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Applications of the Redox-Relay Heck Reaction in the Synthesis of Heterocyclic Scaffolds

A thesis submitted to the University of Nottingham for the degree of Doctor of Philosophy

By

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Declaration

I hereby declare that, except where specific reference is made to other sources, the work contained within this thesis is the original work of my own research since the registration of my PhD degree in September 2018, and any collaboration is clearly indicated.

This thesis has been composed by myself and has not been submitted, in whole or part, for any other degree, diploma or other qualification. The candidate confirms that the work submitted is his own, except where work which has formed part of jointly-authored publications has been included. The contribution of the candidate and the other authors to this work has been explicitly indicated below. The candidate confirms that the appropriate credit has been given within the thesis where reference has been made to the work of others.

Acknowledgements

Firstly, I would like to thank Dr. James Cuthbertson for giving me the opportunity to work in his group, I have felt privileged to have been here during the early years. Working with you has been an absolute pleasure and I am excited to see what the future holds for you and the group.

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Since day one, I have shared an office with the Amabilino Group and I have been very grateful for their time, generosity and friendship, especially as a new PhD starting in a new research group. As the years progressed, it's been great to build friendships outside of the lab that will endure post-studies.

I would like to thank the Lam group also. After completing my master's project in the group, the friendships developed there have continued as members of the group have moved on.

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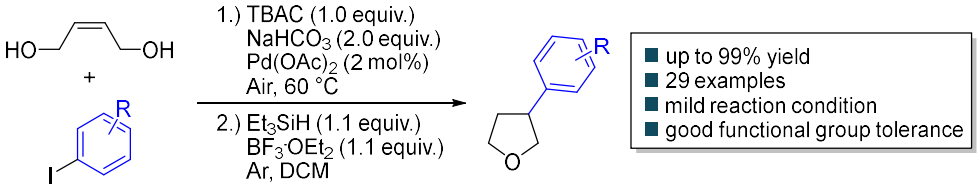
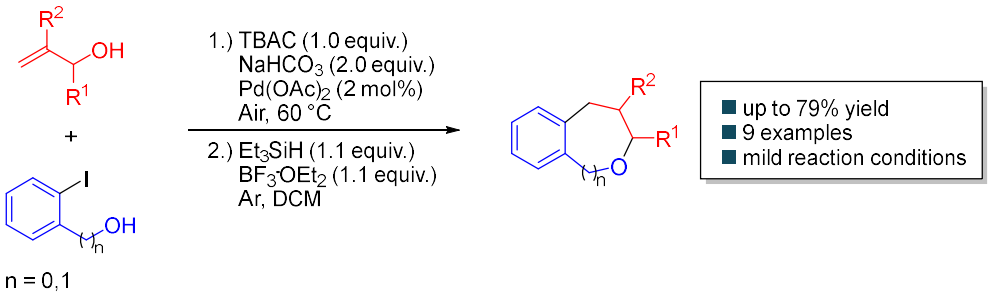
Abstract

We disclose an efficient method for the synthesis of 3-aryl substituted THFs utilising a redox-relay Heck/reduction protocol, achieving yields of up to 99% over two steps. Excellent functional group tolerance is observed including moieties such as: halide, nitrile, ester, ketone, alcohol, nitro and those that contain fluorine. Applications of the chemistry in the synthesis of the natural products calyxolanes A and B are demonstrated.



This methodology has been further extended to larger ring sizes including tetrahydropyrans and oxepanes.



Additionally, work has also been undertaken to provide further understanding of different roles played in the reaction such as the beneficial use of $NaHCO_3$ over K_2CO_3 or the requirement of a chloride quaternary ammonium salt for accessing yields in excess of 50%.

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Abbreviations

9-BBN	9-Borabicyclo[3.3.1]nonane
Ac_2O	Acetic anhydride
acac	Acetylacetone
AIBN	Azobisisobutyronitrile
aq.	Aqueous
BINAP	(2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl)
Boc	*tert*-Butoxycarbonyl
Boc_2O	Di-*tert*-butyl dicarbonate
BOX	Bis(oxazoline)
B(pin)	(Pinacolato)boron
bpy	2,2'-Bipyridine
br	Broad
CAN	Ceric(IV) ammonium nitrate
Cbz	Carbobenzyloxy
CFL	Compact fluorescent lamp
cod	1,5-Cyclooctadiene
COSY	Correlation spectroscopy
Cp	Cyclopentadienyl
CPME	Cyclopentyl methyl ether
CTAB	Cetyltrimethylammonium bromide
d	Doublet
DBCE	Debenzylative cycloetherification
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCE	1,2-Dichloroethane
DCM	Dichloromethane
DEAD	Diethyl azodicarboxylate
DFT	Density functional theory
DHF	Dihydrofuran
DIBAL-H	Di*iso*butylaluminium hydride
DIPEA	Di*iso*propylethylamine
DMA	Dimethylacetamide

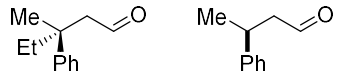
DMAP	4-*N*,*N*-Dimethylaminopyridine
DME or dme	Dimethoxyethane
DMF	*N*,*N*-Dimethylformamide
DMI	Demethylation inhibitor
DMP	Dess-Martin periodinane
DMPU	1,3-Dimethyl-3,4,5,6-tetrahydro-2(*1H*)-pyrimidinone
DMSO	Dimethyl sulfoxide
DNA	Deoxyribonucleic acid
dppb	1,4-bis(diphenylphosphino)butane
dppe	1,2-Bis(diphenylphosphino)ethane
dppf	1,1'-bis(diphenylphosphino)ferrocene
dppp	1,3-bis(diphenylphosphino)propane
dr	Diastereomeric ratio
DTBB	4,4′-Di-*tert*-butylbiphenyl
dtbbpy	4,4'-Di-*tert*-butyl-2,2'-dipyridyl
ee	Enantiomeric excess
ESI	Electrospray ionisation
Et_2O	Diethyl ether
EtOAc	Ethyl acetate
EXAFS	Extended x-ray absorption fine structure
FDA	Food and Drug Administration
HAT	Hydrogen atom transfer
Het	Heterocycle
HIV	Human immunodeficiency virus
HMBC	Heteronuclear multiple bond correlation
HMDS	Hexamethyldisilazane
HPLC	High-performance liquid chromatography
HRMS	High resolution mass spectrometry
HSQC	Heteronuclear single quantum correlation
HWE	Horner-Wadsworth-Emmons
i	*Iso*
J	Coupling constant in Hz
k	Kilo

LDA	Lithium di*iso*propylamine
LED	Light emitting diode
LHMDS	Lithium hexamethyldisilazane
L_n	Ligand(s)
m	Multiplet
m	Meta
m/z	Mass to charge ratio
M^+	Molecular ion
Ms	Methanesulfonyl
MS	Mass spectrometry
Nap	Naphthyl
NBS	*N*-Bromosuccinimide
NCS	*N*-chlorosuccinimide
NHC	*N*-heterocyclic carbene
NMP	*N*-Methyl-2-pyrrolidone
NMR	Nuclear magnetic resonance
nOe	Nuclear Overhauser effect
p	*para*
PBB	*para*-Bromobenzyl
PC	Photocatalyst
PCET	Proton-coupled electron transfer
PCC	Pyridinium chlorochromate
PE	Petroleum ether (Fraction which boils at 40–60 °C)
PG	Protecting group
Phth	Phthalimide
Piv	Pivalyl
PMB	*para*-Methoxybenzyl
PMP	*para*-Methoxyphenyl
ppm	Parts per million
PPTS	Pyridinium *p*-toluenesulfonate
ppy	2-Phenylpyridine
Py	Pyridine
PyrOx	Pyridine-oxazoline

q	Quartet
quant.	Quantitative
RCM	Ring-closing metathesis
R*f*	Retention factor
s	Singlet
SET	Single electron transfer
SDS	Sodium dodecyl sulfate
SM	Starting material
S_N	Nucleophilic substitution
t	Triplet
TBDPS	*tert*-Butyldiphenylsilyl
TBME	Methyl *tert*-butyl ether
TBS	*tert*-Butyldimethylsilyl
TEBA	Benzyltriethylammonium chloride
Tf	Trifluoromethanesulfonyl
TFA	Trifluoroacetic acid
TFAA	Trifluoroacetic anhydride
TFE	2,2,2-Trifluoroethanol
TfOH	Trifluoromethanesulfonic acid
THF	Tetrahydrofuran
THP	Tetrahydropyran
TLC	Thin layer chromatography
TMEDA	Tetramethylethylenediamine
TMS	Trimethylsilyl
TMSOTf	Trimethylsilyl trifluoromethanesulfonate
Ts	*para*-Toluenesulfonyl

Stereochemistry:

Throughout this work, 'wedges' have been used to indicate stereochemistry at quaternary centres and 'blocks' have been used to indicate stereochemistry at tertiary centres.

i.e. 

In this thesis, the use of 'wedges' and 'blocks' is unrelated to the distinctions of absolute or relative stereochemistry of a compound.

Numbering:

Throughout this work, the numbering of compounds has been divided up into two sections. Compounds in the introductions are prefaced with the letter '**I**' and are numbered **I1**, **I2**, etc. Compounds in the main text of the results and discussion are not prefaced with a letter and are numbered **1**, **2**, etc. This is consistent throughout both chapters, with the numbering continuing where the previous chapter ended. To avoid confusion, if a compound is in both the introduction and the results and discussion chapters, they have two different numbers to fit in with the relevant section's numbering. Compounds used as ligands are prefaced with the letter **L**.

Synthesis of Substituted Tetrahydrofurans Using a Redox-Relay Heck Strategy

1 Introduction

1.1 Importance of Heterocycles

Heterocycles are cyclic structures that feature one or more heteroatoms within the ring (typically nitrogen, oxygen and/or sulfur). These types of rings are fundamental for life, found in each DNA base pair **I1**–**I4**[1,2] and in vital carbohydrates such as β-D-glucose **I5**[3] and cellulose **I6** (Figure 1).[4]

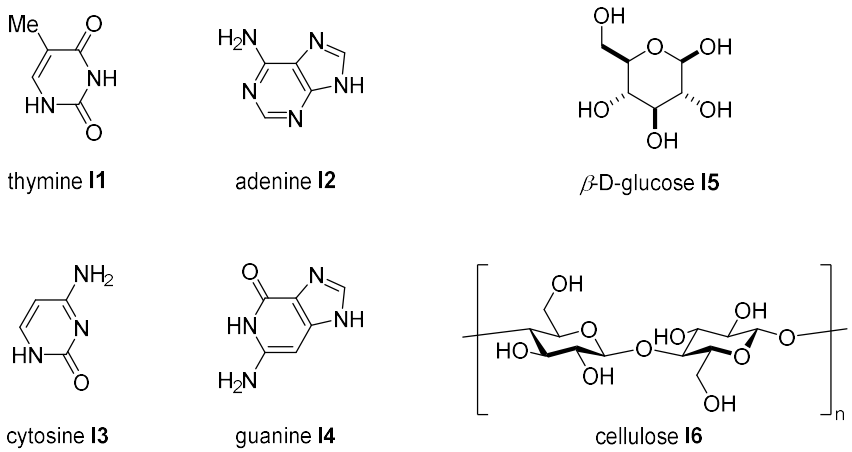
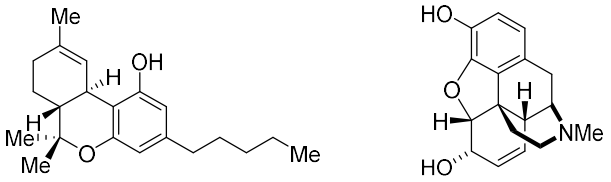


Figure 1 DNA base pairs **I1**–**I4** and sugars fundamental for life **I5** and **I6**.

Heterocycles have been found to have alternative uses within the last 5000 years as humans utilised natural products for medicinal purposes.[5–7] Examples include tetrahydrocannabinol **I7**, found in cannabis, used as a painkiller by the ancient Egyptians,[8] and the analgesic morphine **I8**, found in the opium poppy used in ancient Mesopotamia (Figure 2).[9]



tetrahydrocannabinol **I7** morphine **I8**

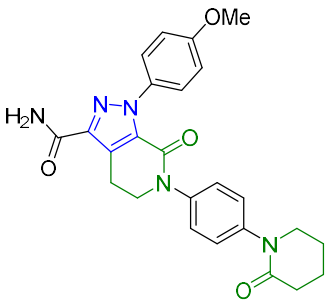
Figure 2 Ancient heterocyclic medications, tetrahydrocannabinol **I7**, and morphine **I8**.

Contemporarily, when analysing the 'Top 200 Small Molecule Pharmaceuticals by Retail Sales in 2020' list produced by the Njarðarson Group,[10] 173 contain at least one heterocycle. This prevalence demonstrates how fundamental heterocycles are to the pharmaceutical industry and consequently, human health.

Aside from maintaining our physiological wellbeing, another major challenge of our times is the global supply of food, especially alongside an ever-growing global population. The significance of heterocycles is equally clear in this context – over 70% of agrochemicals contain at least one heterocycle.[11]

One of the reasons for the ubiquity of heterocycles are their inherent properties which can impart pharmacokinetic differences on drug candidates. When incorporating heterocycles, crucial functions such as solubility, lipophilicity, rigidity, polarity and hydrogen bonding capability can be manipulated to allow for the fine-tuning of properties.[12]

The most common type of heterocycles in drugs are those that contain nitrogen.[13] An important example is apixaban **I9**, an anticoagulant medication, which features two lactam rings (green), one of which is fused to a pyrazole (blue) (Figure 3). Apixaban sales reached over $16 billion in 2021, the highest for a small pharmaceutical compound, highlighting the importance of these types of structures.[10]

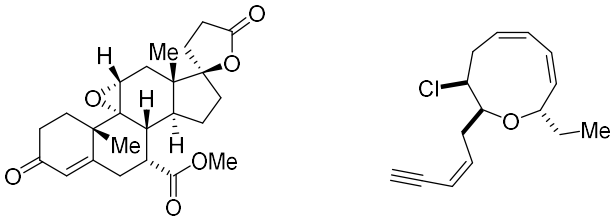


apixaban **I9**

Figure 3 Structure of the anticoagulant medication, apixaban **I9**.

1.1.1 Oxygen-Containing Heterocycles

After *N*-containing heterocycles, *O*-containing heterocycles are the most prevalent.[14] A variety of oxygen-containing rings are seen in natural products from the three-membered epoxide observed in eplerenone **I10**,[15] an aldosterone antagonist used to treat heart failure, to the nine-membered oxonane derivative (+)-brasilenyne **I11**, isolated from *Aplysia brasiliana*, which has been shown to exhibit antifeedant activity (Figure 4).[16]



eplerenone **I10** (+)-brasilenyne **I11**

Figure 4 Three- and nine-membered *O*-heterocycles, eplerenone **I10** and (+)-brasilenyne **I11**.

1.1.1.1 Tetrahydrofurans – Introduction and Importance

Of the oxygen-containing heterocycles, the five-membered ring, tetrahydrofuran (THF) is the most abundant and is found in a large number of biologically active natural products with examples found in annonaceous acetogenins,[17] lignans,[18] polyether ionophores[19] and macrodiolides.[20,21]

As well as being found in numerous natural products, the THF ring is also present in several pharmaceuticals – of all rings featured in U.S. FDA approved drugs, THF is the eleventh most abundant.[22] An example of the beneficial incorporation of the five-membered cyclic ether into drugs was seen when the THF motif was used within HIV-1 protease inhibitor research. Ghosh *et al.* found that replacing a *t*butyl group with a THF ring in their compounds led to greater affinity for the S_2 binding region of the HIV-1 protease enzyme. The researchers observed a tenfold increase in the inhibitory potency of the THF-containing compound **I13** over the original example **I12** (Figure 5).[23]

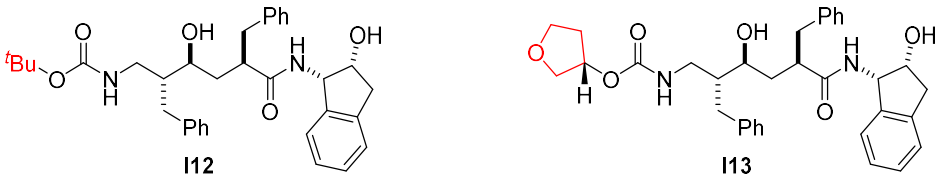
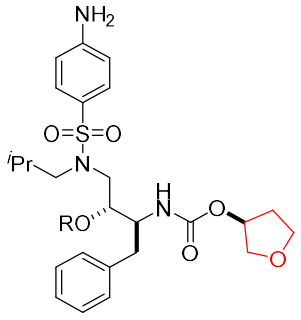


Figure 5 Inhibitory potencies of trial compounds featuring *t*Butyl **I12** and THF **I13** groups.[23]

It was believed that the oxygen atom could participate in hydrogen bonding, whilst the introduction of a ring benefitted compound rigidity.[23,24] The results led to the incorporation of a tetrahydrofuran ring in FDA approved drug, amprenavir **I14** and later its prodrug, fosamprenavir **I15** (Figure 6).



R = H (amprenavir) **I14**, H_2PO_3 (fosamprenavir) **I15**

Figure 6 HIV protease inhibitor, amprenavir **I14** and derived prodrug, fosamprenavir **I15**.

Several THF-containing bioactive compounds feature aromatic substituents, such as: bromuconazole **I16** – a DMI fungicide,[25] magnosalicin **I17** – an antiallergy compound isolated from *Magnolia salicifolia*,[26] metasequirin E **I18**

– isolated from *Metasequoia glyptostroboides*,[27] and calyxolanes A **I19** and B **I20** – both isolated from Caribbean sponge, *Calyx podatypa*[28] (Figure 7).

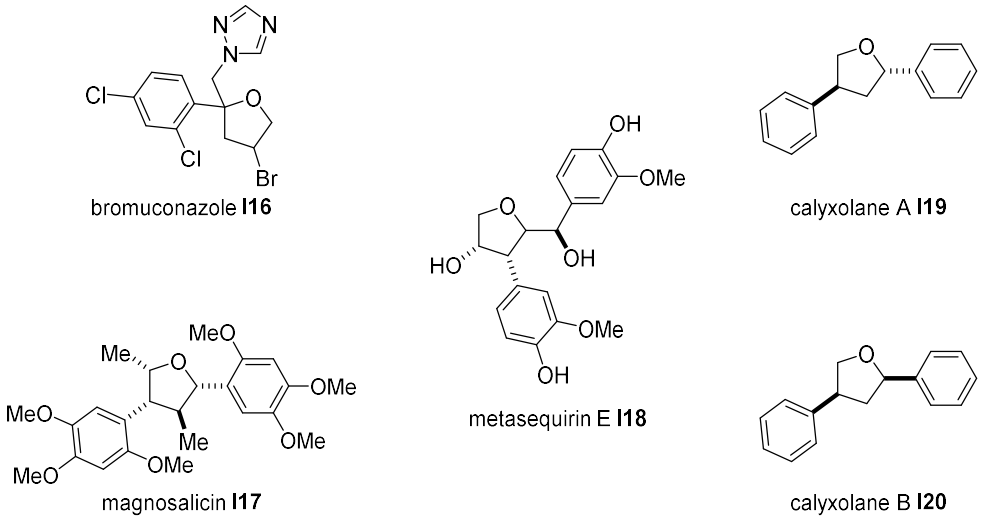
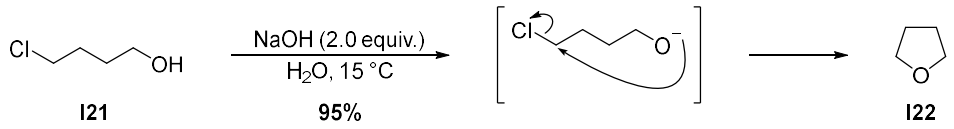


Figure 7 Examples of aryl-substituted THFs.

The ability to synthesise and functionalise THF-containing compounds is therefore of great value to chemists and as such, a variety of different methods to accomplish this have been developed. A short review of selected methodologies is included, demonstrating some of the major advances in the field. Reviews by both Wolfe,[29] and Galano and Oger[30] are available to offer a more comprehensive overview of historical approaches and the current landscape.

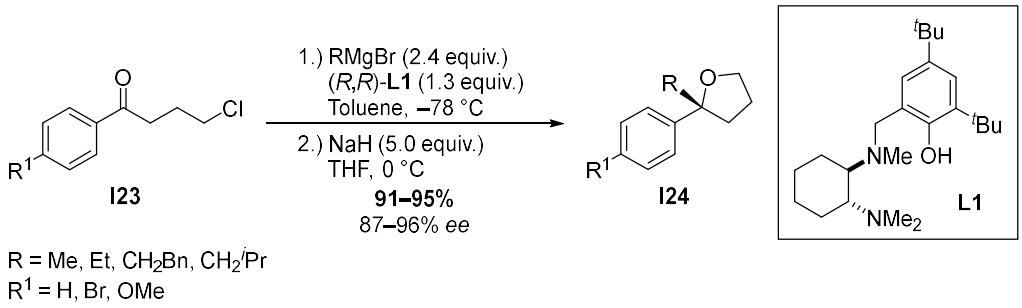
1.2 Synthesis of Tetrahydrofurans

Classically, the Williamson ether synthesis has provided a robust route to ethers, including cyclic ethers. In general, THFs can be synthesised *via* deprotonation of an alcohol, before a nucleophilic attack can take place on a tethered electrophile, commonly an alkyl halide. This simple transformation was demonstrated in a reaction carried out by Heine and Siegfried (Scheme 1).[31]



Scheme 1 Heine and Siegfried's synthesis of THF **I22**.[31]

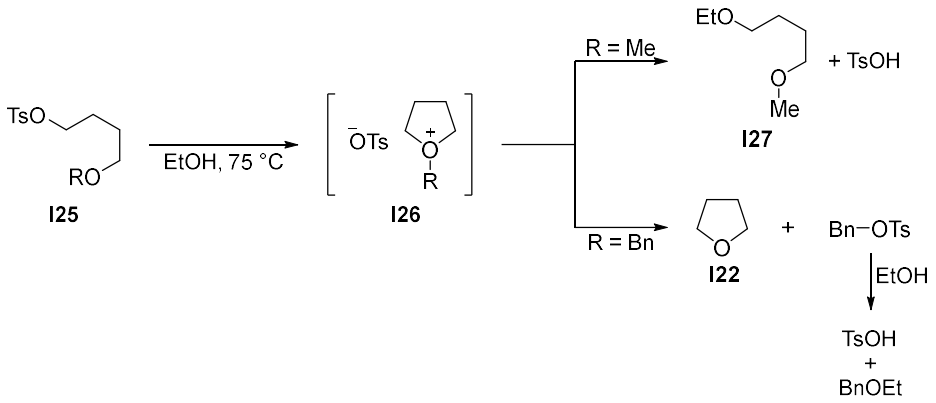
This method from 1850, first described in Williamson's '*Theory of Ætherification*',[32] still finds widespread use today, exemplifying its value. For example, the reaction was used recently by Gilheany and co-workers in their enantioselective formation of 2,2-disubstituted THFs (Scheme 2).[33]



Scheme 2 Gilheany's asymmetric synthesis of 2,2-disubstituted THFs **I24**.[33]

After forming *γ*-chloro tertiary alcohols **I23** *via* an asymmetric Grignard reaction, sodium hydride was used to promote a Williamson etherification reaction to give the desired products **I24**. The reaction was high-yielding with no racemisation of the stereocentre observed.

Debenzylative cycloetherification offers an alternative approach to THF **I22** formation, whilst still utilising an oxygen nucleophile. Barker and co-workers first described the cyclisation of a benzyl ether, tethered to a tosylate when heated in ethanol (Scheme 3).[34]



Scheme 3 Barker's synthesis of tetrahydrofuran **I22**.[34]

This work showed the use of the more labile benzyl ether over a simple alkyl ether to give the cyclised product. Following this early example, more related methodologies have been reported and feature in a review by the Vincent group.[35]

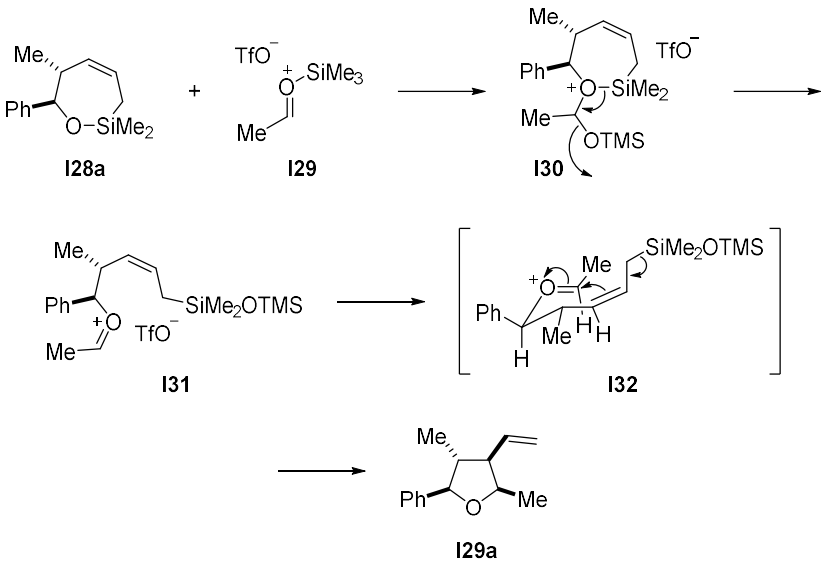
1.2.1 Synthesis of Substituted Tetrahydrofurans: *via* Ionic Pathways

In a different approach to access substituted THFs, Cossy and co-workers employed a ring-contraction strategy.[36] The transformation of cyclic allylsiloxanes **I28** to multi-substituted THFs **I29** utilised a Sakurai-type reaction with an oxonium ion formed *in situ* (Scheme 4).



Scheme 4 Cossy's synthesis of multi-substituted THFs.[36]

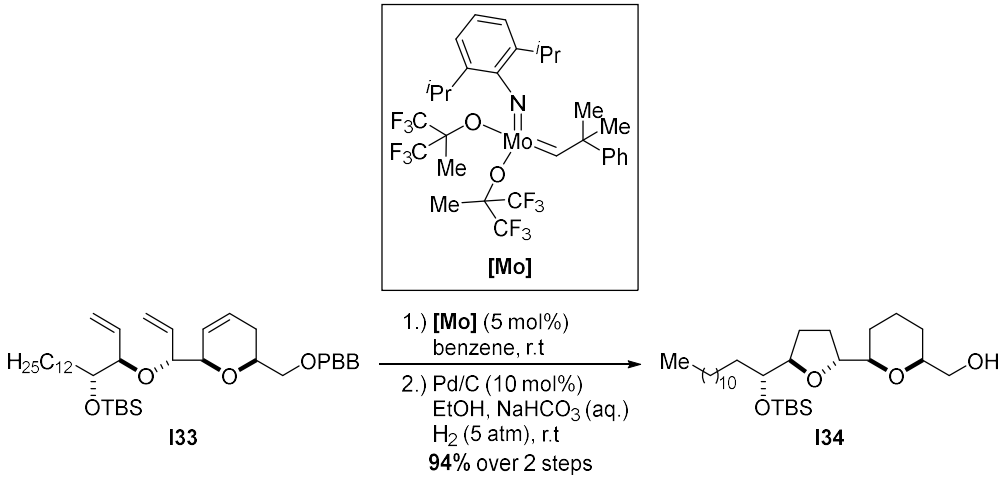
The cyclic products were returned in high diastereoselectivity (up to 19:1 d.r.), derived from a pseudo-equatorial transition state (Scheme 5).



Scheme 5 Postulated mechanism for Cossy's synthesis of multi-substituted THFs **I29a**.[36]

This methodology is able to return structurally complex THFs and as a result was utilised in a strategy to access lignan skeleta.[37] Despite this transformation finding use in natural product synthesis, the starting cyclic allylsiloxanes **I28** have to first be constructed *via* ruthenium-catalysed ring-closing metathesis (RCM), elongating the synthetic route.

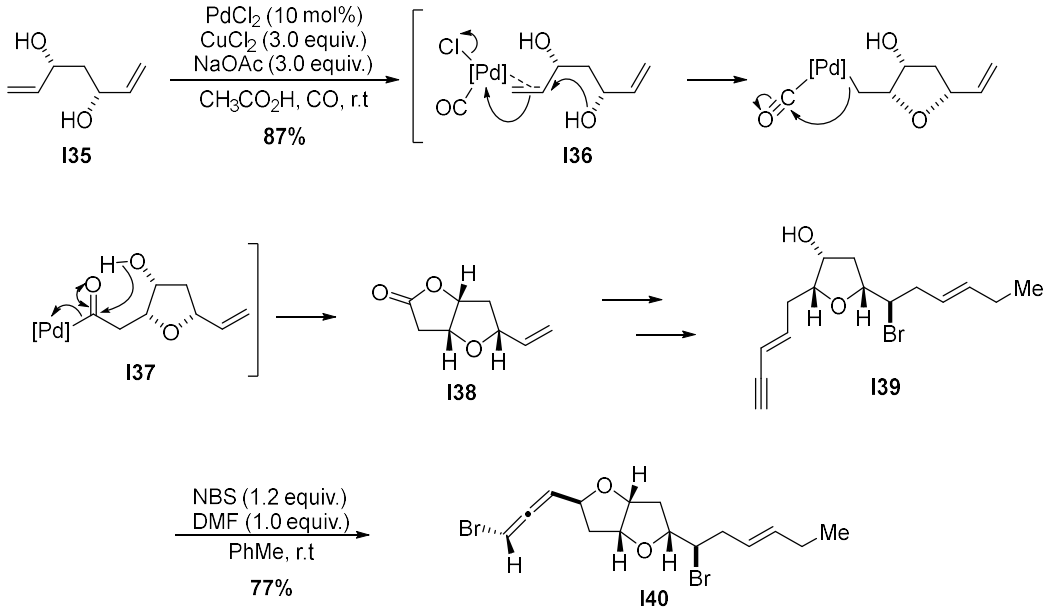
RCM can provide immediate access to substituted THFs as described by Jacobsen and co-workers in their total synthesis of muconin.[38] Having prepared compound **I33**, Shrock's catalyst was used to form a dihydrofuran (DHF) which was then hydrogenated to return a THF-THP derivative **I34** (Scheme 6).



Scheme 6 Jacobsen's THF construction in his total synthesis of muconin.[38]

With a high yield observed for the combined two steps, this example is an effective route to substituted THFs. This work also highlights the prevalence of *O*-containing heterocycles in some natural products.

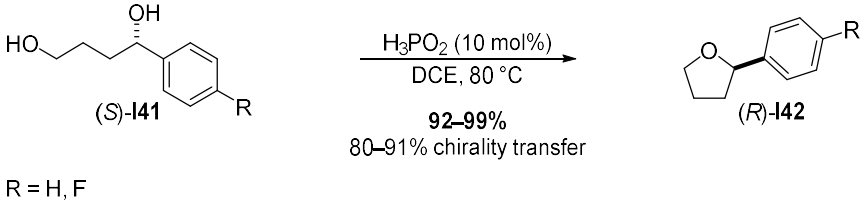
Tang and co-workers described two different methods to construct the fused THF rings found in the natural product, (−)-kumausallene **I40**.[39] Their route relied upon the initial synthesis of asymmetric diol **I35** which underwent a palladium-catalysed oxycarbonylation-lactonisation cascade based on work by Semmelhack to give **I38** as a single enantiomer.[40,41] Although the fused 5,5-bicyclic ring system found in the natural product is formed here, the lactone is later ring-opened to allow for further manipulation in their route to enyne **I39**. The second THF ring in (−)-kumausallene **I40** is installed from enyne **I39** *via* a biomimetic, stereoselective bromoetherification step that also forms the allene (Scheme 7).



Scheme 7 Tang's synthesis of the THF ring in (−)-kumausallene **I40**.[39]

This work, which draws upon previous bromolactonisation work developed by the group,[42,43] was the first diastereo- and enatioselective total synthesis of (−)-kumausallene **I40**, a natural product isolated from the algae, *Laurencia*.

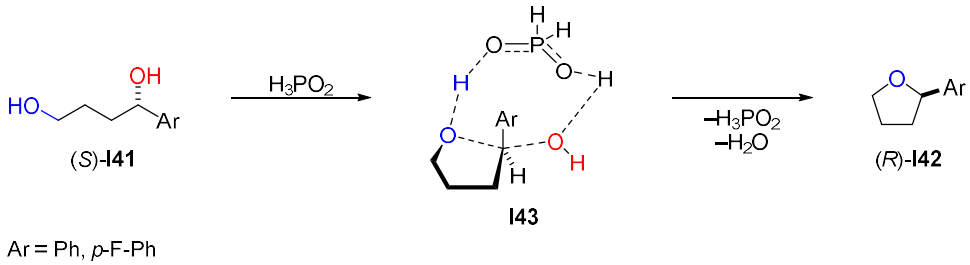
Many strategies take advantage of widely available diols in intramolecular cyclisations. One approach by Samec and co-workers described the use of phosphinic acid as a catalyst for the synthesis of *N*-, *S*- and *O*-heterocycles including 2-aryl-substituted THFs (*R*)-**I42** *via* an intramolecular substitution (Scheme 8).[44]



Scheme 8 Samec's synthesis of 2-substituted THFs (*R*)-**I42**.[44]

The authors claim that their phosphinic acid catalyst acted in a bifunctional Brønsted acid/Brønsted base fashion to activate the nucleophile and leaving group, their findings corroborated by DFT calculations.[44] The hydroxy group of the phosphinic acid protonates the nucleofuge (red) to activate it, whilst the oxo-

group on the acid catalyst deprotonates the nucleophilic heteroatom (blue) (Scheme 9).

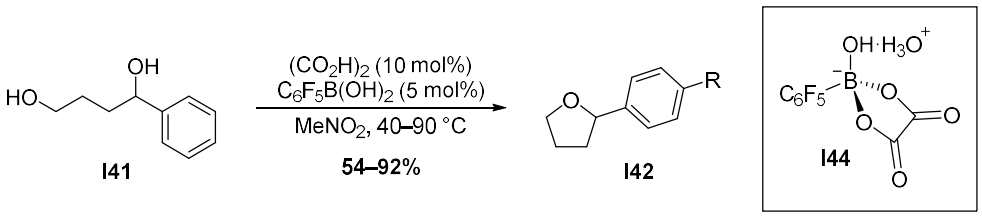


Scheme 9 Postulated mechanism for Samec's synthesis of 2-substituted THFs (*R*)-**I42**.[44]

The conformation adopted to allow this concomitant protonation/deprotonation event in turn promotes an S_N2-type substitution with inversion at the carbon centre. Interestingly, the 1,4 heteroatom distance is vital for this reaction to proceed as the authors were unable to apply this chemistry to the formation of three-, four- or six-membered rings. In addition, with chirality transfer less than 100%, phosphinic acid-promoted epimerisation is feasibly taking place.

Although this method allows access to enantioenriched substituted THFs (*R*)-**I42**, the chiral information is generated as part of a three-step substrate synthesis, lessening the efficiency of this chemistry. In addition, the THF scope is small (two examples), and the reaction is carried out at 80 °C in DCE which is described as an undesirable solvent and having major issues by Pfizer and GlaxoSmithKline (GSK) respectively, with Sanofi banning its use entirely.[45]

Another intramolecular etherification making use of benzylic alcohols **I41** was published by Taylor and co-workers (Scheme 10).[46] It was suggested that pentafluorophenylboronic acid and oxalic acid were in equilibrium with complex **I44** which was acting as a strong Brønsted acid, to promote the cyclisation.



R = H, Me, OMe, CF_3, Cl, Br

Scheme 10 Taylor's synthesis of 2-substituted THFs **I42**.[46]

This complex **I44**, formed *in situ* then proceeds to protonate the benzylic alcohol, which is lost to give a carbocation as part of an ion pair with the boronate ester catalyst. Attack from the tethered nucleophile gives the cyclised product *via* an S_N1 reaction. Because of the planar nature of the carbocation intermediate, only racemic products are accessible using this method.

In contrast to the work of Samec and co-workers, different sized rings can be obtained, including the six-membered tetrahydropyran (THP) and one example of the seven-membered oxepane, albeit in significantly reduced yield. Attempts to access the three- and four-membered rings were unsuccessful returning either a complex mixture or the starting material respectively. This chemistry, similar to the work of Samec and co-workers, requires a multistep synthesis of substrates.

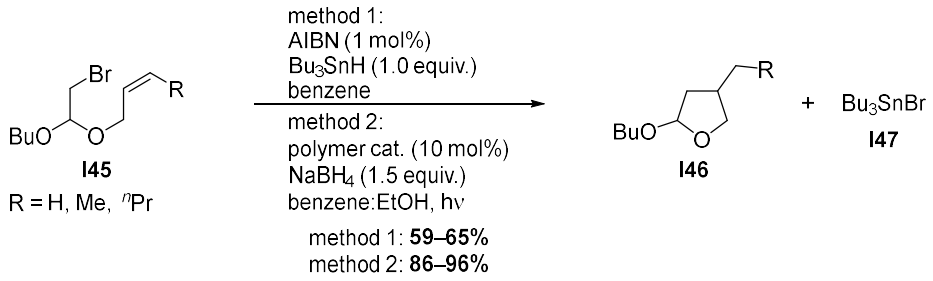
These examples highlight the difficulty in accessing substituted THFs from commercial and readily available substrates. To prepare THFs with desired substituents groups, individual substrate synthesis is required resulting in an inefficient and less general method.

1.2.2 Synthesis of Substituted Tetrahydrofurans *via* Radical Methods

In addition to ionic methods, there have been a number of radical approaches to the synthesis of substituted THFs. During the 20th century, the field of radical chemistry started to develop with the discovery of new reactions based upon the

movement of a single electron. From the outset, radical chemistry was used in the construction of heterocycles,[47] but perhaps the earliest use in the formation of the tetrahydrofuran ring was described by the groups of Ueno and Stork.

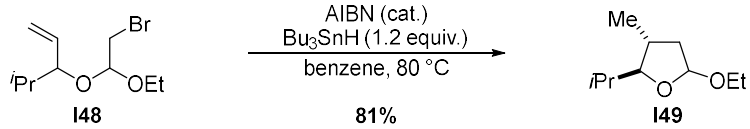
Ueno and co-workers utilised tributyltin hydride and azobisisobutyronitrile (AIBN), to effect their synthesis of THF derivatives.[48] The chemistry is a radical-promoted intramolecular carbocyclisation of haloacetals **I45** (Scheme 11).



Scheme 11 Ueno's synthesis of substituted THFs **I48**.[48]

Initially, the yields for this method (method 1) were only fair; it was suggested that difficulties in isolating the products **I46** from by-product tributyltin bromide **I47** led to the modest yield range. The Ueno group also disclosed an alternative method (method 2) utilising a polymer supported organotin species. The yields for the second method were thought to be more representative of the transformation, with a range from very good to excellent.

This work was followed shortly after by chemistry reported by Stork and co-workers, who described the intramolecular carbocyclisation of alkene **I48** (Scheme 12).[49]

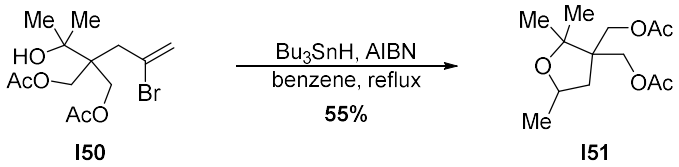


Scheme 12 Stork's synthesis of substituted THFs **I49**.

The conditions were similar to the method of Ueno and later the reaction was named the Ueno-Stork cyclisation. This early work by the two researchers has

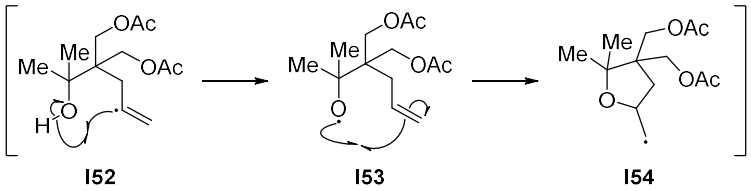
been developed further over the years, with the reaction the focus of a review article by Renaud and co-workers.[50]

Throughout the following years the combination of tributyltin hydride and AIBN have been used countless times to promote radical reactions, such as a method by Ihara and co-workers in their synthesis of substituted THFs **I53** (Scheme 13).[51]



Scheme 13 Ihara's synthesis of substituted THFs **I51**.[51]

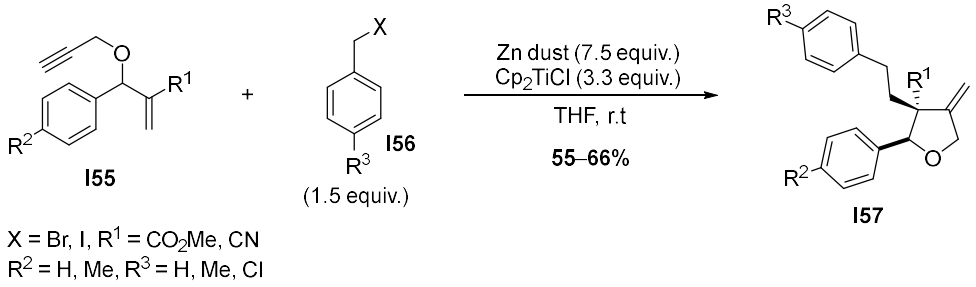
Unexpectedly, the group found that when vinyl bromide **I50** was treated with Bu_3SnH and AIBN, the hydrogen atom of the hydroxy group was abstracted by vinyl radical **I52**. The resultant oxy radical **I53** then undergoes a 5-*exo*-*trig* radical cyclisation to give the THF radical **I54**, with the product **I51** formed following a final HAT step (Scheme 14).



Scheme 14 Postulated mechanism for Ihara's THF synthesis.[51]

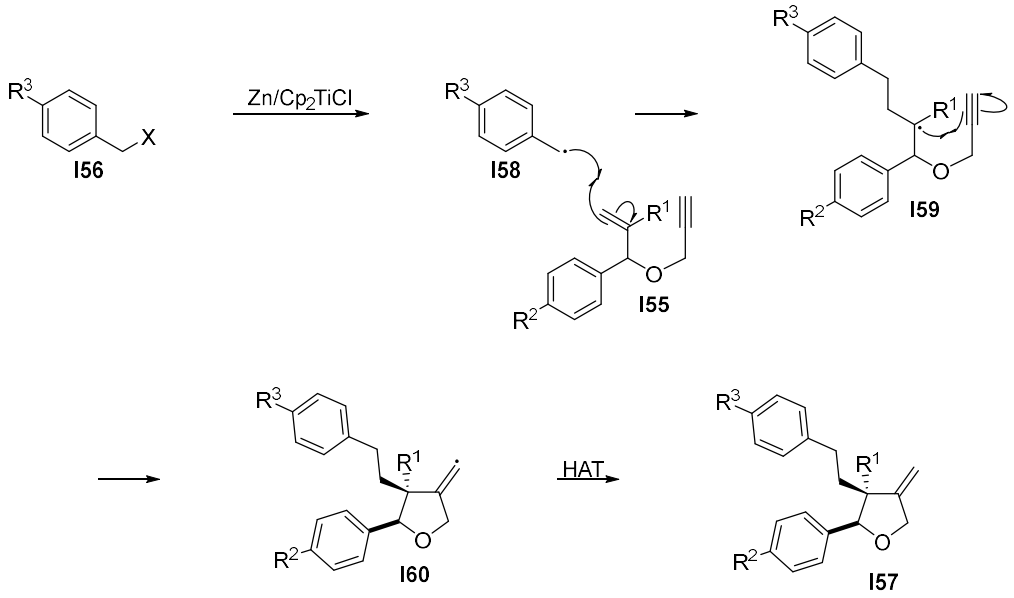
Only seven THF products, with little structural or functional group diversity, were generated using this method with both yield (21–86%) and diastereotopic ratios (1:1–33:1) not consistently satisfactory.

More recently, the Roy group has described a stereoselective synthesis of trisubstituted tetrahydrofurans **I57** *via* a tandem radical cyclisation, this time promoted by a titanocene radical initiator (Scheme 15).[52]



Scheme 15 Roy's stereoselective synthesis of trisubstituted THFs **I57**.[52]

Benzyl radicals **I58** were formed from halogenated precursors **I56** which then attacked alkene **I55** to give intermediate radicals **I61**. The radicals **I61** then cyclised to give the radicals **I62** before a HAT gave the THF products **I57** exclusively as single isomers (Scheme 16).



Scheme 16 Mechanism for Roy's trisubstituted THF synthesis.[52]

This stereoselective chemistry is an effective route to trisubstituted THFs **I57**, but unfortunately the yields are modest, and the methodology requires a two-step synthesis of substrates.

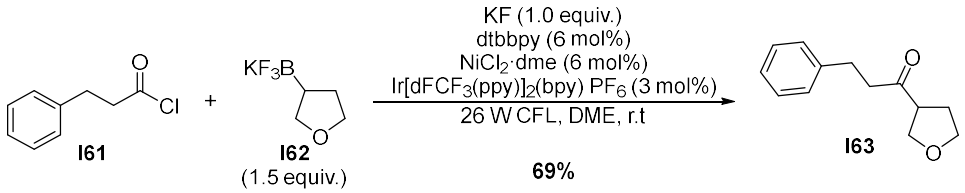
To continue the advances in organic chemistry, increased time, money, and effort are going into developing greener, more efficient syntheses. The ability to access desired compounds without prefunctionalisation is inherently more efficient, not just in terms of reactants used but the volume of solvents associated

with work-ups and even more so, column chromatography. Furthermore, methodologies that can incorporate multiple transformations in the same pot can provide part of the answer to growing sustainability demands.[53]

1.2.3 Recent Advances in the Synthesis of Substituted THFs

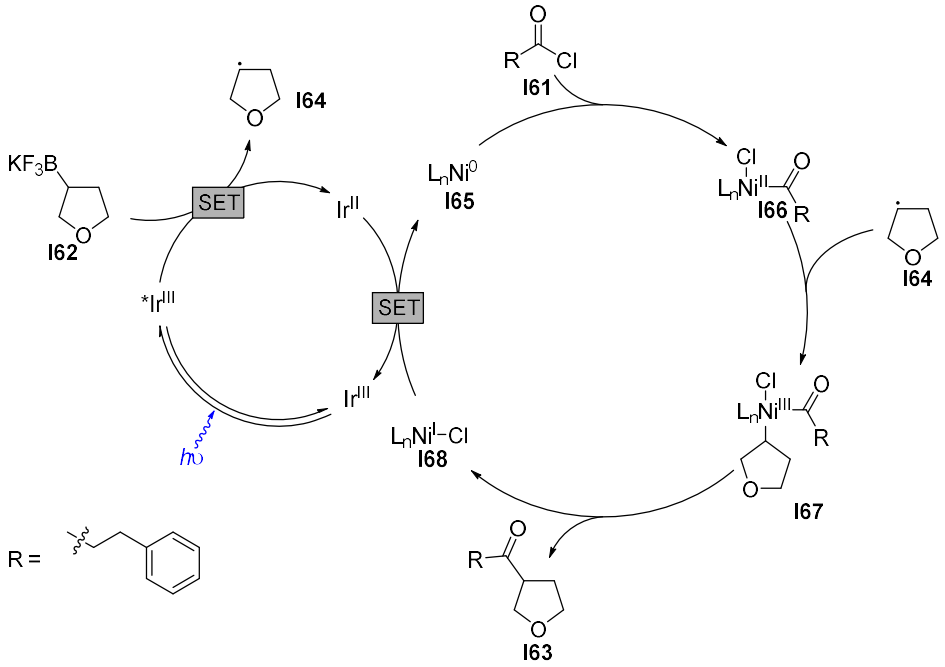
In recent years, radical processes have undergone somewhat of a renaissance with photoredox and electrochemistry techniques at the forefront of modern chemistry.[54–57] New methodologies based on these techniques have unsurprisingly been applied to THF synthesis.

Molander and co-workers employed a synergistic photoredox/nickel catalysis strategy to cross-couple acyl chlorides **I61** with potassium alkyltrifluoroborates **I62**. This work demonstrates that the synthesis of substituted THFs does not rely exclusively on cyclisation methodologies but can utilise THF itself or a substituted derivative such as alkyltrifluoroborate **I62**. The substrate **I62** was subjected to the reaction conditions and gave the 3-substituted THF **I63** in 69% yield (Scheme 17).[58]



Scheme 17 Molander's photocatalytic synthesis of substituted THF **I63**.[58]

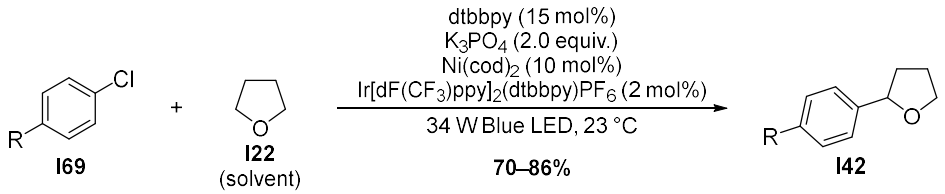
The proposed mechanism begins with the excitation of Ir(III) to *Ir(III) which facilitates the oxidation of alkyltrifluoroborate **I62** to give radical **I64**. Separately, the Ni(0) species **I65** undergoes oxidative addition with acyl chloride **I61** to give the Ni(II) species **I66** which combines with THF radical **I64**, resulting in Ni(III) intermediate **I67**. Reductive elimination provides 3-substituted THF **I63** along with Ni(I) complex **I68** which is subsequently oxidised by Ir(II) to regenerate the Ni(0) species **I65** and complete the cycle (Scheme 18).[58,59]



Scheme 18 Proposed catalytic cycle for Molander's substituted THF synthesis.[58,59]

Although, this method allows access to 3-substituted THFs, the starting materials are problematic. Acyl chlorides are highly reactive and generally require strictly anhydrous conditions while alkyltrifluoroborate **I62** is made over two steps from the corresponding boronic ester which itself is not readily available.

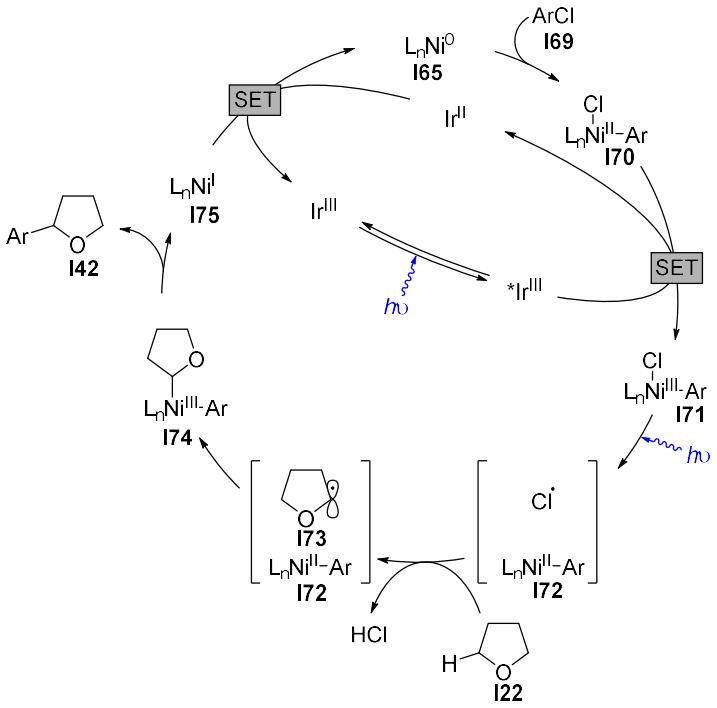
An example from Doyle and co-workers used more readily available reagents in a photocatalysed C(sp^3)–H cross coupling reaction (Scheme 19).[60]



Scheme 19 Doyle's photocatalytic synthesis of 2-aryl substituted THFs **I42**.[60]

Initially, the reaction of Ni(0) **I65** and an aryl chloride **I69** gave the oxidative addition product **I70** which was oxidised by an excited *Ir(III) photocatalyst to Ni(III) species **I71**. Light-induced homolytic cleavage of the Ni–Cl bond by blue

LEDs generated the chlorine radical which was then able to abstract a hydrogen atom from THF **I22** to give carbon centred radical **I73**. Combination of radical **I73** with the Ni(II) aryl species **I72** gave intermediate **I74** which then underwent a reductive elimination step to give the desired product **I42**. The resultant Ni(I) species **I75** was reduced to Ni(0) **I65** following a single electron transfer (SET) from the Ir(II) photocatalyst to complete the cycle (Scheme 20).[60]



Scheme 20 Proposed catalytic cycle for Doyle's C–H functionalisation.[60]

This work takes advantage of the weak C–H bond (92 kcal mol^{-1}) adjacent to oxygen to enable the transformation alongside a novel method for the generation of a chlorine radical.

As a result, this method exhibits excellent regioselectivity, but this positive element may also be considered a drawback. Accessing 3-substituted THFs is clearly unlikely with these conditions due to a higher bond dissociation energy in the associated position. The ability to access THFs with aromatic substitution in the 3/4-position remains an important challenge given the prevalence of the motif in natural products (Figure 8).

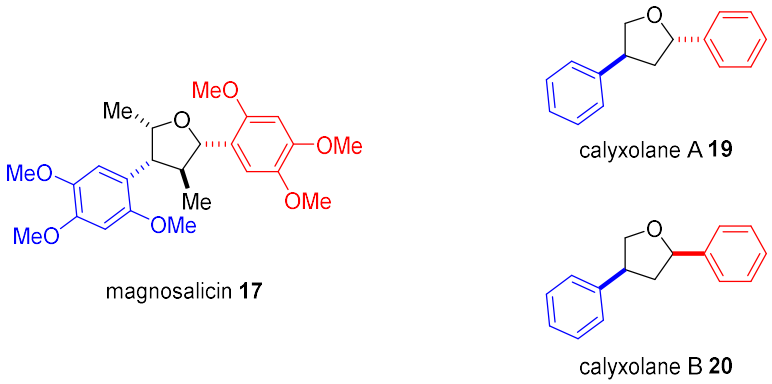
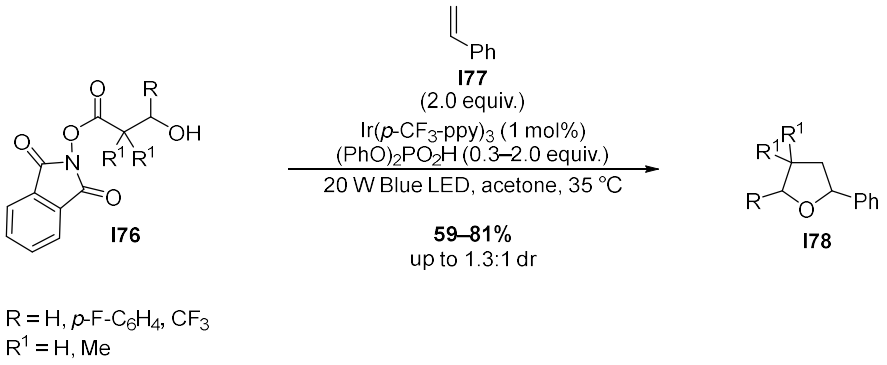


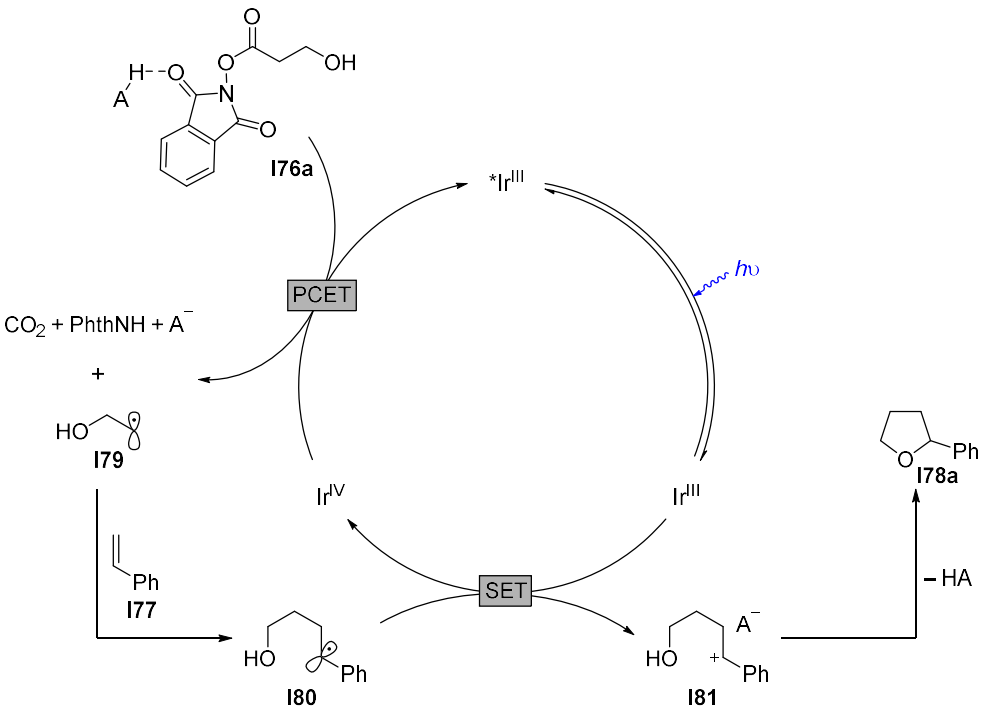
Figure 8 Natural products that feature 3/4-substituted THFs.

Doyle and co-workers, in collaboration with the Knowles group, recently disclosed another photocatalytic approach to access substituted THFs **I78** but from phthalimide esters **I76** and styrene **I77** (Scheme 21).[61]



Scheme 21 Knowles and Doyle's photocatalytic synthesis of substituted THFs **I79**.[61]

The proposed mechanism commences with the excitation of Ir(III) to *Ir(III) which is then able to reduce the phthalimide ester radical precursor **I76a** to give alkyl radical **I79** and fragmentation products phthalimide and CO_2. The alkyl radical **I79** then undergoes an anti-Markovnikov addition to styrene **I77** to give benzylic radical **I80**. A single electron transfer facilitated by Ir(IV) gives carbocation **I81** which cyclises to give substituted THF **I78a** (Scheme 22).[61]



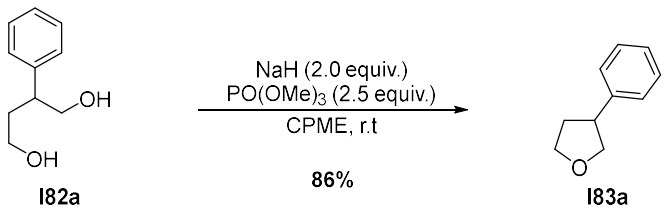
Scheme 22 Proposed catalytic cycle for Knowles and Doyle's substituted THF synthesis.[61]

This versatile chemistry, that relies upon the incorporation of a tethered nucleophile, also provides access to pyrrolidines, piperidines, lactones, morpholines and a dioxanone. This method could allow access to a large number of 2-aryl substituted THFs by varying the styrene used. Unfortunately, this approach is also unsuitable in the synthesis of simple 3-aryl substituted THFs. The relative stability of the benzylic radical **I80** leads to 2-aryl substituted products.

Unfortunately, as described previously, the preparation of 3-aryl THFs is often overlooked in favour of 2-aryl THFs. This is in part because of easier synthesis of substrates that precede 2-aryl THFs or the weaker C–H bond adjacent to the oxygen in THF **I22**. Therefore, the preparation of 3-aryl THFs presents a greater synthetic challenge for chemists.

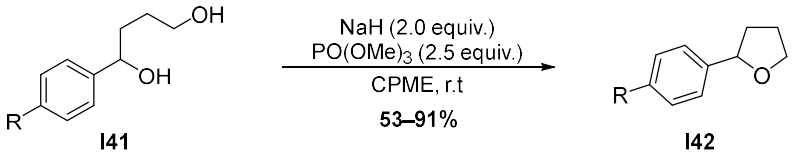
1.2.3.1 3-Aryl Substituted Tetrahydrofurans

Sawama and co-workers employed a diol **I82a** in their synthesis of 3-phenyltetrahydrofuran **I83a**, facilitated by catalyst, trimethyl phosphate (Scheme 23).[62]



Scheme 23 Sawama's synthesis of 3-phenyltetrahydrofuran **I83a**.[62]

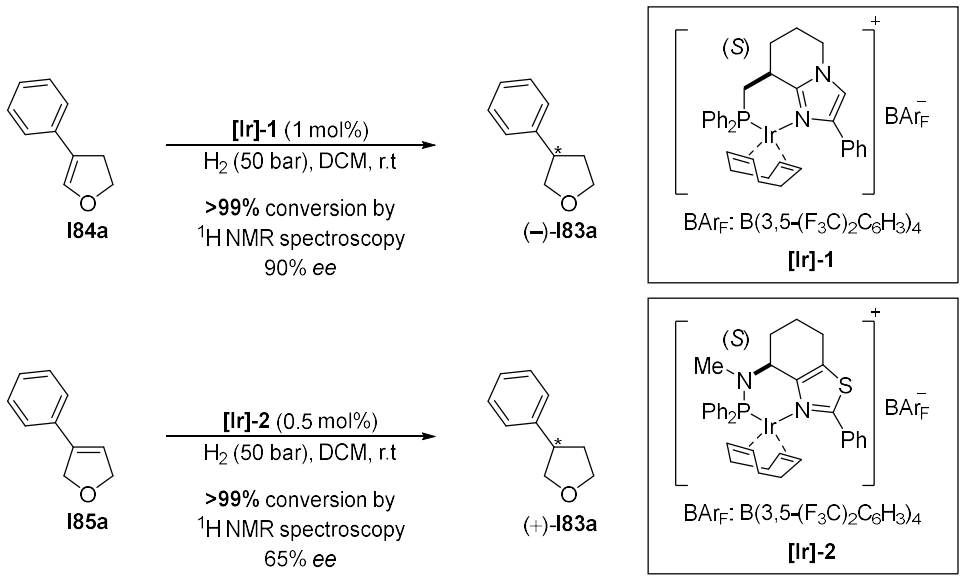
The authors describe the trimethyl phosphate activation of one alcohol and the deprotonation of the other to affect their successful intramolecular nucleophilic substitution reaction. Although high yielding, only one example of a 3-aryl substituted THF was given. Diol **I82** was prepared from the reduction of phenylsuccinic acid – alternative aryl substituted succinic acids are not commercially available, limiting this strategy. The majority of examples reported by the Sawama group were 2-aryl substituted THFs **I42** (Scheme 24),[62] most likely due to the relative ease of the respective substrate synthesis.



R = H, OMe, Me, Cl, F

Scheme 24 Sawama's synthesis of 2-aryl substituted tetrahydrofurans **I42**.[62]

Andersson and co-workers were able to access both 3-phenyltetrahydrofuran enantiomers (−)-**I42** and (+)-**I42** from two different DHFs (**I84** and **I85**) in their Ir-catalysed asymmetric hydrogenation (Scheme 25).[63]

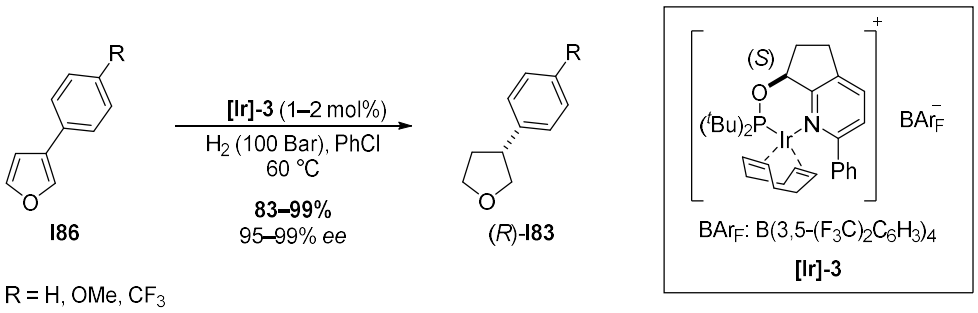


Scheme 25 Andersson's synthesis of 3-aryltetrahydrofuran (−)-**I83a** and (+)-**I83a**.[63]

Different conditions were used for the two DHFs **I84a** and **I85a** with access to both enantiomers achieved with excellent conversion observed for both reactions. Enantioselectivity was less consistent, and the authors could not determine the absolute configuration of the products. Unfortunately, the synthesis of dihydrofurans **I84a** and **I85a** required four and three steps respectively.[64,65]

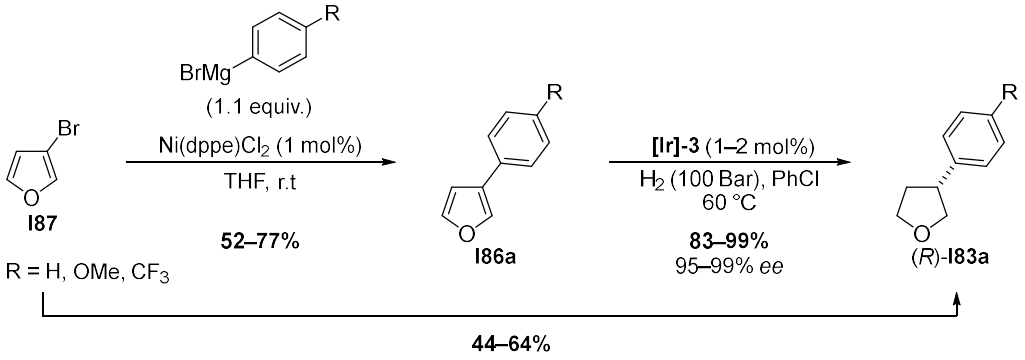
Routes to 3-aryl substituted THFs that do not require prefunctionalisation have been limited. Recently, new methods have been disclosed that have begun to fill this chemical space.

Pfaltz and co-workers described an advancement in the route to 3-aryl substituted THFs achieved through asymmetric Ir-catalysed hydrogenation. Substituted furans underwent Pfaltz's conditions with the 3-aryltetrahydrofuran products (*R*)-**I83a** generated in up to 99% yield, with excellent enantioselectivity. (Scheme 26).[66]



Scheme 26 Pfaltz's synthesis of 3-aryl substituted THFs (*R*)-**I83a**.[66]

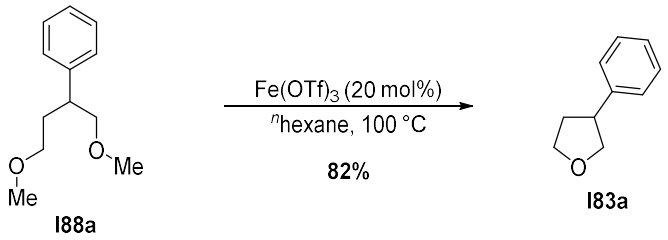
Unfortunately, the chiral ligand **[Ir]-3** is not commercial and is made over five steps in 30% overall yield.[67] The yields described are high, yet this THF-forming methodology should be considered as a two-step process from readily available starting materials as has been detailed in the supporting information associated with the article. The first step of this sequence is a Kumada coupling in which the yields are less impressive. When incorporating this initial step, the range in yield drops from 83–99% to 46–64% (Scheme 27), exemplifying the difficulty in attaining high yields from a multi-step methodology.



Scheme 27 Pfaltz's two-step route to substituted THFs.[66]

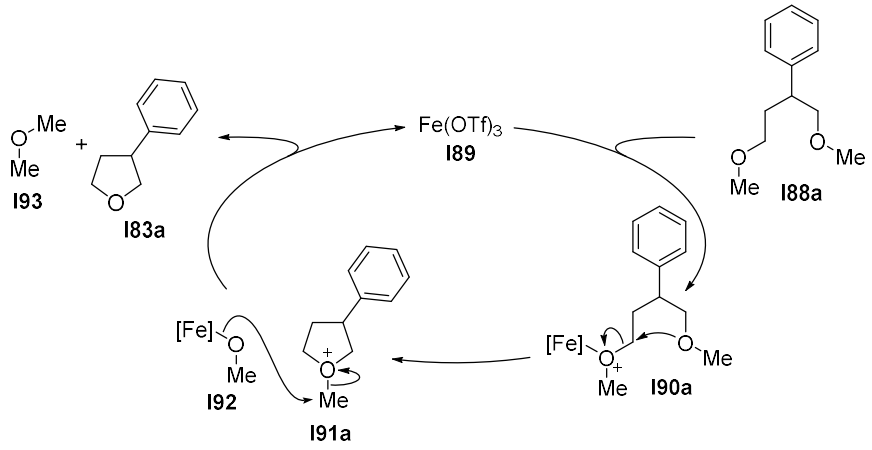
These criticisms aside, this work has some important advantages such as the modular aspect of the cross-coupling which could potentially lead to the generation of a vast library of substituted THFs. In addition, the methodology is able to return the products **I83** in excellent enantioselectivity and in comparison, to the methods described previously, with only one additional transformation needed prior to the key hydrogenation reaction, this THF synthesis represents an improvement in efficiency.

Morandi and co-workers described the first example of a catalytic ring-closing metathesis reaction using two C(sp^3)–O bonds, in their synthesis of 3-phenyl tetrahydrofuran **I83a** (Scheme 28).[68]



Scheme 28 Morandi's Synthesis of 3-phenyltetrahydrofuran **I83a**.[68]

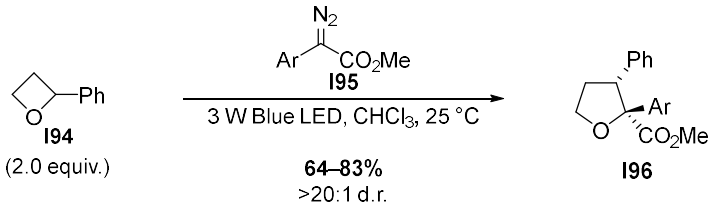
The authors propose that Lewis-acid **I89** activation of one ether gives complex **I90a** which undergoes an intramolecular, nucleophilic attack from the other, unactivated alcohol. The resultant oxonium ion **I91a** is then attacked by iron methoxide complex **I92** to give the THF product **I83a** and dimethyl ether **I93** whilst turning over the catalyst **I89** to complete the cycle (Scheme 29).[68]



Scheme 29 Proposed catalytic cycle for Morandi's synthesis of 3-phenyltetrahydrofuran **I83a**.[68]

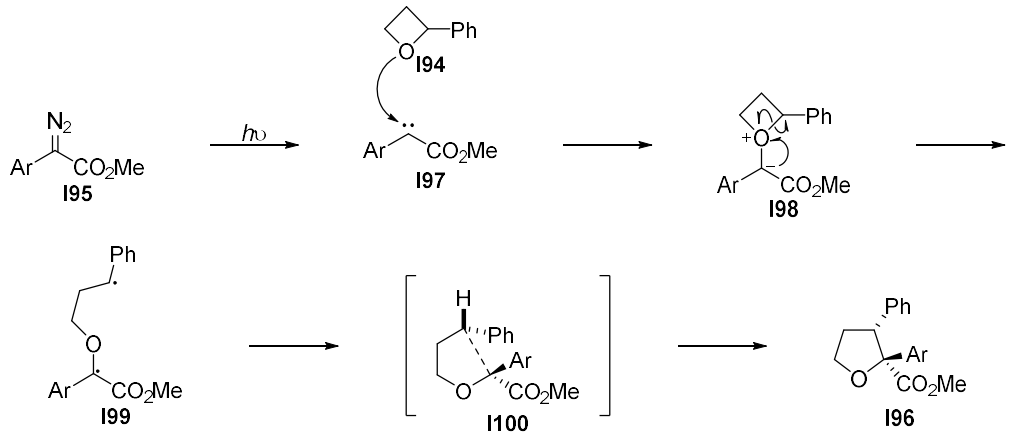
Although this novel work returns the product in very good yield, the substrate precursor is a diol which could potentially undergo a cyclisation reaction using some of the chemistry previously described in this thesis such as the work of the Samec,[44] Taylor[46] and Sawama groups.[62]

Another novel strategy to access 3-aryltetrahydrofurans was reported by Xu, Koenigs and co-workers.[69] Their method was based on an oxygen ylide mediated photochemical ring expansion of oxetanes **I94** (Scheme 30).



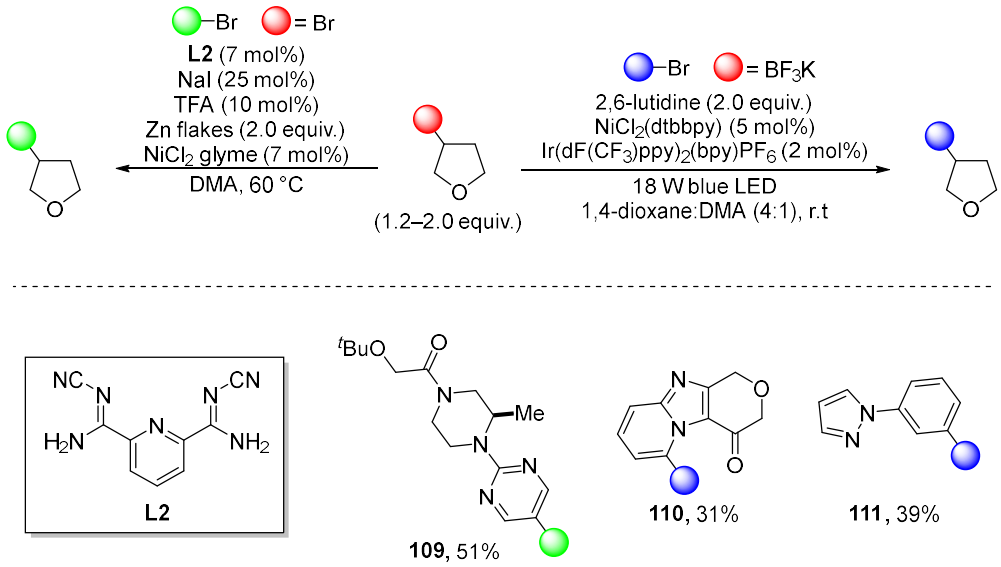
Scheme 30 Xu and Koenigs' synthesis of 3-phenyltetrahydrofurans.[69]

This mild, metal-free methodology delivers good yields with excellent diastereoselectivity. Mechanistically, carbene **I97** formation from diazoalkanes **I95** occurs upon irradiation with blue LEDs. Ylide **I98** is then formed from the oxetane **I94** and newly formed carbenes **I97**. DFT calculations then suggest a homolytic cleavage of the C–O bond to give diradical **I99** which undergoes an intramolecular radical-radical coupling to give the tetrahydrofuran products **I96**. The high diastereoselectivity is determined by a lower energy for the transition state **I100**, with the aromatic groups positioned on opposite faces (Scheme 31).[69]



Scheme 31 Proposed mechanism for Xu and Koenigs' 3-phenyltetrahydrofuran formation.[69]

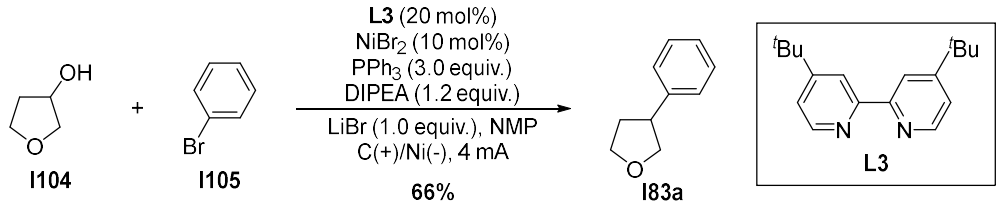
Dombrowski, Gesmundo *et al.* from AbbVie recently isolated three tetrahydrofuran products **I101**–**I103** featuring aromatic substitution in the 3-position (Scheme 32).[70] Their work was to determine the most appropriate methods for C(sp^2)–C(sp^3) cross coupling reactions for medicinal chemists.[70]



Scheme 32 Dombrowski and Gesmundo's synthesis of 3-substituted THFs.[70]

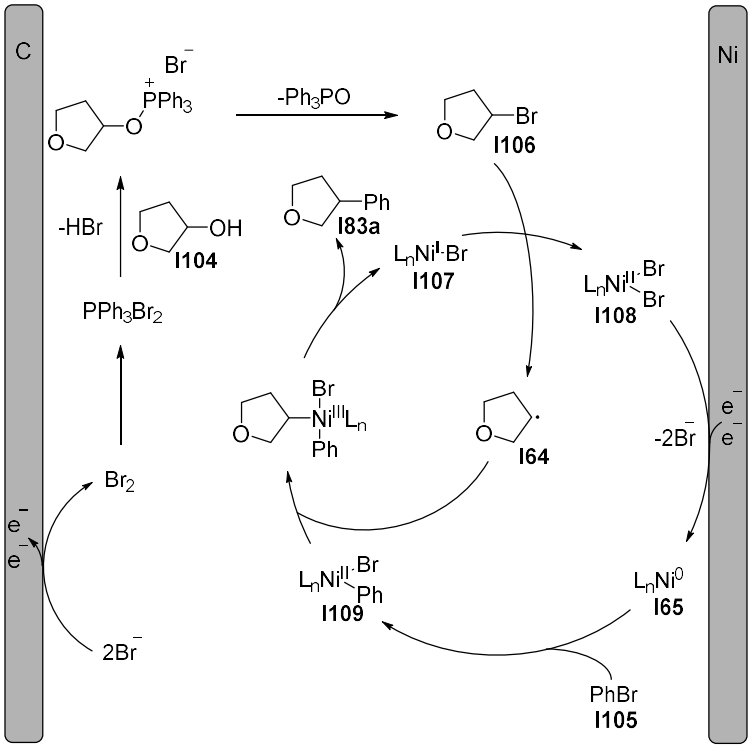
In addition to their isolated THF products **I101**–**I103**, the group also showed the ability for tetrahydrofurans derivatives to undergo other somewhat successful cross-coupling reactions. This included Suzuki/BF_3K coupling, nickel/photoredox decarboxylative coupling, and nickel/photoredox cross-electrophile coupling.[70] Unfortunately, all the reactions were low yielding (<50%), nevertheless, this work by AbbVie highlights the demand for installation of the tetrahydrofuran motif from the pharmaceutical industry.

More recently, access to 3-phenyltetrahydrofuran **I83a** has been achieved electrochemically by the Li group in their nickel-catalysed dehydroxylative cross-coupling of alcohols and aryl halides. The focus of this work was on alcohols generally so only one example of a substituted THF was described (Scheme 33).[71]



Scheme 33 Li's electrosynthesis of 3-phenyltetrahydrofuran **I83a**.[71]

Mechanistically, they suggested that the alcohol **I104** first undergoes an anodic Appel reaction to give an alkyl bromide **I106**. Bromide **I106** is then reduced *via* a SET reduction to give carbon centred radical **I64** while the Ni(I) species **I107** is oxidised to a Ni(II) complex **I108**. The Ni(II) complex **I108** is then reduced to Ni(0) **I65** *via* two SETs at the cathode as two bromide ions are released into solution. The bromide ions can then be oxidised at the anode to produce small quantities of molecular bromine able to promote the catalytic Appel reaction. The Ni(0) species **I65** is able to undergo an oxidative addition step with the aryl halide **I105** starting material to give Ni(II) complex **I109** which is able to combine with the alkyl radical **I64**. Reductive elimination then affords the desired cross-coupled product **I83a**, and the Ni(I) catalyst is turned over (Scheme 34).[71]



Scheme 34 Proposed electrochemical mechanism.[71]

This methodology is a significant development for electrochemistry because it allows for the coupling of two extremely common motifs; alcohols and aryl bromides. In addition, many natural products and pharmaceuticals feature alcohol motifs, meaning this technique could be used for late-stage functionalisation applications. One drawback of the method is the inability to control enantioselectivity, unsurprisingly seen during the Li group's mechanistic studies, when they subjected enantiopure tetrahydrofuran-3-ol to the reaction conditions and observed almost total erosion of enantiomeric excess to <2%.

Both the work of Dombrowski and Gesmundo,[70] and Li[71] require the use of expensive tetrahydrofuran derivatives, lowering the appeal for their chemistry (all prices obtained from SigmaAldrich website, accessed 23/01/23) (Figure 9).[72–74]

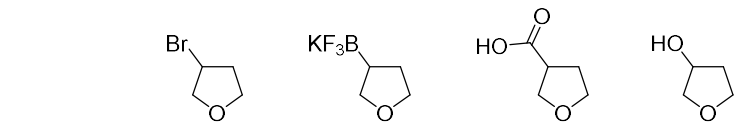
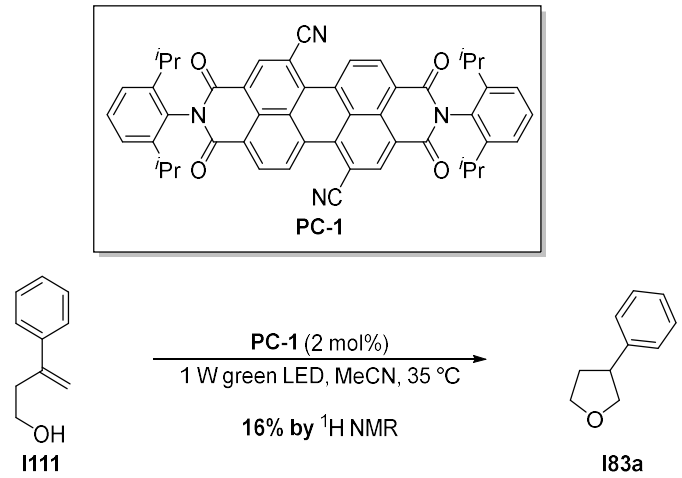


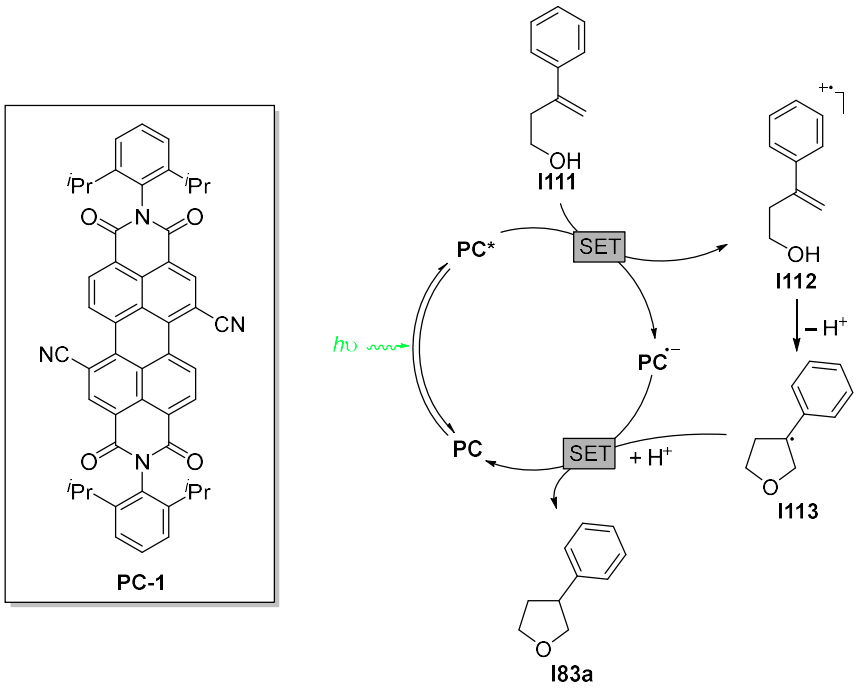
Figure 9 Cost per gram of tetrahydrofuran derivatives used for cross-coupling reactions.[72–74]

Most recently, Wagenknecht and co-workers demonstrated the ability of photocatalyst **PC-1** to facilitate the intramolecular cyclisation of unsaturated alcohol **I111** to give 3-phenyltetrahydrofuran **I83a** (Scheme 35).[75]



Scheme 35 Wagenknecht's synthesis of 3-phenyltetrahydrofuran **I83a**.[75]

The authors propose that following excitation of the photocatalyst **PC-1**, an electron is transferred from unsaturated alcohol **I111**. The resultant radical cation **I112** then undergoes an intramolecular nucleophilic attack to give cyclised radical **I113** along with loss of a proton. A second single electron transfer takes place to return the neutral photocatalyst **PC-1** and, along with addition of a proton, the product, 3-phenyltetrahydrofuran **I83a** (Scheme 36).[75]



Scheme 36 Proposed catalytic cycle for Wagenknecht's synthesis of 3-phenyltetrahydrofuran **I83a**.[75]

In contrast to most other methods described previously, the starting material **I111** for this transformation is prepared in just one step. This approach is also metal-free and proceeds under mild conditions. Unfortunately, the yield is very poor and the photocatalyst is prepared through a multistep, metal-catalysed synthetic route.[75]

These recent methods that produce 3-aryl tetrahydrofurans are an advancement in the field, but they share the same drawback as earlier syntheses of substituted THFs. The methods are reliant on the use of prefunctionalised substrates in which the substituents are installed prior to formation of the ring. For examples that do not require the need for prefunctionalised substrates, the use of expensive starting materials is often necessitated. As a result, there remains a demand for methods that use simple substrates or that enable late-stage functionalisation of the THF ring.

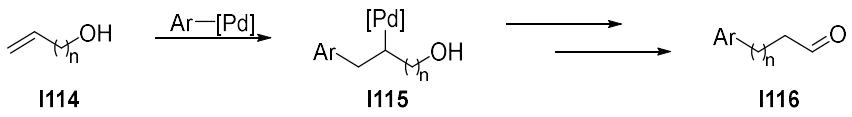
1.3 An Alternative Approach to Substituted THF Synthesis

As has been alluded to, performing multiple steps in one-pot as a part of a cascade reaction is an attractive strategy.[53] By carrying out multiple steps in one vessel, which would otherwise be carried out as individual reactions, significant increases in efficiency are possible. In particular, the amount of solvent needed and time taken for work-ups and purifications is reduced. Although appealing, these cascade opportunities are rare – often when exploring new chemical space, it can be challenging to perform a single transformation successfully.

An alternative method that embodies this approach in synthesising DHF derivatives was reported by Chalk and co-workers using the 'redox-relay Heck'. In this example, three steps were carried out: installation of a substituent, oxidisation of a remote alcohol and cyclisation all within the one pot.

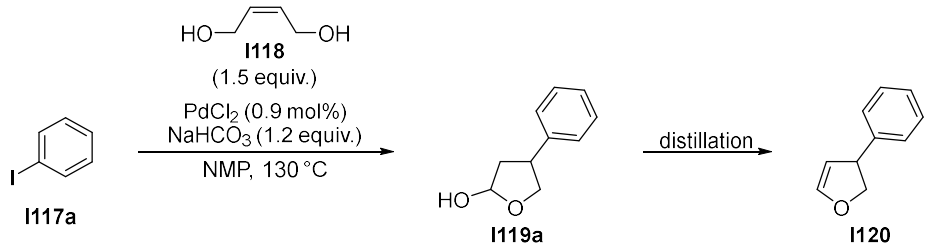
1.3.1 Synthesis of 4-Arylbutyrolactones *via* a Redox-Relay Heck Reaction

The redox-relay Heck reaction describes the Pd-catalysed cross-coupling of aryl and vinyl halides or pseudo halides with unsaturated alcohols. A general scheme shows that after the migratory insertion of an alkene **I114** into an arylpalladium bond that is associated with the standard Heck reaction, a distal hydroxy group then becomes oxidised to a carbonyl **I116** (Scheme 37). This reaction is named redox-relay as the alkene is reduced and the alcohol oxidised with the palladium relaying the redox information along the carbon backbone.



Scheme 37 General scheme of the redox-relay Heck reaction.

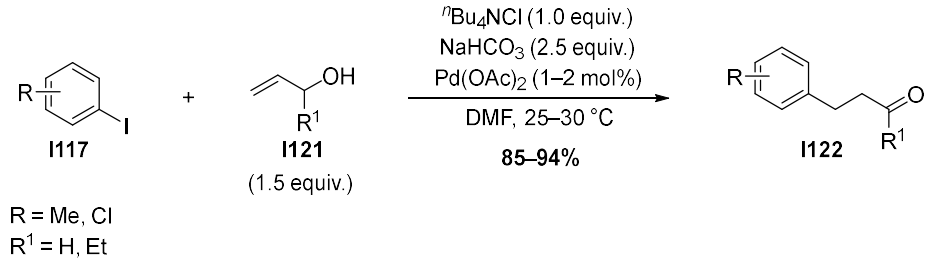
In the first report of the redox-relay Heck reaction, (simultaneously published alongside the work of Heck and co-workers)[76] the Chalk group subjected *cis*-2-butene-1,4-diol **I118** to their developed reaction conditions.[77] They found that after the first alcohol was oxidised to an aldehyde, the second spontaneously attacked the carbonyl to give the cyclised product, 4-phenyltetrahydrofuran-2-ol **I119a**. In attempting to isolate the product *via* distillation, they believed that the alcohol group was eliminated to give 3-phenyl-2,3-dihydrofuran **I120** (Scheme 38).[77]



Scheme 38 Chalk's synthesis of 3-phenyl-2,3-dihydrofuran **I120** *via* 4-phenyltetrahydrofuran-2-ol **I119a**.[77]

Chalk's initial report, which focused mainly on simple unsaturated alcohols, only exhibited one example of using a diol to access a cyclised product.

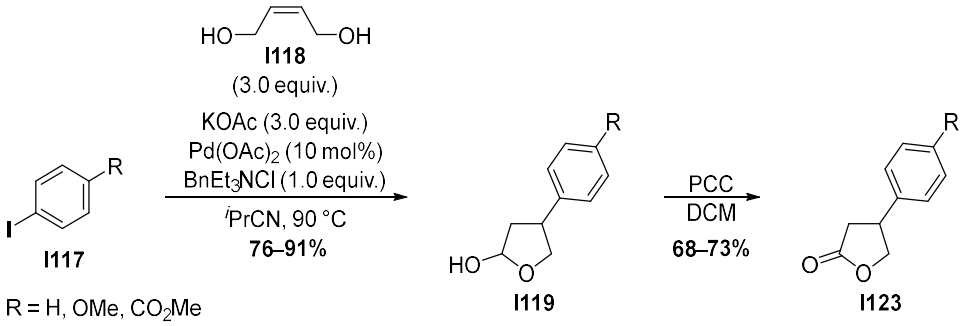
Further advancements in the general redox-relay Heck reaction were described by Jeffrey.[78] He demonstrated it was possible to generate *β*-substituted carbonyls **133** at or near room temperature by the addition of tetrabutylammonium chloride (Scheme 39).



Scheme 39 Jeffrey's use of tetrabutylammonium chloride.[78]

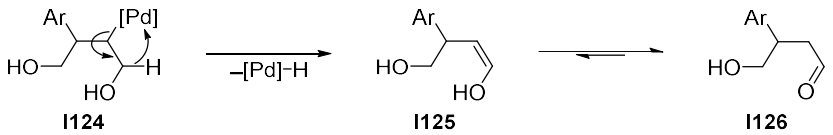
His conditions, commonly referred to as 'Jeffrey conditions', promoted the room temperature redox-relay Heck reaction,[78] while he later provided alternative conditions for the non-relay Heck reaction, also at room temperature.[79]

A redox-relay Heck strategy employing 'Jeffrey conditions' was used by Mandai and co-workers as they shed more light on the reaction between aryl iodides **I117** and *cis*-butene-1,4-diol **I118** (Scheme 40).[80]



Scheme 40 Mandai's synthesis of 4-substituted butyrolactones **136**.[80]

Mechanistically, they suggest that an enol **I125** is generated by the reaction which undergoes tautomerisation to the aldehyde **I126** (Scheme 41).[80]

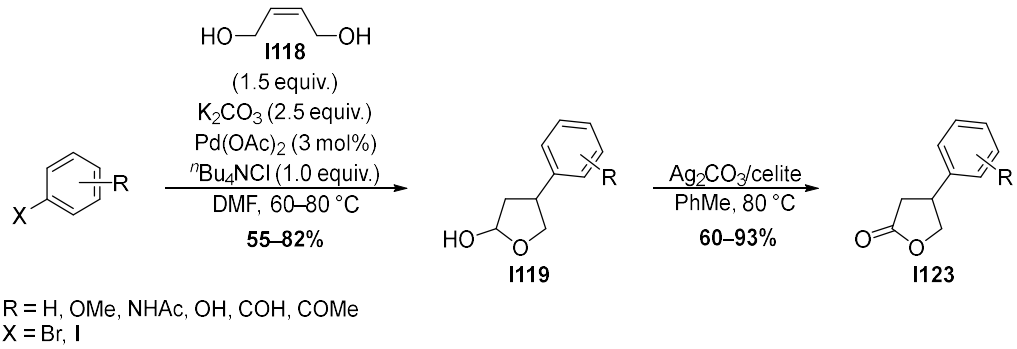


Scheme 41 Mandai's proposed mechanism for formation of hydroxyaldehyde **I126**.[80]

The hemiacetals **I119** they prepared were found to be unstable so oxidation with pyridinium chlorochromate (PCC) was used to give 4-butyrolactones **I123** as stable products.

Although this publication represented the first dedicated study into the synthesis of these cyclised redox-relay Heck products, the scope is extremely small, with only four aryl iodides tested. In addition, the conditions are somewhat wasteful with 10 mol% of palladium and three equivalents of base and diol required.

A more comprehensive study was published a year later by Cacchi and co-workers who mainly focused on using vinyl triflates to access 4-substituted butyrolactones, again with only a small number of aryl halides trialled (Scheme 42).[81]

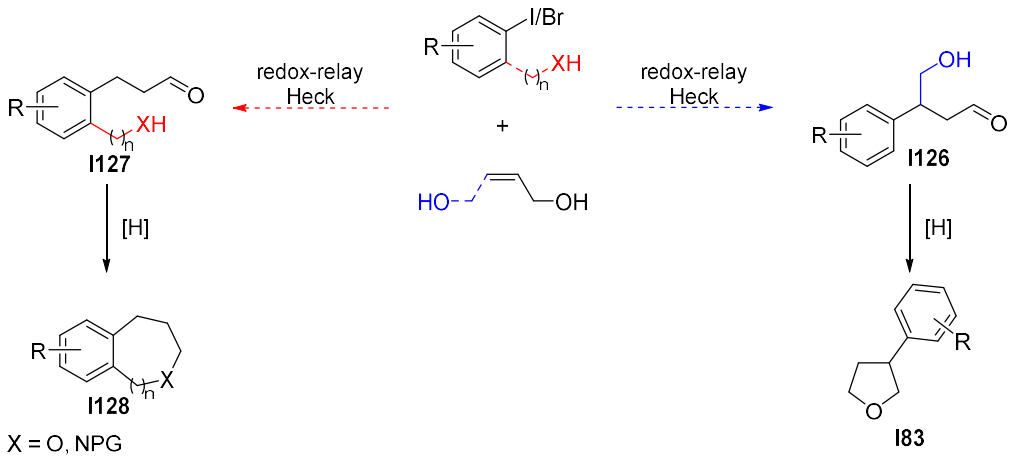


Scheme 42 Cacchi's synthesis of 4-substituted butyrolactones **I123**.[81]

Their conditions improved the reaction stoichiometry by reducing the equivalents of diol **I118**, base, and catalyst. Nevertheless, the predominant use of the less readily available vinyl triflates and the undesirable solvent DMF highlight the drawbacks of their method.

1.3.2 Preliminary Results in the Cuthbertson Group

The redox-relay Heck reaction has the potential to be an extremely valuable strategy for the efficient synthesis of a variety of heterocyclic compounds **I83** and **I128**, largely in part to the *in situ* generation of a carbonyl moiety that can undergo further transformation in the same pot to give new products (Scheme 43).

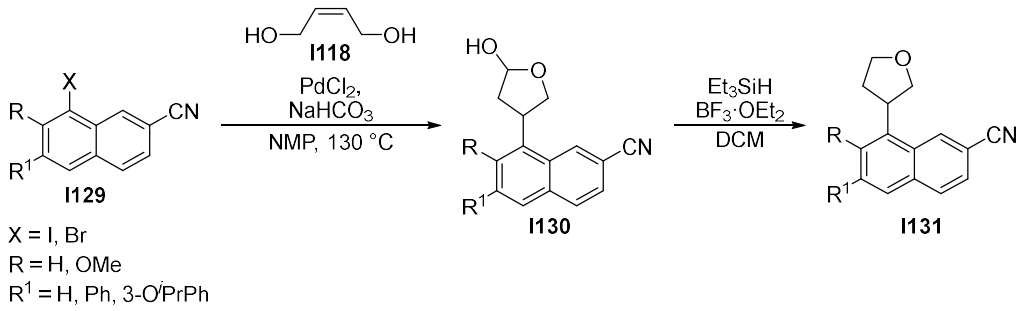


Scheme 43 Proposed synthesis of heterocycles **I83** and **I128** *via* a redox-relay Heck strategy.

The approach would allow for the construction of functionalised compounds from simple, readily available, and inexpensive reagents. The absence of prefunctionalised substrates or transformations that use stoichiometric chemical activators would allow for quick and efficient syntheses. At the same time this would reduce additional reagents, solvents, and wasteful intermediate purifications to realise more sustainable chemical methodologies.

As a starting point for the group in this area, we were interested in the use of inexpensive *cis*-2-butene-1,4-diol **I118** (£0.14 per g)[82] as a pre-cursor to cyclic hemiacetals which could then be reduced to access 3-aryl substituted THFs, in contrast to the oxidised butyrolactone products formed by the Mandai and Cacchi groups.[80,81]

The approach has previously been used by Wendt and co-workers in their search for potent urokinase inhibitors for cancer treatment. The group synthesised a selection of candidates with three containing the THF moiety **I131** (Scheme 44).[83]

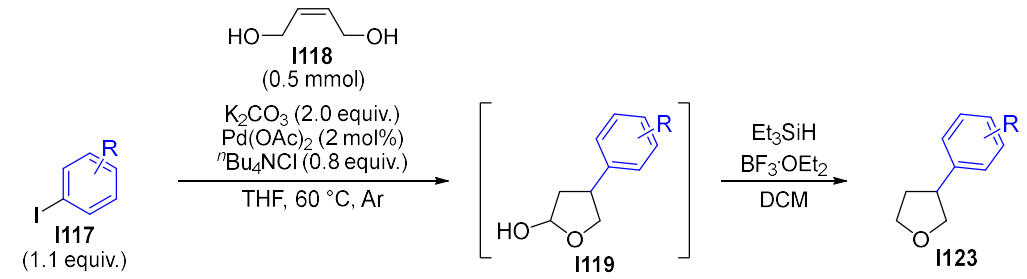


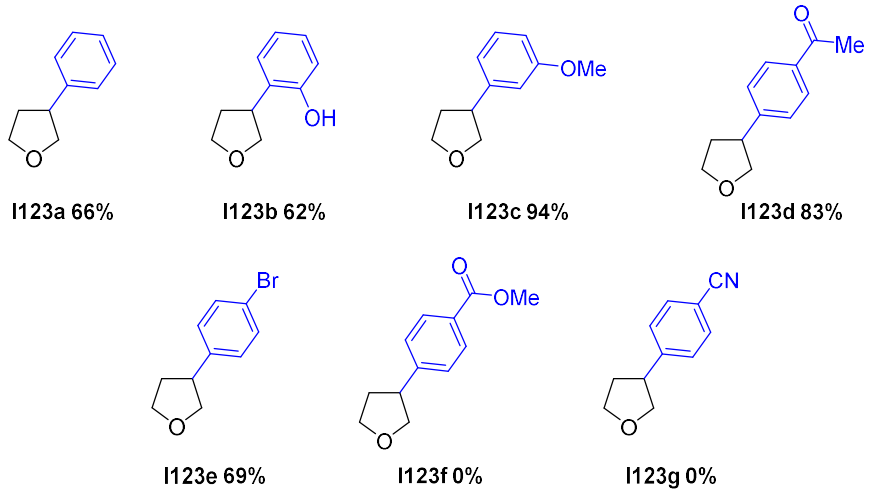
Scheme 44 Wendt's synthesis of 3-subtituted THF derivatives **I131**.[83]

Their procedure (which omitted reagent quantities and yield) used palladium(II) chloride as catalyst at a temperature of 130 °C in NMP. Although this work does act as a proof of concept for our proposed studies, the conditions used are harsh and only three examples are described. As such, there remains a need for a mild, efficient, and general synthesis of THFs substituted in the 3-position.

Early investigations within our group by Megan Mylrea into the redox-relay Heck reaction for the synthesis of aryl-substituted THFs demonstrated that a move away from the adverse solvents DMF or NMP was viable (Table 1).[84]

Table 1 Preliminary results for the synthesis of substituted THFs **I123**.[a,b]





[a]Reaction performed by Megan Mylrea.[84] [b]Isolated yields.

It was also found that several aryl iodides were able to take part in the reaction in fair to excellent yields **I123a–I123e**. Unfortunately, the study showed that a few electron-deficient aryl iodides would not participate in the reaction, returning only starting materials **I123f**, **I123g**. It should be noted, as a result of a miscalculation of the quantity of $^{n}Bu_4NCl$ required, preliminary studies inadvertently used 0.8 equivalents rather than 1.0 equivalents as intended. This could have led to a reduction in either nanoparticle stabilisation, efficient biphasic mixing or both.

Satisfied with the potential of the project based on the initial results, a full investigation into the reaction was proposed.

2 Results and Discussion

2.1 Aims and Objectives

With preliminary results in-hand, the project would begin by undertaking a thorough optimisation process in order to develop a broadly applicable redox-relay Heck reaction for the synthesis of 3-substituted THFs **5**.

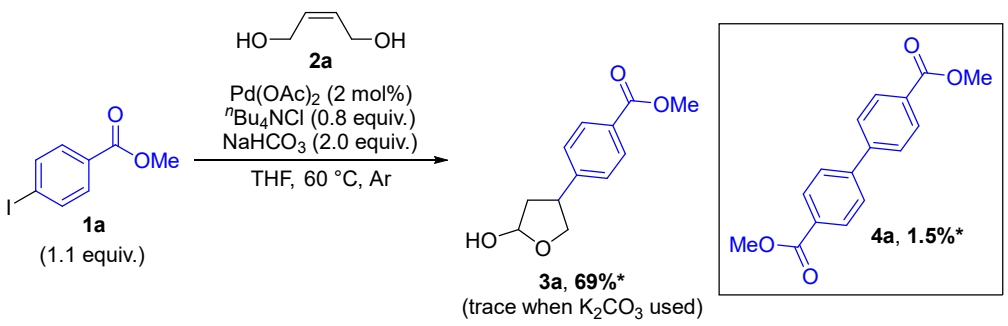
The predominant use of commercial reagents would be employed for the preparation of 3-aryl substituted THFs **5** which would act as an improvement in accessibility and efficiency compared to other methods previously described.

Next, the possibility of accessing 2,4-disubstituted THFs using our two-step sequence would be investigated. Relevant substrate synthesis would be required for this aspect of the project. Finally, further studies would then be undertaken to provide insights into the mechanism of the reaction.

2.2 Reaction Optimisation

Previous studies by Megan Mylrea had shown the use of $NaHCO_3$ as a base in place of K_2CO_3 facilitated the reaction of the previously unreactive, electron-deficient aryl iodide, methyl-4-iodobenzoate **1a**.[84]

Repeating the reaction using the conditions developed by Megan Mylrea gave hemiacetal **3a** in 69% yield (Scheme 45).[85]



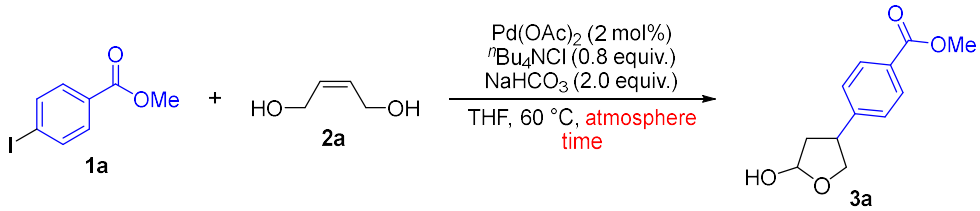
*yield determined by ^{1}H NMR spectroscopy using 1,3-benzodioxole as internal standard

Scheme 45 Preliminary results.

The remainder of the mass balance for the reaction was attributed to unreacted starting materials **1a** (~37%) and **2a** (~30%) and trace quantities of a homo-coupled biphenyl side-product **4a** (1.5%), presumably formed through a reductive homocoupling of the aryl iodide **1a**.[86]

The reaction stoichiometry with respects to the two coupling partners was first investigated using methyl-4-iodobenzoate **1a** as the substrate (Table 2).

Table 2 Optimisation of reaction stoichiometry.



Entry[a]	Time h	Alkene equivalents	Aryl iodide equivalents	Atmosphere	Yield %[b]
1	24	1.0	1.1	Ar	69
2	24	1.0	1.0	Ar	61
3	24	1.1	1.0	Ar	82
4	48	1.1	1.0	Ar	87
5	74	1.1	1.0	Ar	94
6	14	1.1	1.0	Ar	72
7	14	1.1	1.0	Air	71

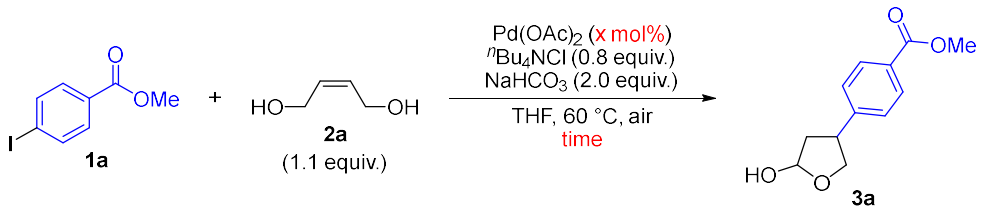
[a]Reaction performed on a 0.50 mmol scale. [b]Yield determined by ^{1}H NMR spectroscopy using 1,3-benzodioxole as an internal standard.

This experiment revealed that a reverse of stoichiometry was beneficial (Entry 3). Furthermore, the reaction was found to carry on producing product after 24 hours, albeit at extremely slow rate, with yield as determined by ^{1}H NMR spectroscopy reaching 94% after 74 hours (Entry 5).

Finally, upon replacing the argon atmosphere with air, no significant loss in yield was observed (Entries 6 and 7). The ability to perform the transformation in an aerobic environment is an important development with greater ease of set-up, accessibility, and cost.

Having optimised the reaction stoichiometry, the catalyst loading was the next variable to be investigated (Table 3).

Table 3 Optimisation of catalyst loading.



Entry[a]	Catalyst loading %	Time h	Yield %[b]
1a	2	1	38
1b	2	3	55
1c	2	5	62
1d	2	24	81
2a	3	1	48
2b	3	3	63
2c	3	5	69
2d	3	24	82
3a	4	1	49
3b	4	3	62
3c	4	5	66
3d	4	24	77

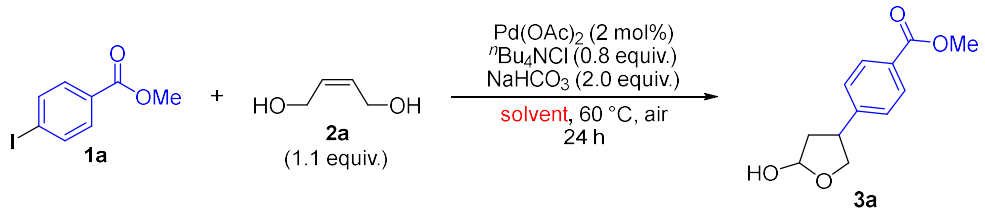
[a]Reaction performed on a 0.50 mmol scale. [b]Samples of the reaction mixture were analysed at the specified time points and the yield was determined by ^{1}H NMR spectroscopy using 1,3-benzodioxole which was added at the beginning of the reactions as an internal standard.

When analysing the effect of catalyst loading, the yield was determined at four time points. Despite the desire for a shorter reaction time, clearly, the reaction does require up to 24 hours to reach very good yield. However, useful yields of over 50% can be obtained within 3 hours.

An increased catalyst loading had a negligible effect on the reaction, with 2, 3 and 4% palladium loading returning yields within experimental error (Entries 1d–3d). When interpreting the ^{1}H NMR spectroscopic data, peaks thought to be associated with the homo-coupled biphenyl side-product **4a**[87] were observed in greater percentage yield when 4 mol% palladium was used than seen with lower catalyst loadings, presumably due to greater concentration of the oxidative addition product.[88] It seems that increasing the catalyst loading beyond 3% promotes an unproductive pathway that has a mildly detrimental effect on product yield. With a minimal difference in the product yield seen for the catalyst loading study (Entries 1d–3d), the optimisation proceeded with the lower loading of 2 mol%.

Although replacing DMF with THF was a positive step previously achieved in the project, due to the hazardous nature of the former solvent, it was hoped that a more sustainable solvent could be identified given THF itself registers as a 'red solvent' on GSK's solvent sustainability guide.[89] A solvent screen was therefore undertaken (Table 4).

Table 4 Optimisation of reaction solvent.



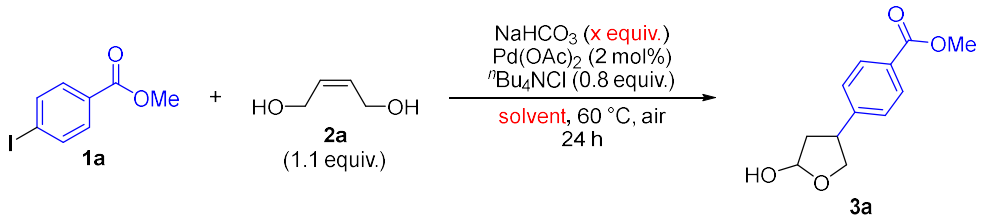
Entry[a]	Solvent	Yield %[b]
1	2-MeTHF	76
2	MeCN	84
3	THF	81
4	MeCN:H_2O (1:1)	53

[a]Reaction performed on a 0.50 mmol scale. [b]Yield determined by ^{1}H NMR spectroscopy using 1,3-benzodioxole as an internal standard.

A small screen was carried out, revealing MeCN to be the best solvent (Entry 2), although THF also returned a very good yield (Entry 3). Interestingly, when water and MeCN (1:1) were used as co-solvents the reaction still returned product **3a** albeit in significantly reduced yield (Entry 4).

The quantity of base in the reaction was next investigated using the two best performing solvents, THF and MeCN (Table 5).

Table 5 Optimisation of base equivalents and solvent.



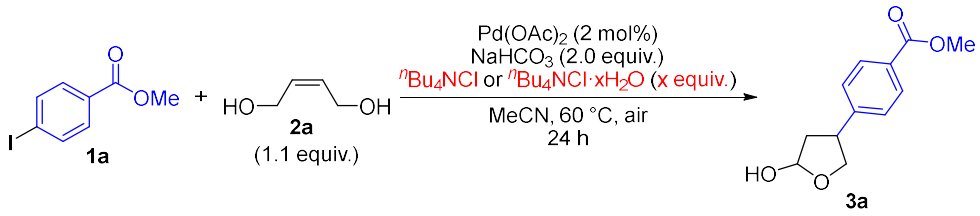
Entry[a]	Solvent	Base equivalents	Yield %[b]
1	THF	1.0	79
2	THF	1.5	78
3	THF	2.0	81
4	MeCN	1.0	82
5	MeCN	1.5	82
6	MeCN	2.0	84

[a]Reaction performed on a 0.50 mmol scale. [b]Yield determined by ^{1}H NMR spectroscopy using 1,3-benzodioxole as an internal standard.

No clear trend was observed when changing the quantity of base in the reaction when THF was solvent (Entries 1–3). When using MeCN, there was an increase in yield when raising the equivalents of $NaHCO_3$ (Entries 4–6), although this was within experimental error. Reactions for optimisation were performed once, to improve confidence in our results, triplicate reactions could have been performed. Nevertheless, when considering the combined results, the highest yields corresponded to a higher loading of base. Although the benefit in yield is slight, it was decided to proceed with the higher quantity of base.

The next variable to be investigated was the tetrabutylammonium chloride salt. ^{n}Bu$_4$NCl is a hygroscopic compound and during optimisation it became clear that water was being inadvertently introduced into the reaction. This led to questions over the effect of the level of water in the reaction. Given that when water is used as co-solvent the reaction is less effective (Table 4, entry 4), it was of interest to see the effect of lower levels of water on the reaction. The hydrated form, ^{n}Bu$_4$NCl·×H$_2$O was used alongside ^{n}Bu$_4$NCl in the next study that also varied the equivalents used (Table 6). It was at this point that the error in the miscalculation of ^{n}Bu$_4$NCl quantity was realised.

Table 6 Optimisation of quaternary ammonium salt.



Entry[a]	Quaternary ammonium salt	Equivalents	Yield %[b]
1	$^{n}Bu_4NCl\cdot\times H_2O$	0.5	58
2	$^{n}Bu_4NCl\cdot\times H_2O$	1.0	92
3	$^{n}Bu_4NCl\cdot\times H_2O$	1.5	93
4	$^{n}Bu_4NCl$	0.5	62
5	$^{n}Bu_4NCl$	0.8	84
6	$^{n}Bu_4NCl$	1.0	91
7	$^{n}Bu_4NCl$	1.5	94
8	none	N/A	58

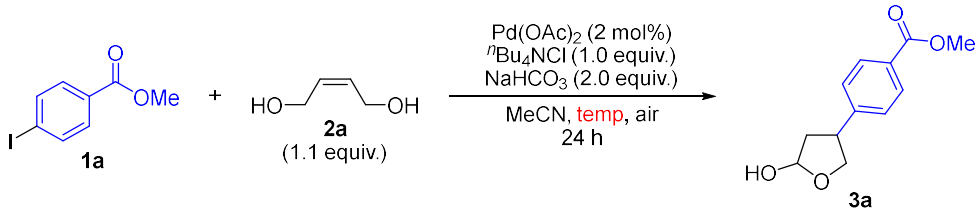
[a]Reaction performed on a 0.50 mmol scale. [b]Yield determined by ^{1}H NMR spectroscopy using 1,3-benzodioxole as an internal standard.

The experiments showed very similar results for either $^{n}Bu_4NCl$ or the hydrated $^{n}Bu_4NCl\cdot\times H_2O$ indicating small amounts of water make little difference to the reaction. However, the hydrated salt proved more difficult to weigh accurately and so with no obvious improvement in yield, it was excluded from further study. It is worth noting that strictly anhydrous conditions are not required in this methodology given that small amounts of water have little to no effect on yield.

With respect to quantity of quaternary ammonium salt, it was found that yield is significantly improved when increasing equivalents from 0.5 to 0.8 to 1.0 (Entries 4–6). The difference between 1.0 and 1.5 equivalents is relatively small and given the high molecular weight of $^{n}Bu_4NCl$ (277.92 $gmol^{-1}$) and our aim to provide a sustainable, atom efficient methodology, it was decided to limit the quantity to 1.0 equivalents (Entry 6).

Despite the yield improving, small quantities of both starting materials **1a** and **2a** were still observed. In an effort to obtain complete conversion, a study with an increased temperature was carried out (Table 7).

Table 7 Effect of temperature increase on conversion.



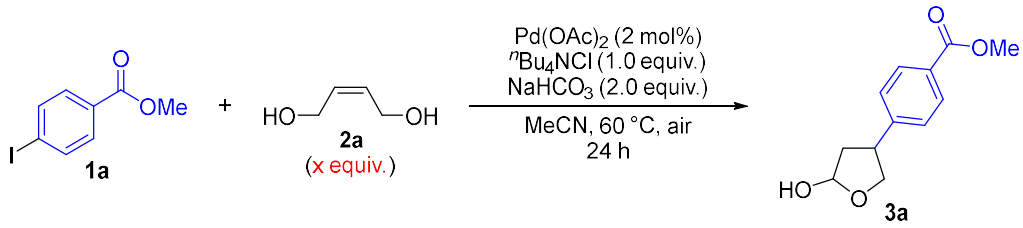
Entry[a]	Temperature °C	Yield %[b]	Side-product 4a yield %[b]
1	60	88	3
2	80	85	5

[a]Reaction performed on a 0.50 mmol scale. [b]Yield determined by ^{1}H NMR spectroscopy using 1,3-benzodioxole as an internal standard.

Complete consumption of aryl iodide **1a** was observed at the elevated temperature but unfortunately the product **3a** formation was reduced. Instead, the formation of homo-coupled side-product **4a** increased, with 5% yield of the biaryl **4a** observed by quantitative ^{1}H NMR spectroscopic analysis (Entry 2). Consequently, the reaction remained at the lower temperature (60 °C).

When analysing the results of the optimisation studies, it was noted that the greatest improvement in yield arose from the investigation of substrate stoichiometry. With other aspects optimised it was decided to re-visit how different equivalents of diol **2a** influence the reaction (Table 8).

Table 8 Optimisation of diol equivalents.



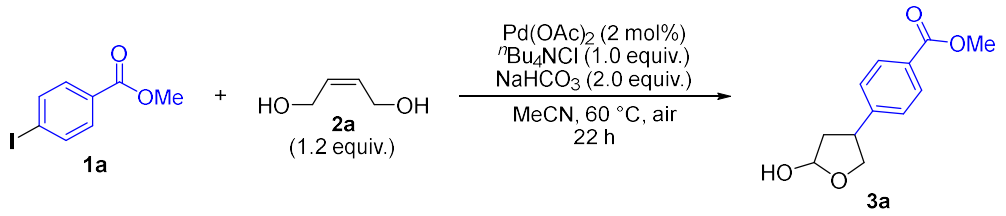
Entry[a]	Diol equivalents	Yield %[b]
1	1.1	89
2	1.2	95
3	1.3	96
4	1.4	97
5	1.5	96

[a]Reaction performed on a 0.50 mmol scale. [b]Yield determined by ^{1}H NMR spectroscopy using 1,3-benzodioxole as an internal standard.

Gratifyingly, increasing equivalents of *cis*-2-butene-1,4-diol **2a** did have a positive effect on the yield. All examples with ≥ 1.2 equivalents gave yields of 95% and above (Entries 2–5). With the improvement in yield minimal from 1.2 to 1.5 diol equivalents, 1.2 equivalents of diol **2a** were used in further studies.

Finally, the concentration of the reaction was investigated. The reaction was run at concentrations higher and lower than the 0.4 mol dm^{-3} used previously however, no improvement in yield was observed (Table 9).

Table 9 Optimisation of concentration.



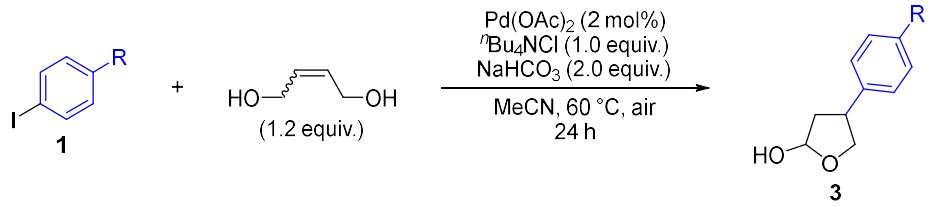
Entry[a]	Concentration mol dm^{-3}	Yield %[b]
1	0.2	86
2	0.4	94
3	0.6	91

[a]Reaction performed on a 0.50 mmol scale. [b]Yield determined by ^{1}H NMR spectroscopy using 1,3-benzodioxole as an internal standard.

The optimisation work was carried out on *cis*-2-butene-1,4-diol **2a** because it is a readily available and inexpensive reagent. The isomer *trans*-2-butene-1,4-diol is less readily available and as such is a more expensive diol. Nevertheless, it was of interest to see how the *E*-isomer may perform in the reaction compared to *cis*-diol **2a**. It was found that the butene-1,4-diol bearing *E*-configuration performed significantly worse than the *Z*-isomer when electronically diverse aryl iodides were trialled (Table 10). This could be related to a less incumbered

approach from the arylpalladium species to the *Z*-alkene prior to carbometallation compared to the *E*-alkene.

Table 10 *trans vs. cis* Alkenes in the redox-relay Heck reaction.



Entry[a]	R	Alkene geometry	Yield[b]
1	OMe	*cis*	quant.
2	OMe	*trans*	85
3	CO_2Me	*cis*	96
4	CO_2Me	*trans*	61

[a]Reaction performed on a 1.00 mmol scale. [b]Yield determined by ^{1}H NMR spectroscopy using 1,3-benzodioxole as an internal standard.

Having identified optimised conditions, with respect to reagents and temperature, we next wanted to re-visit the time profile of the reaction. Samples were taken hourly over the course of 20 hours, providing an insight into product **3a** and homo-coupled side-product **4a** formation and aryl iodide **1a** consumption over time (Figure 10).

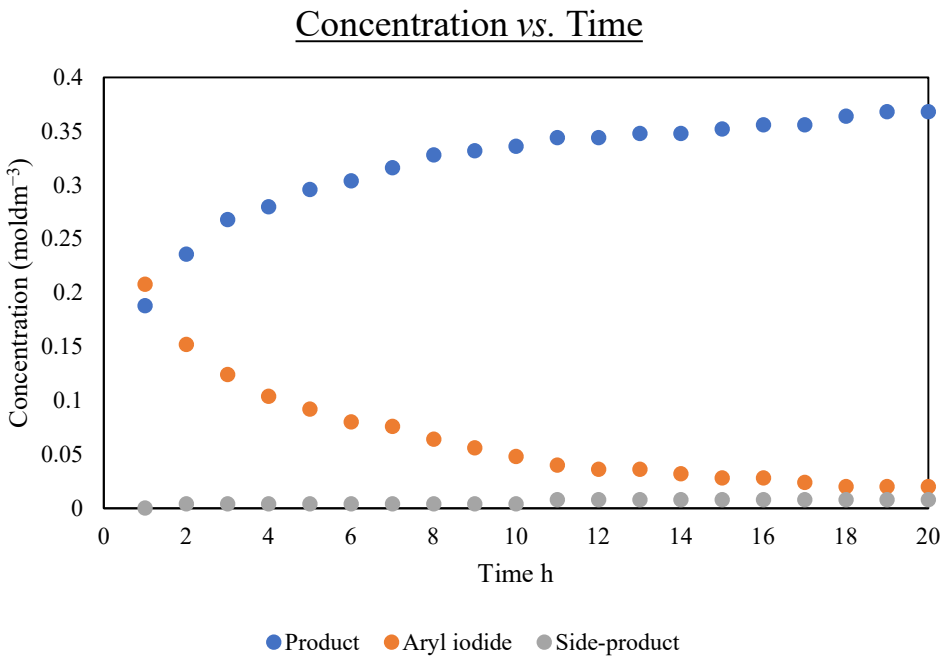


Figure 10 Reaction profile for the optimised redox-relay Heck reaction.

This study confirmed that the reaction proceeds quickly before slowing over time.

A first order reaction with respect to methyl-4-iodobenzoate **1a** was supported by a second plot displaying the natural log of the concentration of aryl iodide **1a** against time, showing a near straight line ($R^2 = 0.9754$) (Figure 11).

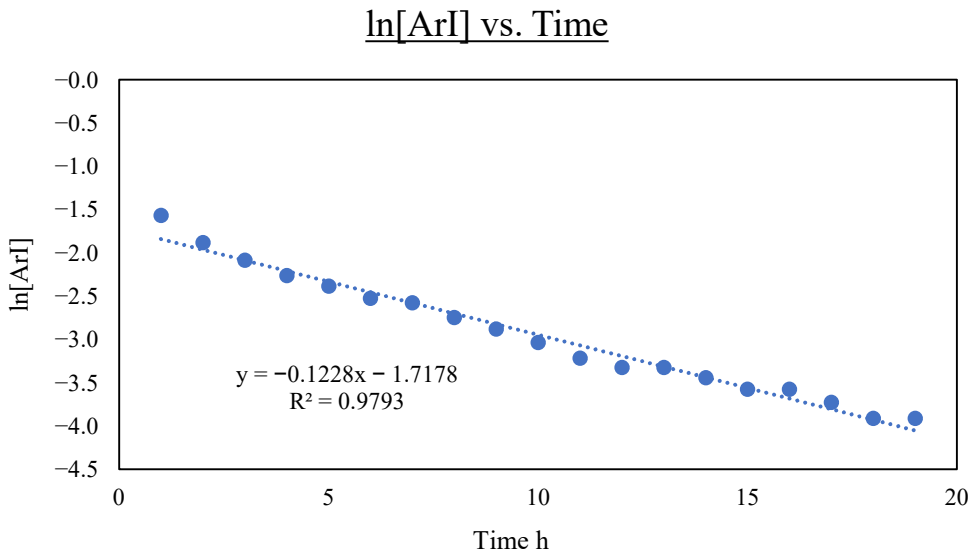


Figure 11 Natural log of the concentration of methyl-4-iodobenzoate **1a** over time.

The first order of reaction with respect to the aryl iodide was reinforced when the inverse concentration was plotted against time. A straight line was not observed, to suggest the reaction is not second order with respect to the aryl iodide **1a** (Figure 12).

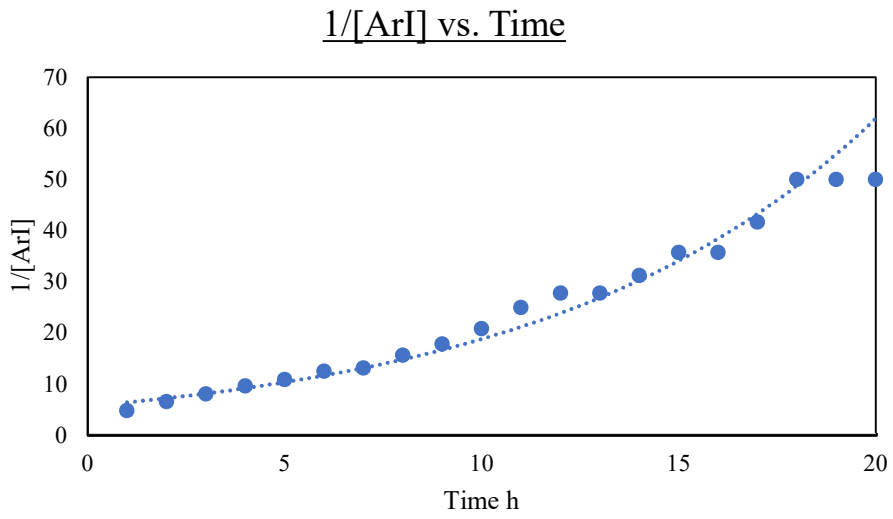


Figure 12 Inverse of the concentration of methyl-4-iodobenzoate **1a** over time.

Previous studies showed that the reaction will continue to form product over the course of multiple days (Table 2). With the aim of producing a general set of

conditions for the synthesis of 3-aryl substituted THFs **5**, it was decided that 24 hours would be a reasonable amount of time for the reaction whilst returning high yields.

2.2.1 Observation from Optimisation Studies

During optimisation, the visible formation of palladium black was consistently observed after 2–4 hours of the reactions. This was not entirely unexpected as the formation of this unreactive substance has been associated with other 'ligandless' palladium catalysed reactions.[90–93] Palladium black is formed through the conglomeration of palladium nanoparticles, which have also been linked to 'ligandless' palladium chemistry including some work related to the redox-relay Heck reaction.[93–99]

The presence of insoluble palladium black provides an opportunity to recover the metal through centrifugation which would be of significance to industrial chemists. Reports have shown up to >99% of the palladium metal precipitates,[90] the metal recovered has then later been shown able to reactivate after treatment with bromine or iodine.[97]

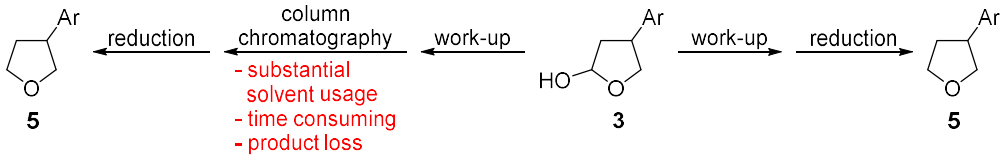
2.2.2 Reduction and Process Development

Having identified optimised conditions for the synthesis of hemiacetals **3**, efforts focused on how to develop an effective reduction process. A high-yielding reduction step is essential for the overall efficiency of this two-step synthesis.

In the preliminary studies carried out by Megan Mylrea, the hemiacetals were purified before undergoing a $BF_3 \cdot OEt_2/Et_3SiH$ reduction to give the substituted THF products **5**.

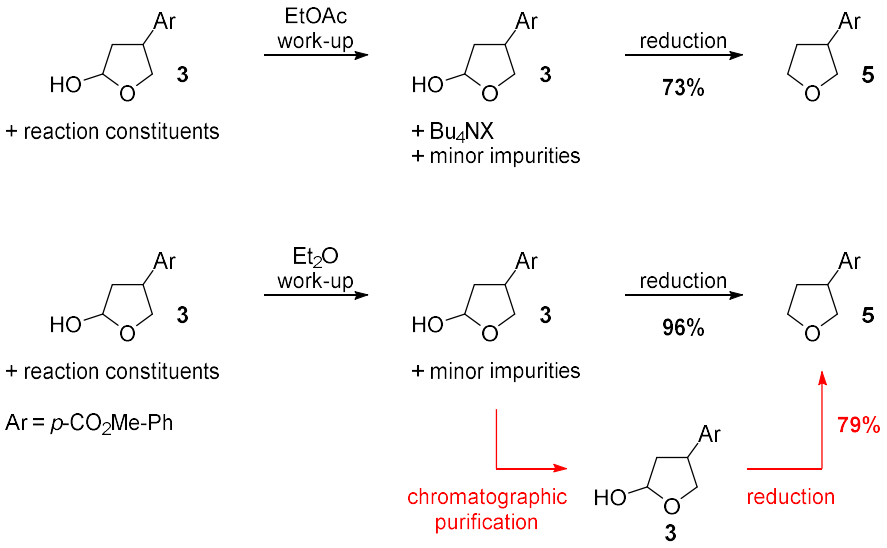
Mandai had reported that the hemiacetals they generated were unstable upon standing which led to his group immediately oxidising the lactols **3** to butyrolactones.[80] We initially found that the hemiacetals **3** were stable in our

hands. Nevertheless, if it was possible to immediately reduce the lactols **3**, a column chromatographic purification step could be circumvented. If the crude lactols **3** could be directly reduced without purification, then we would immediately increase the speed, sustainability, and efficiency of the sequence. In addition, if any hemiacetals **3** were in fact unstable on standing, then product degradation would be minimised (Scheme 46).



Scheme 46 Column chromatographic *vs*. telescoped route to substituted THFs **5**.

The choice of solvent used for working up the redox-relay Heck reactions proved crucial for the success of the telescoped process. When using EtOAc during work-up, the quaternary ammonium salt remained in the organic phase and was therefore present during the reduction step. This was detrimental to the reduction of the lactol and led to a reduced yield (73%). If instead Et_2O was used as work-up solvent, the quaternary ammonium salt transferred into the aqueous layer and was therefore washed from the crude material, allowing for an efficient reduction step (Scheme 47). In order to ensure the column-free process could give comparable yields to a standard chromatographic approach, the two methods were trialled side-by-side before undergoing the reduction and isolation. Pleasingly, the telescoped approach gave superior yield *vs*. the purified lactol route (red arrows, Scheme 47).



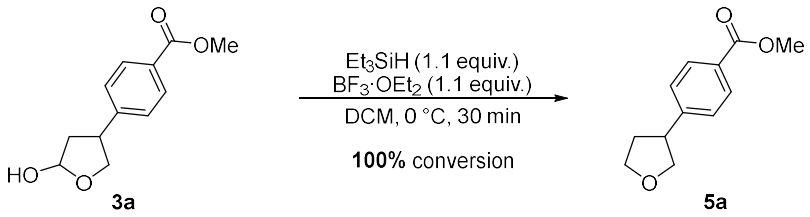
Scheme 47 The effect of work-up solvents and purification on the reduction of lactol **3**.

Looking to further improve the efficiency of the process, an alternative work-up was designed. It was hoped that by passing the crude material through a small pad of silica, before reduction, could further reduce the amount of solvent and time needed. Unfortunately, consistent results were difficult to achieve through this method. Lactols are somewhat polar in nature resulting in the requirement of EtOAc or a similar solvent being used to elute the product through the silica. This led to small quantities of quaternary ammonium salt also eluting, which had been shown to be detrimental to the following reduction reaction. Following the investigation into work-up procedures, we were satisfied by the improvements made that incorporated a Et_2O work-up.

A consequence of this approach was the unknown quantity of product in the crude mass. Given the generally high yields seen in previous examples, it was decided to assume quantitative yield of the hemiacetals **3** prior to the reduction step. This decision would lead in some cases to a greater excess of reducing agent employed than necessary, but it was concluded to be the best approach in our efforts to provide a straightforward and general methodology.

The reduction conditions used are well known for forming THFs from lactols,[100–102] and in our hands the reduction also worked effectively, returning product in up to 94% yield as detailed previously. In initial attempts, the reaction was run for 24 hours; however, this reaction time could be shortened consistent

with previous literature reports.[100–102] When monitoring the reaction over time, it was found that complete consumption of hemiacetal **3** was achieved after 30 minutes, significantly shortening the two-step process (Scheme 48).



Scheme 48 Optimised conditions for the reduction of hemiacetal **3a** to substituted THF **5a**.

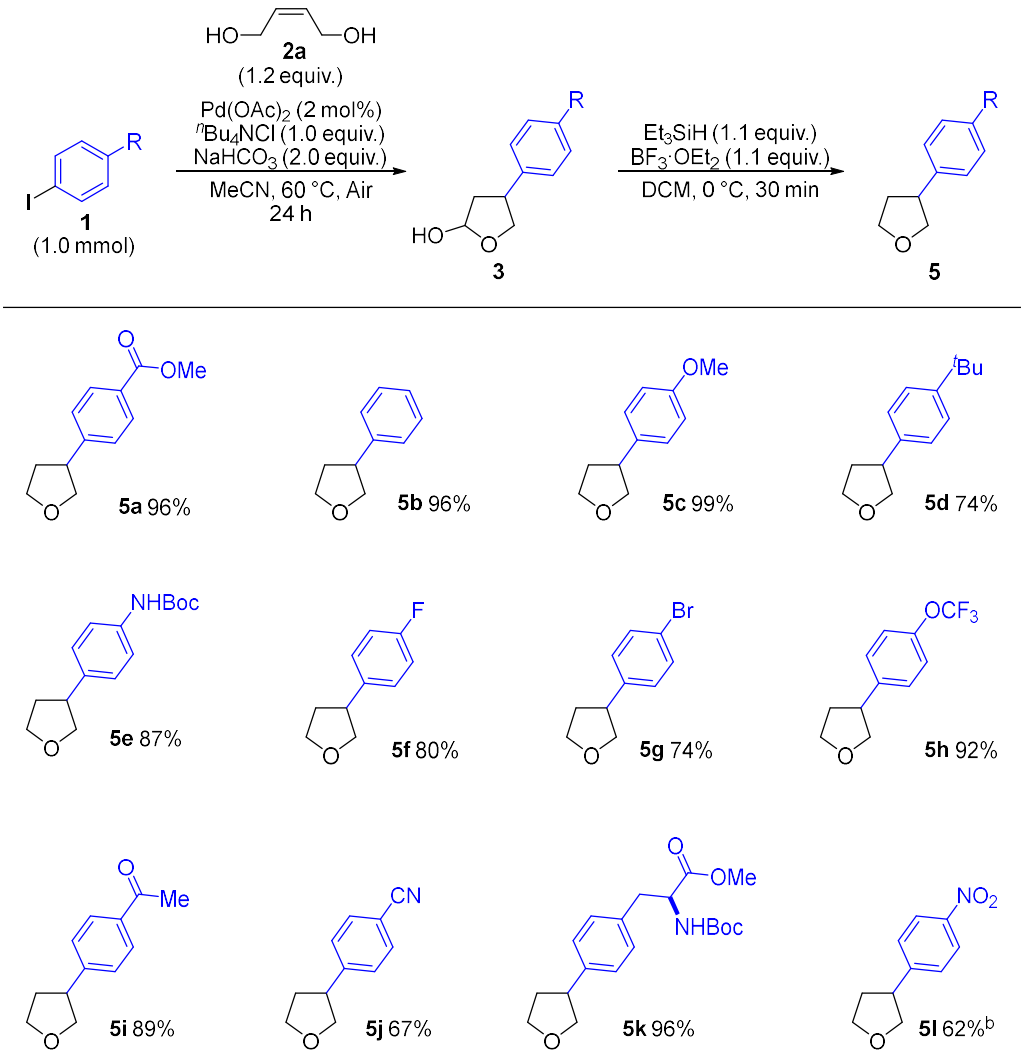
With the optimised conditions for the two-step process in hand, focus turned to exploring the scope of the reaction. In the first instance investigations focused on the aryl iodide coupling partner **3**.

2.3 Aryl Iodide Scope

2.3.1 *para*-Substituted Aryl Iodide Scope

A range of *para*-substituted aryl iodides **1a**–**1l** were first subjected to the optimised, two-step redox-relay Heck/reduction protocol (Table 11).

Table 11 *para*-Substituted aryl iodide scope.[a]



[a]Isolated yield after purification by column chromatography. [b]Hemiacetal required purification prior to reduction.

Pleasingly, yields were generally good to excellent for reactions using *para*-substituted aryl iodides **1a**–**1l**. The simple 3-phenyltetrahydrofuran **5b** was isolated in an excellent yield and a near quantitative yield of the anisole derivative product **5c** was obtained. The *t*butyl substituted example also proved successful returning the desired product **5d** in 74% yield.

A variety of functionality was tolerated in the two-step process including: an *N*-Boc protected aniline (**5e**), halides (**5f–5h**), carbonyls (**5a** and **5i**) and a nitrile (**5j**). Noteworthy was the high selectivity for the iodide in the presence of a bromide (**5g**), the lack of reaction at the bromide could allow for further transformations *via* the plethora of palladium-mediated couplings.[103] Also

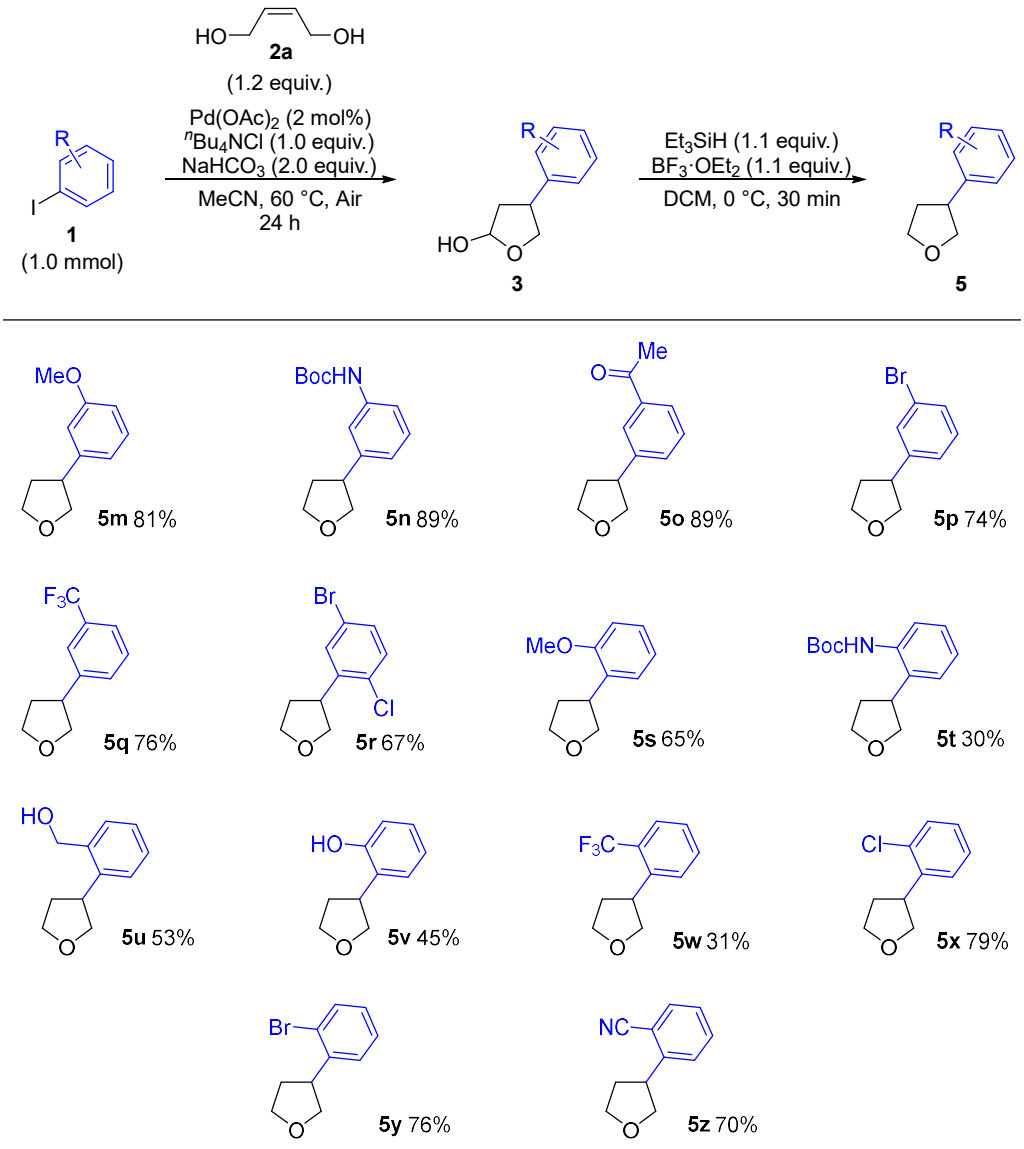
obtained was a novel amino acid derivative **5k** returned in excellent yield (Table 11).

All reactions attempted were successful although there was difficulty separating side-products from the nitro-containing example **5l** leading to an additional purification *via* column chromatography prior to the reduction step (Entry 12). Reduced yields were observed for this example and others featuring strongly electron-withdrawing substituents such as the nitrile group **5j**. Perhaps the electronically deficient arylpalladium species participates in a slower migratory insertion event than the more nucleophilic, electron-rich examples such as **5c**, as observed by the Sigman group.[104]

2.3.2 *meta*- and *ortho*-Substituted Aryl Iodide Scope

Subsequent scope investigations focused on the substrates with substitution at the *meta*- and *ortho*-positions (Table 12).

Table 12 *meta*- and *ortho*-Substituted aryl iodide **1** scope.[a]



[a]Isolated yield after purification by column chromatography.

Gratifyingly, *meta*-substituted aryl iodides **1m**–**1f** also performed well. An anisole derivative was returned in very good yield (**5m**). A protected aniline **5n**

and an acetophenone **5o** example were both delivered in near excellent yields. Unsurprisingly, given mesomeric effects are generally smaller from the meta-position, the electronic nature of aryl iodides seemed to have less of an effect for these examples. Nevertheless, the poorest yields remained associated with electron-deficient examples (**5p** (σ_m = +0.39), **5q** (σ_m = +0.43) and **5r**).[105]

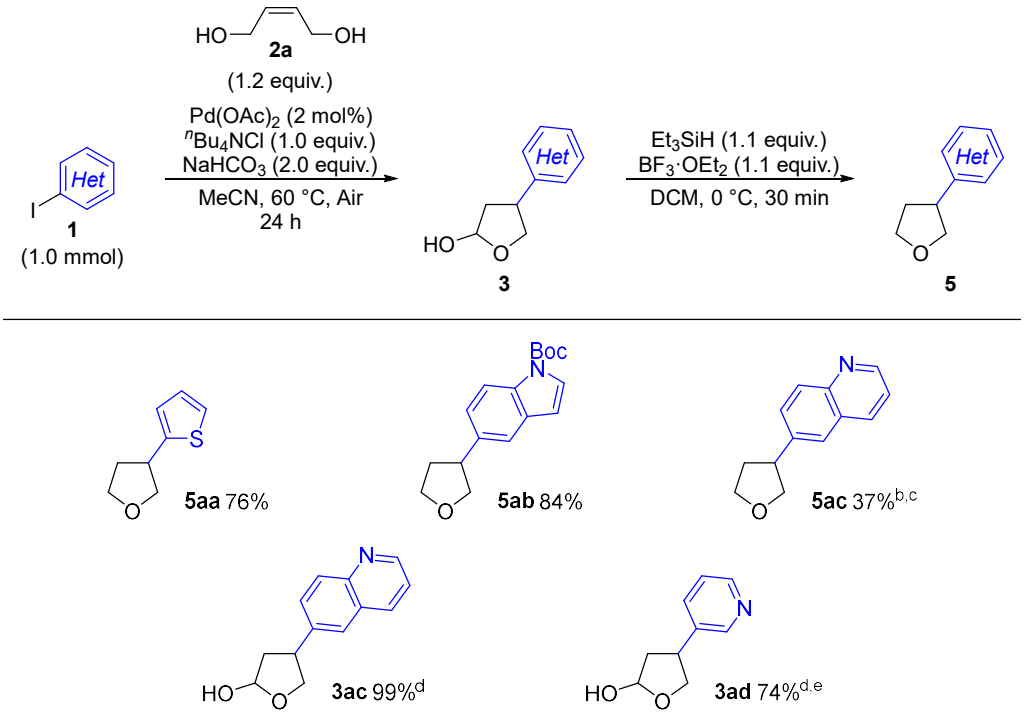
The yields observed for *ortho*-substituted aryl iodides **1f**–**1z** were much more varied. The anisole example **5s** was obtained in good 65% yield, although this represented a significant decrease from the *para* **5c** and *meta* **5m** equivalent substrates which gave 99% and 81% yield respectively. The same pattern was observed from the *N*-Boc protected aniline example **5t** which was formed in 30% yield. Pleasingly, an alcohol and phenol were tolerated in the reaction without the need of protecting groups (**5u** and **5v**). A further example of a trifluoromethyl-containing compound **5w** was returned albeit in a disappointing 30% yield. Gratifyingly, other electron deficient aryl iodides such as those with halide and nitrile substituents were observed in good yield (**5x**–**5z**).

The yields are consistently lower for *ortho*-substituted examples compared to when the same functional groups are in either *meta*- or *para*-positions. The only exceptions are those that are small in nature i.e. nitrile **5z** or chloride **5x** and the bromide **5y** that retains a remarkably similar yield in all positions. This implies larger steric bulk as being detrimental to product yield. Presumably, greater steric hindrance results in higher energy, intermediate species required for an effective oxidative addition step. This is supported by the presence of unreacted aryl iodides and lack of side-products within the remainder of the mass balance. Steric effects could be quantified in future by the use of sterimol steric parameters to further advance our understanding of the reaction. Nevertheless, despite a reduction in yield for aryl iodides bearing substituents in the *ortho*-position, synthetically useful yields of product were obtained in all cases.

2.3.3 Aromatic Heterocyclic Iodide Scope

Aromatic heterocycles are ubiquitous in natural products and pharmaceuticals, and so their tolerance of the reaction conditions would be incredibly valuable. Therefore, to further expand the applicability of the methodology, a trial of aromatic heterocyclic iodides **1aa**–**1ac** was undertaken (Table 13).

Table 13 Aromatic heterocycle scope.[a]



[a]Isolated yield after purification by column chromatography. [b]Redox-relay Heck reaction carried out in THF. [c]Reaction performed at 0.04 M. [d]Yield of isolated hemiacetal. [e]Reaction performed using $Pd(OAc)_2$ (5 mol%).

Pleasingly, aromatic heterocycles **1aa**–**1ac** were tolerated in the reaction with good yields observed for the thiophene and indole cores respectively (**5aa** and **5ab**). Substrates incorporating a basic nitrogen were able to undergo the redox-relay Heck successfully after minor condition alterations (**3ac** and **3ad**). This included an almost quantitative yield achieved for the quinoline-containing hemiacetal **3ac** when performed in THF as opposed to MeCN (~44% determined by ^{1}H NMR spectroscopy). Unfortunately, when subjected to the reduction conditions, a gummy precipitate formed and following work-up only starting

material was returned. It was postulated that the basic nitrogen coordinated to the Lewis acid, forming complex **6** that was largely insoluble in DCM and effectively shutting down the reduction (Figure 13).

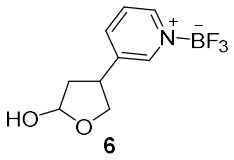
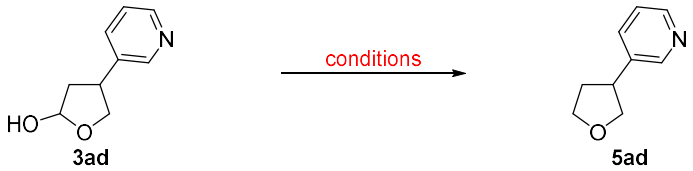


Figure 13 Postulated pyridinium complex **6**.

In an effort to solubilise the complex **6**, an increased quantity of solvent was used. This proved somewhat effective for accessing quinoline-containing product **5ac** but was ineffective for the reduction of pyridine variant **3ad**. A variety of different reduction conditions were evaluated in order to facilitate the synthesis of the THF derived from the pyridine-containing hemiacetal **3ad**. These attempts included increasing the equivalents of $BF_3{\cdot}OEt_2$ or using TFA/Et_3SiH,[106] Amberlyst® 15/Et_3SiH,[107] TsCl/$NaBH_4$ or hydrogenation conditions.[108] Unfortunately, in all cases, no desired product was observed (Table 14).

Table 14 Unsuccessful attempts of reducing hemiacetal **3ad**.



Entry[a]	Conditions	Yield %
1	$BF_3{\cdot}OEt_2$ (2.2 equiv.), Et_3SiH (1.1 equiv.), DCM, 0 °C	n.r
2	TFA (2.5 equiv.), Et_3SiH (2.0 equiv.), DCM, 0 °C	n.r
3	TsCl (1.5 equiv.), Et_3N (2.4 equiv.), $NaBH_4$ (2.0 equiv.) DMSO, 80 °C	n.r
4	Amberlyst® 15, Et_3SiH (2.0 equiv.), DCM, r.t	n.r
5	Pd/C (0.3 equiv.), H_2, AcOH:H_2O (9:1), r.t	n.r

[a]Reactions performed on a 0.18 mmol scale.

Despite the unsuccessful reduction of the pyridine derived hemiacetal **3ad**, it is gratifying that the redox-relay Heck reaction does perform well. Having successfully demonstrated the ability of the methodology to accommodate a variety of aromatic iodides with a range of functionality positioned at *para*-, *meta*- and *ortho*-positions as well as aromatic heterocyclic examples, the scope of the diol coupling partner was investigated.

2.4 Synthesis and Scope of Unsaturated Diols

cis-2-Butene-1,4-diol **2a** is a cheap and readily available reagent. Unfortunately, however, substituted analogues that would be required for the synthesis of more complex THFs are not commercially available and require their own synthesis.

With the synthesis of natural products featuring a 2,4-disubstitution pattern in mind (Figure 14A), diols featuring substitution at the α-position to one of the alcohols were required (Figure 14B).

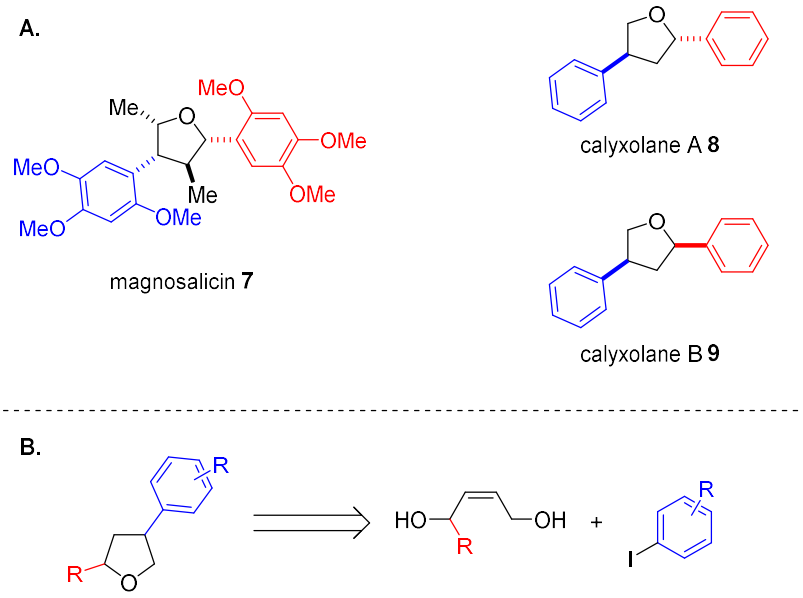
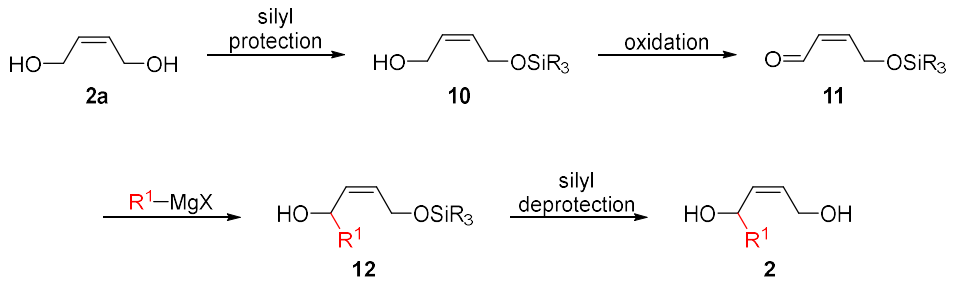


Figure 14 A. Tetrahydrofuran natural products exhibiting 2,4-disubstitution and B. Retrosynthetic approach to 2,4-disubstituted THFs.

2.4.1 Routes to 1-Substituted 2-Butene-1,4-Diols

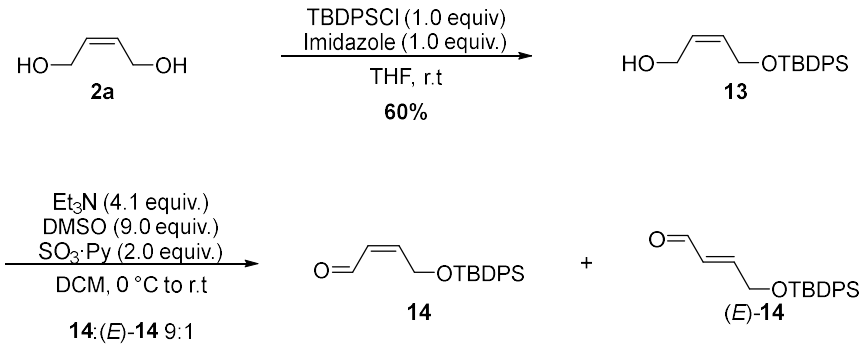
Originally, it was proposed that these secondary alcohols could be accessed from *cis*-2-butene-1,4-diol **2a**. Protection of one alcohol and subsequent oxidation of the other would give enal **11**. Grignard reagents could then be used to install a variety of substituents before a silyl deprotection to give the desired substrates **2** (Scheme 49).



Scheme 49 Proposed synthesis of substituted diols **2**.

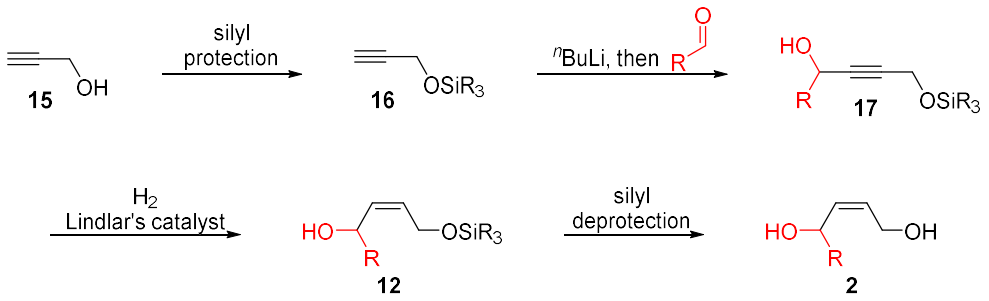
Unfortunately, when testing the route, problems were encountered. Whilst the silyl protection proceeded in good yield following a procedure of Trost,[109] it was found that during the oxidation step isomerisation from the *cis*-product **14** to the *trans*-product (*E*)-**14** took place (Scheme 50). Given that previous attempts using a *trans*-diol gave reduced yield relative to the *cis*-isomer (61% vs 96%), it

was decided to seek a synthetic route that could selectively deliver the *Z*-isomer.[110]



Scheme 50 Unsuccessful route to substituted diols **2**.

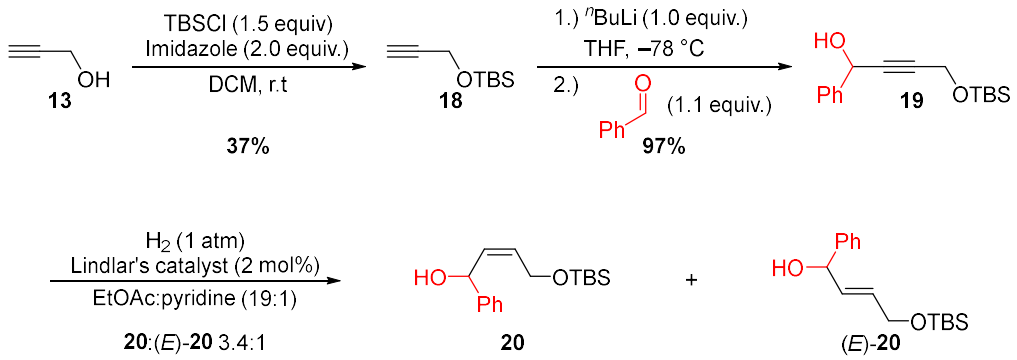
A second approach to accessing the substituted *cis*-diols **2** aimed to take advantage of readily available propargyl alcohol **15**. A silyl protection of the alcohol would begin the sequence, followed by deprotonation to generate the acetylide. The anion generated would be trapped by various aldehydes to give substituted diols **17** before a hydrogenation step with Lindlar's catalyst to selectively reduce the alkynes to the *cis*-alkenes **12**. Finally, a deprotection of the silyl protecting group would return the desired products **2** (Scheme 51).



Scheme 51 Proposed synthesis of substituted diols **2**.

When this reaction plan was tested a similar drawback was observed. Following successful silyl protection and lithiation steps,[111,112] which gave modest and excellent yields respectively, issues arose during the hydrogenation reaction.

During the hydrogenation step,[113] the alkyne **19** was converted into the *cis*-product **20** but unfortunately, within the reaction media, the desired *Z*-alkene **20** then began to isomerise to the undesired *trans*-isomer (*E*)-**20** (Scheme 52).

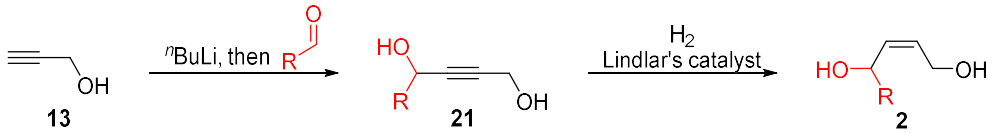


Scheme 52 Second unsuccessful route to substituted diols **2**.

This result in accordance with the previous synthetic route suggests that having bulky alcohol protecting groups is detrimental to selectively accessing the *cis*-isomer.

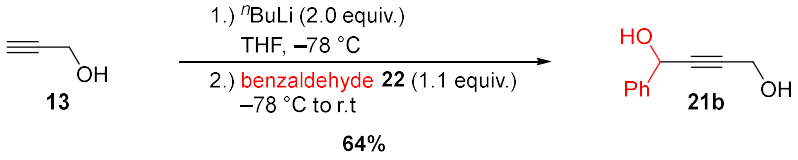
Due to the difficulties encountered with previous approaches, and looking to eliminate a wasteful protecting group approach, a third strategy was envisioned.

Commencing from propargyl alcohol **13**, it was reasoned that two equivalents of *n*BuLi could act to twice deprotonate, resulting in a dianionic species. The introduction of aldehydes would return alkynes **21** which could then give the *cis*-alkenes **2** exclusively when considering the absence of any bulky protecting groups (Scheme 53).



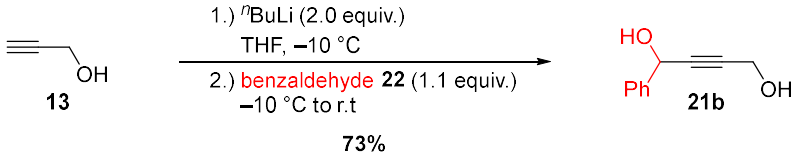
Scheme 53 Postulated synthesis of substituted diols **2**.

If feasible, this would be an attractive pathway following the exclusion of protection/deprotection steps. In a first attempt alkyne diol **21b** was formed in 64% isolated yield from propargyl alcohol **13** and benzaldehyde **22** using two equivalents of ^{n}BuLi following the procedure reported by Jirgensons and co-workers (Scheme 54).[114]



Scheme 54 Synthesis of alkyne diol **21b**.

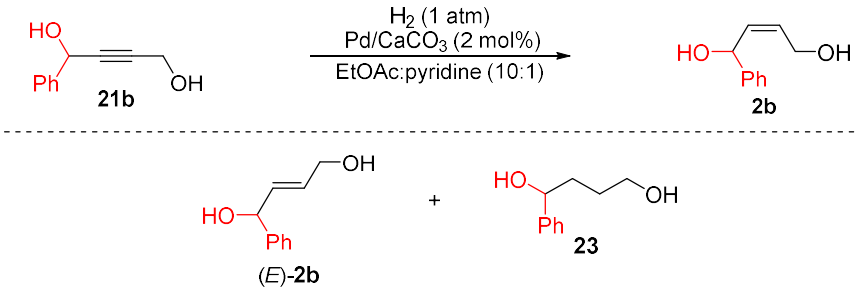
It was of interest to see whether the lithiation step could take place without the need for cryogenic temperatures. A repeated experiment at the elevated temperature of −10 °C was undertaken and the product was isolated in a slightly improved 73% yield (Scheme 55).



Scheme 55 Synthesis of alkyne diol **21b** at −10 °C.

With the double deprotonation approach returning product **21b** and at a more accessible temperature, the key hydrogenation step was then tested using a procedure based on that reported by Knight and co-workers (Table 15).[115]

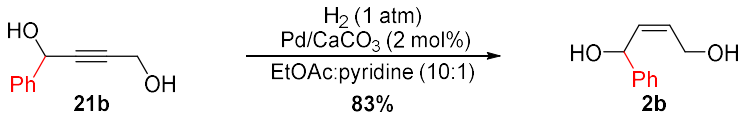
Table 15 Product ratio for alkyne hydrogenation step



Entry[a]	Time (min)	Ratio[b]			
		Starting material 21b	Product 2b	*trans*-Product (*E*)-2b	Fully reduced product 23
1	10	1.00	1.08	trace	/
2	60	/	1.18	1.00	2.00

[a]Reaction performed on a 0.31 mmol scale. [b]Ratios determined by ^{1}H NMR spectroscopy.

Pleasingly, a sample taken at ten minutes showed greater than 50% conversion to the desired alkene with only trace amounts of the undesired *trans*-diol (*E*)-**2b** (Entry 1). A second sample was taken at one hour which showed complete consumption of the starting material **21b** but unfortunately there was now a significant quantity of the *trans*-diol (*E*)-**2b** and a large amount of the fully reduced alkane diol **23** (Entry 2). The reaction was repeated and samples were taken and analysed by thin layer chromatography (TLC) analysis at twenty, forty and seventy minutes. In all cases the starting material **21b** was present but in decreasing quantities. After ninety minutes the starting material was consumed with the desired product **2b** isolated in 83% yield (Scheme 56). This increase in time required may have been related to a new batch of catalyst being used.



Scheme 56 Synthesis of phenyl-substituted alkene diol **2b**.

These results indicated that the reaction is somewhat capricious with respect to the time required and the batch of catalyst used, and so it was decided to

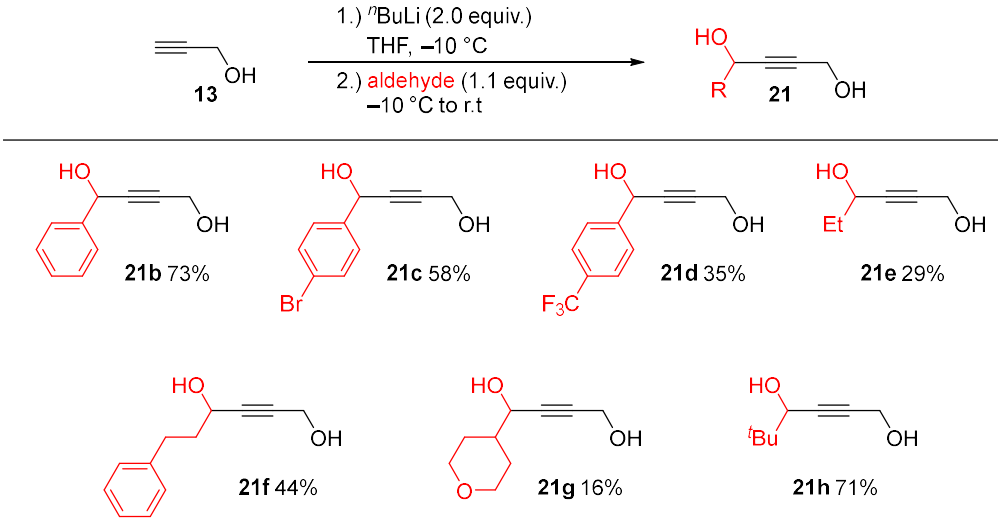
regularly monitor this step of the route *via* TLC analysis to determine the optimum time for each reaction.

Content with the developed route, the synthesis of a number of substituted diols **2** was then undertaken.

2.4.2 Synthesis of 1-Substituted 2-Butene-1,4-Diols

The synthesis of 1-substituted 2-butene-1,4-diols **2** began by first preparing 1-substituted 2-butyne-1,4-diols **21** *via* the direct double deprotonation of propargyl alcohol **13** (Table 16).

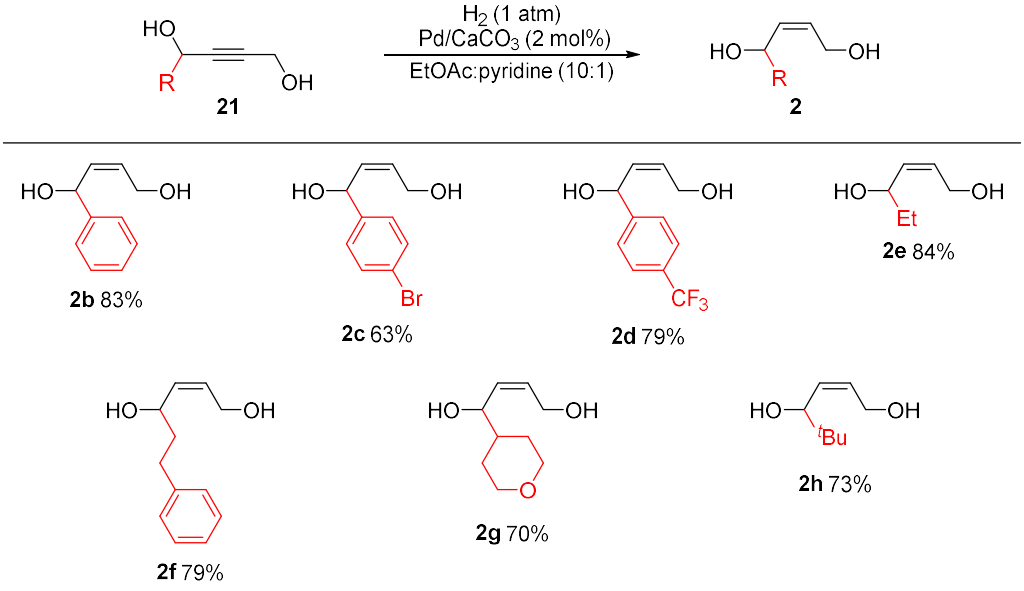
Table 16 Synthesis of 1-substituted 2-butyne-1,4-diols.[a,b]



[a]Reactions performed on a variety of scales, see experimental for details. [b]Isolated yield after purification by column chromatography.

The synthesis of alkynes for the study included both aromatic (**21b**–**21d**) and primary (**21e** and **21f**), secondary (**21g**) and tertiary (**21h**) aliphatic substituents adjacent to the alcohol. The yields observed showed significant variation with a range of 16–73%, suggesting the reaction might need further optimisation. With the alkynes in-hand, work to access the reduced *cis*-alkenes commenced (Table 17).[115]

Table 17 Synthesis of 1-substituted 2-butene-1,4-diols.[a,b,c]

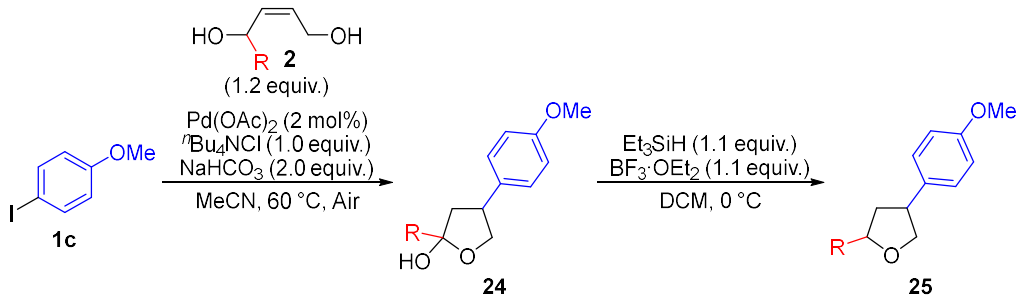


[a]Reactions performed on a variety of scales, see experimental for details. [b]Isolated yield after purification by column chromatography. [c]In all examples *cis*:*trans* ratio was >20:1.

Gratifyingly, the majority of yields were good to very good (63–84%) and more consistent than seen for the alkyne lithiation reactions (Table 16). The successful generation of 1-substituted butene-1,4-diols **2** allowed for the attempted 2,4-disubstituted THF synthesis.

2.4.3 1-Substituted 2-Butene-1,4-Diol Scope

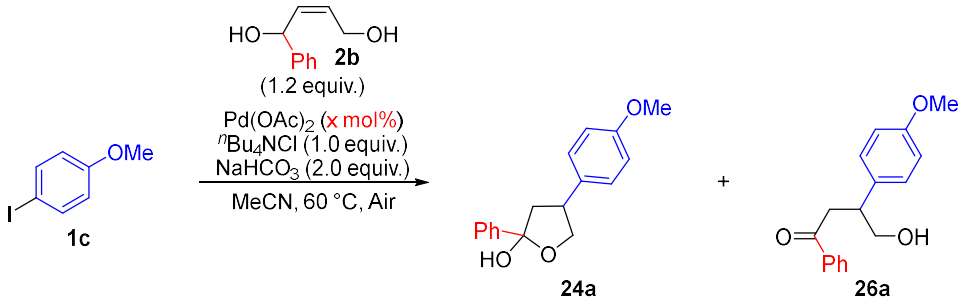
When selecting a suitable aryl iodide for the substituted diol scope, it seemed logical to proceed with the best performing substrate, 4-iodoanisole **1c** for the generation of 2,4-disubstituted THFs **25** (Scheme 57).



Scheme 57 Proposed synthesis of 2,4-disubstituted THFs **25** from 4-iodoanisole **1c**.

When monitoring the first redox-relay Heck reaction carried out with (*Z*)-1-phenylbut-2-ene-1,4-diol **2b**, it was clear by ^{1}H NMR spectroscopy that the reaction had not reached completion after 24 h. In order to maximise yield, a brief screen of catalyst loadings was undertaken (Table 18).

Table 18 Optimisation of catalyst loading.

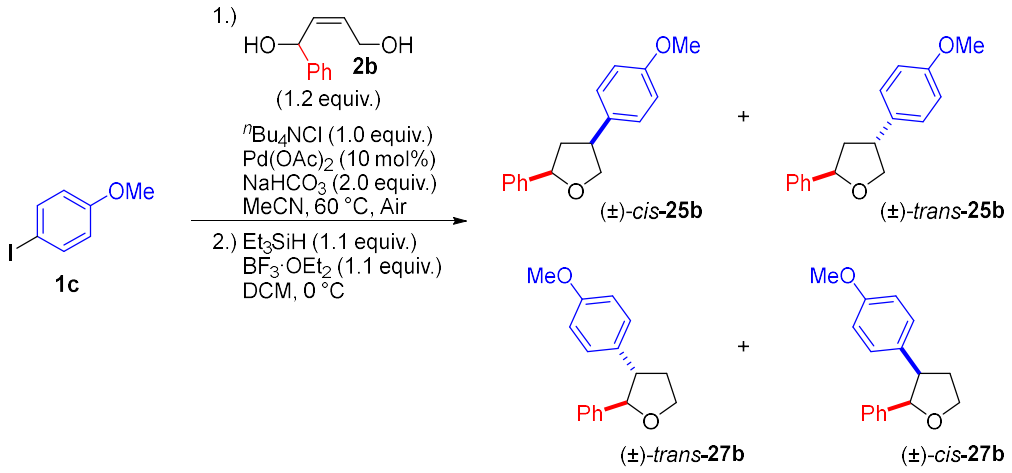


Entry[ab]	Pd loading mol%	Alkene consumption %[c]	Aryl iodide consumption %[c]
1	2	70	81
2	5	75	89
3	10	83	100

[a]Reaction performed on a 0.25 mmol scale. [b]Accurate product yields were not recorded due to the various product isomers and/or uncyclised carbonyls. [c]Consumption determined by ^{1}H NMR spectroscopy using 1,3-benzodioxole as an internal standard.

Gratifyingly, increasing the palladium loading to 10 mol% led to complete consumption of the limiting reagent, 4-iodoanisole **1c** (Entry 3). Following the brief optimisation study, an investigation of the diol scope commenced.

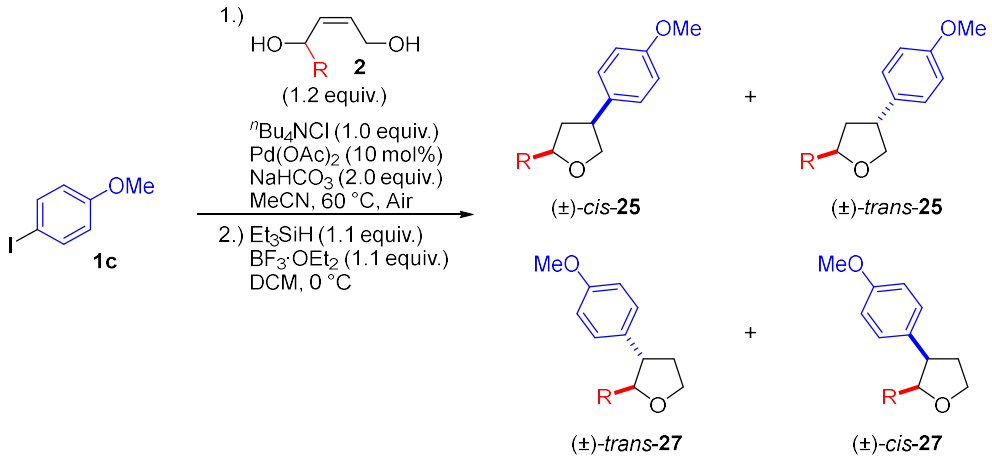
Expecting two diastereoisomers deriving from the second stereogenic centre present in the 2,4-disubstituted products, it was surprising to observe additional signals in the ^{1}H NMR spectrum of the unpurified reaction mixture. Upon further analysis it became clear that four products had formed, two of which were the expected 2,4-diastereomeric products (±)-*cis*-**25** and (±)-*trans*-**25** (Scheme 58). The other two products were identified, through analysis of NMR spectroscopic data, as regiomeric diastereomers, 2,3-disubstituted THFs (±)-*trans*-**27** and (±)-*cis*-**27**, later confirmed by comparison with literature data.[116]

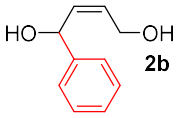
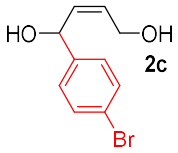
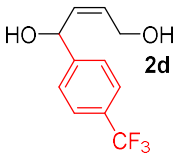
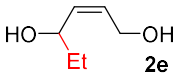
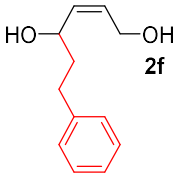
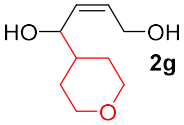
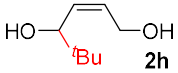


Scheme 58 Observed isomeric products from the redox-relay Heck reaction of 4-iodoanisole **1c** and diol **2b**.

Unfortunately, the four products proved to be inseparable by column chromatography. This result was disappointing in the sense that a proportion of the substrates were undergoing an unproductive pathway to give undesired 2,3-disubstituted THFs. Despite this setback, the results could provide insight into the factors that control the formation of the four different products generated. With this in mind, the substituted diols **2** were then subjected to the redox-relay Heck/reduction conditions (Table 19).

Table 19 1-Substituted-*cis*-butene-1,4-diol **2** scope.

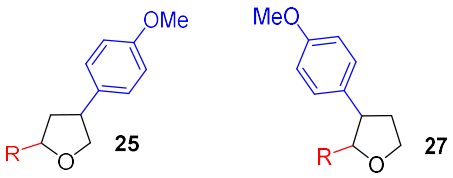


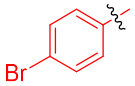
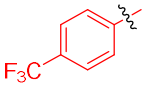
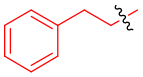
Entry[a]	Substrate	Combined yield %[b]	Product distribution ratio[c]			
			cis-**25**	*trans*-**25**	*trans*-**27**	*cis*-**27**
1	 **2b**	77	14.8	3.3	3.4	1.0
2	 **2c**	44	10.5	1.9	3.2	1.0
3	 **2d**	54	4.9	1.0	1.5	n.r[d]
4	 **2e**	69	6.5	1.5	2.2	1.0
5	 **2f**	79	4.5	1.2	2.4	1.0
6	 **2g**	77	complex overlap of characteristic signals			
7	 **2h**	42	2.7	1.2	1.0	n.r[d]

[a]Reaction performed on a 0.75 mmol scale. [b]Isolated combined yield. [c]Figures obtained by ^{1}H NMR spectroscopic analysis of the unpurified reaction mixture. [d]No clear corresponding signals observed.

By analysing the product ratios, the effects of the substituents on the regioselectivity of the transformation becomes clearer to observe. It should be noted that this analysis is from a relatively small sample, from data that is difficult to accurately interpret and based on only small differences in ratio from aromatic to aliphatic substituents. Consequently, these results and analysis were omitted from the publication that is associated with this work. This thesis allows for the communication of these preliminary findings in conjunction with caveats described (Table 20).

Table 20 Ratio of 2,4-disubstituted THFs **25** *vs*. 2,3-disubstituted THFs **27**.



Entry[a]	R	2,4-Products[b]	2,3-Products[b]
1		4.1	1.0
2		3.0	1.0
3		3.9	1.0
4		2.5	1.0
5		1.7	1.0
6		complex overlap of characteristic signals	
7		3.9	1.0

[a]Reaction performed on a 0.75 mmol scale. [b]Figures obtained from ^{1}H NMR data of the unpurified THF products.

However, it does seem that when the substituent is aromatic, there is a slightly greater preference for the palladium to insert proximal (Entries 1–3). When aliphatic substituents are present, this preference is reduced, with the exception of the ^{t}Butyl example (Entry 7). The slight difference in ratio between the two

examples with primary aliphatic substituents is unexpected given their electronic and steric similarities (Entries 4 and 5). The exception to this trend is Entry 7, which displays almost four times more of the 2,4-disubstituted THF **25h** compared to the 2,3-disubstituted equivalent **27h**.

In the Sigman group's mechanistic work on the redox-relay Heck reaction, they described how the palladium preferentially inserts proximal to the alcohol, due to the subtle electronic differences of the olefinic bond caused by the electronegative alcohol. As a result, selectivity has been shown to diminish when longer distances are observed between the alcohol and the olefin. However, double bond polarity can also be induced by the approach of the arylpalladium species (Figure 15).[104,117,118]

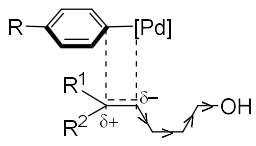
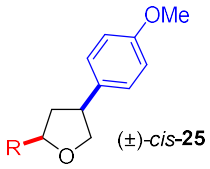


Figure 15 Site selectivity influenced by subtle polarisation of alkene bond.[104,117,118]

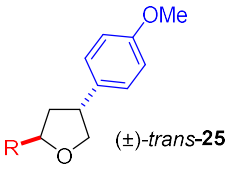
With the double bond centred between two alcohol groups in our diol examples, electron donating effects of the aliphatic groups may cause subtle polarisation of the alkene. However, this electronic effect can be overcome when the alkyl substituent is sterically large in nature, rationalised by examining the ^{t}Butyl example (Entry 7). The tertiary substituent has the greatest electron donating effect whilst also exhibiting the largest steric bulk. This example, relative to other alkyl substituents, produces the greatest proportion of the 2,4-disubstituted products, implicating a stronger influence of sterics over electronics in this particular context.

Following an analysis of the regioselectivity of the transformation, focus turned toward how the substituents may influence stereoselectivity, beginning with the 2,4-disubstituted THFs (Table 21).

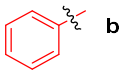
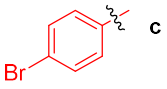
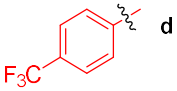
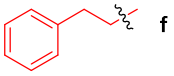
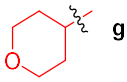
Table 21 Ratio of *cis vs*. *trans* products for 2,4-disubstituted THFs **25**.



(±)-*cis*-**25**



(±)-*trans*-**25**

Entry[a]	R	*cis*[b]	*trans*[b]
1	 **b**	4.5	1
2	 **c**	5.5	1
3	 **d**	4.9	1
4	 **e**	4.2	1
5	 **f**	3.7	1
6	 **g**	Undeterminable due to complexity	
7	 **h**	2.3	1

[a]Reaction performed on a 0.75 mmol scale. [b]Figures obtained from ^{1}H NMR data of the unpurified THF products.

In all cases the *cis*-product was preferentially formed. The selectivity of the *cis*-product can be rationalised by considering the oxonium intermediate, whereby delivery of hydride is favoured on the opposite side to the aromatic group installed in the initial Heck coupling. This results in the positioning of the R substituent onto the same face as the aromatic group (Figure 16).

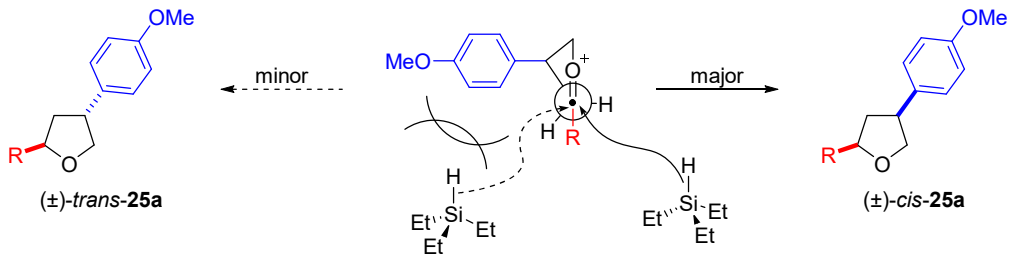
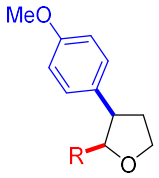


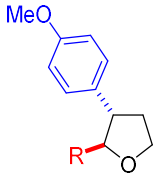
Figure 16 Proposed rationale for excess *cis*-product formation.

Unfortunately, no clear trend is observed for the effect of the α-substituent for the 2,4-disubstituted products **25**. It is difficult to come to any solid conclusions from the data obtained, and five of the examples display similar ratios (Entries 1–5). The example with the most sterically hindered substituent (Entry 7) shows the smallest excess of the *cis*-product implying sterics is influential here. Future work may involve repeating these experiments and increasing the sample size so that trends can be derived with confidence. A different picture is revealed for the 2,3-disubstituted THFs **27** (Table 22).

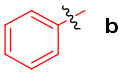
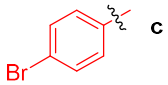
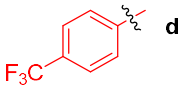
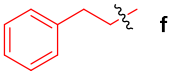
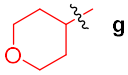
Table 22 Ratio of *cis vs*. *trans* products for 2,3-disubstituted THFs **27**.



(±)-*cis*-**27**



(±)-*trans*-**27**

Entry[a]	R	*cis*[b]	*trans*[b]
1	 **b**	1.0	3.4
2	 **c**	1.0	3.2
3	 **d**	n.d[c]	
4	 **e**	1.0	2.2
5	 **f**	1.0	2.4
6	 **g**	n.d[c]	
7	 **h**	n.d[d]	

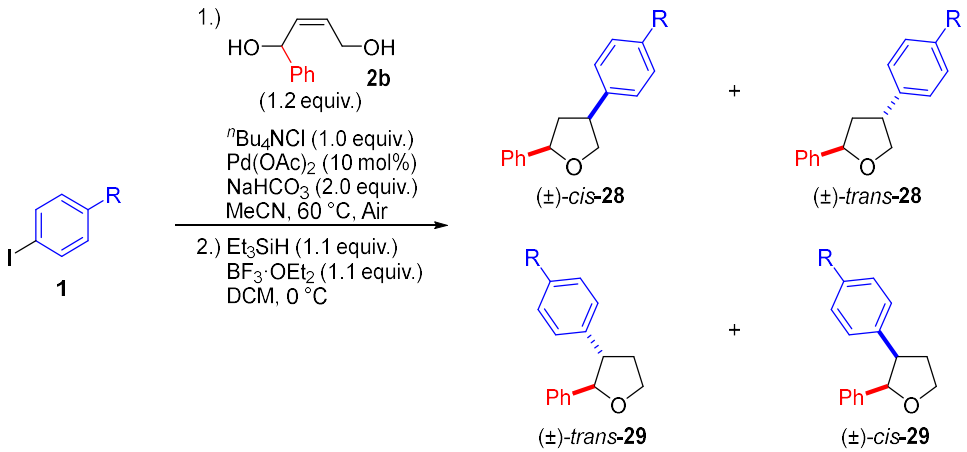
[a]Reaction performed on a 0.25 mmol scale. [b]Figures obtained from ^{1}H NMR spectroscopic data of the unpurified THF products. [c]Not determined due to overlap of signals. [d]Not determined due to no observable 2,3-*trans*-product.

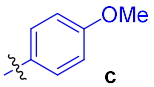
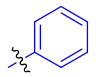
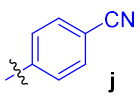
The aryl substituted examples lead to more of the *trans*-products (Entries 1 and 2) relative to when the substituents are aliphatic (Entries 4 and 5). In all cases, the excess of *trans*-products is reduced compared to the respective 2,4-

disubstituted THF examples (Table 21). Unfortunately, due to a complex overlap of signals, a full analysis of the data was unattainable (Entries 3 and 6). A ratio for the ^{t}Butyl-substituted products was also not possible due to no observable signals for the 2,3-*cis*-product (Entry 7).

Following these experiments, it was decided to investigate whether the electronic nature of the aryl iodide used in the Heck reaction could influence the product distribution. In a small study, the phenyl-substituted diol **2b** was used as a control with three electronically diverse aryl iodides; 4-iodobenzonitrile **1j**, iodobenzene **1b** and 4-iodoanisole **1c** (Table 23). In the case of the reaction using iodobenzene the synthesis of the natural products calyxolanes A **8** and B **9** would be achieved, along with the 2,3-disubstituted isomers.

Table 23 Product distribution ratio with electronically diverse aryl iodides.

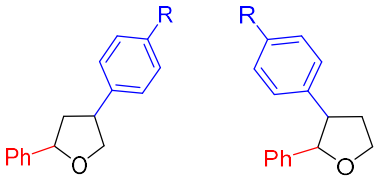


Entry[a]	R	Hammett constant σ[105]	Product distribution ratio[b]			
			cis-**28**	*trans*-**28**	*trans*-**29**	*cis*-**29**
1	 **c**	−0.27	13.0	3.1	3.6	1.0
2	 **b**	0.00	10.3	3.2	2.4	1.0
3	 **j**	+0.66	2.6	1.0	1.9	0

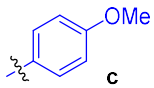
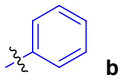
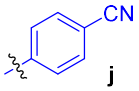
[a]Reaction performed on a 0.25 mmol scale. [b]Figures obtained from ^{1}H NMR spectroscopic data of the unpurified THF products.

Unfortunately, the results from this investigation do not provide any further clarity regarding the causes of the observed product distribution. Again, the interpretation becomes easier when the data is broken down to 2,4- *vs*. 2,3-products and *cis*- *vs*. *trans*-products (Table 24).

Table 24 Ratio of 2,4- *vs*. 2,3-products with electronically diverse aryl iodides.



(±)-**28** (±)-**29**

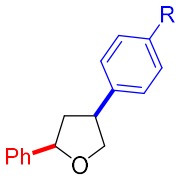
Entry[a]	R	Hammett constant σ[105]	2,4-Products[b]	2,3-Products[b]
1	 **c**	−0.27	3.5	1.0
2	 **b**	0.00	4.0	1.0
3	 **j**	+0.66	1.9	1.0

[a]Reaction performed on a 0.25 mmol scale. [b]Figures obtained from ^{1}H NMR spectroscopic data of the unpurified THF products.

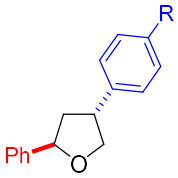
Although, the data are from a small sample, there is no observable trend in relation to Hammett parameters, and therefore the electronic effects of the aryl substituents on regioselectivity.

Seemingly, when focusing on the ratio of diastereoisomers formed, the more electron rich aryl substituents give more of the *cis*-product **28** (Table 25), The reason for this remains unclear.

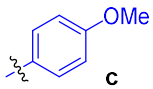
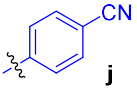
Table 25 Ratio of *cis vs*. *trans* products for 2,4-disubstituted THFs with electronically diverse aryl iodides.



(±)-**28**



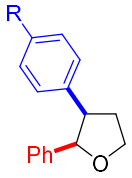
(±)-**28**

Entry[a]	R	*cis*[b]	*trans*[b]
1	 **c**	4.2	1.0
2	 **b**	3.2	1.0
3	 **j**	2.6	1.0

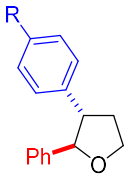
[a]Reaction performed on a 0.25 mmol scale. [b]Figures obtained by ^{1}H NMR spectroscopic analysis of the unpurified reaction mixture.

When the data for the 2,3-disubstituted products **29** was analysed (Table 26), the lack of signal for the electronically poor aryl iodide example (Entry 3) resulted in a no observed trend.

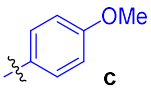
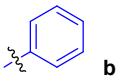
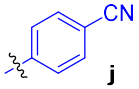
Table 26 Ratio of *cis vs. trans* products for 2,3-disubstituted THFs with electronically diverse aryl iodides.



(±)-29



(±)-29

Entry[a]	R	*cis*[b]	*trans*[b]
1	 **c**	1.0	3.6
2	 **b**	1.0	2.4
3	 **j**	n.d[c]	

[a]Reaction performed on a 0.25 mmol scale. [b]Figures obtained from ^{1}H NMR data of the unpurified THF products. [c]Not determined due to no observable 2,3-*trans*-product.

The analysis is difficult based on the small sample size and exacerbated by the absence of an observable signal for the 2,3-*cis* product (Entry 3).

The 1-substituted 2-butene-1,4-diol **2** scope proved frustrating, as a result of the complex mixtures of products formed. Further experimentation would be required to conclusively determine trends in this chemistry. The results do however highlight a long-standing challenge of Heck chemistry – controlling regioselectivity with olefins that feature little to no electronic bias.[119,120]

2.4.4 Benzyl-Substituted Tetrahydrofurans

Following the investigation of 1-substituted 2-butene-1,4-diols **2** featuring an internal olefin, it was of interest to see how a 1,1-disubstituted alkene diol **33** might behave under the reaction conditions. The redox-relay Heck/reduction sequence would give benzyl-substituted THFs, a motif that, like aryl substituted-THFs, holds significant value.

For example, benzyl-substituted THFs are seen in (+)-lariciresinol **30** which exhibits significant antibacterial activity,[121] cordigol **31** which exhibits fungicidal activity,[122] and ifetroban **32**, a thromboxane-prostanoid receptor antagonist currently being assessed as an anti-cancer treatment (Figure 17).[123,124]

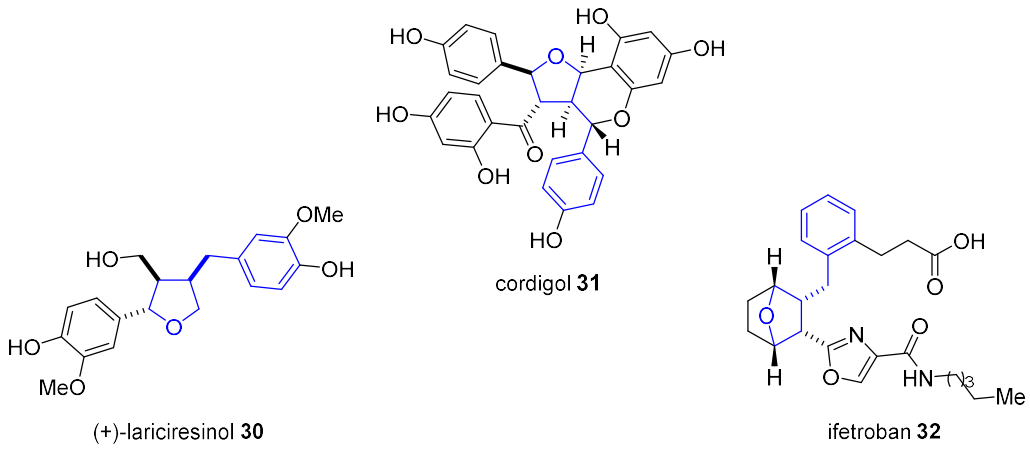
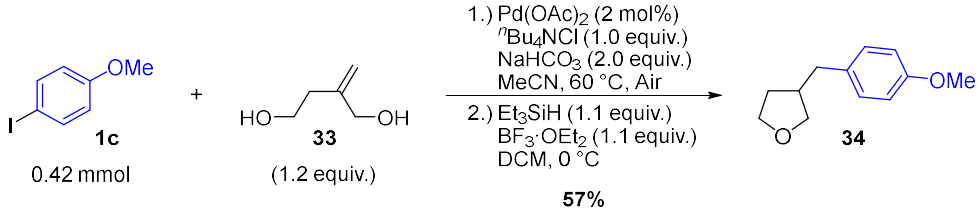


Figure 17 Examples of benzyl-substituted THFs in natural products and pharmaceuticals.[121–124]

Gratifyingly, in a one-off reaction using the previously optimised conditions, benzyl-substituted THF **34** was formed in a 57% isolated yield, demonstrating the applicability of the chemistry to 1,1-disubstituted alkenes (Scheme 59).

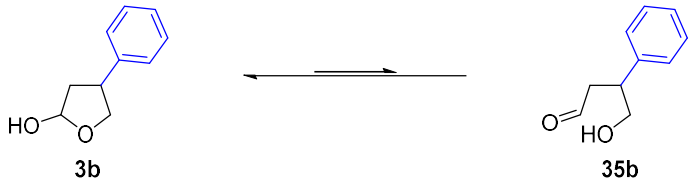


Scheme 59 Synthesis of benzyl-substituted THF **34**.

2.5 Derivatisation of Hemiacetals

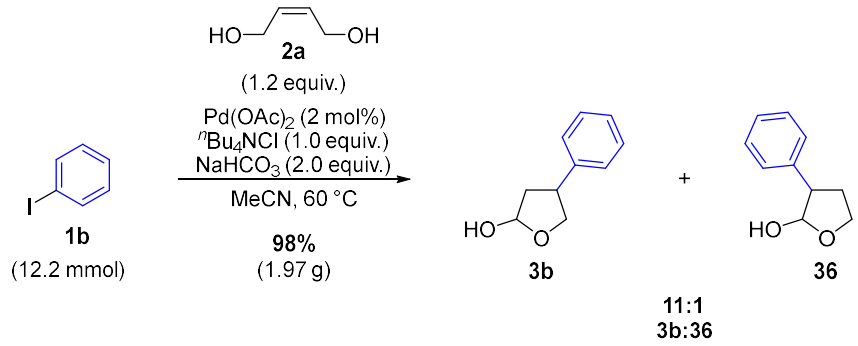
With the reaction scope for aryl iodides and diols investigated, there was an interest in further demonstrating the value of this chemistry by derivatising the

hemiacetal **3b** which exists in equilibrium with hydroxy aldehyde **35** (Scheme 60).



Scheme 60 Equilibrium of hemiacetal **3b** and hydroxy aldehyde **35b**.

Pleasingly, when increasing the scale of the reaction to 12.2 mmol to produce sufficient hemiacetal **3b** for the derivatisation work, an excellent yield was observed. Interestingly, when analysing the isolated product **3b**, a small quantity of hemiacetal **36** was observed (11:1 **3b**:**36**).



Scheme 61 12.2 mmol Scale reaction of hemiacetal **3b** and observed 2,3-substituted side-product **36**.

The formation of this species was inconsequential during the synthesis of 3-aryl THFs due to the eventual reduction of the alcohol. However, trace amounts of this side-product **36** or the products derived from it were observed in three of the derivatisation reactions (Scheme 62a–c).

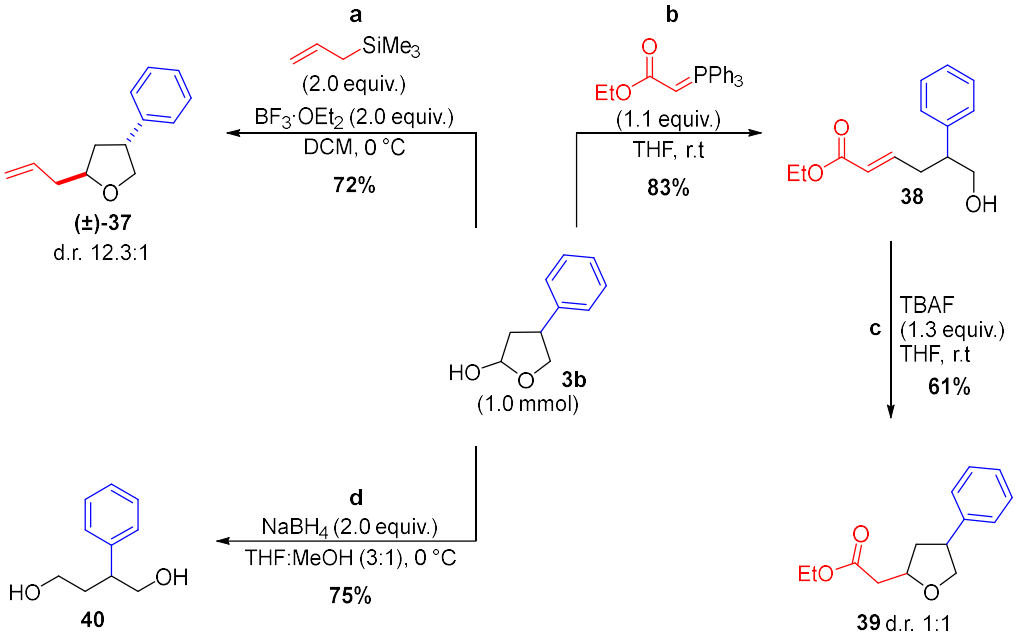
A useful transformation of cyclic hemiacetals was described by the group of Reißig.[125] The reaction involves a similar Lewis acid activation followed by dehydration to give an oxonium ion; the cation generated can then be attacked

by silanes. This approach proved successful with THF (±)-**37** isolated in 72% yield with high diastereoselectivity (Scheme 62a). The *trans* selectivity is borne out of the approach of the nucleophile from the least hindered face.

Lactols in the form of sugar derivatives have been shown to undergo the Wittig reaction[126,127] and gratifyingly our hemiacetal **3b** underwent a successful reaction to the ring opened alkene **38** in an isolated 83% yield (Scheme 62b).

Given our aims to produce substituted heterocycles, we next envisioned the TBAF-promoted cyclisation of the α,β-unsaturated ester **38** based on work by Kobayashi.[128] The reaction gave a 1:1 mixture of 2,4-disubstituted THF diastereoisomers **39** in 61% isolated yield (Scheme 62c).

Again, by utilising the aldehyde species **35b** in equilibrium with hemiacetal **3b**, a borohydride reduction could give access to the monosubstituted diol **40**. This straightforward approach gave the desired product in 75% isolated yield (Scheme 62d).



Scheme 62 Derivatisation of hemiacetal **3b**.

These derivatisation examples showcase the potential of the hemiacetals generated from the operationally simple and functional group tolerant redox-

relay Heck methodology. Given the diverse range of products that can be formed it is hoped that the chemistry may find applications in the synthesis of useful building blocks.

2.6 Synthesis of Calyxolanes A 8 and B 9

We sought to develop a route to calyxolanes A **8** and B **9** that would limit the accompanied formation of the unwanted 2,3-disubtituted diastereomeric products.

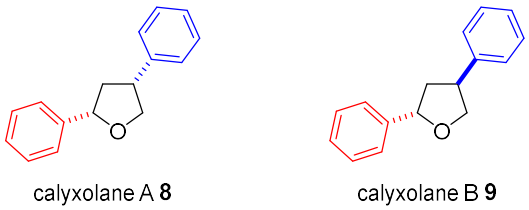
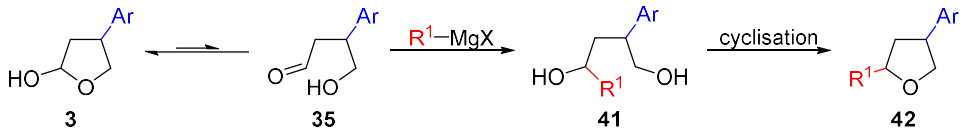


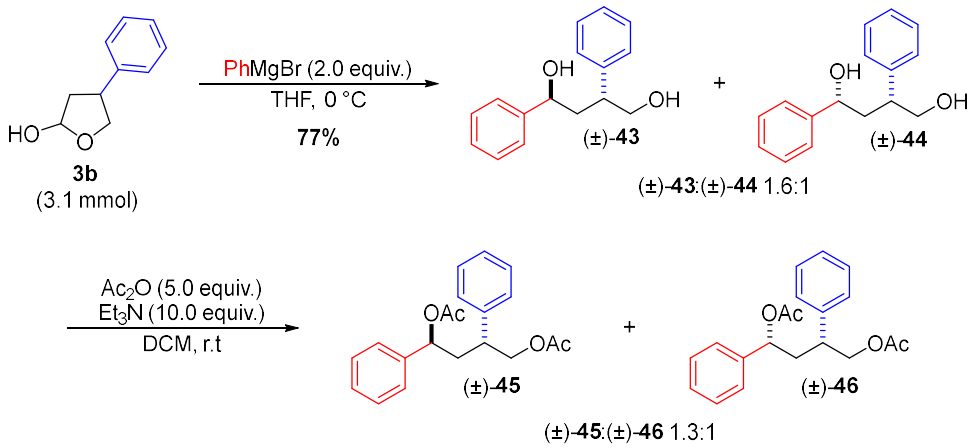
Figure 18 Natural products calyxolanes A **8** and B **9**.

We envisioned adding Grignard reagents to the hemiacetals, taking advantage of the carbonyl reactivity present in the equilibrium of the hemiacetals **3** to give diols. This would be followed by a cyclisation reaction to return the 2,4-disubstituted THF products **42** (Scheme 63).



Scheme 63 Proposed synthesis of 2,4-disubstituted THFs **42** *via* hydroxy aldehyde **35**.

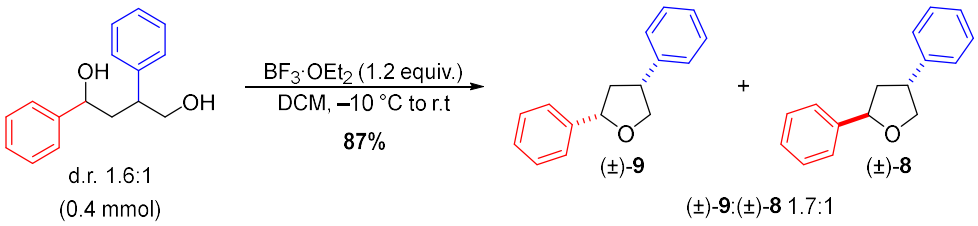
Gratifyingly, addition of phenylmagnesium bromide was successful, giving the disubstituted diol in 77% isolated yield and as a mixture of diastereoisomers (±)-**43** and (±)-**44** (Scheme 64).



Scheme 64 Synthesis of disubstituted diols (±)-**43** and (±)-**44** *via* a Grignard reaction and subsequent synthesis of known diacetates (±)-**45** and (±)-**46**.[129]

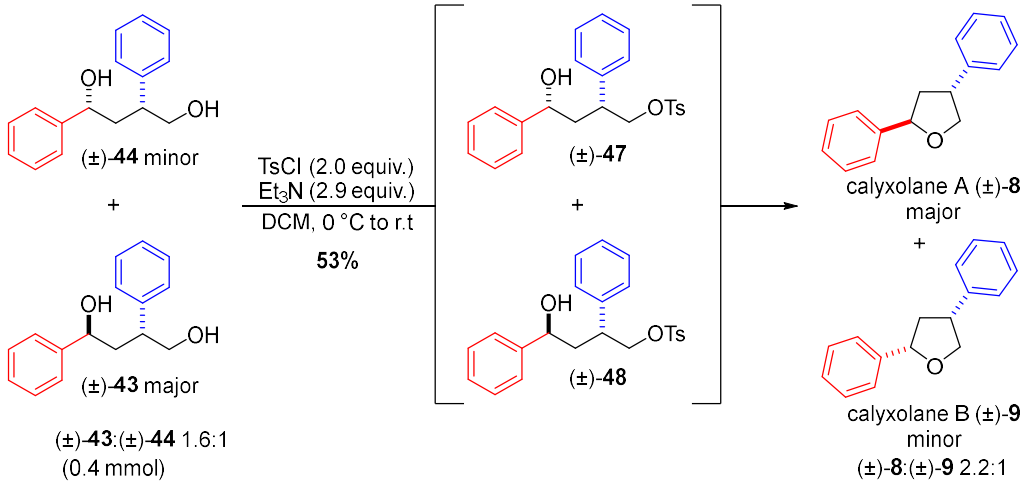
The stereochemistry was assigned by acetylating the alcohols following a procedure by Sumida *et al.* to give the known diacetate derivatives (±)-**45** and (±)-**46** which were not isolated.[129] The disparity in ratio between the alcohols and acetates can be rationalised by the reaction not reaching completion ((±)-**43** and (±)-**44**: (±)-**45** and (±)-**46**, 1:6.3). In the unpurified reaction mixture, small quantities of the alcohols (±)-**43** and (±)-**44** were observed in a ratio of 10:1.

With the disubstituted diol in-hand, focused turned toward the cyclisation and therefore synthesis of the natural products, calyxolanes A **8** and B **9**. Two approaches were trialled for the transformation, the first was based on a Lewis acid-promoted activation of the benzylic alcohol, allowing for the attack from the primary alcohol following a modified procedure of Luo, Gong and co-workers.[130] The approach proved successful, returning a 1.7:1 mixture of diastereoisomers in an 87% isolated yield, with calyxolane B **9** identified as the major component (Scheme 65).



Scheme 65 Synthesis of calyxolanes B (±)-**9** and A (±)-**8**.

The second approach aimed to take advantage of the more readily tosylated primary alcohol before a cyclisation reaction. The tosylation/cyclisation reaction was trialled in one-pot and gave interesting results. It was surprising to observe the mixture of the natural products but with an excess of the *trans*-product, calyxolane A (±)-**8** (Scheme 66). Also isolated following the conclusion of the reaction was tosylated intermediate (±)-**48**.



Scheme 66 Synthesis of calyxolanes A (±)-**8** and B (±)-**9** in a 2.2:1 ratio.

The tosylated species **48** was only observed for the diastereoisomer **43** that precedes calyxolane B (±)-**9**. Fortuitously, this allows for two cyclisation procedures that give mixtures enriched in either calyxolane A (±)-**8** or B (±)-**9**.

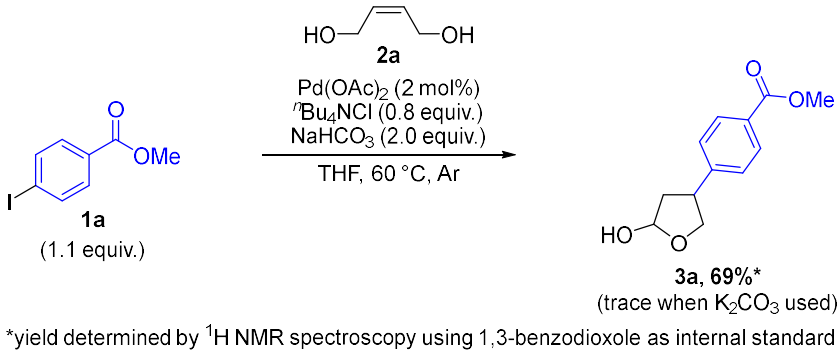
Using this approach, it would be straightforward to access a library of different calyxolane analogues by simply changing the aryl iodide used in the redox-relay Heck step, or the aryl Grignard reagent added to the hemiacetal.

The calyxolane synthesis concluded the synthetic investigations. However, questions remained in relation to some mechanistic elements.

2.7 Mechanistic Investigations

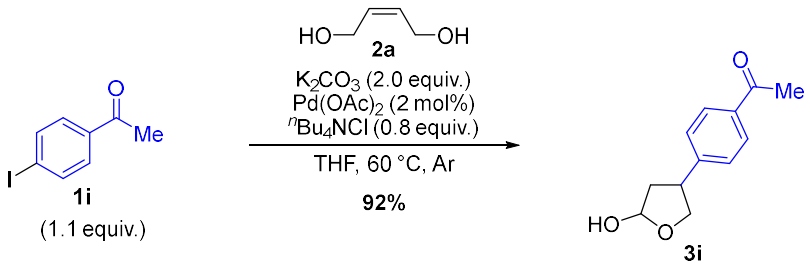
2.7.1 Base Effects

From the beginning of the project, questions had arisen over the ability of sodium hydrogen carbonate to facilitate the coupling of *cis*-butene-1,4-diol **2a** and certain electron deficient aryl iodides where potassium carbonate had failed (Scheme 67).



Scheme 67 Early result displaying effect of $NaHCO_3$ vs. K_2CO_3 with an electron-deficient aryl iodide **1a**.

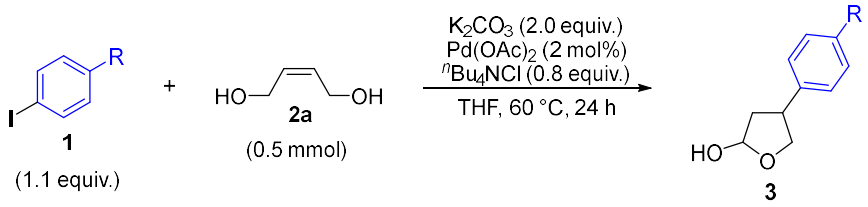
Initially, it was believed that the electron-deficiency of the aryl iodides caused this effect. However, this postulation was discarded when it was observed that 4-iodoacetophenone **1i** gave product in reactions carried out by Megan Mylrea (Scheme 68).[84]



Scheme 68 Synthesis of hemiacetal **3i** carried out by Megan Mylrea.[84]

Aryl iodide **1i** has a Hammett constant that is situated between two unsuccessful electron-deficient examples: methyl-4-iodobenzoate **1a** and 4-iodobenzonitrile **1j** (Table 27).

Table 27 Early result into the effect of base for the redox-relay Heck reaction.[a]

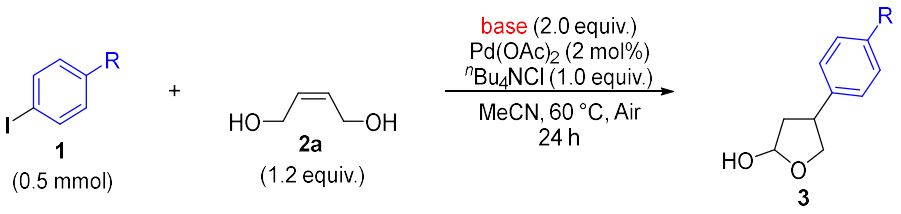


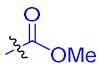
Entry[b]	R	Yield %[c]	Hammett constant σ_p[105]
1		0	+0.45
2		92	+0.50
3		0	+0.66

[a]Work undertaken by Megan Mylrea.[84] [b]Reaction performed on a 0.50 mmol scale. [c]Yield of isolated products.

Previous studies had shown that sodium hydrogen carbonate could facilitate the reaction of methyl-4-iodobenzoate **1a** where potassium carbonate could not (Scheme 67). This result suggested that perhaps the potassium ion itself might be causing the deleterious effect. It was decided to explore this in greater depth by submitting four aryl iodides **1c**, **1a**, **1i** and **1j** to the reaction conditions whilst varying the base used (Table 28).

Table 28 Investigation into base effects.



Entry[a]	R	Yield %[b]						Hammett constant σ_p[105]
		a Li_2CO_3	b Na_2CO_3	c $NaHCO_3$	d K_2CO_3	e $KHCO_3$	f Cs_2CO_3	
1		9	93	100	84	94	37	−0.27
2		16	90	95	11	95	n.r[c]	+0.45
3		17	92	94	38	90	n.r[c]	+0.50
4		19	74	91	n.r	76	n.r[c]	+0.66

[a]Reaction performed on a 0.50 mmol scale. [b]Yield determined by ^{1}H NMR spectroscopy using 1,3-benzodioxole as an internal standard. [c]No observable quantity of product.

Firstly, it can be seen that lithium carbonate is not an effect base for the reaction with product yield never exceeding 20%, irrespective of the aryl iodide used (Entries 1a–4a). Interestingly, yields increase as the aryl iodide becomes more electron-deficient; this is not a trend observed with any other base tested.

Sodium carbonate is, on the other hand, an effective base. Yields are excellent for all examples although slightly lower for the nitrile-substituted aryl iodide (Entry 4b). Sodium hydrogen carbonate was found to be an even better base for the reaction with all yields above 90% (Entries 1c–4c). There is also a potential trend here, showing increased performance with more electron-rich aryl iodides – a trend also seen during the aryl iodide scope studies.

As already noted, potassium carbonate gives some mixed results. The anisole derivative is returned in very good yield (Entry 1d), but the remaining three aryl iodides, all of which are electron-deficient, give low to no yield (Entries 2d–3d). The acetyl-containing example, breaking any trend between yield and the electronics (Entry 3d). Conversely, potassium hydrogen carbonate gives

excellent yields for three examples (Entries 1e–3e), the nitrile species performing similarly to when sodium carbonate was used (Entry 4e). Although the nitrile is prepared in lower yield, it is noteworthy that it gives much higher yield (76%) than when potassium carbonate is employed (n.r.).

Why potassium hydrogen carbonate is so much more effective in promoting the reaction than potassium carbonate remains unclear. If it is a potassium ion deleterious effect, perhaps the lower concentration of potassium ions found in the reaction with potassium hydrogen carbonate allows for the reaction to proceed effectively (Entries 1e–4e).

Caesium carbonate, a base with somewhat different solubility characteristics to others in this study,[131] provided different results. It gives a poor conversion to the anisole-containing hemiacetal (Entry 1f) and no observable quantity of the products from the other aryl iodides (Entries 2f–4f). However, interesting results were obtained from the reactions with caesium carbonate as base. A new series of minor signals were observed for two of the reactions with caesium carbonate (Entries 2f and 4f), suggesting the base had led to alternative products within the system. Insufficient data was gathered for a complete analysis of the different product(s) generated from the reactions. An area of future work may be the further scrutinisation of the product(s) generated.

It would also be worth investigating the role of the reaction solvent. As seen in Table 27, the conditions initially developed result in no observable quantity of the ester or nitrile containing products when potassium carbonate was used in THF. This result is in contrast to the optimised conditions, where small quantities of the ester were observed when the reaction was run in MeCN. Future experimentation could focus on which variable is facilitating the reaction. It is of note, that the best solvent during optimisation was shown to be MeCN. However, on one occasion, changing the solvent to THF had previously been shown to dramatically improve the reaction performance for quinoline derivative **3ac**.

It is evident that further research is required to uncover the reasons for such stark differences in reaction performance. The findings of such work could lead to an enhanced understanding of the Heck reaction and the redox-relay variant. With

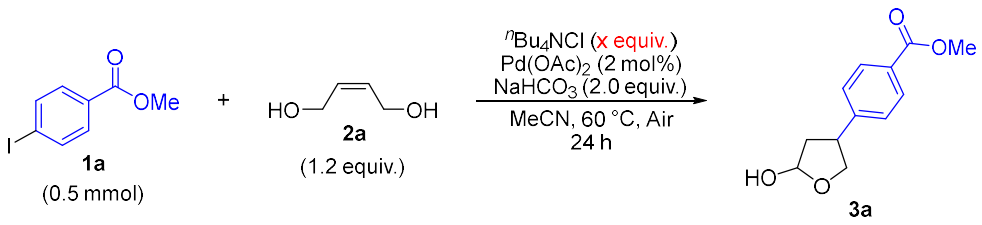
the prevalence of the Heck reaction in chemistry, understanding of the combinatory role base and solvents play could have genuine impact in the field.

2.7.2 Tetraalkylammonium Salt Effects

Another element of the reaction believed to warrant further investigation was the nature of the tetraalkylammonium salt used and how it interacts with the catalyst.

The effect of $^{n}Bu_4NCl$ on the redox-relay Heck reaction is significant as displayed by the large reduction in yield when sub-stoichiometric quantities of the salt are used (Entry 2) or when it is excluded completely (Entry 3) (Table 29). This may be rationalised by considering the interaction between tetraalkylammonium salts and the catalyst.

Table 29 Effect of tetrabutylammonium chloride on the redox-relay Heck reaction.



Entry[a]	$^{n}Bu_4NCl$ equiv.	Yield %[b]
1	1.0	98
2	0.5	63
3	0.0	53

[a]Reaction performed on a 0.50 mmol scale. [b]Yield determined by ^1H NMR spectroscopy using 1,3-benzodioxole as an internal standard.

It is believed that the palladium in the reaction media exists as nanoparticle clusters.[91] In these clusters, the individual palladium atoms at the surface can undergo oxidative addition before detaching from the nanoparticle bulk for the reaction to proceed. Nanoparticle clusters can be stabilised by a variety of

different approaches that include polymers,[132,133] dendrimers,[134,135] ionic liquids[136,137] and ionic surfactants such as $^{n}Bu_4NCl$.

The additives act to limit detrimental metal aggregation through offering steric stabilisation, electrostatic stabilisation, or both.[138] When the aggregation of palladium reaches a certain level, the unreactive palladium black is formed.

De Vries and co-workers suggest that a nanoparticle cluster is constituted of palladium atoms ligated to available halide anions.[90] This mechanism then allows for the ammonium cations to form electrostatic interactions with the cluster, limiting the possibility of inter-palladium interactions and subsequent metal aggregation (Figure 19).

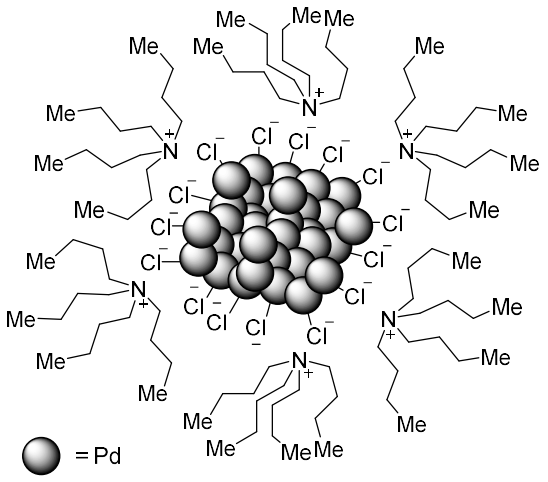
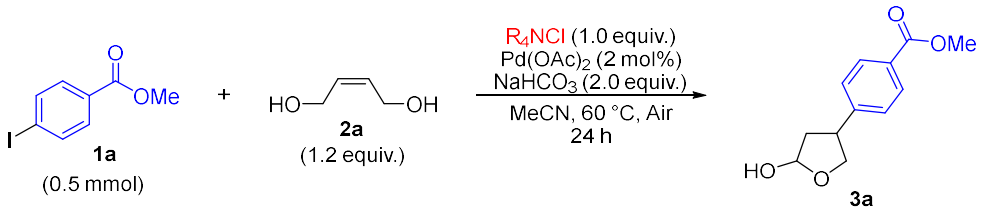


Figure 19 Palladium nanoparticle cluster stabilised by $^{n}Bu_4NCl$.

If this proposal is correct, then the length of carbon chain could have an influence on inter-cluster distances, palladium aggregation and therefore reactivity. To test the effect of chain length on the reaction, a variety of different ammonium salts were used in the reaction (Table 30). It is also worth considering that by shortening the alkyl chains present on quaternary ammonium salts, the solubilising ability will be reduced.

Table 30 Investigation of the carbon chain length of ammonium chloride salt.

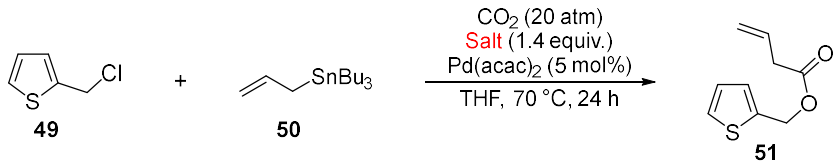


Entry[a]	R	Yield %[b]
1	Me	98
2	Et	88
3	^{n}Pr	93
4	^{n}Bu	98
5	^{n}Hp	87

[a]Reaction performed on a 0.50 mmol scale. [b]Yield determined by ^{1}H NMR spectroscopy using 1,3-benzodioxole as an internal standard.

Under the standard conditions, all salts gave excellent yields. The best results were obtained when methyl or butyl groups are used (Entries 1 and 4) but, clearly the length of carbon chain has negligible impact. This is in contrast to a study carried out by Sun *et al.* in their carboxylative coupling reaction of thiophene derivative **49** and allyltributylstannane **50** (Table 31).[139]

Table 31 Effect of carbon chain length on carboxylative coupling reported by Gao.[139]



Entry	Ammonium salt	Yield %
1	Me_4NBr	0
2	$^{n}Bu_4NBr$	73
3	$^{n}Oct_4NBr$	57
4	CTAB	20

They observed significant aggregation and poor yields for short and long chains (Entry 1 and 4). Dispersed colloids were seen for both tetrabutylammonium

bromide and tetraoctylammonium bromide and this translated into higher yields of 73 and 57% respectively (Entries 2 and 3).

Although Sun *et al.* use bromide salts and an alternative palladium pre-catalyst in what is a fundamentally different reaction, the results suggest that chain length may play a part in colloid formation and therefore reactivity.

It was of interest to investigate further the nature of the ammonium salt in our redox-relay Heck chemistry and how, crucially, it is removed during work-up to enable a successful subsequent reduction step.

During the reaction optimisation, it was found that removal of the quaternary ammonium salt during a work-up procedure allowed for an effective and efficient reduction to take place on the crude hemiacetal material. This was centred upon the idea that the salt is insoluble in Et_2O leading to the transfer of the salt into the aqueous solution. This was supported by the observation of precipitation when the reaction mixture was diluted with Et_2O.

When analysing literature data related to the the soluibility of quaternary ammonium salts in various solvents, measured by percentage of salt in the organic phase, it was surprising to see that $^{n}Bu_4NCl$ and $^{n}Bu_4NBr$ are both barely soluble in EtOAc (2 and 3% of the salts were observed in the organic layer respectively), the solvent that had detrimentally carried through the salt. Interestingly, 58% of tetrabutylammonium iodide is observed in the EtOAc layer, suggesting that it may have been the precipitated material. The experiments by Fox and Qiu involved the addition of 100 mg of salt to a 1:1 mixture of water and organic solvent (4 mL).[140]

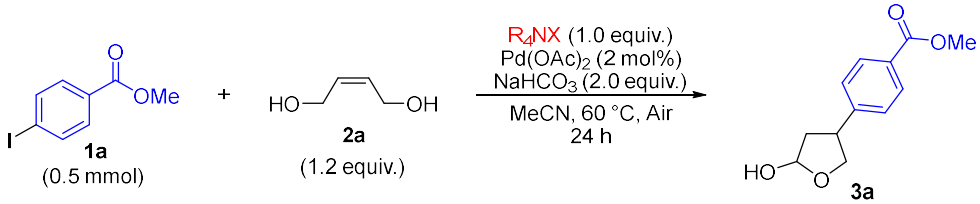
To investigate this, the salt from the reaction was isolated, dissolved in water, acidified with nitric acid and then treated with a solution of silver nitrate.[141,142] In what is a classical educational reaction for school children, precipitate formed with a pale-yellow colour associated with silver iodide. To reduce doubt over the nature of the precipitate formed, a solution of aqueous ammonia was added which did not dissolve the precipitate. Silver iodide is insoluble in ammonia whilst silver chloride is soluble, further supporting the existence of $^{n}Bu_4NI$ as the salt isolated. In this experiment, samples of pure $^{n}Bu_4NCl$ and $^{n}Bu_4NI$ were subjected to the same conditions, and it was clear that $^{n}Bu_4NI$ and the unknown

salt had the same characteristic results. Although this evidence is not conclusive, it goes some distance to confirming that $^{n}Bu_4NI$ was the isolated precipitate from the work up.

The reaction media contains a mixture of different ions. The relatively large volume of Et_2O added may act to preferentially precipitate out the quaternary ammonium salt containing the iodide anion over the chloride. Regardless, the ability to remove the ammonium salt is crucial to the efficiency of the two-step methodology and so the presence of the iodide anion could be particularly important in this respect. Undoubtedly, it is clear that halides play an important, yet complex role in this chemistry.

To further investigate the effect of the halide anion, quaternary butyl, and ethyl ammonium salts with either chloride, bromide, or iodide as the counterion were were used in the reaction. From these results, it was clear that chloride salts were superior to bromide and iodide salts. The result was the same for both ethyl and butyl ammonium species (Table 32**)**.

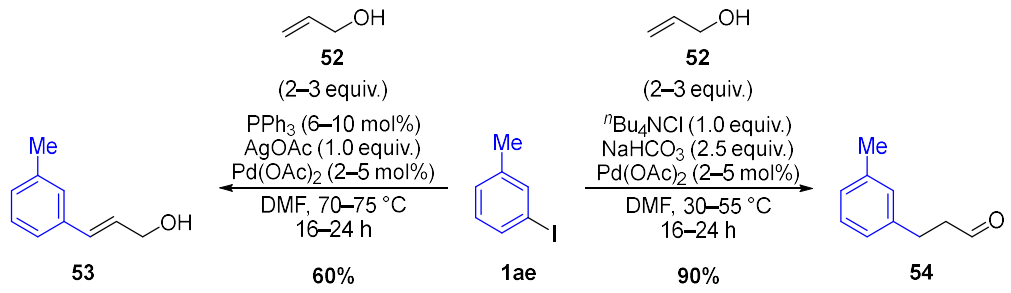
Table 32 Investigation of halide ion and carbon chain length.



Entry[a]	X	R	Yield %[b]
1	Cl	Et	88
2	Br	Et	64
3	I	Et	21
4	Cl	^{n}Bu	98
5	Br	^{n}Bu	71
6	I	^{n}Bu	17
7	no quaternary salt		53

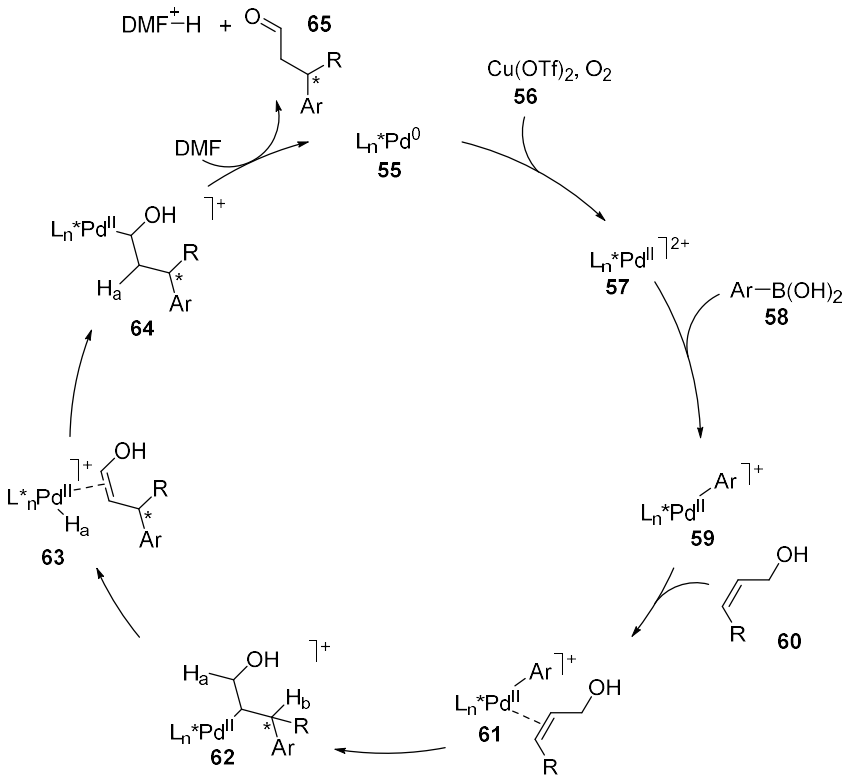
[a]Reaction performed on a 0.50 mmol scale. [b]Yield determined by ^1H NMR spectroscopy using 1,3-benzodioxole as an internal standard.

Interestingly, the use of iodide salts resulted in lower yields than the reaction described earlier that was carried out with no quaternary ammonium salt (Entry 7), suggesting that high concentrations of the iodide have a detrimental effect on the reaction. This study again shows the importance of the halide present. Jeffrey and co-workers reported in 1991, a reaction that supports the importance of halides.[79] They modified the conditions from their standard redox-relay Heck reaction and replaced sodium hydrogen carbonate and $^{n}Bu_4NCl$ with silver acetate and a sub-stoichiometric quantity of triphenylphosphine (Scheme 69).[79]



Scheme 69 Effect of alternative conditions for Jeffrey's Heck coupling.[79]

This modification shut down the redox-relay and returned the standard Heck product. Silver acetate is known to act as a halide scavenger, enforcing a cationic mechanism.[143] The inability of these cationic palladium conditions to give the redox-relay Heck product is contrary to the findings of the Sigman group who were able to effectively demonstrate how a cationic palladium catalyst could promote an enantioselective redox-relay Heck reaction. Their work has indicated a cationic mechanism (Scheme 70).



Scheme 70 Cationic palladium catalysed redox-relay Heck reaction based on Sigman's work.[104,117]

The cycle starts with a palladium(0) source **55** which undergoes oxidation with copper(II) triflate **56** and molecular oxygen to give a palladium(II) species **57**. The triflate anions (not included for clarity) lead to a cationic cycle. Transmetallation then occurs with the boronic acid **58** to yield an arylpalladium(II) species **59** which can coordinate to the olefin of the alkenol **60**. A *syn*-addition of the aryl and palladium groups gives palladium(II) species **62**, with regio- and enantioselectivity determined from substrate and ligand effects respectively. A *β*-hydride elimination then proceeds with the selective removal of H_a over H_b to drive the relay toward intermediate **64**, the thermodynamic driving force for the reaction. Solvent-induced[144] 'oxidative deprotonation' then takes place to give the carbonyl product **65** and turnover the catalyst back to palladium(0) **55**.[145]

The current literature suggests the redox-relay Heck reaction under 'Jeffrey conditions' proceeds *via* an anionic mechanism. Figure 20 shows a postulated mechanism for an anionic redox-relay Heck reaction drawing upon the general literature consensus from related reactions.[90–92,97,146,147] It is worth predicating

the postulated mechanism (Figure 20) with the fact that no study has examined an anionic pathway for the redox-relay Heck reaction.

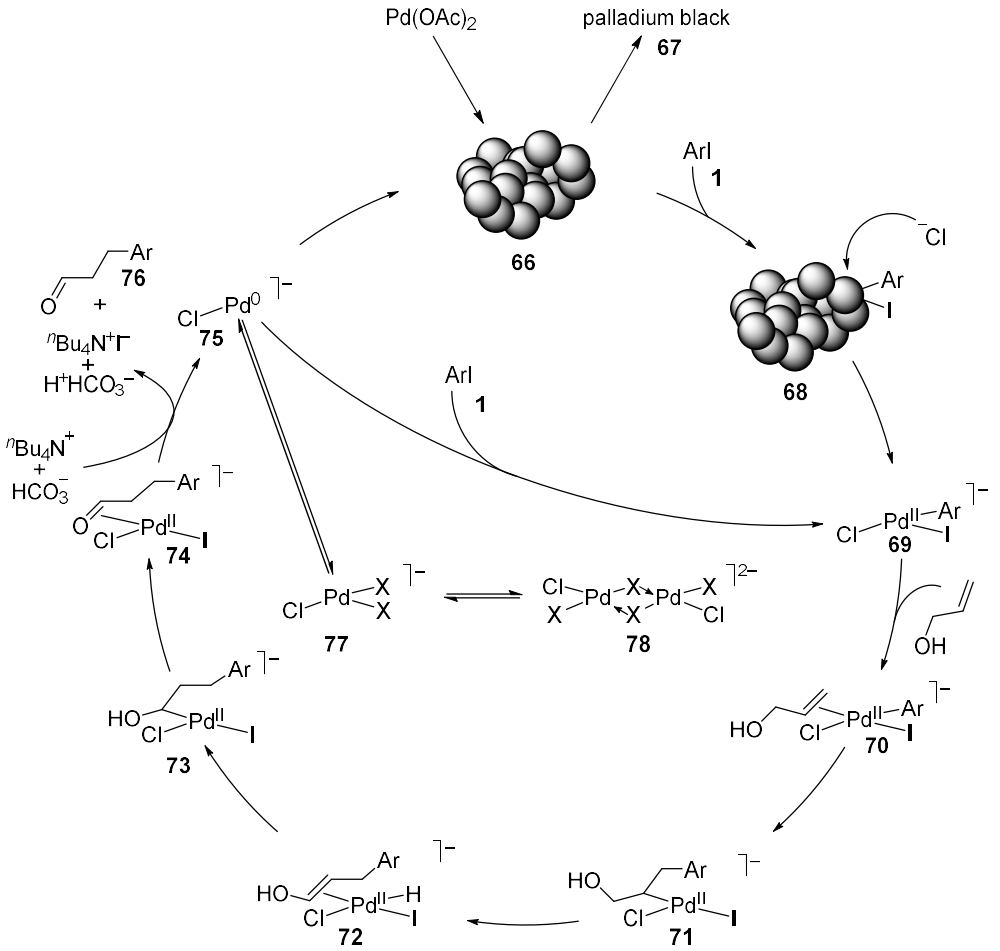


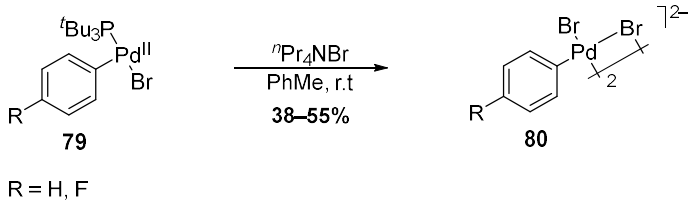
Figure 20 Postulated anionic mechanism for the redox-relay Heck reaction.

Palladium(II) acetate is reduced to palladium(0) which aggregates to form nanoparticles **66**, supported by quaternary ammonium salts as described in Figure 19.[90] The nanoparticles **66** have the potential to aggregate further which leads to unproductive, palladium black **67** formation. Generally, the nanoparticles are well supported by the quaternary ammonium salt and participate in an oxidative addition event that most likely occurs on the nanoparticle surface to give **68**.[98,99] The addition of a chloride ion allows for the negatively charged palladium(II) species **69** to dissociate fully from the cluster. As in standard Heck reactions, the alkene then coordinates to the palladium(II)

species before the initial migratory insertion takes place to give **71**. β-hydride elimination and a second migratory insertion are then undertaken to place palladium at the α-position of the alcohol to give species **73**. A base induced 'oxidative deprotonation' event is then likely to take place, yielding the carbonyl product **76**.[145] The new palladium(0) species **75** can either recombine with a nanoparticle cluster **66** and undergo a further oxidative addition event, or take part in the oxidative addition step to **69** without first recombining.

The role of halides is central in these mechanisms, species **77** and **78** have been observed in 'ligandless' Heck and redox-relay Heck reactions using ES-MS and EXAFS techniques, respectively.[96,97] DeVries and co-workers believe these species originate from palladate(0) species **75** and molecular iodine, although they cannot rationalise the formation of the iodine.

Following the discovery of the dimeric species, Hartwig and co-workers demonstrated the activity of similar dianionic dimers after firstly isolating them through the reaction of palladium(II) compounds with quaternary ammonium halides (Scheme 71).[95]

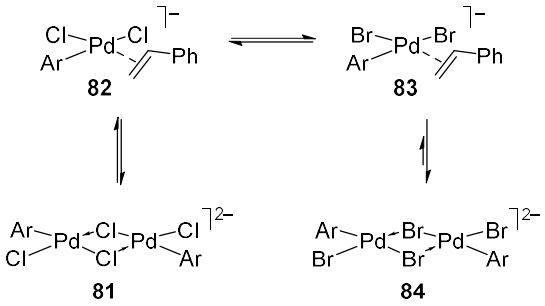


Scheme 71 Hartwig's synthesis of anionic species **80**.[95]

The isolation of the dimers **80** allowed for the first characterisation of the species. The complexes **80**, found to be air-stable crystalline compounds, were then used as catalysts in other Heck reactions. Hartwig and co-workers demonstrated that the anionic complexes react faster than neutral, phosphine-ligated analogues.[95]

Clearly the dimeric anionic complexes **80** are important intermediates in the 'ligandless' Heck reaction. Strassner and co-workers reported the results of a computational study focused on the 'ligandless' Heck reaction with aryl

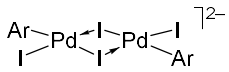
chlorides in 2018.[94] Although they did not use aryl iodides as coupling partner, they did detail some interesting observations that might be applicable. They suggested that dimeric species **81** was the resting state of the catalyst, in equilibrium with the active catalyst **82**. They found that increasing concentration of bromide ions resulted in more of species **83** forming. The related dimeric species **84** was found to be significantly lower in energy, pushing the equilibrium to the unproductive resting state **84**, decreasing catalytic activity (Scheme 72).



Scheme 72 Potential catalyst resting states.

With the Hartwig group finding the same bromide rich dimers being catalytically active or at least readily preceding a catalytically active species,[95] other elements of the reaction media are likely playing influential roles in either system.

Our experiments detailed in this thesis show that reactions carried out with quaternary ammonium chloride salts gave significantly higher yield (>60% increase) than those with quaternary iodide salts (Table 32). Also, the use of $^{n}Bu_4NI$ gave lower yield than when no quaternary ammonium salt was used. One logical explanation might be that as the reaction progresses, the concentration of iodide in the reaction media is increased. This increased iodide concentration may lead to greater inclusion of the halide in the formation of an anionic dimer **85** (Figure 21).



85

Figure 21 Postulated anionic dimer **85**.

If the iodide behaves similarly to the bromide, then the dimer formed could be an unproductive catalytic intermediate. Further analytical work including the use of ES-MS and EXAFS or DFT calculations could be undertaken to determine whether this is the case within our reaction system.

Unfortunately, because the proposed mechanism for the anionic Heck reaction was proposed after much of the early work was carried out on the redox-relay Heck reaction under 'Jeffrey conditions', there is a void in the understanding of the anionic redox-relay Heck reaction. Evidence of faster reaction rates compared to neutral pathways should prompt further investigation into the potential of this system.

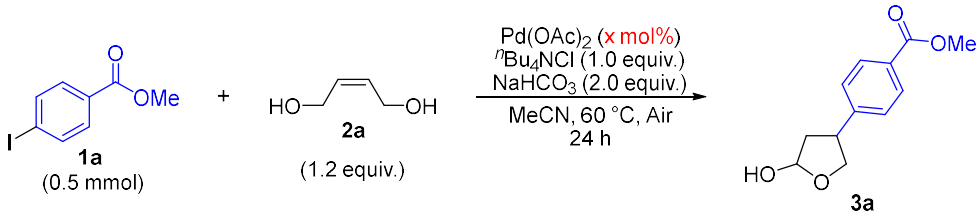
2.7.3 'Homeopathic' Palladium

As well as employing quaternary ammonium salts to reduce aggregation to palladium black, another method has also been used. It is believed that by reducing the palladium in the reaction to 'homeopathic' levels (0.01% to 0.1% catalyst loading), the probability of metal-metal interaction would be minimal. On the other hand, the relatively large quantity of substrates in the reaction would result in productive interactions with the catalyst. This approach, which can dramatically reduce the amount of expensive palladium needed, or the need for quaternary ammonium salts, has been pioneered by the groups of Reetz[91,148] and De Vries.[92,147]

This method has also been adopted unintentionally; some researchers previously believed their 'transition-metal-free' Suzuki reaction was taking place in the absence of catalyst only to be disproved when traces of palladium were found in the sodium carbonate being used.[149,150]

As an initial look into this area, different solutions with varying concentration of palladium were prepared and used as the palladium source in the standard optimisation reaction (Table 33).

Table 33 Redox-relay Heck reaction with 'homeopathic' palladium.



Entry[a]	Palladium loading mol%	Yield %[b]
1	2.0	87
2	8.0×10^{-2}	2
3	2.0×10^{-2}	>1%
4	12.5×10^{-4}	>1%

[a]Reaction performed on a 0.50 mmol scale. [b]Yield determined by ^{1}H NMR spectroscopy using 1,3-benzodioxole as an internal standard.

The control reaction (Entry 1) gave ~10% lower yield than under standard conditions suggesting adding palladium as a solution may have had an adverse effect on activity. When replicating the quantities of palladium used by others in this field, product **3a** was observed only in trace amounts (Entries 2–4).

Notably, this was a one-off study and some optimisation in this area may yield better results. For example, with the palladium sparsely located perhaps the presence of a quaternary salt to stop aggregation is unnecessary or even detrimental in this context.

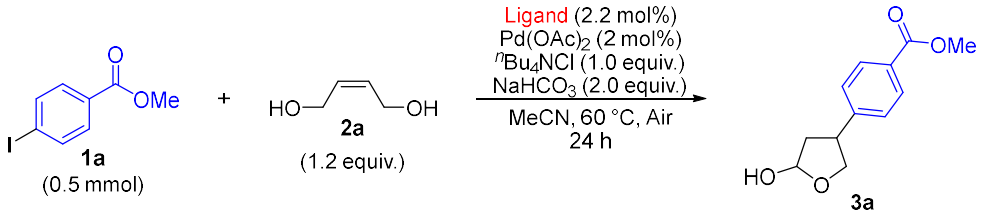
The benefits of realising such a system would be significant. Elimination of ^{n}Bu$_4$NCl, 'homeopathic' quantities of catalyst and the possibility to recycle the insoluble palladium black combined would reduce cost and waste in an industrial setting.[97]

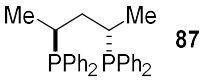
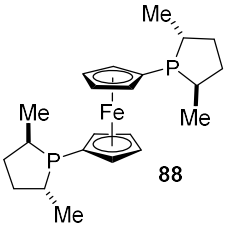
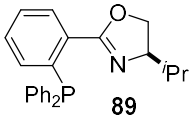
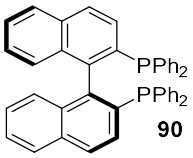
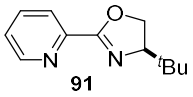
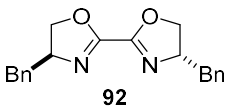
2.7.4 Chiral Ligands and Enantioselectivity

Assuming the mechanism for this reaction does proceed *via* a 'ligandless' anionic route, it was of interest to see the effect of introducing ligands to the reaction. Furthermore, if the reaction could take place in the presence of ligands, then perhaps the enantioselective generation of products could be possible.

To test the feasibility of an enantioselective THF synthesis, a selection of different chiral ligands was chosen (Table 34). Additionally, in one example triphenylphosphine was used to observe the effect of a simple achiral ligand against the standard conditions.

Table 34 Redox-relay Heck reaction with ligands.



Entry[a]	Ligand	Yield %[b]
1	none	98
2	PPh_3 **86**	79[c]
3	 **87**	8
4	 **88**	10
5	 **89**	10
6	 **90**	55
7	 **91**	83
8	 **92**	98

[a]Reaction performed on a 0.50 mmol scale. [b]Yield determined by ^{1}H NMR spectroscopy using ^{n}Bu$_4$NCl as an internal standard. [c]4.4 mol% of ligand used.

The use of triphenylphosphine **86** led to a yield almost 20% lower than the control (Entry 2). This reinforces the view that the 'ligandless' form of palladium has greater activity than when complexed with a ligand typically known to enhance stability. Other phosphine-based ligands **87**–**89** gave poor yields (Entries 3–5), the exception being axially chiral (*S*)-BINAP **90** which

gave product in 55% yield (Entry 6). Palladium with PyrOx and BOX ligands (**91** and **92**) seemed to catalyse the reaction effectively (Entries 7 and 8). It is worth noting that no other reactivity was observed, with just starting material accounting for remaining mass balance.

Unfortunately, when attempting to determine the enantioselectivity by HPLC, finding suitable conditions to separate the two diastereoisomers was challenging. This was due to the similarity between the products, the tendency for the products to degrade under certain column conditions and the presence of the equilibrium products, hydroxy aldehydes. To resolve this issue, the two experiments that returned the best yields (Entries 7 and 8) were reduced to the associated THF product **5b** to determine enantioselectivity. This allowed for the two enantiomers to be separated for analysis but, disappointingly, for both examples, the products were racemic.

As it stands, achieving an enantioselective redox-relay Heck synthesis of substituted THFs under these conditions seems unlikely. There are however modifications that could facilitate an asymmetric methodology. By using diazonium salts, boronic acids or triflates, the cationic pathway opens, allowing for a stable bidentate ligand-catalyst chiral structure throughout the duration of the reaction, this approach has been well developed by Sigman and co-workers.[104,117,145,151–153]

An interesting possibility that has received little attention is an enantioselective redox-relay Heck reaction that proceeds *via* an anionic pathway. This could potentially be achieved using chiral bidentate ligands that carry a formal negative charge such as NHC ligands. Palladate complexes have recent precedence for catalysing Heck reactions,[154–156] including one study that observed alkene migration.[157] To the best of our knowledge an enantioselective Heck reaction using anionic palladium has yet to be realised.

3 Conclusion

In summary, the synthesis of 3-substituted THFs has been achieved through an efficient, redox-relay Heck/reduction protocol.

The methodology tolerates a wide variety of commercially available aryl iodides containing numerous functional groups. Included were *N*-Boc protected aniline derivatives (**5e**, **5n** and **5t**) and an amino acid derivative (**5k**). Halides were also tolerated potentially allowing for further transformation *via* the numerous palladium-mediated coupling reactions. The aryl iodides successfully returned products when substituted in *para*- and *meta*-positions and to a lesser extent *ortho*-positions with steric hindrance seemingly having a deleterious effect on yield.

When expanding the reaction to include different diols, mixed results were obtained. A series of α-substituted diols were prepared in two steps with the aim of accessing 2,4-disubstituted THFs. It was found that four diastereomeric products were obtained, ratios of the products were reported but clear trends were difficult to rationalise with confidence. However, the use of a 1,1-disubstituted alkene diol **33** allowed for the synthesis of a useful benzyl-substituted THF **34** in good yield without optimisation.

In an effort to further demonstrate the utility of the redox-relay Heck reaction, a number of derivatisation reactions were shown from hemiacetal **3b**. A Grignard addition to hemiacetal **3b** gave diol diastereoisomers **43** and **44** which could be cyclised to give the calyxolane natural products (±)-**8** and (±)-**9**. The use of two different cyclisation procedures allowed for either calyxolane A (±)-**8** or calyxolane B (±)-**9** to be prepared in excess.

Finally, with the reaction scope investigated, the details of the methodology were more closely scrutinised. The results of which provided further insight into the role of base, tetraalkylammonium salts, halides, and the possibility of 'homeopathic' palladium in this redox-relay Heck system.

4 Future Work

Further work for this project could focus on elaborating more on these elements of the reaction to gain greater understanding of the influential factors. In particular, finding evidence of anionic dimer **85** could prove important in our understanding of the reaction mechanism.

The next logical step for this work is to assess the possibility of an enantioselective variant reaction. How different ligands act may also provide more information on the electronic nature of palladium during the reaction.

Another area for further study is the different reactivity observed in the presence of other bases. Isolation of alternative products would aid us in our understanding of the popular Heck reaction.

During this project, the total synthesis of calyxolanes A (**±**)-**8** and B (**±**)-**9** and analogues was undertaken. To our knowledge, an assessment of their biological activity is unknown and so, investigations into this area could prove fruitful and further expand the utility of this work.

Finally, the redox-relay Heck/reduction protocol was carried out on *cis*-2-butene-1,4-diol **2a** in order to access the 5-membered THF ring. The application of this protocol to larger rings and with different heteroatoms was a logical next step and as such, is featured in the following chapter.

Synthesis of Substituted Benzoxepanes Using a Redox-Relay Heck Strategy

1 Introduction

Benzoxepanes are seven-membered oxygen-containing heterocycles fused to a phenyl ring. Like the five-membered THF, the benzoxepane motif is found in numerous bioactive compounds and natural products such as cyclosiphonodictyol A **I132**, isolated from Caribbean sponge *Aka coralliphagum*,[158] doxepin **I133**, an anti-depressant treatment,[159] and novel pentaketide ansamycin, microansamycin F **I134** (Figure 22).[160]

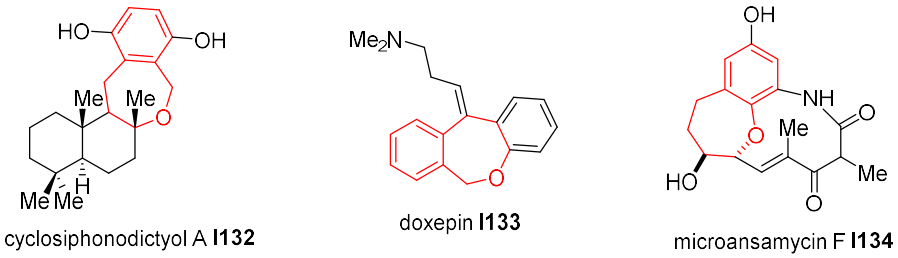
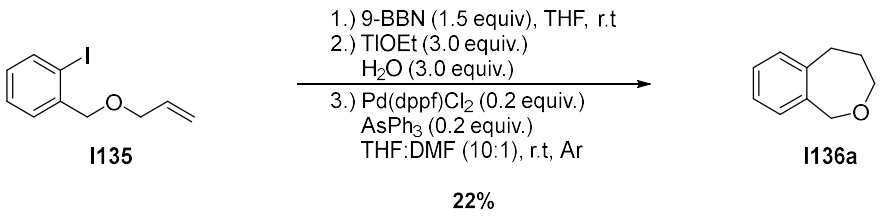


Figure 22 Bioactive compounds and natural products featuring the benzoxepane motif.

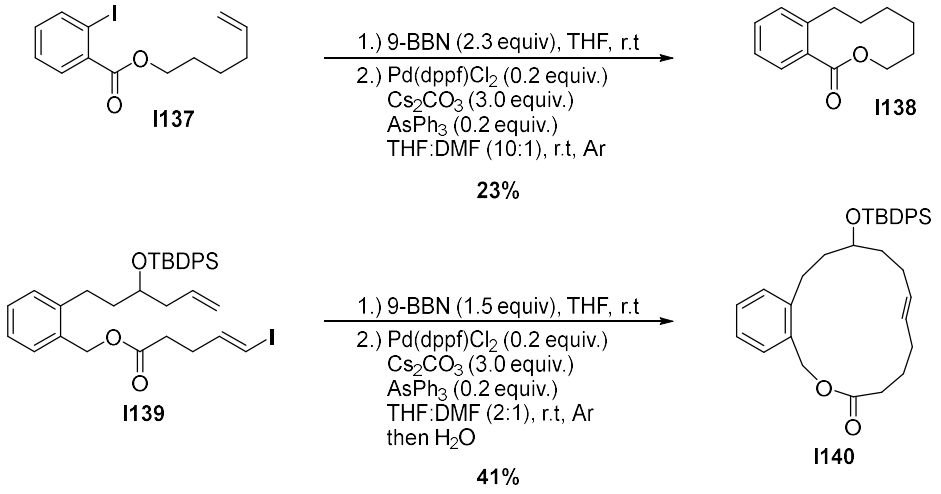
1.1 Synthesis of Benzoxepanes

Several approaches have been utilised to access benzoxepane cores, which is arguably a tougher synthetic challenge than THF synthesis given the entropic disadvantage of forming a seven-membered ring compared to a five-membered equivalent.[161] Danishefsky and co-workers employed an intramolecular *B*-alkyl Suzuki reaction to form benzoxepane **I136a** from benzyl ether **I135** (Scheme 73).[162]



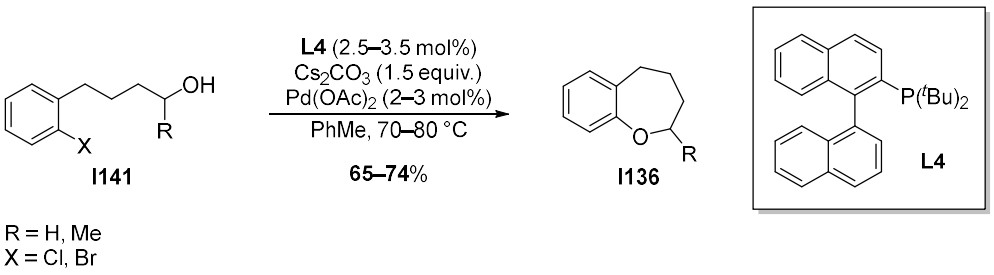
Scheme 73 Danishefsky's synthesis of benzoxepane **I136a**.[162]

This strategy gave a poor yield of benzoxepane **I136a**, whilst a similar yield was observed for the formation of the larger ten-membered ring **I138**. Both these examples start from *ortho*-substituted aryl iodides. The Danishefsky group later directed the activity away from the aryl ring by using a distal vinyl halide **I139**, although the product yield increased significantly, it remained modest (Scheme 74). Unfortunately, applying this approach to the synthesis of a benzoxepane would result in the formation of an unsaturated benzoxepine.



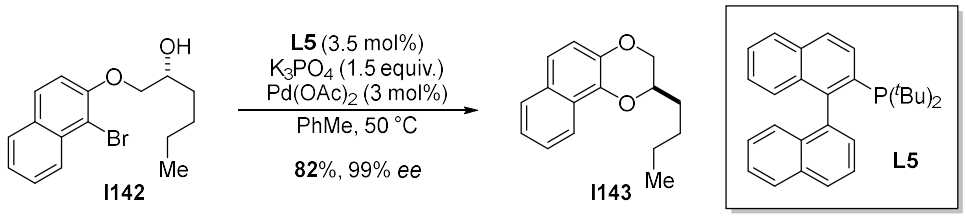
Scheme 74 Danishefsky's synthesis of large rings **I138** and **I140**.[162]

The Buchwald group generated a number of phenyl-fused *O*-heterocycles by also using palladium catalysis. They made two benzoxepanes **I136** from both aryl bromides and chlorides (Scheme 75).[163]



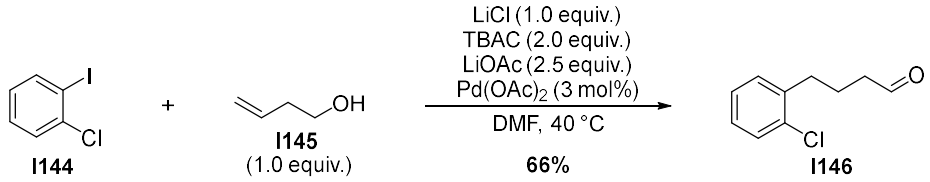
Scheme 75 Buchwald's synthesis of benzoxepanes **I136**.[163]

This method allows access to benzoxepanes in good yield and has the potential to return enantioenriched products when using enantioenriched substrates as Buchwald demonstrated when forming other heterocycles such as substituted 1,4-dioxane **I143** (Scheme 76).[163]



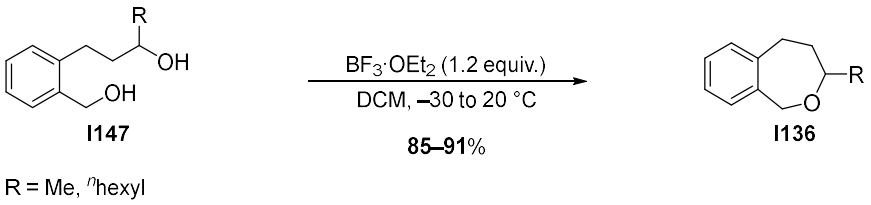
Scheme 76 Buchwald's synthesis of substituted 1,4-dioxane **I143**.[163]

Interestingly, Buchwald and co-workers employed a redox-relay Heck reaction in their substrate synthesis (Scheme 77).[163] Instead of using the carbonyl functionality generated, Buchwald reduced it to give the alcohols required for his chemistry.



Scheme 77 Buchwald's synthesis of aldehyde **I146** *via* the redox-relay Heck reaction.[163]

The Buchwald group's method can provide better yields of the benzoxepane than the method of Danishefsky and co-workers, but the need for two palladium-catalysed reactions within their synthetic route is unappealing. In a different approach described by Yus and co-workers, diols were subjected to a Lewis acid-mediated cyclisation to give substituted benzoxepanes (Scheme 78).[164]



Scheme 78 Yus' synthesis of benzoxepanes **I136**.[164]

In addition to the examples in Scheme 78, Yus and co-workers also demonstrated the chemistry in the synthesis of spirocycle **I148** and cyclohexane-fused benzoxepane, returned as a single diastereoisomer **I149** (Figure 23).[164]

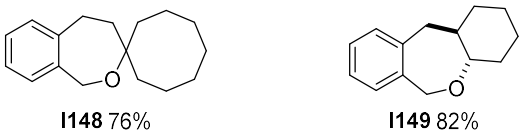
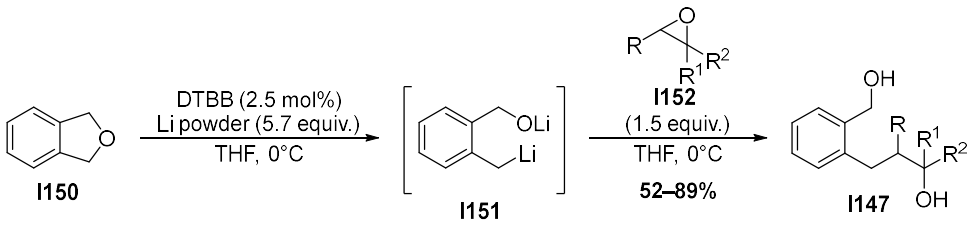


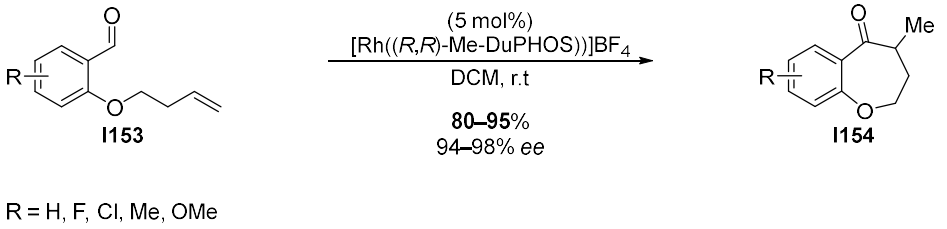
Figure 23 Spirocycle **I148** and cyclohexane-fused benzoxepane **I149**.[164]

Although, generally high yielding, the diols were first prepared following an initial sequence from 1,3-dihydroisobenzofuran **I150** in varied yield (Scheme 79).



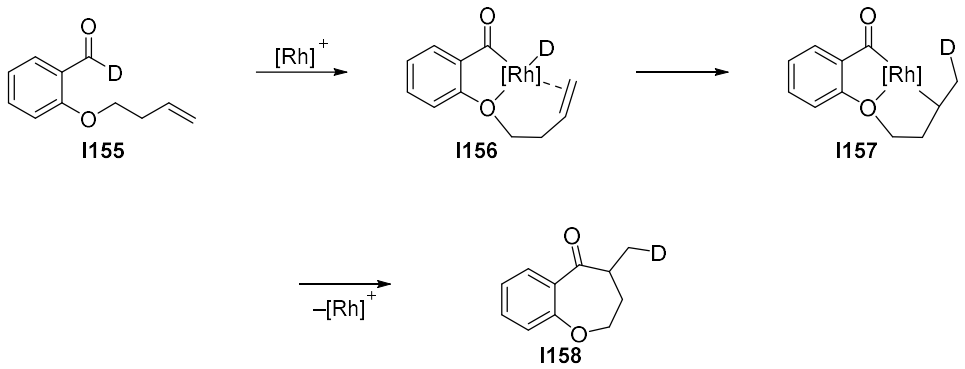
Scheme 79 Yus' synthesis of diols **I147** as benzoxepane precursors.

Dong and co-workers were able to demonstrate a rhodium-catalysed enantioselective intramolecular hydroacylation reaction to access benzoxepanes **I154**. With eight examples, yields exceeding 80% and excellent enantioselectivity, this simple method is an important contribution to benzoxepane synthesis (Scheme 80).[165]



Scheme 80 Dong's enantioselective synthesis of benzoxepanes **I154**.[165]

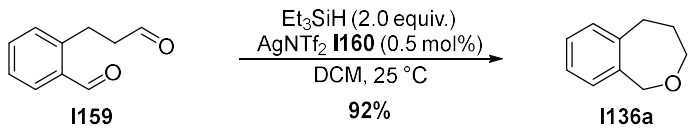
The Dong group's proposed mechanism, which is supported by deuterium labelling studies, begins with rhodium inserting in the C–H/D bond before alkene insertion to give **I157**. A reductive elimination step then follows to give the product **I158** (Scheme 81).[165]



Scheme 81 Proposed mechanism for Dong's benzoxepane synthesis supported by deuterium labelling.[165]

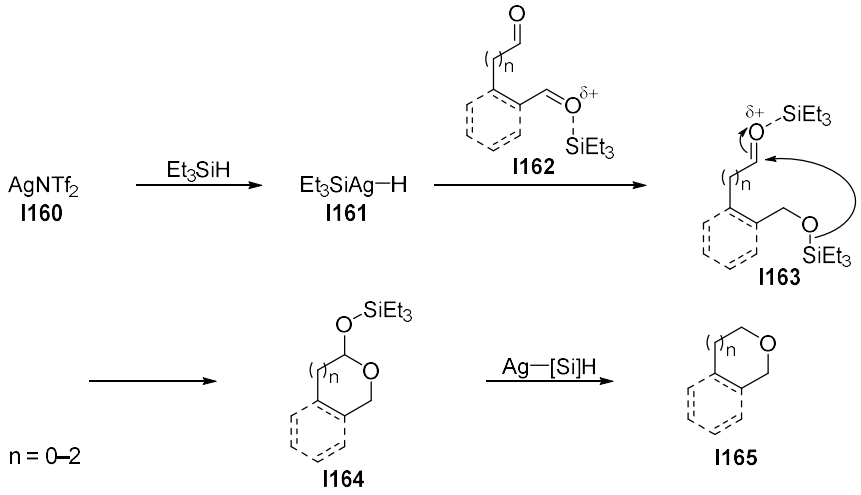
More recently, Xu and co-workers described a silver(I)-catalysed reductive annulation of dialdehydes. The method was used to construct a variety of

different ring sizes from 5-membered to 11-membered cycles including benzoxepane **I136a** in excellent yield (Scheme 82).[166]



Scheme 82 Xu's synthesis of benzoxepane **I136a**.[166]

Only small qualities of silver salt $AgNTf_2$ **I160** were needed in combination with Et_3SiH to form silver hydride species **I161**, which the authors propose, reduces an activated carbonyl to give silylated alcohols **I163**. Intramolecular attack from the alcohol to the second activated aldehyde gives cyclised hemiacetal derivatives **I164** which are then reduced to the annulated products **I65** (Scheme 83).[166]



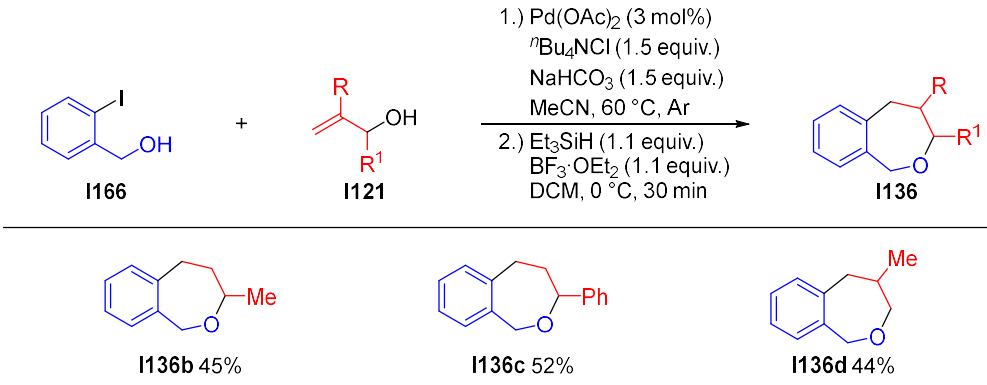
Scheme 83 Proposed mechanism for Xu's reductive cyclisation.[166]

Whilst the methods described in this chapter provide access to a few benzoxepanes, often they are one-off examples and lack substitution on either the aryl or aliphatic rings. The redox-relay Heck/reduction protocol developed for the synthesis of substituted THFs could address these problems and provide a straightforward alternative.

1.1.1 Application of the Redox-Relay Heck Reaction to Benzoxepanes

A study was carried out by fourth year project student Jacob Wills (Cuthbertson Group) to prove the applicability of the redox-relay Heck/reduction strategy to access to benzoxepanes.[167] After developing modified conditions, which included the purification of the Heck product prior to reduction, he found it was possible to form the 7-membered heterocycle **I136b**–**I136d**. Unfortunately, the yields observed were markedly lower than for the THF study (Table 35).

Table 35 Preliminary results for the synthesis of substituted benzoxepanes.[a]



[a]Reactions performed by Jacob Wills.[167] [b]Isolated yield after purification by column chromatography.

These promising results prompted a more thorough investigation with the aim of expanding the reaction scope and improving yield.

2 Results and Discussion

2.1 Aims and Objectives

With preliminary results obtained (Table 35), this project would also begin with optimisation studies. This would be followed by an investigation into the reaction scope which would require the preparation of some additional substrates.

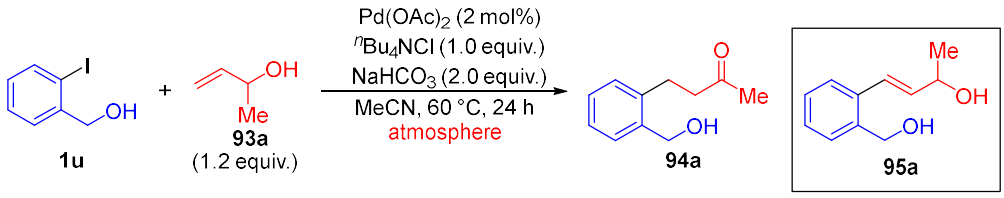
Finally, an investigation into the applicability of this method in the formation of other heterocycles would be carried out, focusing on different ring sizes and alternative heteroatoms.

2.2 Reaction Optimisation

The preliminary studies had indicated that specific areas of the reaction were influential in increasing yield; substrate stoichiometry, reaction atmosphere and equivalence of $^{n}Bu_4NCl$. With other differences in the conditions found to have little effect, work began on a focused optimisation study.

The atmosphere of the system was the first part of the reaction to be investigated. 3-Buten-2-ol **93a** and 2-iodobenzyl alcohol **1u** were used as substrates in a reaction carried out under the optimised conditions from the THF project (Table 36). When analysing the ^{1}H NMR spectrum of the unpurified reaction mixture, it became clear that there was another compound in the crude material, thought to be the Heck product **95a**, supported by the presence of two signals corresponding to olefinic protons in a *trans*-configuration (J = 15.8 Hz).

Table 36 Investigation of reaction atmosphere.

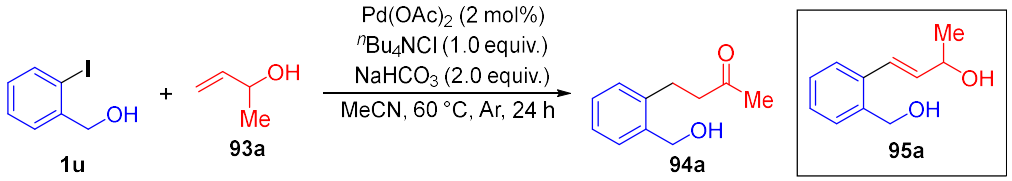


Entry[a]	Atmosphere	Yield %[b]	95a %[b]
1	Air	55	24
2	Ar	68	16

[a]Reaction performed on a 0.50 mmol scale. [b]Yield determined by ^{1}H NMR spectroscopy using 1,3-benzodioxole as an internal standard.

Interestingly, with these substrates, the reaction performs marginally worse (55% vs. 68%) under aerobic conditions than when under argon (Entries 1 and 2). The amount of side-product **95a** was also lower under anaerobic conditions leading to the expulsion of oxygen in future studies. The second variable to be investigated was the stoichiometry of the two coupling partners (Table 37).

Table 37 Optimisation of reaction stoichiometry.

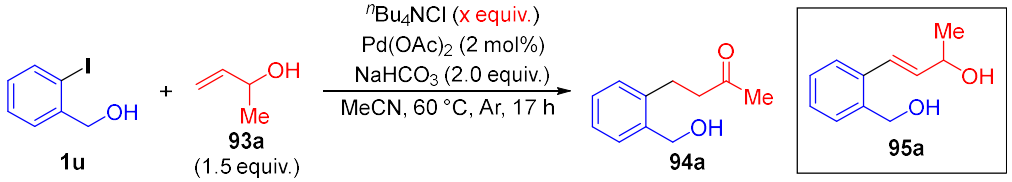


Entry[a]	Aryl iodide equivalents	Alkene equivalents	Yield %[b]	95a %[b]
1	1.2	1.0	59	15
2	1.1	1.0	61	15
3	1.0	1.0	63	13
4	1.0	1.1	62	16
5	1.0	1.2	73	15
6	1.0	1.5	80	16
7	1.0	2.0	80	16

[a]Reaction performed on a 0.50 mmol scale. [b]Yield determined by ^{1}H NMR spectroscopy using 1,3-benzodioxole as an internal standard.

Similarly to the THF project (Chapter 2), higher yields are obtained when the equivalents of the unsaturated alcohol **93a** and the reaction time are increased (Entries 1–6). When 1.5 equivalents of the allylic alcohol were used, the yield reached 80% (Entry 6), increasing the alcohol **93a** to 2.0 equivalents gave no improvement (Entry 7). With the small but useful increase in yield seen when 1.5 equivalents of alcohol used, we proceeded to investigate how the quantity of the quaternary ammonium salt may influence the reaction (Table 38).

Table 38 Investigation of $^{n}Bu_4NCl$ equivalents.

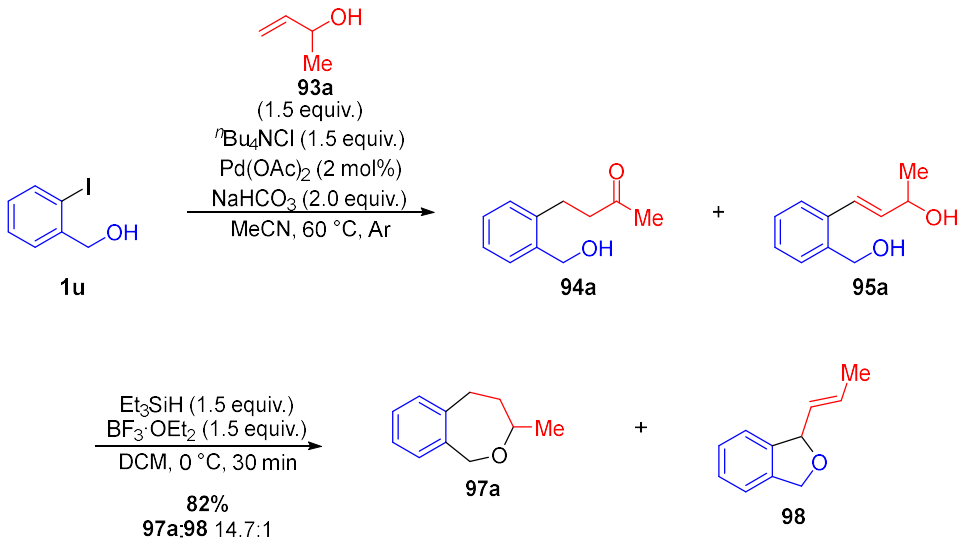


Entry[a]	$^{n}Bu_4NCl$ equivalents	Yield %[b]	95a %[b]
1	1.0	65	16
2	1.5	77	18

[a]Reaction performed on a 0.50 mmol scale. [b]Yield determined by ^{1}H NMR spectroscopy using 1,3-benzodioxole as an internal standard.

Pleasingly, increasing the equivalents from 1.0 (Entry 1) to 1.5 led to higher yield (Entry 2). These results, which were obtained after a shortened 17 hour reaction, indicated that a 24 hour reaction gave greater conversion.

During the THF project, it was possible to eliminate the chromatographic purification of the redox-relay Heck product before the reduction step. Unfortunately, when employing the same approach in the synthesis of benzoxepanes, the co-elution of postulated minor side-product **98** was observed. It was thought to have resulted from cyclisation of the standard Heck product **95a** detected in the first step of the sequence.



Scheme 84 Undesired side-product **97** derived from the redox-relay Heck/reduction sequence.

Therefore, it was decided that a purification step following the redox-relay Heck reaction was necessary, as the redox-relay Heck **94a** and standard Heck **95a** products were found to be readily separable at this stage.

Content with the optimisation studies, and aware of the need for a chromatographic purification prior to reduction, an investigation of the reaction scope was next investigated.

2.3 Synthesis of Substrates and Scope Investigations

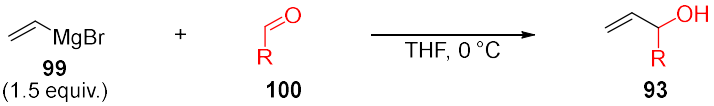
The first area to be investigated was the scope of allylic alcohols in the reaction. Pleasingly, some allylic alcohols are commercial, leading to an expedited synthesis of benzoxepane derivatives. However, some other allylic alcohols we sought were unavailable, necessitating synthetic preparation.

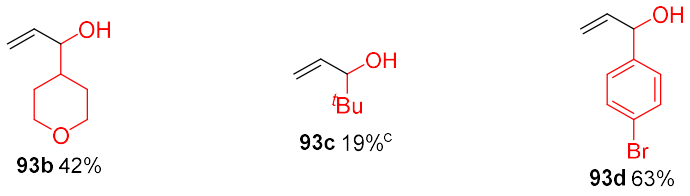
2.3.1 Synthesis of Allylic Alcohols

A simple synthesis of substituted allyl alcohol derivatives **93** was planned. Following a general procedure reported by Taylor and Smith,[168]

vinylmagnesium bromide **99** was added to different aldehydes **100** to access the desired substrates **93** (Table 39).

Table 39 Synthesis of allylic alcohols with substitution at the α-position.[a,b]





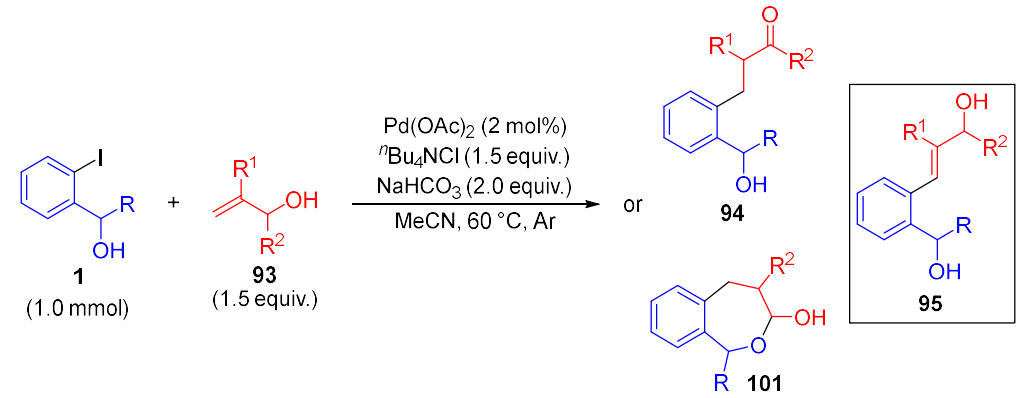
[a]Reactions performed on a variety of scales, see experimental for details. [b]Isolated yield after purification by column chromatography. [c]Obtained as a solution due to volatility.

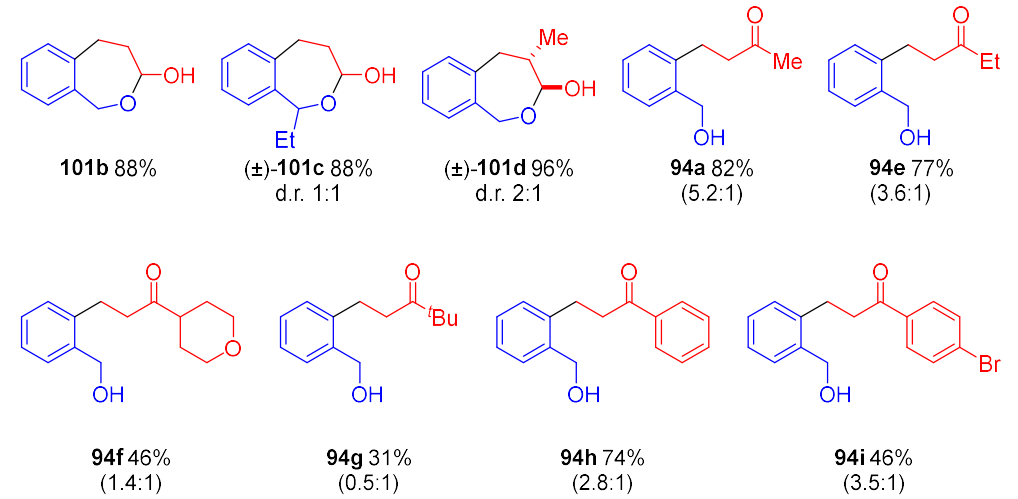
Although the yields obtained were mixed, the alcohols **93b**–**93d** were prepared in sufficient quantity to test the allylic alcohol scope of the redox-relay Heck reaction along with a variety of commercial substrates.

2.3.2 Allylic Alcohol Scope

With a selection of allylic alcohols substituted in both α- and β-positions in-hand, an investigation of the scope for the redox-relay Heck reaction was undertaken using the optimised conditions (Table 40).

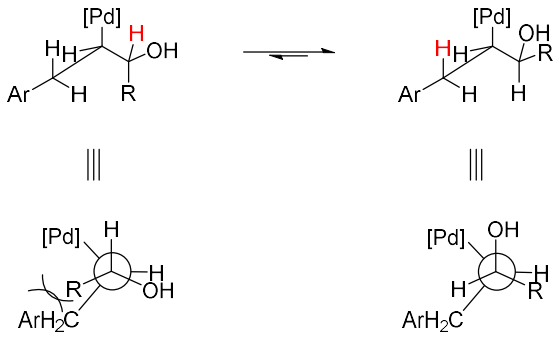
Table 40 Allylic alcohol scope.[a,b]





[a]Isolated yield after purification by column chromatography. [b]Ratio in parentheses corresponds to quantity of desired product **94** relative to undesired Heck side-product **95** in the unpurified reaction mixture.

Unsurprisingly, when aldehydes are formed in the redox-relay Heck reaction, spontaneous cyclisation takes place to give hemiacetal products **101b–101d**. This is in contrast to the uncyclised ketones **94a** and **94e–94i**, derived from α-substituted allylic alcohols. Yields for the redox-relay Heck reaction varied, although, allylic alcohols featuring primary aliphatic substitution or no substitution at the α-position gave very good yields **94a–94e**. When allylic alcohols featured secondary or, to a greater extent, tertiary substitution at the α-position, conversion to the redox-relay Heck product is reduced in favour of the standard Heck product. This is likely because of a less favoured β-elimination of the hydride required for a redox-relay event. The elimination is less favoured because of the conformation adopted to accomodate larger substituent groups (Scheme 85).

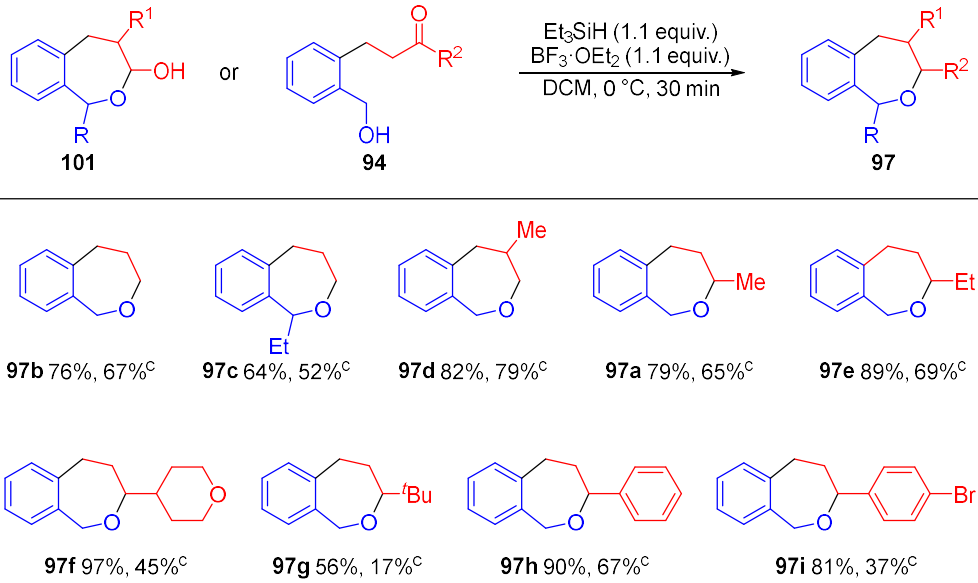


Scheme 85 Proposed rationale for the increased quantity of Heck product with larger R groups.

The phenyl substituted product **94h** was obtained in good yield in contrast to the more modest yield observed for the aryl bromide-containing example **94i**. Analysis of the unpurified reaction mixture showed no significant presence of other side-products for this example, unfortunately, due to time constraints a repeat of the reaction was unviable.

Following the redox-relay Heck reaction, attention turned to the reduction step of the sequence to give the desired benzoxepane products (Table 41).

Table 41 Reduction of redox-relay Heck products to benzoxepanes **97**.[a,b]



[a]Reactions performed on a variety of scales, see experimental for details. [b]Isolated yield after purification by column chromatography. [c]Combined yield for the two-step sequence.

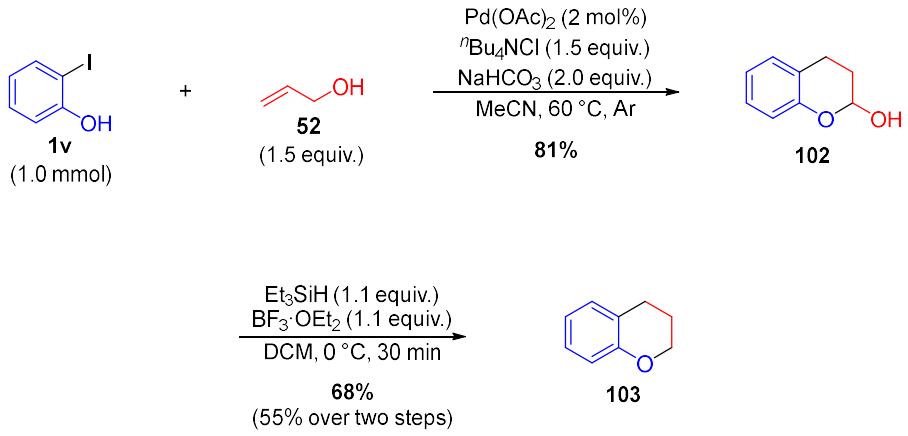
The reduction step of the sequence proved to be straightforward in most cases with yields ranging between 56% and 97%. Unfortunately, due to time constraints, the lower yielding examples **97c** and **97g** were not repeated.

The combined yield over the two-step sequence is generally good. Pleasingly, the reaction allows for the preparation of benzoxepanes bearing substituents at three different positions around the oxepane ring.

2.3.3 Accessing Alternative Heterocycles

Following the successful demonstration of the two-step sequence to prepare the 7-membered benzoxepanes, we next investigated the utility of the methodology to access alternative heterocycles.

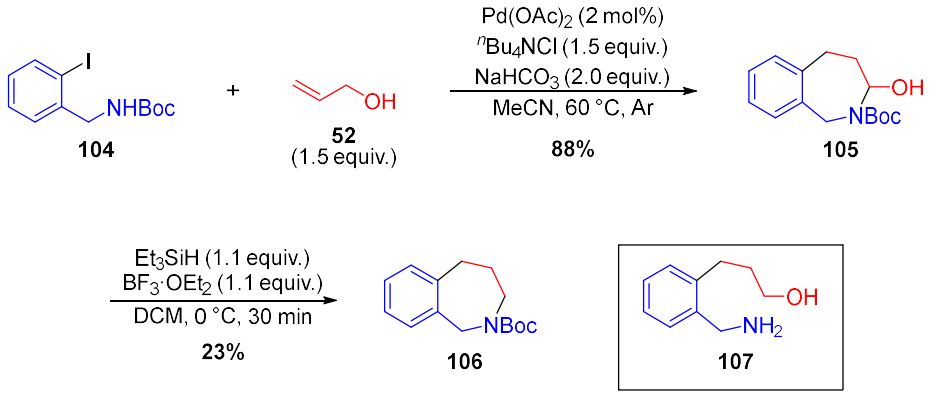
Firstly, to prepare the 6-membered, chromane **103**, we would require the coupling of 2-iodophenol **1v** and allyl alcohol **52**. Using conditions developed for the benzoxepane synthesis, hemiacetal **102** was returned in very good yield before the reduction reaction gave chromane **103** in 68% yield (55% yield over two steps) (Scheme 86).



Scheme 86 Synthesis of chromane **103** *via* chroman-2-ol **102**.

Gratified with the synthesis of chromane **103**, we next explored the potential of the methodology with a different heteroatom. Reaction of *N*-Boc-2-

iodobenzylamine **104** with allyl alcohol **52** gave access to cyclised product **105** in excellent yield. Following the reduction step, benzazapane **106** was observed as a minor product in the unpurified reaction mixture alongside postulated side-product **107** in a ratio of 1:3.6 (**106**:**107**). Consequently, desired product **106** was isolated in a poor 23% yield (Scheme 87).



Scheme 87 Synthesis of *N*-Boc-Benzazapane **106** *via* compound **105**.

Due to time constraints, full characterisation data were not obtained for the novel redox-relay Heck product **105** or the known *N*-Boc-benzazapane **106**. Although, comparison of NMR spectroscopic data with those previously reported provided confidence in the preparation of **106**.[169]

These two examples demonstrate the potential of our two-step sequence toward the synthesis of diverse heterocycles. The synthesis of chromane **103** was effective, whilst the preparation of azapane derivative **106** gave mixed results. The initial redox-relay Heck reaction was very good, but the reduction step requires further optimisation. Alteration of the reduction conditions could allow for a more effective two-step route to 7-membered nitrogen heterocycles.

2.4 Conclusion

In conclusion, further optimisation studies were carried out to allow for the application of our redox-relay Heck/reduction strategy to the synthesis of benzoxepanes.

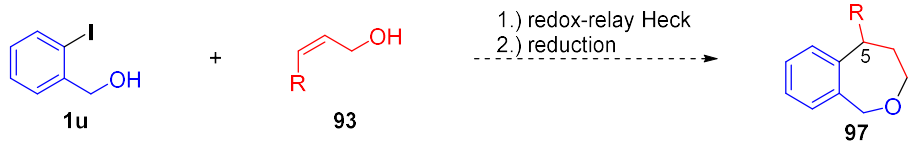
Substrates **93b**–**93d** were then prepared to supplement those that were commercially available, before an investigation of the reaction scope was carried out. Gratifyingly, a number of benzoxepanes **97a–97i** were prepared in generally good yield, featuring substitution at three different positions of the oxepane ring.

Following the synthesis of benzoxepanes, a small investigation into the application of our conditions to other heterocycles **103** and **106** was undertaken, providing good, yet improvable results.

2.5 Future Work

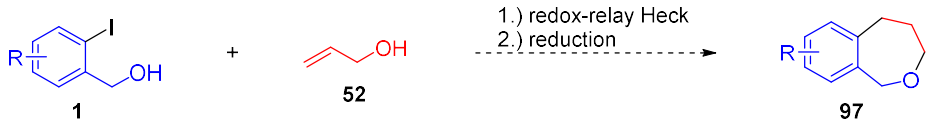
Additional scope investigations for the benzoxepane synthesis should be carried out, to reinforce assumptions made regarding the effects of different substituents in different locations. In particular, the effect of sterically hindered substituents or electron deficient groups at the α-position of allylic alcohols.

The use of γ-substituted allylic alcohols would provide access to benzoxepane products with substitution at the 5-position of the oxepane ring (Scheme 88).



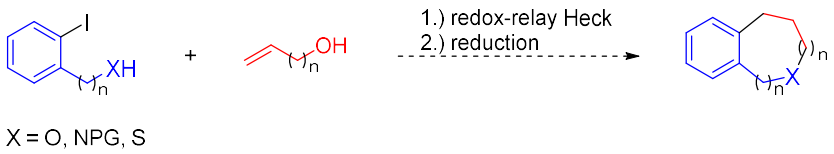
Scheme 88 Possible synthesis of 5-substituted benzoxepanes **97**.

This would complement the use of other allylic alcohols that give benzoxepanes substituted in every other possible position of the oxepane ring. In addition to substitution on the oxepane ring, different iodobenzyl alcohols could be prepared to offer products with aromatic substitution (Scheme 89).



Scheme 89 Possible synthesis of benzoxepanes featuring aromatic substitution **97**.

Finally, due to time constraints, it was not possible to fully explore the application of our methodology to alternative heterocycles. Extended ring sizes may be possible by the incorporation of additional methylene units. In addition, Following the promising azapane synthesis, other heteroatoms could feature within the preparation of diverse heterocyclic products (Scheme 90).



Scheme 90 Possible synthesis of diverse heterocycles.

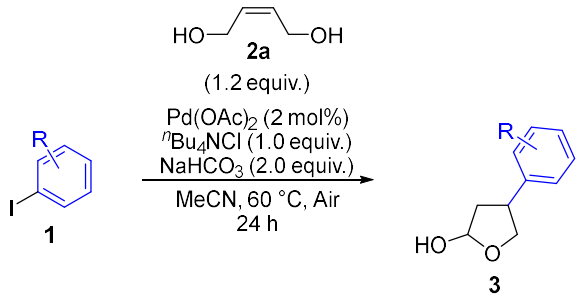
3 Experimental

3.1 General Information

All reagents and solvents used were of laboratory grade and were used as received without further purification, including all anhydrous solvents. All reactions were carried with magnetic stirring. TLC was performed on Merck TLC Al foils $60F_{254}$ precoated plates and was visualised by exposure to ultraviolet (UV) light (254 nm) or by dipping the plates into a solution of $KMnO_4$ or vanillin followed by gentle heating. Flash column chromatography was carried out using silica gel (Merck Supelco 60 Å particle size 40–63 μm) and the specified eluent. Petrol refers to the fraction of petroleum ether that boils in the range 40–60 °C. High-resolution electrospray ionisation time-of-flight (ESI-TOF) mass spectra were recorded using a Bruker MicroTOF II mass spectrometer. High-resolution electron impact ionisation (EI) mass spectra were recorded using a JEOL AccuTOF-GCx mass spectrometer. Melting points were recorded on a Stuart SMP20 melting point apparatus and are uncorrected. Infra-red (IR) spectra were recorded on a Bruker platinum alpha FTIR instrument on the neat compound using the attenuated total refraction technique. ^{1}H NMR, ^{13}C NMR and ^{19}F NMR spectra were acquired on Bruker Avance III 400HD or Avance III 500HD spectrometers. Chemical shifts (δ) are reported in parts per million (ppm); coupling constants (*J*) are quoted in Hertz (Hz) and are reported to the nearest 0.1 Hz. ^{1}H and ^{13}C chemical shifts are reported relative to tetramethylsilane, and are referenced to the appropriate residual solvent peaks (^{1}H NMR: $CDCl_3$ at 7.26 ppm; ^{13}C NMR: $CDCl_3$ at 77.0 ppm). ^{1}H NMR spectral data are reported as follows; chemical shift, number of protons, multiplicity and coupling constant. The following abbreviations (and combinations of) are used to label multiplicities: s (singlet), d (doublet), t (triplet), q (quartet), quint (quintet), m (multiplet), br (broad), and app (apparent). HSQC, DEPT, NOESY and COSY experiments were used to assist structural assignments.

3.2 General Procedures

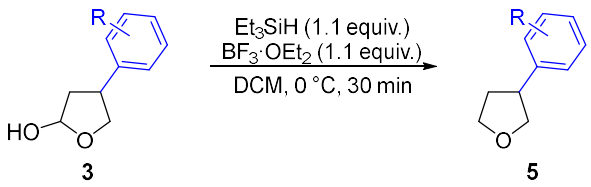
General procedure A – Redox-Relay Heck Reaction (THF Synthesis):



To a microwave vial containing a mixture of $NaHCO_3$ (2.00 equiv.), $Pd(OAc)_2$ (0.02 equiv.), $^nBu_4NCl$ (1.00 equiv.) and aryl iodide (1.00 equiv.) in MeCN (0.40 M) was added diol (1.20 equiv.) at r.t, the vial was capped, then the reaction was heated to 60 °C in a heating block and stirred (1200 rpm) for 24 h. The reaction mixture was cooled to r.t and diluted with Et_2O and water, then the aqueous phase was extracted with Et_2O (× 3). The combined organic layers were washed with brine, dried ($MgSO_4$) and concentrated *in vacuo* to afford the hemiacetal which was immediately reduced using general procedure B.

Note: Use of Et_2O in the work up is important to ensure effective removal of the tetrabutylammonium salt which was found to have a deleterious effect on the reduction step.

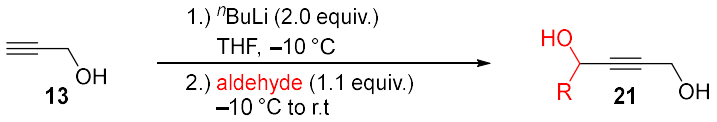
General procedure B – Reduction of Redox-Relay Heck Products:



To a stirred solution of hemiacetal (1.00 equiv.) in DCM (0.20 M) at 0 °C was added Et_3SiH (1.10 equiv.) and $BF_3{\cdot}OEt_2$ (1.10 equiv.) dropwise over 2 min. The reaction was stirred at 0 °C for 40 min then was quenched with sat. aq. $NaHCO_3$. The reaction was diluted with DCM then the aqueous phase was separated and extracted with DCM (× 3). The combined organic layers were

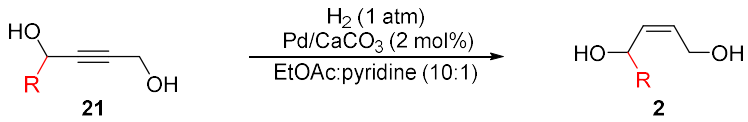
washed with 1 M aq. HCl (except for acid sensitive compounds), brine, dried ($MgSO_4$) and concentrated *in vacuo* to afford the crude product.

General procedure C – Synthesis of Alkynes:



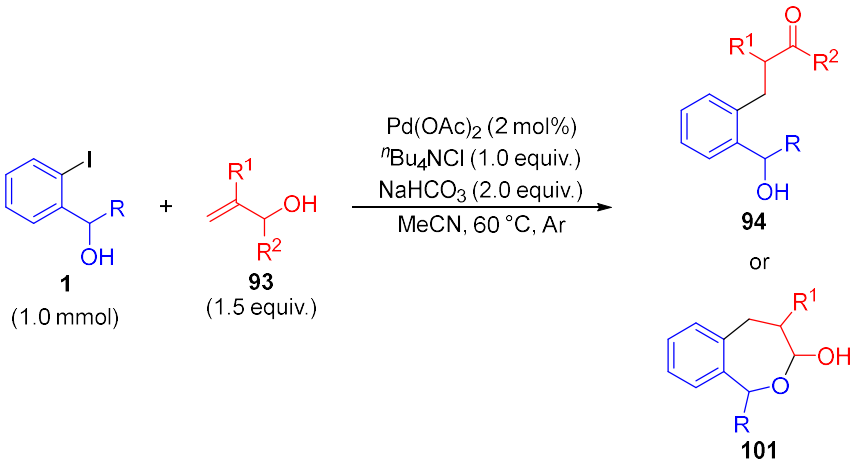
To a solution propargyl alcohol (1.00 equiv.) in THF (0.58 M) at −10 °C under argon was added ^{n}BuLi (2.00 equiv., 2.50 M in hexanes) dropwise. The mixture was left to stir for 1 h, then aldehyde (1.10 equiv.) was added slowly over 10 min. The mixture was left to stir for 5 h before being quenched with sat. aq. NH_4Cl. The aqueous layer was extracted with EtOAc (×3) then the combined organic layers were washed with brine, dried ($MgSO_4$) and concentrated *in vacuo* to afford the crude product.

General procedure D – Hydrogenation of Alkynes:



To a solution of alkyne (1.00 equiv.) in EtOAc:pyridine (10:1, 0.35 M) was added $Pd/CaCO_3$ (5 wt. % loading, 0.01 equiv.). The flask was sealed and then evacuated and backfilled with H_2 three times before stirring at r.t. The reaction was monitored by TLC until consumption of starting material was observed. The mixture was filtered, then concentrated to give the crude product.

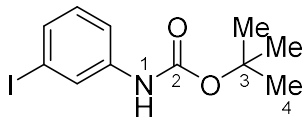
General procedure E – Redox-Relay Heck Reaction (Benzoxepane Synthesis):



To a microwave vial containing a mixture of $NaHCO_3$ (2.00 equiv.), $Pd(OAc)_2$ (0.02 equiv.), $^{n}Bu_4NCl$ (1.50 equiv.) and aryl iodide (1.00 equiv.) in MeCN (0.40 M) was added diol (1.50 equiv.) at r.t, the vial was capped, sparged with argon, then the reaction was heated to 60 °C in a heating block and stirred (1200 rpm) for 24 h. The reaction mixture was cooled to r.t and diluted with Et_2O and water, then the aqueous phase was extracted with Et_2O (× 3). The combined organic layers were washed with brine, dried ($MgSO_4$) and concentrated *in vacuo* to afford the crude product.

3.3 Substrate Synthesis

3.3.1 Synthesis of Aryl Iodides



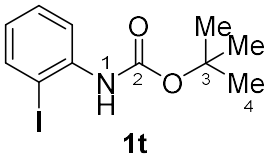
1n

$C_{11}H_{14}INO_2$

tert-Butyl (3-iodophenyl)carbamate (Compound 1n): Prepared using a modification of the procedure reported by *Singh et al.*[170] To a flask was added 3-iodoaniline (657 mg, 3.00 mmol, 1.00 equiv.) and Boc_2O (655 mg, 3.00 mmol,

1.00 equiv.). The flask was then heated to 80 °C on a rotary evaporator under reduced pressure for 30 min to give the title compound **1n** (849 mg, 2.66 mmol, 89%) that was sufficiently pure to use without purification as an off-white crystalline solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (1H, dd, *J* = 1.9, 1.8 Hz, ArH), 7.36 (1H, ddd, *J* = 7.9, 1.8, 1.0 Hz, ArH), 7.28–7.24 (1H, m, ArH), 6.99 (1H, dd, *J* = 8.0, 7.9 Hz, ArH), 1.51 (9H, s, H-4).

Data are consistent with those reported in the literature.[171]

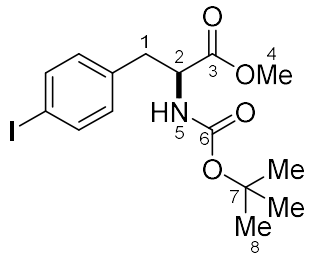


1t

$C_{11}H_{14}INO_2$

tert-Butyl (2-iodophenyl)carbamate (Compound 1t): prepared using a modification of the procedure reported by *Lera, Álvarez et al*.[172] To a solution of 2-iodoaniline (500 mg, 2.28 mmol, 1.00 equiv.) in THF (4 mL) under argon was added Boc_2O (797 mg, 3.68 mmol, 1.61 equiv.). The mixture was heated at reflux for 24 h in a heating block, then was poured into H_2O (10 mL). The aqueous layer was extracted with EtOAc (3 × 10 mL) then the organic layers were washed with brine (15 mL), dried ($MgSO_4$) and concentrated *in vacuo* to afford the crude product. Purification by flash column chromatography (SiO_2, Cyclohexane 100% → Cyclohexane : EtOAc – 9:1) gave the title compound **1t** (650 mg, 2.04 mmol, 89%) as a colourless crystalline solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (1H, app dd, *J* = 8.1, 1.6 Hz, ArH), 7.74 (1H, dd, *J* = 7.9, 1.5 Hz, ArH), 7.31 (1H, dddd, *J* = 8.1, 7.3, 1.5, 0.5 Hz, ArH), 6.82 (1H, br s, H-1), 6.76 (1H, ddd, *J* = 7.9, 7.3, 1.6 Hz, ArH), 1.54 (9H, s, H-4).

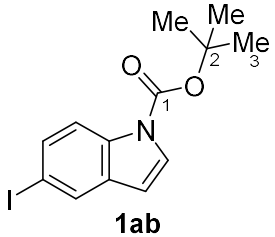
Data are consistent with those reported in the literature.[173]



1k
$C_{15}H_{20}INO_4$

Methyl (*S*)-2-[(tert-butoxycarbonyl)amino]-3-(4-iodophenyl)propanoate (Compound 1k): prepared using a modification of the procedure reported by Verniest *et al*.[174] To a solution of *N*-Boc-4-iodo-L-phenylalanine (1.00 g, 2.56 mmol, 1.00 equiv.) in DMF (10 mL) was added $NaHCO_3$ (645 mg, 7.68 mmol, 3.00 equiv.), then iodomethane (727 mg, 5.12 mmol, 2.00 equiv.) was added dropwise over 30 min. The mixture was stirred for 24 h at r.t. then was poured into H_2O (20 mL). The aqueous layer was extracted with EtOAc (3 × 20 mL) then the organic layers were washed with brine (5 × 20 mL), dried ($MgSO_4$) and concentrated *in vacuo* to afford the crude product. Purification by flash column chromatography (SiO_2, Cyclohexane : EtOAc – 9:1) gave the title compound **1k** (893 mg, 2.20 mmol, 86%) as a colourless crystalline solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (2H, d, *J* = 8.1 Hz, ArH), 6.87 (2H, d, *J* = 8.1 Hz, ArH), 4.97 (1H, d, *J* = 7.7 Hz, H-5), 4.56 (1H, ddd, *J* = 7.7, 6.4, 6.0 Hz, H-2), 3.71 (3H, s, H-4), 3.07 (1H, dd, *J* = 13.8, 6.0 Hz, H-1a), 2.98 (1H, dd, *J* = 13.8, 6.4 Hz, H-1b), 1.42 (9H, s, H-8).

Data are consistent with those reported in the literature.[174]

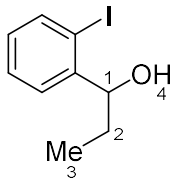


1ab
$C_{13}H_{14}INO_2$

***tert*-Butyl 5-iodo-1*H*-indole-1-carboxylate (Compound 1ab)**: prepared using a modification of the procedure reported by Kazmaier *et al*.[175] To a solution of 5-iodoindole (608 mg, 2.50 mmol, 1.00 equiv.) in DCM (10 mL) was added

DMAP (15.9 mg, 0.13 mmol, 0.05 equiv.), triethylamine (759 mg, 7.50 mmol, 3.00 equiv.) and Boc_2O (600 mg, 2.75 mmol, 1.10 equiv.), then the mixture was stirred for 2 h at r.t. The mixture was concentrated *in vacuo* to give the crude material. Purification by flash column chromatography (SiO_2, Cyclohexane : EtOAc – 30:1) gave the title compound **1ab** (811 mg, 2.36 mmol, 95%) as an off-white crystalline solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91–7.88 (2H, m, ArH), 7.57 (1H, dd, *J* = 8.7, 1.8 Hz, ArH), 7.55 (1H, d, *J* = 3.7 Hz, ArH), 6.49 (1H, d, *J* = 3.7 Hz, ArH), 1.67 (9H, s, H-3).

Data are consistent with those reported in the literature.[175]



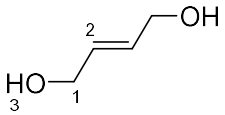
1ae

$C_9H_{11}IO$

1-(2-Iodophenyl)propan-1-ol (Compound 1ae): To a flask containing a solution of 2-iodobenzaldehyde (464 mg, 2.00 mmol, 1.00 equiv.) in THF (11 mL) was added ethylmagnesium bromide (1.00 mL, 3.00 mmol, 1.5 equiv., 3.00 M in Et_2O) at 0 °C under argon. The mixture was stirred for 2 h before being quenched with sat. aq. NH_4Cl (10 mL). The aqueous layer was extracted with Et_2O (3 × 10 mL) then the combined organic layers were washed with brine (15 mL), dried ($MgSO_4$) and concentrated in vacuo to afford the crude product. Purification by flash column chromatography (~40 g SiO_2, cyclohexane : EtOAc – 10:1) gave the title compound **1ae** (322 mg, 1.23 mmol, 61%) as a colourless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (1H, dd, *J* = 7.9, 1.2 Hz, ArH), 7.49 (1H, dd, *J* = 7.8, 1.7 Hz, ArH), 7.41–7.33 (1H, m, ArH), 7.00–6.92 (1H, m, ArH), 4.83 (1H, dd, *J* = 8.0, 4.4 Hz, H-1), 2.00 (1H, br s, H-4), 1.82 (1H, dqd, *J* = 13.9, 7.4, 4.4 Hz, H-2a), 1.74–1.59 (1H, m, H-2b), 1.02 (3H, app t, *J* = 7.4 Hz, H-3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 146.4 (C, ArC), 139.3 (CH, ArCH), 129.1 (CH, ArCH), 128.5 (CH, ArCH), 127.0 (CH, ArCH), 97.8 (C, ArC), 78.6 (CH, C-1), 30.7 (CH_2, C-2), 10.2 (CH_3, C-3).

Data are consistent with those published.[176]

3.3.2 Synthesis of Diols

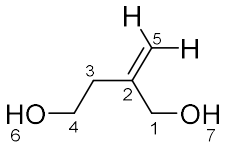


(*E*)-**2a**

$C_4H_8O_2$

***trans*-2-Butene-1,4-diol [Compound (*E*)-2a]:** Prepared using a modification of the procedure reported by Organ *et al*.[177] To a suspension of $LiAlH_4$ (91 mg, 2.40 mmol, 1.20 equiv.) in THF at 0 °C was added a cooled (0 °C) solution of 2-butyne-1,4-diol (172 mg, 2.00 mmol, 1.00 equiv.) in THF (4.5 mL) dropwise over 3 min, the reaction was then stirred and heated at reflux for 5 h in a heating block. The reaction was cooled to r.t. and diluted with Et_2O (10 mL) then was quenched by slow addition of sodium sulfate decahydrate until effervescence ceased. The mixture was then filtered and concentrated *in vacuo* to give the crude product. Purification by flash column chromatography (SiO_2, Pet. ether : EtOAc – 1:3) gave the title compound (*E*)-**2a** (84 mg, 0.95 mmol, 48%) as a colourless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.90 (2H, s, H-2), 4.18 (4H, s, H-1), 1.42 (2H, s, H-3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 130.5 (2 × CH, C-2) 63.0 (2 × CH_2, C-1).

Data are consistent with those reported in the literature.[178]



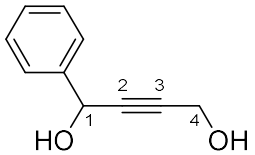
33

$C_5H_{10}O_2$

2-Methylenebutane-1,4-diol (Compound 33): To a suspension of $LiAlH_4$ (264 mg, 6.96 mmol, 1.10 equiv.) in Et_2O (22 mL) at 0 °C was added a solution of dimethyl itaconate (1.00 g, 6.32 mmol, 1.00 equiv.) in Et_2O (6 mL) dropwise over 30 min. The reaction was warmed to r.t and stirred for 22 h, then was quenched by slow addition of sodium sulfate decahydrate until effervescence ceased. The mixture was filtered and then concentrated *in vacuo* to give the

crude product. Purification by flash column chromatography (SiO_2, Et_2O) gave the title compound **33** (107 mg, 1.05 mmol, 17%) as a pale-yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.15–5.12 (1H, m, H-5a), 4.99 (1H, app d, *J* = 1.4 Hz, H-5b), 4.12–4.11 (2H, m, H-1), 3.77 (2H, t, *J* = 5.9 Hz, H-4), 2.38 (2H, td, *J* = 5.9, 1.2 Hz, H-3), 2.09–2.02 (2H, m, H-6, H-7).

Data are consistent with those reported in the literature.[179]

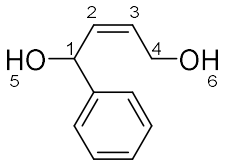


21b

$C_{10}H_{10}O_2$

1-Phenylbut-2-yne-1,4-diol (Compound 21b): Prepared according to general procedure C using propargyl alcohol (520 µL, 8.92 mmol, 1.00 equiv.), ^{n}BuLi (7.12 mL, 17.8 mmol, 2.50 M, 2.00 equiv.) and benzaldehyde (997 µL, 9.81 mmol, 1.10 equiv.) in THF (10 mL). Purification by flash column chromatography (SiO_2, Cyclohexane : EtOAc – 3:2) gave the title compound **21b** (1.06 g, 6.56 mmol, 73%) as an off-white microcrystalline solid; mp. 88–90 °C (Lit.[180] 82–84 °C); R_f = 0.20 (Cyclohexane/EtOAc, 1:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57–7.49 (2H, m, ArH), 7.43–7.29 (3H, m, ArH), 5.51 (1H, app t, *J* = 1.8 Hz, H-1), 4.36 (2H, d, *J* = 1.8 Hz, H-4), 1.98 (2H, br s, H-5, H-6); ^{13}C NMR (101 MHz, $CDCl_3$) δ 140.3 (C, ArC), 128.7 (2 × CH, ArCH), 128.5 (CH, ArCH), 126.6 (2 × CH, ArCH), 85.5 (C, C≡C), 84.9 (C, C≡C), 64.6 (CH, C-1), 51.2 (CH_2, C-4).

Data are consistent with those reported in the literature.[181]

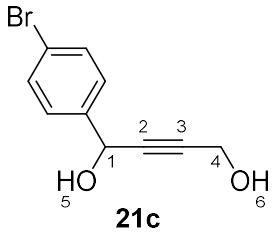


2b

$C_{10}H_{12}O_2$

(*Z*)-1-Phenylbut-2-ene-1,4-diol (Compound 2b): Prepared according to a modified version (increased Pd loading) of general procedure D using 1-phenylbut-2-yne-1,4-diol **21b** (200 mg, 1.23 mmol, 1.00 equiv.) and $Pd/CaCO_3$ (5 wt. % loading, 60.0 mg, 28.1 μmol, 0.02 equiv.) in EtOAc:pyridine (10:1, 6 mL). Purification by flash column chromatography (SiO_2, Cyclohexane : EtOAc – 5:4) gave the title compound **2b** (169 mg, 1.03 mmol, 83%) as an off-white microcrystalline solid; mp. 69–71 °C (Lit.[182] 73–75 °C); R_f = 0.13 (Cyclohexane/EtOAc, 1:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40–7.27 (5H, m, ArH), 5.81–5.76 (2H, m, H-2, H-3), 5.61–5.50 (1H, m, H-1), 4.47–4.35 (1H, m, H-4a), 4.28–4.22 (1H, m, H-4b); ^{13}C NMR (101 MHz, $CDCl_3$) δ 143.0 (C, ArC), 134.6 (C, C-2 or C-3), 130.0 (C, C-3 or C-2), 128.7 (2 × CH, ArCH), 127.7 (CH, ArCH), 126.0 (2 × CH, ArCH), 70.0 (CH, C-1), 58.7 (CH_2, C-4).

Data are consistent with those reported in the literature.[183,184]

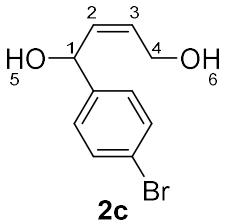


21c

$C_{10}H_9BrO_2$

1-(4-Bromophenyl)but-2-yne-1,4-diol (Compound 21c): Prepared according to general procedure C using propargyl alcohol (291 μL, 5.00 mmol, 1.00 equiv.), ^{n}BuLi (4.00 mL, 10.0 mmol, 2.50 M, 2.00 equiv.) and 4-bromobenzaldehyde (1.02 g, 5.50 mmol, 1.10 equiv.) in THF (10 mL). Purification by flash column chromatography (SiO_2, Cyclohexane : EtOAc – 3:2) gave the *title compound* **21c** (706 mg, 2.93 mmol, 58%) as an off white microcrystalline solid; mp. 78–80 °C; R_f = 0.34 (Cyclohexane/EtOAc, 1:2); υ_{max}/cm^{-1} (thin film) 3231, 2924, 2855, 1483, 1009; ^{1}H NMR (400 MHz, $CDCl_3$)

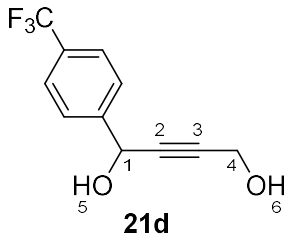
δ 7.50 (2H, d, J = 8.4 Hz, ArH), 7.40 (2H, d, J = 8.4 Hz, ArH), 5.46 (1H, app. t, 1.9 Hz, H-1), 4.35 (2H, d, J = 1.9 Hz, H-4), 2.25 (2H, br s, H-5, H-6); ^{13}C NMR (101 MHz, $CDCl_3$) δ 139.2 (C, ArC), 131.8 (2 × CH, ArCH), 128.3 (2 × CH, ArCH), 122.5 (C, ArC), 85.1 (C, C≡C), 85.0 (C, C≡C), 63.9 CH, C-1), 51.1 (CH_2, C-4); HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{10}H_9{}^{79}BrNaO_2$, 262.9678; Found 262.9671 (2.70 ppm error).



2c

$C_{10}H_{11}BrO_2$

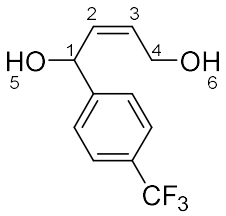
(*Z*)-1-(4-Bromophenyl)but-2-ene-1,4-diol (Compound 2c): Prepared according to general procedure D using 1-(4-bromophenyl)but-2-yne-1,4-diol **21c** (500 mg, 2.07 mmol, 1.00 equiv.) and $Pd/CaCO_3$ (5 wt. % loading, 44.0 mg, 20.7 μmol, 0.01 equiv.) in EtOAc:pyridine (10:1) was added. Purification by flash column chromatography (SiO_2, Cyclohexane : EtOAc – 1:1) gave the *title compound* **2c** (319 mg, 1.31 mmol, 63%) as an off-white microcrystalline solid; mp. 79–81 °C; R_f = 0.18 (Cyclohexane/EtOAc, 1:2); υ_{max}/cm^{-1} (thin film) 3320, 2926, 1487, 1010; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (2H, d, J = 8.4 Hz, ArH), 7.25 (2H, d, J = 8.4 Hz, ArH), 5.83–5.69 (2H, m, H-2, H-3), 5.51 (1H, d, J = 7.6 Hz, H-1), 4.40 (1H, dd, J = 13.3, 6.5 Hz, H-4a), 4.23 (1H, dd, J = 13.3, 5.4 Hz, H-4b); ^{13}C NMR (101 MHz, $CDCl_3$) δ 141.9 (C, ArC), 134.3 (CH, C-2), 131.7 (2 × CH, ArCH), 130.3 (CH, C-3), 127.7 (2 × CH, ArCH), 121.5 (C, ArC), 69.3 (CH, C-1), 58.6 (CH_2, C-4); HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{10}H_{11}{}^{79}BrNaO_2$, 264.9835; Found 264.9835 (2.60 ppm error).



21d

$C_{11}H_9F_3O_2$

1-[4-(Trifluoromethyl)phenyl]but-2-yne-1,4-diol (Compound 21d): Prepared according to general procedure C using propargyl alcohol (291 µL, 5.00 mmol, 1.00 equiv.), ^{n}BuLi (4.00 mL, 10.0 mmol, 2.50 M, 2.00 equiv.) and 4-(trifluoromethyl)benzaldehyde (958 mg, 5.5 mmol, 1.10 equiv.) in THF (10 mL). Purification by flash column chromatography (SiO_2, Cyclohexane : EtOAc – 3:2) gave the *title compound* **21d** (404 mg, 1.76 mmol, 35%) as an off white microcrystalline solid; mp. 40–42 °C; R_f = 0.24 (Cyclohexane/EtOAc, 3:2); υ_{max}/cm^{-1} (thin film) 3310, 2153, 1326, 1124; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (4H, s, ArH), 5.57 (1H, app. t, J = 1.8 Hz), 4.36 (2H, d, J = 1.8 Hz), 2.22 (2H, br s); ^{13}C NMR (101 MHz, $CDCl_3$) δ 143.9 (C, ArC), 130.6 (C, q, J = 32.3 Hz, ArC), 126.8 (2 × CH, ArCH), 125.6 (2 × CH, q, J = 3.9 Hz, ArCH), 123.9 (C, q, J = 272.2 Hz, CF_3), 85.3 (C, C≡C), 84.9 (C, C≡C), 63.8 (CH, C-1), 51.0 (CH_2, C-4); ^{19}F NMR (376 MHz, $CDCl_3$) δ −62.6; HRMS (ESI-TOF) m/z: [M + Na]$^+$ calcd for $C_{11}H_9{}^{19}F_3NaO_2$, 253.0447; Found 253.0448 (0.30 ppm error).

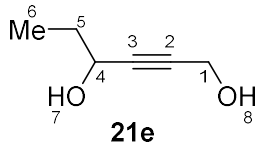


2d

$C_{11}H_{11}F_3O_2$

(*Z*)-1-[4-(Trifluoromethyl)phenyl]but-2-ene-1,4-diol (Compound 2d): Prepared according to general procedure D using 1-(4-(trifluoromethyl)phenyl)but-2-yne-1,4-diol **21d** (404 mg, 1.76 mmol, 1.00 equiv.) and Pd/$CaCO_3$ (5 wt. % loading, 38.0 mg, 17.8 µmol, 0.01 equiv.) in EtOAc:pyridine (10:1, 5 mL). Purification by flash column chromatography (SiO_2, Cyclohexane : EtOAc – 3:2) gave the *title compound* **2d** (192 mg, 0.826

mmol, 47%) as a yellow oil; R_f = 0.16 (Cyclohexane/EtOAc, 3:2); υ_{max}/cm^{-1} (thin film) 3321, 2927, 1325, 1122; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (2H, d, *J* = 8.1 Hz, ArH), 7.51 (2H, d, *J* = 8.1 Hz, ArH), 5.89–5.79 (2H, m, H-3), 5.78–5.72 (1H, m, H-2), 5.64 (1H, d, *J* = 7.9 Hz, H-1), 4.45 (1H, ddd, *J* = 13.3, 6.6, 1.2 Hz, H-4a), 4.30 (1H, ddd, *J* = 13.3, 5.7, 1.1 Hz, H-4b); ^{13}C NMR (126 MHz, $CDCl_3$) δ 146.8 (C, ArC), 134.1 (CH, C-2), 130.6 (CH, C-3), 129.8 (C, q, *J* = 32.3 Hz, ArC), 126.2 (2 × CH, ArCH), 125.5 (2 × CH, q, *J* = 3.7 Hz, ArCH), 124.1 (C, q, *J* = 272.1 Hz, CF_3), 69.3 (CH, C-1), 58.7 (CH_2, C-4); ^{19}F NMR (376 MHz, $CDCl_3$) δ −62.5; HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{11}H_{11}{}^{19}F_3NaO_2$, 255.0603; Found 255.0596 (2.70 ppm error).

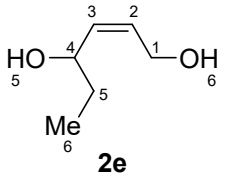


21e

$C_6H_{10}O_2$

Hex-2-yne-1,4-diol (Compound 21e): Prepared according to general procedure C using propargyl alcohol (582 µL, 10.0 mmol, 1.00 equiv.), ^{n}BuLi (8.00 mL, 20.0 mmol, 2.50 M, 2.00 equiv.) and propanal (794 µL, 11.0 mmol, 1.10 equiv.) in THF (20 mL). Purification by flash column chromatography (SiO_2, Cyclohexane : EtOAc – 2:1) gave the title compound **21e** (329 mg, 2.89 mmol, 29%) as a yellow oil; R_f = 0.16 (Cyclohexane/EtOAc, 2:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.36 (1H, dddd, *J* = 6.4, 6.4, 1.7, 1.7 Hz, H-4), 4.31 (2H, d, *J* = 1.7 Hz, H-1a, H-1b), 2.19–2.04 (2H, m, H-7, H-8), 1.80–1.65 (2H, m, H-5a, H-5b), 1.01 (3H, t, *J* = 7.4 Hz, H-6); ^{13}C NMR (101 MHz, $CDCl_3$) δ 86.6 (C, C≡C), 83.1 (C, C≡C), 63.7 (CH, C-4), 51.0 (CH_2, C-1), 30.7 (CH_2, C-5), 9.4 (CH_3, C-6).

Data are consistent with those published.[185]

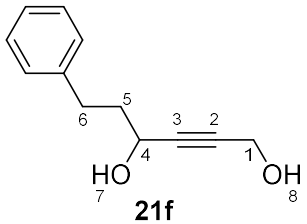


2e

$C_6H_{12}O_2$

(*Z*)-Hex-2-ene-1,4-diol (Compound 2e): Prepared according to general procedure D using hex-2-yne-1,4-diol **21e** (568 mg, 4.98 mmol, 1.00 equiv.) and $Pd/CaCO_3$ (5 wt. % loading, 108 mg, 50.7 μmol, 0.01 equiv.) in EtOAc:pyridine (10:1) (14 mL). Purification by flash column chromatography (SiO_2, Cyclohexane : EtOAc – 1:1) gave the title compound **2e** (484 mg, 4.17 mmol, 84%) as a pale yellow oil; R_f = 0.04 (Cyclohexane/EtOAc, 1:2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.80–5.68 (1H, m, H-2), 5.60–5.50 (1H, m, H-3), 4.41–4.26 (2H, m, H-1a, H-4), 4.13 (1H, dd, *J* = 13.0, 5.8 Hz, H-1b), 2.43–2.21 (2H, m, H-7, H-8), 1.63 (1H, dqd, *J* = 14.0, 7.6, 6.6 Hz, H-5a), 1.56–1.44 (1H, m, H-5b), 0.91 (3H, dd, *J* = 7.6, 7.6 Hz, H-6); ^{13}C NMR (101 MHz, $CDCl_3$) δ 135.1 (CH, C-3), 130.5 (CH, C-2), 69.2 (CH, C-4), 58.7 (CH_2, C-5), 30.3 (CH_2, C-1), 9.6 (CH_3, C-6).

Data are consistent with those published.[186]



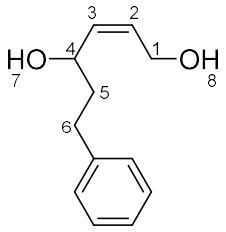
21f

$C_{12}H_{14}O_2$

6-Phenylhex-2-yne-1,4-diol (Compound 21f): Prepared according to general procedure C using propargyl alcohol (520 μL, 8.92 mmol, 1.00 equiv.), ^{n}BuLi (7.12 mL, 17.8 mmol, 2.50 M, 2.00 equiv.) and hydrocinnamaldehyde (1.29 mL, 9.81 mmol, 1.10 equiv.) in THF (10 mL). Purification by flash column chromatography (SiO_2, Cyclohexane : EtOAc – 2:1) gave the title compound **21f** (752 mg, 3.95 mmol, 44%) as a pale yellow oil; R_f = 0.20 (Cyclohexane/EtOAc, 1:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31–7.24 (2H, m, ArH), 7.23–7.15 (3H, m, ArH), 4.39 (1H, dddd, *J* = 6.6, 6.6, 1.7, 1.7 Hz, H-4),

4.29 (2H, d, *J* = 1.7 Hz, H-1a, H-1b), 2.78 (2H, t, *J* = 7.8 Hz, H-6), 2.08–1.96 (2H, m, H-5a, H-5b); ^{13}C NMR (101 MHz, $CDCl_3$) δ 141.1 (C, ArC), 128.5 (2 × CH, ArCH), 128.4 (2 × CH, ArCH), 126.0 (CH, ArCH), 86.6 (C, C≡C), 83.5 (C, C≡C), 61.7 (CH, C-4), 51.0 (CH_2, C-1), 39.0 CH_2, C-5), 31.3 (CH_2, C-6).

Data are consistent with those published.[187]

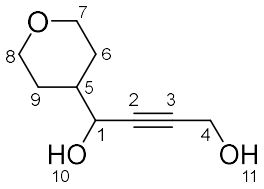


2f

$C_{12}H_{16}O_2$

(*Z*)-6-Phenylhex-2-ene-1,4-diol (Compound 2f): Prepared according to general procedure D using 6-phenylhex-2-yne-1,4-diol **21f** (500 mg, 2.63 mmol, 1.00 equiv.) and Pd/$CaCO_3$ (5 wt. % loading, 56 mg, 26.3 µmol, 0.01 equiv.) in EtOAc:pyridine (10:1, 8 mL). Purification by flash column chromatography (SiO_2, Cyclohexane : EtOAc – 1:1) gave the title compound (398 mg, 2.07 mmol, 79%) as a pale yellow oil; R_f = 0.11 (Cyclohexane/EtOAc, 1:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32–7.25 (2H, m, ArH), 7.21–7.16 (3H, m, ArH), 5.74 (1H, dddd, *J* = 11.2, 7.1, 5.9, 1.1 Hz, H-2), 5.61 (1H, dddd, *J* = 11.2, 7.6, 1.4, 1.3 Hz, H-3), 4.45 (1H, dddd, *J* = 7.6, 7.0, 5.9, 1.1 Hz, H-4), 4.24 (1H, ddd, *J* = 13.1, 7.1, 1.4 Hz, H-1a), 4.11 (1H, ddd, *J* = 13.1, 5.9, 1.3 Hz, H-1b), 2.77–2.62 (2H, m, H-6a, H-6b), 2.10–2.06 (2H, m, H-7, H-8), 1.95 (1H, dddd, *J* = 13.5, 9.1, 7.0, 7.0 Hz, H-5a), 1.80 (1H, dddd, *J* = 13.5, 9.1, 6.8, 5.9 Hz, H-5b); ^{13}C NMR (101 MHz, $CDCl_3$) δ 141.5 (C, ArC), 135.1 (CH, C-3), 130.5 (CH, C-2), 128.4 (2 × CH, ArCH), 128.4 (2 × CH, ArCH), 125.9 (CH, ArCH), 67.2 (CH, C-4), 58.7 (CH_2, C-1), 38.8 (CH_2, C-5), 31.6 (CH_2, C-6).

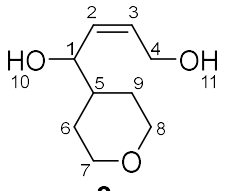
Data are consistent with those published.[188]



21g

$C_9H_{14}O_3$

1-(Tetrahydro-*2H*-pyran-4-yl)but-2-yne-1,4-diol (Compound 21g): Prepared according to general procedure C using propargyl alcohol (510 µL, 8.76 mmol, 1.00 equiv.), ^{n}BuLi (7.00 mL, 17.5 mmol, 2.50 M, 2.00 equiv.) and tetrahydro-*2H*-pyran-4-carbaldehyde (1.10 g, 9.64 mmol, 1.10 equiv.) in THF (15 mL). Purification by flash column chromatography (SiO_2, Cyclohexane : EtOAc – 3:2) gave the *title compound* **21g** (243 mg, 1.43 mmol, 16%) as a yellow oil; R_f = 0.09 (Cyclohexane/EtOAc, 1:1); υ_{max}/cm^{-1} (thin film) 3316, 2945, 2853, 2099, 1085, 1015; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.30 (2H, d, *J* = 1.7 Hz, H-4), 4.22 (1H, dt, *J* = 6.4, 1.7 Hz, H-1), 4.02 (2H, ddd, *J* = 11.7, 4.6, 2.2 Hz, H-7_{eq}, H-8_{eq}), 3.39 (2H, dddd, *J* = 11.8, 11.7, 3.8, 2.2 Hz, H-7_{ax}, H-8_{ax}), 2.62 (2H, br s, H-10, H-11), 1.88–1.67 (3H, m, H-6_{ax} or H-6_{eq}, H-9_{ax} or H-9_{eq}, H-5), 1.59–1.39 (2H, m, H-6_{ax} or H-6_{eq}, H-9_{ax} or H-9_{eq}); ^{13}C NMR (101 MHz, $CDCl_3$) δ 84.9 (C, C≡C), 84.4 (C, C≡C), 67.6 (CH_2, C-7, C-8), 66.3 (CH, C-1), 50.8 (CH_2, C-4), 41.2 (CH, C-5), 28.6 (CH_2, C-6 or C-9), 28.0 (CH_2, C-6 or C-9); HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_9H_{14}NaO_3$, 193.0835; Found 193.0833 (1.00 ppm error).

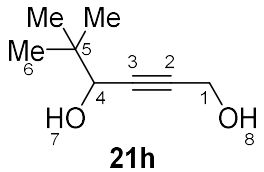


2g

$C_9H_{16}O_3$

(*Z*)-1-(Tetrahydro-*2H*-pyran-4-yl)but-2-ene-1,4-diol (Compound 2g): Prepared according to general procedure D using 1-(tetrahydro-*2H*-pyran-4-yl)but-2-yne-1,4-diol **21g** (300 mg, 1.76 mmol, 1.00 equiv.) and $Pd/CaCO_3$ (5 wt. % loading, 38 mg, 17.9 µmol, 0.01 equiv.) in EtOAc:pyridine (10:1, 5 mL). Purification by flash column chromatography (SiO_2, EtOAc : Cyclohexane –

3:1) gave the *title compound* **2g** (211 mg, 1.22 mmol, 70%) as a colourless oil; R_f = 0.05 (Cyclohexane/EtOAc, 1:1); υ_{max}/cm^{-1} (thin film) 3338, 2949, 2917, 2850, 1086, 1017; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.78–5.69 (1H, m, H-3), 5.54–5.45 (1H, m, H-2), 4.26 (1H, ddd, *J* = 12.9, 7.9, 1.4 Hz, H-4), 4.11 (1H, dd, *J* = 8.1, 7.9 Hz, H-1), 4.05–3.88 (3H, m, H-4b, H-7_{eq}, H-8_{eq}), 3.50 (2H, br s, H-10, H-11), 3.38–3.28 (2H, m, H-7_{ax}, H-8_{ax}), 1.78 (1H, m, H-6_{ax} or H-6_{eq}), 1.65–1.52 (1H, m, H-5), 1.51–1.40 (1H, m, H-9_{ax} or H-9_{eq}), 1.39–1.19 (2H, m, H-6_{ax} or H-6_{eq}, H-9_{ax} or H-9_{eq}); ^{13}C NMR (101 MHz, $CDCl_3$) δ 133.1 (CH, C-2), 131.0 (CH, C-3), 71.0 (CH, C-1), 67.7 (CH_2, C-7 or C-8), 67.6 (CH_2, C-7 or C-8), 58.1 (CH_2, C-4), 40.8 (CH, C-5), 28.9 (CH_2, C-6 or C-9), 28.5 (CH_2, C-6 or C-9); HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_9H_{16}NaO_3$, 195.0992; Found 195.0994 (1.30 ppm error).

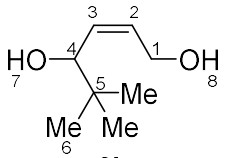


21h

$C_8H_{14}O_2$

5,5-Dimethylhex-2-yne-1,4-diol (Compound 21h): Prepared according to general procedure C using propargyl alcohol (520 µL, 8.92 mmol, 1.00 equiv.), ^{n}BuLi (7.12 mL, 17.8 mmol, 2.50 M, 2.00 equiv.) and pivaldehyde (1.07 mL, 9.81 mmol, 1.10 equiv.) in THF (10 mL). Purification by flash column chromatography (SiO_2, Cyclohexane : EtOAc – 7:4) gave the title compound **21h** (905 mg, 6.37 mmol, 71%) as a yellow oil; R_f = 0.24 (Cyclohexane/EtOAc, 1:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.32 (2H, d, *J* = 1.8 Hz, H-1a, H-1b), 4.06 (1H, dd, *J* = 1.8, 1.8 Hz, H-4), 1.88–1.72 (2H, m, H-7, H-8), 0.99 (9H, s, H-6); ^{13}C NMR (101 MHz, $CDCl_3$) δ 85.5 (C, C≡C), 83.9 (C, C≡C), 71.4 (CH, C-4), 51.1 CH_2, C-1), 35.8 (C, C-5), 25.2 (3 × CH_3, C-6).

Data are consistent with those published.[189]



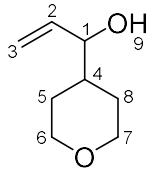
2h

$C_8H_{16}O_2$

(*Z*)-5,5-Dimethylhex-2-ene-1,4-diol (Compound 2h): Prepared according to general procedure D using 5,5-dimethylhex-2-yne-1,4-diol **21h** (274 mg, 1.93 mmol, 1.00 equiv.) and Pd/$CaCO_3$ (5 wt. % loading, 41 mg, 19.3 µmol, 0.01 equiv.) in EtOAc:pyridine (10:1) (6 mL). Purification by flash column chromatography SiO_2, Cyclohexane : EtOAc – 1:1) gave the title compound **2h** (204 mg, 1.41 mmol, 73%) as a pale yellow oil; R_f = 0.15 (Cyclohexane/EtOAc, 1:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.84–5.72 (1H, m, H-2), 5.66–5.55 (1H. m, H-3), 4.33 (1H, dddd, *J* = 13.0, 7.9, 1.3, 1.3 Hz, H-1a), 4.17–4.02 (2H, m, H-1b, H-4), 2.69–2.21 (2H, m, H-7, H-8), 0.90 (9H, d, *J* = 1.4 Hz, 1.4 Hz, H-6); ^{13}C NMR (101 MHz, $CDCl_3$) δ 131.9 (CH, C-3), 131.3 (CH, C-2), 75.0 (CH, C-4), 58.4 (CH_2, C-1), 34.9 (C, C-5), 25.4 (CH_3, C-6).

Data are consistent with those published.[189]

3.3.3 Synthesis of Allylic Alcohols



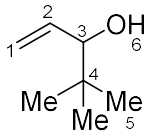
93b

$C_8H_{14}O_2$

1-(Tetrahydro-2*H*-pyran-4-yl)prop-2-en-1-ol (Compound 93b): To a solution of tetrahydropyran-4-carbaldehyde (600 mg, 5.26 mmol, 1.00 equiv.) in THF (24 mL) was added vinylmagnesium bromide (7.89 mL, 7.89 mmol, 1.50 equiv., 1.00 M in THF) dropwise at 0 °C. The reaction was allowed to warm to r.t then stirred for 5 h. The reaction was poured into sat. aq. NH_4Cl (20 mL) and extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine (10 mL), dried ($MgSO_4$) and concentrated *in vacuo* to afford the crude

material. Purification by flash column chromatography (SiO_2, cyclohexane : EtOAc – 3:2) gave the title compound **93b** (340 mg, 2.39 mmol, 45%) as a colourless oil; R_f = 0.20 (cyclohexane/EtOAc, 1:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.81 (1H, ddd, *J* = 17.2, 10.4, 6.8 Hz, H-2), 5.20 (1H, ddd, *J* = 17.2, 1.4, 1.3 Hz, H-3$_{trans}$), 5.15 (1H, ddd, *J* = 10.4, 1.4, 1.3 Hz, H-3$_{cis}$), 4.01–3.90 (2H, m, H-6$_{eq}$, H-7$_{eq}$), 3.81 (1H, dddd, *J* = 6.9, 6.8, 1.3, 1.3 Hz, H-1), 3.41–3.24 (2H, m, H-6$_{ax}$, H-7$_{ax}$), 2.09 (1H, s, H-9), 1.77–1.70 (1H, m, H-5$_{ax}$ or H-5$_{eq}$ or H-8$_{ax}$ or H-8$_{eq}$), 1.65–1.55 (1H, m, H-4), 1.53–1.45 (1H, m, H-5$_{ax}$ or H-5$_{eq}$ or H-8$_{ax}$ or H-8$_{eq}$), 1.42–1.29 (2H, m, H-5$_{ax}$ or H-5$_{eq}$, H-8$_{ax}$ of H-8$_{eq}$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 139.1 (CH, C-2), 116.2 (CH_2, C-3), 77.0 (CH, C-1), 67.8 (CH_2, C-6 or C-7), 67.7 (CH_2, C-6 or C-7), 40.7 (CH, C-4), 28.7 (CH_2, C-5 or C-8), 28.6 (CH_2, C-5 or C-8).

Data are consistent with those published.[190]



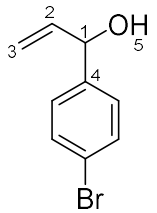
93c

$C_7H_{14}O$

4,4-Dimethylpent-1-en-3-ol (Compound 93c): To a solution of 4-pivaldehyde (1.00 g, 11.6 mmol, 1.00 equiv.) in THF (60 mL) was added vinylmagnesium bromide (17.1 mL, 17.1 mmol, 1.50 equiv., 1.00 M in THF) dropwise at 0 °C. The reaction was allowed to warm to r.t then stirred for 5 h. The reaction was poured into sat. aq. NH_4Cl (20 mL) and extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with brine (30 mL), dried ($MgSO_4$) and concentrated *in vacuo* to afford the crude material. Purification by flash column chromatography (SiO_2, cyclohexane : EtOAc – 9:1) gave the title compound **93c** (Note: as compound was volatile, it was isolated in solution of cyclohexane and Et_2O, calculated by 1H NMR to be 69% product by weight) (255 mg, 2.23 mmol, 19%) as a colourless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.93 (1H, ddd, *J* = 17.2, 10.5, 6.8 Hz, H-2), 5.23 (1H, ddd, *J* = 17.2, 1.6, 1.4 Hz, H-1a), 5.20 (1H, ddd, *J* = 10.5, 1.8, 1.6 Hz, H-1b), 3.75 (1H, ddd, *J* = 6.8, 1.4, 1.2 Hz, H-3), 1.50 (1H,

br s, H-6), 0.91 (9H, s, H-6); ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.1 (CH, C-2), 116.3 (CH_2, C-1), 81.2 (CH, C-3), 34.7 (C, C-4), 25.6 (3 × CH_3, C-5).

Data are consistent with those published.[191]



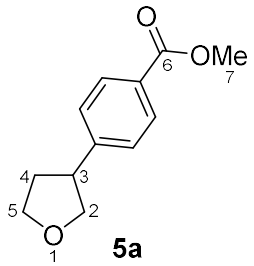
93d

C_9H_9BrO

1-(4-Bromophenyl)prop-2-en-1-ol (Compound 93d): To a solution of 4-bromobenzaldehyde (600 mg, 3.24 mmol, 1.00 equiv.) in THF (15 mL) was added vinylmagnesium bromide (4.86 mL, 4.86 mmol, 1.50 equiv., 1.00 M in THF) dropwise at 0 °C. The reaction was allowed to warm to r.t then stirred for 5 h. The reaction was poured into sat. aq. NH_4Cl (20 mL) and extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine (10 mL), dried ($MgSO_4$) and concentrated *in vacuo* to afford the crude material. Purification by flash column chromatography (SiO_2, cyclohexane : EtOAc – 8:1) gave the title compound **93d** (432 mg, 2.03 mmol, 63%) as a colourless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (2H, d, *J* =8.4 Hz, ArH), 7.25 (2H, d, *J* = 8.4 Hz, ArH), 6.00 (1H, ddd, *J* = 17.1, 10.3, 6.0 Hz, H-2), 5.34 (1H, ddd, *J* = 17.1, 1.3, 1.3 Hz, H-3a), 5.21 (1H, ddd, *J* = 10.3, 1.3, 1.3 Hz, H-3b), 5.19–5.11 (1H, m, H-1), 1.94 (1H, d, *J* = 3.8 Hz, H-5); ^{13}C NMR (101 MHz, $CDCl_3$) δ 141.5 (C, ArC), 139.8 (CH, C-2), 131.6 (2 × CH, ArCH), 128.0 (2 × CH, ArCH), 121.6 (C, ArC), 115.7 (CH_2, C-3), 74.7 (CH, C-1).

Data are consistent with those published.[192]

3.4 Synthesis of 3-Substituted Tetrahydrofurans

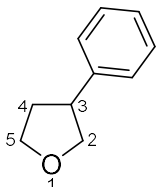


5a

$C_{12}H_{14}O_3$

Methyl 4-(tetrahydrofuran-3-yl)benzoate (Compound 5a): Prepared according to general procedure A using $NaHCO_3$ (168 mg, 2.00 mmol, 2.00 equiv.), $Pd(OAc)_2$ (4.5 mg, 0.02 mmol, 0.02 equiv.), $^{n}Bu_4NCl$ (278 mg, 1.00 mmol, 1.00 equiv.), methyl 4-iodobenzoate (262 mg, 1.00 mmol, 1.00 equiv.), *cis*-2-butene-1,4-diol (99 µL, 1.20 mmol, 1.20 equiv.) in MeCN (2.5 mL). The crude material was then immediately reduced according to general procedure B using hemiacetal (222 mg, 1.00 mmol, 1.00 equiv.), Et_3SiH (176 µL, 1.10 mmol, 1.10 equiv.), $BF_3{\cdot}OEt_2$ (136 µL, 1.10 mmol, 1.10 equiv.) in DCM (5 mL). Purification by flash column chromatography (SiO_2, Cyclohexane : EtOAc – 15:1) gave the title compound **5a** (197 mg, 0.955 mmol, 96%) as a pale yellow oil; R_f = 0.52 (Pet. ether/EtOAc, 1:1); ν_{max}/cm^{-1} (thin film) 2951, 2860, 1716, 1610, 1435, 1274, 1107, 706; ^1H NMR (400 MHz, $CDCl_3$) δ 7.97 (2H, d, *J* = 8.3 Hz, ArH), 7.31 (2H, d, *J* = 8.3 Hz, ArH), 4.19–4.01 (2H, m, H-2a, H-5a), 3.94–3.88 (4H, m, H-5b, H-7), 3.74 (1H, dd, *J* = 8.3, 7.3 Hz, H-2b), 3.45 (1H, app quint, *J* = 7.6 Hz, H-3), 2.39 (1H, app dtd, *J* = 12.8, 7.8, 4.7 Hz, H-4a), 2.00 (1H, dddd, *J* = 12.8, 8.2, 8.0, 7.7 Hz, H-4b); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.9 (C, C-6), 148.4 (C, ArC), 129.9 (2 × CH, ArCH), 128.4 (C, ArC), 127.2 (2 × CH, ArCH), 74.4 (CH_2, C-2), 68.4 (CH_2, C-5), 52.0 (CH_3, C-7), 44.9 (CH, C-3), 34.6 (CH_2, C-4); HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{12}H_{14}NaO_3$, 229.0835; Found 229.0834 (0.30 ppm error).

Data are consistent with those reported in the literature.[193]

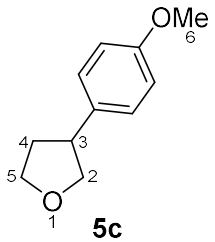


5b

$C_{10}H_{12}O$

3-Phenyltetrahydrofuran (Compound 5b): Prepared according to general procedure A using $NaHCO_3$ (168 mg, 2.00 mmol, 2.00 equiv.), $Pd(OAc)_2$ (4.5 mg, 20.0 μmol, 0.02 equiv.), $^nBu_4NCl$ (278 mg, 1.00 mmol, 1.00 equiv.), iodobenzene (204 mg, 1.00 mmol, 1.00 equiv.), *cis*-2-butene-1,4-diol (99 μL, 1.20 mmol, 1.20 equiv.) in MeCN (2.5 mL). The crude material was then immediately reduced according to general procedure B using hemiacetal (164 mg, 1.00 mmol, 1.00 equiv.), Et_3SiH (176 μL, 1.10 mmol, 1.10 equiv.), $BF_3{\cdot}OEt_2$ (136 μL, 1.10 mmol, 1.10 equiv.) in DCM (5 mL). Purification by flash column chromatography (SiO_2, Cyclohexane : Et_2O – 9:1) gave the title compound **5b** (142 mg, 0.958 mmol, 96%; Yield at 100% purity: 141 mg, 0.951 mmol, 95%) containing traces of triethylsilanol (<1%) as a pale yellow oil; R_f = 0.53 (Pet. ether/EtOAc, 1:1); ν_{max}/cm^{-1} (thin film) 2968, 2928, 2856; ^1H NMR (400 MHz, $CDCl_3$) δ 7.37–7.17 (5H, m, ArH), 4.15 (1H, app t, J = 8.0 Hz, H-2a), 4.08 (1H, app td, J = 8.4, 4.5 Hz, H-5a), 3.97–3.88 (1H, m, H-5b), 3.73 (1H, app t, J = 8.0 Hz, H-2b), 3.41 (1H, app quint, J = 7.9 Hz, H-3), 2.43–2.30 (1H, m, H-4a), 2.10–1.94 (1H, m, H-4b); ^{13}C NMR (101 MHz, $CDCl_3$) δ 142.6 (C, ArC), 128.6 (2 × CH, ArCH), 127.2 (2 × CH, ArCH), 126.5 (CH, ArCH), 74.7 (CH_2, C-2), 68.5 (CH_2, C-5), 45.0 (CH, C-3), 34.6 (CH_2, C-4); HRMS (EI-MS) m/z: $[M]^+$ calcd for $C_{10}H_{12}O$, 148.0883; Found 148.0883 (0.18 ppm error).

Data are consistent with those reported in the literature.[62]

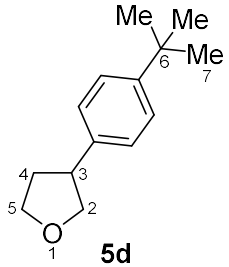


5c

$C_{11}H_{14}O_2$

3-(4-Methoxyphenyl)tetrahydrofuran (Compound 5c): Prepared according to general procedure A using $NaHCO_3$ (168 mg, 2.00 mmol, 2.00 equiv.), $Pd(OAc)_2$ (4.5 mg, 20.0 µmol, 0.02 equiv.), $^nBu_4NCl$ (278 mg, 1.00 mmol, 1.00 equiv.), 4-iodoanisole (234 mg, 1.00 mmol, 1.00 equiv.), *cis*-2-butene-1,4-diol (99 µL, 1.20 mmol, 1.20 equiv.) in MeCN (2.5 mL). The crude material was then immediately reduced according to general procedure B using hemiacetal (194 mg, 1.00 mmol, 1.00 equiv.), Et_3SiH (176 µL, 1.10 mmol, 1.10 equiv.), $BF_3{\cdot}OEt_2$ (136 µL, 1.10 mmol, 1.10 equiv.) in anhydrous DCM (5 mL). Purification by flash column chromatography (SiO_2, Cyclohexane : Et_2O – 9:1) gave the title compound **5c** (174 mg, 0.976 mmol, 98%; Yield at 100% purity: 140 mg, 0.954 mmol, 95%) containing traces of triethylsilanol (<3%) as a pale yellow oil; R_f = 0.47 (Cyclohexane/EtOAc, 12:1); ν_{max}/cm^{-1} (thin film) 2933, 2857, 1512; ^1H NMR (400 MHz, $CDCl_3$) δ 7.17 (2H, d, *J* = 8.5 Hz, ArH), 6.86 (2H, d, *J* = 8.5 Hz, ArH), 4.12 (1H, app t, *J* = 8.0 Hz, H-2a), 4.06 (1H, app td, *J* = 8.3, 4.4 Hz, H-5a), 3.91 (1H, app q, *J* = 7.8 Hz, H-5b), 3.79 (3H, s, H-6), 3.68 (1H, app t, *J* = 8.0 Hz, H-2b), 3.36 (1H, app quint, *J* = 7.9 Hz, H-3), 2.40–2.27 (1H, m, H-4a), 1.99 (1H, app dq, *J* = 12.3, 8.2 Hz, H-4b); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.2 (C, ArC), 134.5 (C, ArC), 128.2 (2 × CH, ArCH), 114.0 (2 × CH, ArCH), 74.7 (CH_2, C-2), 68.5 (CH_2, C-5), 55.3 (CH_3, C-6), 44.2 (CH, C-3), 34.7 (CH_2, C-4); HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{11}H_{15}O_2$, 179.1067; Found 179.1065 (1.10 ppm error).

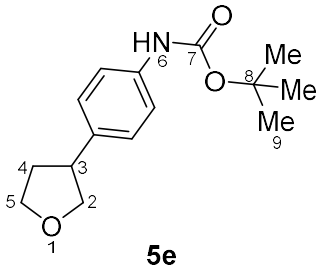
Data are consistent with those reported in the literature.[194]



5d

$C_{14}H_{20}O$

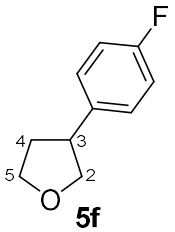
3-[4-(*tert*-Butyl)phenyl]tetrahydrofuran (Compound 5d): Prepared according to general procedure A using $NaHCO_3$ (168 mg, 2.00 mmol, 2.00 equiv.), $Pd(OAc)_2$ (4.5 mg, 20.0 μmol, 0.02 equiv.), $^{n}Bu_4NCl$ (278 mg, 1.00 mmol, 1.00 equiv.), 4-*tert*-butyliodobenzene (260 mg, 1.00 mmol, 1.00 equiv.), *cis*-2-butene-1,4-diol (99 μL, 1.20 mmol, 1.20 equiv.) in MeCN (2.5 mL). The crude material was then immediately reduced according to general procedure B using hemiacetal (220 mg, 1.00 mmol, 1.00 equiv.), Et_3SiH (176 μL, 1.10 mmol, 1.10 equiv.), $BF_3{\cdot}OEt_2$ (136 μL, 1.10 mmol, 1.10 equiv.) in DCM (5 mL). Purification by flash column chromatography (SiO_2, Cyclohexane : EtOAc – 15:1) gave the *title compound* **5d** (152 mg, 0.742 mmol, 74%) as a pale yellow oil; R_f = 0.68 (Pet. ether/EtOAc, 1:1); ν_{max}/cm^{-1} (thin film) 2960, 2904, 2865; ^1H NMR (400 MHz, $CDCl_3$) δ 7.38 (2H, d, *J* = 8.4 Hz, ArH), 7.23 (2H, d, *J* = 8.4 Hz, ArH), 4.18 (1H, dd, *J* = 8.1, 8.0 Hz, H-2a), 4.10 (1H, app td, *J* = 8.3, 4.5 Hz, H-5a), 3.95 (1H, ddd, *J* = 8.3, 8.2, 7.4 Hz, H-5b), 3.76 (1H, app t, *J* = 8.1 Hz, H-2b), 3.42 (1H, dddd, *J* = 8.3, 8.2, 8.1, 8.0 Hz, H-3), 2.38 (1H, dddd, *J* = 12.4, 8.3, 7.4, 4.5 Hz, H-4a), 2.05 (1H, app dq, *J* = 12.4, 8.2 Hz, H-4b), 1.36 (9H, s, H-7); ^{13}C NMR (101 MHz, $CDCl_3$) δ 149.3 (C, ArC), 139.3 (C, ArC), 126.9 (2 × CH, ArCH), 125.4 (2 × CH, ArCH), 74.6 (CH_2, C-2), 68.5 (CH_2, C-5), 44.5 (CH, C-3), 34.6 (CH_2, C-4), 34.3 (C, C-6), 31.3 (3 × CH_3, C-7); HRMS (ESI-TOF) m/z: $[M + NH_4]^+$ calcd for $C_{14}H_{24}NO$, 222.1852; Found 222.1844 (4.00 ppm error).



5e

$C_{15}H_{21}NO_3$

***tert*-Butyl [4-(tetrahydrofuran-3-yl)phenyl]carbamate (Compound 5e)**: Prepared according to general procedure A using $NaHCO_3$ (168 mg, 2.00 mmol, 2.00 equiv.), $Pd(OAc)_2$ (4.5 mg, 20.0 µmol, 0.02 equiv.), $^nBu_4NCl$ (278 mg, 1.00 mmol, 1.00 equiv.), *tert*-butyl (4-iodophenyl)carbamate (319 mg, 1.00 mmol, 1.00 equiv.), *cis*-2-butene-1,4-diol (99 µL, 1.20 mmol, 1.20 equiv.) in MeCN (2.5 mL). The crude material was then immediately reduced according to general procedure B using hemiacetal (279 mg, 1.00 mmol, 1.00 equiv.), Et_3SiH (176 µL, 1.10 mmol, 1.10 equiv.), $BF_3{\cdot}OEt_2$ (136 µL, 1.10 mmol, 1.10 equiv.) in DCM (5 mL). Purification by flash column chromatography (SiO_2, Cyclohexane : EtOAc – 15:1) gave the *title compound* **5e** (230 mg, 0.874 mmol, 87%) as a colourless crystalline solid; mp. 114–116 °C; R_f = 0.51 (Pet. ether/EtOAc, 1:1); ν_{max}/cm^{-1} (thin film) 3303, 2975, 2931, 2870, 1724, 1703, 1525, 1235, 1159, 1051; ^1H NMR (400 MHz, $CDCl_3$) δ 7.30 (2H, d, *J* = 8.4 Hz, ArH), 7.15 (2H, d, *J* = 8.4 Hz, ArH), 6.71 (1H, s, H-6), 4.11 (1H, dd, *J* = 8.4, 7.6 Hz, H-2a), 4.05 (1H, dd, *J* = 8.3, 8.3, 4.5 Hz, H-5a), 3.90 (1H, ddd, *J* = 8.3, 8.2, 7.3 Hz, H-5b), 3.67 (1H, dd, *J* = 8.4, 7.7 Hz, H-2b), 3.35 (1H, dddd, *J* = 8.0, 7.9, 7.7, 7.6 Hz, H-3), 2.32 (1H, dddd, *J* = 12.5, 7.9, 7.3, 4.5 Hz, H-4a), 1.95 (1H, dddd, *J* = 12.5, 8.3, 8.2, 8.0 Hz, H-4b), 1.51 (9H, s, H-9); ^{13}C NMR (101 MHz, $CDCl_3$) δ 152.8 (C, C-7), 137.0 (C, ArC), 136.8 (C, ArC), 127.6 (2 × CH, ArCH), 118.8 (2 × CH, ArCH), 80.3 (C, C-8), 74.5 (CH_2, C-2), 68.4 (CH_2, C-5), 44.3 (CH, C-3), 34.5 (CH_2, C-4), 28.3 (3 × CH_3, C-9); HRMS (ESI-TOF) m/z: $[M + NH_4]^+$ calcd for $C_{15}H_{25}NO_3$, 281.1860; Found 281.1859 (0.20 ppm error).

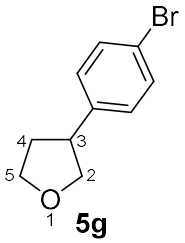


5f

$C_{10}H_{11}FO$

3-(4-Fluorophenyl)tetrahydrofuran (Compound 5f): Prepared according to general procedure A using $NaHCO_3$ (168 mg, 2.00 mmol, 2.00 equiv.), $Pd(OAc)_2$ (4.5 mg, 20.0 μmol, 0.02 equiv.), $^nBu_4NCl$ (278 mg, 1.00 mmol, 1.00 equiv.), 4-fluoroiodobenzene (222 mg, 1.00 mmol, 1.00 equiv.), *cis*-2-butene-1,4-diol (99 μL, 1.20 mmol, 1.20 equiv.) in MeCN (2.5 mL). The crude material was then immediately reduced according to general procedure B using hemiacetal (182 mg, 1.00 mmol, 1.00 equiv.), Et_3SiH (176 μL, 1.10 mmol, 1.10 equiv.), $BF_3{\cdot}OEt_2$ (136 μL, 1.10 mmol, 1.10 equiv.) in DCM (5 mL). Purification by flash column chromatography (SiO_2, Cyclohexane : EtOAc – 15:1) gave the title compound **5f** (132 mg, 0.796 mmol, 80%) as a pale yellow oil; R_f = 0.52 (Pet. ether/EtOAc, 1:1); ν_{max}/cm^{-1} (thin film) 2971, 2933, 2862, 1509, 1222; ^1H NMR (500 MHz, $CDCl_3$) δ 7.26–7.14 (2H, m, ArH), 7.04–6.94 (2H, m, ArH), 4.11 (1H, dd, *J* = 8.5, 7.6 Hz, H-2a), 4.06 (1H, ddd, *J* = 8.5, 8.2, 4.6 Hz, H-5a), 3.90 (1H, ddd, *J* = 8.5, 8.1, 7.9 Hz, H-5b), 3.69 (1H, dd, *J* = 8.5, 7.4 Hz, H-2b), 3.38 (1H, dddd, *J* = 7.8, 7.7, 7.6, 7.4 Hz, H-3), 2.35 (1H, dddd, *J* = 12.5, 8.1, 7.7, 4.6 Hz, H-4a), 1.96 (1H, dddd, *J* = 12.5, 8.2, 7.9, 7.8 Hz, H-4b); ^{13}C NMR (126 MHz, $CDCl_3$) δ 161.5 (C, d, *J* = 245.1 Hz, ArCF), 138.4 (C, d, *J* = 3.2 Hz, ArC), 128.6 (2 × CH, d, *J* = 7.8 Hz, ArCH), 115.3 (2 × CH, d, *J* = 20.9 Hz, ArCH), 74.6 (CH_2, C-2), 68.4 (CH_2, C-5), 44.2 (CH, C-3), 34.7 (CH_2, C-4); ^{19}F NMR (376 MHz, $CDCl_3$) δ −116.7; HRMS (EI-MS) m/z: $[M]^+$ calcd for $C_{10}H_{11}FO$, 166.0788; Found 166.0788 (0.46 ppm error).

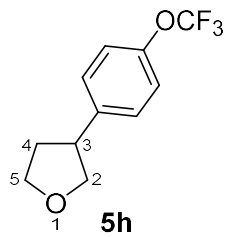
Data are consistent with those reported in the literature.[194]



5g

$C_{10}H_{11}BrO$

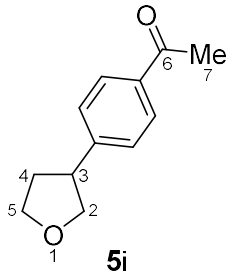
3-(4-Bromophenyl)tetrahydrofuran (Compound 5g): Prepared according to general procedure A using $NaHCO_3$ (168 mg, 2.00 mmol, 2.00 equiv.), $Pd(OAc)_2$ (4.5 mg, 20.0 μmol, 0.02 equiv.), $^nBu_4NCl$ (278 mg, 1.00 mmol, 1.00 equiv.), 4-bromoiodobenzene (283 mg, 1.00 mmol, 1.00 equiv.), *cis*-2-butene-1,4-diol (99 μL, 1.20 mmol, 1.20 equiv.) in MeCN (2.5 mL). The crude material was then immediately reduced according to general procedure B using hemiacetal (243 mg, 1.00 mmol, 1.00 equiv.), Et_3SiH (176 μL, 1.10 mmol, 1.10 equiv.), $BF_3{\cdot}OEt_2$ (136 μL, 1.10 mmol, 1.10 equiv.) in DCM (5 mL). Purification by flash column chromatography (SiO_2, Cyclohexane : EtOAc – 15:1) gave the *title compound* **5g** (182 mg, 0.741 mmol, 74%) as a yellow oil; R_f = 0.61 (Pet. ether/EtOAc, 1:1); ν_{max}/cm^{-1} (thin film) 2969, 2930, 2856, 1489; ^1H NMR (400 MHz, $CDCl_3$) δ 7.42 (2H, d, *J* = 8.5 Hz, ArH), 7.12 (2H, d, *J* = 8.5 Hz, ArH), 4.14–4.00 (2H, m, H-2a, H-5a), 3.90 (1H, ddd, *J* = 8.4, 8.0, 7.9 Hz, H-5b), 3.69 (1H, dd, *J* = 8.3, 7.1 Hz, H-2b), 3.36 (1H, app quint, *J* = 7.7 Hz, H-3), 2.36 (1H, dddd, *J* = 12.7, 7.9, 7.8, 4.7 Hz, H-4a), 1.95 (1H, dddd, *J* = 12.7, 8.2, 8.0, 7.8 Hz, H-4b); ^{13}C NMR (101 MHz, $CDCl_3$) δ 141.9 (C, ArC), 131.6 (2 × CH, ArCH), 128.9 (2 × CH, ArCH), 120.1 (C, ArC), 74.4 (CH_2, C-2), 68.4 (CH_2, C-5), 44.4 (CH, C-3), 34.6 (CH_2, C-4); HRMS (EI-MS) m/z: $[M]^+$ calcd for $C_{10}H_{11}{}^{79}BrO$, 225.9988; Found 225.9989 (0.62 ppm error).



5h

$C_{11}H_{11}F_3O_2$

3-[4-(Trifluoromethoxy)phenyl]tetrahydrofuran (Compound 5h): Prepared according to general procedure A using $NaHCO_3$ (168 mg, 2.00 mmol, 2.00 equiv.), $Pd(OAc)_2$ (4.5 mg, 20.0 µmol, 0.02 equiv.), $^nBu_4NCl$ (278 mg, 1.00 mmol, 1.00 equiv.), 4-(trifluoromethoxy)iodobenzene (288 mg, 1.00 mmol, 1.00 equiv.), *cis*-2-butene-1,4-diol (99 µL, 1.20 mmol, 1.20 equiv.) in MeCN (2.5 mL). The crude material was then immediately reduced according to general procedure B using hemiacetal (248 mg, 1.00 mmol, 1.00 equiv.), Et_3SiH (176 µL, 1.10 mmol, 1.10 equiv.), $BF_3{\cdot}OEt_2$ (136 µL, 1.10 mmol, 1.10 equiv.) in DCM (5 mL). Purification by flash column chromatography (SiO_2, Cyclohexane : EtOAc – 15:1) gave the *title compound* **5h** (213 mg, 0.917 mmol, 92%) as a pale yellow oil; R_f = 0.57 (Pet. ether/EtOAc, 1:1); ν_{max}/cm^{-1} (thin film) 2974, 2936, 2865, 1595, 1252, 1216, 1154, 1056; ^1H NMR (400 MHz, $CDCl_3$) δ 7.27 (2H, d, *J* = 8.7 Hz, ArH), 7.15 (2H, d, *J* = 8.7 Hz, ArH), 4.15–4.03 (2H, m, H-2a, H-5a), 3.91 (1H, ddd, *J* = 8.5, 7.8, 7.7 Hz, H-5b), 3.72 (1H, dd, *J* = 8.6, 7.1 Hz, H-2b), 3.41 (1H, dddd, *J* = 7.9, 7.8, 7.4, 7.1 Hz, H-3), 2.37 (1H, dddd, *J* = 12.4, 7.8, 7.7, 4.6 Hz, H-4a), 1.97, (1H, dddd, *J* = 12.4, 8.3, 7.9, 7.8 Hz, H-4b); ^{13}C NMR (101 MHz, $CDCl_3$) δ 147.7 (C, q, *J* = 1.8 Hz, ArC), 141.7 (C, ArC), 128.4 (2 × CH, ArCH), 121.1 (2 × CH, ArCH), 120.5 (C, q, *J* = 256.6 Hz, CF_3), 74.5 (CH_2, C-2), 68.3 (CH_2, C-5), 44.3 (CH, C-3), 34.6 (CH_2, C-4); ^{19}F NMR (376 MHz, $CDCl_3$) δ −57.9; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{11}H_{12}F_3O_2$, 233.0784; Found 233.0789 (2.20 ppm error).

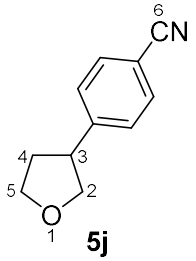


5i

$C_{12}H_{14}O_2$

1-[4-(Tetrahydrofuran-3-yl)phenyl]ethan-1-one (Compound 5i): Prepared according to general procedure A using $NaHCO_3$ (168 mg, 2.00 mmol, 2.00 equiv.), $Pd(OAc)_2$ (4.5 mg, 20.0 μmol, 0.02 equiv.), $^nBu_4NCl$ (278 mg, 1.00 mmol, 1.00 equiv.), 4'-iodoacetophenone (246 mg, 1.00 mmol, 1.00 equiv.), *cis*-2-butene-1,4-diol (99 μL, 1.20 mmol, 1.20 equiv.) in MeCN (2.5 mL). The crude material was then immediately reduced according to general procedure B using hemiacetal (206 mg, 1.00 mmol, 1.00 equiv.), Et_3SiH (176 μL, 1.10 mmol, 1.10 equiv.), $BF_3{\cdot}OEt_2$ (136 μL, 1.10 mmol, 1.10 equiv.) in DCM (5 mL). Purification by flash column chromatography (SiO_2, Cyclohexane : EtOAc – 15:1 → 11:1) gave the title compound **5i** (170 mg, 0.894 mmol, 89%) as a pale yellow oil; R_f = 0.41 (Pet. ether/EtOAc, 1:1); ν_{max}/cm^{-1} (thin film) 2969, 2929, 2860, 1678, 1606; ^1H NMR (400 MHz, $CDCl_3$) δ 7.87 (2H, d, *J* = 8.2 Hz, ArH), 7.31 (2H, d, *J* = 8.2 Hz, ArH), 4.10 (1H, dd, *J* = 8.2, 7.4 Hz, H-2a), 4.05 (1H, ddd, *J* = 8.2, 8.0, 4.7 Hz, H-5a), 3.89 (1H, ddd, *J* = 8.2, 7.9, 7.7 Hz, H-5b), 3.72 (1H, dd, *J* = 8.2, 7.2 Hz, H-2b), 3.43 (1H, dddd, *J* = 7.7, 7.6, 7.5, 7.2 Hz, H-3), 2.55 (3H, s, H-7), 2.37 (1H, dddd, *J* = 12.5, 7.9, 7.7, 4.7 Hz, H-4a), 1.97 (1H, dddd, *J* = 12.5, 8.0, 7.7, 7.6 Hz, H-4b); ^{13}C NMR (101 MHz, $CDCl_3$) δ 197.5 (C, C-6), 148.6 (C, ArC), 135.4 (C, ArC), 128.6 (2 × CH, ArCH), 127.3 (2 × CH, ArCH), 74.3 (CH_2, C-2), 68.3 (CH_2, C-5), 44.8 CH, C-3), 34.5 (CH_2, C-4), 26.4 (CH_3, C-7); HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{12}H_{14}NaO_2$, 213.0886; Found 213.0884 (0.90 ppm error).

Data are consistent with those reported in the literature.[194]

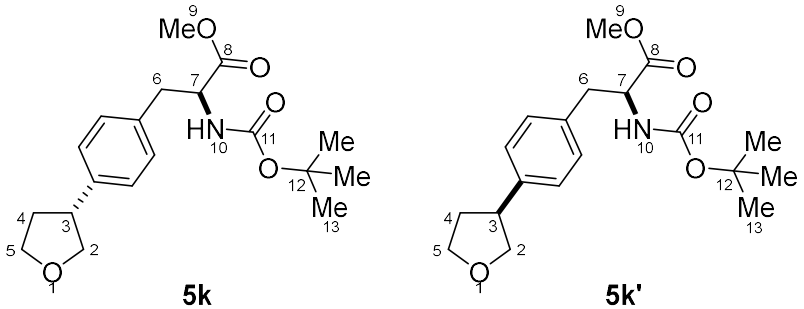


5j

$C_{11}H_{11}NO$

4-(Tetrahydrofuran-3-yl)benzonitrile (Compound 5j): Prepared according to general procedure A using $NaHCO_3$ (168 mg, 2.00 mmol, 2.00 equiv.), $Pd(OAc)_2$ (4.5 mg, 20.0 μmol, 0.02 equiv.), $^nBu_4NCl$ (278 mg, 1.00 mmol, 1.00 equiv.), 4-iodobenzonitrile (229 mg, 1.00 mmol, 1.00 equiv.), *cis*-2-butene-1,4-diol (99 μL, 1.20 mmol, 1.20 equiv.) in MeCN (2.5 mL). The crude material was then immediately reduced according to general procedure B using hemiacetal (189 mg, 1.00 mmol, 1.00 equiv.), Et_3SiH (176 μL, 1.10 mmol, 1.10 equiv.), $BF_3{\cdot}OEt_2$ (136 μL, 1.10 mmol, 1.10 equiv.) in DCM (5 mL). Purification by flash column chromatography (SiO_2, Cyclohexane : EtOAc – 15:1) gave the title compound **5j** (117 mg, 0.675 mmol, 68%) as a pale yellow oil; R_f = 0.43 (Pet. ether/EtOAc, 1:1); ν_{max}/cm^{-1} (thin film) 2972, 2935, 2864, 2226, 1054, 834, 561; ^1H NMR (400 MHz, $CDCl_3$) δ 7.58 (2H, d, *J* = 8.2 Hz, ArH), 7.35 (2H, d, *J* = 8.2 Hz, ArH), 4.14–4.01 (2H, m, H-2a, H-5a), 3.90 (1H, ddd, *J* = 8.3, 7.9, 7.8 Hz, H-5b), 3.74 (1H, dd, *J* = 8.6, 6.5 Hz, H-2b), 3.45 (1H, dddd, 7.7, 7.6, 7.4, 6.5 Hz, H-3), 2.40 (1H, dddd, *J* = 12.6, 7.8, 7.6, 4.7 Hz, H-4a), 1.96 (1H, app dq, *J* = 12.6, 7.7 Hz, H-4b); ^{13}C NMR (101 MHz, $CDCl_3$) δ 148.8 (C, ArC), 132.3 (2 × CH, ArCH), 128.0 (2 × CH, ArCH), 118.8 (C, C-6), 110.3 (C, ArC), 74.2 (CH_2, C-2), 68.3 (CH_2, C-5), 44.9 (CH, C-3), 34.5 (CH_2, C-4); HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{11}H_{11}NNaO$, 196.0733; Found 196.0732 (0.20 ppm error).

Data are consistent with those reported in the literature.[194]

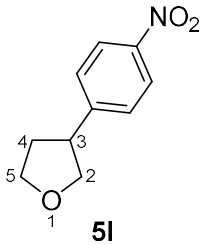


$C_{19}H_{27}NO_5$

Methyl (*S*)-2-[(*tert*-butoxycarbonyl)amino]-3-{4-[(*R*)-tetrahydrofuran-3-yl]phenyl}propanoate and Methyl (S)-2-[(*tert*-butoxycarbonyl)amino]-3-{4-[(*S*)-tetrahydrofuran-3-yl]phenyl}propanoate (Compound 5k and 5k'): Prepared according to general procedure A using $NaHCO_3$ (168 mg, 2.00 mmol, 2.00 equiv.), $Pd(OAc)_2$ (4.5 mg, 20.0 µmol, 0.02 equiv.), $^{n}Bu_4NCl$ (278 mg, 1.00 mmol, 1.00 equiv.), *N*-boc-4-iodo-L-phenylalanine methyl ester (405 mg, 1.00 mmol, 1.00 equiv.), *cis*-2-butene-1,4-diol (99 µL, 1.20 mmol, 1.20 equiv.) in MeCN (2.5 mL). The crude material was then immediately reduced according to general procedure B using hemiacetal (365 mg, 1.00 mmol, 1.00 equiv.), Et_3SiH (176 µL, 1.10 mmol, 1.10 equiv.), $BF_3{\cdot}OEt_2$ (136 µL, 1.10 mmol, 1.10 equiv.) in DCM (5 mL). Purification by flash column chromatography (SiO_2, Cyclohexane : EtOAc – 12:1) gave an inseparable mixture of *title compounds* **5k** and **5k'** (335 mg, 0.958 mmol, 96%, d.r. 1:1) as a colourless oil; R_f = 0.45 (Pet. ether/EtOAc, 1:1); ν_{max}/cm^{-1} (thin film) 3327, 2974, 2932, 2866, 1745, 1711, 1513; ^1H NMR (500 MHz, $CDCl_3$) δ 7.17 (2H, d, *J* = 7.8 Hz, ArH), 7.06 (2H, d, *J* = 7.8 Hz, ArH), 4.99 (1H, d, *J* = 7.9 Hz, H-10), 4.57 (1H, ddd, *J* = 7.9, 6.2, 5.4 Hz, H-7), 4.11 (1H, app t, *J* = 8.0 Hz, H-2a), 4.05 (1H, ddd, *J* = 8.2, 8.1, 4.5 Hz, H-5a), 3.90 (1H, ddd, *J* = 8.1, 8.0, 7.8 Hz, H-5b), 3.71 (3H, s, H-9), 3.68 (1H, app t, *J* = 8.0 Hz, H-2b), 3.36 (1H, app qd, *J* = 8.0, 7.7 Hz, H-3), 3.09 (1H, dd, *J* = 14.0, 5.4 Hz, H-6a), 3.00 (1H, dd, *J* = 14.0, 6.2 Hz, H-6b), 2.33 (1H, dddd, *J* = 12.3, 7.8, 7.7, 4.5 Hz, H-4a), 1.97 (1H, app dq, *J* = 12.3, 8.0 Hz, H-4b), 1.40 (9H, s, H-13); ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.3 (C, C-8), 155.0 (C, C-11), 141.3 (C, ArC), 134.1 (C, ArC), 129.5 (2 × CH, ArCH), 127.4 (2 × CH, ArCH), 79.8 (C, C-12), 74.6 (CH_2, C-2), (74.5 (CH_2, C-2)), 68.4 (CH_2, C-5), 54.3 (CH, C-7), 52.2 (CH_3, C-9), 44.6 (CH, C-3), 37.9 (CH_2, C-6), 34.6 (CH_2,

C-4), (34.5 (CH_2, C-4)), 28.2 (CH_3, C-13); HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{19}H_{28}NO_5$, 350.1962; Found 350.1966 (1.20 ppm error).

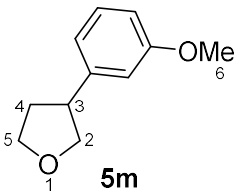
Note: The ^{13}C signals for both diastereoisomers overlap, except for those reported in parentheses.



5l

$C_{10}H_{11}NO_3$

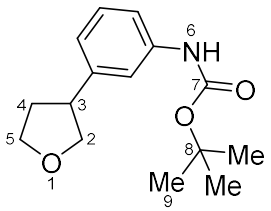
3-(4-Nitrophenyl)tetrahydrofuran (Compound 5l): Prepared according to general procedure A using $NaHCO_3$ (168 mg, 2.00 mmol, 2.00 equiv.), $Pd(OAc)_2$ (4.5 mg, 20.0 µmol, 0.02 equiv.), $^nBu_4NCl$ (278 mg, 1.00 mmol, 1.00 equiv.), 1-iodo-4-nitrobenzene (249 mg, 1.00 mmol, 1.00 equiv.), *cis*-2-butene-1,4-diol (99 µL, 1.20 mmol, 1.20 equiv.) in MeCN (2.5 mL). Purification by flash column chromatography (~10 g SiO_2, Cyclohexane : EtOAc – 4:1 → 1:1) gave the hemiacetal intermediate (151 mg, 0.721 mmol, 72%). The intermediate was then reduced according to general procedure B using hemiacetal (151 mg, 0.72 mmol, 1.00 equiv.), Et_3SiH (126 µL, 0.79 mmol, 1.10 equiv.), $BF_3{\cdot}OEt_2$ (98 µL, 0.79 mmol, 1.10 equiv.) in DCM (4 mL). Purification by flash column chromatography (SiO_2, Cyclohexane : EtOAc – 8:1) gave the *title compound* **5l** (120 mg, 0.623 mmol, 87%, 62% over two steps) as a yellow oil; R_f = 0.43 (Pet. ether/EtOAc, 1:1); ν_{max}/cm^{-1} (thin film) 2973, 2937, 2861, 1598, 1513; ^1H NMR (400 MHz, $CDCl_3$) δ 8.12 (2H, d, *J* = 8.7 Hz, ArH), 7.39 (2H, d, *J* = 8.7 Hz, ArH), 4.13–4.03 (2H, m, H-2a, H-5a), 3.89 (1H, ddd, *J* = 8.2, 7.9, 7.8 Hz, H-5b), 3.75 (1H, dd, *J* = 8.7, 6.7 Hz, H-2b), 3.49 (1H, dddd, *J* = 8.0, 7.9, 7.5, 6.7 Hz, H-3), 2.42 (1H, dddd, *J* = 12.6, 8.0, 7.9, 4.8 Hz, H-4a), 1.97 (1H, dddd, *J* = 12.6, 8.1, 7.8, 7.5 Hz, H-4b); ^{13}C NMR (101 MHz, $CDCl_3$) δ 151.1 (C, ArC), 146.5 (C, ArC), 127.9 (2 × CH, ArCH), 123.7 (2 × CH, ArCH), 74.2 (CH_2, C-2), 68.2 (CH_2, C-5), 44.7 (CH, C-3), 34.5 (CH_2, C-4); HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{10}H_{11}NNaO_3$, 216.0631; Found 216.0630 (0.60 ppm error).



5m

$C_{11}H_{14}O_2$

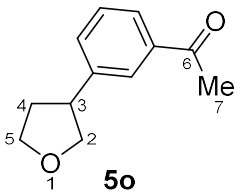
3-(3-Methoxyphenyl)tetrahydrofuran (Compound 5m): Prepared according to general procedure A using $NaHCO_3$ (168 mg, 2.00 mmol, 2.00 equiv.), $Pd(OAc)_2$ (4.5 mg, 20.0 µmol, 0.02 equiv.), $^nBu_4NCl$ (278 mg, 1.00 mmol, 1.00 equiv.), 3-iodoanisole (234 mg, 1.00 mmol, 1.00 equiv.), *cis*-2-butene-1,4-diol (99 µL, 1.20 mmol, 1.20 equiv.) in MeCN (2.5 mL). The crude material was then immediately reduced according to general procedure B using hemiacetal (194 mg, 1.00 mmol, 1.00 equiv.), Et_3SiH (176 µL, 1.10 mmol, 1.10 equiv.), $BF_3{\cdot}OEt_2$ (136 µL, 1.10 mmol, 1.10 equiv.) in DCM (5 mL). Purification by flash column chromatography (SiO_2, Cyclohexane : EtOAc – 15:1) gave the *title compound* **5m** (145 mg, 0.813 mmol, 81%) as a pale yellow oil; R_f = 0.61 (Pet. ether/EtOAc, 1:1); ν_{max}/cm^{-1} (thin film) 2935, 2860, 1601, 1583; ^1H NMR (400 MHz, $CDCl_3$) δ 7.24 (1H, dd, *J* = 8.1, 7.7 Hz, ArH), 6.86 (1H, d, *J* = 7.7 Hz, ArH), 6.82 (1H, s, ArH), 6.80–6.75 (1H, m, ArH), 4.14 (1H, app t, *J* = 8.0 Hz, H-2a), 4.07 (1H, app td, *J* = 8.2, 4.5 Hz, H-5a), 3.92 (1H, ddd, *J* = 8.2, 8.0, 7.8 Hz, H-5b), 3.81 (3H, s, H-6), 3.74 (1H, dd, *J* = 8.0, 7.9 Hz, H-2b), 3.39 (1H, app quint, *J* = 7.7 Hz, H-3), 2.36 (1H, dddd, *J* = 12.3, 7.8, 7.7, 4.5 Hz, H-4a), 2.02 (1H, dddd, *J* = 12.3, 8.2, 8.0, 7.9 Hz, H-4b); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.7 (C, ArC), 144.3 (C, ArC), 129.4 (CH, ArCH), 119.5 (CH, ArCH), 113.1 (CH, ArCH), 111.4 (CH, ArCH), 74.4 (CH_2, C-2), 68.4 (CH_2, C-5), 55.0 (CH_3, C-6), 44.9 (CH, C-3), 34.5 (CH_2, C-4); HRMS (ESI-TOF) m/z: $[M + NH_4]^+$ calcd for $C_{11}H_{18}NO_2$, 196.1332; Found 196.1328 (1.90 ppm error).



5n

$C_{15}H_{21}NO_3$

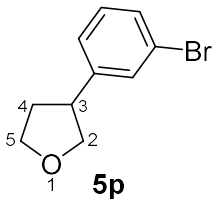
***tert*-Butyl [3-(tetrahydrofuran-3-yl)phenyl]carbamate (Compound 5n)**: Prepared according to general procedure A using $NaHCO_3$ (168 mg, 2.00 mmol, 2.00 equiv.), $Pd(OAc)_2$ (4.5 mg, 20.0 µmol, 0.02 equiv.), $^nBu_4NCl$ (278 mg, 1.00 mmol, 1.00 equiv.), *tert*-butyl (3-iodophenyl)carbamate (319 mg, 1.00 mmol, 1.00 equiv.), *cis*-2-butene-1,4-diol (99 µL, 1.20 mmol, 1.20 equiv.) in MeCN (2.5 mL). The crude material was then immediately reduced according to general procedure B using hemiacetal (180 mg, 1.00 mmol, 1.00 equiv.), Et_3SiH (176 µL, 1.10 mmol, 1.10 equiv.), $BF_3{\cdot}OEt_2$ (136 µL, 1.10 mmol, 1.10 equiv.) in DCM (5 mL). Purification by flash column chromatography (SiO_2, Cyclohexane : EtOAc – 15:1 → 10:1) gave the *title compound* **5n** (234 mg, 0.887 mmol, 89%) as a colourless oil; R_f = 0.57 (Pet. ether/EtOAc, 1:1); ν_{max}/cm^{-1} (thin film) 3308, 2974, 2931, 2871, 1725, 1701; ^1H NMR (400 MHz, $CDCl_3$) δ 7.32 (1H, dd, *J* = 1.9, 1.8 Hz, ArH), 7.22 (1H, dd, *J* = 8.2, 7.6 Hz, ArH), 7.17 (1H, ddd, *J* = 8.2, 1.9, 1.6 Hz, ArH), 6.92 (1H, ddd, *J* = 7.6, 1.8, 1.6 Hz, ArH), 6.56 (1H, br s, H-6), 4.12 (1H, dd, *J* = 8.4, 7.7 Hz, H-4a), 4.05 (1H, ddd, *J* = 8.4, 8.2, 4.6 Hz, H-5a), 3.90 (1H, ddd, *J* = 8.4, 7.9, 7.7 Hz, H-5b), 3.72 (1H, dd, *J* = 8.4, 7.7, H-4b), 3.37 (1H, app quint, *J* = 7.7 Hz, H-3), 2.34 (1H, dddd, *J* = 12.4, 8.1, 7.7, 4.6 Hz, H-4a), 2.00 (1H, dddd, *J* = 12.4, 8.2, 8.0, 7.9 Hz, H-4b), 1.52 (9H, s, H-9); ^{13}C NMR (101 MHz, $CDCl_3$) δ 152.7 (C, C-7), 143.7 (C, ArC), 138.6 (C, ArC), 129.1 (CH, ArCH), 121.8 (CH, ArCH), 117.4 (CH, ArCH), 116.7 (CH, ArCH), 80.5 (C, C-8), 74.5 (CH_2, C-2), 68.5 (CH_2, C-5), 45.0 (CH, C-3) 34.5 (CH_2, C-4), 28.3 (3 × CH_3, C-9); HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{15}H_{21}NNaO_3$, 286.1414; Found 286.1411 (0.80 ppm error).



5o

$C_{12}H_{14}O_2$

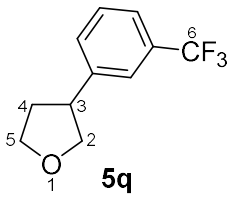
1-[3-(Tetrahydrofuran-3-yl)phenyl]ethan-1-one (Compound 5o): Prepared according to general procedure A using $NaHCO_3$ (168 mg, 2.00 mmol, 2.00 equiv.), $Pd(OAc)_2$ (4.5 mg, 20.0 µmol, 0.02 equiv.), $^nBu_4NCl$ (278 mg, 1.00 mmol, 1.00 equiv.), 3'-iodoacetophenone (246 mg, 1.00 mmol, 1.00 equiv.), *cis*-2-butene-1,4-diol (99 µL, 1.20 mmol, 1.20 equiv.) in MeCN (2.5 mL). The crude material was then immediately reduced according to general procedure B using hemiacetal (206 mg, 1.00 mmol, 1.00 equiv.), Et_3SiH (176 µL, 1.10 mmol, 1.10 equiv.), $BF_3{\cdot}OEt_2$ (136 µL, 1.10 mmol, 1.10 equiv.) in DCM (5 mL). Purification by flash column chromatography (SiO_2, Cyclohexane : EtOAc – 15:1) gave the *title compound* **5o** (170 mg, 0.894 mmol, 89%) as a pale yellow oil; R_f = 0.55 (Pet. ether/EtOAc, 1:1); ν_{max}/cm^{-1} (thin film) 2968, 2931, 2860, 1681; ^1H NMR (400 MHz, $CDCl_3$) δ 7.84 (1H, dd, *J* = 1.8, 1.7 Hz, ArH), 7.80 (1H, ddd, *J* = 7.6, 1.8, 1.6 Hz, ArH), 7.46 (1H, ddd, *J* = 7.6, 1.7, 1.6 Hz, ArH), 7.41 (1H, app t, *J* = 7.6 Hz, ArH), 4.15 (1H, dd, *J* = 8.5, 7.6 Hz, H-2a), 4.08 (1H, ddd, *J* = 8.5, 8.2, 4.6 Hz, H-5a), 3.92 (1H, ddd, *J* = 8.5, 7.7, 7.5 Hz, H-5b), 3.74 (1H, dd, *J* = 8.5, 7.5 Hz, H-2b), 3.46 (1H, dddd, *J* = 8.1, 7.9, 7.6, 7.5 Hz, H-3), 2.60 (3H, s, H-7), 2.40 (1H, dddd, *J* = 12.5, 8.1, 7.5, 4.6 Hz, H-4a), 2.02 (1H, dddd, *J* = 12.5, 8.2, 7.9, 7.7 Hz, H-4b) ; ^{13}C NMR (101 MHz, $CDCl_3$) δ 198.1 (C, C-6), 143.5 (C, ArC), 137.4 (C, ArC), 131.9 (CH, ArCH), 128.8 (CH, ArCH), 126.9 (CH, ArCH), 126.7 (CH, ArCH), 74.5 (CH_2, C-2), 68.4 (CH_2, C-5), 44.8 (CH, C-3), 34.6 (CH_2, C-4), 26.7 (CH_3, C-7); HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{12}H_{14}NaO_2$, 213.0886; Found 213.0887 (0.40 ppm error).



5p

$C_{10}H_{11}BrO$

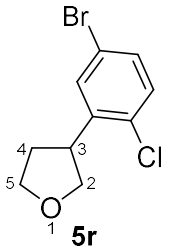
3-(3-Bromophenyl)tetrahydrofuran (Compound 5p): Prepared according to general procedure A using $NaHCO_3$ (168 mg, 2.00 mmol, 2.00 equiv.), $Pd(OAc)_2$ (4.5 mg, 0.02 mmol, 0.02 equiv.), $^nBu_4NCl$ (278 mg, 1.00 mmol, 1.00 equiv.), 3-bromoiodobenzene (283 mg, 1.00 mmol, 1.00 equiv.), *cis*-2-butene-1,4-diol (105.7 mg, 99 µL, 1.20 mmol, 1.20 equiv.) in MeCN (2.5 mL). The crude material was then immediately reduced according to general procedure B using hemiacetal (243 mg, 1.00 mmol, 1.00 equiv.), Et_3SiH (127.9 mg, 176 µL, 1.10 mmol, 1.10 equiv.), $BF_3{\cdot}OEt_2$ (156 mg, 136 µL, 1.10 mmol, 1.10 equiv.) in anhydrous DCM (5 mL). Purification by flash column chromatography (~25 g SiO_2, cyclohexane : EtOAc – 15:1) gave the *title compound* **5p** (168 mg, 0.74 mmol, 74%) as a colourless oil; R_f = 0.57 (Pet. ether/EtOAc, 1:1); υ_{max}/cm^{-1} (thin film) 2970, 2930, 2857, 1565, 1476, 1055, 779, 694; ^1H NMR (400 MHz, $CDCl_3$) δ 7.44–7.38 (1H, m, ArH), 7.37–7.30 (1H, m, ArH), 7.21–7.14 (2H, m, ArH), 4.17–3.98 (2H, m, H-2a, H-5a), 3.90 (1H, ddd, *J* = 8.1, 7.9, 7.7 Hz, H-5b), 3.71 (1H, dd, *J* = 8.6, 7.1 Hz, H-2b), 3.36 (1H, dddd, *J* = 7.8, 7.6, 7.4, 7.1 Hz, H-3), 2.36 (1H, dddd, *J* = 12.5, 7.8, 7.7, 4.6 Hz, H-4a), 1.97 (1H, dddd, *J* = 12.5, 7.9, 7.9, 7.6 Hz, H-4b); ^{13}C NMR (101 MHz, $CDCl_3$) δ 145.3 (C, ArC), 130.3 (CH, ArCH), 130.1 (CH, ArCH), 129.5 (CH, ArCH), 125.8 (CH, ArCH), 122.6 (C, ArC), 74.4 (CH_2, C-2), 68.3 (CH_2, C-5), 44.6 (CH, C-3), 34.5 (CH_2, C-4); HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{10}H_{11}{}^{79}BrNaO$, 248.9885; Found 248.9884 (0.50 ppm error).



5q

$C_{11}H_{11}F_3O$

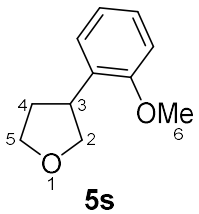
3-[3-(Trifluoromethyl)phenyl]tetrahydrofuran (Compound 5q): Prepared according to general procedure A using $NaHCO_3$ (168 mg, 2.00 mmol, 2.00 equiv.), $Pd(OAc)_2$ (4.5 mg, 0.02 mmol, 0.02 equiv.), $^{n}Bu_4NCl$ (278 mg, 1.00 mmol, 1.00 equiv.), 3-iodobenzotrifuoride (272 mg, 1.00 mmol, 1.00 equiv.), *cis*-2-butene-1,4-diol (105.7 mg, 99 µL, 1.20 mmol, 1.20 equiv.) in MeCN (2.5 mL). The crude material was then immediately reduced according to general procedure B using hemiacetal (232 mg, 1.00 mmol, 1.00 equiv.), Et_3SiH (127.9 mg, 176 µL, 1.10 mmol, 1.10 equiv.), $BF_3{\cdot}OEt_2$ (156 mg, 136 µL, 1.10 mmol, 1.10 equiv.) in anhydrous DCM (5 mL). Purification by flash column chromatography (~25 g SiO_2, cyclohexane : EtOAc – 15:1) gave the *title compound* **5q** (163 mg, 0.76 mmol, 76%) as a yellow oil; R_f = 0.61 (Pet. ether/EtOAc, 1:1); υ_{max}/cm^{-1} (thin film) 2972, 2933, 2860, 1324; ^1H NMR (400 MHz, $CDCl_3$) δ 7.55–7.36 (4H, m, ArH), 4.14 (1H, dd, *J* = 8.6, 7.6 Hz, H-2a), 4.09 (1H, ddd, *J* = 8.5, 8.2, 4.7 Hz, H-5a), 3.92 (1H, ddd, *J* = 8.5, 7.7, 7.7 Hz, H-5b), 3.75 (1H, dd, *J* = 8.6, 7.3 Hz, H-2b), 3.46 (1H, dddd, *J* = 8.4, 8.0, 7.6, 7.3 Hz, H-3), 2.41 (1H, dddd, *J* = 12.6, 8.4, 7.7, 4.7 Hz, H-4a), 2.00 (1H, dddd, *J* = 12.6, 8.2, 8.0, 7.7 Hz, H-4b); ^{13}C NMR (101 MHz, $CDCl_3$) δ 144.0 (C, ArC), 130.8 (C, q, *J* = 31.8 Hz, ArC), 130.6 (CH, ArCH), 129.0 (CH, ArCH), 124.1 (CF_3, q, *J* = 272.3 Hz, C-6), 124.0 (CH, q, *J* = 3.8 Hz, ArCH), 123.3 (CH, q, *J* = 4.0 Hz, ArCH), 74.4 (CH_2, C-2), 68.4 (CH_2, C-5), 44.8 (CH, C-3), 34.6 (CH_2, C-4); ^{19}F NMR (376 MHz, $CDCl_3$) δ −62.61; HRMS (EI-MS) m/z: $[M]^+$ calcd for $C_{11}H_{11}F_3O$, 216.0757; Found 216.0747 (4.60 ppm error).



5r

$C_{10}H_{10}BrClO$

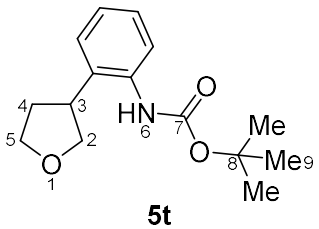
3-(5-Bromo-2-chlorophenyl)tetrahydrofuran (Compound 5r): Prepared according to general procedure A using $NaHCO_3$ (168 mg, 2.00 mmol, 2.00 equiv.), $Pd(OAc)_2$ (4.5 mg, 20.0 µmol, 0.02 equiv.), $^nBu_4NCl$ (278 mg, 1.00 mmol, 1.00 equiv.), 5-bromo-2-chloroiodobenzene (317 mg, 1.00 mmol, 1.00 equiv.), *cis*-2-butene-1,4-diol (99 µL, 1.20 mmol, 1.20 equiv.) in MeCN (2.5 mL). The crude material was then immediately reduced according to general procedure B using hemiacetal (278 mg, 1.00 mmol, 1.00 equiv.), Et_3SiH (176 µL, 1.10 mmol, 1.10 equiv.), $BF_3{\cdot}OEt_2$ (136 µL, 1.10 mmol, 1.10 equiv.) in DCM (5 mL). Purification by flash column chromatography (SiO_2, Cyclohexane : EtOAc – 15:1) gave the *title compound* **5r** (174 mg, 0.667 mmol, 67%) as a pale yellow oil; R_f = 0.73 (Pet. ether/EtOAc, 1:1); ν_{max}/cm^{-1} (thin film) 2974, 2932, 2861, 1465, 1039; ^1H NMR (400 MHz, $CDCl_3$) δ 7.49–7.43 (1H, m, ArH), 7.28–7.23 (1H, m, ArH), 7.22–7.16 (1H, m, ArH), 4.11–3.98 (2H, m, H-2a, H-5a), 3.93–3.85 (1H, m, H-5b), 3.84–3.72 (2H, m, H-2b, H-3), 2.45–2.30 (1H, m, H-4a), 2.03–1.85 (1H, m, H-4b); ^{13}C NMR (101 MHz, $CDCl_3$) δ 142.8 (C, ArC), 132.7 (C, ArC), 130.7 (CH, ArCH), 130.5 (CH, ArCH), 130.3 (CH, ArCH), 120.8 (C, ArC), 73.0 (CH_2, C-2), 67.8 (CH_2, C-5), 41.0 (CH, C-3), 33.1 (CH_2, C-4); HRMS (EI-MS) m/z: $[M]^+$ calcd for $C_{10}H_{10}{}^{79}Br^{35}ClO$, 259.9598; Found 259.9599 (0.35 ppm error).



5s

$C_{11}H_{14}O_2$

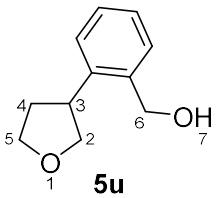
3-(2-Methoxyphenyl)tetrahydrofuran (Compound 5s): Prepared according to general procedure A using $NaHCO_3$ (168 mg, 2.00 mmol, 2.00 equiv.), $Pd(OAc)_2$ (4.5 mg, 20.0 µmol, 0.02 equiv.), $^nBu_4NCl$ (278 mg, 1.00 mmol, 1.00 equiv.), 2-iodoanisole (234 mg, 1.00 mmol, 1.00 equiv.), *cis*-2-butene-1,4-diol (99 µL, 1.20 mmol, 1.20 equiv.) in MeCN (2.5 mL). The crude material was then immediately reduced according to general procedure B using hemiacetal (194 mg, 1.00 mmol, 1.00 equiv.), Et_3SiH (176 µL, 1.10 mmol, 1.10 equiv.), $BF_3{\cdot}OEt_2$ (136 µL, 1.10 mmol, 1.10 equiv.) in DCM (5 mL). Purification by flash column chromatography (SiO_2, Cyclohexane : EtOAc – 15:1) gave the *title compound* **5s** (115 mg, 0.647 mmol, 65%) as a pale yellow oil; R_f = 0.64 (Pet. ether/EtOAc, 1:1); ν_{max}/cm^{-1} (thin film) 2937, 2863, 1600, 1585, 1492; ^1H NMR (400 MHz, $CDCl_3$) δ 7.29–7.16 (2H, m, ArH), 6.96 (1H, app t, *J* = 7.5 Hz, ArH), 6.89 (1H, d, *J* = 8.1 Hz, ArH), 4.17 (1H, dd, *J* = 7.2, 6.9 Hz), 4.05 (1H, ddd, *J* = 8.1, 7.9, 4.9 Hz, H-2a), 3.94 (1H, ddd, *J* = 7.9, 7.6, 7.5 Hz, H-5a), 3.85 (3H, s, H-6), 3.82–3.70 (2H, m, H-3, H-2b), 2.31 (1H, dddd, *J* = 12.4, 7.5, 7.3, 4.9 Hz, H-4a), 2.05 (1H, dddd, *J* = 12.4, 8.1, 7.7, 7.6 Hz, H-4b); ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.2 (C, ArC), 130.5 (C, ArC), 127.3 (CH, ArCH), 126.9 (CH, ArCH), 120.5 (CH, ArCH), 110.2 (CH, ArCH), 73.2 (CH_2, C-2), 68.1 (CH_2, C-5), 55.2 (CH_3, C-6), 38.3 (CH, C-3), 32.6 (CH_2, C-4); HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{11}H_{15}O_2$, 179.1067; Found 179.1065 (0.90 ppm error).



5t

$C_{15}H_{21}NO_3$

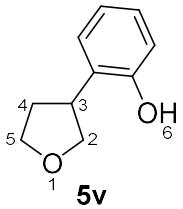
***tert*-Butyl [2-(tetrahydrofuran-3-yl)phenyl]carbamate (Compound 5t)**: Prepared according to general procedure A using $NaHCO_3$ (168 mg, 2.00 mmol, 2.00 equiv.), $Pd(OAc)_2$ (4.5 mg, 20.0 µmol, 0.02 equiv.), $^nBu_4NCl$ (278 mg, 1.00 mmol, 1.00 equiv.), *tert*-butyl (2-iodophenyl)carbamate (319 mg, 1.00 mmol, 1.00 equiv.), *cis*-2-butene-1,4-diol (99 µL, 1.20 mmol, 1.20 equiv.) in MeCN (2.5 mL). The crude material was then immediately reduced according to general procedure B using hemiacetal (279 mg, 1.00 mmol, 1.00 equiv.), Et_3SiH (176 µL, 1.10 mmol, 1.10 equiv.), $BF_3{\cdot}OEt_2$ (136 µL, 1.10 mmol, 1.10 equiv.) in DCM (5 mL). Purification by flash column chromatography (SiO_2, Cyclohexane : EtOAc – 10:1) gave the *title compound* **5t** (79.9 mg, 0.303 mmol, 30%) as a yellow oil; R_f = 0.39 (Pet. ether/EtOAc, 1:1); ν_{max}/cm^{-1} (thin film) 3427, 2974, 2929, 1672, 1491, 1366 ; ^1H NMR (400 MHz, $CDCl_3$) δ 7.65 (1H, app d, J = 8.2 Hz, ArH), 7.23–7.13 (2H, m, ArH), 7.03 (1H, ddd, J = 7.5, 7.4, 1.3 Hz, ArH), 3.86–3.71 (3H, m, H-2a, H-5a, H-2b), 3.66 (1H, ddd, J = 12.9, 6.8, 5.3 Hz, H-5b), 3.01 (1H, app quint, J = 6.1 Hz, H-3), 2.09–1.94 (2H, m, H-4a, H-4b), 1.69 (1H, br s, H-6), 1.52 (9H, s, H-9); ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.8 (C, C-7), 139.2 (C, ArC), 129.6 (C, ArC), 128.2 (CH, ArCH), 126.4 (CH, ArCH), 124.5 (CH, ArCH), 123.5 (CH, ArCH), 80.9 (C, C-8), 66.2 (CH_2, C-2), 42.4 (CH_2, C-5), 39.1 (CH, C-3), 28.4 (3 × CH_3, C-9), 26.0 (CH_2, C-4); HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{15}H_{21}NNaO_3$, 286.1414; Found 286.1418 (1.50 ppm error).



5u

$C_{11}H_{14}O_2$

[2-(Tetrahydrofuran-3-yl)phenyl]methanol (Compound 5u): Prepared according to general procedure A using $NaHCO_3$ (168 mg, 2.00 mmol, 2.00 equiv.), $Pd(OAc)_2$ (4.5 mg, 20.0 μmol, 0.02 equiv.), $^nBu_4NCl$ (278 mg, 1.00 mmol, 1.00 equiv.), 2-iodobenzyl alcohol (234 mg, 1.00 mmol, 1.00 equiv.), *cis*-2-butene-1,4-diol (99 μL, 1.20 mmol, 1.20 equiv.) in MeCN (2.5 mL). The crude material was then immediately reduced according to general procedure B using hemiacetal (194 mg, 1.00 mmol, 1.00 equiv.), Et_3SiH (176 μL, 1.10 mmol, 1.10 equiv.), $BF_3{\cdot}OEt_2$ (136 μL, 1.10 mmol, 1.10 equiv.) in DCM (5 mL). Purification by flash column chromatography (SiO_2, Cyclohexane : EtOAc – 12:1) gave the *title compound* **5u** (94.9 mg, 0.532 mmol, 53%) as a yellow oil; R_f = 0.25 (Pet. ether/EtOAc, 1:1); ν_{max}/cm^{-1} (thin film) 3392, 2970, 2932, 2868, 1488, 1452; ^1H NMR (400 MHz, $CDCl_3$) δ 7.39–7.28 (3H, m, ArH), 7.21 (1H, app td, *J* = 7.4, 1.5 Hz, ArH), 4.73 (2H, s, H-6), 4.14–4.02 (2H, m, H-2a, H-5a), 3.91 (1H, app q, *J* = 7.8 Hz, H-5b), 3.81–3.70 (2H, m, H-2b, H-3), 2.42–2.30 (1H, m, H-4a), 2.15–1.93 (2H, m, H-7, H-4b); ^{13}C NMR (101 MHz, $CDCl_3$) δ 141.6 (C, ArC), 138.2 (C, ArC), 128.6 (2 × CH, ArCH), 126.4 (CH, ArCH), 126.3 (CH, ArCH), 74.7 (CH_2, C-2), 68.4 (CH_2, C-5), 63.6 (CH_2, C-6), 39.8 (CH, C-3), 34.8 (CH_2, C-4); HRMS (ESI-TOF) m/z: $[M + NH_4]^+$ calcd for $C_{11}H_{18}NO_2$, 196.1332; Found 196.1329 (1.50 ppm error).

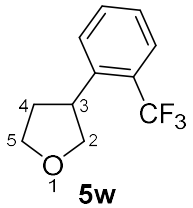


5v

$C_{10}H_{12}O_2$

2-(Tetrahydrofuran-3-yl)phenol (Compound 5v): Prepared according to general procedure A using $NaHCO_3$ (168 mg, 2.00 mmol, 2.00 equiv.),

$Pd(OAc)_2$ (4.5 mg, 20.0 µmol, 0.02 equiv.), $^nBu_4NCl$ (278 mg, 1.00 mmol, 1.00 equiv.), 2-iodophenol (220 mg, 1.00 mmol, 1.00 equiv.), *cis*-2-butene-1,4-diol (99 µL, 1.20 mmol, 1.20 equiv.) in MeCN (2.5 mL). The crude material was then immediately reduced according to general procedure B using hemiacetal (180 mg, 1.00 mmol, 1.00 equiv.), Et_3SiH (176 µL, 1.10 mmol, 1.10 equiv.), $BF_3{\cdot}OEt_2$ (136 µL, 1.10 mmol, 1.10 equiv.) in DCM (5 mL). Purification by flash column chromatography (SiO_2, Cyclohexane : EtOAc – 15:1 → 10:1) gave the *title compound* **5v** (74.2 mg, 0.452 mmol, 45%) as a pale yellow oil; R_f = 0.50 (Pet. ether/EtOAc, 1:1); ν_{max}/cm^{-1} (thin film) 3241, 2953, 2875; ^1H NMR (400 MHz, $CDCl_3$) δ 7.33 (1H, br s), 7.14–7.08 (2H, m, ArH), 6.86–6.80 (2H, m, ArH), 4.25 (1H, ddd, *J* = 8.7, 8.6, 3.9 Hz, H-5a), 4.04 (1H, dd, *J* = 9.1, 4.1 Hz, H-2a), 3.98 (1H, dd, *J* = 9.1, 7.3 Hz, H-2b), 3.79 (1H, app q, *J* = 8.5 Hz, H-5b), 3.59 (1H, dddd, *J* = 9.7, 7.3, 5.4, 4.1 Hz, H-3), 2.43 (1H, dddd, *J* = 12.9, 9.7, 7.9, 3.9 Hz, H-4a), 2.05 (1H, dddd, *J* = 12.9, 8.7, 8.6, 5.4 Hz, H-4b); ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.0 (C, ArC), 129.5 (C, ArC), 129.0 (CH, ArCH), 127.9 (CH, ArCH), 120.0 (CH, ArCH), 116.6 (CH, ArCH), 73.4 (CH_2, C-2), 68.9 (CH_2, C-5), 41.2 (CH, C-3), 33.0 (CH_2, C-4); HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{10}H_{12}NaO_2$, 187.0730; Found 187.0726 (1.90 ppm error).

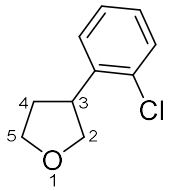


5w

$C_{11}H_{11}F_3O$

3-[2-(Trifluoromethyl)phenyl]tetrahydrofuran (Compound 5w): Prepared according to general procedure A using $NaHCO_3$ (168 mg, 2.00 mmol, 2.00 equiv.), $Pd(OAc)_2$ (4.5 mg, 20.0 µmol, 0.02 equiv.), $^nBu_4NCl$ (278 mg, 1.00 mmol, 1.00 equiv.), 2-iodobenzotrifluoride (272 mg, 1.00 mmol, 1.00 equiv.), *cis*-2-butene-1,4-diol (99 µL, 1.20 mmol, 1.20 equiv.) in MeCN (2.5 mL). The crude material was then immediately reduced according to general procedure B using hemiacetal (232 mg, 1.00 mmol, 1.00 equiv.), Et_3SiH (176 µL, 1.10 mmol, 1.10 equiv.), $BF_3{\cdot}OEt_2$ (136 µL, 1.10 mmol, 1.10 equiv.) in DCM (5 mL). Purification by flash column chromatography (SiO_2, Cyclohexane : EtOAc –

15:1) gave the *title compound* **5w** (67.5 mg, 0.312 mmol, 31%) as a yellow oil; R_f = 0.64 (Pet. ether/EtOAc, 1:1); ν_{max}/cm^{-1} (thin film) 2955, 2923, 2853, 1738, 1462; ^1H NMR (400 MHz, $CDCl_3$) δ 7.62 (1H, d, *J* = 7.8 Hz, ArH), 7.55–7.51 (2H, m, ArH), 7.34–7.27 (1H, m, ArH), 4.15–4.05 (2H, m, H-5a, H-2a), 3.91 (1H, app dt, *J* = 8.6, 7.6 Hz, H-5b), 3.85–3.79 (2H, m, H-3, H-2b), 2.43 (1H, app dtd, *J* = 12.8, 7.8, 4.9 Hz, H-4a), 2.03–1.92 (1H, m, H-4b); ^{13}C NMR (101 MHz, $CDCl_3$) δ 143.1 (C, q, *J* = 1.8 Hz, ArC), 132.3 (CH, ArCH), 128.4 (C, q, *J* = 29.4 Hz, ArC), 127.8 (CH, ArCH), 126.2 (CH, ArCH), 125.6 (CH, q, *J* = 6.0 Hz, ArCH), 124.5 (C, q, *J* = 273.4 Hz, CF_3), 75.3 (CH_2, C-2), 68.5 (CH_2, C-5), 40.0 (CH, q, *J* = 2.0 Hz, C-3), 35.7 (CH_2, C-4); ^{19}F NMR (376 MHz, $CDCl_3$) δ −58.7; HRMS (EI-MS) m/z: $[M]^+$ calcd for $C_{11}H_{11}F_3O$, 216.0757; Found 216.0740 (7.68 ppm error).

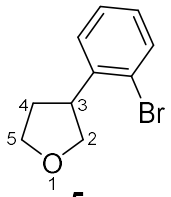


5x

$C_{10}H_{11}ClO$

3-(2-Chlorophenyl)tetrahydrofuran (Compound 5x): Prepared according to general procedure A using $NaHCO_3$ (168 mg, 2.00 mmol, 2.00 equiv.), $Pd(OAc)_2$ (4.5 mg, 20.0 µmol, 0.02 equiv.), $^nBu_4NCl$ (278 mg, 1.00 mmol, 1.00 equiv.), 2-chloroiodobenzene (239 mg, 1.00 mmol, 1.00 equiv.), *cis*-2-butene-1,4-diol (99 µL, 1.20 mmol, 1.20 equiv.) in MeCN (2.5 mL). The crude material was then immediately reduced according to general procedure B using hemiacetal (199 mg, 1.00 mmol, 1.00 equiv.), Et_3SiH (176 µL, 1.10 mmol, 1.10 equiv.), $BF_3{\cdot}OEt_2$ (136 µL, 1.10 mmol, 1.10 equiv.) in DCM (5 mL). Purification by flash column chromatography (SiO_2, Cyclohexane : EtOAc – 15:1) gave the *title compound* **5x** (144 mg, 0.789 mmol, 79%) as a pale yellow oil; R_f = 0.59 (Pet. ether/EtOAc, 1:1); ν_{max}/cm^{-1} (thin film) 2974, 2933, 2861, 1475, 1442; ^1H NMR (400 MHz, $CDCl_3$) δ 7.36 (1H, dd, *J* = 8.0, 1.4 Hz, ArH), 7.35 (1H, dd, *J* = 7.7, 1.8 Hz, ArH), 7.24 (1H, ddd, *J* = 7.7, 7.6, 1.4 Hz, ArH), 7.15 (1H, ddd, *J* = 8.0, 7.6, 1.8 Hz, ArH), 4.13 (1H, dd, *J* = 8.4, 6.8 Hz, H-2a),

4.04 (1H, ddd, *J* = 8.3, 8.0, 5.5 Hz, H-5a), 3.96–3.84 (2H, m, H-5b, H-3), 3.80 (1H, dd, *J* = 8.4, 6.3 Hz, H-2b), 2.39 (1H, dddd, *J* = 12.5, 8.0, 7.5, 5.5 Hz, H-4a), 1.99 (1H, dddd, *J* = 12.5, 8.0, 7.0, 6.7 Hz, H-4b); ^{13}C NMR (101 MHz, $CDCl_3$) δ 140.4 (C, ArC), 133.9 (C, ArC), 129.5 (CH, ArCH), 127.5 (CH, ArCH), 127.2 (CH, ArCH), 127.1 (CH, ArCH), 73.3 (CH_2, C-2), 68.0 (CH_2, C-5), 41.1 (CH, C-3), 33.2 (CH_2, C-4); HRMS (EI-MS) m/z: $[M]^+$ calcd for $C_{10}H_{11}{}^{35}ClO$, 182.0493; Found 182.0502 (4.72 ppm error).

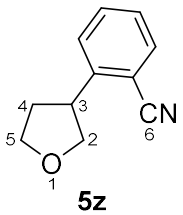


5y

$C_{10}H_{11}BrO$

3-(2-Bromophenyl)tetrahydrofuran (Compound 5y): Prepared according to general procedure A using $NaHCO_3$ (168 mg, 2.00 mmol, 2.00 equiv.), $Pd(OAc)_2$ (4.5 mg, 20.0 µmol, 0.02 equiv.), ^{n}Bu$_4$NCl (278 mg, 1.00 mmol, 1.00 equiv.), 2-bromoiodobenzene (283 mg, 1.00 mmol, 1.00 equiv.), *cis*-2-butene-1,4-diol (99 µL, 1.20 mmol, 1.20 equiv.) in MeCN (2.5 mL). The crude material was then immediately reduced according to general procedure B using hemiacetal (243 mg, 1.00 mmol, 1.00 equiv.), Et_3SiH (176 µL, 1.10 mmol, 1.10 equiv.), $BF_3{\cdot}OEt_2$ (136 µL, 1.10 mmol, 1.10 equiv.) in DCM (5 mL). Purification by flash column chromatography (SiO_2, Cyclohexane : EtOAc – 15:1) gave the *title compound* **5y** (172 mg, 0.756 mmol, 76%) as a colourless oil; R_f = 0.61 (Pet. ether/EtOAc, 1:1); ν_{max}/cm^{-1} (thin film) 3060, 2973, 2860, 1470; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (1H, dd, *J* = 7.8, 1.4 Hz, ArH), 7.34 (1H, dd, *J* = 7.9, 1.8 Hz, ArH), 7.28 (1H, ddd, 7.9, 7.5, 1.4 Hz, ArH), 7.07 (1H, ddd, *J* = 7.8, 7.5, 1.8 Hz, ArH), 4.12 (1H, dd, *J* = 8.4, 6.8 Hz, H-2a), 4.04 (1H, ddd, *J* = 8.3, 8.1, 5.5 Hz, H-5a), 3.92 (1H, ddd, *J* = 8.3, 7.5, 6.9 Hz, H-5b), 3.87 (1H, dddd, *J* = 7.9, 6.9, 6.8, 5.8 Hz, H-3), 3.80 (1H, dd, *J* = 8.4, 5.8 Hz, H-2b), 2.40 (1H, dddd, *J* = 13.0, 7.9, 7.5, 5.5 Hz, H-4a), 1.97 (1H, dddd, *J* = 13.0, 8.1, 6.9, 6.6 Hz, H-4b); ^{13}C NMR (101 MHz, $CDCl_3$) δ 142.2 (C, ArC), 132.8 (CH, ArCH), 127.8 (CH, ArCH), 127.7 (CH, ArCH), 127.3 (CH, ArCH), 124.7 (C,

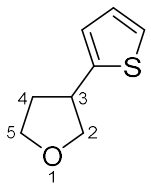
ArC), 73.4 (CH_2, C-2), 68.0 (CH_2, C-5), 43.7 (CH, C-3), 33.5 (CH_2, C-4); HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{10}H_{11}{}^{79}BrNaO$, 248.9885; Found 248.9890 (1.70 ppm error).



5z

$C_{11}H_{11}NO$

2-(Tetrahydrofuran-3-yl)benzonitrile (Compound 5z): Prepared according to general procedure A using $NaHCO_3$ (168 mg, 2.00 mmol, 2.00 equiv.), $Pd(OAc)_2$ (4.5 mg, 20.0 µmol, 0.02 equiv.), $^nBu_4NCl$ (278 mg, 1.00 mmol, 1.00 equiv.), 2-iodobenzonitrile (229 mg, 1.00 mmol, 1.00 equiv.), *cis*-2-butene-1,4-diol (99 µL, 1.20 mmol, 1.20 equiv.) in MeCN (2.5 mL). The crude material was then immediately reduced according to general procedure B using hemiacetal (189 mg, 1.00 mmol, 1.00 equiv.), Et_3SiH (176 µL, 1.10 mmol, 1.10 equiv.), $BF_3{\cdot}OEt_2$ (136 µL, 1.10 mmol, 1.10 equiv.) in DCM (5 mL). Purification by flash column chromatography (SiO_2, Cyclohexane : EtOAc – 15:1) gave the *title compound* **5z** (121 mg, 0.697 mmol, 70%) as a pale yellow oil; R_f = 0.55 (Pet. ether/EtOAc, 1:1); ν_{max}/cm^{-1} (thin film) 2973, 2954, 2936, 2866, 2223; ^1H NMR (400 MHz, $CDCl_3$) δ 7.60 (1H, d, *J* = 7.6 Hz, ArH), 7.55 (1H, dd, *J* = 8.2, 7.2 Hz, ArH), 7.45 (1H, d, *J* = 8.2 Hz, ArH), 7.30 (1H, dd, *J* = 7.6, 7.2 Hz, ArH), 4.15–4.03 (2H, m, H-2a, H-5a), 3.90 (1H, ddd, *J* = 8.1, 7.8, 7.4 Hz, H-5b), 3.87–3.78 (2H, m, H-2b, H-3), 2.47 (1H, dddd, *J* = 12.8, 7.8, 7.6, 5.1 Hz, H-4a), 1.97 (1H, dddd, *J* = 12.8, 7.9, 7.4, 6.7 Hz, H-4b); ^{13}C NMR (101 MHz, $CDCl_3$) δ 147.4 (C, ArC), 133.2 (CH, ArCH), 132.7 (CH, ArCH), 126.8 (CH, ArCH), 126.7 (CH, ArCH), 117.9 (C, C-6), 112.2 (C, ArC), 73.8 (CH_2, C-2), 68.2 (CH_2, C-5), 42.7 (CH, C-3), 34.4 (CH_2, C-4); HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{11}H_{11}NNaO$, 196.0733; Found 196.0730 (1.60 ppm error).

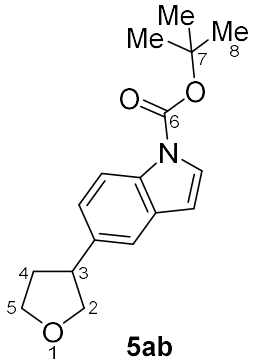


5aa

$C_8H_{10}OS$

3-(Thiophen-2-yl)tetrahydrofuran (Compound 5aa): Prepared according to general procedure A using $NaHCO_3$ (168 mg, 2.00 mmol, 2.00 equiv.), $Pd(OAc)_2$ (4.5 mg, 20.0 μmol, 0.02 equiv.), $^nBu_4NCl$ (278 mg, 1.00 mmol, 1.00 equiv.), 2-iodothiophene (210 mg, 1.00 mmol, 1.00 equiv.), *cis*-2-butene-1,4-diol (99 μL, 1.20 mmol, 1.20 equiv.) in MeCN (2.5 mL). The crude material was then immediately reduced according to general procedure B using hemiacetal (170 mg, 1.00 mmol, 1.00 equiv.), Et_3SiH (176 μL, 1.10 mmol, 1.10 equiv.), $BF_3{\cdot}OEt_2$ (136 μL, 1.10 mmol, 1.10 equiv.) in DCM (5 mL). Purification by flash column chromatography (SiO_2, Cyclohexane : EtOAc – 15:1) gave the title compound **5aa** (118 mg, 0.764 mmol, 76%) as a yellow oil; R_f = 0.66 (Pet. ether/EtOAc, 1:1); ν_{max}/cm^{-1} (thin film) 2955, 2924, 2854, 1737; ^1H NMR (400 MHz, $CDCl_3$) δ 7.16 (1H, dd, *J* = 5.1, 1.1 Hz, ArH), 6.95 (1H, dd, *J* = 5.1, 3.5 Hz, ArH), 6.90 (1H, dt, *J* = 3.5, 1.0 Hz, ArH), 4.15 (1H, dd, *J* = 7.1, 7.0 Hz, H-2a), 4.05 (1H, ddd, *J* = 8.5, 8.1, 5.1 Hz, H-5a), 3.93 (1H, app dt, *J* = 8.5, 7.5 Hz, H-5b), 3.76–3.64 (2H, m, H-2b, H-3), 2.40 (1H, dddd, *J* = 12.5, 7.6, 7.5, 5.1 Hz, H-4a), 2.05 (1H, dddd, *J* = 12.5, 8.1, 7.7, 7.5 Hz, H-4b); ^{13}C NMR (101 MHz, $CDCl_3$) δ 145.7 (C, ArC), 126.7 (CH, ArCH), 123.5 (CH, ArCH), 123.2 (CH, ArCH), 74.7 (CH_2, C-2), 68.1 (CH_2, C-5), 40.3 (CH, C-3), 35.1 (CH_2, C-4); HRMS (EI-MS) m/z: $[M]^+$ calcd for $C_8H_{10}OS$, 154.0447; Found 154.0440 (4.30 ppm error).

Data are consistent with those reported in the literature.[194]

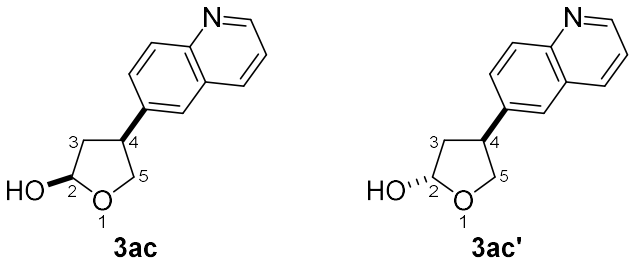


5ab

$C_{17}H_{21}NO_3$

***tert*-Butyl 5-(tetrahydrofuran-3-yl)-1*H*-indole-1-carboxylate (Compound 5ab)**: Prepared according to general procedure A using $NaHCO_3$ (168 mg, 2.00 mmol, 2.00 equiv.), $Pd(OAc)_2$ (4.5 mg, 20.0 μmol, 0.02 equiv.), $^nBu_4NCl$ (278 mg, 1.00 mmol, 1.00 equiv.), *N*-Boc-5-iodoindole **1ab** (343 mg, 1.00 mmol, 1.00 equiv.), *cis*-2-butene-1,4-diol (99 μL, 1.20 mmol, 1.20 equiv.) in MeCN (2.5 mL). The crude material was then immediately reduced according to general procedure B using hemiacetal (303 mg, 1.00 mmol, 1.00 equiv.), Et_3SiH (176 μL, 1.10 mmol, 1.10 equiv.), $BF_3{\cdot}OEt_2$ (136 μL, 1.10 mmol, 1.10 equiv.) in DCM (5 mL). Purification by flash column chromatography (SiO_2, Cyclohexane : EtOAc – 15:1) gave the title compound **5ab** (242 mg, 0.840 mmol, 84%) as an off-white crystalline solid; mp. 47–49 °C; R_f = 0.64 (Pet. ether/EtOAc, 1:1); ν_{max}/cm^{-1} (thin film) 2974, 2931, 2865, 1728; ^1H NMR (500 MHz, $CDCl_3$) δ 8.07 (1H, d, *J* = 8.6 Hz, ArH), 7.59 (1H, d, *J* = 3.7 Hz, ArH), 7.44 (1H, d, *J* = 1.8 Hz, ArH), 7.22 (1H, dd, *J* = 8.6, 1.8 Hz, ArH), 6.53 (1H, d, *J* = 3.7 Hz, ArH), 4.18 (1H, app t, *J* = 8.0 Hz, H-2a), 4.11 (1H, ddd, *J* = 8.2, 8.1, 4.5 Hz, H-5a), 3.95 (1H, ddd, *J* = 8.1, 8.0, 7.8 Hz, H-5b), 3.78 (1H, dd, *J* = 8.0, 7.8 Hz, H-2b), 3.50 (1H, dddd, *J* = 8.2, 8.0, 7.8, 7.7 Hz, H-3), 2.40 (1H, dddd, *J* = 12.2, 7.8, 7.7, 4.5 Hz, H-4a), 2.06 (1H, app dq, *J* = 12.2, 8.0 Hz, H-4b), 1.67 (9H, s, H-8); ^{13}C NMR (126 MHz, $CDCl_3$) δ 149.7 (C, C-6), 137.0 (C, ArC), 133.9 (C, ArC), 130.8 (C, ArC), 126.2 (CH, ArCH), 123.6 (CH, ArCH), 119.1 (CH, ArCH), 115.2 (CH, ArCH), 107.1 (CH, ArCH), 83.6 (C, C-7), 74.9 (CH_2, C-2), 68.5 (CH_2, C-5), 44.9 (CH, C-3), 35.0 (CH_2, C-4), 28.2 (3 × CH_3, C-8); HRMS (ESI-TOF) m/z: $[M + NH_4]^+$ calcd for $C_{17}H_{25}N_2O_3$, 305.1860; Found 305.1858 (0.50 ppm error).

Data are consistent with those reported in the literature.[195]

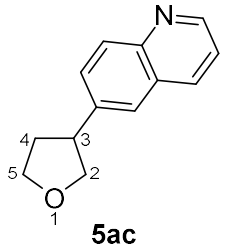


$C_{13}H_{13}NO_2$

(2*R,4*S**)-4-(Quinolin-6-yl)tetrahydrofuran-2-ol and (2*S**,4*S**)-4-(Quinolin-6-yl)tetrahydrofuran-2-ol (Compound 3ac and Compound 3ac')**: Prepared according to a modified version (reaction carried out on a 0.59 mmol scale using THF as the solvent) of general procedure A using $NaHCO_3$ (99.1 mg, 1.18 mmol, 2.00 equiv.), $Pd(OAc)_2$ (2.7 mg, 0.012 mmol, 0.02 equiv.), $^nBu_4NCl$ (164 mg, 0.59 mmol, 1.00 equiv.), 6-iodoquinoline (150 mg, 0.59 mmol, 1.00 equiv.), *cis*-2-butene-1,4-diol (58.4 μL, 0.71 mmol, 1.20 equiv.) in THF (1.5 mL). Purification by flash column chromatography (SiO_2, EtOAc) gave the *title compounds* **3ac** and **3ac'** (112 mg, 0.520 mmol, 88%, d.r. 1.7:1) as an off-white microcrystalline solid; mp. 138–140 °C; R_f = 0.17 (EtOAc); ν_{max}/cm^{-1} (thin film) 3171, 2942, 2872, 1502, 1025; **Major diastereoisomer:** ^1H NMR (400 MHz, $CDCl_3$) δ 8.95–8.80 (1H, m, ArH), 8.15–8.05 (2H, m, ArH), 7.80–7.58 (2H, m, ArH), 7.44–7.35 (1H, m, ArH), 5.88–5.74 (1H, m, H-2), 4.59–4.47 (1H, m, H-5a), 4.01–3.86 (2H, m, H-5b, H-4), 2.46 (1H, ddd, *J* = 12.9, 7.1, 1.0 Hz, H-3a), 2.30–2.18 (1H, m, H-3b); ^{13}C NMR (101 MHz, $CDCl_3$) δ 150.0 (CH, ArCH), 147.3 (C, ArC), 140.7 (C, ArC), 135.8 (CH, ArCH), 129.8 (CH, ArCH), 129.2 (CH, ArCH), 128.2 (C, ArC), 125.4 (CH, ArCH), 121.4 (CH, ArCH), 99.0 (CH, C-2), 73.8 (CH_2, C-5), 42.5 CH, C-4), 42.0 (CH_2, C-3); **Minor diastereoisomer:** ^1H NMR (400 MHz, $CDCl_3$) δ 8.95–8.80 (1H, m, ArH), 8.15–8.05 (2H, m, ArH), 7.70–7.58 (2H, m, ArH), 7.44–7.35 (1H, m, ArH), 5.88–5.74 (1H, m, H-2), 4.31 (1H, app t, *J* = 8.2 Hz, H-5a), 4.08 (1H, app t, *J* = 9.0 Hz, H-5b), 3.69–3.57 (2H, m, H-4, H-6), 2.73 (1H, ddd, *J* = 13.6, 10.0, 5.5 Hz, H-3a), 2.12 (1H, ddd, *J* = 13.6, 8.0, 2.9 Hz, H-3b); ^{13}C NMR (101 MHz, $CDCl_3$) δ 150.0 (CH, ArCH), 147.3 (C, ArC), 139.7 (C, ArC), 135.9 (CH, ArCH), 129.8 (CH, ArCH), 129.7 (CH, ArCH), 128.2 (C, ArC), 125.9 (CH, ArCH), 121.3 (CH, ArCH), 99.2 (CH, C-2), 73.1 (CH_2, C-5), 44.4 (CH, C-4), 41.8 (CH_2, C-3);

HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{13}H_{14}NO_2$, 216.1019; Found 216.1021 (0.80 ppm error).

Note: The relative stereochemistry of the major and minor diastereoisomers was not determined.

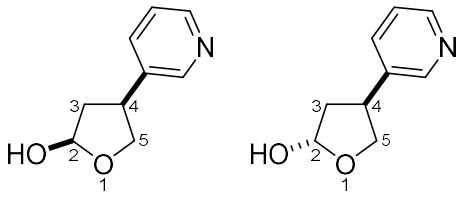


5ac

$C_{13}H_{13}NO$

6-(Tetrahydrofuran-3-yl)quinoline (Compound 5ac): Prepared according to a modified version (THF as solvent) of general procedure A using $NaHCO_3$ (168 mg, 2.00 mmol, 2.00 equiv.), $Pd(OAc)_2$ (4.5 mg, 20.0 μmol, 0.02 equiv.), $^nBu_4NCl$ (278 mg, 1.00 mmol, 1.00 equiv.), 6-iodoquinoline (255 mg, 1.00 mmol, 1.00 equiv.), *cis*-2-butene-1,4-diol (99 μL, 1.20 mmol, 1.20 equiv.) in THF (2.5 mL). The crude material was then immediately reduced according to general procedure B using hemiacetal (215 mg, 1.00 mmol, 1.00 equiv.), Et_3SiH (176 μL, 1.10 mmol, 1.10 equiv.), $BF_3{\cdot}OEt_2$ (136 μL, 1.10 mmol, 1.10 equiv.) in DCM (25 mL). Purification by flash column chromatography (SiO_2, Cyclohexane : EtOAc – 15:1 → 6:1) gave the *title compound* **5ac** (74.0 mg, 0.371 mmol, 37%) as a colourless oil; R_f = 0.04 (Cyclohexane/EtOAc, 9:1); ν_{max}/cm^{-1} (thin film) 2926, 2854, 1499, 1054; ^1H NMR (400 MHz, $CDCl_3$) δ 8.85 (1H, dd, *J* = 4.3, 1.7 Hz, ArH), 8.11–8.01 (2H, m, ArH), 7.65–7.55 (2H, m, ArH), 7.35 (1H, dd, *J* = 8.2, 4.2 Hz, ArH), 4.17 (1H, dd, *J* = 8.6, 7.4 Hz, H-2a), 4.10 (1H, ddd, *J* = 8.4, 8.1, 4.7 Hz, H-5a), 3.93 (1H, ddd, *J* = 8.4, 8.0, 7.8 Hz, H-5b), 3.83 (1H, dd, *J* = 8.6, 7.3 Hz, H-2b), 3.57 (1H, dddd, *J* = 8.1, 7.8, 7.5, 7.3 Hz, H-3), 2.42 (1H, dddd, *J* = 12.6, 8.1, 8.0, 4.7 Hz, H-4a), 2.07 (1H, app ddt, *J* = 12.6, 8.1, 7.8 Hz, H-4b); ^{13}C NMR (101 MHz, $CDCl_3$) δ 149.9 (CH, ArCH), 147.3 (C, ArC), 141.2 (C, ArC), 135.6 (CH, ArCH), 129.7 (CH, ArCH), 129.3 (CH, ArCH), 128.1 (C, ArC), 125.2 (CH, ArCH), 121.2 (CH, ArCH), 74.4 (CH_2, C-2), 68.4 (CH_2, C-5), 44.8 (CH, C-3), 34.6 (CH_2, C-4); HRMS (ESI-

TOF) m/z: $[M + H]^+$ calcd for $C_{13}H_{14}NO$, 200.1070; Found 200.1069 (0.30 ppm error).



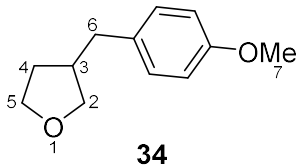
$C_9H_{11}NO_2$

(2*R,4*S**)-4-(Pyridin-3-yl)tetrahydrofuran-2-ol and (2*S**,4*S**)-4-(Pyridin-3-yl)tetrahydrofuran-2-ol (Compound 3ad and Compound 3ad')**: Prepared according to a modified version (increased Pd loading) of general procedure C using $NaHCO_3$ (168 mg, 2.00 mmol, 2.00 equiv.), $Pd(OAc)_2$ (11.2 mg, 0.05 mmol, 0.05 equiv.), $^n Bu_4NCl$ (278 mg, 1.00 mmol, 1.00 equiv.), 3-iodopyridine (205 mg, 1.00 mmol, 1.00 equiv.), *cis*-2-butene-1,4-diol (99 µL, 1.20 mmol, 1.20 equiv.) in MeCN (2.5 mL). Purification by flash column chromatography (SiO_2, Cyclohexane : EtOAc – 1:1) gave an inseparable mixture of *title compounds* **3ad** and **3ad'**(131 mg, 0.790 mmol, 79%, d.r. 1.5:1) as a yellow microcrystalline solid; mp. 89–91 °C; R_f = 0.11 (EtOAc); υ_{max}/cm^{-1} (thin film) 3363, 3184, 2945, 2877, 1428, 1025; **Major diastereoisomer:** ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.53–8.41 (2H, m, ArH), 7.57 (1H, dd, *J* = 8.0, 2.0 Hz, ArH), 7.29–7.21 (1H, m, ArH), 5.77–5.69 (1H, m, H-2), 4.86 (1H, br s, H-6), 4.44 (1H, dd, *J* = 8.1, 7.9 Hz, H-5a), 3.80 (1H, dd, *J* = 7.9, 7.7 Hz, H-5b), 3.72 (1H, dddd, *J* = 8.5, 8.1, 8.0, 7.7 Hz, H-4), 2.37 (1H, ddd, *J* = 12.8, 8.0, 1.1 Hz, H-3a), 2.09 (1H, ddd, *J* = 12.8, 8.5, 5.0 Hz, H-3b); ^{13}C NMR (101 MHz, $CDCl_3$) δ 148.6 (CH, ArCH), 147.7 (CH, ArCH), 138.1 (C, ArC), 134.7 (CH, ArCH), 123.7 (CH, ArCH), 98.6 (CH, C-2), 73.4 (CH_2, C-5), 41.8 (CH_2, C-3), 40.1 (CH, C-4); **Minor diastereoisomer:** ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.53–8.41 (2H, m), 7.76 (1H, dd, *J* = 8.0, 2.0 Hz), 7.29–7.21 (1H, m), 5.77–5.69 (1H, m, H-2), 4.86 (1H, br s, H-6), 4.22 (1H, dd, *J* = 8.9, 8.6 Hz, H-5a), 3.93 (1H, dd, *J* = 9.0, 8.9 Hz, H-5b), 3.41 (1H, dddd, *J* = 9.8, 9.0, 8.6, 8.5 Hz, H-4), 2.63 (1H, ddd, *J* = 13.6, 9.8, 5.5 Hz, H-3a), 1.96 (1H, ddd, *J* = 13.6, 8.5, 2.9 Hz, H-3b); ^{13}C NMR (101 MHz, $CDCl_3$) δ 149.0 (CH, ArCH), 147.7 (CH, ArCH), 137.3 (C, ArC), 135.4 (CH,

ArCH), 123.7 (CH, ArCH), 98.9 (CH, C-2), 72.8 (CH_2, C-5), 41.6 (CH, C-4), 41.5 (CH_2, C-3); HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_9H_{11}NNaO_2$, 188.0682; Found 188.0680 (0.90 ppm error).

Note: The relative stereochemistry of the major and minor diastereoisomers was not determined.

3.5 Diol Scope Studies

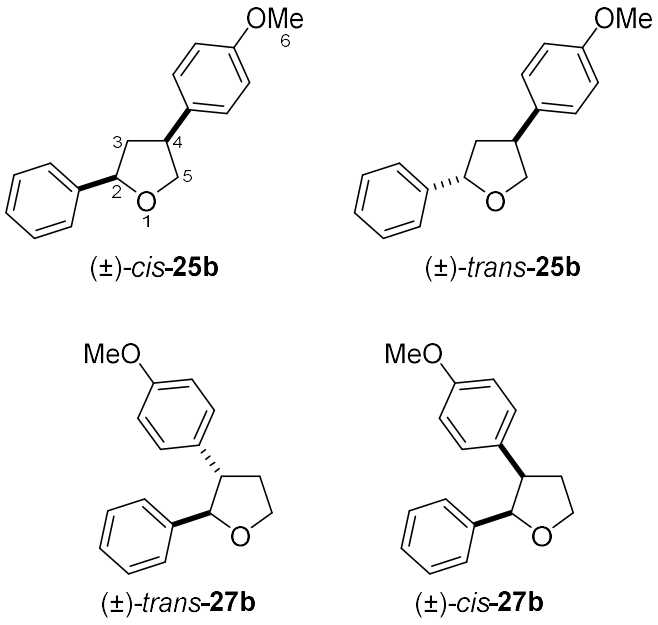


34

$C_{12}H_{16}O_2$

3-(4-Methoxybenzyl)tetrahydrofuran (Compound 34): Prepared according to a modification of general procedure A (0.42 mmol scale) using $NaHCO_3$ (70.6 mg, 0.84 mmol, 2.00 equiv.), $Pd(OAc)_2$ (1.8 mg, 0.01 mmol, 0.02 equiv.), $^nBu_4NCl$ (117 mg, 0.42 mmol, 1.00 equiv.), 4-iodoanisole (98.3 mg, 0.42 mmol, 1.00 equiv.), 2-methylenebutane-1,4-diol **33** (51.1 mg, 0.50 mmol, 1.20 equiv.) in MeCN (2 mL). The crude material was then immediately reduced according to general procedure B using hemiacetal (87.5 mg, 0.42 mmol, 1.00 equiv.), Et_3SiH (73.5 µL, 0.46 mmol, 1.10 equiv.), $BF_3{\cdot}OEt_2$ (56.8 µL, 0.46 mmol, 1.10 equiv.) in DCM (2 mL). Purification by flash column chromatography (SiO_2, Cyclohexane : EtOAc – 15:1) gave the *title compound* **34** (49.5 mg, 0.257 mmol, 61%) as a pale yellow oil; R_f = 0.25 (Cyclohexane/EtOAc, 9:1); ν_{max}/cm^{-1} (thin film) 2930, 2850, 1612, 1511, 1243, 1034; ^1H NMR (500 MHz, $CDCl_3$) δ 7.09 (2H, d, *J* = 8.6 Hz, ArH), 6.83 (2H, d, *J* = 8.6 Hz, ArH), 3.89 (1H, ddd, *J* = 8.3, 7.9, 5.0 Hz, H-5a), 3.82 (1H, dd, *J* = 8.4, 7.0 Hz, H-2a), 3.79 (3H, s, H-7), 3.76 (1H, ddd, *J* = 8.3, 7.5, 7.4 Hz, H-5b), 3.45 (1H, dd, *J* = 8.4, 6.9 Hz, H-2b), 2.68–2.58 (2H, m, H-6), 2.53–2.43 (1H, m, H-3), 1.99 (1H, dddd, *J* = 12.4, 7.5, 7.4, 5.0 Hz, H-4a), 1.61 (1H, dddd, *J* = 12.4, 7.9, 7.4, 7.3 Hz, H-4b); ^{13}C NMR (126 MHz, $CDCl_3$) δ 157.9 (C, ArC), 132.9 (C, ArC), 129.5 (2 × CH, ArCH), 113.8 (2 × CH, ArCH), 73.0 (CH_2, C-2), 67.9 (CH_2, C-5), 55.2 (CH_3, C-7), 41.1 (CH,

C-3), 38.4 (CH_2, C-6), 32.1 (CH_2, C-4); HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{12}H_{16}NaO_2$, 215.1043; Found 215.1041 (0.60 ppm error).

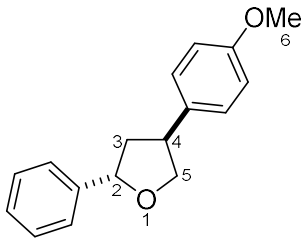


(2*R,4*S**)-4-(4-Methoxyphenyl)-2-phenyltetrahydrofuran [Compound (±)-*cis*-25b]**: To a microwave vial containing a mixture of $NaHCO_3$ (126 mg, 1.50 mmol, 2.00 equiv.), $Pd(OAc)_2$ (18 mg, 0.08 mmol, 0.10 equiv.), $^nBu_4NCl$ (208 mg, 0.75 mmol, 1.00 equiv.), and 4-iodoanisole (176 mg, 0.75 mmol, 1.00 equiv.), in MeCN (1.9 mL, 0.4 M) was added (*Z*)-1-phenylbut-2-ene-1,4-diol **2b** (148 mg, 0.90 mmol, 1.20 equiv.). The vial was capped, then the reaction was heated at 60 °C in a heating block and was held for 24 h. The reaction mixture was cooled to r.t and diluted with Et_2O (10 mL) and water (15 mL), then the aqueous phase was extracted with Et_2O (3 × 10 mL). The combined organic layers were washed with brine (15 mL), dried ($MgSO_4$) and concentrated *in vacuo* to afford the ketone intermediate which was immediately reduced using general procedure B using ketone (203 mg, 0.75 mmol, 1.00 equiv.), Et_3SiH (133 µL, 0.83 mmol, 1.10 equiv.), $BF_3{\cdot}OEt_2$ (102 µL, 0.83 mmol, 1.10 equiv.) in DCM (3.75 mL). Purification by flash column chromatography (SiO_2, Cyclohexane : EtOAc – 15:1) gave an inseparable mixture of the title compound (±)-*cis*-**25b** and isomeric products (±)-*trans*-**25b**, (±)-*trans*-**27b**, and (±)-*cis*-**27b**

(147 mg, 0.576 mmol, 77%, 15.7:3.9:3.2:1.0) as a colourless oil; **Compound** (±)-*cis*-**25b**: R_f = 0.33 (Cyclohexane/EtOAc, 9:1); ν_{max}/cm^{-1} (thin film) 3032, 2935, 1612, 1584, 1248; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46–7.28 (5H, m, ArH), 7.20 (2H, d, *J* = 8.7 Hz, ArH), 6.86 (2H, d, *J* = 8.7 Hz, ArH), 5.08 (1H, dd, *J* = 10.4, 5.8 Hz, H-2), 4.34 (1H, dd, *J* = 8.4, 8.2 Hz, H-5a), 3.97 (1H, dd, *J* = 8.4, 8.3 Hz, H-5b), 3.80 (3H, s, H-6), 3.60 (1H, dddd, *J* = 10.7, 8.3, 8.2, 7.7 Hz, H-4), 2.74 (1H, ddd, *J* = 12.5, 7.7, 5.8 Hz, H-3a), 1.98 (1H, ddd, *J* = 12.5, 10.7, 10.4 Hz, H-3b); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.3 (C, ArC), 142.8 (C, ArC), 133.5 (C, ArC), 128.4 (2 × CH, ArCH), 128.2 (2 × CH, ArCH),127.4 (CH, ArCH), 125.7 (2 × CH, ArCH), 114.0 (2 × CH, ArCH), 81.8 (CH, C-2), 75.2 (CH_2, C-5), 55.3 (CH_3, C-6), 45.3 (CH, C-4), 43.8 (CH_2, C-3); HRMS (ESI-TOF) m/z: $[M + NH_4]^+$ calcd for $C_{17}H_{22}NO_2$, 272.1645; Found 272.1638 (2.60 ppm error).

Data are consistent with those reported in the literature.[116]

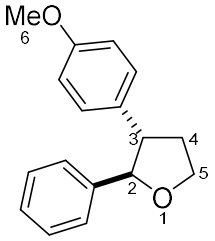
Resolved signals for the minor isomers are reported below.



(±)-*trans*-**25b**

(2*S,4*S**)-4-(4-Methoxyphenyl)-2-phenyltetrahydrofuran [Compound (±)-*trans*-25b]**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46–7.28 (5H, m, ArH), 7.25–7.22 (2H, m, ArH), 6.85–6.83 (2H, m, ArH), 5.23 (1H, dd, *J* = 7.8, 5.7 Hz, H-2), 4.45 (1H, dd, *J* = 8.4, 7.5 Hz, H-5a), 3.91 (1H, dd, *J* = 8.4, 8.1 Hz, H-5b), 3.81–3.78 (3H, m, H-6), 3.50 (1H, dddd, *J* = 8.1, 7.9, 7.8, 7.5 Hz, H-4), 2.54–2.38 (1H, m, H-3a), 2.36–2.17 (1H, m, H-3b).

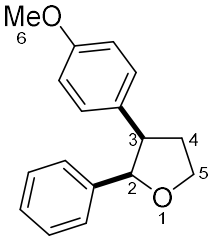
Data are consistent with those reported in the literature.[116]



(±)-*trans*-**27b**

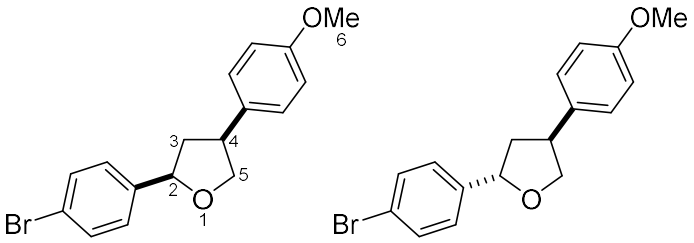
(2*R,3*S**)-3-(4-Methoxyphenyl)-2-phenyltetrahydrofuran [Compound (±)-*trans*-27b]**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46–7.28 (5H, m, ArH), 7.10 (2H, d, *J* = 8.7 Hz, ArH), 6.88–6.83 (2H, m, ArH), 4.78 (1H, d, *J* = 8.5 Hz, H-2), 4.27–4.21 (2H, m, H-5a, H-5b), 3.81–3.78 (3H, m, H-6), 3.17 (1H, ddd, *J* = 8.6, 8.6, 8.5 Hz, H-3), 2.49–2.38 (1H, m, H-4a), 2.36–2.18 (1H, m, H-4b).

Data are consistent with those reported in the literature.[196]

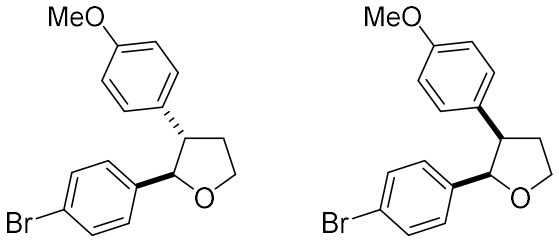


(±)-*cis*-**27b**

(2*R,3*R**)-3-(4-Methoxyphenyl)-2-phenyltetrahydrofuran [Compound (±)-*cis*-27b]**: ^{1}H NMR (400 MHz, $CDCl_3$) 5.16 (1H, d, *J* = 6.8 Hz, H-2).



(±)-*cis*-**25c** (±)-*trans*-**25c**



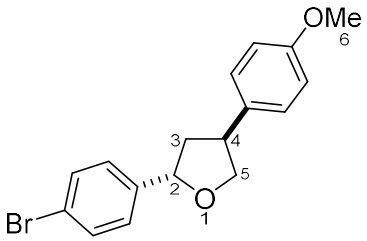
(±)-*trans*-**27c** (±)-*cis*-**27c**

(10.5:1.9:3.2:1.0)

$C_{17}H_{17}BrO_2$

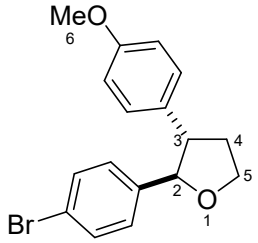
(2*R,4*S**)-2-(4-Bromophenyl)-4-(4-methoxyphenyl)tetrahydrofuran [Compound (±)-*cis*-25c]**: Prepared according to a modified version (increased Pd loading) of general procedure A using $NaHCO_3$ (126 mg, 1.50 mmol, 2.00 equiv.), $Pd(OAc)_2$ (18 mg, 0.08 mmol, 0.10 equiv.), $^nBu_4NCl$ (208 mg, 0.75 mmol, 1.00 equiv.), 4-iodoanisole (176 mg, 0.75 mmol, 1.00 equiv.), (*Z*)-1-(4-bromophenyl)but-2-ene-1,4-diol **2c** (219 mg, 0.90 mmol, 1.20 equiv.) in MeCN (1.9 mL). The crude material was then immediately reduced according to general procedure B using ketone (262 mg, 0.75 mmol, 1.00 equiv.), Et_3SiH (133 µL, 0.83 mmol, 1.10 equiv.), $BF_3{\cdot}OEt_2$ (102 µL, 0.83 mmol, 1.10 equiv.) in DCM (3.75 mL). Purification by flash column chromatography (SiO_2, Cyclohexane : EtOAc – 19:1) gave an inseparable mixture of the *title compound* (±)-*cis*-**25c** and isomeric products (±)-*trans*-**25c**, (±)-*trans*-**27c**, and (±)-*cis*-**27c** (109 mg, 0.327 mmol, 44%, 10.5:1.9:3.2:1.0) as a colourless oil; **Compound** (±)-*cis*-**25c**: R_f = 0.20 (Cyclohexane/EtOAc, 19:1); υ_{max}/cm^{-1} (thin film) 2931, 2854, 1514, 1249; ^1H NMR (400 MHz, $CDCl_3$) δ 7.48 (2H, d, *J* = 8.4 Hz, ArH), 7.28 (2H, d, *J* = 8.4 Hz, ArH), 7.17 (2H, d, *J* = 8.6 Hz, ArH), 6.86 (2H, d, *J* = 8.6 Hz, ArH), 5.02 (1H, dd, *J* = 10.2, 5,8 Hz, H-2), 4.32 (1H, dd, *J* = 8.4, 8.2 Hz, H-5a), 3.95 (1H, dd, *J* = 8.4, 8.3 Hz, H-5b), 3.79 (3H, s, H-6), 3.59 (1H, dddd, *J* = 10.6, 8.3, 8.2, 7.7 Hz, H-4), 2.72 (1H, ddd, *J* = 12.5, 7.7, 5.8 Hz, H-3a), 1.90 (1H, ddd, *J*

= 12.5, 10.6, 10.2 Hz, H-3b); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.4 (C, ArC), 141.9 (C, ArC), 140.8 (C, ArC), 131.5 (2 × CH, ArCH), 128.2 (2 × CH, ArCH), 127.4 (2 × CH, ArCH), 121.1 (C, ArC), 114.1 (2 × CH, ArCH), 81.1 (CH, C-2), 68.5 (CH_2, C-5), 55.3 (CH_3, C-6), 53.8 (CH, C-3), 35.6 (CH_2, C-4); HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{17}H_{17}{}^{79}BrNaO_2$, 355.0304; Found 355.0289 (4.30 ppm error).



(±)-*trans*-**25c**

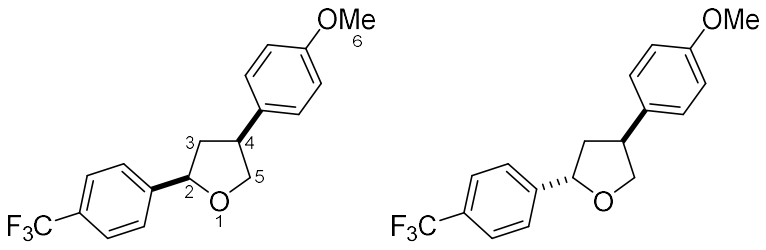
(2*S,4*S**)-2-(4-Bromophenyl)-3-(4-methoxyphenyl)tetrahydrofuran [Compound (±)-*trans*-25c]**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48–7.45 (2H, m, ArH), 7.27–7.24 (2H, m, ArH), 7.24–7.20 (2H, m, ArH), 6.89–6.86 (2H, m, ArH), 5.17 (1H, dd, *J* = 7.8, 5.7 Hz, H-2), 4.42 (1H, dd, *J* = 8.4, 7.5 Hz, H-5a), 3.90 (1H, dd, *J* = 8.4, 8.0 Hz, H-5b), 3.80 (3H, s, H-6), 3.46 (1H, dddd, *J* = 8.0, 7.8, 7.7, 7.5 Hz, H-4), 2.49–2.38 (1H, m, H-3a), 2.34–2.19 (1H, m, H-3b).



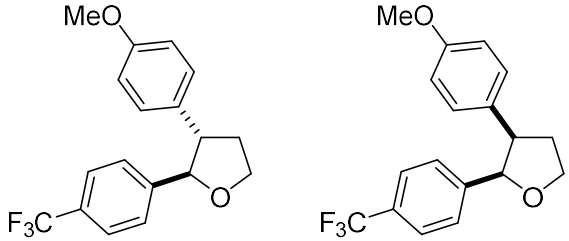
(±)-*trans*-**27c**

(2*R,3*S**)-2-(4-Bromophenyl)-3-(4-methoxyphenyl)tetrahydrofuran [Compound (±)-*trans*-27c]**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (2H, d, *J* = 8.4 Hz, ArH), 7.07 (2H, d, *J* = 8.7 Hz, ArH), 7.03 (2H, d, *J* = 8.4 Hz, ArH), 6.91–6.81 (2H, m, ArH), 4.70 (1H, d, *J* = 8.7 Hz, H-2), 4.26–4.20 (2H, m, H-5a, H-5b), 3.80 (3H, s, H-6), 3.06 (1H, ddd, *J* = 8.8, 8.8, 8.7 Hz, H-3), 2.49–2.38 (1H, m, H-4a), 2.32–2.20 (1H, m, H-4b); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.5 (C,

ArC), 133.2 (C, ArC), 132.1 (C, ArC), 131.3 (2 × CH, ArCH), 128.7 (2 × CH, ArCH), 127.5 (2 × CH, ArCH), 121.2 (C, ArC), 114.1 (2 × CH, ArCH), 87.1 (CH, C-2), 68.5 (CH_2, C-5), 55.3 (CH_3, C-6), 53.8 (CH, C-3), 35.6 (CH_2, C-4).



(±)-*cis*-**25d** (±)-*trans*-**25d**

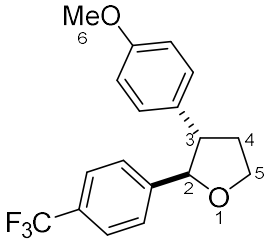


(±)-*trans*-**27d** (±)-*cis*-**27d**

(4.9:1.0:1.5:n.d)
$C_{18}H_{17}F_3O_2$

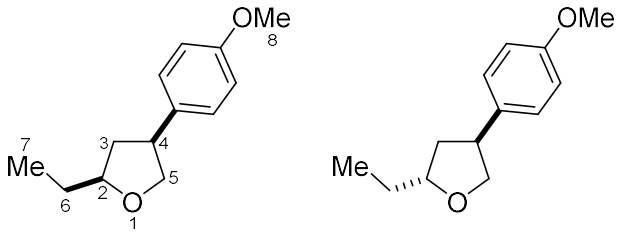
(2*R,4*S**)-4-(4-Methoxyphenyl)-2-[4-(trifluoromethyl)phenyl]tetrahydrofuran [Compound (±)-*cis*-25d]**: Prepared according to a modified version (increased Pd loading) of general procedure A using $NaHCO_3$ (126 mg, 1.50 mmol, 2.00 equiv.), $Pd(OAc)_2$ (18 mg, 0.08 mmol, 0.10 equiv.), $^nBu_4NCl$ (208 mg, 0.75 mmol, 1.00 equiv.), 4-iodoanisole (176 mg, 0.75 mmol, 1.00 equiv.), (*Z*)-1-(4-(trifluoromethyl)phenyl)but-2-ene-1,4-diol **2d** (209 mg, 0.90 mmol, 1.20 equiv.) in MeCN (1.9 mL). The crude material was then immediately reduced according to general procedure B using ketone (254 mg, 0.75 mmol, 1.00 equiv.), Et_3SiH (133 µL, 0.83 mmol, 1.10 equiv.), $BF_3{\cdot}OEt_2$ (102 µL, 0.83 mmol, 1.10 equiv.) in DCM (3.75 mL). Purification by flash column chromatography (SiO_2, Cyclohexane : EtOAc – 19:1) gave an inseparable mixture of the *title compound* (±)-*cis*-**25d** and isomeric products (±)-*trans*-**25d**, (±)-*trans*-**27d**, and (±)-*cis*-**27d** (131 mg, 0.406 mmol, 54%, 4.9:1.0:1.5:n.d) as a colourless oil; **Compound** (±)-

cis-**25d**: R_f = 0.18 (Cyclohexane/EtOAc, 19.9:1); υ_{max}/cm^{-1} (thin film) 2937, 1513, 1247, 1116, 1065; ^1H NMR (400 MHz, $CDCl_3$) δ 7.62 (2H, d, *J* = 8.1 Hz, ArH), 7.52 (2H, d, *J* = 8.1 Hz, ArH), 7.17 (2H, d, *J* = 8.7 Hz, ArH), 6.86 (2H, d, *J* = 8.7 Hz, ArH), 5.13 (1H, dd, *J* = 10.1, 5.9 Hz, H-2), 4.36 (2H, dd, *J* = 8.4, 8.2 Hz, H-5a), 3.97 (1H, dd, *J* = 8.4, 8.4 Hz, H-5b), 3.79 (3H, s, H-6), 3.62 (1H, dddd, *J* = 10.8, 8.4, 8.2, 7.7 Hz, H-4) 2.78 (1H, ddd, *J* = 12.6, 7.7, 5.9 Hz, H-3a), 1.92 (1H, ddd, *J* = 12.6, 10.8, 10.1 Hz, H-3b); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.4 (C, ArC), 147.1 (C, ArC), 132.9 (C, ArC), 129.5 (C, q, *J* = 32.2 Hz, ArC), 128.1 (2 × CH, ArCH), 125.8 (2 × CH, ArCH), 125.4 (2 × CH, q, *J* = 3.8 Hz, ArCH), 124.2 (C, q, *J* = 272.1 Hz, CF_3), 114.1 (2 × CH, ArCH), 81.0 (CH, C-2), 75.3 (CH_2, C-5), 55.3 (CH_3, C-6), 45.2 (CH, C-4), 43.8 (CH_2, C-3); ^{19}F NMR (376 MHz, $CDCl_3$) δ −62.4; HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{18}H_{17}{}^{19}F_3NaO_2$, 345.1073; Found 345.1070 (0.90 ppm error).



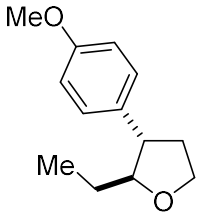
(±)-*trans*-**27d**

(2*R,3*S**)-3-(4-Methoxyphenyl)-2-[4-(trifluoromethyl)phenyl]tetrahydrofuran [Compound (±)-*trans*-27d]**: ^1H NMR (400 MHz, $CDCl_3$) δ 7.55–7.48 (2H, m, ArH), 7.26 (2H, d, *J* = 8.0 Hz, ArH), 7.09 (2H, d, *J* = 8.7 Hz, ArH), 6.88–6.84 (2H, m, ArH), 4.82 (1H, d, *J* = 8.6 Hz, H-2), 4.28–4.23 (2H, m, H-5a, H-5b), 3.81 (3H, s, H-6), 3.08 (1H, ddd, *J* = 9.7, 8.6, 8.2 Hz, H-3), 2.46 (1H, dddd, *J* = 12.5, 8.2, 6.3, 4.7 Hz, H-4a), 2.28 (1H, dddd, *J* = 12.5, 9.7, 8.4, 8.4 Hz, H-4b).

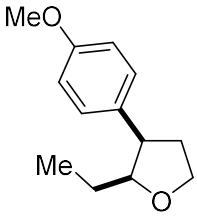


(±)-*cis*-**25e**

(±)-*trans*-**25e**



(±)-*trans*-**27e**



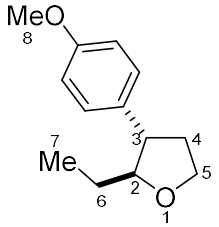
(±)-*cis*-**27e**

(6.5:1.5:2.2:1.0)

$C_{13}H_{18}O_2$

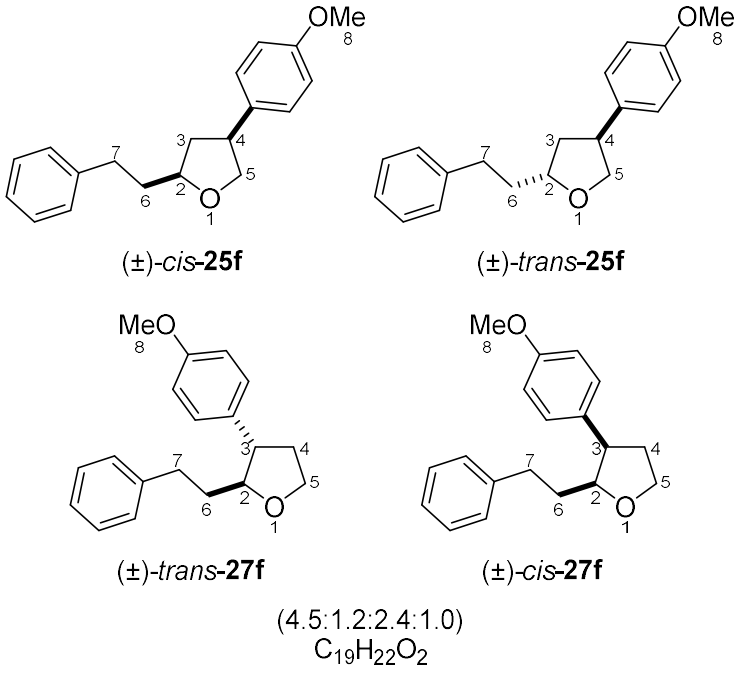
(2*S,4*S**)-2-Ethyl-4-(4-methoxyphenyl)tetrahydrofuran [Compound (±)-*cis*-25e]**: Prepared according to a modified version (increased Pd loading) of general procedure A using $NaHCO_3$ (126 mg, 1.50 mmol, 2.00 equiv.), $Pd(OAc)_2$ (18 mg, 0.08 mmol, 0.10 equiv.), $^nBu_4NCl$ (208 mg, 0.75 mmol, 1.00 equiv.), 4-iodoanisole (176 mg, 0.75 mmol, 1.00 equiv.), (*Z*)-hex-2-ene-1,4-diol **2e** (176 mg, 0.90 mmol, 1.20 equiv.) in MeCN (1.9 mL). The crude material was then immediately reduced according to general procedure B using ketone (167 mg, 0.75 mmol, 1.00 equiv.), Et_3SiH (133 µL, 0.83 mmol, 1.10 equiv.), $BF_3{\cdot}OEt_2$ (102 µL, 0.83 mmol, 1.10 equiv.) in DCM (3.75 mL). Purification by flash column chromatography (SiO_2, Cyclohexane : EtOAc – 19:1) gave an inseparable mixture of the *title compound* (±)-*cis*-**25e** and isomeric products (±)-*trans*-**25e**, (±)-*trans*-**27e**, and (±)-*cis*-**27e** (106 mg, 0.516 mmol, 69%, 6.5:1.5:2.2:1.0) as a colourless oil; **Compound** (±)-*cis*-**25e**: R_f = 0.20 (Cyclohexane/EtOAc, 19:1); υ_{max}/cm^{-1} (thin film) 2961, 2932, 1512, 1245, 1033; ^1H NMR (400 MHz, $CDCl_3$) δ 7.17 (2H, d, *J* = 8.6 Hz, ArH), 6.85 (2H, d, *J* = 8.6 Hz, ArH), 4.12 (1H, dd, *J* = 8.2, 8.2 Hz, H-5a), 3.99–3.90 (1H, m, H-2), 3.79 (3H, s, H-8), 3.74 (1H, dd, *J* = 8.2, 8.1 Hz, H-5b), 3.41 (1H, dddd, *J* = 10.2, 8.2, 8.1, 7.8 Hz, H-4), 2.40 (1H, ddd, *J* = 12.8 7.8, 5.5 Hz, H-3a), 1.80–1.66 (2H, m, H-6), 1.64–1.53 (1H, m, H-3b), 0.98 (3H, t, *J* = 7.5 Hz, H-7); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.2 (C, ArC), 134.6 (C, ArC), 128.1 (2 × CH, ArCH), 114.0 (2 × CH, ArCH), 81.8 (CH, C-2), 74.3 (CH_2, C-5), 55.3 (CH_3, C-8), 44.8 (CH,

C-4), 40.7 (CH_2, C-3), 28.7 (CH_2, C-6), 10.5 (CH_3, C-7); HRMS (ESI-TOF) m/z: $[M + NH_4]^+$ calcd for $C_{13}H_{22}NO_2$, 224.1645; Found 224.1642 (1.50 ppm error).



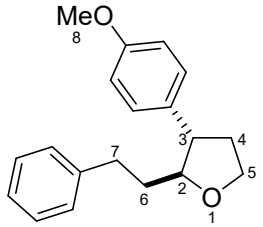
(±)-*trans*-**27e**

(2*S,3*S**)-2-Ethyl-3-(4-methoxyphenyl)tetrahydrofuran [Compound (±)-*trans*-27e]**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20–7.13 (2H, m, ArH), 6.90–6.80 (2H, m, ArH), 4.08–4.00 (2H, m), 3.80 (3H, s), 3.71–3.63 (1H, m), 2.85 (1H, ddd, *J* = 8.6, 8.6, 8.6 Hz), 2.37–2.28 (1H, m), 2.11–2.02 (1H, m), 1.64–1.54 (2H, m), 0.92 (3H, t, *J* = 7.4 Hz).



(2*S,4*S**)-4-(4-Methoxyphenyl)-2-phenethyltetrahydrofuran [Compound (±)-*cis*-25f]**: Prepared according to a modified version (increased Pd loading) of general procedure A using $NaHCO_3$ (126 mg, 1.50 mmol, 2.00 equiv.),

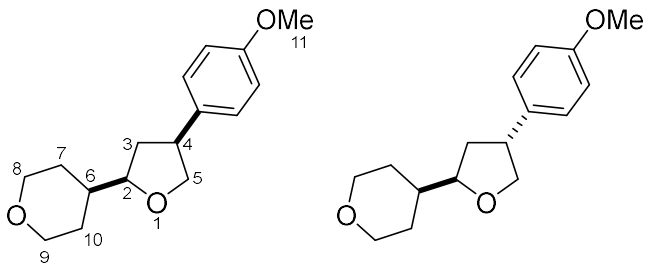
$Pd(OAc)_2$ (18 mg, 0.08 mmol, 0.10 equiv.), $^nBu_4NCl$ (208 mg, 0.75 mmol, 1.00 equiv.), 4-iodoanisole (176 mg, 0.75 mmol, 1.00 equiv.), (*Z*)-6-phenylhex-2-ene-1,4-diol **2f** (173 mg, 0.90 mmol, 1.20 equiv.) in MeCN (1.9 mL). The crude material was then immediately reduced according to general procedure B using ketone (224 mg, 0.75 mmol, 1.00 equiv.), Et_3SiH (133 μL, 0.83 mmol, 1.10 equiv.), $BF_3{\cdot}OEt_2$ (102 μL, 0.83 mmol, 1.10 equiv.) in DCM (3.75 mL). Purification by flash column chromatography (SiO_2, Cyclohexane : EtOAc – 19:1) gave an inseparable mixture of the *title compound* (±)-*cis*-**25f** and isomeric products (±)-*trans*-**25f**, (±)-*trans*-**27f**, and (±)-*cis*-**27f** (167 mg, 0.591 mmol, 79%, 4.5:1.2:2.4:1.0) as a colourless oil; **Compound** (±)-*cis*-**25f**: R_f = 0.18 (Cyclohexane/EtOAc, 19:1); υ_{max}/cm^{-1} (thin film) 2930, 2859, 1513, 1247, 1036; ^1H NMR (400 MHz, $CDCl_3$) δ 7.33–7.11 (7H, m, ArH), 6.86 (2H, d, *J* = 8.6 Hz, ArH), 4.14 (1H, dd, *J* = 8.2, 8.2 Hz, H-5a), 4.08–3.98 (1H, m, H-2), 3.80 (3H, s, H-8), 3.79–3.74 (1H, m, H-5b), 3.47–3.37 (1H, m, H-4), 2.86–2.77 (1H, m, H-7a), 2.71 (1H, ddd, *J* = 13.8, 9.8, 6.5 Hz, H-7b), 2.43 (1H, ddd, *J* = 12.7, 7.5, 5.5 Hz, H-3a), 2.13–1.98 (1H, m, H-6a), 1.96–1.78 (1H, m, H-6b), 1.71–1.57 (1H, m, H-3b); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.2 (C, ArC), 142.0 (C, ArC), 134.4 (C, ArC), 128.4 (2 × CH, ArH), 128.3 (2 × CH, ArH), 128.1 (2 × CH, ArCH), 125.8 (CH, ArCH), 114.0 (2 × CH, ArCH), 79.6 (CH, C-2), 74.3 (CH_2, C-5), 55.3 (CH_3, C-8), 44.8 (CH, C-4), 41.1 (CH_2, C-3), 37.5 (CH_2, C-6), 32.7 (CH_2, C-7); HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{19}H_{23}O_2$, 283.1693; Found 283.1694 (0.40 ppm error).



(±)-*trans*-**27f**

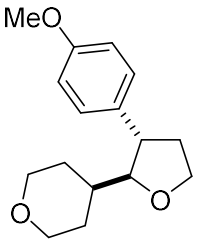
(2*S,3*S**)3-(4-Methoxyphenyl)-2-phenethyltetrahydrofuran [Compound (±)-*trans*-27f]**: ^1H NMR (400 MHz, $CDCl_3$) δ 7.33–7.11 (7H, m, ArH), 6.88–6.81 (2H, m, ArH), 4.09–3.97 (2H, m, H-5a, H-5b), 3.82–3.76 (1H, m, H-2), 3.80 (3H, s, H-8), 2.89 1H, ddd, *J* = 8.0, 8.0, 7.3 Hz, H-3), 2.87–2.79 (1H, m,

H-7a), 2.64–2.54 (1H, m, H-7b), 2.42–2.36 (1H, m, H-4a), 2.13–2.08 (1H, m, H-4b), 1.95–1.78 (2H, m, H-6a, H-6b).

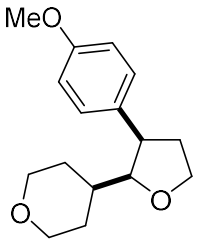


(±)-*cis*-**25g**

(±)-*trans*-**25g**



(±)-*trans*-**27g**



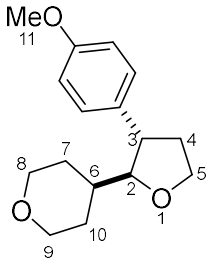
(±)-*cis*-**27g**

(ratio not determinable)

$C_{16}H_{22}O_3$

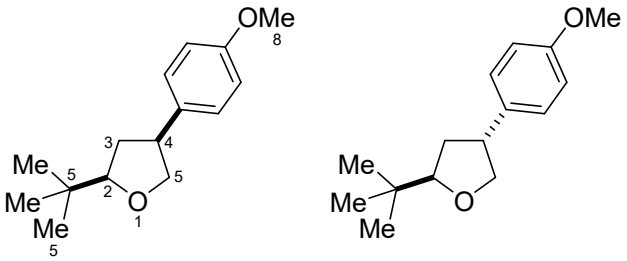
4-[(2*R,4*S**)-4-(4-Methoxyphenyl)tetrahydrofuran-2-yl]tetrahydro-*2H*-pyran [Compound (±)-*cis*-25g]**: Prepared according to a modified version (increased Pd loading) of general procedure A using $NaHCO_3$ (126 mg, 1.50 mmol, 2.00 equiv.), $Pd(OAc)_2$ (18 mg, 0.08 mmol, 0.10 equiv.), $^nBu_4NCl$ (208 mg, 0.75 mmol, 1.00 equiv.), 4-iodoanisole (176 mg, 0.75 mmol, 1.00 equiv.), (*Z*)-1-(tetrahydro-*2H*-pyran-4-yl)but-2-ene-1,4-diol **2g** (155 mg, 0.90 mmol, 1.20 equiv.) in MeCN (1.9 mL). The crude material was then immediately reduced according to general procedure B using ketone (209 mg, 0.75 mmol, 1.00 equiv.), Et_3SiH (133 µL, 0.83 mmol, 1.10 equiv.), $BF_3{\cdot}OEt_2$ (102 µL, 0.83 mmol, 1.10 equiv.) in DCM (3.75 mL). Purification by flash column chromatography (SiO_2, Cyclohexane : EtOAc – 19:1 → 4:1) gave an inseparable mixture of the *title compound* (±)-*cis*-**25g** and isomeric products (±)-*trans*-**25g**, (±)-*trans*-**27g**, and (±)-*cis*-**27g** (151 mg, 0.577 mmol, 77%, ratio not determinable) as a colourless oil; **Compound** (±)-*cis*-**25g**: R_f = 0.02 (Cyclohexane/EtOAc, 19:1); υ_{max}/cm^{-1} (thin film) 2930, 2837, 1512, 1244, 1034; ^1H NMR (400 MHz, $CDCl_3$) δ 7.16 (2H, d, *J* = 8.7 Hz, ArH), 6.85 (2H,

d, *J* = 8.7 Hz, ArH), 4.13 (1H, dd, *J* = 8.3, 8.1 Hz, H-5a), 4.05–3.94 (2H, m, H-8_{eq}, H-9_{eq}), 3.79 (3H, s, H-11), 3.49–3.33 (3H, m, H-8_{ax}, H-9_{ax}, H-4), 2.36 (1H, ddd, *J* = 12.5, 7.4, 5.4 Hz, H-3a), 1.93–1.82 (1H, m, H-7_{ax} or H-7_{eq}), 1.78–1.68 (2H, m, H-6, H-10_{ax} or H-10_{eq}), 1.69–1.59 (1H, m, H-3b), 1.54–1.47 (1H, m, H-10_{ax} or H-10_{eq}), 1.47–1.37 (1H, m, H-7_{ax} or H-7_{eq}); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.3 (C, ArC), 134.1 (C, ArC), 128.1 (2 × CH, ArCH), 114.0 (2 × CH, ArCH), 84.2 (CH, C-2), 74.3 (CH_2, C-5), 67.9 (CH_2, C-8 or C-9), 67.7 (CH_2, C-8 or C-9), 55.3 (CH_3, C-11), 44.6 (CH, C-4), 40.7 (C, C-6), 38.7 (CH_2, C-3), 30.2 (CH_2, C-7), 28.9 (CH_2, C-10); HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{16}H_{23}O_3$, 263.1642; Found 263.1637 (1.80 ppm error).

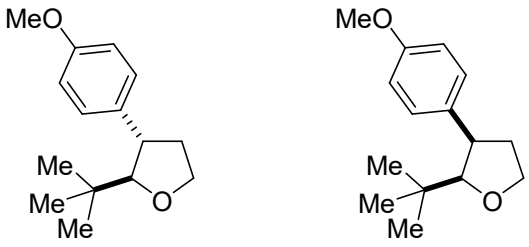


(±)-*trans*-**27g**

4-[(2*S,3*S**)-3-(4-Methoxyphenyl)tetrahydrofuran-2-yl]tetrahydro-*2H*-pyran [Compound (±)-*trans*-27g]**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19–7.14 (2H, m, ArH), 6.88–6.82 (2H, m, ArH), 4.11–3.92 (2H, m, H-5a, H-5b), 3.94–3.88 (2H, m, H-8_{eq}, H-9_{eq}), 3.80–3.79 (3H, m, H-11), 3.73–3.66 (1H, m, H-2), 3.36–3.30 (2H, m, H-8_{ax}, H-9_{ax}), 3.05 (1H, ddd, *J* =8.4, 8.4, 8.4 Hz, H-3), 2.42–2.30 (1H, m, H-4a), 2.07–1.99 (1H, m, H-4b), 1.78–1.66 (3H, m, H-7_{ax} or H-7_{eq}, H-10_{ax} or H-10_{eq}, H-6), 1.39–1.30 (2H, m, H-7_{ax} or H-7_{eq}, H-10_{ax} or H-10_{eq}).



(±)-*cis*-**25h** (±)-*trans*-**25h**

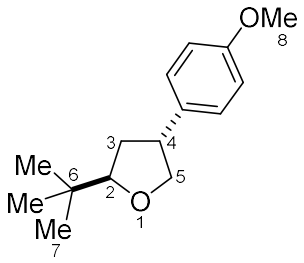


(±)-*trans*-**27h** (±)-*cis*-**27h**

(2.7:1.2:1.0:n.d)
$C_{15}H_{22}O_2$

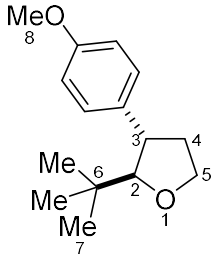
(2*R,4*S**)-2-(*tert*-Butyl)-4-(4-methoxyphenyl)tetrahydrofuran [Compound (±)-*cis*-25h]**: Prepared according to a modified version (increased Pd loading) of general procedure A using $NaHCO_3$ (126 mg, 1.50 mmol, 2.00 equiv.), $Pd(OAc)_2$ (18 mg, 0.08 mmol, 0.10 equiv.), $^nBu_4NCl$ (208 mg, 0.75 mmol, 1.00 equiv.), 4-iodoanisole (176 mg, 0.75 mmol, 1.00 equiv.), (*Z*)-5,5-dimethylhex-2-ene-1,4-diol **2h** (130 mg, 0.90 mmol, 1.20 equiv.) in MeCN (1.9 mL). The crude material was then immediately reduced according to general procedure B using ketone (188 mg, 0.75 mmol, 1.00 equiv.), Et_3SiH (133 μL, 0.83 mmol, 1.10 equiv.), $BF_3{\cdot}OEt_2$ (102 μL, 0.83 mmol, 1.10 equiv.) in DCM (3.75 mL). Purification by flash column chromatography (SiO_2, Cyclohexane : EtOAc – 19:1) gave an inseparable mixture of the *title compound* (±)-*cis*-**25h** and isomeric products (±)-*trans*-**25h**, (±)-*trans*-**27h** (74.5 mg, 0.318 mmol, 42%, 2.7:1.2:1.0:n.d) as a colourless oil; **Compound** (±)-*cis*-**25h**: R_f = 0.20 (Cyclohexane/EtOAc, 19:1); υ_{max}/cm^{-1} (thin film) 2955, 2867, 1513, 1246, 730; ^1H NMR (400 MHz, $CDCl_3$) δ 7.49 (2H, d, *J* = 8.8 Hz, ArH), 6.97 (2H, d, *J* = 8.8 Hz, ArH), 4.17 (1H, dd, *J* = 8.0, 8.0 Hz, H-5a), 3.85 (3H, s, H-8), 3.81–3.75 (1H, m, H-2), 3.73–3.64 (1H, m, H-5b), 3.47–3.36 (1H, m, H-4), 2.21 (1H, ddd, *J* = 12.5, 7.3, 5.7 Hz, H-3a), 1.77 (1H, ddd, *J* = 12.5, 10.8, 10.8 Hz, H-3b), 0.97 (9H, s, H-7); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.7 (C, ArC), 133.4 (C, ArC),

127.7 (2 × CH, ArCH), 114.1 (2 × CH, ArCH), 88.3 (CH, C-2), 74.7 (CH_2, C-5), 55.3 (CH_3, C-8), 44.7 (CH, C-4), 35.9 (CH_2, C-3), 25.8 (3 × CH_3, C-7); HRMS (ESI-TOF) m/z: $[M + NH_4]^+$ calcd for $C_{15}H_{26}NO_2$, 252.1958; Found 252.1949 (3.70 ppm error).



(±)-*trans*-**25h**

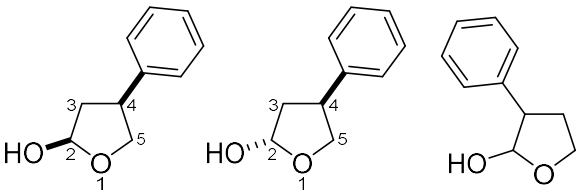
(2*R,4*R**)-2-(*tert*-Butyl)-4-(4-methoxyphenyl)tetrahydrofuran [Compound (±)-*trans*-25h]**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22–7.12 (2H, m, ArH), 6.92–6.78 (2H, m, ArH), 4.18 (1H, dd, *J* = 8.5, 7.0 Hz, H-5a), 3.88–3.82 (1H, m, H-2), 3.80 (3H, s, H-8), 3.76–3.67 (1H, m, H-5b), 3.30 (1H, dddd, *J* = 9.0, 7.0, 7.0, 6.8 Hz, H-4), 2.16–2.09 (1H, m, H-3a), 1.88 (1H, ddd, *J* = 12.8, 8.0, 6.8 Hz, H-3b), 0.94 (9H, s, H-7).



(±)-*trans*-**27h**

(2*R,3*S**)-2-(*tert*-Butyl)-3-(4-methoxyphenyl)tetrahydrofuran [Compound (±)-*trans*-27h]**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22–7.12 (2H, m, ArH), 6.92–6.78 (2H, m, ArH), 4.08–4.00 (1H, m, H-5a), 3.92 (1H, ddd, *J* = 8.2, 6.9, 6.8 Hz, H-5b), 3.80 (3H, s, H-8), 3.78–3.72 (1H, m, H-2), 3.13 (1H, ddd, *J* = 8.2, 8.0, 8.0 Hz, H-3), 2.31 (1H, dddd, *J* = 12.1, 8.2, 6.8, 5.3 Hz, H-4a), 2.01–1.93 (1H, m, H-4b), 0.87 (9H, s, H-7).

3.6 Synthesis and Derivatisation of Hemiacetal 3b

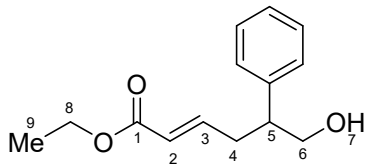


(2*R,4*S**)-4-Phenyltetrahydrofuran-2-ol and (2*R**,4*S**)-4-Phenyltetrahydrofuran-2-ol (Compounds 3b and 3b')**: Prepared according to general procedure A using $NaHCO_3$ (2.05 g, 24.4 mmol, 2.00 equiv.), $Pd(OAc)_2$ (53.9 mg, 240 μmol, 0.02 equiv.), $^{n}Bu_4NCl$ (3.39 g, 12.2 mmol, 1.00 equiv.), iodobenzene (1.37 mL, 12.2 mmol, 1.00 equiv.), *cis*-2-butene-1,4-diol (1.20 mL, 14.6 mmol, 1.20 equiv.) in MeCN (31 mL). Purification by flash column chromatography (SiO_2, Cyclohexane : EtOAc – 4:1 → 3:1) gave the title compound **3b** and **3b'** (1.97 g, 12.0 mmol, 98%, d.r. 1.8:1) as a colourless oil; R_f = 0.35 (Cyclohexane/EtOAc, 1:1); ν_{max}/cm^{-1} (thin film) 3397, 2948, 2883, 983, 697; **Major Diastereoisomer:** ^1H NMR (400 MHz, $CDCl_3$) δ 7.37–7.30 (3H, m, ArH), 7.30–7.20 (2H, m, ArH), 5.77–5.69 (1H, m, H-2), 4.47 (1H, dd, *J* = 8.1, 7.9 Hz, H-5a), 3.85 (1H, dd, *J* = 8.1, 8.0 Hz, H-5b), 3.75 (1H, dddd, *J* = 9.7, 8.0, 7.9, 7.5 Hz, H-4), 2.37 (1H, ddd, *J* = 12.8, 7.5, 1.0 Hz, H-3a), 2.14 (1H, ddd, *J* = 12.8, 9.7, 5.0 Hz, H-3b); **Major Diastereoisomer:** ^{13}C NMR (101 MHz, $CDCl_3$) δ 141.8 (C, ArC), 128.6 (2 × CH, ArCH), 127.1 (2 × CH, ArCH), 126.6 (CH, ArCH), 98.9 (CH, C-2), 74.1 (CH_2, C-5), 42.4 (CH, C-4), 41.8 (CH_2, C-3); **Minor Diastereoisomer:** ^1H NMR (400 MHz, $CDCl_3$) δ 7.37–7.30 (3H, m, ArH), 7.30–7.20 (2H, m, ArH), 5.77–5.69 (1H, m, H-2), 4.22 (1H, dd, *J* = 8.5, 8.3 Hz, H-5a), 3.99 (1H, dd, *J* = 9.8, 8.3 Hz, H-5b), 3.44 (1H, dddd, *J* = 9.8, 9.5, 9.0, 8.5 Hz, H-4), 2.66 (1H, ddd, *J* = 13.4, 9.5, 5.5 Hz, H-3a), 2.03 (1H, ddd, *J* = 13.4, 9.0, 3.3 Hz, H-3b); **Minor Diastereoisomer:** ^{13}C NMR (101 MHz, $CDCl_3$) δ 140.8 (C, ArC), 128.6 (2 × CH, ArCH), 127.6 (2 × CH, ArCH), 126.6 (CH, ArCH), 99.2 (CH, C-2), 73.0 (CH_2, C-5), 44.5 (CH, C-4), 41.6 (CH_2, C-3); HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{10}H_{12}NaO_2$, 187.0730; Found 187.0734 (2.40 ppm error).

Data are consistent with those reported in the literature.[197]

Note 1: It was not possible to assign the relative stereochemistry of the major and minor diastereoisomers.

Note 2: Traces of a regioisomeric species believed to be 2,3-substituted tetrahydrofuran **36** were evident in the ^{1}H NMR spectrum.

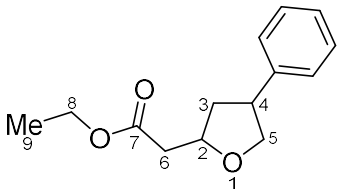


38

$C_{14}H_{18}O_3$

Ethyl (*E*)-6-hydroxy-5-phenylhex-2-enoate (Compound 38): To a solution of 4-phenyltetrahydrofuran-2-ol **3b** (164 mg, 1.00 mmol, 1.00 equiv.) in THF (4 mL) was added (carbethoxymethylene)triphenylphosphorane (383 mg, 1.10 mmol, 1.10 equiv.), the mixture was stirred for 24 h at r.t. The reaction was poured into sat. aq. $NaHCO_3$ (10 mL) and extracted with EtOAc (3 × 7 mL), the combined organics were washed with brine (10 mL), dried ($MgSO_4$) and concentrated *in vacuo* to afford the crude material. Purification by flash column chromatography (SiO_2, Cyclohexane : EtOAc – 5:1) gave the *title compound* **38** (195 mg, 0.832 mmol, 83%) as a colourless oil; R_f = 0.38 (Cyclohexane/EtOAc, 1:1); ν_{max}/cm^{-1} (thin film) 3419, 2930, 1713, 1040; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37–7.30 (2H, m, ArH), 7.28–7.18 (3H, m, ArH), 6.86 (1H, ddd, *J* = 15.6, 7.6, 7.0 Hz, H-3), 5.81 (1H, ddd, *J* = 15.6, 1.6, 1.5 Hz, H-2), 4.14 (2H, q, *J* = 7.1 Hz, H-8), 3.77 (2H, app d, *J* = 6.4 Hz, H-6), 2.97 (1H, app dq, *J* = 8.4, 6.4 Hz, H-5), 2.67 (1H, dddd, *J* = 14.8, 7.6, 6.4, 1.5 Hz, H-4a), 2.54 (1H, dddd, *J* = 14.8, 8.4, 7.0, 1.6 Hz, H-4b), 1.50 (1H, br s, H-7), 1.25 (3H, t, *J* = 7.1 Hz, H-9); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.3 (C, C-1), 146.4 (CH, C-3), 140.9 (C, ArC), 128.8 (2 × CH, ArCH), 127.9 (2 × CH, ArCH), 127.1 (CH, ArCH), 123.0 (CH, C-2), 66.8 (CH_2, C-6), 60.2 (CH_2, C-8), 47.4 (CH, C-5), 34.7 (CH_2, C-4), 14.2 (CH_3, C-9); HRMS (ESI-TOF) m/z: $[M + NH_4]^+$ calcd for $C_{14}H_{22}NO_3$, 252.1594; Found 252.1594 (0.10 ppm error).

Note: Traces of a minor isomeric compound, formed from the regioisomeric 2,3-hemiacetal **S3**, were observed in the $^{1}H/^{13}C$ NMR spectra of the purified product.

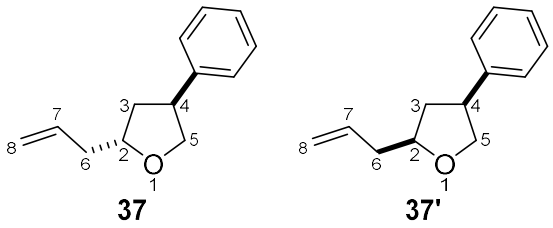


39

$C_{14}H_{18}O_3$

Ethyl 2-(4-phenyltetrahydrofuran-2-yl)acetate (Compound 39): To a solution of ethyl (*E*)-6-hydroxy-5-phenylhex-2-enoate **38** (117 mg, 0.50 mmol, 1.00 equiv.) in THF (2 mL) at r.t was added TBAF (0.65 mL, 0.65 mmol, 1.30 equiv., 1.00 M), the reaction was then stirred for 28 h. The mixture was then concentrated *in vacuo* to afford the crude material. Purification by flash column chromatography (SiO_2, Cyclohexane : EtOAc – 15:1) gave an inseparable mixture of *title compound* **39** (72 mg, 0.306 mmol, 61%, d.r. 1:1) as a colourless oil; R_f = 0.62 (Cyclohexane/EtOAc, 1:1); ν_{max}/cm^{-1} (thin film) 3029, 2978, 1733; **Diastereoisomer 1**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34–7.28 (2H, m, ArH), 7.27–7.20 (3H, m, ArH), 4.59 (1H, dddd, *J* = 7.3, 6.9, 6.6, 6.0 Hz, H-2), 4.26 (1H, dd, *J* = 8.5, 7.7 Hz, H-5a), 4.21–4.14 (2H, m, H-8), 3.74 (1H, dd, *J* = 8.5, 8.3 Hz, H-5b), 3.56–3.41 (1H, m, H-4), 2.79–2.49 (2H, m, H-6a, H-6b), 2.24 (1H, ddd, *J* = 12.8, 7.5, 7.3 Hz, H-3a), 2.12 (1H, ddd, *J* = 12.8, 8.7, 6.0 Hz, H-3b), 1.28 (3H, t, *J* = 7.1 Hz, H-9); **Diastereoisomer 2:** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34–7.28 (2H, m, ArH), 7.27 (3H, m, ArH), 4.45 (1H, app ddt, *J* = 9.8, 7.2, 5.7 Hz, H-2), 4.21–4.14 (3H, m, H-5a, H-8), 3.83 (1H, dd, *J* = 8.4, 8.3 Hz, H-5b), 3.56–3.41 (1H, m, H-4), 2.79–2.49 (3H, m, H-6a, H-6b, H-3a), 1.76 (1H, ddd, *J* = 12.3, 10.0, 9.8 Hz, H-3b), 1.28 (3H, t, *J* = 7.1 Hz, H-9); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.14 (C, C-7), 171.09 (C, C-7), 142.0 (C, ArC), 141.8 (C, ArC), 128.6 (4 × CH, ArCH), 127.24 (2 × CH, ArCH), 127.15 (2 × CH, ArCH), 126.62 (CH, ArCH), 126.58 (CH, ArCH), 76.2 (CH, C-2), 75.6 (CH, C-2), 74.7 (CH_2, C-5), 74.3 (CH_2, C-5), 60.54 (CH_2, C-8), 60.53 (CH_2, C-8), 45.4 (CH, C-4), 44.4 (CH, C-4), 41.1 (CH_2, C-6), 40.7 (CH_2, C-6), 40.6 (CH_2, C-3), 39.4 (CH_2, C-3), 14.2 (2 × CH_3, C-9); HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{14}H_{19}O_3$, 235.1329; Found 235.1327 (0.90 ppm error).

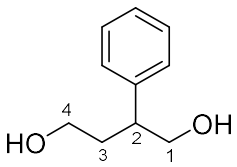
Note: It was not possible to assign the ^{13}C signals to the two diastereoisomers. The ^{13}C NMR spectroscopic data are therefore reported as single list.



$C_{13}H_{16}O$

(2*R,4*S**)-2-Allyl-4-phenyltetrahydrofuran and (2*S**,4*S**)-2-allyl-4-phenyltetrahydrofuran (Compound 37 and 37')**: To a solution of 4-phenyltetrahydrofuran-2-ol **6b** (164 mg, 1.00 mmol, 1.00 equiv.) in DCM (4 mL) at 0 °C was added $BF_3 \cdot OEt_2$ (247 µL, 2.00 mmol, 2.00 equiv.) followed by allyltrimethylsilane (318 µL, 2.00 mmol, 2.00 equiv.). The reaction was allowed to warm to r.t and stirred for 24 h. The reaction was poured into sat. aq. $NaHCO_3$ (10 mL) and extracted with DCM (3 × 10 mL), then the combined organics were dried ($MgSO_4$) and concentrated *in vacuo* to afford the crude material. Purification by flash column chromatography (SiO_2, Cyclohexane : EtOAc – 19:1) gave an inseparable mixture of the title compounds **37** and **37'** (136 mg, 0.722 mmol, 72%, d.r. 12.6:1) as a colourless oil; R_f = 0.29 (Cyclohexane/EtOAc, 19:1); **Major Diastereoisomer 37:** ^1H NMR (500 MHz, $CDCl_3$) δ 7.34–7.29 (2H, m, ArH), 7.27–7.20 (3H, m, ArH), 5.87 (1H, app ddt, *J* = 17.1, 10.2, 6.9 Hz, H-7), 5.14 (1H, dddd, *J* = 17.1, 1.9, 1.7, 1.6 Hz, H-8a), 5.10 (1H, app ddt, *J* = 10.2, 1.9, 1.1 Hz, H-8b), 4.26 (1H, dd, *J* = 8.6, 7.4 Hz, H-5a), 4.26–4.20 (1H, m, H-2), 3.73 (1H, dd, *J* = 8.6, 7.9 Hz, H-5b), 3.44 (1H, app quint, *J* = 7.7, Hz, H-4), 2.45–2.39 (1H, m, H-6a), 2.36–2.30 (1H, m, H-6b), 2.15–2.05 (2H, m, H-3a, H-3b); **Major Diastereoisomer 37:** ^{13}C NMR (126 MHz, $CDCl_3$) δ 142.5 (C, ArC), 134.8 (CH, C-7), 128.5 (2 × CH, ArCH), 127.3 (2 × CH, ArCH), 126.5 (CH, ArCH), 117.1 (CH_2, C-8), 78.7 (CH, C-2), 74.7 CH_2, C-5), 44.5 (CH, C-4), 40.4 (CH_2, C-6), 39.1 (CH_2, C-3).

Data are consistent with those reported in the literature.[125]

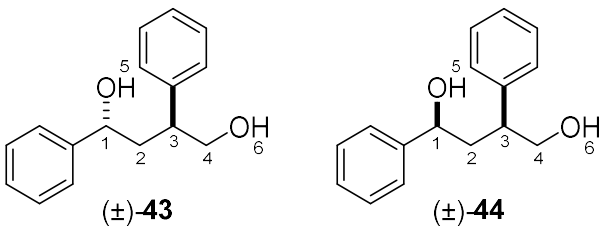


40

$C_{10}H_{14}O_2$

2-Phenylbutane-1,4-diol (Compound 40): To a solution of 4-phenyltetrahydrofuran-2-ol **3b** (164 mg, 1.00 mmol, 1.00 equiv.) in THF:MeOH (3:1, 5 mL) at 0 °C was added $NaBH_4$ (76 mg, 2.00 mmol), then the mixture was stirred for 5 h. The reaction was poured into H_2O (15 mL) and extracted with DCM (3 × 10 mL). The combined organic layers were washed with brine (10 mL) which was then back extracted with DCM (2 × 10 mL). The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo* to afford the crude material. Purification by filtration through a plug of silica gave the title compound **40** (125 mg, 0.751 mmol, 75%) as a colourless oil. R_f = 0.04 (Cyclohexane/EtOAc, 1:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36–7.31 (2H, m, ArH), 7.27–7.21 (3H, m, ArH), 3.79 (2H, d, *J* = 6.6 Hz, H-1), 3.70 (1H, ddd, *J* = 10.8, 6.0, 5.6 Hz, H-4a), 3.59 (1H, ddd, *J* = 10.8, 8.1, 5.4 Hz, H-4b), 2.97 (1H, dddd, *J* = 8.3, 6.6, 6.5, 6.3 Hz, H-2), 2.03 (1H, dddd, *J* = 14.0, 8.1, 6.3, 6.0 Hz, H-3a), 1.90 (1H, dddd, *J* = 14.0, 8.3, 5.6, 5.4 Hz, H-3b), 1.72 (2H, br s, H-5, H-6); ^{13}C NMR (101 MHz, $CDCl_3$) δ 142.4 (C, ArC), 128.5 (2 × CH, ArCH), 127.7 (2 × CH, ArCH), 126.6 (CH, ArCH), 67.2 (CH_2, C-1), 60.7 (CH_2, C-4), 45.7 (CH, C-2), 35.7 (CH_2, C-3).

Data are consistent with those reported in the literature.[198]



(±)-**43** (±)-**44**

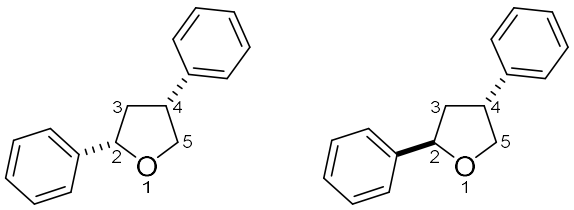
$C_{16}H_{18}O_2$

(1*R,3*S**)-1,3-Diphenylbutane-1,4-diol [Compound (±)-43] and (1*S**,3*S**)-1,3-Diphenylbutane-1,4-diol [Compound (±)-44]**: To a solution of 4-phenyltetrahydrofuran-2-ol **3b** (500 mg, 3.05 mmol, 1.00 equiv.) in THF (13

mL) at 0 °C was added phenylmagnesium bromide (2.03 mL, 6.10 mmol, 3.00 M in Et_2O) dropwise over 5 min, then the mixture was stirred for 5 h. The reaction was poured into sat. aq. NH_4Cl (20 mL) and extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine (10 mL), dried ($MgSO_4$) and concentrated *in vacuo* to afford the crude material. Purification by flash column chromatography (SiO_2, Cyclohexane : EtOAc – 8:1 → 2:1) gave an inseparable mixture of title compounds (±)-**43** and (±)-**44** (571 mg, 2.36 mmol, 77%, d.r. 1.5:1) as a colourless oil. R_f = 0.19 (Cyclohexane/EtOAc, 1:1); **Major Diastereoisomer (±)-43:** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38–7.18 (10H, m, ArH), 4.57 (1H, dd, *J* = 10.2, 2.8 Hz, H-4), 3.80 (2H, app d, *J* = 6.6 Hz, H-1), 3.18 (1H, app dq, *J* = 8.6, 6.4 Hz, H-3), 2.35–2.06 (1H, m, H-2a), 2.00 (1H, ddd, *J* = 14.4, 8.6, 2.8 Hz, H-2b), 1.58 (2H, br s, H-5, H-6); ^{13}C NMR (101 MHz, $CDCl_3$) δ 145.0 (C, ArC), 142.3 (C, ArC), 128.8 (2 × CH, ArCH), 128.5 (2 × CH, ArCH), 128.0 (2 × CH, ArCH), 127.6 (CH, ArCH), 126.9 (CH, ArCH), 125.5 (2 × CH, ArCH), 72.7 (CH, C-1), 67.9 (CH_2, C-4), 46.2 (CH, C-3), 42.8 (CH_2, C-2); **Minor Diastereoisomer (±)-44:** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38–7.18 (10H, m, ArH), 4.65 (1H, app t, *J* = 6.8 Hz, H-4), 3.75 (2H, d, *J* = 6.8 Hz, H-1), 2.76 (1H, app dtd, *J* = 8.2, 6.8, 6.4 Hz, H-3), 2.35–2.06 (4H, m, H-2a, H-2b, H-5, H-6); ^{13}C NMR (101 MHz, $CDCl_3$) δ 144.0 (C, ArC), 142.0 (C, ArC), 128.8 (2 × CH, ArCH), 128.6 (2 × CH, ArCH), 128.0 (2 × CH, ArCH), 127.8 (CH, ArCH), 127.0 (CH, ArCH), 126.2 (2 × CH, ArCH), 72.7 (CH, C-1), 67.4 (CH_2, C-4), 44.8 (CH, C-3), 41.5 (CH_2, C-2).

Data are consistent with those reported in the literature.[199]

Note: The relative stereochemistry was determined by conversion of the diols into the known *bis*-acetoxylated derivatives following the procedure reported by Oshima.[129]



calyxolane B, (±)-**9** calyxolane A, (±)-**8**

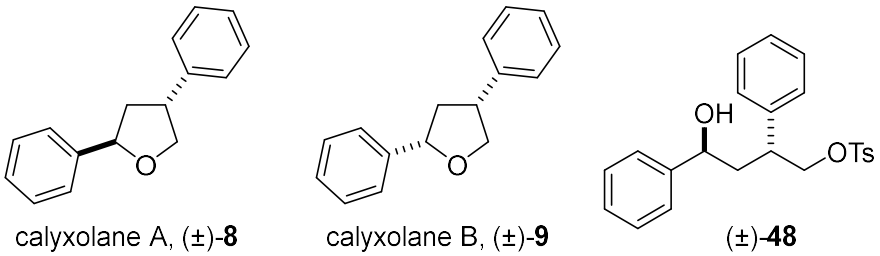
$C_{16}H_{16}O$

(2*S,4*R**)-2,4-Diphenyltetrahydrofuran [Compound (±)-9, calyxolane B] and (2*R**,4*R**)-2,4-Diphenyltetrahydrofuran [Compound (±)-8, calyxolane A]**: To a solution of 1,3-diphenylbutane-1,4-diol (±)-**43** and (±)-**44** (100 mg, 0.413 mmol, 1.00 equiv.) in DCM (4 mL) at −10 °C was added $BF_3{\cdot}OEt_2$ (61.1 μL, 0.495 mmol, 1.20 equiv.) dropwise over 2 min, then the mixture was stirred for 1 h. The reaction was poured into sat. aq. $NaHCO_3$ (10 mL) and extracted with DCM (3 × 10 mL). The combined organic layers were washed with brine (15 mL), dried ($MgSO_4$) and concentrated *in vacuo* to afford the crude material. Purification by flash column chromatography (SiO_2, Cyclohexane : EtOAc – 48:1) gave an inseparable mixture of title compound (±)-**9** and (±)-**8** (80.6 mg, 0.359 mmol, 87%, d.r. 1.7:1) as a colourless oil. R_f = 0.33 (Cyclohexane/EtOAc, 19:1); ν_{max}/cm^{-1} (thin film) 3061, 2863, 1494, 1063, 753, 698; **Major diastereoisomer [calyxolane B, (±)-9]:** ^1H NMR (400 MHz, $CDCl_3$) δ 7.45–7.18 (10H, m, ArH), 5.11 (1H, dd, *J* = 10.3, 5.7 Hz, H-1), 4.40 (1H, dd, *J* = 8.3, 8.1 Hz, H-5a), 4.06 (1H, dd, *J* = 8.3, 8.2 Hz, H-5b), 3.67 (1H, dddd, *J* = 10.6, 8.2, 8.1, 7.6 Hz, H-4), 2.79 (1H, ddd, *J* = 12.6, 7.6, 5.7 Hz, H-3a), 2.06 (1H, ddd, *J* = 12.6, 10.6, 10.3 Hz, H-3b); ^{13}C NMR (101 MHz, $CDCl_3$) δ 142.7 (C, ArC), 141.7 (C, ArC), 128.6 (2 × CH, ArCH), 128.4 (2 × CH, ArCH), 127.4 (CH, ArCH), 127.2 (2 × CH, ArCH), 126.6 (CH, ArCH), 125.7 (2 × CH, ArCH), 81.8 (CH, C-1), 75.1 (CH_2, C-5), 46.0 (CH, C-4), 43.7 (CH_2, C-3); **Minor diastereoisomer [calyxolane A, (±)-9]:** ^1H NMR (400 MHz, $CDCl_3$) δ 7.45–7.18 (10H, m, ArH), 5.27 (1H, dd, *J* = 7.8, 5.8 Hz, H-1), 4.51 (1H, dd, *J* = 8.3, 7.5 Hz, H-5a), 3.99 (1H, dd, *J* = 8.3, 8.0 Hz, H-5b), 3.57 (1H, dddd, *J* = 8.1, 8.0, 7.7, 7.5 Hz, H-4), 2.52 (1H, ddd, *J* = 12.5, 7.8, 7.7 Hz, H-3a), 2.35 (1H, ddd, *J* = 12.5, 8.1, 5.8 Hz, H-3b); ^{13}C NMR (101 MHz, $CDCl_3$) δ 143.6 (C, ArC), 142.0 (C, ArC), 128.6 (2 × CH, ArCH), 128.3 (2 × CH, ArCH), 127.3 (2 × CH, ArCH), 127.2 (CH, ArCH), 126.6 (CH, ArCH), 125.5 (2 × CH, ArCH), 80.6 (CH, C-1),

75.1 (CH_2, C-5), 44.4 (CH, C-4), 42.7 (CH_2, C-3); HRMS (ESI-TOF) m/z: [M + Na]$^+$ calcd for $C_{16}H_{16}NaO$, 247.1093; Found 247.1089 (1.60 ppm error).

Data are consistent with those reported in the literature.[200]

Note: Traces of a minor isomeric compound, formed from the regioisomeric 2,3-hemiacetal **36**, were observed in the ^{1}H NMR spectrum of the purified product.

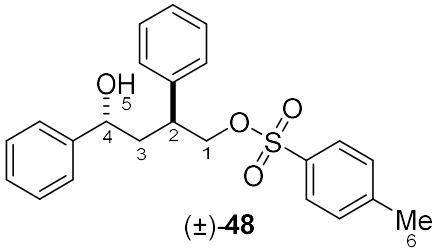


calyxolane A, (±)-**8** calyxolane B, (±)-**9** (±)-**48**

$C_{16}H_{16}O$ $C_{23}H_{24}O_4S$

(2*R,4*R**)-2,4-Diphenyltetrahydrofuran [Compound (±)-8, calyxolane A] and (2*S**,4*R**)-2,4-Diphenyltetrahydrofuran [Compound (±)-9, calyxolane B]**: To a solution of 1,3-diphenylbutane-1,4-diol **20** (100 mg, 0.413 mmol, 1.00 equiv.) in DCM (4 mL) was added tosyl chloride (157 mg, 0.826 mmol, 2.00 equiv.) and triethylamine (164 µL, 1.18 mmol, 2.85 equiv.), then the mixture was heated to 40 °C in a heating block and stirred for 48 h. The reaction was poured into sat. aq. NH_4Cl (10 mL) and extracted with DCM (3 × 10 mL). The combined organic layers were washed with brine (15 mL), dried ($MgSO_4$) and concentrated *in vacuo* to afford the crude material. Purification by flash column chromatography (SiO_2, Cyclohexane : EtOAc – 48:1) gave an inseparable mixture of title compounds (±)-**8** and (±)-**9** (48.7 mg, 0.217 mmol, 53%, d.r. 2.2:1) as a colourless oil and the tosylated species **48** (39.6 mg, 99.9 µmol) as a colourless crystalline solid.

The characterisation data for compound (±)-**8** and (±)-**9** are consistent with those reported above.

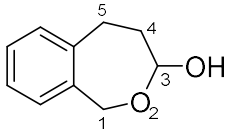


(±)-**48**

$C_{23}H_{24}O_4S$

(2*S,4*R**)-4-Hydroxy-2,4-diphenylbutyl 4-methylbenzenesulfonate (Compound 48)**: R_f = 0.29 (Cyclohexane/EtOAc, 2:1); ν_{max}/cm^{-1} (thin film) 3029, 2924, 1697, 1598, 1494, 1357, 1173; ^1H NMR (400 MHz, $CDCl_3$) δ 7.64 (2H, d, *J* = 8.3 Hz, ArH), 7.34–7.13 (12H, m, ArH), 4.37 (1H, dd, *J* = 10.3, 3.0 Hz, H-4), 4.17 (1H, dd, *J* = 9.6, 6.8 Hz, H-1a), 4.12 (1H, dd, *J* = 9.6, 6.6 Hz, H-1b), 3.35 (1H, dddd, *J* = 10.8, 6.8, 6.6, 4.3 Hz, H-2), 2.42 (3H, s, H-6), 2.12 (1H, ddd, *J* = 14.2, 10.3, 4.3 Hz, H-3a), 1.89 (1H, ddd, *J* = 14.2, 10.8, 3.0 Hz, H-3b), 1.81 (1H, br s, H-5); ^{13}C NMR (101 MHz, $CDCl_3$) δ 144.6 (C, ArC), 144.5 (C, ArC), 139.6 (C, ArC), 132.8 (C, ArC), 129.7 (2 × CH, ArCH), 128.7 (2 × CH, ArCH), 128.5 (2 × CH, ArCH), 128.0 (2 × CH, ArCH), 127.8 (2 × CH, ArCH), 127.6 (CH, ArCH), 127.2 (CH, ArCH), 125.5 (2 × CH, ArCH), 73.9 (CH_2, C-1), 71.4 (CH, C-4), 41.9 (CH, C-2), 41.2 (CH_2, C-3), 21.6 (CH_3, C-6); HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{23}H_{24}NaO_4S$, 419.1288; Found 419.1279 (1.90 ppm error).

3.7 Synthesis of Substituted Benzoxepanes and Related Compounds

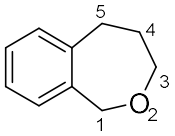


101b

$C_{10}H_{12}O_2$

1,3,4,5-Tetrahydrobenzo[*c*]oxepin-3-ol (Compound 101b): Prepared according to general procedure E using $NaHCO_3$ (168 mg, 2.00 mmol, 2.00 equiv.), $Pd(OAc)_2$ (4.5 mg, 0.02 mmol, 0.02 equiv.), $^nBu_4NCl$ (417 mg, 1.50

mmol, 1.50 equiv.), 2-iodobenzyl alcohol (234 mg, 1.00 mmol, 1.00 equiv.), allyl alcohol (102 μL, 1.50 mmol, 1.50 equiv.) in MeCN (2.5 mL). Purification by flash column chromatography (~30 g SiO_2, cyclohexane : EtOAc – 4:1) gave the *title compound* **101b** (144 mg, 0.88 mmol, 88%) as a colourless oil with trace uncyclised aldehyde; R_f = 0.28 (cyclohexane/EtOAc, 3:2); υ_{max}/cm^{-1} (thin film) 3391, 2940, 2852, 1453, 1024, 757; ^1H NMR (500 MHz, $CDCl_3$) δ 7.23–7.13 (4H, m, ArH), 5.25 (1H, dd, *J* = 7.0, 3.0 Hz, H-3), 5.11 (1H, d, *J* = 14.1 Hz, H-1a), 4.43 (1H, d, *J* = 14.1 Hz, H-1b), 3.59 (1H, br s, OH), 3.05 (1H, ddd, *J* = 15.7, 8.8, 1.8 Hz, H-5a), 2.86 (1H, ddd, *J* = 15.7, 10.8, 1.9 Hz, H-5b), 2.09 (1H, ddd, *J* = 14.0, 8.8, 3.0, 1.9 Hz, H-4a), 1.92 (1H, dddd, *J* = 14.0, 10.8, 7.0, 1.8 Hz, H-4b); ^{13}C NMR (126 MHz, $CDCl_3$) δ 141.2 (C, ArC), 138.8 (C, ArC), 129.2 (CH, ArCH), 128.0 (CH, ArCH), 127.8 (CH, ArCH), 126.1 (CH, ArCH), 98.3 (CH, C-3), 65.3 (CH_2, C-1), 34.2 (CH_2, C-4), 29.1 (CH_2, C-5); HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{10}H_{12}NaO_2$, 187.0730; Found 187.0727 (1.10 ppm error).

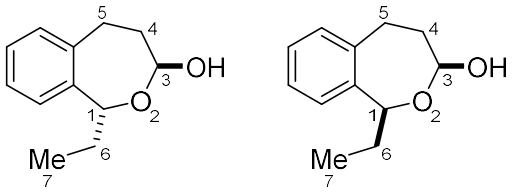


97b

$C_{10}H_{12}O$

1,3,4,5-Tetrahydrobenzo[*c*]oxepine (Compound 97b): Prepared according to general procedure B using 1,3,4,5-tetrahydrobenzo[*c*]oxepin-3-ol (144 mg, 0.876 mmol, 1.00 equiv.), Et_3SiH (155 μL, 0.97 mmol, 1.10 equiv.) and $BF_3{\cdot}OEt_2$ (120 μL, 0.97 mmol, 1.10 equiv.) in DCM (4.4 mL). Purification by flash column chromatography (~30 g SiO_2, cyclohexane : EtOAc – 97:3) gave the title compound **97b** (133 mg, 0.899 mmol, 90%, 79% over two steps) as a pale yellow oil; ^1H NMR (500 MHz, $CDCl_3$) δ 7.23–7.14 (4H, m, ArH), 4.68 (2H, s, H-1), 4.09–4.05 (2H, m, H-3), 3.04–3.00 (2H, m, H-5), 1.89–1.83 (2H, m, H-4); ^{13}C NMR (126 MHz, $CDCl_3$) δ 142.6 (C, ArC), 139.9 (C, ArC), 129.0 (CH, ArCH), 128.5 (CH, ArCH), 127.8 (CH, ArCH), 126.0 (CH, ArCH), 75.6 (CH_2, C-3), 75.0 (CH_2, C-1), 35.4 (CH_2, C-5), 30.3 (CH_2, C-4).

Data are consistent with those published.[201]



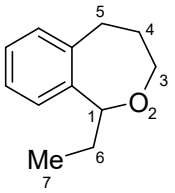
101c **101c'**

$C_{12}H_{16}O_2$

(1*R,3*S**)-1-Ethyl-1,3,4,5-tetrahydrobenzo[*c*]oxepin-3-ol and (1*S**,3*S**)-1-Ethyl-1,3,4,5-tetrahydrobenzo[*c*]oxepin-3-ol (Compound 101c and 101c')**: Prepared according to general procedure E using $NaHCO_3$ (168 mg, 2.00 mmol, 2.00 equiv.), $Pd(OAc)_2$ (4.5 mg, 0.02 mmol, 0.02 equiv.), $^nBu_4NCl$ (417 mg, 1.50 mmol, 1.50 equiv.), 1-(2-iodophenyl)propan-1-ol **1ae** (262 mg, 1.00 mmol, 1.00 equiv.), allyl alcohol (102 µL, 1.50 mmol, 1.50 equiv.) in MeCN (2.5 mL). Purification by flash column chromatography (~30 g SiO_2, cyclohexane : EtOAc – 7:1) gave an inseparable mixture of the *title compounds* **101c** and **101c'** (157 mg, 0.88 mmol, 82%, d.r. 1:1) as a colourless oil with trace uncyclised aldehyde; R_f = 0.14 (cyclohexane/EtOAc, 3:2); **Diastereoisomer 1**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25–7.12 (4H, m, ArH), 5.07 (1H, dd, *J* = 9.0, 3.0 Hz, H-3), 4.52 (1H, dd, *J* = 8.3, 4.9 Hz, H-1), 3.01–2.84 (2H, m, H-5a, H-5b), 2.17 (1H, app dtd, *J* = 13.5, 6.8, 3.0 Hz, H-4a), 2.10–1.96 (2H, m, H-6), 1.62 (1H, app dtd, *J* = 13.5, 9.0, 4.5 Hz, H-4b), 1.14–1.06 (3H, m, H-7); **Diastereoisomer 2**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25–7.12 (4H, m, ArH), 5.42 (1H, app t, *J* = 3.8 Hz, H-3), 5.24 (1H, dd, *J* = 9.3, 4.2 Hz, H-1), 3.35 (1H, ddd, *J* = 15.2, 11.4, 1.8 Hz, H-5a), 2.70 (1H, ddd, *J* = 15.2, 8.2, 2.0 Hz, H-5b), 2.10–1.83 (4H, m, H-4a, H-4b, H-6), 1.14–1.06 (3H, m, H-7).

Note: It was not possible to fully assign the ^{13}C signals to the two diastereoisomers. The ^{13}C NMR spectroscopic data are therefore reported as single list. ^{13}C NMR (101 MHz, $CDCl_3$) δ 142.4 (C, ArC), 141.7 (C, ArC), 141.1 (C, ArC), 140.3 (C, ArC), 129.5 (CH, ArCH), 129.1 (CH, ArCH), 127.5 (CH, ArCH), 127.2 (CH, ArCH), 126.3 (CH, ArCH), 126.0 (CH, ArCH), 125.1 (CH, ArCH), 125.0 (CH, ArCH), 100.4 (CH, C-3, D1), 94.6 (CH, C-3, D2), 77.7 (CH, C-1, D1), 69.4 (CH, C-1, D2), 35.8 (CH_2, C-4, D1), 33.3 (CH_2, C-4 or C-6, D2),

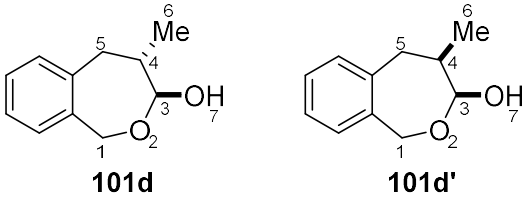
30.1 (CH_2, C-5, D1), 28.6 (CH_2, C-5, D2), 26.8 (CH_2, C-6, D1), 25.6 (CH_2, C-4 or C-6, D2), 11.1 or 10.8 (CH_3, C-7).



97c

$C_{12}H_{16}O$

1-Ethyl-1,3,4,5-tetrahydrobenzo[*c*]oxepine (Compound 97c): Prepared according to general procedure B using 1-Ethyl-1,3,4,5-tetrahydrobenzo[*c*]oxepin-3-ol (157 mg, 0.817 mmol, 1.00 equiv.), Et_3SiH (143 µL, 0.90 mmol, 1.10 equiv.) and $BF_3{\cdot}OEt_2$ (110 µL, 0.90 mmol, 1.10 equiv.) in DCM (4.1 mL). Purification by flash column chromatography (~30 g SiO_2, cyclohexane : EtOAc – 49:1) gave the *title compound* **97c** (91.6 mg, 0.520 mmol, 64%, 52% over two steps) as a pale yellow oil; R_f = 0.37 (cyclohexane/EtOAc, 49:1) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24–7.10 (4H, m, ArH), 4.46 (1H, dd, *J* = 7.3, 6.0 Hz, H-1), 4.23 (1H, ddd, *J* = 12.0, 5.0, 2.7 Hz, H-3a), 3.82 (1H, app td, *J* = 12.0, 3.4 Hz, H-3b), 3.06–2.95 (2H, m, H-5a, H-5b), 1.94 (1H, app quint, *J* = 7.3 Hz, H-6), 1.90–1.81 (1H, m, H-4a), 1.81–1.71 (1H, m, H-4b), 1.08 (3H, t, *J* = 7.3 Hz, H-7).

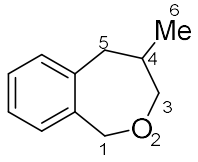


101d **101d'**

$C_{11}H_{14}O_2$

(3*S,4*S**)-4-Methyl-1,3,4,5-tetrahydrobenzo[*c*]oxepin-3-ol and (3*S**,4*R**)-4-Methyl-1,3,4,5-tetrahydrobenzo[*c*]oxepin-3-ol (Compound 101d and 101d')**: Prepared according to general procedure E using $NaHCO_3$ (168 mg, 2.00 mmol, 2.00 equiv.), $Pd(OAc)_2$ (4.5 mg, 0.02 mmol, 0.02 equiv.), $^nBu_4NCl$ (417 mg, 1.50 mmol, 1.50 equiv.), 2-iodobenzyl alcohol (234 mg, 1.00 mmol, 1.00

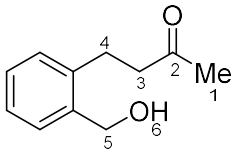
equiv.), 2-methyl-2-propen-1-ol (108 mg, 1.50 mmol, 1.50 equiv.) in MeCN (2.5 mL). Purification by flash column chromatography (~30 g SiO_2, cyclohexane : EtOAc – 4:1) gave an inseparable mixture of the *title compounds* **101d** and **101d'** (171 mg, 0.959 mmol, 96%, d.r. 2:1) as an off-white crystalline solid in an inseparable mixture of diastereoisomers with trace uncyclised aldehyde; mp. 58–60 °C; R_f = 0.32 (cyclohexane/EtOAc, 2:1); υ_{max}/cm^{-1} (thin film) 3373, 2958, 1454, 1034, 741; **Major diastereoisomer 101d**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23–7.07 (4H, m, ArH), 5.19 (1H, d, *J* = 14.3 Hz, H-1a), 4.87 (1H, dd, *J* = 6.4, 3.6 Hz, H-3), 4.41 (1H, d, *J* = 14.3 Hz, H-1b), 3.77–3.66 (1H, d, *J* = 3.6, H-7), 2.94 (1H, app d, *J* = 15.3 Hz, H-5a), 2.81 (1H, dd, 15.3, 9.5 Hz, H-5b), 2.18–1.99 (1H, m, H-4), 1.02 (3H, d, *J* = 6.8 Hz, H-6); ^{13}C NMR (101 MHz, $CDCl_3$) δ 139.6 (C, ArC), 138.5 (C, ArC), 129.9 (CH, ArCH), 127.4 (2 × CH, ArCH), 126.0 (CH, ArCH), 102.3 (CH, C-5), 64.9 (CH_2, C-1), 37.7 (CH, C-4), 37.3 (CH_2, C-5), 17.7 (CH_3, C-6); **Minor diastereoisomer 101d'**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23–7.07 (4H, m, ArH), 5.14 (1H, dd, *J* = 4.2, 2.3 Hz, H-3), 5.07 (1H, d, *J* = 13.6 Hz, H-1a), 4.37 (1H, d, *J* = 13.6 Hz, H-1b), 3.66 (1H, d, *J* = 4.2 Hz, H-7), 3.13 (1H, dd, *J* = 14.8, 9.1 Hz, H-5a), 2.70 (1H, dd, *J* = 14.8, 2.0 Hz, H-5b), 2.18–1.99 (1H, m, H-4), 0.91 (3H, d, *J* = 7.0 Hz, H-6); ^{13}C NMR (101 MHz, $CDCl_3$) δ 140.4 (C, ArC), 138.8 (C, ArC), 129.5 (CH, ArCH), 128.2 (CH, ArCH), 127.9 (CH, ArCH), 126.2 (CH, ArCH), 101.0 (CH, C-3), 65.8 (CH_2, C-1), 37.3 (CH, C-4), 36.4 (CH_2, C-5), 14.5 (CH_3, C-6); HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{11}H_{14}NaO_2$, 201.0886; Found 201.0886 (0.10 ppm error).



97d
$C_{11}H_{14}O$

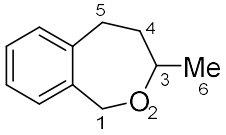
4-Methyl-1,3,4,5-tetrahydrobenzo[*c*]oxepine (Compound 97d): Prepared according to general procedure B using 4-methyl-1,3,4,5-tetrahydrobenzo[*c*]oxepin-3-ol (171 mg, 0.959 mmol, 1.00 equiv.), Et_3SiH (169 µL, 1.06 mmol, 1.10 equiv.) and $BF_3{\cdot}OEt_2$ (130 µL, 1.06 mmol, 1.10 equiv.) in

DCM (4.8 mL). Purification by flash column chromatography (~40 g SiO_2, cyclohexane : EtOAc – 97:3) gave the *title compound* **97d** (128 mg, 0.787 mmol, 82%, 79% over two steps) as a colourless oil; R_f = 0.29 (cyclohexane/EtOAc, 97:3); υ_{max}/cm^{-1} (thin film) 2927, 2839, 1457, 1128, 1098, 770, 738; ^1H NMR (400 MHz, $CDCl_3$) δ 7.24–7.10 (4H, m, ArH), 4.71–4.60 (2H, m, H-1a, H-1b), 4.08 (1H, dd, *J* = 12.0, 3.4 Hz, H-3a), 3.63 (1H, dd, *J* = 12.0, 8.2 Hz, H-3b), 2.95–2.84 (2H, m, H-5a, H-5b), 2.05–1.93 (1H, m, H-4, 0.91 (3H, d, *J* = 6.9 Hz, H-6); ^{13}C NMR (101 MHz, $CDCl_3$) δ 140.9 (C, ArC), 139.8 (C, ArC), 129.6 (CH, ArCH), 128.3 (CH, ArCH), 127.8 (CH, ArCH), 126.1 (CH, ArCH), 81.3 (CH_2, C-3), 74.9 (CH_2, C-1), 43.0 (CH_2, C-5), 33.9 (CH, C-4), 17.7 (CH_3, C-6); HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{11}H_{15}O$, 163.1117; Found 163.1112 (3.30 ppm error).



94a
$C_{11}H_{14}O_2$

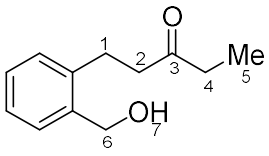
4-[2-(Hydroxymethyl)phenyl]butan-2-one (Compound 94a): Prepared according to general procedure E using $NaHCO_3$ (168 mg, 2.00 mmol, 2.00 equiv.), $Pd(OAc)_2$ (4.5 mg, 0.02 mmol, 0.02 equiv.), $^nBu_4NCl$ (417 mg, 1.50 mmol, 1.50 equiv.), 2-iodobenzyl alcohol (234 mg, 1.00 mmol, 1.00 equiv.), 3-buten-2-ol (130 µL, 1.50 mmol, 1.50 equiv.) in MeCN (2.5 mL). Purification by flash column chromatography (~30 g SiO_2, cyclohexane : EtOAc – 3:2) gave the *title compound* **94a** (150 mg, 0.840 mmol, 84%) as a pale yellow oil; R_f = 0.20 (cyclohexane/EtOAc, 1:1); υ_{max}/cm^{-1} (thin film) 3405, 2892, 1710, 1634; ^1H NMR (400 MHz, $CDCl_3$) δ 7.34 (1H, dd, *J* = 7.2, 1.8 Hz, ArH), 7.25–7.12 (3H, m, ArH), 4.68 (2H, s, H-5), 2.94 (2H, t, *J* = 7.1 Hz, H-4), 2.85–2.75 (3H, m, H-3, H-6), 2.12 (3H, s, H-1); ^{13}C NMR (101 MHz, $CDCl_3$) δ 208.5 (CO, C-2), 139.2 (C, ArC), 138.4 (C, ArC), 128.9 (2 × CH, ArCH), 128.0 (CH, ArCH), 126.4 (CH, ArCH), 63.0 (CH_2, C-5), 44.6 (CH_2, C-3), 29.9 (CH_3, C-1), 25.6 (CH_2, C-4); HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{11}H_{14}NaO_2$, 201.0886; Found 201.0888 (0.90 ppm error).



97a

$C_{11}H_{14}O$

3-Methyl-1,3,4,5-tetrahydrobenzo[*c*]oxepine (Compound 97a): Prepared according to general procedure B using 4-(2-(hydroxymethyl)phenyl)butan-2-one (146 mg, 0.818 mmol, 1.00 equiv.), Et_3SiH (144 μL, 0.90 mmol, 1.10 equiv.) and $BF_3{\cdot}OEt_2$ (111 μL, 0.90 mmol, 1.10 equiv.) in DCM (4.1 mL). Purification by flash column chromatography (~40 g SiO_2, cyclohexane : EtOAc – 97:3) gave the *title compound* **97a** (105 mg, 0.647 mmol, 79%, 65% over two steps) as a colourless oil; R_f = 0.21 (cyclohexane/EtOAc, 49:1); υ_{max}/cm^{-1} (thin film) 2969, 2929, 2841, 1082, 754; ^1H NMR (400 MHz, $CDCl_3$) δ 7.24–7.13 (4H, m, ArH), 4.74–4.65 (2H, m, H-1a, H-1b), 3.91 (1H, dqd, *J* = 10.3, 6.2, 2.0 Hz, H-3), 3.11 (1H, ddd, *J* = 15.0, 12.2, 1.9 Hz, H-5a), 2.87 (1H, ddd, *J* = 15.0, 6.8, 1.9 Hz, H-5b), 1.91 (1H, dddd, *J* = 14.1, 6.8, 2.0, 1.9 Hz, H-4a), 1.56 (1H, dddd, *J* = 14.1, 12.2, 10.3, 1.9 Hz, H-4b), 1.26 (3H, d, *J* = 6.2 Hz, H-6); ^{13}C NMR (101 MHz, $CDCl_3$) δ 142.3 (C, ArC), 140.0 (C, ArC), 128.9 (CH, ArCH), 128.3 (CH, ArCH), 127.8 (CH, ArCH), 126.1 (CH, ArCH), 81.2 (CH, C-3), 73.5 (CH_2, C-1), 36.5 (CH_2, C-4), 34.3 (CH_2, C-5), 22.9 (CH_3, C-6); HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{11}H_{15}O$, 163.1117; Found 163.1121 (2.10 ppm error).

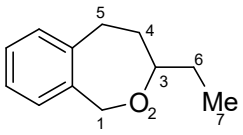


94e

$C_{12}H_{16}O_2$

1-[2-(Hydroxymethyl)phenyl]pentan-3-one (Compound 94e): Prepared according to general procedure E using $NaHCO_3$ (168 mg, 2.00 mmol, 2.00 equiv.), $Pd(OAc)_2$ (4.5 mg, 0.02 mmol, 0.02 equiv.), $^nBu_4NCl$ (417 mg, 1.50 mmol, 1.50 equiv.), 2-iodobenzyl alcohol (234 mg, 1.00 mmol, 1.00 equiv.), 1-penten-3-ol (154 μL, 1.50 mmol, 1.50 equiv.) in MeCN (2.5 mL). Purification

by flash column chromatography (~25 g SiO_2, cyclohexane : EtOAc – 2:1) gave the *title compound* **94e** (149 mg, 0.774 mmol, 77%) as a pale yellow oil; R_f = 0.30 (cyclohexane/EtOAc, 1:1); υ_{max}/cm^{-1} (thin film) 3422, 2976, 2939, 1709, 1455; ^1H NMR (400 MHz, $CDCl_3$) δ 7.35 (1H, dd, *J* = 7.2, 1.8 Hz, ArH), 7.28–7.15 (3H, m, ArH), 4.72 (2H, d, *J* = 5.6 Hz, H-6), 2.97 (2H, t, *J* = 7.1 Hz, H-1), 2.84 (2H, t, *J* = 7.1 Hz, H-2), 2.41 (2H, q, *J* = 7.3 Hz, H-4), 2.34 (1H, t, *J* = 5.6 Hz, H-7), 1.03 (3H, t, *J* = 7.3 Hz, H-5); ^{13}C NMR (101 MHz, $CDCl_3$) δ 208.4 (CO, C-2), 139.4 (C, ArC), 138.4 (C, ArC), 129.1 (CH, ArCH), 129.0 (CH, ArCH), 128.2 (CH, ArCH), 126.5 (CH, ArCH), 63.4 (CH_2, C-6), 44.8 (CH_2, C-2), 30.1 (CH_3, C-1), 25.7 (CH_2, C-5); HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{11}H_{14}NaO_2$, 201.0886; Found 201.0888 (0.90 ppm error).

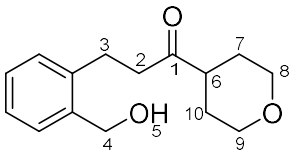


97e

$C_{12}H_{16}O$

3-Ethyl-1,3,4,5-tetrahydrobenzo[*c*]oxepine (Compound 97e): Prepared according to general procedure B using 1-(2-(hydroxymethyl)phenyl)pentan-3-one (149 mg, 0.774 mmol, 1.00 equiv.), Et_3SiH (136 µL, 0.85 mmol, 1.10 equiv.) and $BF_3{\cdot}OEt_2$ (105 µL, 0.85 mmol, 1.10 equiv.) in DCM (3.85 mL). Purification by flash column chromatography (~35 g SiO_2, cyclohexane : EtOAc – 97:3) gave the *title compound* **97e** (121 mg, 0.689 mmol, 89%, 69% over two steps) as a pale yellow oil; R_f = 0.41 (cyclohexane/EtOAc, 97:3); υ_{max}/cm^{-1} (thin film) 2960, 2841, 1083, 754; ^1H NMR (400 MHz, $CDCl_3$) δ 7.22–7.12 (4H, m, ArH), 4.72 (1H, d, *J* = 13.6 Hz, H-1a), 4.67 (1H, d, *J* = 13.6 Hz, H-1b), 3.62 (1H, dddd, *J* = 9.7, 7.2, 5.1, 2.0 Hz, H-3), 3.08 (1H, ddd, *J* = 14.6, 12.0, 2.0 Hz, H-5a), 2.88 (1H, ddd, *J* = 14.6, 6.8, 1.9 Hz, H-5b), 1.92 (1H, dddd, *J* = 14.1, 6.8, 2.0, 2.0 Hz, H-4a), 1.66–1.43 (3H, m, H-4b, H-6a, H-6b), 0.98 (3H, t, *J* = 7.5 Hz, H-7); ^{13}C NMR (101 MHz, $CDCl_3$) δ 142.4 (C, ArC), 140.2 (C, ArC), 128.9 (CH, ArCH), 128.3 (CH, ArCH), 127.8 (CH, ArCH), 126.1 (CH, ArCH), 86.8 (CH, C-3), 73.7 (CH_2, C-1), 34.5 (CH_2, C-4), 34.3 (CH_2, C-5), 29.9 (CH_2, C-6),

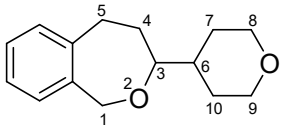
10.3 (CH_3, C-7);HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{12}H_{17}O$, 177.1274; Found 177.1263 (6.30 ppm error).



94f

$C_{15}H_{20}O_3$

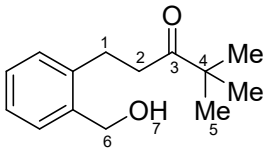
3-[2-(Hydroxymethyl)phenyl]-1-(tetrahydro-2*H*-pyran-4-yl)propan-1-one (Compound 94f): Prepared according to general procedure E using $NaHCO_3$ (168 mg, 2.00 mmol, 2.00 equiv.), $Pd(OAc)_2$ (4.5 mg, 0.02 mmol, 0.02 equiv.), $^nBu_4NCl$ (417 mg, 1.50 mmol, 1.50 equiv.), 2-iodobenzyl alcohol (234 mg, 1.00 mmol, 1.00 equiv.), 1-(tetrahydro-2*H*-pyran-4-yl)prop-2-en-1-ol **93b** (213 mg, 1.50 mmol, 1.50 equiv.) in MeCN (2.5 mL). Purification by flash column chromatography (~30 g SiO_2, cyclohexane : EtOAc – 2:1) gave the *title compound* **94f** (115 mg, 0.463 mmol, 46%) as a pale yellow oil; R_f = 0.09 (cyclohexane/EtOAc, 2:1); υ_{max}/cm^{-1} (thin film) 3435, 2952, 2924, 2850, 1705, 1089, 1016; ^1H NMR (400 MHz, $CDCl_3$) δ 7.34 (1H, dd, J = 6.8, 1.6 Hz, ArH), 7.25–7.12 (3H, m, ArH), 4.71 (2H, s, H-4), 3.95 (2H, ddd, J = 11.5, 4.2, 2.6 Hz, H-8_{eq}, H-9_{eq}), 3.38 (2H, ddd, J = 11.5, 11.4, 2.9 Hz, H-8_{ax}, H-9_{ax}), 2.97 (2H, t, J = 7.3 Hz, H-3), 2.84 (2H, t, J = 7.3 Hz, H-2), 2.50 (1H, app tt, J = 10.9, 4.3 Hz, H-6), 2.34 (1H, br s, H-5), 1.77–1.58 (4H, m, H-7_{ax}, H-7_{eq}, H-10_{ax}, H-10_{eq}); ^{13}C NMR (101 MHz, $CDCl_3$) δ 211.4 (C, C-1), 139.4 (C, ArC), 138.4 (C, ArC), 129.1 (CH, ArCH), 129.0 (CH, ArCH), 128.2 (CH, ArCH), 126.5 (CH, ArCH), 67.2 (2 × CH_2, C-8, C-9), 63.3 (CH_2, C-4), 47.6 (CH, C-6), 41.5 (CH_2, C-2), 28.0 (2 × CH_2, C-7, C-10), 25.7 (CH_2, C-3); HRMS (ESI-TOF) m/z: $[M + NH_4]^+$ calcd for $C_{15}H_{24}NO_3$, 266.1751; Found 266.1751 (0.10 ppm error).



97f

$C_{15}H_{20}O_2$

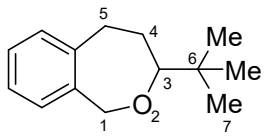
3-(Tetrahydro-2*H*-pyran-4-yl)-1,3,4,5-tetrahydrobenzo[*c*]oxepine (Compound 97f): Prepared according to general procedure B using 3-(2-(hydroxymethyl)phenyl)-1-(tetrahydro-2*H*-pyran-4-yl)propan-1-one **94f** (115 mg, 0.463 mmol, 1.00 equiv.), Et_3SiH (81.5 µL, 0.51 mmol, 1.10 equiv.) and $BF_3{\cdot}OEt_2$ (63.0 µL, 0.51 mmol, 1.10 equiv.) in DCM (2.3 mL). Purification by filtration through a plug of silica gave the *title compound* **97f** as a colourless crystalline solid (105 mg, 0.451 mmol, 97%, 45% over two steps); mp. 78–81 °C; R_f = 0.30 (cyclohexane/EtOAc, 6:1); υ_{max}/cm^{-1} (thin film) 2944, 2931, 1082, 763; ^1H NMR (400 MHz, $CDCl_3$) δ 7.22–7.13 (4H, m, ArH), 4.72 (1H, d, *J* = 13.6 Hz, H-1a), 4.64 (1H, d, *J* = 13.6 Hz, H-1b), 4.03–3.93 (2H, m, H-8_{eq}, H-9_{eq}), 3.44 (1H, ddd, *J* = 10.6, 6.7, 2.1 Hz, H-3), 3.41–3.29 (2H, m, H-8_{ax}, H-9_{ax}), 3.04 (1H, ddd, *J* = 14.5, 11.7, 2.1 Hz, H-5a), 2.92 (1H, ddd, *J* = 14.5, 6.8, 2.2 Hz, H-5b), 1.94 (1H, dddd, *J* = 13.9, 6.8, 2.1, 2.1 Hz, H-4a), 1.87–1.77 (1H, m, H-7_{ax} or H-7_{eq} or H-10_{ax} or H-10_{eq}), 1.69–1.59 (1H, m, H-6), 1.58–1.36 (4H, m, H-4b, H-7_{ax} or H-7_{eq} or H-10_{ax} or H-10_{eq}, H-7_{ax} or H-7_{eq}, H-10_{ax} or H-7_{eq}); ^{13}C NMR (101 MHz, $CDCl_3$) δ 142.2 (C, ArC), 140.1 (C, ArC), 129.0 (CH, ArCH), 128.1 (CH, ArCH), 127.8 (CH, ArCH), 126.1 (CH, ArCH), 88.8 (CH, C-3), 74.0 (CH_2, C-1), 68.2 (CH_2, C-8 or C-9), 67.8 (CH_2, C-8 or C-9), 41.1 (CH, C-6), 34.2 (CH_2, C-5), 31.6 (CH_2, C-4), 29.2 (CH_2, C-7 or C-10), 29.2 (CH_2, C-7 or C-10); HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{15}H_{21}O_2$, 233.1536; Found 233.1533 (1.40 ppm error).



94g

$C_{14}H_{20}O_2$

1-(2-(Hydroxymethyl)phenyl)-4,4-dimethylpentan-3-one (Compound 94g): Prepared according to general procedure E using $NaHCO_3$ (168 mg, 2.00 mmol, 2.00 equiv.), $Pd(OAc)_2$ (4.5 mg, 0.02 mmol, 0.02 equiv.), $^nBu_4NCl$ (417 mg, 1.50 mmol, 1.50 equiv.), 2-iodobenzyl alcohol (234 mg, 1.00 mmol, 1.00 equiv.), 4,4-dimethylpent-1-en-3-ol **93c** (171 mg, 1.50 mmol, 1.50 equiv., as a solution in Et_2O and cyclohexane) in MeCN (2.5 mL). Purification by flash column chromatography (~30 g SiO_2, cyclohexane : EtOAc – 5:2) gave the *title compound* **94g** (68.9 mg, 0.313 mmol, 31%) as a yellow oil; R_f = 0.41 (cyclohexane/EtOAc, 3:2); υ_{max}/cm^{-1} (thin film) 3396, 2966, 2928, 2871, 1701, 1478, 1366, 756; ^1H NMR (400 MHz, $CDCl_3$) δ 7.35 (1H, dd, J = 7.2, 1.8 Hz, ArH), 7.26–7.14 (3H, m, ArH), 4.72 (2H, s, H-6), 2.98–2.92 (2H, m, H-1), 2.90–2.84 (2H, m, H-2), 2.34 (1H, br s, H-7), 1.10 (9H, s, H-5); ^{13}C NMR (101 MHz, $CDCl_3$) δ 215.6 (C, C-3), 139.7 (C, ArC), 138.5 (C, ArC), 129.0 (CH, ArCH), 129.0 (CH, ArCH), 128.1 (CH, ArCH), 126.4 (CH, ArCH), 63.3 (CH_2, C-6), 44.1 (C, C-4), 37.9 (CH_2, C-2), 26.3 (3 × CH_3, C-5), 26.0 (CH_2, C-1); HRMS (ESI-TOF) m/z: $[M + NH_4]^+$ calcd for $C_{14}H_{24}NO_2$, 238.1802; Found 238.1802 (0.20 ppm error).



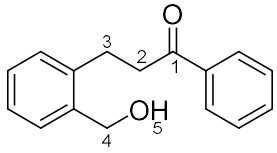
97g

$C_{14}H_{20}O$

3-(^{t}Butyl)-1,3,4,5-tetrahydrobenzo[*c*]oxepine (Compound 97g): Prepared according to general procedure B using 1-(2-(hydroxymethyl)phenyl)-4,4-dimethylpentan-3-one **94g** (68.9 mg, 0.313 mmol, 1.00 equiv.), Et_3SiH (54.9 µL, 0.344 mmol, 1.10 equiv.) and $BF_3{\cdot}OEt_2$ (42.4 µL, 0.344 mmol, 1.10 equiv.) in DCM (1.6 mL). Purification by filtration through a plug of silica gave the *title*

compound **97g** as a pale yellow oil (35.7 mg, 0.175 mmol, 56%, 18% over two steps); R_f = 0.35 (cyclohexane/EtOAc, 49:1); υ_{max}/cm^{-1} (thin film) 2950, 2842, 1088, 752; ^1H NMR (400 MHz, $CDCl_3$) δ 7.23–7.12 (4H, m, ArH), 4.78 (1H, d, *J* = 13.7 Hz, H-1a), 4.63 (1H, d, *J* = 13.7 Hz, H-1b), 3.28 (1H, dd, *J* = 10.7, 1.8 Hz, H-3), 3.04–2.91 (2H, m, H-5a, H-5b), 2.03–1.91 (1H, m, H-4a), 1.54 (1H, dddd, *J* = 14.0, 10.7, 10.6, 3.5 Hz, H-4b), 0.93 (9H, s, H-7); ^{13}C NMR (101 MHz, $CDCl_3$) δ 142.4 (C, ArC), 140.5 (C, ArC), 129.0 (CH, ArCH), 128.0 (CH, ArCH), 127.6 (CH, ArCH), 126.0 (CH, ArCH), 93.5 (CH, C-3), 74.7 (CH_2, C-1), 35.1 (C, C-6), 34.8 (CH_2, C-5), 29.0 (CH_2, C-4), 26.4 (3 × CH_3, C-7); HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{14}H_{20}O$, 205.1587; Found 205.1582 (2.30 ppm error).

Note: reaction underwent work-up, NMR showed ~50% conversion. Reaction re-submitted to conditions for further 3 hours.

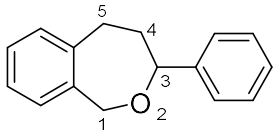


94h

$C_{16}H_{16}O_2$

3-[2-(Hydroxymethyl)phenyl]-1-phenylpropan-1-one (Compound 94h): Prepared according to general procedure E using $NaHCO_3$ (168 mg, 2.00 mmol, 2.00 equiv.), $Pd(OAc)_2$ (4.5 mg, 0.02 mmol, 0.02 equiv.), $^nBu_4NCl$ (417 mg, 1.50 mmol, 1.50 equiv.), 2-iodobenzyl alcohol (234 mg, 1.00 mmol, 1.00 equiv.), α-vinylbenzyl alcohol (201 mg, 1.50 mmol, 1.50 equiv.) in MeCN (2.5 mL). Purification by flash column chromatography (~35 g SiO_2, cyclohexane : EtOAc – 2:1) gave the *title compound* **94h** (178 mg, 0.740 mmol, 74%) as an off-white solid; mp. 69–71 °C; R_f = 0.16 (cyclohexane/EtOAc, 2:1); υ_{max}/cm^{-1} (thin film) 3414, 3062, 1682, 1449, 1206, 745; ^1H NMR (400 MHz, $CDCl_3$) δ 7.99–7.90 (2H, m, ArH), 7.60–7.57 (1H, m, ArH), 7.48–7.40 (2H, m, ArH), 7.38 (1H, dt, *J* = 6.9, 1.3 Hz, ArH), 7.27–7.18 (3H, m, ArH), 4.76 (2H, d, *J* = 4.5 Hz, H-4), 3.37 (2H, t, *J* = 7.4 Hz, H-2), 3.14 (2H, t, *J* = 7.4 Hz, H-3), 2.74–2.66 (1H, m, H-5); ^{13}C NMR (101 MHz, $CDCl_3$) δ 199.6 (C, C-1), 139.5 (C, ArC), 138.5

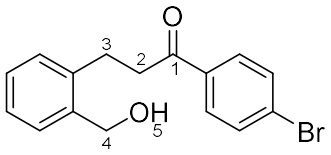
(C, ArC), 136.7 (C, ArC), 133.1 (CH, ArCH), 129.1 (CH, ArCH), 129.0 (CH, ArCH), 128.5 (2 × CH, ArCH), 128.1 (CH, ArCH), 128.0 (2 × CH, ArCH), 126.5 (CH, ArCH), 63.2 (CH_2, C-4), 39.9 (CH_2, C-2), 26.2 (CH_2, C-3); HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{16}H_{17}O_2$, 241.1223; Found 241.1223 (0.20 ppm error).



97h

$C_{16}H_{16}O$

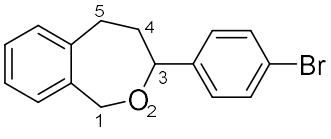
3-Phenyl-1,3,4,5-tetrahydrobenzo[*c*]oxepine (Compound 97h): Prepared according to general procedure B using 3-(2-(hydroxymethyl)phenyl)-1-phenylpropan-1-one **94h** (178 mg, 0.740 mmol, 1.00 equiv.), Et_3SiH (129 μL, 0.81 mmol, 1.10 equiv.) and $BF_3{\cdot}OEt_2$ (100 μL, 0.81 mmol, 1.10 equiv.) in DCM (3.7 mL). Purification by flash column chromatography (~40 g SiO_2, cyclohexane : EtOAc – 97:3) gave the *title compound* **97h** (149 mg, 0.666 mmol, 90%, 67% over two steps) as a colourless crystalline solid; mp. 64–66 °C; R_f = 0.24 (cyclohexane/EtOAc, 97:3); υ_{max}/cm^{-1} (thin film) 3025, 2928, 2847, 1493, 1451, 1090, 1074, 754, 699; ^1H NMR (400 MHz, $CDCl_3$) δ 7.41–7.34 (4H, m, ArH), 7.32–7.22 (5H, m, ArH), 4.92–4.84 (2H, m, H-1a, H-1b), 4.81 (1H, dd, *J* = 10.6, 2.2 Hz, H-3), 3.29 (1H, ddd, *J* = 14.9, 12.1, 2.0 Hz, H-5a), 3.02 (1H, ddd, *J* = 14.9, 6.8, 1.8 Hz, H-5b), 2.17 (1H, dddd, *J* = 14.1, 6.8, 2.2, 2.0 Hz, H-4a), 1.95 (1H, dddd, *J* = 14.1, 12.1, 10.6, 1.8 Hz, H-4b); ^{13}C NMR (101 MHz, $CDCl_3$) δ 143.6 (C, ArC), 142.1 (C, ArC), 1400 (C, ArC), 129.0 (CH, ArCH), 128.5 (CH, ArCH), 128.3 (CH, 2 × ArCH) (2 × ArCH), 127.9 (CH, ArCH), 127.3 (CH, ArCH), 126.2 (CH, ArCH), 125.9 (CH, 2 × ArCH) (2 × ArCH), 87.5 (CH, C-3), 74.0 (CH_2, C-1), 37.2 (CH_2, C-4), 34.6 (CH_2, C-5); HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{16}H_{16}NaO_2$, 247.1093; Found 247.1089 (1.60 ppm error).



94i

$C_{16}H_{15}BrO_2$

1-(4-Bromophenyl)-3-[2-(hydroxymethyl)phenyl]propan-1-one (Compound 94i): Prepared according to general procedure E using $NaHCO_3$ (168 mg, 2.00 mmol, 2.00 equiv.), $Pd(OAc)_2$ (4.5 mg, 0.02 mmol, 0.02 equiv.), $^nBu_4NCl$ (417 mg, 1.50 mmol, 1.50 equiv.), 2-iodobenzyl alcohol (234 mg, 1.00 mmol, 1.00 equiv.), 1-(4-bromophenyl)prop-2-en-1-ol **93d** (320 mg, 1.50 mmol, 1.50 equiv.) in MeCN (2.5 mL). Purification by flash column chromatography (~45 g SiO_2, cyclohexane : EtOAc – 4:1) gave the *title compound* **94i** (146 mg, 0.456 mmol, 46%) as an pale yellow solid; mp. 80–82 °C; R_f = 0.30 (cyclohexane/EtOAc, 2:1); υ_{max}/cm^{-1} (thin film) 3420, 2924, 1682, 1585, 1398, 1203, 1070, 761; ^1H NMR (400 MHz, $CDCl_3$) δ 7.80 (2H, d, *J* = 8.6 Hz, ArH), 7.57 (2H, d, *J* = 8.6 Hz, ArH), 7.38–7.33 (1H, m, ArH), 7.29–7.18 (3H, m, ArH), 4.74 (2H, s, H-4), 3.32 (2H, t, *J* = 7.4 Hz, H-2), 3.12 (2H, t, *J* = 7.4 Hz, H-3), 2.53 (1H, br s, H-5); ^{13}C NMR (101 MHz, $CDCl_3$) δ 198.6 (C, C-1), 139.4 (C, ArC), 138.4 (C, ArC), 135.4 (C, ArC), 131.9 (2 × CH, ArCH), 129.6 (2 × CH, ArCH), 129.2 (CH, ArCH), 129.1 (CH, ArCH), 128.3 (C, ArC), 128.2 (CH, ArCH)126.6 (CH, ArCH), 63.3 (CH_2, C-4), 40.0 (CH_2, C-2), 26.2 (CH_2, C-3); HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{16}H_{15}{}^{79}BrNaO_2$, 341.0148; Found 341.0147 (0.20 ppm error).

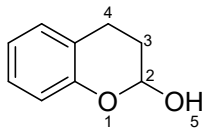


97i

$C_{16}H_{15}BrO$

3-(4-Bromophenyl)-1,3,4,5-tetrahydrobenzo[*c*]oxepine (Compound 97i): Prepared according to general procedure B using 1-(4-bromophenyl)-3-(2-(hydroxymethyl)phenyl)propan-1-one **94i** (146 mg, 0.740 mmol, 1.00 equiv.), Et_3SiH (81.5 μL, 0.51 mmol, 1.10 equiv.) and $BF_3{\cdot}OEt_2$ (63.0 μL, 0.51 mmol,

1.10 equiv.) in DCM (2.3 mL). Purification by flash column chromatography (~35 g SiO_2, cyclohexane : EtOAc – 98:2) gave the *title compound* **97i** (113 mg, 0.373 mmol, 81%, 37% over two steps) as a colourless crystalline solid; mp. 108–111 °C; R_f = 0.35 (cyclohexane/EtOAc, 49:1); υ_{max}/cm^{-1} (thin film) 2930, 2852, 1486, 1083, 1007, 793, 756; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 (2H, d, *J* = 8.5 Hz, ArH), 7.28–7.19 (6H, m, ArH), 4.88–4.79 (2H, m, H-1a, H-1b), 4.75 (1H, dd, *J* = 10.6, 2.1 Hz, H-3), 3.24 (1H, ddd, *J* = 14.8, 12.2, 2.0 Hz, H-5a), 2.98 (1H, ddd, *J* = 14.8, 6.8, 1.8 Hz, H-5b), 2.11 (1H, dddd, *J* = 14.2, 6.8, 2.1, 2.0 Hz, H-4a), 1.85 (1H, dddd, *J* = 14.2, 12.2, 10.6, 1.8 Hz, H-4b); ^{13}C NMR (101 MHz, $CDCl_3$) δ 142.6 (C, ArC), 141.9 (C, ArC), 139.8 (C, ArC), 131.3 (CH, 2 × ArCH), 129.1 (CH, ArCH), 128.5 (CH, ArCH), 128.1 (CH, ArCH), 127.6 (CH, 2 × ArCH), 126.3 (CH, ArCH), 121.1 (C, ArC), 86.6 (CH, C-3), 74.0 (CH_2, C-1), 37.2 (CH_2, C-4), 34.4 (CH_2, C-5); HRMS (ESI-TOF) m/z: [M + Na]$^+$ calcd for $C_{16}H_{15}{}^{79}BrNaO$, 325.0198; Found 325.0191 (2.20 ppm error).

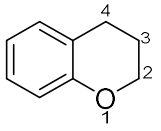


102
$C_9H_{10}O_2$

Chroman-2-ol (Compound 102): Prepared according to general procedure E using $NaHCO_3$ (168 mg, 2.00 mmol, 2.00 equiv.), $Pd(OAc)_2$ (4.5 mg, 0.02 mmol, 0.02 equiv.), ^{n}Bu$_4$NCl (417 mg, 1.50 mmol, 1.50 equiv.), 2-iodophenol (220 mg, 1.00 mmol, 1.00 equiv.), allyl alcohol (102 µL, 1.50 mmol, 1.50 equiv.) in MeCN (2.5 mL). Purification by flash column chromatography (~25 g SiO_2, cyclohexane : EtOAc – 5:1) gave the title compound **102** (171 mg, 0.814 mmol, 81%) as an yellow oil; R_f = 0.30 (cyclohexane/EtOAc, 3:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.12 (1H, ddd, *J* = 8.1, 7.6, 1.5 Hz, ArH), 7.08 (1H, dd, *J* = 7.5, 1.5 Hz, ArH), 6.89 (1H, ddd, *J* = 7.6, 7.5, 1.2 Hz, ArH), 6.83 (1H, dd, *J* = 8.1, 1.2 Hz, ArH), 5.64–5.60 (1H, m, H-2), 3.25 (1H, br s, OH), 3.00 (1H, ddd, *J* = 16.5, 10.4, 6.3 Hz, H-4a), 2.71 (1H, ddd, *J* = 16.5, 5.3, 5.3 Hz, H-4b), 2.10–1.94 (2H, m, H-3a, H-3b); ^{13}C NMR (101 MHz, $CDCl_3$) δ 151.9 (C, ArC), 129.3

(CH, ArCH), 127.4 (CH, ArCH), 122.0 (C, ArC), 120.8 (CH, ArCH), 116.9 (CH, ArCH), 92.1 (CH, C-2), 27.0 (CH_2, C-3), 20.2 (CH_2, C-4).

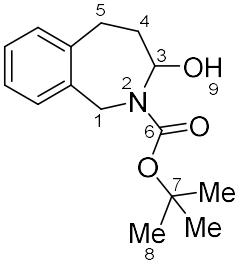
Data are consistent with those published.[202]



103
$C_9H_{10}O$

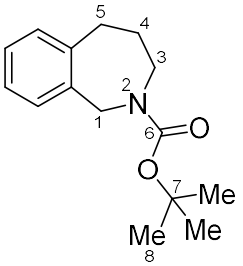
Chromane (Compound 103): Prepared according to general procedure B using chroman-2-ol **102** (122 mg, 0.814 mmol, 1.00 equiv.), Et_3SiH (143 µL, 0.895 mmol, 1.10 equiv.) and $BF_3{\cdot}OEt_2$ (110 µL, 0.895 mmol, 1.10 equiv.) in DCM (4.1 mL). Purification by flash column chromatography (~25 g SiO_2, cyclohexane : EtOAc – 49:1) gave the title compound **103** (74.3 mg, 0.554 mmol, 68%, 55% over two steps) as a colourless oil; R_f = 0.26 (cyclohexane/EtOAc, 49:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.08 (1H, ddd, *J* = 8.3, 7.5, 1.6 Hz, ArH), 7.04 (1H, dd, *J* = 7.5, 1.6 Hz, ArH), 6.83 (1H, ddd, *J* = 7.5, 7.5, 1.2 Hz, ArH), 6.79 (1H, dd, *J* = 8.3, 1.2 Hz, ArH), 4.21–4.16 (2H, m, H-2a, H-2b), 2.80 (2H, app t, *J* = 6.5 Hz, H-4a, H-4b), 2.05–1.97 (2H, m, H-3a, H-3b); ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.9 (C, ArC), 129.8 (CH, ArCH), 127.2 (CH, ArCH), 122.2 (C, ArC), 120.1 (CH, ArCH), 116.7 (CH, ArCH), 66.4 (CH_2, C-2), 24.9 (CH_2, C-4), 22.4 (CH_2, C-3).

Data are consistent with those published.[203]



105
$C_{15}H_{21}NO_3$

***tert*-Butyl 3-hydroxy-1,3,4,5-tetrahydro-2*H*-benzo[*c*]azepine-2-carboxylate (Compound 105)**: Prepared according to general procedure E using $NaHCO_3$ (168 mg, 2.00 mmol, 2.00 equiv.), $Pd(OAc)_2$ (4.5 mg, 0.02 mmol, 0.02 equiv.), $^nBu_4NCl$ (417 mg, 1.50 mmol, 1.50 equiv.), *N*-Boc-2-iodobenzylamine (333 mg, 1.00 mmol, 1.00 equiv.), allyl alcohol (102 µL, 1.50 mmol, 1.50 equiv.) in MeCN (2.5 mL). Purification by flash column chromatography (~30 g SiO_2, cyclohexane : EtOAc – 5:1) gave the *title compound* **105** (232 mg, 0.881 mmol, 88%) as an yellow oil; $R_f = 0.19$ (cyclohexane/EtOAc, 4:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19–7.10 (4H, m, ArH), 5.92–5.75 (1H, m, H-3), 4.69–4.56 (1H, m, H-1a), 4.43–4.31 (1H, m, H-1b), 3.16 (1H, app dd, $J = 16.0, 9.7$ Hz, H-5a), 2.76–2.65 (1H, m, H-5b), 2.22–2.09 (1H, m, H-4a), 2.07–1.98 (1H, m, H-4b), 1.40 (9H, s, H-8).



106
$C_{15}H_{21}NO_2$

***tert*-Butyl 1,3,4,5-tetrahydro-2*H*-benzo[*c*]azepine-2-carboxylate (Compound 106)**: Prepared according to general procedure B using *tert*-Butyl 3-hydroxy-1,3,4,5-tetrahydro-2*H*-benzo[*c*]azepine-2-carboxylate **105** (232 mg, 0.881 mmol, 1.00 equiv.), Et_3SiH (155 µL, 0.968 mmol, 1.10 equiv.) and $BF_3{\cdot}OEt_2$ (119 µL, 0.968 mmol, 1.10 equiv.) in DCM (4.4 mL). Purification by flash column chromatography (~30 g SiO_2, cyclohexane : EtOAc – 15:1) gave

the title compound **106** (56.5 mg, 0.228 mmol, 26%, 23% over two steps) as a colourless oil; R_f = 0.26 (cyclohexane/EtOAc, 9:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.20–7.10 (4H, m, ArH), 4.46–4.34 (2H, m, H-1), 3.75–3.61 (2H, m, H-3), 2.98–2.89 (2H, m, H-5), 1.83–1.70 (2H, m, H-4), 1.39 (9H, s, H-8); ^{13}C NMR (126 MHz, $CDCl_3$) δ 155.0 (C, C-6), 142.0 (C, ArC), 138.8 (C, ArC), 129.5 (CH, ArCH), 129.1 (CH, ArCH), 127.4 (CH, ArCH), 125.7 (CH, ArCH), 79.5 (C, C-7), 52.3 (CH_2, C-1), 50.3 (CH_2, C-3), 35.4 (CH_2, C-5), 28.4 (3 × CH_3, C-8), 28.0 (CH_2, C-4)

Data are consistent with those published.[204]

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