC**H**$_2$), 1.95 (1H, dddd, *J* = 9.9, 5.8, 5.0, 2.1, B 1 × CHC**H**$_2$), 1.78 (1H, dtd, *J* = 14.1, 9.4, 4.8, A 1 × CHC**H**$_2$), 1.61 (3H, s, B 1 × $C(CH_3)_2$), 1.57 (3H, s, A 1 × $C(CH_3)_2$), 1.56 (3H, s, A 1 × $C(CH_3)_2$), 1.55-1.49 (1H, m, B 1 × CHC**H**$_2$), 1.46 (3H, s, B 1 × $C(CH_3)_2$), 1.45-1.36 (2H, m, A C**H$_2$**CH_3), 0.99 (3H, t, *J* = 7.4, A CH_2C**H$_3$**), 0.95 (3H, t, B CH_2C**H$_3$**); **^{13}C NMR** ($CDCl_3$, 150 MHz) δ 138.8, 138.6, 136.1 (B), 132.9 (A), 129.7 (A), 129.1 (A), 128.0 (B), 127.9 (B), 100.6

(A), 99.8 (B), 81.0 (A) 79.4 (A), 77.9 (A), 74.0 (B), 55.0 (B), 35.5 (B), 34.7 (A), 29.9, 29.6, 21.4, 21.4, 19.7, 19.4, 19.1, 18.1, 13.9, 13.9; **LRMS** (CI) 426 (49%, $[M_A+NH_4]^+$, 2 × ^{81}Br), 424 (100%, $[M_A+NH_4]^+$, ^{79}Br, ^{81}Br), 422 (51%, $[M_A+NH_4]^+$, 2 × ^{79}Br), 368 (23%), 366 (48%), 364 (48%), 346 (11%, $[M_B+NH_4]^+$, ^{81}Br), 344 (11%, $[M_B+NH_4]^+$, ^{79}Br), 312 (87%, $[M_B-CH_3]^+$, ^{81}Br), 310 (85%, $[M_B-CH_3]^+$, ^{79}Br), 296 (47%), 294 (50%), 279 (54%), 277 (54%); **HRMS** Found 422.0325, $C_{16}H_{23}Br_2O_2+NH_4]^+$ requires 422.0325; **IR** ν_{max} (film/cm^{-1}) 2955 (C-H), 2919 (C-H), 2868 (C-H), 2850 (C-H), 1513, 1455. nOe interaction used to confirm stereochemistry is shown below.

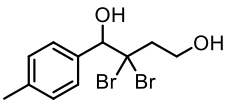


General Procedure I: Preparation of 1,4 diols



$NaBH_4$ (23 mg, 0.60 mmol) was added to a stirred solution of lactol (0.50 mmol) in MeOH (4 mL) at 0 °C. After 10 min, NH_4Cl (5 mL) was added and the organic phase extracted with EtOAc (2 × 5 mL). The organic layer was washed with brine (2 × 5 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The resultant residue was purified by column chromatography (30% EtOAc in petrol) to give the diol.

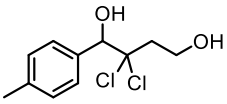
2,2-Dibromo-1-(*p*-tolyl)butane-1,4-diol (168)



General Procedure I using **150a** (168 mg, 0.500 mmol): 169 mg, quantitative, white solid, mp 105-107 °C; **^{1}H NMR** ($CDCl_3$, 600 MHz) δ 7.47 (2H, d, *J* = 8.0, ArH), 7.18 (2H, d, *J* = 8.0, ArH), 5.01 (1H, d, *J* = 1.9, CH), 4.11-4.00 (2H, m, C**H$_2$**OH), 3.84 (1H, d, *J* = 1.6, CHO**H**), 2.76 (1H, dt, *J* = 15.0, 6.4, 1 × CH_2CBr_2), 2.63 (1H, dt, *J* = 15.0, 5.7, 1 × CH_2CBr_2), 3.04 (3H, s, CH_3), 2.26 (1H, s, CH_2O**H**); **^{13}C NMR** ($CDCl_3$, 150 MHz) δ 138.9, 134.1, 129.1, 128.6, 82.3, 79.4, 61.7, 48.1, 21.4; **LRMS** (EI) 340 (42%, M^+, 2 × ^{81}Br), 338 (84%, M^+, ^{79}Br, ^{81}Br), 336 (41%, M^+, 2 × ^{79}Br), 160 (100%); **HRMS**

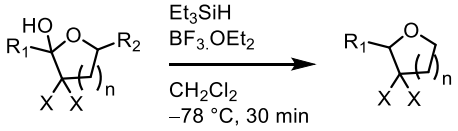
Found 335.9352, $C_{11}H_{14}Br_2O_2$ requires 335.9355; **IR** ν_{max} (solid/cm^{-1}) 3338 (O-H), 2902 (C-H), 1515 (C=C)

2,2-Dichloro-1-(*p*-tolyl)butane-1,4-diol (169)



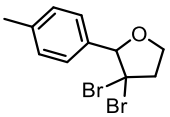
General Procedure I using **151a** (124 mg, 0.500 mmol): 84 mg, 68%, white solid, mp 92-93 °C; **^{1}H NMR** ($CDCl_3$, 600 MHz) δ 7.42 (2H, d, J = 8.0, ArH), 7.18 (2H, d, J = 8.0, ArH), 5.01 (1H, s, CH), 4.07-3.95 (2H, m, CH_2CCl_2), 2.61 (1H, ddd, J = 15.0, 7.1, 5.6, 1 × CH_2CBr_2), 2.54 (1H, s, CH_2O**H**), 2.45 (1H, dt, J = 15.0, 5.5, 1 × CH_2CCl_2), 2.37 (3H, s, CH_3); **^{13}C NMR** ($CDCl_3$, 150 MHz) δ 138.8, 133.8, 128.9, 128.6, 95.5, 81.2, 59.4, 46.1, 21.4; **LRMS** (EI) 252 (1%, $[M]^+$, 2 × ^{37}Cl), 250 (5%, $[M]^+$, ^{35}Cl, ^{37}Cl), 248 (7%, $[M]^+$, 2 × ^{35}Cl), 167 (6%), 149 (11%), 121 (100%); **HRMS** Found 248.0365, $C_{11}H_{14}Cl_2O_2$ requires 248.0365; **IR** ν_{max} (solid/cm^{-1}) 3220 (O-H), 2900 (C-H), 2849 (C-H)

General Procedure J: Preparation of dihalogenated cyclic ethers



Using flame dried glassware and under an argon atmosphere, $BF_3.OEt_2$ (213 mg, 1.50 mmol) was added to a solution of lactol (0.50 mmol) and Et_3SiH (116 mg, 1.00 mmol) in CH_2Cl_2 (1 mL) at –78 °C. The reaction was stirred at –78 °C for 5 min and then allowed to warm to rt over 30 min. Solvent was removed *in vacuo* and the resultant residue purified by column chromatography (10% EtOAc in petrol).

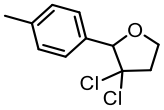
3,3-Dibromo-2-(*p*-tolyl)tetrahydrofuran (170)



General Procedure J using **150a** (168 mg, 0.500 mmol): 158 mg, quantitative, colourless oil; **^{1}H NMR** ($CDCl_3$, 600 MHz) δ 7.49 (2H, d, J = 8.1, ArH), 7.21 (2H, d, J

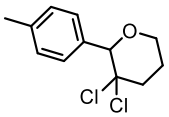
= 8.1, ArH), 5.02 (1H, s, ArCH), 4.29 (1H, td, *J* = 8.5, 7.4, 1 × CH_2O), 4.16-4.07 (1H, m, 1 × CH_2O), 3.23-3.16 (2H, m, CH_2CBr_2), 2.39 (3H, s, CH_3); **^{13}C NMR** ($CDCl_3$,150 MHz) *δ* 138.8, 133.2, 128.6, 127.5, 90.7, 66.8, 65.7, 50.2, 21.5; **LRMS** ($APCI^+$) 323 (34%, $[M+H]^+$, 2 × ^{81}Br), 321 (42%, $[M+H]^+$, ^{79}Br, ^{81}Br), 319 (30%, $[M+H]^+$, 2 × ^{79}Br), 305 (34%, $[M+H-H_2O]^+$, 2 × ^{81}Br), 303 (61%, $[M+H-H_2O]^+$, ^{79}Br, ^{81}Br), 301 (34%, $[M+H-H_2O]^+$, 2 × ^{79}Br), 241 (100%, $[M+H-Br]^+$, ^{81}Br), 239 (96%, $[M+H-Br]^+$, ^{79}Br); **HRMS** Found 300.9225, $C_{11}H_{11}Br_2$ ($[M+H-H_2O]^+$) requires 300.9228; **IR** ν_{max} (film/cm^{-1}) 2953 (C-H), 2892 (C-H)

3,3-Dichloro-2-(*p*-tolyl)tetrahydrofuran (171)



General Procedure J using **151a** (124 mg, 0.500 mmol): 118 mg, quantitative, colourless oil; **^{1}H NMR** ($CDCl_3$, 600 MHz) *δ* 7.45 (2H, d, *J* = 8.0, ArH), 7.24 (2H, d, *J* = 8.0, ArH), 5.10 (1H, s, CH), 4.30 (1H, td, *J* = 8.6, 7.2, 1 × CH_2O), 4.21 (1H, td, *J* = 8.6, 3.7, 1 × CH_2O), 3.02 (1H, ddd, *J* = 13.5, 7.2, 3.7, 1 × CH_2CCl_2), 2.96 (1H, dt, *J* = 13.5, 8.9, 1 × CH_2CCl_2) 2.41 (3H, s, CH_3); **^{13}C NMR** ($CDCl_3$, 150 MHz) *δ* 138.7, 132.1, 128.7, 127.5, 89.7, 89.7, 65.5, 47.7, 21.5; **LRMS** (EI) 234 (11%, $[M]^+$, 2 × ^{37}Cl), 232 (58%, $[M]^+$, ^{35}Cl,^{37}Cl), 230 (100%, $[M]^+$, 2 × ^{35}Cl), 215 (34%), 217 (24%), 194 (44%); **HRMS** Found 230.02585, $C_{11}H_{12}Cl_2O$ requires 230.02597; **IR** ν_{max} (film/cm^{-1}) 2953 (C-H), 2894 (C-H)

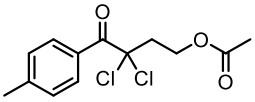
3,3-Dichloro-2-(*p*-tolyl)tetrahydro-2*H*-pyran (172)[192]



General Procedure J using 3,3-dichloro-2-(*p*-tolyl)tetrahydro-2*H*-pyran-2-ol (131 mg, 0.500 mmol): 74.1 mg, 60%, colourless oil; **^{1}H NMR** ($CDCl_3$, 500 MHz) *δ* 7.44 (2H, d, *J* = 8.1, ArH), 7.18 (2H, d, *J* = 8.1, ArH), 4.55 (1H, s, CH), 4.21 (1H, ddt, *J* = 11.6, 4.8, 1.5, 1 × OCH_2), 3.71-3.60 (1H, m, 1 × OCH_2), 2.87-2.78 (1H, m, 1 × CCl_2CH_2), 2.50 (1H, td, *J* = 13.5, 4.2, 1 × CCl_2CH_2), 2.37 (3H, s, CH_3), 2.36-2.28 (1H, m, 1 × $OCH_2C\mathbf{H}_2$), 1.73-1.65 (1H, m, 1 × $OCH_2C\mathbf{H}_2$); **^{13}C NMR** ($CDCl_3$, 125 MHz) *δ* 138.4, 133.0, 129.2, 128.1, 89.7, 87.1, 69.0, 45.5, 24.7, 21.3; **IR** ν_{max} (film/cm^{-1}) 2927 (C-H), 2931 (C-H), 2863 (C-H), 1524, 1439

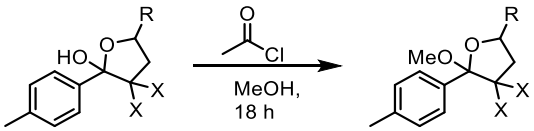
3.3.6 Preparation of halofurans

3,3-Dichloro-4-oxo-4-(*p*-tolyl)butyl acetate (176)



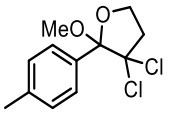
Et_3N (52 µL, 0.37 mmol) was added dropwise to a stirring solution of **151a** (58 mg, 0.25 mmol) in CH_2Cl_2 (1 mL) at 0 °C. After 10 min, Ac_2O (31 mg, 0.30 mmol) was added followed by DMAP (6 mg, 0.05 mmol). The reaction was stirred for 1 h and then quenched with a saturated solution of NH_4Cl (2 mL). The organic layer was separated and the aqueous layer extracted with EtOAc (2 × 3 mL). The organic layers were washed with H_2O (2 × 3 mL) and then brine (2 × 3 mL). The solution was dried (Na_2SO_4), filtered and concentrated *in vacuo*. The resultant residue was purified by column chromatography (5% EtOAc in petrol) to give **176** as a colourless oil (34.1 mg, 47%). **^{1}H NMR** ($CDCl_3$, 600 MHz) δ 8.19 (2H, d, *J* = 8.3, ArH), 7.28 (2H, d, *J* = 8.3, ArH), 4.48 (2H, t, *J* = 7.1, CH_2O), 2.90 (2H, t, *J* = 7.1, CCl_2CH_2), 2.44 (3H, s, $ArCH_3$), 2.04 (3H, s, $C(O)CH_3$); **^{13}C NMR** ($CDCl_3$, 150 MHz) δ 187.3, 170.9, 145.0, 131.4, 129.0, 128.6, 84.4, 60.8, 43.2, 21.9, 21.0; **LRMS** (NSI) 310 (10%, $[M+NH_4]^+$, 2 × ^{37}Cl), 308 (62%, $[M+NH_4]^+$, ^{35}Cl, ^{37}Cl), 306 (100%, $[M+NH_4]^+$, 2 × ^{37}Cl), 233 (7%, $[M-OAc]^+$, 2 × ^{37}Cl), 231 (54%, $[M-OAc]^+$, ^{35}Cl, ^{37}Cl), 229 (87%, $[M-OAc]^+$, 2 × ^{35}Cl); **HRMS** Found 306.0661, $[C_{20}H_{14}Cl_2O_3+NH_4]^+$ requires 306.0658; **IR** ν_{max} (film/cm^{-1}) 2955 (C-H), 2927 (C-H), 2866 (C-H), 1742 (C=O), 1684 (C=O), 1606, 1595, 1575

General Procedure K: Preparation of 3,3-dihalo-2-methoxy-tetrahydrofurans



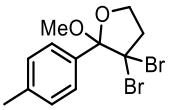
A solution of acetyl chloride in MeOH (1 M, 2 mL.mmol^{-1}) was added to lactol in MeOH (0.5 mLmmol^{-1}) and the reaction stirred for 18 h. The reaction mixture was concentrated *in vacuo* and the product used without further purification.

3,3-Dichloro-2-methoxy-2-(*p*-tolyl)tetrahydrofuran (177)



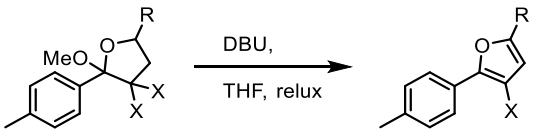
General Procedure K using **151a** (352 mg, 1.42 mmol) and acetyl chloride in MeOH (1 M, 2.8 mL): 372 mg, quantitative, white solid, mp 96-97 °C; **^{1}H NMR** ($CDCl_3$, 600 MHz) δ 7.56 (2H, d, *J* = 8.2, ArH), 7.21 (2H, d, *J* = 8.2, ArH), 4.26 (1H, ddd, *J* = 9.0, 8.4, 7.4, 1 × OCH_2), 4.12 (1H, ddd, *J* = 9.6, 8.4, 2.2, 1 × OCH_2), 3.24-3.16 (1H, m, 1 × CH_2CCl_2), 3.13 (3H, s, OCH_3), 2.90 (1H, ddd, *J* = 13.0, 7.3, 2.2, 1 × CH_2CCl_2), 2.39 (3H, s, $ArCH_3$); **^{13}C NMR** ($CDCl_3$, 150 MHz) δ 139.1, 131.0, 128.6, 128.3, 108.9, 91.4, 64.3, 50.9, 44.6, 21.4; **LRMS** (CI) 264 (1%, $[M]^+$, 2 × ^{37}Cl), 262 (8%, $[M]^+$, ^{37}Cl, ^{35}Cl), 260 (13%, $[M]^+$, 2 × ^{35}Cl), 233 (13%, $[M-OCH_3]^+$, 2 × ^{37}Cl), 231 (67%, $[M-OCH_3]^+$, ^{35}Cl, ^{37}Cl) 229 (100%, $[M-OCH_3]^+$, 2 × ^{35}Cl); **HRMS** Found 260.0366, $C_{12}H_{14}Cl_2O_2$ requires 260.0365; **IR** ν_{max} (solid/cm^{-1}) 2966 (C-H), 2936 (C-H), 2349, 1509, 1436

3,3-Dibromo-2-methoxy-2-(*p*-tolyl)tetrahydrofuran (178)



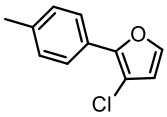
General Procedure K using **150a** (494 mg, 2.00 mmol) and acetyl chloride in MeOH (1 M, 4 mL): 540 mg, 77%, white solid, mp 106-107 °C; **^{1}H NMR** ($CDCl_3$, 400 MHz) 7.63 (2H, d, *J* = 8.0, ArH), 7.21 (2H, d, *J* = 8.0, ArH), 4.29 (1H, ddd, *J* = 9.0, 8.3, 7.0, 1 × OCH_2), 4.03 (1H, ddd, *J* = 10.1, 8.3, 2.0, 1 × OCH_2), 3.44 (1H, dt, *J* = 13.3, 9.5, 1 × CH_2CBr_2) 3.12 (3H, s, OCH_3), 3.07 (1H, ddd, *J* = 13.3, 7.0, 2.0, 1 × CH_2CBr_2), 2.39 (3H, s, $ArCH_3$); **^{13}C NMR** ($CDCl_3$, 100MHz) 139.1, 131.8, 128.4, 127.4, 105.9, 68.3, 64.8, 51.4, 47.2, 21.4; **LRMS** (CI) 352 (5%, $[M]^+$, 2 × ^{81}Br), 350 (11%, $[M]^+$, ^{79}Br, ^{81}Br), 348 (4%, $[M]^+$, 2 × ^{79}Br), 321 (50%, $[M-OCH_3]^+$, 2 × ^{81}Br), 319 (100%, $[M-OCH_3]^+$, ^{79}Br, ^{81}Br), 317 (48%, $[M-OCH_3]^+$, 2 × ^{79}Br); **HRMS** Found 347.9356, $C_{12}H_{14}Br_2O_2$ requires 347.9355; **IR** ν_{max} (solid/cm^{-1}) 2958 (C-H), 2932 (C-H)

General Procedure L: Preparation of 3-halofurans



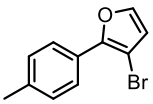
DBU (10 eq.) was added to dihalo-2-methoxytetrahydrofuran (1 eq.) in THF (2 mL.mmol^{-1}) and the mixture heated at reflux until the reaction was complete by TLC. Acetyl chloride in MeOH (1 M) was added to acidify the mixture which was then concentrated *in vacuo*. The residue was purified by column chromatography (petrol) to give the 3-halofuran.

3-Chloro-2-(*p*-tolyl)furan (179)



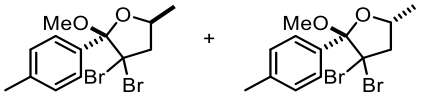
General Procedure L using **177** (163 mg, 0.626 mmol), DBU (953 mg, 6.26 mmol) and THF (1.3 mL): 53 mg, 44%, colourless oil; **^{1}H NMR** ($CDCl_3$, 600 MHz) δ 7.81 (2H, d, *J* = 8.3, ArH), 7.38 (1H, d, *J* = 2.0, OCH), 7.24 (2H, d, *J* = 8.3, ArH), 6.47 (1H, d, *J* = 2.0, CHCCl), 2.39 (3H, s, CH_3); **^{13}C NMR** ($CDCl_3$, 150 MHz) δ 147.7, 140.8, 137.9, 129.4, 126.9, 125.1, 114.1, 110.9, 21.5; **LRMS** (APCI$^+$) 194 (34%, $[M]^+$, ^{37}Cl), 192 (100%, $[M]^+$, ^{35}Cl), 179 (87%), 161 (47%); **HRMS** Found: 192.0346, $C_{11}H_9ClO$ requires 192.0342; **IR** ν_{max} (film/cm^{-1}) 3035 (C-H), 2920 (C-H), 1519, 1490

3-Bromo-2-(*p*-tolyl)furan (180)



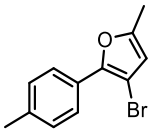
General Procedure L using **178** (194 mg, 0.553 mmol), DBU (842 mg, 5.53 mmol) and THF (1.1 mL): 101 mg, 77%, colourless oil; **^{1}H NMR** ($CDCl_3$, 600 MHz) δ 7.85 (2H, d, *J* = 8.0, ArH), 7.40 (1H, d, 1.4, OCH), 7.25 (2H, d, *J* = 8.0, ArH), 6.52 (1H, d, *J* = 1.4, CBrCH), 2.38 (3H, s, CH_3); **^{13}C NMR** ($CDCl_3$, 150 MHz) δ 149.3, 141.5, 138.1, 129.3, 127.1, 125.6, 116.2, 95.4, 21.5; **LRMS** (EI) 238 (100%, $[M]^+$, ^{81}Br), 236 (98%, $[M]^+$, ^{79}Br), 209 (26%), 207 (24%), 157 (16%, $[M-Br]^+$), 129 (100%); **HRMS** was not obtained due to instability; **IR** ν_{max} (film/cm^{-1}) 3026 (C-H), 2920 (C-H), 1565, 1519, 1490

3,3-Dibromo-2-methoxy-5-methyl-2-(*p*-tolyl)tetrahydrofuran (181)



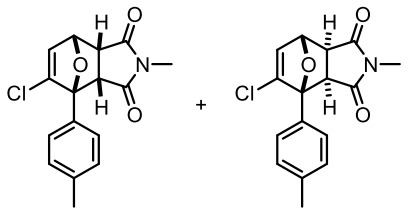
General Procedure K using **150b** (200 mg, 0.569 mmol) and acetyl chloride in MeOH (1 M, 1.2 mL): Isolated as a mixture of diastereomers A:B 1:2.7; 207 mg, quantitative, pale pink gum; **^{1}H NMR** ($CDCl_3$, 600 MHz) δ 7.70-7.56 (4H, m, major ArH, minor ArH), 7.25-7.18 (4H, m, major ArH, minor ArH), 4.72-4.62 (1H, m, major CH), 4.46-4.36 (1H, m, minor CH), 3.61 (1H, dd, J = 13.9, 9.4, minor 1 × CH_2), 3.17-3.12 (7H, m, major OCH_3, minor OCH_3, major 1 × CH_2); 3.09 (1H, dd, J = 13.2, 9.2, major 1 × CH_2), 2.97 (1H, dd, J = 14.0, 3.2, minor 1 × CH_2), 2.40 (3H, s, minor $ArCH_3$), 2.40 (3H, s, major $ArCH_3$), 1.56 (3H, d, J = 6.4, minor CHC**H$_3$**), 1.45 (3H, d, J = 6.3, major CHC**H$_3$**); **^{13}C NMR** ($CDCl_3$, 150 MHz) δ 139.1, 139.0, 136.0, 132.6, 131.9, 128.4, 128.4, 127.4, 109.3, 109.1, 74.5, 72.2, 69.3, 67.5, 54.4, 53.8, 51.4, 51.1, 21.9, 21.5, 21.5, 21.2; **LRMS** (APCI$^+$) 335 (48%, $[M-OCH_3]^+$, 2 × ^{81}Br), 333 (100%, $[M-OCH_3]^+$, ^{79}Br, ^{81}Br), 331 (49%, $[M-OCH_3]^+$, 2 × ^{79}Br), 179 (12%); **HRMS** Found 330.9326, $C_{12}H_{13}OBr_2$ requires 330.9333; **IR** ν_{max} (film/cm^{-1}) 2974 (C-H), 2927 (C-H), 1649 (C=C), 1606, 1512

3-Bromo-5-methyl-2-(*p*-tolyl)furan (182)



General Procedure L using **181** (80 mg, 0.22 mmol), DBU (335 mg, 2.20 mmol) and THF (0.50 mL): 42 mg, 76%, orange oil; **^{1}H NMR** ($CDCl_3$, 600 MHz) δ 7.82 (2H, d, J = 8.3, ArH), 7.22 (2H, d, J = 8.3, ArH), 6.12 (1H, q, J = 0.9, CH), 3.27 (3H, s, $ArCH_3$), 2.35 (3H, d, J = 0.9, $OCCH_3$); **^{13}C NMR** ($CDCl_3$, 150 MHz) δ 151.4, 147.5, 137.5, 129.2, 127.4, 125.2, 112.2, 95.8, 21.5, 13.8; **LRMS** (EI) 252 (98%, $[M]^+$, ^{81}Br), 250 (100%, $[M]^+$, ^{79}Br), 209 (22%), 207 (24%), 143 (21%), 128 (36%); **HRMS** Found 249.9989, $C_{11}H_{12}BrO$ requires 249.9988; **IR** ν_{max} (film/cm^{-1}) 3022 (C-H), 2915 (C-H), 1599, 1553, 1497

(3a*S*,4*S*,7*S*,7a*R*)-5-Chloro-2-methyl-4-(*p*-tolyl)-3a,4,7,7a-tetrahydro-1*H*-4,7-epoxyisoindole-1,3(2*H*)-dione (*endo*-183) and (3a*R*,4*S*,7*S*,7a*S*)-5-Chloro-2-methyl-4-(*p*-tolyl)-3a,4,7,7a-tetrahydro-1*H*-4,7-epoxyisoindole-1,3(2*H*)-dione (*exo*-183)



endo-**183** *exo*-**183**

N-Methylmaleimide (40 mg, 0.36 mmol) was added to a solution of **179** (14 mg, 0.075 mmol) in MeOD-d_4 (0.6 mL) and the reaction mixture placed in an NMR tube. After 7 days the reaction was complete by NMR and the reaction mixture was concentrated *in vacuo* and purified by column chromatography (10% EtOAc in petrol) to give *endo*-**183** (5.8 mg, 25%). Further elution gave *exo*-**183** (6.6 mg, 29%).

(3a*S*,4*S*,7*S*,7a*R*)-5-Chloro-2-methyl-4-(*p*-tolyl)-3a,4,7,7a-tetrahydro-1*H*-4,7-epoxyisoindole-1,3(2*H*)-dione (*endo*-183)

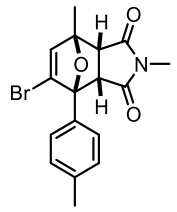
5.8 mg, 25%, white solid, mp 106-109 °C; **^{1}H NMR** (MeOD-d_4, 600 MHz) δ 7.70 (2H, d, J = 8.2, ArH), 7.26 (2H, d, J = 8.2, ArH), 6.46 (1H, d, J = 2.0, C=CH), 5.37 (1H, dd, J = 5.5, 2.0, OCH), 3.91 (1H, dd, J = 7.5, 5.5, OCHC**H**), 3.79 (1H, d, J = 7.5, ArCCH), 2.87 (3H, s, NCH_3), 2.38 (3H, s, $ArCH_3$); **^{13}C NMR** (MeOD-d_4, 150 MHz) δ 176.4, 175.3, 142.0, 140.1, 132.7, 130.2, 129.9, 128.9, 94.5, 79.7, 51.6, 51.2, 24.9, 21.3; **LRMS** (CI) 323 (40%, $[M+NH_4]^+$, ^{37}Cl), 321 (100 %, $[M+NH_4]^+$, ^{35}Cl), 193 (17%); **HRMS** Found 321.1001, $C_{16}H_{18}ClN_2O_3$+ ($[M+NH_4]^+$) requires 321.1000; **IR** ν_{max} (solid/cm^{-1}) 2922 (C-H), 1772, 1689 (C=O), 1589, 1519

(3a*R*,4*S*,7*S*,7a*S*)-5-Chloro-2-methyl-4-(*p*-tolyl)-3a,4,7,7a-tetrahydro-1*H*-4,7-epoxyisoindole-1,3(2*H*)-dione (*exo*-183)

6.6 mg, 29%, white solid, mp 143-144 °C; **^{1}H NMR** (MeOD-d_4, 600 MHz) δ 7.42 (2H, d, J = 8.2, ArH), 7.21 (2H, d, J = 8.2, ArH), 6.57 (1H, d, J = 2.1, C=CH), 5.31 (1H, d, J = 2.1, OCH), 3.53 (1H, d, J = 6.4, OCHC**H**), 3.37 (1H, d, J = 6.4, ArCCH), 2.79 (3H, s, NCH_3), 2.36 (3H, s, $ArCH_3$); **^{13}C NMR** (MeOD-d_4, 150 MHz) δ 177.5, 175.2, 144.7,

139.5, 132.0, 130.0, 129.3, 128.3, 95.0, 81.7, 53.6, 50.0, 24.9, 21.3; **LRMS** (CI) 323 (40%, $[M+NH_4]^+$, ^{37}Cl), 321 (100 %, $[M+NH_4]^+$, ^{35}Cl), 193 (18%); **HRMS** Found 321.1001, $C_{16}H_{18}ClN_2O_3$ requires 321.1000; **IR** ν_{max} (solid/cm^{-1}) 2920 (C-H), 1764, 1687 (C=O), 1591, 1519

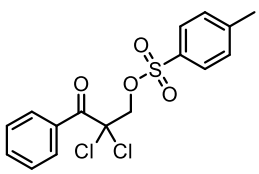
(3a*S*,4*S*,7*S*,7a*R*)-5-Bromo-2,7-dimethyl-4-(*p*-tolyl)-3a,4,7,7a-tetrahydro-1*H*-4,7-epoxyisoindole-1,3(2*H*)-dione (*endo*-184)



N-Methylmaleimide (63 mg, 0.57 mmol) was added to a stirring solution of **182** (24 mg, 0.096 mmol) in dimethylcarbonate (1 mL). The reaction was stirred for 3 days at rt. The reaction mixture was concentrated *in vacuo* and purified by column chromatography (10% EtOAc in petrol) to give *endo*-**184** as a pale orange solid (29 mg, 84%, mp 114-116 °C). **^{1}H NMR** ($CDCl_3$, 600 MHz) δ 7.72 (2H, d, *J* = 8.2, ArH), 7.27 (2H, d, *J* = 8.2, ArH), 6.42 (1H, s, C=CH), 3.84 (1H, d, *J* = 7.5, CH_3CC**H**), 3.38 (1H, d, *J* = 7.5, ArCC**H**), 2.93 (3H, s, NCH_3), 2.40 (2H, s, $ArCH_3$), 1.88 (3H, s, CCH_3); **^{13}C NMR** ($CDCl_3$, 150 MHz) δ 174.7, 173.5, 139.1, 136.4, 134.3, 131.8, 129.2, 127.7, 93.8, 88.5, 54.7, 52.6, 25.0, 21.4, 19.0; **LRMS** ($APCl^+$) 364 (7%, $[M+H]^+$, ^{81}Br), 362 (8%, $[M+H]^+$, ^{79}Br), 282 (22%, $[M-Br]^+$), 269 (98%, $[M-C_7H_7]^+$, ^{81}Br), 267 (100%, $[M-C_7H_7]^+$, ^{79}Br), 187 (23%), 172 (43%); **HRMS** Found 362.0384, $C_{17}H_{17}BrNO_3$ requires 362.0392; **IR** ν_{max} (solid/cm^{-1}) 2918 (C-H), 2851 (C-H), 1689 (C=O), 1584, 1431

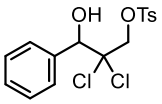
3.3.7 Oxetane synthesis

2,2-Dichloro-3-oxo-3-phenylpropyl 4-methylbenzenesulfonate (186)



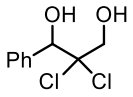
4-Toluenesulfonyl chloride (1.55 g, 8.14 mmol) and pyridine (1.5 mL, 12.2 mmol) were added to a stirring solution of **185** (928 mg, 4.07 mmol) in CH_2Cl_2 (8 mL) at 0 °C. The reaction was stirred at 0 °C for 1 h and then allowed to warm to rt and stirred for 18 h. H_2O (10 mL) was added and the organic phase extracted with CH_2Cl_2 (2 × 10 mL). The organic layer was washed with saturated $CuSO_4$ (10 mL), dried ($MgSO_4$) and filtered. The solution was concentrated *in vacuo* and the resultant residue purified by column chromatography (10% EtOAc in petrol) to give **186** as a white solid (1.20 g, 79%, mp 85-86°C). **^{1}H NMR** ($CDCl_3$, 600 MHz) *δ* 8.22 (2H, dd, *J* = 8.6, 1.2, ArH), 7.87 (2H, d, *J* = 8.4, ArH), 7.64-7.59 (1H, m, ArH), 7.51-7.46 (2H, m, ArH), 7.39 (2H, d, *J* = 8.4, ArH), 4.65 (2H, s, CH_2), 2.47 (3H, s, CH_3); **^{13}C NMR** ($CDCl_3$, 150 MHz) *δ* 186.4, 145.5, 134.4, 132.5, 131.0, 130.8, 130.1, 128.4, 128.4, 80.4, 73.4, 21.9; **LRMS** (APCI$^+$) 377 (5%, $[M+H]^+$, 2 × ^{37}Cl), 375 (18%, $[M+H]^+$, ^{35}Cl, ^{37}Cl), 373 (24%, $[M+H]^+$, 2 × ^{37}Cl), 205 (11%, $[M-OTs]^+$, 2 × ^{37}Cl) 203 (67%, $[M-OTs]^+$, ^{35}Cl, ^{37}Cl), 201 (100%, $[M-OTs]^+$, 2 × ^{35}Cl); **HRMS** Found 373.0062, $C_{16}H_{15}Cl_2O_4S$ requires 373.0068; **IR** ν_{max} (solid/cm^{-1}) 3067 (C-H), 1693 (C=O), 1365

2,2-Dichloro-3-hydroxy-3-phenylpropyl 4-methylbenzenesulfonate (187)



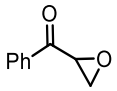
$NaBH_4$ (182 mg, 4.82 mmol) was added to a stirring solution of **186** in MeOH (20 mL) at 0 °C. The reaction was stirred at 0 °C for 10 min and then concentrated *in vacuo*. The resultant residue was purified by column chromatography (8% EtOAc in petrol) to give **187** as a white solid (753 mg, 63%, mp 85-86 °C). **^{1}H NMR** ($CDCl_3$, 400 MHz) *δ* 7.84 (2H, d, *J* = 8.3, ArH), 7.49 (2H, dd, *J* = 7.4, 2.2, ArH), 7.42-7.31 (5H, m, ArH), 5.14 (1H, d, *J* = 4.9, C**H**OH), 4.60 (1H, d, *J* = 10.6, 1 × CH_2), 4.18 (1H, d, *J* = 10.6, 1 × CH_2), 2.90 (1H, d, *J* = 4.9, OH), 2.48 (3H, s, CH_3); **^{13}C NMR** ($CDCl_3$, 100 MHz) *δ* 145.8, 135.9, 132.2, 130.2, 129.3, 128.7, 128.3, 128.1, 90.1, 77.0, 73.0, 21.9; **LRMS** (NSI) 396 (11%, $[M+NH_4]^+$, 2 × ^{37}Cl), 394 (66%, $[M+NH_4]^+$, ^{35}Cl, ^{37}Cl), 392 (100%, $[M+NH_4]^+$, 2 × ^{35}Cl); **HRMS** Found 392.0484, $C_{16}H_{20}Cl_2NO_4S$ ($[M+NH_4]^+$) requires 392.0485; **IR** ν_{max} (solid/cm^{-1}) 3526 (O-H), 1593, 1452, 1445, 1401

2,2-Dichloro-1-phenylpropane-1,3-diol (191)[192]



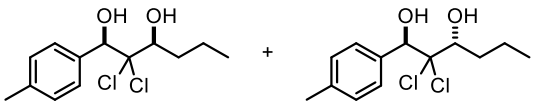
$NaBH_4$ (113 mg, 3.00 mmol) was added to a stirring solution of **185** (456 mg, 2.08 mmol) in MeOH (10 mL) at 0 °C. The reaction was stirred at 0 °C for 30 min and then concentrated *in vacuo*. The resultant residue was purified by column chromatography (10% EtOAc in petrol) to give **191** as a pale yellow solid (236 mg, 51%, mp 98-99 °C (lit. 104-195 °C)[192]). **^{1}H NMR** ($CDCl_3$, 600 MHz) δ 7.58-7.52 (2H, m, ArH), 7.41-7.37 (3H, m, ArH), 5.23 (1H, s, CH), 4.11 (1H, dd, J = 12.5, 6.1, 1 × CH_2), 3.89 (1H, dd, J = 12.5, 7.0, 1 × CH_2), 3.12 (1H, br s, OH), 2.69 (1H, br s, OH); **^{13}C NMR** ($CDCl_3$, 150 MHz) δ 136.7, 129.1, 128.6, 128.1, 95.3, 78.6, 70.3; **IR** ν_{max} (solid/cm^{-1}) 3324 (O-H), 3205 (O-H), 2949 (C-H), 2920 (C-H), 2849 (C-H), 1492, 1450

Oxiran-2-yl(phenyl)methanone (193)[261]



A solution of methanesulfonyl chloride (74 mg, 0.64 mmol) in CH_2Cl_2 (5 mL) was added dropwise to a solution of **191** (140 mg, 0.61 mmol) and Et_3N (74 mg, 0.73 mmol) in CH_2Cl_2 (20 mL) at 0 °C. The reaction was stirred at 0 °C for 30 min and then allowed to warm to rt and stirred for 18 h. The mixture was washed with H_2O (2 × 15 mL). Bu_4NHSO_4 (20 mg, 0.06 mmol) was added to the organic layer followed by aqueous NaOH (50% w/w, 20 mL). The reaction mixture was stirred vigorously for 1.5 h. The layers were separated and the organic layer dried ($MgSO_4$), filtered and concentrated *in vacuo* to give **193** as an orange oil (103 mg, quantitative yield). **^{1}H NMR** ($CDCl_3$, 600 MHz) δ 8.06 (2H, d, J = 8.4, ArH), 7.64 (1H, t, J = 7.4, ArH), 7.56-7.49 (2H, m, ArH), 4.26 (1H, dd, J = 4.5, 2.5, CH), 3.13 (1H, dd, J = 6.5, 4.5, 1 × CH_2), 2.97 (1H, dd, J = 6.5, 2.5, 1 × CH_2); **^{13}C NMR** δ ($CDCl_3$, 150 MHz) 194.8, 135.5, 134.1, 129.0, 128.5, 51.2, 47.8

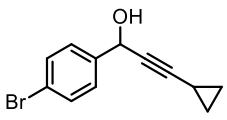
2,2-Dichloro-1-(*p*-tolyl)hexane-1,3-diol (199)



$NaBH_4$ (199 mg, 5.26 mmol) was added to a solution of **198** (960 mg, 3.50 mmol) in MeOH (20 mL) at 0 °C. The reaction was stirred for 10 min at 0 °C. NH_4Cl (15 mL) was added and the reaction extracted with EtOAc (2 × 20 mL). The organic layer was washed with brine (2 × 20 mL), dried ($MgSO_4$) and filtered. Solvents were removed *in vacuo* to give **199** as a white solid that was used without further purification (962 mg, quantitative yield, mp 197-198 °C). Diol **199** was isolated as a mixture of diastereomers A:B 3:1. **^{1}H NMR** (MeOD-d_4, 600 MHz) δ 7.47 (2H, d, J = 8.0, major ArH), 7.42 (2H, d, J = 8.0, minor ArH), 7.13 (2H, d, J = 8.0, minor ArH), 7.08 (2H, d, J = 8.0, major ArH), 5.23 (1H, s, minor ArCH), 4.96 (1H, s, major ArCH), 4.14 (1H, dd, J = 9.9, 1.9, minor CH_2C**H**), 3.96 (1H, dd, J = 9.3, 1.4, major CH_2C**H**), 2.32 (3H, s, major $ArCH_3$), 2.31 (3H, s, minor $ArCH_3$), 2.02-1.94 (1H, m, minor 1 × CHC**H**$_2$), 1.94-1.85 (1H, m, major 1 × CHC**H**$_2$), 1.76-1.65 (2H, m, major 1 × CHC**H**$_2$, minor 1 × C**H**$_2CH_3$), 1.64-1.56 (1H, m, major 1 × C**H**$_2CH_3$), 1.49-1.36 (2H, m, major 1 × C**H**$_2CH_3$, minor 1 × C**H**$_2CH_3$), 1.34-1.24 (1H, m, minor 1 × C**H**$_2CH_3$), 0.99 (3H, J = 7.4, minor CH_2C**H**$_3$), 0.97 (3H, t, J = 7.4, major CH_2C**H**$_3$); **^{13}C NMR** (MeOD-d_4, 150 MHz) δ 138.9 (minor), 138.1 (major), 137.9 (major), 137.3 (minor), 131.1 (major), 130.6 (minor), 128.8 (minor), 128.2 (major), 100.2 (minor), 96.6 (major), 83.3 (major), 80.8 (major), 77.7 (minor), 76.4 (minor), 35.2 (major), 35.1 (minor), 21.3 (major), 21.2 (minor), 20.6 (major), 20.5 (minor), 14.6 (major), 14.3 (minor); **LRMS** (NSI) 303 (10%, $[M+NH_4]^+$, 2 × ^{37}Cl), 301 (68%, $[M+NH_4]^+$, ^{35}Cl, ^{37}Cl), 299 (100%, $[M+NH_4]^+$, 2 × ^{35}Cl), 245 (17%), 187 (7%); **HRMS** Found 299.0578, $C_{13}H_{18}Cl_2O_2Na$ requires 299.0576; **IR** ν_{max} (solid/cm^{-1}) 3267 (O-H), 2957 (C-H), 2869 (C-H), 2349, 1514, 1452

3.3.8 Cyclopropane ring expansion products

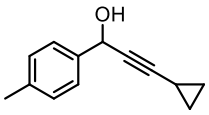
1-(4-Bromophenyl)-3-cyclopropylprop-2-yn-1-ol (202)



General Procedure F using ethynylcyclopropane (1.97 g, 29.7 mmol), *n*-butyllithium (22.3 mL, 35.7 mmol), THF (29.7 mL) and 4-bromobenzaldehyde (5.50 g, 29.7 mmol): 7.47 g, quantitative, orange oil. **^{1}H NMR** ($CDCl_3$, 600 MHz) δ 7.46 (2H, d, J = 8.4, ArH), 7.36 (2H, d, J = 8.4, ArH), 5.33 (1H, s, C**H**OH), 2.82 (1H, br s, OH), 1.36-1.29 (1H, m, C**H**CH_2), 0.82-0.78 (2H, m, 2 × CH_2), 0.76-0.71 (2H, m, 2 × CH_2); **^{13}C NMR** ($CDCl_3$, 150 MHz) δ 140.3, 131.7, 128.5, 122.2, 91.0, 74.9, 64.1, 8.5, 0.4; **LRMS** (CI)

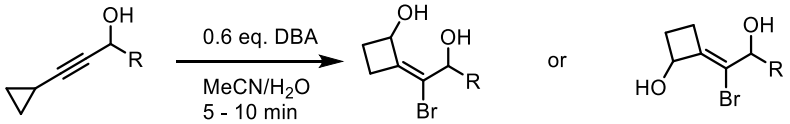
252 (11%, $[M+H]^+$, ^{81}Br), 250 (13%, $[M+H]^+$, ^{79}Br), 235 (98%, $[M-OH]^+$, ^{81}Br), 233 (100%, $[M-OH]^+$, ^{79}Br); **HRMS** Found 249.9989, $C_{12}H_{11}BrO$ requires 249.9988; **IR** ν_{max} (film/cm^{-1}) 3349 (O-H), 3006 (C-H), 2877 (C-H), 2230 (C≡C), 1585, 1482

3-Cyclopropyl-1-(*p*-tolyl)prop-2-yn-1-ol (205)[262]



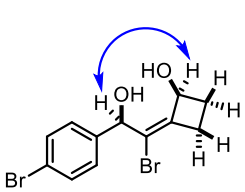
General Procedure F using ethynylcyclopropane (2.63 g, 39.7 mmol),), *n*-butyllithium (29.8 mL, 47.7 mmol), THF (40 mL) and 4-methylbenzaldehyde (4.77 g, 39.7 mmol): 1.85 g, 25%, colourless oil. **^{1}H NMR** ($CDCl_3$, 600 MHz) δ 7.41 (2H, d, J = 8.1, ArH), 7.18 (2H, d, J = 8.1, ArH), 5.39 (1H, s, C**H**OH), 2.36 (3H, s, CH_3), 2.07 (1H, br s, OH), 1.36-1.29 (1H, m, C**H**CH_2), 0.82-0.78 (2H, m, 2 × CH_2), 0.76-0.71 (2H, m, 2 × CH_2); **^{13}C NMR** ($CDCl_3$, 150 MHz) δ 138.5, 138.2, 129.3, 126.7, 90.6, 75.4, 64.8, 21.3, 8.4, 0.3; **LRMS** (CI) 186 (18%, M+), 170 (100%, $[M-OH]^+$); **HRMS** Found 186.1040, $C_{13}H_{14}O$ requires 186.1039; **IR** ν_{max} (film/cm^{-1}) 3370 (O-H), 3007 (C-H), 2917 (C-H), 2862 (C-H), 2232 (C≡C), 1601, 1509

<u>General Procedure M: Preparation of halogenated cyclobutanols</u>

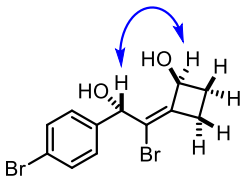


Dibromoisocyanuric acid (0.6 eq.) was added to a stirring solution of propargylic alcohol **202** or **205** (1.0 eq.) in MeCN:H_2O (7:3, 8.5 mL.$mmol^{-1}$). The solution was stirred for 1 h. Saturated $Na_2S_2O_3$ was added and the organic layer extracted with EtOAc. The organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The resultant residue was purified by column chromatography (10% EtOAc in petrol) to give ring expanded products.

(*E*)-2-(1-Bromo-2-hydroxy-2-(*p*-tolyl)ethylidene)cyclobutan-1-ol (204)



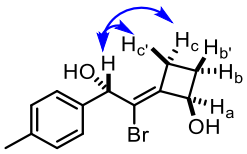
(*R,S*)/(*S,R*)-204



(*R,R*)/(*S,S*)-204

General Procedure M using **202** (126 mg, 0.500 mmol), DBA (86 mg, 0.30 mmol) and MeCN/H_2O (4.3 mL): isolated as a mixture of diastereomers: 1:1.1; 68 mg, 39%, pale yellow oil. **^{1}H NMR** ($CDCl_3$, 600 MHz) δ 7.51-7.50 (2H, m, major ArH), 7.50-7.48 (2H, m, minor ArH), 7.36 (2H, d, 8.2, minor ArH), 7.31 (2H, d, *J* = 8.2, major ArH), 5.57 (1H, s, minor ArCH), 5.56 (1H, s, major ArH), 4.98-4.90 (2H, m, major CH_2C**H**, minor CH_2C**H**), 2.61-2.49 (2H, m, major 1 × C=CCH_2, minor 1 × C=CCH_2), 2.42-2.30 (4H, m, major 1 × C=CCH_2, major 1 × CHC**H**$_2$, minor 1 × C=CCH_2, minor 1 × CHC**H**$_2$), 2.05-1.94 (2H, m, major 1 × CHC**H**$_2$, minor 1 × CHC**H**$_2$); **^{13}C NMR** ($CDCl_3$, 150 MHz) δ 145.4 (minor), 145.3 (major), 140.0 (minor), 139.9 (major), 131.8 (major), 131.7 (minor), 128.8 (major), 128.7 (minor), 122.3 (major), 122.3 (minor), 121.6 (minor), 120.2 (major), 75.1 (major), 75.1 (minor), 70.9 (major), 70.6 (minor), 27.7 (major), 27.6 (minor), 25.7 (minor), 25.2 (major); **LRMS** (NSI) 373 (51%, $[M+Na]^+$, 2 × ^{81}Br), 371 (100%, $[M+Na]^+$, ^{81}Br, ^{79}Br), 369 (49%, $[M+Na]^+$, 2 × ^{79}Br), **HRMS** Found 370.9076; $C_{12}H_{12}Br_2O_2Na$ requires 370.9076; **IR** ν_{max} (film/cm^{-1}) 3313 (O-H), 2947 (C-H), 1691, 1591

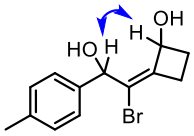
(*E*)-2-(1-Bromo-2-hydroxy-2-(*p*-tolyl)ethylidene)cyclobutan-1-ol (206)



General Procedure M using **205** (373 mg, 2.00 mmol), DBA (344 mg, 1.2 mmol) and MeCN/H_2O (17 mL): isolated as a single diastereomer, 39 mg, 7%, pale yellow oil. **^{1}H NMR** ($CDCl_3$, 600 MHz) δ 7.30 (2H, d, *J* = 8.0, ArH), 7.18 (2H, d, *J* = 8.0, ArH), 5.35 (1H, s, ArCH), 4.83-4.77 (1H, m, H_a), 2.79 (1H, ddd, *J* = 15.9, 11.0, 4.9, $H_{c'}$), 2.54 (1H, ddd, 15.9, 9.5, 8.3, H_c), 2.40 (1H, dddd, *J* = 12.1, 9.5, 8.3, 4.9, H_b), 2.36 (3H, s, CH_3), 2.01 (1H, dddd, *J* = 12.1, 11.0, 8.3, 5.9, $H_{b'}$); **^{13}C NMR** ($CDCl_3$, 150 MHz) δ 144.1, 138.0, 137.4, 129.3, 126.1, 120.7, 73.1, 71.5, 27.1, 25.5, 21.3; **LRMS** (CI) 284 (96%, $[M]^+$, ^{81}Br), 282 (100%, $[M]^+$, ^{79}Br), 267 (17%, $[M-OH]^+$, ^{81}Br), 265 (18%, $[M-OH]^+$,

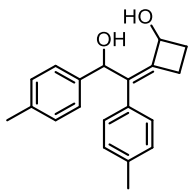
^{79}Br), 185 (19%); **HRMS** Found 282.02508, $C_{13}H_{15}BrO_2$ requires 282.02499; **IR** ν_{max} (film/cm^{-1}) 3264 (O-H), 2983 (C-H), 2943 (C-H), 2920 (C-H), 1671, 1511, 1416; Relative stereochemistry assigned based on NOESY spectra with key correlations indicated.

(*E*)-2-(1-Bromo-2-hydroxy-2-(*p*-tolyl)ethylidene)cyclobutan-1-ol (207)



General Procedure M using **205** (746 mg, 4.00 mmol), DBA (688 mg, 2.4 mmol) and MeCN/H_2O (34 mL): Isolated as a mixture of diastereomers A:B 1:1.6; 168 mg, 15%, pale yellow oil. **^{1}H NMR** ($CDCl_3$, 600 MHz) δ 7.35 (2H, d, 8.1, minor ArH), 7.33 (2H, d, *J* = 8.1, major ArH), 7.19 (4H, d, *J* = 8.1, minor ArH, major ArH), 5.54 (1H, br d, *J* = 3.6, major ArCH), 5.52 (1H, br s, minor ArCH), 4.97-4.89 (2H, m, major CH_2C**H**, minor CH_2C**H**), 3.58 (1H, br d, *J* = 5.7, OH), 3.50 (1H, br d, *J* = 3.6, OH), 3.48 (1H, br s, OH), 3.28 (1H, br s, OH), 2.63-2.48 (2H, m, major 1 × C=CC**H**$_2$, minor 1 × C=CC**H**$_2$), 2.42-2.29 (4H, m, major 2 × CHC**H$_2$**, minor 2 × CHC**H$_2$**), 2.36 (6H, s, major CH_3, minor CH_3); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 144.7 (major), 144.7 (minor), 138.3, 138.2, 138.0, 137.9, 129.4, 127.0 (major), 126.9 (minor), 121.7 (minor), 120.5 (major), 76.3, 75.9, 70.9, 70.5, 27.5, 27.2, 25.8, 25.3, 21.4; **LRMS** (CI) 284 (96%, [M]$^+$, ^{81}Br), 282 (100%, [M]$^+$, ^{79}Br), 267 (17%, [M−OH]$^+$, ^{81}Br), 265 (18%, [M−OH]$^+$, ^{79}Br), 185 (19%); **HRMS** Found 282.02508, $C_{13}H_{15}BrO_2$ requires 282.02499; **IR** ν_{max} (film/cm^{-1}) 3313 (O-H), 2977 (C-H), 2945 (C-H), 2917 (C-H), 1683, 1510, 1418; Relative stereochemistry assigned based on NOESY spectra with key correlations indicated.

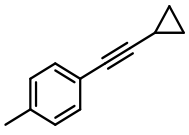
(*Z*)-2-(2-Hydroxy-1,2-di-*p*-tolylethylidene)cyclobutan-1-ol (215)



Using flame dried glassware and under an argon atmosphere, *p*-tolylboronic acid (82 mg, 0.60 mmol), $Pd(OAc)_2$ (5.6 mg, 0.025 mmol), PPh_3 (20 mg, 0.075 mmol) and K_2CO_3 (207 mg, 1.5 mmol) were dissolved in toluene (8 mL) and the solution stirred

for 15 min. A solution of vinyl halide **204** (142 mg, 0.50 mmol) in EtOH (4 mL) was added and the reaction stirred for 18 h at 90 °C. H_2O (8 mL) was added and the organic phase extracted with CH_2Cl_2 (2 × 8 mL). The organic layers were washed with brine (2 × 5 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The resultant residue was purified by column chromatography (15% EtOAc in petrol) to give **215** as a yellow oil (48 mg, 33%). Alkene **215** was isolated as a mixture of diastereomers A:B 1:1; **^{1}H NMR** ($CDCl_3$, 600 MHz) δ 7.31 (2H, d, *J* = 8.0, isomer A ArH), 7.25 (2H, d, *J* = 8.0, isomer B ArH), 7.12 (2H, d, *J* = 8.0, isomer A ArH), 7.09 (2H, d, *J* = 8.0, isomer B ArH), 7.07 (2H, d, *J* = 7.8, isomer B ArH), 7.03 (2H, d, *J* = 7.8, isomer B ArH), 6.99 (2H, d, *J* = 7.9, isomer A ArH), 6.89 (2H, d, *J* = 7.9, isomer B ArH), 5.63 (1H, s, isomer B ArCH), 5.59 (1H, s, isomer A ArCH), 5.12 (1H, td, *J* = 7.6, 2.7, isomer A CH_2C**H**OH), 4.88 (1H, td, *J* = 6.9, 2.8, isomer B CH_2C**H**OH), 3.97 (2H, br s, 2 × OH), 3.75 (1H, br s, OH), 3.52 (1H, br s, OH), 2.54-2.34 (6H, m, isomer A CCH_2, isomer A 1 × C**H**$_2$CHOH, isomer B CCH_2, isomer B 1 × C**H**$_2$CHOH), 2.32 (3H, s, isomer A $ArCH_3$), 2.31 (3H, s, isomer B $ArCH_3$), 2.30 (3H, s, isomer B $ArCH_3$), 2.27 (3H, s, isomer A $ArCH_3$), 2.08-1.91 (2H, m, isomer A 1 × C**H**$_2$CHOH, isomer B 1 × C**H**$_2$CHOH); **^{13}C NMR** ($CDCl_3$, 150 MHz) δ 142.5 (A), 142.5 (B), 140.2 (B), 139.9 (A), 137.4, 137.2, 137.1 (B), 136.6, 136.4, 136.0, 135.1, 134.4 (A), 129.3 (B), 129.1 (A), 128.9 (B), 128.8 (A), 128.3 (A), 128.1 (B), 127.7 (A), 126.5 (B), 76.5 (B), 76.3 (A), 71.5 (A), 70.9 (B), 29.0 (A), 28.5 (B), 24.3 (B), 23.8 (A), 21.3, 21.3, 21.2, 21.2; **LRMS** (CI) 294 (100%, $[M]^+$), 277 (62%), 259 (30%); **HRMS** Found 294.1615, $C_{20}H_{22}O_2$ requires 294.1614; **IR** ν_{max} (film/cm^{-1}) 3318 (O-H), 2980 (C-H), 2942 (C-H), 2866 (C-H), 1611 (C=C), 1510, 1444

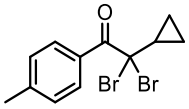
1-(Cyclopropylethynyl)-4-methylbenzene (216)[233]



Using flame dried glassware and under an argon atmosphere, $Pd(OAc)_2$ (15.4 mg, 0.0687 mmol) was added to PPh_3 (72.1 mg, 0.275 mmol) and CuI (26.1 mg, 0.137 mmol) in anhydrous THF (20 mL). 4-Iodotoluene (1.50 g, 6.87 mmol) was added, followed by diisopropylamine (1.44 mL, 10.3 mmol) and then cyclopropylacetylene (500 mg, 7.56 mmol) and the reaction was stirred for 18 h. The mixture was filtered through neutral alumina which was washed with Et_2O (2 × 5 mL). The filtrate was concentrated *in vacuo* and purified by column chromatography (petrol) to give **216** as

an orange oil (1.06 g, quantitative yield). **^{1}H NMR** ($CDCl_3$, 300 MHz) δ 7.27 (2H, d, J = 7.8, ArH), 7.07 (2H, d, J = 7.8, ArH), 2.31 (3H, s, CH_3), 1.51-1.38 (1H, m, CH), 0.93-0.71 (4H, m, 2 × CH_2); **^{13}C NMR** ($CDCl_3$, 125 MHz) δ 137.5, 131.6, 129.0, 120.9, 92.6, 75.9, 21.5, 8.8, 8.6, 0.2; **LRMS** (EI) 156 (100 %, M^+), 141 (80%, $[M-CH_3]^+$), 128 (55%)

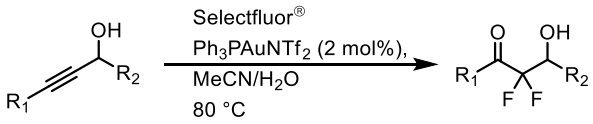
2,2-Dibromo-2-cyclopropyl-1-(*p*-tolyl)ethan-1-one (217)



General Procedure M using **216** (78 mg, 0.5 mmol), DBA (81 mg, 0.30 mmol) and MeCN/H_2O (4.3 mL): 36 mg, 22%, colourless oil. **^{1}H NMR** (300MHz, $CDCl_3$) δ 8.29 (2H, d, J = 8.2, ArH), 7.25 (2H, d, J = 8.2, ArH), 2.43 (3H, s, CH_3), 2.00-1.83 (1H, m, CH), 0.97-0.82 (4H, m, 2 × CH_2); **^{13}C NMR** (75 MHz, $CDCl_3$) 188.1, 144.3, 131.5, 130.1, 128.8, 71.5, 25.5, 21.8, 7.6; **LRMS** (CI) 352 (48%, $[M+NH_4]^+$, 2 × ^{81}Br), 350 (100%, $[M+NH_4]^+$, ^{79}Br, ^{81}Br), 348 (50%, %, $[M+NH_4]^+$, 2 × ^{79}Br), 335 (6%, $[M+H]^+$, 2 × ^{81}Br), 333 (11%, $[M+H]^+$, ^{79}Br, ^{81}Br), 331 (5%, $[M+H]^+$, 2 × ^{79}Br), 270 (34%); **HRMS** Found 329.9250, $C_{12}H_{12}Br_2O$ requires 329.9249

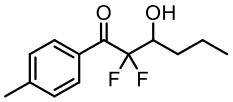
3.3.9 Synthesis and reactions of difluoroketoalcohols

General Procedure N: Preparation of difluoroketoalcohols



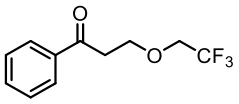
Alkyne (1 eq.) was dissolved in MeCN:H_2O (7:3, 2 mL.mmol^{-1}) in a plastic Falcon tube. $Ph_3PAuNTf_2$ (2 mol%) was added followed by Selectfluor® (2 eq.). The reaction was stirred at 80 °C until the reaction was complete by TLC. H_2O was added and the organic phase extracted with EtOAc. The organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The resultant residue was purified by column chromatography (10% EtOAc in petrol).

2,2-Difluoro-3-hydroxy-1-(*p*-tolyl)hexan-1-one (218)



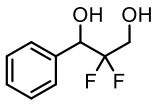
General Procedure N using **141g** (58 mg, 0.31 mmol), $Ph_3PAuNTf_2$ (9.8 mg, 6.2 µmol), Selectfluor® (219 mg, 0.619 mmol) and MeCN/H_2O (0.7 mL): 18 mg, 24%, colourless oil. **^{1}H NMR** ($CDCl_3$, 500 MHz) *δ* 8.02 (2H, d, *J* = 8.2, ArH), 7.30 (2H, d, *J* = 8.2, ArH), 4.29-4.18 (1H, m, C**H**OH), 2.44 (3H, s, $ArCH_3$), 1.74-1.60 (3H, m, CHC**H**$_2$, 1 × C**H**$_2$$CH_3$), 1.54-1.38 (1H, m, 1 × C**H**$_2$$CH_3$), 0.98 (3H, t, *J* = 7.1, CH_2C**H**$_3$); **^{13}C NMR** ($CDCl_3$, 125 MHz) *δ* 190.3 (t, *J* = 31.3), 146.0, 130.5 (t, *J* =3.3), 129.8, 129.5, 116.6 (dd, *J* = 262.9, 257.1), 71.2 (dd, *J* = 27.2, 24.4), 30.9, 21.9, 18.7, 13.9; **^{19}F NMR** ($CDCl_3$, 282 MHz) δ −107.8 (d, *J* = 295.8), −117.0 (d, *J* = 295.8); **LRMS** (NSI) 265 (100%, $[M+Na]^+$); **HRMS** Found 265.1016, $C_{13}H_{16}F_2O_2Na$ ($[M+Na]^+$) requires 265.1011; **IR** ν_{max} (film/cm^{-1}) 3431 (O-H), 2958 (C-H), 2927 (C-H), 2871 (C-H), 1689 (C=O), 1603, 1569, 1502, 1454, 1408

1-Phenyl-3-(2,2,2-trifluoroethoxy)propan-1-one (220)



3-Phenylpropyn-1-ol (33 mg, 0.25 mmol) was dissolved in trifluoroethanol/H_2O (95:5, 4 mL.$mmol^{-1}$) in a plastic Falcon tube. $Ph_3PAuNTf_2$ (2 mol%) was added followed by Selectfluor® (178 mg, 0.50 mmol). The reaction was stirred at 80 °C 18 h. Solvents were removed *in vacuo* and the residue purified by column chromatography (10% EtOAc in petrol) to give **220** as a colourless oil (43 mg, 74%). **^{1}H NMR** ($CDCl_3$, 600 MHz) *δ* 8.00-7.95 (2H, m, ArH), 7.61-7.57 (1H, m, ArH), 7.51-7.46 (2H, m, ArH), 4.08 (2H, t, *J* = 6.3, CH_2C**H**$_2$O), 3.90 (2H, q, *J* = 8.8, CH_2CF_3), 3.31 (2H, t, *J* = 6.3, C(O)CH_2); **^{13}C NMR** ($CDCl_3$, 150 MHz) *δ* 197.7, 136.8, 133.5, 128.8, 128.2, 124.0 (q, J_{CF} = 279.0), 68.9 (q, J_{CF} = 33.8), 68.0, 38.7; **LRMS** (CI) 250 (100%, $[M+NH_4]^+$), 233 (9%, $[M+H]^+$); **HRMS** Found 233.07838; $C_{11}H_{12}F_3O_2$ requires 233.07839; **IR** ν_{max} (film/cm^{-1}) 2952 (C-H), 2942 (C-H), 2923 (C-H), 2864 (C-H), 1608 (C=O), 1540, 1469, 1448, 1431

2,2-Difluoro-1-phenylpropane-1,3-diol (223)



$NaBH_4$ (12 mg, 0.32 mmol) was added to a stirred solution of **222** (37 mg, 0.20 mmol) in MeOH (2 mL) at 0 °C. After 10 min, saturated NH_4Cl (2 mL) was added and the organic phase extracted with EtOAc (2 × 3 mL). The organic layer was washed with brine (2 × 3 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The resultant residue was purified by column chromatography (10% EtOAc in petrol) to give **223** as a colourless oil (31 mg, 82%). **^{1}H NMR** ($CDCl_3$, 600 MHz) δ 7.49-7.42 (2H, m, ArH), 7.43-7.35 (3H, m, ArH), 5.04 (1H, dd, J = 14.0, 8.5, CH), 3.94 (1H, td, J = 16.4, 12.0, 1 × CH_2), 3.74 (1H, q, J = 12.0, 1 × CH_2); **^{13}C NMR** ($CDCl_3$, 150 MHz) δ 136.0, 129.1, 128.6, 127.6, 120.5 (dd, J_{CF} = 248.1, 247.1), 73.6 (dd, J_{CF} = 28.9, 25.9), 62.2 (dd, J_{CF} = 31.6, 24.9); **LRMS** (NSI) 211 (100%, $[M+Na]^+$), 199 (26%), 149 (24%); **HRMS** Found 211.0542, $C_9H_{10}F_2O_2Na$ ($[M+Na]^+$) requires 211.0541; **IR** ν_{max} (film/cm^{-1}) 3345 (O-H), 2918 (C-H), 2849 (C-H), 1494, 1454

Chapter 4 References

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